Organic Reactions

VOLUME I

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PREFACE

In the course of nearly every program of research in organic chemistry the investigator finds it necessary to use several of the better-known synthetic reactions. To discover the optimum conditions for the application of even the most familiar one to a compound not previously subjected to the reaction often requires an extensive search of the literature; even then a series of experiments may be necessary. When the results of the investigation are published, the synthesis, which may have required months of work, is usually described without comment. The background of knowledge and experience gained in the literature search and experimentation is thus lost to those who subsequently have occasion to apply the general method. The student of preparative organic chemistry faces similar difficulties. The textbooks and laboratory manuals furnish numerous examples of the application of various syntheses, but only rarely do they convey an accurate conception of the scope and usefulness of the processes.

For many years American organic chemists have discussed these problems. The plan of compiling critical discussions of the more important reactions thus was evolved. Volume I of *Organic Reactions* is a collection of twelve chapters, each devoted to a single reaction, or a definite phase of a reaction, of wide applicability. The authors have had experience with the processes surveyed. The subjects are presented from the preparative viewpoint, and particular attention is given to limitations, interfering influences, effects of structure, and the selection of experimental techniques. Each chapter includes several detailed procedures illustrating the significant modifications of the method. Most of these procedures have been found satisfactory by the author or one of the editors, but unlike those in *Organic Syntheses* they have not been subjected to careful testing in two or more laboratories. When all known examples of the reaction are not mentioned in the text, tables are given to list compounds which have been prepared by or subjected to the reaction. Every effort has been made to include in the tables all such compounds and references; however, because of the very nature of the reactions discussed and their frequent use as one of the several steps of syntheses in which not all of the intermediates have been isolated, some instances may well have been missed. Nevertheless, the

investigator will be able to use the tables and their accompanying bibliographies in place of most or all of the literature search so often required.

Because of the systematic arrangement of the material in the chapters and the entries in the tables, users of the book will be able to find information desired by reference to the table of contents of the appropriate chapter. In the interest of economy the entries in the index have been kept to a minimum, and, in particular, the compounds listed in the tables are not repeated in the index.

The success of this publication, which will appear periodically in volumes of about twelve chapters, depends upon the cooperation of organic chemists and their willingness to devote time and effort to the preparation of the chapters. They have manifested their interest already by the almost unanimous acceptance of invitations to contribute to the work. The editors will welcome their continued interest and their suggestions for improvements in *Organic Reactions.*

CONTENTS

CHAPTER		PAGE
1	THE REFORMATSKY REACTION—*Ralph L Shriner*	1
2	THE ARNDT-EISTERT SYNTHESIS—*W. E. Bachmann* and *W S Struve*	38
3.	CHLOROMETHYLATION OF AROMATIC COMPOUNDS—*Reynold C Fuson* and *C. H. McKeever*	63
4.	THE AMINATION OF HETEROCYCLIC BASES BY ALKALI AMIDES—*Marlin T. Leffler*	91
5.	THE BUCHERER REACTION—*Nathan L Drake*	105
6.	THE ELBS REACTION—*Louis F. Fieser*	129
7.	THE CLEMMENSEN REDUCTION—*Elmore L Martin*	155
8.	THE PERKIN REACTION AND RELATED REACTIONS—*John R. Johnson*	210
9.	THE ACETOACETIC ESTER CONDENSATION AND CERTAIN RELATED REACTIONS—*Charles R. Hauser* and *Boyd E Hudson, Jr*	266
10.	THE MANNICH REACTION—*F. F. Blicke*	303
11.	THE FRIES REACTION—*A. H. Blatt*	342
12	THE JACOBSEN REACTION—*Lee Irvin Smith*	370
	INDEX	385

CHAPTER 1

THE REFORMATSKY REACTION

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Indiana University

CONTENTS

PAGE

GENERAL CONSIDERATIONS 2
Relative Reactivities of Reagents 4
Side Reactions 4

THE USE OF THE REFORMATSKY REACTION 5
Lengthening the Carbon Chain 6
Synthesis of Arylacetic Acids 9
Synthesis of β-Ketoesters 9

DEHYDRATION OF THE β-HYDROXYESTERS 11
Table I 13

SELECTION OF EXPERIMENTAL CONDITIONS. PROCEDURES 14
Ethyl β-Phenyl-β-hydroxypropionate 16
Ethyl 1-Hydroxycyclohexylacetate 17
Ethyl α-Methyl-β-phenyl-β-hydroxybutyrate 17
Dimethyl Ester of 7-Methoxy-2-methyl-2-carboxy-1-hydroxy-1,2,3,4-tetrahydrophenanthrene-1-acetic Acid 18

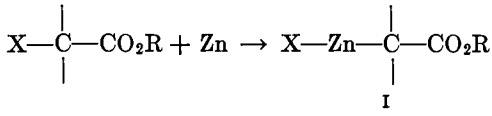
EXAMPLES OF THE REFORMATSKY REACTION 19
Aldehydes. Table II 20
Ketones. Table III 24
Esters. Table IV 33
Substituted Amides 34

VARIATIONS OF THE REFORMATSKY REACTION. 34
Use of Halogen Compounds Other Than α-Haloesters 34
Table V 35
Use of Compounds Other Than Carbonyl Derivatives 36

GENERAL CONSIDERATIONS

The reaction which takes place between a carbonyl compound such as an aldehyde, a ketone, or an ester and an α-haloester in the presence of zinc is commonly known as the Reformatsky reaction.[1] It represents an extension of the reactions of carbonyl compounds with a dialkylzinc or an alkylzinc halide, but possesses the advantage that the isolation of the organozinc compound is unnecessary. The process creates a new carbon-carbon linkage and appears to involve the following steps.[2]

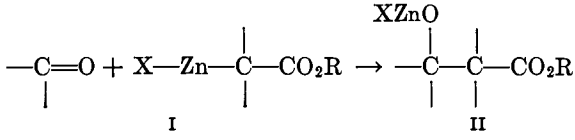
1. Formation of an organozinc halide.



[1]

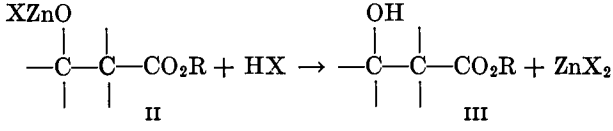
(X represents Cl, Br, I; R is an alkyl group.)

2. Addition to the carbonyl group of the aldehyde or ketone.



[2]

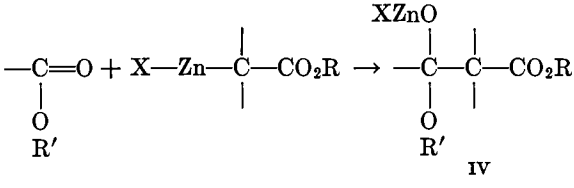
3. Decomposition by dilute acids.



[3]

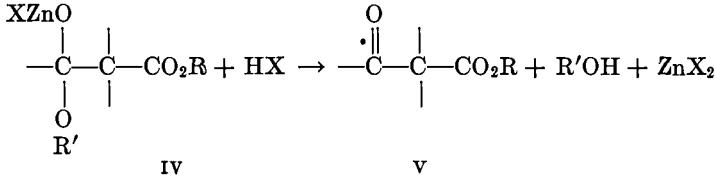
Thus an aldehyde or a ketone leads to a β-hydroxyester (III) as the final product. Subsequent or simultaneous dehydration may produce an unsaturated ester.

When an ester is used instead of an aldehyde or ketone the addition product IV is formed.

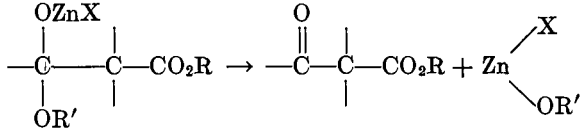


[1] Reformatsky, *Ber.*, **20**, 1210 (1887).
[2] Reformatsky, *J. prakt. Chem.*, **54**, 469 (1896).

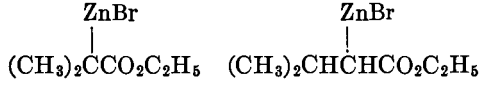
If this addition complex is stable, then the product obtained by hydrolysis of the reaction mixture is a β-ketoester.



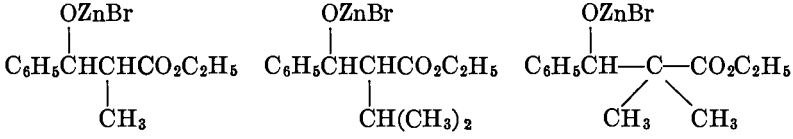
If the addition product decomposes spontaneously, the β-ketoester (V) may again be the final product, or if the keto group in this ketoester is reactive and an excess of the organozinc halide (I) is present further reaction may take place as in equations 2 and 3 above.



Evidence for the existence of the organozinc halide (I) as an intermediate was provided by G. Dain,[3] who isolated and analyzed the following compounds.



Three addition products corresponding to the complex II were also obtained.



These complexes, therefore, parallel the intermediates formed in the well-known reactions involving the Grignard reagent or similar organometallic halides and carbonyl compounds. Indeed, magnesium may be used in place of zinc (p. 16), and apparently the intermediate complexes are analogous. Grignard reagents cannot be prepared from α-haloesters and magnesium alone; hence the Reformatsky reaction offers a pro-

[3] Dain, *J. Russ. Phys. Chem. Soc.*, **28**, 593 (1896).

cedure by which the equivalent of a Grignard reagent from an α-haloester is available for synthetic work. In the subsequent discussion these intermediates will not always be written and only the reactants and main products will be shown. It is to be understood, however, that the steps shown above are always involved.

Relative Reactivities of Reagents. The order of reactivity of carbonyl compounds in the Reformatsky reaction is $RCHO > R_2CO > RCO_2C_2H_5$. The order of reactivity of the haloacetates is $ICH_2CO_2C_2H_5 > BrCH_2CO_2C_2H_5 > ClCH_2CO_2C_2H_5$. The α-chloroacetic esters often react slowly or not at all, and the α-iodoesters are not readily available. Consequently, most Reformatsky reactions have been carried out with the α-bromoesters. Esters containing a secondary or tertiary α-chlorine atom are much more reactive than the corresponding primary derivatives and in some cases are reported to give good yields. The three types of α-bromoesters appear to react equally well.

Side Reactions. Various side reactions may be expected whenever the Reformatsky reaction is carried out. The intermediate organozinc halide may add to the carbonyl group of the α-haloester used as the reagent; for example, Hann and Lapworth [4a] have reported that zinc and ethyl bromoacetate react to produce ethyl γ-bromoacetoacetate.

$$2BrCH_2CO_2C_2H_5 + Zn \rightarrow BrCH_2\underset{\underset{OC_2H_5}{|}}{\overset{\overset{OZnBr}{|}}{C}}\text{—}\dot{C}H_2CO_2C_2H_5$$

$$\downarrow$$

$$BrCH_2COCH_2CO_2C_2H_5 + C_2H_5OZnBr$$

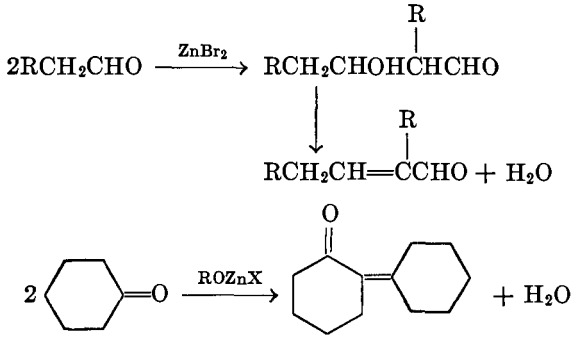
Since aldehydes and ketones possess far greater carbonyl reactivity than the ester group, this side reaction is not important when aldehydes and ketones are used. Moreover, its significance may be minimized by using an excess of the bromoester and adding the latter in successive portions.

A common side reaction is the coupling of the haloester by the zinc.

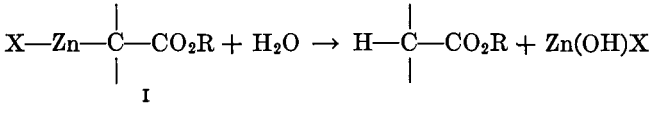
$$2BrCH_2CO_2C_2H_5 + Zn \rightarrow ZnBr_2 + \begin{array}{c} CH_2CO_2C_2H_5 \\ | \\ CH_2CO_2C_2H_5 \end{array}$$

When aliphatic aldehydes or aliphatic or alicyclic ketones are used, these may undergo aldolization under the influence of the zinc salts.

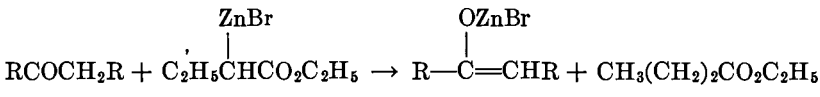
[4a] Hann and Lapworth, *Proc. Chem. Soc.*, **19**, 189 (1903).



Not only does aldolization use up the aldehyde or ketone, but also the dehydration of the aldol produces water which decomposes the intermediate organozinc halide (I).



The organozinc compound may also induce enolization.[4b]



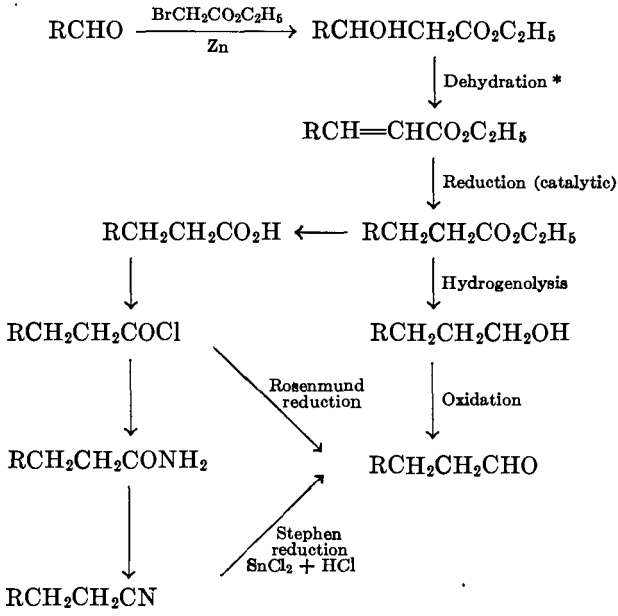
Subsequent hydrolysis of the bromozinc enolate regenerates the original ketone. This reaction accounts for the recovery of appreciable amounts of the starting material and the presence of ethyl *n*-butyrate among the reaction products.

THE USE OF THE REFORMATSKY REACTION

From a synthetic point of view the Reformatsky reaction not only constitutes a method for preparing β-hydroxyesters and the corresponding unsaturated esters and acids but also is a valuable procedure for lengthening the carbon chain by two carbon atoms. The chain may be branched on the α-, β-, or α- and β-carbon atoms by proper choice of reactants. Since the product contains the carbethoxy group, it is possible by a proper sequence of reactions to repeat the chain-lengthening process. Several examples have been chosen to illustrate the utility of the condensation and to point out the part played by the Reformatsky reaction in a synthetic sequence.

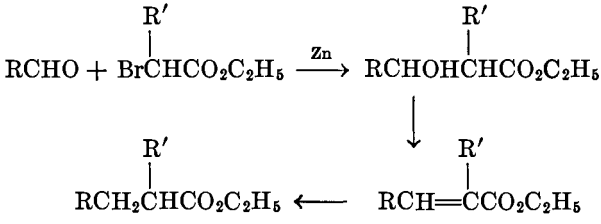
[4b] Newman, *J. Am. Chem. Soc.*, **62**, 870 (1940).

Lengthening the Carbon Chain. *Lengthening the Carbon Chain of an Aldehyde without Branching the Chain.*

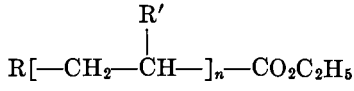


The process may be repeated, leading to $R(CH_2)_4CHO$.

Lengthening the Carbon Chain with Branching on the α-Carbon Atom.

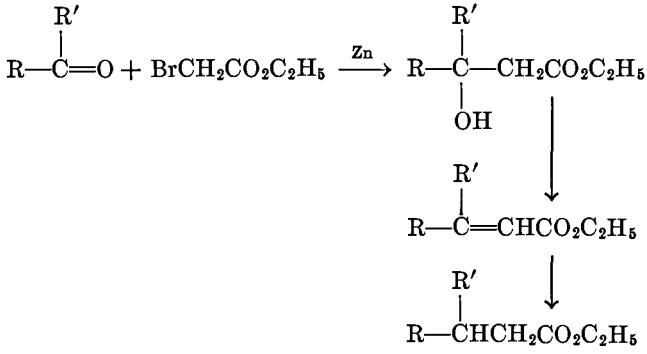


Use of the sequence of reactions outlined under the first example to convert the ester group into an aldehyde group leads to the synthesis of branched-chain esters of the following type.

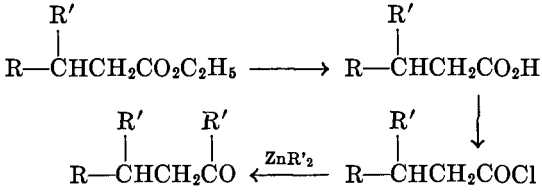


* The dehydration of β-hydroxyesters frequently produces a mixture of α,β- and β,γ-unsaturated esters (see p. 12). Both may be reduced catalytically to the saturated ester.

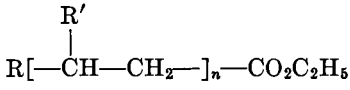
Lengthening the Carbon Chain with Branching on the β-Carbon Atom.



The ester group of the final product may be converted into a keto group by the following reactions.

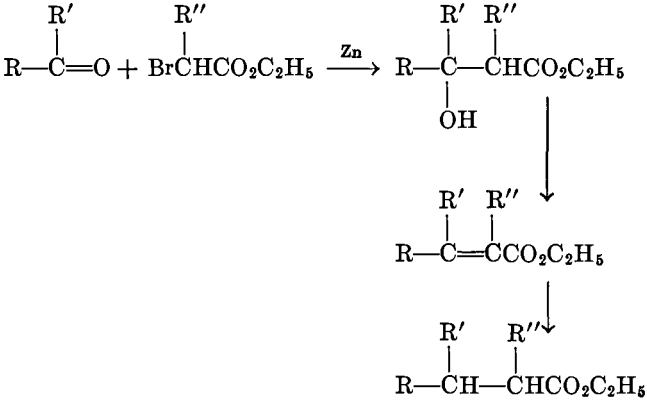


Repetition of these sequences of reactions leads to the preparation of a second type of branched-chain ester.



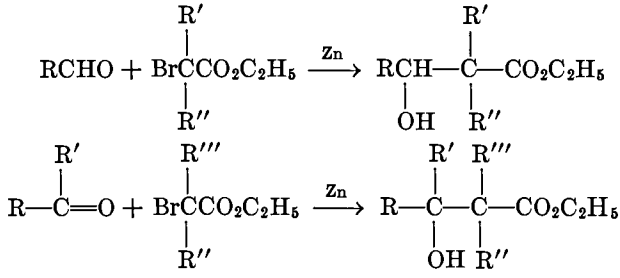
The nature of the R′ group is determined by the starting ketone and the zinc alkyl used in converting the acid chloride into the final ketone. The R′ groups may be alike or different.

Lengthening the Carbon Chain with Branching on Both α- and β-Carbon Atoms.



The nature of the R and R′ groups is determined by the ketone and that of the R″ group by the haloester.

Lengthening the Carbon Chain with Double Branching on the α-Carbon Atom.



Occasionally, hydroxyesters of this type may be dehydrated to β,γ-unsaturated esters which can then be reduced to the saturated esters. However, conversion of these α,α-disubstituted-β-hydroxyesters to the saturated esters is usually best effected by refluxing with phosphorus and hydriodic acid.

These five general types of reactions therefore constitute methods for synthesizing straight-chain and branched-chain hydroxyesters and unsaturated and saturated esters and acids.

Whether or not the Reformatsky reaction is the best method for lengthening a given carbon chain depends on a number of factors. For example, cinnamic acid may be prepared by any of the following reactions.

Perkin reaction — *Yield, %**

$$C_6H_5CHO + (CH_3CO)_2O \xrightarrow[(C_5H_5N)]{CH_3CO_2Na} C_6H_5CH{=}CHCO_2H \qquad 80$$

Claisen condensation

$$C_6H_5CHO + CH_3CO_2C_2H_5 \xrightarrow{NaOC_2H_5} C_6H_5CH{=}CHCO_2C_2H_5 \qquad 74$$

$$\downarrow$$

$$C_6H_5CH{=}CHCO_2H \qquad 72$$

Reformatsky reaction

$$C_6H_5CHO + BrCH_2CO_2C_2H_5 \xrightarrow{Zn} C_6H_5\overset{OH}{C}H{-}CH_2CO_2C_2H_5 \qquad 64$$

$$\downarrow -H_2O$$

$$C_6H_5CH{=}CHCO_2C_2H_5 \qquad 57$$

$$\downarrow$$

$$C_6H_5CH{=}CHCO_2H \qquad 55$$

Knoevenagel condensation

$$C_6H_5CHO + CH_2(CO_2H)_2 \xrightarrow{NH_3} C_6H_5CH{=}C(CO_2H)_2$$

$$\downarrow -CO_2$$

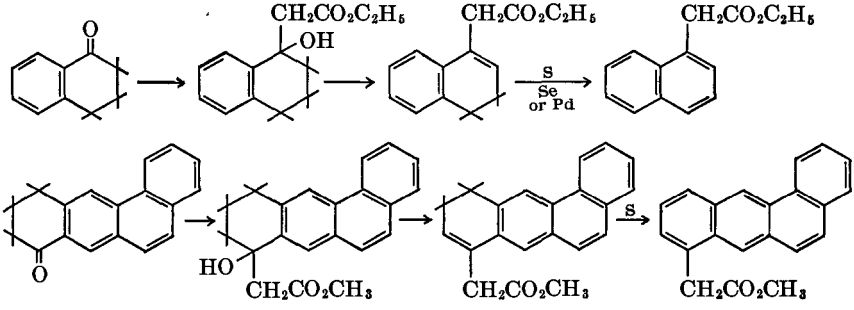
$$C_6H_5CH{=}CHCO_2H \qquad 80$$

* These figures represent the over-all yields of the products shown, based on benzaldehyde.

On the basis of yields alone, the Knoevenagel or Perkin condensation would be preferred for preparing cinnamic acid. From an economic point of view, the reaction chosen would depend on the relative cost of the reagents and the time involved in the preparation. The Reformatsky reaction would not be selected.

However, in the synthesis of an unsaturated acid with branching on the β-carbon atom ($C_6H_5C(R)=CHCO_2H$) from the ketone (C_6H_5COR) the Reformatsky is the only method of these four which will give good yields; the Perkin reaction fails to take place, the Claisen condensation leads to an entirely different product (a 1,3-diketone), and the Knoevenagel condensation gives low yields for small R groups and fails if R is large. Branching of the chain on *both* α- and β-carbon atoms can be accomplished only by the Reformatsky method.

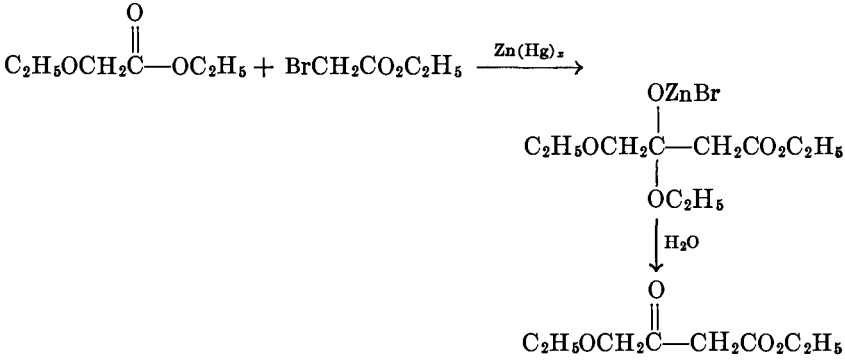
Synthesis of Arylacetic Acids. The Reformatsky reaction is also particularly well adapted to the synthesis of arylacetic acids or their esters. Thus, ketones such as 1-tetralone or 1-ketotetrahydrophenanthrene[5] give hydroxyesters which are readily dehydrated to dihydroarylacetic esters. The latter may be easily dehydrogenated to the aromatic compounds.



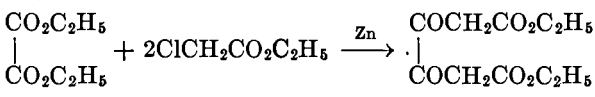
Synthesis of β-Ketoesters. Very few applications of the Reformatsky reaction to the synthesis of β-ketoesters by reactions involving the carbonyl group of an ester are recorded. Ethyl γ-bromoacetoacetate is formed by the action of zinc or magnesium on ethyl bromoacetate.[4a] Hamel [6] reported 56% yields of ethyl γ-chloroacetoacetate by the action of amalgamated magnesium on ethyl chloroacetate. Ethyl γ-ethoxyacetoacetate has been prepared in 10 to 33% yields from ethyl ethoxy-

[5] Bachmann, *J. Org. Chem.*, **3**, 434 (1938).
[6] Hamel, *Bull. soc. chim.*, [4] **29**, 390 (1921); Stolle, *Ber.*, **41**, 954 (1908).

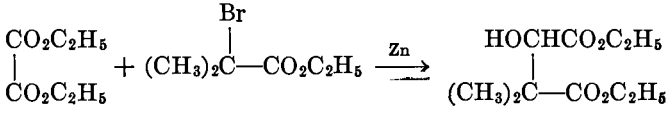
acetate and ethyl bromoacetate [7] by using amalgamated zinc. If ethyl α-bromopropionate is used, the α-methyl derivative is produced.[8]



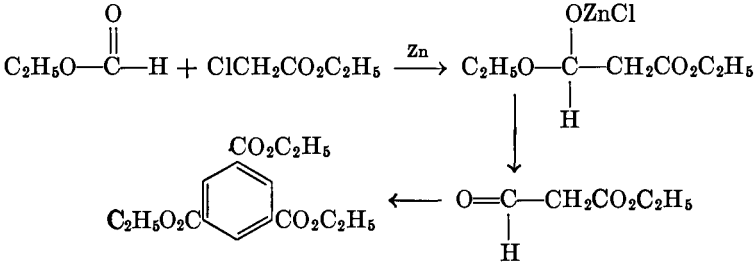
Ethyl 3,4-diketoadipate [9] has been obtained from ethyl oxalate, ethyl chloroacetate, and zinc.



On the other hand, ethyl α-bromoisobutyrate is reported to react with ethyl oxalate to form ethyl α,α-dimethylmalate.[10] It is evident that reduction takes place during this reaction.



The chief product from ethyl formate, ethyl chloroacetate, and zinc is ethyl trimesate.[11] Ethyl formate undergoes the normal Reformatsky reaction to produce the aldehydoester which then trimerizes.



[7] Sommelet, *Bull. soc. chim.*, [4] **29**, 553 (1921); *Compt. rend.*, **154**, 706 (1912).

[8] Johnson, *J. Am. Chem. Soc.*, **35**, 582 (1913); Johnson and Chernoff, *J. Am. Chem. Soc.*, **35**, 585 (1913); **36**, 1742 (1914).

[9] Fittig and Daimler, *Ber.*, **20**, 202 (1887).

[10] Rassow and Bauer, *Ber.*, **41**, 963 (1908).

[11] Reformatsky, *J. Russ. Phys. Chem. Soc.*, **30**, 280 (1898); *J. prakt. Chem.*, **54**, 477 (1896).

With ethyl α-bromopropionate, the presence of the α-methyl group in the intermediate aldehydoester prevents the trimerization. Hence a second Reformatsky reaction occurs leading to ethyl 2,4-dimethyl-3-hydroxyglutarate.[12] Ethyl α-bromoisobutyrate, ethyl formate, and zinc react in a similar fashion to produce ethyl 2,2,4,4-tetramethyl-3-hydroxyglutarate.[13]

Oxidation* of the β-hydroxyesters, obtained by the Reformatsky reaction on aldehydes, by means of the calculated amount of chromic acid in glacial acetic acid as the solvent, produces β-ketoesters in low yields (30–50%).

$$RCHOHCH_2CO_2CH_3 \xrightarrow{CrO_3} RCOCH_2CO_2CH_3$$

Thus, β-ketoesters with no α-substituents may be obtained. This is useful since the Claisen condensation of esters (other than ethyl acetate) yields α-substituted β-ketoesters (see Chapter 9).

DEHYDRATION OF THE β-HYDROXYESTERS

If the temperature of the reaction mixture is high it occasionally happens that the product from the Reformatsky reaction is the unsaturated ester. However, if the reaction is run in the usual solvents, such as ether or benzene (p. 15), the chief constituent of the reaction mixture is the hydroxyester. Because of their tendency to lose water during distillation or saponification,[14] the β-hydroxyesters and their derivatives can sometimes be isolated in the pure state only with difficulty and in poor yields, whereas dehydration of the crude reaction mixtures leads to higher yields of the unsaturated products.

Dehydration may be accomplished by heating the β-hydroxyester with acetic anhydride, acetic anhydride and acetyl chloride,[15] fused potassium acid sulfate,[16] 85% formic acid,[17] anhydrous formic acid,[5, 18, 19] zinc chloride in acetic acid,[20] or sulfuric acid [21] of various strengths (20 to

*See p. 22, reference 48.

[12] Reformatsky, *Ber.*, **28**, 3262 (1895).

[13] Blaise, *Compt. rend.*, **126**, 1808 (1898).

[14] Schroeter, *Ber.*, **37**, 1090 (1904); **40**, 1589 (1907).

[15] Stoermer and Frederici, *Ber.*, **41**, 324 (1908).

[16] Wallach, *Ann.*, **365**, 255 (1909).

[17] Rupe, *Ann.*, **369**, 321 (1909).

[18] Cook, *J. Chem. Soc.*, 2524 (1931); Bachmann and Edgerton, *J. Am. Chem. Soc.*, **62**, 2971 (1940).

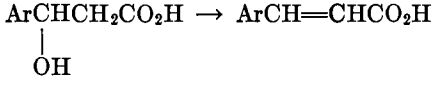
[19] Bergmann and Bograchov, *J. Am. Chem. Soc.*, **62**, 3017 (1940).

[20] Wallach, *Ann.*, **314**, 147 (1901); Tetry, *Bull. soc. chim.*, [3] **27**, 600 (1902).

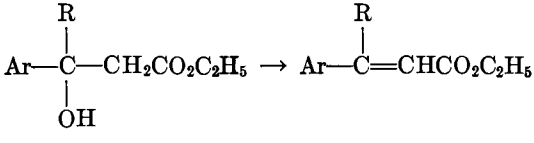
[21] Jaworsky and Reformatsky, *Ber.*, **35**, 3633 (1902).

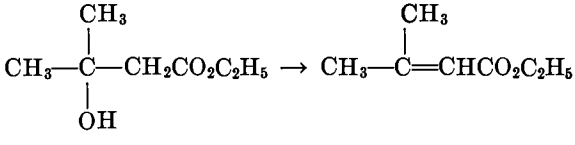
65%); or by refluxing a benzene solution of the β-hydroxyester with iodine,[22] acetic anhydride, acetic anhydride and sodium acetate,[23] phosphorus pentoxide,[24] phosphorus oxychloride,[24, 25] or thionyl chloride and pyridine.[24, 26] Passing dry hydrogen chloride through the β-hydroxyester at 90–100° followed by distillation is also a very satisfactory method [27] (90–95% yields) of dehydration.

For many years it had been assumed that the product of the dehydration reaction was the conjugated α,β-unsaturated ester. When the β-hydroxyl group is secondary, or when an aryl group is attached to the β-carbon atom, the chief product (and in many cases the only one isolated) is, indeed, the α,β-unsaturated ester or acid.

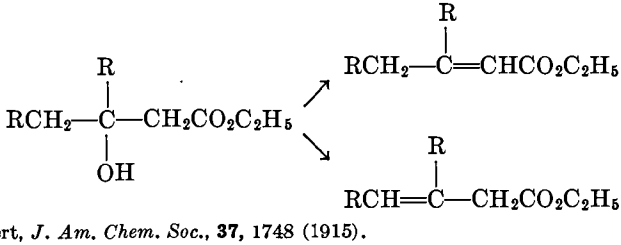


However, when the hydroxyl group is tertiary the structure of the dehydration product is determined by the nature of the substituents. The α,β-unsaturated ester is the chief product when an aryl group or two methyl groups are attached to the β-carbon atom.





However, when one of the alkyl groups is other than methyl then both α,β- and β,γ-unsaturated esters are produced.



[22] Hibbert, *J. Am. Chem. Soc.*, **37**, 1748 (1915).

[23] Rupe and Busolt, *Ber.*, **40**, 4537 (1907).

[24] Kon and Nargund, *J. Chem. Soc.*, 2461 (1932); Phalnikar and Nargund, *J. Indian Chem. Soc.*, **14**, 736 (1937).

[25] Lindenbaum, *Ber.*, **50**, 1270 (1917).

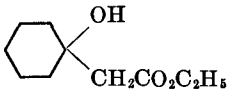
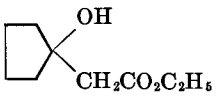
[26] Darzens, *Compt. rend.*, **152**, 1601 (1911).

[27] Natelson and Gottfried, *J. Am. Chem. Soc.*, **61**, 970 (1939).

The proportion of the two isomeric esters depends on the reagent used and on the structure of the compound. The dehydration of a number of β-hydroxyesters by means of four dehydrating agents has been studied by Kon and Nargund.[24] The total yield of the mixture of α,β- and β,γ-unsaturated esters was 80–95%. In Table I is shown the percentage of the total product which was the α,β-unsaturated ester.

TABLE I

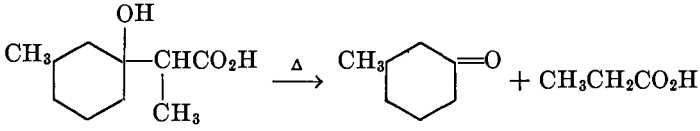
DEHYDRATION OF β-HYDROXYESTERS

β-Hydroxyester	[Percentage of α,β-Unsaturated Ester			
	P_2O_5	$POCl_3$	$SOCl_2$	(fused) $KHSO_4$
$C_2H_5-C(CH_3)(OH)-CH_2CO_2C_2H_5$	39	62	53	57
$C_2H_5-C(C_2H_5)(OH)-CH_2CO_2C_2H_5$	23	68	50	63
$C_3H_7-C(C_3H_7)(OH)-CH_2CO_2C_2H_5$	24	51	31	51
$C_2H_5-C(C_2H_5)(OH)-CH(CH_3)CO_2C_2H_5$	28	43	33	28
	19	43	62	54
	30	58	50	38

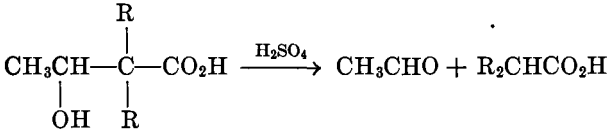
It is occasionally possible to obtain either one of the isomeric dehydration products by proper choice of the experimental conditions. For example, dehydration of ethyl 1-hydroxycyclohexylacetate with acetic anhydride followed by saponification gives Δ^1-cyclohexenylacetic acid;

if the ester is first saponified and the 1-hydroxycyclohexylacetic acid is dehydrated with acetic anhydride the chief product is cyclohexylidene acetic acid.[16] In syntheses of saturated esters or acids it is unnecessary to separate the α,β- and β,γ-esters or acids before reduction.

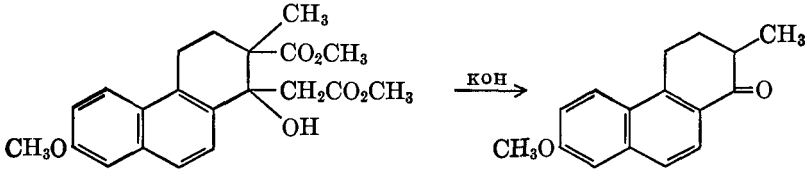
Sometimes cleavage occurs as a side reaction in dehydration of β-hydroxyacids. Thus heat causes the decomposition of α-(1-hydroxy-3-methylcyclohexyl) propionic acid.[16]



Sulfuric acid causes the cleavage of α,α-dialkyl-β-hydroxy acids.[11]



Hot concentrated alkalies may also cause cleavage of the molecule in certain instances.



In order to obtain the unsaturated compound and avoid this cleavage it is essential to dehydrate before hydrolyzing.[28, 29]

SELECTION OF EXPERIMENTAL CONDITIONS. PROCEDURES

In the earlier experiments,[2, 30] the α-haloester, carbonyl compound, and zinc dust were mixed at room temperature and cooled in order to moderate the initial reaction which may cause a considerable temperature rise (60° to 120°). The mixture was allowed to stand at room temperature for periods ranging from two days to three months. After a final warming to 60–70° for two to three hours the mixture was decomposed with dilute acid. The ester was separated or extracted by a solvent, dried, and distilled in vacuum.

[28] Bachmann, Cole, and Wilds, *J. Am. Chem. Soc.*, **62**, 824 (1940).
[29] Bachmann and Wilds, *J. Am. Chem. Soc.*, **62**, 2086 (1940).
[30] Reformatsky and Plesconossoff, *Ber.*, **28**, 2838 (1895).

Control of the initial exothermic reaction may be accomplished by addition of the zinc dust in portions to the other reactants or by the use of a solvent. In most of the recent applications of the Reformatsky reaction a solvent has been employed. This permits better control of the temperature and facilitates stirring. It is essential that the surface of the zinc be kept clean. The formation of an oily product which coats the zinc may stop the reaction. By the proper selection of the solvent mixture it is often possible to keep the addition product in solution or to cause it to crystallize so that it is more readily shaken from the metal by the stirrer. The zinc may be suspended in a copper basket [31] in order to facilitate removal of the addition compounds.

By raising the temperature to the boiling point of the solution the condensation can be effected in a much shorter time (usually one-half to three hours). A prolonged reaction time[32a, 32b] even at a low temperature reduces the yield of β-hydroxyester and increases the amount of high-boiling by-products. The solvents used have been ethyl ether, butyl ether, benzene, toluene, and xylene. A mixture of equal amounts of benzene and toluene,[27] which permits refluxing at temperatures between 90° and 105°, is especially advantageous when the carbonyl reagent is a ketone. Somewhat lower temperatures (70–80°) are better when an aliphatic aldehyde is employed. However, where paraformaldehyde is introduced into the reaction mixture as a source of formaldehyde, the temperature must be high enough (80–100°) to cause depolymerization.

The reagents should be pure and dry. The apparatus should also be clean and dry and protected from the moisture of the air. The observance of strictly anhydrous conditions not only improves the yield but also reduces the induction period so that the reaction usually starts immediately. If difficulty is experienced, the addition of a few crystals of iodine, a little amalgamated zinc, or a very little methylmagnesium iodide may help in initiating the reaction. The copper complex of ethyl acetoacetate has been used as a catalyst.[33] Once started, the reaction is quite vigorous. For this reason, only a small portion of the reactants should be used at the start and the bulk of the materials should be added gradually. Since α-haloesters are lachrymators and skin irritants, precautions should be taken to avoid contact with them.

Zinc dust, zinc foil, granulated zinc, and mossy zinc have been used. Variations in the quality of the zinc are responsible for differences of opinion concerning yields, catalysts, and purification procedures. It is

[31] Kohler and Gilman, *J. Am. Chem. Soc.*, **41**, 683 (1919).
[32a] Nieuwland and Daly, *J. Am. Chem. Soc.*, **53**, 1842 (1931).
[32b] Lipkin and Stewart, *ibid.*, **61**, 3295 (1939).
[33] Kohler, Heritage, and Macleod, *Am. Chem. J.*, **46**, 221 (1911).

desirable that the zinc be as pure as possible and have a fresh clean surface. Any of the forms of zinc may be purified by washing rapidly with 2% hydrochloric or hydrobromic acid, then with water, alcohol, acetone, and absolute ether. The zinc is then warmed in a vacuum oven at 100° for a short time and used immediately. A very active metal has been obtained by immersing 30-mesh zinc in hot (100°) concentrated sulfuric acid containing a few drops of nitric acid.[34] After about fifteen minutes the surface becomes bright and the acid is diluted with a large volume of water. The zinc is washed with water and acetone and then dried. Zinc foil may be cleaned with sandpaper and cut into small strips.

In certain instances amalgamated zinc and a mixture of zinc dust and copper powder [32a] have been used to effect the condensation. Cadmium powder and mixed cadmium-copper powder are ineffective.[32a] Magnesium has also been employed in place of zinc but usually results in lower yields. For example, Zelinsky and Gutt [35] used magnesium to effect the reaction between cyclic ketones and α-bromo- and α-iodo-esters. The yields ranged from 20 to 50%, whereas other investigators report that when zinc was employed the yields were 56 to 70% for the same reactants. Kon and Nargund [24] obtained yields of 48% in the condensation of aliphatic ketones with α-chloroesters and magnesium.

Many different experimental conditions have been described in connection with the Reformatsky reaction, and inspection of the literature reveals that there is no uniformity as regards the procedures. Hence the yields shown in Tables II, III, and IV of the succeeding part do not necessarily represent the highest attainable.

Four procedures have been chosen to illustrate the best methods available at the present time. These procedures not only illustrate the use of different forms of zinc but also bring out other experimental variations. One of the first three procedures should be selected when the reactants are easily available. Procedure 1 illustrates the Reformatsky reaction on an aldehyde, and procedures 2 and 3 on ketones. If the carbonyl compound is one which does not readily undergo self-condensation in the presence of zinc salts, then higher yields can be obtained by treating it repeatedly with zinc and the α-haloester as illustrated by procedure 4. This method is especially advantageous when the ketone is available in only small amounts.

Ethyl β-Phenyl-β-hydroxypropionate.[36] In a clean, dry 500-cc. three-necked flask fitted with a mechanical stirrer, a 250-cc. separatory funnel,

[34] Fieser and Johnson, *J. Am. Chem. Soc.*, **62**, 575 (1940).

[35] Zelinsky and Gutt, *Ber.*, **35**, 2140 (1902); Willstätter and Hatt, *Ann.*, **418**, 148 (1919).

[36] Hauser and Breslow, *Org. Syntheses*, **21**, 51 (1941).

and a reflux condenser, the upper end of which is protected by a calcium chloride drying tube, is placed 40 g. (0.62 mole) of purified zinc dust or granulated zinc. A solution of 83.5 g. (0.50 mole) of ethyl bromoacetate and 65 g. (0.61 mole) of benzaldehyde in 80 cc. of dry benzene and 20 cc. of absolute ether is placed in the separatory funnel. About 15 cc. of this solution is added to the zinc and the flask is warmed until the reaction starts. The mixture is then stirred and the rest of the solution introduced at such a rate that gentle refluxing occurs, about one hour being required. Refluxing is continued for an additional half hour. The flask is then cooled in an ice bath and the contents poured into 300 cc. of ice-cold 10% sulfuric acid with vigorous stirring. The acid layer is drawn off and the benzene solution extracted twice with 50-cc. portions of ice-cold 5% sulfuric acid. The benzene solution is washed once with 25 cc. of cold 10% aqueous sodium carbonate, then with 25 cc. of cold 5% sulfuric acid, and finally with two 25-cc. portions of water. The combined acid extracts are washed with two 50-cc. portions of ether, and the combined ether and benzene solutions are dried with 5 g. of anhydrous magnesium sulfate or Drierite. After filtration, the solvent is removed by distillation at atmospheric pressure on a steam bath and the residue is fractionated in vacuum. The ester is collected at 151–154°/11–12 mm. or 128–132°/5–7 mm. The yield is 59–62 g. (61–64%).

Ethyl 1-Hydroxycyclohexylacetate.[27] A mixture of 800 cc. of benzene and 700 cc. of toluene with 334 g. (2 moles) of ethyl bromoacetate and 196 g. (2 moles) of cyclohexanone is prepared. To 300 cc. of this mixture in a 5-l. three-necked flask fitted with mechanical stirrer, condenser with drying tube, and dropping funnel is added 130 g. (2 moles) of zinc foil which has been cleaned with sandpaper and cut in strips. A few crystals of iodine are introduced, the stirrer is started, and heat is applied by means of a boiling water bath. A vigorous reaction sets in. The remainder of the reaction mixture is now added through the dropping funnel at a rate designed to maintain gentle refluxing. Stirring is then continued for two hours. Practically all the zinc dissolves. The mixture is cooled and the condensation product is decomposed with dilute sulfuric acid (sufficient to dissolve all the zinc hydroxide). The benzene-toluene layer is separated, dried over anhydrous sodium sulfate, and distilled in vacuum. The product is collected at 86–89°/2 mm. The yield ranges from 219 to 278 g. (56–71%).

Ethyl α-Methyl-β-phenyl-β-hydroxybutyrate.[37] A mixture of 110 g. of acetophenone, 162 g. of ethyl α-bromopropionate, and 200 cc. of dry benzene is placed in a 500-cc. separatory funnel inserted in one opening

[37] Rupe, Steiger, and Fiedler, *Ber.*, **47**, 68 (1914); Burton and Shopee, *J. Chem. Soc.*, 1160 (1935); Kloetzel, *J. Am. Chem. Soc.*, **62**, 1708 (1940).

of a 2-l. three-necked flask fitted with a mechanical stirrer and a reflux condenser.

In the flask is placed 70 g. of zinc dust (which has been cleaned with 5% hydrobromic acid, washed with water, alcohol, and acetone, and dried). About 50 cc. of the mixture is added to the zinc dust, the stirrer is started, and the mixture is heated by means of a steam bath until the reaction starts. The remainder of the solution is added at such a rate that gentle refluxing takes place. After the addition is complete, the stirring and refluxing are continued for one hour. The mixture is then cooled to room temperature and hydrolyzed by the addition of 400 cc. of ice-cold 20% sulfuric acid. The benzene layer is separated and the aqueous layer extracted with two 50-cc. portions of benzene. The combined benzene extracts are washed with a 50-cc. portion of cold 5% sulfuric acid, then with 25 cc. of 10% aqueous sodium carbonate, and finally with two 25-cc. portions of water. The benzene solution is dried with about 25 g. of anhydrous magnesium sulfate and the solvent removed by distillation from a steam bath. The residual oil is distilled in vacuum. The ester is a colorless oil boiling at 134–135°/9 mm. The yield ranges from 150 to 161 g. (75–81%).

Dimethyl Ester of 7-Methoxy-2-methyl-2-carboxy-1-hydroxy-1,2,3,4-tetrahydrophenanthrene-1-acetic Acid.[28] To 2.5 g. of granulated zinc (20-mesh, previously washed with dilute hydrochloric acid, water, acetone, and dried) and 0.07 g. of iodine in a mixture of 25 cc. of dry benzene (thiophene-free) and 25 cc. of anhydrous ether, are added 1.5 g. of 7-methoxy-2-methyl-2-carbomethoxy-1-keto-1,2,3,4-tetrahydrophenanthrene and 0.75 cc. of methyl bromoacetate. As the mixture is refluxed on a water bath, the iodine color fades and the solution becomes cloudy. After five to ten minutes a colorless addition product is deposited. Five additions of 2.5 g. of zinc and a trace of iodine are made at forty-five-minute intervals and an additional 0.75 cc. of methyl bromoacetate is introduced after one and one-half hours. The mixture is refluxed for a total of four hours, with occasional vigorous shaking to keep the zinc free from adhering crystals.

The addition product is dissolved by adding a little acetic acid and methanol, and the solution is decanted from the zinc into water. The mixture is acidified with acetic acid. The ether-benzene layer is separated, the aqueous solution is extracted with benzene, and the combined extracts are washed with water and then with dilute aqueous ammonia until no more color is removed. The residue obtained by evaporation of the ether-benzene solution crystallizes readily from methanol. The yield is 1.5–1.6 g. The product is recrystallized from methanol containing a few drops of acetone; colorless leaflets, m.p.

125–125.5° are obtained. By reworking the mother liquors a total yield of 85–90% may be obtained.

EXAMPLES OF THE REFORMATSKY REACTION

In the tables which follow, a number of examples of the Reformatsky, reaction have been collected to indicate its applicability in synthesis. The tables are undoubtedly incomplete because the reaction frequently has been used as merely one step in a synthesis and hence may not be indexed as a Reformatsky process. As pointed out previously (p. 16), because of the wide variations in the experimental conditions employed by different investigators, the yields given are not necessarily the best obtainable. For the same reason comparisons of yields reported by different authors and often referred to different standards of purity are not significant.

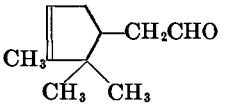
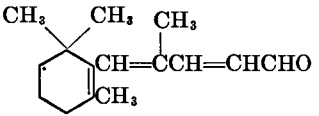
Aldehydes (Table II). Aliphatic and aromatic aldehydes, saturated and unsaturated aldehydes undergo the reaction easily. The reaction has been reported to fail with phenolic aldehydes,[38a] but recent work by Connor[38b] indicates that a reaction does take place.

[38a] Reformatsky, *J. prakt. Chem.*, **54**, 469, 477 (1896).
[38b] Ralph Connor, private communication.

TABLE II

REFORMATSKY REACTIONS ON ALDEHYDES

Aldehyde	α-Haloester	Product Isolated	Yield, %	Reference
HCHO	$CH_3CHBrCO_2C_2H_5$	Hydroxyester	45	39
HCHO	$C_2H_5CHBrCO_2C_2H_5$	Hydroxyester	46	40
HCHO	$(CH_3)_2CBrCO_2C_2H_5$	Hydroxyester	60	41
HCHO	$CH_3(CH_2)_2CHBrCO_2C_2H_5$	Hydroxyester	67	40
HCHO	$C_2H_5CBr(CH_3)CO_2C_2H_5$	Hydroxyester	60	42
HCHO	$(CH_3)_2CHCHBrCO_2C_2H_5$	Hydroxyester	41	40
HCHO	$CH_3(CH_2)_3CHBrCO_2C_2H_5$	Hydroxyester	52	40
HCHO	$(n)C_7H_{15}CHBrCO_2C_2H_5$	Hydroxyester	—	40
CH_3CHO	$ClCH_2CO_2C_2H_5$	None	—	43
CH_3CHO	$C_2H_5CHBrCO_2C_2H_5$	Hydroxyester	—	44
CH_3CHO	$(CH_3)_2CBrCO_2C_2H_5$	Hydroxyester	70	45, 46
CH_3CHO	$(CH_3)_2CHCHBrCO_2C_2H_5$	Hydroxyester	—	47
CH_3CH_2CHO	$ClCH_2CO_2C_2H_5$	None	—	43
CH_3CH_2CHO	$BrCH_2CO_2C_2H_5$	Hydroxyester	39	48
CH_3CH_2CHO	$(CH_3)_2CBrCO_2C_2H_5$	Hydroxyester	24	38*a*
CH_3CH_2CHO	$(n)C_3H_7CHBrCO_2C_2H_5$	Hydroxyester	50	49
$CH_3(CH_2)_2CHO$	$BrCH_2CO_2C_2H_5$	Hydroxyester	25	48
$(CH_3)_2CHCHO$	$BrCH_2CO_2C_2H_5$	Hydroxyester	35	48
$(CH_3)_2CHCHO$	$CH_3CHBrCO_2C_2H_5$	Hydroxyester	41	50
$(CH_3)_2CHCHO$	$(CH_3)_2CBrCO_2C_2H_5$	Hydroxyester	58	51, 52
$(CH_3)_2CHCH_2CHO$	$CH_3CHBrCO_2C_2H_5$	Hydroxyester	—	53
$(CH_3)_2CHCH_2CHO$	$(CH_3)_2CBrCO_2C_2H_5$	Hydroxyester	65	54
$(CH_3)_2CHCH_2CHO$	$(CH_3)_2CHCHBrCO_2C_2H_5$	Hydroxyester	—	55
$CH_3(CH_2)_5CHO$	$BrCH_2CO_2C_2H_5$	Hydroxyester	54	48, 56

$CH_3(CH_2)_5CHO$	$(CH_3)_2CBrCO_2C_2H_5$	Hydroxyester	—	57
$CH_2{=}CHCHO$	$(CH_3)_2CBrCO_2C_2H_5$	Hydroxyester	40	58
$CH_3CH{=}CHCHO$	$BrCH_2CO_2C_2H_5$	Unsaturated acid	60	21
$CH_3CH{=}CHCHO$	$CH_3CHBrCO_2C_2H_5$	Unsaturated acid	60	21
$CH_3CH{=}CHCHO$	$CH_3CHBrCO_2C_2H_5$	Hydroxyester	32	59
$CH_3CH{=}CHCHO$	$C_2H_5CHBrCO_2C_2H_5$	Hydroxyester	50	59
$CH_3CH{=}CHCHO$	$C_2H_5CHBrCO_2C_2H_5$	Unsaturated acid	55	21
$CH_3CH{=}CHCHO$	$(CH_3)_2CBrCO_2C_2H_5$	Hydroxyester	—	21, 60
$(CH_3)_2C{=}CHCHO$	$BrCH_2CO_2C_2H_5$	Hydroxyester	43	61
Furfural	$(CH_3)_2CBrCO_2C_2H_5$	Unsaturated ester	61	38*a*
	$BrCH_2CO_2C_2H_5$	Hydroxyester	—	62
	$BrCH_2CO_2C_2H_5$	Hydroxyester	53	63
	$BrCH_2CO_2C_2H_5$	Unsaturated acid	—	20
C_6H_5CHO	$ClCH_2CO_2C_2H_5$	Unsaturated ester	35	43
C_6H_5CHO	$ClCH_2CO_2C_2H_5$	Unsaturated acid	35	32
C_6H_5CHO	$BrCH_2CO_2C_2H_5$	Hydroxyester	61	48, 64
C_6H_5CHO	$CH_3CHBrCO_2C_2H_5$	Hydroxyester	78	3
C_6H_5CHO	$C_2H_5CHBrCO_2C_2H_5$	Hydroxyester	52	65
C_6H_5CHO	$(CH_3)_2CBrCO_2C_2H_5$	Hydroxyester	78	66
C_6H_5CHO	$(CH_3)_2CHCHBrCO_2C_2H_5$	Hydroxyester	60	38*a*

NOTE. References 39–71*a* appear on p. 22.

TABLE II—*Continued*

REFORMATSKY REACTIONS ON ALDEHYDES

Aldehyde	α-Haloester	Product Isolated	Yield, %	Reference
C_6H_5CHO	$C_6H_5CHClCO_2C_2H_5$	Unsaturated ester	18	32
C_6H_5CHO	$C_2H_5CHClCO_2C_2H_5$	Unsaturated acid	33	32
m-$CH_3C_6H_4CHO$	$CH_3CHBrCO_2C_2H_5$	Hydroxyester	—	67
p-$CH_3C_6H_4CHO$	$BrCH_2CO_2C_2H_5$	Hydroxyester	—	68
p-$CH_3C_6H_4CHO$	$CH_3CHBrCO_2C_2H_5$	Hydroxyester	—	69
p-$(CH_3)_2CHC_6H_4CHO$	$BrCH_2CO_2C_2H_5$	Hydroxyester	—	70
p-$(CH_3)_2CHC_6H_4CHO$	$CH_3CHBrCO_2C_2H_5$	Hydroxyester	—	71*a*
o-HOC_6H_4CHO	$BrCH_2CO_2C_2H_5$	None	0	38*a*

[39] Blaise and Herman, *Ann. chim. phys.*, [8] **17**, 371 (1909).
[40] Blaise and Luttringer, *Bull. soc. chim.*, [3] **33**, 635 (1905).
[41] Blaise and Marcilly, *Bull. soc. chim.*, [3] **31**, 110 (1904).
[42] Blaise and Marcilly, *Bull. soc. chim.*, [3] **31**, 319 (1904).
[43] Reformatsky, *J. Russ. Phys. Chem. Soc.*, **22**, 194 (1890).
[44] Blaise and Bagard, *Ann. chim. phys.*, [8] **11**, 127 (1907).
[45] Courtot, *Bull. soc. chim.*, [3] **35**, 114 (1906).
[46] Effrussi, *J. Russ. Phys. Chem. Soc.*, **28**, 600 (1896).
[47] Maturewitsch, *J. Russ. Phys. Chem. Soc.*, **41**, 1319 (1909).
[48] Conard, Ph.D. thesis, Univ. of Ill., 1934.
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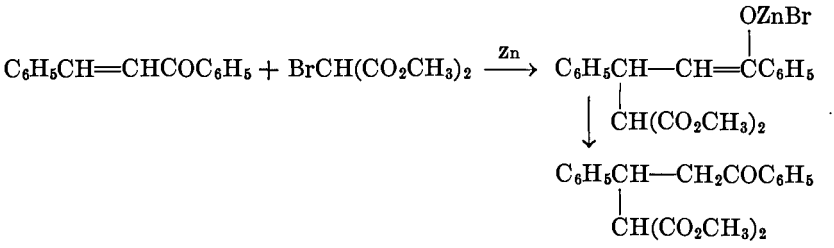
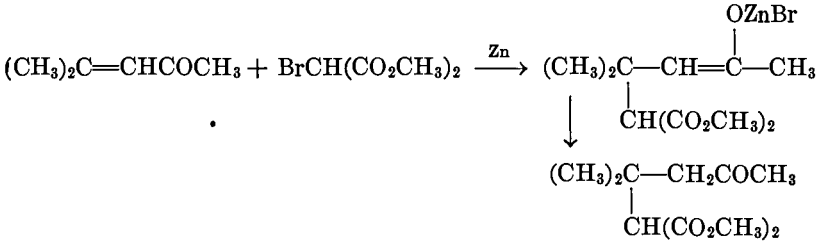
[50] Prospjechov, *J. Russ. Phys. Chem. Soc.*, **29**, 420 (1897).
[51] Michel and Spitzauer, *Monatsh.*, **22**, 1113 (1901).
[52] Reformatsky, *Ber.*, **28**, 2842 (1895).
[53] Raichstein, *J. Russ. Phys. Chem. Soc.*, **39**, 587 (1907).
[54] Kukulesco, *J. Russ. Phys. Chem. Soc.*, **28**, 293 (1896).
[55] Reformatsky, *J. Russ. Phys. Chem. Soc.*, **33**, 242 (1901).
[56] Harding and Weizmann, *J. Chem. Soc.*, **97**, 302 (1910).
[57] Barylowitsch, *J. Russ. Phys. Chem. Soc.*, **28**, 360 (1896).
[58] Blaise and Courtot, *Bull. soc. chim.*, [3] **35**, 360 (1906).
[59] Jaworski, *J. Russ. Phys. Chem. Soc.*, **35**, 277 (1903).
[60] Jaworski, *J. Russ. Phys. Chem. Soc.*, **35**, 285 (1903).
[61] Fischer and Löwenberg, *Ann.*, **494**, 263 (1932).
[62] Arbuzow, *Ber.*, **68**, 1430 (1935).
[63] Davies, Heilbron, Jones, and Lowe, *J. Chem. Soc.*, 584 (1935).
[64] Andrijewski, *J. Russ. Phys. Chem. Soc.*, **40**, 1635 (1908).
[65] Andres, *J. Russ. Phys. Chem. Soc.*, **28**, 283 (1896).
[66] Dain, *J. Russ. Phys. Chem. Soc.*, **28**, 159 (1896).
[67] Gubarew, *J. Russ. Phys. Chem. Soc.*, **44**, 1865 (1912).
[68] Andrijewski, *J. Russ. Phys. Chem. Soc.*, **40**, 770 (1908).
[69] Strzalkowski, *J. Russ. Phys. Chem. Soc.*, **41**, 18 (1909).
[70] Bronstein, *J. Russ. Phys. Chem. Soc.*, **39**, 578 (1907).
[71*a*] Grigorowitsch, *J. Russ. Phys. Chem. Soc.*, **32**, 325 (1900).

Ketones (Table III). Aliphatic, aromatic, cyclic, saturated, and unsaturated ketones have been found to undergo the reaction smoothly. In the case of a ketoester, it is the keto group which reacts with the haloester. The reaction follows an abnormal course with halogenated aliphatic ketones and fails with phenolic ketones. Most α,β-unsaturated ketones undergo the normal Reformatsky reaction with α-haloesters of monobasic acids. However, it has been observed by Kohler, Heritage, and Macleod [33] that methyl bromozincmalonate adds 1,4 to benzalacetophenone. Ethyl α-bromoisobutyrate also adds 1,4 to benzalacetophenone [31] in the presence of zinc. When acetone is treated with methyl bromomalonate in the presence of zinc, the only product isolated is that corresponding to 1,4-addition of the haloester to mesityl oxide.[71b] Evidently, mesityl oxide is formed by the condensation of acetone induced by the RZnX complex.



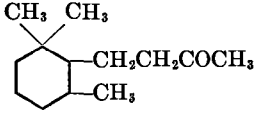
$$2CH_3COCH_3 \rightarrow (CH_3)_2C{=}CHCOCH_3$$

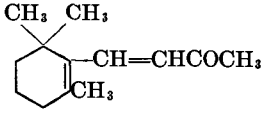
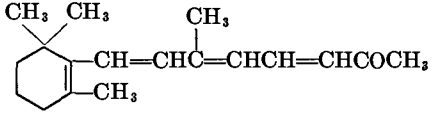
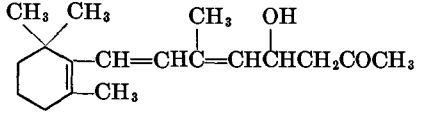
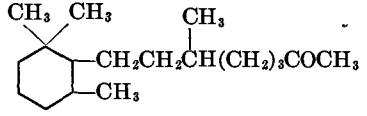


[71b] Iyer, *J. Indian Chem. Soc.*, **17**, 215 (1940).

TABLE III

REFORMATSKY REACTIONS ON KETONES

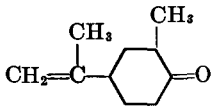
Ketone	α-Haloester	Product	Yield, %	Reference
CH_3COCH_3	$ClCH_2CO_2C_2H_5$	Hydroxyester	—	1
CH_3COCH_3	$ICH_2CO_2C_2H_5$	Hydroxyester	—	1
CH_3COCH_3	$CH_3CHBrCO_2C_2H_5$	Hydroxyester	28	72
CH_3COCH_3	$C_2H_5CHClCO_2CH_3$	Hydroxyester	33	32
CH_3COCH_3	$C_2H_5CHBrCO_2C_2H_5$	Unsaturated acid	39	38*a*
CH_3COCH_3	$(CH_3)_2CBrCO_2C_2H_5$	Hydroxyester	25	30
CH_3COCH_3	$(CH_3)_2CHCHBrCO_2C_2H_5$	Hydroxyester	50	38*a*
$CH_3COC_3H_7(n)$	$ClCH_2CO_2C_2H_5$	Hydroxyester	50	38*a*
$C_2H_5COC_2H_5$	$ClCH_2CO_2C_2H_5$	Hydroxyester	87	38*a*
$(n)C_3H_7COC_3H_7(n)$	$ClCH_2CO_2C_2H_5$	Hydroxyester	95	38*a*
$(n)C_3H_7COC_3H_7(n)$	$(CH_3)_2CBrCO_2C_2H_5$	Hydroxyacid	—	38*a*
$CH_3COCH{=}CHCH_3$	$BrCH_2CO_2CH_3$	Hydroxyester	55	73
$CH_3COCH{=}C(CH_3)_2$	$BrCH_2CO_2C_2H_5$	Unsaturated ester	—	74
$CH_3CO(CH{=}CH)_2CH_3$	$BrCH_2CO_2CH_3$	Hydroxyester	30	73
$CH_3COCH{=}CHCH{=}C(CH_3)_2$	$BrCH_2CO_2CH_3$	Hydroxyester	25	73
$CH_3COCH{=}CHCH{=}C(CH_3)_2$	$BrCH_2CO_2CH_3$	Unsaturated ester	80	61
$CH_3COCH{=}CHCH_2CH(CH_3)_2$	$BrCH_2CO_2C_2H_5$	Hydroxyester	50	75
$CH_3COCH{=}CHCH_2CH(CH_3)_2$	$ICH_2CO_2C_2H_5$	Hydroxyester	—	76
	$BrCH_2CO_2C_2H_5$	Hydroxyester	—	77

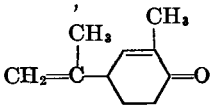
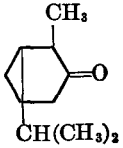
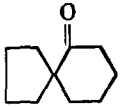
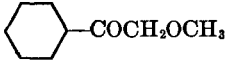
	$BrCH_2CO_2C_2H_5$	Unsaturated ester	88	77, 78
	$BrCH_2CO_2C_2H_5$	Unsaturated ester	—	79
	$BrCH_2CO_2C_2H_5$	Unsaturated ester	64	72
	$BrCH_2CO_2C_2H_5$	Hydroxyester	19	80
$C_6H_5COCH_3$	$ClCH_2CO_2C_2H_5$	Hydroxyester	40	32
$C_6H_5COCH_3$	$BrCH_2CO_2C_2H_5$	Hydroxyester	92	25
$C_6H_5COCH_3$	$CH_3CHBrCO_2C_2H_5$	Hydroxyester	75	37
p-$CH_3C_6H_4COCH_3$	$ClCH_2CO_2C_2H_5$	Unsaturated ester	13	32
p-$CH_3C_6H_4COCH_3$	$BrCH_2CO_2C_2H_5$	Hydroxyester	87	25
o-$CH_3OC_6H_4COCH_3$	$BrCH_2CO_2C_2H_5$	Hydroxyester	88	25
p-$CH_3OC_6H_4COCH_3$	$ClCH_2CO_2C_2H_5$	Unsaturated ester	52	32
p-$CH_3OC_6H_4COCH_3$	$BrCH_2CO_2C_2H_5$	Hydroxyester	85	25
p-$CH_3OC_6H_4COCH_3$	$C_6H_5CHClCO_2C_2H_5$	Hydroxyester	27	32
$C_6H_5COC_2H_5$	$ClCH_2CO_2C_2H_5$	Unsaturated ester	33	32
$C_6H_5COC_6H_5$	$ClCH_2CO_2C_2H_5$	Hydroxyester	30	32

NOTE. References 72–99*b* appear on p. 32.

TABLE III—*Continued*

REFORMATSKY REACTIONS ON KETONES

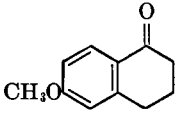
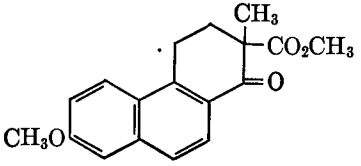
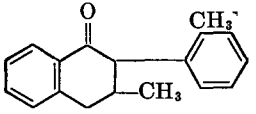
Ketone	α-Haloester	Product	Yield, %	Reference
$C_6H_5COC_6H_5$	$BrCH_2CO_2C_2H_5$	Hydroxyester	75	23
$C_6H_5COCH_2C_6H_5$	$BrCH_2CO_2C_2H_5$	Hydroxyester	—	81
$C_6H_5COCH{=}CHC_6H_5$	$BrCH_2CO_2CH_3$	Unsaturated ester	28	73
$C_6H_5(CH{=}CH)_2COC_6H_5$	$BrCH_2CO_2CH_3$	Unsaturated ester	12	73
Cyclopentanone	$CH_3CHBrCO_2C_2H_5$	Hydroxyester	—	16
3-Methylcyclopentanone	$BrCH_2CO_2C_2H_5$	Hydroxyester	—	20
Cyclohexanone	$BrCH_2CO_2C_2H_5$	Hydroxyester	56	82
Cyclohexanone	$CH_3CHBrCO_2C_2H_5$	Hydroxyester	74	83
Cyclohexanone	$C_2H_5CHBrCO_2C_2H_5$	Hydroxyester	68	83
Cyclohexanone	$(CH_3)_2CBrCO_2C_2H_5$	Hydroxyester	—	83
2-Methylcyclohexanone	$(CH_3)_2CBrCO_2C_2H_5$	Hydroxyester	—	83
3-Methylcyclohexanone	$BrCH_2CO_2C_2H_5$	Hydroxyester	42	20
3-Methylcyclohexanone	$CH_3CHBrCO_2C_2H_5$	Hydroxyester	77	83
3-Methylcyclohexanone	$C_2H_5CHBrCO_2C_2H_5$	Hydroxyester	81	83
3-Methylcyclohexanone	$(CH_3)_2CBrCO_2C_2H_5$	Hydroxyester	—	83
4-Methylcyclohexanone	$BrCH_2CO_2C_2H_5$	Hydroxyester	75	16
4-Methylcyclohexanone	$CH_3CHBrCO_2C_2H_5$	Hydroxyester	81	16, 83
4-Methylcyclohexanone	$C_2H_5CHBrCO_2C_2H_5$	Hydroxyester	87	83
4-Methylcyclohexanone	$(CH_3)_2CBrCO_2C_2H_5$	Hydroxyester	—	83
4-Methoxycyclohexanone	$BrCH_2CO_2C_2H_5$	Hydroxyester	66	84
	$BrCH_2CO_2C_2H_5$	Hydroxyester	50	20

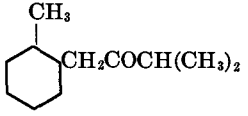
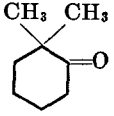
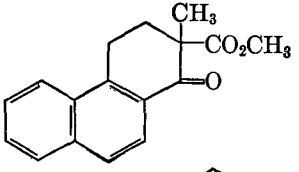
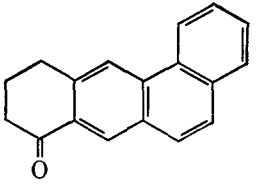
	$BrCH_2CO_2C_2H_5$	Hydroxyester	50	20
	$BrCH_2CO_2C_2H_5$	Hydroxyester	—	20
	$BrCH_2CO_2C_2H_5$	Hydroxyester	29	85
$(CH_2)_6CO$	$BrCH_2CO_2CH_3$	Hydroxyester	42	20
Isatin	$BrCH_2CO_2C_2H_5$	None	0	86
O-Methylisatin	$BrCH_2CO_2C_2H_5$	None	0	86
N-Methylisatin	$BrCH_2CO_2C_2H_5$	Hydroxyester	76	86
N-Ethylisatin	$BrCH_2CO_2C_2H_5$	Hydroxyester	76	86
N-Methylsuccinimide	$BrCH_2CO_2C_2H_5$	Unsaturated ester	20	87
	$BrCH_2CO_2C_2H_5$	Hydroxyester	—	88
$CH_3COCH_2CO_2C_2H_5$	$ClCH_2CO_2C_2H_5$	Hydroxyester	27	32
$CH_3COCH_2CO_2C_2H_5$	$(CH_3)_2CBrCO_2C_2H_5$	Unsaturated ester	10	89

NOTE. References 72–99*b* appear on p. 32.

TABLE III—*Continued*

REFORMATSKY REACTIONS ON KETONES

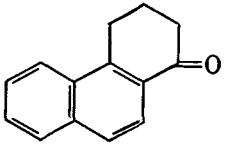
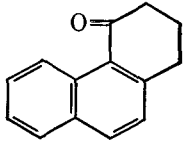
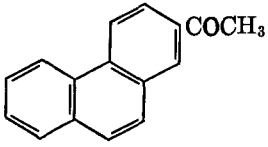
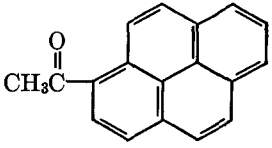
Ketone	α-Haloester	Product	Yield, %	Reference
$CH_3COC(CH_3)_2CO_2C_2H_5$	$BrCH_2CO_2C_2H_5$	Unsaturated ester	25	89
$COCO_2C_2H_5$ $CH_2CO_2C_2H_5$	$BrCH_2CO_2C_2H_5$	Hydroxyester	6	90
	$BrCH_2CO_2C_2H_5$	Hydroxyester	—	91
	$BrCH_2CO_2CH_3$	Hydroxyester	85–90	28
	$BrCH_2CO_2CH_3$	Unsaturated acid	17	92

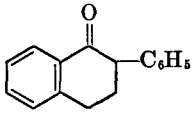
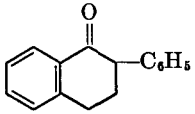
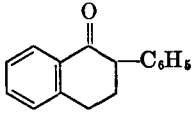
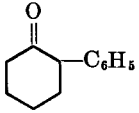
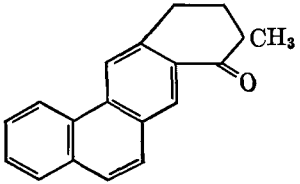
$C_6H_5CH{=}CHCOC_6H_5$	$BrCH(CO_2CH_3)_2$	Keto ester 1,4-addition	—	33
$C_6H_5CH{=}CHCOC_6H_5$	$(CH_3)_2CBrCO_2C_2H_5$	Keto ester 1,4-addition	75	31
$(CH_3)_2C{=}CHCOCH_3$	$BrCH(CO_2CH_3)_2$	Keto ester 1,4-addition	—	71b
	$CH_3CHBrCO_2C_2H_5$	Hydroxyester	—	93
	$CH_3CHBrCO_2C_2H_5$	Hydroxyester	73	94
	$BrCH_2CO_2CH_3$	Hydroxyester	93	29
	$BrCH_2CO_2CH_3$	Unsaturated ester	91	5

NOTE. References 72–99b appear on p. 32.

TABLE III—*Continued*

REFORMATSKY REACTIONS ON KETONES

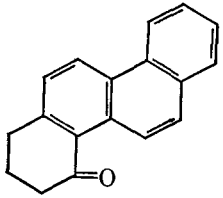
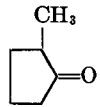
Ketone	α-Haloester	Product	Yield, %	Reference
	$BrCH_2CO_2C_2H_5$	Unsaturated ester	91	95
	$BrCH_2CO_2CH_3$	Unsaturated ester	93	18
	$BrCH_2CO_2CH_3$	Hydroxyester	—	96
	$BrCH_2CO_2CH_3$	Unsaturated ester	40	19

	$BrCH_2CO_2C_2H_5$	Unsaturated acid	68	97
	$CH_3CHBrCO_2C_2H_5$	Unsaturated acid	37	4*a*
	$(CH_3)_2\overset{\overset{Br}{\vert}}{C}CO_2C_2H_5$	Unsaturated acid	27	4*a*
	$BrCH_2CO_2C_2H_5$	Hydroxyester	70	98
	$BrCH_2CO_2CH_3$	Unsaturated ester	60	99*a*

NOTE. References 72–99*b* appear on p. 32.

TABLE III—*Continued*

REFORMATSKY REACTIONS ON KETONES

Ketone	α-Haloester	Product	Yield, %	Reference
	$BrCH_2CO_2CH_3$	Unsaturated acid	49	34
	$(CH_3)_2CBrCO_2C_2H_5$	Hydroxy ester	56	99*b*

[72] Gilaroff, *J. Russ. Phys. Chem. Soc.*, **28**, 501 (1896).
[73] Kuhn and Hoffer, *Ber.*, **65**, 651 (1932).
[74] Rupe and Lotz, *Ber.*, **36**, 15 (1903).
[75] Tiemann, *Ber.*, **33**, 563 (1900).
[76] Barbier and Bouveault, *Compt. rend.*, **122**, 393 (1896).
[77] Karrer, Salomon, Morf, and Walker, *Helv. Chim. Acta*, **15**, 878 (1932).
[78] Kuhn and Morris, *Ber.*, **70**, 853 (1937).
[79] Heilbron, Jones, Lowe, and Wright, *J. Chem. Soc.*, 561 (1936).
[80] Karrer and Morf, *Helv. Chim. Acta*, **16**, 625 (1933).
[81] Phalnikar and Nargund, *J. Univ. Bombay*, **8**, Pt. III, 184 (1939).
[82] Wallach, *Ann.*, **347**, 328 (1906).
[83] Wallach, *Ann.*, **360**, 26 (1908).
[84] Greenlee, Ph.D. thesis, Univ. of Ill., 1939.
[85] Clemo and Ormston, *J. Chem. Soc.*, 1778 (1932).
[86] Myers and Lindwall, *J. Am. Chem. Soc.*, **60**, 644 (1938).
[87] Lukeš, *Collection Czechoslov. Chem. Commun.*, **4**, 81 (1932).
[88] Fried, Rubin, Paist, and Elderfield, *Science*, **91**, 435 (1940).
[89] Perkin and Thorpe, *J. Chem. Soc.*, **71**, 1169 (1897).
[90] Lawrence, *J. Chem. Soc.*, **71**, 457 (1897).
[91] Haberland, *Ber.*, **69**, 1380 (1936).
[92] Newman, *J. Am. Chem. Soc.*, **62**, 2295 (1940).
[93] Bradfield, Hedge, Rao, Simonsen, and Gillam, *J. Chem. Soc.*, 667 (1936).
[94] Adamson, Marlow, and Simonsen, *J. Chem. Soc.*, 774 (1938).
[95] Hoch, *Compt. rend.*, **207**, 921 (1938).
[96] Bergmann and Hillemann, *Ber.*, **66**, 1302 (1933).
[97] Newman, *J. Am. Chem. Soc.*, **60**, 2947 (1938).
[98] Cook, Hewett, and Lawrence, *J. Chem. Soc.*, 71 (1936).
[99*a*] Bergmann and Blum-Bergmann, *J. Am. Chem. Soc.*, **59**, 1573 (1937).
[99*b*] Shive, Crouch, and Lochte, *J. Am. Chem. Soc.*, **63**, 2979 (1941).

TABLE IV

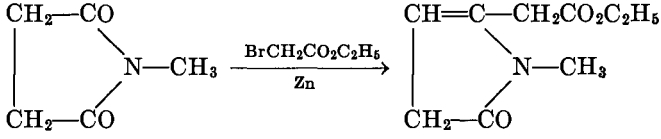
REFORMATSKY REACTIONS ON ESTERS

Ester	Haloester	Product	Yield, %	Reference
$HCO_2C_2H_5$	$ClCH_2CO_2C_2H_5$	Ethyl trimesate	—	11
$HCO_2C_2H_5$	$BrCH_2CO_2C_2H_5$	Ethyl trimesate	—	38*a*
$HCO_2C_2H_5$	$CH_3\overset{\overset{Br}{\vert}}{C}HCO_2C_2H_5$	Ethyl 2,4-dimethyl-3-hydroxyglutarate	41	12
$HCO_2C_2H_5$	$(CH_3)_2\overset{\overset{Br}{\vert}}{C}CO_2C_2H_5$	Ethyl 2,2,4,4-tetramethyl 3-hydroxyglutarate	—	13
$C_2H_5OCH_2CO_2C_2H_5$	$BrCH_2CO_2C_2H_5$	Ethyl γ-ethoxyacetoacetate	15–33	7, 8
$C_2H_5OCH_2CO_2C_2H_5$	$CH_3\overset{\overset{Br}{\vert}}{C}HCO_2C_2H_5$	Ethyl α-methyl-γ-ethoxyacetoacetate	9	8
$BrCH_2CO_2C_2H_5$	$BrCH_2CO_2C_2H_5$	Ethyl γ-bromoacetoacetate	—	4*a*
$ClCH_2CO_2C_2H_5$	$ClCH_2CO_2C_2H_5$	Ethyl γ-chloroacetoacetate	56	6
$\begin{array}{c}CO_2C_2H_5\\\vert\\CO_2C_2H_5\end{array}$	$ClCH_2CO_2C_2H_5$	Ethyl β,γ-diketoadipate	—	9
$\begin{array}{c}CO_2C_2H_5\\\vert\\CO_2C_2H_5\end{array}$	$\overset{\overset{Br}{\vert}}{(CH_3)_2C}CO_2C_2H_5$	Ethyl α,α-dimethylmalate	—	10
$\overset{\overset{Br}{\vert}}{(CH_3)_2C}CO_2C_2H_5$	$\overset{\overset{Br}{\vert}}{(CH_3)_2C}CO_2C_2H_5$	Ethyl isobutyrylisobutyrate	67	100

[100] Salkind, *J. Russ. Phys. Chem. Soc.*, **38**, 97 (1906); Zeltner, *Ber.*, **41**, 592 (1908).

Esters (Table IV). There are relatively few examples of the Reformatsky reaction involving the ester group. The yields appear to be uniformly poor.

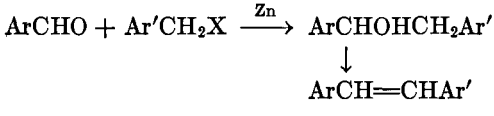
Substituted Amides. Lukeš[87] has obtained ethyl 1-methyl-2-pyrrolone-5-acetate in about 20% yield by treating N-methyl succinimide with ethyl bromoacetate and zinc.



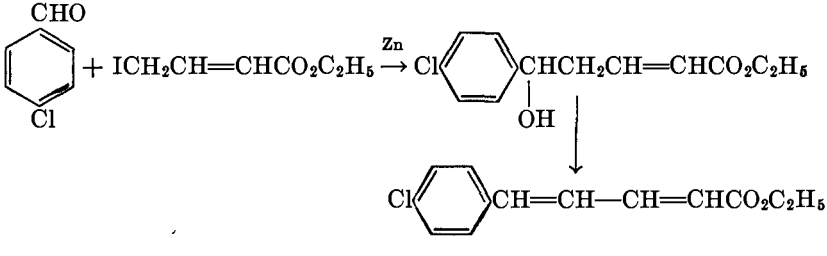
VARIATIONS OF THE REFORMATSKY REACTION

Use of Halogen Compounds Other Than α-Haloesters. Aromatic aldehydes react with β- and γ-bromo- and iodo-esters in the presence of zinc, but the yields are very low (1 to 3%). 6-Methoxy-1-tetralone reacts with ethyl β-bromopropionate in the presence of magnesium to give a 22% yield of the unsaturated acid.[101]

Certain reactive halogen compounds, other than α-haloesters, have been found to condense with aromatic aldehydes in the presence of zinc. Benzyl halides yield substituted stilbenes since the carbinols are easily dehydrated during the reaction.



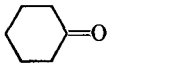
The vinylogs of the α-haloesters undergo the Reformatsky reaction;[102] thus *p*-chlorobenzaldehyde, ethyl γ-iodocrotonate, and zinc react to form the expected condensation product in 42% yield.



[101] Haberland and Heinrich, *Ber.*, **72**, 1222 (1939).
[102] Fuson, Arnold, and Cooke, *J. Am. Chem. Soc.*, **60**, 2272 (1938).

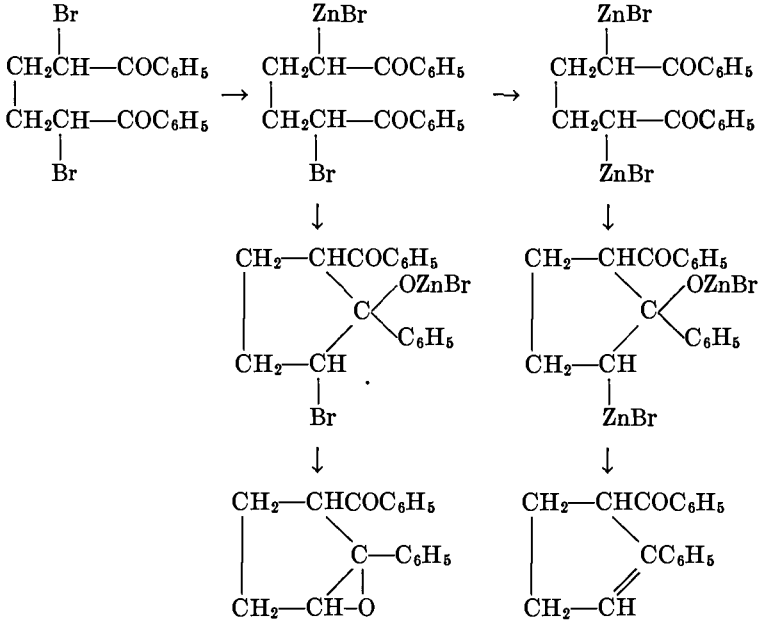
TABLE V

VARIATIONS OF THE REFORMATSKY REACTION

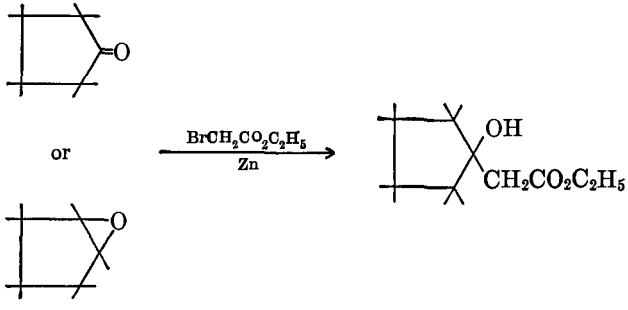
Aldehyde or Ketone	Halogen Compounds	Product	Yield, %	Reference
C_6H_5CHO	$ClCH_2CH{=}CHCO_2C_2H_5$	None	0	103
C_6H_5CHO	$BrCH_2CH{=}CHCO_2C_2H_5$	Hydroxyester	6	102
C_6H_5CHO	$ICH_2CH{=}CHCO_2C_2H_5$	Hydroxyester	13	102
p-ClC_6H_4CHO	$I(CH_2)_3CO_2C_2H_5$	Unsaturated ester	2	102
p-ClC_6H_4CHO	$ICH_2CH{=}CHCO_2C_2H_5$	Hydroxyester and unsaturated ester	42	102
6-Methoxy-1-tetralone	$BrCH_2CH_2CO_2C_2H_5$	Unsaturated acid	22	34
C_6H_5CHO	$C_6H_5CH_2Cl$	Stilbene	24	104
C_6H_5CHO	$BrCH_2C_6H_4CO_2CH_3(p)$	Substituted stilbene	21	104
p-ClC_6H_4CHO	$BrCH_2C_6H_4CO_2CH_3(p)$	Substituted stilbene	22	104
p-ClC_6H_4CHO	$BrCH_2C_6H_4CO_2CH_3(m)$	Substituted stilbene	22	104
p-BrC_6H_4CHO	$BrCH_2C_6H_4CO_2CH_3(p)$	Substituted stilbene	20	104
p-$CH_3O_2CC_6H_4CHO$	$ClC_6H_4CH_2Br(p)$	Substituted stilbene	19	104
	$ICH_2CH{=}CHCO_2C_2H_5$	Unsaturated ester	51	102
$C_6H_5COCH_3$	$Cl_2CHCO_2C_2H_5$	Hydroxychloroester	90	105
CH_3COCH_3	$ICH_2CH_2CH_2COCH_3$	Hydroxyketone	—	106

[103] Arnold, Ph.D. thesis, University of Illinois, 1937.
[104] Fuson and Cooke, *J. Am. Chem. Soc.*, **62**, 1180 (1940).
[105] Darzens, *Compt. rend.*, **203**, 1374 (1936).
[106] Verley, *Bull. soc. chim.*, [3] **17**, 192 (1897).

The formation of substituted cyclopentene and cyclopentene oxide derivatives by the action of zinc on 1,4-dibromo-1,4-dibenzoylbutane may be regarded as an intramolecular Reformatsky reaction.[107]

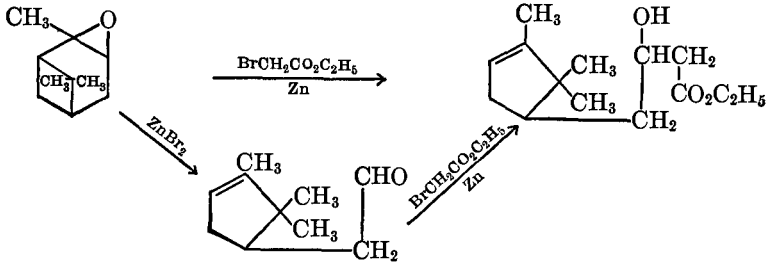


Use of Compounds Other than Carbonyl Derivatives. Certain oxides react with α-haloesters in the presence of zinc to produce hydroxyesters analogous to those obtained from ketones or aldehydes in the normal Reformatsky reaction. Ethyl 1-hydroxycyclopentylacetate is formed from either cyclopentanone or cyclopentene oxide by condensation with ethyl bromoacetate.[108]

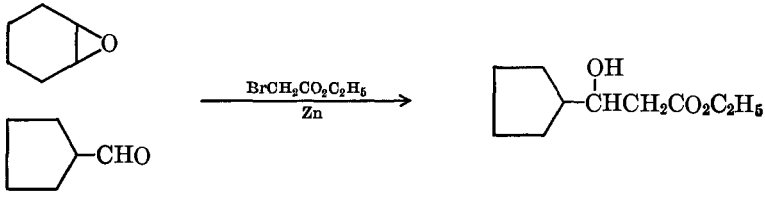


[107] Fuson and Farlow, *J. Am. Chem. Soc.*, **56**, 1593 (1934).
[108] Clemo and Ormston, *J. Chem. Soc.*, 362 (1933).

When certain oxides are used in place of carbonyl compounds, rearrangements may occur. For example, α-pinene oxide gives the same hydroxyester as the aldehyde formed by rearrangement.[62] It has been shown that zinc bromide causes rearrangement of the oxide to the aldehyde which then reacts with ethyl bromoacetate to produce the hydroxyester. Camphene oxide,[109] norpinene oxide,[109] and *d*-Δ^3-carene oxide [84] react similarly.



Cyclohexene oxide produces ethyl β-cyclopentyl-β-hydroxypropionate when treated with ethyl bromoacetate and zinc. The same ester is obtained from cyclopentanealdehyde,[108] demonstrating that ring contraction has taken place during the condensation with cyclohexene oxide.



9,10-Octahydronaphthalene oxide [85] reacts with ethyl bromoacetate and zinc to form a ketospiran and a hydroxyester whose structure is uncertain.

[109] Arbuzov, *J. Gen. Chem.* (*U.S.S.R.*), **9**, 255 (1939).

CHAPTER 2

THE ARNDT-EISTERT SYNTHESIS

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CONTENTS

PAGE

Introduction 38

The Scope and Limitations of the Synthesis 42

Experimental Conditions and Procedures 47
- Preparation of Diazomethane 50
  - From *N*-Nitrosomethylurea 50
  - From *N*-Nitrosomethylurethan 50
- Preparation of Acids 50
  - α-Naphthylacetic Acid 50
  - Decane-1,10-dicarboxylic Acid 51
- Preparation of Amides 51
  - *p*-Homoanisamide 51
  - Anthraquinone-2-acetanilide 52
  - 2-Hydroxy-3-naphthylacetanilide 52
- Preparation of Esters 52
  - Ethyl α-Naphthylacetate 52
  - Dimethyl Ester of 7-Methoxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-β-propionic Acid 53

Survey of the Arndt-Eistert Synthesis 53
- Table of Products and Yields 55

INTRODUCTION

The Arndt-Eistert synthesis is a procedure for converting an acid to its next higher homolog or to a derivative of the homologous acid, such as an ester or amide. The synthesis, which is applicable to both aliphatic and aromatic acids, involves the following three operations.

1. Formation of the acid chloride.

$$R—CO_2H \rightarrow R—COCl \qquad (R = \text{an alkyl or aryl group})$$

2. Reaction of the acid chloride with diazomethane to yield a diazoketone.

$$R{-}COCl + 2CH_2N_2 \rightarrow R{-}\underset{\underset{O}{\|}}{C}{-}CHN_2 + CH_3Cl + N_2$$

3. Rearrangement of the diazoketone, with loss of nitrogen, in the presence of suitable reagents and a catalyst (colloidal silver, platinum, copper). An acid is formed in the presence of water, an ester is produced in an alcohol, and an amide results when ammonia or an amine is used.

$$R{-}\underset{\underset{O}{\|}}{C}{-}CHN_2 + HOH \xrightarrow{Ag} R{-}CH_2CO_2H + N_2$$

$$R{-}\underset{\underset{O}{\|}}{C}{-}CHN_2 + R'OH \xrightarrow{Ag} R{-}CH_2CO_2R' + N_2$$

$$R{-}\underset{\underset{O}{\|}}{C}{-}CHN_2 + NH_3 \xrightarrow{Ag} R{-}CH_2CONH_2 + N_2$$

$$R{-}\underset{\underset{O}{\|}}{C}{-}CHN_2 + R'NH_2 \xrightarrow{Ag} R{-}CH_2CONHR' + N_2$$

The discovery that diazoketones can be converted into derivatives of an acid was made by Wolff [1] and this phase of the synthesis is known as the Wolff rearrangement. Wolff found, for example, that the treatment of ω-diazoacetophenone, $C_6H_5{-}CO{-}CHN_2$, with ethanolic ammonia and silver oxide gave phenylacetamide, $C_6H_5{-}CH_2{-}CONH_2$, in good yield. This reaction had no synthetic value at the time, for Wolff prepared the diazoketones through a complex series of reactions.

The practical application of the Wolff rearrangement as part of a preparative procedure awaited the discovery of a method of obtaining the diazoketones conveniently. This discovery arose from a study of the reaction between acid chlorides and diazomethane. Nierenstein and his collaborators [2] made an extensive study of the reaction between aromatic acid halides and diazomethane, but, strangely enough, they never observed the formation of diazoketones but always obtained ω-halo-

[1] Wolff, *Ann.*, **394**, 25 (1912).

[2] Clibbens and Nierenstein, *J. Chem. Soc.*, **107**, 1491 (1915); Lewis, Nierenstein, and Rich, *J. Am. Chem. Soc.*, **47**, 1728 (1925); Malkin and Nierenstein, *ibid.*, **52**, 1504 (1930).

methyl ketones, $RCOCH_2X$ (X = halogen). However, Arndt and co-workers,[3, 4, 5] and shortly thereafter Robinson and Bradley,[6] showed that diazoketones were obtained in nearly quantitative yield when the acid chloride was added slowly to a cold solution of an excess of diazomethane. This procedure varied from that of Nierenstein, who usually added one mole of diazomethane to the acid chloride, sometimes at slightly elevated temperatures (35°). According to Arndt and co-workers and Bradley and Schwarzenbach,[7] the following reactions take place when an acid chloride is added to diazomethane.

(*a*) $$RCOCl + CH_2N_2 \rightarrow RCOCHN_2 + HCl$$

(*b*) $$HCl + CH_2N_2 \rightarrow CH_3Cl + N_2$$

(*c*) $$RCOCHN_2 + HCl \rightarrow RCOCH_2Cl + N_2$$

The initial reaction is the formation of the diazoketone with liberation of hydrogen chloride (*a*). The hydrogen chloride then reacts with a second molecule of diazomethane to form methyl chloride (*b*). If any of the hydrogen chloride is not destroyed in this reaction, it will react with the diazoketone to yield the ω-chloromethylketone (*c*). In general, where there is always an excess of diazomethane, reaction (*c*) takes place to a very limited extent, because the excess diazomethane reacts with the hydrogen chloride almost as fast as the hydrogen chloride is formed. However, when the reaction is run so that there is always an excess of acid chloride (by adding the diazomethane slowly to the acid chloride), some chloromethyl ketone is formed, especially at higher temperatures, although the high yields of this product obtained by Nierenstein have not been duplicated by other investigators.[7]

With the diazoketones readily available, Arndt and Eistert [8] made a study of the Wolff rearrangement and showed that it was of quite general application. They pointed out that a combination of the two reactions, the formation of the diazoketone from acid chlorides and the Wolff rearrangement, constituted a new method of lengthening a carbon chain by one methylene group.

The diazoketones are believed to decompose by way of intermediates similar to those involved in the Curtius rearrangement of acid

[3] Arndt, Eistert, and Partale, *Ber.*, **60**, 1364 (1927).
[4] Arndt and Amende, *Ber.*, **61**, 1122 (1928).
[5] Arndt, Eistert, and Amende, *Ber.*, **61**, 1949 (1928).
[6] Robinson and Bradley, *J. Chem. Soc.*, 1310 (1928).
[7] Bradley and Schwarzenbach, *J. Chem. Soc.*, 2904 (1928).
[8] Arndt and Eistert, *Ber.*, **68**, 200 (1935).

azides.[1, 9, 10, 11] The nitrogen is eliminated, and a short-lived radical is produced which rearranges to the corresponding ketene.

$$RCOCHN_2 \rightarrow N_2 + [RCOCH{=}] \rightarrow RCH{=}C{=}O$$

$$RCON_3 \rightarrow N_2 + [RCON{=}] \rightarrow RN{=}C{=}O$$

In several cases the intermediate ketenes have been isolated,[12] but ordinarily they are converted to the acids, esters, or amides by the water, alcohol, ammonia, or amine present in the reaction mixture.

$$\begin{aligned} RCH{=}C{=}O + HOH &\rightarrow RCH_2CO_2H \\ + R'OH &\rightarrow RCH_2CO_2R' \\ + NH_3 &\rightarrow RCH_2CONH_2 \\ + R'NH_2 &\rightarrow RCH_2CONHR' \end{aligned}$$

The rearrangement of optically active diazoketones, in which the carbon atom attached to the carbonyl group was asymmetric, resulted in the formation of optically active products except in one or two instances.[10, 11] This result is similar to that observed in the rearrangement of optically active acid azides.

It is considered that the metal catalyst which is usually required for the reaction accelerates the decomposition of the diazoketone to the ketene, since in the absence of such a catalyst no rearrangement takes place and the product formed is a derivative of the ketone. Thus, if diazoacetophenone is heated with water at 70–80°, benzoylcarbinol is obtained.[1, 4]

$$C_6H_5COCHN_2 + H_2O \rightarrow C_6H_5COCH_2OH + N_2$$

If silver is present, rearrangement takes place and phenylacetic acid is formed. Wolff [1] found that the addition of powdered silver did not catalyze the decomposition of diazoacetone in the presence of ammonia, but that the reaction was rapid if either silver oxide or silver nitrate was added. Thus, it appears that the catalyst, if it is metallic silver, must be colloidally dispersed. Arndt and Eistert [8] found that even with highly purified diazoketone there was always a small amount of reduction of the silver salts which could account for the production of the necessary catalyst. Powdered copper and platinum have also been used as catalysts in the rearrangement but much less frequently.

[9] Eistert, *Ber.*, **68**, 208 (1935).

[10] Lane, Willenz, Weissberger, and Wallis, *J. Org. Chem.*, **5**, 276 (1940).

[11] Lane and Wallis, *J. Org. Chem.*, **6**, 443 (1941).

[12] Schroeter, *Ber.*, **42**, 2346 (1909); **49**, 2704 (1916); Staudinger and Hirzel, *Ber.*, **49**, 2522 (1916).

THE SCOPE AND LIMITATIONS OF THE SYNTHESIS

It is apparent that by the Arndt-Eistert synthesis an acid can be converted to its next higher homolog by a three-step process. The over-all yield is ordinarily between 50 and 80%. Other well-known methods for accomplishing the same result include the following processes, which are presented in outline form.

[1] $RCO_2H \rightarrow RCOCl \rightarrow RCHO \rightarrow RCH_2OH \rightarrow RCH_2Br \rightarrow$

RCH_2CN (or RCH_2MgBr) $\rightarrow RCH_2CO_2H$

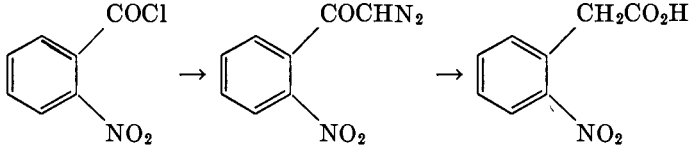
[2] $RCO_2H \rightarrow RCO_2C_2H_5 \rightarrow RCH_2OH \rightarrow RCH_2Br \rightarrow RCH_2CN$

(or RCH_2MgBr) $\rightarrow RCH_2CO_2H$

[3] $RCO_2H \rightarrow RCOCl \rightarrow RCOCN \rightarrow RCOCO_2H \rightarrow RCH_2CO_2H$

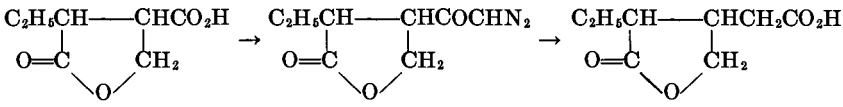
The choice of the method to be used depends on several factors, such as the amount of the acid desired, the type of acid, and the over-all yields possible. Methods 1 and 2, which consist of more steps than the Arndt-Eistert reaction, often give lower over-all yields and require a longer working time. Method 3 generally gives poor yields of the product. The Arndt-Eistert reaction can be carried through rapidly, one day usually being sufficient for the complete synthesis, and it is thus an ideal method when only small amounts of the final product are desired. It is of interest that Eistert [13] and Burger and Avakian [14] have worked successfully with amounts of diazoketone as large as 100 g.

Each of the three methods outlined above involves a more or less drastic reduction which may interfere with its application to a compound containing a nitro, quinone, keto, lactone, ester, or other reducible group. The Arndt-Eistert reaction involves no such step and can be used for the preparation of molecules which are sensitive to reducing agents. For example, the nitrophenylacetic acids can be prepared easily and in good yields from the nitrobenzoyl chlorides.[8, 15]



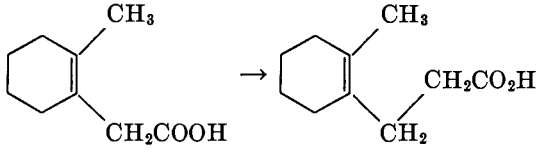
[13] Eistert, *Ber.*, **69**, 1074 (1936).
[14] Burger and Avakian, *J. Org. Chem.*, **5**, 606 (1940).
[15] Bachmann and Holmes, unpublished results.

d-Homopilopic acid can be prepared from *d*-pilopic acid, the lactone ring remaining intact throughout the synthesis.[16, 16a]

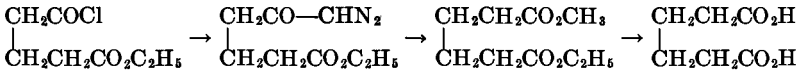


d-Pilopic acid *d*-Homopilopic acid

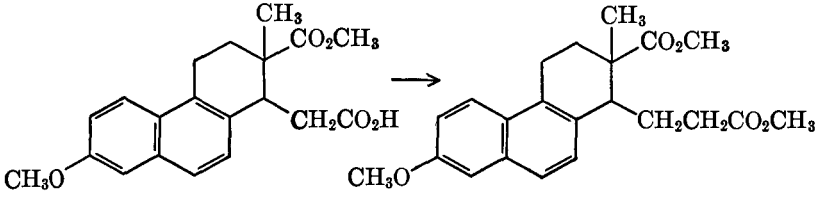
An illustration of the conversion of a β,γ-unsaturated acid to its homolog is the preparation of β-(2-methylcyclohexenyl)-propionic acid from 2-methylcyclohexenylacetic acid.[17]



A dicarboxylic acid can be converted, through its acid ester, to its next higher homolog, a process which would be difficult to accomplish by other methods. Thus, glutaric acid has been converted to adipic acid through the intermediate ester chloride.[18]

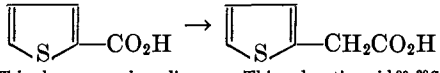


The Arndt-Eistert reaction is ideal for use on complex molecules. The reaction is carried out at moderately low temperatures so that the chances of decomposing the molecule are not as great as in some of the other syntheses. An interesting example in the synthesis of the sex hormone equilenin is the conversion of one of the intermediates to its next higher homolog in good yield (80–84%).[19]

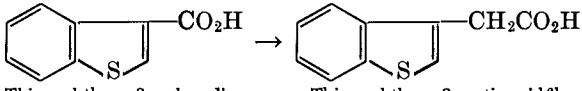


[16] Preobrashenski, Poljakowa, and Preobrashenski, *Ber.*, **68**, 850 (1935).
[16a] Poljakowa, Preobrashenski, and Preobrashenski, *Ber.*, **69**, 1314 (1936).
[17] Plentl and Bogert, *J. Org. Chem.*, **6**, 669 (1941).
[18] Bachmann and Sheehan, unpublished results.
[19] Bachmann, Cole, and Wilds, *J. Am. Chem. Soc.*, **62**, 824 (1940).

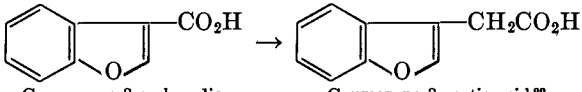
The following are some of the syntheses that have been carried out in the heterocyclic series by means of the Arndt-Eistert synthesis.



Thiophene-α-carboxylic acid → α-Thienylacetic acid [20, 20a]



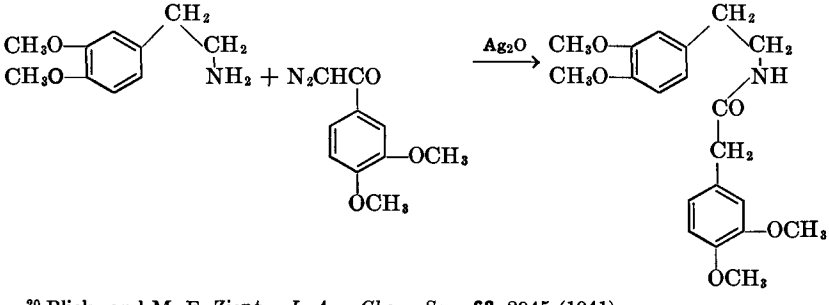
Thionaphthene-3-carboxylic acid → Thionaphthene-3-acetic acid [21]



Coumarone-3-carboxylic acid → Coumarone-3-acetic acid [22]

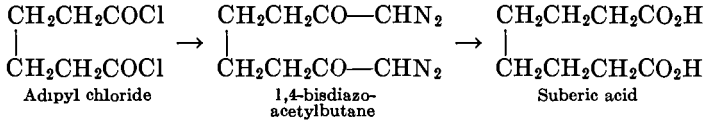
Although diazoketones have been prepared successfully from 2-,[23] 3-,[24] and 4-pyridinecarboxylic acid [24] and from 4-quinolinecarboxylic acid,[24a] the Wolff rearrangement on the diazoketones has not been reported. The complete synthesis has been carried out on *N*-methylpyrrole-2-carboxylic acid.[20a]

An ingenious application of the synthesis has been made in a synthesis of papaverine. The diazoketone prepared from the acid chloride of veratric acid and diazomethane was allowed to react with homoveratrylamine to give the substituted amide of homoveratric acid, which was then cyclized and dehydrogenated to papaverine.[25]



[20] Blicke and M. F. Zienty, *J. Am. Chem. Soc.*, **63**, 2945 (1941).
[20a] Arndt and Eistert, Ger. pat., 650,706 [*C. A.*, **32**, 595 (1938)].
[21] Crook and Davies, *J. Chem. Soc.*, 1697 (1937).
[22] Titoff, Müller, and Reichstein, *Helv. Chim. Acta*, **20**, 883 (1937).
[23] Winterfeld and Cosel, *Arch. Pharm.*, **289**, 70 (1940).
[24] Baumgarten and Dornow, *Ber.*, **73**, 44 (1940); Dornow, *Ber.*, **73**, 185 (1940).
[24a] King and Work, *J. Chem. Soc.*, 1307 (1940).
[25] Eistert, *Angew. Chem.*, **54**, 124 (1941).

Since the product obtained in the Arndt-Eistert synthesis is an acid, or a derivative which can be hydrolyzed to an acid, it is possible to continue the chain-lengthening process. The method is particularly adapted for the preparation of a homologous series of acids. In a number of cases two methylene groups have been added to the chain of an acid by carrying out two successive Arndt-Eistert syntheses.[17, 26, 27] Two methylene groups have been introduced into dicarboxylic acids in one operation (bishomologation) by the Arndt-Eistert method. Thus, adipic acid has been converted to suberic acid, and sebacic acid to decane-1,10-dicarboxylic acid through the intermediate bisdiazoketones.[28, 29]

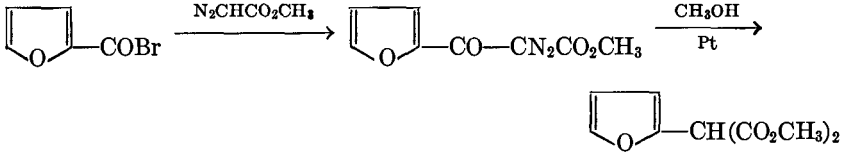


Little work has been done on the use of diazo compounds other than diazomethane in the Arndt-Eistert synthesis. It has been reported that the diazoketone obtained from *p*-nitrobenzoyl chloride and diazoethane yielded *p*-nitrophenylmethylacetanilide when rearranged in aniline.[30]

$$p\text{-}NO_2C_6H_4COCl \xrightarrow{CH_3CHN_2} p\text{-}NO_2C_6H_4CO{-}C(CH_3)N_2$$

$$p\text{-}NO_2C_6H_4CO{-}C(CH_3)N_2 + C_6H_5NH_2 \rightarrow p\text{-}NO_2C_6H_4CH(CH_3)CONHC_6H_5 + N_2$$

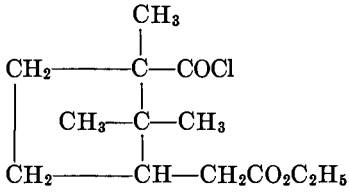
Several carboalkoxydiazoketones, $RCO{-}CN_2CO_2R'$, formed by interaction of acid chlorides and diazoacetic ester,[31] have been submitted to rearrangement.[12] The diazoketone prepared from α-furoyl bromide and methyl diazoacetate yielded dimethyl α-furylmalonate when rearranged in methanol in the presence of platinum.[32]

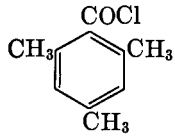


The chlorides of two hindered acids have been found to resist the action of diazomethane; these are the chloride of the acid ester of homocam-

[26] Bachmann and Edgerton, *J. Am. Chem. Soc.*, **62**, 2550 (1940).
[27] Bachmann and Holmes, *J. Am. Chem. Soc.*, **62**, 2750 (1940).
[28] Walker, *J. Chem. Soc.*, 1304 (1940).
[29] Work, *J. Chem. Soc.*, 1315 (1940).
[30] Eistert, unpublished results. See ref. 25.
[31] Staudinger and Machling, *Ber.*, **49**, 1973 (1916); Staudinger, Becker, and Hirzel, *Ber.*, **49**, 1978 (1916).
[32] Reichstein and Morsman, *Helv. Chim. Acta*, **17**, 1119 (1934).

phoric acid in which the acid chloride group is attached to a tertiary carbon atom [33] and mesitoyl chloride.[18]





Unlike the acid chlorides of carboxylic acids, sulfonyl chlorides fail to react with diazomethane.[34]

Functional groups as phenolic hydroxyl, aldehyde, active methylene, and α,β-unsaturated carbonyl groups, which are capable of reacting with diazomethane, might be expected to interfere in the Arndt-Eistert synthesis. Only a few acid chlorides containing such groups have been studied. From 4-fluorenonecarboxylic acid chloride, the methyl ester of 4-fluorenoneacetic acid was obtained in 84% yield,[35] although the parent ketone, fluorenone, reacts with diazomethane.[36] Likewise, 2-hydroxy-3-naphthoyl chloride yields the diazoketone without methylation of the hydroxyl group.[37] However, it is not certain that the acid chloride group in other compounds containing reactive groups will react preferentially with the diazomethane.

One of the side reactions that occurs in the preparation of the diazoketones is the formation of ω-halomethyl ketones. As has already been pointed out, this reaction is not significant if the reaction is carried out at low temperature in the presence of an excess of diazomethane. If the diazoketone is treated with halogen acids, the ω-halomethyl ketone can be obtained in excellent yield, and this reaction has been used recently for preparative purposes.[24a, 28, 29, 38]

$$R-\underset{\underset{O}{\|}}{C}-CHN_2 + HCl \rightarrow R-\underset{\underset{O}{\|}}{C}-CH_2Cl + N_2$$

Other side reactions apparently accompany the formation of some diazoketones, since the latter are sometimes contaminated with impurities as yet unidentified. In view of the reaction between acid chlorides and diazoacetic ester,[31, 32] there is a possibility that the diazoketone formed

[33] Litvan and Robinson, *J. Chem. Soc.*, 1997 (1938).
[34] Arndt and Scholz, *Ber.*, **66**, 1012 (1933).
[35] Bachmann and Sheehan, *J. Am. Chem. Soc.*, **62**, 2687 (1940).
[36] Schultz, Schultz, and Cochran, *J. Am. Chem. Soc.*, **62**, 2902 (1940).
[37] Krzikalla and Eistert, *J. prakt. Chem.*, **143**, 50 (1935).
[38] Haberland, *Ber.*, **72**, 1215 (1939).

initially may react with a second molecule of the acid chloride, but this has not been established.

EXPERIMENTAL CONDITIONS AND PROCEDURES

The acid chloride used in the first step of the Arndt-Eistert reaction may be prepared by any of the usual methods, but it should be carefully purified, by distillation whenever possible. The solvents and apparatus must be scrupulously dry, especially when aliphatic chlorides are employed, in order to avoid hydrolysis. Any free acid formed by hydrolysis will be converted to the methyl ester by the diazomethane, thus contaminating the product and decreasing the yield.

Diazomethane must be prepared with care. It is extremely toxic, and repeated exposure to even very low concentrations causes increased sensitivity to the substance. An account of a case of acute diazomethane poisoning has been published.[39] A good hood with a forced draft is strongly recommended for work with diazomethane. Diazomethane is explosive in the gaseous state, and, although the ethereal solutions, which are generally used, are safe to handle at room temperature or lower, a certain amount of care must be exercised. Fortunately, an ether solution of diazomethane can be prepared at 0° from *N*-nitrosomethylurea,[40, 41] and the solution can be used without purification by distillation. An inexpensive method for preparing *N*-nitrosomethylurea from urea and methylamine hydrochloride has been described.[42] It should be mentioned that *N*-nitrosomethylurea has been known to explode when kept at room temperature, but when stored in a cold place the compound remains unchanged for months.

The preparation of diazomethane from *N*-nitrosomethylurethan [43] by von Pechmann's method is convenient for small amounts, although the diazomethane usually requires purification by distillation. The method consists in decomposing the urethan by means of a sodium alcholate. Higher alcohols, such as propanol [19] and ethylene glycol,[44] have been used to make the alcoholate in order to minimize contamination of the diazomethane.

Diazomethane has been prepared also from hydrazine, chloroform, and potassium hydroxide.[45] A new method which appears attractive, but

[39] Sunderman, Connor, and Fields, *Am. J. Med. Sci.*, **195**, 469 (1938).

[40] Arndt, *Org. Syntheses*, **15**, 4 (1935).

[41] Hofmann, *Ber.*, **14**, 2725 (1881); Odenwald, *Ann.*, **416**, 228 (1918); **418**, 317 (1919); Werner, *J. Chem. Soc.*, **115**, 1096 (1919).

[42] Arndt, Loewe, and Avan, *Ber.*, **73**, 606 (1940).

[43] Hartman and Phillips, *Org. Syntheses*, **13**, 84 (1933).

[44] Meerwein and Burneleit, *Ber.*, **61**, 1845 (1928).

[45] Staudinger and Kupfer, *Ber.*, **45**, 501 (1912).

which has not yet found extensive use, consists in the treatment of nitrosomethylaminomesityl oxide with sodium isopropoxide.[46] The requisite intermediate is obtained readily from mesityl oxide, methylamine, and nitrous acid.

The concentration of diazomethane in a solution is estimated best by titration with benzoic acid according to the procedure of Marshall and Acree.[47]

From a consideration of the reactions which occur on interaction of an acid chloride and diazomethane, it is evident that the *acid chloride should be added to an excess of diazomethane*, for in this manner the side reaction leading to the formation of the ω-halomethyl ketone is suppressed. A solution (or suspension) of the acid chloride (1 mole) in ether or benzene is added slowly to a cold (0–5°) solution of diazomethane (3 moles) in ether or benzene with swirling or mechanical stirring of the mixture. Generally a brisk evolution of nitrogen takes place. With reactive acid chlorides, such as most aliphatic acid chlorides, the reaction appears to be complete as soon as addition has been made, but usually the mixture is allowed to stand at 20–25° for an hour or two. With aromatic and other less reactive acid chlorides, two hours and more (sometimes twelve to twenty-four hours) is generally allowed.

Some diazoketones crystallize from the solution as they are formed, or when the solution is cooled to −10° or lower. Usually they are isolated by evaporating the solvent under reduced pressure from a water bath held at 20–30°. As a rule, the residual diazoketone is satisfactory for rearrangement without further purification. If it is crystalline, the diazoketone may be purified by trituration with a small volume of cold solvent in order to dissolve oily impurities, and many diazoketones have been recrystallized. Purification by distillation is not recommended. Diazoacetone explodes when distilled at atmospheric pressure (113–115°), but it has been distilled without decomposition under reduced pressure.[1] While most diazoketones appear to be stable under ordinary conditions, and some even in cold methanolic potassium hydroxide solution,[48] the crystalline diazoketone obtained from cinnamoyl chloride and diazomethane is unstable and decomposes on standing.[7]

For the rearrangement of the diazoketones to yield acids, esters, amides, and substituted amides, silver oxide is frequently employed. Freshly prepared silver oxide and commercial silver oxide have been used with equal success. The silver oxide may be prepared by adding a dilute solution of sodium hydroxide to a solution of silver nitrate (10%)

[46] Adamson and Kenner, *J. Chem. Soc.*, 286 (1935).
[47] Marshall and Acree, *Ber.*, **43**, 2323 (1910).
[48] Reichstein and v. Euw, *Helv. Chim. Acta*, **22**, 1209 (1939); **23**, 136 (1940).

until precipitation is just complete, an excess of alkali being avoided. The silver oxide is washed several times with distilled water by decantation and then filtered by suction and washed well with water.

In order to prepare an acid, a dioxane solution of the diazoketone is added slowly to a warm (60–70°) aqueous solution of silver nitrate and sodium thiosulfate or to a suspension of silver oxide in a dilute solution of sodium thiosulfate. If the conversion to the acid fails to give good results, it may be advisable to employ the procedures for making the ester or amide, which are obtained generally in higher yields than the acids, and obtain the free acid by hydrolysis of the derivative.

Esters of the homologous acids are prepared by adding silver oxide to a hot solution or suspension of the diazoketone in an anhydrous alcohol. Methanol, ethanol, and propanol have been used, methanol most frequently. The silver oxide is added generally in the form of a slurry in the alcohol, best results being obtained if it is added in portions over a period of an hour or two rather than in one lot.[49] The silver oxide is reduced by hot methanol to metallic silver, which usually deposits as a mirror on the sides of the flask.

There is an appreciable difference in the rates with which various diazoketones rearrange and form esters. Sometimes the reaction is complete in an hour; however, as much as twelve hours may be necessary for completion of the reaction. The presence of unreacted diazoketone may be detected by the evolution of nitrogen which takes place when a sample of the solution is treated with a drop or two of concentrated hydrochloric acid.[13] If the reaction is slow, it may be advisable to continue the addition of more silver oxide. In a few resistant cases, the solution was filtered from the sludge of silver and silver oxide and the filtrate was treated with fresh silver oxide. In one preparation,[35] best results were obtained by refluxing a suspension of silver oxide in methanol until a thin silver mirror was formed (about fifteen minutes), then adding the diazoketone and continuing the refluxing.

The conversion of a diazoketone to an acid amide has been accomplished by passing ammonia into a cold solution of the diazoketone in ethanol containing a small amount of silver oxide. The procedure has been reversed also and the diazoketone added to an ethanolic solution of ammonia, followed by the addition of silver oxide or silver nitrate. A more widely used scheme consists in treating a warm solution of the diazoketone in dioxane with a 10–28% aqueous solution of ammonia containing a small amount of silver nitrate, after which the mixture is heated for some time.[8, 14] It would appear desirable to take precautions

[49] Arndt and Eistert, *Ber.*, **69**, 1805 (1936).

(use of shield) when heating mixtures containing ammoniacal silver nitrate.

A number of procedures have been employed to prepare anilides from the diazoketones. Some have been prepared by the gradual addition of the diazoketone to boiling aniline;[1, 37] after each addition one waits until the evolution of nitrogen has ceased before making another addition. A better procedure consists in warming a solution of the diazoketone and aniline in ethanol or dioxane containing a small amount of aqueous silver nitrate.[8]

Occasionally the product obtained in a reaction may contain traces of colloidal silver or silver salts. These may be removed by filtering a solution of the compound through alumina, after first making the solution alkaline if an acid is the product.

Preparation of Diazomethane

From *N*-Nitrosomethylurea.[40] A mixture of 150 cc. of ordinary ether and 45 cc. of 40% aqueous potassium hydroxide is cooled to 5°. To this is added, with continuous cooling and efficient stirring or swirling, 15 g. of finely powdered *N*-nitrosomethylurea in small portions as rapidly as the crystals dissolve (a few minutes). The deep yellow ethereal solution of diazomethane can be separated from the aqueous layer by decantation or by means of a separatory funnel. The solution, which contains about 4.2 g. of diazomethane, is dried for several hours over pellets of pure potassium hydroxide or over soda-lime. A solution of diazomethane in benzene may be prepared in the same way. Larger runs may be made by varying the amounts of material accordingly.

From *N*-Nitrosomethylurethan.[19] A solution of 2.8 g. of powdered potassium hydroxide (85%) in 10 cc. of warm propanol is prepared in a 125-cc. Claisen flask; 60 cc. of anhydrous ether is added to the solution, and the flask is attached to a dry condenser, which is connected to a receiver (a suction flask fitted with a drying tube) containing about 10 cc. of anhydrous ether. The end of the condenser dips below the surface of the ether in the receiver. Through a dropping funnel a solution of 4.5 cc. of nitrosomethylurethan in 10 cc. of anhydrous ether is dropped into the alkaline mixture; the diazomethane is distilled from the mixture as it is formed. The ethereal solution contains between 0.72 and 0.9 g. of diazomethane and is suitable for reaction without drying.

Preparation of Acids

Conversion of α-Naphthoic Acid to α-Naphthylacetic Acid.[8, 25] A solution of 19 g. of α-naphthoyl chloride in 50 cc. of absolute ether is added

at 5–10° to a solution of diazomethane prepared from 35 g. of nitrosomethylurea in 500 cc. of ether. After several hours at 20–25°, the ether is removed under reduced pressure, finally at 30°. The crystalline yellow residue of α-naphthoyldiazomethane (m.p. of a sample after recrystallization from benzene, 54–55°) weighs 18 g. (92%).

A solution of 15 g. of the diazoketone in 100 cc. of dioxane is added dropwise with stirring to a mixture of 2 g. of silver oxide, 5 g. of anhydrous sodium carbonate, and 3 g. of sodium thiosulfate in 200 cc. of water at 50–60°. Stirring is continued for one hour after addition is complete, and the temperature of the mixture is raised finally to 90–100°. The solution is cooled, diluted with water, and acidified with dilute nitric acid. The α-naphthylacetic acid, which precipitates, is filtered from the mixture and recrystallized from water; yield, 10–12 g. (79–88%); m.p. 130°.

Bishomologation. Sebacic Acid to Decane-1,10-dicarboxylic Acid (p. 45). An ethereal solution of sebacyl chloride prepared from 20 g. of sebacic acid is added slowly to an ethereal solution of diazomethane (prepared from 50 g. of nitrosomethylurea), and the mixture is allowed to stand overnight. The ether and excess of diazomethane are removed under reduced pressure, and the residual crystalline 1,8-bisdiazoacetyloctane is collected; yield, 19.3 g. (77%, based on the acid); m.p. 91°, after recrystallization from benzene.[29]

A solution of 6.8 g. of the diazoketone in 100 cc. of warm dioxane is added with stirring to a suspension of 7 g. of freshly precipitated silver oxide in 250 cc. of an aqueous solution containing 11 g. of sodium thiosulfate at 75°. A brisk evolution of nitrogen occurs. After one and one-half hours at 75°, the black silver residue is removed by filtration, the clear, almost colorless filtrate is acidified with nitric acid, and the decane-1,10-dicarboxylic acid is extracted with ether. From the ether extract, 4.5 g. (72%) of crude acid is obtained. After recrystallization from 20% aqueous acetic acid, it melts at 127–128°.[28]

Preparation of Amides

Conversion of *p*-Anisoyl Chloride to the Amide of *p*-Homoanisic Acid.[14] To an ethereal solution of diazomethane obtained from 380 g. of nitrosomethylurea 150 g. of *p*-anisoyl chloride is added, and the solution is allowed to stand overnight. The solvent is removed by distillation, and the crystalline diazoketone is recrystallized from benzene, from which it separates as transparent, hexagonal prisms; m.p. 90–91°; yield, 109 g. (70.3%).

A solution of 20 g. of the diazoketone in 100 cc. of dioxane is treated with 150 cc. of aqueous ammonia (sp. gr. 0.9) and 30 cc. of 10% aqueous silver nitrate solution at 60–70°. The mixture is boiled under reflux for two hours, cooled, and the *p*-homoanisamide is precipitated by the addition of water. Recrystallization from ethanol yields 15 g. (81%) of the pure amide; m.p. 188–189°.

Preparation of Anthraquinone-2-acetanilide.[8] To a solution of diazomethane in dioxane (prepared from 35 g. of nitrosomethylurea) is added 27 g. of anthraquinone-2-carboxylic acid chloride. When the reaction is complete, a few cubic centimeters of water are added and then 30 cc. of aniline and 30 cc. of 10% aqueous silver nitrate solution. A renewed evolution of gas occurs. The reaction is completed by heating on a steam bath. The product begins to separate while the mixture is still warm; after cooling, the product is filtered, dried, and recrystallized from xylene, from which the anilide is obtained as small, colorless needles; m.p. 267–268°.

Preparation of 2-Hydroxy-3-naphthylacetanilide.[37] To an ethereal solution of diazomethane prepared from 35 g. of nitrosomethylurea is added 25 g. of 2-acetoxy-3-naphthoyl chloride. After one-quarter hour at room temperature, the mixture is cooled for one hour at −15°, and the precipitated diazoketone [23 g. (90%); m.p. 122–123°, dec.] is filtered from the mixture.

Ten grams of the diazoketone is added in portions to 30 g. of boiling aniline; after each addition the reaction is allowed to run to completion before the next portion is added. The mixture is boiled for a short time after all the diazoketone has been added, cooled, and poured into dilute hydrochloric acid. The anilide is filtered from the mixture and recrystallized from ethanol or acetic acid; m.p. 215–216°; yield, 7.1 g. (58%).

Preparation of Esters

Preparation of the Ethyl Ester of α-Naphthylacetic Acid.[25, 8] The diazoketone is prepared from the acid chloride of α-naphthoic acid in the manner described (p. 50). To a solution of 10 g. of the diazoketone in 150 cc. of ethanol at 55–60° is added a small amount of a slurry of silver oxide, prepared from 10 cc. of 10% aqueous silver nitrate and stirred with 30 cc. of ethanol. As soon as the evolution of nitrogen subsides, more of the silver oxide is introduced, and this process is continued until all the slurry has been added. The mixture is then refluxed for a short time, treated with charcoal, filtered, and evaporated. Distillation yields 8–9 g. (73–82%) of ethyl α-naphthylacetate, boiling at 175–178°/11 mm.

Preparation of the Dimethyl Ester of 7-Methoxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-β-propionic Acid [19] (p. 43). To 4 cc. of ice-cold dry benzene in a 125-cc. filter flask fitted with a drying tube are added 2 drops of pyridine and then 1.5 cc. of pure thionyl chloride. To the cold solution is added 1.71 g. of 7-methoxy-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid (p. 43) in powdered form. After standing at room temperature for one-half hour, the mixture is warmed to about 40° for ten minutes. The orange-yellow solution, containing some pyridine hydrochloride in suspension, is evaporated under reduced pressure; 2 cc. of benzene is added, and the solution is evaporated again in order to remove traces of thionyl chloride. The crystalline acid chloride is dissolved in 16 cc. of warm benzene; the solution is cooled somewhat and decanted carefully (through a small plug of cotton in the side arm of the flask) drop by drop into a cold (5°) solution of diazomethane in ether (prepared from 4.5 cc. of nitrosomethylurethane); during the addition the diazomethane solution is swirled constantly.

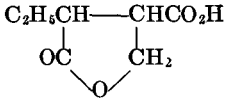
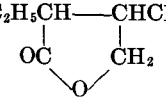
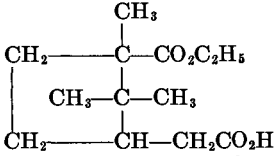
After fifteen to thirty minutes, the ether and excess of diazomethane are removed under reduced pressure at room temperature. To the crystalline diazoketone is added 35 cc. of anhydrous methanol, and to the warm (50°) mixture is added one-half of the silver oxide which has been prepared from 3.6 cc. of 10% aqueous silver nitrate solution and made into a slurry with methanol. The mixture is warmed on a water bath at about 60° with frequent swirling. Nitrogen is evolved, and after fifteen to twenty minutes all of the rather insoluble diazoketone has gone into solution. At this time a small amount of silver oxide is added and the heating is continued; further additions of silver oxide are made every five minutes, so that after six additions all of it has been added. Then the mixture is refluxed for fifteen minutes, treated with Norit, filtered, and concentrated to a small volume. On cooling, the product crystallizes; yield, 1.48–1.56 g. (80–84%); m.p. 97–101°. If the crystals darken on exposure to light, a benzene solution of the product is passed through a short column of alumina in order to remove traces of silver compounds present.

SURVEY OF THE ARNDT-EISTERT SYNTHESIS

In the following table are given nearly all the examples of the synthesis which had been reported prior to November, 1941. The first column gives the name or formula, or both, of the acid used as the starting material. The acids are listed in the following order: aliphatic, cycloalkyl, arylalkyl, aromatic, and heterocyclic acids. Frequently an

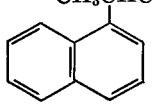
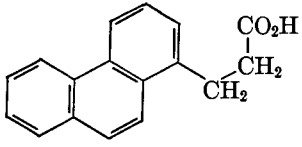
ester or amide of the homologous acid was prepared in the synthesis, and the derivative was then hydrolyzed to the free acid, the weight of which was recorded. The second column shows the product (acid, ester, or amide) which was prepared initially, and the third column indicates the compound which was isolated. The yields, which are reported in the fourth column, represent the conversion of the starting acid to the compound which was isolated and are the over-all yields for the three steps: preparation of the acid chloride, formation of the diazoketone, and rearrangement of the diazoketone.

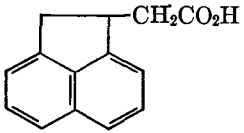
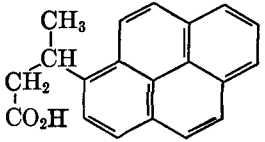
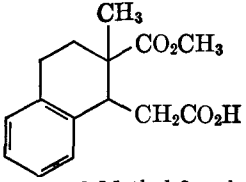
PRODUCTS AND YIELDS OBTAINED IN THE ARNDT-EISTERT SYNTHESIS

Starting Acid	Primary Product	Compound Isolated	Yield, %	Reference *
Acetic acid	Amide	Propionamide		1, 5
Ethyl hydrogen glutarate	Ester	Adipic acid	69	18
Adipic acid	Amide	Suberic acid	75	28
Sebacic acid	Acid	Decane-1,10-dicarboxylic acid	55	28
	Amide	Decane-1,10-dicarboxylic acid amide	66	28
 *d*-Pilopic acid	Acid	 *d*-Homopilopic acid	68	16
rac-Isopilopic acid	Acid	*rac*-Homoisopilopic acid		16*a*
	Amide	*rac*-Homoisopilopamide	—	16*a*
	Ester	*rac*-Ethyl homoisopilopate	—	16*a*
2-Methylcyclohexenylacetic acid (p. 43)	Acid	β-(2-Methylcyclohexenyl)-propionic acid	—	17
	Amide	Amide of the above acid	—	17
	Ester	Ethyl ester of the above acid	—	17
β-(2-Methylcyclohexenyl)-propionic acid	Acid	γ-(2-Methylcyclohexenyl)-butyric acid	—	17
 Ethyl hydrogen homocamphorate	Acid	Hydrocamphorylacetic acid	53	33

* References 50–72 appear on p 62

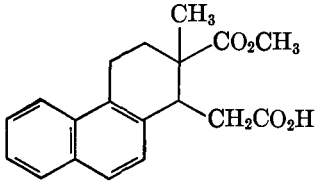
PRODUCTS AND YIELDS OBTAINED IN THE ARNDT-EISTERT SYNTHESIS—*Continued*

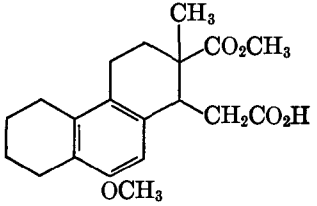
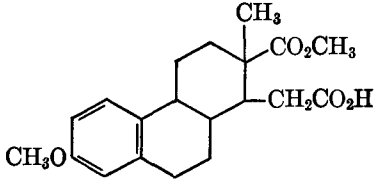
Starting Acid	Primary Product	Compound Isolated	Yield, %	Reference *
$C_6H_5CH_2CH_2CO_2H$	Acid	γ-Phenylbutyric acid	60	33
β-Phenylpropionic acid	Ester	γ-Phenylbutyric acid	74	50
$C_6H_5CH_2(CH_3)CHCO_2H$	Acid	β-Methyl-γ-phenylbutyric acid	—	10
α-Methyl-β-phenylpropionic acid	Amide	Amide of the above acid		10
$C_6H_5(CH_3)(C_2H_5)CCO_2H$ Methylethylphenylacetic acid	Acid	β,β,β-Methylethylphenylpropionic acid	—	10
$C_6H_5(CH_3)CH(CH_3)CHCO_2H$ α-Methyl-β-phenylbutyric acid	Acid	β-Methyl-γ-phenylvaleric acid	81	51
$CH_3CHCH_2CO_2H$  β-(1-Naphthyl)-butyric acid	Ester	γ-(1-Naphthyl)-valeric acid	68	52
 β-(1-Phenanthryl)-propionic acid	Ester	γ-(1-Phenanthryl)-butyric acid	61	53
β-(2-Phenanthryl)-butyric acid	Ester	γ-(2-Phenanthryl)-valeric acid	80	53
β-(3-Phenanthryl)-butyric acid	Ester	γ-(3-Phenanthryl)-valeric acid	80	54
	Amide	γ-(3-Phenanthryl)-valeramide	72	54
4-Methyl-1-phenanthrylacetic acid	Ester	β-(4-Methyl-1-phenanthryl)-propionic acid	42	55
β-(4-Methyl-1-phenanthryl)-propionic acid	Ester	γ-(4-Methyl-1-phenanthryl)-butyric acid	41	55

 7-Acenaphthylacetic acid	Ester	β-(7-Acenaphthyl)-propionic acid	78	56
1-Ethyl-7-acenaphthylacetic acid	Ester	β-(1-Ethyl-7-acenaphthyl)-propionic acid	60	57
 β-Methyl-β-(3-pyrenyl)-propionic acid	Ester	γ-Methyl-γ-(3-pyrenyl)-butyric acid	87	58
α-Methyl-β-(3-pyrenyl)-propionic acid	Ester	β-Methyl-γ-(3-pyrenyl)-butyric acid	92	58
 α-2-Methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene-1-acetic acid	Ester	α-Methyl ester of the homologous acid	77	59
β-Form of the above compound	Ester	β-Form of the above compound	68	59
α-2-Methyl-2-carbomethoxy-1,2,3,4,-tetrahydronaphthalene-1-β-propionic acid	Ester	α-Methyl ester of the homologous acid	75	59
α-6-Methoxy-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene-1-acetic acid	Ester	α-Methyl ester of the homologous acid	—	60
β-Form of the above acid	Ester	β-Form of the above compound	—	60

* References 50–72 appear on p. 62.

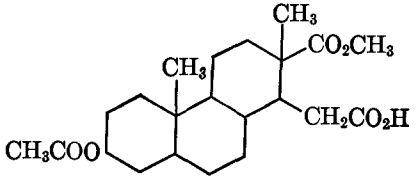
PRODUCTS AND YIELDS OBTAINED IN THE ARNDT-EISTERT SYNTHESIS—*Continued*

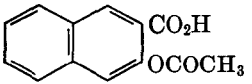
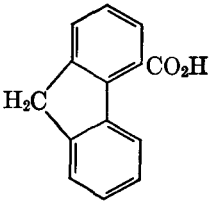
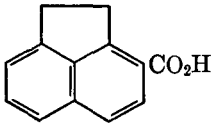
Starting Acid	Primary Product	Compound Isolated	Yield, %	Reference *
	Ester	α-Methyl ester of the homologous acid	90	61
α-2-Methyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid				
β-Form of the above acid	Ester	β-Form of the above compound	50	61
α-7-Methoxy-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid	Ester	α-Methyl ester of the homologous acid	74	19
β-Form of the above acid	Ester	β-Form of the above compound	80–84	19
α-7-Methoxy-2-ethyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid	Ester	α-Methyl ester of the homologous acid	88	62
β-Form of the above acid	Ester	β-Form of the above compound	78	62
α-7-Methoxy-2-*n*-propyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid	Ester	α-Methyl ester of the homologous acid	40–50	63
β-Form of the above acid	Ester	β-Form of the above compound	86	63
α-7-Methoxy-2-*n*-butyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid	Ester	α-Methyl ester of the homologous acid	85	63
β-Form of the above acid	Ester	β-Form of the above compound	—	63
α-7-Methoxy-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-1-β-propionic acid	Ester	α-Methyl ester of the homologous acid	40	63
β-Form of the above acid	Ester	β-Form of the above compound	49	63

α-9-Methoxy-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid	Ester	α-Methyl ester of the homologous acid	82	64
β-Form of the above acid	Ester	β-Form of the above compound	74	64
α-9-Methoxy-2-ethyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid	Ester	α-Methyl ester of the homologous acid	81	64
β-Form of the above acid	Ester	β-Form of the above compound	77	64
α-9-Methoxy-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-1-β-propionic acid	Ester	α-Methyl ester of the homologous acid	48	64
β-Form of the above acid	Ester	β-Form of the above compound	41	64
 α-9-Methoxy-2-methyl-2-carbomethoxy-*sym*-octahydrophenanthrene-1-acetic acid	Ester	α-Methyl ester of the homologous acid	80	65
β-Form of the above acid	Ester	β-Form of the above compound	82	65
 Monomethyl ester of O-methylestric acid	Acid	Dimethyl ester of O-methylhomoestric acid	Poor	33

* References 50–72 appear on p. 62.

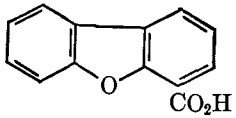
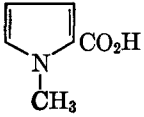
PRODUCTS AND YIELDS OBTAINED IN THE ARNDT-EISTERT SYNTHESIS—*Continued*

Starting Acid	Primary Product	Compound Isolated	Yield, %	Reference *
 Monomethyl ester of 3-acetoxyetiobilianic acid	Ester	Ethyl ester of the homologous acid	—	66
Benzoic acid	Amide	Phenylacetamide	69	8
	Anilide	Phenylacetanilide	41	8
o-Nitrobenzoic acid	Amide	*o*-Nitrophenylacetamide	55	8
m-Nitrobenzoic acid	Ester	*m*-Nitrophenylacetic acid	65	15
p-Nitrobenzoic acid	Anilide	*p*-Nitrophenylmethylacetanilide (Using diazoethane)	—	25
o-Bromobenzoic acid	Acid	*o*-Bromophenylacetic acid	62	67
p-Anisic acid	Amide	*p*-Homoanisamide	57	14
3,4-Dimethoxybenzoic acid	Amide	3,4-Dimethoxyphenylacetic acid	65	8
3,4,5-Trimethoxybenzoic acid	Amide	3,4,5-Trimethoxyphenylacetic acid	—	68
3,5-Dibenzyloxy-4-methoxybenzoic acid	Ester	3,5-Dibenzyloxy-4-methoxyphenylacetic acid	—	69
2-Biphenylcarboxylic acid	Acid	2-Biphenylacetic acid	52–68	70
2′-Nitro-6′-methyl-2-biphenylcarboxylic acid	Anilide	*o*-(2-Methyl-6-nitrophenyl)-α-toluanilide	—	11
α-Naphthoic acid	Acid	α-Naphthylacetic acid	45	8
	Amide	α-Naphthylacetamide	82	8
	Ester	Ethyl α-naphthylacetate	65–75	8, 25
	Anilide	α-Naphthylacetanilide	—	8

 2-Acetoxy-3-naphthoic acid	Ester	2-Hydroxy-3-naphthylacetic acid	85–88	13, 37
	Anilide	2-Hydroxy-3-naphthylacetanilide	62	37
 4-Fluorenecarboxylic acid 4-Fluorenonecarboxylic acid	Ester	4-Fluoreneacetic acid	89	35
	Ester	Methyl 4-fluorenoneacetate	84	35
 1-Acenaphthenecarboxylic acid	Acid	1-Acenaphthylacetic acid	63	67
Anthraquinone-2-carboxylic acid	Anilide	Anthraquinone-2-acetanilide	—	8
1-Chloroanthraquinone-2-carboxylic acid	Anilide	1-Chloroanthraquinone-2-acetanilide	—	8
1-Nitroanthraquinone-2-carboxylic acid	Anilide	1-Nitroanthraquinone-2-acetanilide	—	8
α-Thiophenecarboxylic acid (p. 44)	Ester	Ethyl α-thienylacetate	58	20, 20*a*
	Ester	Methyl α-thienylacetate	—	20
Thionaphthene-3-carboxylic acid (p. 44)	Acid	Thionaphthyl-3-acetic acid	65	21
Coumarone-3-carboxylic acid (p. 44)	Ester	Coumarone-3-acetic acid	20	22
	Amide	Coumarone-3-acetamide	—	22
	Ester	Ethyl coumarone-3-acetate	24	22

* References 50–72 appear on p. 62.

PRODUCTS AND YIELDS OBTAINED IN THE ARNDT-EISTERT SYNTHESIS—*Continued*

Starting Acid	Primary Product	Compound Isolated	Yield, %	Reference *
 4-Dibenzofurancarboxylic acid	Amide	4-Dibenzofurylacetamide	67	71
4,6-Dimethoxy-1-dibenzofurancarboxylic acid	Amide	4,6-Dimethoxy-1-dibenzofurylacetamide	14	72
α-Furoic acid	Ester	Dimethyl α-furylmalonate (Using methyl diazoacetate)	30	32
 N-Methylpyrrole-2-carboxylic acid	Ester	Ethyl N-methylpyrrole-2-acetate	—	20a

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[53] Bachmann and Struve, *J. Org. Chem.*, **5**, 416 (1940).
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CHAPTER 3

CHLOROMETHYLATION OF AROMATIC COMPOUNDS

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University of Illinois

CONTENTS

PAGE

INTRODUCTION 64

THE SCOPE AND LIMITATIONS OF THE REACTION 64

PROCEDURES FOR CHLOROMETHYLATION 66
- Chloromethylation of Benzene 67
- Chloromethylation of 1,3,5-Triisopropylbenzene 68
- Chloromethylation of *p*-Xylene 69
- Chloromethylation of Naphthalene 70
- Chloromethylation of *p*-Nitrophenol 71
- Chloromethylation of Acetomesitylene 71

RELATED REACTIONS 72
- Bromomethylation 72
- Iodomethylation 72
- Chloroethylation 72
- Chloropropylation 73
- Chlorobutylation 73

TABLES OF DATA ON CHLOROMETHYLATION 74
- I. Chloromethylation of Hydrocarbons 75
- II. Chloromethylation of Halogen and Nitro Derivatives of Hydrocarbons 80
- III. Chloromethylation of Phenols and Aryl Esters 83
- IV. Chloromethylation of Ethers and Thioethers 86
- V. Chloromethylation of Aldehydes and Ketones 89

INTRODUCTION

The replacement of a hydrogen atom by a chloromethyl group in a single operation has come to be known as chloromethylation. The process may be illustrated by the earliest example, a synthesis of benzyl chloride carried out by Grassi and Maselli [1] in 1898. These authors used benzene, hydrogen chloride, paraformaldehyde, and zinc chloride.

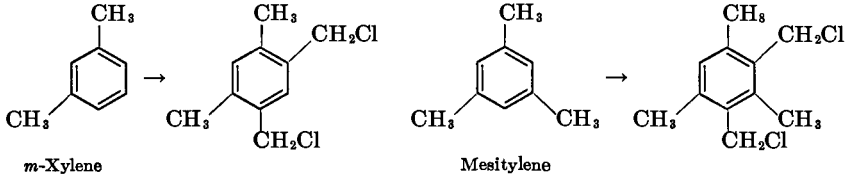
$$C_6H_6 + CH_2O + HCl \rightarrow C_6H_5CH_2Cl + H_2O$$

Chloromethylation is of value in synthetic work inasmuch as the —CH_2Cl group can be converted to other groups such as —CH_2OH, —CHO, CH_2CN, and —CH_3.

The present review has been limited to nuclear chloromethylation of aromatic compounds. Typical procedures are given, and an attempt has been made to indicate the scope and limitations of the reaction. The reactions are listed in tabular form.

THE SCOPE AND LIMITATIONS OF THE REACTION

Chloromethylation is generally applicable to aromatic hydrocarbons. Benzene, naphthalene, anthracene, phenanthrene, biphenyl, and many of their derivatives have been converted to chloromethyl derivatives. Terphenyl, however, resists chloromethylation altogether.[2] Monoalkyl benzene derivatives yield *para* chloromethyl compounds frequently accompanied by lesser amounts of the *ortho* isomers. A second chloromethyl group usually can be introduced, and sometimes excellent yields of dichloromethyl derivatives are obtained. Examples are the dichloromethyl derivatives of *m*-xylene [3] and mesitylene.[4]

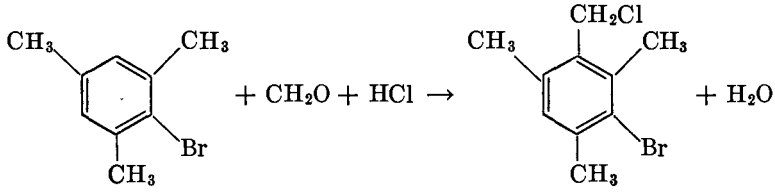


m-Xylene Mesitylene

The presence of a halogen atom on the ring causes the reaction to be more difficult to effect. Although such compounds as bromo- and chlorobenzene, bromo- and chlorotoluenes, and *p*-dichlorobenzene can be chloromethylated, the yields are frequently low. More highly halo-

[1] Grassi and Maselli, *Gazz. chim. ital.*, **28**, II, 477 (1898).
[2] v. Braun, Irmish, and Nelles, *Ber.*, **66**, 1471 (1933).
[3] v. Braun and Nelles, *Ber.*, **67**, 1094 (1934).
[4] Nauta and Dienske, *Rec. trav. chim.*, **55**, 1000 (1936).

genated derivatives generally fail to undergo chloromethylation. As might be expected, however, halogen derivatives of polymethylbenzenes sometimes react readily to give high yields of chloromethyl compounds. Bromomesitylene is an example.[5]



Nitro groups tend to inhibit the reaction. Nitrobenzene,[6, 7] *o*-nitrotoluene,[6] *p*-nitrotoluene,[6] nitromesitylene,[7] and 1-nitronaphthalene have been found to give chloromethyl derivatives, but usually in low yields. *m*-Dinitrobenzene and 1,3,5-trinitrobenzene, as well as *o*- and *p*-chloronitrobenzene, fail to react.[6]

Ketones are generally unreactive. Acetophenone appears to react,[7] but benzophenone [8] and anthraquinone [6] are recovered unchanged. However, chloromethylation is successful with ketones such as acetomesitylene, acetoisodurene, and 2,4,6-triethylacetophenone.[8]

Phenols, as might be expected, react so readily that the reaction generally goes too far, yielding polymeric materials. The presence of a nitro group counteracts this tendency; satisfactory yields from nitrophenols have been reported.[9, 10, 11] A suitable device for getting around the difficulty with phenols is to convert them to esters by treatment with ethyl chlorocarbonate; the ethyl aryl carbonates can be chloromethylated successfully.[12, 13, 14]

The most important side reaction is that leading to the formation of the corresponding diarylmethane derivative. Highly reactive compounds of many sorts—naphthalene, anisole, phenols, polymethylbenzenes, etc.—tend to yield this type of product, and it is often difficult or impossible to isolate the intermediate chloromethyl derivative. Examples are α- and β-naphthol.[15]

[5] Fuson, Kneisley, Lindsey, Rabjohn, and Sperati, unpublished work.
[6] Stephen, Short, and Gladding, *J. Chem. Soc.*, **117**, 510 (1920).
[7] Vavon, Bolle, and Calin, *Bull. soc. chim.*, (5) **6**, 1025 (1939).
[8] Fuson and McKeever, *J. Am. Chem. Soc.*, **62**, 784 (1940).
[9] Stoermer and Behn, *Ber.*, **34**, 2455 (1901).
[10] Buehler, Kirchner, and Diebel, *Org. Syntheses*, **20**, 59 (1940).
[11] Ger. pat., 132,475 (1900) [*Chem. Zentr.*, **73**, II, 81 (1902)].
[12] Sommelet, *Bull. soc. chim.*, [4] **53**, 853 (1933).
[13] Sommelet and Marszak, *Compt. rend.*, **198**, 2256 (1934).
[14] Sommelet, *Compt. rend.*, **197**, 256 (1933).
[15] Castiglioni, *Gazz. chim. ital.*, **67**, 324 (1937).

Aromatic amines react very readily, but it has not been possible to isolate their simple chloromethyl derivatives.[16] These could hardly be expected to be stable, since the highly reactive chloromethyl group would undoubtedly condense with any amino group that might be present in the molecule.

In a study of the effect of substituents on the ease of chloromethylation of benzene by chloromethyl ether in the absence of a catalyst, Vavon, Bolle, and Calin [7] have found that the rate is increased by $—CH_3$, $—C_2H_5$, $—C_3H_7$, $—OCH_3$, and $—OC_3H_7$, and diminished by —Cl, —Br, —I, $—CH_2Cl$, $—CO_2H$, and $—NO_2$. These effects are illustrated by the following relative rates of reaction.

Benzene	1
Toluene	3
m-Xylene	24
Mesitylene	600
Anisole	1,300
3,5-Dimethylanisole	100,000
Chloromesitylene	2
Nitrobenzene	Too slow to measure
Nitromesitylene	Too slow to measure

PROCEDURES

The procedure for chloromethylation has been modified in numerous ways. The formaldehyde may be added as formalin, or it may be generated in the reaction mixture by depolymerization of paraformaldehyde (trioxymethylene). (The terms paraformaldehyde and trioxymethylene, used interchangeably in the literature, refer to the polyoxymethylenes—polymers having the structure $HOCH_2O(CH_2O)_nCH_2OH$. The trimer $(CH_2O)_3$, melting at 62–63°, is called *alpha*-trioxymethylene.[17] It is anhydrous, whereas paraformaldehyde generally contains from 2 to 5% of water.) Instead of formaldehyde and hydrochloric acid, diethyl or dimethyl formal and hydrochloric acid may be used. When chloromethyl ethers or dichloromethyl ether are employed, the reaction usually can be effected without hydrochloric acid.

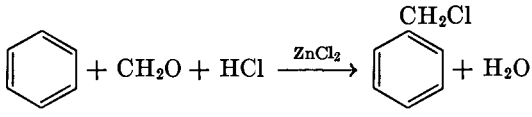
Catalysts may or may not be required. Among the catalysts which have been found to be especially useful are zinc chloride, sulfuric acid, and acetic acid. Yields with *p*-bromotoluene are increased about threefold by mixing a little aluminum chloride with the fused zinc chloride.[18]

[16] Wagner, *J. Am. Chem. Soc.*, **55**, 724 (1933).
[17] Pratesi, *Gazz. chim. ital.*, **14**, 139 (1884).
[18] Fieser and Seligman, *J. Am. Chem. Soc.*, **57**, 942 (1935).

Blanc [19] introduced the —CH_2Cl group into aromatic hydrocarbons by means of a mixture of formalin or paraformaldehyde and hydrochloric acid in the presence of zinc chloride. Darzens and Lévy,[20] in their syntheses of derivatives of naphthalene, employed paraformaldehyde and hydrochloric acid in acetic acid solution. Quelet and his co-workers,[21–28] who have carried out numerous syntheses starting with aryl ethers, employed formalin and hydrochloric acid, with or without a catalyst, and modified the technique according to the sensitiveness of the chloromethylation product which was expected. Vavon, Bolle, and Calin,[7] as has already been stated, developed a technique permitting them to follow the course of the reaction and to study the influence of substituents on the ease of introduction of the —CH_2Cl group. They used chloromethyl ether, without a catalyst, usually in acetic acid solution.

The most successful method for the chloromethylation of aromatic hydrocarbons is that of Blanc.[19] It has been modified in various ways. The preparation of benzyl chloride illustrates one of these variations.

Chloromethylation of Benzene [19]
(Method of Blanc)



A mixture of 600 g. (7.7 moles) of benzene, 60 g. (2 moles) of paraformaldehyde,* and 60 g. of pulverized zinc chloride † is heated to 60° with stirring. While this temperature is maintained, a rapid stream of hydrogen chloride is passed into the reaction mixture until no more gas is absorbed (about twenty minutes). The organic layer is removed,

* It is possible to use 40% formalin in place of paraformaldehyde. In this case more zinc chloride is required. The following proportions are most satisfactory: 400 g. of benzene, 75 g. of 40% formalin, and 100 g. of pulverized zinc chloride. The reaction is carried out as described; if allowed to run twelve hours, a 70% yield of diphenylmethane is obtained.

† If the proportion of zinc chloride is increased, the yield of dichloromethyl derivative is correspondingly greater; if less zinc chloride is used, almost no dichloromethyl compound is produced but the yield of benzyl chloride is diminished.

[19] Blanc, *Bull. soc. chim.*, [4] **33**, 313 (1923).

[20] Darzens and Lévy, *Compt. rend.*, **202**, 73 (1936).

[21] Quelet, *Compt. rend.*, **198**, 102 (1934).

[22] Quelet and Anglade, *Bull. soc. chim.*, [5] **3**, 2200 (1936).

[23] Quelet and Allard, *Bull. soc. chim.*, [5] **4**, 620 (1937).

[24] Quelet, *Bull. soc. chim.*, [4] **53**, 510 (1933).

[25] Quelet, *Compt. rend.*, **196**, 1411 (1933).

[26] Quelet, *Bull. soc. chim.*, [5] **1**, 539 (1934).

[27] Quelet, *Bull. soc. chim.*, [5] **1**, 904 (1934).

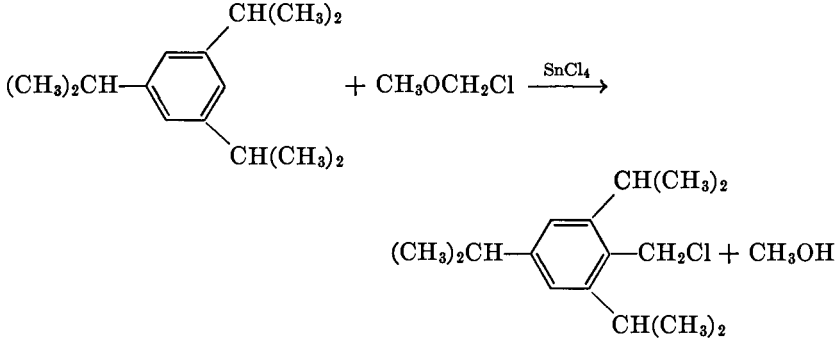
[28] Quelet and Allard, *Compt. rend.*, **205**, 238 (1937).

washed with water and then with dilute sodium bicarbonate,* dried over calcium chloride, and fractionally distilled. After the excess benzene has been removed there is obtained 200 g. (79%) of benzyl chloride; b.p. 70° (15 mm.).

There are also produced about 12 g. of *p*-xylylene dichloride, m.p. 100°, and a small amount of diphenylmethane.

Although the reaction usually is carried out with zinc chloride as the catalyst, sulfuric acid and aluminum chloride have been used also. These catalysts are sometimes objectionable because they tend to favor the formation of diphenylmethane derivatives. For the chloromethylation of compounds which do not react readily, stannic chloride has sometimes been found to be a superior catalyst.[5, 29] The use of stannic chloride as the catalyst is exemplified by the preparation of 2,4,6-triisopropylbenzyl chloride. This method is interesting also because chloromethyl ether is used in place of formaldehyde or paraformaldehyde.

Chloromethylation of 1,3,5-Triisopropylbenzene [5]



The chloromethyl ether is prepared by the method of Reyschuler.[30] Three hundred grams of paraformaldehyde and 200 cc. of methanol are mixed and cooled. A rapid stream of hydrogen chloride is passed through the mass until two layers form and all the paraformaldehyde has disappeared. It is necessary to keep the mixture cool to prevent the formation of methylal. About 300–400 g. of hydrogen chloride is required. The upper layer is separated, dried over calcium chloride, and fractionated several times. The product boils at 57–59° and is about 90% pure. By washing with concentrated hydrochloric acid, it is possible to obtain a product which is 95% chloromethyl ether.

* It is absolutely necessary to remove all the zinc salt by the washings. Without this precaution the product almost completely resinifies during the distillation period.

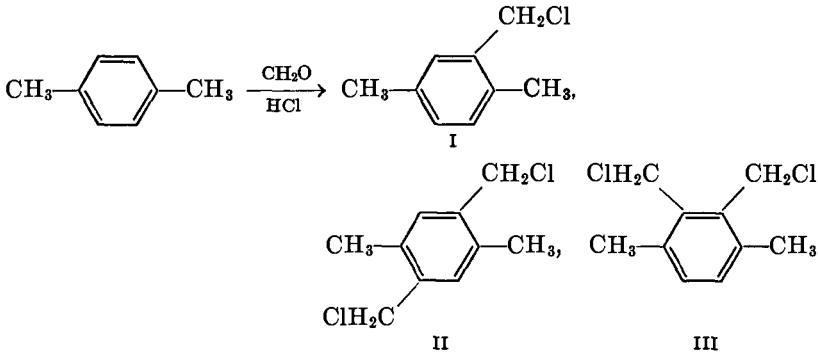
[29] Sommelet, *Compt. rend.*, **157**, 1443 (1913).

[30] Reyschuler, *Bull. soc. chim.*, [4] **1**, 1195 (1907).

A mixture of 300 g. (1.47 moles) of 1,3,5-triisopropylbenzene* and 200 g. (2.5 moles) of chloromethyl ether is diluted with 600 cc. of carbon disulfide and cooled to 0°. To this solution is added, over a period of one hour, 120 g. (0.46 mole) of stannic chloride. The reaction mixture is stirred during the addition and for one hour afterward. It is poured on ice, and the organic layer is separated and dried over calcium chloride. Removal of the solvent and distillation of the residue in vacuum gives the benzyl chloride in yields of 300–315 g. (81–85%); b.p. 129–130° (4 mm.).

The chloromethylation of highly alkylated benzenes generally can be accomplished without any catalyst. It is sufficient to treat the hydrocarbon with a mixture of formaldehyde and concentrated hydrochloric acid.[3,4] The chloromethylation of *p*-xylene, for example, is conducted in the following manner.

Chloromethylation of *p*-Xylene [3]



One mole of the hydrocarbon is mixed with an equal weight of 37% formalin (1.3 moles of formaldehyde) and five times its weight of concentrated hydrochloric acid. The mixture is stirred at 60–70° for seven hours, during which time a stream of hydrogen chloride is introduced. The resulting oil is taken up in ether, and the solution is dried. Distillation gives 106 g. of a fraction which is chiefly 2,5-dimethylbenzyl chloride (I); b.p. 103° (12 mm.). A second fraction, amounting to about 10 g., consists mainly of α^1,α^4-dichlorodurene (II); m.p. 133°. A very small amount of α^2,α^3-dichloroprehnitene (III) (m.p. 68–70°) also can be isolated.

The chloromethylation of naphthalene has received much attention. Although, by the use of petroleum ether in the Blanc method, the reac-

* The Dow Chemical Company product, Alkazene-13, was used.

tion gives yields of 30% of the theoretical amount,[19] other methods have been found to be more useful. Darzens and Lévy [20] and, more recently, Ruggli and Burckhardt,[31] Jones,[32] Fieser and Novello,[33] Fieser and Gates,[34] and Cambron [35] have obtained the chloromethyl derivative by using a large amount of glacial acetic acid as a solvent for the hydrocarbon. Cole and Dodds [36] preferred to carry out the reaction in an aqueous mixture with sulfuric acid as the catalyst.

The procedure of Cambron is as follows.

Chloromethylation of Naphthalene [35]

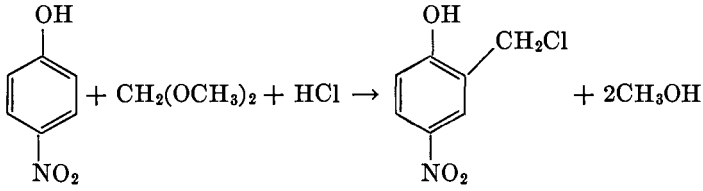
A mixture of 288 g. (2.25 moles) of the hydrocarbon, 90 g. (3 moles) of paraformaldehyde, 250 g. of glacial acetic acid, 280 cc. of concentrated hydrochloric acid, and 135 cc. of syrupy phosphoric acid is heated, with efficient stirring, at 98–100° for four and one-half hours. The reaction mixture is then poured into 2 l. of cold water. The aqueous layer is decanted from the heavy oily layer, which is washed two or three times with 2-l. portions of water. After each washing the water is removed by decantation. The oil is filtered to remove the small amount of solid material and distilled under reduced pressure. The yield of α-chloromethylnaphthalene is 223 g.; b.p. 145–160° (6–8 mm.). This is 56.5% of the theoretical yield based on the amount of naphthalene used.

Phenols and their ethers, as has been indicated, react much more readily than the hydrocarbons. For anisole and the methyl cresyl ethers, monochloromethylation with 35–40% formalin and hydrochloric acid is most successful if conducted at 0–15° and without a catalyst. Higher temperatures and the presence of zinc chloride favor the formation of diphenylmethane derivatives and also dichloromethylation products. Phenyl esters, hydroxy aldehydes, ethers of hydroxy aldehydes, nitrophenols, nitrophenyl ethers, and highly alkylated ketones generally require mild conditions also.

An interesting illustration is the synthesis of 2-hydroxy-5-nitrobenzyl chloride by chloromethylation of *p*-nitrophenol. Methylal is used as the source of formaldehyde, and a little sulfuric acid is added to accelerate the reaction.

[31] Ruggli and Burckhardt, *Helv. Chim. Acta*, **23**, 441 (1940).
[32] Jones, U. S. pat., 2,212,099 [*C. A.*, **35**, 462 (1941)].
[33] Fieser and Novello, *J. Am. Chem. Soc.*, **62**, 1855 (1940).
[34] Fieser and Gates, *J. Am. Chem. Soc.*, **62**, 2335 (1940).
[35] Cambron, *Can. J. Research*, **17B**, 10 (1939).
[36] Coles and Dodds, *J. Am. Chem. Soc.*, **60**, 853 (1938).

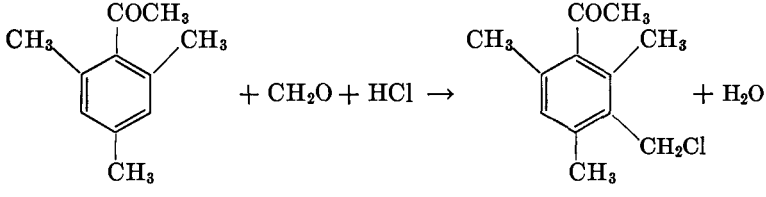
Chloromethylation of *p*-Nitrophenol [10]



A mixture of 50 g. (0.36 mole) of *p*-nitrophenol, 650 cc. of concentrated hydrochloric acid, 5 cc. of concentrated sulfuric acid, and 76 g. (1 mole) of methylal is stirred for four to five hours at 70–72°. During this period hydrogen chloride is passed into the reaction mixture. About an hour after the reaction is begun the 2-hydroxy-5-nitrobenzyl chloride begins to separate. It is removed by filtration after the reaction mixture has been chilled. The yield is 46 g. (69%).

Ketones having mesityl, duryl, isoduryl, or other highly alkylated aryl radicals undergo chloromethylation in yields of 25 to 88%.[8] The procedure employs paraformaldehyde and concentrated hydrochloric acid, but no catalyst. The chloromethylation of acetomesitylene gives very satisfactory results.

Chloromethylation of Acetomesitylene [8]



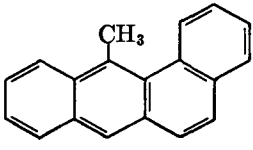
A mixture of 40 g. (0.25 mole) of acetomesitylene, 9 g. (0.3 mole) of paraformaldehyde, and 150 cc. of concentrated hydrochloric acid is shaken on a mechanical shaker overnight at room temperature. The α^3-chloroacetoisodurene precipitates from the reaction mixture in clusters of almost white needles. These are removed by filtration and washed with water. They are recrystallized from low-boiling petroleum ether, then from methanol. There is obtained 40 g. (77%) of pure material; m.p. 74.5–75.5°.

RELATED REACTIONS

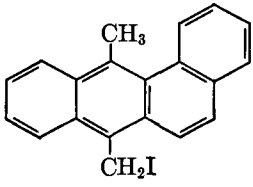
The expectation that condensations analogous to chloromethylation would take place if other aldehydes or other halogen acids were employed has been realized in a number of instances.

Bromomethylation. By the use of hydrogen bromide in place of hydrogen chloride it has been possible to prepare bromomethyl derivatives.[37] α-Bromomethylnaphthalene,[20] benzyl bromide,[6] *p*-chlorobenzyl bromide,[6] and α^1,α^4-dibromo-*p*-xylene [6] have been made in this way. Ethyl anisate,[7] salicylaldehyde,[38] salicylic acid,[39] and phenyl ether [40] also undergo bromomethylation. Darzens [41] states that the method is general but that the yields are lower than in chloromethylation.

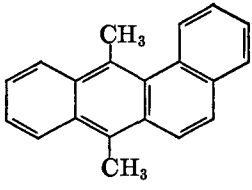
Iodomethylation. Iodomethylation has been reported by Sandin and Fieser [42] who converted 9-methyl-1,2-benzanthracene (I) to 9,10-dimethyl-1,2-benzanthracene (III) through the intermediate iodomethyl derivative (II). The iodomethylation was carried out by treating the hydrocarbon with chloromethyl ether or paraformaldehyde in glacial



I



II



III

acetic acid solution and then adding hydriodic acid (sp. gr. 1.7). The bright yellow iodomethyl compound formed in yields of 90%.

This preparation is especially interesting in the light of the failure of Badger and Cook to isolate the corresponding chloromethylation product.[43]

Chloroethylation. By the use of paraldehyde in place of formaldehyde it has been possible to effect chloroethylation. Anisole and its homologs, when treated with paraldehyde and hydrochloric acid, give the corre-

[37] Tschunkur and Eichler, Ger. pat., 509,149 [*C. A.*, **25**, 711 (1931); *Chem. Zentr.*, **102**, I, 360 (1931)].

[38] Ger. pat., 114,194 (1900) [*Chem. Zentr.*, **71**, II, 928 (1900)].

[39] F. Bayer and Company, Ger. pat., 113,723 (1900).

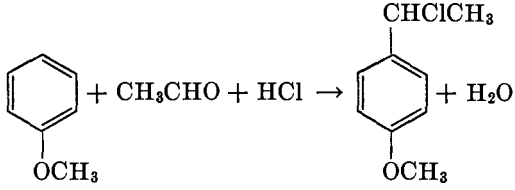
[40] Brunner, Ger. pat., 569,570 [*Chem. Zentr.*, II, 609 (1933)].

[41] Darzens, *Compt. rend.*, **208**, 818 (1939).

[42] Sandin and Fieser, *J. Am. Chem. Soc.*, **62**, 3098 (1940).

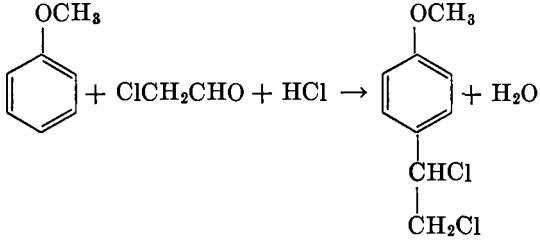
[43] Badger and Cook, *J. Chem. Soc.*, 802 (1939).

sponding chloroethyl derivatives in yields of 40–60%.[27, 44, 45, 46, 47] The synthesis of 4-methoxy-α-chloroethylbenzene is an example.

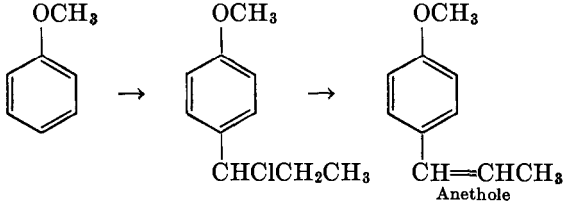


Xylene also has been chloroethylated.[45] The chloroethyl derivatives readily lose hydrogen chloride, yielding the corresponding vinyl derivatives. Anisole gives a 90% yield of *p*-vinylanisole accompanied by a 10% yield of the *ortho* isomer.[46]

Chloroacetaldehyde can be used also; with anisole it gives α,β-dichloroethylanisole.[48]



Chloropropylation. Chloropropylation of anisole followed by dehydrochlorination furnishes a synthesis of anethole.[46]



Chlorobutylation. Chlorobutylation of anisole has also been reported.[45, 46, 49] By using butyraldehyde, Ducasse [49] obtained 2-methoxy-5-methyl-α-chlorobutylbenzene in a yield of 30%. Chloroisobutylation of anisole has likewise been effected.[45]

[44] Quelet, *Compt. rend.*, **199**, 150 (1934).
[45] Sommelet and Marszak, Fr. pat., 787,655 [*C. A.*, **30**, 1185 (1936)].
[46] Quelet, *Bull. soc. chim.*, [5] **7**, 196 (1940).
[47] Quelet, *Bull. soc. chim.*, [5] **7**, 205 (1940).
[48] Quelet and Allard, *Bull. soc. chim.*, [5] **7**, 215 (1940).
[49] Ducasse, *Bull. soc. chim.*, [5] **3**, 2202 (1936).

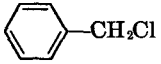
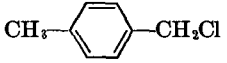
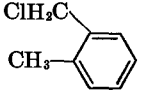
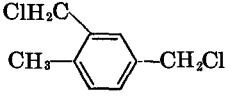
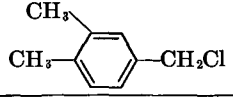
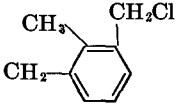
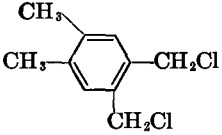
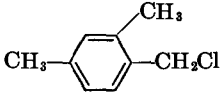
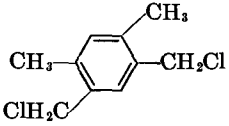
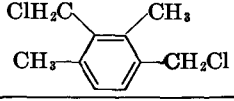
TABLES OF DATA ON CHLOROMETHYLATION

The following tables list compounds which have been chloromethylated, together with the reaction products. References have been given to pertinent literature sources. Where available, the per cent yield is indicated in parentheses following the reference number.

The compounds have been arranged, according to the nature of the parent substances, in five groups: hydrocarbons (Table I), halogen and nitro derivatives of hydrocarbons (Table II), phenols and phenyl esters (Table III), ethers and thioethers (Table IV), and aldehydes and ketones (Table V).

TABLE I

CHLOROMETHYLATION OF HYDROCARBONS

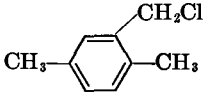
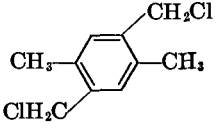
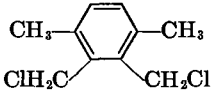
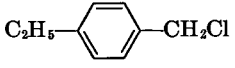
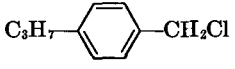
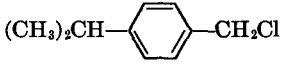
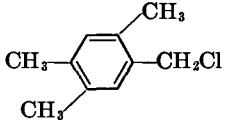
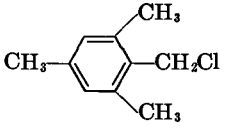
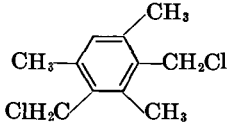
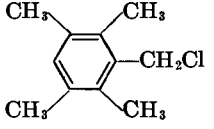
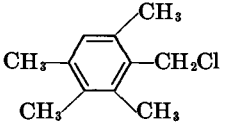
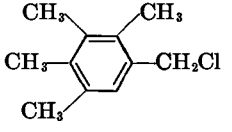
Parent Compound, References,* and Yields †	Product
Benzene 1, 6(**36**), 7, 19(**80**), 29(**30**), 37(**52**), 50, 51, 52	
Benzene 6, 19	
Toluene 6, 7, 19(**82**), 29(**35**), 41, 50, 51, 52	
Toluene 41, 53	
Toluene 19	
o-Xylene 3(**69**), 7, 29, 37, 41, 50, 51	
o-Xylene 3(**9**)	
o-Xylene 3(**35**)	
m-Xylene 3(**62**), 6, 7, 19, 29, 37, 41, 50(**60**), 51, 52, 53	
m-Xylene 3(**76**), 19	
m-Xylene 3	

* References 50–90 appear on p. 90.

† Figures in parentheses indicate the per cent yields.

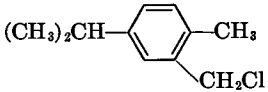
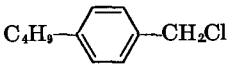
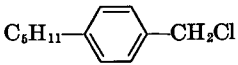
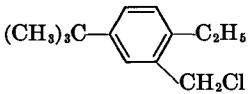
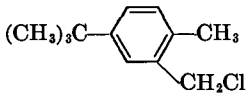
TABLE I—*Continued*

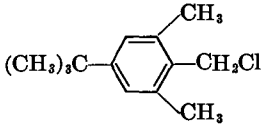
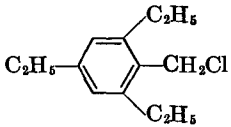
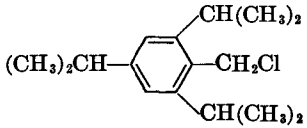
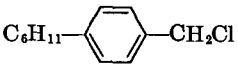
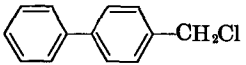
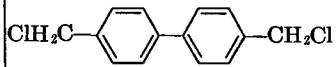
CHLOROMETHYLATION OF HYDROCARBONS—*Continued*

Parent Compound, References,* and Yields †	Product
p-Xylene 3(**69**), 7, 29, 37, 41, 50, 51, 52	
p-Xylene 3(**7**)	
p-Xylene 3	
Ethylbenzene 7, 19(**94**), 50, 52, **54**	
Propylbenzene 52	
Cumene 7, 19(**75**), 29, 41, 50, 52, **54**	
Pseudocumene 7, 37, 50(**60**), 52, 55(**70**)	
Mesitylene 4, 7, 29, 50(**85**), 53	
Mesitylene 4(**77**)	
Durene 5(**70**)	
Isodurene 5(**49**)	
Prehnitene 7	

* References 50–90 appear on p. 90.

† Figures in parentheses indicate the per cent yields.

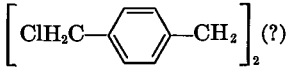
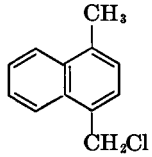
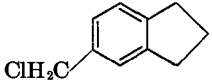
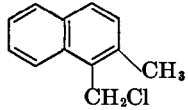
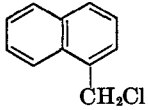
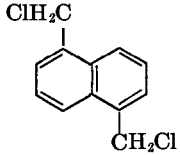
Parent Compound, References,* and Yields †	Product
p-Cymene 19(**76**), 29, 37, 52	
Isobutyl-*p*-cymene 56	Not isolated
n-Butylbenzene 52	
t-Amylbenzene 52	
p-*t*-Butylethylbenzene 57	 (?)
p-*t*-Butyltoluene 52, 57	 (?)

Parent Compound, References,* and Yields †	Product
1,3-Dimethyl-5-*t*-butylbenzene 5	
1,3,5-Triethylbenzene 5(**72**)	
1,3,5-Triisopropylbenzene 5(**80**), 56(**94**)	
Cyclohexylbenzene 2(**50**)	
Biphenyl 2(**20**), 7, 37, 50	
Biphenyl 2(**12**),6	

* References 50–90 appear on p. 90.
† Figures in parentheses indicate the per cent yields.

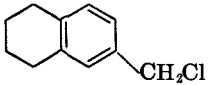
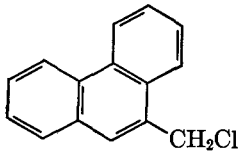
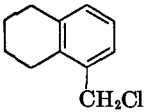
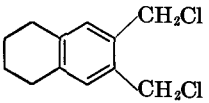
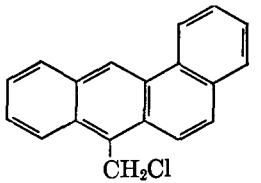
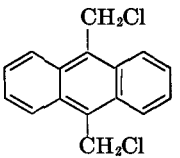
TABLE I—*Continued*

CHLOROMETHYLATION OF HYDROCARBONS—*Continued*

Parent Compound, References,* and Yields †	Product	Parent Compound, References,* and Yields †	Product
Bibenzyl 58		α-Methylnaphthalene 7, 20	
Hydrindene 59		β-Methylnaphthalene 20	
Naphthalene 6, 7, 19(**35**), 20(**95**), 31(**62**), 32, 33(**45**), 34(**63**), 35(**56**), 36(**70**), 37, 59*a*(**42**), 60, 61, 63		Isononylnaphthalene 56(**90**)	
		Diisopropylnaphthalene 56(**86**)	
Naphthalene 59*a*, 64, 65		Isododecylnaphthalene 56(**92**)	
		n-Dodecylnaphthalene 56(**50**)	

* References 50–90 appear on p. 90.

† Figures in parentheses indicate the per cent yields.

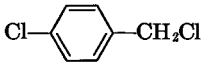
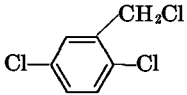
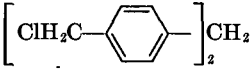
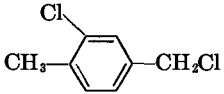
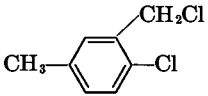
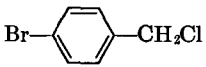
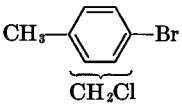
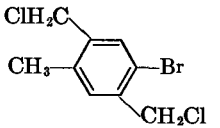
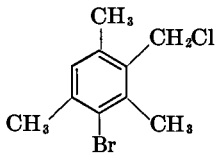
Parent Compound, References,* and Yields †	Product	Parent Compound, References,* and Yields †	Product
Tetralin 7(**50**), 66, 67, 68		Phenanthrene 64, 70, 71	
Tetralin 7(**9**)			
Tetralin 64, 69	 (?)	1,2-Benzanthracene 43(**68**), 68, 72,	
Acenaphthene 64	Not isolated	9-Methyl-1,2-benzanthracene 43	Not isolated
Anthracene 6, 43, 64		3,4-Benzpyrene 43	Not isolated
		20-Methylcholanthrene 43	Not isolated

* References 50–90 appear on p. 90.

† Figures in parentheses indicate the per cent yields.

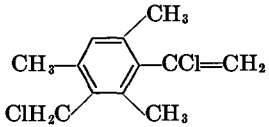
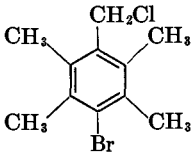
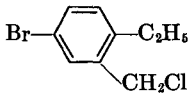
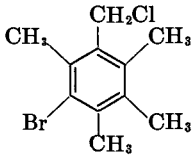
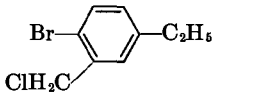
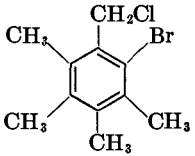
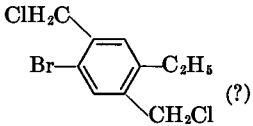
TABLE II

CHLOROMETHYLATION OF HALOGEN AND NITRO DERIVATIVES OF HYDROCARBONS

Parent Compound, References,* and Yields †	Product	Parent Compound, References,* and Yields †	Product
Chlorobenzene 6, 19, 37		Benzyl chloride 6	
p-Dichlorobenzene 6		Benzyl chloride 58(**5**)	
o-Chlorotoluene 6		Benzyl bromide 6	
p-Chlorotoluene 6, 37		Bromobenzene 6	
p-Bromotoluene 18		Chloromesitylene 7	Not isolated
p-Bromotoluene 18(**8**)		Bromomesitylene 5(**68**), 7	

* References 50–90 appear on p. 90.

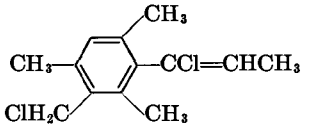
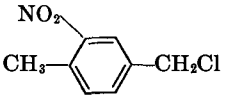
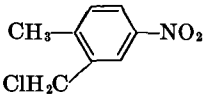
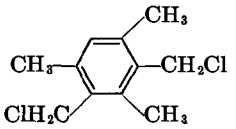
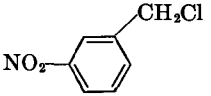
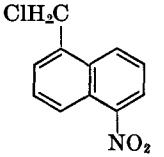
† Figures in parentheses indicate the per cent yields.

Parent Compound, References,* and Yields †	Product	Parent Compound, References,* and Yields †	Product
Iodomesitylene 7	Not isolated	1-Chloro-1-mesitylethylene 74(**80**)	
Bromodurene 73*a*(**42**)		*p*-Bromoethylbenzene 75	
Bromoisodurene 73*a*(**45**)		*p*-Bromoethylbenzene 75	
Bromoprehnitene 73*a*(**36**)		*p*-Bromoethylbenzene 75	 (?)

* References 50–90 appear on p. 90.
† Figures in parentheses indicate the per cent yields.

TABLE II—*Continued*

CHLOROMETHYLATION OF HALOGEN AND NITRO DERIVATIVES OF HYDROCARBONS—*Continued*

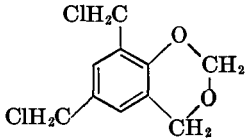
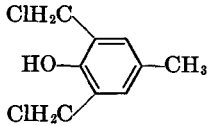
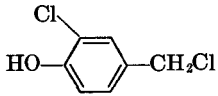
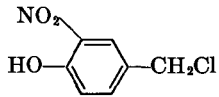
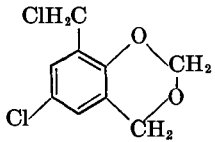
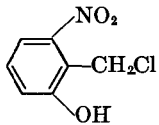
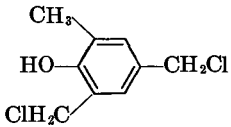
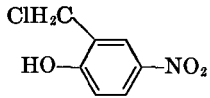
Parent Compound, References,* and Yields †	Product	Parent Compound, References,* and Yields †	Product
1-Chloro-1-mesitylpropene 74(**79**)		*o*-Nitrotoluene 6	
		p-Nitrotoluene 6	
α^2-Chloroisodurene 7		Nitromesitylene 7	Not isolated
Nitrobenzene 6, 7		1-Nitronaphthalene 76	

* References 50–90 appear on p. 90.

† Figures in parentheses indicate the per cent yields.

TABLE III

CHLOROMETHYLATION OF PHENOLS AND ARYL ESTERS

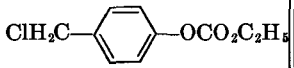
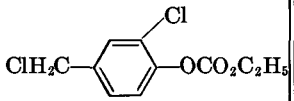
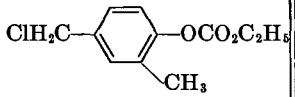
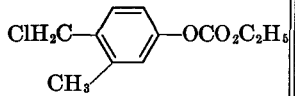
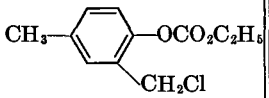
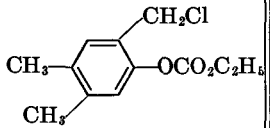
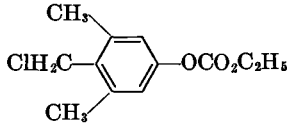
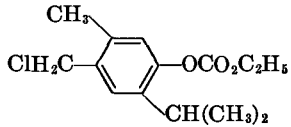
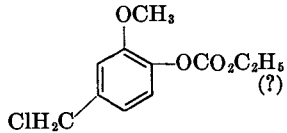
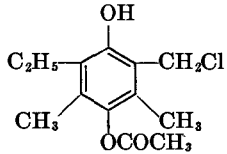
Parent Compound, References,* and Yields †	Product	Parent Compound, References,* and Yields †	Product
Phenol 77		*p*-Cresol 77	
o-Chlorophenol 9, 11, 61, 78		*o*-Nitrophenol 9, 11	
p-Chlorophenol 79(**90**)		*m*-Nitrophenol 79*a*(**15**)	
o-Cresol 77		*p*-Nitrophenol 10(**69**), 11	

* References 50–90 appear on p. 90.

† Figures in parentheses indicate the per cent yields.

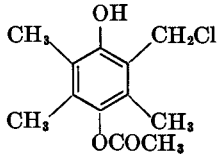
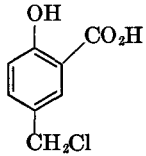
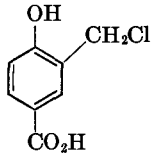
TABLE III—*Continued*

CHLOROMETHYLATION OF PHENOLS AND ARYL ESTERS—*Continued*

Parent Compound, References,* and Yields †	Product
Ethyl phenyl carbonate 12(**50**), 14(**50**)	
Ethyl *o*-chlorophenyl carbonate 14	
Ethyl *o*-cresyl carbonate 12, 14	
Ethyl *m*-cresyl carbonate 12, 13(**30**), 14	
Ethyl *p*-cresyl carbonate 12, 14	
Ethyl 3,4-xylyl carbonate 12	
Ethyl 3,5-xylyl carbonate 12,13(**60**)	
Ethyl thymyl carbonate 12, 14	
Ethyl guaiacol carbonate 13(**60**)	
Diacetate of 2,6-Dimethyl-3-ethylhydroquinone 79*b*(**33**)	

* References 50–90 appear on p. 90.

† Figures in parentheses indicate the per cent yields.

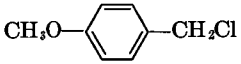
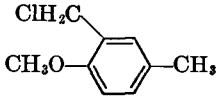
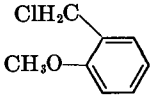
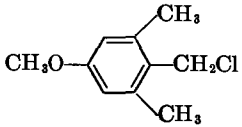
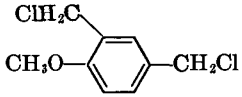
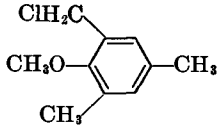
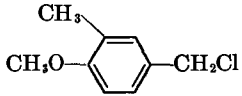
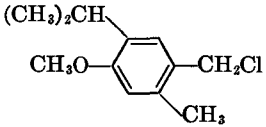
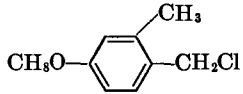
Parent Compound, References,* and Yields †	Product	Parent Compound, References,* and Yields †	Product
Diacetate of pseudocumohydroquinone 79c(**73**)		Salicylic acid 39	
		m-Hydroxybenzoic acid 39	
Ethyl anisate 7	Not isolated	*p*-Hydroxybenzoic acid 39	
Anisyl acetate 7	Not isolated	β-Hydroxynaphthoic acid 39	
		m-Cresotinic acid 39	

* References 50–90 appear on p. 90.

† Figures in parentheses indicate the per cent yields.

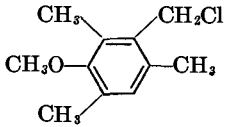
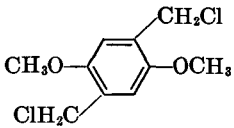
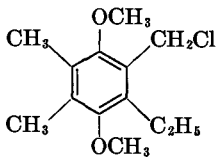
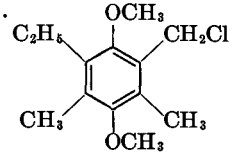
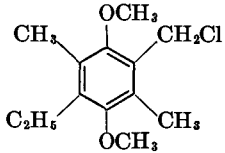
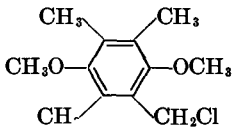
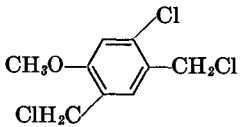
TABLE IV

CHLOROMETHYLATION OF ETHERS AND THIOETHERS

Parent Compound, References,* and Yields †	Product	Parent Compound, References,* and Yields †	Product
Anisole 6, 7, 13(**60**), 21(**50**), 22, 45, 79*d*(**60**), 80, 82(**60**), 83, 84		Methyl *p*-cresyl ether 7, 21(**75**), 22(**60**), 81, 83(**75**), 85, 86, 86*a*(**90**)	
Anisole 79*d*(**7**), 84		Methyl 3,5-xylyl ether 7	
Anisole 22(**50**), 79*d*, 81, 82, 85, 86		Methyl 2,4-xylyl ether 7	
Methyl *o*-cresyl ether 21, 22(**40**), 83		Methyl thymyl ether 7, 21(**70**), 23	
Methyl *m*-cresyl ether 7, 21, 83(**25**)		Phenetole 13(**70**), 21, 45	

* References 50–90 appear on p. 90.

† Figures in parentheses indicate the per cent yields.

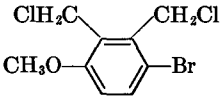
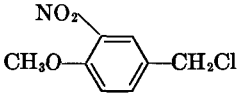
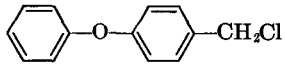
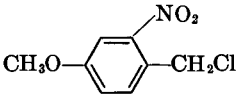
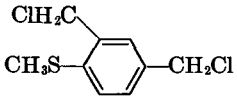
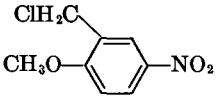
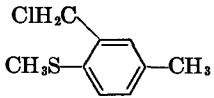
Parent Compound, References,* and Yields †	Product
n-Butyl phenyl ether 13, 45	
Methyl mesityl ether 7	
Hydroquinone dimethyl ether 81, 85, 86	
Dimethyl ether of 2,3-dimethyl-5-ethylhydroquinone 79*b*(**99**)	
Dimethyl ether of 2,6-dimethyl-3-ethylhydroquinone 79*b*(**100**)	
Dimethyl ether of 2,5-dimethyl-3-ethylhydroquinone 79*b*(**100**)	
3,6-Dimethoxypseudocumene 55(**60**)	
m-Chloroanisole 81, 85, 86	

* References 50–90 appear on p. 90.

† Figures in parentheses indicate the per cent yields.

TABLE IV—*Continued*

CHLOROMETHYLATION OF ETHERS AND THIOETHERS—*Continued*

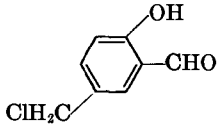
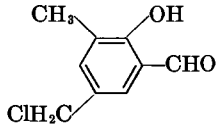
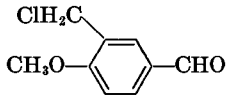
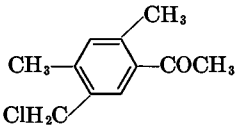
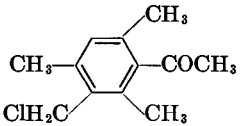
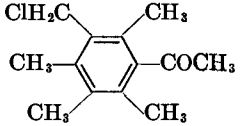
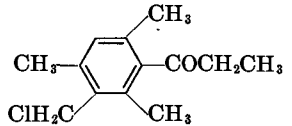
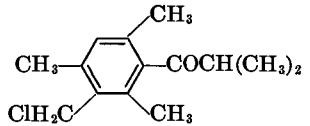
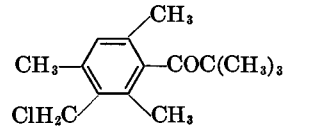
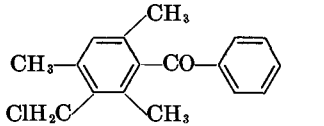
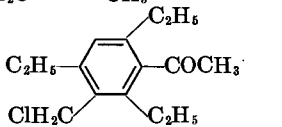
Parent Compound, References,* and Yields †	Product	Parent Compound, References,* and Yields †	Product
p-Bromoanisole 7, 24(**45**), 25(**45**), 26(**80**), 27(**80**), 83(**45**), 87(**50**), 88(**80**)		Anisic acid 7	Not isolated
o-Nitroanisole 24, 25, 26(**80**), 41(**96**), 81, 85, 86, 89(**98**)		Phenyl ether 40	
m-Nitroanisole 24, 25, 26		Methyl phenyl thioether 81, 85, 86, 90	
p-Nitroanisole 24(**70**), 25, 26(**75**)		Methyl *p*-tolyl thioether 81, 85, 86, 90	

* References 50–90 appear on p. 90.

† Figures in parentheses indicate the per cent yields.

TABLE V

CHLOROMETHYLATION OF ALDEHYDES AND KETONES

Parent Compound, References,* and Yields †	Product
Salicylaldehyde 9, 38	
o-Homosalicylaldehyde 9	
Anisaldehyde 28(**90**)	
Acetophenone 7	Not isolated
2,4-Dimethylacetophenone 8(**58**)	
Acetomesitylene 8(**77**)	
Acetoisodurene 8(**75**)	
Propiomesitylene 8(**88**)	
Isobutyromesitylene 8(**78**)	
Pivalylmesitylene 8(**25**)	
Benzoylmesitylene 8(**35**)	
2,4,6-Triethylacetophenone 8(**57**)	

* References 50–90 appear on p. 90.

† Figures in parentheses indicate the per cent yields.

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[51] Sommelet, *Bull. soc. chim.*, [4] **15**, 107 (1914).
[52] Bert, *Compt. rend.*, **186**, 373 (1928).
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[55] Smith and McMullen, *J. Am. Chem. Soc.*, **58**, 629 (1936).
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[61] Buehler, Brown, Holbert, Fulmer, and Parker, *J. Org. Chem.*, **6**, 902 (1941).
[62] Manske and Ledingham, *Can. J. Research*, **17B**, 14 (1939).
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[64] I. G. Farbenindustrie, Fr. pat., 695,095 (1930) [*Chem. Zentr.*, **102**, I, 2396 (1931)].
[65] Brunner and Greune, U. S. pat., 1,910,462 (1933) [*C. A.*, **27**, 4092 (1933); *Chem. Zentr.*, **104**, II, 4355 (1933)].
[66] Reddelien and Lange, Ger. pat., 519,807 (1929) [*C. A.*, **25**, 3363 (1931); *Chem. Zentr.*, **102**, II, 124 (1931)].
[67] Lange, Ger. pat., 533,132 (1930) [*C. A.*, **26**, 4064 (1932); *Chem. Zentr.*, **102**, II, 2659 (1931)].
[68] Reddelien and Lange, U. S. pat., 1,853,083 (1932) [*Chem. Zentr.*, **103**, I, 3894 (1932)].
[69] Brunner and Greune, Ger. pat., 533,850 (1929) [*C. A.*, **26**, 734 (1932); *Chem. Zentr.*, **103**, II, 3159 (1932)].
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[71] v. Braun, *Ber.*, **70**, 979 (1937).
[72] E. Kamp, Dissertation, Frankfurt, 1936.
[73] Wood and Fieser, *J. Am. Chem. Soc.*, **62**, 2674 (1940).
[73a] Smith and Horner, *J. Am. Chem. Soc.*, **62**, 1349 (1940).
[74] Miller, Ph.D. thesis, University of Illinois, 1940.
[75] Bruce and Kahn, *J. Am. Chem. Soc.*, **60**, 1017 (1938).
[76] I. G. Farbenindustrie, Brit. pat., 473,522 (1937) [*C. A.*, **32**, 1946 (1938)].
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[79] Buehler, Bass, Darling, and Lubs, *J. Am. Chem. Soc.*, **62**, 890 (1940).
[79a] Buehler, Deebel, and Evans, *J. Org. Chem.*, **6**, 216 (1941).
[79b] Smith and Opie, *J. Am. Chem. Soc.*, **63**, 937 (1941).
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[79d] Quelet and Anglade, *Compt. rend.*, **203**, 262 (1936).
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[81] Brunner, U. S. pat., 1,887,396 (1933) [*C. A.*, **27**, 1359 (1933)].
[82] Quelet and Allard, *Bull. soc. chim.*, [5] **3**, 1794 (1936).
[83] Quelet, *Bull. soc. chim.*, [4] **53**, 851 (1933).
[84] Ofner, *Helv. Chim. Acta*, **18**, 951 (1935).
[85] I. G. Farbenindustrie, Fr. pat., 695,477; Brit. pat., 347,892 (1930) [*Chem. Zentr.*, **103**, I, 2997 (1932)].
[86] I. G. Farbenindustrie, Brit. pat., 347,892 (1930) [*C. A.*, **26**, 2750 (1932)].
[86a] Ducasse, *Bull. soc. chim.*, [5] **2**, 1283 (1935).
[87] Quelet, *Compt. rend.*, **195**, 155 (1932).
[88] Quelet, *Compt. rend.*, **198**, 2107 (1934).
[89] Quelet and Germain, *Compt. rend.*, **202**, 1442 (1936).
[90] Brunner, Ger. pat., 569,569 (1933) [*C. A.*, **27**, 3723 (1933)].

CHAPTER 4

THE AMINATION OF HETEROCYCLIC BASES BY ALKALI AMIDES

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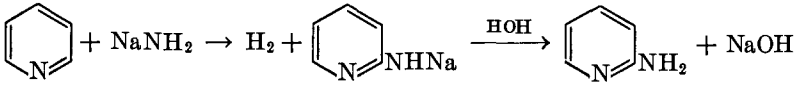
CONTENTS

	PAGE
INTRODUCTION	91
THE SCOPE AND LIMITATIONS OF THE REACTION	92
EXPERIMENTAL CONDITIONS	96
The Alkali Amides	96
The Solvent	97
Temperature	97
Mole Ratio	98
General Precautions	98
EXPERIMENTAL PROCEDURES	98
Preparation of Sodium Amide	98
Preparation of 2-Aminopyridine	99
Preparation of 4-Amino-2-phenylquinoline	100
SUMMARY OF AMINATIONS OF HETEROCYCLIC BASES (TABLE)	102

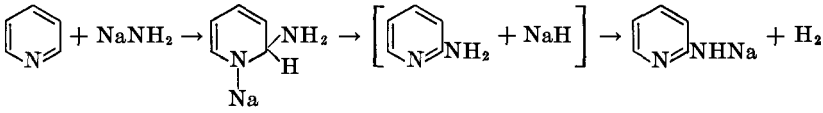
INTRODUCTION

Heterocyclic bases such as pyridine and quinoline and their derivatives react with metal amides to yield amino derivatives. For example, pyridine is converted to 2-aminopyridine by the action of sodium amide; an intermediate metal derivative is formed, and this is hydrolyzed to the free amine. (This reaction was discovered by Chichibabin [1] in 1914.)



[1] Chichibabin and Seide, *J. Russ. Phys. Chem. Soc.*, **46**, 1216 (1914).

It has been suggested [2, 3, 4] that the initial step in the reaction is the addition of the metal amide to the —CH=N— group; the resulting product is then transformed to the metal derivative of the amine, either through intramolecular rearrangement or through decomposition to the amino compound and sodium hydride which interact to give the metal derivative.



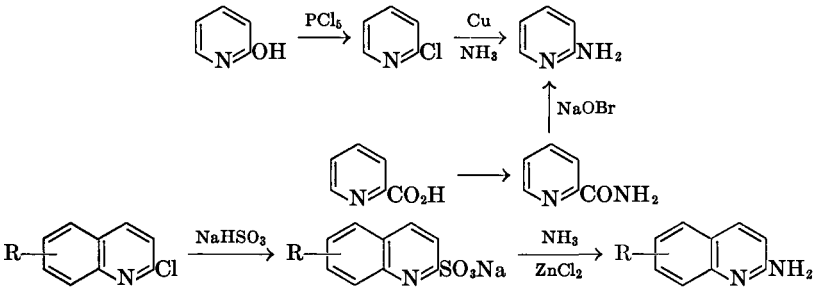
This mechanism accounts for the formation of small amounts of 4-aminopyridine (by 1,4-addition) and for the lack of formation of the 3-isomer. Evidence of the formation of an unstable addition product has actually been obtained for quinoline.[5]

THE SCOPE AND LIMITATIONS OF THE REACTION

The study of the amination of molecules containing the —CH=N— group has been confined almost entirely to the heterocyclic compounds. The few Schiff's bases (which also contain the —CH=N— group) which have been aminated in this way have given yields of 20% or less [3, 4] and the products are more readily synthesized by other methods. Of the heterocyclic bases only pyridine and quinoline and their derivatives give satisfactory results; amino derivatives of other heterocyclic bases such as pyrazines, pyrimidines, and thiazoles are not obtained readily by this reaction (see table). The amino derivatives of pyridines and quinolines, which are very difficultly available by other methods, are obtained directly in yields ranging from 50 to 100% by the use of alkali amides.

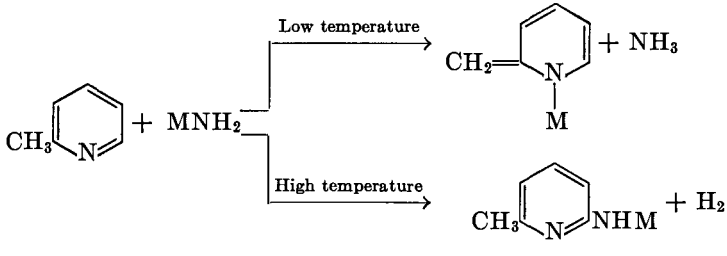
The more common methods of preparing aromatic amines, such as the reduction of nitro compounds, are generally of little value because of the difficulty in obtaining the desired intermediates. For example, nitration of pyridine with nitric acid is unsuccessful, and nitration with nitrogen peroxide (NO_2) gives a 10% yield of 3-nitropyridine.[6] Other methods of synthesis of aminopyridines and aminoquinolines are illustrated in the following scheme.

[2] Ziegler and Zeiser, *Ber.*, **63**, 1848 (1930).
[3] Kirsanov and Ivaschenko, *Bull. soc. chim.*, [5] **2**, 2109 (1935).
[4] Kirsanov and Polyakova, *Bull. soc. chim.*, [5] **3**, 1600 (1936).
[5] Bergstrom, *J. Org. Chem.*, **2**, 411 (1937).
[6] Shoruigin and Topchiev, *Ber.*, **69**, 1874 (1936).



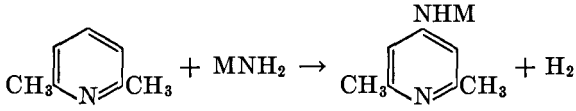
The synthesis of 2-aminopyridine from the hydroxy derivative,[7] as indicated above, results in over-all yields of less than 50%, and both this procedure and that involving the Hofmann degradation [8] are long and tedious. The latter method is useful, however, for the preparation of 3-aminopyridines, which cannot be obtained by direct amination. The synthesis of 2-aminoquinoline derivatives from the alkali sulfonates is a convenient method when the corresponding 2-chloro derivatives are available.[9] By contrast with these methods, the direct amination process is a convenient and economical one.

The ease with which a substituted base undergoes amination is affected by the nature of the substitutents. When 2-alkylpyridines are treated with alkali amides in liquid ammonia, the only reaction observed is the formation of the salt of the enamic modification,[10] but in hydrocarbon solvents at higher temperatures the 2-alkyl-6-aminopyridines are produced.[11]



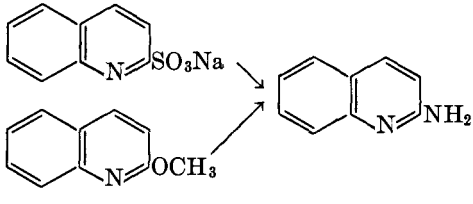
If both the 2- and 6-positions are occupied by alkyl groups, the amino group is forced into the 4-position. Thus, 2,6-dimethylpyridine and sodium amide in boiling xylene form 4-amino-2,6-dimethylpyridine.[12]

[7] Fargher and Furness, *J. Chem. Soc.*, **107**, 690 (1915); Räth, Ger. pat., 510, 432 (1930).
[8] Camps, *Arch. Pharm.*, **240**, 347 (1902).
[9] Zerweck and Kunze, U. S. pat., 2,086,691 (1937); Ger. pat., 615,184 (1935).
[10] Bergstrom, *J. Am. Chem. Soc.*, **53**, 4065 (1931).
[11] Seide, *J. Russ. Phys. Chem. Soc.*, **50**, 534 (1920).
[12] Chichibabin, *J. Russ. Phys. Chem. Soc.*, **47**, 835 (1915); Chichibabin and Vidonova, *J. Russ. Phys. Chem. Soc.*, **53**, 238 (1921).



A study has been made of the effect of various substituents on the course of amination of the quinoline nucleus in liquid ammonia.[13] In this solvent good yields of aminoquinolines are generally obtained, but, if an alkyl group is present in either positions 2 or 4, then salt formation occurs unless more vigorous conditions are employed. For example, 4-methylquinoline is converted to 2-amino-4-methylquinoline when the reaction is carried out in dimethylaniline at 120°,[14] but none of the product is obtained when the reaction is attempted in liquid ammonia at 20°.[15] It might be expected that other salt-forming groups, such as amido, amino (aromatic), carboxyl, ethynyl, hydroxyl, imino, isonitroso, and active methylene groups, would exert the same effect on amination. This is not always true. Thus, a carboxyl group in the 2- or 4-position actually increases the rate of the reaction and improves the yield.[13] 2-Aminoquinoline-4-carboxylic acid and 4-aminoquinoline-2-carboxylic acid are obtained in yields of 70 and 81% respectively from the corresponding acids, potassium amide, and potassium nitrate in liquid ammonia; under the same conditions, 2-aminoquinoline is obtained from quinoline in only 50% yield.[13] On the other hand, an amino group in position 2 of quinoline prevents the amination, as does also a hydroxyl group in either position 2 or 8.[13]

When a sulfonic acid or methoxyl group is present in the 2-position of quinoline, it is replaced by an amino group by the action of potassium amide in liquid ammonia.[13]



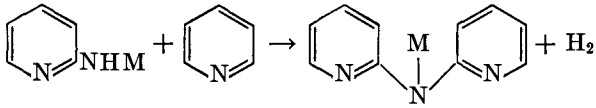
Ordinarily the amination of pyridine and its derivatives can be controlled so that only one amino group is introduced. For example, from the reaction of pyridine with sodium amide in dimethylaniline at temperatures below 120°, 2-aminopyridine is obtained in yields of about 75%;[16] a small amount of the 4-isomer may or may not be formed,

[13] Bergstrom, *J. Org. Chem.*, **3**, 233 (1938).
[14] Leffler, unpublished observations.
[15] Bergstrom, *J. Am. Chem. Soc.*, **53**, 3027 (1931).
[16] Schering A.-G., Ger. pat., 663,891 (1938).

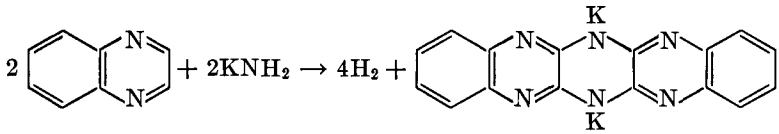
depending on the quality and quantity of the sodium amide used.[14, 17, 18, 19] By increasing the amount of the amide and operating at temperatures near 170°, either in dimethylaniline [16] or in the absence of a solvent,[17] 2,6-diaminopyridine is obtained as the major product; a small amount of 4-aminopyridine is formed at the same time, but 2,4-diaminopyridine has not been isolated. 2,4,6-Triaminopyridine is formed only at high temperature and in the presence of a large excess of the metal amide.[16]

When quinoline is treated with potassium amide in liquid ammonia, 2- and 4-aminoquinolines are formed in the ratio 5:1. Substitution of barium amide for the potassium amide prevents the formation of the 4-isomer.[5] It is probable that a similar result is not to be expected if the reaction is carried out in solvents other than liquid ammonia.

Secondary reactions, in which the alkali salt of the aminoheterocyclic base acts as an aminating agent, are sometimes observed. Thus, dipyridylamine has been isolated as a by-product in the preparation of 2-aminopyridine.[18]



Quinoxaline is converted to fluorubin by potassium amide.[20, 21]



The only recorded attempt to produce a secondary amine by the reaction of substituted alkali amides with heterocyclic bases is the reaction of sodium phenylamide and pyridine; a small amount of 2-phenylaminopyridine was obtained.[1]

Another side reaction that takes place in the amination reaction is coupling. Bipyridyls are always produced in the preparation of aminopyridines. Thus, 2,2′-bipyridyl, 4,4′-bipyridyl and also dihydro-4,4′-bipyridyl have been isolated as by-products in the amination of pyridine.[17, 18, 22] These products are often formed in significant quantities

[17] Shreve, Riechers, Rubenkoenig, and Goodman, *Ind. Eng. Chem.*, **32**, 173 (1940).
[18] Wibaut and Dingemanse, *Rec. trav. chim.*, **42**, 240 (1923).
[19] Chichibabin and Seide, *J. Russ. Phys. Chem. Soc.*, **50**, 522 (1920).
[20] Bergstrom and Ogg, *J. Am. Chem. Soc.*, **53**, 245 (1931).
[21] Bergstrom and Fernelius, *Chem. Rev.* **12**, 162 (1933).
[22] Bergstrom and Fernelius, *Chem. Rev.*, **12**, 156 (1933).

when hydrocarbon solvents are employed but their formation is suppressed when the reaction is carried out in dialkylanilines.

The coupled products may undergo amination if the conditions of reaction are sufficiently strenuous. For example, 2,2′-bipyridyl is only slightly attacked by sodium amide in boiling toluene but undergoes appreciable reaction in boiling xylene.[23] The 4,4′-isomer is more readily aminated.[24]

Similar coupling products are formed from other heterocyclic bases [25] and are often the major products of the reaction between metal amides and complex heterocyclic substances.[26]

EXPERIMENTAL CONDITIONS

Direct amination is usually effected by treating the heterocyclic base with an alkali amide in the presence of a solvent. Potassium nitrate is often used to accelerate the amination of quinoline and its derivatives (see p. 100). The exact manner in which it functions is unknown but appears to be related to the oxidizing capacity of the nitrate ion.

The Alkali Amides. Many patents have been granted and much has been written about the preparation and properties of various metal amides, particularly of sodium amide.[27] In the selection of the proper amide for any amination, the character of the compound to be aminated and the type of solvent to be used must be considered. On a manufacturing scale, the fact that sodium amide is much less expensive than other metal amides may be the determining factor.

Certain precautions must be rigorously observed in the handling of any metal amide. Most of the knowledge of this class of compound has been gained from the study of sodium amide, because of its wide use. It is especially important that the alkali amide be freshly prepared for each reaction. This is necessary, not only from the standpoint of the reproducibility of the experimental results, but also for reasons of safety. It has been shown a number of times [27] that alkali amides react with the oxygen, carbon dioxide, and water of the air to give dangerously explosive mixtures containing the hydroxides, carbonates, and nitrites. A patent has been granted to Ziegler [28] for the preparation of a homogeneous paste by grinding an alkali amide with several times its weight

[23] Tjeen Willink, Jr., and Wibaut, *Rec. trav. chim.*, **54**, 281 (1935).

[24] Horsters and Dohrn, Ger. pat., 398,204 (1924).

[25] Chichibabin and Zatzepina, *J. Russ. Phys. Chem. Soc.*, **50**, 553 (1920).

[26] Chichibabin and Shchukina, *J. Russ. Phys. Chem. Soc.*, **62**, 1189 (1930).

[27] For a review, "The Chemistry of Alkali Amides," see (*a*) Bergstrom and Fernelius, *Chem. Rev.*, **12**, 43 (1933); (*b*) Bergstrom and Fernelius, *ibid.*, **20**, 413 (1937).

[28] Ziegler, Ger. pat., 601,047 (1934).

of an inert liquid such as benzene. It is reported that such a paste can be handled and transported with safety. Even when stored under a dry hydrocarbon, an alkali amide should be carefully protected from the air and samples which develop a yellow or green or darker color should be discarded.

Sodium amide is employed in most aminations except those in which liquid ammonia is used as the solvent. Because of its insolubility in liquid ammonia, it is inferior to potassium or barium amide, both of which are soluble. Wibaut and Dingemanse [18] found that an especially pure sodium amide [29] failed to react with pyridine under conditions which were very satisfactory when a commercial grade of sodium amide was used. This and other reports indicate that the amination is influenced by impurities, probably the substances used as catalysts in the preparation of the amide (p. 99).

The Solvent. Various hydrocarbons (such as benzene, toluene, xylene, cumene, mesitylene, and petroleum fractions), dimethylaniline, diethylaniline, and liquid ammonia have been used as solvents. The amination of pyridine in the absence of a solvent is also successful.[17] With quinolines and isoquinolines good yields are obtained in liquid ammonia solution,[5, 13] but, since the reactions must be carried out at room temperature or above, special apparatus must be used to prevent the development of dangerous pressures due to the hydrogen evolved. The yield of 2-aminopyridine obtained in reactions employing liquid ammonia as a solvent is less than 30%. By the use of hydrocarbon solvents such as toluene, yields as high as 80% of this product have been reported;[30] however, it has been the general experience of several workers [14, 18] that the pure material is usually obtained in yields of 50% or less.

The introduction of dialkylanilines [16, 31] as solvents has greatly increased the practical value of amination of pyridine and its homologs. For example, 2-aminopyridine is obtained in 70–80% yields from pyridine and sodium amide in dimethylaniline at 90–115°, and 2,6–diaminopyridine in yields of 80–90% at 150–180°.[16] It is probable that the value of dimethylaniline and diethylaniline [14] depends on their solvent action on sodium amide and on the sodium amide-pyridine addition compounds. Unfortunately, the investigation of these solvents in aminations of heterocyclic bases other than pyridines has been very limited.

Temperature. An amination should be carried out at the lowest temperature which will promote the desired reaction. In monoaminations this is usually the temperature at which a steady evolution of

[29] Titherley, *J. Chem. Soc.*, **65**, 504 (1894).
[30] Vieweg, Ger. pat., 476,458 (1929).
[31] Ostromislensky, *J. Am. Chem. Soc.*, **56**, 1713 (1934).

hydrogen occurs. Temperatures higher than necessary are to be avoided because of increased diamination, coupling, etc. For the preparation of monoaminopyridines the temperatures reported are usually in the range of 100–150°. Aminoquinolines have nearly always been prepared in liquid ammonia at room temperature.

Mole Ratio. In the preparation of monoaminopyridine in the presence of dialkylanilines, the alkali amide is used in about 25% excess over the theoretical amount.[16, 14] In the older experiments using hydrocarbon solvents the ratio of amide to pyridine was usually 2: 1, and because of the large excess of amide there was often pronounced conversion to diamino derivatives and coupled products. In the amination of pyridine without a solvent, it is recommended that the amide be used in the amount theoretically required for the introduction of the desired number of amino groups.[17]

General Precautions. The reagents and apparatus employed should be dried. In laboratory preparations it is advisable to use the alkali amide in the flask in which it is prepared, thus avoiding possible exposure to the air in transferring the material. Apparatus should be carefully washed with alcohol or dilute aqueous sodium hydroxide, after the reaction is complete, to prevent the formation of explosive mixtures from any remaining alkali amide.

EXPERIMENTAL PROCEDURES

Preparation of Sodium Amide

Sodium amide is prepared on a commercial scale by the action of dry ammonia on molten sodium at 350°. Because of the slowness of the conversion, various catalysts, such as sodium hydroxide, sodium oxide, and oxides of chromium or related metals,[27] are usually added, and samples of the commercial material may be expected to contain varying amounts of one or more of these substances.

The procedures described in *Organic Syntheses*[32] and *Inorganic Syntheses*,[33] involving the use of gaseous ammonia and molten sodium, are quite adequate in detail and are satisfactory when large quantities of the amide are desired. However, for use in ordinary laboratory operations, the amide is more conveniently prepared by the liquid ammonia process described below. This method has the further advantage of allowing the amination to be carried out in the same flask in which the amide is prepared. The method may also be adapted to the preparation of small amounts of potassium amide.

[32] Bergstrom, *Org. Syntheses*, **20**, 86 (1940).
[33] Dennis and Brown, *Inorg. Syntheses*, **1**, 74 (1939).

Procedure.[34] A 500-cc. three-necked flask is equipped with a gas-tight mechanical stirrer, a bubbling tube, and an outlet tube attached to a wide-bore soda-lime tube. Approximately 250 cc. of liquid ammonia from a tank is collected in the flask, and 0.15 g. of ferric nitrate (anhydrous or hydrated) is added. About 0.5 g. of clean sodium is then added, and after it has dissolved the solution is stirred and dry air is slowly bubbled in until the blue color has disappeared. The oxide so formed acts as a catalyst in the subsequent reaction. The bubbling tube is removed and 11.5 g. (0.5 atom) of clean sodium is added to the stirred solution in portions sufficiently small to prevent vigorous reaction. The mixture is stirred for fifteen to twenty minutes after the addition of the sodium is complete.

If the amide is to be used in a solvent other than ammonia, the ammonia is allowed to evaporate while the new solvent is slowly added from a dropping funnel. If the dry amide is desired, the product may be freed from ammonia by evacuation at 100°. In any event, sodium amide prepared by this method must be used immediately. Because of its finely divided condition and the presence of oxides, it rapidly changes to explosive substances.

Preparation of 2-Aminopyridine [14, 16, 31]

The flask containing the suspension of sodium amide in liquid ammonia (preceding paragraph) is fitted with a small dropping funnel, and 45 cc. of dry dimethylaniline is added cautiously, the ammonia being allowed to escape through the soda-lime tube. After all the ammonia has been driven out, the soda-lime tube is removed and a dry vertical condenser, protected by a calcium chloride tube, is attached. The mixture is stirred and 31.6 g. (0.4 mole) of dry pyridine is added through the dropping funnel. The funnel is then replaced by a thermometer which dips into the reaction mixture. The flask is heated in an oil bath, the temperature of the reaction mixture being maintained at 105–110° until the evolution of hydrogen has ceased. Hydrogen is produced rapidly at first, as shown by the continuous stream of bubbles observed when a rubber tube connected to the calcium chloride tube is dipped under water. After eight to ten hours the formation of hydrogen is negligible. Near the end of this period it may be necessary to discontinue the stirring because of the formation of a solid cake in the reaction flask.

When the reaction is complete, the mixture is cooled and 5% aqueous sodium hydroxide solution (about 75 cc.) is gradually added until the vigorous decomposition has stopped. Water (about 300 cc.) is then

[34] Vaughn, Vogt, and Nieuwland, *J. Am. Chem. Soc.*, **56**, 2120 (1934).

added to complete the hydrolysis of the sodium salt. The mixture is extracted with 75 cc. of petroleum ether (b.p. 30–60°) to remove the dimethylaniline; if necessary more water may be added to assist in the separation of the layers. The aqueous solution is cooled to 15°, saturated with solid sodium hydroxide, and extracted several times with benzene. The combined benzene extracts are dried over anhydrous sodium sulfate, and the residue from the distillation of the solvent is distilled under diminished pressure. The product boiling at 117–120°/36 mm. weighs 23–28.6 g. (66–76%). The residue consists of 4,4′-bipyridyl, 2,2′-dipyridylamine, and other unidentified products.[17]

Preparation of 4-Amino-2-phenylquinoline [35]

In leg *A* of the two-legged tube (Fig. 1) are placed 1.05 g. (0.27 atom) of potassium and 0.02 g. of ferric oxide. Tube *C* is closed with a stopper, and legs *A* and *B* are sealed off as indicated by the dotted lines while a

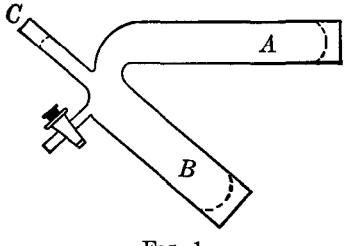


FIG. 1

stream of ammonia is passed in through the stopcock. Through tube *C* 1.83 g. (0.0089 mole) of 2-phenylquinoline and 1.61 g. (0.016 mole) of potassium nitrate are introduced into leg *B*. Tube *C* is then sealed off as indicated. At intervals ammonia is condensed in leg *A*, by cooling *A* in a solid carbon dioxide-acetone bath, until the rapid conversion of potassium to potassium amide is complete. Hydrogen is occasionally vented during this operation. Ammonia is then condensed in the apparatus until 15–20 cc. is present and the contents of the tubes are mixed thoroughly by shaking. The apparatus is allowed to stand at room temperature, with the stopcock closed, for four hours.

The ammonia is evaporated from the reaction mixture and the contents of the tube are rinsed out with ethanol and benzene. Water is added to the mixture, and the greater part of the organic solvents is removed by distillation. The 4-amino-2-phenylquinoline which separates is collected by filtration. The dry, nearly pure product weighs

[35] Bergstrom, *J. Org. Chem.*, **3**, 424 (1938).

1.96 g. (99.7%). After recrystallization from benzene or dilute ethanol, it melts at 164–165°.

Runs of larger size should not be attempted in the apparatus described. Apparatus for larger runs has been devised.[36]

SUMMARY OF AMINATIONS OF HETEROCYCLIC BASES (TABLE)

In the table are summarized the aminations of heterocyclic bases reported prior to January 1, 1941. It is possible that many of the yields recorded in the table, particularly in connection with preparations in which hydrocarbon solvents were used, might be improved by carrying out the reactions in dimethylaniline solution.

[36] Bergstrom, *J. Org. Chem.*, **2**, 423 (1937).

TABLE

HETEROCYCLIC BASES AMINATED BY ALKALI AMIDES

Heterocyclic Base	Alkali Amide	Solvent and Temperature	Amino Heterocyclic Base	Yield,%	Reference*
Acridine	KNH_2	Ammonia	9-Aminoacridine		37
	$Ba(NH_2)_2$	Ammonia	9-Aminoacridine		37
2,2'-Bipyridyl	$NaNH_2$	Toluene, 110°	(?)-Diamino-2,2'-bipyridyl	Poor	23, 38
4,4'-Bipyridyl	$NaNH_2$	Cumene, 200°	2,2'-Diamino-4,4'-bipyridyl		24
Isoquinoline	KNH_2	Ammonia, 25°	1-Aminoisoquinoline	83	39, 40
Isoquinoline-4-carboxylic acid	KNH_2	Ammonia	1-Aminoisoquinoline-4-carboxylic acid	71	41
Phenanthridine	$NaNH_2$	Xylene 110–130°	6-Aminophenanthridine	60–80	42
	KNH_2	Ammonia	6-Aminophenanthridine	90	43
6-Phenylphenanthridine	KNH_2 or $Ba(NH_2)_2$	Ammonia	6-Aminophenanthridine		43
Pyrazine	KNH_2	Ammonia	No products isolated		20
2,5-Dimethylpyrazine	$NaNH_2$	Xylene	3-Amino-2,5-dimethylpyrazine	Poor	26
Pyridine	$NaNH_2$	Dimethylaniline 100–115°	2-Aminopyridine	75–85	16, 44
	$2NaNH_2$	Dimethylaniline 170°	2,6-Diaminopyridine	82–90	16, 45
	$3NaNH_2$	Dimethylaniline	2,4,6-Triaminopyridine		16
2,6-Dimethylpyridine	$NaNH_2$	Toluene	4-Amino-2,6-dimethylpyridine		12
4-Ethylpyridine	$NaNH_2$	Hydrocarbon, 150°	2-Amino-4-ethylpyridine		24
5-Ethyl-2-methylpyridine	$NaNH_2$	Hydrocarbon, 150°	6-Amino-5-ethyl-2-methylpyridine		12
3-Hydroxypyridine	$NaNH_2$	*p*-Cymene, 210°	2,6-Diaminopyridine		46
2-Methylpyridine	$NaNH_2$		6-Amino-2-methylpyridine		47
2-Methylpyridine	$NaNH_2$	200°	4,6-Diamino-2-methylpyridine		48
3-Methylpyridine	$NaNH_2$	Xylene 135–140°	2-Amino-3-methylpyridine	52	49
4-Methylpyridine	$NaNH_2$		2-Amino-4-methylpyridine		50
3-(2'-N-Methylpiperidyl)-pyridine [N-Methylanabasine]	$NaNH_2$	Xylene (reflux)	α-Amino-(and α'-amino)-N-methyl-anabasine	40–50	51

3-(2'-N-Methylpyrrolidyl)-pyridine [Nicotine]	$NaNH_2$	Xylene, 140°	α-Aminonicotine	30	52
			α'-Aminonicotine	30	52
3-(2'-Piperidyl)-pyridine [Anabasine]	$NaNH_2$	Dimethylaniline 120–150°	2-Aminoanabasine		38, 51
			6-Aminoanabasine	40	38, 51
2-Propylpyridine	$NaNH_2$	200°	4,6-Diamino-2-propylpyridine		48
6-Methylpyrimidine	$NaNH_2$	130–160°	2-Amino-(and 2,4-diamino)-6-methyl-pyrimidine		53
Quinoline	KNH_2 (KNO_3)	Ammonia, 50–70°	2-Aminoquinoline and	53	5, 17, 25
			4-Aminoquinoline	10 (?)	5
	$Ba(NH_2)_2$	Ammonia, 25°	2-Aminoquinoline	80	5
5,6-Benzoquinoline	KNH_2 (KNO_3)	Ammonia, 25°	2-(?)-Amino-5,6-benzoquinoline	98	35
7,8-Benzoquinoline	$Ba(NH_2)_2$	Ammonia, 25°	2-(?)-Amino-7,8-benzoquinoline	88	35
2-Carboxyquinoline	KNH_2 (KNO_3)	Ammonia, 25°	4-Amino-2-carboxyquinoline	81	13
4-Carboxyquinoline	KNH_2 (KNO_3)	Ammonia, 25°	2-Amino-4-carboxyquinoline	70	13
6-Carboxyquinoline	KNH_2 (KNO_3)	Ammonia, 25°	(?)-Amino-6-carboxyquinoline	60	13
6-Dimethylaminoquinoline	$Ba(NH_2)_2$	Ammonia, 25°	(?)-Amino-6-dimethylaminoquinoline	34	13
8-Ethoxyquinoline	$Ba(NH_2)_2$	Ammonia, 25°	(?)-Amino-8-ethoxyquinoline	76	13
4-Methylquinoline	$NaNH_2$	Dimethylaniline 115–125°	2-Amino-4-methylquinoline	46	14
6-Methylquinoline	$Ba(NH_2)_2$	Ammonia, 25°	(?)-Amino-6-methylquinoline	35	13
7-Methylquinoline	$Ba(NH_2)_2$	Ammonia, 25°	Unsuccessful	0	13
8-Methylquinoline	$Ba(NH_2)_2$	Ammonia, 25°	(?)-Amino-8-methylquinoline	35	13
2-Methoxyquinoline	KNH_2	Ammonia, 25°	2-Aminoquinoline	51	13
6-Methoxyquinoline	$Ba(NH_2)_2$	Ammonia, 25°	(?)-Amino-6-methoxyquinoline	76	13
2-Phenylquinoline	KNH_2 (KNO_3)	Ammonia, 25°	4-Amino-2-phenylquinoline	92–100	35

*References 37–56 appear on p. 104.

TABLE—*Continued*

HETEROCYCLIC BASES AMINATED BY ALKALI AMIDES

Heterocyclic Base	Alkali Amide	Solvent and Temperature	Amino Heterocyclic Base	Yield,%	Reference*
6-Phenylquinoline	$Ba(NH_2)_2$	Ammonia, 25°	(?)-Amino-6-phenylquinoline	87	35
8-Phenylquinoline	$Ba(NH_2)_2$	Ammonia, 25°	(?)-Amino-8-phenylquinoline	88	35
2-Sulfoquinoline	KNH_2	Ammonia, 25°	2-Aminoquinoline	73	13
6-Sulfoquinoline	$Ba(NH_2)_2$	Ammonia, 25°	(?)-Amino-6-sulfoquinoline	83	13
Quinoxaline	KNH_2	Ammonia, 25°	Fluorubin (K salt)		20
2,3-Dimethylquinoxaline	KNH_2	Ammonia, 25°	Dipotassium salt		54, 55
2,3-Dimethyl-6-methylquinoxaline	KNH_2	Ammonia, 25°	Dipotassium salt		55
2,3-Diphenylquinoxaline	KNH_2	Ammonia, 130–140°	2-Amino-3-phenylquinoxaline		55
2,3-Diphenyl-6-methylquinoxaline	KNH_2	Ammonia, 130–140°	2-Amino-6-methyl-3-phenylquinoxaline		55
6-Methylquinoxaline	KNH_2	Ammonia			55
4-Methylthiazole	$NaNH_2$	150°	2-Amino-4-methylthiazole		56

[37] Reference 27*a*, p. 163.
[38] Kabatchnik and Katzelsohn, *Bull. soc. chim.*, [5] **2**, 576 (1935).
[39] Bergstrom, *Ann.*, **515**, 34 (1934).
[40] Chichibabin and Oparina, *J. Russ. Phys. Chem. Soc.*, **50**, 543 (1920).
[41] Bergstrom and Rodda, *J. Am. Chem. Soc.*, **62**, 3030 (1940).
[42] Morgan and Walls, *J. Chem. Soc.*, 2229 (1932).
[43] Reference 27*b*, p. 472.
[44] Reference 27*a*, pp. 154–158; 5*b*, p. 463.
[45] Philipp, U. S. pat., 1,789,022 (1931).
[46] Plazek, *Roczniki Chem.*, **16**, 403 (1936).
[47] Seide, *J. Russ. Phys. Chem. Soc.*, **50**, 534 (1920).
[48] Schneiderwirth, U. S. pat., 2,062,680 (1936).
[49] Seide, *Ber.*, **57**, 1802 (1924).
[50] Seide, *Ber.*, **57**, 791 (1924).
[51] Menschikov, Grigorovitch, and Orechoff, *Ber.*, **67**, 289 (1934).
[52] Chichibabin and Kirsanov, *Ber.*, **57**, 1163 (1924).
[53] Ochiai and Karii, *J. Pharm. Soc. Japan*, **59**, 18 (1939).
[54] Ogg and Bergstrom, *J. Am. Chem. Soc.*, **53**, 1849 (1931).
[55] Reference 27*a*, p. 162.
[56] Ochiai, *J. Pharm. Soc. Japan*, **58**, 1040 (1938).

CHAPTER 5

THE BUCHERER REACTION

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University of Maryland

CONTENTS

PAGE

INTRODUCTION 105

MECHANISM 106

SCOPE 107

Conversion of Amines to Hydroxyl Compounds 108

Reactions of Primary Amines 108

Reactions of Secondary and Tertiary Amines 110

Conversion of Hydroxyl Compounds to Amines 110

Preparation of Primary Amines 110

Preparation of Secondary Amines 111

Preparation of Secondary Amines from Primary Amines 113

Reactions Involving Hydrazines 114

The Use of Bisulfite Addition Products in the Preparation of Azo Compounds 117

SELECTION OF EXPERIMENTAL CONDITIONS 118

EXPERIMENTAL PROCEDURES 120

2-Naphthylamine 120

7-Methyl-1-naphthylamine 120

2-*p*-Tolylamino-5-hydroxynaphthalene-7-sulfonic Acid 121

2-(4'-Hydroxyphenylamino)-8-naphthol-6-sulfonic Acid and 2-(4'-Hydroxyphenylamino)-naphthalene-6-sulfonic Acid 121

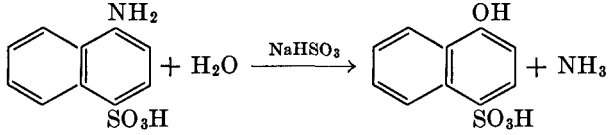
TABLE OF COMPOUNDS PREPARED BY THE BUCHERER REACTION 122

INTRODUCTION

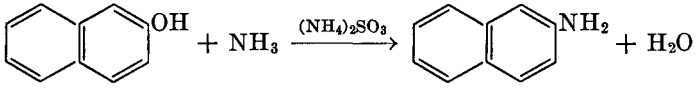
The Bucherer reaction is the reversible conversion of a naphthylamine to a naphthol in the presence of an aqueous sulfite or bisulfite. It has proved to be of value in the synthesis of naphthalene derivatives, particularly in the manufacture of dye intermediates. In certain instances it is conveniently used in the preparation of naphthols from naphthyla-

mines; in others it is employed for the reverse transformation, the synthesis of naphthylamines from naphthols.

(1)



(2)



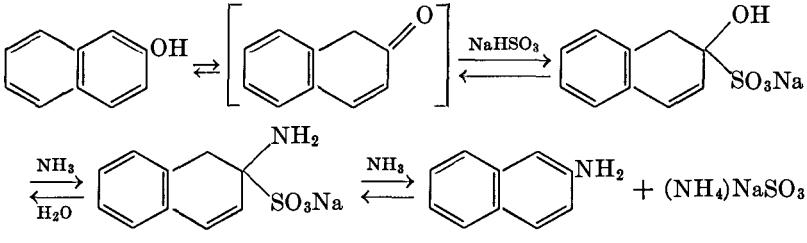
The second reaction has been extended to the synthesis of certain alkyl- and aryl-aminonaphthalenes by the use of alkyl- and aryl-amines and sodium bisulfite, to the synthesis of naphthylhydrazines by the use of hydrazine sulfite, and to the synthesis of carbazoles by the use of phenylhydrazine and bisulfite.

Although Lepetit [1, 2] was the first to discover the amazingly easy transformation of naphthionic acid to 1-naphthol-4-sulfonic acid (equation 1), Hans T. Bucherer [3] discovered the reaction independently, recognized its usefulness, and demonstrated its reversibility. As a consequence, the name Bucherer has continued to be associated with these transformations.

MECHANISM

Studies of the mechanism of the formation of a naphthylamine from a naphthol, sodium bisulfite, and ammonia [4] indicate that the reaction involves addition of the bisulfite to the keto form of the naphthol.

(3)



The reaction of the addition product with ammonia is similar to that of the sodium bisulfite addition product of formaldehyde, which yields sodium aminomethanesulfonate.[5] Compounds similar to the bisulfite

[1] Lepetit, pli cacheté No. 888, May 16, 1896; *Bull. soc. ind. Mulhouse*, 326 (1903).
[2] Friedländer, *Ber.*, **54**, 620 (1921).
[3] Bucherer, *J. prakt. Chem.*, [2] **69**, 49 (1904).
[4] Fuchs and Stix, *Ber.*, **55**, 658 (1922).
[5] Raschig, *Ber.*, **59**, 859 (1926).

addition product pictured in (3) have been isolated from hydroquinone,[6] resorcinol,[7] phloroglucinol,[8] disodium 2-naphthol-1-sulfonate,[9] 2,7-dihydroxynaphthalene,[4] 1,5-dihydroxynaphthalene,[4] and many other substances.[3] In some instances the action of bisulfite leads to the introduction of sulfonate residues in addition to the one on the carbonyl carbon.[4, 6, 7]

The mechanism of the Bucherer replacement of an amino group by a hydroxyl group is well illustrated by the behavior of naphthionic acid and sodium bisulfite.[3] After naphthionic acid has been boiled for some time with a 40% solution of sodium bisulfite and the mixture has been made acid to Congo paper and boiled to expel excess sulfur dioxide, a small quantity (*ca.* 15%) of 1-naphthol-4-sulfonic acid can be isolated. The remainder is present as addition product (*cf.* reaction 3). If this mixture is now made alkaline to phenolphthalein and boiled, ammonia is driven off and disodium 1-naphthol-4-sulfonate is produced. When the resultant mixture is again acidified to Congo paper and boiled, more sulfur dioxide is removed and the remainder of the starting material can be accounted for as 1-naphthol-4-sulfonic acid. It is apparent that the intermediate bisulfite addition product is quite stable toward dilute acid but is readily decomposed by alkali.

If, after the excess bisulfite has been decomposed as above, the resulting mixture is heated with excess ammonia, the original naphthionic acid is regenerated. The papers of Fuchs and co-workers [4, 6, 7, 8, 9a] describe the properties of a variety of such addition products.

SCOPE OF THE BUCHERER REACTION

The replacement of hydroxyl by amino groups, or of amino by hydroxyl groups, is limited practically to naphthalene derivatives and resorcinol. Benzene derivatives containing one hydroxyl or one amino group are much less reactive than similar naphthalene derivatives. Polyfunctional benzenes react more readily, but with the exception of resorcinol they undergo reactions which are complicated by secondary processes. Hydroxyanthraquinones do not react.

Dihydroxy or diamino derivatives of naphthalene in which the substituents are in different rings usually undergo replacement of only one of the two groups; the second group may, however, be involved to a limited extent (*cf.* behavior of naphthols with hydrazine sulfite and

[6] Fuchs and Elsner, *Ber.*, **52**, 2281 (1919).
[7] Fuchs and Elsner, *Ber.*, **53**, 886 (1920).
[8] Fuchs, *Ber.*, **54**, 245 (1921).
[9] Woroshtzow, *Ber.*, **62**, 57 (1929).
[9a] Fuchs and Pirak, *Ber.*, **59**, 2458 (1926).

hydrazine, p. 114). For example, 1,5-diaminonaphthalene, heated under reflux with sodium bisulfite solution,[3] is slowly converted into an addition product which, after destruction of the excess bisulfite, can be salted out in considerable quantity. This addition product is converted into 1-amino-5-naphthol by heating with alkali. Concurrently with the production of this addition product, a small amount of the addition product of 1,5-dihydroxynaphthalene is formed, and it, too, can be salted out (it is more sparingly soluble than the one previously mentioned). A small quantity of free aminonaphthol and dihydroxynaphthalene as well are formed during the reaction. The total yield of aminonaphthol is about 80%.

Conversion of Amines to Hydroxyl Compounds

Reactions of Primary Amines. Both α- and β-naphthylamines can be converted to naphthols in practically quantitative yields. Addition products are first formed, and these are decomposed by treatment with alkali, although a varying, usually small, amount of the addition product decomposes during the first stage of the preparation. Most substituted naphthylamines (except those having an N-aryl substituent) also react within the limitations discussed below. Naphthylamine- and aminonaphtholsulfonic acids are important dye intermediates, and the application of the Bucherer reaction to these compounds has been studied extensively.

The effect of various experimental conditions on the conversion of sodium 1-amino-5-naphthalenesulfonate to the corresponding naphthol has been studied by Kogan,[10] who found that the reaction proceeded best in a slightly acid solution with about seven moles of bisulfite per mole of aminonaphthalenesulfonate.

The effects of a sulfonic acid group on the replacement of the amino group by hydroxyl may be summarized as follows.

(*a*) A 1,4-relationship of amino group and sulfonic acid group promotes the reaction.

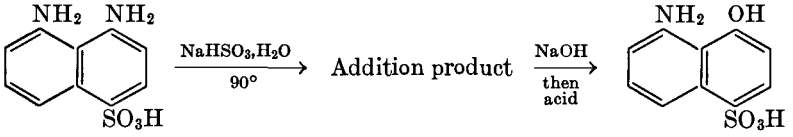
(*b*) A 1,2-, 1,3-, or 2,3-relationship of the same groups hinders the reaction.

(*c*) A relationship such that the two groups are in different rings has little effect on the ease with which the reaction takes place.

Because of the effect of the position of a sulfonic acid group on the reactivity of the amino group, the Bucherer reaction of diaminonaphthalenesulfonic acids often takes only one of two possible courses. For

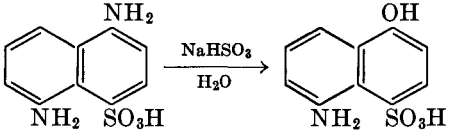
[10] Kogan and Nikolaeva, *J. Applied Chem.* (*U.S.S.R.*), **11**, 652 (in French 659) (1938) [*C. A.*, **32**, 7031 (1938)].

example, 1,8-diaminonaphthalene-4-sulfonic acid is easily converted into

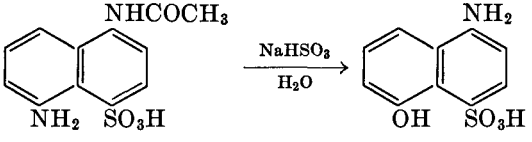


8-amino-1-naphthol-4-sulfonic acid, rather than into 8-hydroxy-1-naphthylamine-4-sulfonic acid.[3]

Similarly, 1,5-diaminonaphthalene-4-sulfonic acid yields 5-amino-1-naphthol-4-sulfonic acid.

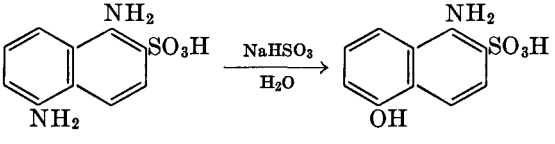


However, if the amino group at position 1 is acetylated, then the amino group in position 5 takes part in the reaction.



Evidently the acetyl group is removed by hydrolysis after the Bucherer reaction is complete, for the product is the free amine.

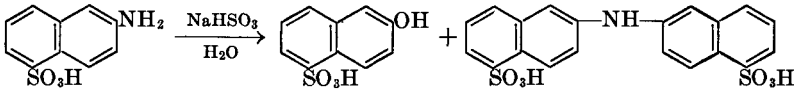
The hindering effect of a sulfonic acid group on the replacement of an adjacent amino group is seen in the reaction of 1,5-diaminonaphthalene-2-sulfonic acid; the product is 1-amino-5-naphthol-2-sulfonic acid.



Occasionally secondary amines are formed as by-products of the Bucherer reaction with naphthylamines. For example, treatment of 2-naphthylamine-5-sulfonic acid with even a large excess of sodium bisulfite (10–20 moles) leads to a mixture containing the dinaphthylaminesulfonic acid as well as 2-naphthol-5-sulfonic acid, but even after long heating demonstrable quantities of the original naphthylaminesulfonic acid are present.[11] This behavior is obviously a result of reaction between the

[11] Bucherer and Stohmann, *J. prakt. Chem.*, [2] **71**, 433 (1905).

addition complex and the amine and corresponds to the reaction type discussed below.



Reactions of Secondary and Tertiary Amines. N-Mono- and N,N-dialkyl derivatives of naphthylamines can be converted to naphthols by treatment with aqueous sodium bisulfite.[12] These reactions frequently take place with greater ease than those of primary amines. In the case of the N-monobenzyl derivatives of 1-naphthylamine-4,7- and -4,8-disulfonic acids the yield of benzylamine varies from 60 to 77%. In the case of N-monobenzyl-1-naphthylamine-4-sulfonic acid the yield of benzylamine is smaller and the time for conversion longer;[13] one would anticipate a ready cleavage because of the activating effect of the sulfonic acid group, but the sparing solubility of the compound hinders the reaction. The disulfonic acid, which is more soluble, reacts more readily. Apparently the N,N-dibenzyl derivatives of the same compounds are not cleaved at all under comparable conditions or even by heating in a closed container at 125–150°.[13]

Conversion of Hydroxyl Compounds to Amines

Preparation of Primary Amines. 1- and 2-Naphthols and their derivatives can be converted into primary amines by treatment with ammonia and ammonium sulfite or by the action of ammonia on their bisulfite addition products.[13] The effect of substituents on ease of replacement is the same as that mentioned above. Hydroxyquinolines may be aminated similarly.[14]

Inasmuch as 2-nitronaphthalene cannot be obtained by direct nitration, the Bucherer process for preparing 2-naphthylamine and its derivatives is of considerable importance. In the preparation of 2-naphthylamine from 2-naphthol, reaction begins around 100° but proceeds much more rapidly in an autoclave at about 150°.[3] Yields given range from 88%[15] to "practically quantitative."[3] Other references to 2-naphthylamine will be found under $C_{10}H_9N$ in the table of compounds prepared by the Bucherer reaction on p. 122. An advantage of the Bucherer method for the preparation of 2-naphthylamine is that the process can be carried out at a temperature such that there is practically

[12] Bucherer, *J. prakt. Chem.*, [2] **70**, 345 (1904).
[13] Bucherer and Seyde, *J. prakt. Chem.*, [2] **75**, 249 (1907).
[14] Woroshtzow and Kogan, *Ber.*, **65**, 142 (1932).
[15] Bezzubetz, *J. Chem. Ind. (Moscow)*, **7**, 908 (1930) [*C. A.*, **25**, 4545 (1931)].

no formation of 2-2′-dinaphthylamine; 2-naphthylamine is filtered from the cooled reaction mixture, and the mother liquor can be used again.[3]

2,8-Dihydroxynaphthalene-6-sulfonic acid, "G acid," is converted to 2-amino-8-naphthol-6-sulfonic acid in 80% yield.[3] Similarly, 2,5-dihydroxynaphthalene-7-sulfonic acid yields 2-amino-5-naphthol-7-sulfonic acid, and 1,5-dihydroxynaphthalene-7-sulfonic acid yields 1-amino-5-naphthol-7-sulfonic acid. In these instances the hindering effect of the sulfonic acid group causes the reaction to take place in the other ring.

The behavior of 2-hydroxy-3-naphthoic acid in the Bucherer reaction is worthy of note. This acid undergoes decarboxylation below 100° when heated in the presence of aqueous sodium bisulfite, although the acid itself can be heated in water for eighteen hours at 125° without change.[16] When heated with ammonia and ammonium sulfite at 150–155° for nine hours it is converted into 2-naphthylamine (67%) and 2,2′-dinaphthylamine (23%). The bisulfite addition product of 2-hydroxy-3-naphthoic acid is related to a β-keto acid; the decarboxylation is therefore to be expected. The observed [13] stability of ethyl 2-hydroxy-3-naphthoate toward boiling sodium bisulfite solution is understandable; no loss of carbon dioxide would be expected even though the bisulfite addition product of the keto form were produced, for β-keto esters are quite stable. Bucherer's experiments do not prove whether or not the bisulfite addition product of the keto ester is formed, but they do demonstrate that replacement of the 2-hydroxyl group by an amino group does not occur. The hindering effect of the carbethoxy group is thus to be compared with the similar influence of the sulfonic acid group.

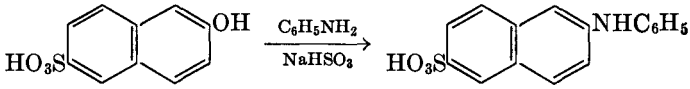
8-Hydroxyquinoline is converted "almost quantitatively" into 8-aminoquinoline by heating with ammonia and ammonium sulfite in a closed vessel at 150–160° for six to seven hours.[14] 6-Hydroxyquinoline and 8-hydroxyquinoline-5-sulfonic acid are similarly converted to the corresponding aminoquinolines.

Preparation of Secondary Amines. Conversions of naphthols to N-alkyl- or N,N-dialkyl-aminonaphthalenes require more vigorous conditions than are necessary for the production of primary amines by means of ammonia and ammonium sulfite. For example, amination of 1-naphthol-4-sulfonic acid takes place smoothly at 90°, but the substitution of methylamine for ammonia necessitates carrying out the process at 150° in an autoclave.[12] It is possible in such instances to heat together one mole of naphthol, one mole of alkylamine sulfite, and one mole of alkylamine in an autoclave at 125–150° until reaction is complete (test for residual naphtholsulfonic acid), or to prepare the addition product from the naphthol and excess sodium bisulfite and, after acidification

[16] Bucherer, *Z. Farb. Text. Chem.*, **1**, 477 (1903).

and expulsion of sulfur dioxide by heating, to heat the addition product with two moles of amine. The excess amine can be recovered in either case. Numerous examples of this process involving ethanolamine, ethylenediamine, methylamine, etc., are to be found in the patent literature.[17, 18, 19, 20]

The introduction of arylamino residues occurs more readily with naphthols of the β-series [11] (see also the next section). 1-Naphthol-4-sulfonic acid does not react with aniline and sodium bisulfite at 100°, but 2-naphthol-6-sulfonic acid reacts smoothly at this temperature, yielding 2-phenylaminonaphthalene-6-sulfonic acid.[11, 21, 22] The corresponding 2-phenylamino-8-sulfonic acid has been prepared in a similar manner.[21, 22] The yield of 34% (recrystallized product) obtained after boiling for nineteen hours could undoubtedly be increased by operation at a more elevated temperature in an autoclave provided with a stirrer.



There is wide variation in the tendency of aromatic amines to undergo this reaction. The table below lists a number of common amines in the order of increasing reactivity toward β-naphthols.

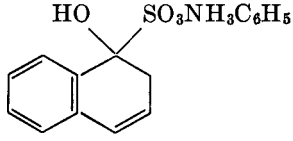
Reactivity of Some Arylamines in the Bucherer Amination Process [11]

Relatively unreactive	Benzidine
	β-Naphthylamine
	Aminonaphthol ethers
	Xylidine
	o- and *p*-Toluidine
	Aniline
Moderately reactive	*p*-Phenetidine
	Sulfanilic acid
	Metanilic acid
Extremely reactive	*p*-Aminophenol
	p-Phenylenediamine

Later work [22a] has shown that arylamination may be extended to

[17] Brit. pat., 249,717 [*C. A.*, **21**, 916 (1927)].
[18] Brit. pat., 436,805 [*C. A.*, **30**, 2203 (1936)].
[19] U. S. pat., 1,543,569 [*C. A.*, **19**, 2345 (1925)].
[20] Fr. pat., 788,707 [*C. A.*, **30**, 1586 (1936)].
[21] Bucherer, *Z. Farb. Text. Chem.*, **3**, 57 (1904).
[22] Bucherer, *Z. Farb. Text. Chem.*, **2**, 193 (1903).
[22a] U. S. pat., 2,059,466 [*C. A.*, **31**, 418 (1937)].

1-naphthols under special conditions. The salt of an arylamine will react at a temperature between 100° and 200° with a molecular equivalent of the isolated bisulfite addition product of a 1-naphthol; the product, an arylaminonaphthalene, is formed in good yield. The reaction may also be carried out in aqueous solution; the bisulfite addition product is prepared in the usual way in aqueous medium, excess bisulfite is neutralized or removed by acid, the requisite amount of amine hydrochloride is added, and the mixture is heated in an autoclave. It has been suggested [22a] that the intermediate involved is a salt of the addition product and the amine.



In many cases it is possible to isolate such saltlike addition products, which, on heating, yield the expected amine, sulfur dioxide, and water.

The usefulness of any particular arylamine in the Bucherer process is determined not only by its own tendency to enter the reaction but also by the reactivity of the bisulfite addition compound of the naphthol with which it is being condensed. *p*-Toluidine in the presence of bisulfite does not react rapidly with 2-naphthol-6-sulfonic acid; however, the yield is practically quantitative when the isomeric 2,8-acid is used.[11] Likewise, benzidine, which reacts with β-naphthols only with extreme difficulty, reacts much more readily with 2-hydroxy-3-naphthoic acid and with 2,8-dihydroxy-3-carboxynaphthalene-6-sulfonic acid, both of which are notable for the ease with which they undergo amination by the Bucherer process.

It is possible to use relatively complex amines in this process. Thus *p*-rosaniline reacts readily in the presence of sodium bisulfite with 2-naphthol-6-sulfonic acid to form substituted rosanilines.[11, 21] The exact constitution of the reaction products has not been established.

The effects of substituent sulfonic acid groups in the naphthol nucleus upon the ease of reaction with an arylamine are identical with those mentioned earlier (p. 108).

Preparation of Secondary Amines from Primary Amines

2-Naphthylamines can be substituted for 2-naphthols in any of the reactions described on pp. 110–113; 1-naphthylamines can be substituted for 1-naphthols only in those processes involving alkylamination or dial-

kylamination. The 2-naphthylamines react more easily than the corresponding naphthols.[11] Thus 1-methylamino-7-naphthol-4-sulfonic acid can be prepared from 1-amino-7-naphthol-4-sulfonic acid by treatment with sodium bisulfite and methylamine.[23] Likewise, 2-(4′-hydroxyphenylamino)-naphthalene can be prepared from 2-naphthylamine and *p*-aminophenol,[24] and 2-phenylaminonaphthalene-6-sulfonic acid can be prepared from 2-aminonaphthalene-6-sulfonic acid.[11, 21]

2-Amino-8-naphthol-6-sulfonic acid, 2-aminonaphthalene-6,8-disulfonic acid, and 2-amino-5-naphthol-7-sulfonic acid all react in the presence of sodium bisulfite with *p*-rosaniline to form substituted rosanilines.[11]

The process discussed above may be summarized as follows.

$$\mathrm{ArNH_2} \xrightarrow[\substack{\mathrm{Ar'NH_2} \\ \text{or} \\ \mathrm{R_2NH}}]{\mathrm{NaHSO_3}} \mathrm{ArNHAr'} \text{ or } \mathrm{ArNR_2} \qquad (\mathrm{R} = \text{alkyl or hydrogen})$$

It should be noted that no useful reversal of the Bucherer reaction takes place when N-aryl-2-naphthylamines are heated with sodium bisulfite solution.

Reactions Involving Hydrazines

Arylhydrazines are formed in the reaction of hydrazine sulfite and hydrazine with naphthols.[25, 26, 27] Thus hydrazines can be prepared from 1- and 2-naphthol, and 2,7-dihydroxynaphthalene yields 7-hydroxy-2-naphthylhydrazine (82%) with a very small amount of dihydrazine under the conditions used.[26b] Both hydroxyl groups of 2,3-dihydroxynaphthalene can be replaced by hydrazine residues;[26a] the yield of crude product is about 57%. Similarly resorcinol yields *m*-phenylenedihydrazine.[26c] The latter compound cannot be isolated as such but can be obtained as its reaction product with benzaldehyde (yield 50%). Pyrocatechol, hydroquinone, 3,4-diaminotoluene, and salicylic acid do not undergo the reaction.[26c] It is to be noted that both 1- and 2-naphthols undergo this reaction, and that more than one hydrazine residue can be introduced readily.

When phenylhydrazine, sodium bisulfite, and a naphthol (or naphthylamine) are heated together a rather complicated series of reactions takes

[23] Ger. pat., 676,856 [*C. A.*, **33**, 7319 (1939)].

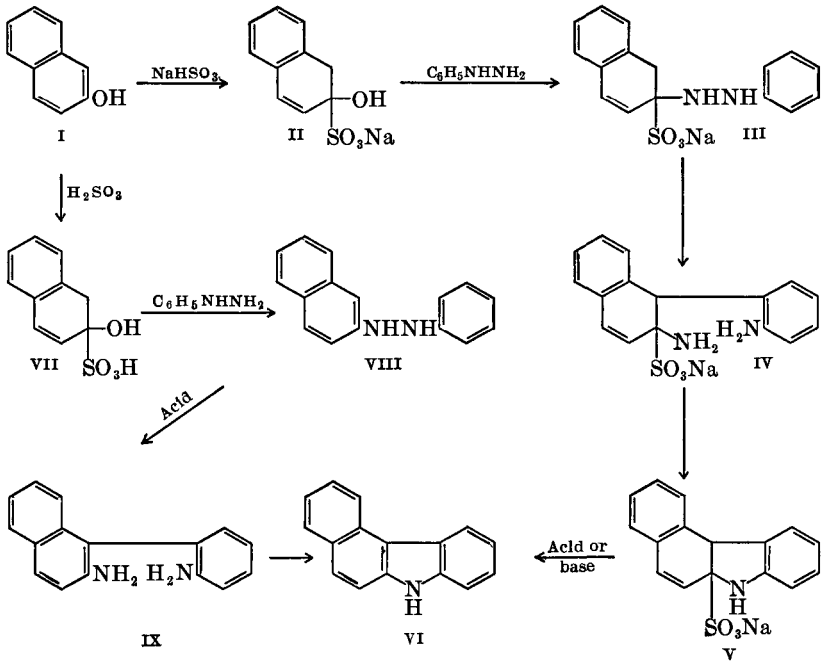
[24] Brit. pat., 479,447 [*C. A.*, **32**, 5003 (1938)].

[25] Franzen, *Habilitationsschrift*, Heidelberg (1904).

[26] (*a*) Franzen, *J. prakt. Chem.*, **76**, 205 (1907); (*b*) **78**, 143 (1908); (*c*) **78**, 157 (1908); (*d*) *Ber.*, **38**, 266 (1905).

[27] Bucherer and Schmidt, *J. prakt. Chem.*, [2] **79**, 369 (1909).

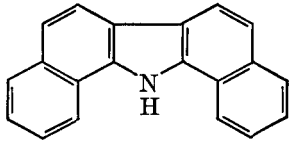
place. The process has been carefully studied by Fuchs and Niszel,[28] who have presented the mechanism shown below.



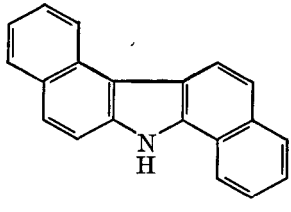
Bucherer and co-workers [29, 30] investigated the reaction earlier but concluded that products corresponding to V were probably carbazole-N-sulfonic acids because of the ease with which they lost the sulfonic acid residues and yielded carbazoles. These investigators also noted the formation of diamines (corresponding to IV) as by-products. Fuchs' proof that the transformations I → VII → VIII → IX → VI can actually be carried out [28] makes the reaction of naphthols or 2-hydroxy-3-naphthoic acid with phenylhydrazine and bisulfite, and that of naphthylhydrazines with bisulfite, quite understandable. Thus phenylhydrazine and 2-hydroxy-3-naphthoic acid react to give a 70% yield of a compound of type V which is readily cleaved by acid with the formation of 5,6-benzocarbazole.[27] If 2-naphthol is substituted for hydroxynaphthoic acid, the reaction takes place much more sluggishly and the yield of carbazole is only 46% after several days at 130°.[27] *p*-Tolylhydrazine yields similar products.[27]

[28] Fuchs and Niszel, *Ber.*, **60**, 209 (1927).
[29] Bucherer and Seyde, *J. prakt. Chem.*, [2] **77**, 403 (1908).
[30] Bucherer and Sonnenberg, *J. prakt. Chem.*, [2] **81**, 1 (1910).

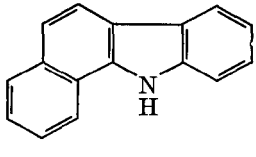
When a naphthylhydrazine reacts with aqueous bisulfite the first reaction apparently is removal of the hydrazine residue with the formation of the bisulfite addition compound of the parent naphthol [27] which then combines with unchanged naphthylhydrazine to form a compound similar to III. If 1-naphthylhydrazine is used, this product is apparently stable [27] but is converted by treatment with hot mineral acids into 1,2,7,8-dibenzocarbazole.



2-Naphthylhydrazine behaves somewhat differently in that the principal products are 3,4,5,6-dibenzocarbazole and a compound of type V. This substance loses its sulfonic acid group readily to form the corresponding carbazole. Experiments [27] have shown that it is possible to prepare the type V compound from 2-hydroxynaphthoic acid directly by treatment with 2-naphthylhydrazine in sodium bisulfite solution. 1-Naphthylhydrazine also condenses easily with 2-hydroxy-3-naphthoic acid; the condensation product (type V) is formed in good yield and is readily transformed into 1,2,5,6-dibenzocarbazole by the action of mineral acid.[27]



1-Naphthylamine-4-sulfonic acid and the corresponding naphtholsulfonic acid react readily with phenylhydrazine in the presence of bisulfite. Apparently the reaction proceeds to a type III compound; evidence for the structure of this compound is its conversion by oxidation in alkaline solution into 1-phenylazonaphthalene-4-sulfonic acid. Treatment with hot concentrated hydrochloric acid converts the hydrazo compound in part into 1,2-benzocarbazole.[30]



During the treatment with acid the nuclear sulfonic acid group is cleaved by hydrolysis.

The action of phenylhydrazine and sodium bisulfite on a number of naphthylamine- and naphthol-sulfonic acids has been studied.[30, 31, 32, 33] In all instances the reactions which occur can be interpreted in terms of the mechanism proposed by Fuchs and Niszel. These investigations [30] indicate that reactions which involve compounds of the 1-series and phenylhydrazine usually proceed only to type III compounds (except 1-naphthol- and 1-naphthylamine-5-sulfonic acid). The hydrazo compound can be converted by treatment with mineral acid into a carbazole. Reactions which involve members of the 2-series proceed to type V compounds from which the sulfonic acid group is readily cleaved by hydrolysis in mineral acid solution. Numerous examples of carbazoles prepared by this method will be found in the table of compounds prepared by the Bucherer reaction (pp. 124–7).

Reactions involving aminonaphtholsulfonic acids, phenylhydrazine, and bisulfite are complex.[30, 32, 33] Azo dyes also react with sodium bisulfite and phenylhydrazine, but here again the reactions are complex and the nature of the products is obscure.

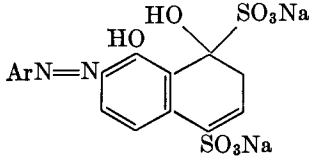
In general the reaction of a hydrazine with a naphthol (or naphthylamine) in the presence of bisulfite takes place more readily than the corresponding reaction involving an amine and a naphthol (or naphthylamine). In this connection it is interesting to note that "R acid" (2-naphthol-3,6-disulfonic acid), which does not react with amines [30] in the presence of bisulfite because of the hindering effect of the 3-sulfonic acid, condenses readily with phenylhydrazine under similar conditions.

The Use of Bisulfite Addition Products in the Preparation of Azo Compounds

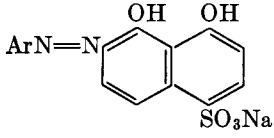
Bisulfite addition products obtained from dihydroxy- or diaminonaphthalenes can be employed in the preparation of azo dyes. Those compounds containing a free amino group in the aromatic ring of the addition complex can be converted into diazonium salts which couple in the usual way. After the coupling the hydroxyl group can be regenerated by treatment with alkali or the addition product can be converted into an amine. Obviously a bisulfite addition product can be coupled with any diazonium salt provided that there is an activating group (hydroxyl or amino) in the *aromatic* ring; coupling must take place in the

[31] König and Haller, *J. prakt. Chem.*, **101**, 38 (1920).
[32] Bucherer and Zimmermann, *J. prakt. Chem.*, **103**, 277 (1921).
[33] Bucherer and Wahl, *J. prakt. Chem.*, **103**, 253 (1921).

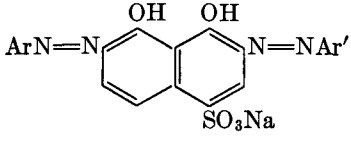
ring containing the free aromatically bound amino or hydroxyl group (directed coupling). For example, diazonium salts might couple with 1,8-dihydroxynaphthalene-4-sulfonic acid in either the 2- or the 7-position. Actually the first mole of diazo compound couples almost exclusively in the 2-position. When sodium bisulfite reacts with 1,8-dihydroxynaphthalene-4-sulfonic acid, the ring holding the sulfonic acid group is involved (activating influence of the 4-sulfonic acid). The reaction product couples with a diazo compound to form a substance of the following structure.



When this compound is warmed with alkali, it is reconverted to a dihydroxynaphthalenesulfonic acid.



Thus a directed coupling has been accomplished. This azo compound could be again coupled with a different diazonium salt with formation of a *bis*-azo dye.[12]



Suitably located amino groups can be diazotized more cleanly in addition compounds because the hydroxyl-containing rings are considerably less reactive toward chance excess of nitrous acid than those of the parent aminonaphthols.[12]. Azo dyes related to a naphthol can be made sufficiently water-soluble as addition compounds with bisulfite, even though they contain originally no sulfonic acid group, so that they can be applied to the fiber. The combined bisulfite can be removed when the dye is on the fiber.[12]

SELECTION OF EXPERIMENTAL CONDITIONS

Experimental conditions necessarily vary over a wide range. Reaction may take place at a temperature as low as 90°, or it may proceed

satisfactorily only in the neighborhood of 150°. If some of the reactants are only sparingly soluble, intimate mixing of the phases is essential to the success of the process. Aminations involving the use of ammonia and ammonium sulfite are ordinarily conducted in closed vessels at temperatures from 100–150°. Arylaminations will proceed slowly under reflux but take place more rapidly in an autoclave at about 150°. General directions for preparation of N-aryl-2-naphthylamine derivatives are given by Bucherer.[21] The requisite 2-naphthol- or naphthylamine-sulfonic acid is dissolved in a minimum of boiling water and then gradually mixed at 80–90° with a warm solution of sodium bisulfite. If a sulfonic acid should be salted out by the mixing, the salt is brought back into solution by warming on the water bath. The aromatic amine is next added either as such or as a mixture of the hydrochloride and an equivalent of aqueous sodium hydroxide.

The mixture is then heated under reflux until a titration with *p*-nitrobenzenediazonium chloride shows no more decrease in original naphthol and no increase in product. To carry out the test for complete reaction a small test portion of the mixture is made distinctly alkaline to phenolphthalein and freed of the excess of the amine used as aminating agent by steam distillation. The mixture is then made acid to Congo red with sulfuric acid and boiled until all the sulfur dioxide has been expelled. Diazonium salt solution is then added dropwise from a calibrated pipet until a drop of the mixture on filter paper shows no color in the run-out either with the diazonium salt solution or with Schaeffer's acid (2-hydroxynaphthalene-6-sulfonic acid). As soon as this point is reached, the precipitated dye is filtered from the main test portion and washed with a little saturated sodium chloride solution, the washings being added to the test portion. Sodium acetate is then added to the test solution, and the solution is again titrated with the same diazonium salt solution. The ratio of the volume of diazonium salt solution employed in the coupling in acid solution and the volume used in the coupling in sodium acetate solution gives the proportion between the newly formed amine and the remaining naphthol.

If specific directions for the preparation of the desired compound are not available, orientation experiments controlled as above, using relatively small quantities of material, are necessary in order to determine optimum conditions of time, temperature, and proportions of reactants.

The following examples illustrate both simple amination and arylamination.

EXPERIMENTAL PROCEDURES

Preparation of 2-Naphthylamine

One hundred forty-four grams (1 mole) of 2-naphthol is placed in a suitable pressure vessel together with a solution of ammonium sulfite prepared by passing sulfur dioxide into 400 cc. of cooled, concentrated ammonia (sp. gr. 0.90) until 100 g. of gas has been absorbed. An apparatus such as that employed for high-pressure hydrogenation will serve; it is essential that provision be made for shaking or stirring the reaction mixture. The autoclave is closed and heated at 150° with continual shaking or stirring for eight hours and is then allowed to cool *with shaking*.

The reaction mixture is removed from the autoclave, which is rinsed with about 500 cc. of water. The product is filtered on a Büchner funnel, and the crude material is dissolved in a boiling mixture of 150 cc. of concentrated hydrochloric acid and 400 cc. of water and then diluted with 1 l. of water. Ten grams of Norit is added, and the mixture is boiled for five minutes. After filtration (heated funnel) from any undissolved dinaphthylamine, the product is precipitated by pouring the hot solution with stirring into a solution of 120 g. of sodium hydroxide in 500 cc. of water. The resulting slurry, which should be alkaline to phenolphthalein, is cooled with stirring to 20°, filtered, and washed with 2 l. of cold water.

The product is dried to constant weight at 50°. It is a light tan powder and weighs 135–137 g. (94–96% of the amount theoretically possible). The product melts at 111–112°.

Preparation of 7-Methyl-1-naphthylamine [34, 35]

A mixture of 50 g. of 7-methyl-1-naphthol, 150 cc. of water, 75 cc. of freshly prepared ammonium sulfite solution (prepared from aqueous ammonia [sp.gr. 0.90] and sulfur dioxide), and 75 cc. of aqueous ammonia solution (sp.gr.0.90) is prepared in a 35-mm. Pyrex tube approximately 400 mm. in length. The tube is carefully sealed and heated in an electrically heated furnace constructed of iron pipe and attached to a shaking machine.

The furnace is heated to a temperature of 160–165° as recorded by a thermometer under the resistance wire, and the furnace and its contents are shaken at this temperature for thirty to thirty-five hours. The shaker is then stopped and the furnace allowed to cool to room temperature before it is opened.

[34] Ruzicka and Morgeli, *Helv. Chim. Acta*, **19**, 377 (1936).
[35] Howard, Ph.D. thesis, University of Maryland, p. 25 (1938).

The contents of the tube are extracted with three 250-cc. portions of ether; the extracts are combined and extracted with 10% hydrochloric acid until a small test portion of the last extract gives no precipitate of amine when made alkaline with 10% aqueous sodium hydroxide. The extracts are made alkaline with 10% aqueous sodium hydroxide, whereupon the amine precipitates and is filtered and dried in vacuum. The yield is 40–45 g. (80–90%). The combined yields of several such runs are distilled from a sausage flask under 3 mm. pressure. The bulk of the material boils at 139–140°/3 mm.; the product melts at 58–59°. If desired the amine can be crystallized from petroleum ether, from which it separates in the form of fine needles.

Preparation of 2-*p*-Tolylamino-5-hydroxynaphthalene-7-sulfonic Acid

A mixture of 216 g. (2 moles) of distilled *p*-toluidine, 215 g. (0.9 mole) of 2-amino-5-hydroxynaphthalene-7-sulfonic acid ("J acid"), 167 g. of sodium bisulfite, and 500 cc. of water, in a 3-l. three-necked round-bottomed flask provided with a reflux condenser and a mechanical stirrer, is heated under reflux with stirring for thirty hours. Sodium carbonate is then added until the mixture is alkaline and the excess *p*-toluidine is removed by steam distillation. The residual solution is cooled in a refrigerator until crystallization is complete, and the crystals are sucked dry on a Büchner funnel and washed with about 50 cc. of cold saturated sodium chloride solution. The product is dissolved in about 700 cc. of hot water to which enough hydrochloric acid is added to make the mixture acid to Congo red. The mixture is allowed to stand in a refrigerator until crystallization is complete; the crystalline acid is filtered and washed on the filter with a little ice-cold hydrochloric acid and then twice with small portions of cold water. The 2-*p*-tolylamino-5-hydroxy-7-sulfonic acid is dried at 100°; it weighs about 185 g. (65%).

Preparation of 2-(4′-Hydroxyphenylamino)-8-naphthol-6-sulfonic Acid and 2-(4′-Hydroxyphenylamino)-naphthalene-6-sulfonic Acid [21]

A mixture of 25 g. of "γ acid" (2-amino-8-hydroxynaphthalene-6-sulfonic acid), 50 cc. of water, 250 g. of sodium bisulfite solution (33%), 20 g. of *p*-aminophenol hydrochloride, and 16 g. of sodium hydroxide is boiled under reflux for twenty hours. When the mixture has cooled to room temperature, it is acidified to Congo paper and the crude product is filtered on a Büchner funnel. It is purified by solution in alkali and reprecipitation by acid. The pure product weighs about 13 g. (37.5%).

Substitution of 25 g. of "Schaeffer's acid" (2-hydroxynaphthalene-6-sulfonic acid) for "γ acid" above results in a yield of 20 g. (61%) of 2-(4′-hydroxyphenylamino)-naphthalene-6-sulfonic acid.

Compounds Prepared by the Bucherer Reaction

(Types of reaction are referred to by numbers as follows.)

I. ArOH → $ArNH_2$
II. $ArNH_2$ → ArOH
III. ArOH or $ArNH_2$ → ArNHR or $ArNR_2$
IV. ArOH or $ArNH_2$ → ArNHAr'
V. ArOH or $ArNH_2$ → $ArNHNH_2$
VI. ArOH or $ArNH_2$ → A carbazole

Formula	Name of Compound	Type	Yield, %	Reference *
$C_6H_6O_2$	Resorcinol	II	—	51
C_6H_7ON	*m*-Aminophenol	I	—	48
$C_6H_8N_2$	*m*-Phenylenediamine	I	80	3, 48
$C_6H_{10}N_4$	1,3-Phenylenedihydrazine	V	20, 75	22*a*, 26*c*
$C_7H_8O_2$	2,4-Dihydroxytoluene	II	—	51
$C_9H_8N_2$	6-Aminoquinoline	I	—	14
$C_9H_8N_2$	8-Aminoquinoline	I	Almost quant.	14
$C_9H_8O_3NS$	8-Aminoquinoline-5-sulfonic acid	I	—	14
$C_{10}H_9N$	2-Naphthylamine	I	67, 87–88	2, 3, 15, 16, 36, 37, 48
$C_{10}H_{10}N_2$	1,5-Diaminonaphthalene	I	—	48
$C_{10}H_{10}N_2$	2,7-Diaminonaphthalene	I	90	3
$C_{10}H_{10}N_2$	1-Naphthylhydrazine	V	—	26*d*
$C_{10}H_{12}N_4$	2,3-Naphthylenedihydrazine	V	57	26*d*
$C_{10}H_8O_4S$	1-Naphthol-4-sulfonic acid	II	Quant.	1, 2, 3, 12, 38, 39
$C_{10}H_8O_4S$	1-Naphthol-6-sulfonic acid	II	—	39
$C_{10}H_8O_4S$	1-Naphthol-7-sulfonic acid	II	—	2, 12
$C_{10}H_8O_4S$	1-Naphthol-8-sulfonic acid	II	—	12
$C_{10}H_8O_4S$	2-Naphthol-6-sulfonic acid	II	—	51, 53
$C_{10}H_8O_4S$	2-Naphthol-8-sulfonic acid	II	—	53
$C_{10}H_8O_5S$	1,5-Dihydroxynaphthalene-4-sulfonic acid	II	—	40
$C_{10}H_8O_5S$	1,5-Dihydroxynaphthalene-7-sulfonic acid	II	—	32, 40
$C_{10}H_8O_5S$	1,8-Dihydroxynaphthalene-4-sulfonic acid	II	—	2, 39
$C_{10}H_8O_5S$	1,8-Dihydroxynaphthalene-5-sulfonic acid	II	—	2
$C_{10}H_8O_5S$	2,5-Dihydroxynaphthalene-1-sulfonic acid	II	—	33
$C_{10}H_8O_5S$	2,5-Dihydroxynaphthalene-7-sulfonic acid	II	90	3, 51, 53
$C_{10}H_8O_7S_2$	1-Naphthol-4,6-disulfonic acid	II	—	12
$C_{10}H_8O_7S_2$	1-Naphthol-4,7-disulfonic acid	II	—	12
$C_{10}H_8O_7S_2$	1-Naphthol-4,8-disulfonic acid	II	Quant.	3, 12

* References 36 to 58 appear on p. 128.

COMPOUNDS PREPARED BY THE BUCHERER REACTION—*Continued*

Formula	Name of Compound	Type †	Yield, %	Reference *
$C_{10}H_8O_7S_2$	1-Naphthol-6,8-disulfonic acid	II	—	12
$C_{10}H_8O_8S_2$	1,8-Dihydroxynaphthalene-4,6-disulfonic acid	II	—	32
$C_{10}H_8O_{10}S_3$	1-Naphthol-4,6,8-trisulfonic acid	II	—	12
$C_{10}H_9ON$	1-Amino-2-naphthol	I	—	8*a*
$C_{10}H_9ON$	1-Amino-4-naphthol	I	35	8*a*
$C_{10}H_9ON$	1-Amino-5-naphthol	II	80	3
$C_{10}H_9ON$	1-Amino-8-naphthol	II	—	12
$C_{10}H_9ON$	2-Amino-7-naphthol	II	—	53
$C_{10}H_{10}ON_2$	7-Hydroxy-2-naphthylhydrazine	V	82	26*b*
$C_{10}H_9O_3NS$	1-Naphthylamine-4-sulfonic acid	I	—	48
$C_{10}H_9O_3NS$	2-Naphthylamine-1-sulfonic acid	I	—	12
$C_{10}H_9O_3NS$	2-Naphthylamine-6-sulfonic acid	I	—	12, 22
$C_{10}H_9O_3NS$	2-Naphthylamine-7-sulfonic acid	I	—	12
$C_{10}H_9O_3NS$	2-Naphthylamine-8-sulfonic acid	I	—	22
$C_{10}H_9O_4NS$	1-Amino-5-naphthol-2-sulfonic acid	II	—	40
$C_{10}H_9O_4NS$	1-Amino-5-naphthol-4-sulfonic acid	II, I	—	40
$C_{10}H_9O_4NS$	1-Amino-5-naphthol-7-sulfonic acid	I	—	48
$C_{10}H_9O_4NS$	1-Amino-5-naphthol-8-sulfonic acid	II	—	40
$C_{10}H_9O_4NS$	1-Amino-7-naphthol-4-sulfonic acid	I	—	23
$C_{10}H_9O_4NS$	1-Amino-8-naphthol-5-sulfonic acid	II	—	12, 39, 49
$C_{10}H_9O_4NS$	2-Amino-5-naphthol-7-sulfonic acid	I	—	3
$C_{10}H_9O_4NS$	2-Amino-8-naphthol-6-sulfonic acid	I	80, 59	3, 13
$C_{10}H_9O_6NS_2$	2-Naphthylamine-6,8-disulfonic acid	I	—	12
$C_{10}H_{10}O_3N_2S$	1,5-Diaminonaphthalene-4-sulfonic acid	I	—	40
$C_{10}H_{10}O_3N_2S$	2,5-Diaminonaphthalene-1-sulfonic acid	I	Quant.	33
$C_{11}H_{11}O_3NS$	1-Methylaminonaphthalene-4-sulfonic acid	III	—	12, 50
$C_{11}H_{11}O_3NS$	2-Methylaminonaphthalene-6-sulfonic acid	III	—	50
$C_{11}H_{11}O_3NS$	2-Amino-1-naphthylmethane sulfonic acid	I	—	52
$C_{11}H_{11}O_4NS$	1-Methylamino-7-naphthol-4-sulfonic acid	III	—	23
$C_{12}H_{14}N_2$	1-(β-Aminoethylamino)-naphthalene	III	—	17
$C_{12}H_{12}ON_2$	3-Hydroxy-4'-aminodiphenylamine	IV	—	41
$C_{12}H_{13}ON$	2-(β-Hydroxyethylamino)-naphthalene	III	—	56
$C_{12}H_{13}O_2N$	1-(β-Hydroxyethylamino)-5-naphthol	III	—	18
$C_{12}H_{19}ON$	2-Hexyl-5-aminophenol	I	70–80	42
$C_{12}H_{13}O_4NS$	2-(β-Hydroxyethylamino)-naphthalene-7-sulfonic acid	III	—	56
$C_{12}H_{13}O_4NS$	1-(β-Hydroxyethylamino)-naphthalene-4-sulfonic acid	III	—	56

* References 36 to 58 appear on p. 128.
† See p. 122.

COMPOUNDS PREPARED BY THE BUCHERER REACTION—*Continued*

Formula	Name of Compound	Type †	Yield, %	Reference *
$C_{12}H_{13}O_5NS$	2-(β-Hydroxyethylamino)-8-hydroxynaphthalene-6-sulfonic acid	III	—	56
$C_{12}H_{14}O_3N_2S$	1-(β-Aminoethylamino)-naphthalene-4-sulfonic acid	III	—	19
$C_{13}H_{14}O_2N_2$	2-(β-Aminoethylamino)-naphthalene-6-carboxylic acid	III	—	57
$C_{13}H_{15}ON$	2-(Methyl-β-hydroxyethylamino)-naphthalene-6-sulfonic acid	III	—	56
$C_{13}H_{15}O_5NS$	2-(β-Hydroxyethylamino)-8-methoxynaphthalene-6-sulfonic acid	III	—	56
$C_{14}H_{18}N_2$	2-(ω-Aminobutylamino)-naphthalene	III	—	17
$C_{14}H_{19}N_3$	2-(ω-Aminoethylaminoethylamino)-naphthalene	III	—	17
$C_{14}H_{12}O_2N_2$	1,5-Bis(β-hydroxyethylamino)-naphthalene	III	—	18
$C_{14}H_{15}ON$	1-(4'-Hydroxyphenylamino)-naphthalene	IV	—	43
$C_{15}H_{18}O_2N_2$	2-(ω-Aminobutylamino)-naphthalene-6-carboxylic acid	III	—	57
$C_{16}H_{11}N$	Benzo-(1,2)-carbazole	VI	75	29, 30
$C_{16}H_{11}N$	Benzo-(3,4)-carbazole	VI	46	28, 29, 30
$C_{16}H_{11}N$	Benzo-(5,6)-carbazole	VI	—	32
$C_{16}H_{13}N$	2-Phenylaminonaphthalene	IV	65	21, 24, 44
$C_{16}H_{14}N_2$	2-(4'-Aminophenylamino)-naphthalene	IV	64	13
$C_{16}H_{11}ON$	1-Hydroxybenzo-(3,4)-carbazole	VI	—	28
$C_{16}H_{11}ON$	4'-Hydroxybenzo-(3,4,1',2')-carbazole	VI	60	28
$C_{16}H_{11}ON$	1'-Hydroxybenzo-(3,4,2',3')-carbazole	VI	—	33
$C_{16}H_{13}ON$	1-Phenylamino-4-naphthol	IV	—	43
$C_{16}H_{13}ON$	1-Phenylamino-5-naphthol	IV	96	22*a*, 43
$C_{16}H_{13}ON$	2-Phenylamino-5-naphthol	IV	70	22*a*, 33
$C_{16}H_{13}ON$	1-(4'-Hydroxyphenylamino)-naphthalene	IV	—	24, 45
$C_{16}H_{13}ON$	2-(4'-Hydroxyphenylamino)-naphthalene	IV	74	21
$C_{16}H_{13}O_2N$	2-(4'-Hydroxyphenylamino)-7-naphthol	IV	—	24
$C_{16}H_{11}O_3NS$	Benzo-(1,2)-carbazole-3-sulfonic acid	VI	—	27
$C_{16}H_{11}O_3NS$	Benzo-(1,2,1',2')-carbazole-4'-sulfonic acid	VI	—	30
$C_{16}H_{11}O_3NS$	Benzo-(1,2,1',2')-carbazole-5'-sulfonic acid	VI	—	32
$C_{16}H_{11}O_3NS$	Benzo-(3,4,1',2')-carbazole-5'-sulfonic acid	VI	—	30
$C_{16}H_{11}O_4NS$	3'-Hydroxybenzo-(1,2,1',2')-carbazole-5'-sulfonic acid	VI	—	32
$C_{16}H_{11}O_4NS$	1'-Hydroxybenzo-(3,4,2',3')-carbazole-5'-sulfonic acid	VI	—	32

* References 36 to 58 appear on p. 128.
† See p. 122.

COMPOUNDS PREPARED BY THE BUCHERER REACTION—*Continued*

Formula	Name of Compound	Type †	Yield, %	Reference *
$C_{16}H_{11}O_4NS$	5'-Hydroxybenzo-(3,4,3',4')-carbazole-1'-sulfonic acid	VI	—	32
$C_{16}H_{11}O_6NS_2$	Benzo-(3,4,1',2')-carbazole-1,5'-disulfonic acid	VI	—	30
$C_{16}H_{13}O_3NS$	2-Phenylaminonaphthalene-6-sulfonic acid	IV	—	11,21,22, 58
$C_{16}H_{13}O_3NS$	2-Phenylaminonaphthalene-8-sulfonic acid	IV	34	21, 22
$C_{16}H_{13}O_3NS$	2-Phenylaminonaphthalene-3'-sulfonic acid	IV	—	13
$C_{16}H_{13}O_4NS$	2-(4'-Hydroxyphenylamino)-naphthalene-6-sulfonic acid	IV	—	21
$C_{16}H_{13}O_4NS$	2-(4'-Hydroxyphenylamino)-naphthalene-8-sulfonic acid	IV	98	21
$C_{16}H_{13}O_4NS$	2-Phenylamino-5-naphthol-7-sulfonic acid	IV	—	21
$C_{16}H_{13}O_4NS$	2-Phenylamino-8-naphthol-6-sulfonic acid	IV	86	21
$C_{16}H_{13}O_5NS$	2-(4'-Hydroxyphenylamino)-8-naphthol-6-sulfonic acid	IV	—	21
$C_{16}H_{13}O_6NS_2$	2-Phenylaminonaphthalene-6,4'-disulfonic acid	IV	83	21
$C_{16}H_{13}O_6NS_2$	2-Phenylaminonaphthalene-6,3'-disulfonic acid	IV	89	21
$C_{16}H_{13}O_6NS_2$	2-Phenylaminonaphthalene-5,7-disulfonic acid	IV	—	2
$C_{16}H_{13}O_6NS_2$	2-Phenylaminonaphthalene-6,8-disulfonic acid	IV	—	2
$C_{16}H_{13}O_7NS_2$	2-(4'-Hydroxyphenylamino)-naphthalene-6,8-disulfonic acid	IV	84	13
$C_{16}H_{14}O_3N_2S$	1-(4'-Aminophenylamino)-naphthalene-4-sulfonic acid	IV	—	41
$C_{16}H_{14}O_3N_2S$	2-(4'-Aminophenylamino)-naphthalene-6-sulfonic acid	IV	72	21
$C_{16}H_{14}O_6N_2S_2$	2-(4'-Aminophenylamino)-naphthalene-6,8-disulfonic acid	IV	82	13
$C_{17}H_{13}N$	6-Methylbenzo-(3,4)-carbazole	VI	—	29
$C_{17}H_{15}N$	2-*p*-Tolylaminonaphthalene	IV	82	13
$C_{17}H_{15}N$	2-(3'-Methylphenylamino)-naphthalene	IV	34	13
$C_{17}H_{15}N$	2-(2'-Methylphenylamino)-naphthalene	IV	28	13
$C_{17}H_{16}N_2$	2-(3'-Amino-4'-methylphenylamino)-naphthalene	IV	55	13

* References 36 to 58 appear on p. 128.
† See p. 122.

COMPOUNDS PREPARED BY THE BUCHERER REACTION—*Continued*

Formula	Name of Compound	Type †	Yield, %	Reference *
$C_{17}H_{13}ON$	4'-Methoxybenzo-(3,4,1',2')-carbazole	VI	—	28
$C_{17}H_{13}O_2N$	2-(2'-Carboxyphenylamino)-naphthalene	IV	17	13
$C_{17}H_{13}O_3N$	2-(3'-Carboxy-4'-hydroxyphenylamino)-naphthalene	IV	—	13
$C_{17}H_{15}ON$	1-(4'-Methoxyphenylamino)-naphthalene	IV	—	24, 45
$C_{17}H_{15}ON$	2-(4'-Methoxyphenylamino)-naphthalene	IV	74	13
$C_{17}H_{15}ON$	2-(2'-Methoxyphenylamino)-naphthalene	IV	27	13
$C_{17}H_{13}O_6NS$	1-(4'-Hydroxy-3'-carboxyphenylamino)-naphthalene-4-sulfonic acid	IV	—	47
$C_{17}H_{13}O_6NS$	2-(4'-Hydroxy-3'-carboxyphenylamino)-naphthalene-7-sulfonic acid	IV	—	46, 47
$C_{17}H_{13}O_6NS$	2-(4'-Hydroxy-3'-carboxyphenylamino)-naphthalene-6-sulfonic acid	IV	—	47
$C_{17}H_{13}O_6NS$	2-(4'-Hydroxy-3'-carboxyphenylamino)-naphthalene-8-sulfonic acid	IV	—	47
$C_{17}H_{13}O_7NS$	2-(4'-Hydroxy-3'-carboxyphenylamino)-8-naphthol-6-sulfonic acid	IV	—	47
$C_{17}H_{13}O_9NS_2$	1-(4'-Hydroxy-3'-carboxyphenylamino)-naphthalene-3,8-disulfonic acid	IV	—	47
$C_{17}H_{13}O_9NS_2$	1-(4'-Hydroxy-3'-carboxyphenylamino)-naphthalene-6,8-disulfonic acid	IV	—	47
$C_{17}H_{15}O_3NS$	2-*o*-Tolylaminonaphthalene-6-sulfonic acid	IV	51	21
$C_{17}H_{15}O_3NS$	2-*p*-Tolylaminonaphthalene-6-sulfonic acid	IV	35	21
$C_{17}H_{15}O_3NS$	2-*p*-Tolylaminonaphthalene-8-sulfonic acid	IV	Pract. quant., 76	11, 21
$C_{17}H_{15}O_4NS$	2-*p*-Tolylamino-8-naphthol-6-sulfonic acid	IV	—	13
$C_{17}H_{15}O_6NS_2$	2-*p*-Tolylaminonaphthalene-6,8-disulfonic acid	IV	—	21
$C_{18}H_{16}N_2$	N-N-Diphenyl-*m*-phenylenediamine	IV	—	43
$C_{18}H_{17}N$	2-(2',4'-Dimethylphenylamino)-naphthalene	IV	—	13
$C_{18}H_{13}O_5N$	8-Phenylamino-2-naphthol-3,2'-dicarboxylic acid	IV	—	43
$C_{18}H_{15}O_4N$	8-(4'-Methoxyphenylamino)-2-naphthol-3-carboxylic acid	IV	—	43

* References 36 to 58 appear on p. 128.
† See p. 122.

COMPOUNDS PREPARED BY THE BUCHERER REACTION—*Continued*

Formula	Name of Compound	Type †	Yield, %	Reference *
$C_{18}H_{17}ON$	2-(4'-Ethoxyphenylamino)-naphthalene	IV	61	13
$C_{18}H_{17}O_3NS$	2-(2',4'-Dimethylphenylamino)-naphthalene-6-sulfonic acid	IV	58	21
$C_{18}H_{17}O_4NS$	2-*p*-Ethoxyphenylaminonaphthalene-6-sulfonic acid	IV	69	21
$C_{18}H_{17}O_4NS$	2-*p*-Ethoxyphenylaminonaphthalene-8-sulfonic acid	IV	50	21
$C_{18}H_{17}O_5NS$	2-*p*-Ethoxyphenylamino-8-naphthol-6-sulfonic acid	IV	86	21
$C_{20}H_{13}N$	Dibenzo-(3,4,5,6)-carbazole	VI	—	27
$C_{20}H_{13}N$	Dibenzo-(1,2,7,8)-carbazole	VI	—	27
$C_{20}H_{15}ON$	1-(2'-Naphthylamino)-7-naphthol	IV	—	43
$C_{20}H_{15}ON$	8-(2'-Naphthylamino)-2-naphthol	IV	84	22*a*
$C_{20}H_{15}ON$	1-(4'-Hydroxyphenylamino)-anthracene	IV	82	22*a*
$C_{20}H_{15}O_6NS_2$	2,2'-Dinaphthylamine-6,6'-disulfonic acid	IV	—	11
$C_{22}H_{14}N_2$	Carbazolo-(3,4,3',4')-carbazole	VI	—	28
$C_{22}H_{18}O_2N_2$	2,7-Di(4'-hydroxyphenylamino)-naphthalene	IV	—	45
$C_{22}H_{18}O_4N_2S$	N-(5''-Hydroxy-7''-sulfo-2''-naphthyl)-benzidine	IV	—	54, 55
$C_{22}H_{18}O_4N_2S$	N-(8''-Hydroxy-6''-sulfo-2''-naphthyl)-benzidine	IV	—	54
$C_{22}H_{18}O_7N_2S_2$	N-(5''-Hydroxy-7''-sulfo-2''-naphthyl)-benzidine-3'-sulfonic acid	IV	—	54, 55
$C_{22}H_{18}O_7N_2S_2$	N-(8''-Hydroxy-6''-sulfo-2''-naphthyl)-benzidine-3'-sulfonic acid	IV	—	54
$C_{24}H_{22}O_4N_2S$	N-(5''-Hydroxy-7''-sulfo-2''-naphthyl)-tolidine	IV	—	55
$C_{24}H_{22}O_6N_2S$	N-(5''Hydroxy-7''-sulfo-2''-naphthyl)-dianisidine	IV	—	55
$C_{24}H_{22}O_7N_2S_2$	N-(5''-Hydroxy-7''-sulfo-2''-naphthyl)-tolidine-3'-sulfonic acid	IV	—	55
$C_{28}H_{23}O_3N_3S$	N-(2-Naphthyl-6-sulfo)-*p*-rosaniline	IV	—	21
$C_{32}H_{24}O_2N_2$	N,N'-Bis(5''-hydroxy-1''-naphthyl)-benzidine	IV	—	43
$C_{34}H_{21}O_7NS_2$	Dibenzoate of dinaphthocarbazole from "J acid"	VI	—	31

* References 36 to 58 appear on p. 128.
† See p. 122.

[36] Levi, *Giorn. chim. ind. applicata*, **3**, 97 (1921).
[37] Brit. pat., 184,284 [*C. A.*, **17**, 110 (1923)].
[38] U. S. pat., 1,880,701 [*C. A.*, **27**, 515 (1933)].
[39] Ger. pat., 109,102 [*Frdl.* **5**, 164 (1897–1900)].
[40] Bucherer and Uhlmann, *J. prakt. Chem.*, [2] **80**, 201 (1909).
[41] Ger. pat., 451,980 [*C. A.*, **22**, 4130 (1928)].
[42] Hartung, Minnick, and Koehler, *J. Am. Chem. Soc.*, **63**, 507 (1941).
[43] Ger. pat., 643,221 [*C. A.*, **31**, 4342 (1937)]; Brit. pat., 451,348 [*C. A.*, **31**, 113 (1937)].
[44] Fr. pat., 750,243 [*C. A.*, **28**, 779 (1934)].
[45] Fr. pat., 807,765 [*C. A.*, **31**, 5813 (1937)]; *cf.* Fr. pat., 645,150, and Ger. pat., 642,549.
[46] Fr. pat., 789,589 [*C. A.*, **30**, 2019 (1936)].
[47] Brit. pat., 437,798 [*C. A.*, **30**, 2203 (1936)].
[48] Ger. pat., 117,471 [*Frdl.*, **6**, 190 (1900–02)].
[49] Ger. pat., 120,016 [*Chem. Zentr.*, I, 1074 (1901)].
[50] Ger. pat., 121,683 [*Frdl.*, **6**, 192 (1900–02)].
[51] Ger. pat., 126,136 [*Frdl.*, **6**, 189 (1900–02)].
[52] Ger. pat., 132,431 [*Frdl.*, **6**, 193 (1900–02)].
[53] Ger. pat., 134,401 [*Frdl.*, **6**, 186 (1900–02)].
[54] Ger. pat., 254,510 [*C. A.*, **7**, 1617 (1913)].
[55] Brit. pat., 11,427 [*C. A.*, **6**, 3023 (1912)].
[56] Ger. pat. 442,310 [*Frdl.*, **15**, 511 (1927–29)].
[57] U. S. pat. 1,727,506 [*cf.* Ger. pat., 468,811 (*C. A.*, **23**, 2723 [1929]); *Frdl.*, **16**, 510 (1927–29)].
[58] Ger. pat., 122,570 [*Frdl.*, **6**, 194 (1900–02)].

General Reference, Bucherer Reaction

BUCHERER, "Lehrbuch der Farbenchemie," 2nd ed., p. 200, Otto Spamer, Leipzig, 1914.

CHAPTER 6

THE ELBS REACTION

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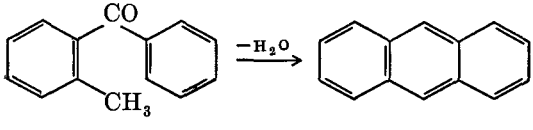
CONTENTS

	PAGE
INTRODUCTION	129
EXAMPLES OF THE REACTION	131
Synthesis of Anthracene Homologs	131
1,2,5,6-Dibenzanthracene Series	134
1,2-Benzanthracene Series	139
Synthesis of Cholanthrenes	142
Pyrolysis of Diketones	147
Summary of Side Reactions	147
EXPERIMENTAL PROCEDURES	149
Preparation of the Required Ketones	149
Selection of Conditions for the Pyrolysis	150
Examples: 1,2,5,6-Dibenzanthracene	151
1,2-Benzanthracene	152
Methylcholanthrene	153

INTRODUCTION

Diaryl ketones having a methyl or methylene substituent adjacent to the carbonyl group often suffer cyclodehydration when submitted to pyrolysis and afford a certain amount of the corresponding anthracene derivative. Although an early instance of the production of a hydro-



carbon by this process was reported briefly by Behr and van Dorp,[1] the

[1] Behr and van Dorp, *Ber.*, **6**, 753 (1873); **7**, 16 (1874).

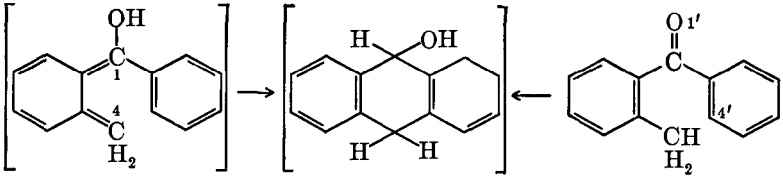
reaction is generally accredited to Elbs,[2-8] for this investigator was the first to explore the generality and synthetic uses of the reaction. Elbs and his co-workers studied the pyrolysis of various polyalkylbenzophenones and, finding that some of these substances failed to condense while others afforded anthracene homologs in no better than 20–25% yield (Table I), were inclined to discount the value of the method, particularly where the hydrocarbon in question can be obtained by the phthalic anhydride synthesis of the anthraquinone, followed by reduction. From the accumulated data now available, it has become apparent that, although the Elbs condensation in general is subject to many limitations and shortcomings, there are instances in which the reaction proceeds smoothly and affords the best known means of obtaining important hydrocarbons. The reaction also has found significant use in the synthetic preparation of hydrocarbons not available by other known methods. A low yield in the pyrolysis is often offset by the ready availability of the required ketone.

The reaction usually is carried out by heating the ketone without catalyst or solvent at the reflux temperature, or at a temperature in the range 400–450°, until water is no longer evolved. At the high temperature required to effect ring closure considerable carbonization may occur and much material may be lost as the result of cleavage of the ketone by the water liberated, elimination or degradation of alkyl substituents, and molecular rearrangements. The main hydrocarbon reaction product may not be that normally expected on the basis of the structure of the starting material, and the product is frequently, if not always, accompanied by related hydrocarbons. With the exception of a few particularly favorable applications of the reaction, a product of the Elbs condensation usually requires extensive purification, and the probable structure as inferred from analogy should be investigated by independent methods. The total weight of the crude hydrocarbon fraction obtained from the pyrolysis mixture by distillation and initial crystallization usually does not provide a reliable index of the true yield unless the melting point can be shown to be reasonably close to that of a single, fully purified product.

The mechanism of the condensation is not known. Cook [9] suggested

[2] Elbs and Larsen, *Ber.*, **17**, 2847 (1884).
[3] Claus and Elbs, *Ber.*, **18**, 1797 (1885).
[4] Elbs and Olberg, *Ber.*, **19**, 408 (1886).
[5] Elbs, *J. prakt. Chem.*, **33**, 180 (1886).
[6] Elbs, *J. prakt. Chem.*, **35**, 465 (1887).
[7] Elbs, *J. prakt. Chem.*, **41**, 1 (1890).
[8] Elbs, *J. prakt. Chem.*, **41**, 121 (1890).
[9] Cook, *J. Chem. Soc.*, 487 (1931).

that the ketone may undergo tautomerism to an enolic form having a diene system to which intramolecular addition of the attached aryl group may occur, giving the dihydroanthranol. Fieser and Dietz [10]



suggested that the same intermediate, which at the pyrolysis temperature certainly would undergo rapid dehydration to the hydrocarbon, may result alternately from a forced 1,4-addition of the methyl substituent to the conjugated system comprising the carbonyl group and the aryl nucleus. There is no evidence bearing on either hypothesis, and a suggested analogy [11] to the formation of anthracene derivatives by the cyclization of *o*-benzylbenzaldehyde [11] and *o*-benzyl diaryl ketones [12] does not appear applicable because these cyclizations proceed under the influence of an acid catalyst and at a low temperature and hence under conditions wholly unlike those required for the non-catalytic high-temperature pyrolysis.

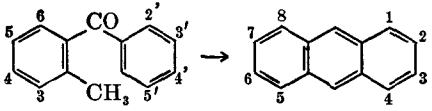
EXAMPLES OF THE REACTION

Synthesis of Anthracene Homologs. Observations concerning the pyrolysis of mono-, di-, tri-, tetra-, and penta-methyl derivatives of benzophenone are included in Table I. In most instances the material pyrolyzed was the total distilled product of the condensation of a hydrocarbon with an acid chloride or with phosgene, and the published data on the pyrolysis temperatures and the yields are not very specific. Seer and co-workers [13, 14] followed Elbs' practice of refluxing the ketone gently for a prolonged period but obtained only very low yields. Morgan and Coulson [15, 16] found it expedient to shorten the time of reaction and to remove the hydrocarbon formed from time to time in order to protect it from destruction. Although this technique apparently represented a marked improvement, the yields reported refer merely to materials of unspecified purity and consequently are ambiguous. The data

[10] Fieser and Dietz, *Ber.*, **62**, 1827 (1929).
[11] E. Bergmann, *J. Org. Chem.*, **4**, 1 (1939).
[12] Bradsher, *J. Am. Chem. Soc.*, **62**, 486, 1077 (1940).
[13] Seer and Stanka, *Monatsh.*, **32**, 143 (1911).
[14] Seer and Ehrenzweig, *Monatsh.*, **33**, 33 (1912).
[15] Morgan and Coulson, *J. Chem. Soc.*, 2203 (1929).
[16] Morgan and Coulson, *J. Chem. Soc.*, 2551 (1929).

TABLE I

ANTHRACENE DERIVATIVES



Benzophenone Derivative	Preparation	Pyrolysis	Anthracene Derivative	Yield, %	Reference
2-Methyl		With Zn	Anthracene	?	1
2,4-Dimethyl	ArH + C_6H_5COCl	Refl. 6–10 hr.	No condensation	0	7
2,5-Dimethyl	ArH + C_6H_5COCl	Refl. 12 hr. (b.p. 303°)	2-Methyl	10–20	2, 7
2-Methyl-5-isopropyl	ArH + C_6H_5COCl	Refl. 8 days (b.p. 345°)	Trace of anthracene (loss of *i*-Pr)	0	3, 6
2,4,5-Trimethyl	ArH + C_6H_5COCl	Refl. several days (b.p. 329°)	No condensation	0	6
2,4,6-Trimethyl	ArH + C_6H_5COCl	Refl. several days (b.p. 319°)	No condensation	0	6
2,4,3'-Trimethyl	ArH + Ar'COCl	Refl. 5 days (b.p. 320°)	2,6-Dimethyl	?	13
		Brief heating, removal of product		"Good"	15
2,4,4'-Trimethyl	ArH + Ar'COCl (82%)	350–360°, 6 hr.	2,7-Dimethyl	(59 crude)	15
2,5,4'-Trimethyl	ArH + Ar'COCl	350–360°, 6 hr.	2,6-Dimethyl	(70 crude)	15
2,4,5,4'-Tetramethyl	ArH + Ar'COCl	Refl. 8 hr.	2,3,6-Trimethyl + trimethylanthrone	?	16

2,4,2',4'-Tetramethyl	$2C_6H_4(CH_3)_2 + COCl_2$ (70–80%)	Refl.	1,3,6-Trimethyl	20–25	8
2,5,2',5'-Tetramethyl	$2C_6H_4(CH_3)_2 + COCl_2$ (40%)	Refl. 6 hr. (b.p. 327°)	1,4,6-Trimethyl	20–25	4, 6
2,4,6,3',5'-Pentamethyl	ArH + Ar'COCl	Refl. 6 days	1,3,5,7-Tetramethyl (as quinone)	3	14
2-Methyl-2'-phenyl	ArCOCl + Ar'MgI (55%)	Refl. 7.5 hr.	1-Phenyl	18	17

RELATED EXAMPLES

Ketone	Preparation	Pyrolysis	Product	Yield, %	Reference
Di-(4-hydrindyl) ketone	ArLi + Ar'CN (51%)	415–420°, 30 min.	1,2-Cyclopenteno-5,10-aceanthrene	21	18
4-(2',3'-Dimethylbenzoyl)-hydrindene	ArCN + Ar'MgBr (56%)	420–430°, 2 hr.	1,2-Dimethyl-5,10-aceanthrene and 1-methyl-5,6-cyclopentenoanthracene	1.3 and 3	18

[17] Cook, *J. Chem. Soc.*, 1087 (1930).
[18] Fieser and Hershberg, *J. Am. Chem. Soc.*, **59**, 394 (1937).

for the series of homologs hardly warrant any general conclusion except that some *o*-methylbenzophenones afford anthracene derivatives in low yields while others, under the conditions investigated, gave only negative results. Although 2,4-dimethylbenzophenone apparently failed to undergo cyclization under conditions adequate for the formation of a certain amount of 2-methylanthracene from the isomeric 2,5-dimethylbenzophenone, a corresponding difference was not noted with the 2,4,4′- and 2,5,4′-trimethyl compounds.

Table I includes an instance of the elimination of an isopropyl group in the course of the pyrolysis and an example of the formation of an anthrone derivative along with the corresponding hydrocarbon. The anthrone may possibly arise by the dehydrogenation of the postulated intermediate dihydroanthranol. The last entry of the table shows that cyclization can occur in both of two possible directions, the one involving an *ortho* methyl group and the other an *ortho* methylene substituent.

1,2,5,6-Dibenzanthracene Series (Table II). The Elbs reaction affords by far the most rapid and economical method known for the synthesis of 1,2,5,6-dibenzanthracene (III), a hydrocarbon widely used for the experimental production of cancer in animals. A number of points of general interest have been discovered in the extensive studies of this example of the reaction. One is the occurrence of a rearrangement in the pyrolysis of α,α'-dinaphthyl ketones. Although 2′-methyl-2,1′-dinaphthyl ketone (I) and 2-methyl-1,1′-dinaphthyl ketone (II) would be expected to yield isomeric hydrocarbons,[19, 10] Cook [24] showed that they both afford III as the chief product. Cook suggested that the ketone

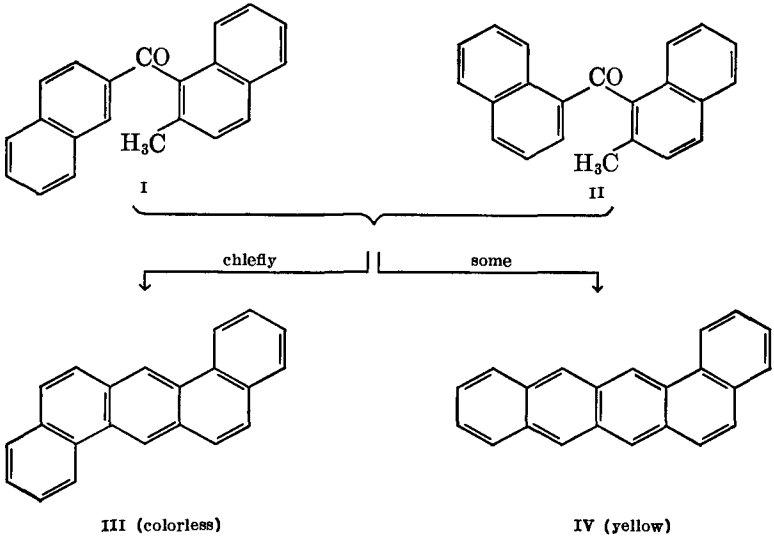
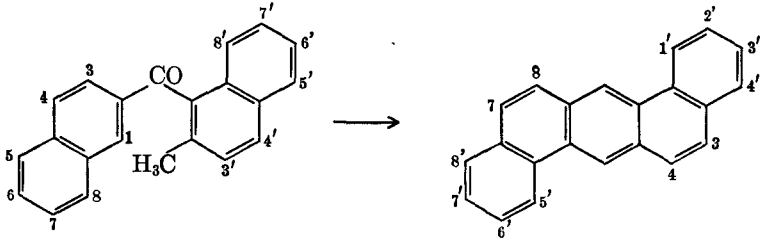


TABLE II

1,2,5,6-DIBENZANTHRACENE DERIVATIVES

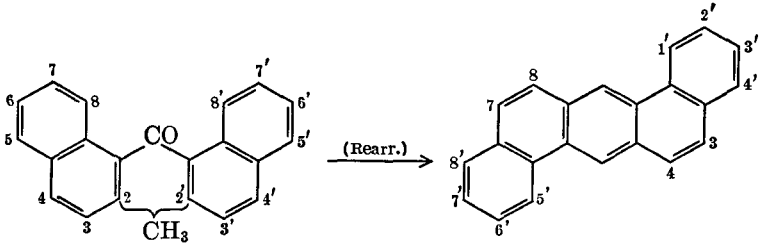


2,1'-Dinaphthyl Ketone Derivative	Preparation	Pyrolysis	1,2,5,6-Dibenzanthracene Derivative	Yield, %	Reference
2'-Methyl	ArCOCl + Ar'H	Refl. 20 min.	1,2,5,6-Dibenzanthracene	About 20	19
	ArCOCl + Ar'H	Refl. 30 min.		32	10
	ArCN + Ar'MgBr (63%)	420° with Zn, $1\frac{3}{4}$ hr.		50	20
2'-Methyl-5,6,7,8-tetrahydro	ArH + Ar'COCl (70%)	430–450°, 2 hr.	1,2,5,6-Dibenzanthracene (dehydrogenation)	?	21
2'-Ethyl	ArCOCl + Ar'H (91% crude)	425–430°, $1\frac{1}{2}$ hr.	1,2,5,6-Dibenzanthracene (loss of CH_3)	23	22
2',3'-Dimethyl	ArCOCl + Ar'H (31%)	445°, 2 hr.	4-Methyl	?	23
2',6'-Dimethyl	ArCOCl + Ar'H (75%)	Refl. 2 hr.	3'-Methyl	35	10
2',7'-Dimethyl	ArCOCl + Ar'H (40%)	Refl. 440–450°, about 1 hr.	2'-Methyl	?	24

NOTE. References 19–28 appear on p. 137.

TABLE II—*Continued*

SYNTHESIS OF OTHER POLYNUCLEAR HYDROCARBONS FROM MONOKETONES



1,1'-Dinaphthyl Ketone Derivative	Preparation	Pyrolysis	1,2,5,6-Dibenzanthracene Derivative	Yield, %	Reference
2-Methyl	ArCOCl + Ar'H	Refl. 20 min. Refl. 5 hr.	1,2,5,6-Dibenzanthracene	About 20 32	19, 9 10, 9
2,4'-Dimethyl	ArCOCl + Ar'H	440–450°, about 1 hr.	1,2,5,6-Dibenzanthracene (loss of CH_3)	?	24
2,6-Dimethyl	ArCOCl + Ar'H (50%)	440–450°, about 1 hr.	3'-Methyl	?	24
2,7-Dimethyl	ArCOCl + Ar'H (70%)	440–450°, about 1 hr.	2'-Methyl	?	24
2',3'-Dimethyl	ArCOCl + Ar'H	445°, 2 hr.	4-Methyl	?	23
2,4',7'-Trimethyl	ArCOCl + Ar'H	440–450°, about 1 hr.	2'-Methyl (loss of CH_3)	?	24
4,2',6'-Trimethyl	ArCOCl + Ar'H	440–450°, about 1 hr.	3'-Methyl (loss of CH_3)	?	24
4,2',7'-Trimethyl	ArCOCl + Ar'H (45%)	440–450°, about 1 hr.	2'-Methyl (loss of CH_3)	?	24
2'-Methyl-4',5'-dimethylene	ArCOCl + Ar'H (65%)	430–450°, $\frac{1}{2}$–2 hr.	Phenanthraacenaphthene	6	21

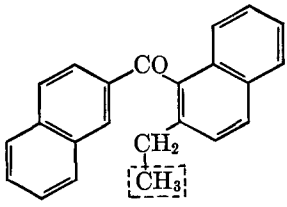
Ketone mixture	o-$C_6H_4(CH_3)COCl$ + Phenanthrene	Refl.	1,2,3,4-Dibenzanthracene, 2,3-(Naphtho-2′,3′)-phenanthrene, 1,2-(Naphtho-2′,3′)-phenanthrene	?	19, 25
9-o-Toluylphenanthrene	C_7H_7MgX + $C_{14}H_9CN$(83%)	400–420° with Zn, 3 hr.	1,2,3,4-Dibenzanthracene	56	25a
9-(2,4-Dimethylbenzoyl)-phenanthrene	C_8H_9MgX + $C_{14}H_9CN$(75%)	420°, $2\frac{1}{2}$ hr.	6-Methyl-1,2,3,4-dibenzanthracene	12	25a
2-Methyl-3-(1′-naphthoyl)-tetralin	$C_{10}H_7COCl$ + Tetralin	Refl. with Cu, 20 min.	2,3-(Naphtho-2′,3′)-phenanthrene	?	25
2-Methyl-3-(2′-naphthoyl)-tetralin	$C_{10}H_7COCl$ + Tetralin	Refl. with Cu, 20 min.	2,3-(Naphtho-2′,3′)-phenanthrene	?	25
3-o-Toluylphenanthrene	C_7H_7MgX + $C_{14}H_9CN$(79%)	400–420° with Zn, 2 hr.	2,3-(Naphtho-2′,3′)-phenanthrene	22	25a
2-Methyl-1-(9′-phenanthroyl)-naphthalene	$C_{14}H_9COCl$ + $C_{10}H_7CH_3$	Refl. 2 hr.	1,2,3,4,5,6-Tribenzanthracene	24	10
	$C_{11}H_9MgX$ + $C_{14}H_9CN$(65%)	410° with Zn, $2\frac{3}{4}$ hr.		44	25a
2-Methyl-1-(3′-phenanthroyl)-naphthalene	$C_{14}H_9COCl$ + $C_{10}H_6(CH_3)MgBr$	430–440°, $\frac{1}{2}$–2 hr.	2′,3′-Phenanthra-2,3-phenanthrene	15	21
2-Methyl-1-(1′-anthroyl)-naphthalene	α-$C_{14}H_9COCl$ + $C_{10}H_6(CH_3)MgBr$	430–440°, $\frac{1}{2}$–2 hr.	2′,3′-Phenanthra-1,2-anthracene	?	21
2-Methyl-1-(2′-anthroyl)-naphthalene	β-$C_{14}H_9COCl$ + $C_{10}H_7CH_3$	Refl. 20 min.	2′,3′-Phenanthra-1,2 anthracene	?	26
2-Methyl-1-(2′-fluorenyl)-naphthalene	$C_{10}H_6(CH_3)COCl$ + $C_{13}H_{10}$ (85%)	430–450°, $\frac{1}{2}$–2 hr.	2,3-Phenanthra-3′,2′-(or 1′,2′)-fluorene	15	21
3-o-Toluylpyrene	o-$CH_3C_6H_4COCl$ + $C_{16}H_{10}$	420–440°, 2 hr.	2′,3′-Naphtha-1,2-pyrene	7	27, 28

[19] Clar, *Ber.*, **62**, 350, 1378 (1929).
[20] Bachmann, *J. Org. Chem.*, **1**, 347 (1937).
[21] Cook, *J. Chem. Soc.*, 499 (1931).
[22] Fieser and Newman, *J. Am. Chem. Soc.*, **58**, 2376 (1936).
[23] Cook, *J. Chem. Soc.*, 1592 (1933).
[24] Cook, *J. Chem. Soc.*, 489 (1931).
[25] Clar, *Ber.*, **62**, 1574 (1929).
[25a] Bachmann and Pence, *J. Am. Chem. Soc.*, **59**, 2339 (1937).
[26] Winterstein and Schön, *Z. physiol. Chem.*, **230**, 146 (1934).
[27] Cook and Hewett, *J. Chem. Soc.*, 398 (1933).
[28] Clar, *Ber.*, **69**, 1671 (1936).

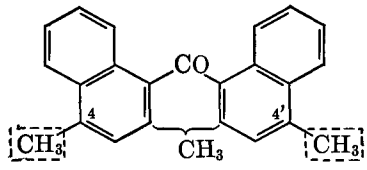
(II) which reacts abnormally may undergo rearrangement to the isomer I at the pyrolysis temperature, and indeed it has been shown [10] that the abnormal pyrolysis of II proceeds far more slowly than the normal condensation of I. The several examples listed in the second section of Table II demonstrate the generality of the rearrangement.

The hydrocarbon prepared from either ketone retains a bright yellow color not altered by distillation or repeated crystallization,[19, 10] but Cook [9] found that pure 1,2,5,6-dibenzanthracene is colorless and that the color is due to the presence of a persistent chrysogen which Winterstein and Schön [26] later identified as the isomeric 1,2,6,7-dibenzanthracene (IV). The chrysogen, which evidently arises from the ketone I by condensation of the methyl group into the β-position of the second naphthyl nucleus, constitutes about 10% of the hydrocarbon mixture. Various methods have been reported for the removal of the yellow contaminant based upon its greater affinity for chemical reagents or adsorbents. These include (*a*) preferential sulfonation of the mixture in xylene solution [9, 24] (extensive losses), (*b*) chromatographic adsorption [26] (10–20% recovery), (*c*) treatment with maleic anhydride in boiling xylene,[29] and treatment with lead tetraacetate in acetic acid solution [30] (70–83% recovery).

In this series there are several instances of the loss of methyl groups in the course of the Elbs reaction. The pyrolysis of the ethyl-substituted ketone V affords 1,2,5,6-dibenzanthracene in relatively high yield, the



V



VI

methyl group which normally would appear at a reactive *meso* position of the product being completely eliminated. 1,1′-Dinaphthyl ketones having methyl groups at the 4- or 4′-positions (VI) are prone to lose these substituents, and there appears to be a general tendency for the elimination of substituents from α-positions in the carbonyl-containing rings of the dinaphthyl ketones.[31] Another change observed in the course of a pyrolysis is dehydrogenation. The 5,6,7,8-tetrahydride of

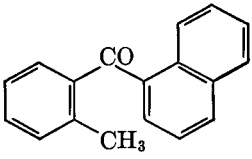
[29] Cook, *J. Chem. Soc.*, 3273 (1931); Cook, Hieger, Kennaway, and Mayneord, *Proc. Roy. Soc.*, **B111**, 469 (1932).

[30] Fieser and Hershberg, *J. Am. Chem. Soc.*, **60**, 1893 (1938).

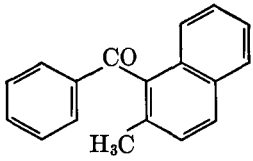
[31] Fieser and Peters, *J. Am. Chem. Soc.*, **54**, 3742 (1932).

the ketone I affords the fully aromatized hydrocarbon III when heated at 430–450°,[21] and other instances studied by Clar [25] are listed in the third section of Table II, which includes data on the synthesis of higher polynuclear hydrocarbons by elaboration of the general scheme already illustrated.

1,2-Benzanthracene Series (Table III). The most noteworthy feature of the data on the conversion of methylated benzoylnaphthalenes into 1,2-benzanthracene derivatives is the striking contrast in the behavior of the 2-methyl and 2′-methyl compounds, VII and VIII. The first ketone on being pyrolyzed for three hours affords 1,2-benzanthracene in as high as 61% yield, whereas the isomer VIII loses water only in the course of twenty-six hours and gives the same hydrocarbon in 10% yield.



VII



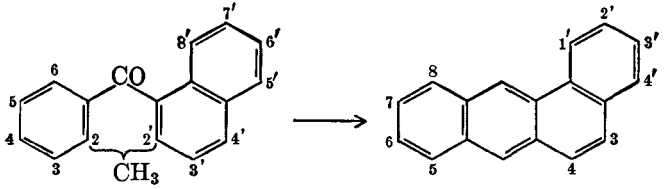
VIII

The difference is understandable in terms of the mechanism suggested by Fieser and Dietz, for in the favorable case (VII) the methyl group condenses into a naphthalene nucleus, while in VIII this group must substitute into a less reactive benzene nucleus. Cook's postulate that the Elbs reaction is dependent upon a process of enolization does not explain the observed difference, since VIII should be more prone to enolize than VII.

The favorable feature of structure encountered in *o*-tolyl α-naphthyl ketone (VII) is met with also in the series of *o*-methyl 2,1′-dinaphthyl ketones listed in Table II, for example ketone I (p. 134), and in this series the yields again are on the whole definitely better than with the methylated benzophenones (Table I). Ketones of the type of 1-benzoyl-2-methylnaphthalene (VIII) thus fall into the same unfavorable class as the benzophenone derivatives, and it will be seen from the data of Table III, which refer almost entirely to ketones of the type of VIII, that the yields are regularly poor. Unfortunately polysubstituted ketones having the *o*-methyl group in the naphthalene nucleus are more readily accessible than the more favorably constituted isomers and have been used exclusively for the synthesis of 1,2-benzanthracene homologs. In this series aroyl rearrangements occur in several instances, and there are examples of the loss and degradation of alkyl groups. Methyl substituents have been found to be eliminated from positions 5 and 8 of the resulting 1,2-benzanthracene, but there are examples of the retention of methyl at these same positions as well as at positions 4, 6, 7, 2′, and 3′.

TABLE III

1,2-BENZANTHRACENE DERIVATIVES



1'-Benzoylnaphthalene Derivative	Preparation	Pyrolysis	1,2-Benzanthracene Derivative	Yield, %	Reference
2-Methyl	ArCN + Ar'MgBr (76%)	410° with Zn, 3 hr.	1,2-Benzanthracene	54	20
		400–410° with Zn, 3 hr.		61	32
2'-Methyl	ArCOCl + Ar'H	Refl. 26 hr.	1,2-Benzanthracene	10	10
2,3-Dimethyl	ArCN + Ar'MgBr (89%)	425–430° with Zn, 2 hr.	5-Methyl, 8-methyl, and 1,2-benzanthracene	Low;rearr., loss of CH_3	33
2,2'-Dimethyl	ArCOCl + Ar'H	See note *a*	1,2-Benzanthracene (loss of CH_3)	5–10	34
3,2'-Dimethyl	ArCOCl + Ar'H	See note *a*	7-Methyl	5–10	34
4,2'-Dimethyl	ArCOCl + Ar'H	See note *a*	6-Methyl	5–10	34
2',3'-Dimethyl	ArCOCl + Ar'H (79%)	Refl. 3–4 hr.	4-Methyl, crude + methyl-1,2-benzanthrone	16, total	31
		415°, 5 hr.	4-Methyl + naphthacene	1	23
2',6'-Dimethyl	ArCOCl + Ar'H	See note *a*	3'-Methyl	5–10	34
2',7'-Dimethyl	ArCOCl + Ar'H	See note *a*	2'-Methyl	5–10	34
4-Isopropyl-2'-methyl	ArCOCl + Ar'H	410–420°, 2 hr.	6-Isopropyl + 6-methyl (degradation of *i*-Pr)	1–2	34
4-Phenyl-2'-methyl	ArCOCl + Ar'H	Refl. ½ hr.	6-Phenyl	8	17
3,4,2'-Trimethyl	ArCOCl + Ar'H	See note *a*	6,7-Dimethyl	5–10	34

3,2',6'-Trimethyl	ArCOCl + Ar'H	See note *a*	3',7-Dimethyl	1	34
3,2',7'-Trimethyl	ArCOCl + Ar'H	See note *a*	2',7-Dimethyl	5–10	34
4,2',6'-Trimethyl	ArCOCl + Ar'H	See note *a*	3',6-Dimethyl	5–10	34
4,2',7'-Trimethyl	ArCOCl + Ar'H	See note *a*	2',6-Dimethyl + 2',7-dimethyl (rearr.)	5–10	34
4-Isopropyl-2',7'-dimethyl	ArCOCl + Ar'H	See note *a*	2',7-Dimethyl (degrad., rearr.)	5–10	34
2-Methyl-4',5'-dimethylene	ArCOCl + Ar'H (23%)	400–410°, 40 min.	3,4'-Dimethylene	23	35
3,4-Trimethylene-2'-methyl	RH + Ar'COCl	450°, 2 hr.	5,6-Cyclopenteno (+ 6,7-isomer?)	2–3	21, 36

RELATED EXAMPLES

Ketone	Preparation	Pyrolysis	Product	Yield, %	Reference
4,4'-Di-α-naphthoyl-3,3'-dimethyldiphenyl	$C_{10}H_7COCl$ + di-*m*-tolyl	430–450°, 2 hr.	1,2,1',2'-Dibenz-6,6'- (or 7,7')-dianthryl	27	21
vic.-*o*-Xylyl β-naphthoyl ketone	ArCN + Ar'MgBr (87%)	420–425° with Zn, $1\frac{1}{2}$ hr.	8-Methyl-1,2-benzanthracene + other subst.	Low	33
1-Benzoylacenaphthene	C_6H_5MgBr + $Ar'CONH_2$ (95%)	420–425°, 40 min.	1',9-Methylene-1,2-benzanthracene	13	33
5-Quinolyl *o*-tolyl ketone	ArMgBr + Ar'CN (33%)	420–425° with Zn, 1 hr.	4'-Aza-1,2-benzanthracene	7	37

[a] In this series of experiments Cook [34] heated the ketone until water was no longer evolved and boiling ceased; usually the pyrolysis was conducted at 440–450° for two hours, or at 410–420° for four hours or sometimes longer. The yield of crude material was 20–25%; the yield of product purified by distillation, crystallization, and (usually) through the picrate was 5–10%.

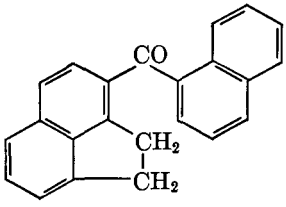
[32] Fieser and Hershberg, *J. Am. Chem. Soc.*, **59**, 2502 (1937).
[33] Fieser and Cason, *J. Am. Chem. Soc.*, **61**, 1740 (1939).
[34] Cook, *J. Chem. Soc.*, 456 (1932).
[35] Geyer and Zuffanti, *J. Am. Chem. Soc.*, **57**, 1787 (1935).
[36] Cook, *J. Chem. Soc.*, 2529 (1931).
[37] Fieser and Hershberg, *J. Am. Chem. Soc.*, **62**, 1640 (1940).

An isopropyl group was in part retained at position 6 and in part degraded to furnish a 6-methyl group.

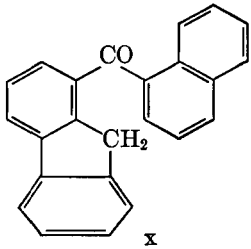
Synthesis of Cholanthrenes (Table IV). The synthesis of a hydrocarbon of the cholanthrene series by the Elbs reaction is illustrated by the formulas shown in Table IV. Although singly linked alkyl substituents are often eliminated at the pyrolysis temperature from the 5- and 10-positions of the 1,2-benzanthracene nucleus, the ace- or dimethylene bridge attached at these points appears to be more stable, for no instance of a rupture of these linkages is on record. Furthermore, both the 4-hydrindyl-α- and β-naphthyl ketones present structures particularly favorable for the Elbs condensation. As with *o*-tolyl α-naphthyl ketone (VII), ring closure involves a substitution into a reactive naphthalene nucleus, and another auspicious circumstance is that the *ortho* methylene group undoubtedly surpasses a corresponding *ortho* methyl group in reactivity. It is thus understandable that the reaction resulting in the formation of a cholanthrene takes place with particular rapidity and probably at a slightly lower critical pyrolysis temperature than in any other known example.

The generally favorable situation is reflected in the fact that the important carcinogens cholanthrene and 20-methylcholanthrene can be prepared in quantity in a thoroughly purified condition in 40–50% yield and that the yields on the whole are definitely better than in any of the other series studied. Methyl groups at the 1-, 6-, and 7-positions of the hydrindene nucleus pass through the pyrolysis unscathed, and the same is true of a methyl situated in the naphthalene nucleus at the 4′(α)-position, whereas in the synthesis of 1,2,5,6-dibenzanthracenes such a group invariably is eliminated. The only troublesome instance of methyl elimination encountered is in the pyrolysis of 2,7-dimethyl-4-(α-naphthoyl)-hydrindene, when the alkyl group which should appear at the highly reactive meso-methylene group (C_{15}) was retained only in part, and was in part lost. Syntheses of the 20-ethyl, 20-isopropyl, and 20-*t*-butyl derivatives have been accomplished successfully, if in low yield. It has even been possible, at least in some instances, to carry methoxyl groups and halogen atoms through the synthesis. A methoxyl substituent located at either the 6′- or 7′-position of the ketone is retained admirably, and the corresponding 3- and 2-methoxycholanthrenes are obtainable in excellent yield. A methoxyl at the vulnerable 4′(α)-position, however, is completely lost. With a chlorine atom at the 4′-position of the naphthoylhydrindene, extensive elimination of the substituent also occurred, but careful fractionation of the reaction mixture afforded a small amount of 6-chloro-20-methylcholanthrene. The 3-chloro isomer was obtained without difficulty.

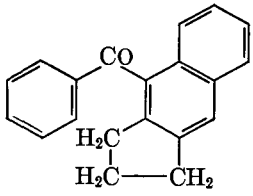
The second section of Table IV lists a number of variations of the cholanthrene synthesis. The ketones IX and X afford the expected 1′,9-dimethylene-1,2-benzanthracene and 15,16-benzdehydrocholanthrene in 32% and 60% yield, respectively. The particularly high yield



IX

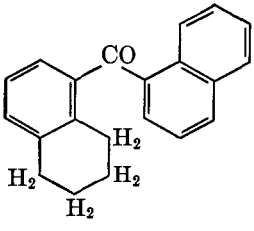


X

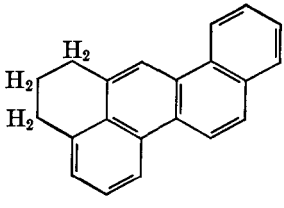


XI

in the latter case probably is associated with the presence in X of a doubly activated methylene group. The ketone XI is convertible into 4,10-ace-1,2-benzanthracene, an isomer of cholanthrene. That the yield is only 10% is attributable to the fact that the condensation involves substitution into the benzene rather than the naphthalene nucleus. *ar*-α-Tetralyl α-naphthyl ketone (XII) would be expected to yield homocholanthrene, but it affords instead 1,12-trimethylenechrysene (XIII), evidently as the result of a disproportionative isomerization to an aromatic structure of greater stability.

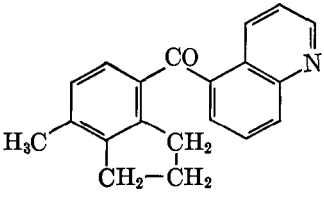


XII

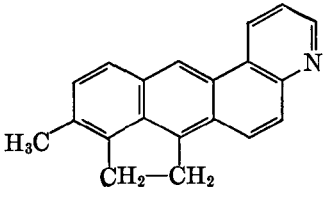


XIII

Another variation consists in the use of certain aryl quinolyl ketones for the synthesis of polynuclear aromatic substances containing a condensed pyridine ring. Thus 5-quinolyl 7-methyl-4-hydrindyl ketone (XIV) on pyrolysis affords 20-methyl-4-azacholanthrene (XV) in 12%



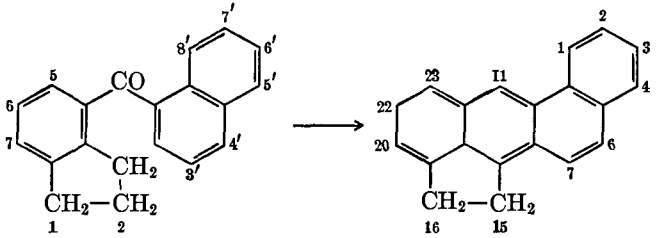
XIV



XV

TABLE IV

CHOLANTHRENE DERIVATIVES



4-(α-Naphthoyl)-hydrindene Derivative	Preparation	Pyrolysis	Cholanthrene Derivative	Yield, %	Reference
Parent ketone	ArMgBr + Ar'COCl (50%)	400–405°, 25 min.	Cholanthrene	34	38
	ArCN + Ar'MgBr (91%)	410°, ½ hr.		42	39
	Mixt. from α- and β-C_9H_9Br	400–410°, ½ hr.		?	40
7-Methyl	ArMgBr + Ar'COCl (50%[41])	405–410°, 25 min.	20-Methyl	About 50	42
	ArCN + Ar'MgBr (89%)	405–410°, 40 min.		49	43
	ArMgBr + Ar'CN (49%)	405–410°, 40 min.		43	20
7-Ethyl	ArCN + Ar'MgBr (61%)	405–410°, ½ hr.	20-Ethyl	29	44
7-Isopropyl	ArCN + Ar'MgBr (82%)	410–415°, 30 min.	20-Isopropyl	3	45
7-*t*-Butyl	ArMgBr + Ar'CN (46%)	400–410°	20-*t*-butyl	8	46
6-Methyl	ArCN + Ar'MgBr (94%)	415°	22-Methyl	27	47
4'-Methyl	ArCN + Ar'MgBr (85%)	400–410°, 40 min.	6-Methyl	24	47
1,7-Dimethyl	ArMgBr + Ar'COCl (59%)	400–405°, 30 min.	16,20-Dimethyl	20	48
2,7-Dimethyl	ArMgBr + Ar'COCl (48%)	405–410°, 30 min.	15,20-Dimethyl + 20-methyl	(23, total)	49
	ArLi + Ar'COCl (low)				41
7,4'-Dimethyl	ArMgBr + Ar'CN (81%)	410°	6,20-Dimethyl	30	47
6,4'-Dimethyl	ArCN + Ar'MgBr (89%)	415°	6,22-Dimethyl	23	47

7-Methyl-4'-methoxy	ArCOCl + Ar'H (82%) ArCN + Ar'MgBr (66%)	405°, 15 min.	20-Methyl (loss of OCH_3)	—	50
7-Methyl-6'-methoxy	ArLi + Ar'CN (50%)	405°, 20 min.	3-Methoxy-20-methyl	35	51
	ArCN + Ar'MgI (63%)	400–405° with Zn, 15 min.		38	52
7-Methyl-7'-methoxy	ArLi + Ar'COCl (48%)	405°, 15 min.; 420°	2-Methoxy-20-methyl	40	50
7-Methyl-4'-chloro	ArCN + Ar'MgBr (72%)	410°, brief heating	6-Chloro-20-methyl + 20-methyl	1.2	50
7-Methyl-6'-chloro	ArCN + Ar'MgBr (63%)	400°, 15 min.	3-Chloro-20-methyl	33	52

RELATED EXAMPLES

Ketone	Preparation	Pyrolysis	Product	Yield, %	Reference
4-(β-Naphthoyl)-hydrindene	ArMgBr + Ar'COCl (46%)	400–405°	8,9-Dimethylene-1,2-benzanthracene	?	38
4-(β-Naphthoyl)-7-methylhydrindene	ArMgBr + Ar'COCl (45%)	400–405°	7-Methyl-8,9-dimethylene-1,2-benzanthracene	50	42
7-Methyl-4-(5'-bromo-2'-naphthoyl)-hydrindene	ArCN + Ar'MgBr (50%)	370°, 8 min.	4-Bromo-7-methyl-8,9-dimethylene-1,2-benzanthracene	38	52
1-(α-Naphthoyl)-acenaphthene	ArLi + Ar'COCl (21%)	400–415°, 15 min.	1',9-Dimethylene-1,2,5,6-dibenzanthracene	32	53
5-Quinolyl 7-methyl-4-hydrindyl ketone	ArLi + Ar'CN (17.5%)	440°, 3–4 min.	20-Methyl-4-azacholanthrene	12	37
8-Quinolyl 7-methyl-4-hydrindyl ketone	ArMgBr + Ar'CN (57%)	400–410° with Pd-C, 10 min.	11-Hydroxy-20-methyl-1-azacholanthrene (?)	50	37
1-Benzoyl-2,3-cyclopentenonaphthalene	Tetrahydride + Se (69%)	405°, 45 min.	4,10-Ace-1,2-benzanthracene	10	54

NOTE. References 38–55 appear on p. 146.

TABLE IV—*Continued*

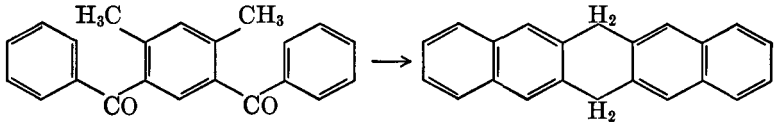
RELATED EXAMPLES

Ketone	Preparation	Pyrolysis	Product	Yield, %	Reference
5-Benzoyl-6,7-cyclopentenotetralin	ArCOCl + Ar'H (90%)	410°, 1 hr.	1',2',3',4'-Tetrahydro-4,10-ace-1,2-benzanthracene + Dehydro-3,4-trimethyleneisobenzanthrene-2	4 and 17–21	54
1-(α-Naphthoyl)-fluorene	ArCOCl + $C_{10}H_7MgBr$ (56%)	415°, 25 min.	15,16-Benzdehydrocholanthrene	60	38
1-(β-Naphthoyl)-fluorene	ArCOCl + $C_{10}H_8$ (84%)	415°, 25 min.	1',2'-Naphtho-1,2-fluorene	?	38
ar-α-Tetralyl α-naphthyl ketone	ArMgBr + Ar'COCl (40%)	395–400°, 45 min.	1,12-Trimethylenechrysene	44	55
ar-α-Tetralyl β-naphthyl ketone	ArMgBr + Ar'COCl (44%)	400°, 30 min.	8,9-Trimethylene-3,4-benzphenanthrene + 2 isomers and a dehydro compound	?	55

[38] Fieser and Seligman, *J. Am. Chem. Soc.*, **57**, 2174 (1935).
[39] Bachmann, *J. Org. Chem.*, **3**, 434 (1939).
[40] Bruce, *J. Am. Chem. Soc.*, **63**, 301 (1941).
[41] Bruce, *J. Am. Chem. Soc.*, **60**, 2277 (1938).
[42] Fieser and Seligman, *J. Am. Chem. Soc.*, **57**, 942 (1935).
[43] Fieser and Seligman, *J. Am. Chem. Soc.*, **58**, 2482 (1936).
[44] Bruce and Kahn, *J. Am. Chem. Soc.*, **60**, 1017 (1938).
[45] Bruce and Todd, *J. Am. Chem. Soc.*, **61**, 157 (1939).
[46] Fieser and Snow, *J. Am. Chem. Soc.*, **60**, 176 (1938).
[47] Fieser and Bowen, *J. Am. Chem. Soc.*, **62**, 2103 (1940).
[48] Fieser and Seligman, *J. Am. Chem. Soc.*, **57**, 1377 (1935).
[49] Bruce with Fieser, *J. Am. Chem. Soc.*, **59**, 479 (1937).
[50] Fieser and Desreux, *J. Am. Chem. Soc.*, **60**, 2255 (1938).
[51] Cook and de Worms, *J. Chem. Soc.*, 1825 (1937).
[52] Fieser and Riegel, *J. Am. Chem. Soc.*, **59**, 2561 (1937).
[53] Fieser and Hershberg, *J. Am. Chem. Soc.*, **57**, 1681 (1935).
[54] Fieser and Seligman, *J. Am. Chem. Soc.*, **59**, 883 (1937).
[55] Fieser and Seligman, *J. Am. Chem. Soc.*, **58**, 478 (1936).

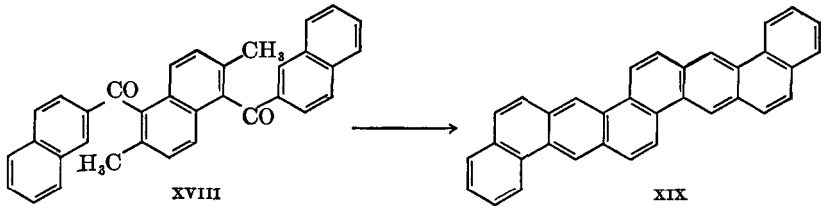
yield. Similarly, 5-quinolyl *o*-tolyl ketone (Table III) yields 4′-aza-1,2-benzanthracene (β-anthraquinoline). With 8-quinolyl 7-methyl-4-hydrindyl ketone the sole reaction product (50%) contains an atom of oxygen and presumably is of a stabilized anthranol type of structure.

Pyrolysis of Diketones (Table V). The Elbs reaction has been applied rather extensively, particularly by Clar and co-workers, to the synthesis from suitable diketones of higher hydrocarbons having two separate or merged anthracenoid groupings (see refs. 57–64 in Table V). One example is the pyrolysis of 4,6-dibenzoyl-1,3-xylene (XVI), which yields a hydrocarbon having the probable structure of mesodihydropentacene (XVII). The formation of the dihydride rather than the fully aromatic



XVI XVII

hydrocarbon doubtless is a consequence of the great reactivity of pentacene. The most extensive elaboration of the method yet accomplished is the synthesis of 2,3,8,9-di-(naphtho-1′,2′)-chrysene (XIX) from the diketone XVIII. The hydrocarbon, which melts at 500°, was



XVIII XIX

obtained in 52% yield. Other examples listed in the table involve diketones which are similar to XVIII but in which one or both naphthoyl groups are replaced by benzoyl radicals.

Summary of Side Reactions. Examples have been cited in the foregoing sections of the occurrence of aroyl migrations in the course of the Elbs pyrolysis, of the elimination of alkyl, halo, and methoxy substituents, of the degradation of isopropyl to methyl, and of processes of hydrogenation, dehydrogenation, and intramolecular disproportionation. The formation of anthrones in three instances represents the production of substances of a stage of oxidation higher than that of the expected hydrocarbon, and there is one instance of an apparent reduction. As a by-product in the synthesis of methylcholanthrene, there was isolated [43] a substance which is resistant to dehydrogenation and which

TABLE V

PYROLYSIS OF DIKETONES

Diketone	Product	Yield	Remarks	Reference
2,5-Dibenzoyl-1,4-xylene	No condensation	0		56
4,6-Dibenzoyl-1,3-xylene	Dihydropentacene (probably meso [58])	?		57
1,4-Di-(*o*-toluyl)-benzene	1,2-(Naphtho-2',3')-anthracene (*a*) and	20–25, total		59, 60
1,2-Di-(*o*-toluyl)-benzene	Dihydropentacene (*b*)	Very low	Rearr. (*b*)	59, 60
1,2-Bis-(2',5'-dimethylbenzoyl)-benzene	7,7'-Dimethyl-1,2-(naphtho-2',3'-anthracene (*a*) and	?		59, 60
1,2-Bis-(2',4'-dimethylbenzoyl)-benzene	2,2'-Dimethyldihydropentacene (*b*)	?	Rearr. (*b*)	59, 60
1,3-Bis-(2',4'-dimethylbenzoyl)-benzene	6',7-Dimethyl-1,2-(naphtho-2',3'-anthracene (*a*) and 2',3'-dimethyldihydropentacene (*b*)		Rearr. (*b*)	59, 60
1-(2,4-Dimethylbenzoyl)-4-(2-methylnaphthoyl-1)-benzene	11-Methyl-3,4-benzpentaphene[a] (?)	?		61
1,3-Bis-(2-methylnaphthoyl-1)-benzene	3,4,9,10-Dibenzpentaphene (?)	Very low	Rearr.	61
1,4-Bis-(2-methylnaphthoyl-1)-benzene		Very low		61
1,5-Dibenzoyl-2,6-dimethylnaphthalene	1,2-(Anthraceno-2',1')-anthracene	?		63
1,8-Dibenzoyl-2,7-dimethylnaphthalene	Hexaphene	?	Rearr.	63, 64
Di-(o-toluyl)-naphthalene	No condensation	0		63
1-Benzoyl-5-(1'-naphthoyl)-2,6-dimethylnaphthalene	4,5-Benz-10,11-(1',2'-naphtho)-chrysene	40		21
1-Benzoyl-5-(2'-naphthoyl)-2,6-dimethylnaphthalene		?		21
2,6-Dimethyl-1,5-di-(2'-naphthoyl)-naphthalene	2,3,8,9-Di-(naphtho-1',2')-chrysene	52		10

[a] For nomenclature, see Clar, ref. 62.

[56] de Diesbach and Strebel, *Helv. Chim. Acta*, **8**, 556 (1925).
[57] Clar and John, *Ber.*, **62**, 3021 (1929).
[58] Clar and John, *Ber.*, **63**, 2967 (1930).
[59] Clar, John and Hawran, *Ber.*, **62**, 940 (1929).
[60] Clar and John, *Ber.*, **64**, 981 (1931).
[61] Clar, *Ber.*, **72**, 2139 (1939).
[62] Clar, *Ber.*, **72**, 2137 (1939).
[63] Clar, Wallenstein, and Avenarius, *Ber.*, **62**, 950 (1929).
[64] Clar, *Ber.*, **73**, 81 (1940).

probably is formed by the reduction of the carbonyl group of the starting ketone. Another side reaction leads to the formation of hydrocarbon fragments such as phenanthrene from a phenanthryl aryl ketone,[10] or anthracene from an anthryl aryl ketone.[59] Apparently the ketone suffers some cleavage by the water evolved, perhaps with subsequent decarboxylation of the acid fragment: $ArCOAr' + H_2O \rightarrow ArCOOH + Ar'H \rightarrow ArH + CO_2 + Ar'H$. Clar [63] reports the formation of benzoic acid and benzaldehyde in the pyrolysis of 1,5-dibenzoyl-2,6-dimethylnaphthalene.

EXPERIMENTAL PROCEDURES

Preparation of the Required Ketones. The ketone required for a given Elbs synthesis is often obtained most readily by the Friedel and Crafts reaction, and in many of the experiments cited the practice has been to distil the total ketone or ketone mixture and submit it as such to pyrolysis. Since the distillate almost invariably consists of a mixture of isomers, this practice introduces uncertainties concerning the nature of the reaction and the yield. Except for the routine preparation of materials by known methods, it is definitely advantageous either to purify and characterize the products obtained by the Friedel and Crafts method or to employ a synthesis from a Grignard or lithium derivative.

The principal variations of this general synthesis have been studied carefully in a number of instances, as summarized in the second column of Tables I–IV. The reaction $ArMgX + ArCOCl$ has been employed in 10 instances with yields ranging from 40 to 59% and with an average yield of 49%. Bruce [41] has found that considerable losses are associated with side reactions resulting in the formation of ArH and $(ArCO)_2O$. The use of a nitrile in place of an acid chloride is definitely advantageous, for in 22 examples the reaction $ArMgX + ArCN$ has given pure ketones in an average yield of 70%. Some of these syntheses represent particularly difficult cases, for example where a cyanoquinoline constitutes one component, and in the more normal instances the yields frequently are in the range 80–90%, particularly when the inherent slowness of the nitrile reaction has been recognized and adequate time allowed. The use of an amide as the second component has been investigated in only one instance, but with marked success. The condensation of phenylmagnesium bromide with 1-acenaphthamide was found to proceed slowly (72 hr.) but very smoothly, affording 1-benzoylacenaphthene in 95% yield.[33] Lithium derivatives have not been employed at all extensively but, except in special cases, probably are less satisfactory than the Grignard reagents. The reaction $ArLi + ArCOCl$ has given yields described as "very low," [41] 48%,[50] and 21%.[53] The last figure applies to the reaction

between 1-acenaphthyllithium and α-naphthoyl chloride, which was found at least more satisfactory than the attempted condensation of 1-acenaphthylmagnesium iodide with the acid chloride. Yields reported for the reaction ArLi + ArCN are 51%,[18] 50%,[51] and 17.5%[37] (cyanoquinoline), and the synthetic method thus appears less advantageous than the condensation of a Grignard reagent with the nitrile.

Selection of Conditions for the Pyrolysis. Attempts to find a catalyst for the Elbs reaction have met with little success. Elbs[5] tried sulfuric acid, potassium bisulfate, phosphorus pentoxide, and zinc chloride with negative results. Morgan and Coulson[15] found piperidine and acetic anhydride also without effect and noted that 2,4,4′-trimethylbenzophenone is cleaved by sulfuric acid to *p*-toluic acid and *m*-xylene.

The pyrolysis frequently has been conducted in the presence of a small amount of zinc dust, and indeed in the first instance of the reaction Behr and van Dorp[1] passed the vapor of *o*-tolyl phenyl ketone over zinc dust. It is still questionable that the use of zinc results in any material improvement. In two sets of parallel experiments[33, 54] conducted with and without zinc dust no difference was observable in the results. In the synthesis of the 2-[50] and 3-methoxy[52] derivatives of methylcholanthrene the yields in small-scale experiments were 36 and 38% in the presence of zinc and 40 and 32% in its absence. It was observed by Hershberg[32] that *o*-tolyl α-naphthyl ketone can be pyrolyzed at 400–410° in the presence of zinc dust to give 1,2-benzanthracene in 61% yield, but that without zinc the reaction proceeds only very slowly at the same temperature. This is the only concrete indication that zinc has any effect, and the effect may be merely to lower slightly the pyrolysis temperature. A comparison of the first three entries in Table III would seem to indicate that the use of zinc improves the yield in the synthesis of 1,2,5,6-dibenzanthracene, but in view of the experiment cited below as an example of the procedure it is probable that the higher yield reported by Bachmann[20] is attributable more to his use of homogeneous Grignard ketone in place of the mixture resulting from the Friedel and Crafts reaction.

Although many of the earlier experiments were conducted by heating the ketone over a free flame at the boiling point without control or measurement of the temperature, most workers now consider it advisable to use a heating bath and to conduct the pyrolysis at the lowest temperature at which a steady liberation of water is observed.[34, 43] As the bath temperature is brought slowly to or above 400°, the critical pyrolysis temperature usually is sharply defined by a brisk bubbling which is hardly noticeable at a temperature 5° lower.[43]

Certain claims concerning modifications in the procedure of conducting

the Elbs reaction have appeared in the patent literature,[65–67] but the supporting data are not sufficiently definitive to warrant acceptance of the claims in the absence of confirmatory evidence. Thus it is stated [65] that ketones can be pyrolyzed to hydrocarbons by dropping the liquid into a metal tube packed with active carbon, alumina, or silica gel at about 400°, but there is no indication that the contact agents play any real role or effect any improvement.

Two isolated and as yet unclarified instances are reported of the use of starting materials other than ketones. Elbs [7] found that, although *m*-xylyl phenyl ketone failed to undergo satisfactory reaction, the corresponding alcohol, *m*-xylyl phenyl carbinol, condensed to β-methylanthracene almost as readily as *p*-xylyl phenyl ketone . On oxidation of α-naphthyl-4-(7-ethylhydrindenyl)-carbinol, Bruce and Kahn [44] obtained an abnormal product regarded as an ether, ArCH(Ar′)OCH(Ar′)Ar, and this on pyrolysis afforded 20-ethylcholanthrene.

Example 1. 1,2,5,6-Dibenzanthracene (Experiment by J. Cason). For best economy, and because of the greater speed and ease in the manipulation of large amounts of material, it is considered advantageous to employ the ketone mixture prepared by the Friedel and Crafts reaction,[19, 10] even though the yield in the pyrolysis may be lower than with the purer Grignard ketone.[20]

A 2-l. three-necked flask is charged with 1.02 moles of β-naphthoic acid and 1.04 moles of phosphorus pentachloride and the mixture heated for one hour on the steam bath. Boiling chips are added, and the phosphorus oxychloride is taken off at water pump vacuum. The residue, which crystallizes on cooling, is dissolved in 575 cc. of carbon bisulfide, 1.23 moles of β-methylnaphthalene is added, and then, while the mixture is stirred mechanically under reflux, 1.31 moles of aluminum chloride is added during thirty minutes. The mixture is refluxed for two hours, cooled, decomposed with ice and hydrochloric acid, and the solvent is removed with steam. The granular brown solid is digested at the boiling point with sodium carbonate solution, collected, and dried thoroughly at room temperature (it becomes gummy at 50°; a trace of water causes troublesome foaming in the distillation). Vacuum distillation gives 264 g. (88%) of crude ketone, b.p. 250–252°/4 mm. (bath, 300–310°). The distillate is a clear, dark reddish oil which sets to a glass on cooling.

The pyrolysis is conveniently carried out in a two-bulb distillation flask [68] having a 300-cc. distillation bulb with an inverted-U side arm

[65] I. G. Farbenindustrie, Brit. pat., 251,270 (1926) [*C. A.*, **21**, 1272 (1927)].

[66] I. G. Farbenindustrie, Brit. pat., 253,911 (1925) [*C. A.*, **21**, 2478 (1927)].

[67] Nicodemus and Berndt, U. S. pat., 1,776,924; 1,776,925 (1930) [*C. A.*, **24**, 5765 (1930)].

[68] Fieser, "Experiments in Organic Chemistry," 2nd ed., p. 250, D. C. Heath and Co., 1941.

sealed on about 11 cm. above the flask and carrying a 100-cc. receiving bulb. The flask is charged with 152 g. of the crude ketone and heated in a nitrate-nitrite bath (care!) at 430° ± 5° (bath). The pyrolysis must be attended constantly and the upper part of the flask warmed occasionally with a free flame to prevent water from condensing and dropping back into the hot mixture. Sweeping of the vessel with dry nitrogen or carbon dioxide perhaps facilitates somewhat the removal of water but is unnecessary and offers no material advantage. The evolution of water slackens noticeably within about three hours, and after three and one-half hours the flask is removed from the bath, some glass wool is pushed down into the bulb to promote even boiling, and the mouth of the flask is sealed off. The product is then distilled at 2–3 mm. pressure, the low-boiling material which comes over in a fore-run being removed from the receiver. The dibenzanthracene distils largely at a bath temperature of 300–320°, and in part on raising the bath to 400°. During distillation the upper part of the flask is kept hot with a free flame. By using a flask with a high side arm and distilling carefully, a clean distillate can be obtained and redistillation is unnecessary. The distillate is melted, poured (and rinsed) into a 4-l. flask, and dissolved in about 3 l. of boiling benzene. The solution is concentrated until crystallization sets in (about 1800 cc.). The yellow dibenzanthracene separating in the first crop and melting at 260–262° (cor.) amounts to 44 g. (31%). The material recovered from the mother liquor when recrystallized melts at 253–258° and weighs 4 g.; total yield of yellow product, 33%. Almost identical yields were obtained in 20-g. and 80-g. runs and in runs conducted with added zinc dust.

In one method for the preparation of colorless dibenzanthracene,[30] a warm solution of 2 g. of lead tetraacetate in 500 cc. of acetic acid is added in small portions to a warm solution of 10 g. of yellow hydrocarbon in 500 cc. of benzene, and the solution is refluxed gently for one hour. The solvent is then distilled slowly until the solution has been reduced in volume to 300–350 cc. On cooling, dibenzanthracene separates in completely colorless plates with a blue fluorescence in ultraviolet light, m.p. 265–266° (cor.) (purest sample, 266–266.5°). The recovery ordinarily amounts to 70–83%. With particularly poor samples of crude hydrocarbon a second treatment with lead tetraacetate may be required; this was true of a sample melting at 250–255°, from which the recovery of thoroughly purified material was 50%.

Example 2. 1,2-Benzanthracene.[20, 32] *o*-Tolyl α-naphthyl ketone is prepared [20] by adding 23.4 g. of *o*-tolunitrile to the Grignard reagent from 50 g. of α-bromonaphthalene in 75 cc. of ether and 75 cc. of benzene. The mixture is refluxed for eight hours, cooled, and hydrolyzed with ice

and 100 cc. of concentrated hydrochloric acid. The sparingly soluble ketimine hydrochloride which crystallizes from the two-phase system is collected by suction filtration and hydrolyzed by boiling with water for one hour. The ketone crystallizes from the cooled mixture and is distilled, b.p. 174°/0.4 mm.; yield 37.8 g. (76%). After crystallization from methanol the ketone melts at 59–61°.

For pyrolysis,[20] a mixture of 34 g. of the ketone and 10 g. of zinc dust is heated for three hours in a metal bath kept at 410°. The hydrocarbon is distilled from the flask at 0.4 mm. and crystallized several times from benzene-alcohol, giving 17.2 g. (54%) of yellow 1,2-benzanthracene. For the removal of chrysogen by Cook's method,[29] the crude hydrocarbon (17.2 g.) is refluxed with 1 g. of maleic anhydride in 50 cc. of benzene for three hours. The hot solution is then shaken with aqueous alkali and the benzene layer is filtered, concentrated to a small volume, and treated with alcohol, when colorless 1,2-dibenzanthracene crystallizes, m.p. 155.5–157°.

In a repetition [32] of this experiment the crude hydrocarbon from the pyrolysis of 6 g. of ketone with 2 g. of zinc dust was purified after distillation by passage through a tower of activated alumina in benzene solution. This afforded, after crystallization, a total of 2.75 g. of colorless 1,2-benzanthracene, m.p. 159.5–160.5° (cor.), and 0.6 g. of yellow product, m.p. 159–160°; total yield 61%.

Example 3. Methylcholanthrene.[43] 7-Methyl-4-(α-naphthoyl)-hydrindene is prepared by condensing the Grignard reagent from 195 g. of redistilled α-bromonaphthalene in ether-benzene with 120 g. of 7-methyl-4-cyanohydrindene and hydrolyzing the resulting ketimine hydrochloride in a boiling mixture of hydrochloric acid, acetic acid, and toluene. The yield of the ketone, obtained as a light yellow, viscous oil, b.p. 211–214°/2 mm., is 194 g. (89%).

The pyrolysis of 168.5 g. of the ketone is conveniently conducted in three lots and the products combined for purification. In a 100-cc. flask with a sealed-on receiving bulb a portion of the ketone is warmed over a free flame and then placed in a preheated nitrate-nitrite bath and heated for forty minutes at a temperature at which brisk bubbling is observed (405–410°, uncor.). In a typical 56.5-g. run the water and hydrocarbon cleavage products collecting in the receiver amounted to 6 g. At the end of the period of heating the flask is removed from the heating bath, cooled somewhat with a blast of air, a capillary is inserted, the receiving bulb is rinsed with acetone, and the hydrocarbon is distilled rather rapidly at 2–3 mm. pressure, and then redistilled to remove traces of entrained tar.

The redistilled material from the three pyrolyses consists of a bright

yellow solid weighing 113.3 g. This is dissolved in 400 cc. of benzene and the solution is cooled slightly and diluted with 1 l. of ether. The bulk of the methylcholanthrene separates in a nearly pure condition as fine yellow needles (72 g.). This is dissolved in 500 cc. of benzene, and 300 cc. of ether is added; on cooling, the hydrocarbon separates as yellow needles of high purity (63 g.), m.p. 178.5–179.5° (cor.) (purest sample, 179.5–180°). The mother liquor from this crystallization when concentrated and treated with 12 g. of picric acid affords 12.5 g. of methylcholanthrene picrate, m.p. 176–177°. The oily material recovered from the original mother liquor is pyrolyzed again and the product distilled, crystallized once from benzene-ether, and converted to the picrate in benzene solution. Recrystallization affords 14.5 g. of satisfactory picrate, m.p. 178–179°. The total yield of material collected as such or as the picrate is 77.1 g. (49%).

CHAPTER 7

THE CLEMMENSEN REDUCTION

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CONTENTS

PAGE

INTRODUCTION 156

TYPES OF COMPOUNDS REDUCED BY THE CLEMMENSEN METHOD 157

Aldehydes 157

Aliphatic Aldehydes 157

Aromatic Aldehydes 157

Ketones 157

Aliphatic and Alicyclic Ketones 157

Aliphatic-Aromatic Ketones 158

Aromatic Ketones 159

Keto Acids 159

α-Keto Acids 159

β-Keto Acids 160

γ-Keto Acids 160

Other Keto Acids 160

α,β-Unsaturated Carbonyl Compounds 161

The Reduction of Other Functional Groups by Amalgamated Zinc and Hydrochloric Acid 161

EXPERIMENTAL PROCEDURES 162

General Discussion 162

Preparation of Zinc Amalgam 163

The Clemmensen Reduction in the Absence of an Organic Solvent (Method I) 164

Reduction of β-(*p*-Toluyl)-propionic Acid 164

Reduction of 2,4-Dihydroxyacetophenone 164

The Clemmensen Reduction in the Presence of a Solvent Miscible with Aqueous Hydrochloric Acid (Method II) 164

Preparation of 4-Chloro-7-methylindan 165

Reduction of γ-Keto-γ-(2-fluorene)-butyric Acid 166

The Clemmensen Reduction in the Presence of a Solvent Immiscible with the Hydrochloric Acid (Method III) 166

Reduction of β-Benzoylpropionic Acid 166

Reduction of β-(*p*-Anisoyl)-propionic Acid 167

Reduction of Stearophenone 167

PAGE
The Clemmensen Reduction in the Presence of Solvents of Both Types (Method IV) 168
The Clemmensen Reduction with Unamalgamated Zinc (Method V) . . . 168
TABLE OF COMPOUNDS REDUCED BY THE CLEMMENSEN METHOD 169–200

INTRODUCTION

The replacement of the oxygen atom of the carbonyl group in an aldehyde or ketone by two hydrogen atoms through the use of amalgamated zinc and hydrochloric acid was first employed in 1913 by Clemmensen [1] and is known as the Clemmensen method of reduction. The process has been applied to a large number of aldehydes and ketones as a step in the synthesis of polynuclear hydrocarbons and alkylated aromatic compounds, including those containing one or more phenolic hydroxyl groups. It has also played an important role in the elucidation of the structures of highly complex natural products.

The formation of hydrocarbons from aldehydes and ketones by the Clemmensen reaction can be illustrated by the following equations:

$$RC(=O)-H + 4(H) \xrightarrow[HCl]{Zn(Hg)x} RCH_3 + H_2O$$

$$RC(=O)-R' + 4(H) \xrightarrow[HCl]{Zn(Hg)x} RCH_2R' + H_2O$$

The method is of peculiar value because nearly all other reducing agents which have been employed convert aldehydes and ketones to the corresponding carbinols or pinacols, rather than to the hydrocarbons. The chief alternative methods of accomplishing the same transformation are catalytic hydrogenation and reduction with hydrazine and alkali (Wolff-Kishner method).

The mechanism of the reduction by amalgamated zinc and hydrochloric acid is not clearly understood. If the carbinol is assumed to be the intermediate, then these same reagents should be suitable for the replacement of an alcoholic hydroxyl group by a hydrogen atom. However, with few exceptions, alcohols are not affected by zinc amalgam and hydrochloric acid. Only activated alcoholic hydroxyl groups, such as those in β-hydroxy acids and benzyl alcohols, are removed by the Clemmensen reagents.

The wide use of this method of reduction has resulted in the development of several modifications of the original procedure. These consist

[1] Clemmensen: (*a*) *Ber.*, **46**, 1838 (1913); (*b*) *Ber.*, **47**, 51 (1914); (*c*) *Ber.*, **47**, 681 (1914).

primarily in the addition of solvents, in some cases miscible and in other cases immiscible with the aqueous hydrochloric acid, and in methods of treating and amalgamating the zinc.

TYPES OF COMPOUNDS REDUCED BY THE CLEMMENSEN METHOD

Aldehydes

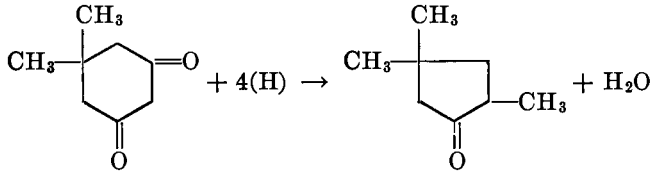
Aliphatic Aldehydes. The conversion of heptaldehyde to *n*-heptane [1a] in 72% yield appears to be the only recorded instance of a Clemmensen reduction of an aliphatic aldehyde.

Aromatic Aldehydes. The number of aromatic aldehydes which have been subjected to the action of zinc amalgam and hydrochloric acid is not large. The original procedure of Clemmensen gives excellent results with certain phenolic aldehydes but is less satisfactory for the reduction of benzaldehyde. Robinson and Shah [2] obtained good yields from aromatic aldehydes by carrying out the reaction in the presence of dilute ethanol with a specially prepared zinc amalgam.

Ketones

Aliphatic and Alicyclic Ketones. Aliphatic and alicyclic ketones of low molecular weight are reduced smoothly, but those of higher molecular weight are attacked only slowly. Apparently small amounts of unsaturated compounds are formed as by-products from some ketones. Both propylene and pinacol are reported to be present in the products of the Clemmensen reduction of acetone.[3] With ketones of the sterol series it is necessary to employ a solvent miscible with the hydrochloric acid to increase the solubility of the carbonyl compound in the reaction mixture. This modification of procedure is not desirable with the simple aliphatic ketones, since with such compounds it favors the formation of resinous by-products.

No reduction of an aliphatic or alicyclic α-diketone has been described. The cyclic β-diketone, 5,5-dimethylcyclohexadione-1,3, undergoes reduction and rearrangement to 2,4,4-trimethylcyclopentanone-1.[4]



[2] Robinson and Shah, *J. Chem. Soc.*, 1491 (1934).
[3] Muller, *Z. Electrochem.*, **33**, 255 (1927).
[4] Dey and Linstead, *J. Chem. Soc.*, 1063 (1935).

Several other β-diketones have been reduced without rearrangement; some of the reactions have been interrupted to produce monoketones.[5]

Aliphatic ketones containing primary,[1c] secondary,[6] or tertiary[7] hydroxyl groups undergo reduction of the carbonyl group without change of the alcohol function. These observations, together with the fact that alcohols have been used satisfactorily as solvents, indicate that alcoholic hydroxyl groups are not ordinarily reduced by amalgamated zinc and hydrochloric acid. However, the direct replacement of an unactivated hydroxyl group has been observed in one case; 3-hydroxy-7,12-diketocholanic acid is reduced to cholanic acid.[8] The reduction of 1,2-glycols, which has been observed with certain sterol derivatives,[9] may depend on preliminary dehydration to ketones which then react in the usual way.

Aliphatic-Aromatic Ketones. Most aliphatic-aromatic ketones react normally, and numerous carbonyl compounds of this type, particularly phenolic ketones, have been reduced by the Clemmensen method. Cyclic ketones obtained by ring closure of γ-arylbutyric acids are also readily converted to hydrocarbons. Ketones of very slight water solubility are best reduced by employing a hydrocarbon solvent and operating in such a way that the amalgamated zinc is in contact with both the aqueous acid and the hydrocarbon solution[10] (see p. 167).

The presence of a carboxyl group attached to the aromatic nucleus frequently causes the reaction to proceed more rapidly and in excellent yields.[11] It is probable that the carboxyl group assists in maintaining the required concentration in the acid mixture by increasing the solubility of the carbonyl compound.

The reduction of aliphatic-aromatic ketones containing one, two, or three hydroxyl or methoxyl groups on the aromatic ring proceeds exceptionally well. Quantitative yields are obtained with the lower members, and even with the higher homologs the yields are very good. The reaction proceeds rapidly, and in some cases it is possible to employ the color produced with ferric chloride as a control test.[12]

[5] (*a*) Wieland and Martz, *Ber.*, **59**, 2352 (1926); (*b*) Qudrat-i-Khuda, *J. Chem. Soc.*, 206 (1930); (*c*) Ruzicka, Koolhaas, and Wind, *Helv. Chim. Acta*, **14**, 1151 (1931); (*d*) Chuang, Ma, and Tien, *Ber.*, **68**, 1946 (1935); (*e*) Friedmann, *J. prakt. Chem.*, **146**, 65 (1936); (*f*) Bardhan and Sengupta, *J. Chem. Soc.*, 2520 (1932).

[6] Marker and Lawson, *J. Am. Chem. Soc.*, **61**, 852 (1939).

[7] Lutz and Small, *J. Org. Chem.*, **4**, 220 (1939).

[8] Borsche and Hallwass, *Ber.*, **55**, 3325 (1922).

[9] Marker, Kamm, Oakwood, Wittle, and Lawson, *J. Am. Chem. Soc.*, **60**, 1067 (1938).

[10] Mikeska, Smith, and Lieber, *J. Org. Chem.*, **2**, 499 (1938).

[11] Cox, *J. Am. Chem. Soc.*, **52**, 352 (1930).

[12] (*a*) Dohme, Cox, and Miller, *J. Am. Chem. Soc.*, **48**, 1688 (1926); (*b*) Cox, *J. Am. Chem. Soc.*, **52**, 352 (1930).

Side reactions accompany the reduction of many aliphatic-aromatic ketones, and in a few cases resinous products are formed in considerable quantities. Styrene, styrene polymers, and the pinacolone of acetophenone (formed by rearrangement of the pinacol) have been isolated as by-products in the preparation of ethylbenzene from acetophenone.[13] In the reaction of 2,6-dihydroxyvalerophenone with amalgamated zinc and aqueous hydrochloric acid, cleavage of the ketone has been observed, but in ethanolic solution the reduction is satisfactory.[14] Although most indandiones which have been studied react normally,[15] the indan produced from 2,2-diethyl-6,7,8,9-tetrahydro-1,3-α-naphthindandione by the ordinary procedure is not completely free of oxygen compounds, and reaction over an extended period yields the 2-alkyl-5,6,7,8-tetrahydronaphthalene, formed by reductive opening of the indan ring.[15a]

Aromatic Ketones. The reduction of benzophenone and its homologs by the original Clemmensen procedure is reported to be unsatisfactory because of the formation of resinous materials. On the other hand, *p*-hydroxybenzophenone [1c] is transformed to *p*-hydroxydiphenylmethane in quantitative yield. 2,4-Dihydroxy [16a] and 2,4,6-trihydroxybenzophenones [16b] give the expected products in somewhat less satisfactory yields. *o*-Benzoylbenzoic acid is converted to *o*-benzylbenzoic acid, but reduction with zinc dust and alkali is more convenient and gives better yields.[17] Either benzil or benzoin is transformed to diphenylethane in good yields by the action of amalgamated zinc and aqueous hydrochloric acid,[1c] but the reduction of benzoin in the presence of ethanol affords stilbene in good yield.[18] 2,4,6,2′,4′,6′-Hexamethylbenzil is unaffected by zinc amalgam and concentrated hydrochloric acid. Anthraquinone [1a] and certain of its derivatives [19] are reduced to dihydroanthracenes.

Keto Acids

α-Keto Acids. The carbonyl group of α-keto acids is attacked under the conditions of the Clemmensen reduction, but the products are the α-hydroxy derivatives rather than the completely reduced acids. For example, phenylglyoxylic acid and its ethyl ester give mandelic acid and

[13] Steinkopf and Wolfram, *Ann.*, **430**, 113 (1923).

[14] Adams, Cain, and Baker, *J. Am. Chem. Soc.*, **62**, 2201 (1940).

[15] (*a*) v. Braun, Kirschbaum, and Schuhmann, *Ber.*, **53**, 1155 (1920); (*b*) Fleischer and co-workers, *Ber.*, **53**, 1255 (1920); **56**, 228 (1923); *Ann.*, **422**, 231, 272 (1921).

[16] (*a*) Klarmann, *J. Am. Chem. Soc.*, **48**, 791 (1926); (*b*) Klarmann and Figdor, *ibid.*, **48**, 803 (1926).

[17] Martin, *J. Am. Chem. Soc.*, **58**, 1438 (1936).

[18] Ballard and Dehn, *J. Am. Chem. Soc.*, **54**, 3969 (1932).

[19] Backer, Strating, and Huisman, *Rec. trav. chim.*, **58**, 761 (1939).

ethyl mandelate, respectively,[13] and ethyl 9-fluoreneglyoxylate yields the corresponding hydroxy ester.[20]

β-Keto Acids. The reduction of a few esters of β-keto acids has been investigated. Ethyl acetoacetate is transformed to ethyl butyrate in 30% yield, and ethyl benzoylacetate to ethyl hydrocinnamate in 59% yield.[13] The reduction of a β-keto ester of the bile acid series, the methyl ester of 6-ketolithobilianic acid,[21] and of two bicyclic di-(β-keto) esters [22] is recorded.

γ-Keto Acids. The most important acids of this type are those obtainable by the Friedel and Crafts reaction of succinic anhydride or its substitution products with aromatic compounds or by the action of an aryl Grignard reagent with such an anhydride. The reduction of these keto acids by one of the Clemmensen procedures is satisfactory, although in certain cases some resinification occurs. A bimolecular byproduct, the dilactone of γ,γ′-diphenyl-γ,γ′-dihydroxysuberic acid, has been isolated from β-benzoylpropionic acid.[23]

β-Aroylpropionic acids with methoxyl groups attached to the aromatic ring are best reduced in the presence of a solvent (toluene) immiscible with the hydrochloric acid.[17] β-(4,8-Dimethoxy-1-naphthoyl)-propionic acid yields γ-(4,8-dimethoxy-1-naphthyl)-butyric acid and an abnormal product, γ-(4-methoxy-5-tetralyl)-butyric acid.[24] The formation of the latter compound involves the reduction of the ring carrying the carbonyl group and the elimination of the methoxyl group from that ring. A side reaction in the reduction of β-(*p*-bromobenzoyl)-propionic acid results in the replacement of the bromine atom by a hydrogen atom.[25] Esters of β-aroylpropionic acids undergo simultaneous reduction and hydrolysis to give γ-arylbutyric acids.[26]

The Clemmensen reduction of purely aliphatic γ-keto acids and their esters has not been studied extensively. Ethyl levulinate [13] yields ethyl valerate, but neither γ-ketopimelic acid nor its dimethyl ester [27] is reduced.

Other Keto Acids. δ-Keto acids and molecules in which the keto group is still further removed from the carboxyl group react normally in both aliphatic and aliphatic-aromatic series. Thus, the reductions

[20] Wislicenus and Weitemeyer, *Ann.*, **436**, 1 (1924).

[21] Windaus, *Ann.*, **447**, 233 (1926).

[22] Guha, *Ber.*, **72**, 1359 (1939).

[23] Overbaugh, Allen, Martin, and Fieser, *Org. Syntheses*, **15**, 64 (1935).

[24] Fieser and Hershberg, *J. Am. Chem. Soc.*, **58**, 2382 (1936).

[25] Fieser and Seligman, *J. Am. Chem. Soc.*, **60**, 170 (1938).

[26] (*a*) Fieser and Peters, *J. Am. Chem. Soc.*, **54**, 4373 (1932); (*b*) Haworth and Mavin, *J. Chem. Soc.*, 2720 (1932).

[27] Komppa, *Ann. Acad. Sci. Fennicae*, **A51**, No. 3 (1938) [*C. A.*, **34**, 2335 (1940)].

of γ-(*p*-anisoyl)-butyric acid,[28] of octacosan-14-one-1,28-dioic acid[29] [$HO_2C(CH_2)_{12}CO(CH_2)_{13}CO_2H$], and of 22-phenyldocosan-13-one-1-oic acid[30] [$C_6H_5(CH_2)_9CO(CH_2)_{11}CO_2H$] have been reported. With the last two compounds extended periods are required for the completion of the reaction.

α,β-Unsaturated Carbonyl Compounds

Little information is available concerning the Clemmensen reduction of α,β-unsaturated compounds. Both the carbonyl group and the ethylenic linkage of unsaturated acids of the β-aroylacrylic acid type[31] are reduced. Similarly, 2,3-diphenylcyclopentene-2-one-1 is converted to 2,3-diphenylcyclopentane.[32] *n*-Butylbenzene is obtained in 50% yield from benzalacetone, but the major product from benzalacetophenone is a bimolecular one, 1,3,4,6-tetraphenylhexane-1,6-dione.[33] Isolated double bonds apparently are not affected by amalgamated zinc and hydrochloric acid.

Chromanones are converted to chromans by means of amalgamated zinc and hydrochloric acid;[34] e.g., 7-hydroxy-2,2-dimethylchromanone is reduced to 7-hydroxy-2,2-dimethylchroman.[34a] Acylated coumarins are reduced to alkyl coumarins by the method of Clemmensen,[35] and it is reported that 6,8-diethyl-5-hydroxy-4-methylcoumarin is obtained by the reduction of 6-acetyl-8-ethyl-5-hydroxy-4-methylcoumarin.[35c]

The Reduction of Other Functional Groups by Amalgamated Zinc and Hydrochloric Acid

Compounds containing sensitive groups in addition to carbonyl sometimes undergo reductions of more than one type. It was mentioned above that an ethylenic link is reduced when it is conjugated with a carbonyl group. The double bond of α,β-unsaturated acids, such as cinnamic acid,[13] is also saturated by zinc amalgam and acid. Pyrroles[36] and

[28] Plant and Tomlinson, *J. Chem. Soc.*, 1092 (1935).

[29] Ruzicka, Brugger, Seidel, and Shinz, *Helv. Chim. Acta*, **11**, 496 (1928).

[30] Hills and Robinson, *J. Chem. Soc.*, 281 (1936).

[31] Sengupta, *J. Indian Chem. Soc.*, **17**, 183 (1940).

[32] Burton and Shoppee, *J. Chem. Soc.*, 567 (1939).

[33] Dippy and Lewis, *Rec. trav. chim.*, **56**, 1000 (1937).

[34] (*a*) Bridge, Crocker, Cubin, and Robertson, *J. Chem. Soc.*, 1530 (1937); (*b*) George and Robertson, *J. Chem. Soc.*, 1535 (1937); (*c*) Anderson and Marrian, *J. Biol. Chem.*, **127**, 647 (1939).

[35] (*a*) Chowdhry and Desai, *Proc. Indian Acad. Sci.*, **8A**, 1 (1938) [*C. A.*, **32**, 9065 (1938)]; (*b*) Limaye and Limaye, *Rasayanam* (*Suppl.*) (1938) [*C. A.*, **33**, 1698 (1939)]; (*c*) Desai and Ekhlas, *Proc. Indian Acad. Sci.*, **8A**, 567 (1938) [*C. A.*, **33**, 3356 (1939)].

[36] (*a*) Wibaut and Hackmann, *Rec. trav. chim.*, **51**, 1157 (1932); (*b*) Wibaut and Oosterhuis, *ibid.*, **52**, 941 (1933).

isoquinolines [37] appear to be easily reduced to pyrrolines and tetrahydroisoquinolines, and in one instance (p. 160) the reduction of a naphthalene to a tetralin has been observed. The hydroxyl group of β-hydroxy acids [38] and of benzyl alcohol [13] is replaced by hydrogen upon treatment with amalgamated zinc and hydrochloric acid. The same reagent reduces γ-aryl-γ-lactones to γ-aryl butyric acids.[39] The halogen of α-halo acids [40] and α-haloketones [41] is substituted by hydrogen under the conditions of the Clemmensen reduction. With a few compounds the removal of a halogen atom attached to a benzene ring has been observed.[25] When ω-dimethylaminoacetophenone is reduced by the Clemmensen method the dimethylamino group is removed and ethylbenzene is produced.[42] Somewhat similar is the formation of ethylresorcinol from 2,4-dihydroxy-ω-butoxyacetophenone.[43] Under certain conditions, highly reactive ketones such as 2,6-dihydroxyvalerophenone (p. 159) and 2,2-diethyl-6,7,8,9-tetrahydro-1,3-naphthindandione [15a] undergo cleavage of carbon chains.

EXPERIMENTAL PROCEDURES

General Discussion

The procedure originally used by Clemmensen is satisfactory for the reduction of many carbonyl compounds which are appreciably soluble in the acid mixture or which melt below the boiling point of the reaction mixture. The exact proportions of zinc and hydrochloric acid employed are not of great importance provided that both are present in large excess. Although most reductions reported in the literature have made use of 20–40% hydrochloric acid, many have been successful with acid as dilute as 5%. It has been shown [23] that the product obtained from β-benzoylpropionic acid in the presence of constant-boiling hydrochloric acid is not as pure as that obtained when concentrated hydrochloric acid is used.

The reduction is carried out generally by heating the mixture under reflux for a period of four to ten hours. Longer reaction periods are required in some instances. Occasionally it is desirable to carry out the

[37] (*a*) Awe, *Ber.*, **67**, 836 (1934); (*b*) Awe and Unger, *Ber.*, **70**, 472 (1937).

[38] Cook and Lawson, *J. Chem. Soc.*, 827 (1933).

[39] (*a*) Martin, *J. Am. Chem. Soc.*, **58**, 1438 (1936); (*b*) Fieser and co-workers, *ibid.*, **58**, 2382 (1936); **60**, 170, 1940 (1938); **61**, 862 (1939); (*c*) Newman and Orchin, *ibid.*, **60**, 586 (1938); (*d*) Hewett, *J. Chem. Soc.*, 293 (1940).

[40] Clemo, Haworth, and Walton, *J. Chem. Soc.*, 2368 (1929).

[41] (*a*) Johnson and Hodge, *J. Am. Chem. Soc.*, **35**, 1014 (1913); (*b*) Funke and Ristic, *J. prakt. Chem.*, **146**, 151 (1936).

[42] v. Braun and Weissbach, *Ber.*, **62**, 2416 (1929).

[43] Hurd and Fowler, *J. Am. Chem. Soc.*, **61**, 249 (1939).

reaction at room temperature, particularly when the carbonyl compound is sensitive to the strong acid mixture. In such cases the reactants are allowed to stand at room temperature for one to two days and the reduction is then completed by heating to reflux for a period ranging from fifteen minutes to two hours. By this method 3,4-dihydroxytoluene has been obtained from 3,4-dihydroxybenzaldehyde,[44] and γ-(α-thienyl)-butyric acid is produced in excellent yield from β-(α-thenoyl)-propionic acid.[45]

An improvement in yield frequently results if the substance to be reduced is first converted to a derivative which has a lower melting point and a greater solubility in the reaction mixture. Although β-3-acenaphthoylpropionic acid [26a] and β-(1-methyl-4-naphthoyl)-propionic acid [26b] are not attacked by amalgamated zinc and hydrochloric acid, their ethyl esters are reduced in yields of about 40%.

The use of mechanical stirring has been reported in the conversion of 4-acylresorcinols [12a] to alkylresorcinols, but in most cases sufficient agitation is provided by the ebullition of the hot acid.

The physical form of the zinc appears not to be critical, since zinc turnings, zinc wool, granulated zinc, zinc powder, and mossy zinc have given good results. Mossy zinc has been most commonly used. It has been reported [2] that a very satisfactory zinc dust can be prepared by pulverizing pure zinc.

The zinc is ordinarily amalgamated by treatment with 5 to 10% of its weight of mercuric chloride in the form of a 5 to 10% aqueous solution. The time required for amalgamation can be diminished by employing a solution of mercuric chloride in very dilute hydrochloric acid.[17] In order to obtain a homogeneous amalgam, it is advisable to shake or stir the mixture during the amalgamation. The quality of the amalgam is said to be improved by three washings of the zinc with hot hydrochloric acid [2] before amalgamation.

Preparation of Zinc Amalgam

A mixture of 100 g. of mossy zinc, 5 to 10 g. of mercuric chloride, 5 cc. of concentrated hydrochloric acid, and 100 to 150 cc. of water is stirred or shaken for five minutes. The aqueous solution is decanted, and the amalgamated zinc is covered with 75 cc. of water and 100 cc. of concentrated hydrochloric acid. The material to be reduced, usually 40 to 50 g., is then added immediately and the reaction is started.

[44] Anshultz and Wenger, *Ann.*, **482**, 25 (1930).
[45] Fieser and Kennelly, *J. Am. Chem. Soc.*, **57**, 1611 (1935).

The Clemmensen Reduction in the Absence of an Organic Solvent (Method I)

Reduction of β-(*p*-Toluyl)-propionic acid.[17] A mixture of amalgamated zinc (prepared from 100 g. of mossy zinc and 5 g. of mercuric chloride as described above), 75 cc. of water, 175 cc. of concentrated hydrochloric acid, and 50 g. of β-(*p*-toluyl)-propionic acid is refluxed vigorously for ten hours in a 1-l. round-bottomed flask. A 50-cc. portion of concentrated hydrochloric acid is added every three hours during the heating period. After the reaction mixture has been cooled to room temperature, the solid γ-(*p*-tolyl)-butyric acid is collected and washed with small amounts of cold water. The filtrate and washings are combined and extracted with three 75-cc. portions of ether. The solid product is dissolved in the combined extracts and, after filtration from a small amount of insoluble material, the solution is dried over calcium chloride. The solvent is then removed and the residue is distilled under diminished pressure. The product, a colorless oil, crystallizes to a white solid melting at 61–62°. The yield is 41 g. (88%).

Reduction of 2,4-Dihydroxyacetophenone.[1b, 41a, 46] A mixture of amalgamated zinc (prepared from 200 g. of mossy zinc and 10 g. of mercuric chloride as described on p. 163), 150 cc. of water, 150 cc. of concentrated hydrochloric acid, and 50 g. of 2,4-dihydroxyacetophenone (resacetophenone) is refluxed in a 1-l. round-bottomed flask until a drop of the liquid in ethanol gives no color with aqueous ferric chloride. A portion of about 10–15 cc. of concentrated hydrochloric acid is added hourly. When the color test indicates the reaction to be complete (three to four hours) the mixture is cooled and the solution is decanted from any unchanged zinc amalgam. The solution is saturated with sodium chloride and extracted with ether to remove the reaction product. Removal of the solvent yields a light yellow solid which crystallizes from benzene or chloroform as thick white prisms, m.p. 97°. The yield is 44 g. (97%).

The Clemmensen Reduction in the Presence of a Solvent Miscible with Aqueous Hydrochloric Acid (Method II)

Certain carbonyl compounds which are not appreciably soluble in the acid mixture are reduced with difficulty by Method I. In such cases the reaction is often facilitated by the addition of a solvent, such as ethanol, acetic acid, or dioxane, which is miscible with the aqueous hydrochloric acid. For example, bilianic acid is reduced by means of a

[46] Brewster and Harris, *J. Am. Chem. Soc.*, **52**, 4866 (1930).

mixture of acetic and hydrochloric acids,[47] and γ-(3-phenanthryl)-butyric acid is obtained in 50% yield by the gradual addition of concentrated hydrochloric acid to a boiling mixture of β-(3-phenanthroyl)-propionic acid, acetic acid, and amalgamated zinc.[48] The use of acetic acid as a solvent in the reduction of a number of natural products has become standard practice (see p. 197). In some cases it is used without the addition of hydrochloric acid.

Ethanol is employed to increase the solubility of α-, β-, and γ-keto esters.[13] It has been reported that γ-keto-γ-(2-fluorene)-butyric acid is unaffected by the Clemmensen reduction according to Method I, but that it is reduced almost quantitatively in the presence of aqueous ethanol.[49] The cleavage of 2,6-dihydroxyvalerophenone is avoided by carrying out the reaction in aqueous ethanol,[14] and the reduction of other hydroxyphenyl alkyl ketones is assisted by the same solvent.[50] The gradual addition of an ethanolic solution of the ketone or aldehyde to a refluxing mixture of aqueous hydrochloric acid and zinc has given excellent yields of reduction products from various indanones [51] and aromatic aldehydes.[2] The preparation of 4-chloro-7-methylindan illustrates this procedure.

Preparation of 4-Chloro-7-methylindan.[52] A solution of 100 g. of a mixture of 4-chloro-7-methyl-1-indanone and 7-chloro-4-methyl-1-indanone [52] in 500 cc. of ethanol is added in portions, over a period of four to five hours, to a refluxing mixture of 100 cc. of water, 40 cc. of ethanol, 250 cc. of concentrated hydrochloric acid, and the amalgamated zinc prepared from 350 g. of granulated zinc and 17.5 g. of mercuric chloride (see p. 163). After the addition is complete the mixture is refluxed for ten hours, during which time 200 cc. of concentrated hydrochloric acid is added in portions. The mixture is cooled; the aqueous layer is decanted and, after dilution with an equal volume of water, is extracted twice with ether. The greater portion of the product is recovered by extraction of the zinc residues with ether. Any lumps of material must be broken up to facilitate the extraction. The ether extracts are combined, and, after removal of the solvent, the residual oil is steam-distilled from an aqueous solution of sodium hydroxide. The colorless oil is separated from the distillate, and the aqueous layer is extracted with ether. The oil is combined with the ether solution and, after drying and removal of the solvent, is distilled under diminished pressure. The

[47] Borsche and Rosenkranz, *Ber.*, **52**, 342 (1919).
[48] Haworth and Mavin, *J. Chem. Soc.*, 1012 (1933).
[49] Koelsch, *J. Am. Chem. Soc.*, **55**, 3885 (1933).
[50] Coulthard, Marshall, and Pyman, *J. Chem. Soc.*, 280 (1930).
[51] Fieser and Seligman, *J. Am. Chem. Soc.*, **57**, 942 (1935).
[52] Fieser and Seligman, *J. Am. Chem. Soc.*, **58**, 2482 (1936).

product is a colorless liquid b.p. 132–133°/25 mm. The yield is 88.5 g. (95%).

Reduction of γ-Keto-γ-(2-fluorene)-butyric Acid.[49] A mixture of 90 g. of γ-keto-γ-(2-fluorene)-butyric acid, 450 cc. of ethanol, 450 cc. of concentrated hydrochloric acid, and 180 g. of amalgamated zinc is refluxed for one hour. A second 450–cc. portion of concentrated hydrochloric acid is then added, and refluxing is continued for eight hours. The mixture is cooled, and the solid is collected and dissolved by boiling with 1000 cc. of 5% aqueous sodium hydroxide. After filtration and acidification the γ-(2-fluorene)-butyric acid separates. The yield of crude product is 85 g. It is readily purified by recrystallization from acetic acid followed by recrystallization from benzene-petroleum ether, yielding white plates, m.p. 151–151.5°.

The Clemmensen Reduction in the Presence of a Solvent Immiscible with the Hydrochloric Acid (Method III)

A large number of carbonyl compounds have been reduced in poor yields by Methods I and II, and, especially in the cases of certain keto acids, the difficulty has been ascribed to the formation of insoluble polymolecular reduction products which coat the surface of the zinc.[17] The addition of a hydrocarbon solvent, such as toluene, which is immiscible with the hydrochloric acid is beneficial in those cases because it keeps most of the material out of contact with the zinc, and in the aqueous layer the reduction occurs at such a high dilution that polymolecular reactions are largely inhibited.

The modification is particularly advantageous with keto acids which contain methoxyl groups. Such compounds may suffer hydrolysis of methoxyl groups during the reduction; consequently it is desirable to treat an alkaline solution of the crude reaction product with methyl sulfate, in the presence of a trace of sodium hydrosulfite if darkening occurs during methylation, to recover any demethylated material.

Certain extremely insoluble compounds cannot be reduced by this method unless both the aqueous layer and the hydrocarbon layer are in contact with the zinc.

Reduction of β-Benzoylpropionic Acid.[17] To 120 g. of mossy zinc, amalgamated as described on p. 163, 75 cc. of water, 175 cc. of concentrated hydrochloric acid, and 100 cc. of toluene is added 50 g. of β-benzoylpropionic acid. The mixture is refluxed briskly for twenty-four to thirty hours, during which time a 50-cc. portion of concentrated hydrochloric acid is added every six hours. The solution is cooled to room temperature, the aqueous layer is separated and, after dilution with 200

cc. of water, is extracted with three 75-cc. portions of ether. The combined ether and toluene solutions are washed with a little water and dried over calcium chloride. The solvents are removed by distillation under diminished pressure, and the residue is distilled. γ-Phenylbutyric acid, b.p. 178–181°/19 mm., is obtained as a colorless oil which solidifies to white crystals, m.p. 46–48°. The yield is 41 g. (90%).

Reduction of β-(*p*-Anisoyl)-propionic Acid.[17] To 120 g. of mossy zinc amalgamated as described on p. 163 are added, in the order given, the following: 75 cc. of water, 175 cc. of concentrated hydrochloric acid, 100 cc. of toluene, and 50 g. of β-(*p*-anisoyl)-propionic acid. The mixture is refluxed briskly for forty-eight hours, during which time a 25-cc. portion of concentrated hydrochloric acid is added every six hours. The solution is cooled to room temperature; the aqueous layer is separated and, after dilution with 200 cc. of water, is extracted with three 75-cc. portions of ether. The toluene and ether extracts are added to 300 cc. of 5% aqueous sodium hydroxide, and the solvents are removed by steam distillation.

The residual alkaline solution is cooled to 80°, and 5 to 10 cc. of methyl sulfate is added. If necessary, aqueous sodium hydroxide is introduced to keep the solution alkaline. After the mixture has been shaken or stirred for thirty to forty-five minutes, the excess alkali is neutralized and the solution is treated with charcoal. The colorless or yellow filtrate is cooled to 10° and acidified by the slow addition of hydrochloric acid. The mixture is kept in an ice bath until the precipitation of the product is complete. It is then filtered and the solid is washed with a little cold water. The crude material, obtained in quantitative yield, is sufficiently pure for most purposes. For purification it is dissolved in ether and the solution is filtered from any insoluble material. The solvent is removed and the residue is distilled under diminished pressure. The yield of γ-(*p*-anisyl)-butyric acid, b.p. 182–186°/4 mm., m.p. 61–62°, is 43 g. (94%). For further purification the acid may be recrystallized from petroleum ether (b.p. 30–60°).

Reduction of Stearophenone.[10] Mossy zinc is added to a weighed 2-l. Erlenmeyer flask until a layer about 8 cm. deep is formed. The weight of the zinc is determined, and the metal is amalgamated by treatment with the appropriate amounts of mercuric chloride, water, and hydrochloric acid (p. 163). To the zinc amalgam is added sufficient concentrated hydrochloric acid to cover about one half of it, followed by a solution of 250 g. of stearophenone in 750 cc. of xylene. The mixture is heated under reflux for seven hours, during which time gaseous hydrogen chloride is passed into the bottom of the flask to replace losses. The xylene layer is separated, the solvent removed, and the product distilled, b.p.

220–235°/5 mm. A residue of about 30 g. of a heavy oil is discarded. The distillate is dissolved in 750 cc. of xylene and treated with another portion of zinc amalgam and hydrochloric acid as described above. The product isolated, b.p. 195–205°/4 mm., m.p. 33°, weighs 190 g. (77%). Crystallization of the *n*-octadecylbenzene from ether yields a product of m.p. 35–36°.

The Clemmensen Reduction in the Presence of Solvents of Both Types (Method IV)

Certain carbonyl compounds of very slight solubility are reduced in the presence of toluene only when a small amount of a solvent such as acetic acid, ethanol, or dioxane is added to the reaction mixture. The water-soluble solvent effects a satisfactory distribution of the compound between the two layers, permitting a low concentration of the material in the aqueous layer. 4-Hydroxy-3-phenylpropiophenone,[53] and 4-methyl-1-keto-1,2,3,4-tetrahydrophenanthrene [54] have been reduced by this modification in yields of 74 and 94%, respectively. The experimental procedure is essentially the same as that of Method III.

The Clemmensen Reduction with Unamalgamated Zinc (Method V)

Unamalgamated zinc has been employed successfully with chlorogenone, cholestanedione-3,6, cholestanone-7, and other ketones of the sterol family.[55] The compound to be reduced is dissolved in 95% ethanol, and 20-mesh granulated zinc is added. To the boiling mixture small amounts of concentrated hydrochloric acid are added over a period of several hours. Apparently this procedure represents another modification suitable for ketones of very low water solubility.

TABLE OF COMPOUNDS REDUCED BY THE CLEMMENSEN METHOD

In the following pages the compounds which have been reduced by the Clemmensen procedure are tabulated. Since many of these reactions were carried out before the development of the modified procedures, it is likely that in many cases the yields reported do not represent the maxima now obtainable.

The compounds in the table are grouped according to the number of carbon atoms present. The method of reduction is indicated, and the yield is included if it is available. The nature of the product is given only when the reaction follows an abnormal course.

[53] Harris and Pierce, *J. Am. Chem. Soc.*, **62**, 2223 (1940).

[54] Bachmann and Edgerton, *J. Am. Chem. Soc.*, **62**, 2219 (1940).

[55] Marker and Rohrmann, *J. Am. Chem. Soc.*, **61**, 846, 946, 1284, 2719, 3314, 3479 (1939).

Compounds Reduced by the Clemmensen Method

C_5–C_7

Formula	Compound	Method	Yield *	Reference †
$C_5H_{10}O_2$	Pentanol-1-one-4	I	70	3
	R.P. ‡ *n*-Amyl alcohol			
$C_6H_8O_2$	Cyclohexadione-1,4	I	—	3
$C_6H_{10}O_3$	Ethyl acetoacetate	II	30	38
$C_6H_9ON_3$	4-Methyl-5-aminoacetylimidazole	I	0	418
C_7H_6O	Benzaldehyde	I	46	1
		I	12	38
$C_7H_{14}O$	*n*-Heptanal	I	72	1
$C_7H_6O_2$	Salicylaldehyde	I	70	2
$C_7H_6O_2$	*m*-Hydroxybenzaldehyde	I	40	2
$C_7H_6O_2$	*p*-Hydroxybenzaldehyde	I	95	2
$C_7H_6O_3$	2,4-Dihydroxybenzaldehyde	I	—	2
		I	—	57
		II	—	253
$C_7H_6O_3$	2,6-Dihydroxybenzaldehyde	I	—	278
$C_7H_{12}O_3$	Ethyl levulinate	II	55	38

C_8

C_8H_8O	Acetophenone	I	80	38
		I	80	1
$C_8H_{12}O$	*cis* and *trans*-β-Bicyclo-0:3:3)-octanone	II	—	153
$C_8H_{12}O$	5,5-Dimethylcyclohexene-2-one-1	I	—	285
$C_8H_8O_2$	*p*-Hydroxyacetophenone	I	Q	2
$C_8H_{12}O_2$	5,5-Dimethylcyclohexadione-1,3	I	—	182
$C_8H_6O_3$	Phenylglyoxylic acid	I	70	38
	R.P.‡ Mandelic acid			
$C_8H_8O_3$	3,4-Dihydroxyacetophenone	I	75	2
$C_8H_8O_3$	2,4-Dihydroxyacetophenone	I	Q	2
		I	Q	5
		I	82	103
		I	Q	57
$C_8H_8O_3$	2,6-Dihydroxyacetophenone	I	49	390
$C_8H_8O_3$	2,5-Dihydroxyacetophenone	I	70	2
		I	—	5
		I	30	426
$C_8H_8O_3$	2-Hydroxy-3-methoxybenzaldehyde	I	49	87
		III	67	345
$C_8H_8O_3$	2,4-Dihydroxy-5-methylbenzaldehyde	II	—	253

* Q, yield reported as quantitative; G, yield reported as good, P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

Formula	Compound	Method	Yield *	Reference †
$C_8H_{12}O_3$	β-(Cyclopentanone-2)-propionic acid	I	72	178
		I	74	180
$C_8H_8O_4$	2,4,6-Trihydroxyacetophenone	I	48	457
$C_8H_8O_4$	2,3,6-Trihydroxy-4-methylbenzaldehyde	I	—	79
$C_8H_8O_4$	2,3,4-Trihydroxyacetophenone	I	95	2
C_8H_6OS	Thiochromanone	I	—	47
$C_8H_{13}ON$	2-Keto-octahydropyrrocoline	I	27	250
$C_8H_{13}ON$	7-Keto-octahydropyrrocoline	I	40	419
$C_8H_7O_2Br$	2-Hydroxy-5-bromoacetophenone	I	—	164
$C_8H_7O_2Cl$	2-Hydroxy-5-chloroacetophenone	I	42	41
		I	—	165
$C_8H_6O_2Cl_2$	3,5-Dichloro-2-hydroxyacetophenone	I	—	408
$C_8H_7O_3Br$	3,4-Dihydroxy-5-bromoacetophenone	I	—	406
	R.P.‡ 4-Ethylresorcinol			
$C_8H_7O_3Cl$	ω-Chloro-3,4-dihydroxyacetophenone	I	G	5
	R.P.‡ 3,4-Dihydroxyethylbenzene			
$C_8H_7O_3Cl$	2,4-Dihydroxy-5-chloroacetophenone	I	—	167
		I	—	406
$C_8H_6O_3Br_2$	2,4-Dihydroxy-3,5-dibromoacetophenone	I	—	103
$C_8H_6O_3Cl_2$	2,4-Dihydroxy-3,5-dichloroacetophenone	I	—	103
$C_8H_8O_3S$	β-(α-Thenoyl)-propionic acid	I	72	468
	C_9			
C_9H_8O	Indanone-1	I	90	3
$C_9H_{10}O$	Propiophenone	I	90	1
$C_9H_{10}O$	Benzyl methyl ketone	I	90	1
$C_9H_{10}O$	*m*-Methylacetophenone	I	G	19
$C_9H_{10}O$	*p*-Methylacetophenone	I	—	19
$C_9H_{10}O$	4-Hydroxy-2,3-dimethylbenzaldehyde	I	—	77
$C_9H_{14}O$	*l-trans*-β-hydrindanone	I	—	181
		I	—	173
$C_9H_{14}O$	2,2-Dimethyl-3-keto-bicyclo(1:2:2)heptane	I	—	24
$C_9H_{10}O_2$	*p*-Methoxyacetophenone	I	59	5
$C_9H_{10}O_2$	*p*-Hydroxypropiophenone	I	Q	2
		II	—	91
		I	73	141
$C_9H_{10}O_2$	2-Hydroxypropiophenone	I	71	141
$C_9H_{10}O_2$	2-Methyl-4-hydroxyacetophenone	I	90	73
$C_9H_{10}O_2$	4-Hydroxy-2,6-dimethylbenzaldehyde	I	40	75
$C_9H_{10}O_2$	2-Hydroxy-4,5-dimethylbenzaldehyde	I	—	75
$C_9H_{10}O_2$	4-Hydroxy-2,6-dimethylbenzaldehyde	I	73	74
$C_9H_{10}O_2$	2-Hydroxy-3-methylacetophenone	I	—	41
		I	79	74
$C_9H_{10}O_2$	2-Hydroxy-4-methylacetophenone	I	75	74

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

Formula	Compound	Method	Yield *	Reference †
$C_9H_{10}O_2$	4-Hydroxy-3-methylacetophenone	I	—	73
$C_9H_{10}O_3$	3,4-Dimethoxybenzaldehyde	I	31	228
$C_9H_{10}O_3$	2,4-Dihydroxy-3-ethylbenzaldehyde	II	87	161
$C_9H_{10}O_3$	2,4-Dihydroxy-5-ethylbenzaldehyde	II	—	161
$C_9H_{10}O_3$	3-Hydroxy-4-methoxyacetophenone	II	—	91
$C_9H_{10}O_3$	2,4-Dihydroxypropiophenone	I	60	57
$C_9H_{10}O_3$	2,4-Dihydroxy-6-methylacetophenone	I	55	161
$C_9H_{10}O_3$	2,6-Dihydroxy-3-methylacetophenone	III	67	312
$C_9H_{10}O_3$	2,6-Dihydroxypropiophenone	I	75	390
$C_9H_{10}O_3$	2,4-Dihydroxypropiophenone	I	—	406
		I	Q	5
$C_9H_{10}O_3$	2,5-Dihydroxypropiophenone	I	30	426
		I	—	5
$C_9H_{12}O_3$	2,3,3-Trimethylcyclopentene-1-one-4-carboxylic acid	I	—	286
	R.P.‡ 1,2,2-Trimethyl-3-cyclopentanecarboxylic acid			
$C_9H_8O_4$	3-Acetyl-2,4-dihydroxybenzaldehyde	II	—	339
$C_9H_8O_4$	3-Acetyl-2,6-dihydroxybenzaldehyde	II	44	330
$C_9H_{10}O_4$	2,4,6-Trihydroxypropiophenone	I	45	457
$C_9H_8O_5$	3-Carbomethoxy-2,6-dihydroxybenzaldehyde	II	72	278
		I	—	246
$C_9H_{14}O_5$	Dimethyl γ-ketopimelate	II	0	409
$C_9H_8O_6$	Bicyclo(2:2:1)heptane-3,7-dione-1,2-dicarboxylic acid	I	—	414
C_9H_7OBr	4-Bromo-1-indanone	II	77	335
		II	77	195
C_9H_7OCl	4-Chloro-1-indanone	II	—	327
$C_9H_9O_2Br$	3-Bromo-6-hydroxypropiophenone	I	—	164
$C_9H_9O_2Cl$	3-Chloro-6-hydroxypropiophenone	I	—	165
$C_9H_9O_2Cl$	3-Chloro-4-methyl-6-hydroxyacetophenone	I	—	165
$C_9H_8O_2Cl_2$	3,5-Dichloro-2-hydroxypropiophenone	I	—	408
$C_9H_9O_3Cl$	3-Chloro-4,6-dihydroxypropiophenone	I	—	406
$C_9H_8O_3Br_2$	3,5-Dibromo-2,4-dihydroxypropiophenone	I	—	103
$C_9H_{15}ON$	4-Keto-5,5'-dimethyldi-(1,2)pyrrolidine	I	—	214
$C_9H_{15}ON$	2-Methyl-3-keto-octahydropyrrocoline	I	—	188
	R.P.‡ 3-Hydroxy-2-methyloctahydropyrrocoline			
$C_9H_{15}ON$	5-Methyl-7-keto-octahydropyrrocoline	I	63	419
$C_9H_{15}ON$	3-Keto-octahydropyridocoline	I	42	188
$C_9H_{15}ON$	4-Ketodecahydroquinoline	I	33	273
$C_9H_{15}ON$	1-Keto-octahydropyridocoline	I	60	101
		I	—	213
$C_9H_{15}ON$	2-Keto-octahydropyridocoline	I	33	213
C_9H_8OS	4-Ketoisothiochroman	I	30	96
	R.P.‡ 1-Methylthiophthalan			
$C_9H_{12}OS$	2,3,5-Trimethyl-4-acetothienone	I	75	95

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

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‡ R.P., reduction product.

C_{10}

Formula	Compound	Method	Yield *	Reference †
$C_{10}H_{10}N_2$	1-Methyl-2-(3-pyridyl)-pyrrole	I	70	147
$C_{10}H_{10}N_2$	1-Methyl-2-(2-pyridyl)-pyrrole	I	12	166
$C_{10}H_{10}O$	Benzalacetone	I	50	288
$C_{10}H_{12}O$	4-Ethylacetophenone	I	—	19
		I	—	76
$C_{10}H_{12}O$	4-Phenyl-2-butanone	I	Q	1
$C_{10}H_{12}O$	Butyrophenone	I	88	1
$C_{10}H_{12}O$	2,5-Dimethylacetophenone	I	80	11
$C_{10}H_{12}O$	3-Methylpropiophenone	I	G	19
$C_{10}H_{12}O$	4-Methylpropiophenone	I	66	19
$C_{10}H_{16}O$	*trans*-β-Decalone	I	—	45
$C_{10}H_{16}O$	*cis*-β-Decalone	II	75	153
$C_{10}H_{16}O$	8-Methylhydrindanone-6	I	—	446
$C_{10}H_{16}O$	5-Methyl-2-isopropyl-bicyclo(5:1:$0^{2,6}$)hexanone-1	I	28	235
$C_{10}H_{16}O$	d-Thujone	I	50	235
$C_{10}H_{12}O_2$	3-Ethyl-4-hydroxy-5-methylbenzaldehyde	I	60	74
$C_{10}H_{12}O_2$	5-Ethyl-4-hydroxy-2-methylbenzaldehyde	I	60	74
$C_{10}H_{12}O_2$	2-Hydroxy-3,4,6-trimethylbenzaldehyde	I	—	74
$C_{10}H_{12}O_2$	3-Hydroxy-2,4,6-trimethylbenzaldehyde	I	—	60
$C_{10}H_{12}O_2$	4-Ethoxyacetophenone	I	58	5
$C_{10}H_{12}O_2$	5-Ethyl-2-hydroxyacetophenone	I	80	73
$C_{10}H_{12}O_2$	2-Hydroxy-3,4-dimethylacetophenone	I	60	73
$C_{10}H_{12}O_2$	2-Hydroxy-4,6-dimethylacetophenone	I	75	8
$C_{10}H_{12}O_2$	2-Hydroxy-4,5-dimethylacetophenone	I	76	74
$C_{10}H_{12}O_2$	5-Hydroxy-2,4-dimethylacetophenone	I	—	73
$C_{10}H_{12}O_2$	4-Hydroxy-3,5-dimethylacetophenone	I	46	73
$C_{10}H_{12}O_2$	4-Hydroxybutrophenone	I	—	451
		II	—	91
$C_{10}H_{12}O_2$	2-Hydroxy-3-methylpropiophenone	I	—	41
$C_{10}H_{14}O_2$	8-Methylhydrindione-4,6	I	—	446
		I	—	185
$C_{10}H_{10}O_3$	2,6-Dihydroxy-3-propionylbenzaldehyde	II	—	376
$C_{10}H_{10}O_3$	Ethyl phenylglyoxylate R.P.‡ Ethyl mandelate	II	57	38
$C_{10}H_{10}O_3$	β-Benzoylpropionic acid	III	90	466
		III	90	465
		I	78	464
$C_{10}H_{10}O_3$	γ-Phenyl-γ-butyrolactone	III	81	465
$C_{10}H_{10}O_3$	3-Ethyl-4,6-dihydroxy-2-methylbenzaldehyde	I	64	455
$C_{10}H_{12}O_3$	2,4-Dihydroxybutyrophenone	I	78	57
$C_{10}H_{12}O_3$	5-Ethyl-2,4-dihydroxyacetophenone	I	82	86
		I	—	454
$C_{10}H_{12}O_3$	2,6-Dimethoxyacetophenone	I	—	240
$C_{10}H_{12}O_3$	3-Ethyl-2,4-dihydroxyacetophenone	I	—	291

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

Formula	Compound	Method	Yield *	Reference †
$C_{10}H_{12}O_3$	3-Hydroxy-4-methoxypropiophenone	II	—	91
$C_{10}H_{12}O_3$	2,4-Dihydroxy-3-methylpropiophenone	I	—	376
$C_{10}H_{12}O_3$	2,4-Dihydroxyphenyl isopropyl ketone	I	71	110
		I	—	53
$C_{10}H_{12}O_3$	2,5-Dihydroxybutyrophenone	I	30	426
		I	—	239
$C_{10}H_{12}O_3$	2,6-Dihydroxybutyrophenone	I	75	390
$C_{10}H_{14}O_3$	Cyclopentanespirocyclopentan-2-one-5-carboxylic acid	I	—	438
$C_{10}H_{16}O_3$	4-Keto-5-cyclopentylvaleric acid	I	—	441
$C_{10}H_{16}O_3$	(1,6-Dimethylcyclohexanone-3)-acetic acid	I	—	329
$C_{10}H_{10}O_4$	1,3-Diacetyl-4,6-dihydroxybenzene	I	82	86
		I	—	54
$C_{10}H_{10}O_4$	β-2-Hydroxybenzoylpropionic acid	I	—	452
		III	96	403
		I	—	432
$C_{10}H_{12}O_4$	2,4,6-Trimethoxybenzaldehyde	I	0	111
$C_{10}H_{12}O_4$	5-Ethyl-2,3,4-Trihydroxyacetophenone	I	75	2
$C_{10}H_{12}O_4$	2-Hydroxy-4-(β-hydroxyethoxy) acetophenone	I	90	184
$C_{10}H_{12}O_4$	2,4,6-Trihydroxybutyrophenone	I	56	457
$C_{10}H_{12}O_4$	3-Carboxy-4-hydroxypropiophenone	I	—	89
$C_{10}H_{14}O_4$	3-Acetyl-2,6-dihydroxyacetophenone	I	46	291
$C_{10}H_{10}O_5$	3-Carboxy-2,6-dimethoxybenzaldehyde	II	—	278
$C_{10}H_{14}O_5$	3-Carboxy-3-methylcyclopentanone-2-β-propionic acid	I	—	412
$C_{10}H_9OBr$	4-Bromo-7-methyl-1-indanone	II	87	175
$C_{10}H_9OBr$	7-Bromo-4-methyl-1-indanone	II	87	175
$C_{10}H_9OCl$	4-Chloro-7-methyl-1-indanone	II	95	222
$C_{10}H_9OCl$	7-Chloro-4-methyl-1-indanone	II	95	222
$C_{10}H_9OCl$	4-Chloro-6-methyl-1-indanone	II	78	395
$C_{10}H_{11}O_2Br$	5-Bromo-2-hydroxybutyrophenone	I	—	164
$C_{10}H_{11}O_2Cl$	5-Chloro-3-ethyl-2-hydroxyacetophenone	I	—	41
$C_{10}H_{11}O_2Cl$	5-Chloro-2-hydroxy-4-methylpropiophenone	I	—	165
$C_{10}H_{11}O_2Cl$	5-Chloro-2-hydroxybutyrophenone	I	—	165
$C_{10}H_{10}O_2Cl_2$	3,5-Dichloro-2-hydroxybutyrophenone	I	—	408
$C_{10}H_9O_3Br$	β-4-Bromobenzoylpropionic acid	III	75	263
$C_{10}H_{11}O_3Cl$	5-Chloro-2,4-dihydroxybutyrophenone	I	79	169
		I	—	167
$C_{10}H_{13}ON$	ω-Dimethylaminoacetophenone	I	—	96
	R.P.‡ Ethylbenzene			
$C_{10}H_{13}ON$	Ethyl (3,5-dimethyl-2-pyridyl) ketone	I	—	299
	R.P.‡ Ethyl (3,5-dimethyl-2-pyridyl) carbinol			
$C_{10}H_{17}ON$	1-Keto-2-methyloctahydropyridocoline	I	—	250
$C_{10}H_{17}ON$	1-Keto-8-methyloctahydropyridocoline	I	74	273
$C_{10}H_{12}OS$	2,7-Dimethyl-3-keto-3,4,5,6-tetrahydro-β-thionaphthen	I	P	287
$C_{10}H_{12}O_3S$	β-(2,5-Dimethyl-3-thenoyl)-propionic acid	I	71	287

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

C_{11}

Formula	Compound	Method	Yield *	Reference †
$C_{11}H_{12}O$	4,7-Dimethyl-1-indanone	I	73	458
$C_{11}H_{12}O$	7-Methyl-1-tetralone	I	44	35
$C_{11}H_{12}O$	Benzocycloheptenone-1	I	40	27
$C_{11}H_{14}O$	2,4,6-Trimethylacetophenone	I	G	19
		I	74	319
$C_{11}H_{14}O$	2,4,5-Trimethylacetophenone	I	77	319
		I	G	19
$C_{11}H_{14}O$	2,4-Dimethylpropiophenone	I	50	386
$C_{11}H_{14}O$	Isovalerophenone	I	—	428
$C_{11}H_{14}O$	*n*-Valerophenone	I	58	471
$C_{11}H_{16}O$	9-Methyl $\Delta^{4,10}$ (or $\Delta^{5,10}$) octalone-1	I	98	206
$C_{11}H_{16}O$	[2,2-Dimethylbicyclo(2:2:1^{3,6})heptyl]-acetaldehyde	I	77	24
$C_{11}H_{18}O$	Dicyclopentyl ketone	I	—	217
$C_{11}H_{20}O$	Cyclohexyl *n*-butyl ketone	I	—	217
$C_{11}H_{20}O$	Cyclohexyl isobutyl ketone	I	—	217
$C_{11}H_{22}O$	Methyl nonyl ketone	I	—	46
		I	88	1
$C_{11}H_{22}O$	3-*n*-Butylheptanone-2	I	16	46
$C_{11}H_{22}O$	Caprone	I	73	46
$C_{11}H_{12}O_2$	5,6-Dimethoxy-1-indanone	III	—	458
$C_{11}H_{12}O_2$	6-Methoxytetralone-1	I	—	432
$C_{11}H_{12}O_2$	Ethyl cinnamate	II	82	38
	R.P.‡ Ethyl hydrocinnamate			
$C_{11}H_{14}O_2$	4-Hydroxy-2-methyl-5-isopropylbenzaldehyde	I	87	2
$C_{11}H_{14}O_2$	4-Ethoxypropiophenone	I	77	5
$C_{11}H_{14}O_2$	2-Hydroxy-5-*n*-propylacetophenone	I	—	106
$C_{11}H_{14}O_2$	5-Ethyl-2-hydroxy-3-methylacetophenone	I	65	73
$C_{11}H_{14}O_2$	5-Ethyl-2-hydroxy-4-methylacetophenone	I	60	73
$C_{11}H_{14}O_2$	3-Ethyl-2-hydroxy-5-methylacetophenone	I	—	73
$C_{11}H_{14}O_2$	4-Ethyl-5-hydroxy-2-methylacetophenone	I	61	60
$C_{11}H_{14}O_2$	2-Hydroxy-3,4,5-trimethylacetophenone	I	75	74
$C_{11}H_{14}O_2$	2-Hydroxy-3,5,6-trimethylacetophenone	I	75	74
$C_{11}H_{14}O_2$	4-Hydroxy-3,5-dimethylpropiophenone	I	50	106
$C_{11}H_{14}O_2$	4-Hydroxyphenyl isobutyl ketone	I	—	428
$C_{11}H_{14}O_2$	2-Hydroxy-3-methylbutyrophenone	II	—	91
$C_{11}H_{14}O_2$	2-Hydroxy-5-methylbutyrophenone	II	—	91
$C_{11}H_{14}O_2$	4-Hydroxy-3-methylbutyrophenone	I	57	106
		II	—	91
$C_{11}H_{14}O_2$	2-Hydroxy-4-methylbutyrophenone	II	—	91
$C_{11}H_{14}O_2$	4-Hydroxyvalerophenone	II	—	91
$C_{11}H_{14}O_2$	Endomethylene-1,4-5,8-diketodecalin	I	59	72
$C_{11}H_{16}O_2$	9-Methyl-2,4-diketodecalin	I	60	114

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

Formula	Compound	Method	Yield *	Reference †
$C_{11}H_{16}O_2$	1,8,8-Trimethylbicyclo(1:2:3) octane-2,4-dione	I	—	90
$C_{11}H_{10}O_3$	3-Carboxy-1-keto-1,2,3,4-tetrahydronaphthalene	I	—	64
$C_{11}H_{12}O_3$	β-3-Methylbenzoylpropionic acid	III	84	200
$C_{11}H_{12}O_3$	β-*p*-Toluylpropionic acid	I	80	35
		I	80	135
		III	92	200
$C_{11}H_{12}O_3$	Ethyl benzoylacetate	II	59	38
$C_{11}H_{12}O_3$	γ-Benzoyl-*n*-butyric acid	I	—	230
$C_{11}H_{12}O_3$	α-Methyl-β-benzoylpropionic acid	I	—	35
$C_{11}H_{12}O_3$	7-Hydroxy-2,2-dimethylchromanone-4	I	60	251
$C_{11}H_{14}O_3$	3,5-Diethyl-2,6-dihydroxybenzaldehyde	I	60	455
$C_{11}H_{14}O_3$	2,6-Dimethoxypropiophenone	I	—	240
$C_{11}H_{14}O_3$	3,5-Dimethoxy-propiophenone	I	—	31
$C_{11}H_{14}O_3$	3,4-Dimethoxypropiophenone	I	65	5
$C_{11}H_{14}O_3$	4,5-Dimethoxy-2-methylacetophenone	I	78	228
$C_{11}H_{14}O_3$	4-Hydroxy-3-methoxybutyrophenone	II	—	91
$C_{11}H_{14}O_3$	2,6-Dihydroxyphenyl *n*-butyl ketone	II	73	396
$C_{11}H_{14}O_3$	2,6-Dihydroxyphenyl isobutyl ketone	II	73	226
$C_{11}H_{14}O_3$	2,4-Dihydroxyphenyl isobutyl ketone	I	83	110
		I	—	53
$C_{11}H_{14}O_3$	2,4-Dihydroxyphenyl *n*-butyl ketone	I	—	53
		I	85	396
$C_{11}H_{14}O_3$	3-Ethyl-4,6-dihydroxy-2-methylacetophenone	I	64	455
$C_{11}H_{14}O_3$	2,4-Dihydroxy-3-methylbutyrophenone	I	—	376
$C_{11}H_{14}O_3$	2,5-Dimethoxypropiophenone	I	54	5
		I	—	280
$C_{11}H_{14}O_3$	2,5-Dihydroxyphenyl *n*-butyl ketone	I	18	203
$C_{11}H_{14}O_3$	2,5-Dihydroxyphenyl isobutyl ketone	I	30	426
		I	—	239
$C_{11}H_{14}O_3$	2,5-Dihydroxy-3,4,6-trimethylacetophenone	II	—	315
$C_{11}H_{12}O_4$	β-*m*-Anisoylpropionic acid	III	60	465
		I	15	467
		I	67	207
$C_{11}H_{12}O_4$	β-*p*-Anisoylpropionic acid	III	90	475
		III	85	465
		I	—	452
		I	—	432
		I	—	284
		I	—	163
		I	—	35
$C_{11}H_{12}O_4$	α-Methyl-β-2-hydroxybenzoylpropionic acid	I	—	437
$C_{11}H_{12}O_4$	3-Carboxy-4-hydroxybutyrophenone	I	—	89
$C_{11}H_{12}O_4$	5,7-Dihydroxy-2,2-dimethylchromanone-4	II	65	227
$C_{11}H_{12}O_4$	3-Acetyl-4-ethyl-2,6-dihydroxybenzaldehyde	II	—	339
$C_{11}H_{14}O_4$	2,4,6-Trimethoxyacetophenone	I	23	111

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

Formula	Compound	Method	Yield *	Reference †
$C_{11}H_{14}O_4$	2,4,6-Trihydroxyphenyl *n*-butyl ketone	I	25	457
$C_{11}H_{14}O_4$	2,4,6-Trihydroxyphenyl isobutyl ketone	II	63	341
$C_{11}H_{14}O_4$	4-Carboxy-1,3-diketodecalin	I	—	114
$C_{11}H_{11}OBr$	4-Bromo-2,7-dimethyl-1-indanone	II	87	232
$C_{11}H_{11}OBr$	7-Bromo-2,4-dimethyl-1-indanone	II	87	232
$C_{11}H_{11}OBr$	4-Bromo-7-ethyl-1-indanone	II	80	266
$C_{11}H_{11}OBr$	7-Bromo-4-ethyl-1-indanone	II	80	266
$C_{11}H_{19}ON$	5-Isopropyl-7-keto-octahydropyrrocoline	I	50	419
$C_{11}H_{13}O_2Br$	5-Bromo-2-hydroxyphenyl *n*-butyl ketone	I	—	164
$C_{11}H_{13}O_2Cl$	5-Chloro-2-hydroxyphenyl *n*-butyl ketone	I	—	165
$C_{11}H_{12}O_2Cl_2$	3,5-Dichloro-2-hydroxyphenyl *n*-butyl ketone	I	—	408
$C_{11}H_{13}O_3N$	Ethyl β-2-pyridoylpropionate	I	63	133
$C_{11}H_{13}O_3N$	β-3,5-Dimethyl-2-pyridoylpropionic acid	I	91	299
	C_{12}			
$C_{12}H_{14}$	Di-Δ^1-cyclopentenylacetylene	I	5	261
	R.P.‡ 1,2,3,3*a*,4,5,6,7,8,8*b*-Decahydro-as-indacene			
$C_{12}H_{10}O$	Methyl α-naphthyl ketone	I	55	1
		I	—	126
$C_{12}H_{10}O$	Methyl β-naphthyl ketone	III	52	292
		III	52	220
		I	—	113
$C_{12}H_{12}O$	2,3-Benzobicyclo(0:3:3)-2-octen-4-one	I	—	442
$C_{12}H_{14}O$	7-Ethyl-1-tetralone	I	—	35
$C_{12}H_{14}O$	6-Acetyl-1-tetralin	I	—	22
$C_{12}H_{14}O$	6,7-Dimethyl-1-tetralone	I	80	135
$C_{12}H_{14}O$	5,7-Dimethyl-1-tetralone	I	80	135
		I	—	35
$C_{12}H_{14}O$	5,8-Dimethyl-1-tetralone	I	80	135
$C_{12}H_{14}O$	2,4-Dimethyl-1-tetralone	I	77	393
$C_{12}H_{14}O$	2,2-Dimethyl-1-tetralone	I	81	306
$C_{12}H_{16}O$	4-Ethyl-2,5-dimethylacetophenone	I	83	14
$C_{12}H_{16}O$	*p*-*n*-Propylpropiophenone	I	—	76
$C_{12}H_{16}O$	3-Methyl-1-phenylpentanone-1	I	38	236
$C_{12}H_{16}O$	*n*-Caprophenone	I	56	471
$C_{12}H_{20}O$	Cyclohexyl cyclopentyl ketone	I	—	217
$C_{12}H_{20}O$	8,10-Dimethyl-2-ketodecalin	I	—	115
$C_{12}H_{22}O$	Cyclododecanone	I	76	99
$C_{12}H_6O_2$	7,8-Diketoacenaphthene	I	35	172
$C_{12}H_{10}O_2$	2-Acetyl-1-naphthol	I	60	176
		I	—	415
$C_{12}H_{10}O_2$	4-Acetyl-1-naphthol	I	—	416
$C_{12}H_{14}O_2$	5-Methoxy-4,7-dimethyl-1-indanone	II	90	458

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

Formula	Compound	Method	Yield *	Reference †
$C_{12}H_{14}O_2$	7-Methoxy-2-methyl-1-tetralone	I	59	437
$C_{12}H_{16}O_2$	3,5-Diethyl-2-hydroxyacetophenone	I	60	73
$C_{12}H_{16}O_2$	5-Ethyl-4-methoxy-2-methylacetophenone	I	75	73
$C_{12}H_{16}O_2$	3-Ethyl-2-hydroxy-4,5-dimethylacetophenone	I	66	73
$C_{12}H_{16}O_2$	4-Ethyl-2-hydroxy-3,5-dimethylacetophenone	I	72	73
$C_{12}H_{16}O_2$	2-Hydroxy-5-*n*-propylpropiophenone	I	70	141
$C_{12}H_{16}O_2$	4-Hydroxy-3-*n*-propylpropiophenone	I	70	141
$C_{12}H_{16}O_2$	5-Ethyl-2-hydroxy-3-methylpropiophenone	I	51	106
$C_{12}H_{16}O_2$	3-Ethyl-4-hydroxy-5-methylpropiophenone	I	29	106
$C_{12}H_{16}O_2$	4-Hydroxy-3,5-dimethylbutyrophenone	I	48	106
$C_{12}H_{16}O_2$	2-Hydroxy-3-methylphenyl *n*-butyl ketone	II	—	91
$C_{12}H_{16}O_2$	2-Hydroxy-5-methylphenyl *n*-butyl ketone	II	—	91
$C_{12}H_{16}O_2$	2-Hydroxy-4-methylphenyl *n*-butyl ketone	II	—	91
$C_{12}H_{16}O_2$	4-Hydroxy-3-methylphenyl *n*-butyl ketone	II	—	91
$C_{12}H_{16}O_2$	4-Hydroxycaprophenone	II	—	91
$C_{12}H_{18}O_2$	2,4-Diketo-5,9-dimethyldecalin	I	—	114
$C_{12}H_{18}O_2$	1,1[1]-Ethynylenebiscyclopentanol	I	3	261
$C_{12}H_{12}O_3$	γ-(*p*-Toluyl)-buten-3-oic acid	I	Q	378
$C_{12}H_{12}O_3$	2-Phenylcyclopentanone-3-carboxylic acid	I	—	442
$C_{12}H_{12}O_3$	3,4-Dihydroxy-1,2-benzocycloheptenone-1′-methylene ether	I	—	27
$C_{12}H_{14}O_3$	β-4-Ethylbenzoylpropionic acid	III	91	397
		III	94	338
		I	—	219
		I	—	35
$C_{12}H_{14}O_3$	α,α-Dimethyl-β-benzoylpropionic acid	I	71	306
		I	—	283
$C_{12}H_{14}O_3$	Ethyl β-benzoylpropionate	I	—	36
$C_{12}H_{14}O_3$	β-2,5-Dimethylbenzoylpropionic acid	I	90	116
		I	80	135
$C_{12}H_{14}O_3$	β-2,4-Dimethylbenzoylpropionic acid	I	80	135
		I	—	35
$C_{12}H_{14}O_3$	β-3,4-Dimethylbenzoylpropionic acid	I	80	135
$C_{12}H_{14}O_3$	3-Acetyl-2-hydroxy-4,6-dimethylacetophenone	I	60	8
$C_{12}H_{14}O_3$	6,7-Dimethoxy-1-tetralone	I	70	154
		I	77	122
$C_{12}H_{16}O_3$	3,5-Diethyl-2,6-dihydroxy-4-methylbenzaldehyde	I	—	455
$C_{12}H_{16}O_3$	4-Hydroxy-3-methoxyphenyl *n*-butyl ketone	I	—	118
		II	—	91
$C_{12}H_{16}O_3$	2,4-Dihydroxyphenyl *n*-amyl ketone	I	85	53
		I	84	110
$C_{12}H_{16}O_3$	2,4-Dihydroxyphenyl isoamyl ketone	I	82	110
		I	—	53
$C_{12}H_{16}O_3$	2,5-Dihydroxyphenyl isoamyl ketone	I	30	426
		I	—	239

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp 201–209

‡ R.P., reduction product.

Formula	Compound	Method	Yield *	Reference †
$C_{12}H_{16}O_3$	2-Hydroxy-5-methoxyphenyl *n*-butyl ketone	I	51	280
$C_{12}H_{18}O_3$	3-Carboxy-2-(3-methylspirocyclohexane)-cyclopentanone-1	I	—	429
$C_{12}H_{10}O_4$	8-Acetyl-7-hydroxy-4-methylcoumarin	I	—	424
$C_{12}H_{14}O_4$	α-Methyl-β-*p*-anisoylpropionic acid	I	86	437
$C_{12}H_{14}O_4$	β-4-Methoxy-2-methylbenzoylpropionic acid	I	—	284
$C_{12}H_{14}O_4$	β-2-Methoxy-5-methylbenzoylpropionic acid	I	—	284
$C_{12}H_{14}O_4$	β-3-Methoxy-2-methylbenzoylpropionic acid	II		290
$C_{12}H_{14}O_4$	β-3-Methoxy-4-methylbenzoylpropionic acid	III	86	465
$C_{12}H_{14}O_4$	β-4-Methoxy-3-methylbenzoylpropionic acid	I	—	284
$C_{12}H_{14}O_4$	δ-2-Hydroxybenzoylvaleric acid	III	97	403
$C_{12}H_{14}O_4$	2,4-Dihydroxy-5-propionylpropiophenone	I	—	54
$C_{12}H_{14}O_4$	5-Hydroxy-6,7-dimethoxy-1-tetralone	I	—	432
$C_{12}H_{14}O_4$	5-Hydroxy-7-methoxy-2,2-dimethyl-chromanone-4	II	48	252
$C_{12}H_{14}O_4$	7-Hydroxy-5-methoxy-2,2-dimethyl chromanone-4	II	—	252
$C_{12}H_{16}O_4$	2,4,6-Trihydroxyphenyl *n*-amyl ketone	I	54	457
		I	70	56
$C_{12}H_{16}O_4$	3,4,5-Trimethoxypropiophenone	I	31	112
$C_{12}H_{16}O_4$	ω-Butoxy-2,4-dihydroxyacetophenone	I	—	318
	R.P.‡ Ethyl resorcinol			
$C_{12}H_{14}O_5$	β-2,5-Dimethoxybenzoylpropionic acid	III	42	403
$C_{12}H_{14}O_5$	β-2,4-Dimethoxybenzoylpropionic acid	I	—	432
$C_{12}H_{14}O_5$	β-3,4-Dimethoxybenzoylpropionic acid	III	62	465
		I	—	452
		I	—	122
$C_{12}H_{14}O_6$	β-2-Hydroxy-3,4-dimethoxybenzoylpropionic acid	I	—	432
$C_{12}H_{12}O_6$	3,5-Diacetyl-2,4,6-trihydroxyacetophenone	I	—	54
$C_{12}H_9ON$	4-Benzoylpyridine	I	80	61
$C_{12}H_{13}OBr$	4-Bromo-7-isopropyl-1-indanone	II	87	317
$C_{12}H_{13}OBr$	7-Bromo-4-isopropyl-1-indanone	II	87	317
$C_{12}H_{15}O_2Br$	5-Bromo-2-hydroxyphenyl *n*-amyl ketone	I	—	164
$C_{12}H_{15}O_2Cl$	5-Chloro-2-hydroxyphenyl *n*-amyl ketone	I	—	165
$C_{12}H_{15}O_2Cl$	3-Chloro-6-hydroxy-2-methyl-5-isopropylacetophenone	I	—	165
$C_{12}H_{15}O_3Cl$	5-Chloro-2,4-dihydroxyphenyl *n*-amyl ketone	II	—	167
	C_{13}			
$C_{13}H_{10}O$	6,7-Benzo-1-indanone	I	53	139
$C_{13}H_{10}O$	Benzophenone	I	—	38
$C_{13}H_{12}O$	1-Acetyl-4-methylnaphthalene	I	—	425
$C_{13}H_{12}O$	1-Acetyl-7-methylnaphthalene	II	65	333

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

Formula	Compound	Method	Yield *	Reference †
$C_{13}H_{12}O$	2-Acetyl-6-methylnaphthalene	II	—	333
$C_{13}H_{14}O$	6,7-Cyclopenteno-1-tetralone	II	89	233
		I	—	433
$C_{13}H_{14}O$	3-Keto-1,2,3,4,10,11-hexahydrofluorene	I	—	435
$C_{13}H_{14}O$	1,2,3,10-Tetrahydroperinaphthanone-7	I	—	48
$C_{13}H_{16}O$	6-Acetyl-7-methyltetralin	II	77	383
$C_{13}H_{16}O$	2-Ethyl-5-methyl-1-tetralone	I	59	92
$C_{13}H_{16}O$	3-Ethyl-5-methyl-1-tetralone	I	43	92
$C_{13}H_{16}O$	4-Ethyl-7-methyl-1-tetralone	I	86	149
$C_{13}H_{16}O$	7-Ethyl-3-methyl-1-tetralone	I	—	197
$C_{13}H_{16}O$	2,2,7-Trimethyl-1-tetralone	I	83	306
$C_{13}H_{16}O$	2,3,5-Trimethyl-1-tetralone	I	Q	102
$C_{13}H_{18}O$	Phenyl *n*-hexyl ketone	I	53	471
$C_{13}H_{22}O$	Cyclohexyl 2-methylcyclopentyl ketone	I	—	217
$C_{13}H_{24}O$	Cyclotridecanone	I	—	99
$C_{13}H_{10}O_2$	*p*-Hydroxybenzophenone	I	Q	3
$C_{13}H_{12}O_2$	2-Propionyl-1-naphthol	I	50	176
$C_{13}H_{12}O_2$	9-Keto-7,8,9,12-tetrahydrodibenzopyran	I	0	436
$C_{13}H_{14}O_2$	2,2-Diethyl-indan-1,3-dione	I	75	9
		I	68	13
$C_{13}H_{16}O_2$	5-Ethyl-7-hydroxy-8-methyl-(?)-tetralone	II	—	337
$C_{13}H_{16}O_2$	6-Methoxy-4,7-dimethyl-1-tetralone	I	65	385
$C_{13}H_{16}O_2$	7-Methoxy-5,8-dimethyl-1-tetralone	I	76	458
$C_{13}H_{16}O_2$	Diacetylmesitylene	I	20	474
$C_{13}H_{18}O_2$	4,5-Diethyl-2-hydroxy-3-methylacetophenone	I	—	73
$C_{13}H_{18}O_2$	3,4-Diethyl-2-hydroxy-5-methylacetophenone	I	64	73
$C_{13}H_{18}O_2$	5-Ethyl-4-methoxy-2,3-dimethylacetophenone	I	50	73
$C_{13}H_{18}O_2$	3-Ethyl-4-hydroxy-5-methylbutyrophenone	I	48	106
$C_{13}H_{18}O_2$	2-Hydroxy-3-methylphenyl *n*-amyl ketone	II	—	91
$C_{13}H_{18}O_2$	4-Hydroxy-3-methylphenyl *n*-amyl ketone	II	—	91
$C_{13}H_{18}O_2$	2-Hydroxy-5-methylphenyl *n*-amyl ketone	II	—	91
$C_{13}H_{13}O_2$	2-Hydroxy-4-methylphenyl *n*-amyl ketone	II	—	91
$C_{13}H_{18}O_2$	2-Hydroxyphenyl *n*-hexyl ketone	II	—	91
$C_{13}H_{18}O_2$	4-Hydroxyphenyl *n*-hexyl ketone	II	—	91
$C_{13}H_{20}O_2$	7-Acetyl-1-keto-10-methyl decalin	I	—	115
$C_{13}H_{20}O_2$	1,1′-Ethynylcyclohexanolcyclopentanol	I	6	261
	R.P.‡ 3*a*,4,4*a*,6,7,8,9,9*b*-octahydro-α-naphthindan			
$C_{13}H_{20}O_2$	3-Ethyl-2,4-diketo-9-methyldecalin	I	—	114
$C_{13}H_8O_3$	7,8-Diketo-1-methoxyacenaphthene	I	25	172
$C_{13}H_{10}O_3$	2,4-Dihydroxybenzophenone	I	30	55
$C_{13}H_{14}O_3$	β-5-Indanoylpropionic acid	III	73	233
		I	—	433
$C_{13}H_{14}O_3$	β-(1-Keto-3-tetralyl)propionic acid	I	70	63
$C_{13}H_{14}O_3$	5-*p*-Anisyl-cyclohexane-1,3-dione	I	80	211
$C_{13}H_{16}O_3$	Ethyl α-methyl-β-benzoylpropionate	I	—	36
$C_{13}H_{16}O_3$	β,β-Dimethyl-γ-benzoylbutyric acid	I	—	230

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

Formula	Compound	Method	Yield *	Reference †
$C_{13}H_{16}O_3$	α,α-Dimethyl-β-*p*-toluylpropionic acid	I	82	306
$C_{13}H_{16}O_3$	Ethyl β-*o*-toluylpropionate	II	43	179
$C_{13}H_{16}O_3$	Ethyl β-*p*-toluylpropionate	I	—	36
$C_{13}H_{16}O_3$	β-4-Isopropylbenzoylpropionic acid	I	80	135
$C_{13}H_{16}O_3$	6,7-Dimethoxy-2-methyl-1-tetralone	I	64	134
		I	—	129
$C_{13}H_{16}O_3$	6,7-Dimethoxy-3-methyl-1-tetralone	I	64	134
$C_{13}H_{18}O_3$	2,6-Dimethoxyphenyl isobutyl ketone	I	43	140
$C_{13}H_{18}O_3$	2,5-Dimethoxyphenyl isobutyl ketone	I	48	280
$C_{13}H_{18}O_3$	4-Hydroxy-3-methoxyphenyl *n*-amyl ketone	II	—	91
$C_{13}H_{18}O_3$	2,4-Dihydroxyphenyl *n*-hexyl ketone	I	—	53
$C_{13}H_{10}O_4$	2,4,6-Trihydroxybenzophenone	I	50	56
$C_{13}H_{12}O_4$	8-Acetyl-7-methoxy-4-methylcoumarin	II	—	274
$C_{13}H_{12}O_4$	7-Hydroxy-4-methyl-8-propionylcoumarin	I	—	424
$C_{13}H_{12}O_4$	5-Hydroxy-4-methyl-6-propionylcoumarin	II	—	340
$C_{13}H_{16}O_4$	3-Carboxy-4-hydroxyphenyl isoamyl ketone	I	—	89
$C_{13}H_{16}O_4$	3-Carboxy-4-hydroxy-*n*-caprophenone	I	88	89
$C_{13}H_{16}O_4$	β-4-Methoxy-2,5-dimethylbenzoylpropionic acid	I	92	94
$C_{13}H_{16}O_4$	α-Methyl-β-3-methoxy-2-methylbenzoylpropionic acid	II	—	225
$C_{13}H_{16}O_4$	δ-*p*-Anisoylvaleric acid	I	73	183
$C_{13}H_{16}O_4$	5-Hydroxy-6,7-dimethoxy-2-methyl-1-tetralone	I	—	437
$C_{13}H_{18}O_4$	2,4,6-Trihydroxyphenyl *n*-hexyl ketone	I	30	457
$C_{13}H_{16}O_5$	α-Methyl-β-3,4-dimethoxybenzoylpropionic acid	I	45	129
		I	—	134
$C_{13}H_{16}O_5$	β-Methyl-β-3,4-dimethoxybenzoylpropionic acid	I	—	134
$C_{13}H_{16}O_5$	γ-3,4-Dimethylbenzoylbutyric acid	I	73	448
$C_{13}H_{16}O_6$	α-Methyl-β-2-hydroxy-3,4-dimethoxybenzoylpropionic acid	I	—	437
$C_{13}H_7OBr$	2-, 3-, or 4-Bromofluorenone-9	II	Q	196
$C_{13}H_9OBr$	*o*-Bromobenzophenone	I	—	351
		I	50	88
$C_{13}H_9OBr$	4-Bromo-5,6-benzo-1-indanone	I	—	33
$C_{13}H_{15}OBr$	4-Bromo-7-*t*-butyl-1-indanone	II	70	264
$C_{13}H_{15}OBr$	7-Bromo-4-*t*-butyl-1-indanone	II	70	264
$C_{13}H_{17}O_2Cl$	5-Chloro-2-hydroxyphenyl *n*-hexyl ketone	I	—	165
$C_{13}H_{17}O_3Cl$	5-Chloro-2,4-dihydroxyphenyl *n*-hexyl ketone	II	—	167
$C_{13}H_{15}ON$	1-Keto-5,6-benzo-1,2,3,4,7,8-hexahydropyridocoline	I	37	276
$C_{13}H_{21}ON$	1-Keto-5,6-benzododecahydropyridocoline	I	52	276
$C_{13}H_{11}O_3N$	β-2-Quinolylpropionic acid	I	—	244
$C_{13}H_{17}O_3N$	Ethyl β-(3,5-dimethylpyridyl-2) propionate	I	91	299

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

C_{14}

Formula	Compound	Method	Yield *	Reference †
$C_{14}H_{12}O$	1- and 4-Keto-1,2,3,4-tetrahydrophenanthrenes	IV	69	371
$C_{14}H_{12}O$	8-Methyl-peri-naphthanone-7	IV	70	394
$C_{14}H_{12}O$	3-Acetylacenaphthene	I	—	20
$C_{14}H_{14}O$	1-α-Naphthylbutanone-1	I	—	33
$C_{14}H_{14}O$	1-β-Naphthylbutanone-1	I	—	33
$C_{14}H_{14}O$	1-Acetyl-4-ethylnaphthalene	I	70	126
$C_{14}H_{16}O$	2-(4-Methyl-1-naphthyl)propanol-2	I	—	425
$C_{14}H_{16}O$	1-Keto-1,2,3,4,5,6,7,8-octahydroanthracene	I	—	35
$C_{14}H_{16}O$	9-Keto-1,2,3,4,9,10,11,12-octahydrophenanthrene (*vis* and *trans* isomers)	I	—	331
$C_{14}H_{16}O$	ω-Cyclohexenylacetophenone R.P.‡ β-Phenylethylcyclohexene	II	45	335
$C_{14}H_{18}O$	4,7-Dimethyl-2-isopropyl-1-indanone	I	—	344
$C_{14}H_{18}O$	2,2-Diethyl-1-tetralone	I	63	306
$C_{14}H_{18}O$	5-Methyl-8-isopropyl-1-tetralone	I	52	37
$C_{14}H_{18}O$	6-Acetyl-7-ethyltetralin	I	—	22
$C_{14}H_{18}O$	*o*-Phenylacetophenone	I	66	174
$C_{14}H_{20}O$	9-Ketododecahydrophenanthrene (m.p. 94°)	I	86	336
$C_{14}H_{20}O$	9-Ketododecahydrophenanthrene (m.p. 51°)	I	88	336
$C_{14}H_{20}O$	9-Ketododecahydrophenanthrene	I	81	201
$C_{14}H_{22}O$	9-Ketotetradecahydrophenanthrene (m.p. 48°)	I	Q	336
$C_{14}H_{22}O$	*trans*-3-Methyl-4-propyl-1,2,4*a*,5,6,7,8,8*a*-octahydro-1-naphthalenone	II	62	360
$C_{14}H_{24}O$	2-Acetyl-8,10-dimethyldecalin	I	—	115
$C_{14}H_{26}O$	Cyclotetradecanone	I	87	99
$C_{14}H_8O_2$	Anthraquinone R.P.‡ Dihydro- and hexahydroanthracene	I	—	3
$C_{14}H_{10}O_2$	Benzil	I	Q	3
$C_{14}H_{12}O_2$	Benzoin	I	84	3
		II	50	119
$C_{14}H_{12}O_2$	4-Hydroxy-3-phenylacetophenone	IV	70	398
$C_{14}H_{14}O_2$	2,4-Diketo-1,2,3,4,9,10,11,12-octahydrophenanthrene	I	35	470
$C_{14}H_{14}O_2$	2-*n*-Butyroyl-1-hydroxynaphthalene	I	63	176
$C_{14}H_{16}O_2$	2,2-Diethyl-4-methylindan-1,3-dione	I	29	25
$C_{14}H_{16}O_2$	2,2-Diethyl-5-methylindan-1,3-dione	I	73	25
$C_{14}H_{16}O_2$	7-Hydroxy-9-keto-1,2,3,4,9,10,11,12-octahydrophenanthrene	III	63	331
$C_{14}H_{18}O_2$	5-Ethyl-7-methoxy-8-methyl-1-tetralone	I	70	337
$C_{14}H_{18}O_2$	8-Ethyl-7-methoxy-5-methyl-1-tetralone	I	—	337
$C_{14}H_{18}O_2$	6-Methoxy-3,4,5-trimethyl-1-tetralone	I	—	225
$C_{14}H_{20}O_2$	3,5-Diethyl-2-methoxy-6-methylacetophenone	I	43	73
$C_{14}H_{20}O_2$	2-Hydroxy-4-methylphenyl *n*-hexyl ketone	II	—	91
$C_{14}H_{22}O_2$	3-Ethyl-2,4-diketo-5,9-dimethyldecalin	I	—	114

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

Formula	Compound	Method	Yield *	Reference †
$C_{14}H_{22}O_2$	1,1′-Ethynylenebiscyclohexanol	I	—	260
	R.P.‡ Δ^{11}-Dodecahydrophenanthrene			
$C_{14}H_{12}O_3$	β-1-Naphthoylpropionic acid	III	86	465
		III	—	370
		I	70	121
		I	64	78
$C_{14}H_{12}O_3$	β-2-Naphthoylpropionic acid	III	91	465
		I	70	121
		I	81	78
$C_{14}H_{12}O_3$	β-1- and 2-Naphthoylpropionic acids	IV	78	371
$C_{14}H_{12}O_3$	Benzyl 2,4-dihydroxyphenyl ketone	I	70	55
		I	—	53
$C_{14}H_{12}O_3$	2,4-Dihydroxy-3-methylbenzophenone	I	—	376
$C_{14}H_{16}O_3$	β-1-Tetroylpropionic acid	I	—	44
$C_{14}H_{16}O_3$	β-2-Tetroylpropionic acid	I	—	35
$C_{14}H_{16}O_3$	5-*p*-Anisyl-2-methylcyclohexa-1,3-dione	I	85	211
$C_{14}H_{18}O_3$	6,7-Dimethoxy-2,3-dimethyl-1-tetralone	I	11	122
$C_{14}H_{18}O_3$	α,α-Diethyl-β-benzoylpropionic acid	I	60	306
$C_{14}H_{18}O_3$	β-Ethyl-β-methyl-γ-benzoylbutyric acid	I	—	230
$C_{14}H_{18}O_3$	Ethyl α-methyl-β-*p*-toluylpropionate	I	—	36
$C_{14}H_{18}O_3$	Ethyl β-methyl-β-*p*-toluylpropionate	I	—	36
$C_{14}H_{18}O_3$	β-4-*t*-Butylbenzoylpropionic acid	III	84	465
$C_{14}H_{18}O_3$	6-Hydroxy-2,2,5,7,8-pentamethylchromanon	II	66	314
$C_{14}H_{20}O_3$	2,4-Dihydroxyphenyl *n*-heptyl ketone	I	—	53
$C_{14}H_{20}O_3$	Ketolactone from dihydroisoalantolactone	I	—	109
		I	68	113
$C_{14}H_{26}O_3$	13-Ketomyristic acid	I	—	160
$C_{14}H_8O_4$	Alizarin	I	73	3
	R.P.‡ Hexahydroanthracene			
$C_{14}H_{10}O_4$	3-Benzoyl-2,6-dihydroxybenzaldehyde	I	—	376
$C_{14}H_{12}O_4$	Benzyl 2,4,6-trihydroxyphenyl ketone	I	65	56
$C_{14}H_{12}O_4$	β-2-Hydroxy-3-naphthoylpropionic acid	III	—	313
$C_{14}H_{14}O_4$	6-Butyryl-5-hydroxy-4-methylcoumarin	II	—	340
$C_{14}H_{14}O_4$	8-Butyryl-7-hydroxy-4-methylcoumarin	I	—	424
$C_{14}H_{14}O_4$	6-Acetyl-8-ethyl-5-hydroxy-4-methylcoumarin	I	—	427
$C_{14}H_{18}O_4$	δ-4-Ethoxybenzoylvaleric acid	I	—	183
$C_{14}H_{18}O_4$	β-2-Ethyl-4-methoxy-5-methylbenzoylpropionic acid	I	96	337
$C_{14}H_{18}O_4$	β-5-Ethyl-4-methoxy-2-methylbenzoylpropionic acid	I	80	337
$C_{14}H_{18}O_4$	1,5-Di-*n*-butyryl-2,4-dihydroxybenzene	I	—	54
$C_{14}H_{18}O_5$	α,β-Dimethyl-β-3,4-dimethoxybenzoylpropionic acid	I	—	122
$C_{14}H_{18}O_6$	Diethyl-bicyclo(2:2:2)octadionedicarboxylate	IV	42	349
$C_{14}H_{19}O_2Cl$	5-Chloro-2-hydroxyphenyl *n*-heptyl ketone	I	—	165
$C_{14}H_{19}O_3Cl$	5-Chloro-2,4-dihydroxyphenyl *n*-heptyl ketone	II	—	167

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

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‡ R.P., reduction product.

Formula	Compound	Method	Yield *	Reference †
$C_{14}H_{11}ON$	2-Acetylcarbazole	III	—	155
$C_{14}H_{11}ON$	3-Acetylcarbazole	III	—	155
$C_{14}H_{15}ON$	5-Phenyl-7-ketooctahydropyrrocoline	I	16	419
$C_{14}H_{17}ON$	6-Acetylhexahydrocarbazole	I	32	212
$C_{14}H_{12}OS$	Phenacyl phenyl sulfide	I	20	96
	R.P ‡ (α-Methylbenzyl)phenyl sulfide			
	C_{15}			
$C_{15}H_{12}O$	Benzalacetophenone	I	—	288
	R.P.‡ Tetraphenylhexadione			
$C_{15}H_{14}O$	2-Ethyl-4,5-benzo-1-indanone	I	—	33
$C_{15}H_{14}O$	1-Keto-2-methyl-1,2,3,4-tetrahydrophenanthrene	I	—	121
$C_{15}H_{14}O$	1-Keto-4-methyl-1,2,3,4-tetrahydrophenanthrene	IV	94	397
$C_{15}H_{14}O$	1-Keto-9-methyl-1,2,3,4-tetrahydrophenanthrene	I	—	132
$C_{15}H_{14}O$	4-Keto-3-methyl-1,2,3,4-tetrahydrophenanthrene	I	—	121
$C_{15}H_{14}O$	4-Keto-7-methyl-1,2,3,4-tetrahydrophenanthrene	I	—	125
$C_{15}H_{14}O$	8-Ethylperinaphthanone-7	I	64	33
$C_{15}H_{16}O$	1-Keto-3,4,5,6,12,13-hexahydro-peribenzoacenaphthene	I	—	65
$C_{15}H_{16}O$	α-Keto-octahydromethylenephenanthrene	I	70	65
$C_{15}H_{18}O$	6,7-Cyclopenteno-1-keto-2,2-dimethyl-1,2,3,4-tetrahydronaphthalene	I	—	433
$C_{15}H_{18}O$	7-Methyl-1-keto-1,2,3,4-tetrahydronaphthalene-2,2-spirocyclopentane	I	—	410
$C_{15}H_{18}O$	1-Keto-1,2,3,4-tetranaphthalene-2,2-spirocyclohexane	I	—	248
$C_{15}H_{22}O$	Acetyldiethylmesitylene	I	45	474
$C_{15}H_{22}O$	Phenyl *n*-octyl ketone	I	51	471
$C_{15}H_{24}O$	4*a*,5,6,7,8,8*a*-Hexahydro-3-*n*-propyl-4-ethyl-1(2)-naphthalenone	I	54	259
$C_{15}H_{14}O_2$	4-Hydroxy-3,5-dimethylbenzophenone	I	40	106
$C_{15}H_{14}O_2$	4-Hydroxy-3-phenylpropiophenone	IV	74	398
$C_{15}H_{16}O_2$	4,5-Cyclohexenyl-2,2-dimethylindan-1,3-dione	I	70	26
		I	—	22
$C_{15}H_{16}O_2$	1-Hydroxy-2-naphthyl *n*-butyl ketone	I	50	176
$C_{15}H_{22}O_2$	2-Hydroxy-3,5-di-*n*-propylpropiophenone	I	71	141
$C_{15}H_{22}O_2$	2-Hydroxy-3,5-dimethylphenyl *n*-hexyl ketone	I	60	106
$C_{16}H_{22}O_2$	4-Hydroxy-3,5-dimethylphenyl *n*-hexyl ketone	I	53	106

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Formula	Compound	Method	Yield *	Reference †
$C_{15}H_{26}O_2$	1-(1-Cyclohexanol)-3-*n*-propyl-1-hexyne-3-ol	I	6	259
	R.P.‡ 1,2,4*a*,5,6,7,8,8*a*-Octahydro-3-*n*-propyl-4-ethylnaphthalene			
$C_{16}H_{28}O_2$	Dihydrocalameone	I	—	413
$C_{15}H_{10}O_3$	1,4-Diketo-3-phenylisochroman	I	—	304
	R.P.‡ Dibenzyl-*o*-carboxylic acid			
$C_{15}H_{14}O_3$	2,4-Dihydroxy-3-methylphenyl benzyl ketone	I	—	376
$C_{15}H_{14}O_3$	α-Methyl-β-1-naphthoylpropionic acid	I	—	121
$C_{15}H_{14}O_3$	α-Methyl-β-2-naphthoylpropionic acid	I	75	121
$C_{15}H_{14}O_3$	β-Methyl-β-2-naphthoylpropionic acid	I	—	150
$C_{15}H_{14}O_3$	β-5-Methyl-1-naphthoylpropionic acid	II	90	150
$C_{15}H_{14}O_3$	β-8-Methyl-2-naphthoylpropionic acid	I	—	163
$C_{15}H_{14}O_3$	β-Phenylpropionylresorcinol	I	—	53
		I	50	54
$C_{15}H_{18}O_3$	1-Phenacylcyclopentane-1 acetic acid	I	—	230
$C_{15}H_{18}O_3$	α,α-Dimethyl-β-5-indanoylpropionic acid	I	—	433
$C_{15}H_{18}O_3$	α,α-3-Methylcyclopentane-β-benzoylpropionic acid	I	—	283
$C_{15}H_{18}O_3$	α,α-Cyclopentane-β-(*p*-toluyl)-propionic acid	I	—	410
$C_{15}H_{18}O_3$	α,α-Cyclohexane-β-benzoylpropionic acid	I	—	248
		I	—	283
$C_{15}H_{22}O_3$	2,4-Dihydroxyphenyl *n*-octyl ketone	I	—	53
$C_{15}H_{22}O_3$	Tetrahydrosantonin	I	53	100
		I	—	108
		I	G	158
$C_{15}H_{12}O_4$	2,6-Dihydroxy-3-(phenylacetyl)-benzaldehyde	I	—	376
$C_{16}H_{14}O_4$	β-Phenyl-2,4,6-trihydroxypropiophenone	I	—	54
$C_{16}H_{14}O_4$	β-4-Methoxy-1-naphthoylpropionic acid	IV	60	402
		I	—	242
$C_{15}H_{14}O_4$	β-5-Methoxy-1-naphthoylpropionic acid	II	58	334
		III	51	254
$C_{15}H_{14}O_4$	β-3-Methoxy-2-naphthoyl propionic acid	III	62	298
		III	—	301
$C_{15}H_{14}O_4$	6-Acetyl-7-hydroxycyclohexeno-(1',2',3,4)-coumarin	I	—	311
$C_{15}H_{18}O_4$	α-1-Keto-7-methoxy-5,8-dimethyl-1,2,3,4-tetrahydronaphthyl-2-acetic acid	I	75	94
$C_{15}H_{22}O_4$	Humulinic acid	II	38	50
$C_{15}H_{24}O_4$	Dihydrohumulinic acid	II	—	50
$C_{15}H_{16}O_5$	δ-2,5-Dimethylbenzoyl-δ-hydroxybutane-β,γ-dicarboxylic acid lactone	I	—	107
$C_{15}H_{18}O_5$	δ-2,5-Dimethylbenzoylbutane-β,γ-dicarboxylic acid	I	39	107
$C_{15}H_{20}O_6$	Diethyl bicyclo(3:2:2)nonadionedicarboxylate	IV	—	349

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Formula	Compound	Method	Yield *	Reference †
$C_{15}H_{19}O_4Cl$	Ethyl α-chloro β-4-methoxy-2,5-dimethylbenzoylpropionate	I	—	94
	R.P.‡ γ-4-Methoxy-2,5-dimethylphenylbutyric acid			
	C_{16}			
$C_{16}H_{12}O$	4-Keto-1,2,3,4-tetrahydrofluoranthene	I	70	80
$C_{16}H_{12}O$	2-Acetylphenanthrene	I	46	138
		I	10	142
$C_{16}H_{12}O$	3-Acetylphenanthrene	I	—	138
		I	10	142
$C_{16}H_{14}O$	3-Phenyl-1-tetralone	I	—	67
		I	—	156
$C_{16}H_{14}O$	7-Phenyl-1-tetralone	III	—	382
$C_{16}H_{14}O$	1'-Methyl-3'-keto-2,3-cyclopentenoacenaphthene	IV	85	356
$C_{16}H_{14}O$	3-*o*-Tolyl-1-indanone	I	G	68
$C_{16}H_{14}O$	3-*p*-Tolyl-1-indanone	I	G	68
$C_{16}H_{14}O$	1-Keto-as-hexahydropyrene	IV	65	404
$C_{16}H_{14}O$	1-Keto-1,2,3,4-tetrahydro-8,9-acephenanthrene	I	P	476
$C_{16}H_{16}O$	3-Acetyl-4-ethyl-acenaphthene	I	—	20
$C_{16}H_{16}O$	9-Acetyl-1,2,3,4-Tetrahydrophenanthrene	IV	88	371
$C_{16}H_{16}O$	1-Keto-2,2-dimethyl-1,2,3,4-tetrahydrophenanthrene	I	70	343
$C_{16}H_{16}O$	1-Keto-2,9-dimethyl-1,2,3,4-tetrahydrophenanthrene	I	—	150
$C_{16}H_{16}O$	1-Keto-4,8-dimethyl-1,2,3,4-tetrahydrophenanthrene	I	—	150
$C_{16}H_{16}O$	4-Keto,1,7-dimethyl-1,2,3,4-tetrahydrophenanthrene	I	—	125
$C_{16}H_{16}O$	4-Keto-3,7-dimethyl-1,2,3,4-tetrahydrophenanthrene	I	—	150
$C_{16}H_{16}O$	4-Keto-3,3-dimethyl-1,2,3,4-tetrahydrophenanthrene	I	73	343
$C_{16}H_{16}O$	4-Keto-6,7-dimethyl-1,2,3,4-tetrahydrophenanthrene	I	—	150
$C_{16}H_{18}O$	1-Keto-decahydropyrene	I	—	65
$C_{16}H_{20}O$	2-Methyl-2-(2',4'-Dimethylphenyl)-Δ^3-tetrahydrobenzaldehyde	I	81	202
$C_{16}H_{20}O$	7-Ethyl-1-keto-1,2,3,4-tetrahydronaphthalene-2,2-spirocyclopentane	I	—	410
$C_{16}H_{20}O$	1-Keto-7-methyl-1,2,3,4-tetrahydronaphthalene-2,2-spirocyclohexane	I	—	248

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‡ R.P., reduction product.

Formula	Compound	Method	Yield *	Reference †
$C_{16}H_{22}O$	5-Acetyl-6,7-diethyl-1,2,3,4-tetrahydronaphthalene	I	—	22
$C_{16}H_{30}O$	Cyclohexadecanone	I	—	99
$C_{16}H_{30}O$	Muscon (β-methylcyclopentadecanone)	I	—	51
$C_{16}H_{12}O_2$	7-Keto-7,8,9,10-tetrahydrobenzo(*b*)-naphtho(2,3-*d*)furan	II	10	353
$C_{16}H_{16}O_2$	4-Keto-7-methoxy-1-methyl-1,2,3,4-tetrahydrophenanthrene	I	—	191
$C_{16}H_{16}O_2$	4-Keto-7-methoxy-8-methyl-1,2,3,4-tetrahydrophenanthrene	I	37	190
$C_{16}H_{20}O_2$	1,4,5,8-Di-(endomethylene)-9,10-diketotetradecahydroanthracene	I	36	72
$C_{16}H_{24}O_2$	3-Ethyl-4-hydroxy-5-methylphenyl *n*-hexyl ketone	I	53	106
$C_{16}H_{28}O_2$	Cyclohexadecan-1,9-dione	I	—	82
$C_{16}H_{14}O_3$	4,4'-Diacetyldiphenyl ether	I	—	310
$C_{16}H_{14}O_3$	β-1-Acenaphthoylpropionic acid	I	60	476
$C_{16}H_{14}O_3$	β-3-Acenaphthoylpropionic acid	IV	50	465
		I	0	476
$C_{16}H_{14}O_3$	β-4-Phenylbenzoylpropionic acid	III	—	382
		II	—	381
$C_{16}H_{14}O_3$	α-Phenyl-β-benzoylpropionic acid	III	—	307
		I	76	322
$C_{16}H_{14}O_3$	β-Phenyl-β-benzoylpropionic acid	I	—	230
$C_{16}H_{16}O_3$	α,α-Dimethyl-β-1-naphthoylpropionic acid	I	49	343
$C_{16}H_{16}O_3$	α,α-Dimethyl-β-2-naphthoylpropionic acid	I	55	343
$C_{16}H_{16}O_3$	β-4-Ethyl-1-naphthoylpropionic acid	IV	94	371
$C_{16}H_{16}O_3$	α-Ethyl-β-1-naphthoylpropionic acid	I	—	150
$C_{16}H_{16}O_3$	Methyl β-4-methyl-1-naphthoylpropionate	I	88	132
$C_{16}H_{16}O_3$	β-6,7-Dimethyl-2-naphthoylpropionic acid	I	90	150
$C_{16}H_{16}O_3$	α-Methyl-β-4-methyl-1-naphthoylpropionic acid	I	75	150
$C_{16}H_{16}O_3$	α-Methyl-β-5-methyl-1-naphthoylpropionic acid	I	—	132
$C_{16}H_{16}O_3$	α-Methyl-β-6-methyl-2-naphthoylpropionic acid	I	70	150
$C_{16}H_{16}O_3$	β-Methyl-β-6-methyl-2-naphthoylpropionic acid	I	—	150
$C_{16}H_{20}O_3$	1-Phenacylcyclohexane-1-acetic acid	I	—	230
$C_{16}H_{20}O_3$	α,α-3-Methylcyclopentane-β-*p*-toluylpropionic acid	I	—	283
$C_{16}H_{20}O_3$	α,α-cyclopentane-β-*p*-ethylbenzoylpropionic acid	I	—	410
$C_{16}H_{20}O_3$	α,α-Spirocyclohexane-β-*p*-toluylpropionic acid	I	—	248
$C_{16}H_{20}O_3$	γ-1-Keto-7-ethyl-1,2,3,4-tetrahydronaphthyl-2-*n*-butyric acid	IV	85	397

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‡ R.P., reduction product.

Formula	Compound	Method	Yield *	Reference †
$C_{16}H_{20}O_3$	α,α-Cyclopentane-β-4-ethylbenzoylpropionic acid	I	—	410
$C_{16}H_{20}O_3$	α,α-Cyclohexane-β-*p*-toluylpropionic acid	I	—	248
$C_{16}H_{24}O_3$	2,4-Dihydroxyphenyl *n*-nonyl ketone	I	—	53
$C_{16}H_{28}O_3$	ω-2-Ketocyclopentylundecylic acid	I	—	439
$C_{16}H_{12}O_4$	β-2-Dibenzofuroylpropionic acid	III	83	364
$C_{16}H_{16}O_4$	Anisoin	III	72	387
$C_{16}H_{16}O_4$	β-4-Methoxy-6-methyl-1-naphthoylpropionic acid	I	50	116
$C_{16}H_{16}O_4$	β-6-Methoxy-5-methyl-2-naphthoylpropionic acid	I	53	190
$C_{16}H_{16}O_4$	6-Acetyl-7-hydroxy-5'-methylcyclohexeno-1',2',4,3-coumarin	I	—	311
$C_{16}H_{16}O_4$	6-Acetyl-7-hydroxy-4'-methylcyclohexeno-1',2',4,3-coumarin	I	—	311
$C_{16}H_{20}O_4$	α-1-Keto-7-methoxy-5,8-dimethyl-1,2,3,4-tetrahydronaphthyl-2-propionic acid	I	84	94
$C_{16}H_{16}O_5$	β-2,6-Dimethoxy-1-naphthoylpropionic acid	III	54	221
$C_{16}H_{16}O_5$	β-4,8-Dimethoxy-1-naphthoylpropionic acid	IV	25	221
		II	20	255
$C_{16}H_{18}O_5$	δ-4-Methoxy-2,5-dimethylbenzoylbutane-β,γ-dicarboxylic anhydride	I	99	93
$C_{16}H_{18}O_6$	δ-4-Methoxy-2,5-dimethylbenzoyl-δ-hydroxybutane-β,γ-dicarboxylic acid lactone	I	83	107
$C_{16}H_{20}O_6$	δ-4-Methoxy-2,5-dimethylbenzoylbutane-β,γ-dicarboxylic acid	I	53	94
$C_{16}H_{18}O_8$	γ-4-Methoxy-2,5-dimethylbenzoylpropane-α,α,β-tricarboxylic acid	I	84	94
$C_{16}H_{12}O_3S$	3,6-Diacetylphenoxthine	I	—	310
$C_{16}H_{10}O_3SCl_2$	3,6-*bis*-(Chloroacetyl)-phenoxthine	I	—	310

C_{17}

$C_{17}H_{12}O$	1'-Keto-1,2-cyclopentenophenanthrene	II	—	258
$C_{17}H_{12}O$	3'-Keto-1,2-cyclopentenophenanthrene	IV	59	258
$C_{17}H_{12}O$	3'-Keto-3,4-cyclopentenophenanthrene	IV	70	258
$C_{17}H_{12}O$	1'-Keto-9,10-cyclopentenophenanthrene	I	92	271
$C_{17}H_{12}O$	5,6-Benzo-1,2-dihydro-3-benzonaphthenone	I	30	258
$C_{17}H_{14}O$	2-Propionylphenanthrene	IV	83	369
$C_{17}H_{14}O$	3-Propionylphenanthrene	IV	77	369
$C_{17}H_{14}O$	1-Acetyl-4-methylphenanthrene	IV	95	397
$C_{17}H_{14}O$	3-Acetyl-5-methylphenanthrene	IV	—	397
$C_{17}H_{14}O$	4'-Keto-1',2',3',4'-tetrahydro-2,3-benzofluorene	I	65	143

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

Formula	Compound	Method	Yield *	Reference †
$C_{17}H_{14}O$	1′-Keto-1,2-cyclopenteno-9,10-dihydrophenanthrene	IV	—	295
$C_{17}H_{14}O$	3′-Keto-3,4-dihydro-1,2-cyclopentenophenanthrene	II	—	215
$C_{17}H_{14}O$	3′-Keto-1,2-cyclopenteno-9,10-dihydrophenanthrene	IV	—	295
$C_{17}H_{14}O$	1-Keto-2,3-cyclopenteno-1,4-dihydrophenanthrene	I	55	421
$C_{17}H_{14}O$	4-Keto-2,3-cyclopenteno-1,4-dihydrophenanthrene	I	—	249
		I	55	421
$C_{17}H_{14}O$	2,3-Diphenylcyclopentene-2-one-1	I	—	332
	R.P.‡ 1,2-Diphenylcyclopentane			
$C_{17}H_{16}O$	2,3-Diphenylcyclopentanone-1 (*cis*)	III	54	305
		I	—	332
$C_{17}H_{16}O$	2,3-Diphenylcyclopentanone-1 (*trans*)	III	66	305
		I	—	332
$C_{17}H_{16}O$	?-Isobutyrylfluorene	I	—	15
$C_{17}H_{16}O$	2-Benzyltetralone-1	I	—	64
$C_{17}H_{16}O$	4-Methyl-3-phenyltetralone-1	I	—	156
$C_{17}H_{16}O$	1-Keto-2,3-cyclopentano-1,2,3,4-tetrahydrophenanthrene	I	72	297
$C_{17}H_{18}O$	1,5-Diphenylpentanone-3	I	76	3
$C_{17}H_{18}O$	1-Keto-2,2,9-trimethyl-1,2,3,4-tetrahydrophenanthrene	I	70	343
$C_{17}H_{18}O$	1-Ethyl-4-keto-7-methyl-1,2,3,4-tetrahydrophenanthrene	I	Q	131
$C_{17}H_{18}O$	4-Keto-1,2,7-trimethyl-1,2,3,4-tetrahydrophenanthrene	I	—	124
$C_{17}H_{18}O$	4-Keto-1,3,7-trimethyl-1,2,3,4-tetrahydrophenanthrene	I	—	124
$C_{17}H_{18}O$	4-Keto-1,6,7-trimethyl-1,2,3,4-tetrahydrophenanthrene	I	—	124
$C_{17}H_{20}O$	3-Keto-1,2-cyclopentano-3,4,9,10,11,12-hexahydrophenanthrene	I	—	209
$C_{17}H_{20}O$	1-Keto-6,7-cyclopenteno-1,2,3,4-tetrahydronaphthalene-2,2-spirocyclopentane	I	—	421
		I	—	249
$C_{17}H_{22}O$	7-Ethyl-1-keto-1,2,3,4-tetrahydronaphthalene-2,2-spirocyclohexane	I	—	248
$C_{17}H_{28}O$	4*a*,5,6,7,8*a*-Hexahydro-3-*n*-butyl-4-*n*-propyl-1(2)-naphthalenone	I	57	259
$C_{17}H_{32}O$	Civetone	I	—	81
$C_{17}H_{18}O_2$	1-Methyl-2-(6-methoxynaphthyl-2)-cyclopentanone-5	III	—	373
$C_{17}H_{18}O_2$	4-Keto-7-methoxy-1,2-dimethyl-1,2,3,4-tetrahydrophenanthrene	I	55	152

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

Formula	Compound	Method	Yield *	Reference †
$C_{17}H_{18}O_2$	2,2-Dimethyltetrahydroacenaphth-α,β-indan-1,3-dione	I	92	26
$C_{17}H_{20}O_2$	2,2-Diethyltetrahydronaphth-α,β-indan-1,3-dione	I	—	26
		I	—	22
		I	—	21
$C_{17}H_{20}O_2$	2,2-Diethyltetrahydronaphth-β,β-indan-1,3-dione	I	45	26
		I	—	22
$C_{17}H_{22}O_2$	2,2,5-Triethyl-4,7-dimethylindan-1,3-dione	I	81	12
$C_{17}H_{22}O_2$	2,2-Diethyl-4-methyl-7-isopropylindan-1,3-dione	I	76	25
$C_{17}H_{14}O_3$	1-(α-Naphthoyl)-Δ^1-cyclopentene-2-carboxylic acid	I	—	421
		I	—	249
$C_{17}H_{14}O_3$	1-(β-Naphthoyl)-Δ^1-cyclopentene-2-carboxylic acid	I	—	249
		I	—	421
$C_{17}H_{14}O_3$	4-Keto-1-phenyl-1,2,3,4-tetrahydronaphthoic acid	III	78	192
$C_{17}H_{14}O_3$	β-2-Fluoroylpropionic acid	II	Q	143
$C_{17}H_{14}O_3$	Ethyl 9-fluoroylformate	I	80	43
	R.P.‡ Fluorenhydroxyacetic acid			
$C_{17}H_{16}O_3$	8-Acetyl-4-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene	I	—	422
$C_{17}H_{16}O_3$	Methyl β-3-acenaphthoylpropionate	III	60	465
		I	47	476
$C_{17}H_{16}O_3$	1-(α-Naphthoyl)-cyclopentane-2-carboxylic acid	I	79	297
$C_{17}H_{18}O_3$	1,3-Di-*p*-anisylpropanone-1	III	81	387
$C_{17}H_{18}O_3$	β-6-Isopropyl-2-naphthoylpropionic acid	I	60	150
$C_{17}H_{18}O_3$	γ-2-Naphthyl-α,β,γ-trimethylbutyrolactone	III	87	377
$C_{17}H_{20}O_3$	α,α-Spirocyclopentane-β-(5-indanoyl)-propionic acid	I	—	421
		I	—	249
$C_{17}H_{22}O_3$	α,α-Cyclohexane-β-(*p*-ethylbenzoyl)-propionic acid	I	—	248
$C_{17}H_{26}O_3$	2,4-Dihydroxyphenyl *n*-decyl ketone	I	—	53
$C_{17}H_{16}O_4$	7,4'-Dimethoxy-2,3-dihydroisoflavone	II	24	350
$C_{17}H_{16}O_4$	Homopterocarpin	III	—	380
$C_{17}H_{16}OS$	2,6-Diphenylpenthianone	I	40	97

* Q, yield reported as quantitative; G, yield reported as good. P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

C_{18}

Formula	Compound	Method	Yield *	Reference †
$C_{18}H_{14}O$	1'-Keto-3'-methyl-1,2-cyclopentenophenanthrene	I	—	144
$C_{18}H_{14}O$	4-Keto-1,2,3,4-tetrahydrochrysene	IV	60	369
		I	94	138
$C_{18}H_{14}O$	1-Keto-1,2,3,4-tetrahydro-5,6-benzanthracene	I	—	138
$C_{18}H_{14}O$	1'-Keto-1',2',3',4'-tetrahydro-3,4-benzphenanthrene	IV	71	404
$C_{18}H_{14}O$	4-Keto-1,2,3,4-tetrahydrotriphenylene	II	71	296
$C_{18}H_{16}O$	*cis*-6-Keto-5,6,11,12,13,14-hexahydrochrysene	I	55	307
$C_{18}H_{16}O$	3-Ketohexahydrochrysene	IV	—	346
$C_{18}H_{18}O$	ω-Cyclohexenyl-1-acetylnaphthalene	II	42	335
$C_{18}H_{18}O$	2-γ-Phenylpropyl-1-indanone	I	—	67
$C_{18}H_{18}O$	1-Keto-1,2,3,4-tetrahydrophenanthrene-2,2-spirocyclopentane	I	—	241
		I	—	417
$C_{18}H_{18}O$	1-Keto-1,2,3,4,9,10,11,12-octahydrotriphenylene	IV	74	371
$C_{18}H_{20}O$	2-Keto-1,2,3,4,5,6,7,8,13,14,15,16-dodecahydrochrysene	III	—	208
$C_{18}H_{22}O$	4-Ketododecahydrotriphenylene	I	—	270
$C_{18}H_{26}O$	$\Delta^{17,18}$-Hexadecahydrochrysenone-6	IV	60	400
$C_{18}H_{26}O$	$\Delta^{1,2}$-Hexadecahydro-1,2-benzanthrone-3	IV	47	400
$C_{18}H_{28}O$	Laurophenone	I	—	440
		I	47	471
$C_{18}H_{14}O_2$	1-Benzoyl-4-methoxynaphthalene	IV	30	465
$C_{18}H_{14}O_2$	2,2-Dimethyl-α-fluorenindan-1,3-dione	I	—	15
$C_{18}H_{14}O_2$	*trans*-2,11-Diketo-1,2,9,10,11,18-hexahydrochrysene	I	75	136
$C_{18}H_{14}O_2$	*cis*-2,11-Diketo-1,2,9,10,11,18-hexahydrochrysene	I	70	136
$C_{18}H_{14}O_2$	*rac.*-2,11-Diketo-1,2,9,10,11,18-hexahydrochrysene	I	—	117
$C_{18}H_{16}O_2$	3-Desoxy-11-ketoequilenin R.P. ‡ Desoxyequilenin	II	—	366
$C_{18}H_{16}O_2$	3-Desoxy-11-ketoequilenin R.P.‡ Monoketodesoxyequilenin	V	—	366
$C_{18}H_{16}O_2$	7-Methoxy-3'-keto-3,4-dihydro-(cyclopentenoe-1',2':1,2-phenanthrene)	IV	83	348
$C_{18}H_{20}O_2$	4-Hydroxy-3-phenyl-*n*-caprophenone	IV	60	398
$C_{18}H_{22}O_2$	Oestrone	II	62	145
		II	—	146
$C_{16}H_{22}O_2$	1,1'-Ethynylenetetrahydronaphtholcyclohexanol R.P.‡ 1,2,2*a*,3,4,5,6,6*a*,7,8-Decahydrochrysene	I	—	261

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

Formula	Compound	Method	Yield *	Reference †
$C_{18}H_{32}O_2$	Cyclooctadecan-1,10-dione	I	—	82
$C_{18}H_{14}O_3$	β-2-Anthroylpropionic acid	IV	70	445
$C_{18}H_{14}O_3$	β-2-Phenanthroylpropionic acid	II	50	138
$C_{18}H_{14}O_3$	β-3-Phenanthroylpropionic acid	II	50	138
$C_{18}H_{14}O_3$	β-9-Phenanthroylpropionic acid	III	79	365
$C_{18}H_{16}O_3$	β-[2-(9,10-Dihydrophenanthroyl)]-propionic acid	IV	92	369
		IV	85	295
$C_{18}H_{16}O_3$	3-Keto-2,5-diphenylcyclopentane-1-carboxylic acid	I	—	83
$C_{18}H_{16}O_3$	*o*-(6-Tetroyl)benzoic acid	I	83	39
$C_{18}H_{18}O_3$	α,α-Spirocyclopentane-β-1-naphthoylpropionic acid	I		417
		I	—	241
$C_{18}H_{18}O_3$	α,β-Dimethyl-α-phenyl-β-benzoylpropionic acid	IV	80	401
$C_{18}H_{18}O_3$	β-[9-(1,2,3,4-Tetrahydrophenanthroyl)-propionic acid	IV	96	371
$C_{18}H_{20}O_3$	1,4-Di-*p*-anisylbutanone-1	III	53	387
$C_{18}H_{20}O_3$	β-6-*t*-Butyl-2-naphthoylpropionic acid	IV	78	465
$C_{18}H_{20}O_3$	β-5,6,7,8-Tetramethyl-2-naphthoylpropionic acid	III	—	377
$C_{18}H_{20}O_3$	Methyl α,α-dimethyl-β-4-methyl-1-naphthoylpropionate	I	44	343
$C_{18}H_{22}O_3$	β-[9-(1,2,3,4,5,6,7,8-octahydrophenanthroyl)]-propionic acid	I	—	270
$C_{18}H_{22}O_3$	β-[6-(1,2,3,4,9,10,11,12-octahydrophenanthroyl)]-propionic acid	I	—	331
$C_{18}H_{22}O_3$	β-(5 or 6)-Cyclohexane-1-spirohydrindoylpropionic acid	I	—	331
$C_{18}H_{28}O_3$	2,4-Dihydroxyphenyl *n*-undecyl ketone	I	—	53
		I	—	54
$C_{18}H_{18}O_4$	Methyl β-4-methoxy-4′-xenoylpropionate	I	20	216
$C_{18}H_{18}O_4$	Methyl β-4-methoxy-3-xenoylpropionate	I	58	216
$C_{18}H_{26}O_4$	1,5-Di-*n*-caproyl-2,4-dihydroxybenzene	I	—	54
$C_{18}H_{18}O_5$	α-Phenyl-β-3,4-dimethoxybenzoylpropionic acid	I	91	187
$C_{18}H_{13}ON$	2-Phenyl-5-benzoylpyridine	I	0	40
$C_{18}H_{21}O_3N$	Dihydrocodeinone	I	—	29
$C_{18}H_{21}O_4N$	Dihydrohydroxycodeinone	I	—	71
		I	42	368
	R.P.‡ Dihydrohydroxythebainone			
$C_{18}H_{23}O_3N$	Dihydrothebainone	I	—	71

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

C_{19}

Formula	Compound	Method	Yield *	Reference †
$C_{19}H_{14}O$	4,5-Methylene-7-keto-7,8,9,10-tetrahydrochrysene	IV	59	391
$C_{19}H_{14}O$	4,5-Methylene-10-keto-7,8,9,10-tetrahydrochrysene	IV	41	391
$C_{19}H_{16}O$	1'-Methyl-5-keto-5,6,7,8-tetrahydro-1,2-benzanthracene	IV	85	399
$C_{19}H_{16}O$	2-Methyl-4-keto-1,2,3,4-tetrahydrochrysene	IV	83	369
$C_{19}H_{16}O$	1-Keto-1,2,3,4-tetrahydro-11-methylchrysene	IV	86	399
$C_{19}H_{16}O$	2-Methyl-1-keto-1,2,3,4-tetrahydrotriphenylene	III	77	365
$C_{19}H_{20}O$	Methyl β-9-fluorenyl-β-methyl-*n*-propyl ketone	I	—	256
$C_{19}H_{20}O$	1-Keto-9-methyl-1,2,3,4-tetrahydrophenanthrene-2,2-spirocyclopentane	I	—	417
		I	—	241
$C_{19}H_{22}O$	2-Keto-10-methyl-2,3,4,5,6,7,8,9,10,11-decahydrochrysene	I	—	279
$C_{19}H_{22}O$	4-Keto-1-ethyl-7-isopropyl-1,2,3,4-tetrahydrophenanthrene	I	Q	131
$C_{19}H_{28}O$	Androstenone	I	40	342
$C_{19}H_{38}O$	Methyl *n*-heptadecyl ketone	I	Q	1
$C_{19}H_{14}O_2$	Lactone of 2-(α-hydroxy-*o*-methylbenzyl)-1-naphthoic acid	III	38	220
$C_{19}H_{14}O_2$	Lactone of 2-(α-hydroxy-α-methylbenzyl)-1-naphthoic acid	II	74	220
$C_{19}H_{22}O_2$	2,2-Diethyl-5-cyclohexenylindan-1,3-dione	I	68	26
$C_{19}H_{22}O_2$	2,2-Diethyltetrahydroacenaphtho-α,β-indan-1,3-dione	I	62	26
		I	—	22
$C_{19}H_{24}O_2$	Oestrone methyl ether	II	—	146
$C_{19}H_{24}O_2$	2,2-Diethyltetrahydronaphtho-α,β-indan-1,3-dione	I	74	34
$C_{19}H_{28}O_2$	Androstan-3,17-dione	II	35	224
$C_{19}H_{14}O_3$	β-(4,5-Methylene-1-phenanthroyl)-propionic acid	IV	55	391
$C_{19}H_{16}O_3$	β-4-Methyl-1-phenanthroylpropionic acid	IV	57	399
$C_{19}H_{16}O_3$	β-5-Methyl-3-phenanthroylpropionic acid	IV	88	399
$C_{19}H_{16}O_3$	β-Methyl-β-2-phenanthroylpropionic acid	IV	50	369
$C_{19}H_{16}O_3$	α-Methyl-β-9-phenanthroylpropionic acid	III	77	365
$C_{19}H_{16}O_3$	β-(4,5-Methylene-9,10-dihydro-2-phenanthroyl)-propionic acid	IV	44	391
$C_{19}H_{20}O_3$	α,α-Spirocyclopentane-β-(4-methyl-1-naphthoyl)-propionic acid	I	—	417
$C_{19}H_{22}O_3$	1,5-Di-*p*-anisylpentan-3-one	III	63	387
$C_{19}H_{28}O_3$	Androstan-3,17-dion-?-ol	I	64	224
$C_{19}H_{30}O_3$	2,4-Dihydroxyphenyl *n*-dodecyl ketone	I	—	53

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

Formula	Compound	Method	Yield *	Reference †
$C_{19}H_{20}O_4$	6-Acetyl-7-hydroxy-*trans*-octalino-(2',3',4,3)-coumarin	I	—	311
$C_{19}H_{17}ON$	Methyl-8-phenyl-1-keto-2-(benzo-6,7-indoledihydride-2,8)	I	95	69
	R.P.‡ 1-Methyl-2-naphthylacetic acid			
$C_{19}H_{23}O_4N$	Sinomenine	I	—	460
		I	—	71
$C_{19}H_{25}O_4N$	Dihydrosinomenine	I	—	71
$C_{19}H_{16}ONBr$	Methyl-8-phenyl-1-keto-2-(bromo-4'-benzo-2',1')-6,7-indoldihydride-2,8	I	95	69
	R.P.‡ 6-Bromo-1-methyl-2-naphthylacetic acid			
$C_{19}H_{16}O_2S_2$	Thianthrene-diethylindandione	I	50	25
$C_{19}H_{13}O_2Cl$	Lactone of 2-(*p*-chloro-α-hydroxy-α-methylbenzyl)-1-naphthoic acid	II	70	265

C_{20}

$C_{20}H_{12}O$	1-Ketocholanthrene	IV	22	327
$C_{20}H_{14}O$	11-Acetylchrysene	II	—	198
$C_{20}H_{14}O$	12-Acetylchrysene	II	53	198
$C_{20}H_{16}O$	1-Keto-2*a*,3,4,5-tetrahydrocholanthrene	II	93	327
$C_{20}H_{24}O$	2-Keto-1,10-dimethyl-2,3,4,5,6,7,8,9,10,11-decahydrochrysene	I	—	279
$C_{20}H_{82}O$	Phenyl *n*-tridecyl ketone	I	39	471
$C_{20}H_{16}O_2$	Lactone of 2-(α-hydroxy-8,α-dimethyl-2-naphthylmethyl)-benzoic acid	II	70	263
$C_{20}H_{16}O_2$	Lactone of 2-(α-hydroxy-*o*,α-dimethylbenzyl)-1-naphthoic acid	II	76	220
$C_{20}H_{18}O_2$	2,11-Diketo-5,14-dimethylhexahydrochrysene	III	68	444
$C_{20}H_{20}O_2$	Lactone of 2-(α-hydroxy-6,α-dimethyl-7-tetrolylmethyl) benzoic acid	II	36	272
$C_{20}H_{22}O_2$	Dimesityl diketone	II	0	120
$C_{20}H_{24}O_2$	2,2,5,5-Tetramethyltetrahydronaphtho-di-indan-4,6-dione	I	—	22
		I	—	26
$C_{20}H_{26}O_2$	2,2-Diethyl-6,7-(2',2'-diethylcyclopenteno)-indan-1,3-dione	I	—	13
$C_{20}H_{26}O_2$	2,2-Diethyl-5,6-(2',2'-diethylcyclopenteno)-indan-1,3-dione	I	—	13
$C_{20}H_{28}O_2$	Hinokione	I	—	430
$C_{20}H_{32}O_2$	1,4-Myristylphenol	I	Q	10
$C_{20}H_{32}O_2$	4-Hydroxy-3,5-dimethylphenyl *n*-undecyl ketone	I	45	106
$C_{20}H_{36}O_2$	Cycloeicosan-1,11-dione	I	—	62
	R.P.‡ Cycloeicosanone			

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

Formula	Compound	Method	Yield *	Reference †
$C_{20}H_{16}O_3$	5-Keto-8-methyl-5,6,7,8-tetrahydro-1,2-benz-7-anthroic acid	IV	61	445
$C_{20}H_{18}O_3$	Methyl α-methyl-β-(3-phenanthroyl)-propionate	I	P	151
$C_{20}H_{22}O_3$	Methyl α,α-spirocyclopentane-β-(4-methyl-1-naphthoyl)-propionate	I	—	241
$C_{20}H_{30}O_3$	3-Ketoetiocholanic acid	II	—	375
$C_{20}H_{30}O_3$	3-Ketoetioallocholanic acid	II	42	375
$C_{20}H_{32}O_3$	2-Hydroxy-5-methoxy-4-*n*-pentylphenyl *n*-heptyl ketone	I	—	280
$C_{20}H_{32}O_3$	1-Myristyl-3,4-dihydroxybenzene	I	—	6
$C_{20}H_{14}O_4$	9,10,11,12-Tetraketo-2,6-dimethyl-9,10,11,12,15,16-hexahydronaphthacene	I	—	157
$C_{20}H_{18}O_4$	2,11-Diketo-5,14-dimethoxy-1,2,9,10,11,18-hexahydrochrysene	I	47	136
		I	45	186
$C_{20}H_{18}O_4$	2,11-Diketo-6,15-dimethoxy-1,2,9,10,11,18-hexahydrochrysene	III	27	186
$C_{20}H_{22}O_4$	1,4-Di-*p*-anisoylbutane	III	62	387
		I	43	183
$C_{20}H_{22}O_4$	1,6-Di-(2-hydroxy-4-methylphenyl)-hexane-1,6-dione	I	—	168
$C_{20}H_{28}O_4$	3,11-(?)-Diketoetiocholanic acid	I	19	303
$C_{20}H_{20}O_6$	3,4'-Diethyl-2,3'-diformyl-6'-methoxy-5,6-methylenedioxy-1,1'-diphenyl ether	III	—	316
$C_{20}H_{34}O_6$	2,15-Dimethylhexadecane-5,12-dione-1,16-dicarboxylic acid	I	—	168
$C_{20}H_{18}OBr$	2-(Bromoacetyl)-chrysene	I	—	218
$C_{28}H_{23}O_5Br$	1-(3',4'-Dimethoxyphenyl)-4-(2'-bromo-4',5'-dimethoxyphenyl)-butanone-1	I	93	159
$C_{28}H_{17}ON$	Dimethyl-3,8-phenyl-1-keto-2-(benzo-6,7-indoledihydride-2,8)	I	—	69
	R.P.‡ Methyl-(1-methyl-2-naphthyl)-acetic acid			
$C_{20}H_{18}O_4N$	Berberinium	I	92	294
	Used Zn-Cd and Zn-Pb mixture			
	R.P.‡ 16,17-Dihydrodesoxyberberin			
$C_{20}N_{27}O_4N$	Dihydromethylsinomenine	I	—	98
$C_{20}H_{17}O_6N$	Carbazole-3,6-bis-γ-ketobutyric acid	II	54	212
		II	—	293

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp 201–209.

‡ R.P., reduotion product.

C_{21}

Formula	Compound	Method	Yield *	Reference †
$C_{21}H_{30}O$	5-Acetyl-2,2,4-triethyl-6,7-cyclohexenoindan	I	53	34
$C_{21}H_{42}O$	Di-*n*-decyl ketone	I	31	234
$C_{21}H_{30}O_2$	Cryptomeria resin constituent	I	—	420
$C_{21}H_{60}O_2$	Methylhinokione	I	—	430
$C_{21}H_{60}O_2$	Methyl ether of sugiol	I	—	431
$C_{21}H_{32}O_2$	Allopregnanedione-3,20	II	—	267
		I	34	302
$C_{21}H_{62}O_2$	Allopregnanedione-3,20	II	55	324
	R.P.‡ Allopregnanone-20			
$C_{21}H_{32}O_2$	Pregnanedione-3,20	II	—	324
	R.P.‡ Pregnanone-20			
$C_{21}H_{32}O_2$	Uranedione-3,11	V	85	363
	R.P.‡ Uraneone-11			
$C_{21}H_{32}O_2$	Uranedione-?,?	II	—	267
$C_{21}H_{34}O_2$	Allopregnanol-20(α)-one-3	II	10	324
$C_{21}H_{34}O_2$	3-Ethyl-4-hydroxy-5-methylphenyl *n*-undecyl ketone	I	30	106
$C_{21}H_{22}O_3$	Methyl β-tetrahydroacephenanthroyl-propionate	I	35	476
$C_{21}H_{30}O_3$	Allopregnanetrione-3,11,20	I	71	302
		II	—	362
$C_{21}H_{30}O_3$	Allopregnanetrione-3,6,20	II	—	405
$C_{21}H_{30}O_3$	Uranetrione-3,11,20	V	—	363
		II	—	267
	R.P.‡ Uranedione-11,20			
$C_{21}H_{32}O_6$	13-Keto-15-phenylpentadecanoic acid	I	94	189
$C_{21}H_{34}O_3$	3,4-Dihydroxyphenyl *n*-tetradecyl ketone	I	—	6
$C_{21}H_{30}O_4$	Methyl 3,7-diketoetioallocholanate	II	30	374
$C_{21}H_{24}O_4NI$	Papaverin methiodide	I	—	294
	R.P.‡ *d,l*-Laudenosin			

C_{22}

$C_{22}H_{14}O$	8-Acetyl-1,2-benzpyrene	II	24	328
$C_{22}H_{16}O$	1′-Keto-1′,2′,3′,4′-tetrahydro-1,2-benzchrysene	II	—	300
	R.P.‡ 1′-Hydroxy-1′,2′,3′,4′-tetrahydro-1,2-benzchrysene			
$C_{22}H_{16}O$	?-Acetyl-12-ethylchrysene	I	—	218
$C_{22}H_{16}O$	2,3-Diphenyltetralone-1	I	50	322
$C_{22}H_{22}O$	1′-Keto-3′-methyl-5,6-cyclopentenoretene	I	—	231
$C_{22}H_{44}O$	*t*-Butyl *n*-heptadecyl ketone	I	—	234
$C_{22}H_{24}O_2$	1,2,3,4,5,6,7,8-Octamethylanthraquinone	IV	82	372

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

Formula	Compound	Method	Yield *	Reference †
$C_{22}H_{30}O_2$	2,2-Diethyl-4,7-dimethyl-5,6-(2′,2′-diethylcyclopenteno)-indan-1,3-dione	I	88	12
$C_{22}H_{36}O_2$	1,4-Myristylethoxybenzene	I	Q	10
$C_{22}H_{40}O_2$	Cyclodocosan-1,12-dione	I	32	99
$C_{22}H_{16}O_6$	β-1-Chrysenoylpropionic acid	II	—	300
$C_{22}H_{16}O_3$	β-2-Chrysenoylpropionic acid	II	—	300
$C_{22}H_{16}O_6$	α,β-Diphenyl-β-benzoylpropionic acid	I	30	322
$C_{22}H_{22}O_3$	β-8-Methyl-2-isopropyl-3-phenanthroylpropionic acid	II	58	257
$C_{22}H_{32}O_3$	Ketolactone from tigogenin	II	97	193
$C_{22}H_{34}O_3$	3-Ketobisnorallocholanic acid	II	—	148
$C_{22}H_{36}O_6$	1-Myristyl-3,4-dimethoxybenzene	I	—	4
		I	Q	10
		I	—	58
$C_{22}H_{36}O_3$	1-(3′,4′-Dimethoxyphenyl)-tetradecanone-3	I	—	6
$C_{22}H_{36}O_3$	1-Myristyl-2,5-dimethoxybenzene	I	G	10
$C_{22}H_{26}O_4$	1,4-Di-(*p*-ethoxybenzoyl)-butane	I	—	183
$C_{22}H_{34}O_4$	Keto acid from sarsasapogenin acetate	II	—	355
$C_{22}H_{26}O_5$	1-Keto-6,7-dimethoxy-2-(3′,4′-dimethoxybenzyl)-3-methyl-1,2,3,4-tetrahydronaphthalene	I	50	275
$C_{22}H_{22}O_6$	2,11-Diketo-5,6,14,15-tetramethoxy-1,2,9,10,11,18-hexahydrochrysene	III	—	186
$C_{22}H_{24}O_7$	4-Keto-6,7-dimethoxy-1-veratryl-3-methyl-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid	I	—	449
$C_{22}H_{24}O_3N_2$	N-Methyl-*sec.*-*ps.*-strychnine	I	2	289

C_{23}

$C_{23}H_{16}O$	2-Benzylidene-3-phenyl-3-methyl-indanone-1	I	—	447
$C_{23}H_{44}O$	Cyclotricosanone	I	—	130
$C_{23}H_{46}O$	Di-*n*-undecyl ketone	I	32	234
$C_{23}H_{16}O$	2-α-(α-Hydroxy-α,1′-naphthylethyl-1-naphthoic acid lactone	III	74	325
$C_{23}H_{32}O_3$	Methyl-6-acetyldehydroabietate	IV	77	384
$C_{23}H_{36}O_6$	Allopregnanol-20(β)-one-3-acetate	II	—	324
	R.P.‡ Allopregnanol-20(β)			
$C_{23}H_{36}O_3$	Pregnanol-20(α)-one-3-acetate	II	—	324
$C_{23}H_{36}O_3$	1-(2′,3′-Dimethoxyphenyl)-pentadecanone-3	I	—	7
$C_{23}H_{36}O_6$	1-(3′,4′-Dimethoxyphenyl)-pentadecanone-3	I	—	6
$C_{23}H_{38}O_3$	3,4-Dimethoxyphenyl *n*-tetradecyl ketone	I	—	4
		I	—	58
$C_{23}H_{32}O_4$	Tetrahydroanhydrosarmentogenone	II	—	223

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

Formula	Compound	Method	Yield *	Reference †
$C_{23}H_{32}O_4$	Tetrahydroanhydrodigoxigenone	II	—	223
		II	—	205
$C_{23}H_{34}O_4$	Desoxypyrolithobilianic acid	II	—	59
$C_{23}H_{34}O_5$	Digitoxanondiacid	II	—	194
$C_{26}H_{22}O_6$	Rotenone	I	—	104
$C_{23}H_{22}O_6$	Isorotenone	II	—	104
$C_{23}H_{26}O_7$	Ethyl 4-keto-6,7-dimethoxy-1-veratryl-1,2,3,4-tetrahydronaphthalene-2-carboxylate	I	—	177
$C_{23}H_{19}O_6Cl$	1,2,α-Triacetoxy-4-(*p*-chlorobenzyl)-naphthalene	I	—	321
	R.P.‡ 4-(*p*-chlorobenzyl)-1,2-dihydroxynaphthalene			

C_{24}

$C_{24}H_{40}O$	Stearophenone	III	77	450
		III	24	320
$C_{24}H_{46}O$	Cyclohexyl *n*-heptadecyl ketone	I	45	234
$C_{24}H_{46}O$	2,2-Dimethyl-*n*-docosanone-5	I	31	234
$C_{24}H_{34}O_2$	2,2-Diethyl-4-methyl-7-isopropyl-5,6-(2′,2′-diethylcyclopenteno)-indan-1,3-dione	I	73	25
$C_{24}H_{40}O_2$	1,4-Palmitylethoxybenzene	I	60	10
$C_{24}H_{44}O_2$	Cyclotetracosan-1,13-dione	I	39	99
$C_{24}H_{36}O_3$	1-Cyclopentenyl-13-(2,4-dihydroxyphenyl)-*n*-tridecanone-13 (Chaulmoogrylresorcinol)	I	—	84
$C_{24}H_{36}O_3$	1-Cyclopentyl-13-(2,4-dihydroxyphenyl)-*n*-tridecanone-13 (Dihydrochaulmoogrylresorcinol)	I	—	84
$C_{24}H_{40}O_3$	Trihydroxycholene	I	—	407
$C_{24}H_{40}O_3$	3,4-Dimethoxyphenyl *n*-pentadecyl ketone	I	—	4
		I	Q	10
		I	—	58
$C_{24}H_{30}O_4$	1,8-Di-*p*-anisoyloctane	III	58	387
$C_{24}H_{36}O_4$	Dehydrohyodesoxycholic acid	II	—	42
$C_{24}H_{36}O_4$	3,12-Diketocholanic acid	V	—	463
	R.P.‡ 12-Ketocholanic acid			
$C_{24}H_{36}O_4$	3-Hydroxy-7-ketocholanic acid	I	—	237
$C_{24}H_{40}O_4$	Ursodesoxycholic acid	II	—	461
$C_{24}H_{34}O_5$	Dehydrocholic acid	II	—	23
	R.P.‡ 7,12-Diketocholanic acid	II	—	462
		II	—	18
$C_{24}H_{34}O_5$	α-Triketocholanic acid	II	—	434
$C_{24}H_{34}O_5$	Dehydrocholic acid	II	—	32
		II	—	423
		II	—	23
$C_{24}H_{30}O_6$	Diethyl β,β′-di-*p*-anisyl-β,β′-dihydroxyadipate	I	—	137

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

C_{25}—C_{26}

Formula	Compound	Method	Yield *	Reference †
$C_{25}H_{16}O$	12-Benzoylchrysene	II	79	198
$C_{25}H_{36}O_3$	1-Cyclopentenyl-13-(2-hydroxy-4-methoxyphenyl)-*n*-tridecanone-13	I	—	84
$C_{25}H_{36}O_5$	Pregnandiol-3,4-one-20 diacetate	II	—	268
	R.P.‡ Allopregnane			
$C_{26}H_{42}O$	2-*n*-Pentadecyl-5,6,7,8-tetrahydronaphthyl ketone	II	63	388
$C_{26}H_{24}O_2$	1,2,3,4,5,6,7,8-Tetracyclopentenoanthraquinone	IV	73	372
$C_{26}H_{46}O_2$	Cyclohexacosan-1,14-dione	I	51	99
$C_{26}H_{40}O_3$	1-Cyclopentenyl-13-(2,4-dimethoxyphenyl)-*n*-tridecanone-13	I	—	84
$C_{26}H_{44}O_3$	Ketocarboxylic acid obtained from cholesterol	II	80	128
		II	75	66

C_{27}

$C_{27}H_{46}O$	Cholestanone-6	II	—	469
$C_{27}H_{46}O$	Cholestanone-7	V	—	326
$C_{27}H_{46}O$	Zymostanone	II	—	472
$C_{27}H_{54}O$	14-Heptacosane (myristone)	I	—	127
$C_{27}H_{44}O_2$	Desoxysarsasapogenone	II	—	354
$C_{27}H_{44}O_2$	Cholestanedione-3,6	V	—	326
		II	—	238
$C_{27}H_{46}O_2$	Epicoprostanol-3-one-24	II	0	210
$C_{27}H_{42}O_3$	Sarsasapogenone	IV	68	359
		V	45	354
		II	81	323
		IV	43	308
$C_{27}H_{42}O_3$	Isosarsasapogenone	V	—	323
		II	—	323
$C_{27}H_{42}O_3$	Pseudosarsasapogenone	V	—	389
$C_{27}H_{42}O_3$	Tigogenone	V	—	367
		II	P	358
		V	—	357
$C_{27}H_{44}O_3$	Tigogenin	II	—	357
$C_{27}H_{40}O_4$	Anhydrosarsasapogenoic acid	II	20	309
$C_{27}H_{40}O_4$	Chlorogenone	V	—	326
		II	—	367
$C_{27}H_{44}O_5$	Ketodicarboxylic acid from cholestanone	II	—	28
$C_{27}H_{42}O_7$	6-Ketolithobilianic acid trimethyl ester	II	—	59
$C_{27}H_{41}ON$	Solatubenone	I	—	411
$C_{27}H_{25}O_4N$	9-*o,m,p*-Tolyldesoxyberberin	II	G	170
$C_{27}H_{29}O_4N$	9-Phenyldesoxypalmatin	I	—	294
	R.P.‡ 9-Phenyl-2,3,11,12-tetramethoxyberbin			
$C_{27}H_{25}O_5N$	9-o-Anisyldesoxyberberin	II	G	170

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

C_{28}

Formula	Compound	Method	Yield *	Reference †
$C_{26}H_{40}O$	Ergostatrienone	I	—	123
$C_{28}H_{42}O$	α-Ergostadienone	III	—	123
$C_{26}H_{44}O$	α-Ergostenone	I	—	123
$C_{28}H_{46}O$	2-*n*-Heptadecyl-5,6,7,8-tetrahydronaphthyl ketone	III	68	450
$C_{26}H_{44}O_2$	Campnospermonyl metyl ether	I	—	85
$C_{28}H_{52}O_2$	Cyclo-octacosan-1,15-dione	I	51	99
$C_{26}H_{46}O_3$	13-Keto-22-phenylbehenic acid	I	30	189
$C_{28}H_{42}O_3$	Ergostanedionol	II	—	162
$C_{26}H_{40}O_5$	Triketobufosterocholenic acid	II	—	459
$C_{26}H_{40}O_5$	Triketoisosterocholenic acid	I	—	453
$C_{26}H_{42}O_5$	Triketobufosterocholanic acid	II	—	459
$C_{28}H_{27}O_6N$	9-Veratryldesoxyberberin	II	6	170

C_{29}

$C_{29}H_{46}O$	Norechinocystenone	II	—	392
$C_{29}H_{46}O$	Oleanone	I	—	456
		II	—	473
$C_{29}H_{46}O$	2-Methyl-3-*n*-pentadecyl-5,6,7,8-tetrahydronaphthyl ketone	II	50	383
$C_{29}H_{50}O$	Bombicestanone	I	—	281
		II	72	388
$C_{29}H_{50}O$	Inagostanone	II	—	282
$C_{29}H_{56}O$	Cyclononacosanone	I	—	99
$C_{29}H_{56}O$	15-Nonacosanone (laurone)	I	—	127
$C_{29}H_{56}O$	9-Nonacosanone	I	—	127
$C_{29}H_{56}O$	10-Nonacosanone	I	—	127
$C_{29}H_{53}O$	12-Nonacosanone	I	—	127
$C_{29}H_{44}O_2$	Norechinocystendione	II	—	392
$C_{29}H_{44}O_2$	Sapogenol diketone	II	—	247
$C_{29}H_{42}O_4$	Diketolactone of quillaic acid	II	—	379
$C_{29}H_{46}O_4$	5-Hydroxy-3-stearoyl-4,6,7-trimethylisocoumaranone	II	Q	277

* Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

C_{30}—C_{31}

Formula	Compound	Method	Yield *	Reference †
$C_{30}H_{44}O$	*n*-Heptadecyl biphenyl ketone	III	73	450
$C_{30}H_{50}O$	Lupanone	II	—	443
$C_{30}H_{56}O$	Cyclotriacontanone	I	34	82
$C_{30}H_{32}O_2$	1,2,3,4,5,6,7,8-Tetracyclohexenoanthraquinone	IV	82	372
$C_{30}H_{56}O_2$	Cyclotriacontan-1,16-dione	I	51	82
		I	32	99
$C_{30}H_{46}O_3$	Oleanonic acid	II	—	245
$C_{30}H_{50}O_3$	Methyl hedragon	II	—	347
$C_{30}H_{56}O_3$	13-Keto-*n*-triacontanoic acid	I	—	160
$C_{30}H_{44}O_4$	Methyl ester of diketoquillaic acid	II	60	379
$C_{30}H_{56}O_5$	14-Keto-octacosane-1,28-dicarboxylic acid	I	—	82
$C_{30}H_{25}O_4N$	9-α-Naphthyldesoxyberberin	II	G	170
$C_{31}H_{52}O$	*ar*.-2-Methyl-3-phytyltetralin	II	95	383
$C_{31}H_{62}O$	16-Hentriacontanone (palmitone)	I	—	127
$C_{31}H_{46}O_3$	Methyl oleanonate	II	—	245
$C_{31}H_{46}O_4$	Oxidation product of methyl echinocystate	II	85	352

C_{32}—C_{67}

$C_{32}H_{60}O_2$	Cyclodotriacontan-1,17-dione	I	—	171
$C_{32}H_{44}O_4$	Ergosteron-3-maleic anhydride addition product	II	35	204
$C_{32}H_{46}O_5$	Ketoacetyloleanolic acid	II	—	245
$C_{33}H_{56}O_4$	Diacetate of 4-hydroxystigmastanol	II	—	269
	R.P.‡ Stigmastane			
$C_{34}H_{20}O_2$	3,9-Dibenzoylperylene	I	—	105
$C_{34}H_{64}O_2$	Cyclotetratriacontan-1,18-dione	I	—	171
$C_{34}H_{66}O_3$	13-Ketotetratriacontanoic acid	I	80	229
$C_{35}H_{70}O$	Pentatriacontanone-18 (Stearone)	I	—	127
		I	Q	1
$C_{36}H_{46}O_4$	Ketone acetate from desoxysarsasapogenin	II	6	308
$C_{39}H_{30}O$	Triphenylmethyl 4-(diphenylmethyl)phenyl ketone	I	—	70
$C_{41}H_{24}O_3$	Tribenzoylperylene	II	—	199
	R.P.‡ Benzyldibenzoylperylene			
$C_{46}H_{90}O_3$	13-Ketohexatetracontanoic acid	I	86	229
$C_{67}H_{134}O$	*n*-Heptahexacontanone-34	I	—	229

* Q, yield reported as quantitative; G, yield reported as good, P, yield reported as poor. A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201–209.

‡ R.P., reduction product.

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CHAPTER 8

THE PERKIN REACTION
AND RELATED REACTIONS

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CONTENTS

PAGE

INTRODUCTION 211

SCOPE OF THE REACTION 217
- Carbonyl Components 217
  - Table I. Yields of Cinnamic Acids from Substituted Benzaldehydes . . 218
- Acid Components 223
- Comparison with Other Synthetic Methods 233

SELECTION OF EXPERIMENTAL CONDITIONS 236

USE OF THE PERKIN REACTION IN SYNTHESIS 240
- α,β-Unsaturated Acids 240
- Other Unsaturated Acids 241
- Cyclic Compounds 242
- Indirect Syntheses 243

LABORATORY PROCEDURES 248
- Cinnamic Acid 248
  - Using Acetic Anhydride and Potassium Acetate 248
  - Using Malonic Acid and a Pyridine Base 248
- *p*-Methoxycinnamic Acid 249
- β-Piperonylacrylic Acid (3,4-Methylenedioxycinnamic Acid) 249
- 3-Methoxy-4-Hydroxycinnamic Acid (Ferulic Acid) 250
- α-Methylcinnamic Acid 251
- α-Phenylcinnamic Acid 252
- β-*n*-Hexylacrylic Acid (α,β-Nonenoic Acid) 252
- *o*-Nitrophenylpyruvic Acid 253
  - Azlactone from Aceturic Acid and *o*-Nitrobenzaldehyde 253
  - Hydrolysis of the Azlactone 253

SUMMARY 255
- Table II. Yields of Cinnamic Acid under Various Conditions 255
- Table III. Ring-Substituted Cinnamic Acids 256

INTRODUCTION

In 1868 W. H. Perkin [1] described a synthesis of coumarin by heating the sodium salt of salicylaldehyde with acetic anhydride. Further study of this reaction led to the discovery of a new method for preparing cinnamic acid and its analogs by means of a synthesis of very general application, which became known as the Perkin reaction.[2] This reaction is brought about by heating an aldehyde of aromatic type with the anhydride of an aliphatic acid of the general formula RCH_2CO_2H, in the presence of the sodium salt of the acid.

$$C_6H_5CH{=}O + (CH_3CO)_2O + CH_3CO_2Na \rightarrow C_6H_5CH{=}CHCO_2H$$

$$C_6H_5CH{=}O + (RCH_2CO)_2O + RCH_2CO_2Na \rightarrow C_6H_5CH{=}\underset{\underset{R}{|}}{C}CO_2H$$

Since the resulting β-arylacrylic acids can be subjected to a variety of chemical transformations, the Perkin reaction gives access indirectly to a number of other types of compounds such as arylethylenes and acetylenes, arylacetaldehydes, arylethylamines, arylpropionic and propiolic acids, and their derivatives. Several modifications and extensions of the Perkin reaction, such as the paraconic acid synthesis of Fittig and the azlactone synthesis of Erlenmeyer, have served to broaden the scope and usefulness of the original process.

In the course of an extensive study of unsaturated acids Fittig [3] and his collaborators made several important contributions to the mechanism of the Perkin reaction. He showed that the aldehyde condenses with the *alpha* methylene group of the acid component (salt or anhydride) and concluded that the reaction is an addition process, like an aldol condensation, involving an intermediate β-hydroxy compound that loses water to form the α,β-unsaturated acid.

$$C_6H_5CH{=}O + (CH_3CH_2CO)_2O + CH_3CH_2CO_2Na \rightarrow$$

$$\left[C_6H_5CHOH\underset{\underset{CH_3}{|}}{C}HCO_2H\right] \rightarrow C_6H_5CH{=}\underset{\underset{CH_3}{|}}{C}CO_2H$$

Perkin [2] had assumed, without experimental proof, that the carbon atom farthest removed from the carboxyl group was probably the one which

[1] Perkin, *J. Chem. Soc.*, **21**, 53, 181 (1868).
[2] Perkin, *J. Chem. Soc.*, **31**, 388 (1877).
[3] Fittig, *Ann.*, **195**, 169 (1879); **216**, 97 (1883); **227**, 48 (1885); *Ber.*, **14**, 1824 (1881); **16**, 1436 (1883); **27**, 2658 (1897).

condenses with the aldehyde, but Fittig and others,[4, 5] quickly disproved Perkin's tentative hypothesis.*

The view that the Perkin reaction involves an intermediate addition product of the aldol type is generally accepted at the present time. It is supported by the actual isolation of derivatives of the intermediate addition products in certain cases where the normal elimination of water does not occur. For example, benzaldehyde, sodium isobutyrate, and isobutyric anhydride (or acetic anhydride) on heating at 100° give rise to the isobutyryl derivative of β-phenyl-β-hydroxypivalic acid (α,α-dimethyl-β-hydroxy-β-phenylpropionic acid)[6] and the mixed anhydride of this acid with isobutyric acid.

$$C_6H_5CH{=}O + (CH_3)_2CHCOOCOCH(CH_3)_2 + (CH_3)_2CHCO_2Na \rightarrow$$

$$C_6H_5\underset{\underset{OCOC_3H_7}{|}}{CH}{-}C(CH_3)_2CO_2H \quad \textit{and} \quad C_6H_5\underset{\underset{OCOC_3H_7}{|}}{CH}{-}C(CH_3)_2COOCOC_3H_7$$

The total yield, calculated as β-phenyl-β-hydroxypivalic acid, is about 33% of the theoretical.[7] At 150° the same reactants give the unsaturated hydrocarbon, 2-methyl-1-phenylpropene,[8] which is formed presumably from the above intermediates by loss of carbon dioxide and isobutyric acid (or anhydride).

$$C_6H_5\underset{\underset{OCOC_3H_7}{|}}{CH}{-}C(CH_3)_2CO_2H \rightarrow C_6H_5CH{=}C(CH_3)_2 + CO_2 + C_3H_7CO_2H$$

Likewise, furfural on heating with isobutyric anhydride and sodium isobutyrate gives only 2-methyl-1-furylpropene,[9] even at temperatures as low as 100°.

In typical examples of the Perkin reaction, involving derivatives of acetic acid or monosubstituted acetic acids, decarboxylation has been observed in a few instances, notably with isovaleric acid.[10] This side

* For an interesting account of early work on the Perkin reaction see Lachmann, "The Spirit of Organic Chemistry," The Macmillan Co., London (1899), pp. 12–20; also, Cohen, "Organic Chemistry for Advanced Students," fifth edition, Longmans, Green and Co., New York (1928), Part I, pp. 288–293. An excellent review of recent work is given by Watson, *Ann. Repts. Chem. Soc.* (*London*), **36**, 210 (1939).

[4] Baeyer and Jackson, *Ber.*, **13**, 115 (1880).

[5] Conrad and Bischoff, *Ann.*, **204**, 183 (1880).

[6] Fittig and Jayne, *Ann.*, **216**, 115 (1883); Fittig and Ott, *Ann.*, **227**, 119 (1885).

[7] Hauser and Breslow, *J. Am. Chem. Soc.*, **61**, 793 (1939).

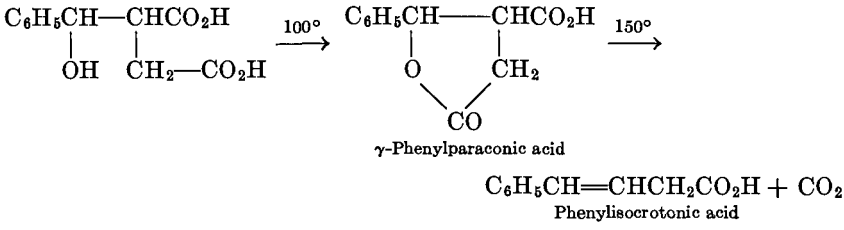
[8] Perkin, *J. Chem. Soc.*, **35**, 138 (1879).

[9] Baeyer and Tonnies, *Ber.*, **10**, 1364 (1877).

[10] Schaarschmidt, Georgeacopol, and Herzenberg, *Ber.*, **51**, 1059 (1918).

reaction is generally negligible at the temperatures usually employed (140–175°) but may become important at higher temperatures. Thus, anisaldehyde on heating at 170° with propionic anhydride and sodium propionate yields mainly *p*-anisyl-α-methylacrylic acid,[11] but at 200° anethole (*p*-propenylanisole) is obtained.[12]

Further evidence for the formation of an intermediate of the aldol type is afforded by the reaction of benzaldehyde with succinic anhydride (or acetic anhydride) and sodium succinate. Fittig and Jayne [13] showed that if the reaction is carried out at 100° the product is γ-phenylparaconic acid, formed by lactonization of the intermediate hydroxy acid.



γ-Phenylparaconic acid

Phenylisocrotonic acid

On heating to 150°, γ-phenylparaconic acid loses carbon dioxide and gives the β,γ-unsaturated acid, phenylisocrotonic acid, which Perkin had obtained directly by carrying out the original condensation at 150°.

The relative significance of the acid anhydride and the sodium salt in the intimate mechanism of the Perkin condensation has been the subject of numerous investigations extending over a period of more than fifty years. Perkin [2] believed that the cinnamic acids are formed by condensation between the aldehyde and the acid anhydride, with the sodium salt functioning as a catalyst. He found that cinnamic acid is formed alone when benzaldehyde and acetic anhydride are heated at 180° with sodium acetate, butyrate or valerate, whereas benzaldehyde on heating with propionic anhydride and sodium acetate gives only α-methylcinnamic acid. Fittig [3] then studied the reaction with several anhydride-salt combinations, particularly at lower temperatures. He found that benzaldehyde, acetic anhydride, and sodium acetate (in equimolecular amounts) do not react at 100° even on long-continued heating; when sodium *n*-butyrate was used in place of the acetate, reaction occurred slowly and only α-ethylcinnamic acid was formed, but at 150° a mixture containing one part of α-ethylcinnamic to two parts of cinnamic acid was obtained, and at 180° the product contained only one part of

[11] Perkin, *J. Chem. Soc.*, **31**, 415 (1877); **32**, 669 (1878).

[12] Moureu and Chauvet, *Bull. soc. chim.*, [3] **17**, 412 (1897); Moureu, *Ann. chim.*, [7] **15**, 135 (1898).

[13] Fittig and Jayne, *Ann.*, **216**, 100 (1883).

α-ethylcinnamic to ten parts of cinnamic acid.[14] From these results Fittig concluded that at 100° the reaction occurs between the aldehyde and the salt, and explained the formation of cinnamic acid at 150° and 180° by assuming that an anhydride-salt exchange occurs at the higher temperatures (but not at 100°), giving rise to sodium acetate, which then reacts with the aldehyde. Fittig considered, therefore, that the observed behavior of anhydride-salt combinations was compatible only with the view that the aldehyde always condenses with the salt.

Michael [15] was led by theoretical considerations to doubt the validity of Fittig's views and brought forward strong experimental evidence in favor of Perkin's contention that the condensation occurs between the aldehyde and anhydride. Michael and Hartman [16] showed that the anhydride-salt exchange postulated by Fittig occurs rapidly even at 100° and the position of equilibrium is very far on the side of the higher anhydride and sodium acetate. They found that acetic anhydride on heating with sodium butyrate or caproate for a short time at 100° gave excellent yields of butyric or caproic anhydride, while butyric anhydride and sodium acetate do not react appreciably under these conditions.

$$2C_3H_7CO_2Na + (CH_3CO)_2O \overset{100^\circ}{\rightleftharpoons} 2CH_3CO_2Na + (C_3H_7CO)_2O$$

These results show unmistakably that, in Fittig's experiment with benzaldehyde, acetic anhydride, and sodium butyrate at 100°, the reaction mixture must have contained considerable butyric anhydride and sodium acetate and but little acetic anhydride and sodium butyrate. Consequently, the formation of α-ethylcinnamic acid as the main product under these conditions affords strong evidence that the reaction proceeds between the aldehyde and the anhydride. Recently Breslow and Hauser [17] found that the same relative quantities of cinnamic and α-ethylcinnamic acids were formed when benzaldehyde was condensed with a mixture of either acetic anhydride and sodium butyrate, or butyric anhydride and sodium acetate, which had in each case been heated previously for several hours to establish equilibrium.* At 100° the product contained about 80% α-ethylcinnamic and 20% cinnamic acid; at 180° there is a larger proportion of acetic anhydride in the reac-

* In these experiments the original anhydride-salt mixtures contained one mole of anhydride to two moles of the salt; in Fittig's and Michael's experiments the anhydride and salt were used in equimolecular quantities, and in Perkin's less than one-half mole of salt was used per mole of anhydride.

[14] Fittig and Slocum, *Ann.*, **227**, 53 (1885).

[15] Michael, *J. prakt. Chem.*, [2] **60**, 364 (1899).

[16] Michael and Hartman, *Ber.*, **34**, 918 (1901); see also Michael, *Am. Chem. J.*, **50**, 411 (1913).

[17] Breslow and Hauser, *J. Am. Chem. Soc.*, **61**, 786 (1939).

tion mixture and the product is made up of about 30% of α-ethylcinnamic and 70% cinnamic acid.

Fittig's view that the salt condenses with the aldehyde appeared to be strongly supported by Stuart's observation [17] that benzaldehyde, sodium malonate, and acetic anhydride react at room temperature with evolution of carbon dioxide and formation of cinnamic acid. Fittig regarded this as a convincing proof of his view since he believed that malonic acid was incapable of forming an anhydride and the reaction must have occurred between the aldehyde and sodium malonate. Michael pointed out that this argument also is not valid since a mixed anhydride of malonic and acetic acid could be formed and, in any event, malonic acid is much more reactive in condensation reactions than the anhydrides or salts of monobasic acids. This view is confirmed by recent work [17] which has shown that sodium malonate does not react with benzaldehyde to any appreciable extent unless glacial acetic acid is present.

In spite of Michael's objections, Fittig's interpretation was widely accepted for many years and still persists in several of the current textbooks of organic chemistry. However, the results of a number of workers now provide substantial evidence in favor of Perkin's and Michael's view that it is the anhydride and not the salt that undergoes condensation with the aldehyde. Kalnin [18] has shown that benzaldehyde condenses readily with acetic anhydride in the presence of inorganic and organic bases (potassium carbonate, triethylamine, etc.) but does not condense with sodium acetate in the presence of these catalysts (or in the presence of inorganic dehydrating agents [19]). These and other results [20, 21] indicate that the Perkin reaction is essentially an aldol condensation of the aldehyde and anhydride, in which the salt of the acid functions merely as a base and promotes enolization of the anhydride. In this connection it is of interest to note that ketene, which may be regarded as an intramolecular anhydride of acetic acid, reacts readily at 25° with benzaldehyde in the presence of potassium acetate to give a mixed anhydride of cinnamic and acetic acids, along with styrene.[22]

$$C_6H_5CHO + 2CH_2{=}C{=}O \xrightarrow{CH_3CO_2K} C_6H_5CH{=}CHCOOCOCH_3$$

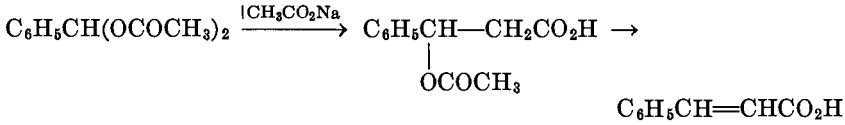
$$C_6H_5CHO + CH_2{=}C{=}O \longrightarrow C_6H_5CH{=}CH_2 + CO_2$$

This reaction does not take place with tributylamine in place of potassium acetate, and with small amounts of the latter (0.1 mole per mole of

[16] Kalnin, *Helv. Chim. Acta*, **11**, 977 (1928).
[19] Bakunin and Peccerillo, *Gazz. chim. ital.*, **65**, 1145 (1935).
[20] Kuhn and Ishikawa, *Ber.*, **64**, 2347 (1931).
[21] Müller, *Ann.*, **491**, 251 (1931).
[22] Hurd and Thomas, *J. Am. Chem. Soc.*, **55**, 275 (1933).

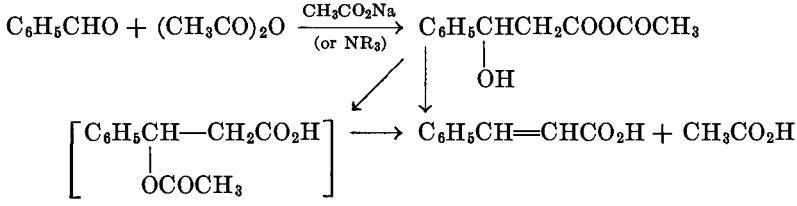
benzaldehyde) produces about 70% of styrene and only 30% of cinnamic acid.[23]

Perkin [24] suggested that the aldehyde and anhydride combine to form benzal diacetate, which then undergoes rearrangement under the influence of sodium acetate.



The intermediate formation of benzal diacetate appeared plausible in view of Caro's synthesis [25] of cinnamic acid by heating benzal chloride with excess sodium acetate. This idea was elaborated by Nef,[26] who postulated the formation of the nascent phenylacetoxymethylene radical, C_6H_5—CH—$OCOCH_3$, in the process. Experiments showed, however, that benzal diacetate and sodium acetate give only small amounts of cinnamic acid at 160–180° under the usual conditions of the Perkin reaction, and higher temperatures (200–220°) are required to obtain a good conversion. Other work [27] indicates also that the aldehyde diacetates are not intermediates in the Perkin reaction, but that they react by decomposing into the aldehyde and acid anhydride.

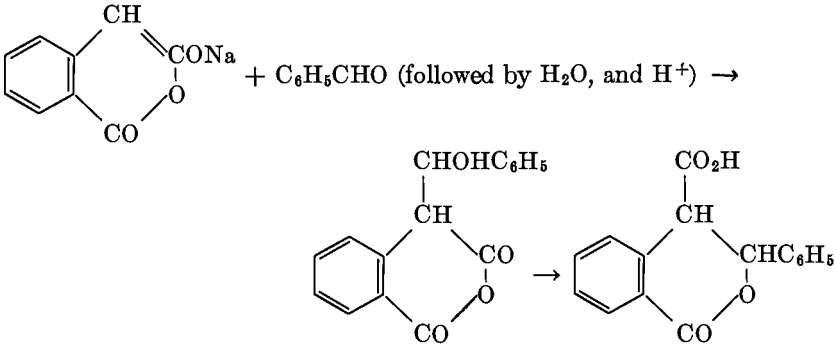
The modern view of the mechanism of the Perkin reaction is essentially that the aldehyde reacts with the sodium salt of the enol form (enolate anion) of the acid anhydride, formed by interaction of the anhydride with the sodium salt or other base; the addition product then decomposes into cinnamic acid.



The intimate details of the process may be envisaged in several ways,[7, 22] all leading to the same result. The notion of enolization of the anhydride is supported by Müller's observation [21] that the sodium derivative of homophthalic anhydride reacts instantly with benzaldehyde at room

[23] Vittum, Thesis, Cornell University, 1933.
[24] Perkin, *J. Chem. Soc.*, **31**, 424 (1877); **49**, 317 (1886).
[25] Ger. pats., 17,467, 18,232 (1880) (*Frdl.*, **1**, 26, 28).
[26] Nef, *Ann.*, **298**, 302 (1897); see also references 174 and 175, p. 264.
[27] Böck, Lock, and Schmidt, *Monatsh.*, **64**, 401 (1934).

temperature. This reaction is analogous to the paraconic acid syntheses involving succinic anhydride, and leads eventually to a lactone-acid.



Likewise, Hauser and Breslow [7] have shown that benzaldehyde reacts instantly at room temperature with the sodium enolates of ethyl acetate and isobutyrate to form β-phenyl-β-hydroxy esters.

SCOPE OF THE REACTION

The Perkin reaction may be regarded essentially as the condensation of a carbonyl component A and an acid anhydride-salt combination B. In the resulting acrylic acids, substituents in the carbonyl component appear in the β-position and those in the acid component appear in the α-position.

$$\underset{\text{A}}{RCH{=}O} + \underset{\text{B}}{(CH_3CO)_2O} \rightarrow \underset{\beta\text{-Substituted acrylic acids}}{RCH{=}CHCO_2H}$$

$$RCH{=}O + (R'CH_2CO)_2O \rightarrow \underset{\alpha,\beta\text{-Disubstituted acrylic acids}}{RCH{=}C(R')CO_2H}$$

The following discussion gives a survey of the types of carbonyl components and acid anhydride-salt combinations that can be used, and of the yields that can be obtained under favorable conditions.

Carbonyl Components

In general the usual Perkin reaction is limited for practical purposes to aldehydes of the aromatic series and closely related types. Table I gives a brief survey of the yields of β-arylacrylic acids obtained from various substituted benzaldehydes, with acetic anhydride and sodium acetate,

under similar conditions of reaction.[27, 28, 29] The yields given are typical but do not always represent the maximum that can be secured with a given aldehyde, as the optimum conditions of reaction (temperature, duration of heating, catalytic effects, etc.) vary somewhat for different substituents.

TABLE I

YIELDS OF CINNAMIC ACIDS FROM SUBSTITUTED BENZALDEHYDES [a]

Substituent	Yield (per cent)	Substituent	Yield (per cent)
None [27]	45–50 [b]	2-Methoxy [60]	55
2-Methyl [27]	15	2,5-Dimethoxy [31]	56
3-Methyl [27]	23	4-Methoxy [30]	30
4-Methyl [27]	33	4-Ethoxy [32]	36
2,6-Dimethyl [27]	0	4-Hydroxy [30]	62
2-Iodo [29]	85	4-Dimethylamino [29]	0
2-Chloro [27]	71	2-Nitro [27]	75
3-Chloro [27]	63	3-Nitro [27]	75
4-Chloro [27]	52	4-Nitro [27]	82
2,6-Dichloro [27]	82	2,4-Dinitro [27]	70 [c]

[a] The conditions were very similar but not identical in all experiments. In general, 1 mole of the aldehyde was heated for eight hours at 180° with about 2 moles of acetic anhydride and 0.7 mole of sodium acetate.

[b] It has been reported [33] that the yield of cinnamic acid can be increased to 80–85% by adding a little pyridine as catalyst; this result could not be checked in the Cornell laboratory. The yield is increased to 70–75% (without addition of pyridine) by heating for twenty-four hours.[27]

[c] This yield is obtained with eight hours' heating at 150°; with four hours' heating at 180° the yield is about 20%, and longer heating gives lower yields.

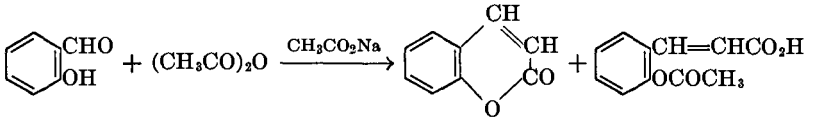
These results indicate that the activity of substituted benzaldehydes in the Perkin reaction is similar to the trends observed in other reactions involving the carbonyl group. A halogen or nitro group in any position increases the rate of reaction and the yield; a methyl group in any position decreases the rate and the yield, and this effect falls off in the order: *ortho* > *meta* > *para*. A methoxyl group in the *ortho* position has a small favorable influence, but in the *para* position it has a definitely unfavorable effect on the rate and the yield.

The behavior of *ortho*-substituted benzaldehydes indicates that the reaction is not adversely affected unless the type of substituent is unfavorable. Thus, 2,6-dichlorobenzaldehyde and 2,6-dinitrobenzaldehyde

[26] Lock and Bayer, *Ber.*, **72**, 1064 (1939).
[29] Meyer and Beer, *Monatsh.*, **34**, 649 (1913).
[30] Posner, *J. prakt. Chem.*, [2] **82**, 425 (1910).
[31] Kauffmann and Burr, *Ber.*, **40**, 2355 (1907).
[32] Stoermer, *Ber.*, **61**, 2326 (1928).
[33] Bacharach and Brogan, *J. Am. Chem. Soc.*, **50**, 3333 (1928).

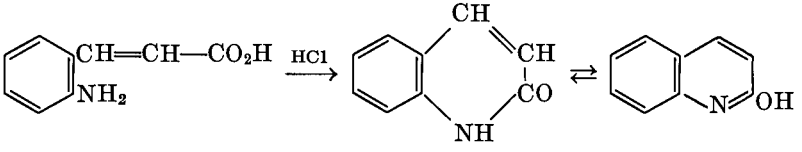
give excellent yields, but 2,6-dimethylbenzaldehyde and 2,4,6-trimethylbenzaldehyde do not react appreciably.[27]

Substituted benzaldehydes with hydroxyl groups in the *meta* or *para* positions give satisfactory results. In the course of reaction the hydroxyl group is acetylated and the product is the corresponding acetoxycinnamic acid. The latter need not be isolated and can be saponified readily to give the free hydroxy acid. Salicylaldehyde gives coumarin,[1] the lactone of the *cis* form of *o*-hydroxycinnamic acid (coumarinic acid), together with the acetyl derivative of the *trans* form (coumaric acid).[34]



The action of alkalies on coumarin gives salts of coumarinic acid, but the acid is unknown in the free state as it undergoes ring closure spontaneously to regenerate coumarin. Strong alkalies or alcoholic sodium ethoxide convert coumarin into salts of coumaric acid, from which the free acid can be obtained by acidification. Methylation of sodium coumarate gives *trans-o*-methoxycinnamic acid, which is identical with the acid obtained from *o*-methoxybenzaldehyde in the Perkin reaction.

The aminocinnamic acids are not prepared directly by the Perkin reaction but are obtained by reduction of the corresponding nitrocinnamic acids with ferrous sulfate and ammonia.[35] The ordinary (stable) form of *o*-nitrocinnamic acid, obtained from *o*-nitrobenzaldehyde in the Perkin reaction, gives *trans-o*-aminocinnamic acid, which on long heating with hydrochloric acid is converted to carbostyril (the nitrogen analog of coumarin).[36]



The aminocinnamic acids can be diazotized and subjected to the usual diazonium replacement reactions; this method has served for the preparation of the chloro-, bromo-, and iodocinnamic acids,[35] and *o*- and *p*-fluorocinnamic acids.[37]

[34] Tiemann and Herzfeld, *Ber.*, **10**, 285 (1877).

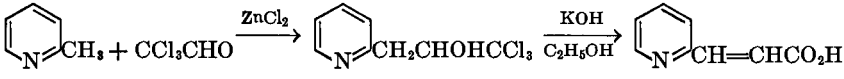
[35] Gabriel, *Ber.*, **15**, 2294 (1882); Gabriel and Herzberg, *Ber.*, **16**, 2038 (1883).

[36] Baeyer and Jackson, *Ber.*, **13**, 115 (1880); Tiemann, *Ber.*, **13**, 2069 (1880); Posner, *Ann.*, **389**, 45 (1912); Stoermer and Heymann, *Ber.*, **45**, 3099 (1912).

[37] Griess, *Ber.*, **18**, 961 (1885); Kindler, *Ann.*, **464**, 278 (1928).

The Perkin reaction has been carried out with aldehydes of the biphenyl [38] and naphthalene series. 1-Naphthaldehyde [39] and 4-bromo-1-naphthaldehyde [40] react quite satisfactorily, but 2-naphthaldehyde [39] gives only a small yield of β-2-naphthylacrylic acid. 2-Hydroxy-1-naphthaldehyde gives a 30% yield of β-naphthocoumarin.[41]

Furfural [42] (and substituted 2-furanaldehydes) and 2-thiophenealdehyde [43] take part readily in the Perkin reaction, but there appears to be no report of the use of aldehydes of the pyridine and quinoline series. The 2- and 4-pyridineacrylic acids, and the corresponding quinoline derivatives, are prepared conveniently by condensation of the 2- or 4-methyl derivative with chloral, followed by hydrolysis.[44]



The condensation of indole-3-aldehyde with hippuric acid in the presence of acetic anhydride and sodium acetate (Erlenmeyer's azlactone synthesis) has been reported.[45]

Cinnamaldehyde, which is a vinylog of benzaldehyde, gives excellent yields of β-styrylacrylic acids under the usual conditions of the Perkin reaction.[2]

$$C_6H_5CH{=}CHCHO + (CH_3CO)_2O \xrightarrow[165^\circ]{CH_3CO_2Na} C_6H_5CH{=}CHCH{=}CHCO_2H$$

On heating cinnamaldehyde with phenylacetic acid in the presence of acetic anhydride and litharge, decarboxylation occurs and 1,4-diphenylbutadiene is obtained in 30% yield.[46]

$$C_6H_5CH{=}CHCHO + C_6H_5CH_2CO_2H \xrightarrow[(CH_3CO)_2O]{PbO} C_6H_5CH{=}CHCH{=}CHC_6H_5$$

[38] Hey, *J. Chem. Soc.*, 2478 (1931); see also Vorländer, *Ber.*, **68**, 453 (1935), and reference 28, p. 1069.

[39] Rousset, *Bull. soc. chim.*, [3] **17**, 813 (1897).

[40] Mayer and Sieglitz, *Ber.*, **55**, 1839 (1922).

[41] Kaufmann, *Ber.*, **16**, 685 (1883).

[42] Baeyer, *Ber.*, **10**, 357 (1877); Gibson and Kahnweiler, *Am. Chem. J.*, **12**, 314 (1890); Johnson, *Org. Syntheses*, **20**, 55 (1940).

[43] Biedermann, *Ber.*, **19**, 1855 (1886); Cohn, *Z. physiol. Chem.*, **17**, 283 (1890).

[44] Einhorn, *Ber.*, **18**, 3465 (1885); *Ann.*, **287**, 27 (1895); Koenigs and Miller, *Ber.*, **37**, 1338 (1904); Rabe and Kindler, *Ber.*, **55**, 532 (1922); Alberts and Bachman, *J. Am. Chem. Soc.*, **57**, 1284 (1937).

[45] Ellinger and Flamand, *Ber.*, **40**, 3031 (1907); *Z. physiol. Chem.*, **55**, 15 (1908).

[46] Kuhn and Winterstein, *Helv. Chim. Acta.*, **11**, 103 (1928); Corson, *Org. Syntheses*, **16**, 28 (1936).

Under the same conditions two moles of cinnamaldehyde react with one of succinic acid to give 1,8-diphenyloctatetrene.[46]

The bifunctional aromatic aldehydes, phthalaldehyde,[47] isophthalaldehyde,[48] and terephthalaldehyde,[49, 50] can be converted to the corresponding benzenediacrylic acids in 20, 80, and 50% yields, respectively. Under mild conditions terephthaldehyde gives the monoacrylic acid, 4-formylcinnamic acid;[49] on prolonged heating a mixture of the mono- and di-acrylic acids is obtained (25% and 50% yields, respectively).[50]

2,2′-Biphenyldialdehyde gives an 8–9% yield of 2,2′-biphenyldiacrylic acid.[51]

4-Cyanobenzaldehyde [52] and 4-carboethoxybenzaldehyde [49] have been converted to the corresponding cinnamic acids, apparently in satisfactory yields. 2-Cyanocinnamic acid has been prepared through Caro's modification of the Perkin reaction, by heating 2-cyanobenzal chloride with acetic anhydride and sodium acetate.[53]

Aliphatic aldehydes such as valeraldehyde and heptaldehyde give mainly condensation products when heated with acetic anhydride and sodium acetate, and only small amounts of the β-alkylacrylic acids are formed.[54] Acetaldehyde with propionic anhydride and sodium propionate (thirty hours at 120–130°) gives a small yield of tiglic acid, and isobutyraldehyde with the same reagents (thirty hours at 190–200°) gives a 15–20% yield of isomeric 4-methylpentenoic acids.[55] The reaction with sodium phenylacetate and acetic anhydride, sometimes called Oglialoro's modification of the Perkin reaction,[56] is somewhat more satisfactory; with these reagents paraldehyde gives α-phenylcrotonic acid (methylatropic acid).[57]

[47] Thiele and Falk, *Ann.*, **347**, 117 (1906).
[48] Ruggli and Staub, *Helv. Chim. Acta*, **17**, 1523 (1934).
[49] Löw, *Ann.*, **231**, 375 (1885).
[50] Ephraim, *Ber.*, **34**, 2784 (1901).
[51] Weitzenbock, *Monatsh.*, **34**, 208 (1913).
[52] Moses, *Ber.*, **33**, 2625 (1900); see also Shoppee, *J. Chem. Soc.*, 985 (1930).
[53] Drory, *Ber.*, **24**, 2574 (1891).
[54] Fittig and Schneegans, *Ann.*, **227**, 79 (1885); Fittig and Hoffken, *Ann.*, **304**, 334 (1899).
[55] Kietreiber, *Monatsh.*, **19**, 735 (1898).
[56] Oglialoro, *Gazz. chim. ital.*, **8**, 429 (1878); **9**, 428, 432 (1879); **10**, 481 (1880); and later papers.
[57] Rupe, *Ann.*, **369**, 332 (1909).

Although the Perkin reaction in its simplest form is quite unsatisfactory with aliphatic aldehydes, modifications involving the replacement of the monobasic acid components by succinic acid (Fittig's synthesis of paraconic acids and β,γ-unsaturated acids)[13, 54, 58] and by malonic acid (Doebner,[59] Knoevenagel [60]) are useful preparative methods in the aliphatic and aromatic series.

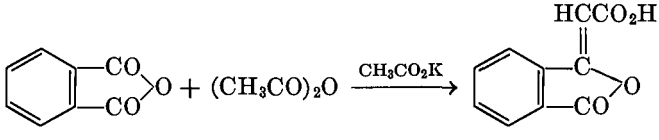
Simple aliphatic and aromatic ketones cannot be used as carbonyl components in the Perkin reaction, or in the paraconic acid synthesis. Acetone condenses with malonic acid in the presence of acetic anhydride,[61] or ammonia,[62] to give β,β-dimethylacrylic acid. The best results are obtained by Doebner's method using malonic acid and pyridine, which gives a 60% yield; [63] under these conditions diethyl ketone gives β,β-diethylacrylic acid in 30% yield, but cyclohexanone gives less than 5% of the corresponding acrylic acid.

α-Ketonic acids react with acetic anhydride and sodium acetate, with loss of carbon dioxide, to give β-substituted acrylic acids.[64] Pyruvic acid gives crotonic acid, and arylglyoxylic acids give the corresponding cinnamic acids.

$$RCOCO_2H + (CH_3CO)_2O \xrightarrow{CH_3CO_2Na} RCH{=}CHCO_2H + CO_2 + CH_3CO_2H$$

Pyruvic acid reacts in a similar way with sodium succinate in the presence of acetic anhydride, to form dimethylmaleic anhydride. These reactions have little preparative value as the same products can usually be obtained from more readily accessible reactants.

Michael and Gabriel made the remarkable discovery that phthalic anhydride may be used as the carbonyl component in a Perkin reaction. On heating phthalic anhydride with acetic anhydride and potassium acetate, for ten minutes at 150–160°, phthalylacetic acid is formed in 50% yield.[65]



[56] Fittig and Frankel, *Ann.*, **255**, 18 (1889); Fittig and Politio, *Ann.*, **255**, 293 (1889).

[59] Doebner, *Ber.*, **33**, 2140 (1900); *Ber.*, **35**, 1137 (1902).

[60] Knoevenagel, *Ber.*, **31**, 2598 (1898); Ger. pats., 97,734, 156,560, 161,171 (*Frdl.*, **7**, 736; **8**, 1268).

[61] Massot, *Ber.*, **27**, 1225, 1574 (1894).

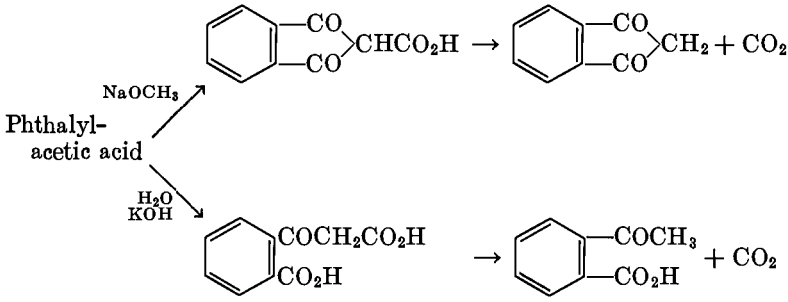
[62] Knoevenagel, Ger. pat., 162,281 (*Frdl.*, **8**, 1267).

[63] Dutt, *J. Indian Chem. Soc.*, **1**, 297 (1925); *C. A.*, **19**, 2475 (1925).

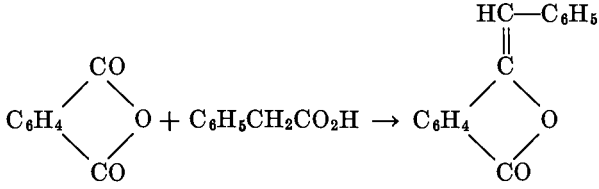
[64] Homolka, *Ber.*, **18**, 987 (1885); Claus and Wollner, *Ber.*, **18**, 1861 (1885).

[65] Gabriel and Michael, *Ber.*, **10**, 1554 (1877); Gabriel and Neumann, *Ber.*, **26**, 952 (1893).

This acid undergoes a number of interesting transformations; on treatment with sodium methoxide and subsequent warming with hydrochloric acid, carbon dioxide is evolved and 1,3-diketohydrindene is obtained. Cold aqueous alkalies open the lactone ring of phthalylacetic acid to form 2-carboxybenzoylacetic acid, which loses carbon dioxide readily to yield 2-acetylbenzoic acid.



Phthalic anhydride reacts with phenylacetic acid and sodium acetate, with evolution of carbon dioxide, to give benzalphthalide in 71–74% yields.[66]



Benzalphthalide is converted by sodium methoxide into 1,3-diketo-2-phenylhydrindene,[67] and by concentrated aqueous alkalies into 2-phenacetylbenzoic acid. These transformations of the phthalic anhydride condensation products are useful preparative methods.

Acid Components

Although the Perkin reaction is considered to occur with the acid anhydride, there are numerous instances in which the resulting acrylic acid corresponds to the salt used and not the anhydride. Thus, sodium phenylacetate and acetic anhydride react with benzaldehydes to produce α-phenylcinnamic acids in excellent yields (Oglialoro's modification),[56] and α-acylaminoacetic acids react with benzaldehydes in the presence of acetic anhydride and sodium acetate at 100° to give derivatives of

[66] Gabriel, *Ber.*, **18**, 3470 (1885); Weiss, *Org. Syntheses*, **13**, 10 (1933).
[67] Nathanson, *Ber.*, **26**, 2576 (1893); Eibner, *Ber.*, **39**, 2203 (1906).

α-acylaminocinnamic acids (azlactone synthesis).[68] Owing to the exchange reactions that occur in mixtures of acids, salts, and anhydrides, even at 100°, the product will depend primarily upon the relative active-methylene reactivity of the various acid species present. For this reason it will be convenient in the present discussion to refer merely to the acid component that undergoes reaction, without necessarily specifying whether it is introduced as the free acid, salt, or anhydride.

The Perkin reaction is limited practically to acetic and monosubstituted acetic acids, RCH_2CO_2H, as two α-hydrogen atoms must be eliminated to form the α,β-unsaturation. Disubstituted acetic acids such as isobutyric acid give β-hydroxy-α,α-dialkylpropionic acids, but this reaction has little preparative significance as the Claisen or Reformatsky reaction (p. 8) is usually more satisfactory for such compounds; at higher temperatures the dialkylacetic acids yield dialkylstyrenes (p. 212). The present survey is restricted to monosubstituted acetic acids and related types, which are considered according to the nature of the substituent in the α-position.

Alkylacetic acids having a straight-chain alkyl substituent react quite readily with benzaldehyde to give α-alkylcinnamic acids in satisfactory yields.[2] Propionic, *n*-butyric,[3] and *n*-caproic [16] anhydrides react with aromatic aldehydes at lower temperatures (100°) than acetic anhydride, and often give slightly higher yields. Palmitic anhydride and sodium palmitate are reported to give a 55% yield of α-*n*-tetradecylcinnamic acid.[69]

Isocaproic acid appears to react normally [16] to form α-isobutylcinnamic acid, but isovaleric acid gives very small yields of the α-isopropyl derivatives.[10] Even at temperatures as low as 70°, a mixture of valeric anhydride, sodium valerate, and benzaldehyde evolves carbon dioxide, and isopropylstyrene is the main product; the same behavior occurs with *p*-anisaldehyde and with furfural. The decarboxylation is believed to occur at an intermediate stage since the α-isopropylacrylic acids, once formed, are stable above 100°. Cycloalkylacetic acids apparently have not been used in the Perkin reaction.

Crotonic anhydride, which is a vinylog of acetic anhydride, reacts with benzaldehyde in the presence of triethylamine (but not potassium crotonate) to give α-vinylcinnamic acid in 40% yield.[20]

$$C_6H_5CHO + (CH_3CH{=}CHCO)_2O \xrightarrow[125^\circ]{NEt_3} C_6H_5CH{=}\underset{\underset{CH{=}CH_2}{|}}{C}CO_2H$$

[68] Erlenmeyer, *Ann.*, **271**, 164 (1892); **337**, 265 (1904); see also Plöchl, *Ber.*, **16**, 2815 (1883).

[69] Krafft and Rosing, *Ber.*, **33**, 3578 (1900).

The reaction is considered to involve a preliminary 1,4-enolization of the γ-methyl group to give the system $CH_2{=}CH{-}CH{=}C(OH)OAc$, and subsequent addition of benzaldehyde at the α-position. Under similar conditions β,β-dimethylacrylic anhydride gives α-isopropenylcinnamic acid (38% yield);[70] the corresponding α-isopropenyl derivatives have been obtained also from *o*-nitrobenzaldehyde, *p*-anisaldehyde, piperonal, cinnamaldehyde, and furfural.

Phenylacetic acid and other α-arylacetic acids react very satisfactorily with aromatic aldehydes to give α-arylcinnamic acids. Oglialoro[56] showed that sodium phenylacetate and acetic anhydride give α-phenylcinnamic acid, and only a trace of cinnamic acid is formed. This modification, with subsequent refinements,* is a convenient preparative method as it obviates the necessity of isolating the arylacetic anhydride. The good yields obtained in this reaction are undoubtedly due to the ability of α-aryl groups to enhance the active-methylene activity, as the order of reactivity of anhydride-salt combinations follows the sequence: α-aryl $\gg$ alkyl $>$ hydrogen.[71] Tolylacetic acids[72] and other substituted arylacetic acids also give satisfactory yields.

Homologs of phenylacetic acid such as β-phenylpropionic and γ-phenylbutyric acids are much less reactive than phenylacetic acid, and the Oglialoro modification gives poor yields owing to the formation of large quantities of cinnamic acid.[73, 74] The reaction is used nevertheless as a preparative method since the products cannot be synthesized conveniently in other ways. Sodium β-phenylpropionate with benzaldehyde and acetic anhydride gives α-benzylcinnamic acid;[73] salts of *p*-chloro-, bromo-, iodo-, and dimethylamino-phenylpropionic acids give the corresponding substituted benzyl derivatives in low yields.[74] Potassium γ-phenylbutyrate with benzaldehyde and acetic anhydride (twelve days at 100°) gives α-phenethylcinnamic acid in 14% yield.[73]

Phenylisocrotonic acid (styrylacetic or β-benzalpropionic acid), a vinylog of phenylacetic acid, reacts satisfactorily when the sodium salt is used in combination with acetic anhydride.[75]

$$C_6H_5CHO + C_6H_5CH{=}CHCH_2CO_2Na \xrightarrow{Ac_2O} C_6H_5CH{=}\underset{\underset{CH{=}CHC_6H_5}{|}}{C}CO_2H$$

* For an example of the laboratory procedure see p. 252.

[70] Ishikawa and Kato, *Sci. Repts. Tokyo Bunrika Daigaku*, I, 289 (1934); *C. A.*, **28**, 2698 (1934).

[71] Bakunin, *Gazz. chim. ital.*, **31**, II, 77 (1901); Bakunin and Fisceman, *ibid.*, **46**, I, 77 (1916).

[72] Pschorr, *Ber.*, **39**, 3110 (1906).

[73] Rupe, *Ann.*, **395**, 106, 411 (1913).

[74] Shoppee, *J. Chem. Soc.*, 968 (1930).

[75] Thiele, *Ann.*, **306**, 154 (1899).

This reaction can be carried out in 20–25 minutes at 140°; the product is 1,4-diphenylbutadiene-2-carboxylic acid, which is structurally analogous to the acids obtained from crotonic and dimethylacrylic anhydrides (p. 224).

Malonic acid, owing to the powerful activating effect of two carboxyl groups on the same carbon atom, undergoes condensation with aliphatic and aromatic aldehydes under very mild conditions. In this particular case it is likely that the acid itself (in the enol form) reacts with the aldehyde, and the condensation can be effected satisfactorily under a wide variety of conditions. Undoubtedly the use of malonic acid is the best and most general preparative method for β-substituted acrylic acids. Until quite recently malonic acid has been a relatively expensive reagent and its use has been restricted largely to the less common aromatic aldehydes. It has also proved especially useful for aliphatic aldehydes and for various aromatic aldehydes that give poor results in the simple Perkin reaction (alkyl-, alkoxy-, dimethylamino-benzaldehydes, etc.).

The condensation of malonic acid with various aliphatic aldehydes (paraldehyde,[76] propionaldehyde,[77] isobutyraldehyde,[78] isovaleraldehyde,[79] etc.) was first effected in glacial acetic acid and a little acetic anhydride. Knoevenagel [60] found that the reaction can be carried out with much better results using ammonia or primary or secondary amines (especially piperidine) as catalysts. Unfortunately neither of these modifications is a good preparative method in the aliphatic series as mixtures of α,β- and β,γ-unsaturated acids are obtained.[80] The most satisfactory method in the aliphatic (and aromatic) series is Doebner's modification [59] using pyridine, which has been studied by von Auwers.[81] He found that acetaldehyde gives exclusively crotonic acid (60% yield).

$$CH_3CHO + CH_2(CO_2H)_2 \xrightarrow[20^\circ]{C_5H_5N} CH_3CH{=}CHCO_2H + CO_2$$

Propionaldehyde gives almost pure α,β-pentenoic acid, with only a trace of the β,γ-isomer; isobutyraldehyde, isovaleraldehyde, and *n*-heptaldehyde give almost entirely α,β-unsaturated acids. With *n*-heptaldehyde [80] the β,γ-unsaturated acid amounts to 5–10%; the latter can be removed by stirring with 85% sulfuric acid at 80°,[82] which converts it to the γ-lactone (insoluble in sodium carbonate solution).

[76] Komnenos, *Ann.*, **218**, 149 (1883).

[77] Fittig, *Ann.*, **283**, 85 (1894).

[78] Braun, *Monatsh.*, **17**, 213 (1896).

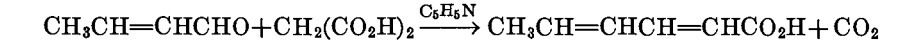
[79] Schryver, *J. Chem. Soc.*, **63**, 1331, 1334 (1893).

[80] Zaar, *Ber. Schimmel & Co. Akt. Ges.*, Jubilee Number, 299 (1929); *C. A.*, **24**, 2107 (1930).

[81] von Auwers, Meisnner, Seydel, and Wissebach, *Ann.*, **432**, 46 (1923).

[82] Shukow and Schestakow, *J. Russ. Phys. Chem. Soc.*, **40**, 830 (1908); *Chem. Zentr.*, II, 1415 (1908).

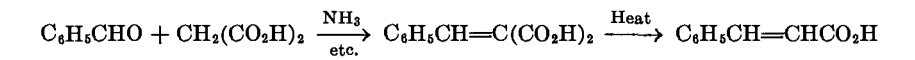
Acrolein [59] and crotonaldehyde [59, 83] can be condensed with malonic acid in pyridine to give butadienecarboxylic acid and sorbic acid in satisfactory yields.



$$CH_3CH{=}CHCHO + CH_2(CO_2H)_2 \xrightarrow{C_5H_5N} CH_3CH{=}CHCH{=}CHCO_2H + CO_2$$

Cinnamaldehyde reacts with malonic acid in the presence of ammonia or aniline,[60] or in the presence of pyridine;[59, 63, 83] if the reaction is carried out at moderate temperatures cinnamalmalonic acid is obtained, but at higher temperatures carbon dioxide is evolved and cinnamalacetic acid is produced.

Aromatic aldehydes react with malonic acid in the presence of ammonia and primary and secondary amines [60] to give benzalmalonic acids, which, on heating, lose carbon dioxide to form β-arylacrylic acids.



$$C_6H_5CHO + CH_2(CO_2H)_2 \xrightarrow[\text{etc.}]{NH_3} C_6H_5CH{=}C(CO_2H)_2 \xrightarrow{\text{Heat}} C_6H_5CH{=}CHCO_2H$$

In the presence of large amounts of ammonia or methylamine the corresponding β-amino-β-arylpropionic acids are obtained in 50–60% yields, together with some of the cinnamic acid.[84]

The arylacrylic acids are obtained directly by the Doebner modification using pyridine as the solvent, and a small amount of piperidine. The reaction mixture is warmed for a short period on the steam bath and then refluxed for a few minutes. This is the outstanding preparative method for β-arylacrylic acids and often gives high yields of products which cannot be obtained by the ordinary Perkin reaction. Thus, 4-dimethylaminobenzaldehyde [63, 83] and 2,4,6-trimethoxybenzaldehyde [85] do not react in the usual Perkin synthesis, but with malonic acid and pyridine they give the corresponding cinnamic acids in 65–85% and 70% yields, respectively. The Doebner method is also of great preparative value for hydroxycinnamic acids,[86] and it has been reported recently that the reaction can be carried out successfully with only a small amount of pyridine instead of using pyridine as a solvent.[87] There is little doubt

[83] Riedel, *Ann.*, **361**, 89 (1908).

[84] Rodionov and collaborators, *Ber.*, **59**, 2952 (1926); *Arch. Pharm.*, **266**, 116 (1928); *J. Am. Chem. Soc.*, **51**, 847 (1929).

[85] Herzig, Wenzel, and Gehringer, *Monatsh.*, **24**, 868 (1903).

[86] Vorsatz, *J. prakt. Chem.*, [2] **145**, 265 (1936).

[87] Kurien, Pandya, and Surange, *J. Indian Chem. Soc.*, **11**, 823 (1934); *C. A.*, **29**, 3325 (1935). See also a series of papers by Pandya and collaborators, dealing with specific aldehydes:

(*a*) Salicylaldehyde: *Proc. Indian Acad. Sci.*, **1A**, 440 (1935); *C. A.*, **29**, 3325 (1935), *Chem. Zentr.*, II, 2362 (1935).

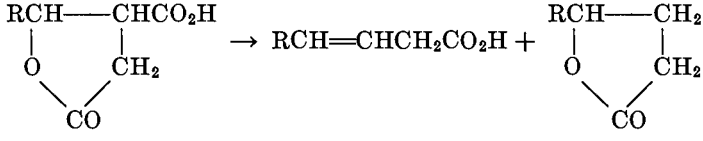
(*b*) Piperonal: *Proc. Indian Acad. Sci.*, **2A**, 402 (1935); *C. A.*, **30**, 1775 (1936), *Chem. Zentr.*, I, 4433 (1936).

[*Footnote continued on page 228.*]

that pyridine exerts a definite catalytic effect; substituted pyridine bases differ quantitatively in their effectiveness.[87] Bachmann and Kloetzel [88] have reported excellent yields of the corresponding acrylic acids from *o*-chlorobenzaldehyde and from several phenanthraldehydes (1-, 2-, 3-, and 10-), using malonic acid and a small amount of pyridine.

Fittig [3] observed that sodium methylmalonate reacted with benzaldehyde in the presence of acetic anhydride to form α-methylcinnamic acid. No doubt other alkyl- and aryl-malonic acids would react with benzaldehyde to give α-substituted cinnamic acids, but these reactions would be of little preparative value.

Fittig discovered that aromatic [13] and aliphatic [54] aldehydes react readily with sodium succinate and acetic anhydride at 100°, to give γ-phenyl- and γ-alkyl-paraconic acids (p. 213) in satisfactory yields. These acids lose carbon dioxide on heating and form the β,γ-unsaturated acids, together with a small amount of the γ-butyrolactone.



This reaction affords a useful extension of the Perkin synthesis and has been used as a preparative method for a number of γ-substituted vinylacetic acids.[58] Methylsuccinic acid gives a mixture of the isomeric α,γ- and β,γ-disubstituted paraconic acids.[89] Phenylsuccinic acid and benzaldehyde react at 125° to give β,γ-diphenylvinylacetic acid.[90]

(*c*) Anisaldehyde: *Proc. Indian Acad. Sci.*, **4A**, 134 (1936); *C. A.*, **30**, 8149 (1936), *Chem. Zentr.*, I, 2767 (1937).

(*d*) *p*-Hydroxybenzaldehyde: *Proc. Indian Acad. Sci.*, **4A**, 140 (1936); *C. A.*, **30**, 8149 (1936), *Chem. Zentr.*, I, 2768 (1937).

(*e*) *m*-Hydroxybenzaldehyde: *Proc. Indian Acad. Sci.*, **4A**, 144 (1936); *C. A.*, **30**, 8149 (1936), *Chem. Zentr.*, I, 2768 (1937).

(*f*) o-Methoxy- and *m*-methoxybenzaldehyde: *Proc. Indian Acad. Sci.*, **5A**, 437 (1937); *C. A.*, **31**, 7412 (1937), *Chem. Zentr.*, II, 3313 (1937).

(*g*) 2-Hydroxy-1-naphthaldehyde: *Proc. Indian Acad. Sci.*, **6A**, 181 (1937); *C. A.*, **32**, 1260 (1938), *Chem. Zentr.*, I, 1356 (1938).

(*h*) 2,4-Dihydroxybenzaldehyde: *Proc. Indian Acad. Sci.*, **7A**, 381 (1938); *C. A.*, **32**, 7435 (1938), *Chem. Zentr.*, II, 2736 (1938).

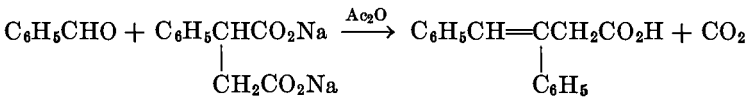
(*i*) *p*-Tolualdehyde: *Proc. Indian Acad. Sci.*, **9A**, 508 (1939); *C. A.*, **33**, 8589 (1939).

(*j*) 3,4-Dihydroxy-, 3-methoxy-4-hydroxy-, and 3,4-dimethoxybenzaldehyde: *Proc. Indian Acad. Sci.*, **9A**, 511 (1939); *C. A.*, **33**, 8589 (1939), *Brit. Chem. Abstracts*, AII, 478 (1939).

[66] Bachmann, *J. Org. Chem.*, **3**, 444 (1938); Bachmann and Kloetzel, *J. Am. Chem. Soc.*, **59**, 2209 (1937).

[69] Fittig, *Ann.*, **255**, 5, 7, 108, 126, 257 (1889).

[90] Fichter and Latzko, *J. prakt. Chem.*, [2] **74**, 330 (1906).

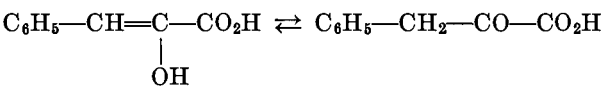


Phenylsuccinic acid and cinnamaldehyde [91] give only a small amount of the vinylogous unsaturated acid as the latter is transformed mainly into 2,5-diphenylphenol.

Glutaric acid reacts with benzaldehyde to form only a trace of δ-phenyl-γ,δ-pentenoic acid ($C_6H_5CH{=}CHCH_2CH_2CO_2H$),[92] but phenylglutaric acid reacts more satisfactorily and gives γ,δ-diphenyl-γ, δ-pentenoic acid.[93]

The Perkin reaction is unsuitable for the direct preparation of α-halogenated cinnamic acids. When benzaldehyde is heated with sodium chloroacetate and acetic anhydride only a trace of α-chlorocinnamic acid is formed.[94, 95] Sodium bromoacetate [94] and fluoroacetate [96] under similar conditions give none of the corresponding α-halogenated cinnamic acids. α-Bromocinnamic acid (in a variety of crystalline forms) can be obtained by the action of bases on the bromide of cinnamic acid under carefully controlled conditions; aqueous sodium carbonate or acetate converts the dibromide largely to β-bromostyrene.

α-Phenoxy- and cresoxy-cinnamic acids can be prepared by heating the sodium salts of aryloxyacetic acids with benzaldehyde and acetic anhydride,[97] but some cinnamic acid is formed also. The parent compound, α-hydroxycinnamic acid, is the enol form of phenylpyruvic acid.

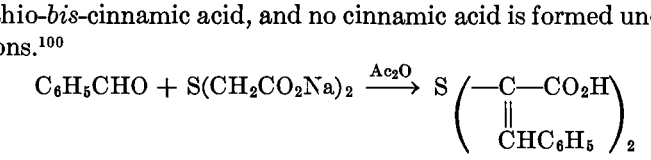


Owing to this relationship certain derivatives of α-thiolcinnamic acid (benzalrhodanine, etc.)[98] and α-acylaminocinnamic acid (azlactones, etc.) can be hydrolyzed to give phenylpyruvic acid, and this forms an elegant preparative method for arylpyruvic acids [99] and related compounds.[98]

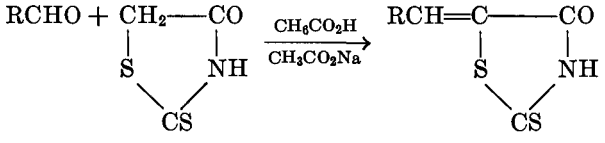
Several derivatives of α-thiolcinnamic acid can be obtained from the corresponding α-thiolacetic acids. Sodium thiodiglycolate reacts with

[91] Fichter and Grether, *Ber.*, **36**, 1407 (1903).
[92] Fittig, *Ann.*, **282**, 334 (1894).
[93] Fichter and Merkens, *Ber.*, **34**, 4177 (1901).
[94] Plöchl, *Ber.*, **15**, 1945 (1882).
[95] Michael, *J. prakt. Chem.*, [2] **40**, 64 (1889).
[96] Swarts, *Bull. soc. chim.*, [4] **25**, 325 (1919).
[97] Oglialoro, *Gazz. chim. ital.*, **10**, 483 (1880); **20**, 505 (1890).
[98] Gränacher, *Helv. Chim. Acta*, **5**, 610 (1922).
[99] Buck and Ide, *Org. Syntheses*, **15**, 33 (1935); Herbst and Shemin, *ibid.*, **19**, 77 (1939).

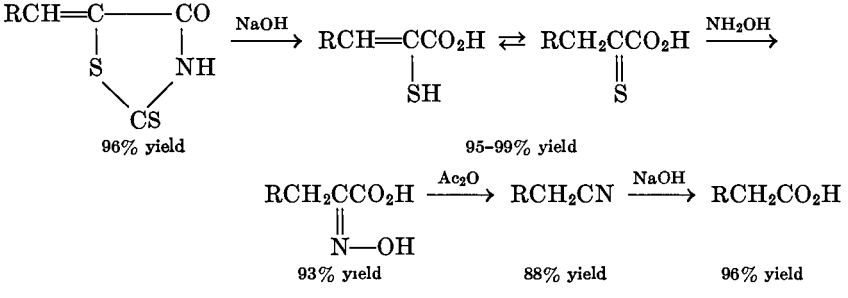
two molecules of benzaldehyde in the presence of acetic anhydride to give α-thio-*bis*-cinnamic acid, and no cinnamic acid is formed under these conditions.[100]



The most significant reaction of this type for preparative purposes is the condensation of cyclic sulfur compounds, such as rhodanine (and related heterocyclic derivatives), with aromatic aldehydes. This condensation can be effected readily under various conditions as the methylene group of rhodanine is quite active;* excellent yields are obtained using a combination of glacial acetic acid and sodium acetate.[101]



The resulting derivatives are useful intermediates for the preparation of arylthiopyruvic acids,[98] β-arylalanines,[98] arylacetonitriles, arylacetic acids, β-arylethylamines, etc.[101, 102] These reactions have been particularly useful in the furan series [98, 102] and for alkoxyphenyl compounds.[101] Furfural has been converted to 2-furanacetic acid [102] in an over-all yield of 73% by the following typical series of transformations (five steps).



It is difficult to find another series of reactions that gives such uncommonly good yields. It is of interest to note that the process does not require strong mineral acids at any stage and consequently is well adapted for use with acid-sensitive groups.

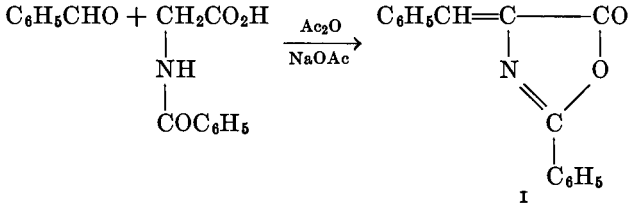
* For a survey of earlier references to these condensations see Grånacher, reference 98.

[100] Loeven, *Ber.*, **18**, 3242 (1885); see also Hinsberg, *J. prakt. Chem.*, [2] **84**, 192 (1911).

[101] Julian and Sturgis, *J. Am. Chem. Soc.*, **57**, 1126 (1935).

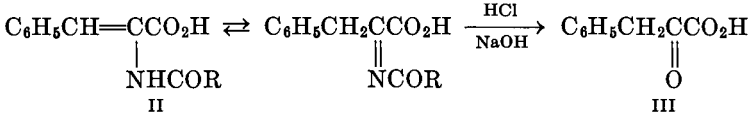
[102] Plucker and Amstutz, *J. Am. Chem. Soc.*, **62**, 1512 (1940).

A large number of derivatives of aminoacetic acid undergo condensation with benzaldehyde and other aldehydes of aromatic type, in essentially the same manner as rhodanine. The most familiar example is the condensation of hippuric acid with benzaldehyde in the presence of acetic anhydride and sodium acetate (Erlenmeyer's azlactone synthesis).[68]



The yields of azlactones (substituted oxazolones)* from hippuric acid are usually quite good (62–64% with benzaldehyde,[103] 69–73% with 3,4-dimethoxybenzaldehyde [104]), and similar or somewhat better results are obtained when aceturic acid is used (74–77% yield of azlactone from benzaldehyde).[105]

Mild hydrolysis of the azlactones with alkalies gives the α-acylaminocinnamic acids (II), and further hydrolysis yields the arylpyruvic acids (III).[68, 99]



For this type of reaction the α-acetamido compounds [105] are preferable to the α-benzamidocinnamic acids, as the former are less resistant to hydrolysis. This is particularly true for azlactones derived from *o*-nitrobenzaldehydes, which undergo a variety of side reactions on warming with alkalies.[106] The arylpyruvic acids are useful intermediates in synthetic work; on oxidation with hydrogen peroxide they give arylacetic acids in good yields.[99] The azlactones and α-acylaminocinnamic acids can be transformed into β-aryl-α-aminopropionic acids by warming with phosphorus and hydriodic acid,[68, 103] or by catalytic reduction and subsequent hydrolysis.[105]

* In *Chemical Abstracts* and *Beilstein's Handbuch* the azlactone (I) from hippuric acid and benzaldehyde is named 2-phenyl-4-benzal-5-oxazolone; that from aceturic acid is 2-methyl-4-benzal-5-oxazolone. In British usage the former (I) is called 5-keto-2-phenyl-4-benzylidene-4:5-dihydroöxazole.

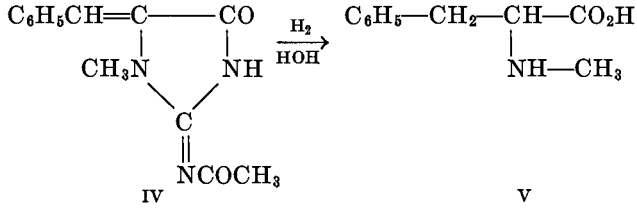
[103] Gillespie and Snyder, *Org. Syntheses*, **14**, 81 (1934).

[104] Buck and Ide, *Org. Syntheses*, **13**, 8 (1933); see also *ibid.*, **15**, 31, 33 (1935).

[105] Herbst and Shemin, *Org. Syntheses*, **19**, 1 (1939); see also pp. 67 and 77.

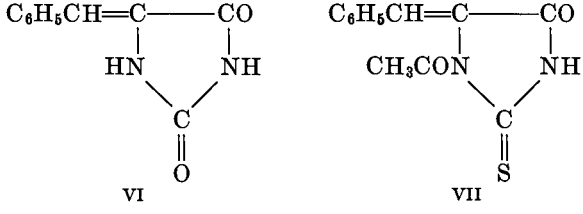
[106] Burton, *J. Chem. Soc.*, 1265 (1935); 402 (1937).

Erlenmeyer found that N-phenylglycine (i.e., its acetyl derivative, which has no hydrogen on the nitrogen atom) does not give an azlactone, but he showed that creatine can be condensed with benzaldehyde in the presence of acetic anhydride and sodium acetate. Under improved conditions [107] an 80% yield of N-acetyl-5-benzalcreatine (IV) is ob-



tained, and this on reduction and hydrolysis can be transformed into N-methylphenylalanine (V); this affords a useful general method for N-methyl derivatives of β-substituted alanines.[107, 108]

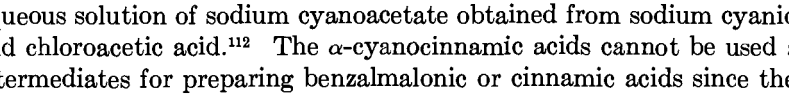
Hydantoin condenses with a variety of aromatic aldehydes (including anisaldehyde, piperonal, furfural, etc.) in the presence of acetic acid, sodium acetate, and a little acetic anhydride.[109] The corresponding 5-benzalhydantoins (VI) are obtained in good yields (70–85%) and are useful intermediates for amino acid syntheses. Similar condensation



products (VII) can be obtained from acylthiohydantoins [109] under similar conditions. It has been reported recently that 92–98% yields of 1-acetyl-5-benzal-2-thiohydantoins (VII) are secured from acetylthiohydantoin by using pyridine and a trace of diethylamine or pyridine,[110] but this procedure gives inferior yields (30–40%) with hydantoin itself.

Cyanoacetic acid reacts readily with aromatic aldehydes to give α-cyanocinnamic acids, which can be decarboxylated by heating to give the β-arylacrylonitriles.[111]

[107] Nicolet and Campbell, *J. Am. Chem. Soc.*, **50**, 1155 (1928).
[108] Deulofeu and Mendivelzua, *Ber.*, **68**, 783 (1935).
[109] Wheeler and Hoffman, *Am. Chem. J.*, **45**, 369 (1911); see also Wheeler, Nicolet, and Johnson, *ibid.*, **46**, 471 (1911).
[110] Boyd and Robson, *Biochem. J.*, **29**, 542 (1935); *C. A.*, **29**, 5094 (1935).
[111] Fiquet, *Bull. soc. chim.*, [3] **7**, 11 (1892); *Ann. chim.*, [6] **29**, 433 (1893).



The α-cyanocinnamic acids are prepared conveniently by using an aqueous solution of sodium cyanoacetate obtained from sodium cyanide and chloroacetic acid.[112] The α-cyanocinnamic acids cannot be used as intermediates for preparing benzalmalonic or cinnamic acids since they are resistant to hydrolysis by acids and are cleaved into benzaldehyde and malonic acid by strong alkalies.[111] The addition of sodium cyanide to ethyl α-cyanocinnamate and subsequent hydrolysis with acids gives phenylsuccinic acid in 90–95% yields.[113] The addition of ethyl malonate to ethyl α-cyanocinnamate leads in a similar way to α-phenylglutaric acid in 75–85% yields.[114]

The condensation of benzylcyanide with aromatic aldehydes leads directly to the nitriles of α-arylcinnamic acids, $C_6H_5CH{=}C(C_6H_5)CN$,[115] which have limited application in synthetic work.

Comparison with Other Synthetic Methods

From the standpoint of its application in organic synthesis the Perkin reaction is used most generally for the preparation of β-arylacrylic and α-substituted-β-arylacrylic acids. Two other methods of very general utility are available for the same purpose—the Claisen condensation of aldehydes with esters and the Reformatsky reaction. For the purpose of this discussion the condensations of malonic acid in the presence of ammonia and primary or secondary amines will be designated as the Knoevenagel modification * of the Perkin reaction, and the use of malonic acid in pyridine (usually with a little piperidine added) will be designated as the Doebner modification.† A general comparison of these reactions may be made for a simple example, such as the preparation of cinnamic acid from benzaldehyde (see also p. 8).

Perkin: Acetic anhydride; potassium acetate; five hours' heating at 175–180°; yield, 55%.

* The term Knoevenagel reaction is used very broadly to include the condensation of esters, nitriles, nitroparaffins, etc., with a variety of carbonyl components in the presence of ammonia or primary or secondary amines.

† The term Doebner reaction is often used for the synthesis of α-alkyl- and α-arylcinchoninic acids from aromatic amines, aldehydes, and pyruvic acid.

[112] Lapworth and McRae, *J. Chem. Soc.*, **121**, 1699 (1922); Lapworth and Baker, *Org. Syntheses Coll. Vol.*, **I**, 175 (1932).

[113] Lapworth and Baker, *Org. Syntheses Coll.* Vol., **I**, 440 (1932).

[114] Manske, *J. Am. Chem. Soc.*, **53**, 1106 (1931).

[115] Frost, *Ann.*, **250**, 157 (1889); Walther, *J. prakt. Chem.*, [2] **53**, 454 (1896); Brand and Löhr, *ibid.*, [2] **109**, 365 (1925).

Knoevenagel: Malonic acid; ammonia, piperidine, or diethylamine; alcohol as solvent; two to four hours' heating at 100°; yield, 70–80%.

Doebner: Malonic acid; trace of piperidine; pyridine as solvent; one to two hours' heating at 100°; yield, 80–90%.

Claisen: Ethyl acetate, absolute; metallic sodium and a trace of alcohol; excess of ethyl acetate serves as solvent; two hours at 0–5°; yield, 68–74%.[116]

Reformatsky: * Ethyl bromoacetate; metallic zinc; benzene as solvent; one to two hours at 100°, followed by heating and distillation (to dehydrate intermediate β-hydroxy ester); yield, 50–60%.

In the Claisen reaction the product is an ester, which can be saponified readily to obtain the acid; in the Reformatsky reaction, the intermediate β-hydroxy ester is subjected to dehydration and the resulting cinnamic ester distilled and saponified.

$$C_6H_5CHO + CH_3CO_2C_2H_5 \xrightarrow[C_2H_5OH]{Na} C_6H_5CH{=}CHCO_2C_2H_5 + H_2O$$

(Claisen reaction)

$$C_6H_5CHO + BrCH_2CO_2C_2H_5 \xrightarrow[(Mg)]{Zn} C_6H_5CHOHCH_2CO_2C_2H_5 \xrightarrow{Heat} C_6H_5CH{=}CHCO_2C_2H_5$$

(Reformatsky reaction)

The direct formation of an ester may be advantageous in many instances, as the purification of an ester by distillation is likely to be more convenient and less wasteful of material than recrystallization of the solid acid. Moreover, the esters are often desired in preference to the free acids for use in subsequent transformations, such as conversion to amides, catalytic hydrogenation, and formation of addition or substitution products.

The Perkin reaction is particularly well suited for reactions involving nitrobenzaldehydes and halogenated benzaldehydes, since especially high yields are obtained with these compounds and these types of substituents are unfavorable for the Claisen or Reformatsky reactions. Benzaldehydes containing a free phenolic group are likewise unsuited for the Claisen or Reformatsky reaction but may be protected by alkylation or acetylation. In the Perkin reaction *o*-hydroxybenzaldehydes give coumarins; the *m*- and *p*-hydroxy compounds yield the corresponding acetoxycinnamic acids, which can be hydrolyzed readily with alkalies. The Doebner modification is suitable for hydroxy compounds and gives

* See Chapter 1.

[116] Marvel and King, *Org. Syntheses Coll. Vol.*, I, 246 (1932).

especially good results if the reaction is carried out by long standing at room temperature.[86]

The Claisen reaction is definitely superior to the ordinary Perkin reaction for alkylbenzaldehydes, alkoxybenzaldehydes, and *p*-dimethylaminobenzaldehyde. These types give 60–85% yields of the corresponding cinnamic esters in the Claisen reaction, and similar good yields in the Doebner modification of the Perkin reaction; the Knoevenagel modification is satisfactory also for such preparations. 2,4,6-Trimethylcinnamic acid is obtained only in traces in the usual Perkin reaction, but the ethyl ester can be prepared in 70% yield by the Claisen method.[27]

The Doebner modification is rapid and convenient, and for large-scale preparations is less hazardous than the Claisen reaction. A large quantity of pyridine is required, and it must be anhydrous for maximum yields. A technical fraction of pyridine bases (b.p. 120–160°), after redistillation and thorough drying, gives as good results as pure pyridine; recent studies indicate that the pyridine bases can be used in stoichiometric quantities [117] and even in catalytic amounts.[87] The Knoevenagel modification is simpler from the standpoint of solvent required, as alcohol is a satisfactory medium. Neither the Doebner nor the Knoevenagel modification is used for α-substituted cinnamic acids as the requisite monosubstituted malonic acids are not readily accessible.

A satisfactory synthesis of substituted cinnamic acids from the corresponding benzyl halides has been developed by von Braun and Nelles.[118] The benzyl halide is converted to the corresponding malonic acid in the conventional way; the resulting β-arylmalonic acid is then brominated, decarboxylated, and treated with alkali.

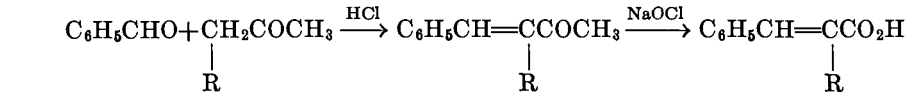
$$\mathrm{RCH_2Br} \rightarrow \mathrm{RCH_2CH(CO_2H)_2} \xrightarrow{\mathrm{Br_2}} \mathrm{RCH_2CBr(CO_2H)_2} \xrightarrow{\mathrm{Heat}}$$
$$\mathrm{RCH_2CHBrCO_2H} \xrightarrow{\mathrm{NaOH}} \mathrm{RCH{=}CHCO_2H}$$

This method is not suitable for aliphatic or alicyclic compounds but gives good over-all yields with a variety of substituted benzyl halides. The advantage of this synthesis over the Perkin or Claisen reaction lies in the circumstance that the benzyl halides are often more readily accessible than the corresponding benzaldehydes.

α-Arylcinnamic acids are prepared most readily by the Perkin reaction, but good yields of the esters can be obtained in the Claisen reaction. α-Alkylcinnamic acids are obtained readily by the Perkin reaction but sometimes more conveniently by the Claisen or Reformatsky reaction. Another method of preparative value involves the condensation of ben-

[117] Dalal and Dutt, *J. Indian Chem. Soc.*, **9**, 309 (1932); *C. A.*, **27**, 279 (1933).
[118] von Braun and Nelles, *Ber.*, **66**, 1464 (1933).

zaldehyde with alkyl derivatives of acetone, and oxidation of the resulting benzalacetones with sodium hypochlorite.[119]



This method has been used for α-*n*-propyl-, *n*-butyl-, and *n*-amyl-cinnamic acids. Benzalacetone itself gives cinnamic acid by hypochlorite oxidation, and a limited number of ring-substituted cinnamic acids have been prepared by this method.

The Doebner modification appears to be the best general method for the preparation of β-alkylacrylic acids and can be used to a limited extent for β,β-dialkylacrylic acids. The acids obtained in this way are less likely to be contaminated with the isomeric β,γ-unsaturated acids.

The Reformatsky reaction is the only one of the reactions that is suited for the direct preparation of β,β-diarylacrylic acids, as benzophenone and its derivatives will react with bromoacetic esters and zinc but will not take part in the Perkin or Claisen reaction.

SELECTION OF EXPERIMENTAL CONDITIONS

A number of studies have been made of factors influencing the yields in the Perkin reaction, but it is difficult to draw any broad generalizations. In many of the preparations described in the literature the proportions of reactants and the general procedure have been essentially those used by Perkin: a mixture of two parts of the benzaldehyde with one part (by weight) of freshly fused sodium acetate and three parts (by weight) of acetic anhydride is heated for about eight hours at 175–180°. These proportions correspond, in the case of benzaldehyde, to about 1.5 moles of acetic anhydride and 0.65 mole of sodium acetate. Meyer and Beer [29] reported that 2.1 moles of acetic anhydride and 0.7 mole sodium acetate per mole of aldehyde gave the best results for a group of substituted aldehydes.

Recent work [27] indicates that a slightly larger proportion of sodium acetate, about 1 mole instead of 0.65–0.7 mole, gives a small improvement in the yields (5–10%). Further increases in the amount of sodium acetate, up to 2 moles, have little effect, but beyond this point the yields fall off. There is generally but little advantage in using more than 1.5 moles of acetic anhydride per mole of aldehyde; the use of 2 moles of anhydride increases the yield only a small amount (1–3%), and a large excess is deleterious. The use of an indifferent solvent such as toluene

[119] Ger. pat., 21,162 (1882) (*Frdl.*, **1**, 28); see also reference 131, p. 243.

or nitrobenzene causes a marked drop in the yield and can impede the reaction completely. The addition of a small amount of pyridine (8 drops for 0.2 mole benzaldehyde) raises the yield of cinnamic acid from 50–60% to 80–85%.[33]

It is reported [27] that the yield of cinnamic acid is increased (using the proportions of Meyer and Beer) by prolonged heating at 180°. The yields were as follows: heating two hours, 6%; four hours, 21%; six hours, 35%; eight hours, 45%; ten hours, 52%; fourteen hours, 61%; twenty-four hours, 72%; fifty hours, 76.5%; one hundred hours, 77%. Although the yields may be increased in this way with certain aldehydes, with others better yields are obtained by shorter periods of heating and at lower temperatures. In general a period of seven to eight hours' heating at 170–180° is adequate when sodium acetate is used. A period of three to five hours' heating at 140–160° may be sufficient if potassium acetate is used, and better yields are secured in this way with some aldehydes.

Meyer and Beer [27] studied the influence of a series of metallic acetates on the yields of various cinnamic acids and observed that potassium acetate gave a definite improvement over sodium acetate (64% yield as against 48%, with benzaldehyde). With *o*-chlorobenzaldehyde and various metallic acetates, using 2.1 moles anhydride and 0.7 mole acetate (eight hours at 180°), the yields were: lithium, 58%; sodium, 71%; potassium, 78%; rubidium, 82%; magnesium, 0%; calcium, 8%; barium, 3%; copper, 3%; lead, 70%; mercury, 37%.

Kalnin [18] carried out an extensive study of various factors influencing the yields in the Perkin reaction.* He found that tertiary amines catalyze the formation of cinnamic acid from benzaldehyde and acetic anhydride, in the absence of metallic acetates, and that their activity increases with the basic strength of the amine. Likewise, there is an optimum ratio of amine to acid anhydride; with triethylamine this is about one-third mole, but for weaker bases a larger proportion is required. Benzaldehyde, acetic anhydride (1 mole), and triethylamine (0.33 mole), heated at 180° for eight hours, gave a 29% yield of cinnamic acid; the same amount of pyridine gave only 1% yield. These amines were slightly more effective with propionic than with acetic anhydride. A mixture of benzaldehyde (1 mole), phenylacetic anhydride (0.5 mole), acetic anhydride (4 moles), and pyridine (2 moles) gave a 95% yield of α-phenylcinnamic acid after five hours' heating at 150°.

Kalnin [18] also found that metallic salts other than acetates can act as catalysts in the Perkin reaction. The following yields of cinnamic acid were obtained using benzaldehyde (1 mole), acetic anhydride (1.5

* Kalnin's paper also includes a survey and critical review of earlier work in the field.

moles), and various metallic salts (0.65 mole-equivalent), with eight hours' heating at 180°.

Potassium acetate	72%	Potassium sulfite	32%
Potassium carbonate	59%	Tripotassium phosphate	20%
Sodium carbonate	40%	Potassium sulfide	8%
Sodium acetate	39%	Potassium cyanide	0%
Trisodium phosphate	36%	Potassium iodide	0%

The effect of the duration of heating (at 180°) was studied for three of these catalysts, and the following yields were obtained.

	One-Fourth Hour	One Hour	Four Hours	Eight Hours
Potassium carbonate	34%	40%	52%	59%
Sodium carbonate	3%	14%	27%	40%
Sodium acetate	0%	2%	20%	39%

Kalnin's results indicate that potassium carbonate may be substituted advantageously for sodium acetate but that it is not quite so effective as potassium acetate.

Chappell [120] investigated the duration of heating when potassium acetate is used, and compared three aldehydes under similar conditions (1.5 moles anhydride and 0.63 mole potassium acetate, at 180°). The following yields were obtained.

	Two Hours	Four Hours	Six Hours	Eight Hours
Benzaldehyde	52%	55%	58%	60%
Anisaldehyde	30%	35%	30%	20%
Furfural	56%	49%	40%	28%

A parallel series of experiments using sodium acetate showed that the yields increased steadily up to eight hours' heating. It is clear that the optimum conditions with potassium acetate are likely to be quite dissimilar for different types of aldehydes. For furfural the most favorable results were obtained with four to five hours' heating at 150°, or six to seven hours at 140°;[121] when potassium acetate was used the addition of pyridine did not improve the yield.

In the presence of the most active acetates cinnamic acid is formed slowly at 100°; the following yields were obtained by boiling for one minute to dissolve the salt,* and then heating at 100° for sixteen hours:[120] potassium acetate, 2%; rubidium, 19%; cesium, 20%; tetraethylam-

* The solubility of the metallic acetates in the reaction mixture is an important factor and Kalnin attributes the results of Meyer and Beer, in part, to the low solubility of certain of the salts, for example, lithium acetate. Kalnin's rate studies with the alkali carbonates suggest that these bases neutralize the acetic acid formed during the reaction and thereby offset its retarding effect.

[120] Chappell, Thesis, Cornell University, 1933.

[121] Johnson, *Org. Syntheses*, **20**, 55 (1940).

monium, 18%; thallous, 14%; lead, 0%. Rubidium and cesium salts are too rare to be used for preparative purposes, but these results suggest that quaternary ammonium salts might be good catalysts under appropriate conditions.

Michael observed that free acetic acid has a retarding effect on the formation of cinnamic acid. This is readily understandable in terms of the current theory that the reaction involves enolization of the anhydride, since acetic acid would suppress the enolization. Kalnin obtained the following yields of cinnamic acid when increasing amounts of glacial acetic acid were added to the usual reaction mixtures and the reactions were carried out at 180° for eight hours.

Acetate Used	Moles of Acetic Acid Added and Yields				
	None	*0.62 mole*	*1.85 moles*	*3.1 moles*	*4.3 moles*
Potassium	72%	51%	24%	6%	2%
Sodium	39%	32%	17%	—	1%

The effect of acetic acid depends upon the degree of activity of the reacting components. *o*-Chlorobenzaldehyde reacts readily with a mixture of potassium acetate and glacial acetic acid to give *o*-chlorocinnamic acid in 70% yield; with a less reactive salt, sodium acetate, only half of the aldehyde undergoes reaction and the yield is only 24%. With compounds having a very active methylene group (malonic acid, cyanoacetic acid, rhodanine,[101] hydantoin,[109] etc.), excellent yields of condensation products can be obtained in the presence of glacial acetic acid.

The unfavorable effect of acetic acid is reduced in the customary procedures for the Perkin reaction by using an air-cooled condenser, and at the temperatures employed the acetic acid distils out of the reaction mixture. This means of overcoming the retarding effect of the acetic acid formed in the reaction is of considerable importance with benzaldehyde and less reactive aldehydes. It is quite likely that discrepancies in yields reported in the literature are due in large measure to variations in the extent of removal of acetic acid.

The effect of various factors on the reaction of phenylacetic acid (or anhydride) with *o*-nitrobenzaldehyde has been studied exhaustively by Bakunin and Peccerillo.[19] They obtained the following yields of α-*o*-nitrophenylcinnamic acid when a standard reaction mixture (1 mole aldehyde, 1 mole phenylacetic acid, 3 moles acetic anhydride, 1 mole metallic salt or organic base) was heated for twelve hours at 90°.

Sodium acetate	68%	Trimethylamine	89%
Sodium benzoate	60%	Triethylamine	95%
Potassium acetate	70%	Tripropylamine	98%
Ethanolamine	3%	Triisoamylamine	87%
Pyridine	33%	No salt or amine	0%

Thus, with two very reactive components, the tertiary amines proved to be very effective catalysts, whereas Kalnin found that triethylamine gives only a 29% yield of cinnamic acid with benzaldehyde and acetic anhydride. In another series of experiments, using phenylacetic anhydride, Bakunin and Peccerillo [19] obtained the following yields.

Rubidium acetate	80%	Pyridine	42%
Potassium acetate	78%	Trimethylamine	85%
Sodium acetate	72%	Triethylamine	87%
Lithium acetate	34%	Diethylamine	8%
Barium acetate	27%	Piperidine	23%
Without any salt or amine	6%	Aniline	0%
		Ammonia	0%

These workers found that acetic anhydride can be replaced by propionic, butyric, or valeric anhydride, but benzoic anhydride gave low yields of *o*-nitrophenylcinnamic acid. Inorganic dehydrating agents such as phosphorus pentoxide and anhydrous calcium chloride were ineffective. Likewise, ethyl phenylacetate could not be substituted for phenylacetic acid (or anhydride).

USE OF THE PERKIN REACTION IN SYNTHESIS

The Perkin reaction and related condensations afford a means of transforming an aromatic aldehyde group into a variety of side chains. The corresponding reactions can be used only to a limited extent with aliphatic aldehydes (and a few ketones) but are nevertheless of some preparative value in the aliphatic series. The types of compounds that will participate in these reactions have been reviewed in considering the scope of the reaction (pp. 217–233). The following brief summary indicates the types of compounds that can be obtained directly by means of the Perkin reaction in its varied forms.

α,β-Unsaturated Acids

$RCH{=}CHCO_2H$. β-Arylacrylic acids are prepared by the usual Perkin reaction, or by the Knoevenagel and Doebner modifications using malonic acid. 1-Naphthaldehydes, 2-furanaldehydes, and 2-thiophenealdehyde may be used instead of benzaldehyde. β-Alkylacrylic acids can be prepared from aliphatic aldehydes and malonic acid, preferably by the Doebner modification.

$R_2C{=}CHCO_2H$. β,β-Diarylacrylic acids cannot be prepared by the Perkin reaction; the β,β-dialkylacrylic acids can be obtained from dialkyl ketones and malonic acid, preferably by the Doebner modification.

$RCH{=}C(R)CO_2H$. α-Alkyl- and α-aryl-cinnamic acids are prepared readily by the Perkin reaction from benzaldehydes and substituted acetic acids. α-Vinylcinnamic acids may also be prepared (see below).

Other Unsaturated Acids

$RCH{=}CHCH_2CO_2H$. γ-Alkyl and γ-aryl derivatives of vinylacetic acid can be obtained by using sodium succinate and acetic anhydride in the Perkin reaction. Under mild conditions (120°) the intermediate paraconic acids can be obtained (Fittig's modification). β,γ-Disubstituted derivatives are obtained by using sodium methyl- or phenyl-succinate. It is reported that the Knoevenagel modification, using malonic acid and amines, often gives mainly β,γ-unsaturated acids when aliphatic aldehydes are used.[80]

$RCH{=}CHCH_2CH_2CO_2H$. The reaction of sodium glutarate with benzaldehyde gives very low yields of γ-benzalbutyric acid ($R = C_6H_5$). Sodium α-phenylglutarate reacts more satisfactorily and gives γ,δ-diphenyl-γ-pentenoic acid.

$RCH{=}CHCH{=}CHCO_2H$. Butadiene-1-carboxylic acid ($R = H$) and sorbic acid ($R = CH_3$) can be prepared from acrolein and crotonaldehyde, respectively, using the Doebner modification. 4-Phenylbutadiene-1-carboxylic acid ($R = C_6H_5$) can be obtained from cinnamaldehyde in the usual Perkin reaction, and also by the Knoevenagel or Doebner modification.

$RCH{=}CHCH{=}C(R')CO_2H$. 1-Alkyl and 1-aryl derivatives of 4-phenylbutadiene-1-carboxylic acid are prepared from cinnamaldehyde and substituted acetic acids in the usual Perkin reaction.

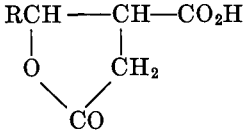
$RCH{=}C(CO_2H)CH{=}CH_2$. 1-Phenylbutadiene-2-carboxylic acid is obtained by condensation of benzaldehyde with crotonic anhydride in the presence of triethylamine.[20] The corresponding 3-methyl homolog is obtained by using β-methylcrotonic anhydride.[70]

$RCH{=}C(CO_2H)CH{=}CHR$. 1,4-Diarylbutadiene-2-carboxylic acids are obtained by condensing benzaldehydes with β-benzalpropionic acid.[122]

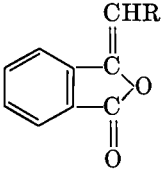
[122] Thiele, *Ann.*, **306**, 154 (1899); Schenck, *J. prakt. Chem.*, [2] **141**, 299 (1934).

$RCH{=}CHC{=}CHCH{=}CHR$ (with CO_2H on the C) A small amount of 1,6-diphenylhexatriene-3-carboxylic acid is formed by condensing cinnamaldehyde with sodium β-benzalpropionate and acetic anhydride under mild conditions,[123] but this does not appear to be a satisfactory preparative method.

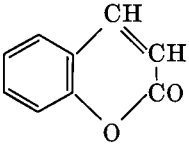
Cyclic Compounds



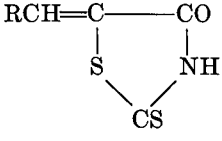
γ-Alkyl- and γ-aryl-paraconic acids are obtained by warming aliphatic and aromatic aldehydes with sodium succinate and acetic anhydride at 100–125° (Fittig's synthesis). At higher temperatures, or on heating the paraconic acids, β,γ-unsaturated acids and γ-butyrolactones are formed.



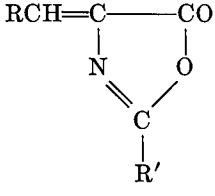
Phthalylacetic acid (R = CO_2H) is prepared from phthalic anhydride, potassium acetate, and acetic anhydride. With phenylacetic acid and others, at higher temperatures, decarboxylation occurs and benzalphthalide (R = C_6H_5, etc.) is formed. Disubstituted compounds can be obtained from phthalic anhydride and disubstituted acetic acids.



Coumarin and ring-substituted coumarins can be prepared by heating salicylaldehydes with acetic anhydride and sodium acetate. α-Alkyl and α-aryl coumarins are obtained from substituted acetic acids. Certain α,β-disubstituted coumarins can be prepared from *o*-hydroxy aryl ketones.[124, 125]



5-Benzalrhodanine and related compounds can be prepared by reaction of benzaldehyde and its derivatives with rhodanine. 3-Substituted rhodanines may also be used.

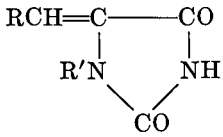


5-Benzal derivatives of 4-oxazolone (azlactones) are prepared from benzaldehydes and hippuric acid (R′ = C_6H_5). Other acyl derivatives of glycine give similar compounds (R′ = CH_3, $CH_2C_2H_5$, etc.).

[123] Knell, Dissertation, Munich (1902); reported by Smedley, *J. Chem. Soc.*, **93**, 373 (1908), and by Kuhn and Winterstein, reference 46, p. 220.

[124] Bargellini, *Gazz. chim. ital.*, **41**, I, 737 (1911); *Atti accad. Lincei*, [6] **2**, 178, 261 (1925); *C. A.*, **20**, 595 (1926).

[125] Flynn and Robertson, *J. Chem. Soc.*, 215 (1936).



5-Benzal derivatives of hydantoin (R′ = H), 2-thiohydantoin, creatinine, and a number of similar compounds can be prepared from benzaldehyde and the appropriate derivatives of glycine.

Indirect Syntheses

The products obtained directly in the Perkin reaction and its various ramifications often serve as intermediates for the preparation of other types of compounds. The following paragraphs are intended merely to indicate in a brief way the essential operations involved in typical syntheses that have some preparative value. For convenience the types are listed for aryl compounds (where the starting material would usually be benzaldehyde). In many instances the reactions used are applicable also to compounds with other organic radicals (R = alkyl, vinyl or propenyl, styryl, 2-furyl, etc.)

RCH=CH$_2$. Styrene and β-alkylstyrenes can be obtained by the thermal decarboxylation of the corresponding cinnamic acid.[126] A very general method that can be applied to alkyl and aryl derivatives of acrylic acid consists in adding hydrobromic acid (or hydriodic acid) at low temperature, and treating the resulting β-haloacid with sodium carbonate.[127, 128]

RCH=CHBr. β-Bromostyrenes are obtained by heating the dibromide of the corresponding cinnamic acid with sodium carbonate solution,[129] or with potassium (or sodium) acetate.[130]

$$\mathrm{RCH{=}CHCO_2H} \xrightarrow{\mathrm{Br_2}} \mathrm{RCHBrCHBrCO_2H} \xrightarrow[\mathrm{(NaOAc)}]{\mathrm{Na_2CO_3}} \mathrm{RCH{=}CHBr} + \mathrm{CO_2}$$

β-Alkyl-β-bromostyrenes [131] can be prepared from the dibromides of α-alkylcinnamic acids by use of alcoholic sodium acetate (75% yields). 1-Bromoölefins can be obtained from alkylacrylic acids, preferably by dehydrohalogenation of the dibromides with pyridine.[132]

RC≡CH. Arylacetylenes and alkylacetylenes may be prepared from the corresponding bromostyrenes or 1-bromoölefins, obtained as de-

[126] Abbott and Johnson, *Org. Syntheses Coll. Vol.*, **I**, 430 (1932).

[127] Fittig and Binder, *Ann.*, **195**, 131 (1879).

[128] Young, Dillon, and Lucas, *J. Am. Chem. Soc.*, **50**, 2533 (1929).

[129] Nef, *Ann.*, **308**, 267 (1899); Straus, *Ann.*, **342**, 220 (1905); Manchot, *Ann.*, **387**, 282 (1912).

[130] Straus, *Ber.*, **42**, 2878 (1909); see also Adams and Johnson, "Laboratory Experiments in Organic Chemistry," The Macmillan Co., New York, third edition (1940), p. 309.

[131] Bogert and Davidson, *J. Am. Chem. Soc.*, **54**, 337 (1932).

[132] Bachman, *J. Am. Chem. Soc.*, **55**, 4279 (1933); Farrell and Bachman, *ibid.*, **57**, 1281 (1935).

scribed above, by dehydrohalogenation with solid potassium hydroxide,[133] alcoholic alkalies,[129] or preferably with sodium amide.[134] Alkyl derivatives of phenylacetylene may be prepared from the corresponding β-alkyl-β-bromostyrenes,[131] or by alkylation of phenylacetylene with alkyl sulfates or toluenesulfonates.[135]

RCH_2CHO. Arylacetaldehydes may be prepared by addition of hypochlorous acid to cinnamic acid, and heating the α-chloro-β-hydroxy acid with sodium hydroxide or carbonate solution.[136]

$$RCH{=}CHCO_2H \xrightarrow{HOCl} RCHOHCHClCO_2H \xrightarrow{NaOH} RCH_2CH{=}O$$

A more refined method consists in treating the acrylic amides with hypochlorite in the presence of methanol, and hydrolysis of the resulting vinyl urethane with dilute acid.

$$RCH{=}CHCONH_2 \xrightarrow[CH_3OH]{NaOCl} RCH{=}CHNHCO_2CH_3 \xrightarrow[H_2SO_4]{HOH} RCH_2CH{=}O + NH_3, \text{ etc.}$$

This procedure, due to Weerman,[137] has permitted the synthesis of several difficultly accessible aldehydes.[138]

$RCH_2CH{=}NOH$. Substituted acetaldehydes may also be obtained via the acetaldoximes, which can be prepared in excellent yields from benzalrhodanines, etc. (see p. 230).[98, 102]

RCH_2CO_2H. Substituted acetic acids may be obtained by peroxide oxidation of the substituted pyruvic acids, which are secured by way of the azlactone synthesis (see p. 230). They are also obtained in good yields from the substituted acetaldoximes, by dehydration to the nitriles, $RCH_2C{\equiv}N$, and subsequent hydrolysis (see p. 230).

$RCH_2C{\equiv}N$. These may be prepared in good yields by dehydration of the corresponding substituted aldoximes (see preceding paragraph).

$RCH_2CH_2NH_2$. β-Substituted ethylamines may be obtained by reduction or by catalytic hydrogenation of $RCH_2CH{=}NOH$, RCH_2CN, or $RCH{=}CHNHCO_2CH_3$ (see under RCH_2CHO).

$RCH_2CH_2CO_2H$. β-Substituted propionic acids are prepared readily from the corresponding acrylic acids by reduction with sodium amalgam, by electrolytic reduction,[139] or by catalytic hydrogenation.

[133] Hessler, *Org. Syntheses Coll. Vol.*, **I**, 428 (1932).

[134] Bourguel, *Ann. chim.*, [10] **3**, 225 (1925); *Org. Syntheses Coll. Vol.*, **I**, 185 (1932).

[135] Truchet, *Ann. chim.*, [10] **16**, 309 (1931); Johnson, Schwartz, and Jacobs, *J. Am. Chem. Soc.*, **60**, 1882 (1938).

[136] Erlenmeyer and Lipp, *Ann.*, **219**, 182 (1883); Forrer, *Ber.*, **11**, 982 (1878).

[137] Weerman, *Ann.*, **401**, 1 (1913); *Rec. trav. chim.*, **29**, 18 (1910); **37**, 1 (1917).

[138] Rinkes, *Rec. trav. chim.*, **39**, 200, 704 (1920); **45**, 819 (1926); **46**, 268 (1927); **48**, 960 (1929).

[139] Ingersoll, *Org. Syntheses Coll. Vol.*, **I**, 304 (1932).

RCH_2CHCO_2H (R′ on the CH). α,β-Disubstituted propionic acids are obtained by reduction of the corresponding acrylic acids.

$RCHCH_2CO_2H$ (R′ on the CH). β,β-Disubstituted propionic acids can be prepared by addition of aromatic hydrocarbons to cinnamic acids in the presence of sulfuric acid,[140] or preferably aluminum chloride.[141] Grignard reagents undergo 1,4-addition to α,β-unsaturated esters to give derivatives of β,β-disubstituted propionic acids.[142]

$RCH{=}CHCN$. β-Substituted acrylonitriles can be prepared by decarboxylation of the α-cyanoacrylic acids, obtained by condensation of cyanoacetic acid with aldehydes. The α-aryl derivatives of β-arylacrylonitriles can be obtained directly by condensation of benzyl cyanide with aromatic aldehydes.

$RC{\equiv}CCO_2H$. Substituted propiolic acids may be obtained by dehydrohalogenation of the dibromides of the corresponding cinnamic esters.[143]

$$RCH{=}CHCO_2C_2H_5 \xrightarrow{Br_2} RCHBrCHBrCO_2C_2H_5 \xrightarrow[EtOH]{KOH} RC{\equiv}CCO_2H$$

The free acid is not used as this would favor decarboxylation to form the β-bromostyrene, which is formed as an accessory product even when the esters are used.

RCH_2COCO_2H. β-Substituted pyruvic acids can be prepared in good yields by hydrolysis of the corresponding azlactones [99] or α-acylamino acids[105] (see p. 253). The corresponding α-thiopyruvic acids can be obtained by hydrolysis of the condensation products formed from rhodanine and aromatic aldehydes (see p. 230).

$RCOCH_2CO_2C_2H_5$ Benzoylacetic ester can be prepared by addition of bromine to ethylcinnamate, dehydrohalogenation under mild conditions to α-bromocinnamic acid, and treatment of the α-bromo ester with cold concentrated sulfuric acid.[144]

$$C_6H_5CHBrCHBrCO_2C_2H_5 \xrightarrow[etc.]{KOH} C_6H_5CH{=}CBrCO_2C_2H_5 \xrightarrow{H_2SO_4} C_6H_5COCH_2CO_2C_2H_5$$

The aroylacetic esters can also be obtained from the corresponding

[140] Liebermann and Hartmann, *Ber.*, **25**, 960, 2124 (1892).
[141] Wislicenus and Eble, *Ber.*, **50**, 253 (1917).
[142] Kohler and Heritage, *Am. Chem. J.*, **33**, 21 (1905).
[143] Abbott, *Org. Syntheses*, **12**, 60 (1932); see also Perkin, *J. Chem. Soc.*, **45**, 172 (1884); Liebermann and Sachse, *Ber.*, **24**, 4113 (1891).
[144] Michael and Browne, *Ber.*, **19**, 1392 (1886).

arylpropiolic ester by hydration with cold sulfuric acid,[145] or by addition of a secondary amine and subsequent hydrolysis of the β-dialkylaminocinnamic ester.[146]

o-$RCH_2COC_6H_4CO_2H$. Acetophenone-o-carboxylic acid (R = H) and ω-substituted derivatives (R = C_6H_5, etc.) can be obtained by hydrolysis of phthalylacetic acids or benzalphthalides, produced by interaction of phthalic anhydride and acetic anhydride, phenylacetic acid, etc. (see p. 223).

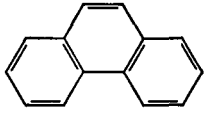
RCH_2CHCO_2H (NH$_2$). Substituted alanines can be obtained from the corresponding azlactones by reduction (or catalytic hydrogenation) and hydrolysis of the resulting saturated acylamino derivative (see p. 231). The details of the procedure may be varied according to the nature of the groups present, and this series of transformations has been used for a variety of substituted alanines.

The condensation products from aldehydes and rhodanine may be used in a similar way to obtain substituted alanines.[88]

$RCHCH_2CO_2H$ (NH_2). Derivatives of β-alanine may be obtained by the action of an excess of hydroxylamine on substituted acrylic acids, or their esters.[147] If a large excess of ammonia or methylamine is used in the Knoevenagel modification, β-aryl-β-aminopropionic acids may be formed in considerable amount along with the β-arylacrylic acid.[84]

$RCH_2CH_2CH_2NH_2$. γ-Substituted propylamines can be obtained by reduction or catalytic hydrogenation of β-substituted acrylonitriles (RCH=CHCN), obtained from aldehydes and cyanoacetic acid as outlined above.

$RCH_2CH_2CH_2CO_2H$. γ-Substituted butyric acids can be obtained by hydrogenation of the β,γ-unsaturated acids obtained by Fittig's paraconic acid synthesis.



Derivatives of cinnamic acid have been of great value for the synthesis of a number of polycyclic systems. In 1898 Pschorr[148] developed a very general method for the synthesis of phenanthrene and its derivatives, and this has found wide application

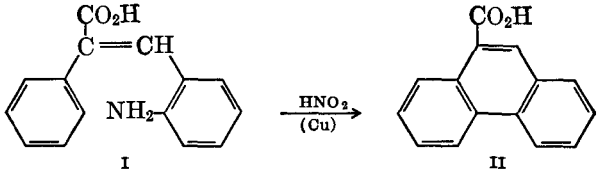
[145] Perkin, *J. Chem. Soc.*, **45**, 174 (1884).

[146] Moureu and Lazennec, *Bull. soc. chim.*, [3] **35**, 1191 (1906).

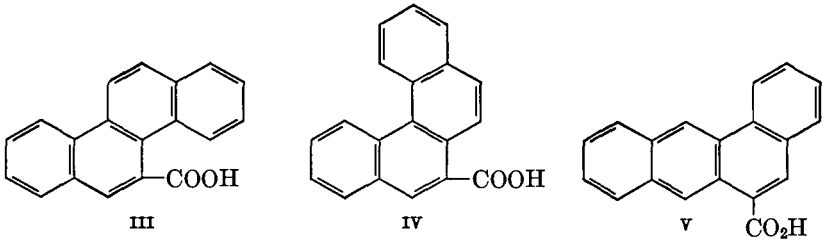
[147] Posner, *Ber.*, **36**, 4309 (1903); **38**, 2320 (1905); *Ann.*, **389**, 33 (1912).

[146] Pschorr and collaborators, *Ber.*, **29**, 496 (1896); **33**, 162, 176, 1810, 1826, 1829 (1900); **34**, 3998 (1901); **35**, 4400, 4412 (1902); **39**, 3106 (1906); *Ann.*, **391**, 40 (1912), and other papers. For an excellent survey of Pschorr's synthesis see Fieser, reference 149.

in studies of morphine derivatives, carcinogenic hydrocarbons, etc.[149] The essential features of Pschorr's synthesis are illustrated by the method used to prepare phenanthrene-9-carboxylic acid. *o*-Nitrobenzaldehyde was condensed with sodium phenylacetate to give α-phenyl-2-nitrocinnamic acid; this was reduced to the corresponding amino acid (I, 77% yield), which was diazotized and treated with copper powder, as catalyst, to effect ring closure to phenanthrene-9-carboxylic acid (II, 93% yield). The latter gave phenanthrene upon decarboxylation (64% yield).



A similar series of reactions starting from *o*-nitrobenzaldehyde and sodium α-naphthylacetate leads to chrysene-5-carboxylic acid (III),[150] which yields chrysene on decarboxylation. When *o*-nitrobenzaldehyde



and sodium β-naphthylacetate are used as starting materials, the subsequent ring closure takes place at the 1- or 3-position of the naphthalene ring leading respectively to 3,4-benzo-4-phenanthroic acid (IV, 40%) and 1,2-benz-4-anthroic acid (V, 60%).[151] The first synthesis of 1,2,5,6-dibenzanthracene was accomplished by means of the Pschorr synthesis starting from the acid obtained by a double condensation of 1,4-benzenediacetic acid with two moles of *o*-nitrobenzaldehyde.[152]

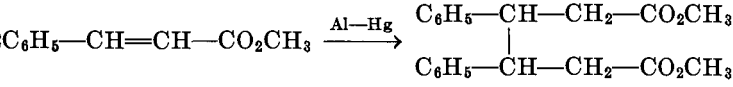
[149] Fieser, "The Chemistry of Natural Products Related to Phenanthrene," second edition, Reinhold Publishing Corporation, New York (1937), pp. 28–31, 96–98, 343.

[150] Weitzenböck and Lieb, *Monatsh.*, **33**, 557 (1912).

[151] Cook, *J. Chem. Soc.*, 2524 (1931). Earlier workers mistook 1,2-benzanthracene for 3,4-benzophenanthrene; see Weitzenböck and Lieb, reference 150, and Mayer and Oppenheimer, *Ber.*, **51**, 513 (1918).

[152] Weitzenböck and Klinger, *Monatsh.*, **39**, 315 (1918).

The bimolecular reduction of methyl cinnamate by means of amalgamated aluminum leads to methyl β,β'-diphenyladipate (*meso* and racemic forms).



Although low yields are obtained in this reduction, it has served as a source of β,β'-diphenyladipic acid, which has been used for the synthesis of chrysene derivatives and of chrysene itself.[153]

LABORATORY PROCEDURES

Cinnamic Acid

Using Acetic Anhydride and Potassium Acetate.* A mixture of 21 g. (0.2 mole) of freshly distilled benzaldehyde, 30 g. (0.3 mole) of 95% acetic anhydride, and 12 g. (0.12 mole) of freshly fused potassium acetate is refluxed in an oil bath at 170–175° continuously for five hours, using an air-cooled condenser.

The hot reaction mixture is poured into about 1200 cc. of warm water, part of which is used to rinse the reaction flask, and unchanged benzaldehyde is removed by steam distillation. The residual liquid is cooled slightly, 3–4 g. of decolorizing carbon is added, and the mixture is boiled gently for five to ten minutes. The liquid is filtered rapidly through a fluted filter paper; the clear filtrate is heated to boiling, 12–14 cc. of concentrated hydrochloric acid is added carefully, and the hot solution is cooled rapidly with good stirring. After the cinnamic acid has crystallized completely the crystals are filtered with suction, washed with several small portions of water, and dried. The acid obtained in this way melts at 131.5–132° and is pure enough for most purposes. The yield is 16–18 g. (55–60%).

Using Malonic Acid and a Pyridine Base.[117] A mixture of 10.6 g. benzaldehyde (0.1 mole), 10.4 g. malonic acid (0.1 mole), and 9.3 g. α-picoline (0.1 mole) is heated for three to four hours in a water bath at 70°. At the end of this period evolution of carbon dioxide has ceased, and the reaction mixture is then treated with 500 cc. of water and 25 cc. of concentrated hydrochloric acid. Unchanged benzaldehyde is removed by steam distillation, and the cinnamic acid is isolated as described in

* The advantage of potassium acetate over sodium acetate is that a shorter period of heating is required to obtain comparable yields.

[153] von Braun and Irmisch, *Ber.*, **64**, 2461 (1931); see also Robinson and collaborators, *J. Chem. Soc.*, 607 (1933); 1412, 1414 (1935).

the preceding paragraph. The product melts at 131.5–132.5° and weighs 8–8.5 g. (54–57%). Substituted benzaldehydes usually give higher yields (80–95%) in this reaction.

p-Methoxycinnamic Acid

A solution of 13.6 g. (0.1 mole) of anisaldehyde and 12.6 g. (0.12 mole) of malonic acid in a small quantity of 95% ethyl alcohol is treated with 21 g. of an 8% solution of ammonia (0.1 mole) in 95% ethyl alcohol, and the mixture is heated on a steam bath. After the alcohol has distilled, the oily residue is heated on a vigorously boiling water bath until evolution of carbon dioxide has ceased and the mixture becomes solid (about two hours).

The product is treated with warm water and dissolved by the addition of a minimum amount of sodium carbonate. The solution is boiled a few minutes with 1–2 g. of decolorizing charcoal and filtered through a fluted paper. The warm filtrate is poured with stirring into an excess of cold 20% sulfuric acid containing some chopped ice. After the acid has crystallized completely it is collected with suction, washed with several small portions of cold water, and dried. The yield is 8–9 g. (45–50%),* and the product melts at 166–168°.

β-Piperonylacrylic Acid (3,4-Methylenedioxycinnamic Acid)

Forty-five grams of piperonal (0.3 mole), 60 g. of malonic acid (0.576 mole), 120 cc. of *dry* pyridine, and 3 cc. of piperidine are placed in a 300-cc. round-bottomed flask fitted with a reflux condenser and calcium chloride tube, and heated for one hour on a steam bath. The solution, which at the end of that time is clear, is then boiled gently over a flame for twenty minutes (or merely heated for an additional hour on the steam bath). The contents of the flask are cooled and poured with stirring *into* a mixture of 175 cc. of concentrated hydrochloric acid and 300 g. of chopped ice. The precipitate is filtered with suction, then washed once with 25 cc. of 10% hydrochloric acid and twice with 25-cc. portions of water. After drying, the acid melts at 227–230° (uncor.), and weighs 49–53 g. (85–90%). The recorded melting point of β-piperonylacrylic acid is 233° (cor.).

A large excess of malonic acid is used to obtain a good conversion of the aldehyde. A ratio of 1.9 moles per mole of aldehyde was found to be near the optimum; with 1.6 moles the yield was 75%, and with 1 mole it fell to 65%. The Doebner modification is used generally for the less

* Higher yields are reported in the literature (see Table III, p. 260) but could not be duplicated in the Cornell laboratory.

common aldehydes, where a good yield is important, and also for aldehydes that do not give good yields in the usual Perkin reaction.

The presence of water in the reagents causes a marked lowering of the yields. Pyridine should be dried thoroughly over solid caustic and redistilled; higher-boiling pyridine bases (boiling up to 165°) give as good yields as pyridine, when dried thoroughly and distilled. When higher bases are used the reaction mixture is heated for two hours on the steam bath instead of one hour followed by twenty minutes' boiling.

This general procedure is essentially that described in the literature for several alkoxybenzaldehydes.[154, 155] By the directions given above, 4-methoxy- and 3,4-dimethoxy-benzaldehyde furnish *p*-anisyl- and veratryl-acrylic acids, respectively, in 80% yields. *p*-Dimethylaminobenzaldehyde is reported to give the corresponding cinnamic acid in 80% yield by a similar procedure.[74]

3-Methoxy-4-Hydroxycinnamic Acid (Ferulic Acid)

A solution of 15.2 g. (0.1 mole) of vanillin, 23 g. (0.22 mole) of malonic acid, and 1 g. (1.2 cc., 0.012 mole) of piperidine in 50 cc. of dry pyridine is allowed to stand at room temperature for three weeks. During this time the reaction mixture is protected by a soda-lime tube but must not be corked as carbon dioxide is evolved; a Bunsen valve may be used.

The reaction mixture is poured with stirring into a mixture of 60 cc. of concentrated hydrochloric acid and 100 g. of chopped ice. The acid precipitates at once, and after standing until separation is complete it is filtered with suction. The product is washed with 10 cc. of 5% hydrochloric acid, followed by two 10-cc. portions of water, and then dried. The yield of ferulic acid, m.p. 173° (cor.), is 14–17 g. (70–85%).

This procedure is an adaptation of the Doebner modification developed by Vorsatz [86] and is particularly advantageous for preparing cinnamic acids having a free phenolic group. These compounds give low yields at 100° in the Doebner procedure, presumably owing to the ease of decarboxylation of the hydroxycinnamic acids.

The following yields were reported by Vorsatz with other substituted benzaldehydes, with the same proportions of aldehyde and malonic acid: 2,4-dihydroxycinnamic acid (caffeic acid), using 1.4 g. aniline instead of piperidine, allowing to stand overnight, and then warming at 50–55° until evolution of carbon dioxide was essentially complete (about three hours), in 87% yield; 3,4-methylenedioxycinnamic acid (piperonylacrylic acid), using piperidine and standing four weeks at room temperature,

[154] Cain, Simonsen, and Smith, *J. Chem. Soc.*, **53**, 1035 (1913).
[155] Haworth, Perkin, and Rankin, *J. Chem. Soc.*, **125**, 1693 (1924).

in 83% yield after recrystallization from 75% alcohol; 3,4-dihydroxycoumarin-α-carboxylic acid (daphnetin-3-carboxylic acid), using aniline or pyridine and warming for twenty hours at 37°, in 83% yield.

If a large excess of ammonia (60 moles) or methylamine is used in this reaction a mixture of the β-aminopropionic and acrylic acids is formed.[84]

α-Methylcinnamic Acid [2]

A mixture of 21 g. (0.2 mole) of freshly distilled benzaldehyde, 32 g. (0.25 mole) of propionic anhydride, and 20 g. (0.2 mole) of fused sodium propionate is heated with occasional shaking for thirty hours in an oil bath at 130–135°. The warm mixture is poured into about 500 cc. of water, stirred thoroughly, and neutralized by the addition of sodium carbonate solution. After removal of unchanged benzaldehyde by steam distillation (or ether extraction), the solution is warmed with 3–4 g. of decolorizing carbon and filtered while hot. The warm filtrate is poured slowly, with stirring, into an excess of concentrated hydrochloric acid mixed with chopped ice. After the acid has crystallized completely it is collected with suction, washed with several portions of water, and dried. The crude product, amounting to 21–25 g., is recrystallized from ligroin and gives 19–23 g. (60–70% yield) of purified material.

The acid obtained in this way may melt at 81° or 74°, as α-methylcinnamic acid exists in two different crystalline forms. Both forms have the same configuration (*trans* $C_6H_5:CO_2H$) and give the same ester. Occasionally a mixture of the two *trans* forms is obtained which melts at 77–78°. The true geometrical isomer, *allo*-α-methylcinnamic acid (*cis* $C_6H_5:CO_2H$), melts at 91° and can be obtained by long exposure of the ordinary acid to ultra-violet light.

Very little cinnamic acid is formed in this reaction when sodium acetate is used as catalyst. Although some acetic anhydride is formed by the anhydride-salt exchange, the concentration is low and its rate of reaction at 135° is much less than that of propionic anhydride. At higher temperatures more cinnamic acid is formed (p. 213).

The procedure given is essentially that of Edeleano;[156] α-methylcinnamic acid has also been prepared using propionic anhydride and sodium propionate,[2] or acetic anhydride and sodium propionate at 100°,[14] and by heating benzal chloride with sodium propionate at 150° (Erdmann [156]).

[156] Edeleano, *Ber.*, **20**, 617 (1887); see also Rupe and Busolt, *Ann.*, **369**, 320 (1909); Erdmann, *Ann.*, **227**, 248 (1885).

α-Phenylcinnamic Acid [157]

In a 200-cc. round-bottomed flask, 17.4 g. (0.10 mole) of dry potassium phenylacetate, 5 g. of dry potassium carbonate (0.035 mole), 0.5 cc. pyridine, 10.6 g. (0.10 mole) freshly distilled benzaldehyde, and 15.3 g. (0.15 mole) freshly distilled acetic anhydride are mixed thoroughly under nitrogen. An air-cooled reflux condenser is attached, and the flask is carefully inserted in an oil bath at 180°. A vigorous bubbling takes place for a few minutes, after which the reaction proceeds quietly. Heating is continued at 180–190° for two hours. The mixture is allowed to cool, and 300–400 cc. water is added with gentle heating to break up lumps. Potassium hydroxide solution (6 *N*) is added until the solution is basic (about 30 cc. is required), but care should be taken not to add a large excess of base as the potassium salt of the acid is easily salted out of solution. The mixture is heated until all soluble material has dissolved; some oily material will remain undissolved. The flask is cooled under the water tap and the solution extracted with 300–400 cc. of ether to remove unchanged benzaldehyde and a little stilbene (*ca.* 1 g.). The water solution is acidified with 6 *N* hydrochloric acid (15–20 cc. is required), the precipitated acid filtered off, and the filtrate tested with more acid for completeness of precipitation. The precipitate is conveniently dried on a porous plate in a vacuum desiccator. The yield of crude acid, melting about 160°, is 13–15 g. (60–65% of the theoretical). It can be recrystallized by dissolving in 50% ethanol at boiling temperature and adding water until the solution is just cloudy. The solution is cooled very slowly, and long needles form gradually. The purified acid amounts to 11–12 g. (50–55% of theoretical) and melts at 168–170° (uncor.). The acid obtained in this way is the *trans* form.

β-*n*-Hexylacrylic Acid (α,β-Nonenoic Acid)

In a large flask 114 g. (1.1 moles) of malonic acid is dissolved in 185 cc. of dry pyridine; the reaction is slightly exothermic. The solution is cooled in ice water, and 114 g. (1 mole) of freshly distilled *n*-heptaldehyde is added with stirring or good shaking. After a part of the aldehyde has been added the mixture rapidly sets to a mush of crystals, but moderate stirring is possible. The mixture is allowed to stand at room temperature for sixty hours with frequent shaking. During this time the mixture froths owing to evolution of carbon dioxide, and at the end most of the

[157] This procedure was furnished through the courtesy of Professor C. R. Hauser and Miss Mildred Patterson, of Duke University. It is a modern version of the Oglialoro modification incorporating results of Bakunin and collaborators, and the use of potassium carbonate and pyridine, as suggested by Kalnin's studies.

malonic acid has been consumed. The reaction mixture finally is warmed on a steam bath for eight to nine hours (until evolution of carbon dioxide has ceased) and then poured into an equal volume of water. The oily layer is separated and shaken thoroughly with 300 cc. of 25% hydrochloric acid to remove pyridine. The product is taken up in benzene, washed with water, dried, and distilled under diminished pressure. After a small fore-run of heptaldehyde (3–4 g.), the acid is collected at 130–132°/2 mm.; there is little high-boiling residue. With small quantities the yield is 75–80%, but with larger amounts (1 kg. of heptaldehyde) the yield is 80–85%.*

Zaar [80] reported that the acid prepared in this way contains about 5% of the β,γ-isomer, whereas the Knoevenagel procedure using piperidine gives a lower yield and much more impure material. Zaar removed the β,γ-isomer as the γ-lactone by treating the distilled acid with an equal weight of 85% sulfuric acid and stirring for 6 hours at 80°,[82] washing with water, and then treating the product with sodium carbonate solution. This converts the β,γ-unsaturated acid to γ-*n*-amylbutyrolactone (b.p. 110–112°/3 mm.), which is insoluble in carbonate and can be removed by extraction with a solvent. From the alkaline solution the purified α,β-nonenoic acid is regenerated by acidification and redistilled.

o-Nitrophenylpyruvic Acid †

Azlactone from Aceturic Acid and *o*-Nitrobenzaldehyde. Six grams (0.04 mole) of *o*-nitrobenzaldehyde, 5.5 g. (0.047 mole) of aceturic acid, and 2.6 g. (0.032 mole) of fused sodium acetate are mixed thoroughly (by grinding in a mortar) and placed in a 125-cc. Erlenmeyer flask. To the mixture is added 15 cc. (16.2 g., 0.142 mole) of 90–95% acetic anhydride, and the open flask is then heated on the steam bath for two and one-half hours. The flask is cooled to room temperature and allowed to stand for two hours, during which time crystallization occurs. The solid cake of crystals is broken up and washed with three 20-cc. portions of water. The finely crystalline yellow product is dried for twelve hours in a vacuum desiccator over sodium hydroxide and calcium chloride. The yield is 6 g. of crude product (65%) melting at 110–112°. It may be recrystallized from petroleum ether (b.p. 90–100°) to give bright yellow needles of m.p. 113.5–114.5°.

Hydrolysis of the Azlactone. Eight grams (0.0345 mole) of the crude azlactone is refluxed with 200 cc. of 1 *N* hydrochloric acid for two and one-

* This procedure is due to Zaar,[60] who reported also the following yields with higher aldehydes: *n*-octaldehyde to α,β-decenoic acid, 75%; *n*-decaldehyde to α,β-dodecenoic acid, 58%; *n*-undecaldehyde to α,β-tridecenoic acid, 67%.

† These directions were furnished by Mr. Richard B. Hasbrouck, Cornell University.

half hours in a reflux apparatus fitted with ground-glass joints. To the hot (90°) solution is added 1–2 g. of charcoal, and the whole is boiled for a few minutes. The boiling solution is then filtered and cooled to room temperature. Most of the *o*-nitrophenylpyruvic acid separates as an oil, but seeding or scratching causes crystallization to begin. After standing at room temperature for two hours, the mixture is cooled at 0° overnight. The light tan crystals of *o*-nitrophenylpyruvic acid are filtered, washed with 5 cc. of cold water, and dried in a vacuum desiccator. The product weighs 4.3 g. and melts at 117–120°. The aqueous mother liquor is concentrated in vacuum to about 50 cc., and the oily product is seeded and worked up as before. The second crop of crystals weighs 1.7 g. and melts at 119–120°. The total yield of product is 6.0 g. or 83% of the theoretical. This product is sufficiently pure for synthetic purposes: it may be recrystallized from water with small loss.

TABLE II

YIELDS OF CINNAMIC ACID UNDER VARIOUS CONDITIONS

Carbonyl Component	Acid Components m = moles per mole aldehyde	Conditions		Yield, %	Reference
		Temperature, °C.	Time, hours		
Benzaldehyde	Ac_2O (1.5 m) + NaOAc (0.65 m)	180	8	48, 52	29, 27
	—same, + trace C_5H_5N	180	8	85	33
	Ac_2O (2.1 m) + KOAc (0.7 m)	180	8	64	29
	Ac_2O (1.5 m) + KOAc (0.65 m)	180	8	60, 72	18, 120
	Ac_2O (1.5 m) + K_2CO_3 (0.65 m)	180	8	59	18
	Malonic (1.2 m) + NH_3 (2 m)	100	3	80–85	60
	Malonic acid + C_5H_5N + $C_5H_{11}N$	115	3–4	90	63
Benzalaniline	Malonic acid (1 m)	20–100	24	70	63
Benzal chloride	NaOAc (4–5 m) or KOAc	200	10–20	Good	25
Benzal diacetate	HOAc (4 m) + NaOAc (4 m)	160–180	10	20	26

TABLE III

RING-SUBSTITUTED CINNAMIC ACIDS

Substituted Benzaldehyde (or Other Carbonyl Component)	Acid Components	Conditions		Substituted Cinnamic Acid (or Other Product)*	Yield, %	Reference†
		Temperature, °C.	Time, hours			
3-Fluoro-	Malonic (1.2 *m*) + NH_3 (2.5 *m*)	100, 180	4	3-Fluoro-	50	158
2-Chloro-	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180–200	8	2-Chloro-	66, 71	29, 27
	Ac_2O (2.1 *m*) + KOAc (0.7 *m*)	180–200	8		72	29
(2-Chlorobenzal chloride)	HOAc (1.8 *m*) + KOAc (5 *m*)	210	40	2-Chloro-	Good	159
3-Chloro-	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180	8	3-Chloro-	63	27
4-Chloro-	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180	8	4-Chloro-	52	27
2-Chloro-6-fluoro-	Malonic (1.5 *m*) + HOAc	100	6	2-Chloro-6-fluoro-	90	160
2,5-Dichloro-	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180	8	2,5-Dichloro-	78	27
2,6-Dichloro-	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180	8	2,6-Dichloro-	82	27, 161
3,5-Dichloro-	Ac_2O (0.8 *m*) + NaOAc (1.3 *m*)	190	18	2,5-Dichloro-	76	162
3,5-Dichloro-2-nitro-	Ac_2O (1.5 *m*) + NaOAc (1 *m*)	180	7	3,5-Dichloro-2-nitro-	65	163
2,3,4-Trichloro-	Ac_2O + NaOAc	(180)	(8)	2,3,4-Trichloro-	Good	164
2,3,6-Trichloro-	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180	8	2,3,6-Trichloro-	66	27
2,4,5-Trichloro-	Ac_2O + NaOAc	(180)	(8)	2,4,5-Trichloro-	Good	164
Pentachloro-	Ac_2O(3.5 *m*) + NaOAc (1 *m*)	170–180	60	Pentachloro-	30	179
2-Bromo-	Malonic (1.8 *m*) + HOAc (1.5 *m*)	100, 190	6	2-Bromo-	Good	160
2-Bromobenzal diacetate	Ac_2O + NaOAc	165–190	9		Good	165
3-Bromo-	Malonic acid + C_5H_5N + $C_5H_{11}N$	115	3–4	3-Bromo-	83	63
3,4,5-Tribromo-	Ac_2O (25 *m*) + NaOAc (4 *m*)	Refl.	7	3,4,5-Tribromo-	53	180

Tribromo-2-nitro-	Ac_2O (25 *m*) + NaOAc (4 *m*)	Refl.	6	Tribromo-2-nitro-	68	180
2-Iodo-	Ac_2O (9 *m*) + NaOAc (1.5 *m*)	150	8.5	2-Iodo-	85	51
3-Iodo-	Ac_2O (1.3 *m*) + NaOAc (0.65 *m*)	Refl.	8	3-Iodo-	(90)	166
2-Nitro-	Ac_2O (2 *m*) + KOAc (1 *m*)	135	0.25	2-Nitro-	67	167
	Ac_2O(2.1 *m*) + NaOAc (0.7 *m*)	180	8		75	27
	Ac_2O (2.1 *m*) + NaOAc (1 *m*)	190	16		95	168
	Malonic acid + C_5H_5N + $C_5H_{11}N$	115	3–4		73	63
2-Nitrobenzalaniline	Malonic (1.2 *m*)	100	1		50	60
3-Nitro-	Ac_2O (2 *m*) + NaOAc (1.5 *m*)	180	13	3-Nitro-	76	169
	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180	8		75	27
	Malonic acid + C_5H_5N + $C_5H_{11}N$	115	3–4		82	63
	Malonic (1.3 *m*) + NH_3 (2 *m*)	100	2		72	60
4-Nitro-	Ac_2O (2 *m*) + NaOAc (0.8 *m*)	180	8	4-Nitro-	90	170
	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180	8		82	27
	Malonic acid + C_5H_5N + $C_5H_{11}N$	100			90	63
	Malonic (1.3 *m*) + NH_3 (1 *m*)	100	2		90	60
2-Nitro-4-chloro-	Ac_2O (7.5 g.) + NaOAc (1 g.)	Refl.	6	2-Nitro-4-chloro-	50	171
2-Nitro-5-chloro-	Ac_2O (1.4 g.) + NaOAc (0.6 g.)	145	8	2-Nitro-5-chloro-	..	172
3-Nitro-4-chloro-	Ac_2O (7.5 g.) + NaOAc (1 g.)	Refl.	7	3-Nitro-4-chloro-	80	171
2-Nitro-4-bromo-	Ac_2O (7.5 g.) + NaOAc (1 g.)	Refl.	5	2-Nitro-4-bromo-	40	171
2-Nitro-5-bromo-	Ac_2O (1.6 g.) + NaOAc (0.7 g.)	145	7	2-Nitro-5-bromo-	..	173
3-Nitro-4-bromo-	Ac_2O (8 g.) + NaOAc (1 g.)	Refl.	7	3-Nitro-5-bromo-	55	171
2,4-Dinitro-	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	150	8	2,4-Dinitro-	70	27
2,6-Dinitro-	Ac_2O (excs) + NaOAc (1 *m*)	145	8	2,6-Dinitro-	Good	174
2,4,6-Trinitro-	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	Varied	Varied	None	0	27
2-Methyl-	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180	8	2-Methyl-	15	27
3-Methyl-	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180	8	3-Methyl-	23	27
3-Methyl-6-nitro-	Malonic acid + C_5H_5N + $C_5H_{11}N$	100		3-Methyl-6-nitro-		181

* A name in italics is synonymous to that immediately preceding.
† References 158–232 appear on pp. 264–265.

TABLE III—*Continued*

RING-SUBSTITUTED CINNAMIC ACIDS

Substituted Benzaldehyde (or Other Carbonyl Component)	Acid Components	Conditions		Substituted Cinnamic Acid (or Other Product) *	Yield, %	Reference†
		Temperature, °C.	Time, hours			
4-Methyl-	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180	8	4-Methyl-	23, 15	27, 28
	Ac_2O (2.4 *m*) + NaOAc (0.7 *m*)	170	24		70	175
	Malonic acid + C_5H_5N + $C_5H_{11}N$	115	3–4		87, 70	63, 74
	Malonic (1 *m*) + C_5H_5N (0.15 *m*)	100	4–5		84, 95	87, 87*i*
	Malonic (1 *m*) + Quinoline.(1 *m*)	85	1		70	117
4-Methyl-2-chloro-	Malonic acid + C_5H_5N	100	6	4-Methyl-2-chloro-	(50)	182
4-Methyl-3-nitro-	Ac_2O (2 g.) + NaOAc (1 g.)	170	10	4-Methyl-3-nitro-	75	175
4-Ethyl-	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180–200	8	4-Ethyl-	Trace	28
	Malonic acid + C_5H_5N + $C_5H_{11}N$	115	3–4		83	28
2,4-Dimethyl-	Malonic (1 g.) + $C_6H_5NH_2$	100	3	2,4-Dimethyl-	..	176, 177
	Malonic (1.2 *m*) + NH_3	100			..	178
2,5-Dimethyl-	Malonic (1 g.) + $C_6H_5NH_2$	100	3+	2,5-Dimethyl-	..	177
2,6-Dimethyl-	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180	8–50	2,6-Dimethyl-	0	27
3,4-Dimethyl-	Malonic (1.2 *m*) + $C_6H_5NH_2$	20–100	24, 1	3,4-Dimethyl-	Good	178
2,3,4-Trimethyl-	Malonic (1 *m*) + $C_5H_{11}N$ (trace)	100	12	2,3,4-Trimethyl-	(90)	183
2,4,5-Trimethyl-3,6-dinitro-	Ac_2O (2.3 g.) + NaOAc (0.7 g.)	145	8	2,4,5-Trimethyl-3,6-dinitro-	30	184
2,4,6-Trimethyl-	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180	50	2,4,6-Trimethyl-	7	27
	Malonic acid + C_5H_5N + $C_5H_{11}N$	115	3–4		10	28
2,4,6-Trimethyl-3,5-dinitro	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180–200	8	2,4,6-Trimethyl-3,5-dinitro-	60	28

4-Isopropyl	Ac_2O (2.1 *m*) + NaOAc (0.9 *m*)	175	6	4-Isopropyl-	42	2
	Malonic (1.2 *m*) + C_5H_5N + $C_5H_{11}N$	100	2		64	185
2-Isopropyl-5-methyl-	Malonic acid + C_5H_5N + $C_5H_{11}N$	100, 115	2, $1\frac{1}{2}$	2-Isopropyl-4-methyl-	(50)	186
4-Phenyl-	Ac_2O (8 *m*) + NaOAc (1.2 *m*)	Refl.	8	4-Phenyl-	..	38
	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180–200	8		Trace	28
	Malonic (1.1 *m*) + CH_3CO_2H	100	12		..	38
2-Hydroxy-	Ac_2O (1.6 g.) + NaOAc (1.3 g.)	Refl.	3–4	2-Acetoxy-(and coumarin)	..	1, 34
	Malonic acid + C_5H_5N + $C_5H_{11}N$	115	4	(*o*-Coumaric acid)	20	63
	Malonic (1 *m*) + C_5H_5N (0.15 *m*)	100, 65	4, 4	(Coumarin-α-carboxylic acid)	50	87, 87*a*
2-Methoxy-	Ac_2O (2 g.) + NaOAc (0.7 g.)	Refl.	9	2-Methoxy-	55	30, 2
	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180–200	8		44	28
	Malonic (1.2 *m*) + C_5H_5N + $C_5H_{11}N$	100	3–4		80	185
	Malonic (1 *m*) + C_5H_5N (0.15 *m*)	100	4–5		80	87*f*
2-Methoxy-3-nitro-	Ac_2O (2.1 g.) + NaOAc (1.5 g.)	175	3	2-Methoxy-3-nitro-	..	187
2-Methoxy-5-nitro-	Ac_2O (3 g.) + NaOAc (1 g.)	Refl.	6	2-Methoxy-5-nitro-	65	188
2-Ethoxy-	Ac_2O + NaOAc	165		2-Ethoxy-	..	189
2-Ethoxy-5-nitro-	Ac_2O (3 g.) + NaOAc (1 g.)	Refl.	6	2-Ethoxy-5-nitro-	..	190
3-Hydroxy-	Ac_2O (2.5 g.) + NaOAc (2 g.)	Refl.	5	3-Acetoxy-	Good	30, 191
	Malonic (1 *m*) + Quinoline (1 *m*)	80	10	3-Hydroxy-	70	117
	Malonic (1 *m*) + C_5H_5N (0.15 *m*)	110	8		95	87*e*
	Malonic acid + C_5H_5N + $C_5H_{11}N$	100	2		90	87*e*
3-Methoxy-	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180–200	8	3-Methoxy-	40	28, 191
	Malonic acid + NH_3	120			..	30
	Malonic (1 *m*) + C_5H_5N (0.15 *m*)	100	4–5		90+	87*f*, 192
	Malonic (1.2 *m*) + C_5H_5N + $C_5H_{11}N$	100, 115	2, $\frac{1}{2}$		90, 70	193, 195
3-Methoxy-2-nitro-	Malonic (2 *m*) + C_5H_5N + $C_5H_{11}N$	100, 115	2	3-Methoxy-2-nitro-	95	194
3-Methoxy-4-nitro-	Same	100, 115	2	3-Methoxy-4-nitro-	95	194
3-Methoxy-6-nitro-	Same	100, 115	2	3-Methoxy-6-nitro-	95	194

* A name in italics is synonymous to that immediately preceding.
† References 158–232 appear on pp. 264–265.

TABLE III—*Continued*

RING-SUBSTITUTED CINNAMIC ACIDS

Substituted Benzaldehyde (or Other Carbonyl Component)	Acid Components	Conditions		Substituted Cinnamic Acid (or Other Product)*	Yield, %	Reference†
		Temperature, °C.	Time, hours			
3-Ethoxy-	Ac_2O (1 g.) + NaOAc (1 g.)	Refl.	5	3-Ethoxy-	..	195
4-Hydroxy-	Ac_2O (3 *m*) + NaOAc (2.3 *m*)	145	24	4-Hydroxy-(after hydrolysis of acetate)	60, 50	30, 196
4-Hydroxy-3,5-diiodo-	Ac_2O (8 *m*) + NaOAc (3.5 *m*)	135	12	4-Hydroxy-3,5-diiodo-	60	200
4-Methoxy-	Ac_2O (2.2 *m*) + NaOAc (1 *m*)	Refl.	6	4-Methoxy-	30	30
	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180–200	8		20	28
	Ac_2O (1.5 *m*) + KOAc (0.6 *m*)	180	4		35	120
	Malonic (1.2 *m*) + NH_3 (1 *m*)	100	3		90, 78	60, 197
	Malonic (1.8 *m*) + C_5H_5N + $C_5H_{11}N$	100, 115	2, $\frac{1}{2}$		80–90	154, 198, 199, 63
	Malonic (1 *m*) + C_5H_5N (0.15 *m*)	100	4		78, 84	87, 87*c*
4-Methoxy-3-nitro-	Ac_2O (2.5 *m*) + NaOAc (1.3 *m*)	145	8	4-Methoxy-3-nitro-	45	201
4-Ethoxy-	Ac_2O (0.8 g.) + NaOAc (0.5 g.)	175	10	4-Ethoxy-	36	32
4-*n*-Propoxy-	Ac_2O (0.8 g.) + NaOAc (0.5 g.)	175	10	4-*n*-Propoxy-	40	32
4-*n*-Butoxy-	Ac_2O (1.5 g.) + NaOAc (0.5 g.)	210	9	4-*n*-Butoxy	40	32
4-Hydroxy-2,5-dimethyl-	Malonic (2.5 *m*) + C_5H_5N + $C_5H_{11}N$	100	2	4-Hydroxy-2,5-dimethyl-	..	202
4-Methoxy-2,5-dimethyl-	Malonic (2.5 *m*) + C_5H_5N + $C_5H_{11}N$	100, 115	5, $\frac{1}{2}$	4-Methoxy-2,5-dimethyl-	90	202
2-Hydroxy-3-methoxy-	Ac_2O (4.5 *m*) + NaOAc (4 *m*)	180	8	2-Acetoxy-3-methoxy-(and 8-methoxycoumarin)	20, 15	203

2,3-Dimethoxy-	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180–200	8	2,3-Dimethoxy-	15	28
	Ac_2O (6.5 *m*) + NaOAc (1.7 *m*)	200	24		70	204
	Malonic (2 *m*) + C_5H_5N + $C_5H_{11}N$	100, 115	$1\frac{1}{2}$, $\frac{1}{4}$		95	205
2,3-Methylenedioxy-	Malonic (2.5 *m*) + C_5H_5N + $C_5H_{11}N$	100	$1\frac{1}{2}$	2,3-Methylenedioxy-	Good	206
2-Ethoxy-3-methoxy-	Malonic (2 *m*) + C_5H_5N + $C_5H_{11}N$	100, 115	1, $\frac{1}{10}$	2-Ethoxy-3-methoxy-	95	207
2,3-Diethoxy-	Malonic (2 *m*) + C_5H_5N + $C_5H_{11}N$	100, 115	1, $\frac{1}{10}$	2,3-Diethoxy-	90	207
2,4-Dihydroxy-	Ac_2O + NaOAc	170	8	(7-Acetoxycoumarin,	30	87*h*, 208
	Malonic (1 *m*) + C_5H_5N (0.15 *m*)	105		7-hydroxycoumarin, or *umbelliferone*)	43	87*h*
2,4-Dimethoxy-	Ac_2O (2.5 *m*) + NaOAc (1.2 *m*)	Refl.	6	2,4-Dimethoxy-	70	209, 210
	Malonic (1.2 *m*) + C_5H_5N + $C_5H_{11}N$	100			95	185
2,5-Dimethoxy-	Ac_2O (2.7 *m*) + NaOAc (1.2 *m*)	180	8	2,5-Dimethoxy-	55	211
2,6-Dimethoxy-	Ac_2O + NaOAc			2,6-Dimethoxy-	0	
	Malonic acid + C_5H_5N				35	212
3,4-Dihydroxy-	Ac_2O (3 g.) + NaOAc (1 g.)	Refl.	4	3,4-Diacetoxy-	..	213
	Malonic (1.3 *m*) + CH_3CO_2H	100	10	3,4-Dihydroxy-	25	30
	Malonic (2 *m*) + C_5H_5N + $C_6H_5NH_2$	55	3	or *caffeic acid*	87	86
	Malonic (1 *m*) + C_5H_5N (0.15 *m*)	70–100			44	87*j*
	Malonic (2 *m*) + C_5H_5N + $C_5H_{11}N$	10–25	3 weeks		83	87*j*
3-Hydroxy-4-methoxy-	Malonic (1.5 *m*) + C_5H_5N + $C_5H_{11}N$	100, 115	3, $\frac{1}{2}$	3-Hydroxy-4-methoxy- or *hesperetic acid*, or *isoferulic acid*	90	214
3-Methoxy-4-hydroxy-	Ac_2O (3 g.) + NaOAc (1 g.)	Refl.	5–6	3-Methoxy-4-acetoxy-	..	213
	Malonic (1.5 *m*) + NH_3 (1.2 *m*)	100	$\frac{1}{2}$	3-Methoxy-4-hydroxy- or *ferulic acid*	50	30
	Malonic (3 *m*) + C_5H_5N + $C_5H_{11}N$	100	$1\frac{1}{2}$		80	215
	Malonic (2 *m*) + C_5H_5N + $C_5H_{11}N$	20	3 weeks		83	86, 87*j*

* A name in italics is synonymous to that immediately preceding.
† References 158–232 appear on pp. 264–265.

TABLE III—*Continued*

RING-SUBSTITUTED CINNAMIC ACIDS

Substituted Benzaldehyde (or Other Carbonyl Component)	Acid Components	Conditions		Substituted Cinnamic Acid (or Other Product)*	Yield, %	Reference†
		Temperature, °C.	Time, hours			
3-Methoxy-4-hydroxy-5-chloro-	Ac_2O (4 *m*) + NaOAc (2 *m*)	Refl.	3	3-Methoxy-4-acetoxy-5-chloro-	95	216
3,4-Methylenedioxy-	Ac_2O (1.8 *m*) + NaOAc (1 *m*)	Refl.	6–7	3,4-Methylenedioxy-	..	217
	Malonic (1.1 *m*) + NH_3 (1 *m*)	100	2		85, 45	60, 30
	Malonic (1.2 *m*) + C_5H_5N + $C_5H_{11}N$	100	2		85–90	185
	Same	20	4 weeks		83	86
	Malonic (1 *m*) + C_5H_5N (0.15 *m*)	100	4		95	87, 87*b*
3,4-Methylenedioxy-6-nitro-	Ac_2O (2.3 *m*) + NaOAc (1.7 *m*)	Refl.	3	3,4-Methylenedioxy-6-nitro-	..	217
3,4-Carbonyldioxy-	Malonic acid + HCO_2H	65	10	3,4-Carbonyldioxy- (after decarboxylation)	60	218
3,4-Dimethoxy-	Ac_2O (5 *m*) + NaOAc (2 *m*)	170	20	3,4-Dimethoxy-	40	210
	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180–200	8		20	28
	Malonic (1.9 *m*) + C_5H_5N + $C_5H_{11}N$	100	2		85	198
	Malonic (1 *m*) + C_5H_5N (0.15 m)	70–100			60	87*j*
3,4-Dimethoxy-2,6-dibromo-	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180–200	8	3,4-Dimethoxy-2,6-dibromo-	6	28
3,4-Dimethoxy-5-nitro-	Ac_2O (3 *m*) + NaOAc (2 *m*)	180	8	3,4-Dimethoxy-5-nitro-	60	219
3,4-Dimethoxy-6-nitro-	Malonic (1 *m*) + $C_5H_{11}N$	125	3	3,4-Dimethoxy-6-nitro-	70	220

3-Methoxy-4-ethoxy-	Malonic (1.2 *m*) + C_5H_5N + $C_5H_{11}N$	100	2–3	3-Methoxy-4-ethoxy-	90	185, 221
3-Ethoxy-4-methoxy-	Malonic acid + C_5H_5N + $C_5H_{11}N$	100	2–3	3-Ethoxy-4-methoxy-	(Good)	221
3,4-Dimethoxy-2-methyl-	Ac_2O + NaOAc	180	12	3,4-Dimethoxy-2-methyl-	..	222
3,5-Dihydroxy-	Malonic (1 *m*) + $C_5H_{11}N$ + EtOH	100	1	3,5-Dihydroxy-	..	223
3-Hydroxy-5-methoxy-	Malonic (1.5 *m*) + $C_5H_{11}N$ + EtOH	100	1	3-Hydroxy-5-methoxy-	..	224
3,5-Dimethoxy-	Malonic (1.2 *m*) + $C_5H_{11}N$ + EtOH	100	1	3,5-Dimethoxy-	..	223
2,3,4-Trihydroxy-	Malonic (2 *m*) + C_5H_5N + $C_6H_5NH_2$	37	20	(7,8-Dihydroxycoumarin-3-carboxylic acid or *Daphnetin-3-carboxylic acid*)	83	86
2,3-Dihydroxy-4-methoxy-	Ac_2O + NaOAc	180	8	(7-Methoxy-8-hydroxycoumarin)	..	225
	Malonic (1 *m*) + $C_6H_5NH_2$ + EtOH	100			85	225
2,3,4-Trimethoxy-	Malonic (1.2 *m*) + C_5H_5N + $C_5H_{11}N$	100, 115	7	2,3,4-Trimethoxy-	94	185
2,4,5-Trimethoxy-	Malonic (2 *m*) + C_5H_5N + $C_5H_{11}N$	100, 115	2, $\frac{1}{2}$	2,4,5-Trimethoxy-	80	226
2,4,6-Trimethoxy-	Malonic (2 *m*) + C_5H_5N	100	3	2,4,6-Trimethoxy-	70	227
3,4,5-Trihydroxy-	Malonic (1 *m*) + $C_5H_{11}N$	100	$\frac{1}{2}$	3,4,5-Trihydroxy-	50	228
	Ac_2O (20 g.) + NaOAc (1 g.)	155	18	3,4,5-Triacetoxy-	..	229
3,5-Dimethoxy-4-hydroxy-	Malonic (4 *m*) + CH_3CO_2H	100, 220	16, $\frac{1}{10}$	3,5-Dimethoxy-4-hydroxy- or *sinapic acid*	80	230
3,4,5-Trimethoxy-	Ac_2O (7 *m*) + NaOAc (3 *m*)	145	5	3,4,5-Trimethoxy-	60	231
	Malonic (1.2 *m*) + C_5H_5N + $C_5H_{11}N$	100	12		80	185
2-Acetamido-5-nitro-	Ac_2O (3 *m*) + NaOAc (1.5 *m*)	160	8	(6-Nitrocarbostyryl)	..	232
4-Acetamido-	Malonic acid + C_5H_5N + $C_5H_{11}N$	100		4-Acetamido-	78	74
4-Acetamido-3-nitro-	Ac_2O (3 *m*) + NaOAc (1.5 *m*)	165	7		..	232
4-Dimethylamino-	Ac_2O (2.1 *m*) + NaOAc (0.7 *m*)	180–200	8	4-Dimethylamino-	0	29
	Ac_2O (2.1 *m*) + KOAc (0.7 *m*)	180–200	8		5	29
	Malonic (1 *m*) + C_5H_5N + $C_5H_{11}N$	100			85	74

* A name in italics is synonymous to that immediately preceding.
† References 158–232 appear on pp. 264–265.

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CHAPTER 9

THE ACETOACETIC ESTER CONDENSATION AND CERTAIN RELATED REACTIONS

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CONTENTS

PAGE

MECHANISM 267

SCOPE AND LIMITATIONS 270
Side Reactions 272
Cyclizations (Dieckmann Reaction) 274
Acylation of Esters with Acid Chlorides 275

EXPERIMENTAL CONDITIONS AND PROCEDURES 276
Choice of Base 276
Selection of Experimental Conditions with Sodium Alkoxides 278
Procedures 279
Powdered Sodium 279
Alcohol-Free Sodium Alkoxides 279
Self-Condensation of Various Alkyl Acetates, Ethyl Propionate, and Ethyl Butyrate in the Presence of Sodium Alkoxides 280
Forced Self-Condensation of Ethyl Esters of *n*-Valeric and Higher Aliphatic Acids in the Presence of Sodium Ethoxide 281
Condensation of Two Different Esters in the Presence of Sodium. Preparation of Ethyl γ,γ-Diethoxyacetoacetate and Ethyl Benzoylacetate . . . 282
Self-Condensation Followed by Cyclization. Preparation of Ethyl Succinylsuccinate by the Use of Sodium Ethoxide or Sodium 283
Condensation of Two Different Esters Followed by Cyclization. Preparation of 3,5-Dicarboethoxycyclopentanedione-1,2 284
Selection of Experimental Conditions with Triphenylmethylsodium 284
Procedures 286
Triphenylmethylsodium 286
Self-Condensation. Ethyl α-Isovalerylisovalerate 288
Mixed Ester Condensation. Ethyl α-Ethoxalylisobutyrate 288

EXAMPLES OF THE ACETOACETIC ESTER CONDENSATION 289

SURVEY OF METHODS OF SYNTHESIS OF SIMPLE β-KETOESTERS 297

MECHANISM

The acetoacetic ester condensation* consists in the reaction, in the presence of certain bases, of an ester having hydrogen on the α-carbon atom with a second molecule of the same ester or with another ester (which may or may not have hydrogen on the α-carbon atom) to form a β-ketoester. The bases capable of effecting such reactions include sodium alkoxides, triphenylmethylsodium, sodium amide, and certain Grignard reagents such as mesitylmagnesium bromide and isopropylmagnesium bromide; also, metallic sodium effects certain condensations, the sodium alkoxide which is formed in the reaction mixture probably serving as the active condensing agent.[1] The classical example of the acetoacetic ester reaction is the formation of acetoacetic ester itself by condensation of ethyl acetate by means of sodium ethoxide, for which the following reaction may be written.

$$CH_3CO_2C_2H_5 + CH_3CO_2C_2H_5 + NaOC_2H_5 \rightarrow CH_3C(ONa){=}CHCO_2C_2H_5 + 2C_2H_5OH$$

The reaction probably involves an ionic mechanism,[2, 3] the first step of which is an acid-base exchange; in the presence of the ethoxide ion the hydrogen on the α-carbon atom is ionized as a proton to form the ester anion (enolate anion), which is probably a resonance hybrid of the two structures $^{-}CH_2{-}C{=}O(OC_2H_5)$ and $CH_2{=}C{-}O^{-}(OC_2H_5)$.

$$(1) \qquad CH_3CO_2C_2H_5 + {}^{-}OC_2H_5 \rightleftarrows (CH_2CO_2C_2H_5)^{-} + C_2H_5OH$$

The second step involves the condensation of the ester anion with the carbonyl group of a molecule of unchanged ester, presumably forming an intermediate anion (with the charge on the oxygen) which, on release of the ethoxide ion, forms acetoacetic ester.

$$(2) \quad CH_3C(=O)(OC_2H_5) + (CH_2CO_2C_2H_5)^{-} \rightleftarrows CH_3C(O^{-})(OC_2H_5){-}CH_2CO_2C_2H_5 \rightleftarrows CH_3COCH_2CO_2C_2H_5 + {}^{-}OC_2H_5$$

* This type of condensation is frequently called a Claisen reaction—a term that is used also for certain other types of condensation effected by bases, including ketone-ester condensations to form 1,3-diketones and such aldol reactions as the condensations of ethyl acetate with benzaldehyde to form ethyl cinnamate and of acetophenone with benzaldehyde to form benzalacetophenone.

[1] Snell and McElvain, *J. Am. Chem. Soc.*, **53**, 2310 (1931).

[2] Hauser and Renfrow, *J. Am. Chem. Soc.*, **59**, 1823 (1937).

[3] Hauser, *J. Am. Chem. Soc.*, **60**, 1957 (1938); Arndt and Eistert, *Ber.*, **69**, 2384 (1936).

Acetoacetic ester is then converted into its anion by the action of the ethoxide ion; this third step involves an acid-base reaction in which a hydrogen on the α-carbon atom of the β-ketoester is ionized.

$$(3)\quad CH_3COCH_2CO_2C_2H_5 + {}^{-}OC_2H_5 \rightleftarrows (CH_3COCHCO_2C_2H_5)^{-} + C_2H_5OH$$

Evidence that esters form anions according to the first step of the mechanism is furnished by the racemization of esters of optically active disubstituted acetic acids in the presence of ethoxide ion,[4] and by the hydrogen-deuterium exchange of ethyl acetate and other esters with α-hydrogen atoms in the presence of this base and deutero alcohol.[5] That ester anions are the active intermediates in the condensation is shown by the fact that they may be prepared by means of the stronger base, triphenylmethyl ion, and condensed with esters or other reagents.[6, 7, 8, 9]

With ethoxide ion and most esters the equilibrium of the first step is on the side of unchanged ester, and in order for this base to effect the condensation the β-ketoester formed must be converted largely into its anion, that is, the third step must take place. With triphenylmethyl ion, however, the equilibrium of the first step is on the side of the ester anion, and the third step is not required for the condensation, although this acid-base reaction does take place when the β-ketoester has an enolizable hydrogen. Thus, in the presence of the triphenylmethyl ion, ethyl isobutyrate may be condensed with ethyl benzoate to form ethyl benzoyldimethylacetate [10] even though this β-ketoester is incapable of forming an enolate anion. Ethyl isobutyrate also undergoes self-condensation in the presence of the triphenylmethyl ion (but not in the presence of ethoxide ion) to form ethyl isobutyrylisobutyrate,[2] which is converted into its anion by the ethyl isobutyrate anion or the triphenylmethyl ion; the hydrogen on the γ-carbon atom of the β-ketoester is involved in this third step.[11] These reactions may be represented as follows.

$$HC(CH_3)_2CO_2C_2H_5 + (C_6H_5)_3C^{-} \rightleftarrows [C(CH_3)_2CO_2C_2H_5]^{-} + (C_6H_5)_3CH$$

$$C_6H_5CO_2C_2H_5 + [C(CH_3)_2CO_2C_2H_5]^{-} \rightleftarrows C_6H_5COC(CH_3)_2CO_2C_2H_5 + {}^{-}OC_2H_5$$

[4] Kenyon and Young, *J. Chem. Soc.*, 216 (1940).
[5] Brown and Eberly, *J. Am. Chem. Soc.*, **62**, 113 (1940).
[6] Schlenk, Hillemann, and Rodloff, *Ann*, **487**, 135 (1931).
[7] Muller, Gawlick, and Kreutzmann, *Ann.*, **515**, 97 (1934).
[8] Hauser and Renfrow, *Org. Syntheses*, **19**, 43 (1939).
[9] Hudson and Hauser, *J. Am. Chem. Soc.*, **62**, 2457 (1940).
[10] Renfrow and Hauser, *J. Am. Chem. Soc.*, **60**, 463 (1938).
[11] Hudson and Hauser, *J. Am. Chem. Soc.*, **61**, 3568 (1939).

$$HC(CH_3)_2CO_2C_2H_5 + [C(CH_3)_2CO_2C_2H_5]^- \rightleftarrows HC(CH_3)_2COC(CH_3)_2CO_2C_2H_5 + {}^-OC_2H_5$$

$$HC(CH_3)_2COC(CH_3)_2CO_2C_2H_5 + [C(CH_3)_2CO_2C_2H_5]^- \rightleftarrows [C(CH_3)_2COC(CH_3)_2CO_2C_2H_5]^- + HC(CH_3)_2CO_2C_2H_5 \text{ or } (C_6H_5)_3CH$$

$$\text{or } (C_6H_5)_3C^-$$

The reversibility of the acetoacetic ester condensation is well established. Certain β-ketoesters, especially those having one or two substituents on the α-carbon atom, are cleaved by alcoholic sodium ethoxide to form esters. Thus, although ethyl α-propionylpropionate is formed by the self-condensation of ethyl propionate in the presence of sodium ethoxide, when treated with alcoholic sodium ethoxide it reverts to ethyl propionate;[12] similarly, ethyl diethylacetoacetate is cleaved by alcoholic sodium ethoxide to form ethyl diethylacetate and ethyl acetate.[12]

$$CH_3CH_2COCH(CH_3)CO_2C_2H_5 \xrightarrow[C_2H_5OH]{NaOC_2H_5} 2CH_3CH_2CO_2C_2H_5$$

$$CH_3COC(C_2H_5)_2CO_2C_2H_5 \xrightarrow[C_2H_5OH]{NaOC_2H_5} HC(C_2H_5)_2CO_2C_2H_5 + CH_3\dot{C}O_2C_2H_5$$

An interesting example is the reversion of the product from ethyl isobutyrate and ethyl benzoate. Although ethyl benzoyldimethylacetate is obtained by short treatment of these esters with triphenylmethylsodium,[10] on standing in the presence of sodium ethoxide and triphenylmethane (both of which are by-products of the condensation) it reverts to ethyl benzoate and ethyl isobutyrate, the latter undergoing self-condensation to form ethyl isobutyrylisobutyrate which is converted into its sodium derivative.[13] These reactions can be followed from the ionic equations represented above.

There seems little doubt that the acetoacetic ester condensation is influenced in the first step by the acidic strength of the ester [5] and by the basic strength of the condensing agent,[2] in the second step by the rate and position of equilibrium of the reaction of the ester anion with ester,[14] and in the third step by the acidic strength of the β-ketoester and the strength of the base. At least with triphenylmethylsodium the first and third steps are relatively rapid and complete and the second step is relatively slow. Apparently, the influence of structure on the overall reaction is most pronounced in the second step.[14] In general, it may be

[12] Dieckmann, *Ber.*, **33**, 2670 (1900).
[13] Hudson and Hauser, *J. Am. Chem. Soc.*, **62**, 62 (1940).
[14] Abramovitch and Hauser, unpublished observations.

stated that the acetoacetic ester type of condensation will take place when a base is formed which is weaker than that used as the condensing agent. Thus, in the formation of ethyl acetoacetate from ethyl acetate and sodium ethoxide, the enolate anion, $(CH_3COCHCO_2C_2H_5)^-$, is weaker than the ethoxide ion, and in the formation of ethyl benzoyldimethylacetate from ethyl isobutyrate and ethyl benzoate in the presence of triphenylmethylsodium the ethoxide ion (a by-product of the condensation) is weaker than the triphenylmethyl ion.

SCOPE AND LIMITATIONS

The acetoacetic ester type of reaction is used to prepare a variety of β-ketoesters and certain other types of compounds. The self-condensation of esters having hydrogen on the α-carbon atom may be effected readily; this amounts to an acylation of the ester by another molecule of the same ester.

$$RCH_2CO_2C_2H_5 + H{-}CHRCO_2C_2H_5 \rightarrow RCH_2COCHRCO_2C_2H_5 + C_2H_5OH$$

$$R_2CHCO_2C_2H_5 + H{-}CR_2CO_2C_2H_5 \rightarrow R_2CHCOCR_2CO_2C_2H_5 + C_2H_5OH$$

The condensation between two different ethyl esters may be indicated as follows.

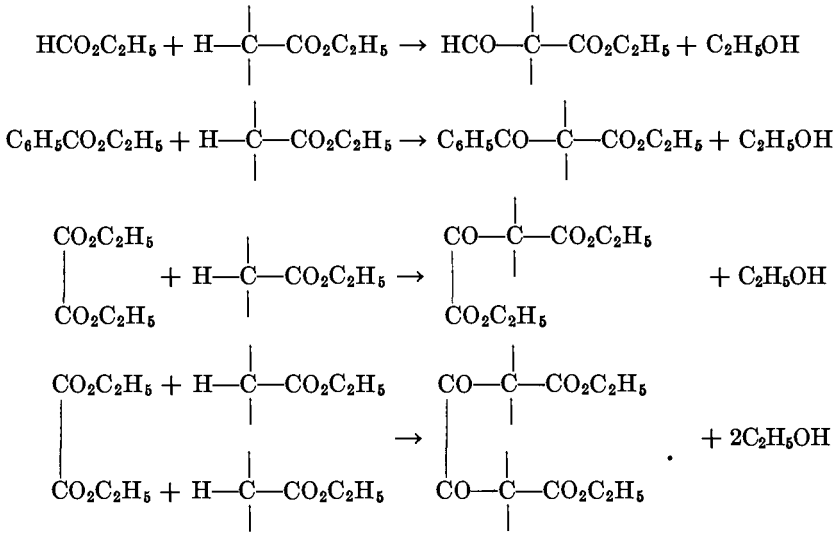
$$RCO_2C_2H_5 + H{-}\overset{|}{\underset{|}{C}}{-}CO_2C_2H_5 \rightarrow RCO\overset{|}{\underset{|}{C}}CO_2C_2H_5 + C_2H_5OH$$

The first ester may be designated as the acylating ester. This condensation is generally satisfactory only when one of the esters (the acylating ester) has no active hydrogen. The condensation of two esters each of which has active hydrogen atoms may result in the formation of a mixture of four different β-ketoesters, the two self-condensation products and the two mixed ester condensation products, although in certain cases one of the latter may be the principal product. Even the application of the special technique of first converting one of the esters largely into its sodium enolate by means of triphenylmethylsodium and then condensing the enolate with an ethyl ester has not been particularly successful thus far, as mixtures of β-ketoesters are still obtained.[15] Certain acylations by means of phenyl or diphenyl esters, however, have been successful.[14]

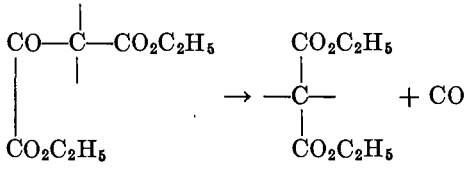
Three of the more common esters which have no active hydrogen and which have served satisfactorily as acylating esters are ethyl formate,

[15] Hudson and Hauser, *J. Am. Chem. Soc.*, **63**, 3156 (1941).

ethyl benzoate, and ethyl oxalate. General reactions with these esters are indicated in the following formulations.



The ethoxalyl derivatives may lose carbon monoxide to form malonic ester derivatives when heated; the reaction serves as a good method for the preparation of certain of these compounds.[16]



Similarly, ethyl formate and ethyl oxalate acylate ethyl crotonate and ethyl sorbate, the vinylogs of ethyl acetate.

$$HCO_2C_2H_5 + CH_3(CH{=}CH)_nCO_2C_2H_5 \rightarrow HCOCH_2(CH{=}CH)_nCO_2C_2H_5 + C_2H_5OH$$
$$(n = 1 \text{ or } 2)$$

$$\begin{array}{l} CO_2C_2H_5 \\ | \\ CO_2C_2H_5 \end{array} + CH_3(CH{=}CH)_nCO_2C_2H_5 \rightarrow \begin{array}{l} COCH_2(CH{=}CH)_nCO_2C_2H_5 \\ | \\ CO_2C_2H_5 \end{array} + C_2H_5OH$$
$$(n = 1 \text{ or } 2)$$

[16] See, for example, Cox and McElvain, *Org. Syntheses*, **17**, 56 (1937).

Apparently, not all esters having hydrogen on the α-carbon atom undergo the acetoacetic ester condensation to form β-ketoesters. Thus, ethyl dichloroacetate when treated with alcoholic sodium ethoxide yields ethyl oxalochloroacetate diethyl acetal and ethyl diethoxyacetate.[17] Although methyl diphenylacetate is converted by triphenylmethylsodium into its sodium enolate (which may be condensed with acid chlorides to form β-ketoesters),[7] the self-condensation of this ester apparently has not been effected. The unsaturated esters, ethyl acrylate [18] and ethyl crotonate,[19] when treated with sodium ethoxide, undergo condensations of the Michael type; however, as indicated above, ethyl crotonate undergoes the acetoacetic ester reaction with certain esters (ethyl oxalate and ethyl formate).

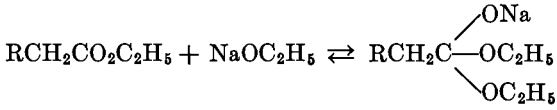
Phenyl acetate fails to condense in the presence of sodium phenoxide.[20] Although purely aliphatic alkyl acetates (in which the alkyl group is methyl, ethyl, propyl, etc.), undergo the normal acetoacetic ester condensation when treated with the corresponding sodium alkoxide (or with metallic sodium), the phenyl-substituted alkyl acetates, benzyl and benzohydryl acetates (and also allyl and cinnamyl acetates) undergo so-called abnormal acetoacetic ester reactions. Thus, benzyl acetate with sodium benzyloxide yields only traces of benzyl acetoacetate,[21] and when heated with metallic sodium this ester yields the "alkylated" product, β-phenylpropionic acid;[21, 22] allyl acetate with sodium undergoes the same type of reaction. Benzohydryl acetate and sodium yield still another "abnormal" product, tetraphenylethane;[23] cinnamyl acetate undergoes the same type of reaction.[23] Benzohydryl acetate with sodium benzohydryloxide yields the "alkylated" product, β,β-diphenylpropionic acid, and other products.[21] It should be pointed out that these so-called abnormal acetoacetic ester reactions presumably require relatively high temperatures (100–300°) and that at least benzyl acetate undergoes the normal acetoacetic ester condensation when treated with triphenylmethylsodium at room temperatures.[24]

Side Reactions

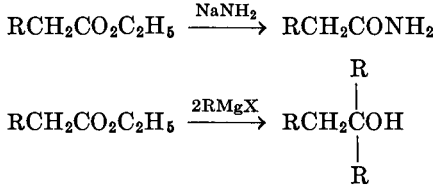
The most important type of side reaction that is encountered when the acetoacetic ester condensation is carried out involves the reaction of the

[17] Cope, *J. Am. Chem. Soc.*, **58**, 570 (1936).
[18] Pechmann and Rohm, *Ber.*, **34**, 428 (1901).
[19] Pechmann and Rohm, *Ber.*, **33**, 3324 (1900).
[20] Fisher and McElvain, *J. Am. Chem. Soc.*, **56**, 1766 (1934).
[21] Bacon, *Am. Chem. J.*, **33**, 68 (1905).
[22] Conrad and Hodgkinson, *Ann.*, **193**, 298 (1878).
[23] Tseou and Wang, *J. Chinese Chem. Soc.*, **5**, 224 (1937).
[24] Hudson and Hauser, unpublished observations.

carbonyl group of the ester with the base used as condensing agent; indeed, this type of reaction is frequently the most characteristic reaction of the ester. Sodium alkoxides may react reversibly with the carbonyl group of the ester.



However, other bases of sufficient strength to ionize the α-hydrogen of esters and effect condensations are also capable of reacting irreversibly with the carbonyl group of esters. Thus, sodium amide effects the ammonolysis of esters,[25] and Grignard reagents react with esters to form ketones or carbinols.



These reactions generally predominate, but sodium (or potassium) amide and certain Grignard reagents react preferentially with the α-hydrogen of certain esters and effect condensations. Although triphenylmethylsodium is capable of reacting with the carbonyl group of esters, this type of reaction occurs apparently only when the ester contains no α-hydrogen; for example, with methyl benzoate a ketone is formed.[26]

$$C_6H_5CO_2CH_3 + (C_6H_5)_3CNa \rightarrow C_6H_5COC(C_6H_5)_3 + NaOCH_3$$

Metallic sodium is capable of reacting with the carbonyl group of esters to form acyloins [27] (RCHOHCOR) and diketones [27] (RCOCOR), but in the presence of excess of ethyl acetate or ethyl propionate, metallic sodium effects only the acetoacetic ester condensation.[28] With ethyl *n*-butyrate or ethyl isobutyrate and sodium, however, the acetoacetic ester condensation does not take place even in the presence of an excess of the ester; instead, acyloins, diketones, and higher-boiling products are formed.[28]

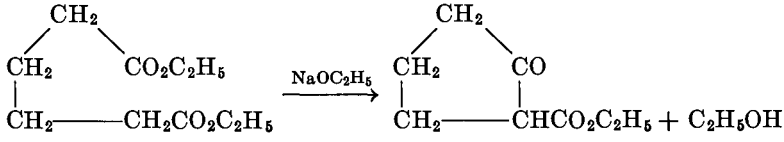
In certain cases, side reactions involving the alcohol portion of the ester are encountered. Thus, in the presence of potassium amide in liquid

[25] See Bergstrom and Fernelius, *Chem. Rev.*, **12**, 142–150 (1933); *ibid.*, **20**, 459 (1937).
[26] Schlenk and Ochs, *Ber.*, **49**, 610 (1916).
[27] Bouveault and Locquin, *Bull. soc. chim.*, [3] **35**, 629 (1906).
[28] Snell and McElvain, *J. Am. Chem. Soc.*, **53**, 750 (1931).

ammonia, β-phenylethyl acetate is converted partly to styrene.[29] The so-called abnormal acetoacetic ester reactions discussed above (p. 272) may also be regarded as other types of side reactions involving the alcohol portion of the ester.

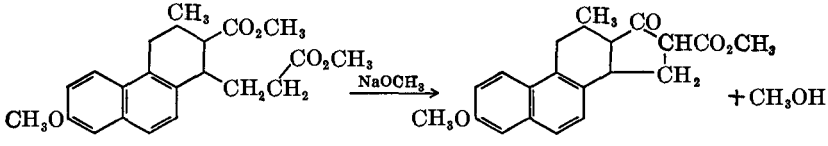
Cyclizations (Dieckmann reaction)

Certain esters having hydrogen on the δ- or ε-carbon atom which is activated (generally by a carbonyl group) undergo intramolecular cyclization. These reactions may be illustrated by the formation of 2-carboethoxycyclopentanone from ethyl adipate.

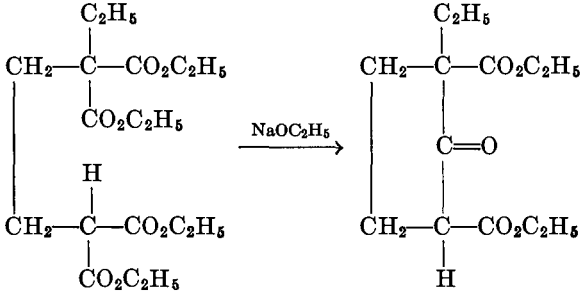


Similarly, ethyl pimelate can be cyclized to a cyclohexanone derivative, but ethyl suberate affords 2-carboethoxycycloheptanone in low yield. The esters of glutaric, azelaic, and sebacic acids fail to cyclize intramolecularly in the presence of sodium ethoxide.

This cyclization has proved particularly useful in preparing polycyclic compounds. For example, the cyclic ketoester which is an intermediate in the synthesis of the sex hormone equilenin can be obtained in practically quantitative yield.[30]



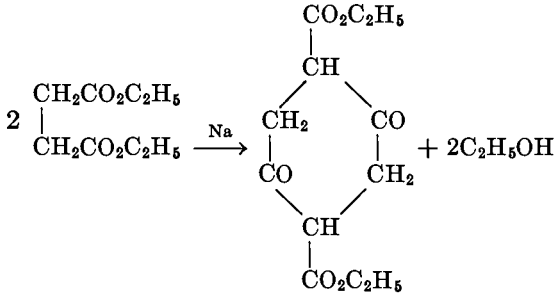
Certain intramolecular cyclizations are accompanied by decarboxylation, illustrated as follows.

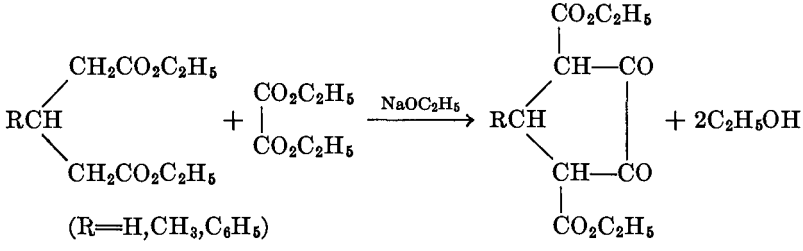


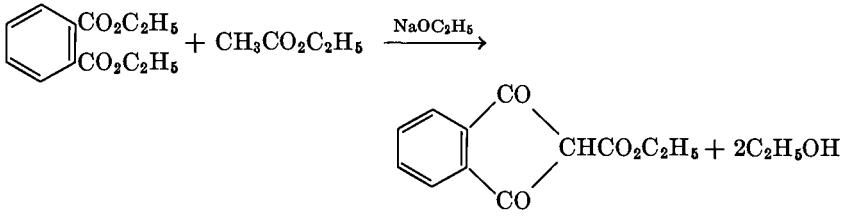
[29] Skell and Hauser, unpublished observations.

[30] Bachmann, Cole, and Wilds, *J. Am. Chem. Soc.*, **62**, 835 (1940).

Five- and six-membered rings may also be formed by intermolecular condensation and cyclization, examples of which may be represented as follows.







The Acylation of Esters with Acid Chlorides

Closely related to the acylation of esters with esters (as occurs in the acetoacetic ester reaction) is the acylation of esters with acid chlorides or anhydrides. For example, ethyl isobutyrate in the form of its sodium enolate (prepared from the ester and triphenylmethylsodium) may be acylated not only with ethyl benzoate [10] or phenyl benzoate,[31] but also with benzoic anhydride [31] or benzoyl chloride; [31] the reactions with the last three reagents (especially the one with the acid chloride), being essentially irreversible, give the best yield of ethyl benzoyldimethylacetate. These reactions may be represented by the following general equa-

[61] Hudson, Dick, and Hauser, *J. Am. Chem. Soc.*, **60**, 1960 (1938).

tion in which X represents ethoxide, phenoxide, benzoate, or chloride groups.

$$C_6H_5COX + Na[C(CH_3)_2CO_2C_2H_5] \rightarrow C_6H_5COC(CH_3)_2CO_2C_2H_5 + NaX$$

The reactions of the sodium enolates of ethyl isobutyrate and other esters of disubstituted acetic acids with various acid chlorides are of particular value for the preparation of α,α-disubstituted β-ketoesters [15] of the type $RCOCR_2CO_2C_2H_5$. The acylation of the sodium enolate of ethyl acetate with acid chlorides does not stop with monoacylation but produces mainly the diacylated acetate [15] $(RCO)_2CHCO_2C_2H_5$.

EXPERIMENTAL PROCEDURES

Choice of Base

The base most commonly used for the acetoacetic ester condensation is the sodium alkoxide that corresponds to the alcohol portion of the ester; for example, sodium ethoxide is used with ethyl esters. These bases are generally readily available and usually they produce no by-products except the corresponding alcohol, which is easily separated from the condensation product. Under the proper conditions, sodium alkoxides effect the condensation of acetates and most esters that have two hydrogens on the α-carbon atom (in reactions of either two similar or two different ester molecules); two such esters, however, ethyl isovalerate [32] and ethyl *t*-butylacetate,[32] as well as esters that have only one α-hydrogen atom (e.g., ethyl isobutyrate [33]) fail to condense in the presence of sodium ethoxide.

The second most useful base is triphenylmethylsodium, which condenses not only ethyl acetate [14] and presumably all esters that are condensed by sodium alkoxides, but also certain esters that cannot be condensed by means of the latter bases. Thus, triphenylmethylsodium effects the self-condensations of ethyl isovalerate [15] and ethyl isobutyrate [2] and the mixed ester condensations between ethyl isobutyrate and esters with no α-hydrogen, for example, ethyl oxalate.[15] Also, triphenylmethylsodium is the only base that has been found to be generally satisfactory for the condensations of esters with acid chlorides.[15] With the proper equipment, triphenylmethylsodium is readily prepared, and it generally produces no appreciable amounts of by-products except triphenylmethane, which usually may be separated readily from the condensation product.

[32] Roberts and McElvain, *J. Am. Chem. Soc.*, **59**, 2007 (1937).
[33] McElvain, *J. Am. Chem. Soc.*, **51**, 3124 (1929).

Mesitylmagnesium bromide [34] effects the self-condensation of ethyl isovalerate and ethyl isobutyrate (and also ethyl *t*-butylacetate), but the yields of products are not so high as those obtained with triphenylmethylsodium. Apparently, mixed ester condensations have not been attempted with mesitylmagnesium bromide, but it seems likely that at least certain of them might be effected; however, an attempt to condense ethyl isobutyrate with benzoyl chloride by means of mesitylmagnesium bromide has been unsuccessful.[15]

Certain other bases have limited application. Although isopropylmagnesium bromide is not satisfactory for the self-condensation of ethyl acetate or ethyl isovalerate,[34] this Grignard reagent does bring about the self-condensations of ethyl phenylacetate [35] (in which the α-hydrogen is activated by the phenyl group) and of *t*-butyl acetate [24] (in which the carbonyl group is deactivated by the *t*-butyl group). Also, potassium amide effects the self-condensation of *t*-butyl acetate,[24] but sodium amide reacts with ethyl acetate to give only a low yield of acetoacetic ester [36] and with ethyl isobutyrate to give little or none of the β-ketoester.[37] Sodium amide is satisfactory, however, for the cyclization of ethyl adipate [38] (and especially for various ketone-ester Claisen condensations).[25] Sodium *n*-amylacetylide, $NaC{\equiv}C{-}(CH_2)_4CH_3$, has been used for the self-condensation of certain esters.[39]

In general, the appropriate sodium alkoxide would be chosen for a condensation if it is capable of effecting the reaction; if not, triphenylmethylsodium would be chosen unless the triphenylmethane produced is difficult to separate from the condensation product, and in that case, mesitylmagnesium bromide would be tried. In special cases, other bases may be chosen; thus for the self-condensation of ethyl phenylacetate, isopropylmagnesium bromide [35] would be used instead of sodium ethoxide, [32] since a considerably better yield of condensation product is obtained with the Grignard reagent. For the self-condensation of *t*-butyl acetate, triphenylmethylsodium,[14] potassium amide,[24] or isopropylmagnesium bromide [24] may be chosen instead of sodium *t*-butoxide, since the first two bases give as good or better yield of condensation product and this particular sodium alkoxide is rather difficult to prepare; [20] the yield of product with the Grignard reagent is slightly lower than yields obtained with the other bases.

[34] Spielman and Schmidt, *J. Am. Chem. Soc.*, **59**, 2009 (1937).

[35] Conant and Blatt, *J. Am. Chem. Soc.*, **51**, 1227 (1929).

[36] Titherly, *J. Chem. Soc.*, **81**, 1520 (1902); Freund and Speyer, *Ber.*, **35**, 2321 (1902).

[37] Scheibler and Stein, *J. prakt. Chem.*, **139**, 107 (1934).

[38] Haller and Cornubert, *Bull. soc. chim.*, [4] **39**, 1626 (1926); *Compt. rend.*, **179**, 315 (1924).

[39] Moureu and De Lange, *Bull. soc. chim.*, [3] **27**, 378 (1902).

Procedures for condensations using the two most generally applicable bases, sodium alkoxides and triphenylmethylsodium, are described below.

Selection of Experimental Conditions with Sodium Alkoxides

A variety of experimental conditions have been used in acetoacetic ester condensations brought about by sodium alkoxides. In general, the basic procedure involves the reaction of the ester or ester mixture with the sodium alkoxide under a reflux condenser. The time and temperature of reaction vary greatly with different esters, ranging from several minutes to a few days at temperatures from 25° to 140°. The reaction mixture is generally neutralized in the cold with dilute acetic or sulfuric acid, and the condensation product isolated, dried, and distilled in vacuum, or, if solid, recrystallized.

Anhydrous alcohol-free sodium alkoxides are to be preferred for most condensations, although in certain reactions the presence of a little alcohol apparently does not decrease the yield appreciably. Ethyl ethoxalylacetate (sodium salt) is prepared commercially from ethyl acetate and ethyl oxalate using an alcoholic solution of sodium ethoxide.[40] It is convenient to generate the sodium alkoxide in the reaction mixture by means of metallic sodium, but this procedure apparently is satisfactory only for the condensations of ethyl acetate and ethyl succinate (and possibly ethyl propionate) [41] with themselves or with certain other esters, and for certain cyclizations. Generally sodium is used in the form of wire or powder.

With alcohol-free sodium alkoxides, esters should be pure and dry. When metallic sodium is used the ester should contain a little but not too much alcohol; except for the alcohol, the ester should be pure and dry. The apparatus should be dry and protected from moisture of the air by means of a calcium chloride tube or a soda-lime tube. When a stirrer is used, it should be provided with a mercury seal. Ordinarily, no special precautions are taken to exclude atmospheric oxygen. Many condensations (especially self-condensations) are carried out with no solvent other than the ester, which may be present in considerable excess. Other condensations (especially cyclizations) are carried out in dry ether, benzene, or toluene.

Certain departures from the basic procedure have led to improved results. When the self-condensations of higher homologs of ethyl acetate are carried out in the presence of sodium ethoxide, removal (by distillation under reduced pressure) of the alcohol formed during the

[40] Private communication from W. L. Johnson, U. S. Industrial Chemicals, Inc., Baltimore, Md.

[41] See reference 28, p. 755, and reference 33, p. 3130.

reactions generally increases the yields of β-ketoesters. These "forced" reactions are of particular value for the self-condensation of ethyl *n*-valerate and higher esters;[42] the lower esters distil with the alcohol and must be used in considerable excess.[33]

The condensation of two different esters is sometimes carried out by first mixing the acylating ester (which should be incapable of self-condensation) with sodium ethoxide and then adding the other ester and heating the mixture. When an ester tends to condense with itself as readily as with the acylating ester, the yield of mixed-ester condensation product may be improved by adding simultaneously to the acylating ester, at intervals, small portions of the ester to be acylated and approximately equivalent amounts of metallic sodium. Ethyl benzoylacetate is prepared commercially essentially according to this scheme.[40] Also, this procedure is successful for the acylation of ethyl acetate with ethyl diethoxyacetate;[43] this reaction is one of the few examples in which two esters both of which have α-hydrogen can be condensed satisfactorily.

Several procedures have been chosen to illustrate the various techniques and to illustrate the following types of reactions: self-condensation of esters; mixed-ester condensation; intramolecular cyclization; intermolecular self-condensation and cyclization; intermolecular mixed-ester condensation and cyclization. Also, the preparations of powdered sodium and of alcohol-free sodium ethoxide are described.

PROCEDURES

Powdered Sodium.[44] Freshly cut sodium is covered with about ten times its weight of xylene (preferably purified with sodium) in a round-bottomed flask equipped with a reflux condenser, and the mixture is heated until the xylene boils and the sodium melts. The flask is stoppered with a cork, wrapped with a towel, and shaken vigorously while the sodium resolidifies. In this manner, as much as 50–60 g. of sodium may be converted into a very fine powder. The xylene may then be decanted and replaced with another inert solvent.

Alcohol-Free Sodium Alkoxides.[44] Powdered sodium is covered with approximately ten times its weight of inert solvent (purified xylene, benzene, ether, or ligroin) in a flask equipped with a mechanical stirrer, dropping funnel, and a reflux condenser carrying a soda-lime tube. The calculated amount of absolute alcohol (1 mole to 1 gram atom of sodium)

[42] Briese and McElvain, *J. Am. Chem. Soc.*, **55**, 1697 (1933).

[43] Dakin and Dudley, *J. Chem. Soc.*, **105**, 2455 (1914); Johnson and Cretcher, *J. Am. Chem. Soc.*, **37**, 2149 (1915); Johnson and Mikeska, *ibid.*, **41**, 812 (1919).

[44] Houben-Weyl, Vol. II, 1925, p. 748.

is diluted with twice its volume of the inert solvent and added dropwise to the vigorously stirred contents of the flask. When the initial reaction subsides, nearly all the sodium has reacted. The mixture is then refluxed with continuous stirring until the sodium has completely disappeared. The solvent may then be distilled, the last traces being removed under reduced pressure.

Sodium methoxide and sodium ethoxide may be prepared in this manner, but the method is not satisfactory for sodium alkoxides higher than sodium ethoxide; methods of preparation of higher alkoxides are described in the literature.[20]

Ethanol-free sodium ethoxide may also be prepared by adding freshly cut sodium to an excess of absolute ethanol contained in a round-bottomed flask which is immediately connected to a condenser set downward for distillation and to a source of dry nitrogen; a filter flask to which a soda-lime tube is attached is used as a receiver. When the reaction has ceased the excess ethanol is removed by distillation. Dry nitrogen is then admitted and the flask is heated in an oil bath at 150°/20 mm. for one hour. Before use the white cake of sodium ethoxide should be pulverized by stirring or shaking in an atmosphere of nitrogen.

Self-Condensation of Various Alkyl Acetates,[20] Ethyl Propionate,[32] and Ethyl Butyrate [32] in the Presence of Sodium Alkoxides. The self-condensation of ethyl acetate by means of sodium is described in detail in *Organic Syntheses*.[45] The following procedure, involving sodium alkoxides, may be applied to a variety of esters of acetic acid as well as to the ethyl esters of propionic and butyric acids.

In a 500-cc. three-necked flask, fitted with a stirrer, reflux condenser, and a thermometer which dips below the surface of the reaction mixture, are placed 0.2 mole of the alcohol-free alkoxide and 1.2 moles of the corresponding ester. The contents of the flask are heated with stirring to the temperature and for the time indicated in Table I. At the end of the reaction time the flask is surrounded by ice and the reaction mixture is cooled to 10°. The reflux condenser is replaced by a dropping funnel, and 36 g. of 33.3% aqueous acetic acid is added dropwise to the mixture at such a rate that the temperature remains below 15°. When the solid material has completely dissolved, the ester layer is separated and the aqueous layer is extracted with four 50-cc. portions of ether. The combined ester layer and ether extracts, after drying over anhydrous sodium sulfate, is fractionally distilled. The conditions of reaction, the maximum yields, and the boiling points of various β-ketoesters obtained are given in Table I.

[45] Inglis and Roberts, *Org. Syntheses, Coll. Vol.*, **1**, 230 (1932).

TABLE I

SELF-CONDENSATION IN THE PRESENCE OF SODIUM ALKOXIDES

Ester Used	Temperature of Reaction, ° C.	Time of Reaction, hr.	Product	
			Yield, %	B.p./mm.*
Ethyl acetate	78	8	75–76	78–80/16
Ethyl propionate	95	16	46–47 [a]	88-90/12
Ethyl *n*-butyrate	95	32	40–42 [a]	102-105/12
Methyl acetate	57	16–32	57–61	—
n-Propyl acetate	77	16	73	78/11
n-Butyl acetate	115	8	71	90/11
Isobutyl acetate	115	4 [b]	71	84.5/11
Isopropyl acetate	87	8	75	69/11
s-Butyl acetate	87	8	80	79.1/11
t-Butyl acetate	77	32	52	71.5/11

a A higher yield of the β-ketoester is obtained by periodic distillations of portions of the ester together with the alcohol that is formed during the reaction (see following procedure), but considerable excess of the pure ester is required in the process.

b Reaction mixture heated at 115° for four hours and then allowed to stand at room temperature for twelve hours.

Forced Self-Condensation of Ethyl Esters of *n*-Valeric[42] and Higher Aliphatic Acids[42] in the Presence of Sodium Ethoxide. In a 125-cc. modified Claisen flask with a fractionating side arm 35 cm. long are placed 0.1 mole of the purified ester and 0.05 mole of ethanol-free sodium ethoxide (prepared from absolute ethanol and powdered sodium under dry ether, p. 279). The reaction flask is attached to the receiving flask (which is not cooled), and this flask in turn is attached through a soda-lime tower and a safety bottle to a manometer and a water pump. The safety bottle contains a stopcock which can be opened to the air and by which the pressure in the system can be regulated. The reaction flask is then heated carefully in an oil bath to a temperature and under a pressure that cause a moderate, but not too vigorous, evolution of ethanol vapor as shown by the ebullition of the reaction mixture. The required temperature and pressure vary with the boiling point of the ester, the more volatile ones requiring lower reaction temperatures and higher pressures in order to avoid loss of ester. Consequently the time necessary for the completion of the reaction in these cases is increased. A summary of the conditions for the reaction of the various esters is given in Table II. Column 2 shows the temperatures and column 3 the pressures which are most satisfactory at the beginning of each reaction to ensure a moderate evolution of alcohol. After the reaction has pro-

ceeded for some time the temperature and pressure can be raised and lowered, respectively, without appreciable loss of ester. Column 4 gives the time required for completion of the reaction; at the end of this period the reaction mass ceases ebullition. The reaction product after cooling is treated with the calculated quantity of 30% acetic acid and shaken vigorously until the sodium salt is completely decomposed. The ketoester is then extracted with 25 cc. of benzene, and the resulting benzene solution, after washing with water, is dried over anhydrous sodium sulfate. The benzene is removed by distillation. Ethyl α-lauryllaurate and ethyl α-myristylmyristate are recrystallized from absolute methanol. The liquid products are purified by distillation. This procedure is quite satisfactory for all the ketoesters except ethyl α-pelargonylpelargonate and ethyl α-caprylcaprate, both of which suffer a small amount of pyrolysis to the corresponding ketone, which appears as a low-boiling solid fraction in the distillate. The yields and boiling (or melting) points of the β-ketoesters are shown in Table II (last column).

TABLE II

CONDITIONS AND TIME REQUIRED FOR FORMATION OF β-KETOESTERS

$RCH_2COCH(R)CO_2C_2H_5$

Ester Used, Ethyl	Reaction Temperature, ° C.	Reaction Pressure, mm.	Time for Completion, hr.	Ketoester	
				Yield, %	B.p./mm. or m.p., ° C.
Valerate	89–90	120–130	7–8	77	109–110/5
Caproate	90–95	75–80	7–8	80	132–133/5
Heptoate	90–95	60–65	7	78	147–148/5
Caprylate	90–95	20–25	5	84	173–175/5
Pelargonate	100–105	15–20	4–5	74	195–200/5
Caprate	105–110	15–20	4	74	220–225/5
Laurate	120–125	15–20	4	79	28–29 (m.p.)
Myristate	125–130	15–20	4	84	37–38 (m.p.)

Condensation of Two Different Esters[46] in the Presence of Sodium. Preparation of Ethyl γ,γ-Diethoxyacetoacetate[43] and Ethyl Benzoylacetate.[40, 47] In a three-necked flask fitted with a stirrer, a dropping

[46] For a detailed procedure for the condensation of ethyl oxalate with ethyl propionate in the presence of sodium ethoxide, see Cox and McElvain, *Org. Syntheses*, **17**, 54 (1937).

[47] Yuoh Fong Chi and Yung Mao Lee, *Trans. Science Soc. China*, **8**, 87–89 (1934).

funnel, and a reflux condenser carrying a calcium chloride tube, 66 g. (0.49 mole) of ethyl diethoxyacetate is heated to 85–90° and portions of 2 g. of sodium wire and 9 cc. of ethyl acetate are added at half-hour intervals until 34 g. (1.5 atoms) of sodium and 130 g. (1.5 moles) of ethyl acetate have been introduced. The reaction is quite vigorous at first, but after it subsides the sodium and ethyl acetate can be added a little more rapidly; the seventeen additions can be made in about six hours. The brown, viscous reaction mixture is stirred continuously, and stirring and heating at 85–90° are continued for four hours after the last addition of sodium and ethyl acetate. Ethanol (30 cc.) is added to dissolve the residual sodium, and then the oil, cooled somewhat but not allowed to become too viscous, is poured into a mixture of 130 cc. of concentrated hydrochloric acid and 130 g. of ice. The oily layer is immediately separated, and the aqueous layer is extracted once with a small quantity of ether. The oily layer and ether extract are combined, washed with sodium carbonate solution, dried, and the ether and ethanol distilled on a bath at 100°. Fractional distillation of the residue gives 76 g. (71%) of ethyl γ,γ-diethoxyacetoacetate boiling at 112°/4–6 mm. A considerable amount of ethyl acetoacetate passes over in the fore-run, along with some ethyl diethoxyacetate.

By a similar procedure ethyl benzoylacetate is obtained in 55–77% yield from ethyl acetate, ethyl benzoate, and sodium.[47] Ethyl benzoylacetate is prepared commercially essentially in this manner [40] in a yield of 68%; much ethyl acetoacetate is also obtained in the same reaction.[40]

By a similar procedure methyl benzoylacetate is obtained in 45–85% yield from methyl acetate, methyl benzoate, and sodium.[40, 48] The method is not very satisfactory, however, for the acylation of ethyl acetate with its purely aliphatic homologs.[48]

Self-Condensation Followed by Cyclization.[49] Preparation of Ethyl Succinylsuccinate by the Use of Sodium Ethoxide[50] or Sodium.[51] To 29 g. (0.43 mole) of ethanol-free sodium ethoxide covered with 140 cc. of dry ether is added 38 g. (0.21 mole) of ethyl succinate. The mixture is refluxed three or four days. The ether is then distilled and the residue is neutralized in the cold with dilute sulfuric acid. The crude crystalline ester is collected and washed with water. It is dissolved in 200 cc. of

[46] Wahl and Doll, *Bull. soc. chim.*, [4] **13**, 265 (1913); Wahl, *ibid.*, [4] **3**, 946 (1908); Wahl and Meyer, *ibid.*, [4] **3**, 957 (1908).

[49] For the cyclization of a number of esters of polyfunctional acids, see Dieckmann, *Ann.*, **317**, 51 (1901); for a detailed procedure for the cyclization of ethyl adipate, see (*a*) Pinkney, *Org. Syntheses*, **17**, 30 (1937), and (*b*) Linstead and Meade, *J. Chem. Soc.*, 940 (1934).

[50] Piutti, *Gazz. chim. ital.*, **20**, 167 (1890).

[51] Upenski and Turin, *Chem. Zentr.*, III, 754 (1923).

95% ethanol, decolorized with 1 g. of charcoal, and allowed to crystallize. The yield of ethyl succinylsuccinate, m.p. 126–127°, is about 60%.

When sodium is used, the procedure involves the addition of a slight excess of powdered [52] sodium (27 g., 1.17 atom) to ethyl succinate (75 g., 0.43 mole) containing a small amount (4 cc.) of absolute ethanol. After the initial reaction, which may require cooling to prevent flooding of the reflux condenser, the mixture is heated to 60° for five hours, then to 100° for two hours, and finally to 110° for twenty-five hours. It is then cooled, added *cautiously* to cold dilute sulfuric acid, and worked up as just described; the yield is about 60%.

Condensation of Two Different Esters Followed by Cyclization. Preparation of 3,5-Dicarboethoxycyclopentanedione-1,2.[53] To 34 g. (0.5 mole) of ethanol-free sodium ethoxide, covered with 200 cc. of anhydrous ether and contained in a flask fitted with a reflux condenser, is added 36.5 g. (0.25 mole) of ethyl oxalate. After mixing thoroughly, 47 g. (0.25 mole) of ethyl glutarate is added over about fifteen minutes and the mixture is heated to refluxing. After approximately one hour, when solution is complete, the ether is distilled and the residue is heated to 120–130° until it changes to a yellow solid (about three hours). The reaction mixture is cooled and washed with ice-cold dilute sulfuric acid (10%), then with ice-water. After drying in the air (twenty-four hours) the crude product, m.p. 90–104°, weighs 43 g. It is recrystallized from 80 cc. of 95% ethanol, and 30 g. (50%) of pure material (m.p. 115°) is obtained.

It is reported that ethyl β-methylglutarate condenses with ethyl oxalate to give an almost quantitative yield [53] of 4-methyl-3,5-dicarboethoxycyclopentanedione-1,2, melting at 108°, and that ethyl β-phenylglutarate with ethyl oxalate gives an excellent yield [53] of the 4-phenyl derivative, m.p. 160–161°. Ethyl β,β-dimethylglutarate with ethyl oxalate gives only a low yield [53] of the 4,4-dimethyl derivative by this procedure, but a considerably better yield is obtained using the corresponding methyl esters and sodium methoxide.[54]

Selection of Experimental Conditions with Triphenylmethylsodium

The first step in procedures for carrying out self-condensations of esters, mixed ester condensations, or ester acid chloride condensations by means of triphenylmethylsodium consists in converting the ester to be acylated into its sodium enolate. This is done simply by adding the

[52] Jeaurenaud, *Ber.*, **22**, 1282 (note 4) (1889).
[53] Dieckmann, *Ber.*, **32**, 1930 (1899); *Ber.*, **27**, 965 (1894).
[54] Komppa, *Ann.*, **368**, 137 (1909).

ester to an equivalent amount of triphenylmethylsodium in ether solution. The formation of the enolate is indicated by the fading or disappearance of the characteristic deep red color of the base. Self-condensation of the ester is effected merely by allowing the enolization mixture to stand, usually at room temperature; the enolate anions are acylated by molecules of unchanged ester with which they are in equilibrium. The acylation of the sodium enolate with other esters or with acid chlorides is effected by adding an equivalent amount of the reagent to the enolization mixture as soon as the characteristic deep red color of the triphenylmethylsodium has nearly or completely disappeared; in this way, self-condensation of the original ester is minimized. The acylation of an ester by another ester or acid chloride will, of course, be successful only when this reaction takes place more rapidly than the self-condensation of the original ester. The reaction mixtures are worked up by first neutralizing them (except when acid chlorides are used) with acetic acid, and extracting the mixture with water. The ether solution (which may be washed with sodium bicarbonate solution) is dried and the ether is distilled. The β-ketoester is isolated from the residue (mainly triphenylmethane) by fractional distillation in vacuum. If the product is a high-boiling liquid (b.p. above 150°/15 mm.), triphenylmethane should be removed before fractionation by cooling and seeding the residue; the solubility of the triphenylmethane is greatly reduced by the addition of one or two volumes of 95% ethanol. Techniques other than distillations may be employed in the isolation of crystalline products or of alkali-soluble products.

The time required for the conversion of an ester into its sodium enolate varies greatly with different esters. For example, with ethyl acetate, the color of the triphenylmethylsodium disappears almost immediately even when the reaction is carried out at 0°, but with ethyl isobutyrate the color changes to light red only after a few minutes at room temperature, while with ethyl diethylacetate there is no noticeable decrease in the depth of color until after a few hours at room temperature. Also, the time required for completion of the acylation varies greatly. For example, the self-condensation of ethyl acetate is practically complete within an hour (a 43% yield of ethyl acetoacetate is obtained within three minutes at room temperature),[31] but the self-condensation of ethyl isobutyrate [2] or ethyl isovalerate [15] requires a day or longer. Acylations of the sodium enolates of esters with acid chlorides or with especially reactive esters such as ethyl oxalate are essentially complete within a few minutes.[15] Although considerable heat is generated in the rapid reactions, no special cooling arrangements are necessary when the triphenylmethylsodium is used in approximately 0.15 molar concentrations (or

less) and at an initial temperature of approximately 20° or less. With more concentrated solutions or when the room temperature is high, the reaction mixture should be cooled by means of an ice bath.

Triphenylmethylsodium is conveniently prepared in almost quantitative yield (90%) by shaking a solution of pure triphenylchloromethane (m.p. 112–113°) in dry ether with an excess of freshly prepared sodium amalgam. Since the base reacts readily with active hydrogen compounds (water, ethanol, etc.) and with oxygen, the materials should be pure and the base should be prepared and used in an atmosphere of dry nitrogen. The base is commonly prepared and used in approximately 0.15 molar concentrations; however, concentrations up to 0.5 molar have been employed.

Procedures have been chosen to illustrate the preparation of triphenylmethylsodium, the self-condensation of an ester, and a mixed ester condensation. An ester acid-chloride condensation is described in detail in *Organic Syntheses*; [8] the reaction on a larger scale is described in the literature.[15]

Procedures

Triphenylmethylsodium.[55, 15] Nine hundred and fifty grams of 1.5% sodium amalgam is prepared in the following manner. In a 250-cc. Pyrex Erlenmeyer flask 14 g. (0.61 atom) of freshly cut sodium is covered to a depth of 2 cm. with high-boiling mineral oil. The flask is heated until the sodium begins to melt. Then 935 g. of mercury, contained in a separatory funnel whose stem passes through a cardboard shield (8 cm. square), is added rapidly to the molten sodium (hood!). The flask is stoppered and shaken until no solid particles of amalgam remain. When the flask has cooled to approximately 80°, or when the amalgam first begins to crystallize, the flask is cooled rapidly to room temperature by swirling in cold water. The oil is decanted, and the amalgam (950 g.) is washed twice with dry benzene or ligroin.

To a mixture of 70 g. (0.25 mole) of triphenylchloromethane (m.p. 112–113°) and 950 g. of freshly prepared 1.5% sodium amalgam in a 2-l. Pyrex glass-stoppered bottle, 1500 cc. of absolute ether is added. The glass stopper is lubricated with a little Lubriseal and firmly inserted. The bottle is clamped securely in a mechanical shaker which makes a 4- to 5-in. stroke and three to four strokes a second. Shaking is begun; if the temperature of the bottle rises above approximately 40°, shaking is interrupted until the bottle cools somewhat. The characteristic deep red color appears after five to fifteen minutes' shaking. After shaking for three to six hours the bottle is cooled to room temperature and

[55] Renfrow and Hauser, *Org. Syntheses*, **19**, 83 (1939).

removed from the shaker. The stopper is clamped down and the mixture allowed to stand undisturbed overnight. Sodium chloride and particles of mercury settle to the bottom.

The solution is analyzed in the following way. A tube delivering a rapid stream of dry nitrogen is held at the mouth of the bottle while the stopper is loosened and slowly removed. A sample is taken in the conventional manner, by means of a 25-cc. pipette, and delivered into a small separatory funnel containing 25 cc. of distilled water. (The bottle should be restoppered immediately.) The separatory funnel is stoppered and shaken. The aqueous layer is drained into a 250-cc. Erlenmeyer flask, and the ether layer is extracted with two additional 25-cc. portions of distilled water. The combined aqueous extracts are titrated with 0.2 *N* sulfuric acid, methyl red being used as the indicator. The average concentration of the triphenylmethyl sodium is 0.14 to 0.15 mole per liter.

The solution is transferred to a nitrogen-filled 2-l. Erlenmeyer flask by means of a pressure siphon, using nitrogen gas under limited pressure (40–80 mm.). For convenience, the receiving flask should be graduated, and the siphon tube provided with a stopcock. A plug of cotton packed around the delivery tube in the neck of the receiving flask serves to prevent the diffusion of air into the flask. By carefully adjusting the depth to which the siphon tube extends into the bottle, it is possible to transfer 1350–1400 cc. of the supernatant solution without carrying over any of the sludge from the bottom of the bottle. When the transfer is complete, the receiving flask is stoppered tightly. The solution should then be used within a few minutes. The quantity of base available for use is usually 0.20–0.21 mole (80–85%).

By using solid sodium amalgam (3%), much higher concentrations of the base may be prepared without special cooling. The modifications necessary in the preparation of approximately 1 mole of triphenylmethylsodium are given below.

The 3% sodium amalgam prepared as described above from 51 g. of sodium and 1649 g. of mercury is poured while hot into a shallow iron pan and allowed to cool. The mineral oil is decanted, and, by means of a hammer and chisel, the amalgam is broken into pieces measuring about 1 cm. on each edge. The amalgam is washed thoroughly with benzene or ligroin and transferred to a 2-l. Pyrex bottle. A solution of 278 g. (1 mole) of triphenylchloromethane (m.p. 112–113°) in 1500 cc. of dry ether is added, and the bottle is stoppered and shaken in the manner already described. The shaking process should be watched very closely and interrupted whenever necessary in order to avoid overheating. The persistent red color of the base appears after one to two hours of shak-

ing; little heat is generated after the appearance of the color. Shaking is continued until no pieces of solid amalgam remain, and then for two hours longer. The bottle is cooled, removed from the shaker, and allowed to stand, as described above. The solution is then analyzed, by removing a 10-cc. aliquot and diluting with 25 cc. of ether before extraction and titration.

Except when alkylations are to be carried out, it is frequently permissible to use the solution of triphenylmethylsodium without separating it from the sludge of sodium chloride and amalgam. The total volume of solution may be considered to be equal to the volume of the ether employed plus 0.77 cc. per g. of triphenylchloromethane used. When the solution is not separated from the amalgam and when the above volume correction is applied in the calculation of the quantity of base available, yields of 85–93% of the theoretical amount are obtained.

Self-Condensation. Ethyl α-Isovalerylisovalerate.[15] To a solution of 0.21 mole of triphenylmethylsodium in approximately 1400 cc. of ether contained in a 2-l. Erlenmeyer flask, is added 31.8 cc. (27.5 g., 0.21 mole) of ethyl isovalerate (b.p. 134–135°). The flask is stoppered well, shaken to effect complete mixing, and allowed to stand at room temperature for sixty hours. The reaction mixture is then acidified by the addition, with shaking, of 15 cc. (approximately 0.25 mole) of glacial acetic acid. The mixture is extracted with 100 cc. of water. The resulting ether solution is washed with 50-cc. portions of 10% sodium carbonate solution until free from excess acid. The ether solution is dried by shaking with anhydrous sodium sulfate and allowing to stand over Drierite. The solution is filtered and the ether distilled on a water bath. The residue is distilled in vacuum. The fraction boiling up to 170°/15 mm. is redistilled through a 6-in. Widmer column, and the fraction boiling at 118–119°/15 mm. is collected. The yield of ethyl α-isovalerylisovalerate is 13.3 g. (63%).

Mixed Ester Condensation. Ethyl α-Ethoxalylisobutyrate.[15] To a solution of 0.205 mole of triphenylmethylsodium in approximately 1400 cc. of ether, contained in a 2-l. Erlenmeyer flask, is added 27.3 cc. (23.8 g., 0.205 mole) of ethyl isobutyrate (b.p. 111–112°). The flask is stoppered, shaken, and allowed to stand. After five minutes, 27.8 cc. (30 g., 0.205 mole) of ethyl oxalate (b.p. 72–74°/10 mm.) is added slowly and with shaking. The reaction is vigorous, and the mixture may boil gently. After standing for ten minutes at room temperature, the reaction mixture is acidified with 15 cc. of glacial acetic acid and extracted with 100 cc. of water. The resulting ether solution is washed free from excess acid with 50-cc. portions of saturated sodium bicarbonate solution. The ether solution is dried by shaking with anhydrous sodium sulfate and

allowing to stand over Drierite. The solution is filtered and the ether distilled on a water bath. The residue is distilled in vacuum, and the fraction boiling up to 200°/50 mm. is fractionated through a 6-in. Widmer column. The yield of ethyl α-ethoxalylisobutyrate (b.p. 122–123/15 mm.) is 27.2 g. (61%).

EXAMPLES OF THE ACETOACETIC ESTER TYPE OF CONDENSATION

In Table III are listed self-condensations of esters; in Table IV, condensations between different esters; in Table V, intramolecular cyclizations; in Table VI, intermolecular condensations and cyclizations; in Table VII, ester-acid chloride condensations.

TABLE III

SELF-CONDENSATIONS OF ESTERS

Ester	Condensing Agent	Product	Yield, %	Reference
Ethyl acetate	Sodium ethoxide	Ethyl acetoacetate	36–76	56, 20, 32
Ethyl acetate	Sodium ethoxide (forced)	Ethyl acetoacetate	68–80	33, 32
Ethyl acetate	Sodium	Ethyl acetoacetate	28–38	45
Ethyl acetate	Sodium (forced)	Ethyl acetoacetate	72	1
Ethyl acetate	Triphenylmethylsodium	Ethyl acetoacetate	81	14
Ethyl acetate	Sodium amide	Ethyl acetoacetate	8	36
Ethyl acetate	Calcium	Ethyl acetoacetate	20	57
Ethyl acetate	Sodium *n*-amylacetylide	Ethyl acetoacetate	31	39
Methyl acetate	Sodium methoxide	Methyl acetoacetate	57–61	20
n-Propyl acetate	Sodium *n*-propoxide	*n*-Propyl acetoacetate	73	20
Isopropyl acetate	Sodium isopropoxide	Isopropyl acetoacetate	75	20
Isopropyl acetate	Sodium *n*-amylacetylide	Isopropyl acetoacetate	35–40	39
n-Butyl acetate	Sodium *n*-butoxide	*n*-Butyl acetoacetate	71	20
Isobutyl acetate	Sodium isobutoxide	Isobutyl acetoacetate	71	20
Isobutyl acetate	Sodium *n*-amylacetylide	Isobutyl acetoacetate	—	39
s-Butyl acetate	Sodium *s*-butoxide	*s*-Butyl acetoacetate	80	20
t-Butyl acetate	Sodium *t*-butoxide	*t*-Butyl acetoacetate	52	20
t-Butyl acetate	Potassium amide	*t*-Butyl acetoacetate	50	24
t-Butyl acetate	Triphenylmethylsodium	*t*-Butyl acetoacetate	63	14
t-Butyl acetate	Isopropylmagnesium bromide	*t*-Butyl acetoacetate	42	24
Amyl acetate	Sodium *n*-amylacetylide	Amyl acetoacetate	50	39
Phenyl acetate	Sodium phenoxide	Phenyl acetoacetate	0	20
Benzyl acetate	Sodium benzyloxide	Benzyl acetoacetate	Trace	21
Benzyl acetate	Triphenylmethylsodium	Benzyl acetoacetate	25	24
Benzhydryl acetate	Sodium benzhydrylate	Benzhydryl acetoacetate	Trace	21
Ethyl propionate	Sodium ethoxide	Ethyl α-propionylpropionate	46–47	32
Ethyl propionate	Sodium ethoxide (forced)	Ethyl α-propionylpropionate	81	33
Ethyl propionate	Sodium	Ethyl α-propionylpropionate	15–32	41
Ethyl propionate	Sodium *n*-amylacetylide	Ethyl α-propionylpropionate	28	39

Isobutyl propionate	Sodium *n*-amylacetylide	Isobutyl α-propionylpropionate	50	39
Ethyl *n*-butyrate	Sodium ethoxide	Ethyl α-butyrylbutyrate	40–42	32
Ethyl *n*-butyrate	Sodium ethoxide (forced)	Ethyl α-butyrylbutyrate	76	33
Ethyl *n*-butyrate	Sodium	Ethyl α-butyrylbutyrate	0	28
Ethyl *n*-butyrate	Sodium *n*-amylacetylide	Ethyl α-butyrylbutyrate	27	39
Amyl *n*-butyrate	Sodium *n*-amylacetylide	Amyl α-butyrylbutyrate	32–35	39
Ethyl isobutyrate	Sodium	Ethyl α-isobutyrylisobutyrate	0	28
Ethyl isobutyrate	Sodium ethoxide (forced)	Ethyl α-isobutyrylisobutyrate	0	33
Ethyl isobutyrate	Triphenylmethylsodium	Ethyl α-isobutyrylisobutyrate	45–60	2, 14
Ethyl isobutyrate	Mesitylmagnesium bromide	Ethyl α-isobutyrylisobutyrate	27	34
Ethyl *n*-valerate	Sodium ethoxide	Ethyl *n*-valeryl-*n*-valerate	34–35	32
Ethyl *n*-valerate	Sodium ethoxide (forced)	Ethyl *n*-valeryl-*n*-valerate	77	42
Ethyl isovalerate	Sodium ethoxide (forced)	Ethyl α-isovalerylisovalerate	0	32
Ethyl isovalerate	Triphenylmethylsodium	Ethyl α-isovalerylisovalerate	63	15
Ethyl isovalerate	Mesitylmagnesium bromide	Ethyl α-isovalerylisovalerate	51	34
Ethyl *t*-butylacetate	Sodium ethoxide (forced)	Ethyl α,γ-di-*t*-butylacetoacetate	0	32
Ethyl *t*-butylacetate	Mesitylmagnesium bromide	Ethyl α,γ-di-t-butylacetoacetate	32	34
Ethyl caproate	Sodium ethoxide (forced)	Ethyl α-caproylcaproate	80	42
Ethyl heptoate	Sodium ethoxide (forced)	Ethyl α-heptoylheptoate	78	42
Ethyl caprylate	Sodium ethoxide (forced)	Ethyl α-caprylylcaprylate	84	42
Ethyl pelargonate	Sodium ethoxide (forced)	Ethyl α-pelargonylpelargonate	74	42
Ethyl caprate	Sodium ethoxide (forced)	Ethyl α-caprylcaprate	74	42
Ethyl laurate	Sodium ethoxide (forced)	Ethyl α-lauryllaurate	79	42
Ethyl myristate	Sodium ethoxide (forced)	Ethyl α-myristylmyristate	84	42
Ethyl stearate	Mesitylmagnesium bromide	Ethyl α-stearylstearate	27	34
Ethyl phenylacetate	Sodium ethoxide	Ethyl α,γ-diphenylacetoacetate	55	32
Ethyl phenylacetate	Isopropylmagnesium bromide	Ethyl α,γ-diphenylacetoacetate	94	35
Ethyl *p*-chlorophenylacetate	Isopropylmagnesium bromide	Ethyl α,γ-di-*p*-chlorophenylacetoacetate	93	58
Ethyl methoxyacetate	Sodium	Ethyl α,γ-dimethoxyacetoacetate	54	59
Methyl methoxyacetate	Sodium	Methyl α,γ-dimethoxyacetoacetate	40–50	59

[56] Higley, *Am. Chem. J.*, **37**, 299 (1907); Kutz and Adkins, *J. Am. Chem. Soc.*, **52**, 4392 (1930).

[57] Perkin and Pratt, *J. Chem. Soc.*, **95**, 161 (1909).

[58] Ivanov and Spasov, *Bull. soc. chim.*, [4] **49**, 375 (1931).

[59] Pratt and Robinson, *J. Chem. Soc.*, **127**, 168 (1925).

TABLE IV

CONDENSATIONS BETWEEN DIFFERENT ESTERS

Acylating Ester	Ester Acylated	Condensing Agent	Product	Yield, %	Reference
Ethyl propionate	Ethyl acetate	Sodium	Ethyl propionylacetate	11	48
Ethyl *n*-butyrate	Ethyl acetate	Sodium	Ethyl *n*-butyrylacetate	19–22	48
Ethyl *n*-valerate	Ethyl acetate	Sodium	Ethyl *n*-valerylacetate	18	48
Ethyl *n*-heptoate	Ethyl acetate	Sodium	Ethyl *n*-heptoylacetate	22	48
Ethyl isovalerate	Ethyl acetate	Sodium	Ethyl isovalerylacetate	9	48
Ethyl hexahydrobenzoate	Ethyl acetate	Sodium	Ethyl hexahydrobenzoylacetate	15–20	48
Ethyl diethoxyacetate	Ethyl acetate	Sodium	Ethyl γ,γ-diethoxyacetoacetate	71	43
Ethyl diethoxyacetate	Ethyl succinate	Sodium	Ethyl γ,γ-diethoxyacetosuccinate	40–48	60
Ethyl formate	Ethyl acetate	Sodium	Ethyl formylacetate (sodium salt 70% pure)	—	61
Ethyl formate	Ethyl acetate	Sodium ethoxide	Ethyl formylacetate (sodium salt 67% pure)	79	62
Ethyl formate	Ethyl propionate	Sodium ethoxide	Ethyl α-formylpropionate	14	62
Ethyl formate	Ethyl isobutyrate	Triphenylmethylsodium	Ethyl α-formylisobutyrate	16	15
Ethyl formate	Ethyl phenylacetate	Sodium ethoxide	Ethyl formylphenylacetate	90	62, 63,
Ethyl formate	Ethyl succinate	Sodium	Ethyl formylsuccinate	60–70	64
Methyl formate	Methyl succinate	Sodium	Methyl formylsuccinate	35	64
Ethyl formate	Ethyl crotonate	Potassium ethoxide	Ethyl γ-formylcrotonate (crude)	70	65
Ethyl formate	Ethyl sorbate	Potassium ethoxide	Ethyl ϵ-formylsorbate (crude)	73	65
Ethyl oxalate	Ethyl acetate	Sodium or sodium ethoxide	Ethyl oxalylacetate (sodium salt)	60–80	66, 67
Ethyl oxalate	Ethyl acetate	Sodium ethoxide (alc. soln.)	Ethyl oxalylacetate (sodium salt)	78	40
Ethyl oxalate	Ethyl acetate (2 moles)	Sodium or sodium ethoxide	Diethyl ketipate	—	66, 68
Ethyl oxalate	Ethyl propionate	Sodium ethoxide	Ethyl α-oxalylpropionate	60–70	46
Ethyl oxalate	Ethyl *n*-butyrate	Sodium	Ethyl α-oxalyl-*n*-butyrate	Low	66
Ethyl oxalate	Ethyl *n*-butyrate	Sodium ethoxide	Ethyl α-oxalyl-*n*-butyrate	Low	66
Ethyl oxalate	Ethyl isobutyrate	Triphenylmethylsodium	Ethyl oxalyldimethylacetate	61	15
Ethyl oxalate	Ethyl phenylacetate	Sodium ethoxide	Ethyl oxalylphenylacetate (sodium salt)	85	69, 68, 70
Ethyl oxalate	Ethyl hydrocinnamate	Sodium or sodium ethoxide	Ethyl oxalylbenzylacetate	—	71, 66
Ethyl oxalate	Ethyl γ-phenyl-*n*-butyrate	Sodium ethoxide	Ethyl α-oxalyl-γ-phenyl-*n*-butyrate	Good	72
Ethyl oxalate	Phthalid	Sodium ethoxide (alc. soln.)	Oxalylphthalid	57	66

Ethyl oxalate	Ethyl crotonate	Sodium or sodium ethoxide	Ethyl γ-oxalylcrotonate (sodium salt)	40	73
Ethyl oxalate	Ethyl crotonate	Potassium ethoxide	Ethyl γ-oxalylcrotonate (potassium salt)	70	74
Ethyl oxalate	Methyl β-methylcrotonate	Potassium ethoxide	Methyl γ-oxalyl β-methylcrotonate (potassium salt)	86	75
Ethyl oxalate	Ethyl sorbate	Potassium ethoxide	Ethyl ε-oxalylsorbate (potassium salt)	60	76
Ethyl oxalate	Ethyl succinate	Sodium ethoxide	Ethyl oxalylsuccinate	70	77
Ethyl oxalate (2 moles)	Ethyl succinate	Sodium ethoxide	Ethyl α,α′-dioxalylsuccinate (sodium salt)	75	77
Ethyl oxalate	Ethyl glutarate	Sodium ethoxide	Ethyl α-oxalylglutarate	65	78
Ethyl oxalate	Ethyl α-methylglutarate	Sodium ethoxide	Ethyl α-oxalyl α′-methylglutarate (not isolated)	—	79
Ethyl benzoate	Ethyl acetate	Sodium ethoxide	Ethyl benzoylacetate	28–37	80, 80*a*
Ethyl benzoate	Ethyl acetate	Sodium	Ethyl benzoylacetate	55–70	47, 40, 62
Methyl benzoate	Methyl acetate	Sodium	Methyl benzoylacetate	45–85	40, 48
Ethyl benzoate	Ethyl propionate	Sodium ethoxide	Ethyl α-benzoylpropionate	19	80
Ethyl benzoate	Ethyl *n*-butyrate	Sodium ethoxide	Ethyl α-benzoyl-*n*-butyrate	4	80
Ethyl benzoate	Ethyl isobutyrate	Triphenylmethylsodium	Ethyl benzoyldimethylacetate	20	10
Ethyl *o*-anisate	Ethyl acetate	Sodium	Ethyl *o*-anisoylacetate	60	48
Ethyl *p*-anisate	Ethyl acetate	Sodium	Ethyl *p*-anisoylacetate	62	48
Ethyl furoate	Ethyl acetate	Sodium	Ethyl furoylacetate	76	48
Phenyl propionate	*n*-Amyl acetate	Triphenylmethylsodium	*n*-Amyl propionylacetate	30	14
p-Diphenylpropionate	Ethyl acetate	Triphenylmethylsodium	Ethyl propionylacetate	44	14

[60] Rugeley and Johnson, *J. Am. Chem. Soc.*, **47**, 2995 (1925).
[61] Pechmann, *Ber.*, **25**, 1047 (1892).
[62] De Combe, *Ann. chim.*, [10] **18**, 87 (1932).
[63] Wislicenus, *Ber.* **20**, 2930 (1887).
[64] Wislicenus, Boklen, and Reuthe, *Ann.*, **363**, 347 (1908); Rothenburg, *J. prakt. Chem.*, [2] **51**, 144 (note 1) (1895).
[65] Borscheu and Manteuffel, *Ann.* **505**, 193 (1933).
[66] Wislicenus, *Ann.*, **246**, 307–355 (1888).
[67] Wislicenus, *Ber.*, **19**, 3225 (1886).
[68] Wislicenus, *Ber.*, **20**, 591 (1887).
[69] Wislicenus, *Ber.*, **27**, 1091 (1894).
[70] Levene and Meyer, *Org. Syntheses*, **16**, 33 (1936).
[72] Hershberg and Fieser, *Org. Syntheses*, **18**, 24 (1938).
[73] Prager, *Ann.*, **338**, 375 (1905); Lapworth, *Proc. Chem. Soc.*, **16**, 132 (1900).
[74] Wislicenus and Schollkoph, *J. prakt. Chem.*, [2] **95**, 270 (note 3) (1917).
[75] Kuhn and Grundmann, *Ber.*, **69**, 1760 (1936).
[76] Borscheu and Manteuffel, *Ber.*, **65**, 868 (1932).
[77] Wislicenus and co-workers, *Ann.*, **285**, 1–34 (1895); *Ber.*, **22**, 885 (1889).
[78] Gault, *Compt. rend*, **148**, 1113 (1909).
[79] Cox, Kroeker, and McElvain, *J. Am. Chem. Soc.*, **56**, 1174 (1934).
[80] Dorsch and McElvain, *J. Am. Chem. Soc.*, **54**, 2960 (1932).

TABLE V

INTRAMOLECULAR CONDENSATIONS (DIECKMANN REACTION)

Ester	Condensing Agent	Product	Yield, %	Reference
Ethyl adipate	Sodium	2-Carboethoxycyclopentanone	74–86	49*a*, 49*b*
Ethyl adipate	Sodium amide	2-Carboethoxycyclopentanone	70–80	38
Ethyl α-methyladipate	Sodium	2-Carboethoxy-5-methylcyclopentanone	70	49
Ethyl β-methyladipate	Sodium	2-Carboethoxy-4-methylcyclopentanone	60–80	49
Ethyl pimelate	Sodium	2-Carboethoxycyclohexanone	60	49
Methyl ester of β-7-methoxy-2-methyl 2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-propionic acid	Sodium methoxide	Methyl ether of *d,l*-16-carbomethoxy-equilenin	97	30
Ethyl glutarate	Sodium	2-Carboethoxycyclobutanone	0	49
Ethyl suberate	Sodium	2-Carboethoxycycloheptanone	Low	49
Ethyl azelate	Sodium	2-Carboethoxycycloöctanone	0	49
Ethyl sebacate	Sodium	2-Carboethoxycyclononanone	0	49
Ethyl α-carboethoxy-α′-ethyladipate	Sodium ethoxide	2-Ethyl 2,5-dicarboethoxycyclopentanone	Low	81
Ethyl α-ethyl-α,α′-dicarboethoxyadipate	Sodium ethoxide	2-Ethyl 2,5-dicarboethoxycyclopentanone	74	82
Ethyl α,α′-dicarboethoxyadipate	Sodium ethoxide	2,5-Dicarboethoxycyclopentanone and 2-Carboethoxycyclopentanone	31 15	82 82
Methyl α-methyl-β-ethylacrylidenemalonate	Sodium hydroxide (alc. soln.)	4,6-Dimethylsalicylic acid	—	83

[81] Meincke and McElvain, *J. Am. Chem. Soc.*, **57**, 1443 (1935).
[62] Meincke, Cox, and McElvain, *J. Am. Chem. Soc.*, **57**, 1133 (1935).
[63] Meerwein, *Ann.*, **358**, 83 (1908).

TABLE VI

INTERMOLECULAR CONDENSATIONS AND CYCLIZATIONS

Acylating Ester	Ester Acylated	Condensing Agent	Product	Yield, %	Reference
Ethyl succinate	Ethyl succinate	Sodium ethoxide	Ethyl ester of cyclohexanedione-1,4-dicarboxylic acid-2,5	65	50
Ethyl succinate	Ethyl succinate	Sodium	Ethyl ester of above acid	80	51, 32
n-Propyl succinate	*n*-Propyl succinate	Sodium	*n*-Propyl ester of above acid	51	84
Isobutyl succinate	Isobutyl succinate	Sodium	Isobutyl ester of above acid	44	84
Allyl succinate	Allyl succinate	Sodium	Allylester of above acid	—	84
Ethyl oxalate	Ethyl glutarate	Sodium ethoxide (alc. soln.)	3,5-Dicarboethoxycyclopentanedione-1,2	80	53
Ethyl oxalate	β-Methylglutarate	Sodium ethoxide (alc. soln.)	3,5-Dicarboethoxy-4-methylcyclopentanedione-1,2	Good	53
Ethyl oxalate	β-Phenylglutarate	Sodium ethoxide (alc. soln.)	3,5-Dicarboethoxy-4-phenylcyclopentanedione-1,2	Good	53
Methyl oxalate	Methyl β,β-dimethylglutarate	Sodium methoxide	Dimethyl diketoapocamphorate	70	54
Ethyl oxalate	Ethyl β,β-dimethylglutarate	Sodium ethoxide	Diethyl diketoapocamphorate	Low	54 (53)
Ethyl phthalate	Ethyl acetate	Sodium or sodium ethoxide	2-Carboethoxy 1,3-diketohydrindene	Good	66
Ethyl oxalate	Ethyl β-ethoxycrotonate	Potassium ethoxide	Potassium enolate of 3-carboethoxy 4-ethoxycyclopentene-3-dione-1,2	90 (crude salt)	85

[84] Liebermann, *Ann.*, **404**, 287 (1914).
[85] Wislicenus and Schollkoph, *J. prakt. Chem.*, [2] **95**, 281 (1917).

TABLE VII

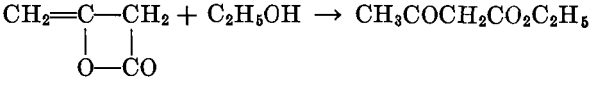
CONDENSATIONS BETWEEN ESTERS AND ACID CHLORIDES

Acid Chloride	Ester	Condensing Agent	Product	Yield, %	Reference
Acetyl chloride	Ethyl isobutyrate	Triphenylmethylsodium	Ethyl α-acetylisobutyrate	51	15
n-Butyryl chloride	Ethyl isobutyrate	Triphenylmethylsodium	Ethyl α-*n*-butyrylisobutyrate	58	15
Isobutyryl chloride	Ethyl isobutyrate	Triphenylmethylsodium	Ethyl α-isobutyrylisobutyrate	55–74	8, 15
Benzoyl chloride	Ethyl isobutyrate	Triphenylmethylsodium	Ethyl α-benzoylisobutyrate	50–65	8, 15
Ethyl chlorocarbonate	Ethyl isobutyrate	Triphenylmethylsodium	Diethyl dimethylmalonate	75	15
Propionyl chloride	Ethyl methylethylacetate	Triphenylmethylsodium	Ethyl propionylmethylethylacetate	52	15
Isovaleryl chloride	Ethyl methylethylacetate	Triphenylmethylsodium	Ethyl isovalerylmethylethylacetate	51	15
Benzoyl chloride	Ethyl methylethylacetate	Triphenylmethylsodium	Ethyl benzoylmethylethylacetate	59	15
Benzoyl chloride	Ethyl diethylacetate	Triphenylmethylsodium	Ethyl benzoyldiethylacetate	62	15
Propionyl chloride (large excess)	Ethyl acetate	Triphenylmethylsodium	Ethyl propionyl acetate and	15	15
			Ethyl dipropionylacetate	39	15
n-Butyryl chloride	Ethyl acetate	Triphenylmethylsodium	Ethyl di-*n*-butyrylacetate	49	15
Acetyl chloride	Methyl diphenylacetate	Triphenylmethylsodium	Methyl acetyldiphenylacetate	—	6
Benzoyl chloride	Methyl diphenylacetate	Triphenylmethylsodium	Methyl benzoyldiphenylacetate	34	6
Methyl chlorocarbonate	Methyl diphenylacetate	Triphenylmethylsodium	Methyl diphenylmalonate	—	6
Benzoyl chloride	9-Carbomethoxyfluorene	Triphenylmethylsodium	9-Benzoyl 9-carbomethoxyfluorene	34	6
Methyl chlorocarbonate	9-Carbomethoxyfluorene	Triphenylmethylsodium	9,9-Dicarbomethoxyfluorene	—	6

BRIEF SURVEY OF METHODS OF SYNTHESIS OF SIMPLE β-KETOESTERS

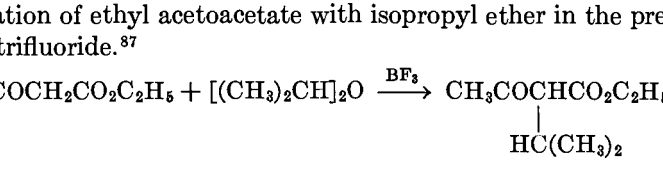
In this section the more important methods of synthesis of various types of simple β-ketoesters are briefly considered.

(A) $CH_3COCH_2CO_2C_2H_5$ and $CH_3COCH_2CO_2R$. For many years ethyl acetoacetate has been prepared in the laboratory and in industry by the self-condensation of ethyl acetate in the presence of sodium. Recently, diketene has become commercially available [86] and is now used to prepare ethyl acetoacetate; the reaction may be represented as follows.



Acetoacetic esters of other alcohols have been prepared satisfactorily by the self-condensation of the appropriate ester (CH_3CO_2R), by the alcoholysis of ethyl acetoacetate, and by the reaction of diketene with the appropriate alcohol; [86] the last method is probably the most convenient when diketene is available.

(B) $CH_3COCHRCO_2C_2H_5$. These β-ketoesters are commonly prepared by the alkylation of the sodium enolate of ethyl acetoacetate with the appropriate alkyl halide. Mixed ester condensations have not been satisfactory for the preparation of β-ketoesters of this type. Ethyl α-isopropylacetoacetate has been prepared in good yield (60–70%) by the alkylation of ethyl acetoacetate with isopropyl ether in the presence of boron trifluoride.[87]



(C) $CH_3COCR_2CO_2C_2H_5$. These β-ketoesters are commonly prepared by the dialkylation of ethyl acetoacetate, that is, by the alkylation of compounds of type B. Ethyl α-acetylisobutyrate (in which R is methyl) has been prepared in good yield (51%) from the sodium enolate of ethyl isobutyrate and acetyl chloride.[15] Methyl α,α-diphenylacetoacetate, $CH_3COC(C_6H_5)_2CO_2CH_3$, has been prepared in a similar manner.[6]

(D) $RCOCH_2CO_2C_2H_5$ (in Which R is an Alkyl or Aryl Group Other Than Methyl). A number of methods have been used for the preparation of β-ketoesters of this type, but none appears to be an entirely satisfactory general method. The following have been used most frequently: (1) the acylation of ethyl acetate by other ethyl esters; (2) the acylation

[86] Boese, *J. Ind. Eng. Chem.*, **32**, 16 (1940).
[87] Hauser and Breslow, *J. Am. Chem. Soc.*, **62**, 2392 (1940).

of acetonitrile by esters and subsequent alcoholysis of the ketonitrile; (3) the acylation of ethyl acetoacetate with acid chlorides or anhydrides and the subsequent ammonolysis or alcoholysis of the product; (4) the reaction of ethyl cyanoacetate with Grignard reagents; (5) the hydration of α,β-acetylenic acids and esterification; (6) the acylation of methyl ketones with ethyl carbonate; and (7) the oxidation of β-hydroxyesters (p. 11).

The acylation of ethyl acetate by another ester (method 1) consists in a mixed ester condensation, which, as already pointed out (p. 270), is in general satisfactory only when the acylating ester has no active hydrogen. The acylation of acetonitrile with esters (method 2) [80, 88] appears to have had a somewhat more limited use than method 1. The nitrile and ester are condensed by means of sodium ethoxide (or triphenylmethylsodium) [89] and the resulting β-ketonitrile alcoholized.[80, 88]

$$RCO_2C_2H_5 + CH_3CN \rightarrow RCOCH_2CN \rightarrow RCOCH_2CO_2C_2H_5$$

Method 3 may be represented as follows.

$$CH_3COCH_2COC_2H_5 \xrightarrow{RCOCl} CH_3COCH(RCO)CO_2C_2H_5 \xrightarrow{NH_3} RCOCH_2CO_2C_2H_5$$

The acylation of ethyl acetoacetate (in the form of its sodium enolate) is readily carried out with acid chlorides or anhydrides,[90] and the ammonolysis (or alcoholysis) of the acyl acetoacetic ester at least in several cases gives good yields of the desired acyl acetate.[91] However, ethyl propionylacetoacetate on ammonolysis gives a mixture of ethyl propionylacetate and ethyl acetoacetate which is difficult to separate.[91]

Method 4 [62, 92] may be represented as follows.

$$RMgX + NCCH_2CO_2C_2H_5 \rightarrow R(NMgX)CCH_2CO_2C_2H_5 \xrightarrow{HOH} RCOCH_2CO_2C_2H_5$$

The Grignard reagent may react not only with the cyanide group, but also with the ester group and with the active hydrogens, resulting in mixtures of products. It has been shown that 1 mole of ethyl cyanoacetate is capable of reacting with 4 moles of Grignard reagent.[93] It should be pointed out, however, that the β-ketoester is not contaminated with ethyl acetoacetate as sometimes happens with methods 1 and 3.

[66] Cox, Kroeker, and McElvain, *J. Am. Chem. Soc.*, **56**, 1172 (1934).
[69] Abramovitch and Hauser, unpublished observations.
[90] Bouveault and Bongert, *Bull. soc. chim.*, [3] **27**, 1046 (1902).
[91] Bouveault and Bongert, *Bull. soc. chim.*, [3] **27**, 1089 (1902).
[92] Blaise, *Compt. rend.*, **132**, 978 (1901).
[93] Brekpot, *Bull. soc. chim. Belg.*, **32**, 386 (1923).

Method 5 [94] may be represented as follows.

$$R{-}C{\equiv}C{-}CO_2H \xrightarrow{HOH} RCOCH_2CO_2H \xrightarrow{C_2H_5OH} RCOCH_2CO_2C_2H_5$$

In general, the hydration of the acetylenic acids appears to give good yields of β-ketoacids,[94] but the esterification of the latter may be difficult. The use of the method is somewhat limited by the fact that the acetylenic acids or hydrocarbons are generally not readily available.

Method 6 [95] may be represented as follows.

$$RCOCH_3 + C_2H_5OCO_2C_2H_5 \xrightarrow{NaOC_2H_5} RCOCH_2CO_2C_2H_5$$

This method consists in heating or digesting the ketone with sodium or potassium ethoxide (or other alkoxide) in a large excess of ethyl carbonate (or other alkyl carbonate). This direct method appears to be very satisfactory for the synthesis of several of the higher acylacetates, but it is not satisfactory for the synthesis of ethyl propionylacetate or ethyl isobutyrylacetate.[95]

In Table VIII are collected the yields that have been reported in the preparation of typical β-ketoesters by these methods. The question

TABLE VIII

PERCENTAGE YIELDS OF ETHYL ACYLACETATES $RCOCH_2CO_2C_2H_5$ BY VARIOUS METHODS

Acyl Group (RCO)	Method 1	Method 2	Method 3	Method 4	Method 5	Method 6
CH_3CH_2CO—	11	—	10–12	10–60	—	?
$CH_3(CH_2)_2CO$—	19–22	17 [97]	75 [a]	40	?	—
$(CH_3)_2CHCO$—	—	36	—	—	—	Poor
$CH_3(CH_2)_3CO$—	18	—	—	15	—	—
$(CH_3)_2CHCH_2CO$—	"Poor"	—	"Excellent" [a]	—	—	60
$CH_3(CH_2)_4CO$—	—	—	"Excellent" [a]	—	50–80	65
$CH_3(CH_2)_5CO$—	22	—	—	—	?	74 [c]
$CH_3(CH_2)_8CO$—	—	—	—	—	76 (crude)	—
C_6H_5CO—	55–70 [d]	42	49–58 [b]	—	—	60

a Yields given are for the methyl acylacetates.
b Over-all yield for both acylation and ammonolysis.
c Yield for *n*-propyl acylacetate.
d With sodium ethoxide as condensing agent the yield is 37%.[60]

[94] Moureu and De Lange, *Bull. soc. chim.*, [3] **29**, 666 (1903).
[95] Wallingford, Homeyer, and Jones, *J. Am. Chem. Soc.*, **63**, 2252 (1941).

mark indicates that the method was used but that no yield was reported. It should be noted that the yields given under method 3, with the exception of ethyl benzoylacetate, are for the ammonolysis reaction only and do not include the yields obtained in the preparation of the acyl acetoacetic esters. The yields given under method 1 are those obtained under "special conditions" with sodium as condensing agent and are calculated without taking into consideration the quantities of starting materials recovered unchanged.

It can be seen from Table VIII that only one of the β-ketoesters listed, ethyl (methyl, in method 3) *n*-butyrylacetate, has been prepared by at least five of the methods. This compound appears to be best prepared by method 3; however, the 75% yield does not include the acylation of ethyl acetoacetate.[91] Ethyl isobutyrylacetate has been prepared in fairly good yield [88] by method 2, while several of the higher aliphatic β-ketoesters have been prepared satisfactorily by methods 3,[91] 5,[94] or 6.[95] Ethyl benzoylacetate has been prepared satisfactorily by methods 1,[47] 2,[80] 3,[96] and 6,[95] the *Organic Syntheses* method [96] being basically the same as 3, and the commercial method [40] basically the same as 1.

None of the methods described above appear to be satisfactory for the preparation of ethyl propionylacetate. One investigator reported a yield of 55% [62] using method 4, but another obtained only a 10–12% yield [93] by this method. Although Fischer and Orth [97] record a yield of 60% by method 4, they point out that the preparation is inferior to method 3, in which the yield is only 10–12%. Ethyl propionylacetate has been obtained in fair yield (44%) by condensing the sodium enolate of ethyl acetate (prepared by means of triphenylmethylsodium) with *p*-diphenyl propionate.[14] In a similar manner, *n*-amyl propionylacetate has been obtained from the sodium enolate of *n*-amyl acetate and phenyl propionate.[14] In both cases essentially pure products were obtained; apparently the only disadvantage of the method is that a relatively large amount of triphenylmethylsodium is required. Ethyl propionylacetate has been prepared also from the sodium enolate of ethyl acetate and a large excess of propionyl chloride, but the yield was only 15%, the main product (39% yield) being the dipropionylacetate.[15] The latter on ammonolysis according to the second step of method 3 gave ethyl propionylacetate in a yield of 50%.[15]

(E) **$RCOCHRCO_2C_2H_5$.** *1. Special Case: $RCH_2COCHRCO_2C_2H_5$, in Which the Two Groups, R, Are the Same.* Most β-ketoesters of this kind are best prepared by the self-condensation of esters of the type $RCH_2CO_2C_2H_5$ or by the action of ethanol on the appropriate diketene.

[96] Shriner, Schmidt, and Roll, *Org. Syntheses*, **18**, 33 (1938).
[97] Fischer and Orth, "Die Chemie des Pyrolles," Vol. I, p. 404 (1934), Leipzig.

The acylation of ketones with ethyl carbonate is also satisfactory in certain cases.[95]

2. General Case: $RCOCHRCO_2C_2H_5$ (the Two Groups, R, May Be the Same or Different). The only general method for the preparation of β-ketoesters of this type consists in the alkylation of unsubstituted β-ketoesters of type D, $RCOCH_2CO_2C_2H_5$. When prepared by method 6 described above, the latter are obtained in the reaction mixture in the form of their sodium enolates and may be alkylated directly.[95] Similarly, the cleavage of acyl acetoacetic esters by means of sodium ethoxide gives the sodium enolates of β-ketoesters of type D, which may be alkylated directly.[98]

$$\underset{\underset{RCO}{|}}{CH_3COCHCO_2C_2H_5} \xrightarrow{NaOC_2H_5} RCOCH_2CO_2C_2H_5 \xrightarrow{RX} RCOCHRCO_2C_2H_5$$

With primary alkyl halides over-all yields of 61–75% are reported.[98] β-Ketoesters of the type $C_6H_5COCHRCO_2C_2H_5$ may be prepared either by the alkylation of the unsubstituted compound,[99] $C_6H_5COCH_2CO_2C_2H_5$, or by the condensation of ethyl benzoate with propionitrile or higher aliphatic nitriles, followed by the alcoholysis of the resulting β-ketonitrile.[80] The latter method has given over-all yields of 37–42% in several different cases.[80]

$$C_6H_5CO_2C_2H_5 + RCH_2CN \xrightarrow{NaOC_2H_5} C_6H_5COCHRCN \xrightarrow{C_2H_5OH} RCOCHRCO_2C_2H_5$$

Ethyl α-benzoylpropionate has been prepared in 37% yield by the acylation of propiophenone with ethyl carbonate.[95]

(F) $RCOCR_2CO_2C_2H_5$. *1. Special Case: $R_2CHCOCR_2CO_2C_2H_5$, in Which the Four Groups Are the Same.* One β-ketoester of this type, namely, ethyl isobutyrylisobutyrate, has been prepared in good yield by the self-condensation of ethyl isobutyrate,[2] and it is possible that others might be prepared in a similar manner. But this β-ketoester is better prepared from the sodium enolate of ethyl isobutyrate and isobutyryl chloride.[15]

2. General Case: $RCOCR_2CO_2C_2H_5$, in Which the Three Groups, R, May Be the Same or Different. Certain β-ketoesters of this type have been prepared by the alkylation of compounds of type E or by the dialkylation of acylacetates (compounds of type D);[99] obviously, the complete synthesis requires several steps and at least in certain cases it is unsatisfactory. A more direct and better method for the synthesis of

[96] Bouveault and Locquin, *Bull. soc. chim.*, [3] **31**, 588 (1904).
[99] See, for example, Hope and Perkin, *J. Chem. Soc.*, **95**, 2042 (1909).

compounds of the type $RCOCR_2CO_2C_2H_5$ consists in condensing the appropriate ester, in the form of its sodium enolate, with a suitable acid chloride.[15] The yields are high (50–75%), and the products are of high purity.

(G) **Miscellaneous β-Ketoesters.** Ethyl ethoxalylacetate and ethyl formylacetate and their homologs are probably best prepared by mixed ester condensations (see p. 271). Also a number of cyclic β-ketoesters are probably best prepared by ester-ester condensations (see pp. 274, 275).

CHAPTER 10

THE MANNICH REACTION

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CONTENTS

PAGE

Introduction 304

The Scope of the Mannich Reaction 307

The Use of Secondary Amines 307

With Ketones 308

With Aldehydes 309

With Acids and Esters 310

With Phenols 311

With Acetylenes 311

With α-Picolines and Quinaldines 312

The Use of Primary Amines 312

With Ketones 312

With Aldehydes 313

With Acids and Esters 313

With Phenols and Acetylenes 314

With α-Picolines and Quinaldines 314

The Use of Ammonia 315

With Ketones 315

With Acids 316

Related Reactions 316

Application of the Mannich Reaction in Synthesis 318

Unsaturated Compounds 318

Preparation of Ethylenic Compounds 318

Preparation of Pyrazolines 319

Use of a Mannich Base as a Source of Unsaturated Ketone for Condensations with an Active Methylene Compound 320

Conversion of a Ketone to Its Next Higher Homolog 322

Syntheses Dependent on the Active Methylene Group in the Aminoketone . 322

Syntheses Dependent on the Activity of the Dimethylamino Group in Dimethylaminomethylphenols 323

Reduction to Aminoalcohols 323

PAGE

Products Derived by Transformation of the Aldehyde Group in β-Dialkylaminoaldehydes . . . 324
β-Monoalkylaminoketone Condensation Products . . . 325
Condensation Products from One Mole of a Primary Amine, Two Moles of Formaldehyde, and Two Moles of a Ketone . . . 326

EXPERIMENTAL CONDITIONS AND PROCEDURES . . . 327
Solvents . . . 327
Nature of Formaldehyde and Time of Reaction . . . 327
Relative Amounts of Components . . . 328
Isolation of Product . . . 328
By-Products . . . 329
Procedures . . . 329
Phenyl β-Piperidinoethyl Ketone Hydrochloride . . . 329
1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-1,2,3,4-tetrahydronaphthalene . . . 329
2,4,6-Tri-(dimethylaminomethyl)-phenol . . . 330

EXAMPLES OF THE MANNICH REACTION . . . 330

INTRODUCTION

The Mannich reaction consists in the condensation of ammonia or a primary or secondary amine, usually as the hydrochloride, with formaldehyde and a compound containing at least one hydrogen atom of pronounced reactivity. The essential feature of the reaction is the replacement of the active hydrogen atom by an aminomethyl or substituted aminomethyl group. The product from acetophenone, formaldehyde, and a secondary amine salt is an example. In the equation the reactive hydrogen atoms are underlined.

$$C_6H_5COC\underline{H}_3 + CH_2O + R_2NH \cdot HCl \rightarrow C_6H_5COC\underline{H}_2CH_2NR_2 \cdot HCl + H_2O$$

The product from a methyl ketone contains reactive hydrogen atoms, and in some cases it is possible to carry the reaction one step further, yielding a compound with two basic groups.

$$C_6H_5COC\underline{H}_2NR_2 \cdot HCl + CH_2O + R_2NH \cdot HCl \rightarrow C_6H_5COCH(CH_2NR_2 \cdot HCl)_2 + H_2O$$

If the substance used in the condensation contains reactive hydrogen atoms on two or more different carbon atoms, then substituted aminomethyl groups may appear at different points in the molecule, leading to a mixture of isomers.

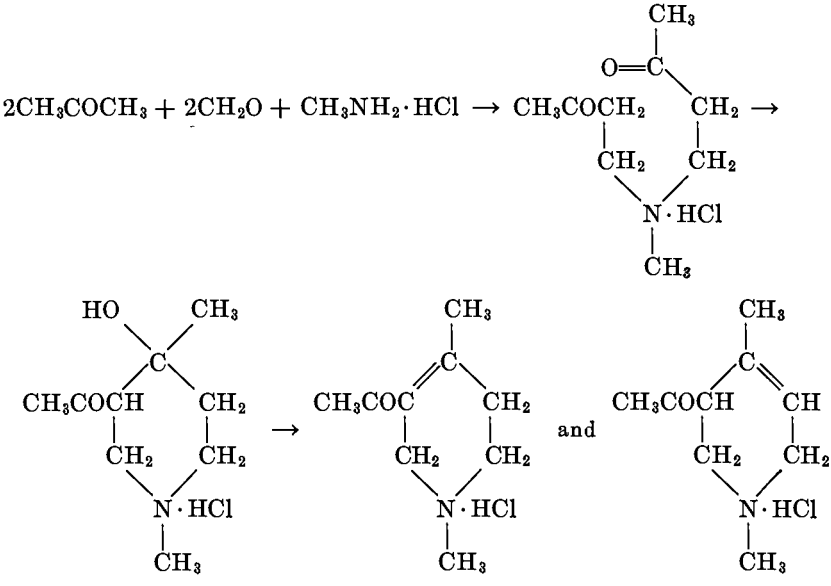
If the condensation is effected with a primary amine or its salt, the product is a secondary amine.

$$C_6H_5COCH_3 + CH_2O + RNH_2 \cdot HCl \rightarrow C_6H_5COCH_2CH_2NHR \cdot HCl + H_2O$$

In many cases the resulting secondary amine reacts further to yield a tertiary amine.

$$C_6H_5COCH_3 + CH_2O + C_6H_5COCH_2CH_2NHR \cdot HCl \rightarrow$$
$$(C_6H_5COCH_2CH_2)_2NR \cdot HCl + H_2O$$

Frequently such products, derived from two molecules of ketone, two molecules of formaldehyde, and one molecule of primary amine, are unstable and readily undergo cyclization. The compounds obtained from acetone, formaldehyde, and methylamine are illustrative.[1]

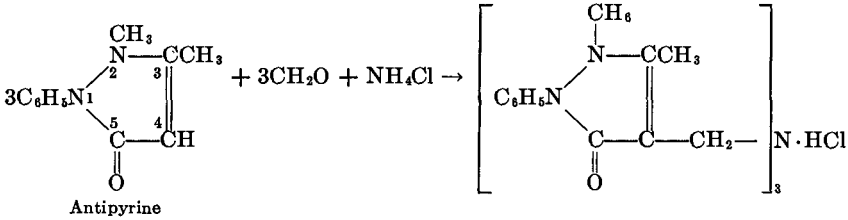


The product to be expected from a Mannich reaction involving an ammonium salt is a primary amine. In many cases, the primary amine so produced reacts further, as above, to form a secondary amine, a tertiary amine, or a cyclic substance. The situation is further complicated by the fact that methylamine, produced from the ammonium salt and formaldehyde, also takes part in the reaction. For example, the compounds shown above as products of acetone, formaldehyde, and

[1](*a*) Mannich and Ball, *Arch. Pharm.*, **264**, 65 (1926); (*b*) Mannich and Ritsert, *ibid.*, **264**, 164 (1926).

methylamine hydrochloride are also obtained from acetone, formaldehyde, and ammonium chloride.[1b]

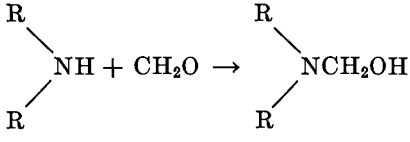
The first observation of a condensation of the type now known as the Mannich reaction was made by Tollens,[2, 3] who isolated the tertiary amine from ammonium chloride, formaldehyde, and acetophenone. Later Petrenko-Kritschenko [4] and his students studied condensations of this kind but failed to recognize the reaction as a general one. The detailed study by Mannich, begun in 1917, was initiated by the observation that antipyrine salicylate, formaldehyde, and ammonium chloride reacted to form a tertiary amine.[5]



Antipyrine

Since Aminopyrine (Pyramidon, 4-dimethylaminoantipyrine) failed to react, it was evident that the reaction involved the hydrogen atom of carbon 4 of antipyrine.

The mechanism of the Mannich reaction has not been established. The addition of the amine to formaldehyde has been considered as a possible primary step.



The fact that, in the case of antipyrine, the reaction of dimethylaminomethanol gives a poorer yield of condensation product than either formaldehyde and the amine or formaldehyde and the amine hydrochloride indicates that this view is not correct.[6] The possibility that the initial step is the formation of the methylol from the ketone has been examined.

$$RCOCH_3 + CH_2O \rightarrow RCOCH_2CH_2OH$$

[2] van Marle and Tollens, *Ber.*, **36**, 1351 (1903).

[3] Schäfer and Tollens, *Ber.*, **39**, 2181 (1906).

[4] Petrenko-Kritschenko and co-workers: (*a*) *Ber.*, **39**, 1358 (1906); (*b*) *Ber.*, **41**, 1692 (1908); (*c*) *Ber.*, **42**, 2020 (1909); (*d*) *Ber.*, **42**, 3683 (1909).

[5] Mannich and Krösche, *Arch. Pharm.*, **250**, 647 (1912).

[6] Bodendorf and Koralewski, *Arch. Pharm.*, **271**, 101 (1933).

The methylols of acetone and cyclohexanone do condense with dimethylamine to give the expected products. However, the methylol from antipyrine does not react at all with dimethylamine.[6] Apparently neither of these processes represents the primary step of the Mannich reaction.

THE SCOPE OF THE MANNICH REACTION

The Use of Secondary Amines

The secondary amines which have been used successfully are listed in Table I.

TABLE I

SECONDARY AMINES IN THE MANNICH REACTION

Dimethylamine	Piperidine
Diethylamine	1,2,3,4-Tetrahydroisoquinoline
Diethanolamine	6-Methoxy-1,2,3,4-tetrahydroisoquinoline
Dipropylamine	Morpholine
Di-*n*-butylamine	Piperazine
Diisoamylamine	ω-Methylaminopropiophenone
Dibenzylamine	β-Acetylethylbenzylamine
Methyldiethylethylenediamine	Benzyl-(2-cyclohexanonylmethyl)-amine
Methylaniline	3,4-Methylenedioxybenzyl-(2-cyclohexanonylmethyl)-amine

Dimethylamine is very reactive and usually leads to excellent yields. Diethylamine appears to be less reactive; it has been reported [7] that the typical condensation does not take place with ethyl methyl ketone, diethylamine, and formaldehyde. On the other hand, formaldehyde and this amine do give normal products with acetone,[8] benzalacetone,[9] acetophenone,[10] and several derivatives of the last.[11, 12] It has been reported that 2-acetylfuran and formaldehyde react normally with salts of dimethylamine, dipropylamine, di-*n*-butylamine, and diethanolamine, but not with the salt of diethylamine.[13] In other cases where dimethylamine, diethylamine, and dipropylamine have given good results, di-*n*-butylamine and diethanolamine have failed to react.[13] The cyclic secondary amines mentioned above generally react about as well as dimethylamine. However, dicyclohexylamine [14] and tetrahydroquinoline [11, 15] are said not to take part in the reaction.

[7] Kermack and Muir, *J. Chem. Soc.*, 3089 (1931).
[8] du Feu, McQuillin, and Robinson, *J. Chem. Soc.*, 53 (1937).
[9] Mannich and Schütz, *Arch. Pharm.*, **265**, 684 (1927).
[10] Blicke and Burckhalter, *J. Am. Chem. Soc.*, **64**, 451 (1942).
[11] Mannich and Lammering, *Ber.*, **55**, 3510 (1922).
[12] Mannich and Dannehl, *Arch. Pharm.*, **276**, 206 (1938).
[13] Levvy and Nisbet, *J. Chem. Soc.*, 1053 (1938).
[14] Burger and Bryant, *J. Am. Chem. Soc.*, **63**, 1054 (1941).
[15] Burger and Mosettig, *J. Am. Chem. Soc.*, **58**, 1570 (1936).

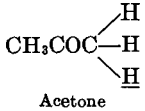
With Ketones. Saturated ketones, cycloalkanones, α,β-unsaturated ketones, aliphatic aromatic ketones, including those in which the aromatic ring is heterocyclic, and certain heterocyclic ketones containing a carbonyl group in the ring all undergo the Mannich reaction with secondary amines, usually in good yields.

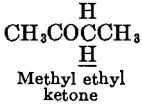
In Table II are listed ketones which have been treated with formaldehyde and salts of secondary amines with the successful formation of a β-dialkylaminoketone. In the formulas the replaceable hydrogen atom is underlined. A detailed list of the Mannich reactions involving these ketones is given in Table V, p. 331.

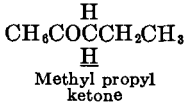
TABLE II

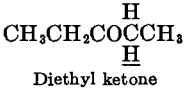
KETONES IN THE MANNICH REACTION

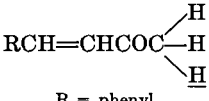
Aliphatic Ketones


Acetone

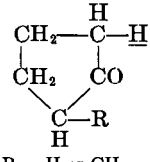

Methyl ethyl ketone

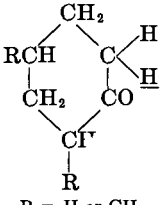

Methyl propyl ketone

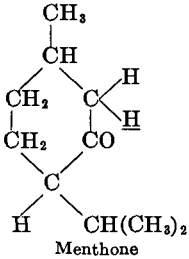

Diethyl ketone


R = phenyl, substituted phenyl or α-furyl

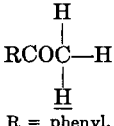
Cycloalkanones

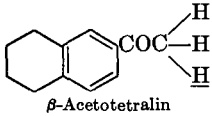

R = H or CH_3
Cyclopentanone
2-Methylcyclopentanone


R = H or CH_3
Cyclohexanone
2-Methylcyclohexanone
4-Methylcyclohexanone


Menthone

Aliphatic Aromatic Ketones


R = phenyl, substituted phenyl, β-naphthyl, 2-, 3-, or 9-phenanthryl, α-furyl, α-thienyl, or 2-(9-methylcarbazyl)


β-Acetotetralin

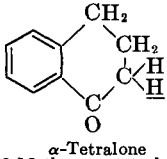
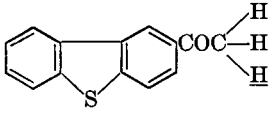

α-Tetralone
6-Methoxy-α-tetralone
6-Acetoxy -α-tetralone
7-Methoxy-α-tetralone
7-Acetoxy -α-tetralone

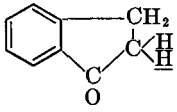
TABLE II—*Continued*

KETONES IN THE MANNICH REACTION—*Continued*

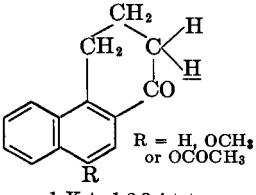
Aliphatic Aromatic Ketones—Continued



2-Acetyldibenzothiophene
4-Acetyldibenzothiophene

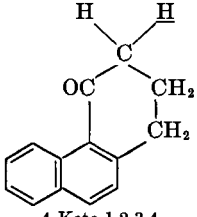


α-Hydrindone
5,6-Dimethoxy-α-hydrindone

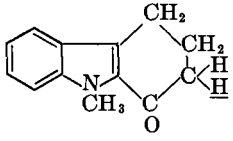


R = H, OCH_3 or $OCOCH_3$

1-Keto-1,2,3,4-tetrahydrophenanthrene, 1-keto-9-methoxy-1,2,3,4-tetrahydrophenanthrene and 1-keto-9-acetoxy-1,2,3,4-tetrahydrophenanthrene

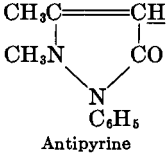


4-Keto-1,2,3,4-tetrahydrophenanthrene

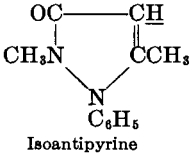


1-Keto-9-methyl-1,2,3,4-tetrahydrocarbazole

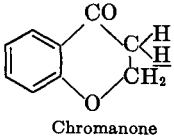
Heterocyclic Ketones



Antipyrine



Isoantipyrine

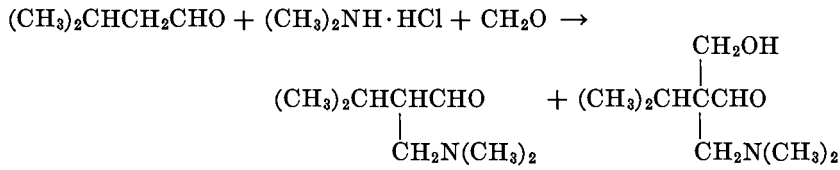


Chromanone

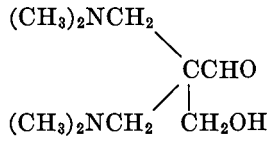
The following ketones have proved to be unreactive: *o*-aminoacetophenone and its acetyl and benzoyl derivatives;[12] *m*-aminoacetophenone (the acetyl and benzoyl derivatives do react in this case [12]); *p*-acetoaminoacetophenone;[11] and β-tetralone.[16] 1-Phenyl-3-methylpyrazolone-5,[17] 1-phenyl-5-methylpyrazolone-3,[17] and barbituric acid [17] do not react.

With Aldehydes. The behavior of aldehydes in the Mannich reaction is similar to that of ketones. The α-hydrogen atom of the aldehyde is substituted by a dialkylaminomethyl group. A secondary reaction which sometimes occurs involves the simultaneous introduction of a methylol group on the α-carbon atom.[18]

[16] Mosettig and May, *J. Org. Chem.*, **5**, 528 (1940).
[17] Mannich and Kather, *Arch. Pharm.*, **257**, 18 (1919).
[16] Mannich, Lesser, and Silten, *Ber.*, **65**, 378 (1932).



In the case of acetaldehyde the only product isolated is one of more complicated nature in which two dimethylaminomethyl groups and one methylol group have entered the molecule.[18]



The aldehydes have been less extensively studied than the ketones and there are recorded merely the condensations of acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde, isovaleraldehyde, and hexahydrobenzaldehyde with dimethylamine or piperidine hydrochloride. The products from the reactions are shown in Table V, p. 331.

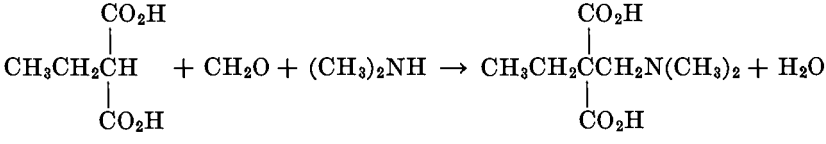
With Acids and Esters. A number of acids containing highly active hydrogen atoms in the α-position can be used instead of aldehydes or ketones. When an acid is employed the free secondary amine, rather than its salt, is used. The acids which have given satisfactory results are listed in Table III. The replaceable hydrogen atoms are underlined.

TABLE III

ACIDS IN THE MANNICH REACTION

$CNC\underline{H}_2CO_2H$	$CH_3COC\underline{H}(R)CO_2H$
p-$NO_2C_6H_4C\underline{H}_2CO_2H$	$C\underline{H}_2(CO_2H)_2$
$C_6H_5COC\underline{H}_2CO_2H$	$RC\underline{H}(CO_2H)_2$
o-$NO_2C_6H_4C\underline{H}(OH)CO_2H$	$RC\underline{H}(CO_2R)CO_2H$
$C\underline{H}_3COCO_2H$	$C_6H_5COCH_2C\underline{H}(CO_2H)_2$
$CH_3COC\underline{H}_2CO_2H$	$HO_2CCH_2C\underline{H}(CO_2H)_2$

The replacement of a lone active hydrogen atom is illustrated by the reaction of ethylmalonic acid, formaldehyde, and dimethylamine.[19]



A side reaction which often occurs involves the decarboxylation of

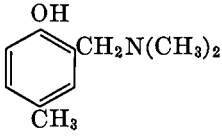
[19] Mannich and Ganz, *Ber.*, **55**, 3486 (1922).

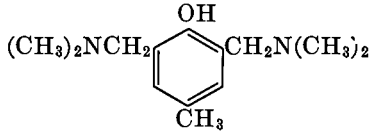
the acid, as in the condensation of ethylacetoacetic acid with formaldehyde and dimethylamine [20]

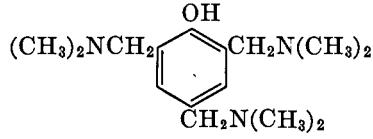
$$CH_3CH_2\underset{\underset{COCH_3}{|}}{\overset{\overset{CO_2H}{|}}{C}}H + CH_2O + (CH_3)_2NH \rightarrow CH_3CH_2\underset{\underset{COCH_3}{|}}{C}HCH_2N(CH_3)_2 + CO_2 + H_2O$$

In those cases where two dialkylamino groups enter the molecule, carbon dioxide is invariably eliminated.

With Phenols. The *o*- and *p*-hydrogens in phenols are sufficiently active to enter into the Mannich reaction. Thus, products from phenol,[21, 22, 23] 4-acetaminophenol,[21] *o*- and *p*-cresol,[22] *m*-cresol,[23] 3,5-dimethylphenol,[24] 2-methyl-4-ethylphenol,[22] 2- and 4-methoxyphenol,[25] β-naphthol,[25] and 8-hydroxyquinoline [21] with formaldehyde and dimethylamine or piperidine or morpholine, have been reported. From *p*-cresol a mono- and a di-substitution product are obtained, and from phenol and *m*-cresol, trisubstitution products.







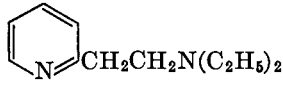
Interaction of 2-methyl-6-ethylphenol, formaldehyde, and dimethylamine is reported to yield a mixture of methylenedi-(2-methyl-6-ethylphenol) and 1-(dimethylaminomethoxy)-2-methyl-6-ethylbenzene.[22]

With Acetylenes. Phenylacetylene and certain substituted phenylacetylenes, such as the 2-nitro, 2-amino, and 4-methoxy derivatives, react readily with formaldehyde and secondary amines.[26]

$$C_6H_5C{\equiv}CH + CH_2O + (C_2H_5)_2NH \rightarrow C_6H_5C{\equiv}CCH_2N(C_2H_5)_2$$

[20] Mannich and Bauroth, *Ber.*, **57**, 1108 (1924).
[21] Ger. pat., 92,309; *Frdl.*, 4, 103 (1899).
[22] Décombe, *Compt. rend.*, **196**, 866 (1933).
[23] Bruson and MacMullen, *J. Am. Chem. Soc.*, **63**, 270 (1941).
[24] Caldwell and Thompson, *J. Am. Chem. Soc.*, **61**, 765 (1939).
[25] Décombe, *Compt. rend.*, **197**, 258 (1933).
[26] Mannich and Chang, *Ber.*, **66**, 418 (1933).

With α-Picolines and Quinaldines. Since an α-methyl group in a pyridine or quinoline nucleus has hydrogens of about the same activity as those in the methyl group of a methyl ketone, the Mannich reaction might be expected to take place with such molecules. α-Picoline,[27] 2-methylquinoline [7, 27, 28] (quinaldine), 2-methyl-4-hydroxyquinoline,[28] 2-methyl-8-nitroquinoline,[28] and 2-ethoxy-4-methylquinoline [28] have been condensed with dimethylamine, diethylamine, methyldiethylenediamine, piperidine, and methylaniline, either as the free amine or as the amine hydrochloride. Thus, α-picoline, formaldehyde, and diethylamine yield 2-(β-diethylaminoethyl)-pyridine.[27]



The Use of Primary Amines

The primary amines listed in Table IV have been used successfully in the Mannich condensation.

TABLE IV

PRIMARY AMINES IN THE MANNICH REACTION

Methylamine	β-Phenylethylamine
Ethylamine	Ethylenediamine
β-Hydroxyethylamine	Ethyl aminoacetate
β-Chloroethylamine	ω-Aminoacetophenone
Allylamine	Tetrahydro-β-naphthylamine
Benzylamine	Aniline *
3, 4-Methylene-dioxybenzylamine	

Hydrazine [17] and guanidine,[17] have failed to react.

* Reacts only in certain instances.

With Ketones. When a primary amine or its salt is used in a Mannich reaction the first product is a secondary amine, but this often reacts with more of the reagents to give a tertiary amine. Aliphatic ketones and primary amines give rise to a number of products; for example, four substances have been isolated from the reaction of formaldehyde, diethylketone, and methylamine hydrochloride.[29] The structures of some of them are still in doubt (see also the reaction of acetone, methylamine, and formaldehyde, p. 305).

[27] Tseou Héou-Féo, *Compt. rend.*, **192**, 1242 (1931).
[28] Ger. pat., 497,907; *Frdl.*, **16**, 2669 (1931).
[29] Mannich, *Arch. Pharm.*, **255**, 261 (1917).

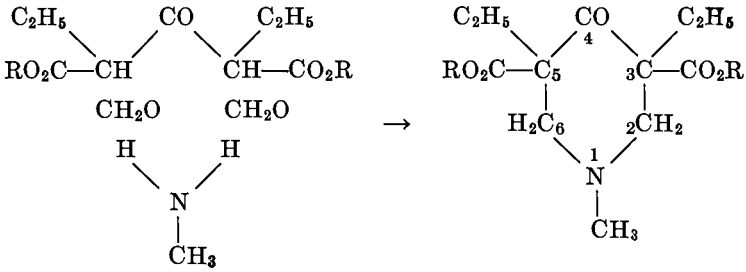
With Aldehydes. Apparently the only known reaction involving an aldehyde, a primary amine, and formaldehyde is that of isobutyraldehyde and methylamine.[30]

$$(CH_3)_2CHCHO + CH_2O + CH_3NH_2 \rightarrow (CH_3)_2C(CH_2NHCH_3)CHO$$

With Acids and Esters. The Mannich reaction of primary amines with acids containing active hydrogen atoms leads to the same types of compounds as described above in connection with secondary amines. As might be expected, the first product often undergoes further condensation to form a tertiary amine. The reaction of methylmalonic acid, formaldehyde, and methylamine is an example.[31]

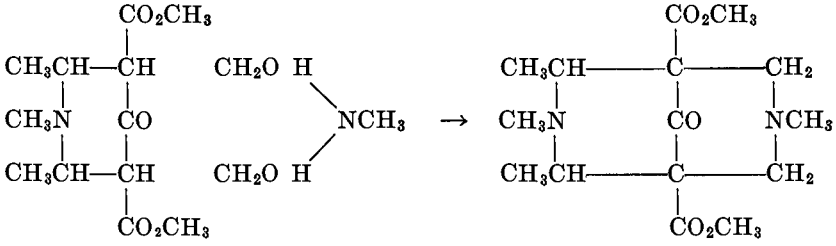
$$2CH_3CH(CO_2H)_2 + 2CH_2O + CH_3NH_2 \rightarrow \left(CH_3C(CO_2H)_2{-}CH_2\right)_2NCH_3$$

When a primary amine is used with a polycarbonyl compound which contains reactive hydrogen atoms on carbon atoms located in the 1,3-positions with respect to each other, then cyclic products may be expected. Thus, esters of α,α-diethylacetonedicarboxylic acid react with formaldehyde and methylamine to give pyridones.[32]



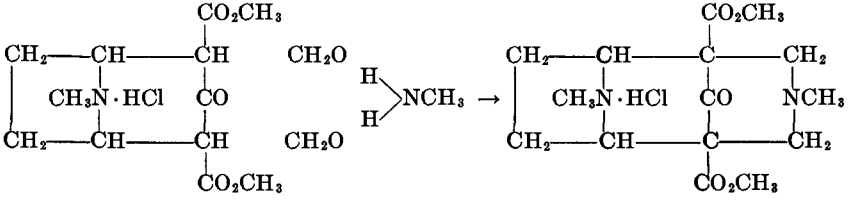
If the pyridone contains hydrogen atoms on the 3- and 5-carbon atoms, the condensation may be carried one step further and a bicyclic system may be produced. For example, the pyridone obtained by a reaction of the Mannich type from methyl acetonedicarboxylate, acetaldehyde, and methylamine can be condensed with formaldehyde and methylamine.[33]

[30] Mannich and Wieder, *Ber.*, **65**, 385 (1932).
[31] Mannich and Kather, *Ber.*, **53**, 1368 (1920).
[32] Mannich and Schumann, *Ber.*, **69**, 2299 (1936).
[33] Mannich and Viet, *Ber.*, **68**, 506 (1935).

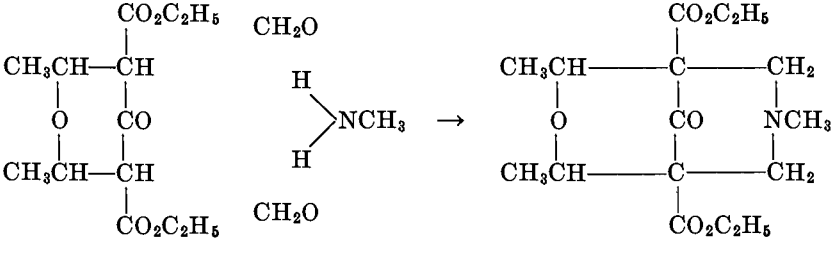


The name "bispidin" has been suggested for the bicyclic ring system produced in such reactions.[33, 34]

This reaction can be used to build up tricyclic systems. Thus, the hydrochloride of methyl tropanone-2,4-dicarboxylate reacts in the same way as the pyridone above.[33]



A similar reaction occurs when a tetrahydropyrone[35] derivative is used in place of the pyridone. For example, a bicyclic product is obtained from ethyl dimethyltetrahydropyronedicarboxylate, formaldehyde, and methylamine.



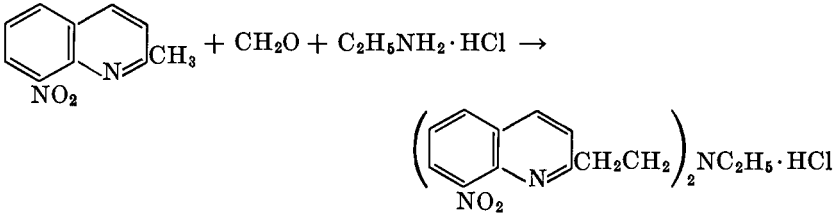
It has been suggested that the bicyclic ring system so formed be termed the "pydin" nucleus.

With Phenols and Acetylenes. No Mannich reactions involving primary amines and either phenols or acetylenes have been reported.

With α-Picolines and Quinaldines. Of the compounds containing a methyl group in the 2-position of a pyridine nucleus only 2-methyl-8-nitroquinoline has been treated with a primary amine and formalde-

[34] Mannich and Mohs, *Ber.*, **63**, 608 (1930).
[35] Mannich and Mück, *Ber.*, **63**, 604 (1930).

hyde. The amine used was ethylamine, and the product was a tertiary amine.[28]



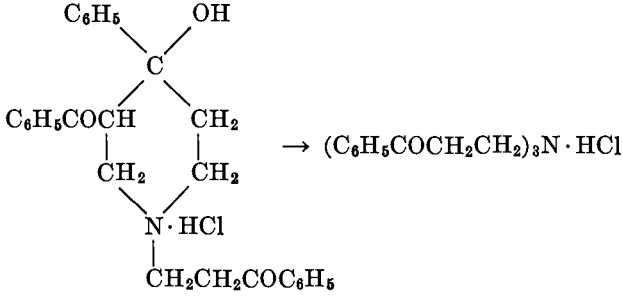
The Use of Ammonia

With Ketones. A primary amine is the first product to be expected from a Mannich reaction in which ammonia or an ammonium salt and formaldehyde react with a compound containing an active hydrogen atom. With the simple ketones subsequent reaction of the primary amine so formed usually leads to the production of tertiary amines. Salts of certain of these primary and secondary amines have been isolated and found to be stable, but the free bases change to the tertiary amines. The disproportionation of the primary and secondary amines obtained from acetophenone, formaldehyde, and ammonia is an example.[36]

$$3C_6H_5COCH_2CH_2NH_2 \rightarrow (C_6H_5COCH_2CH_2)_3N + 2NH_3$$

$$3(C_6H_5COCH_2CH_2)_2NH \rightarrow 2(C_6H_5COCH_2CH_2)_3N + NH_3$$

In some instances cyclic products are obtained from ketones, ammonia, and formaldehyde. From acetophenone, ammonium chloride, and formaldehyde there has been isolated a substance which is believed to be a substituted piperidine.[36] It readily changes to the salt of tri-(β-benzoylethyl)-amine.[3]

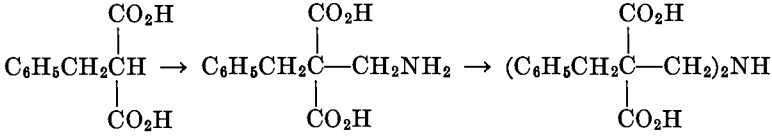


[36] Mannich and Abdullah, *Ber.*, **68**, 113 (1935).

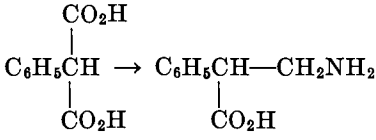
With cyclohexanone the tertiary amine is obtained directly,[5] in analogy with the reaction of antipyrine [5, 37] (p. 306).

The formation of cyclic products derived from methylamine, by reaction of acetone, formaldehyde, and ammonium chloride, has been mentioned (p. 305). The reaction with diethyl ketone takes a similar course, producing a trimethylpiperidone.[29] Presumably, methylamine is first formed from ammonium chloride and formaldehyde.

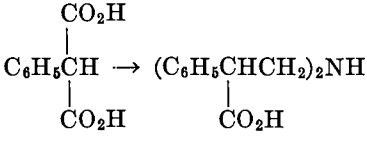
With Acids. From the reaction of benzylmalonic acid, ammonia, and formaldehyde both a primary amine and a secondary amine have been isolated.[19]



In the case of phenylmalonic acid a primary amine is produced and decarboxylation occurs when ammonia is used.[19]



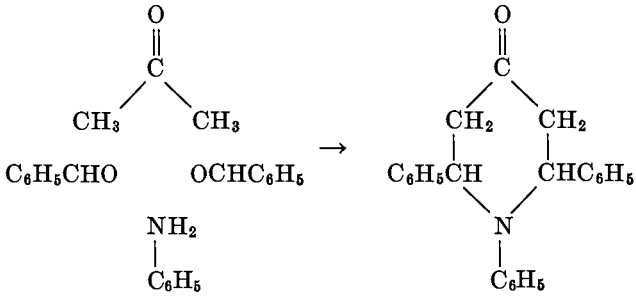
When ammonium chloride is employed the decarboxylated secondary amine is obtained.[19]



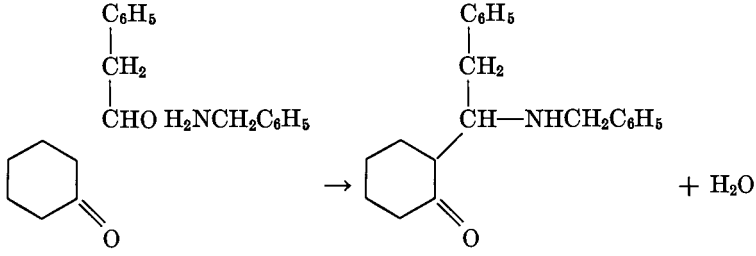
RELATED REACTIONS

Aldehydes other than formaldehyde may be used in certain condensations of the Mannich type. Those which have been studied are acetaldehyde, phenylacetaldehyde, benzaldehyde, and anisaldehyde. These have been employed successfully with acetone, cyclohexanone, and esters of acetonedicarboxylic acid. The reactions appear to be limited to ammonia and primary amines and their salts. With acetone, aniline, and benzaldehyde a piperidone is obtained.[4d]

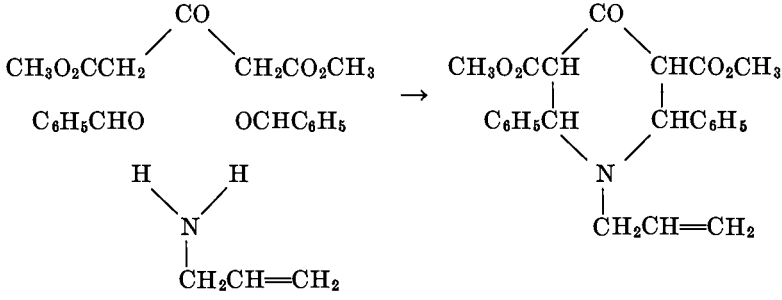
[37] Mannich and Braun, *Ber.*, **53**, 1874 (1920).



An open-chain product is formed from cyclohexanone, phenylacetaldehyde, and benzylamine.[38]



Substituted piperidones are always produced when esters of acetonedicarboxylic acid are employed, as in the reaction of the methyl ester with allylamine and benzaldehyde.[34]



Similar piperidones have been obtained by substituting for allylamine the following: ammonia,[4a] methylamine,[34] ethylamine,[4d] and β-hydroxyethylamine;[34] by employing acetaldehyde, instead of benzaldehyde, with ammonium bromide,[39] methylamine,[39] benzylamine,[39] and β-phenylethylamine;[39] and by using allylamine, anisaldehyde, and methyl acetonedicarboxylate.[34]

[36] Otto Hieronimus, Dissertation, Berlin, 1938.
[39] Peter Peckelhoff, Dissertation, Stuttgart, 1933; Ger. pat., 510,184.

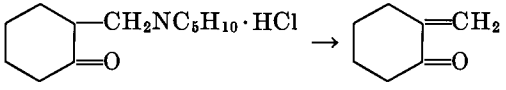
THE APPLICATION OF THE MANNICH REACTION IN SYNTHESIS

Unsaturated Compounds

Preparation of Ethylenic Compounds. The most characteristic property of many of the products obtained in the Mannich reaction, especially those derived from secondary amines, is the decomposition into the amine and an unsaturated compound. The various condensation products exhibit widely different stabilities. Some can be distilled under diminished pressure,[40] but most of them undergo decomposition when heated or subjected to steam distillation.

$$C_6H_5COCH_2CH_2N(CH_3)_2\cdot HCl \rightarrow C_6H_5COCH{=}CH_2 + (CH_3)_2NH\cdot HCl \quad \text{(Ref. 41)}$$

$$(C_6H_5COCH_2CH_2)_2NCH_3\cdot HCl \rightarrow C_6H_5COCH{=}CH_2 + C_6H_5COCH_2CH_2NHCH_3\cdot HCl \quad \text{(Ref. 41)}$$



(Ref. 40)

$$\begin{array}{l} CH_3CHCHO \\ \quad\;\; | \\ \quad CH_2N(CH_3)_2\cdot HCl \end{array} \rightarrow \begin{array}{l} CH_3CCHO \\ \quad\;\; \| \\ \quad\;\; CH_2 \end{array} + (CH_3)_2NH\cdot HCl \quad \text{(Ref. 42)}$$

In a few cases the products from Mannich reactions decompose spontaneously. Thus, from monoethyl ethylmalonate, formaldehyde, and diethylamine there is obtained directly ethyl α-ethylacrylate; undoubtedly, this is formed by elimination of carbon dioxide and diethylamine from the primary reaction product.[43]

$$\begin{array}{l} \quad COOH \\ \quad\;\; | \\ C_2H_5CHCOOC_2H_5 \end{array} + H_2CO + (C_2H_5)_2NH \rightarrow \left[\begin{array}{l} \quad\quad COOH \\ \quad\quad\;\; | \\ C_2H_5CCOOC_2H_5 \\ \quad\quad\;\; | \\ \quad\quad CH_2N(C_2H_5)_2 \end{array}\right]$$

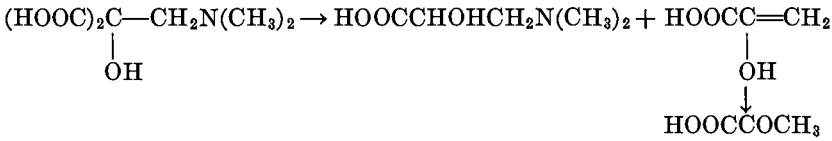
$$+ H_2O \rightarrow \begin{array}{l} C_2H_5CCOOC_2H_5 \\ \quad\;\; \| \\ \quad\;\; CH_2 \end{array} + H_2O + CO_2 + (C_2H_5)_2NH$$

Other β-dimethylaminoketones are sufficiently unstable that they decompose in the presence of sodium ethylate or dilute alkaline solu-

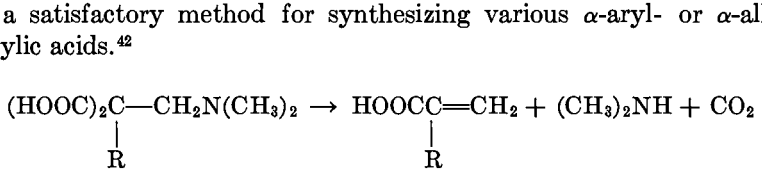
[40] Mannich and Hönig, *Arch. Pharm.*, **265**, 598 (1927).
[41] Mannich and Heilner, *Ber.*, **55**, 356 (1922).
[42] Mannich and Bauroth, *Ber.*, **55**, 3504 (1922).
[43] Mannich and Ritsert, *Ber.*, **57**, 1116 (1924).

tions. Addition of sodium carbonate to an aqueous solution of 2-nitro-β-dimethylaminopropiophenone hydrochloride or 3-acetylamino-β-dimethylaminopropiophenone hydrochloride results in an immediate liberation of dimethylamine.[12]

In some cases, when two carboxyl groups are present one is eliminated during the decomposition.[42]

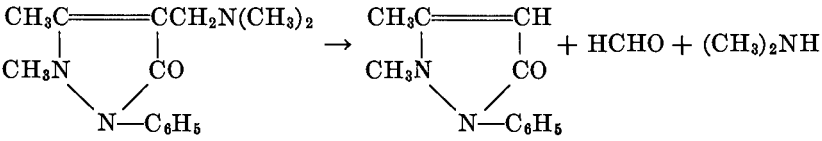


This process, when a monosubstituted malonic acid is employed, serves as a satisfactory method for synthesizing various α-aryl- or α-alkylacrylic acids.[42]



Carter and Jones,[44] in the preparation of α-benzylacrylic acid, found refluxing the Mannich base in neutral aqueous solution to be an excellent method for the decomposition.

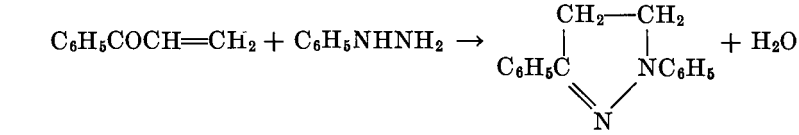
When the active hydrogen atom in the compound reacting with formaldehyde and a dialkylamine is a tertiary one, the product cannot decompose to an ethylenic substance and hence, presumably, may decompose under hydrolytic conditions to the dialkylamine, formaldehyde, and the original compound. This is illustrated by the decomposition of dimethylaminomethylantipyrine to antipyrine, dimethylamine, and formaldehyde, when treated with an aqueous solution of sodium sulfite and sulfurous acid.[17]



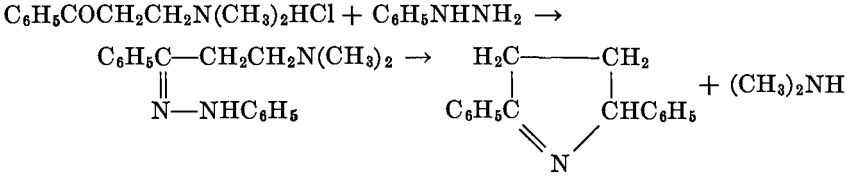
Preparation of Pyrazolines. Another reaction that may depend on intermediate formation of an ethylenic compound is the production of pyrazolines by the action of phenylhydrazine. Kohler [45] demonstrated

[44] H. E. Carter and R. C. Jones, private communication.
[45] Kohler, *Am. Chem. J.*, **42**, 375 (1909).

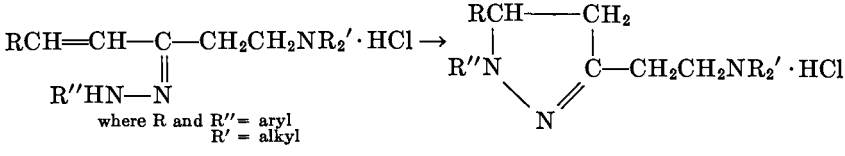
that phenyl vinyl ketone and phenylhydrazine react with surprising ease to yield 1,3-diphenylpyrazoline.



When β-dimethylaminopropiophenone hydrochloride and phenylhydrazine react in the presence of sodium acetate, 1,3-diphenylpyrazoline is formed.[13, 20, 40, 46, 47, 48] In some cases, the intermediate products must be treated with ethanolic hydrogen chloride to effect the cyclization.



It is not impossible that the initial phenylhydrazone decomposes to the phenylhydrazone of the phenyl vinyl ketone, which then cyclizes to the 1,3-diphenylpyrazoline. Such a mechanism is supported by the work of Nisbet,[49, 50, 51, 52] who observed that the phenylhydrazones of β-dialkylaminoketones derived from α,β-unsaturated ketones isomerize readily to pyrazolines and in so reacting make use of the double bond already present in the molecule.

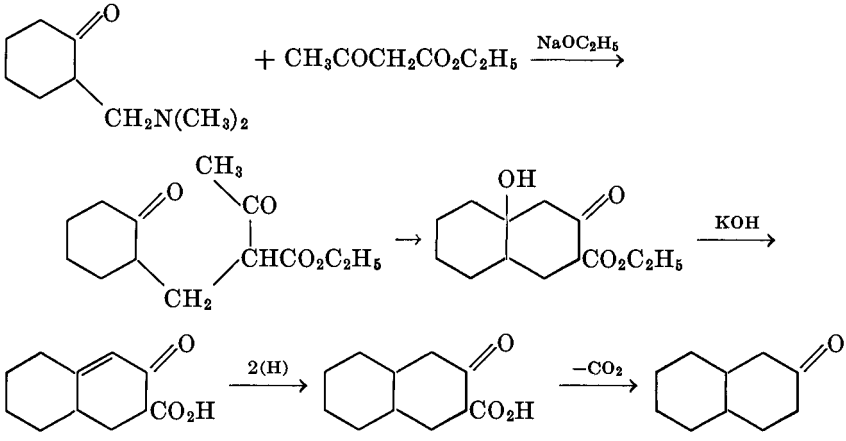


Some of the 1,5-diaryl-3-(β-dialkylaminoethyl)-pyrazoline salts were shown by Nisbet [50, 51, 52] to be local anesthetics.

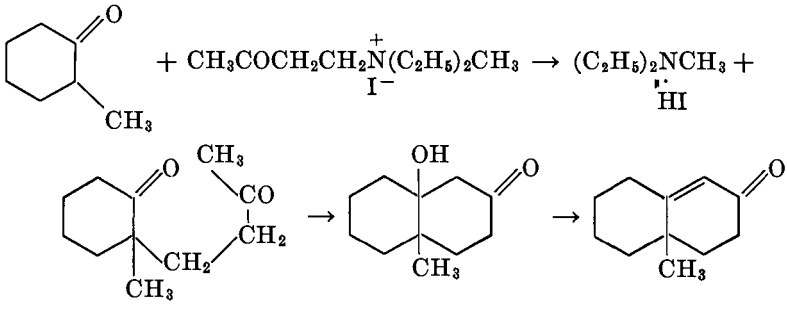
The Use of a Mannich Base as a Source of Unsaturated Ketone for Condensations with an Active Methylene Compound. A reaction which offers many possibilities in synthetic work is the condensation of β-dialkylaminoketones with active methylene compounds in the presence

[46] Jacob and Madinaveitia, *J. Chem. Soc.*, 1929 (1937).
[47] Harradence and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 233 (1938).
[48] Harradence and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **73**, 14 (1939).
[49] Nisbet and Gray, *J. Chem. Soc.*, 839 (1933).
[50] Nisbet, *J. Chem. Soc.*, 1237 (1938).
[51] Nisbet, *J. Chem. Soc.*, 1568 (1938).
[52] Levvy and Nisbet, *J. Chem. Soc.*, 1572 (1938).

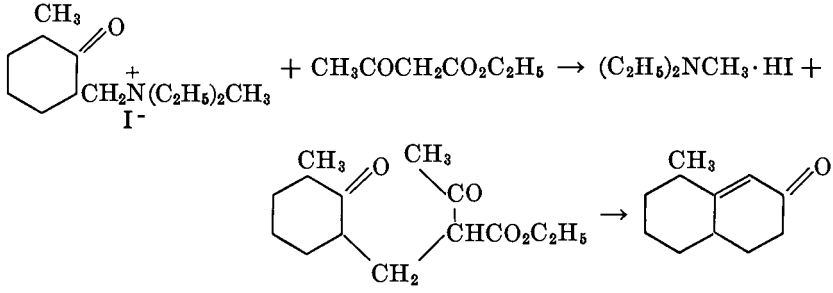
of sodium ethoxide. Apparently a gradual formation of α,β-unsaturated ketone results in a smoother addition reaction than is possible when the α,β-unsaturated ketone is used directly in the Michael condensation. For example, by a condensation with acetoacetic ester Mannich [53] converted 2-dimethylaminomethylcyclohexanone to a β-decalone derivative in excellent yield; the product was subsequently degraded to β-decalone.



Robinson [8] has employed a modification of this procedure for the synthesis of a variety of compounds which are otherwise inaccessible. The modification consists in treating the Mannich base with methyl iodide. A solution of the methiodide, which need not be isolated, is allowed to react with the active methylene compound in the presence of sodium amide or sodium ethoxide. The advantage of the methiodide over the Mannich base presumably lies in the liberation of the α,β-unsaturated ketone at lower concentration and greater reactivity. The following two syntheses illustrate Robinson's modification.



[53] Mannich, Koch, and Borkowsky, *Ber.*, **70**, 355 (1937).

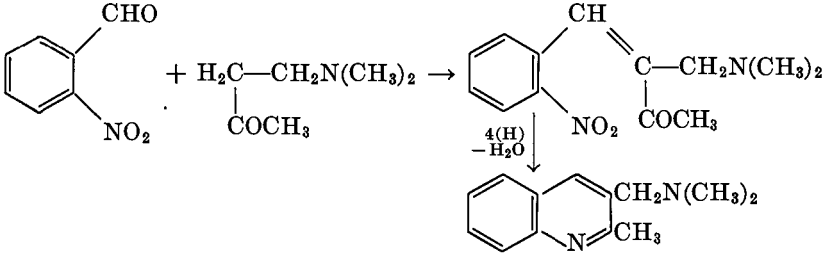


Conversion of a Ketone to Its Next Higher Homolog. Reduction of the unsaturated ketone obtained by decomposition of a Mannich base leads to a ketone with one more methylene group than that used in the preparation of the Mannich base.[11]

$$(p)\ CH_3OC_6H_4COCH_3 \rightarrow (p)\ CH_3OC_6H_4COCH_2CH_2N(CH_3)_2\cdot HCl \rightarrow$$
$$(p)\ CH_3OC_6H_4COCH{=}CH_2 \rightarrow (p)\ CH_3OC_6H_4COCH_2CH_3$$

Syntheses Dependent on the Active Methylene Group in the Aminoketone

Advantage can be taken of the active methylene group in the β-dialkylamino carbonyl compounds for the synthesis of products otherwise inaccessible. Thus β-dimethylaminoethyl methyl ketone and *o*-nitrobenzaldehyde react to give a product which upon reduction loses water to form a substituted quinoline.[54]

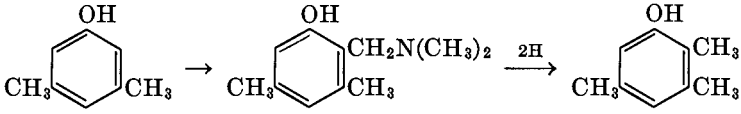


An analogous reaction may be used for the preparation 2-(β-piperidinethyl)-6,7-methylenedioxyquinoline.[55]

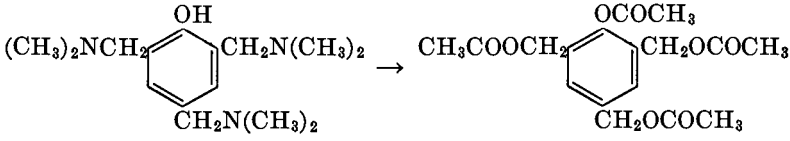
[54] Mannich and Reichert, *Arch. Pharm.*, **271**, 116 (1933).
[55] Mannich and Schilling, *Arch. Pharm.*, **276**, 582 (1938).

Syntheses Dependent on the Activity of the Dimethylamino Group in Dimethylaminomethylphenols

The products obtained by the Mannich reaction with phenols have possible synthetic uses in the introduction of methyl groups into the phenolic ring. Thus, β-dimethylaminomethylxylenol is readily hydrogenolyzed to 2,3,5-trimethylphenol.[24]



It has also been demonstrated that when these phenolic substances are treated with acetic anhydride the dimethylamino groups are replaced by acetoxy groups.[23] 2,4,6-Tri-(dimethylaminomethyl)-phenol is converted into 2,4,6-tri-(acetoxymethyl)-phenyl acetate.



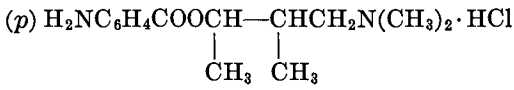
Reduction to Aminoalcohols

The β-substituted aminoketones or aldehydes can be reduced readily to the corresponding γ-substituted aminoalkanols,[11, 12] which are much more stable than the corresponding ketones. This procedure provides an unusually good source of such aminoalcohols. When the ketone contains an asymmetric carbon atom a second one is introduced when the carbinol is formed, and in several cases the two diastereoisomeric modifications have been isolated.[1, 18, 32, 56, 57, 58, 59, 60]

The γ-aminoalcohols, in the form of their benzoates and *p*-aminobenzoates, find application as local anesthetics, and many such physiologically active compounds have been prepared through the Mannich reaction.[9, 11, 18, 37, 40, 41, 56, 57, 61, 62, 63] The commercial local anesthetic Tutocaine is made from the alcohol obtained by reduction of the Mannich base from dimethylamine, formaldehyde, and ethyl methyl ketone;

[56] Mannich and Curtaz, *Arch. Pharm.*, **264**, 741 (1926).
[57] Mannich, *Arch. Pharm.*, **265**, 251 (1927).
[58] Mannich, Borkowsky, and Lin, *Arch. Pharm.*, **275**, 54 (1937).
[59] Mannich and Salzmann, *Ber.*, **72**, 506 (1939).
[60] Mannich and Stein, *Arch. Pharm.*, **264**, 77 (1926).
[61] Mannich and Schaller, *Arch. Pharm.*, **276**, 575 (1938).
[62] Mannich and Hof, *Arch. Pharm.*, **265**, 589 (1927).
[63] Mannich and Horkheimer, *Arch. Pharm.*, **264**, 167 (1926).

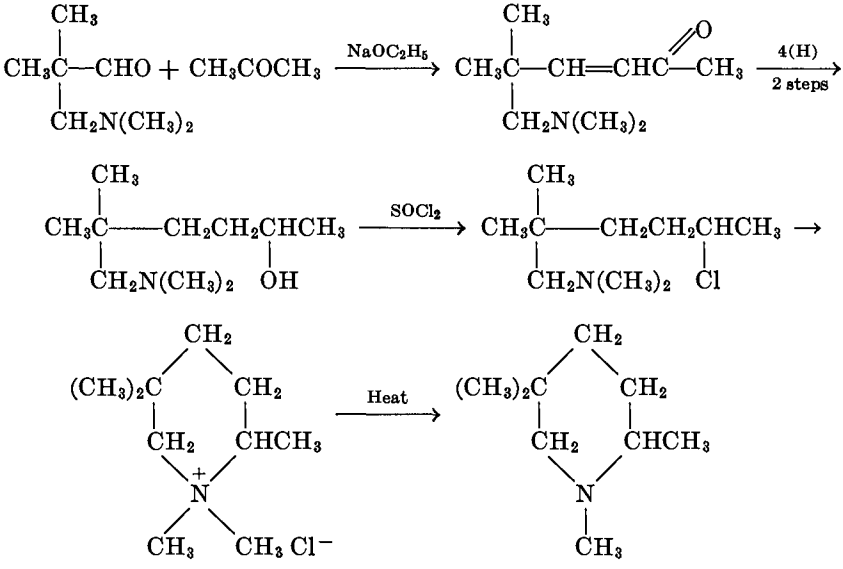
the alcohol is converted to the *p*-aminobenzoate, and the latter is used as the hydrochloride.



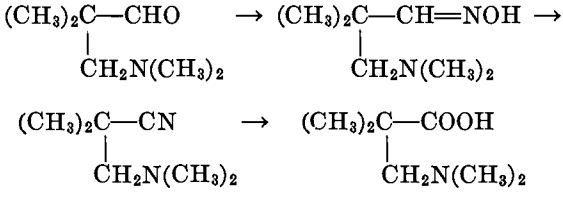
Tutocaine

Products Derived by Transformation of the Aldehyde Group in β-Dialkylaminoaldehydes

Certain of the β-dialkylaminoaldehydes can be transformed into piperidine derivatives. Thus, α,α-dimethyl-β-dimethylaminopropionaldehyde is converted into 1,2,5,5-tetramethylpiperidine.[38]

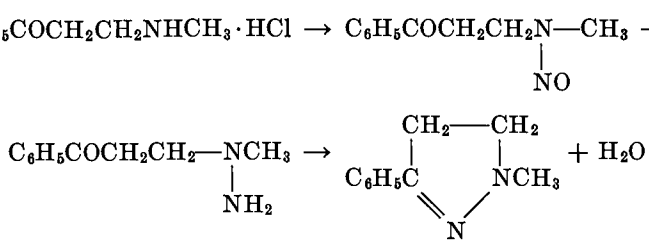


The aminoaldehyde also may be transformed into the corresponding amino acids [18] by the following series of reactions.

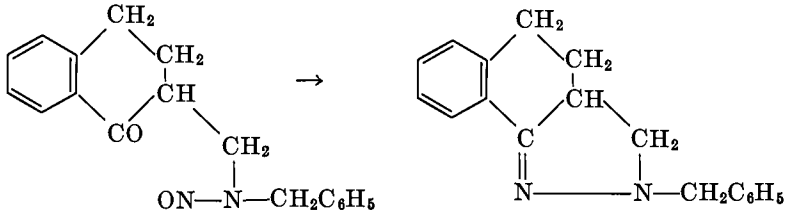


β-Monoalkylaminoketone Condensation Products

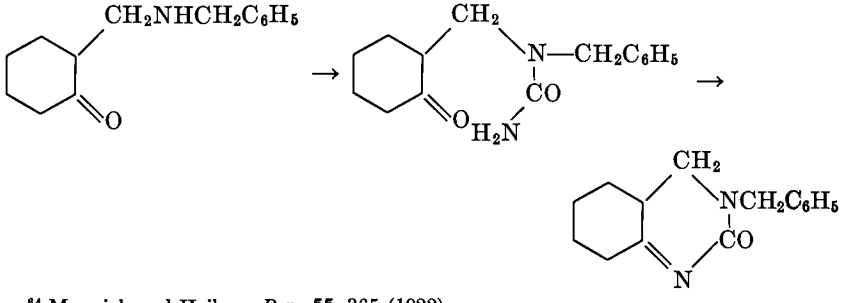
The Mannich bases from one molecule of a primary amine, one of formaldehyde, and one of ketone have been used in a variety of condensations involving both the ketone group and the secondary amine group. The nitroso derivative of β-methylaminopropiophenone is readily reduced to the corresponding β-hydrazinoketone, which cyclizes to 1-methyl-3-phenylpyrazoline.[64]



A similar cyclization occurs in the formation of 2-benzyltetrahydronaphthindazole[38] by reduction of 2-(benzylnitrosaminomethyl)-α-tetralone.

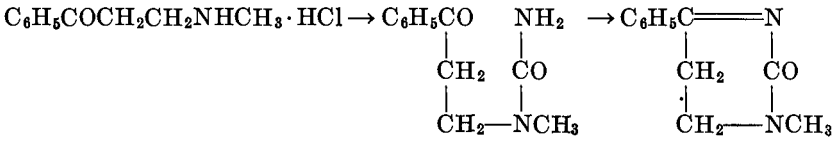


Other types of cyclic compounds may result if properly constructed molecules and appropriate reagents are used. Thus the compound from benzylamine hydrochloride, formaldehyde, and cyclohexanone reacts with potassium cyanate to form a urea which undergoes dehydration to an octahydroquinazoline.[38]



[64] Mannich and Heilner, *Ber.*, **55**, 365 (1922).

An analogous reaction has been used for the synthesis of 1-methyl-2-keto-4-phenyl-1,2,5,6-tetrahydropyrimidine from β-methylaminopropiophenone.[64]

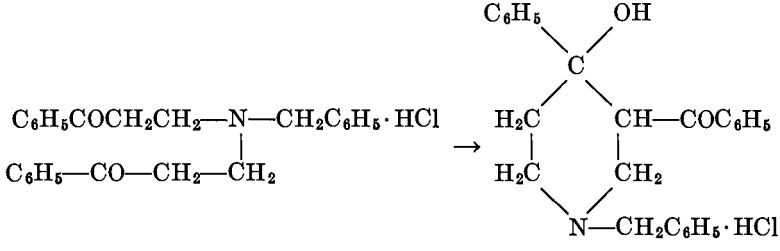


Condensation Products from One Mole of a Primary Amine, Two Moles of Formaldehyde, and Two Moles of a Ketone

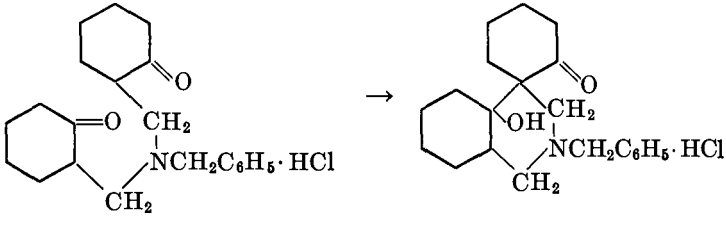
Benzylamine hydrochloride, formaldehyde, and acetophenone react to form a mixture of products:[38] the first from one mole of benzylamine, one of acetophenone, and one of formaldehyde; and the second from one mole of benzylamine, two of acetophenone, and two of formaldehyde. The second is unstable and cyclizes to a piperidine derivative.

$$C_6H_5COCH_3 + HCHO + C_6H_5CH_2NH_2 \cdot HCl \rightarrow C_6H_5COCH_2CH_2NHCH_2C_6H_5 \cdot HCl$$

$$2C_6H_5COCH_3 + 2HCHO + C_6H_5CH_2NH \cdot HCl \rightarrow$$

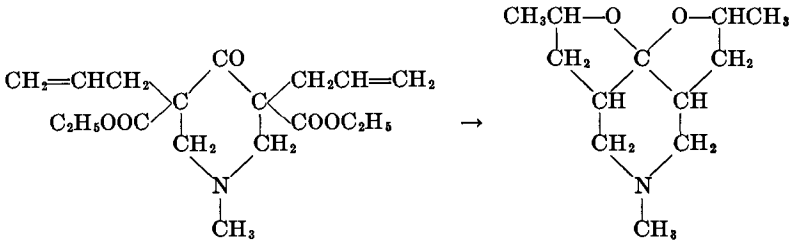


Benzylamine hydrochloride condenses similarly with cyclohexanone,[38] and the product involving two moles of cyclohexanone is converted to a reduced isoquinoline derivative during the reaction.



A tricyclic ring system is formed when the diethyl ester of 1-methyl-3,5-diallyl-4-piperidone-3,5-dicarboxylic acid (obtained from the diethyl

ester of α,α'-diallylacetonedicarboxylic acid, two moles of formaldehyde, and one of methylamine) is hydrolyzed and decarboxylated.[32]



EXPERIMENTAL CONDITIONS AND PROCEDURES

Solvents

When aqueous formaldehyde is used the condensation is ordinarily carried out by shaking or stirring the reactants in the absence of an organic solvent; in some cases[34] methanol has been added to such mixtures. When paraformaldehyde is used an organic solvent is required. If the ketone component is a liquid, such as acetone,[38] cyclopentanone,[47] or cyclohexanone,[47] an excess of it may be used as the solvent. In other cases ethanol (95% or absolute) is added as the solvent. In condensations involving 2-, 3-, or 9-acetylphenanthrene, paraformaldehyde, and salts of secondary amines, isoamyl alcohol is recommended as the solvent.[65] The condensations proceed much faster in the higher-boiling solvent, and the formation of certain by-products, obtained by prolonged heating in ethanol, is avoided. On the other hand, it is stated that, although in ethanol the condensation between 3-acetyl-9-methylcarbazole, formaldehyde, and a secondary amine salt proceeds more slowly than in isoamyl alcohol, it is less subject to side reactions associated with instability of the aminoketone salts at the higher temperature.[66]

Nature of Formaldehyde and Time of Reaction

Formaldehyde is used in the form of a 20–40% aqueous solution or as paraformaldehyde. In certain reactions, such as the condensation of α-tetralone, formaldehyde, and tetrahydroisoquinoline hydrochloride, aqueous formaldehyde is said to be superior to paraformaldehyde.[16]

In a few cases[12, 38, 47] enough concentrated hydrochloric acid is added at the beginning of the reaction to make the mixture acidic to Congo red;

[65] van de Kamp and Mosettig, *J. Am. Chem. Soc.*, **58**, 1568 (1936).
[66] Ruberg and Small, *J. Am. Chem. Soc.*, **63**, 736 (1941).

in other instances[11, 15, 65] the mixture is acidified at the end of the reaction in order to depolymerize unchanged paraformaldehyde and bring it into solution.

The time required for a Mannich reaction depends upon the nature of the ketone and of the amine salt and upon the boiling point of the solvent employed. The reaction between furfuralacetone, paraformaldehyde, and dimethylamine hydrochloride in alcoholic solution is said to be complete after the mixture has been boiled for a few minutes.[49] When 3-acetyl-9-methylcarbazole, paraformaldehyde, and diethylamine hydrochloride are heated in absolute ethanolic solution for five hours the yield of reaction product is 59% but is increased to 83% when the mixture is heated for eight hours.[66]

Relative Amounts of Components

In the preparation of Mannich products, various investigators have mixed the components in the calculated quantities or they have employed an excess of the amine salt and formaldehyde or an excess of the ketone. It is common practice to use 1.00 molecular equivalent of the carbonyl compound, 1.05–1.10 molecular equivalents of the amine salt, and 1.5–2.0 molecular equivalents of formaldehyde. Excellent yields of the basic ketone are obtained by the interaction of cyclohexanone, aqueous formaldehyde, and dimethylamine hydrochloride,[37] or morpholine hydrochloride,[47] when five times the calculated quantity of ketone is allowed to react. When excess formaldehyde is used, the material is added in several portions during the course of the reaction. Part of the formaldehyde reacts with ethanol, when this is used as a solvent, to form methylene diethyl ether.[9]

Due consideration should be given to the manner in which unchanged amine salt and formaldehyde can be separated from the desired product at the termination of the reaction. If difficulties are anticipated in such separations, the advantage to be gained by the employment of any of the components in excess may be questioned. If more than one reaction product is possible, the relative amounts of amine salt and formaldehyde may or may not influence the nature and yield of the product.[18, 19]

Isolation of Product

In a number of cases the salt of the desired product precipitates when the reaction mixture is cooled. Ether may be added to facilitate separation of the product. Occasionally the solvent is removed and crystallization of the residue brought about by washing it with ether or acetone. Sometimes it is advantageous to liberate the basic product from its salt

and purify the former by distillation, provided that the material can be distilled without decomposition.

By-Products

By-products of the reaction have been identified in some instances. They may be formed by some change of the reaction product itself, or they may be produced by condensation of the formaldehyde with the amine or ketone. Thus, diethylamine may be converted to N,N′-tetraethylmethylenediamine,[43] and piperidine to methylenedipiperidine.[56] From reactions involving cyclohexanone, there have been isolated 2-methylene cyclohexanone [37] and di-(2-cyclohexanonylmethyl) ether.[37] Similarly, methylenedi-β-naphthol [25] and methylenedianti-pyrine [17] have been produced in reactions involving β-naphthol and antipyrine, respectively.

Procedures

Preparation of Phenyl β-Piperidinoethyl Ketone Hydrochloride.[11] A mixture of 12.2 g. (0.1 mole) of piperidine hydrochloride, 0.25 cc. of concentrated hydrochloric acid, 4.5 g. (0.15 mole) of paraformaldehyde, 30 cc. of absolute ethanol, and 12.0 g. (0.1 mole) of acetophenone is heated to reflux. After one hour, 3 g. (0.1 mole) of paraformaldehyde is added to the solution and refluxing is continued for two hours. To the hot mixture is added 250 cc. of boiling acetone, and the resulting solution is cooled slowly, finally in ice water. The white crystalline product is collected on a filter; it weighs 21.5 g. (85%) and melts at 185–189°. For purification it is dissolved in 95% ethanol (4 cc. per g.), and the hot solution is diluted with a fourfold volume of boiling acetone. The recovery of material melting at 192–193° is about 80%.

1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-1,2,3,4-tetrahydronaphthalene.[16] A mixture of 5.0 g. (0.034 mole) of α-tetralone, 4.0 g. (0.041 mole) of 30% aqueous formaldehyde, and 6.1 g. (0.036 mole) of tetrahydroisoquinoline hydrochloride is prepared in a small (preferably 50-cc.) three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a tube for admission of nitrogen. A slow stream of nitrogen is passed through the apparatus while the mixture is stirred and heated on the steam bath for one and one-half hours. The brown viscous mass is dissolved in water, and the solution is freed of neutral substances by extraction with ether. Concentrated ammonium hydroxide is then added to the aqueous solution until no further separation of water-insoluble material occurs. The product is collected by extraction with ether. The residue obtained by distillation of the ether solidifies upon washing with cold ethanol. Recrystallization of the crude material

(7.4 g.) from the minimum quantity of ethanol yields 6.6 g. (66%) of the pure aminoketone, m.p. 90–91°.

2,4,6-Tri-(dimethylaminomethyl)-phenol.[23] A mixture of 94 g. (1 mole) of phenol and 720 g. (4 moles) of 25% aqueous dimethylamine solution is cooled to 20° in a 2-l. three-necked flask fitted with a stirrer, a thermometer for reading the internal temperature, and an addition funnel. The mixture is stirred while 350 g. of 30% aqueous formaldehyde is added dropwise over a period of about one-half hour, the reaction mixture being maintained at 25–30°. Stirring at this temperature is continued for one hour after completion of the addition. The addition funnel is then replaced by a reflux condenser, and the solution is stirred and heated on a steam bath for two hours. To the hot solution is added 200 g. of sodium chloride, and stirring and heating are continued for about twenty minutes.

The organic layer is separated from the hot solution and transferred to a 500-cc. Claisen flask. It is distilled under diminished pressure; the fraction boiling at 130–150°/1-2 mm. weighs 228 g. (86%). The slight red color can be removed by redistillation (b.p. 130–135°/1 mm.) with almost no loss.

EXAMPLES OF THE MANNICH REACTION

The reactions summarized in Table V are classified according to the complexity of the basic component of the reaction mixture. Thus, reactions involving ammonia or its salts are listed first, and those involving secondary amines or their salts, last. Only the name or formula of the aminoketone is given in the product column; in reactions involving amine or ammonium salts it is to be understood that the product is also a salt. The yields are those given in the literature; sometimes they refer to purified products, sometimes to crude materials. Undoubtedly, many of the yields could be improved by a thorough study of optimum reaction conditions and processes of isolation and purification.

TABLE V *

EXAMPLES OF THE REACTION

Reactants	Product (Yield)
Ammonia, formaldehyde, and	
Tartronic acid [42]	$HOC(COOH)_2CH_2NH_2$ (39%)
Benzylmalonic acid [19]	$C_6H_5CH_2C(COOH)_2CH_2NH_2$ (65%)
	$[C_6H_5CH_2C(COOH)_2CH_2]_2NH$ (53%)
Phenylmalonic acid [19]	$C_6H_5CH(COOH)CH_2NH_2$ (63%)
Ammonia, benzaldehyde, and	
Dimethyl (and diethyl) acetonedicarboxylate [4d]	Dimethyl (and diethyl) 2,6-diphenyl-4-piperidone-3,5-dicarboxylate (good)
Ammonium chloride, formaldehyde, and	
Acetone [1b] [29]	1,4-Dimethyl-3-acetyl-4-hydroxypiperidine (—)
Diethyl ketone [29]	1,3,5-Trimethyl-4-piperidone (29) (—)
Acetophenone [3, 36]	$(C_6H_5COCH_2CH_2)_3N$ (23–31%)
	1-(β-Benzoylethyl)-3-benzoyl-4-hydroxy-4-phenylpiperidine (27%)
Cyclohexanone [37]	Tri-(2-cyclohexanonylmethyl)-amine (—)
Antipyrine [5]	Tri-(4-antipyrylmethyl)-amine (86%)
p-Tolypyrine [5]	Tri-(*p*-tolypyrylmethyl)-amine (72%)
Homoantipyrine [5]	Tri-(homoantipyrylmethyl)-amine (70%)
Phenylmalonic acid [19]	$[C_6H_5CH(COOH)CH_2]_2NH$ (63%)
Ammonium bromide,† acetaldehyde, and	
Diethyl acetonedicarboxylate [39]	Diethyl 2,6-dimethyl-4-piperidone-3,5-dicarboxylate (46 5%)
Methylamine, formaldehyde, and	
Tartronic acid [42]	$HOC(COOH)_2CH_2NHCH_6$ (33%)
Methylmalonic acid,‡ [31]	$[CH_3C(COOH)_2CH_2]_2NCH_3$ (34%)
Ethylmalonic acid [19]	$CH_3CH_2C(COOH)_2CH_2NHCH_3$ (—)
Benzylmalonic acid [19]	$C_6H_5CH_2C(COOH)_2CH_2NHCH_3$ (very good)
Phenacylmalonic acid [19]	$C_6H_5COCH_2C(COOH)_2CH_2NHCH_3$ (good)
4-Nitrophenylacetic acid [67]	(4)$NO_2C_6H_4CH(COOH)CH_2NHCH_3$ (20%)
Diethyl α,α′-diethylacetonedicarboxylate [32]	Diethyl 1-methyl-3,5-diethyl-4-piperidone-3,5-dicarboxylate (40%)
Diethyl α,α′-diallylacetonedicarboxylate [32]	Diethyl 1-methyl-3,5-diallyl-4-piperidone-3,5-dicarboxylate (65–70%)
Diethyl 2,6-dimethyltetrahydropyrone-3,5-dicarboxylate [35]	A "pydin" § (64%)
Diethyl 2,6-diphenyltetrahydropyrone-3,5-dicarboxylate [35]	A "pydin" (>80%)
Dimethyl 1-methyl-2,6-diphenyl-4-piperidone-3,5-dicarboxylate [34]	A "bispidin" § (74%)
Dimethyl 1-allyl-2,6-diphenyl-4-piperidone-3,5-dicarboxylate [34]	A "bispidin" § (70%)
Dimethyl tropanone-2,4-dicarboxylate [33]	A tricyclic compound § (45–50%)
Methylamine, benzaldehyde, and	
Dimethyl (and diethyl) acetonedicarboxylate [34, 4d]	Dimethyl (and diethyl) 1-methyl-2,6-diphenyl-4-piperidone-3,5-dicarboxylate (65%)

* References 67–74 appear on p 341

† The piperidone was obtained in smaller amount when ammonium chloride was used in place of ammonium bromide, the yield was still lower when ammonia was substituted for an ammonium salt

‡ Malonic acid yielded an unidentified product

§ See p 314

TABLE V *—*Continued*

EXAMPLES OF THE REACTION

Reactants	Product (Yield)
Methylamine hydrochloride, formaldehyde, and	
Acetone [29, 1a]	$(CH_3COCH_2CH_2)_2NCH_3$ (56%)
	1,4-Dimethyl-3-acetyl-4-hydroxypiperidine (—)
Diethyl ketone [29]	$CH_3CH_2COCH(CH_3)CH_2NH(CH_3)$ (—)
	1,3,5-Trimethyl-4-piperidone (—)
	$CH_3CH[CH_2NH(CH_3)]COCH[CH_2NH(CH_3)]CH_3$ or $CH_3CH_2COC[CH_2NH(CH_3)]_2CH_6$ (—)
	$[CH_3CH_2COCH(CH_3)CH_2]_2NCH_3$ (—)
Acetophenone [41, 10]	$C_6H_5COCH_2CH_2NHCH_3$ (70%)
	$(C_6H_5COCH_2CH_2)_2NCH_3$ (34%)
Cyclohexanone [37]	Methyldi-(2-cyclohexanonylmethyl)-amine (2.4%+)
2-Acetylthiophene [10]	Methyl di-[2-(α-thenoyl)-ethyl]-amine (61%)
Antipyrine [17]	Methyldi-(4-antipyrylmethyl)-amine (92%)
Isobutyraldehyde [30]	$(CH_3)_2C(CHO)CH_2NHCH_3$ (70%)
Dimethyl (and diethyl) 1,2,6-trimethyl-4-piperidone-3,5-dicarboxylate [33]	A "bispidin" (70%)
Methylamine hydrochloride, acetaldehyde, and	
Diethyl acetonedicarboxylate [39]	Diethyl 1,2,6-trimethyl-4-piperidone-3,5-dicarboxylate (—)
Ethylamine, benzaldehyde, and	
Diethyl acetonedicarboxylate [4d]	Diethyl 1-ethyl-2,6-diphenyl-4-piperidone-3,5-dicarboxylate (—)
Ethylamine hydrochloride, formaldehyde, and	
2-Methyl-8-nitroquinoline [26]	Ethyldi-[β-(8-nitro-2-quinolyl)-ethyl]-amine (—)
Antipyrine [17]	Ethyldi-(4-antipyrylmethyl)-amine (—)
β-Hydroxyethylamine, benzaldehyde, and	
Dimethyl acetonedicarboxylate [34]	Dimethyl 1-(β-hydroxyethyl)-2,6-diphenyl-4-piperidone-3,5-dicarboxylate (65%)
β-Chloroethylamine hydrochloride, formaldehyde, and	
Dimethyl 1,2,6-trimethyl-4-piperidone-3,5-dicarboxylate [33]	A "bispidin" (63%)
β-Phenylethylamine hydrochloride, formaldehyde, and	
Dimethyl 1,2,6-trimethyl-4-piperidone-3,5-dicarboxylate [33]	A "hispidin" (—)
β-Phenylethylamine hydrochloride, † *acetaldehyde, and*	
Dimethyl acetonedicarboxylate [39]	Dimethyl 1-(β-phenylethyl)-2,6-dimethyl-4-piperidone-3,5-dicarboxylate (—)
Allylamine, formaldehyde, and	
Benzylmalonic acid [19]	$C_6H_5CH_2C(COOH)_2CH_2NHCH_2CH{=}CH_2$ (good)
Dimethyl 1-methyl-2,6-diphenyl-4-piperidone-3,5-dicarboxylate [34]	A "bispidin" (75%)
Allylamine, benzaldehyde, and	
Dimethyl acetonedicarboxylate [34]	Dimethyl 1-allyl-2,6-diphenyl-4-piperidone-3,5-dicarboxylate (70%)

* References 67–74 appear on p. 341.

† Neither the racemic nor the dextro or levo modification of α-phenylethylamine hydrochloride could be made to react with acetaldehyde and the ester of acetonedicarboxylic acid.

TABLE V *—*Continued*

EXAMPLES OF THE REACTION

Reactants	Product (Yield)
Allylamine, anisaldehyde, and Dimethyl acetonedicarboxylate [34]	Dimethyl 1-allyl-2,6-di-*p*-anisyl-4-piperidone-3,5-dicarboxylate (70%)
Allylamine hydrochloride, formaldehyde, and Dimethyl 1,2,6-trimethyl-4-piperidone-3,5-dicarboxylate [33]	A "bispidin" (—)
Antipyrine [17]	Allyldi-(4-antipyrylmethyl)-amine (—)
ω-Aminoacetophenone hydrochloride, formaldehyde, and Antipyrine [17]	$C_6H_5COCH_2NR_2$; R = 4-antipyrylmethyl (98%)
Ethyl aminoacetate hydrochloride, formaldehyde, and Antipyrine [17]	$R_2NCH_2CO_2C_2H_5$; R = 4-antipyrylmethyl (—)
Benzylamine, phenylacetaldehyde, and Cyclohexanone [36]	$C_6H_5CH_2NHCH(CH_2C_6H_5)C_6H_9O$ (1.5%)
Benzylamine hydrochloride, formaldehyde, and Acetone [38]	$CH_3COCH_2CH_2NHCH_2C_6H_5$ (>3%)
Benzalacetone [36]	$C_6H_5CH{=}CHCOCH_2CH_2NHCH_2C_6H_5$ (20%)
	1-Benzyl-3-cinnamyl-4-styryl-4-hydroxypiperidine (10%)
Acetophenone [33]	$C_6H_5COCH_2CH_2NHCH_2C_6H_5$ (53%)
	1-Benzyl-3-benzoyl-4-phenyl-4-hydroxypiperidine (—)
Cyclopentanone [33]	Benzyl-(2-cyclopentanonylmethyl)-amine (—)
Cyclohexanone [36]	Benzyl-(2-cyclohexanonylmethyl)-amine (65%)
	A decahydroisoquinoline † (10–25%)
α-Tetralone [36]	β-(Benzylaminomethyl)-α-tetralone (55%)
Benzylamine hydrochloride, acetaldehyde, and Dimethyl acetonedicarboxylate [39]	Dimethyl 1-benzyl-2,6-dimethyl-4-piperidone-3,5-dicarboxylate (30%)
3,4-Methylenedioxybenzylamine hydrochloride, formaldehyde, and Acetone [36]	$CH_3COCH_2CH_2NHCH_2C_6H_3(O_2CH_2)(3,4)$ (20%)
Benzalacetone [36]	$C_6H_5CH{=}CHCOCH_2CH_2NHCH_2C_6H_3(O_2CH_2)(3,4)$ (52%)
Acetophenone [36]	$C_6H_5COCH_2CH_2NHCH_2C_6H_3(O_2CH_2)(3,4)$ (56%)
Cyclopentanone [36]	2-(3,4-Methylenedioxybenzylaminomethyl)-cyclopentanone (67%)
Cyclohexanone [36]	2-(3,4-Methylenedioxybenzylaminomethyl)-cyclohexanone (—)
	A decahydroisoquinoline † (—)
α-Tetralone [36]	β-(3,4-Methylenedioxybenzylaminomethyl)-α-tetralone (70%)
Aniline, benzaldehyde, and Acetone [4d]	1,2,6-Triphenyl-4-piperidone (—)
Tetrahydro-β-naphthylamine hydrochloride, formaldehyde, and Antipyrine [17]	Tetrahydro-β-naphthyldi-(4-antipyrylmethyl)-amine (—)
Ethylenediamine hydrochloride, formaldehyde, and Antipyrine [17]	Tetra-(4-antipyrylmethyl)-ethylenediamine (77%)

* References 67–74 appear on p. 341.
† See p. 326.

TABLE V *—*Continued*

EXAMPLES OF THE REACTION

Reactants	Product (Yield)
Dimethylamine, formaldehyde, and	
Cyanoacetic acid [19]	$CNCH_2CH_2N(CH_3)_2$ † (—)
4-Nitrophenylacetic acid [67]	(4) $NO_2C_6H_4CH(COOH)CH_2N(CH_3)_2$ (67%)
2,4-Dinitrophenylacetic acid [67]	(2,4) $(NO_2)_2C_6H_3CH[CH_2N(CH_3)_2]_2$ (52%)
Benzoylacetic acid [56]	$C_6H_5COCH_2CH_2N(CH_3)_2$ (—)
Pyruvic acid [20]	$(CH_3)_2NCH_2CHCOCOOCH_2$ ‡ (56%)
Acetoacetic acid [56]	$CH_6COCH_2CH_2N(CH_3)_2$ (42%)
	$CH_6COCH[CH_2N(CH_3)_2]_2$ (28%)
Methylacetoacetic acid [56]	$CH_3COCH(CH_3)CH_2N(CH_6)_2$ (—)
Ethylacetoacetic acid [20]	$CH_3COCH(C_2H_5)CH_2N(CH_6)_2$ ‡ (30%)
Allylacetoacetic acid [56]	$CH_6COCH(CH_2CH{=}CH_2)CH_2N(CH_3)_2$ (38%)
Levulinic acid [20]	$(CH_3)_2NCH_2CH_2COCH_2CH_2COOH$ ‡ (21%)
Malonic acid [31]	$CH(COOH)[CH_2N(CH_3)_2]_2$ (47%)
Methylmalonic acid [31]	$CH_3C(COOH)_2CH_2N(CH_3)_2$ (55%)
Ethylmalonic acid [19]	$CH_3CH_2C(COOH)_2CH_2N(CH_3)_2$ (70%)
Allylmalonic acid [19]	$CH_2{=}CHCH_2C(COOH)_2CH_2N(CH_3)_2$ (90%)
Benzylmalonic acid [19]	$C_6H_5CH_2C(COOH)_2CH_2N(CH_3)_2$ (90%)
Phenylmalonic acid [19]	$C_6H_5CH(COOH)CH_2N(CH_3)_2$ (60%)
γ-Phenylpropylmalonic acid [19]	$C_6H_5CH_2CH_2CH_2C(COOH)_2CH_2N(CH_3)_2$ (90%)
Phenacylmalonic acid [19]	$C_6H_5COCH_2C(COOH)_2CH_2N(CH_3)_2$ (45%)
Tartronic acid [42]	$HOC(COOH)_2CH_2N(CH_3)_2$ (54%)
Ethanetricarboxylic acid [19]	$(HOOC)_2C(CH_2COOH)CH_2N(CH_3)_2$ (46%)
Phenylacetylene [26]	$C_6H_5C{\equiv}CCH_2N(CH_3)_2$ (—)
2-Aminophenylacetylene [26]	(2) $NH_2C_6H_4C{\equiv}CCH_2N(CH_3)_2$ (—)
Antipyrine [6]	4-Dimethylaminomethylantipyrine (60%)
Phenol [21, 22, 23]	2-(Dimethylaminomethyl)-phenol (—)
	2,6-Di-(dimethylaminomethyl)-phenol (poor)
	2,4,6-Tri-(dimethylaminomethyl)-phenol (86%)
4-Acetylaminophenol [21]	2-(Dimethylaminomethyl)-4-acetylaminophenol (—)
o-Cresol [22]	2-(Dimethylaminomethyl)-6-methylphenol (—)
m-Cresol [23]	2,4,6-Tri-(dimethylaminomethyl)-3-methylphenol (—)
p-Cresol [22]	2-(Dimethylaminomethyl)-4-methylphenol (—)
	2,6-Di-(dimethylaminomethyl)-4-methylphenol (—)
2-Methoxyphenol [25]	2-Methoxy-6-(dimethylaminomethyl)-phenol (—)
4-Methoxyphenol [25]	4-Methoxy-6-(dimethylaminomethyl)-phenol (—)
3,5-Dimethylphenol [24]	2-(Dimethylaminomethyl) 3,5-dimethylphenol (34%)
2-Methyl-4-ethylphenol [22]	2-Methyl-4-ethyl-6-(dimethylaminomethyl)-phenol (—)
Catechol [25]	Dimethylaminomethylcatechol (—) ‡
Resorcinol [25]	Dimethylaminomethylresorcinol (—) ‡
Hydroquinone [24, 25]	2,5-*bis*-(Dimethylaminomethyl)-hydroquinone (almost quantitative) ‡
Phloroglucinol [25]	Dimethylaminomethylphloroglucinol (—) ‡
	bis-(Dimethylaminomethyl)-phloroglucinol (—) ‡
Indole [74]	3-Dimethylaminomethylindole (almost quantitative)
β-Naphthol [25]	Dimethylaminomethyl-β-naphthol (—)
Dimethylamine hydrochloride, formaldehyde, and	
Acetone [29, 59]	$CH_3COCH_2CH_2N(CH_3)_2$ § (—) (14%)
	$CH_6COCH[CH_2N(CH_3)_2]_2$ § (—) (58%)
Methyl ethyl ketone [62]	$CH_3COCH(CH_3)CH_2N(CH_3)_2$ (—)
	$CH_3CH_2COCH_2CH_2N(CH_3)_2$ (—)
Methyl propyl ketone [62]	$CH_3COCH(C_2H_5)CH_2N(CH_3)_2$ (—)

* References 67–74 appear on p 341
† The product could not be obtained in crystalline form
‡ In this instance the amine salt was employed
§ The amine base was used

TABLE V *—*Continued*

EXAMPLES OF THE REACTION

Reactants	Product (Yield)
Diethyl ketone [29]	$CH_3CH_2COCH(CH_3)CH_2N(CH_3)_2$ (31%)
Acetophenone [41]	$C_6H_5COCH_2CH_2N(CH_3)_2$ (60%)
2-Nitroacetophenone [12]	(2) $NO_2C_6H_4COCH_2CH_2N(CH_6)_2$ (80–90%)
3-Nitroacetophenone [12]	(3) $NO_2C_6H_4COCH_2CH_2N(CH_3)_2$ (80–90%)
3-Acetylaminoacetophenone [12]	(3) $(CH_3CONH)C_6H_4COCH_2CH_2N(CH_6)_2$ (55%)
3-Benzoylaminoacetophenone [12]	(3) $(C_6H_5CONH)C_6H_4COCH_2CH_2N(CH_6)_2$ (79%)
Acetoanisone [11]	(4) $CH_3OC_6H_4COCH_2CH_2N(CH_3)_2$ (—)
Acetoveratrone [11]	(3,4) $(CH_3O)_2C_6H_3COCH_2CH_2N(CH_3)_2$ (—)
Benzalacetone [50, 54]	$C_6H_5CH{=}CHCOCH_2CH_2N(CH_3)_2$ (25%)
4-Anisalacetone [50]	(4) $CH_3OC_6H_4CH{=}CHCOCH_2CH_2N(CH_3)_2$ (63%)
Piperonalacetone [51]	(3,4) $(CH_2O_2)C_6H_3CH{=}CHCOCH_2CH_2N(CH_6)_2$ (—)
3-Methoxy-4-ethoxybenzalacetone [51]	(3,4) $(CH_6O)(C_2H_5O)C_6H_3CH{=}CHCOCH_2CH_2N(CH_3)_2$ (—)
3-Ethoxy-4-methoxybenzalacetone [51]	(3,4) $(C_2H_5O)(CH_3O)C_6H_3CH{=}CHCOCH_2CH_2N(CH_3)_2$ (—)
6-Nitropiperonalacetone [55]	(3,4) (6) $(CH_2O_2)(NO_2)C_6H_2CH{=}CHCOCH_2CH_2N(CH_3)_2$ (—)
6-Nitroveratralacetone [55]	(3,4,6) $(CH_3O)_2(NO_2)C_6H_2CH{=}CHCOCH_2CH_2N(CH_3)_2$ (20–25%)
Methyl β-naphthyl ketone [68]	β-$C_{10}H_7COCH_2CH_2N(CH_6)_2$ (70%)
β-Acetotetralin [11]	β-(β-Dimethylaminopropionyl)-tetralin (—)
2-Acetylphenanthrene [65]	2-(β-Dimethylaminopropionyl)-phenanthrene (—)
3-Acetylphenanthrene [65]	3-(β-Dimethylaminopropionyl)-phenanthrene (—)
9-Acetylphenanthrene [65]	9-(β-Dimethylaminopropionyl)-phenanthrene (—)
Cyclopentanone [61]	2-(Dimethylaminomethyl)-cyclopentanone (—)
Cyclohexanone [37]	2-(Dimethylaminomethyl)-cyclohexanone (85%)
4-Methylcyclohexanone [40]	2-(Dimethylaminomethyl)-4-methylcyclohexanone (—)
Menthone [40]	Dimethylaminomethylmenthone † (54%)
α-Tetralone [58]	β-(Dimethylaminomethyl)-α-tetralone (70%)
1-Keto-1,2,3,4-tetrahydrophenanthrene [15]	1-Keto-2-dimethylaminomethyl-1,2,3,4-tetrahydrophenanthrene (65%)
4-Keto-1,2,3,4-tetrahydrophenanthrene [15]	4-Keto-3-dimethylaminomethyl-1,2,3,4-tetrahydrophenanthrene (77%)
2-Acetylfuran [13]	2-Furyl β-dimethylaminoethyl ketone (—)
Furfuralacetone [49]	$C_4H_3OCH{=}CHCOCH_2CH_2N(CH_3)_2$ (—)
2-Acetylthiophene [13, 10]	2-Thienyl β-dimethylaminoethyl ketone (47%)
2-Acetyldibenzothiophene [14]	β-Dimethylaminoethyl 2-dibenzothienyl ketone (41%) ‡
2-Propionylthiophene [10]	α-(Dimethylaminomethyl)-ethyl 2-thienyl ketone (60%)
2-Acetyl-4-phenylthiazole [13]	β-Dimethylaminoethyl 4-phenyl-2-thiazolyl ketone (—)
Antipyrine [17]	4-Dimethylaminomethylantipyrine (90%)
Isoantipyrine [17]	1-Phenyl-2,5-dimethyl-4-dimethylaminomethylpyrazolone-3 (74%)
2-Acetyl-9-methylcarbazole [69]	β-Dimethylaminoethyl 2-(9-methylcarbazyl) ketone (18%)
3-Acetyl-9-methylcarbazole [66]	β-Dimethylaminoethyl 3-(9-methylcarbazyl) ketone (61%) ‡
1-Keto-9-methyl-1,2,3,4-tetrahydrocarbazole [69]	1-Keto-2-dimethylaminomethyl-9-methyl-1,2,3,4-tetrahydrocarbazole (10–15%)
Acetaldehyde [16]	$[(CH_6)_2NCH_2]_2C(CH_2OH)CHO$ (practically quantitative)
Propionaldehyde [16]	$CH_3CH[CH_2N(CH_3)_2]CHO$ (15%)
	$CH_3C[CH_2N(CH_3)_2]_2CHO$ (—)

* References 67–74 appear on p. 341.
† A mixture of isomers seems to be formed.
‡ Yield based on the amount of original ketone not recovered from the reaction mixture.

TABLE V *—*Continued*

EXAMPLES OF THE REACTION

Reactants	Product (Yield)
Butyraldehyde [18]	$CH_3CH_2CH[CH_2N(CH_3)_2]CHO$ (—)
	$CH_3CH_2C(=CH_2)CHO$ (—)
Isobutyraldehyde [16]	$(CH_3)_2C[CH_2N(CH_3)_2]CHO$ (70–80%)
Isovaleraldehyde [18]	$(CH_3)_2CHCH[CH_2N(CH_3)_2]CHO$ (—)
	$(CH_3)_2CH(CH_2OH)[CH_2N(CH_3)_2]CHO$ (—)
Hexahydrobenzaldehyde [18]	1-Dimethylaminomethylhexahydrobenzaldehyde (—)
2-Methylquinoline [26]	2-(β-Dimethylaminoethyl)-quinoline (—)
2-Methyl-4-hydroxyquinoline [26]	2-(β-Dimethylaminoethyl)-4-hydroxyquinoline (—)
2-Ethoxy-4-methylquinoline [23]	2-Ethoxy-4-(β-dimethylaminoethyl)-quinoline (—)
Diethylamine, formaldehyde, and	
2,4-Dinitrophenylacetic acid [67]	$(2,4)(NO_2)_2C_6H_3CH[CH_2N(C_2H_5)_2]_2$ (52%)
Benzylacetoacetic acid [56]	$CH_3COCH(CH_2C_6H_5)CH_2N(C_2H_5)_2$ (46%)
Monoethylmalonate [43]	$C_2H_5OOCCH_2CH_2N(C_2H_5)_2$ (21%)
	$C_2H_5OOCCH[CH_2N(C_2H_5)_2]_2$ (—)
Monoethyl methylmalonate [43]	$C_2H_5OOCC(=CH_2)CH_3$ (88%)
Monoethyl ethylmalonate [43]	$C_2H_5OOCC(=CH_2)CH_2CH_3$ (63%)
Monoethyl allylmalonate [43]	$C_2H_5OOCC(=CH_2)CH_2CH{=}CH_2$ (quantitative)
Monoethyl benzylmalonate [43]	$C_2H_5OOCC(=CH_2)CH_2C_6H_5$ (73%)
Diethyl 2,6-dimethyltetrahydropyrone-3,5-dicarboxylate [35]	Diethyl 2,6-dimethyl-3-diethylaminomethyltetrahydropyrone-3,5-dicarboxylate (30%)
Phenylacetylene [26]	$C_6H_5C{\equiv}CCH_2N(C_2H_5)_2$ (80%)
2-Nitrophenylacetylene [26]	$(2)NO_2C_6H_4C{\equiv}CCH_2N(C_2H_5)_2$ (—)
4-Nitrophenylacetylene [26]	$(4)NO_2C_6H_4C{\equiv}CCH_2N(C_2H_5)_2$ (—)
4-Methoxyphenylacetylene [26]	$(4)CH_3OC_6H_4C{\equiv}CCH_2N(C_2H_5)_2$ (—)
α-Picoline [27]	2-(β-Diethylaminoethyl)-pyridine (80%)
Quinaldine [7, 27]	2-(β-Diethylaminoethyl)-quinoline (33%)
Diethylamine hydrochloride, formaldehyde, and	
Acetone [6]	$CH_3COCH_2CH_2N(C_2H_5)_2$ (66%)
Acetophenone [10]	$C_6H_5COCH_2CH_2N(C_2H_5)_2$ (45%)
2-Nitroacetophenone [12]	$(2)NO_2C_6H_4COCH_2CH_2N(C_2H_5)_2$ (80–90%)
3-Nitroacetophenone [12]	$(3)NO_2C_6H_4COCH_2CH_2N(C_2H_5)_2$ (80–90%)
Acetoveratrone [11]	$(3,4)(CH_3O)_2C_6H_3COCH_2CH_2N(C_2H_5)_2$ (—)
Benzalacetone [9]	$C_6H_5CH{=}CHCOCH_2CH_2N(C_2H_5)_2$ (60%)
4-Anisalacetone [50]	$(4)CH_3OC_6H_4CH{=}CHCOCH_2CH_2N(C_2H_5)_2$ (60%)
2-Butoxybenzalacetone [52]	$(2)C_4H_9OC_6H_4CH{=}CHCOCH_2CH_2N(C_2H_5)_2$ (5–10%)
Methylenedioxybenzalacetone [9]	$(3,4)(CH_2O_2)C_6H_6CH{=}CHCOCH_2CH_2N(C_2H_5)_2$ (60%)
3,4-Dimethoxybenzalacetone [9, 51]	$(3,4)(CH_6O)_2C_6H_3CH{=}CHCOCH_2CH_2N(C_2H_5)_2$ (60%)
3-Ethoxy-4-methoxybenzalacetone [51]	$(3,4)(C_2H_5O)(CH_3O)C_6H_3CH{=}CHCOCH_2CH_2N(C_2H_5)_2$ (—)
6-Nitropiperonalacetone [55]	$(3,4,6)(CH_2O_2)(NO_2)C_6H_2CH{=}CHCOCH_2CH_2N(C_2H_5)_2$ (50%)
6-Nitroveratralacetone [55]	$(3,4,6)(CH_3O)_2(NO_2)C_6H_2CH{=}CHCOCH_2CH_2N(C_2H_5)_2$ (40%)
2-Acetylphenanthrene [65]	2-(β-Diethylaminopropionyl)-phenanthrene (—)
3-Acetylphenanthrene [65]	3-(β-Diethylaminopropionyl)-phenanthrene (—)
9-Acetylphenanthrene [65]	9-(β-Diethylaminopropionyl)-phenanthrene (—)
2-Methylcyclopentanone [8]	2-Methyl-5-diethylaminomethylcyclopentanone (71%)
Cyclohexanone [40]	2-Diethylaminomethylcyclohexanone (83%)
2-Methylcyclohexanone [6]	2-Methyl-6-diethylaminomethylcyclohexanone (60–65%)
1-Keto-1,2,3,4-tetrahydrophenanthrene [15]	1-Keto-2-diethylaminomethyl-1,2,3,4-tetrahydrophenanthrene (59%)

* References 67–74 appear on p. 341.

TABLE V *—*Continued*

EXAMPLES OF THE REACTION

Reactants	Product (Yield)
4-Keto-1,2,3,4-tetrahydrophenanthrene [15]	4-Keto-3-diethylaminomethyl-1,2,3,4-tetrahydrophenanthrene (51%)
1-Keto-9-methoxy-1,2,3,4-tetrahydrophenanthrene [70]	1-Keto-2-diethylaminomethyl-9-methoxy-1,2,3,4-tetrahydrophenanthrene (41%)
1-Keto-9-acetoxy-1,2,3,4-tetrahydrophenanthrene [70]	1-Keto-2-diethylaminomethyl-9-acetoxy-1,2,3,4-tetrahydrophenanthrene (20%)
Furfuralacetone [49]	$C_4H_3OCH{=}CHCOCH_2CH_2N(C_2H_5)_2$ (—)
Chromanone [71]	3-Diethylaminomethyl-4-chromanone (—)
2-Acetylthiophene [10]	β-Diethylaminoethyl 2-thienyl ketone (39%)
2-Acetyldibenzothiophene [14]	β-Diethylaminoethyl 2-dibenzothienyl ketone (40%)
Antipyrine [17]	4-Diethylaminomethylantipyrine (—)
2-Acetyl-9-methylcarbazole [69]	β-Diethylaminoethyl 2-(9-methylcarbazyl) ketone (20–25%)
3-Acetyl-9-methylcarbazole [66]	β-Diethylaminoethyl 3-(9-methylcarbazyl) ketone (83%)†
2-Acetyl-4-phenylthiazole [13]	β-Diethylaminoethyl 4-phenyl-2-thiazolyl ketone (—)
Isobutyraldehyde [16]	$(CH_3)_2C[CH_2N(C_2H_5)_2]CHO$ (—)
Diethanolamine hydrochloride, formaldehyde, and	
2-Acetylfuran [13]	Di-β-(β-hydroxyethyl)-aminoethyl 2-furyl ketone (—)
Dipropylamine, formaldehyde, and	
Ethylacetoacetic acid [56]	$CH_3COCH(C_2H_5)CH_2N(C_6H_7)_2$ (40%)
Dipropylamine hydrochloride, formaldehyde, and	
Anisalacetone [50]	(4)$CH_3OC_6H_4CH{=}CHCOCH_2CH_2N(C_3H_7)_2$ (85%)
2-Acetylfuran [13]	β-Dipropylaminoethyl 2-furyl ketone (—)
2-Acetyl-4-phenylthiazole [13]	β-Dipropylaminoethyl 4-phenyl-2-thiazolyl ketone (—)
Dibutylamine hydrochloride, formaldehyde, and	
2-Acetylfuran [13]	β-Dibutylaminoethyl 2-furyl ketone (—)
Anisalacetone [50]	(4)$CH_3OC_6H_4CH{=}CHCOCH_2CH_2N(C_4H_9)_2$ (16%)
Diisoamylamine hydrochloride, formaldehyde, and	
Acetophenone [63]	$C_6H_5COCH_2CH_2N(C_5H_{11})_2$ (54%)
Methyldiethylethylenediamine hydrochloride, formaldehyde, and	
2-Methyl-4-hydroxyquinoline [28]	Methyldiethyl-β-(4-hydroxy-2-quinolyl)-ethylethylenediamine (—)
ω-Methylaminopropiophenone hydrochloride, formaldehyde, and	
Antipyrine [64]	$C_6H_5COCH_2CH_2N(CH_3)R$; R = 4-antipyrylmethyl (—)
β-Acetylethylbenzylamine hydrochloride, formaldehyde, and	
Acetone [38]	1-Benzyl-3-(α-hydroxyethyl)-4-methyl-4-hydroxypiperidine (—)
Dibenzylamine hydrochloride, formaldehyde, and	
Anisalacetone [50]	(4)$CH_6OC_6H_4CH{=}CHCOCH_2CH_2N(CH_2C_6H_5)_2$ (93%)

* References 67–74 appear on p. 341.
† Yield based on the amount of original ketone not recovered from the reaction mixture.

TABLE V *—*Continued*

EXAMPLES OF THE REACTION

Reactants	Product (Yield)
Benzyl-(2-cyclohexanonylmethyl)-amine hydrobromide, formaldehyde, and	
Acetone [36]	2-Benzyl-4-acetyl-10-hydroxydecahydroisoquinoline (73%)
Acetophenone [66]	2-Benzyl-4-benzoyl-10-hydroxydecahydroisoquinoline (7.5%)
3,4-Methylenedioxybenzyl-(2-cyclohexanonylmethyl)-amine hydrobromide, formaldehyde, and	
Acetone [38]	2-(3,4-Methylenedioxybenzyl)-4-acetyl-10-hydroxydecahydroisoquinoline (—)
Methylaniline, formaldehyde, and	
Quinaldine hydrochloride [7]	2-(β-Phenylmethylaminoethyl)-quinoline (—)
Methylaniline hydrochloride, formaldehyde, and	
Antipyrine [17]	4-(Phenylmethylaminomethyl)-antipyrine (49%)
Piperidine, formaldehyde, and	
Antipyrine [6]	4-Piperidinomethylantipyrine (44%)
Cyclohexanone [6]	2-Piperidinomethylcyclohexanone (37%)
4-Nitrophenylacetic acid [67]	(4)$NO_2C_6H_4CH(COOH)CH_2NC_5H_{10}$ (64%)
2,4-Dinitrophenylacetic acid [67]	(2,4)$(NO_2)_2C_6H_3CH(CH_2NC_5H_{10})_2$ (41%)
2-Nitromandelic acid [67]	(2)$NO_2C_6H_4C(OH)(COOH)CH_2NC_5H_{10}$ (75%)
Benzoylacetic acid [56]	$C_6H_5COCH_2CH_2NC_5H_{10}$ (90%)
Pyruvic acid [20]	$C_5H_{10}NCH_2CHCOCOOCH_2$ † (43%)
Methylacetoacetic acid [56]	$CH_3COCH(CH_3)CH_2NC_5H_{10}$ (60%)
Ethylacetoacetic acid [20]	$CH_3COCH(C_2H_5)CH_2NC_5H_{10}$ † (—)
Allylacetoacetic acid [56]	$CH_3COCH(CH_2CH{=}CH_2)CH_2NC_5H_{10}$ (30–45%)
Benzylacetoacetic acid [56]	$CH_3COCH(CH_2C_6H_5)CH_2NC_5H_{10}$ (46%)
Levulinic acid [20]	$CH_2(CH_2NC_5H_{10})COCH_2CH_2COOH$ (48%) †
Benzylmalonic acid [19]	$C_6H_5CH_2C(COOH)_2CH_2NC_5H_{10}$ (85%)
Tartronic acid [42]	$C(OH)(COOH)_2CH_2NC_5H_{10}$ (14%)
Diethyl 2,6-dimethyltetrahydropyrone-3,5-dicarboxylate [35]	Diethyl 2,6-dimethyl-3-(piperidinomethyl)-tetrahydropyrone-3,5-dicarboxylate (73%)
Phenylacetylene [26]	$C_6H_5C{\equiv}CCH_2NC_5H_{10}$ (—)
4-Methoxyphenylacetylene [26]	(4)$CH_3OC_6H_4C{\equiv}CCH_2NC_5H_{10}$ (—)
4-Acetylaminophenol [21]	2-Piperidinomethyl-4-acetylaminophenol (—)
β-Naphthol [25]	Piperidinomethyl-β-naphthol (—)
8-Hydroxyquinoline [21]	Piperidinomethyl-8-hydroxyquinoline (—)
Quinaldine hydrochloride [7]	2-(β-Piperidinoethyl)-quinoline (72%)
Indole [74]	3-Piperidinomethylindole (—)
Piperidine hydrochloride, formaldehyde, and	
Acetone [62]	$CH_6COCH_2CH_2NC_5H_{10}$ (good)
Methyl ethyl ketone [62]	$CH_3COCH(CH_3)CH_2NC_5H_{10}$ (—)
Pinacoline [62]	$(CH_3)_3CCOCH_2CH_2NC_5H_{10}$ (—)
Allylacetone [62]	$CH_2{=}CHCH_2CH_2COCH_2CH_2NC_5H_{10}$ (20%)
	$CH_2{=}CHCH_2CH(CH_2NC_5H_{10})COCH_3$ (—)
Acetophenone [11]	$C_6H_5COCH_2CH_2NC_5H_{10}$ (90%)
2-Nitroacetophenone [12]	(2)$NO_2C_6H_4COCH_2CH_2NC_5H_{10}$ (80–90%)
3-Nitroacetophenone [12]	(3)$NO_2C_6H_4COCH_2CH_2NC_5H_{10}$ (80–90%)
Acetoanisone [11]	(4)$CH_3OC_6H_4COCH_2CH_2NC_5H_{10}$ (—)

* References 67–74 appear on p. 341.
† In this instance the amine hydrochloride was used.

TABLE V *—*Continued*

EXAMPLES OF THE REACTION

Reactants	Product (Yield)
Desoxybenzoin [11]	$C_6H_5COCH(C_6H_5)CH_2NC_5H_{10}$ (—)
Acetoveratrone [11]	$(3,4)(CH_3O)_2C_6H_6COCH_2CH_2NC_5H_{10}$ (—)
Benzalacetone [9, 49, 50]	$C_6H_5CH{=}CHCOCH_2CH_2NC_5H_{10}$ (60%)
2-Methoxybenzalacetone [52]	$(2)CH_3OC_6H_4CH{=}CHCOCH_2CH_2NC_5H_{10}$ (13%)
2-Ethoxybenzalacetone [52]	$(2)C_2H_5OC_6H_4CH{=}CHCOCH_2CH_2NC_5H_{10}$ (30%)
2-Propoxybenzalacetone [52]	$(2)C_3H_7OC_6H_4CH{=}CHCOCH_2CH_2NC_5H_{10}$ (26%)
2-Butoxybenzalacetone [52]	$(2)C_4H_9OC_6H_4CH{=}CHCOCH_2CH_2NC_5H_{10}$ (26%)
Anisalacetone [9, 50]	$(4)CH_3OC_6H_4CH{=}CHCOCH_2CH_2NC_5H_{10}$ (60%)
Piperonalacetone [9, 51]	$(3,4)(CH_2O_2)C_6H_3CH{=}CHCOCH_2CH_2NC_5H_{10}$ (60%)
3,4-Dimethoxybenzalacetone [9, 51]	$(3,4)(CH_3O)_2C_6H_3CH{=}CHCOCH_2CH_2NC_5H_{10}$ (60%)
Ethyl 4-anisyl ketone [11]	$(4)CH_3OC_6H_4COCH(CH_3)CH_2NC_5H_{10}$ (—)
3-Methoxy-4-ethoxybenzalacetone [51]	$(3,4)(CH_3O)(C_2H_5O)C_6H_3CH{=}CHCOCH_2CH_2NC_5H_{10}$ (—)
3-Ethoxy-4-methoxybenzalacetone [51]	$(3,4)(C_2H_5O)(CH_6O)C_6H_3CH{=}CHCOCH_2CH_2NC_5H_{10}$ (—)
6-Nitropiperonalacetone [55]	$(3,4,6)(CH_2O_2)(NO_2)C_6H_2CH{=}CHCOCH_2CH_2NC_5H_{10}$ (60–65%)
6-Nitroveratralacetone [55]	$(3,4,6)(CH_3O)_2(NO_2)C_6H_2CH{=}CHCOCH_2CH_2NC_5H_{10}$ (55–60%)
2-Acetylphenanthrene [65]	2-(β-Piperidinopropionyl)-phenanthrene (—)
3-Acetylphenanthrene [65]	3-(β-Piperidinopropionyl)-phenanthrene (—)
9-Acetylphenanthrene [65]	9-(β-Piperidinopropionyl)-phenanthrene (—)
Methyl β-naphthyl ketone [66]	$(\beta)C_{10}H_7COCH_2CH_2NC_5H_{10}$ (60%)
β-Acetotetralin [11]	β-(β-Piperidinopropionyl)-tetralin (—)
Cyclopentanone [61]	2-Piperidinomethylcyclopentanone (90%)
Cyclohexanone [40]	2-Piperidinomethylcyclohexanone (62%)
4-Methylcyclohexanone [40]	2-Piperidinomethyl-4-methylcyclohexanone (93%)
α-Tetralone [56]	β-Piperidinomethyl-α-tetralone (75%)
1-Keto-1,2,3,4-tetrahydrophenanthrene [15]	1-Keto-2-piperidinomethyl-1,2,3,4-tetrahydrophenanthrene (—)
4-Keto-1,2,3,4-tetrahydrophenanthrene [15]	4-Keto-3-piperidinomethyl-1,2,3,4-tetrahydrophenanthrene (—)
1-Keto-9-methoxy-1,2,3,4-tetrahydrophenanthrene [70]	1-Keto-2-piperidino-9-methoxy-1,2,3,4-tetrahydrophenanthrene (63%)
2-Acetylfuran [13]	β-Piperidinoethyl 2-furyl ketone (—)
Furfuralacetone [49]	$C_4H_6OCH{=}CHCOCH_2CH_2NC_5H_{10}$ (—)
2-Acetylthiophene [10, 13]	β-Piperidinoethyl 2-thienyl ketone (74%)
2-Acetyldibenzothiophene [14]	β-Piperidinoethyl 2-dibenzothienyl ketone (55%) †
4-Acetyldibenzothiophene [14]	β-Piperidinoethyl 4-dibenzothienyl ketone (40%) †
2-Acetyl-4-phenylthiazole [13]	β-Piperidinoethyl 4-phenyl-2-thiazolyl ketone (—)
Antipyrine [6, 17]	4-Piperidinomethylantipyrine (70%)
Chromanone [71]	3-Piperidinomethyl-4-chromanone (28%)
Isobutyraldehyde [18]	$(CH_6)_2C(CH_2NC_5H_{10})CHO$ (—)
Isovaleraldehyde [16]	$(CH_3)_2CHCH(CH_2NC_5H_{10})CHO$ (—)
	$(CH_3)_2CHC(CH_2OH)(CH_2NC_5H_{10})CHO$ (70%)
Hexahydrobenzaldehyde [18]	1-Piperidinomethylhexahydrobenzaldehyde (—)
Tetrahydroisoquinoline hydrochloride, formaldehyde, and	
Acetophenone [11]	2-(β-Benzoylethyl)-1,2,3,4-tetrahydroisoquinoline (—)
2-Acetylphenanthrene [65]	2-(β-1,2,3,4-Tetrahydroisoquinolinopropionyl)-phenanthrene (—)

* References 67–74 appear on p. 341.
† Yield based on the amount of original ketone not recovered from the reaction mixture.

TABLE V *—*Continued*

EXAMPLES OF THE REACTION

Reactants	Product (Yield)
3-Acetylphenanthrene [65]	3-(β-1,2,3,4-Tetrahydroisoquinolinopropionyl)-phenanthrene (—)
9-Acetylphenanthrene [65]	9-(β-1,2,3,4-Tetrahydroisoquinolinopripionyl)-phenanthrene (—)
Cyclohexanone [40]	2-(1,2,3,4-Tetrahydroisoquinolinomethyl)-cyclohexanone (—)
α-Tetralone [16]	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-1,2,3,4-tetrahydronaphthalene (66%)
1-Keto-6-methoxy-1,2,3,4-tetrahydronaphthalene [16]	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene (63%)
1-Keto-6-acetoxy-1,2,3,4-tetrahydronaphthalene [16]	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-6-acetoxy-1,2,3,4-tetrahydronaphthalene (81%)
1-Keto-7-methoxy-1,2,3,4-tetrahydronaphthalene [16]	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-7-methoxy-1,2,3,4-tetrahydronaphthalene (76%)
1-Keto-7-acetoxy-1,2,3,4-tetrahydronaphthalene [16]	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-7-acetoxy-1,2,3,4-tetrahydronaphthalene (61%)
1-Keto-1,2,3,4-tetrahydrophenanthrene [15]	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-1,2,3,4-tetrahydrophenanthrene (61%)
4-Keto-1,2,3,4-tetrahydrophenanthrene [15]	4-Keto-3-(1,2,3,4-tetrahydroisoquinolinomethyl)-1,2,3,4-tetrahydrophenanthrene (34%)
1-Keto-9-methoxy-1,2,3,4-tetrahydrophenanthrene [70]	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-9-methoxy-1,2,3,4-tetrahydrophenanthrene (46%)
1-Keto-9-acetoxy-1,2,3,4-tetrahydrophenanthrene [70]	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-9-acetoxy-1,2,3,4-tetrahydrophenanthrene (72%)
2-Acetyldibenzothiophene [14]	β-(1,2,3,4-Tetrahydroisoquinolino)-ethyl 2-dibenzothienyl ketone (30%)
2-Acetyl-9-methylcarbazole [69]	β-(1,2,3,4-Tetrahydroisoquinolino)-ethyl 2-(9-methyloarbazyl) ketone (37%)
3-Acetyl-9-methylcarbazole [66]	β-(1,2,3,4-Tetrahydroisoquinolino)-ethyl 3-(9-methylcarbazyl) ketone (78%)
6-Methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, formaldehyde, and	
α-Tetralone [16]	1-Keto-2-(6-metnoxy-1,2,3,4-tetrahydroisoquinolinomethyl)-1,2,3,4-tetrahydronaphthalene (68%)
1-Keto-6-methoxy-1,2,3,4-tetrahydronaphthalene [16]	1-Keto-2-(6-methoxy-1,2,3,4-tetrahydroisoquinolinomethyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene (88%)
1-Keto-6-acetoxy-1,2,3,4-tetrahydronaphthalene [16]	1-Keto-2-(6-methoxy-1,2,3,4-tetrahydroisoquinolinomethyl)-6-acetoxy-1,2,3,4-tetrahydronaphthalene (74%)
1-Keto-7-methoxy-1,2,3,4-tetrahydronaphthalene [16]	1-Keto-2-(6-methoxy-1,2,3,4-tetrahydroisoquinolinomethyl)-7-methoxy-1,2,3,4-tetrahydronaphthalene (68%)

* References 67–74 appear on p. 341.

TABLE V—*Continued*

EXAMPLES OF THE REACTION

Reactants	Product (Yield)
1-Keto-7-acetoxy-1,2,3,4-tetrahydronaphthalene [16]	1-Keto-2-(6-methoxy-1,2,3,4-tetrahydroisoquinolinomethyl)-7-acetoxy-1,2,3,4-tetrahydronaphthalene (64%)
Morpholine, formaldehyde, and	
Phenol [23]	2,4,6-Tri-(morpholinomethyl)-phenol (—)
Morpholine hydrochloride, formaldehyde, and	
Acetone [47]	β-Morpholinoethyl methyl ketone (73%)
Diethyl ketone [48]	α-(Morpholinomethyl)-ethyl ethyl ketone (50%)
Acetophenone [47]	β-Morpholinoethyl phenyl ketone (excellent)
Acetoveratrone [47]	β-Morpholinoethyl 3,4-dimethoxyphenyl ketone (56%)
2-Acetylphenanthrene [72]	β-Morpholinoethyl 2-phenanthryl ketone (73%)
3-Acetylphenanthrene [72]	β-Morpholinoethyl 3-phenanthryl ketone (76%)
Cyclopentanone [47]	2-Morpholinomethyl cyclopentanone (90%)
	2,5-Dimorpholinomethylcyclopentanone (—)
Cyclohexanone [47]	2-Morpholinomethylcyclohexanone (practically quantitative)
2-Methylcyclohexanone [47]	2-Methyl-6-morpholinomethylcyclohexanone (—)
4-Methylcyclohexanone [47]	2-Morpholinomethyl-4-methylcyclohexanone (—)
α-Hydrindone * [76]	2-Morpholinomethyl-1-hydrindone (83%)
5,6-Dimethoxy-α-hydrindone [73]	2-Morpholinomethyl-5,6-dimethoxy-1-hydrindone (37%)
1-Keto-1,2,3,4-tetrahydrophenanthrene [72]	1-Keto-2-morpholinomethyl-1,2,3,4-tetrahydrophenanthrene (41%)
4-Keto-1,2,3,4-tetrahydrophenanthrene [72]	3-Morpholinomethyl-4-keto-1,2,3,4-tetrahydrophenanthrene (30%)
2-Acetylthiophene [47]	β-Morpholinoethyl 2-thienyl ketone (46%)
Antipyrine [47]	4-Morpholinomethylantipyrine (46%)
Chromanone [71]	3-Morpholinomethyl-4-chromanone (37%)
Piperazine hydrochloride, formaldehyde, and	
Acetophenone [11]	N,N′-Di-(β-benzoylethyl)-piperazine (—)
Acetoanisone [11]	N,N′-Di-(β-4-methoxybenzoylethyl)-piperazine (—)
Acetoveratrone [11]	N,N′-Di-(β-3,4-dimethoxybenzoylethyl)-piperazine (—)
Malonic acid [19]	$(HOOC)_2CHCH_2NCH_2CH_2N(CH_2CH_2COOH)CH_2CH_2$ † (17%)
	$HOOCCH_2CH_2NCH_2CH_2N(CH_2CH_2COOH)CH_2CH_2$ (19%)
Antipyrine [17]	N,N′-Di-(antipyrylmethyl)-piperazine (—)

* A gummy product was obtained when β-hydrindone was used.
† The piperazine base was used.

[67] Mannich and Stein, *Ber.*, **58**, 2659 (1925).
[66] Blicke and Maxwell, *J. Am. Chem. Soc.*, **64**, 428 (1942).
[69] Ruberg and Small, *J. Am. Chem. Soc.*, **60**, 1591 (1938).
[70] Burger, *J. Am. Chem. Soc.*, **60**, 1533 (1938).
[71] Harradence, Hughes, and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 273 (1938).
[72] Mosettig, Shaver, and Burger, *J. Am. Chem. Soc.*, **60**, 2464 (1938).
[73] Harradence and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 284 (1938).
[74] Kühn and Stein, *Ber.*, **70**, 567 (1937).

CHAPTER 11

THE FRIES REACTION

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CONTENTS

PAGE

Introduction 342

Applicability and Limitations 344
- Temperature 344
- Solvents 345
- Ratio of Ester to Reagent 345
- Structure of the Acyl Radical 345
- Structure of the Phenoxyl Group 347

The Reverse Fries Reaction 353

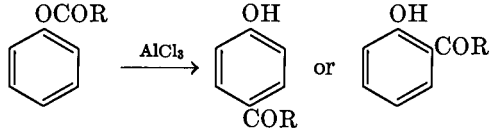
Selection of Experimental Conditions 353

Experimental Procedures 354
- The Low-Temperature Reaction in Nitrobenzene. 2-Methyl-4-hydroxyacetophenone 354
- The Preparation of a *p*-Hydroxyketone in the Absence of a Solvent. 3-Methyl-4-hydroxybenzophenone 355
- The Preparation of an *o*-Hydroxyketone. 2-Hydroxy-5-methylbenzophenone 355
- Formation and Separation of a Mixture of *o*- and *p*-Hydroxyketones. *o*- and *p*-Propiophenol 355

Tabular Survey of the Fries Reaction 356

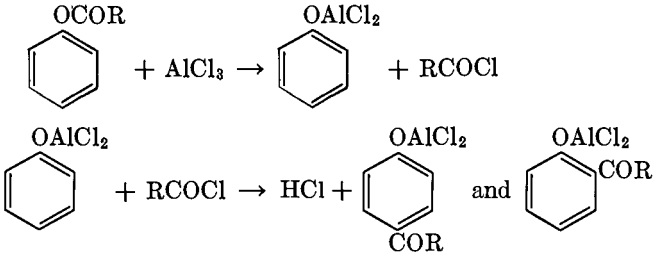
INTRODUCTION

The Fries reaction consists in the conversion of an ester of a phenol to an *o*- or *p*-hydroxyketone, or a mixture of both, by treatment with aluminum chloride.

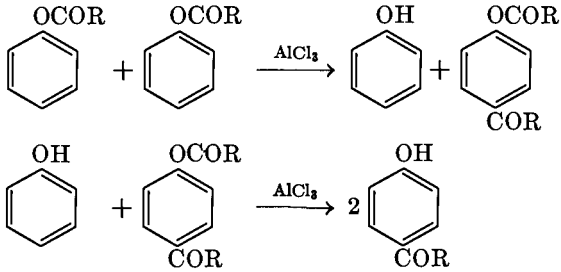


A second method available for the synthesis of similar compounds is the Friedel-Crafts reaction, in which a phenol, or an ether of a phenol, is condensed with an acid chloride or acid anhydride in the presence of aluminum chloride. In spite of the fact that the Fries reaction requires two steps—the preparation of the ester and the rearrangement to the hydroxyketone—as compared to the single step in the Friedel-Crafts synthesis, the Fries method usually is to be preferred for the preparation of phenolic ketones. The yields are ordinarily better and the experimental procedure does not have to be modified greatly to adapt it to a variety of esters.

Three different mechanisms for the Fries rearrangement have received serious consideration. In one of them the ester is assumed to react with aluminum chloride to give an acid chloride and a phenoxyaluminum chloride which combine to form a derivative of the hydroxyketone.



In another scheme, it is proposed that one molecule of the phenyl ester is acylated by another molecule.



In the third mechanism, the Fries reaction is considered to be a true intramolecular rearrangement in which the acyl group shifts directly from the oxygen atom to the carbon atom of the ring.

Certain experimental facts can be cited to support each of these mechanisms,[1] but it has not yet been possible to prove or disprove any one of them.

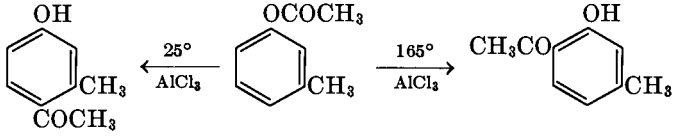
[1] Blatt, *Chem. Rev.*, **27**, 429 (1940).

APPLICABILITY AND LIMITATIONS

The structure of the phenyl ester determines whether or not a Fries reaction will take place. If the reaction does occur with a particular ester, the product may be either the *o*- or *p*-hydroxyketone or a mixture of the two. The nature of the product is influenced not only by the structure of the ester, but also by the temperature, the solvent, and the amount of aluminum chloride used. By variation of these last three factors it is often possible to direct the course of the reaction so that either of the isomeric ketones may be the major product from the same ester. Since it is usually possible to separate the two ketones, the synthesis is often useful even when it cannot be directed to the exclusive production of one isomer.

Temperature

A temperature effect in the Fries reaction has been observed by many workers.[2] A striking example has been reported by Rosenmund and Schnurr,[3] who found that at 25° only the *p*-hydroxyketone (80%) was obtained from *m*-cresyl acetate and aluminum chloride, while at 165° only the *o*-hydroxyketone (95%) was formed.



Similar observations were made in the rearrangement of *m*-cresyl benzoate; below 100° only the *p*-hydroxyketone (60%) was formed, and at 175° the *ortho* isomer was the sole product (95%).

It is not always possible to obtain at will either of the two possible products simply by varying the reaction temperature. For example, the higher aliphatic esters of *m*-cresol yield the *o*-hydroxyketones even at low temperatures,[4] and the esters of *o*-cresol yield *p*-hydroxyketones as the principal products even at high temperatures.[3] Generally, however, low reaction temperatures favor the formation of the *p*-hydroxyketones, and if these are desired it is good practice to keep the reaction temperature at 60° or less.[3]

[2] Eykmann, *Chem. Weekblad*, **1**, 453 (1904).
[3] Rosenmund and Schnurr, *Ann.*, **460**, 56 (1928).
[4] Baltzly and Bass, *J. Am. Chem. Soc.*, **55**, 4292 (1933).

Solvents

The Fries reaction can be carried out in the absence of a solvent, but the temperature at which the reaction proceeds at a useful rate is lowered by the presence of nitrobenzene.[3, 5] No data are available to show whether the other solvents which have been employed, such as tetrachloroethane [6] and chlorobenzene,[7] also exert this influence. Carbon disulfide has been used in the Fries reaction in a rather special way: the reaction is begun in this solvent, the carbon disulfide then removed by distillation, and the reaction is completed by heating in the absence of a solvent.[8, 9] There is little information at present concerning the effect of different solvents on the ratio in which the two isomers are produced. However, it has been shown that, in the rearrangement of phenyl caprylate at 70°, the proportion of the *p*-hydroxyketone formed in nitrobenzene is higher than in tetrachloroethane (71% as compared to 63%).[10]

Ratio of Ester to Reagent

The aluminum chloride and the phenyl ester are generally employed in approximately equimolar quantities. However, in the rearrangement of guaiacol acetate, two moles of aluminum chloride are required.[11] The suggestion has been made that one mole of aluminum chloride is used by complex formation with the alkoxyl group.[11] It would be desirable to have information on the effect of using two moles of aluminum chloride per mole of ester with other, similarly constituted esters, for example the acetate of resorcinol monomethyl ether. It has been found that the proportion of *p*-hydroxyketone produced by rearrangement of phenyl caprylate in the presence of two moles of aluminum chloride is higher (63% *para*, 30% *ortho*) than that in experiments in which only one mole of the reagent is used (45% *para*, 33.5% *ortho*).[10] It should be noted that the increase in yield of the *p*-hydroxyketone is at the expense of unreacted material, not at the expense of *o*-hydroxyketone.

Structure of the Acyl Radical

The acyl radical of the phenyl ester may be either aliphatic or aromatic. Esters of aliphatic acids as large as stearic acid have been used

[5] Barch, *J. Am. Chem. Soc.*, **57**, 2330 (1935).
[6] Blicke and Weinkauff, *J. Am. Chem. Soc.*, **54**, 330 (1932).
[7] Wojahn, *Arch. Pharm.*, **271**, 417 (1933).
[8] Cox, *J. Am. Chem. Soc.*, **52**, 352 (1930).
[9] Fieser and Bradsher, *J. Am. Chem. Soc.*, **58**, 1739, 2337 (1936).
[10] Ralston, McCorkle, and Bauer, *J. Org. Chem.*, **5**, 645 (1940).
[11] Coulthard, Marshall, and Pyman, *J. Chem. Soc.*, 280 (1930).

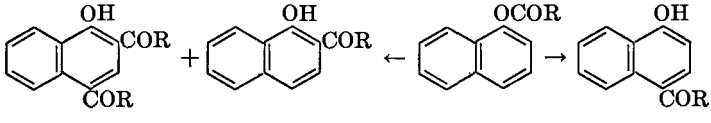
successfully. Esters of haloacetic acids and of alkyl, alkoxyl, and halogen-substituted aromatic acids have been employed. Esters of purely aliphatic unsaturated acids appear not to have been tried, but certain esters of cinnamic acid have been found to rearrange.

Rosenmund and Schnurr [3] studied the relative rates at which the Fries reaction takes place with different esters of the same phenol (thymol). Their observations are summarized in the following list, in which the acyl groups are arranged in the order of decreasing rate of reaction.

$$C_nH_{2n+1}CO\ (n = 1 \text{ to } 5) > C_6H_5CH_2CO > C_6H_5CH_2CH_2CO > C_6H_5CH{=}CHCO > C_6H_5CO$$

As an example of the magnitude of the differences in rate, it may be noted that after five hours in nitrobenzene solution at 20° the rearrangement of thymyl acetate was 60% complete and that of thymyl benzoate only 4% complete. The order of reactivity of the acyl groups is the same for rearrangement to either the *o*- or *p*-hydroxyketone.

The stability of esters containing the less reactive acyl groups sometimes limits the usefulness of the Fries rearrangement. For example, the benzoate of α-naphthol does not undergo a Fries reaction at the ordinary temperature.[12] The butyrate of α-naphthol furnishes, after seventeen to eighteen hours at 0°, 35% of 4-butyryl-1-naphthol and 22% of 2-butyryl-1-naphthol.[12] At 100–120°, the same ester furnishes 3% of 4-butyryl-1-naphthol, 55% of 2-butyryl-1-naphthol, and 2% of 2,4-dibutyryl-1-naphthol.[13]



The rearrangement of *p*-cresyl cinnamate does not take place at temperatures below that at which the ester undergoes decomposition.

With the aliphatic esters of certain phenols, an increase in the size of the acyl group favors the formation of *o*-hydroxyketone. This is particularly true of the aliphatic acid esters of *m*-cresol, for only the acetate can be converted to a *p*-hydroxyketone. The same tendency, although less pronounced, has been observed with aliphatic acid esters of α-naphthol. As indicated by the examples just cited, the importance of the size of the acyl radical in determining the course of the rearrangement depends on the structure of the phenolic residue. Although it is probably correct to state that an increase in the size of the acyl group of a

[12] Lederer, *J. prakt. Chem.*, [2] **135**, 49 (1932).
[13] Stoughton, *J. Am. Chem. Soc.*, **57**, 202 (1935).

particular ester will increase the tendency toward formation of the *o*-hydroxyketone, it is still possible to prepare *p*-hydroxyketones containing very large acyl groups. Phenyl palmitate and phenyl stearate,[10, 14] for example, furnish the *p*-hydroxyketones (19.7%, 21%) when the reaction is carried out by heating the esters to 70° with aluminum chloride in tetrachloroethane. The yield of *p*-hydroxyketone from phenyl palmitate is less than half that from phenyl caprylate but the ratio of *para*- to *ortho*-hydroxyketones is not greatly different with these two esters (1.32 to 1.35).[10]

Structure of the Phenoxyl Group

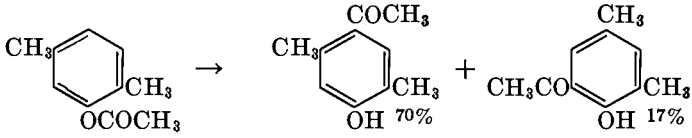
The structure of the phenolic portion of the ester is the factor of greatest importance in determining whether a Fries reaction will take place and whether the product will consist principally of the *o*- or *p*-hydroxyketone. The importance of this factor is revealed by examination of the products from esters of monosubstituted phenols. The presence of a *meta*-directing group on the aromatic portion of the phenyl ester usually interferes with the Fries reaction. For example, the reaction does not occur if the phenolic residue carries a nitro or benzoyl group in either the *ortho* or *para* position; the presence of an acetyl or carboxyl group in the *ortho* position hinders the reaction, and, in the *para* position, prevents it.[3, 8]

If the phenyl ester contains a single alkyl group in the phenolic ring, then the position of this substituent has a profound influence on the nature of the product. For example, esters of *o*-cresol yield predominantly *p*-hydroxyketones, esters of *m*-cresol yield predominantly *o*-hydroxyketones, and esters of *p*-cresol yield exclusively *o*-hydroxyketones. The effect of a *para* substituent has been observed with a variety of alkyl groups and with halogen; the effect of *ortho* substituents has been observed with several alkyl groups; the effect of a *meta* substituent has been determined only with esters of *m*-cresol.

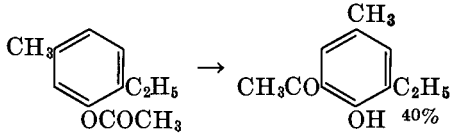
The rearrangement products of more than fifty disubstituted phenol esters are shown in Part C of the tabular survey of the Fries reaction (p. 360). It will be noticed that with three esters, 2,5-dimethylphenyl acetate, 2-ethyl-5-methylphenyl acetate, and 2-methyl-6-ethylphenyl acetate, products formed by migration of an alkyl group were isolated. It is probable that these migrations were the result of the use of high temperatures and prolonged reaction times and that they would not occur if more gentle experimental conditions were used. Thus, the carvacryl and thymyl esters yielded the expected *p*-hydroxyketones without migration of alkyl groups when mild experimental procedures were used.

[14] Bell and Driver, *J. Chem. Soc.*, 835 (1940).

Again, 2-methyl-6-ethylphenyl acetate yielded 50% of the normal product together with some rearrangement product when the reaction mixture was heated for five hours. When more gentle conditions were employed the yield of the normal product rose to 73% and no rearranged product was reported. In many of the esters the acyl group migrated to the *ortho* position even though the *para* position was vacant. This is due in part to the presence of alkyl groups in the *meta* positions. Apparently, it is also due in part to the high temperatures used, since the esters of carvacrol and thymol furnished the *p*-hydroxyketones under the mild conditions employed in their rearrangement.



(Ref. 15)



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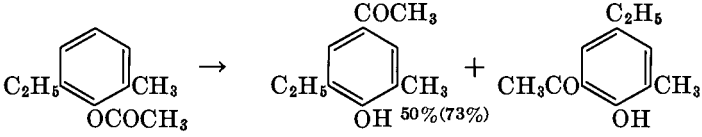


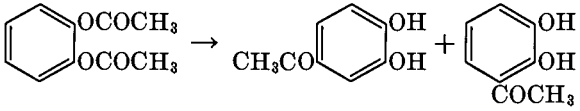
(Ref. 16,17)

In Part D of the tabular survey of the Fries reaction are given the products obtained from the acetates of seven trialkylphenols, each of which has at least one vacant *ortho* or *para* position. In the second experiment, the only product isolated was one involving migration of an alkyl group, and only in the first and seventh were such products entirely absent. In the third experiment the transfer of a methyl group from one molecule to another also occurred. A comparison of the data of Part D of the tabular survey with those of Part C indicates that migrations of alkyl groups occur the more readily as the number of such groups is increased. However, even with the heavily alkylated phenyl esters it is probable that these migrations result from the drastic treatment with aluminum chloride and that they are not an integral part of the Fries reaction.

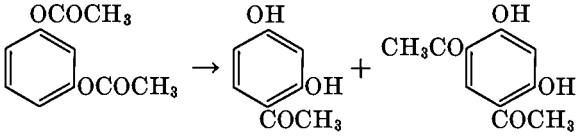
[15] Auwers, Bundesmann, and Wieners, *Ann*, **447**, 162 (1926).
[16] Auwers and Mauss, *Ann.*, **460**, 240 (1928).
[17] Auwers and Janssen, *Ann.*, **483**, 44 (1930).

The migration or removal of an alkyl group sometimes permits the Fries reaction to occur even with esters of 2,4,6-trialkylphenols. However, since very drastic conditions are required, these forced reactions must be investigated in each individual instance before they can be relied upon for preparative purposes. Part D of the tabular survey of the Fries reaction shows the products obtained from the 2,4,6-trialkylphenols.

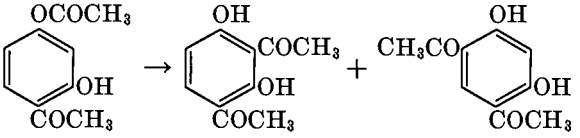
The esters of the three dihydroxybenzenes, catechol, resorcinol, and hydroquinone, undergo the Fries reaction. Esters of catechol yield predominantly 4-acylcatechols and secondarily 3-acylcatechols.



The usual technique may be employed with these esters, but it is preferable to treat an equimolar mixture of a diester and catechol with aluminum chloride.[18, 19] Resorcinol esters can be converted to 4-acylresorcinols or to 4,6-diacylresorcinols using a variety of techniques,[20, 21, 22] but 4-acylresorcinols are so readily obtained directly from resorcinol and the acids or acid chlorides that the Fries reaction is seldom used for their preparation.[23, 24]



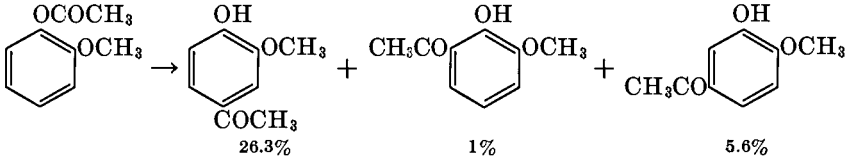
The Fries rearrangement of the acetate of 4-acetylresorcinol furnishes the 2,4- (58%) and the 4,6-diacylresorcinol (42%). The formation of the 1,2,3,4-tetrasubstituted derivative is explained as a consequence of chelation which stabilizes the Kekulé form leading to the 2,4-diacyl compound.[25]



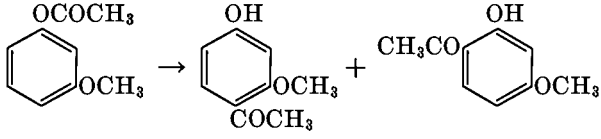
[18] Rosenmund and Lohfert, *Ber.*, **61**, 2601 (1928).
[19] Miller, Hartung, Rock, and Crossley, *J. Am. Chem. Soc.*, **60**, 7 (1938).
[20] Klarmann, *J. Am. Chem. Soc.*, **48**, 2358 (1926).
[21] Rosenmund and Schulz, *Arch. Pharm.*, **265**, 308 (1927).
[22] Rosenmund, Buchwald, and Deligiannis, *Arch. Pharm.*, **271**, 342 (1933).
[23] Cooper, *Org. Syntheses*, **21**, 103 (1941).
[24] Cox, *Rec. trav. chim.*, **50**, 848 (1931).
[25] Baker, *J. Chem. Soc.*, 1684 (1934).

Acyl derivatives of α-resorcyclic acid (3,5-dihydroxybenzoic acid) are reported not to give the Fries reaction.[26]

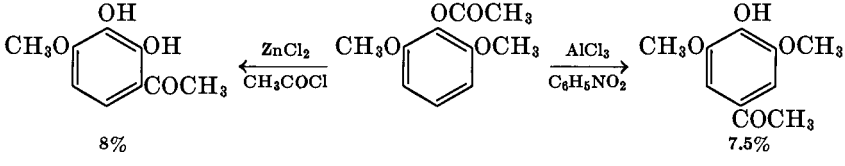
The acetate of guaiacol furnishes three products in the Fries reaction.[27] Particularly to be noted is the presence of a *m*-hydroxyketone among the products, for the formation of *m*-hydroxyketones in the Fries reaction is exceedingly rare.



The Friedel-Crafts reaction with guaiacol and acetyl chloride furnishes the same three products, making it evident that the formation of the *m*-hydroxyketone is related to the *ortho* methoxyl group and is not a peculiarity of the Fries reaction. The resorcinol derivative yields an *o*- and a *p*-hydroxyketone (12%, 11%) but no *m*-hydroxyketone.[26]

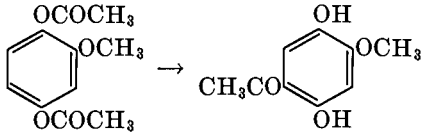


Esters of pyrogallol,[28] phloroglucinol,[28, 29, 30] 1,2,4-trihydroxybenzene,[30] and of a number of hydroxydimethoxybenzenes and dihydroxymethoxybenzenes have been studied. The products obtained from these esters are, with few exceptions, those to be expected and the yields are usually quite small. The use of more than one mole of aluminum chloride per mole of the ester might give better results. It has been reported that 2,6-dimethoxyphenyl acetate, with zinc chloride at room temperature in acetyl chloride as the solvent, furnishes the unsymmetrical product, the acetyl group taking a *meta* position.[31] The same ester on treatment with aluminum chloride yields the *p*-hydroxyketone.[32]

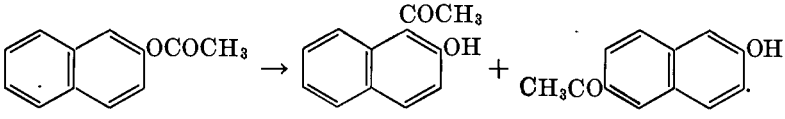


[26] Mauthner, *J. prakt. Chem.*, [2] **136**, 205 (1933).
[27] Reichstein, *Helv. Chim. Acta*, **10**, 392 (1927).
[28] Heller, *Ber.*, **45**, 2389 (1912).
[29] Heller, *Ber.*, **42**, 2736 (1909).
[30] Mauthner, *J. prakt. Chem.*, [2] **139**, 293 (1934).
[31] Mauthner, *J. prakt. Chem.*, [2] **118**, 314 (1928).
[32] Mauthner, *J. prakt. Chem.*, [2] **121**, 255 (1929).

The diacetate of 2-methoxy-1,4-dihydroxybenzene undergoes a Fries reaction and yields the dihydroxyketone (38%).[26]



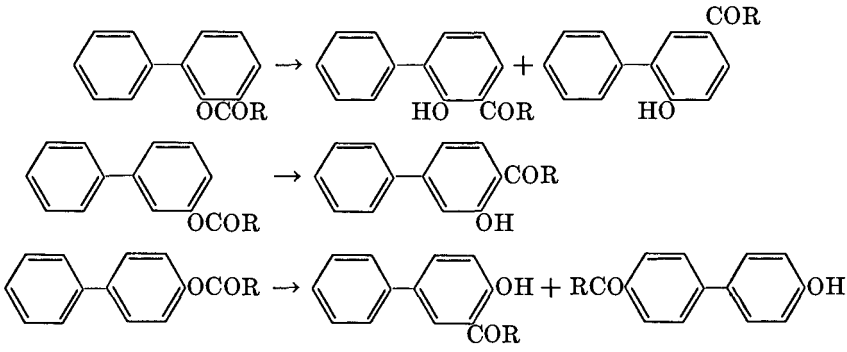
Esters of α-naphthol furnish 4-acylnaphthols at low temperatures.[12, 13, 33] With an increase in the size of the acyl group, the rate of formation of the 4-acylnaphthols falls off to such an extent that the method is of little value for their preparation. Increasing the temperature results in the formation of 2-acylnaphthols and 2,4-diacylnaphthols. β-Naphthyl acetate furnishes 1-acetyl-2-naphthol (33–40%) together with 6-acetyl-2-naphthol (5%).[33, 34, 35]



In the phenanthrene series the Fries reaction offers no advantage over the Friedel-Crafts method for it either leads to difficultly separable or inseparable mixtures (2-acetoxy- and 3-acetoxyphenanthrene) or furnishes the same products as the Friedel-Crafts reaction but in no better yields (9-acetoxyphenanthrene).[36]

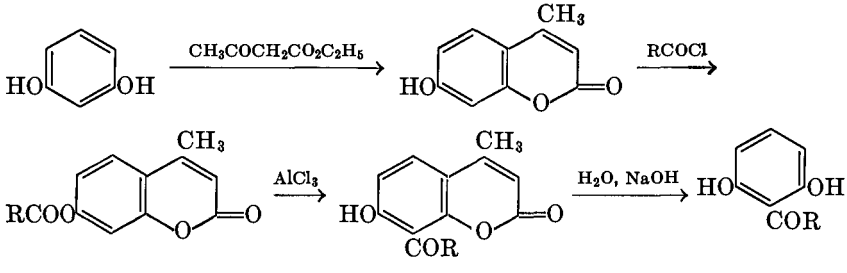
With one interesting exception, the directive influence of the phenyl group in esters of the hydroxybiphenyls is similar to that of the methyl group in esters of the cresols. Thus, esters of 2-hydroxybiphenyl furnish 3-acyl- and 5-acyl-2-hydroxybiphenyls,[37] the yield of the former increasing with the size of the acyl group.[38] Esters of 3-hydroxybiphenyl furnish 4-acyl-3-hydroxybiphenyls.[38] However, with esters of 4-hydroxybiphenyls the acyl group migrates to the *para* position of the second benzene ring, yielding 4′-acyl-4-hydroxybiphenyls as well as the expected 3-acyl-4-hydroxybiphenyls.[6, 9, 39, 40]

[33] Witt and Braun, *Ber.*, **47**, 3216 (1914).
[34] Fries, *Ber.*, **54**, 709 (1921).
[35] Fries and Schimmelschmidt, *Ber.*, **58**, 2835 (1925).
[36] Mosettig and Burger, *J. Am. Chem. Soc.*, **55**, 2981 (1933).
[37] Auwers and Wittig, *J. prakt. Chem.*, [2] **108**, 99 (1924).
[38] Harris and Christiansen, *J. Am. Pharm. Assoc.*, **23**, 530 (1934).
[39] Hey and Jackson, *J. Chem. Soc.*, 802 (1936).
[40] Cheetham and Hey, *J. Chem. Soc.*, 770 (1937).

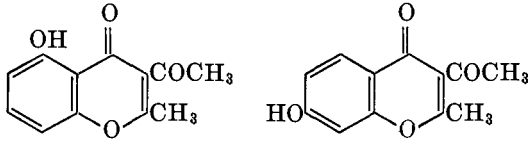


With the acetate of 4-hydroxybiphenyl the 4-hydroxy-3-ketone is the principal product; with the benzoate the 4-hydroxy-4′-ketone is the principal product.

The Fries reaction of esters of hydroxycoumarins proceeds normally to yield the *o*-hydroxyketones.[41, 42, 43, 44] The reaction with the acyl derivatives of 4-methyl-7-hydroxycoumarin, made from resorcinol and acetoacetic ester, provides a synthesis of 2-acylresorcinols.[45]



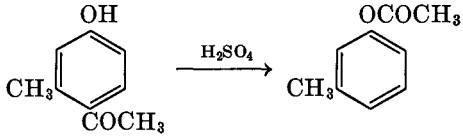
Although esters of hydroxycoumarins rearrange readily, attempts to carry out the Fries reaction with acetates of the following hydroxychromanones have been unsuccessful.[46]



[41] Desai and Hamid, *C. A.*, **32**, 1254 (1938).
[42] Limaye, *Ber.*, **67**, 12 (1934).
[43] Limaye and Munje, *C. A.*, **32**, 2096 (1938).
[44] Sethna, Shah, and Shah, *C. A.*, **32**, 549 (1938).
[45] Russell and Frye, *Org. Syntheses*, **21**, 22 (1941).
[46] Kelkar and Limaye, *C. A.*, **31**, 2214 (1937).

THE REVERSE FRIES REACTION

Rosenmund and Schnurr found that *p*-hydroxyketones having an alkyl group *ortho* to the acyl group are converted to *m*-alkylphenyl esters in excellent yields on heating with sulfuric, camphorsulfonic, or phosphoric acid.



[Quantitative yield]

It has been supposed that the temperature effect in the Fries reaction may be related to this reverse reaction; that is, the *p*-hydroxyketone may revert to the ester, which then rearranges to the *o*-hydroxyketone under the influence of the aluminum chloride and the high temperature. Indeed, the *p*-hydroxyketone shown above is converted to the isomeric *o*-hydroxyketone on heating with aluminum chloride. However, the ester has not been shown to be an intermediate.

SELECTION OF EXPERIMENTAL CONDITIONS

The phenyl esters are conveniently prepared by heating the phenol with the acid chloride, or, if the acid chloride is aromatic, by a Schotten-Baumann acylation. If the starting materials are pure, the crude dry esters often can be used directly.

The temperature at which the Fries reaction is best carried out depends upon whether an *o*- or *p*-hydroxyketone is being prepared, and upon the reactivity of the acyl group. These factors have been discussed in section II. If mild experimental conditions are indicated, a solvent, usually nitrobenzene, is employed. Reaction under more severe conditions is generally carried out without a solvent. Tetrachloroethane and chlorobenzene are useful solvents when the reaction is to be run at temperatures up to their boiling points.

In general, for the preparation of a *p*-hydroxyketone one mole of an ester is dissolved in about five times its weight of dry nitrobenzene, and from 1.2 to 1.3 moles of aluminum chloride is added in small portions. The rate of addition of the aluminum chloride is regulated by the heat evolved in the reaction. The mixture is allowed to stand for twenty-four hours at room temperature or is heated to 60° for an hour. It is then poured onto ice and dilute hydrochloric acid.

For the preparation of an *o*-hydroxyketone, one mole of an ester is mixed intimately with 1.2–1.3 moles of aluminum chloride in a flask con-

nected with an air or water condenser. It is advisable to use a large flask as the mixture often foams during the reaction. The flask is placed in an oil bath, heated slowly to 120°, and kept at that temperature for fifteen minutes. The heating should be done cautiously as the heat of reaction is often large. The upper temperature may be higher than 120°, but it is desirable to keep the temperature as low as possible. After cooling, ice and dilute hydrochloric acid are added.

Boron fluoride has been used to bring about the Fries reaction, but no details of its use are available.[47]

Several procedures are available for working up the reaction mixtures. Nitrobenzene or tetrachloroethane, when present, can be removed by distilling with steam. Alternatively, the reaction mixture can be extracted with ether and the product isolated by extraction of the ether solution with aqueous sodium hydroxide.

Mixtures of *o*- and *p*-hydroxyketones often can be separated by virtue of the fact that the latter are not volatile with steam. If the *o*-hydroxyketone is of such large molecular weight that it is not volatile with steam, a separation may be effected by distillation at ordinary or reduced pressure. Thus, *o*-heptanoylphenol boils at 135–140° (3 mm.) while the *para* isomer boils at 200–207° (4 mm.).[48] If the *o*- and *p*-hydroxyketones are both solids, a separation often can be effected by taking advantage of the fact that the *ortho* isomer will be the more soluble in ligroin. Again, it is frequently possible to separate a pair of isomeric *o*- and *p*-hydroxyketones by extracting with dilute sodium hydroxide an ether solution containing both isomers. The *p*-hydroxyketone is extracted more readily.

EXPERIMENTAL PROCEDURES

The Low-Temperature Reaction in Nitrobenzene

Preparation of 2-Methyl-4-hydroxyacetophenone.[3] To a solution of 10 g. of *o*-cresyl acetate in 50 g. of nitrobenzene is added in small portions 10 g. of aluminum chloride. The reaction mixture is left to stand for twenty-four hours at room temperature and then is poured onto ice and dilute hydrochloric acid. The nitrobenzene is removed by steam distillation, and the residual crude 2-methyl-4-hydroxyacetophenone is purified by vacuum distillation. The yield is 8.0–8.5 g. (80 to 85%) of pure ketone, m.p. 128°.

[47] Meerwein, *Ber.*, **66**, 411 (1933); Auwers, Pötz, and Noll, *Ann.*, **535**, 228 (1938).
[48] Read and Wood, *Org. Syntheses*, **20**, 58 (1940).

The Preparation of a *p*-Hydroxyketone in the Absence of a Solvent

Preparation of 3-Methyl-4-hydroxybenzophenone.[49] Fifty grams of *o*-cresyl benzoate is heated to 130° and stirred while 40 g. of aluminum chloride is added. The temperature is raised to 160° and kept there for forty-five minutes. After cooling, the reaction mixture is decomposed with dilute hydrochloric acid, and the crude product is filtered and dried. On distillation, the material boils at 240–260° (12–15 mm.) and furnishes 45.5 g. (90%) of pure ketone, m.p. 173–174°.

The Preparation of an *o*-Hydroxyketone

Preparation of 2-Hydroxy-5-methylbenzophenone. In a 1-l., three-necked, round-bottomed flask fitted with a thermometer and an air condenser are placed 75 g. (0.35 mole) of *p*-cresyl benzoate and 60 g. (0.44 mole) of aluminum chloride. The reactants are mixed by shaking, and the flask is then placed in an oil bath at 90°. After the reaction mixture has melted, heat is applied to the bath, rapidly until the temperature of the mixture reaches 120°, then slowly until it reaches 140°. The reaction mixture is kept at this temperature for ten minutes, the thermometer is removed from the flask, and the flask is removed from the bath. When the reaction mixture is cold, it is added to a stirred mixture of 250 g. of ice and 150 cc. of concentrated hydrochloric acid. After the ice has melted, the solid product is filtered and dried. The yield is 70–73 g. of a yellow solid which is pure enough for most purposes but which contains a small amount of impurity that lowers the melting point considerably. The ketone may be purified by distillation with superheated steam followed by crystallization from ethanol. It then melts at 83–84°, and the yield is 60 g. (80%).

Formation and Separation of a Mixture of *o*- and *p*-Hydroxyketones

Preparation of *o*- and *p*-Propiophenol.[50] In a 2-l., three-necked, round-bottomed flask fitted with a reflux condenser, a sturdy mechanical stirrer, and a 100-cc. dropping funnel are placed 374 g. (2.8 moles) of aluminum chloride and 400 cc. of carbon disulfide. Stirring is begun, and 375 g. of phenyl propionate is added at such a rate that the solvent boils vigorously. When the addition is complete, the reaction mixture is boiled on the steam bath for about two hours; then the reflux condenser is turned downward and the solvent is removed by distillation. The

[49] Cox, *J. Am. Chem. Soc.*, **49**, 1029 (1927).
[50] Miller and Hartung, *Org. Syntheses*, **13**, 90 (1933).

flask is next heated for three hours in an oil bath maintained at 140–150°, stirring being continued as long as possible.

The reaction mixture is allowed to cool and is decomposed by the cautious addition of a mixture of 300 cc. of water and 300 cc. of concentrated hydrochloric acid, followed by 500 cc. of water. On standing overnight, most of the *p*-propiophenol in the upper oily layer solidifies and is removed by filtration. It is crystallized from 400 cc. of methanol and furnishes 129–148 g. (34–39%) of light yellow material melting at 145–147°. A second crystallization raises the melting point to 147–148°.

The oily filtrate and the concentrated mother liquors from the above recrystallization are dissolved in 500 cc. of 10% aqueous sodium hydroxide and extracted with two 100-cc. portions of ether to remove non-phenolic products. The alkaline solution is acidified, and the oily layer is separated, dried over anhydrous magnesium sulfate, and distilled. The distillation furnishes 120–132 g. (32–35%) of *o*-propiophenol boiling at 110–115° (6 mm.) and 40 g. of *p*-propiophenol boiling at 135–150° (11 mm.). The total yield of crude *p*-propiophenol is 169–188 g. (45–50%).

TABULAR SURVEY OF THE FRIES REACTION

The use of one mole of aluminum chloride per mole of ester is to be understood unless a different ratio of aluminum chloride to ester or a different reagent is specified. The position of the acyl group in the product is always given with reference to the hydroxyl group as 1; if more than one hydroxyl group is present, the numbering is such as to give the lowest numbers to the carbon atoms carrying the hydroxyl groups. Where a product is listed but no yield is given, the product was reported in the literature with no information about the yield.

A. Esters of Phenol

Ester R of Acyl Group	Solvent	Experimental Conditions	Products		Reference *
			% 2-Acyl	% 4-Acyl	
CH_3	$C_6H_5NO_2$	24 hr. at 20–25°	—	75 max.[a]	3
CH_3	—	165°	70 max.	—	3
CH_3	CS_2	2 hr. at b.p., 3 hr. at 140–150°	30	—	51
C_3H_7	—	1–2 hr. at 160–180°	60	19	11
C_5H_{11}	—	1–2 hr. at 160–180°	50	—	11
C_5H_{11}	$CHCl_2CHCl_2$	6 hr. at 70°	33.5	45	10
C_5H_{11}	$CHCl_2CHCl_2$	$2AlCl_3$; 6 hr. at 70°	30	63	10
C_5H_{11}	$C_6H_5NO_2$	$2AlCl_3$; 6 hr. at 70°	20.1	71.4	10
C_6H_5	—	15 min. at 140°	—	Quantitative	3
C_6H_{13}	—	1–2 hr. at 160–180°	58	—	11
$C_6H_4OCH_3$-*p*	—	15 min. at 140°	—	80 [b]	3
$C_{11}H_{23}$	$CHCl_2CHCl_2$	10 hr. at 70°	28	46	10
$C_{11}H_{23}$	—	1 hr. at 150°	Secondary	Principal	14
$C_{13}H_{27}$	$CHCl_2CHCl_2$	10 hr. at 70°	34.5	43	10
$C_{15}H_{31}$	$CHCl_2CHCl_2$	10 hr. at 70°	14 9	19.7	10
$C_{17}H_{35}$	$CHCl_2CHCl_2$	10 hr. at 70°	18.3	21.2	10
$C_{17}H_{35}$	—	1 hr. at 150°	Secondary	Principal	14

* References 51–64 appear on p. 369.

[a] Comparable results are reported [6] with the phenyl esters of other primary, straight-chain, aliphatic acids up to and including caprylic acid.

[b] Demethylation at the ether linkage takes place.

B. Esters of Monosubstituted Phenols

Ester		Experimental Conditions	Products		Reference *
Substituent	R of Acyl Group		% 6-Acyl	% 4-Acyl	
2-CH_3	CH_3	$C_6H_5NO_2$; 24 hr. at 20°	—	85 [a]	3
2-CH_3	CH_3	?	55 max.	—	3
2-CH_3	CH_2Cl	140°	20	No yield	52
2-CH_3	C_2H_5	3 hr. at 120°	40	No yield	53
2-CH_3	C_3H_7	Overnight at room temperature, heat to 100–110°	No yield	47	17
2-CH_3	C_3H_7	½ hr. at 160–180°	60	30	11
2-CH_3	C_3H_7	48 hr. at room temp.	—	30	11
2-CH_3	C_4H_9	½ hr. at 160–180°	46	30	11
2-CH_3	C_5H_{11}	½ hr. at 160–180°	60	25	11
2-CH_3	C_6H_5	15 min. at 140°	—	Quantitative	3
2-CH_3	C_6H_5	Add reagent at 130°; 45 min. at 160°	—	91	49
2-C_2H_5	CH_3	100–120°	No yield	—	16
2-$C_6H_5CH_2$	CH_3	$C_6H_5NO_2$; overnight at room temp., 3–4 hr. at 50–60°	—	70 [b]	7
2-$C_6H_5CH_2$	CH_3	170°	—	No yield	7
3-CH_3	CH_3	$C_6H_5NO_2$; 24 hr. at 20°	—	82 [c]	3
3-CH_3	CH_3	165°	95	—	3
3-CH_3	CH_2Cl	5 hr. at 150°	50	—	54
3-CH_3	C_2H_5	$C_6H_5NO_2$; 10 days at 2°	65	10	4
3-CH_3	C_2H_5	120–140°	93	—	4
3-CH_3	C_3H_7	$C_6H_5NO_2$; 10 days at 2°	72	3	4
3-CH_3	C_3H_7	120–140°	75	—	4
3-CH_3	C_3H_7	$C_6H_5NO_2$; 24 hr. at 20°	88	—	11
3-CH_3	C_4H_9	$C_6H_5NO_2$; 24 hr. at 20°	85	—	11
3-CH_3	C_4H_9	120–140°	80	—	4
3-CH_3	C_5H_{11}	$C_6H_5NO_2$; 24 hr. at 20°	93	—	11
3-CH_3	C_5H_{11}	120–140°	91	—	4
3-CH_3	C_6H_5	$C_6H_5NO_2$; 5 hr. at 60°	—	60	3
3-CH_3	C_6H_5	15 min. at 175°	95	—	3
3-CH_3	C_6H_5	CS_2; 3 hr. at room temp., heat to 90°	50	32	49
3-CH_3	C_6H_{13}	$C_6H_5NO_2$; 24 hr. at 20°	84	—	11
3-CH_3	C_6H_{13}	120–140°	67	—	4
3-CH_3	C_8H_{17}	120–140°	75	—	4

* References 51–64 appear on p. 369.

B. ESTERS OF MONOSUBSTITUTED PHENOLS—*Continued*

Ester		Experimental Conditions	Products		Reference *
Substituent	R of Acyl Group		% 2-Acyl	% 4-Acyl	
4–CH_3	CH_3	10 min. at 120°	90 [d]	—	3
4–CH_3	CH_2Cl	4 hr. at 140°	90	—	54
4–CH_3	C_2H_5	Cold 45 min., warm on steam bath	80	—	55
4–CH_3	C_4H_9	2 hr. at 160°	65	—	11
4–CH_3	C_5H_{11}	10 min. at 120°	88	—	3, 11
4–CH_3	C_6H_5	10 min. at 140°	Quantitative [e]	—	3
4–CH_3	C_6H_5	15 min. at 140°; heat to 200°	94	—	49
4–CH_3	C_6H_{13}	10 min. at 120°	85	—	3
4–CH_3	C_7H_{15}	20 min. at 100°	Quantitative	—	3
4–Cl	CH_3	1 hr. at 120°	Quantitative [f]	—	53
4–Cl	CH_2Cl	5 hr. at 140–150°	No yield	—	56
4–C_2H_5	CH_3	$6\frac{1}{2}$ hr. at 100–110°	70	—	16
4–C_3H_7	CH_3	?	No yield	—	17
4–$C_6H_5CH_2$	CH_3	C_6H_5Cl; 30–45 min. at b.p.	85 [g]	—	7
4–$C_6H_5CH_2CH_2$	CH_3	C_6H_5Cl; 30–45 min. at b.p.	70 [h]	—	7
4–$C_6H_5CH_2CH_2CH_2$	CH_3	C_6H_5Cl; at b.p.	No yield	—	7

* References 51–64 appear on p. 369.

[a] Comparable results are reported [3] with the *o*-cresyl esters of other primary, straight-chain, aliphatic acids up to and including caprylic acid.

[b] Comparable results are reported [7] with the propionate, butyrate, and isobutyrate of *o*-benzylphenol.

[c] Comparable results are reported [3] with esters of *m*-cresol and primary, straight-chain, aliphatic acids up to and including caprylic acid. These results have not been confirmed; [4,11] compare the data in the table above for these esters of *m*-cresol.

[d] Comparable results are reported [3] with the propionate, butyrate, and isovalerate of *p*-cresol.

[e] Comparable results are reported [3] with the *o*-chlorobenzoate, the *o*-bromobenzoate, and the *p*-bromobenzoate of *p*-cresol.

[f] Comparable results are reported [3] with other aliphatic acid esters of *p*-chlorophenol and of *p*-bromophenol.

[g] Comparable results are reported [7] with the propionate, butyrate, and isovalerate of *p*-benzylphenol.

[h] Comparable results are reported [7] with the propionate, butyrate, and isovalerate of *p*-(β-phenylethyl)-phenol.

C. Esters of Disubstituted Phenols

Ester		Experimental Conditions	Products		Reference *
Substituent	R of Acyl Group		% 6-Acyl	% 4-Acyl	
2,3-Dimethyl	CH_3	18 hr. at room temperature, heat to 120°	60	—	16
2,3-Dimethyl	CH_3	Heat on steam bath	69	—	57
2,4-Dimethyl	CH_3	130–140°	No yield	—	15
2,4-Dimethyl	C_6H_{13}	130–140°	74	—	17
2-Methyl-4-ethyl	CH_3	6 hr. at 130–140°	77	—	16
2-Methyl-4-ethyl	C_2H_5	3 hr. at 130–140°	70	—	17
2-Ethyl-4-methyl	CH_3	130–140°	No yield	—	15
2,4-Diethyl	CH_3	$5\frac{1}{2}$ hr. at 130–140°	67	—	16
2-Methyl-4-butyl	CH_3	130–140°	63	—	17
2-Ethyl-4-propyl	CH_3	?	No yield	—	17
2-Chloro-4-methyl	CH_3	10 min. at 120°	Quantitative [a]	—	3
2-Chloro-4-methyl	C_6H_5	10 min. at 140°	92	—	3
2-Ethyl-4-chloro	CH_3	2 hr. at 120°	No yield	—	53
2,5-Dimethyl	CH_3	18 hr. at room temperature, heat to 120°	2,4-Dimethyl-6-acetyl, 17	70	15
2-Ethyl-5-methyl	CH_3	130–140°	2-Ethyl-4-methyl-6-acetyl, 40	—	15
2-Methyl-5-isopropyl	CH_3	$C_6H_5NO_2$; 24 hr. at 25°	—	90 [b]	3
2-Methyl-5-isopropyl	C_6H_5	$C_6H_5NO_2$; 5 hr. at 60°	—	60	3
2-Propyl-5-methyl	CH_3	$C_6H_5NO_2$; 18 hr. at 20°	—	82	3
2-Isopropyl-5-methyl	CH_3	$C_6H_5NO_2$; 24 hr. at 20°	—	87 [c]	3
2-Isopropyl-5-methyl	C_6H_5	$C_6H_5NO_2$; 5 hr. at 60°	—	70	3
2-Isopropyl-5-methyl	$C_6H_5CH{=}CH$	$C_6H_5NO_2$; 48 hr. below 20°	—	80	3
2,6-Dimethyl	CH_3	Overnight at room temp., 6 hr. at 120°	—	81	16

* References 51–64 appear on p. 369.

[a] Comparable results are reported [3] with the propionate and butyrate of 2-chloro-4-methylphenol.

[b] Comparable results are reported [3] with the propionate, butyrate, and isovalerate of carvacrol.

[c] Comparable results are reported [3] with the propionate, butyrate, isovalerate, phenylacetate, caprylate, and hydrocinnamate of thymol.

C. ESTERS OF DISUBSTITUTED PHENOLS—*Continued*

Ester		Experimental Conditions	Products		Reference *
Substituent	R of Acyl Group		% 6-Acyl	% 4-Acyl	
2,6-Dimethyl	C_2H_5	Overnight at room temp., heat at 100–110°	—	59	17
2,6-Dimethyl	C_3H_7	Overnight at room temp., heat at 100–110°	—	67	17
2,6-Dimethyl	C_6H_5	Overnight at room temp., heat at 100–110°	—	47	17
2,6-Dimethyl	C_6H_{13}	Overnight at room temp., heat at 100–110°	—	65	17
2,6-Dimethyl	$C_{11}H_{23}$	Overnight at room temp., heat at 100–110°	—	75	17
2-Methyl-6-ethyl	CH_3	5 hr. at 130–140°	2-Methyl-4-ethyl-6-acetyl	50	16
2-Methyl-6-ethyl	C_2H_5	Overnight at room temp., heat to 100–110°		73 [d]	17
2,6-Diethyl	CH_3	100–120°	Unidentified *o*-hydroxyketone	60	16
2-Methyl-6-propyl	CH_3	?	—	No yield	17
3,4-Dimethyl	CH_3	4 hr. at 130°	No yield	—	15
3-Methyl-4-ethyl	CH_3	$4\frac{1}{2}$ hr. above 100°	70	—	16
3-Methyl-4-ethyl	CH_3	10 min. at 120°	Quantitative	—	3
3-Methyl-4-chloro	CH_3	10 min. at 120°	No yield [e]	—	3
3-Methyl-4-chloro	C_6H_5	10 min. at 140°	Quantitative	—	3
3,5-Dimethyl	CH_3	10 hr. on steam bath	80	—	57
3,5-Dimethyl	CH_3	2 hr. on steam bath	No yield	2,6-diacyl	58, 59
3,5-Diethyl	CH_3	10 hr. at 100–120°	No yield		16

* References 51–64 appear on p. 369.

[d] Comparable results are reported [17] with the butyrate, heptanoate, and dodecanoate of 2-methyl-6-ethylphenol.

[e] Under the same conditions the propionate and butyrate of 3-methyl-4-chlorophenol are reported [3] to furnish the 6-acyl derivatives in yields of more than 90%.

D. Acetates of Trisubstituted Phenols

Substituents	Experimental Conditions	Products	Reference *
2,3,4-Trimethyl	130–140°	6-Acetyl	15
2,3,5-Trimethyl	2½ hr. at 130–140°	2,3,4-Trimethyl-6-acetyl, 86%	15
2,4,5-Trimethyl	4 hr. at 130–140°	2,3,4-Trimethyl-6-acetyl, principal 2,4,5-Trimethyl-6-acetyl, considerable 3,4-Dimethyl-6-acetyl, small 2,3,5,6-Tetramethylphenol, very small	15
2,4-Dimethyl-5-ethyl	6 nr. at 130–140°	2,4-Dimethyl-3-ethyl-6-acetyl, principal 2,4-Dimethyl-5-ethyl-6-acetyl, secondary Total yield, 75%	16
2-Ethyl-4,5-dimethyl	6½ hr. at 130–140°	2-Ethyl-4,5-dimethyl-6-acetyl 2-Ethyl-3,4-dimethyl-6-acetyl	16
2,4-Diethyl-5-methyl	5 hr. at 130–140°	2,4-Diethyl-5-methyl-6-acetyl 2,3-Diethyl-4-methyl-6-acetyl Total yield, 65%	16
3,4,5-Trimethyl	½ hr. at 130°	2-Acetyl	15
2,4,6-Trimethyl	11 hr. at 130–140°	2,3,4-Trimethyl-6-acetyl, 42% 2,6-Dimethyl-4-acetyl, 1%	15, 17
2,4-Dimethyl-6-ethyl	7 hr. at 130–140°	2,4-Dimethyl-3-ethyl-6-acetyl, principal 2-Ethyl-3,4-dimethyl-6-acetyl, secondary Total yield, 70%	16, 17
2,6-Dimethyl-4-ethyl	5 hr. at 130–140°	2,6-Dimethyl-4-acetyl 2,4-Dimethyl-6-acetyl 2,4-Dimethyl-3-ethyl-6-acetyl Total yield, 50%	17 *Cf.* 16
2-Methyl-4,6-diethyl	7 hr. at 130–140°	2-Methyl-3,4-diethyl-6-acetyl, 70%	16, 17
2,6-Diethyl-4-methyl	5 hr. at 130–140°	2,3-Diethyl-4-methyl-6-acetyl, 60%	16

* References 51–64 appear on p. 369.

D. ACETATES OF TRISUBSTITUTED PHENOLS—*Continued*

Substituents	Experimental Conditions	Products	Reference *
2,6-Dimethyl-4-propyl	130–140°	2,6-Dimethyl-4-acetyl, 46% Unidentified *o*-hydroxyketone, 1%	17
2,6-Dimethyl-4-butyl	3 hr. at 130–140°	2,6-Dimethyl-4-acetyl, 40% Unidentified *o*-hydroxyketone, 10%	17
2-Methyl-4-ethyl-6-allyl	4 hr. at 130–140°	2-Methyl-4-ethyl-6-acetyl, 50%	17
2-Methyl-4-ethyl-6-propyl	130–140°	2-Methyl-6-propyl-4-acetyl, 25% Unidentified *o*-hydroxyketone, 25%	17
2-Methyl-4-propyl-6-ethyl	3 hr. at 130–140°	Unidentified *o*-hydroxyketone, 30%	17
2,4,6-Triethyl	6 hr. at 130–140°	2,3,4-Triethyl-6-acetyl, 65%	16
2-Methyl-4-butyl-6-ethyl	4 hr. at 130–140°	2-Methyl-4-butyl-6-acetyl, 46%	17
2,6-Dimethyl-4-benzyl	3 hr. at 130–140°	2,6-Dimethyl-4-acetyl, 65%	17
2,4-Dimethyl-6-heptyl	3 hr. at 130–140°	Unidentified *o*-hydroxyketone, <50%	17
2,6-Dimethyl-4-heptyl	4 hr. at 130–140°	2,6-Dimethyl-4-acetyl, 18% Unidentified *o*-hydroxyketone, 3.5%	17
2-Methyl-4-ethyl-6-benzyl	4 hr. at 130–140°	2-Methyl-4-ethyl-6-acetyl, 63%	17
2-Methyl-4-heptyl-6-ethyl	130–140°	Unidentified *o*-hydroxyketone, 33%	17
2,6-Dimethyl-4-dodecyl	8 hr. at 130–140°	2,6-Dimethyl-4-acetyl, 20%	17
2-Methyl-4-dodecyl-6-ethyl	3 hr. at 130–140°	2-Methyl-6-ethyl-4-acetyl, 5%	17

* References 51–64 appear on p. 369.

E. Esters of Polyhydroxybenzenes

Ester	Solvent	Experimental Conditions	Products	Reference *
Catechol diacetate	$C_6H_5NO_2$	2 hr. at 75°	4-Acyl, 80%	18
Catechol dipropionate	$C_6H_5NO_2$	45 hr. at room temp., warm on steam bath	4-Acyl, 39%	18
Catechol dibutyrate	$C_6H_5NO_2$	½ hr. at 100°	4-Acyl, 35%	18
Catechol dibutyrate	$C_6H_5NO_2$	Add 1 mole catechol; 2 hr. at 80°	4-Acyl, 35%	18
Catechol divalerate	CS_2	Add 1 mole catechol; 4½hr. at 135–140°	4-Acyl, 50%	19
Catechol diisovalerate	CS_2	Same as divalerate	4-Acyl, 69%; 3-acyl	19
Catechol diisovalerate	$C_6H_5NO_2$	Add 1 mole catechol; 1 hr. at 80°	4-Acyl, 40%	18
Catechol dicaproate	CS_2	Same as divalerate	4-Acyl, 72%	19
Catechol diisocaproate	CS_2	Same as divalerate	4-Acyl, 60%; 3-acyl	19
Catechol dibenzoate	$C_6H_5NO_2$	4 hr. at 100°	4-Acyl, Quantitative	18
Catechol distearate	—	1 hr. at 110°	No pure product	18
Guaiacol acetate	—	$ZnCl_2$; heat to b.p.	4-Acyl, 26%; 5-acyl, 5.6%; 6-acyl, 1%	27
Guaiacol acetate	$C_6H_5NO_2$	3 days at room temp.	4-Acyl, 30%	18
Guaiacol propionate	$C_6H_5NO_2$	$2AlCl_3$; ½–1 hr. at 80°, overnight cold	4-Acyl, 50%; 4-acylcatechol [a]	11
Guaiacol propionate	CS_2	$2AlCl_3$; 2 hr. at 140°	4-Acylcatechol, 51%	19
Guaiacol butyrate	CS_2	Same as propionate in CS_2	4-Acylcatechol, 23–62%	19
Guaiacol caproate	CS_2	Same as propionate in CS_2	4-Acylcatechol, 30–47%	19
Guaiacol heptanoate	CS_2	Same as propionate in CS_2	4-Acylcatechol, 8–17%	19
Resorcinol diacetate	—	$2AlCl_3$; 4 hr. at 130°	2,6-Diacyl [b]	22
Resorcinol diacetate	—	$ZnCl_2$; 130°	2,6-Diacyl, 40–50% [c]	20
Resorcinol monomethyl ether acetate	$C_6H_5NO_2$	24 hr. at room temp.	4-Acyl, 11%; 6-acyl, 12%	26
4-Ethylresorcinol diacetate	$C_6H_5NO_2$	$2AlCl_3$. Add 1 mole of 4-ethyl resorcinol; 18 hr. at room temperature, 3–4 hr. at 60°	6-Acyl, Quantitative [d]	22

* References 51–64 appear on p. 369.

[a] Comparable results are reported [11] with the butyrate, valerate, and heptanoate.

[b] Comparable results are reported [22] with the dipropionate, dibutyrate, and divalerate.

[c] Comparable results are reported [20] with the dipropionate, dibutyrate, dicaproate, and dilaurate.

[d] Without the added mole of 4-ethylresorcinol, the yield is 47%. Comparable results are reported [29] with the dipropionate, dibutyrate, diisovalerate, dicaproate, and dibenzoate.

E. ESTERS OF POLYHYDROXYBENZENES—*Continued*

Ester	Solvent	Experimental Conditions	Products	Reference *
4-Ethylresorcinol diacetate	—	$2AlCl_3$; 3–4 hr. at 60–70° or 5 hr. at 110°	2,6-Diacyl, 50%	22
4-Ethylresorcinol dipropionate	—	$2AlCl_3$; 3–4 hr. at 60–70° or 5 hr. at 110°	2,6-Diacyl, 50%	22
4-Propylresorcinol diacetate	$C_6H_5NO_2$	Same as 4-ethylresorcinol diacetate in $C_6H_5NO_2$	6-Acyl [e]	22
4-Propylresorcinol diacetate	$C_6H_5NO_2$	$2AlCl_3$; 4 hr. at 60–70°	2,6-Diacyl, 40%	22
5-Methylresorcinol, 1-acetate 3-monomethyl ether	$C_6H_5NO_2$	24 hr. at room temperature	6-Acyl, 50%	26
4-Benzylresorcinol diacetate	$C_6H_5NO_2$	Add one mole of 4-benzylresorcinol, 3–4 hr. at 50°	6-Acyl, 85% [f]	7
Hydroquinone diacetate	$C_6H_5NO_2$	2 hr. at 75°	2-Acyl, 23%	18
Hydroquinone dipropionate	$C_6H_5NO_2$	2 hr. at 75°	2-Acyl, 24%	18
Pyrogallol triacetate	—	$ZnCl_2$; 2 hr. at 145°	5,6-Diacyl, 26%	28
Pyrogallol monoacetate dimethylether (1,2,3)	$C_6H_5NO_2$	24 hr. at room temperature	6-Acyl, 61%	26
Pyrogallol monoacetate dimethylether (1,2,6)	$C_6H_5NO_2$	24 hr. at room temperature	4-Acyl, 7.5%	32
Pyrogallol monoacetate dimethylether (1,2,6)	—	$ZnCl_2$; 3 hr. at 120°	3-Acetyl-6-methoxy-1,2-dihydroxybenzene, 8%	31
Pyrogallol monoacetate dimethylether (1,2,6)	CH_3COCl	$ZnCl_2$; 4 weeks at room temperature	3-Acetyl-6-methoxy-1,2-dihydroxybenzene, 10%	31
Pyrogallol monochloroacetate dimethylether (1,2,6)	—	8 hr. at 100°	3-Chloroacetylpyrogallol	31

* References 51–64 appear on p. 369.

[e] Comparable results are reported [22] with the dipropionate, dibutyrate, divalerate, dicaproate, and dibenzoate.

[f] Comparable results are reported [7] with the dipropionate, dibutyrate, and diisovalerate of 4-benzylresorcinol and with the same esters of 4-(β-phenylethyl)-resorcinol.

E. Esters of Polyhydroxybenzenes—*Continued*

Ester	Solvent	Experimental Conditions	Products	Reference *
Trihydroxybenzene, 1,4-diacetate-2-methyl ether	$C_6H_5NO_2$	24 hr. at room temperature	5-Acyl, 38%	26
Phloroglucinol triacetate	—	$ZnCl_2$; 3 hr. at 130°	2,4,6-Triacetylphloroglucinol, 60%	20, 29
Phloroglucinol triacetate	$C_6H_5NO_2$	24 hr. at room temperature	2,4,6-Triacetylphloroglucinol, 28%	30
Phloroglucinol tribenzoate	—	30 min. at 130–140°	2,4,6-Tribenzoylphloroglucinol, 30%	18

F. Esters of Naphthols, Hydroxybiphenyls, and Hydroxyphenanthrenes

Ester	Experimental Conditions	Products	Reference *
α-Naphthyl acetate	$C_6H_5NO_2$; 18 hr. at 0°	2-Acyl, 16%; 4-acyl, 42%	12
α-Naphthyl acetate	$C_6H_5NO_2$; 18 hr. at 25°	4-Acyl, 28%	12
α-Naphthyl acetate	2 hr. at 100°, 1 hr. at 120°	2-Acyl, 61%; 4-acyl, 5%; 2,4-diacyl, 4%	13
α-Naphthyl acetate	4 hr. at 125°	2-Acyl, 50%	34
α-Naphthyl acetate	½ hr. at 150°	2-Acyl, 25%; 4-acyl, 10%	60
α-Naphthyl propionate	2 hr. at 100°; 1 hr. 120°	2-Acyl, 54%; 4-acyl, 6%; 2,4-diacyl, 2%	13
α-Naphthyl butyrate	$C_6H_5NO_2$; 18 hr. at 0°	2-Acyl, 22%; 4-acyl, 35%	12
α-Naphthyl butyrate	2 hr. at 100°; 1 hr. at 120°	2-Acyl, 55%; 4-acyl, 3%; 2,4-diacyl, 2%	13
α-Naphthyl valerate	2 hr. at 100°; 1 hr. at 120°	2-Acyl, 40%; 4-acyl, 2%	13
α-Naphthyl phenylacetate	$C_6H_5NO_2$; 24 hr. at 0–10°	2-Acyl, 14%; 4-acyl, 37%	12

* References 51–64 appear on p. 369.

F. Esters of Naphthols, Hydroxybiphenyls, and Hydroxyphenanthrenes—*Continued*

Ester	Experimental Conditions	Products	Reference *
α-Naphthyl benzoate	Room temperature in $C_6H_5NO_2$ or b.p. in CS_2	No reaction	12
β-Naphthyl acetate	CS_2; 1 hr. at b.p., 4 hr. at 120°	1-Acyl, 40%	34
β-Naphthyl acetate	30 min. at 120°	1-Acyl, 33%	60
β-Naphthyl acetate	$ZnCl_2$; 150–160°	6-Acyl, 5%	33
β-Naphthyl chloroacetate	CS_2; 1 hr. at b.p., 4 hr. at 120°	Naphtho[2,1-*b*] furan, 1,2-dihydro-1-one, 20%	61
2-Hydroxybiphenyl acetate	3 hr. at 130°	5-Acyl, 60%; 3-acyl	37
2-Hydroxybiphenyl propionate	30–45 min. at 160°	5-Acyl; 3-acyl, 8%	38
2-Hydroxybiphenyl butyrate	30–45 min. at 160°	5-Acyl, 40%; 3-acyl, 15%	38
2-Hydroxybiphenyl valerate	30–45 min. at 160°	5-Acyl, 40%; 3-acyl, 20%	38
3-Hydroxybiphenyl propionate	30–45 min. at 160°	4-Acyl, 71%	38
4-Hydroxybiphenyl acetate	$CHCl_2CHCl_2$; 2 hr. at 140°	3-Acyl	40
4-Hydroxybiphenyl acetate	CS_2; 30 min. at 140°	3-Acyl; 4′-acyl, 4%	9
4-Hydroxybiphenyl benzoate	$CHCl_2CHCl_2$; 1 hr. at 140°	4′-Acyl	6
4-Hydroxybiphenyl benzoate	$CHCl_2CHCl_2$; 1 hr. at 140°	3-Acyl	39
4-Hydroxybiphenyl benzoate	CS_2; $\frac{1}{2}$ hr. at 160°	4′-Acyl, 22%	9
2-Hydroxyphenanthrene acetate	?	Mixture contains over 10% 1-acyl	36
3-Hydroxyphenanthrene acetate	$AlCl_3$ or $AlBr_3$	No crystalline product	36
9-Hydroxyphenanthrene acetate	$AlBr_3$; $C_6H_5NO_2$; $2\frac{1}{2}$ hr. at room temperature	10-Acyl	36
2-Hydroxy-9,10-dihydrophenanthrene acetate	CS_2; 1 hr. at 140°	3-Acyl, 24%; 7-acyl, 23%	62

* References 51–64 appear on p. 369.

G. Esters of Hydroxycoumarins

Ester	Experimental Conditions	Products	Reference *
4-Methyl-5-hydroxycoumarin acetate	?	6-Acyl	44
4-Methyl-7-hydroxycoumarin acetate	1 hr. at 120–140°	8-Acyl, 15–20%	63
4-Methyl-7-hydroxycoumarin acetate	1 hr. at 140–150°	6-Acyl, 4%; 8-acyl	41
4-Methyl-7-hydroxycoumarin acetate	Rapidly to 125°; then heat during 2 hr. to 170°	8-Acyl, 75%	45
4-Methyl-7-hydroxycoumarin propionate	1 hr. at 165–170°	8-Acyl, 28%; 6-acyl	64
4-Methyl-7-hydroxycoumarin benzoate	1 hr. at 160–170°	8-Acyl, 63%	42
4-Methyl-7-hydroxycoumarin *p*-toluate	?	8-Acyl	64
4-Phenyl-7-hydroxy coumarin acetate	1 hr. at 165–170°	8-Acyl, 50%	43
4-Phenyl-7-hydroxycoumarin benzoate	1 hr. at 165–170°	8-Acyl	43
4-*p*-Bromophenyl-7-hydroxycoumarin acetate	?	8-Acyl	43
4-*p*-Tolyl-7-hydroxycoumarin acetate	1 hr. at 165°	8-Acyl, 7%	64

* References 51–64 appear on p. 369.

H. Some Miscellaneous Esters

Ester	Experimental Conditions	Products	Reference *
Acetylsalicyclic acid	$C_6H_5NO_2$; 4 hr. at 60°	4-Acyl, 60%	3
Caproylsalicylic acid, methyl ester	CS_2; 2 hr. at b.p., heat to 110°	4-Acyl, 82% [a]	8
2-Acetyl-4-methylphenyl acetate	10 min. at 100–120°	2,6-Diacyl, 76%	3
2-Benzoyl-4-methylphenyl benzoate	?	No reaction	3
Phenyl-*o*-(anisoyl) benzoate	$CHCl_2CHCl_2$; 2 hr. at 90°	Phenolphthalein 90%	6
Diphenyl phthalate	$CHCl_2CHCl_2$; $\frac{1}{2}$ hr. at 150°	Phenolphthalein, 63% 1-Hydroxyanthraquinone, 33%	6

[a] Comparable results are reported [6] for the propionate, butyrate, valerate, and isocaprylate.

[51] Mozingo, *Org. Syntheses*, **21**, 45 (1941).
[52] Auwers, *Ber.*, **49**, 812 (1916).
[53] Auwers and Wittig, *Ber.*, **57**, 1270 (1924).
[54] Fries and Finck, *Ber.*, **41**, 4271 (1908).
[55] Auwers, *Ber.*, **47**, 3319 (1914).
[56] Fries, Hasselbach, and Schröder, *Ann.*, **405**, 369 (1914).
[57] Smith and Opie, *J. Org. Chem.*, **6**, 427 (1941).
[58] Auwers, *Ber.*, **48**, 90 (1915).
[59] Auwers and Borsche, *Ber.*, **48**, 1708 (1915).
[60] Imoto, *J. Chem. Soc. Japan*, **58**, 932 (1937) [*C. A.*, **32**, 534 (1938)].
[61] Fries and Frellstedt, *Ber.*, **54**, 717 (1921).
[62] Mosettig and Stuart, *J. Am. Chem. Soc.*, **61**, 1 (1939).
[63] Limaye, *Ber.*, **65**, 375 (1932).
[64] Limaye and Shenolikar, *C. A.*, **32**, 2096 (1938).

CHAPTER 12

THE JACOBSEN REACTION

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CONTENTS

PAGE

INTRODUCTION 371

THE SCOPE OF THE REACTION 372

EXAMPLES OF THE JACOBSEN REACTION 374

Polyalkylbenzenes 374

Tetramethylbenzenes 374

Ethyltrimethylbenzenes 374

Pentamethylbenzene and Pentaethylbenzene 376

Octahydroanthracene 376

Halogenated Polyalkylbenzenes 376

4-Iodo-*m*-xylene 376

5- (and 6-)Halopseudocumenes 377

Halomesitylenes 377

Halotetramethylbenzenes 378

9-Bromoöctahydroanthracene 379

4,6-Dihalo-*m*-xylenes 379

5,6-Dibromopseudocumene 380

3- (and 6-)Halo-5-fluoropseudocumenes 380

Halogenated Benzenes 381

EXPERIMENTAL PROCEDURES 381

1,2,3,4-Tetramethylbenzene (Prehnitene) 381

From Pentamethylbenzene 381

From a Mixture of the 1,2,4,5- and 1,2,3,5-Tetramethylbenzenes (Durene and Isodurene) 382

1,2,3,4-Tetraethylbenzene 383

3-Halopseudocumenes 383

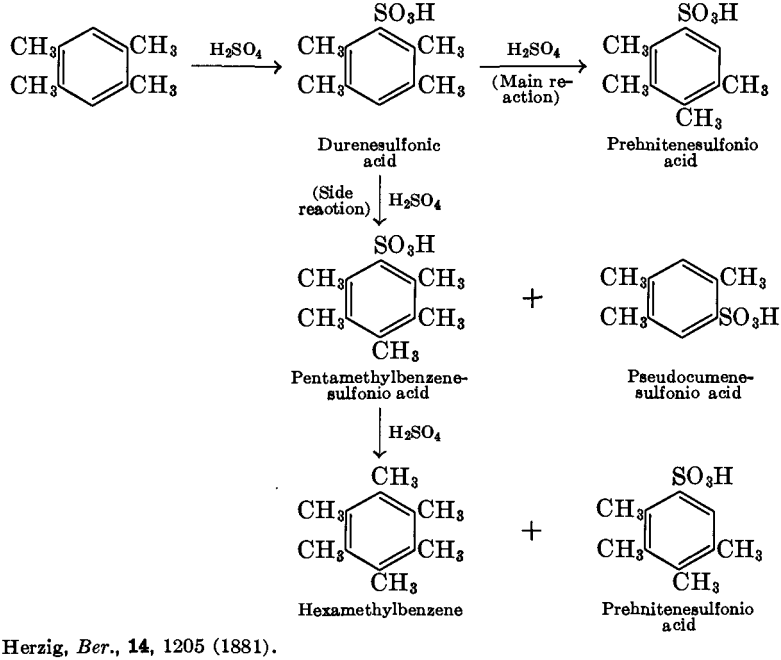
3-Chloropseudocumene 383

3-Bromopseudocumene 384

INTRODUCTION

The migration of an alkyl group or a halogen atom in a sulfonic acid derived from a polyalkylbenzene, a halogenated polyalkylbenzene, or a polyhalogenated benzene is known as the Jacobsen reaction. The reaction is nearly always effected by treating the hydrocarbon or halogenated hydrocarbon with concentrated sulfuric acid and allowing the resulting sulfonic acid to remain in contact with the sulfuric acid. The first observation of a rearrangement of this kind was made by Herzig [1] (1881), who recorded the rearrangement of a polyhalogenated benzenesulfonic acid. However, the reactions have taken the name of Oscar Jacobsen [2] (1886), who discovered the rearrangement of polyalkylbenzenesulfonic acids.

The migrations of the Jacobsen reaction may be divided into two general types: (*a*) intramolecular, in which the migrating group moves from one position to another in the same molecule; and (*b*) intermolecular, in which there is a transfer of one or more groups from one molecule to another. In most cases, migrations of both types occur simultaneously. An important characteristic of the reaction is the migration of the alkyl groups to vicinal positions. The rearrangement of durenesulfonic acid is a typical example.



[1] Herzig, *Ber.*, **14**, 1205 (1881).
[2] Jacobsen, *Ber.*, **19**, 1209 (1886).

It is known with certainty that the rearrangements of the Jacobsen reaction involve the sulfonic acids, not the hydrocarbons.[3] This is shown by the fact that durenesulfonic acid rearranges in contact with phosphorus pentoxide, a reagent which has no effect on durene itself. Also, the sulfonic acid from pentamethylbenzene rearranges when left in a desiccator over concentrated sulfuric acid, whereas the hydrocarbon is unchanged under the same conditions. As yet no completely satisfactory explanation has been advanced regarding the function of the sulfonic acid group in promoting the rearrangement.[4] Nor is it possible to account for the side reactions which occur during the course of the Jacobsen reaction. The by-products are sulfur dioxide and polymeric materials ranging from tars to insoluble, infusible solids. It is known that part of the sulfur dioxide is in some way liberated from the sulfonic acid during rearrangement, while the remainder results from the oxidizing action of sulfuric acid on the organic substances present in the reaction mixture.

THE SCOPE OF THE REACTION

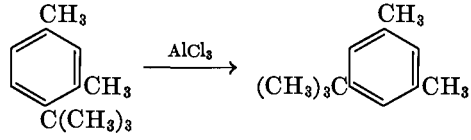
The Jacobsen reaction has been limited, with few exceptions, to the polyalkylbenzenes, halogenated polyalkylbenzenes, and halogen derivatives of benzene. The substituents which have been shown capable of migration are CH_3 and C_2H_5 (the only two alkyl groups studied), I, Br, Cl, and SO_3H. No Jacobsen rearrangement of compounds containing amino, nitro, methoxyl, or carboxyl groups is known.

The ease with which rearrangement takes place depends on the groups attached to the benzene ring. If only halogen is present, rearrangement occurs even when the benzene ring carries but one substituent. If both halogen and alkyl groups are attached to the ring, then rearrangement occurs the more readily the greater the number of alkyl groups, provided that at least one unsubstituted position is present. If only alkyl groups are present, then rearrangement occurs only with the tetra- and pentaalkyl derivatives. Thus, the sulfonic acids derived from the trialkylbenzenes, hemimellitene,[5] pseudocumene,[3] mesitylene,[3] 1,2,4-triethylbenzene,[6] and 1,3,5-triethylbenzene [6] are stable to sulfuric acid.

The synthetic value of the Jacobsen reaction lies in the formation of vicinal derivatives by migration of the alkyl groups of compounds containing these groups in non-vicinal positions. Thus, the tetramethyl-, tetraethyl- and trimethylethyl-benzenes of non-vicinal orientation rear-

[3] Smith and Cass, *J. Am. Chem. Soc.*, **54**, 1614 (1932).
[4] Moyle and Smith, *J. Org. Chem.*, **2**, 112 (1937).
[5] Smith and Moyle, *J. Am. Chem. Soc.*, **58**, 1 (1936).
[6] Smith and Guss, *J. Am. Chem. Soc.*, **62**, 2631 (1940).

range to valuable vicinal derivatives. This is in direct contrast to the orienting effects in rearrangements brought about by aluminum chloride.* In the polyalkylation of benzene by the Friedel and Crafts method, non-vicinal derivatives are formed. For instance, it is certain that the trimethylbenzene fraction produced from benzene, methyl chloride, and anhydrous aluminum chloride contains no 1,2,3-trimethylbenzene (hemimellitene), nor does the tetramethylbenzene fraction contain any 1,2,3,4-tetramethylbenzene (prehnitene).[7] The fact that alkyl groups orient themselves in the *meta* positions in the Friedel and Crafts synthesis may be ascribed to rearrangement of the expected products under the influence of aluminum chloride. Thus, it has been demonstrated that 1,3-dimethyl-4-*t*-butylbenzene is converted to the 1,3,5-isomer by aluminum chloride.[8]



In the halogenated polyalkylbenzenes migration of an alkyl group has been observed only with chlorodurene and chloroisodurene. Several examples of halogen migration are known. In certain cases migration of an alkyl group occurs after the removal of halogen by intermolecular rearrangement. The only applications of synthetic value in connection with the rearrangement of halogenated polyalkylbenzenes are the preparations of 2,4-dibromo- or 2,4-dichloro-*m*-xylene from the 4,6-dihalo-*m*-xylenes, and of 3-bromo- or 3-chloro-pseudocumene from the 5-halo isomers.

The rearrangement of halogenated benzenes leads to mixtures from which pure products can be separated only with difficulty. Consequently, the method cannot be considered of synthetic value. The observations which have been reported do not indicate any tendency toward vicinal orientation in the polyhalogenated rearrangement products.

In the following section are given the detailed results of investigations of the Jacobsen reaction.

* For a review of the subject of alkylation and rearrangement in the presence of aluminum chloride, see Nightingale, *Chem. Rev.*, **25**, 329 (1939).

[7] Smith and Cass, *J. Am. Chem. Soc.*, **54**, 1617 (1932).

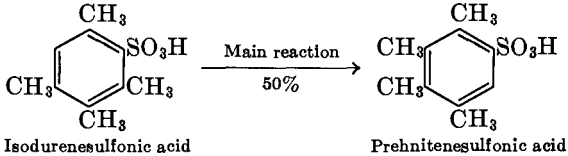
[8] Smith and Perry, *J. Am. Chem. Soc.*, **61**, 1411 (1939).

EXAMPLES OF THE JACOBSEN REACTION

Polyalkylbenzenes

Tetramethylbenzenes. The equation for the rearrangement of durenesulfonic acid [2, 3] is shown on p. 371. Prehnitenesulfonic acid has been obtained in 70% yield when the reaction was carried out by sulfonating durene with concentrated sulfuric acid and allowing the sulfonation mixture to stand for twenty-five days at room temperature.[3] The other products were sulfur dioxide, carbon dioxide, and very small amounts of 5-pseudocumenesulfonic acid and hexamethylbenzene. About 30% of the reaction product was a brown amorphous material.

Isodurenesulfonic acid rearranges to prehnitenesulfonic acid, but the yield is somewhat less than that obtained from durene.[3, 9] The by-products are essentially the same as those from durene.



Isodurenesulfonic acid — Prehnitenesulfonic acid

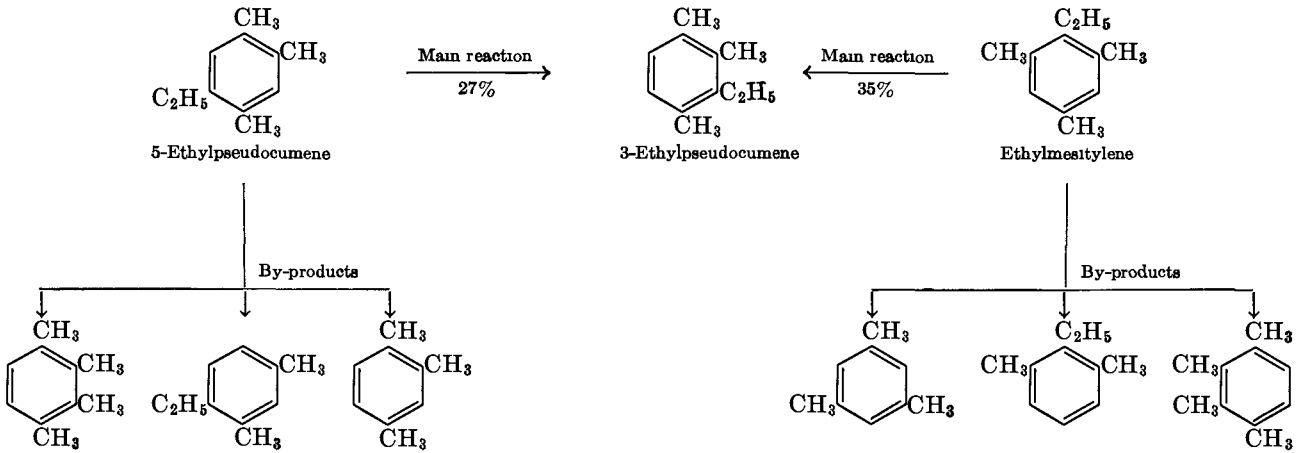
Prehnitene is sulfonated by sulfuric acid, and the sulfonic acid does not rearrange.[3]

The 1,2,4,5- and 1,2,3,5-tetraethylbenzenes [6, 10, 11] rearrange to give products analogous to those obtained from the tetramethyl derivatives. However, the reactions with the tetraethylbenzenes are much more rapid (15 minutes at 100°), and the yield of 1,2,3,4-tetraethylbenzene is 90–92%. The rearrangements of the tetraethylbenzenes are the only recorded instances of Jacobsen reactions in which the tarry, polymeric by-product is entirely absent and practically no sulfur dioxide is evolved.

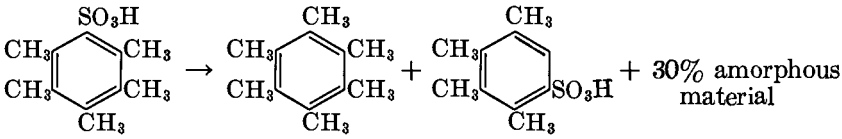
Ethyltrimethylbenzenes.[12, 13] The sulfonic acids of 1,2,4-trimethyl-5-ethylbenzene (5-ethylpseudocumene) and 1,3,5-trimethyl-2-ethylbenzene (ethylmesitylene) rearrange to that of 1,2,4-trimethyl-3-ethylbenzene (3-ethylpseudocumene). The yields are relatively low, owing to side reactions which involve elimination of the ethyl group or one of the methyl groups. In the chart on p. 375, the sulfonic acid groups are not included in the formulas because their exact positions are unknown.

[9] Töhl, *Ber.*, **21**, 904 (1888).
[10] Jacobsen, *Ber.*, **21**, 2814, 2819 (1888).
[11] Galle, *Ber.*, **16**, 1774 (1883).
[12] Töhl and Karchowski, *Ber.*, **25**, 1530 (1892).
[13] Smith and Kiess, *J. Am. Chem. Soc.*, **61**, 989 (1939).

PRODUCTS OF REARRANGEMENT OF 5-ETHYLPSEUDOCUMENE AND ETHYLMESITYLENE



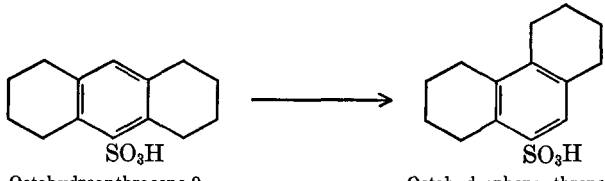
Pentamethylbenzene and Pentaethylbenzene. The rearrangement of pentamethylbenzenesulfonic acid[14, 15] is intermolecular, a methyl group being transferred from one molecule to another.



Pentaethylbenzene[6, 10, 12, 16] undergoes a similar reaction, but the yields (20–30%) are inferior to those obtained in the pentamethylbenzene rearrangement. The by-products are formed in much larger quantities. This is in contrast to the tetraethylbenzenes, which rearrange more readily than the tetramethyl derivatives.

Hexamethylbenzene[2, 3] is not affected by sulfuric acid.

Octahydroanthracene. Octahydroanthracene-9-sulfonic acid[17] is rearranged by sulfuric acid to octahydrophenanthrene-9-sulfonic acid. The reaction is rapid (20 minutes at 90–100°), and yields as high as 85% have been obtained. This is one of the rare cases in which the action of sulfuric acid is improved by the presence of a diluent. Sulfuric acid containing a little acetic acid is used to effect sulfonation and rearrangement.

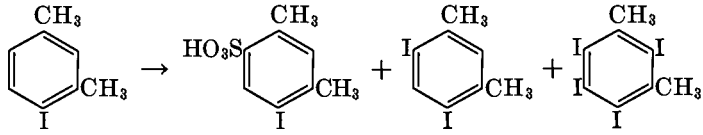


Octahydroanthracene-9-sulfonic acid — Octahydrophenanthrene-9-sulfonic acid

Halogenated Polyalkylbenzenes

4-Iodo-*m*-xylene.[18, 19] When 4-iodo-*m*-xylene is treated with concentrated sulfuric acid and the reaction mixture is allowed to stand for several weeks the products isolated (in unspecified yields) are di- and tetra-iodoxylenes and an iodoxylenesulfonic acid.

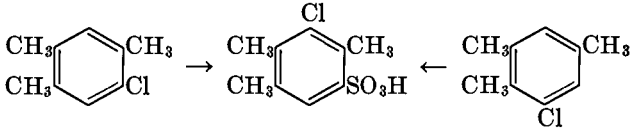
[14] Jacobsen, *Ber.*, **20**, 896 (1887).
[15] Smith and Lux, *J. Am. Chem. Soc.*, **51**, 2994 (1929).
[16] Smith and Guss, *J. Am. Chem. Soc.*, **62**, 2634 (1940).
[17] Schroeter and Götzsky, *Ber.*, **60**, 2035 (1937).
[18] Hammerich, *Ber.*, **23**, 1634 (1890).
[19] Töhl and Bauch, *Ber.*, **23**, 3117 (1890); **26**, 1105 (1893).



4-Iodo-*m*-xylene | 4-Iodo-*m*-xylene-6-sulfonic acid | 4,6-Diiodo-*m*-xylene | 2,4,5,6-Tetraiodo-*m*-xylene

No rearrangements have been reported for monohalogen derivatives of *o*- and *p*-xylenes.

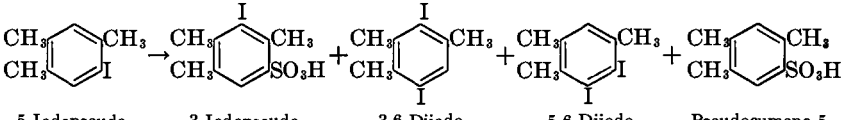
5- (and 6-)Halopseudocumenes. The sulfonic acids of 1,2,4-trimethyl-5-chloro- and 1,2,4-trimethyl-6-chloro-benzenes rearrange to the sulfonic acid of 1,2,4-trimethyl-3-chlorobenzene (3-chloropseudocumene) in yields of 71 and 44%, respectively.[5] Apparently both reactions involve intramolecular migration of the halogen atom.



5-Chloropseudocumene | 3-Chloropseudocumene sulfonic acid | 6-Chloropseudocumene

The corresponding 5-bromo compound is converted to the sulfonic acid of 1,2,4-trimethyl-3-bromobenzene (3-bromopseudocumene) in 90% yield.[5, 20] A small amount of 1,2,4-trimethyl-3,5,6-tribromobenzene (tribromopseudocumene) is obtained as a by-product.

1,2,4-Trimethyl-5-iodobenzene [21] (5-iodopseudocumene) gives rise to two diiodopseudocumenes, an iodopseudocumenesulfonic acid, and pseudocumene-5-sulfonic acid; the yields are not reported.

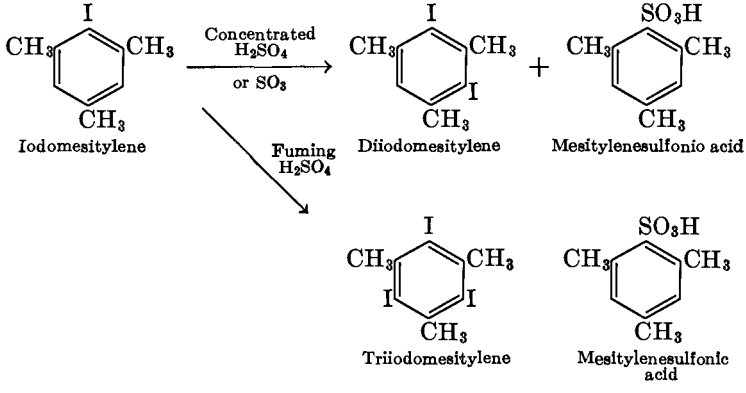


5-Iodopseudocumene | 3-Iodopseudocumene-5-sulfonic acid | 3,6-Diiodopseudocumene | 5,6-Diiodopseudocumene | Pseudocumene-5-sulfonic acid

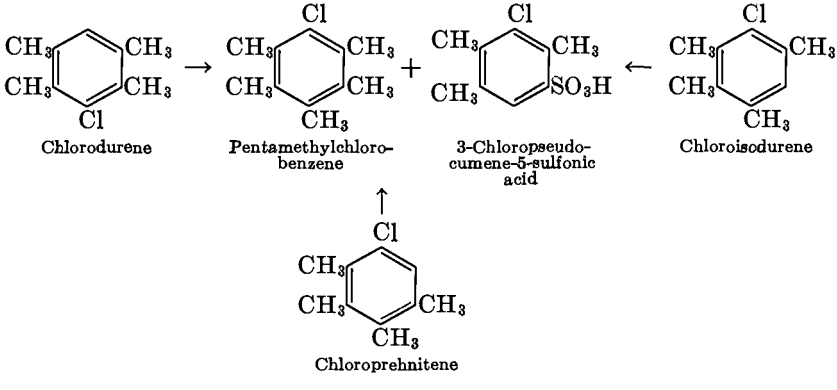
Halomesitylenes.[5, 22, 23] The sulfonic acid of chloromesitylene appears to be stable, but that of bromomesitylene rearranges easily to give a mixture of mesitylenesulfonic acid, dibromomesitylene, and tribromomesitylene. The sulfonation of iodomesitylene leads to analogous

[20] Jacobsen, *Ber.*, **22**, 1580 (1889).
[21] Kurzel, *Ber.*, **22**, 1586 (1889).
[22] Töhl and Eckel, *Ber.*, **26**, 1099 (1893).
[23] Rose, *Ann.*, **164**, 63 (1872).

products, the character of which depends primarily on the reagent. No yields are reported.



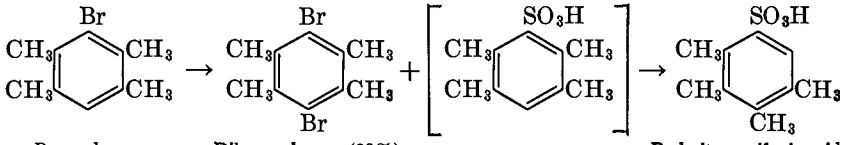
Halotetramethylbenzenes.[5, 24, 25, 26] All three monochlorotetramethylbenzenes[5, 25] (1,2,4,5-tetramethyl-3-chlorobenzene, 1,2,3,5-tetramethyl-4-chlorobenzene, 1,2,3,4-tetramethyl-5-chlorobenzene) rearrange to pentamethylchlorobenzene and 1,2,4-trimethyl-3-chloro-5-benzenesulfonic acid. In these reactions migration of a methyl group must occur.



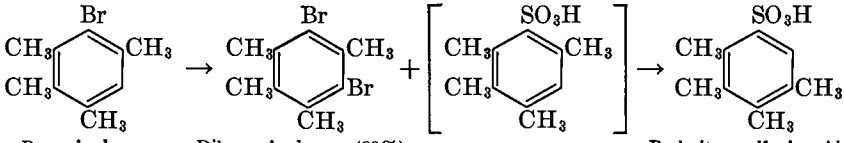
The corresponding bromo compounds, 1,2,4,5-tetramethyl-3-bromobenzene (bromodurene[24, 26]), 1,2,3,5-tetramethyl-4-bromobenzene (bromoisodurene[25]), and 1,2,3,4-tetramethyl-5-bromobenzene (bromoprehnitene) react differently. No migration of a methyl group occurs, but the bromine migrates intermolecularly to give dibromo compounds. The sulfonic acid from which the bromine has been removed is that of durene,

[24] Smith and Moyle, *J. Am. Chem. Soc.*, **55**, 1676 (1933).
[25] Töhl, *Ber.*, **25**, 1527 (1892).
[26] Jacobsen, *Ber.*, **20**, 2837 (1887).

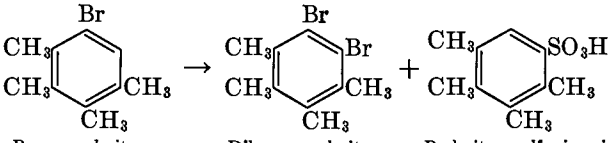
isodurene, or prehnitene, the first two of which rearrange to prehnitenesulfonic acid. The yields of dibromo derivatives are 80–100%, and those of prehnitenesulfonic acid 25–80%. The three isomeric dibromotetramethylbenzenes and bromopentamethylbenzene do not rearrange in contact with sulfuric acid, but all undergo a slow decomposition accompanied by evolution of sulfur dioxide.



Bromodurene — Dibromodurene (99%) — Prehnitenesulfonic acid (25%)

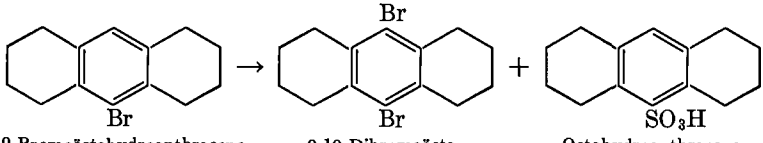


Bromoisodurene — Dibromoisodurene (80%) — Prehnitenesulfonic acid (40%)



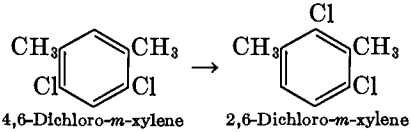
Bromoprehnitene — Dibromoprehnitene (99%) — Prehnitenesulfonic acid (82%)

9-Bromoöctahydroanthracene.[17] The sulfonic acid of 9-bromoöctahydroanthracene rearranges when warmed with fuming sulfuric acid, yielding 9,10-dibromoöctahydroanthracene and an octahydroanthracenesulfonic acid. The structure of the latter has not been proved; it is probably the 9-isomer.



9-Bromoöctahydroanthracene — 9,10-Dibromoöctahydroanthracene — Octahydroanthracene-9-sulfonic acid

4,6-Dihalo-*m*-xylenes. 4,6-Dichloro-*m*-xylene[27] rearranges to 2,4-dichloro-*m*-xylene (12% yield) when subjected to the conditions of the Jacobsen reaction.



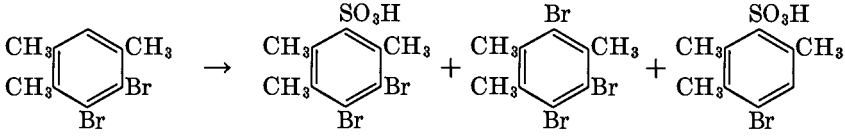
4,6-Dichloro-*m*-xylene — 2,6-Dichloro-*m*-xylene

[27] Koch, *Ber.*, **23**, 2318 (1890).

4,6-Dibromo-*m*-xylene[28] rearranges in the same way, forming 2,4-dibromo-*m*-xylene (about 25% yield). From the behavior of other halogen compounds, it is likely that the halogen atom is the migrating group, although the same products would be produced by migration of a methyl group.

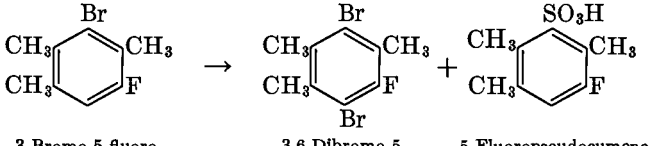
Dihalogen derivatives of *o*- and *p*-xylenes have been reported to rearrange, but the yields of definite products were very low.[27]

5,6-Dibromopseudocumene.[29] 1,2,4-Trimethyl-5,6-dibromobenzene (5,6-dibromopseudocumene) was treated with chlorosulfonic acid by Jacobsen. Sulfonation was accompanied by the formation of tribromopseudocumene and 1,2,4-trimethyl-6-bromobenzene-3-sulfonic acid. The yields were not reported, but the main product isolated was tribromopseudocumene.



5,6-Dibromopseudocumene | 5,6-Dibromopseudocumene-3-sulfonic acid | Tribromopsudocumene | 6-Bromopseudocumene-3-sulfonic acid

3- (and 6-)Halo-5-fluoropseudocumenes.[30] Only a few fluoro compounds have been investigated in connection with the Jacobsen reaction. No instance of migration of a fluorine atom has been reported. For example, 5-fluoropseudocumene undergoes no rearrangement when it is sulfonated and the sulfonic acid is left in contact with sulfuric acid for three months. When 3- (or 6-)bromo-5-fluoropseudocumene is treated with sulfuric acid, rearrangement involving intermolecular migration of the bromine atom occurs. The methyl groups are unaffected. The analogous chloro-5-fluoropseudocumenes give the corresponding dichloro-



3-Bromo-5-fluoropseudocumene | 3,6-Dibromo-5-fluoropseudocumene | 5-Fluoropseudocumene-3-sulfonic acid

fluoropseudocumene and the same fluoropseudocumenesulfonic acid; yields are not reported.

[26] Jacobsen, *Ber.*, **21**, 2827 (1888).
[29] Jacobsen, *Ber.*, **19**, 1221 (1886).
[30] Töhl and Müller, *Ber.*, **26**, 1108 (1893).

Halogenated Benzenes [1]

The reactions of bromobenzene, *p*-dibromobenzene, and 1,3,5-tribromobenzene [1] with sulfuric acid have been studied. In all cases sulfur dioxide and carbon dioxide are evolved and only small yields of definite products result. Bromobenzene is converted to a dibromobenzenesulfonic acid, probably the 1,3,5-isomer; *p*-dibromobenzene yields 1,2,4,5-tetrabromobenzene and hexabromobenzene; 1,3,5-tribromobenzene yields hexabromobenzene.

Iodobenzene [31, 32] is converted by sulfuric acid to *p*-diiodobenzene and benzenesulfonic acid, with liberation of some iodine and hydriodic acid. *o*- and *p*-Iodotoluenes undergo a similar reaction. *p*-Diiodobenzene and fuming sulfuric acid give a mixture of tri- and tetraiodobenzenes;[33] experimental details are lacking.

It is quite obvious that the Jacobsen reaction as applied to halogenated benzenes to form polyhalogenated benzenes is not one of practical synthetic value.

There appear in the literature [34] some rearrangements of 1,8-dichloronaphthalene which resemble the Jacobsen rearrangement. When 1,8-dichloronaphthalene is heated with hydrochloric acid at 290°, a rearrangement to 1,5-dichloronaphthalene occurs. A similar conversion also results from the action of sulfuric acid, but considerable decomposition occurs simultaneously. Heating with phosphoric acid or in the absence of any acid fails to bring about a rearrangement of the dichloronaphthalene. Only the 1,8-dichloro isomer undergoes rearrangement. The 1,8-dichloro-4-naphthalenesulfonic acid is hydrolyzed by acid at 230° to give 1,8-dichloronaphthalene; the 1,8-dichloro-3-naphthalenesulfonic acid, however, undergoes hydrolysis only if a temperature of 285° is reached, and then a mixture of the 1,8-, the 1,5- and the 1,7-dichloro derivatives results.

EXPERIMENTAL PROCEDURES

1,2,3,4-Tetramethylbenzene (Prehnitene)

From Pentamethylbenzene.[15] To 74 g. of pentamethylbenzene (m.p. 52°) heated to 65°, 200 g. of concentrated sulfuric acid is added and the mixture is shaken vigorously. This procedure results in a mush of fine crystals of the hydrocarbon in the sulfuric acid; lumps must be

[31] Neumann, *Ann.*, **241**, 33 (1887).
[32] Cass, Ph.D. thesis, University of Minnesota, 1931.
[33] Boyle, *J. Chem. Soc.*, **95**, 1683 (1909).
[34] Armstrong and Wynne, *Chem. News*, **76**, 69 (1897).

avoided; if any are formed they should be broken up. The reaction mixture of crystals and red liquid is allowed to stand at room temperature for twenty-four hours, then cooled in an ice-salt bath. To it is now added 165–200 g. of cracked ice in three portions with vigorous stirring. The cold mixture is filtered and the filter cake pressed as dry as possible; the precipitate is then stirred with 700 cc. of cold water and again filtered. The product is a mixture of hexamethylbenzene and tar while the red aqueous filtrate contains the prehnitenesulfonic acid.

The filtrate is treated with excess of powdered calcium carbonate, and the precipitated calcium sulfate is filtered and thoroughly washed with water. The calcium prehnitenesulfonate in the combined filtrate and washings is converted to the corresponding sodium salt by addition of a saturated aqueous sodium carbonate solution as long as any precipitate forms. The precipitated calcium carbonate is filtered and washed with water. The filtrate and washings are evaporated to dryness on the steam bath. The residue of sodium prehnitenesulfonate weighs 40 g.

Since the prehnitenesulfonic acid undergoes extensive decomposition when heated with sulfuric acid, the sodium salt is advantageously hydrolyzed to the hydrocarbon by a "flash" method. In a steam-distillation flask, provided with openings for a thermometer and dropping funnel, is placed about 100 cc. of water. Superheated steam is passed into the flask, and concentrated sulfuric acid is then added slowly from the dropping funnel until the temperature of the diluted acid reaches 150–160°. At this point a saturated aqueous solution of 40 g. of sodium prehnitenesulfonate or a thin paste of solid and water is run into the flask at such a rate that the temperature of the mixture remains at 140–150°. Careful control of this temperature is essential. Hydrolysis takes place rapidly, and a pale yellow oil separates from the distillate. The crude oil weighs 20 g. (88%). Upon distillation, over 90% boils at 97–98°/24–25 mm.; m.p. −7.4°. Highly purified prehnitene melts at −6.4°.

From a Mixture of the 1,2,4,5- and 1,2,3,5-Tetramethylbenzenes (Durene and Isodurene). A mixture of durene and isodurene, b.p. 82–84°/15 mm. can be obtained by fractionation of the hydrocarbons produced by the reaction of methyl chloride and aluminum chloride with the mixed xylenes (see ref. 3 for details). A mixture of 100 g. of this fraction, 67 cc. of concentrated sulfuric acid and 33 cc. of 60% fuming sulfuric acid is shaken (in a 500-cc. glass-stoppered Erlenmeyer flask) for about five minutes. The resulting solution is heated to 80° for a period of nine hours. The black, nearly solid reaction mixture is then broken up and poured over 500 g. of crushed ice. After filtration of the insoluble material (18 g.) the solution is cooled to +10° and the sul-

fonic acid is precipitated by the addition of 250 cc. of concentrated sulfuric acid. After cooling, the dark-colored sulfonic acid, m.p. 98–100°, is collected on a filter and pressed dry. It is dissolved in 200 cc. of warm water and is then hydrolyzed by the "flash" method described above. The organic layer from the steam distillation weighs 65 g. and on careful fractionation yields 41.4 g. (41.4%) of prehnitene boiling at 94–96.4°/25 mm. and freezing at −7.2°.

1,2,3,4-Tetraethylbenzene [6]

From the ethylation of benzene,[35] a fraction can be obtained (b.p. 110–113°/10–11.5 mm.) which contains 1,2,4,5- and 1,2,3,5-tetraethylbenzenes. A mixture of 25 g. of this fraction and 100 g. of concentrated sulfuric acid is stirred at 100° for fifteen minutes. The emulsion which first forms darkens in color and the hydrocarbons dissolve. The cooled solution is poured onto 100 g. of ice, whereupon the tan-colored sulfonic acid crystallizes. The product is purified by crystallization from a mixture of benzene and petroleum ether (b.p. 60–68°). It forms white crystals, m.p. 118–120°, which contain one molecule of water of crystallization. The yield is 34–35 g. (90.7–92.3%).

A mixture of 84 g. of the sulfonic acid and 300 cc. of 50% sulfuric acid is heated. Steam is passed through the solution; when the temperature reaches 130° (thermometer in liquid), hydrolysis begins and at 140–150° is rapid. The oil in the distillate is removed and fractionated through a column of the Fenske type packed with glass helices. The product distils at 119–120°/11 mm. and is pure 1,2,3,4-tetraethylbenzene.[36] The yield is 50 g. (90.7%).

3-Halopseudocumenes

Chlorination or bromination of pseudocumene [37] (1,2,4-trimethylbenzene) produces mixtures of the 3- and 5-halopseudocumenes. The 5-halopseudocumenes have relatively high melting points and can be largely removed by cooling and filtering the reaction product. The filtrate consists largely of the 3-halopseudocumene (see ref. 5, p. 8, for details).

3-Chloropseudocumene. In a 250-cc. glass-stoppered Erlenmeyer flask, 30 g. of 5-chloropseudocumene (or 30 g. of the mixture of the 3- and 5-chloropseudocumenes) is dissolved in 100 cc. of 20% fuming sulfuric acid by vigorous shaking of the mixture. The solution is heated to

[35] Smith and Guss, *J. Am. Chem. Soc.*, **62**, 2625 (1940).

[36] Smith and Guss, *J. Am. Chem. Soc.*, **62**, 2630 (1940).

[37] Smith and Cass, *J. Am. Chem. Soc.*, **54**, 1603 (1932); Smith and Lund, *ibid.*, **52**, 4144 (1930).

65–70° for four hours and is then poured over 150 g. of crushed ice. The resulting mixture is cooled in a salt-ice bath until crystallization of the sulfonic acid of 3-chloropseudocumene is complete. The cold mixture is then filtered and the cake is pressed dry. The sulfonic acid is dissolved in 75–125 cc. of water, and the insoluble tar (4.5 g.) is filtered and discarded. The cold solution is treated with an excess of 20% sodium hydroxide, and the precipitate of sodium sulfonate is collected by filtration. The filtrate is concentrated to one-third volume, chilled, and filtered to yield a second crop. The total yield of sodium 3-chloropseudocumenesulfonate, after drying at 110°, is 35.4 g. (71%).

The sodium salt is dissolved in 250 cc. of 50% sulfuric acid, in a 500-cc. flask arranged for steam distillation. The flask is heated in an oil bath until the internal temperature is 135–155°. Steam is passed into the liquid until the distillate is homogeneous. The organic layer of the distillate is separated, dried over a little calcium chloride, and distilled under diminished pressure. The pure 3-chloropseudocumene, boiling at 127°/61 mm., weighs 17.2 g. (79%, based on the sulfonate).

3-Bromopseudocumene. By vigorous shaking, 19.9 g. of crude 5-bromopseudocumene is dissolved in 120 g. of 20% fuming sulfuric acid which is maintained at 70°. After solution is complete the reaction mixture is treated as described in the above procedure. The sodium salt of 3-bromopseudocumenesulfonic acid, which weighs 27.1 g. (90%), is hydrolyzed by steam distillation from 50% sulfuric acid maintained at 175°.[13] The 3-bromopseudocumene boils at 85.5–86.5°/5 mm. and weighs 14.5 g. (80%, based on the sulfonate).

INDEX

Numbers in bold-face type refer to experimental procedures.

4,10-Ace-1,2-benzanthracene, 143
β,3-Acenaphthoylpropionic acid in Clemmensen reduction, 163
Acetoacetic ester condensation, 266–302
  condensing agents in, 267, 276–277, 284–286
  experimental conditions, 278–279, 284–286
  experimental procedures, 279–289
  "forced," 278–279
  mechanism, 267
  reversibility, 269
  scope, 270–272
  side reactions, 272–274
  tables, 290–296
Acetomesitylene, chloromethylation of, **71**
Acetylenes in Mannich reaction, 311, 314
Acids, conversion to next higher homologs, 38
  in Mannich reaction, 310, 313, 316
  preparation by Arndt-Eistert synthesis, **50**
Acylation, with acid anhydrides, 275
  with acid chlorides, 275, 276
    table, 296
  with esters, 266–302
    tables, 290–295
2-Acylresorcinols, synthesis of, 352
Alcohols, reduction by zinc amalgam and acid, 162
Aldehydes, chloromethylation of aromatic, 89
  in Mannich reaction, 309, 313, 316, 317, 324, 327
  reduction by Clemmensen method, 157
  in Reformatsky reaction, 19–22
Alkyl acetates, self-condensation, **280–281**
Alkylacetylenes, 243
α-Alkylcinnamic acids, preparation by Perkin reaction, 224
2-Alkylpyridines, reaction with alkali amides, 93
β-Alkylstyrenes from cinnamic acids, 243
Amides, in Reformatsky reaction, 34
  preparation by Arndt-Eistert synthesis, **51**
Amination of heterocyclic bases, 91–104
  alkali amides in, 96
  experimental conditions, 96–98
  experimental procedures, 98–100
  tables, 102–104
Amines, heterocyclic, preparation of, 91–104
  in Mannich reaction, 307–315
Amino acids from Mannich bases, 324
Amino alcohols by reduction of Mannich bases, 323, 324
Aminocarbonyl compounds, preparation by Mannich reaction, 304–341
4-Amino-2-phenylquinoline, **100**
2-Aminopyridine, **99**
Ammonia in Mannich reaction, 315–316
n-Amyl propionylacetate, 300
β-(*p*-Anisoyl)-propionic acid, reduction by Clemmensen method, **167**
γ-(*p*-Anisyl)-butyric acid, **167**
Anthracene derivatives, preparation, 130, 131, 132–133
β-Anthraquinoline, 147
Anthraquinone-2-acetanilide, **52**
Arndt-Eistert synthesis, 38–62
  experimental conditions, 47–50
  experimental procedures, 50–53
  scope, 42–47
  tables, 55–62
Aroylacetic esters, 245
Arylacetaldehydes, 244

Arylacetic acids, by Arndt-Eistert synthesis, 50
by Perkin reaction, 230
by Reformatsky reaction, 9
Arylacetonitriles, 230
Arylacetylenes from cinnamic acids, 243
β-Arylalanines, 230
Arylamines, reactivity in Bucherer reaction, 112
β-Aryl-β-aminopropionic acids, 246
Arylethylamines, 230
Arylhydrazines in Bucherer reaction, 114–117
Arylpyruvic acids, 229
Arylthiopyruvic acids, 230
4′-Aza-1,2-benzanthracene, 147
Azlactone synthesis, 223–224
Azo compounds, preparation, 117–118

Benzalphthalide, 223
1,2-Benzanthracene, 139, 150, **152**
derivatives, preparation of, 139–141
15,16-Benzdehydrocholanthrene, 143
Benzene, chloromethylation of, **67**
Benzenediacrylic acids, 221
Benzoin, reduction to stilbene, 159
Benzoylacetic ester, **282–283**, 299, 300
o-Benzoylbenzoic acid, reduction of, 159
1-Benzoyl-2-methylnaphthalene, in Elbs reaction, 139
β-Benzoylpropionic acid, Clemmensen reduction of, **166**
α-Benzylacrylic acid, 319
o-Benzylbenzaldehyde, cyclization of, 131
Benzyl chloride, preparation by chloromethylation of benzene, **67**
2,5-dimethyl-, **69**
2-hydroxy-5-nitro-, **71**
2,4,6-triisopropyl-, **68**
2,4,6-trimethyl-3-aceto-, **71**
Benzyl halides, substituted, 63–90
2-Benzyltetrahydronaphthindazole, 325
2,2′-Biphenyldiacrylic acid, 221
Bipyridyls as by-products in amination of pyridine, 95, 100
Bishomologation, 45, **51**
Bromodurene, 378, 379
3-Bromo-5-fluoropseudocumene, 380
6-Bromo-5-fluoropseudocumene, 380
Bromoisodurene, 378, 379
Bromomesitylenesulfonic acid, 377
Bromomethylation, 72
9-Bromoöctahydroanthracene, 379
9-Bromoöctahydroanthracenesulfonic acid, 379
Bromoprehnitene, 378, 379
3-Bromopseudocumene, 373, **384**
5-Bromopseudocumene, 377
3-Bromopseudocumenesulfonic acid, 377
β-Bromostyrenes, 243
Bucherer reaction, 105–128
effect of sulfonic acid groups in, 108–109
experimental conditions, 118–119
experimental procedures, 120–121
mechanism, 106
scope, 107–118
side reactions, 108–109

Carbazoles, preparation by Bucherer reaction, 114–117
Carbonyl compounds, reduction by Clemmensen method, 155–209
α,β-unsaturated, in Clemmensen reduction, 161
preparation by Mannich reaction, 318
Carbostyril, 219
Chlorobutylation, 73
Chlorodurene, 378
Chloroethylation, 72
Chloro-5-fluoropseudocumene, 380
Chloroisobutylation, 73
Chloroisodurene, 378
Chloromethylation of aromatic compounds, 63–90
Blanc method, **67**
catalysts, 66–67
experimental procedures, 67–71
scope, 64–66
side reactions, 65
tables, 74–89
6-Chloro-20-methylcholanthrene, 142
Chloromethyl ether, **68**
4-Chloro-7-methylindan, **165**
4-Chloro-7-methyl-1-indanone, Clemmensen reduction of, **165**
7-Chloro-4-methyl-1-indanone, Clemmensen reduction of, **165**

α-Chloromethylnaphthalene, **70**
Chloroprehnitene, 378
Chloropropylation, 73
3-Chloropseudocumene, 373, **383**
5-Chloropseudocumene, 373
3-Chloropseudocumenesulfonic acid, 377, 378
5-Chloropseudocumenesulfonic acid, 377
Cholanthrene, 142, 144
  derivatives, 142–145
Chromanones, reduction by Clemmensen method, 161
Chrysene, 247
Cinnamic acid, **248–249**
  Caro's synthesis, 216
  comparison of methods of preparation, 8, 233–234
Claisen condensation, 8, 234, 267
Clemmensen reduction, 155–209
  by-products, 157, 158, 159, 160, 161, 162, 166
  experimental procedures, 162–168
    choice of, 162–163, 164, 165
  mechanism of, 156
  solvents for, 164, 165, 166, 168
  tables, 169–200
Coumarin, 219
Creatine in Perkin reaction, 232
Cyanoacetic ester in Perkin reaction, 232
Cyclization, Dieckmann, 274, 294–295
  of Mannich bases, 322, 325–326

β-Decalone, 321
Decane-1,10-dicarboxylic acid, **51**
Decarboxylation, during Mannich reaction, 310, 311
  during Perkin reaction, 212, 220, 224
Diazomethane, **50**
  precautions in use of, 47
1,2,5,6-Dibenzanthracene, 150, **151**, 247
  derivatives, preparation of, 134–137
  purification of, 138
1,5-Dibenzoyl-2,6-dimethylnaphthalene, 149
4,6-Dibenzoyl-1,3-xylene, 147
Dibromodurene, 379
Dibromoisodurene, 379
9,10-Dibromoöctahydroanthracenesulfonic acid, 379
Dibromoprehnitene, 379
Dibromopseudocumene, 380
2,4-Dibromo-*m*-xylene, 373, 380
4,6-Dibromo-*m*-xylene, 373, 380
3,5-Dicarboethoxycyclopentanedione-1,2, **284**
Dichlorodurenes, **69**
Dichlorofluoropseudocumene, 380
1,8-Dichloronaphthalene, 381
1,8-Dichloro-3-naphthalenesulfonic acid, 381
1,8-Dichloro-4-naphthalenesulfonic acid, 381
2,4-Dichloro-*m*-xylene, 373, 379
4,6-Dichloro-*m*-xylene, 373, 379
Dieckmann reaction, 274
  table, 294–295
4,6-Dihalo-*m*-xylenes, 379
Dihydroanthranol as intermediate in Elbs reaction, 131, 134
2,4-Dihydroxyacetophenone, reduction of, **164**
2,6-Dihydroxyvalerophenone, 159
4,6-Diiodo-*m*-xylene, 377
Diketene, 297
α-Diketones in Clemmensen reduction, 157
β-Diketones in Clemmensen reduction, 157, 158
β,β-Dimethylacrylic acid, 222
1,3-Dimethyl-4-*t*-butylbenzene, 373
1,3-Dimethyl-5-*t*-butylbenzene, 373
5,5-Dimethylcyclohexadione-1,3, rearrangement of, 157
1′,9-Dimethylene-1,2-benzanthracene, 143
2,3,8,9-Di-(naphtho-1′,2′)-chrysene, 147, 148
Dinaphthyl ketones in Elbs reaction, 138
1,3-Diphenylpyrazoline, 320
Doebner modification of Perkin reaction. 226, 233
Durene, 371, 374
Durenesulfonic acid, 371, 372, 374

Elbs reaction, 129–154
  preparation of ketones for use in, 149
  procedures, 151–154
  selection of experimental conditions, 150
  side reactions, 147

Erlenmeyer azlactone synthesis, 223–224, 231, **253**
Ester condensation, 266–302
  mixed, table, 292–293
Esters, in Mannich reaction, 310, 313
  in Reformatsky reaction, 33, 34
  of phenols, chloromethylation of, 84, 85
  preparation, by Arndt-Eistert synthesis, **52**
  self-condensation of, 266–302
    table, 290–291
  unsaturated, synthesis of, 11–13
Ethers, aromatic, chloromethylation of, 86–88
Ethyl acylacetates, preparation by various methods, 299
Ethyl benzoylacetate, **282–283**
  preparation by various methods, 299–300
Ethyl α-benzoylpropionate, 301
Ethyl γ-bromoacetoacetate, 4
Ethyl butyrate, self-condensation of, **280–281**
Ethyl *n*-butyrylacetate, preparation by various methods, 299–300
Ethyl caprate, self-condensation of, **281–282**
Ethyl caproate, self-condensation of, **281–282**
Ethyl caprylate, self-condensation of, **281–282**
Ethyl γ-chloroacetoacetate, 9
20-Ethylcholanthrene, 151
Ethyl γ,γ-diethoxyacetoacetate, **282–283**
Ethyl ethoxalylacetate, 278
Ethyl ethoxalylisobutyrate, 288
Ethyl α-ethylacrylate, 318
Ethyl heptoate, self-condensation of, **281–282**
Ethyl 1-hydroxycyclohexylacetate, **17**
Ethyl isobutyrylacetate, preparation by various methods, 299–300
Ethyl α-isopropylacetoacetate, 297
Ethyl α-isovalerylisovalerate, **288**
Ethyl laurate, self-condensation of, **281–282**
Ethylmesitylene, 375
Ethylmesitylenesulfonic acid, 374
Ethyl α-methyl-β-phenyl-β-hydroxybutyrate, **17**
Ethyl myristate, self-condensation of, **281–282**
Ethyl pelargonate, self-condensation of, **281–282**
Ethyl β-phenyl-β-hydroxypropionate, **16**
Ethyl propionate, self-condensation of, **280–281**
Ethyl propionylacetate, preparation by various methods, 299–300
5-Ethylpseudocumene, 374
  -sulfonic acid, 374, 375
3-Ethylpseudocumenesulfonic acid, 374
Ethylresorcinol, **164**
Ethyl succinylsuccinate, **283–284**
Ethyltrimethylbenzenes, 374
Ethyl valerate, self-condensation of, **281–282**

Ferulic acid, **250**
γ-(2-Fluorene)-butyric acid, **166**
5-Fluoropseudocumene, 380
Formaldehyde, in chloromethylation of aromatic compounds, 66
  in Mannich reaction, 327–328
Formalin, 66
Friedel-Crafts synthesis of phenolic ketones, 343
Fries reaction, 342–369
  experimental conditions, 353–354
  experimental procedures, 354–356
  formation of *m*-hydroxyketones in, 350
  mechanism, 343
  migration of alkyl groups, 347–349
  reversal, 353
  scope, 344–353
  solvents, 345
  tables, 356–369
  temperature effect in, 344
2-Furanacetic acid, 230

1,2-Glycols in Clemmensen reduction, 158

α-Halocarbonyl compounds, reduction of, 162
α-Haloesters in Reformatsky reaction, 4, 20–33
3-Halo-5-fluoropseudocumenes, 380
6-Halo-5-fluoropseudocumenes, 380
Halogenated benzenes, 381

Halogenated polyalkylbenzenes, 376
Halomesitylenes, 377
ω-Halomethylketones, 39–40
3-Halopseudocumenes, **383**
5-Halopseudocumenes, 377
6-Halopseudocumenes, 377
Halotetramethylbenzenes, 378
Hemimellitenesulfonic acid, 372
Hexamethylbenzene, 371, 374
β-*n*-Hexylacrylic acid, **252**
Hippuric acid in Perkin reaction, 231
p-Homoanisamide, **51**
Hydantoin in Perkin reaction, 232
β-Hydroxyesters, cleavage of, 14
  dehydration of, 11–13
  reduction of, 8
  synthesis of, 1–37
o- and *p*-Hydroxyketones, separation of mixtures, 354
  synthesis by Fries reaction, 342–369
2-Hydroxy-3-naphthylacetanilide, **52**
2-(4′-Hydroxyphenylamino)-naphthalene-6-sulfonic acid, **121**
2-(4′-Hydroxyphenylamino)-8-naphthol-6-sulfonic acid, **121**
4-Hydroxy-3-phenylpropiophenone, Clemmensen reduction of, 168

Iodomesitylene, 378
Iodomethylation, 72
4-Iodo-*m*-xylene, 376
4-Iodo-*m*-xylene-6-sulfonic acid, 377
Isodurenesulfonic acid, 374
Isoquinolines, reduction by zinc amalgam and acid, 162

Jacobsen reaction, 370–384

Ketene in Perkin reaction, 215
α-Keto acids, reduction by Clemmensen method, 159
γ-Keto acids, reduction by Clemmensen method, 160
β-Keto esters, from β-hydroxy esters, 11
  reduction by Clemmensen method, 160
  survey of methods of synthesis, 297–302
  synthesis by Reformatsky reaction, 9
γ-Keto-γ-(2-fluorene)-butyric acid, Clemmensen reduction of, **166**
Ketones, aromatic, chloromethylation of, 65, 89
  conversion to next higher homolog, 322
  in Mannich reaction, 308, 312, 315, 325, 326
  in Reformatsky reaction, 23–32
  of sterol group, reduction of, 168
  phenolic, reduction, 158, 159
  reduction by Clemmensen method, 157–161
  α,β-unsaturated, from Mannich bases, 318
1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-1,2,3,4-tetrahydronaphthalene, **329**
Knoevenagel modification of Perkin reaction, 226, 233

Magnesium, use in Reformatsky reaction, 16
Malonic acid, 222, 226
Malonic esters, preparation of, 271
Mannich reaction, 303–341
  application in synthesis, 318–327
  by-products, 329
  experimental conditions, 327–328
  experimental procedures, 329–330
  mechanism, 306
  related reactions, 316–317
  reversal, 319
  scope, 307–316
  solvents, 327
  tables, 330–341
Mesitylenesulfonic acid, 372
Mesitylmagnesium bromide in ester condensations, 267, 277
Mesodihydropentacene, 147
p-Methoxycinnamic acid, **249**
3-Methoxy-4-hydroxycinnamic acid, **250**
7-Methoxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-β-propionic acid, dimethyl ester, **53**
Methylal, 66, 71
Methylation of phenols, 166
20-Methyl-4-azacholanthrene, 143
Methyl benzoylacetate, preparation of, 283
20-Methylcholanthrene, 144, **153**
α-Methylcinnamic acid, **251**

4-Methyl-3,5-dicarboethoxycyclopentanedione-1,2, **284**
Methyl β,β′-diphenyladipate, 248
3,4-Methylenedioxycinnamic acid, **249**
2-Methyl-4-hydroxyacetophenone, **354**
3-Methyl-4-hydroxybenzophenone, **355**
1-Methyl-2-keto-4-phenyl-1,2,5,6-tetrahydropyrimidine, 326
4-Methyl-1-keto-1,2,3,4-tetrahydrophenanthrene, Clemmensen reduction of, 168
Methyl 7-methoxy-2-methyl-2-carbomethoxy-1-hydroxy-1,2,3,4-tetrahydrophenanthrene-1-acetate, **18**
7-Methyl-4-(α-naphthoyl)-hydrindene, 153
β-(1-Methyl-4-naphthoyl)-propionic acid in Clemmensen reduction, 163
7-Methyl-1-naphthylamine, **120**
1-Methyl-3-phenylpyrazoline, 325
Michael condensation, use of Mannich bases in, 320–322
Migration, of alkyl groups, 371
  of halogen atoms, 371

Naphthalene, chloromethylation of, **70**
Naphthols in Bucherer reaction, 105–127
α-Naphthylacetic acid, **50**
  ethyl ester, **52**
2-Naphthylamine, **120**
Naphthylamines in Bucherer reaction, 105–127
α-Naphthyl-4-(7-ethylhydrindenyl)-carbinol, 151
p-Nitrophenol, chloromethylation of, 71
o-Nitrophenylpyruvic acid, **253**
N-Nitrosomethylurea, 50
N-Nitrosomethylurethan, 50
α,β-Nonenoic acid, **252**

n-Octadecylbenzene, **167**
Octahydroanthracene, 376
Octahydroanthracene-9-sulfonic acid, 376, 379
Octahydrophenanthrene-9-sulfonic acid, 376
Organozinc halides as intermediates in Reformatsky reaction, 2,3
Oxides, in Reformatsky reaction, 36, 37
  rearrangement of, 37

Paraconic acids, Fittig's synthesis, 222
Paraformaldehyde, 66
Pentaethylbenzene, 376
Pentamethylbenzene, 376
  -sulfonic acid, 371, 372, 376
Pentamethylchlorobenzenesulfonic acid, 378
Perkin reaction, 210–265
  comparison with other methods, 233–236
  experimental conditions, 236–240
  experimental procedures, 248–254
  Oglialoro's modification, 221, 223
  scope, 217–233
  tables, 255–263
  use in synthesis, 240–248
Phenanthrene, 246
Phenolic ketones, synthesis by Fries reaction, 342–369
Phenols, chloromethylation of, 65, 83–85
  in Mannich reaction, 311, 314
2-Phenylaminopyridine, 95
γ-Phenylbutyric acid, **166**
α-Phenylcinnamic acid, **252**
Phenyl β-piperidinoethyl ketone hydrochloride, **329**
Phenylpyruvic acid, 229
Phthalic anhydride in Perkin reaction, 222
Phthalylacetic acid, 223
Picolines in Mannich reaction, 312, 314
β-Piperonylacrylic acid, **249**
Polyalkylbenzenes, 374
Prehnitene, 374, **381–382**
  -sulfonic acid, 371, 374
Propiolic acids, 245
Propionic acids, β-substituted, 244
  α,β-disubstituted, 245
  β,β-disubstituted, 245
o- and *p*-Propiophenol, **355–356**
Pschorr synthesis, 246, 247
Pseudocumenesulfonic acid, 371, 372, 374
Pyrazolines, preparation by Mannich reaction, 319, 325
Pyridine, amination of, 94–95, **99**
Pyridineacrylic acids, 220
Pyrolysis of *o*-methyl diaryl ketones, 150
Pyrroles, reduction by zinc amalgam, 161
Pyruvic acid in Perkin reaction, 222

Quinaldines in Mannich reaction, 312, 314
Quinoline, amination of, 94–95
use of potassium nitrate in, 96

Reformatsky reaction, 1–37, 234
intermediates in, 2, 3
procedures, 14–18
side reactions in, 4, 5
solvents, 15
use of, 5–10
variations of, 34–37
Resacetophenone, Clemmensen reduction of, **164**
Rhodanine, 230

Schiff bases, amination of, 92
Sodium, in ester condensations, 266–302
powdered, **279**
Sodium alkoxides (alcohol-free), **279–280**
in ester condensations, 266–302
Sodium amalgam, **286**, **287–288**
Sodium amide, **98–99**
in ester condensations, 267, 273, 277
precautions in use of, 96–97, 98
Stearophenone, Clemmensen reduction of, **167**
Styrene as by-product in Clemmensen reduction of acetophenone, 159

1,2,3,4-Tetraethylbenzene, **383**
1,2,4,5-Tetraethylbenzene, 374
1,2,3,5-Tetraethylbenzene, 374
2,4,5,6-Tetraiodo-*m*-xylene, 377
ar-α-Tetralyl α-naphthyl ketone, 143
Tetramethylbenzenes, 374
1,2,3,4-Tetramethylbenzene, **381–382**
1,2,4,5-Tetramethyl-3-chlorobenzene, 378
1,2,3,5-Tetramethyl-4-chlorobenzene, 378
1,2,3,4-Tetramethyl-5-chlorobenzene, 378
1,2,5,5-Tetramethylpiperidine, 324
Thioethers, aromatic, chloromethylation of, 88
β-(*p*-Toluyl)-propionic acid, Clemmensen reduction of, **164**
2-*p*-Tolylamino-5-hydroxynaphthalene-7-sulfonic acid, **121**
γ-(*p*-Tolyl)-butyric acid, **164**
o-Tolyl α-naphthyl ketone in Elbs reaction, 139, 150, **152–153**
2,4,6-Tri-(acetoxymethyl)-phenyl acetate, 323
2,4,6-Tri-(dimethylaminomethyl)-phenol, **330**
1,2,4-Triethylbenzenesulfonic acid, 372
1,3,5-Triethylbenzenesulfonic acid, 372
1,3,5-Triisopropylbenzene, chloromethylation of, **68**
2,4,4′-Trimethylbenzophenone, 150
1,2,4-Trimethyl-5-bromobenzenesulfonic acid, 377
1,2,4-Trimethyl-3-chloro-5-benzenesulfonic acid, 378
1,2,4-Trimethyl-5-chlorobenzenesulfonic acid, 377
1,2,4-Trimethyl-6-chlorobenzenesulfonic acid, 377
2,4,4-Trimethylcyclopentanone-1, 157
1,2,4-Trimethyl-5,6-dibromobenzene, 380
1,12-Trimethylenechrysene, 143
1,2,4-Trimethyl-3-ethylbenzenesulfonic acid, 374
1,2,4-Trimethyl-5-ethylbenzenesulfonic acid, 374
1,3,5-Trimethyl-2-ethylbenzenesulfonic acid, 374
1,2,4-Trimethyl-5-iodobenzene, 377
2,3,5-Trimethylphenol, 323
α-Trioxymethylene, 66
Triphenylmethylsodium, **286–287**
in ester condensations, 266–302
Tutocaine, 323–324

α,β-Unsaturated acids, 240, 319
α,β-Unsaturated esters, reduction of, 6
β,γ-Unsaturated esters, reduction of, 6

α-Vinylcinnamic acid, 224

Wolff rearrangement, 39

p-Xylene, chloromethylation of, **69**
m-Xylyl phenyl carbinol, 151
m-Xylyl phenyl ketone, 151

Zinc, amalgamation of, 163
for use in Clemmensen reduction, 163
forms of, 15
purification of, for use in Reformatsky reaction, 16