ORGANIC CHEMISTRY

SECOND EDITION

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The Pennsylvania State College

With the Assistance of a Committee of Colleagues

VOLUME TWO

Part III: Aromatic Compounds

Part IV: Heterocyclic Compounds

Part V: Organophosphorus and Organometallic Compounds

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PART III

AROMATIC OR BENZENE SERIES

I. BENZENE

The distinctive properties of the members of this series are peculiarly those of benzene and can best be shown by a detailed discussion of that substance which was first found in a liquid by-product of the preparation of illuminating gas from whale oil[1] and later in coal tar.[2]

Because of the tremendous amount of work on aromatic compounds and the fact that the latter are obtained from coal tar it might be thought that coal tar and coal are distinctly aromatic in nature. It should be remembered that both coal and coal tar are very complex chemically. In "low temperature" coal tar the amount of aliphatic compounds is considerable.[3]

Chemistry of Coal.[4]

Hydrogenation of Coal.[5]

Chemistry of Coal Utilization.[6]

The Constituents of Coal Tar.[7]

Possible New Uses for Coal.[8]

Benzene and its higher homologs, toluene and the xylenes occur in only small amounts in coal tar but can be obtained in larger quantities by scrubbing coal gas or water gas with suitable high boiling oils and by cyclization of aliphatic hydrocarbons.

Aromatic compounds are found in petroleums to a larger extent than is ordinarily realized. Even Pennsylvania petroleum contains a minute amount of toluene. Other petroleums proved to be the main sources of toluene for the Global War. From one Mid-continent petroleum the following aromatic compounds, arranged in order of increasing boiling points, have been isolated:[9] benzene, toluene, Et-benzene, *p*-xylene, *m*-xylene, *o*-xylene, isopropylbenzene, *n*-propylbenzene, 1-Me-3-Et-benzene, 1-Me-4-Et-benzene, 1,3,5-Me_3-benzene, 1-Me-2-Et-benzene, 1,2,4-Me_3-benzene, 1,2,3-Me_3-benzene, 1,2,3,4-Me_4-benzene, *n*-Amylbenzene, 1,4-Me_2-2-propyl-benzene, H_4-naphthalene, 1,5-Me_2-2-propylbenzene, 1,3,5-Me_3-2-Et-benzene, naphthalene, phenyl-cyclopentane,

[1] Faraday. *Ann. phys.* **5**, 306 (1825).
[2] Hofmann. *Ann.* **55**, 204 (1845).
[3] Morgan. *J. Soc. Chem. Ind.* **51**, 67T (1932).
[4] Tropsch. *Chem. Revs.* **6**, 63 (1929).
[5] Bergius. *Z. Ver. deut. Ing.* **69**, 1313 (1925).
[6] Storch. "Chemistry of Coal Utilization." John Wiley & Son, New York, 1945.
[7] Spielmann. "The Constituents of Coal Tar." Longmans, Green & Co., 1924.
[8] Howard. *Ind. Eng. Chem.* **35**, 156 (1943).
[9] Rossini. *Oil Gas J.* **39**, No. **27**, 158, 159, 219 (1940).

6-Me-H_4-naphthalene, 5-Me-H_4-naphthalene, 2-Me-naphthalene, 1-Me-naphthalene.

Benzene, benzol, C_6H_6, m. 5.4°, b. 80.4°.

Many of the physical properties of benzene indicate a transition point at about 40°.[10]

A. Structure of Benzene

A combustion analysis and molecular weight determination prove its empirical formula. Comparison of this formula with that of hexane, C_6H_{14}, would indicate benzene to be highly unsaturated. It does not, however, give any reaction with $KMnO_4$ or with bromine water, ordinary reagents for unsaturated compounds. Practically all of its reactions are those of substitution instead of addition. Thus

$$C_6H_6 + HNO_3 \rightarrow \underset{\text{Nitrobenzene}}{C_6H_5NO_2} + H_2O$$

$$C_6H_6 + H_2SO_4 \rightarrow \underset{\text{Benzenesulfonic acid}}{C_6H_5SO_3H} + H_2O$$

$$C_6H_6 + Hg(OCOCH_3)_2 \rightarrow \underset{\text{Acetoxymercuribenzene}}{C_6H_5HgOCOCH_3} + CH_3CO_2H$$

$$C_6H_6 + Cl_2 \rightarrow \underset{\text{Chlorobenzene}}{C_6H_5Cl} + HCl$$

The first three of these reactions take place in the aromatic series with an ease which is unknown with aliphatic and alicyclic compounds. Contrary to what might be expected from a C_6 compound, only *one* of each of these monosubstitution products has ever been obtained. No isomer of any of them can be obtained from benzene. Thus only one *monochlorobenzene* has ever been made. It is C_6H_5Cl, m. −45°, b. 132.1°. This means either that the *six H atoms* in benzene are all similarly placed in the molecule so that the same product is obtained no matter which one is replaced or that *one H* atom is so situated that it is more reactive than the others and is always the first to be replaced. A choice between these theoretical possibilities can be reached by a study of the facts regarding further substitution in the benzene molecule. Thus the continued action of chlorine gives the following reaction:

$$C_6H_5Cl + Cl_2 \rightarrow C_6H_4Cl_2 + HCl$$

The resulting product is a *mixture* which can be separated into *three isomeric* dichlorobenzenes with the following properties.

$C_6H_4Cl_2$	m.	b.	d_4^{20}	n_D^{20}
(A)	52.9°	173°	1.458	1.527
(B)	−14.°	179°	1.298	1.549
(C)	−24.8°	173°	1.288	1.546

[10] Menzies, Lacoss. *Proc. Natl. Acad. Sci.* **18**, 144 (1932).

Further chlorination is possible.

$$C_6H_4Cl_2 + Cl_2 \rightarrow C_6H_3Cl_3 + HCl$$

In this way (*A*) gives a homogeneous product, a trichlorobenzene which may be called (*D*). When (*B*) is further chlorinated it gives a product which can be separated into *two* trichlorobenzenes, one of which is identical with (*D*), obtained from (*A*) and a different Cl_3-benzene which may be called (*E*). When the third Cl_2-benzene, (*C*), is chlorinated, it gives a product which is found to be a mixture of *three* trichlorobenzenes, (*D*), (*E*) and a different one which may be called (*F*). The properties of these trichlorobenzenes are as follows:

$C_6H_3Cl_3$	m.	b.
(*D*)	17°	213°
(*E*)	50.8°	219°
(*F*)	63°	208.5°

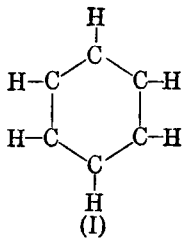
The chlorination of each of these Cl_3-benzenes can be continued.

$$C_6H_3Cl_3 + Cl_2 \rightarrow C_6H_2Cl_4 + HCl$$

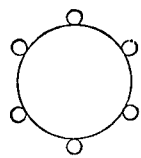
When (*F*), the trichlorobenzene obtainable only from (*C*) and not from (*A*) or (*B*), is chlorinated, the product is a homogeneous tetrachlorobenzene (*G*). Chlorination of (*E*) gives a mixture of (*G*) and another Cl_4-benzene (*H*). Similarly (*D*) gives a mixture of three Cl_4-benzenes, (*G*), (*H*) and (*I*). The properties of these substances are as follows:

$C_6H_2Cl_4$	m.	b.
(*G*)	51°	246°
(*H*)	47°	254°
(*I*)	137.5°	246°

Further chlorination of each of these substances gives only *one* pentachlorobenzene, C_6HCl_5, m. 86°, b. 277°, and *one* hexachlorobenzene, C_6Cl_6, m. 226°, b. 326°. The only explanation of all of the above facts and of countless other facts about benzene and its derivatives, homologs and analogs is that the six carbon and six hydrogen atoms in the benzene molecule are arranged in a symmetrical ring,[11] (I). This conception of the ring nature of benzene was first expressed by Loschmidt (1861)[12] (II).



(I)

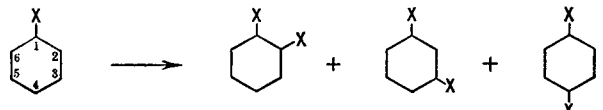


(II)

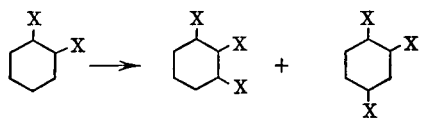
[11] Kekulé. *Bull soc. chim.* [2] 3, 98 (1865).
[12] Anschutz. *Ber.* 45, 539 (1912).

The fourth valence of each carbon in (I) may be neglected for the time-being. In fact, from a practical viewpoint it is nearly always so neglected because it gives evidence of its existence only under the most unusual circumstances. Thus, if benzene were the only carbon compound known, carbon would be believed to have a valence of *three* except under peculiar conditions. The assumption of the *benzene ring* not only explains the above facts but also makes possible the assignment of a structure formula to each of the chlorinated benzenes described above (p. 601). The number of possible substitutions at the corners of a regular hexagon agrees with the number of isomers actually obtained.

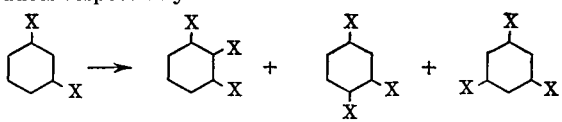
If only one substituent is introduced, only one product can be produced.

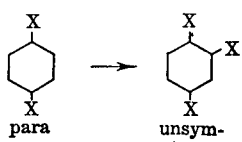


Only three disubstitution products are possible since substitution in the 5 and 6 positions gives the same products as in the 3 and 2 positions respectively.

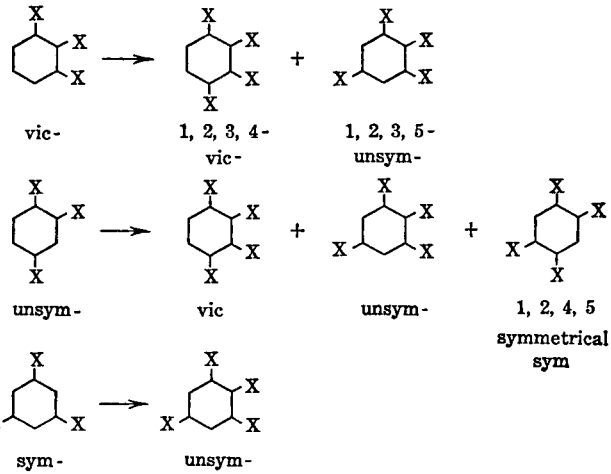


Only *two* trisubstitution products can be derived from the *ortho* compound since the placing of the third group in positions 5 or 6 gives the same *unsym-* and *vic-* products respectively.

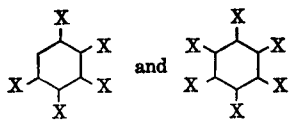




Thus the unsymmetrical trisubstitution product is obtainable from all three disubstitution products while the symmetrical X_3-product comes only from the meta compound and the vicinal X_3-product can be derived from both the ortho and meta compounds.



The unsymmetrical tetrasubstitution product is obtainable from all three trisubstitution products. The symmetrical X_4-product is obtainable only from the unsymmetrical X_3-product. The vicinal X_4-product is derivable from the vicinal and the unsymmetrical X_3-product but not from the symmetrical X_3-product. It is to be noted that the unsubstituted corners in the X_4-products are *o*-, *m*-, and *p*- to each other. The only possible penta- and hexasubstitution products containing X are

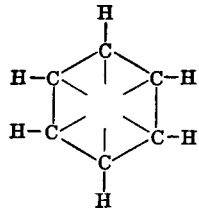


These are obtainable from all of the X_4-products.

On the basis of the above facts alone, the proper formulas can be assigned to the possible chlorinated benzenes (A) to (I) (p. 598) namely: (A) is 1,4-Cl_2-benzene; (B) is 1,2-Cl_2; (C) is 1,3-; (D) is 1,2,4-Cl_3-; (E) is 1,2,3-Cl_3; (F) is 1,3,5-Cl_3; (G) is 1,2,3,5-Cl_4-; (H) is 1,2,3,4-Cl_4; and (I) is 1,2,4,5-Cl_4-benzene.

It should be remembered that the details of this elegant demonstration first suggested by Körner were not completed until long after the scientific world had accepted the original guess of Kekulé that the six carbon atoms of benzene form a ring. Meantime a multitude of facts has accumulated, every one of which is consistent with the original guess. Of the many formulas

suggested, the *centric formula*[13, 14] has survived best probably because it is least definite as to the fourth "bonds."



This formula agrees with the *fact* that the fourth bonds of the carbon atoms in benzene and its derivatives are *different* from ordinary single or double bonds. The formula actually used by organic chemists is the simple hexagon.

Each "vacant" corner is understood to have a hydrogen atom attached to it. This formula simply ignores the fourth bonds or treats them as if they did not exist. This agrees with at least 99.9 per cent of the facts regarding benzene and its derivatives. Moreover it emphasizes the high degree of symmetry of the benzene molecule which is indicated by a multitude of facts including its Raman spectrum.[15]

B. Formation of Benzene

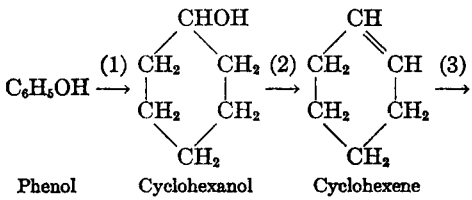
1. From coal. The thermal decomposition of the organic compounds in soft coal forms benzene and its homologs (toluene, xylenes, etc.) and its analogs (naphthalene, anthracene, etc.). Practically all benzene is obtained by scrubbing the gases from by-product coke plants and illuminating gas plants. Commercial "ninety per cent benzol" is a mixture, 90% of which distills below 100°. "Nitration benzol" boils within one degree of the true boiling point 80.4° (760 mm). Its only impurity is a small amount of thiophene (b.p. 84°). "Molecular weight benzene" is free of thiophene and melts at 5° or higher (true m.p. 5.4°). The small amount of thiophene in commercially pure benzene is removed by taking advantage of its greater reactivity. Thus shaking with several portions of H_2SO_4 converts the thiophene to a sulfonic acid without changing the benzene. Similarly, refluxing with mercuric acetate mercurates the thiophene without reacting with the benzene.

2. From other aromatic compounds. Most aromatic compounds can be converted to benzene by relatively simple reactions. Many of them can be converted to hydroxyl compounds (phenols) which yield benzene on distillation

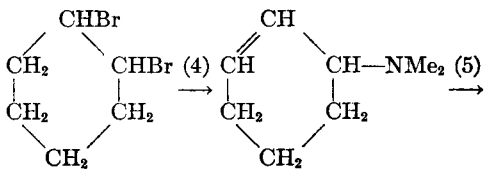
[13] Armstrong. *J. Chem. Soc.* **51**, 264 (1887).
[14] Baeyer. *Ann.* **245**, 121 (1888).
[15] Andrews. *J. Chem. Phys.* **3**, 175 (1935).

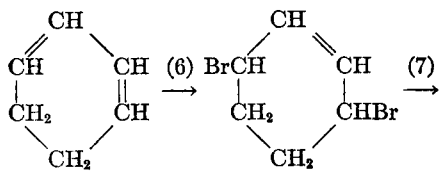
with zinc dust. Homologs and analogs of benzene such as toluene and naphthalene yield carboxylic acids of benzene on vigorous oxidation. These give benzene on heating with soda lime.

3. By synthesis (Willstätter). The steps are as follows:

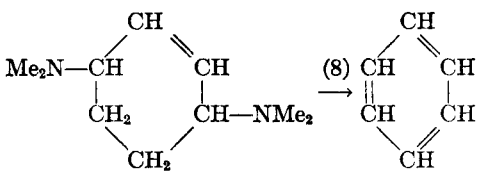


Phenol Cyclohexanol Cyclohexene





1,3-Cyclohexadiene



1,3,5-Cyclohexatriene

The reactions are carried out as follows:

(1) Hydrogenation with a nickel catalyst.

(2) Dehydration by sulfuric acid.

(3) Addition of bromine.

(4) Treatment of the dibromide with an excess of dimethylamine. The first step is the removal of one HBr to give an *allyl system* with a very reactive halogen, $-CH=CH-CHBr-$.

(5) and (8) Exhaustive methylation. Addition of methyl iodide, conversion to the quarternary ammonium hydroxide and destructive distillation to

yield trimethylamine, water and olefinic compounds. In the case of (8) the last step takes place even at 0° if the pressure is greatly reduced.

(6) Addition of bromine at the ends of the conjugated system.

(7) An addition reaction of 2 Me_2NH with the bromine atoms which are parts of reactive allyl systems to form $=CHNMe_2 . HBr$. An inorganic base or excess Me_2NH removes the HBr.

According to the reactions involved, including the final exhaustive methylation, the product should contain three double bonds arranged in alternate or conjugated form around the 6-carbon ring. The final product is benzene, which seldom shows the presence of double bonds. The intermediate compounds, cyclohexene and cyclohexadiene-1,3, differ entirely from the final product in being *highly unsaturated.* For instance they react readily with $KMnO_4$ or bromine water while benzene does not act at all. Thus the introduction of the third "double bond" entirely changes the nature of the molecule. It might be thought that the typical "benzene properties" are entirely due to alternating double and single bonds (Thiele) in a ring. Such is not the case because 1,3,5,7-cyclooctatetraene[16, 17] shows only the properties of a very highly unsaturated compound and none of those shown by benzene. Kekulé had recognized this difficulty about the double bonds in benzene and had also seen that a structure containing a 6-ring and three alternate double bonds should have *four* disubstitution products, the para, meta, and *two* ortho compounds differing by having a double bond or a single bond respectively between the adjacent carbons bearing the two substituting groups. In view of the absence of a second ortho compound, Kekulé proposed his hypothesis of the oscillation of the double bonds in benzene.

The centric formula then becomes a phase half-way in the oscillation. The results of modern mechanics and X-ray studies have added quantitative confirmation of Kekulé's guess.[18, 19] In modern language, the *oscillation* of the conjugated double bonds becomes *resonance.* Evidence for the oscillation or resonance formula is given by the ozonolysis products of *o*-xylene (p. 614).

Benzene structure.[20]

Reactions of Benzene

1. Heat links benzene rings together with the elimination of hydrogen.

$$2\ C_6H_6 \rightarrow H_2 + \underset{\text{Diphenyl}}{C_6H_5-C_6H_5}$$

Smaller amounts of higher products are also formed (p. 709).

[16] Willstätter, Waser. *Ber.* **44**, 3423 (1911).
[17] Willstätter, Heidelberger. *Ber.* **46**, 517 (1913).
[18] Pauling. *J. Chem. Phys.* 1, 362 (1933).
[19] Mack. *J. Am. Chem. Soc.* **54**, 2141 (1932).
[20] Ahrens. *Sammlung Chemische-Technischen Vortrage* **1898**, 1928.

2. Oxidation.

(*a*) Ordinary oxidizing agents have no effect on benzene unless the conditions used are vigorous enough to oxidize it to oxides of carbon and water.

(*b*) Oxidation by air with catalysts like vanadium oxides gives maleic acid.[21]

(*c*) Ozonation gives a tri-ozonide[22] which decomposes with water to give glyoxal and its oxidation products.

(*d*) Potassium chlorate and sulfuric acid give "trichlorophenomalic acid," (trichloroacetoacrylic acid) which reacts with alkali to give chloroform and a maleate.

$$Cl_3CCOCH=CHCO_2H \rightarrow CHCl_3 + NaO_2CCH=CHCO_2Na$$

Benzene has valuable anti-knock properties in motor fuels.

3. Reduction.

(*a*) Hydriodic acid converts benzene into a mixture of hexahydrobenzene (cyclohexane) and methylcyclopentane.

(*b*) Catalytic hydrogenation with nickel gives cyclohexane. This reaction takes place less readily than with substituted benzenes.

4. With halogens.

(*a*) Fluorine reacts violently giving hydrogen fluoride and carbon tetrafluoride.[23,24]

(*b*) In the cold and in darkness, the other halogens merely dissolve in benzene with practically no action. In sunlight, chlorine and bromine *add* to benzene to give compounds, $C_6H_6Cl_6$, benzene hexachloride, and $C_6H_6Br_6$.[25] They exist in stereomeric forms. These halides are unstable. On heating or in the presence of catalysts like ferric salts, they lose 3 HX readily giving *unsymmetrical* trihalogenated benzenes. Iodine does not react with benzene except in the presence of an oxidizing agent like iodic acid or nitric acid, in which case it gives iodobenzene and *p*-diiodobenzene.[26,27]

$$5\ C_6H_6 + 2\ I_2 + HIO_3 \rightarrow 5\ C_6H_5I + 3\ H_2O$$

The function of the oxidizing agent is to remove the HI which would otherwise reverse the reaction.

(*c*) Chlorine and bromine react with hot benzene in the presence of a great variety of catalysts such as iodine and ferric halides to give *substitution* products of benzene.

$$C_6H_6 + Br_2 \rightarrow C_6H_5Br + HBr$$

[21] Weiss, Downs. *Ind. Eng. Chem.* **12**, 228 (1920).
[22] Harries. *Ann. Rep. Chem. Soc.* (London) **1904**, 92.
[23] Bancroft, Jones. *Trans. Am. Electrochem. Soc.* (preprint) **55**, 1929.
[24] Bancroft, Wearty. *Proc. Natl. Acad. Sci.* **17**, 183 (1931).
[25] Smith, Noyes, Haut. *J. Am. Chem. Soc.* **55**, 4444 (1933).
[26] Eginger, Goldberg. *Ber.* **33**, 2876 (1900).
[27] Datta, Chatterjee. *J. Am. Chem. Soc.* **39**, 435 (1917).

Chlorine with isobutylene gives an analogous *substitution* reaction with the formation of isocrotyl chloride and methallyl chloride but no isobutylene dichloride (p. 97).

The mechanism of substitution in the benzene ring may involve the following steps:

(*a*) Addition of positive halogen at one end of a double bond, thus leaving the other carbon with only a sextet of electrons. (*b*) Addition of a negative halogen would satisfy this deficiency but an easier process is the loss of a proton to restore the conjugated system of three double bonds. Compare the mercuration of thiophene (p. 759).

Some dihalogen product is always formed from benzene.

$$C_6H_5Br + Br_2 \rightarrow C_6H_4Br_2 + HBr$$

This is mainly the para compound with small and approximately equal amounts of the ortho and meta compounds.

5. Nitration. Concentrated nitric acid, fuming nitric acid or a mixture of nitric and sulfuric acids converts benzene to nitrobenzene.

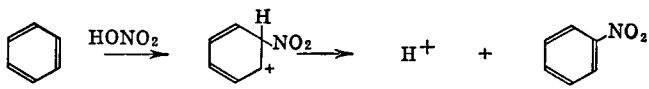
$$C_6H_6 + HNO_3 \rightarrow C_6H_5NO_2 + H_2O$$

The reaction is strongly exothermic. In the laboratory this gives no trouble but on a large scale it necessitates effective cooling. The process is not reversible.

Isobutylene gives a similar nitration.

$$Me_2C{=}CH_2 + HNO_3 \rightarrow Me_2C{=}CHNO_2 + H_2O$$

The nitration of benzene proceeds by the following steps:



The tendency to re-establish the ring conjugation is so great that there is no possibility of the addition of the OH^- to the electronically deficient carbon. Thus a relatively slow bimolecular process is excluded by a very rapid monomolecular process.

Under ordinary conditions the nitration of benzene gives no dinitrated product. Thus the activity of the benzene ring is considerably *lessened* by the introduction of a nitro group. Under vigorous nitration conditions (fuming nitric acid and conc. sulfuric acid) a dinitrobenzene can be obtained.

$$C_6H_5NO_2 + HNO_3 \rightarrow C_6H_4(NO_2)_2 + H_2O$$

This is almost entirely the meta compound with no more than traces of the

ortho and para compounds. Even more vigorous nitration (fuming nitric and fuming sulfuric acids) gives 1,3,5-trinitrobenzene.

The ready formation of nitro compounds in the liquid phase by means of conc. nitric acid is typical of aromatic compounds. Aliphatic hydrocarbons can be nitrated successfully in the vapor phase.[28]

6. Sulfonation. Concentrated sulfuric acid or, more rapidly, fuming sulfuric acid (oleum) forms benzenesulfonic acid.

$$C_6H_6 + H_2SO_4 \rightarrow C_6H_5SO_3H + H_2O$$

The process can be reversed by using superheated steam or by heating the sulfonic acid with concentrated hydrochloric acid. Sulfur trioxide in sulfur dioxide also sulfonates benzene in high yields.[29] Under ordinary conditions there is no tendency for the sulfonation of benzene to introduce a second sulfonic acid group. Thus the activity of the benzene ring is lowered also by the presence of a sulfonic acid group. Vigorous sulfonation with oleum introduces a second group.

$$C_6H_5SO_3H + SO_3 \xrightarrow{H_2SO_4} C_6H_4(SO_3H)_2$$

The product is a mixture of *meta* and *para* compounds with the former predominating. Probably the meta compound is formed first and then rearranges to the para compound until an equilibrium is attained. The reversibility of the sulfonation process makes this rearrangement possible.

$$\underset{\text{Meta}}{C_6H_4(SO_3H)_2} + H_2SO_4 \rightleftharpoons H_2S_2O_7 + C_6H_5SO_3H \rightleftharpoons \underset{\text{Para}}{C_6H_4(SO_3H)_2} + H_2SO_4$$

No ortho-benzenedisulfonic acid has ever been detected among the products. Any such product formed is probably rearranged to the more stable *m*- or *p*-forms. When an anhydrous salt of meta-benzenedisulfonic acid is heated with sulfuric acid, a third sulfonic acid group is introduced.

$$\underset{\text{Meta}}{C_6H_4(SO_3K)_2} + 3\ H_2SO_4 \rightarrow \underset{\text{Sym}}{C_6H_3(SO_3H)_3} + 2\ KHSO_4 + H_2O$$

No isomeric benzenetrisulfonic acids have been obtained by direct sulfonation.

7. Friedel and Crafts Reaction.[30]

(*a*) Alkyl halides react with benzene in the presence of anhydrous aluminum chloride to give alkylbenzenes. Much less than a molecular amount of

[28] Hass et al. *Ind. Eng. Chem.* 28, 339 (1936).

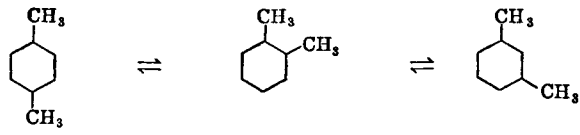
[29] Leiserson, Bost, LeBaron. *Ind. Eng. Chem.* 40, 508 (1948).

[30] "Org. Reactions," Vol. III.

aluminum chloride is sufficient to cause this reaction.

$$C_6H_6 + CH_3Cl \xrightarrow{AlCl_3} C_6H_5CH_3 + HCl$$

Continued treatment with methyl chloride gives all the possible methylated benzenes ending with hexamethylbenzene. This reaction will not only introduce an alkyl group into the benzene ring, but will cause the transfer of a group from one position to another and even from one molecule to another. Thus the following changes take place in presence of $AlCl_3$.



Para-xylene Ortho Meta

$$2\ C_6H_5CH_3 \rightarrow \underset{\text{xylenes}}{C_6H_4(CH_3)_2} + \underset{\text{benzene}}{C_6H_6}$$
$$\text{toluene}$$

The reaction with ethyl halides is similar to that of the methyl halides. With *n*-propyl halides the chief product is isopropylbenzene with only a small amount of *n*-propylbenzene. At 0° *n*-Bu halides give a mixture of *n*-Bu-benzene and *sec*-Bu-benzene. At higher temperatures the latter is the sole product. Isobutyl halides, in which the tendency to rearrangement is always great, ordinarily give only *t*-Bu-benzene even at −18° although the use of mere traces of $AlCl_3$ gives small amounts of isobutylbenzene along with the *t*-Bu compound. Isoamyl halides give isoamylbenzene and *t*-Am-benzene. These rearrangements during the Friedel-Crafts reaction can be explained on the basis of a rearrangement of the halide or of the conversion of the halide to an olefin with the subsequent addition of benzene as H and phenyl according to Markownikoff's Rule. An extreme case of such rearrangement and splitting of the halide has been observed in the furan series.[31] Thus a tertiary butyl derivative is obtained from *n*-amyl chloride, *n*-hexyl bromide and even from *n*-octadecyl bromide.

(*b*) Olefins react with benzene and anhydrous aluminum chloride to give the same products as those obtained from the corresponding alkyl halides. Thus ethylene gives all the possible ethylated benzenes including hexaethylbenzene. With higher olefins the addition of benzene under the influence of aluminum chloride follows Markownikoff's Rule. Thus, propylene gives isopropylbenzene, the *n*-butylenes give *sec*-butylbenzene and isobutylene gives *t*-butylbenzene.

(*c*) Acyl halides and acid anhydrides give carbonyl compounds. In such cases a molecular amount of aluminum chloride must be used since it forms

[31] Gilman, Burtner. *J. Am. Chem. Soc.* **57**, 909 (1935).

very stable addition products with the carbonyl compounds. Typical reactions of this group follow:

$$COCl_2 \rightarrow C_6H_5\underset{\displaystyle Cl}{\overset{|}{C}}{=}O$$

Phosgene Benzoyl chloride

$$CH_3COCl \rightarrow CH_3COC_6H_5$$

Methyl phenyl ketone, Acetophenone

$$(CH_3CH_2CO)_2O \rightarrow CH_3CH_2COC_6H_5$$

Propionic anhydride Propiophenone

$$C_6H_5COCl \rightarrow C_6H_5COC_6H_5$$

Benzophenone

$$HCl + CO \rightarrow C_6H_5\underset{\displaystyle H}{\overset{|}{C}}{=}O$$

Benzaldehyde

Since CO is, in a sense, the anhydride of formic acid it is not surprising that benzene reacts with Ni carbonyl and $AlCl_3$ in the cold to give benzaldehyde. At high temperatures anthracene is the main product.[32]

(*d*) Organic acids work less satisfactorily in the preparation of ketones by the Friedel-Crafts reaction.

The most important of the Friedel-Crafts reactions of benzene is that with phthalic anhydride to make *o*-benzoylbenzoic acid which is readily converted to anthraquinone by sulfuric acid.

The action of benzene itself with $AlCl_3$ and HCl gives a mixture boiling up to 360°. One substance formed is 1-Me-3-Ph-cyclopentane.

(*e*) Benzene also reacts in the presence of aluminum chloride with oxygen, sulfur and carbon dioxide.

$$2\,C_6H_6 + O_2 \xrightarrow{AlCl_3} 2\,C_6H_5OH$$

Phenol

$$C_6H_6 + S \rightarrow C_6H_5SH$$

Thiophenol

$$C_6H_6 + CO_2 \rightarrow C_6H_5CO_2H$$

Benzoic acid

Such reactions may be rendered important practically by the cheap anhydrous aluminum chloride made available by its use in the cracking of petroleum.

[32] *Ann. Rep. Chem. Soc.* (London) **1904**, 88.

8. With alcohols in the presence of dehydrating agents such as P_2O_5 and H_2SO_4, secondary and tertiary alkyl benzenes are obtained.

n-Butyl alcohol → *s*-Butylbenzene
iso-Butyl alcohol → *t*-Butylbenzene

9. With aldehydes in the presence of sulfuric acid, diphenylmethane compounds are obtained.

$$R{-}\overset{H}{\underset{|}{C}}{=}O \rightarrow [RCHOHC_6H_5] \rightarrow R{-}CH(C_6H_5)_2$$

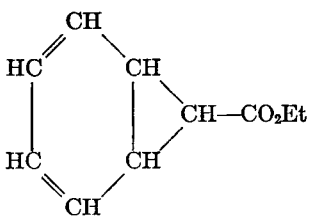
The OH in the intermediate compound is very reactive because of its position alpha to a phenyl group. Formaldehyde gives Ph_2CH_2 and higher products including anthracene.

10. Mercuric acetate mercurates benzene when heated under pressure or on refluxing with an alcoholic solution.[33] In the latter case the EtOH forms ethyl acetate, thus shifting the equilibrium.

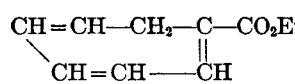
$$C_6H_6 + Hg(OCOCH_3)_2 + C_2H_5OH \rightarrow \underset{\text{Phenylmercuric acetate}\\ \text{Acetoxymercuribenzene}}{C_6H_5HgOCOCH_3} + CH_3CO_2C_2H_5$$

Mercuration is as characteristic of aromatic compounds as nitration or sulfonation.

11. Ethyl diazoacetate reacts with benzene at 130° to give the bi-cyclic compound norcaradienecarboxylic ester (I) and its rearrangement product cycloheptatrienecarboxylic ester (II).



(I)



(II)

12. Metalation. Alkali derivatives of benzene can be made by treating it with alkali alkyls.

$$C_6H_6 + EtK \rightarrow C_6H_5K + EtH$$

Some $C_6H_4K_2$ is also formed. Thus the product of the reaction, when treated with CO_2, gives a 33% yield of benzoate, a 14% yield of terephthalate, a trace of phthalate but apparently little or no isophthalate.

[33] Maynard. *J. Am. Chem. Soc.* **46**, 1510 (1924).

Benzene vapors are very toxic.[34] Even small amounts of the vapors breathed over a period deplete the blood in both white and red corpuscles and greatly lower the resistence to infection. The only ordinary commercial solvent which is more dangerous than benzene is Cl_4-ethane.

II. HOMOLOGS OF BENZENE

A. Toluene

Toluene, methylbenzene, phenylmethane, toluol, $C_6H_5CH_3$, m. $-92°$, b. 110.8°, is obtained after benzene in the distillation of the light oil from scrubbing coal gas.

Preparation. 1. By the Wurtz-Fittig reaction from bromobenzene, methyl iodide and metallic sodium. The yield in the reaction between an aromatic and an aliphatic halide is better than would be expected in view of the three possible products. The first step after the formation of the phenyl radical is probably the formation of sodium phenyl, C_6H_5Na. This reacts readily with the aliphatic halide but not with the aromatic halide. Any ethylene and ethane formed from free methyl radicals escapes during the reaction. Any diphenyl formed from free phenyl radicals is readily separated from the main product because of its lower volatility and higher melting point (71°).

2. By the Friedel-Crafts reaction.

(*a*) From benzene and methyl chloride.

(*b*) From xylenes and benzene

$$C_6H_4(CH_3)_2 + C_6H_6 \xrightarrow{AlCl_3} 2\ C_6H_5CH_3$$

The *reactions of toluene* resemble those of benzene except that there is a chance for the reaction to take place either in the side chain or in the ring and that the methyl group exerts a directing or orienting influence on groups entering the ring, directing them mainly to the para and ortho positions with only a small amount entering the meta position.

1. Heat. At dull red heat toluene forms dibenzyl (1,2-diphenylethane).

$$2\ C_6H_5CH_3 \rightarrow C_6H_5CH_2CH_2C_6H_5 + H_2$$

At high temperatures this loses hydrogen to form stilbene (1,2-diphenylethylene). Greater heat gives very complex changes involving such products as benzene, naphthalene, dibenzyl, anthracene, chrysene, benzerythrene, phenanthrene, diphenyl, styrene and traces of methane, acetylene and ditolyl.

2. Oxidation. As with all aromatic hydrocarbons with *side chains*, toluene can be readily oxidized, the side chain alone being changed.

(*a*) Ordinary oxidizing agents such as dilute nitric acid, potassium permanganate and chromic acid mixture (a dichromate and sulfuric acid) convert

[34] Pierce. *Chem. and Met. Eng.* **49**, No. 8, 80 (1942).

the methyl to a carboxyl.

$$C_6H_5CH_3 + 3[O] \rightarrow \underset{\text{Benzoic acid}}{C_6H_5CO_2H} + H_2O$$

(*b*) Under special conditions it is possible to oxidize toluene to benzaldehyde, C_6H_5CHO. (1) By controlled air oxidation. (2) By oxidation with manganese dioxide and sulfuric acid. (3) By means of chromyl chloride, CrO_2Cl_2.[1]

(*c*) Oxidation with aqueous potassium persulfate gives dibenzyl (1,2-diphenylethane) together with benzaldehyde and benzoic acid.

(*d*) A peculiar oxidation of toluene occurs when it is heated at 200° with sulfur, the main product being stilbene (*sym*-diphenylethylene).

3. Reduction. The catalytic hydrogenation of toluene is much easier than that of benzene. The product is hexahydrotoluene (methylcyclohexane).

Hydriodic acid at 280° gives methylcyclohexane, dimethylcyclopentane and methylcyclopentane.

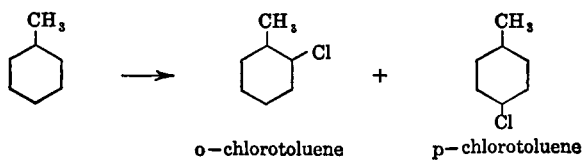
4. With halogens there is no tendency to addition as in benzene. Substitution is easier.

(*a*) Chlorine and bromine react with boiling toluene, especially when exposed to actinic light, to give substitution almost entirely in the methyl group.

$$C_6H_5CH_3 \rightarrow \underset{\text{Benzyl chloride}}{C_6H_5CH_2Cl} \rightarrow \underset{\text{Benzal chloride}}{C_6H_5CHCl_2} \rightarrow \underset{\text{Benzotrichloride}}{C_6H_5CCl_3}.$$

These substances react like aliphatic halides but are much more active because of the benzene ring in the alpha position. Over a 90% yield of benzyl chloride can be obtained from boiling toluene and dry chlorine in the light.

(*b*) Chlorine and bromine in the presence of halogenation catalysts and in the absence of strong light give mixtures of ortho and para products with no more than a trace of meta product.



The nuclear halogens are very unreactive. Further chlorination of the monochlorotoluenes gives mainly the *o,p*- or 2,4-dichlorotoluene. Over an 80% yield of ring-chlorinated toluenes can be obtained from toluene and wet chlorine in the dark. Chlorination with antimony pentachloride or iodine as catalyst gives ortho and para products in the ratio 55:45.[2]

[1] Etard. *Ann. chim. phys.* [5] 22, 218 (1881).
[2] Wertyporoch. *Ann.* 493, 153 (1932).

The formation and separation of the monochlorotoluenes is typical of ring-substitution products of toluene in general. The relative proportions of the *o*- and *p*-products can be somewhat modified by the conditions used. They are usually easily separated because the para compounds are mainly solids while the ortho compounds are liquids. There is only a slight difference in boiling point between the isomers. The *p*-compound can be obtained in a high state of purity by freezing it out of the mixture. The mother liquor consists of the *o*-compound and the small amount of *m*-compound formed, the liquid being saturated with the *p*-compound at the temperature of the original freezing. A further separation can be achieved by fractional distillation followed by freezing to remove more of the para compound. *o*-Chlorotoluene is an important dye-intermediate.

5. Nitration of toluene is far easier than with benzene. It gives mainly *o*- and *p*-nitrotoluenes with about 4% of the meta compound. The large scale on which toluene is nitrated and the refinements of modern commercial distillation make available this small proportion of meta nitrotoluene. Further nitration gives mainly 2,4-dinitrotoluene. This can then be nitrated to 2,4,6-trinitrotoluene (T.N.T.). It is impossible to introduce a fourth nitro group by direct nitration. In the large scale commercial nitration of toluene with nitric acid (d. 1.475) at 30° the following percentages are obtained, para 37, ortho 59, meta 4.

6. Sulfonation of toluene gives a mixture of *o*- and *p*-toluene sulfonic acids. The ortho acid is related to saccharin (p. 697).

7. Friedel-Crafts reactions. Toluene, treated with anhydrous aluminum chloride, gives a mixture of xylenes and benzene. When treated with alkyl halides, olefins, etc. and $AlCl_3$, toluene gives para and meta compounds, mainly the latter. Thus toluene with $AlCl_3$ and isobutyl chloride gives *m*-*t*-Bu-toluene which can be trinitrated to give a musk substitute.[3] When anhydrous $FeCl_3$ is used in place of $AlCl_3$ *p*-*t*-Bu-toluene is the chief product.

Toluene with phthalic anhydride and anhydrous aluminum chloride gives *o*-(*p*-toluyl)-benzoic acid which is converted to beta-methylanthraquinone by sulfuric acid.

8. Alcohols and aldehydes condense with toluene in the presence of concentrated sulfuric acid more readily than with benzene. The products contain *para* tolyl groups almost exclusively.

9. Mercuration of toluene in the *p*- and *o*-positions takes place when it is refluxed with mercuric acetate. The chief product is *p*-tolylmercuric acetate (*p*-acetoxymercuritoluene).

B. Higher Homologs of Benzene

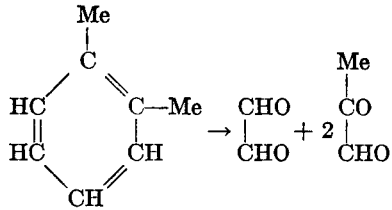
These resemble toluene in properties and reactions.

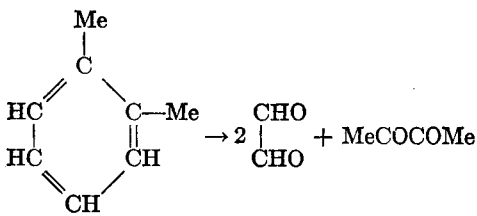
Dimethylbenzenes, xylenes, $C_6H_4(CH_3)_2$, occur in coal tar, the *m*-isomer forming about 70% of the mixture. Whereas only the *o*-xylene can be sepa-

[3] Baur. *Ber.* 24, 2836 (1891).

rated by fractionation, all three isomers can be separated by means of H_2SO_4. The cold conc. acid leaves the para compound unchanged. The solution of the sulfonic acids of the ortho and meta xylenes is treated with $BaCO_3$ and Na_2CO_3 in the usual way to eliminate the excess H_2SO_4 and to form the Na salts. Evaporation causes the *o*-xylene sulfonate to separate first. After recrystallization, this is hydrolyzed to *o*-xylene by HCl at 190°. Meta and para xylenes can also be separated by careful recrystallization from pentane at low temperatures.[4]

o-xylene, m. −27°, b. 144°, can be synthesized from *o*-Br-toluene, MeI and Na. Oxidation by dil. HNO_3 gives *o*-toluic acid. Chromic acid mixture oxidizes it completely to CO_2 and H_2O. Over a vanadium base catalyst with air at 1000° F. *o*-xylene is oxidized to phthalic anhydride.[5] Treatment of *o*-xylene with 15% ozone gives glyoxal and both methylglyoxal and diacetyl.[6,7] This might indicate the existence of both Kekulé forms, but should rather be taken as a result of the resonance between them.



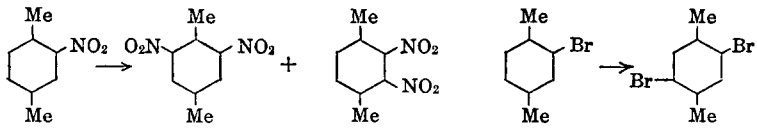


m-Xylene, m. −54°, b. 138.8°, is the most readily available xylene. It can also be prepared from mesitylene by oxidizing one methyl to give mesitylenic acid and eliminating CO_2 from the latter. It is not oxidized by boiling 20% nitric acid but is converted to *m*-toluic acid by 30% nitric acid. Chromic acid mixture converts it to isophthalic acid. Chlorination, nitration and sulfonation of *m*-xylene take place readily in the 4-position which is *o*- and *p*- to the methyl groups. Thus in presence of Hg salts, 50% nitric acid converts *m*-xylene to a mixture of 4-NO_2-*m*-xylene and 4-NO_2-3-Me-benzoic acid, the latter predominating at higher reaction temperatures.

[4] McArdle, Mason. *C. A.* **42**, 2988 (1948).
[5] *Chem. Inds.* **59**, 68 (1946).
[6] Levine, Cole. *J. Am. Chem. Soc.* **54**, 338 (1932).
[7] Wibaut, Haayman. *Science* **94**, 49 (1941).

m-Xylene with isobutyl or *t*-butyl halides or isobutylene in presence of $AlCl_3$ gives 5-*t*-Bu-*m*-xylene in good yield. This, on trinitration, gives an artificial musk. $AlCl_3$ alone converts *m*-xylene to a complex mixture of benzene, toluene, *p*-xylene, mesitylene, pseudocumene, and durene.

***p*-Xylene,** m. 13.2°, b. 138.5°, can be made by the action of Na on MeI and *p*-Br-toluene or *p*-Br_2-benzene. It is readily oxidized to *p*-toluic and terephthalic acids. The dinitration of *p*-xylene gives mainly the 2,6- and 2,3-compounds, with very little of the 2,5-compound. On the other hand dibromination gives mainly the 2,5-compound.



p-Xylene can be sulfonated by fuming sulfuric acid.

The three xylenes have been isolated from an Oklahoma petroleum.[8] They constitute about 0.3% of the crude oil.

Ethylbenzene, phenylethane, $C_6H_5CH_2CH_3$, m. −92.8°, b. 136.2°, can be made in a variety of ways: (1) from benzene with an ethyl halide or ethylene in presence of $AlCl_3$ or HF, (2) from bromobenzene, an ethyl halide and Na and (3) by reduction of styrene, $PhCH=CH_2$. Halogenation attacks mainly the $\alpha-C$. Oxidation gives benzoic acid. Many derivatives of ethylbenzene have been made.[9] It is used in manufacturing styrene for artificial rubber.

Trimethylbenzenes, $C_6H_3(CH_3)_3$, are contained in small amount in coal tar. *Hemimellitene*, 1,2,3-Me_3-benzene, b. 176°, *Pseudocumene*, 1,2,4-Me_3-benzene, m. −57.4°, b. 169.3°, is separated from mesitylene by means of its sparingly soluble sulfonic acid. Its structure is proved by its synthesis from MeI and bromo-*p*-xylene. *Mesitylene*, 1,3,5-Me_3-benzene, m. −53°, b. 164.8°, can be made from acetone or methylacetylene by the action of sulfuric acid.

Propylbenzenes, $C_6H_5C_3H_7$, are synthesized by the usual reactions. *n-Propylbenzene*, $C_6H_5CH_2CH_2CH_3$, m. −101.6°, b. 158°, is made by the Wurtz-Fittig reaction but not by the Friedel-Crafts reaction. *Isopropylbenzene, cumene*, $C_6H_5CH(CH_3)_2$, b. 154°, is made from benzene and either propyl chloride in presence of $AlCl_3$. It is used in improving the performance of aviation fuel.

Benzene is alkylated by cyclopropane with $AlCl_3$ to *n*-propylbenzene.[10]

Cymene, *p*-methylisopropylbenzene, *p*-cymene, $CH_3C_6H_4CH(CH_3)_2$, m. −73.5°, b. 177°, is found in many essential oils, notably in spruce turpentine from which it can be obtained cheaply. It is also formed by heating camphor

[8] White, Rose. *J. Research Natl. Bur. Standards* **9**, 711 (1932).
[9] Cline, Reid. *J. Am. Chem. Soc.* **49**, 3150 (1927).
[10] Grosse, Ipatieff. *J. Org. Chem.* **2**, 447 (1937).

with P_2O_5. Oxidation gives *p*-toluic acid, *p*-methylacetophenone, *p*-isopropylbenzoic acid (*cumic acid*) or terephthalic acid.[11]

Polymethylbenzenes. *Durene*, 1,2,4,5-Me_4-benzene, m. 80°, b. 195°; *isodurene*, 1,2,3,5-Me_4-benzene, m. −24°, b. 197°; *Me_5-benzene*, m. 53°, b. 230°, and *Me_6-benzene* (mellitene), m. 166°, b. 265°, are obtained by the Friedel-Crafts reaction using mixed xylenes and MeCl.[12]

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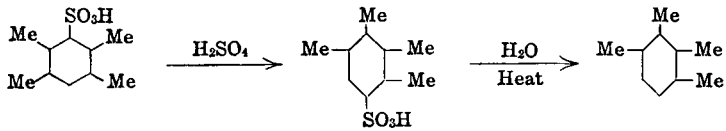

Isodurene undergoes a similar change. Pentamethylbenzene similarly gives hexamethylbenzene and prehnitenesulfonic acid.[14]

A good example of steric hindrance to addition reactions is the failure of trihaloacetyl derivatives of durene and isodurene to give the haloform reaction even on boiling with concentrated alkali.[15]

All except two of the possible *ethylated* benzenes are known. Their boiling points are as follows: ethylbenzene, 136.1°; diethylbenzenes, *o*- 184.5°, *m*- 181.5°, *p*- 183°; triethylbenzenes, *unsym*- 218°, *sym*- 218°; tetraethylbenzenes, *vic*- 254°, *sym*- 250° (m. 13°); Et_5-benzene, 277°; Et_6-benzene, 298° (m. 129°).

III. UNSATURATED BENZENE HYDROCARBONS

Styrene, "styrol," cinnamene, phenylethylene, vinylbenzene,

$$C_6H_5CH=CH_2,$$

b. 146°, is readily obtained by heating cinnamic acid[1] or by the usual methods for introducing a double bond as by elimination of water or HBr from phenylmethylcarbinol, β-phenylethyl alcohol or their bromides. Another method is to add HBr to cinnamic acid and then boil the water solution of the sodium salt of the β-bromohydrocinnamic acid.

$$PhCHBrCH_2CO_2Na \rightarrow NaBr + CO_2 + PhCH=CH_2$$

Styrene is now made commercially by the dehydrogenation of ethylbenzene. A glacial acetic acid solution of H_2SO_4 polymerizes styrene to distyrene, 1,3-

[11] Senseman, Stubbs. *Ind. Eng. Chem.* **24**, 1184 (1932).
[12] Smith, Cass. *J. Am. Chem. Soc.* **54**, 1603, 1609 (1932).
[13] "Org. Reactions," Vol. III.
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[15] Gray et al. *J. Am. Chem. Soc.* **53**, 3494 (1936).
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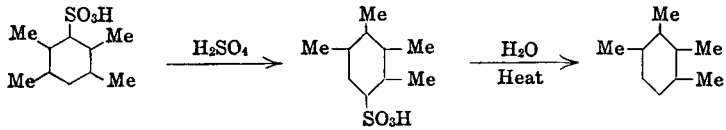

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Ph_2-1-butene, b. 311°. On standing or heating, styrene polymerizes readily to solid metastyrene. Hydroquinone inhibits this polymerization.[2] Styrene adds HBr to give $C_6H_5CH_2CH_2Br$. Nitric acid gives ω-nitrostyrene, $PhCH=CHNO_2$. This reaction is like that of nitric acid with isobutylene. Styrene is used in preparing polystyrene resins and in manufacturing synthetic rubber.

The activating effect of the phenyl group on the double bond is shown not only by the ready polymerization of styrene but by the fact that the treatment of a solution of ethylene in styrene with bromine results in almost exclusive addition to the latter substance.[3] With formaldehyde, styrene gives the following products:[4] $PhCH(CH_2OH)_2$, $PhCH(CH_2O)_2CH_2$.

For diphenylethylenes, etc., see p. 716.

Allylbenzene, $C_6H_5CH_2CH=CH_2$, b. 157°, is made from allyl bromide and a phenyl Grignard reagent in the usual way for 1-olefins. On heating with alcoholic KOH it gives *propenylbenzene*, $C_6H_5CH=CHCH_3$, b. 177° which has been synthesized in many ways including the conversion of ethylphenylcarbinol to its chloride and removal of HCl by alcoholic KOH. The shift of a double bond from the 2-position in relation to a phenyl group to the 1-position is readily achieved in much the same way that a double bond shifts to the αβ-position in relation to a carboxyl group.

1-Phenylbutadiene, $C_6H_5CH=CHCH=CH_2$, has been studied extensively.[5] It adds exclusively in the 3,4- rather than the 1,4-positions. HOCl and HOBr give $PhCH=CHCHOHCH_2X$. The presence of Br or NH_2 in the 4-position does not change the mode of addition.

Phenylacetylene, $C_6H_5C\equiv CH$, b. 142°, can be made in a variety of ways, probably best by dropping ω-bromostyrene into fused KOH (OS). It gives the usual acetylene reactions including the formation of metal derivatives and hydration with sulfuric acid to give acetophenone.

IV. AROMATIC HALOGEN COMPOUNDS

A. Addition Compounds

The long exposure of benzene in sunlight to chlorine or to bromine vapor gives the products $C_6H_6X_6$. Although as many as sixteen isomeric benzene hexachlorides are theoretically possible, only five probable strainless forms, two of which are mirror images, are considered likely of existence.

The separation of the five known isomers has been effected through recrystallization. They are alpha m. 158°, beta 309°, gamma 112.5°, delta 138–139°, epsilon 218°. The approximate composition of the hexachloride

[2] "Org. Syntheses."

[3] Anantakrishnan, Ingold. *J. Chem. Soc.* **1935**, 1396.

[4] *Ann. Rep. Chem. Soc.* (London) **1920**, 79.

[5] Muscat et al. *J. Am. Chem. Soc.* **51**, 2496 (1929); **52**, 1574 (1930); **53**, 252 (1931); **54**, 2001 (1932); **56**, 1239 (1934).

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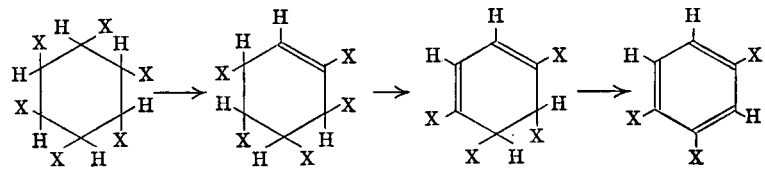
mixture is 70% α, 5% β, 12% γ, 7% δ and 5% ϵ. The gamma form, Gammexane, is the active principle of 666 which has outstanding insecticidal properties.[1,2]

The hexahalides lose 3 HX giving *unsym*-trihalogenbenzenes on treatment with bases. The steps involved may be the following:

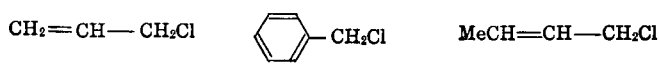


In the first step, no choice is possible because of the symmetry of the molecule. The second step takes place as indicated because of the greater reactivity of the allylic halogen of the system XC=C−CX as compared with that of the system C=CX−CX. Whichever X is removed in the last step, the product is the unsymmetrical trihalide.

B. Substitution Compounds

These are known in great numbers. They fall in two classes depending on whether the halogen is in the side chain or in the ring.

1. Halogen in side chain. These compounds are really arylsubstituted alkyl halides and follow the same regularities as do the parent halides (p. 74) except that a halogen alpha to an aromatic ring, as in benzyl halides, is even more reactive than in the corresponding alkyl halides. A consideration of the formula of benzyl chloride (II) shows it to have an allyl chloride grouping (I).



(I) (II) (III)

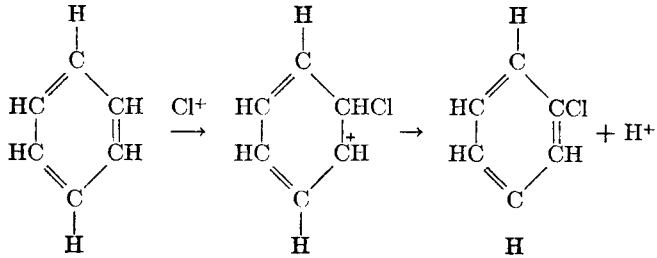
The analogy is strengthened by the fact that the Grignard reagent of (II) gives rearrangements much as does that of crotyl chloride (III) the entering group going in the *o*- and 3-positions respectively.

o- and *p*-Hydroxybenzyl halides are peculiar in not being soluble in alkali. Instead they are converted to methylene quinones (p. 690).

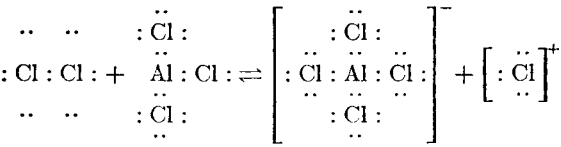
2. Halogen in ring. In presence of catalysts or halogen carriers such as iodine or various metal halides including those of iron and aluminum, chlorine and bromine replace H atoms of the benzene ring readily. This replacement probably resembles that which takes place in the action of chlorine on isobutylene to give an unsaturated chloride instead of the expected isobutylene dichloride (p. 40). In each case, after the first Cl has added, it is easier for a

[1] Slade. *Chemistry & Industry* 23, 314 (1945).
[2] Haller, Bowen. *Agr. Chemicals* 11, 15–17 (1947).

proton to be expelled than for the second Cl to add. In the case of benzene this is probably due to the strong tendency to revert to a completely conjugated system.



The function of the halogen carrier may be to favor the addition of a halogen with 6 electrons to the extra electron pair of one of the benzene double bonds. Thus

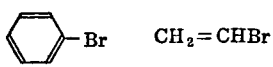


Iodine does not replace aromatic H because the reverse substitution by HI takes place more readily

$$C_6H_6 + I_2 \rightleftharpoons C_6H_5I + HI$$

This tendency can be overcome by using an oxidizing agent such as nitric acid which will destroy the HI.[3] The true aryl halides are peculiarly inactive with the following exceptions:

(*a*) They react with metals such as Mg, Na and Cu[4] to form Grignard reagents and to give coupling reactions, Na being most useful in causing the reaction of an aryl halide with an alkyl halide and Cu to cause the union of two aryl residues. The inactivity of the true aryl halides resembles that of the vinyl halides.



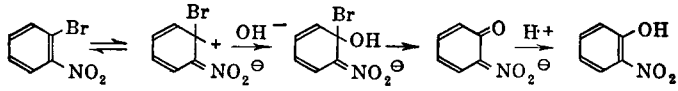
Unlike the vinyl halides, the aryl halides cannot lose HX to give an acetylenic linkage.

(*b*) At high temperatures and pressures they give certain metatheses. Thus chlorobenzene has to be heated with sodium hydroxide solution to about 300° before it reacts to give phenol.[5] With ammonia and copper salts it will

[3] Datta, Chatterjee. *J. Am. Chem. Soc.* **39**, 435 (1917).
[4] Ullmann. *Ann. Rep. Chem. Soc.* (London) **1904**, 87.
[5] Hale. *C. A.* **21**, 249 (1927).

react to give aniline at about 200°.[3] Bromobenzene with KCN or cuprous cyanide at 200° gives PhCN.[6]

(*c*) If a nitro group is in the *o*- or *p*-position, the halogen becomes readily reactive with basic reagents such as NaOH and NH_4OH to give nitrophenols and nitroanilines. The point of attack may be the nitro group and the reactions may proceed by addition rather than by true metathesis.



In the action with ammonia, the groups $-NH_2$ and $=NH$ play the same part as $-OH$ and $=O$.

Preparation. The only compounds of wide importance are the halides of benzene and toluene which will be considered separately (pp. 621, 625).

A. Homologs and substitution products of benzyl halides, $ArCH_2X$. In some cases these can be made directly as in the case of the benzyl halides themselves but usually they are made from the corresponding arylcarbinols which are prepared by the usual reactions.

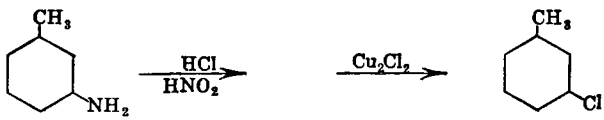
B. True aromatic halides can be made by direct halogenation but the position taken by the halogen is not subject to control. The action of reagents like PCl_5 does not usually replace phenolic OH by Cl but gives stable and unreactive phosphates. An exception is the case of the nitrophenols in which the OH is readily replaced by Cl.

The best method for the controlled introduction of a halogen is by the diazotization of the proper aryl amine. This preparation is especially important for the fluoro and iodo compounds and in the introduction of halogen atoms into positions not possible by direct substitution. The proper amine is treated with a suitable acid and sodium nitrite or N_2O_3 generated by the action of nitric acid on As_2O_3.

1. For fluoro compounds the amine is dissolved in fluoroboric acid, a solution of BF_3 gas in hydrofluoric acid obtained by treatment of boric acid with hydrofluoric acid.

$$ArNH_2 + HBF_4 + HNO_2 \rightarrow 2\,H_2O + ArN_2BF_4 \xrightarrow{\text{heat}} ArF + N_2 + BF_3$$

2. Chloro and bromo compounds are made by treating the diazonium halide with the proper cuprous halide and warming. Thus *m*-chlorotoluene can be made from *m*-toluidine.



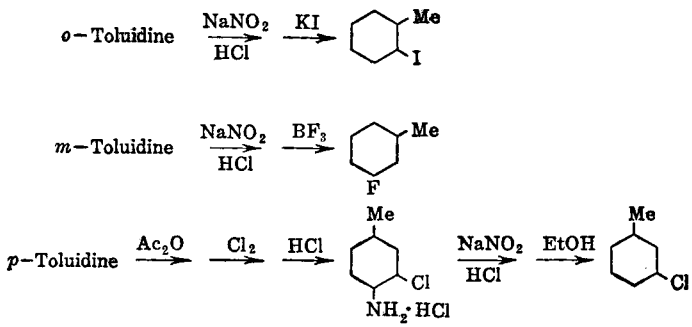
[6] *Ann. Rep. Chem. Soc.* (London) 1920, 77.

An indirect method of achieving the same result is to chlorinate *p*-acetotoluidide, remove the acetyl group, diazotize and remove the diazonium group by reduction with alcohol.

3. Iodo compounds are obtained by simply warming the aryl diazonium chloride with an inorganic iodide.

All of these preparations give tarry by-products and usually some phenols. The halides can be obtained by steam distillation from alkaline solution, the tars and alkali phenolates being nonvolatile with steam.

A few examples of the use of diazotization to prepare aryl halides follow:



Individual Halides of Benzene and its Homologs

Because of the aliphatic nature of their reactions, attention will be turned first to those with halogen in the aliphatic side chain.

Benzyl chloride, $C_6H_5CH_2Cl$, b. 175°, is made by chlorinating boiling toluene in the light, and by chloromethylating benzene.[7,8] The Cl is very reactive. Thus KCN readily gives phenylacetonitrile, $PhCH_2CN$. The reactivity of substituted benzyl halides has been extensively studied.[9] Nitration of benzyl chloride readily gives somewhat over 50 and 30% of the *p*- and *o*-compounds and about 15% *m*-compound. *Benzyl bromide*, b. 198°, is made by direct bromination. *Benzyl iodide*, m. 24°, is readily made by the reaction of benzyl chloride with KI in acetone or methanol. All the benzyl halides, especially the iodide, are lachrymators.

Benzyl chloride is used to make benzaldehyde and to introduce the benzyl group on the nitrogen atom in certain dyes.

The preparation of benzylmagnesium chloride takes place readily to about 95% but at the same time a small amount of di-*p*-tolyl, m. 120°, is formed. This indicates the formation of free radicals.[10] Benzyl magnesium halides

[7] Ginsburg, Whitmore et al. *Ind. Eng. Chem.* **38**, 478 (1946).
[8] "Org. Reactions," Vol. I.
[9] *Ann. Rep. Chem. Soc.* (London) **1929**, 137.
[10] Gilman, Kirby. *J. Am. Chem. Soc.* **51**, 1571 (1929).

give some normal reactions to form benzyl derivatives while in other cases they also give *o*-tolyl derivatives.[11]

Certain compounds in which the benzyl group is "negative" are obtained as follows:

$$PhCH_2MgCl \xrightarrow{HgCl_2} (PhCH_2)_2Hg \xrightarrow{Na} PhCH_2Na \xrightarrow{Me_4NCl} PhCH_2NMe_4$$

The last two compounds are ionized in non-aqueous solvents. Water hydrolyzes them to give toluene.[12]

Further chlorination of benzyl chloride gives benzylidene or *benzal chloride*, $C_6H_5CHCl_2$, b. 203°, and *benzotrichloride*, $C_6H_5CCl_3$, b. 213°. As usual with polyhalides, they are less reactive than the monohalide. They can be converted to benzaldehyde and benzoic acid by vigorous hydrolysis.

Benzotrichloride, with suitable reagents such as AgF or HF, gives *benzotrifluoride*. The oxidation of this substance destroys the benzene ring with formation of F_3CCO_2H thus illustrating the great stability of the C—F linkage. Nitration of benzotrichloride gives mainly the *meta* nitro compound (65%).

Orientation in Benzene Compounds

The different *orienting effects of different groups* in the benzene ring were early observed. At first it was thought that a compound like toluene gave only *ortho* and *para* products when a second group was introduced and that a compound like nitrobenzene gave only *meta* products. The fact is that all possible products are formed in all cases but groups can be divided into two classes, (1) those which direct an entering group mainly to the *ortho* or *para* position and (2) those which direct mainly to the *meta* position. Another way to regard the difference in these two classes of groups is that the first *facilitate* substitution in the *ortho* and *para* positions while the second *hinders* substitution in these positions thus allowing the *meta* position to react. To be effective in allowing meta substitution the change in reactivity has to be perhaps one hundred-fold. Thus, although benzene reacts with chlorine nearly ten times as rapidly as does chlorobenzene, the chlorination of the latter gives mainly *o*- and *p*-dichlorobenzenes.[13]

It is a fact that *o,p*-directing groups speed up substitution whereas *m*-directing groups make it slower.

Much work has been done and a tremendous amount has been written on orientation in benzene compounds.

The original rule on orientation was that of Crum Brown and Gibson.[14] They stated that the group X will be meta-orienting if the compound HX

[11] Gilman et al. *Proc. Iowa Acad. Sci.* 34, 221 (1927).
[12] *Ann. Rep. Chem. Soc.* (London) 1917, 117.
[13] Groggins. "Unit Processes in Org. Chem." 3rd Ed. McGraw Hill, 1947, p. 247.
[14] Crum Brown, Gibson. *J. Chem. Soc.* 61, 367 (1892).

can be oxidized readily to HOX. Since the following take place readily:

$$H(NO_2) \rightarrow HONO_2 \qquad H(SO_3H) \rightarrow HOSO_3H$$
$$H(CHO) \rightarrow HOCHO \qquad H(CO_2H) \rightarrow HOCO_2H$$

the groups NO_2, SO_3H, CHO and CO_2H should be meta-directing. This agrees with facts such as the formation of 90% *m*-, 8% *o*- and 1% *p*-dinitrobenzene from the nitration of nitrobenzene at 30°. Since the following changes *do not* take place readily:

$$H(Cl) \not\rightarrow HOCl \qquad H(OH) \not\rightarrow HO{-}OH$$
$$H(NH_2) \not\rightarrow HONH_2 \qquad H(CH_3) \not\rightarrow HOCH_3$$

the groups Cl, OH, NH_2 and CH_3 should be ortho-para-directing. This agrees with facts such as the formation of over 90% *o*- and *p*-nitrotoluenes in the nitration of toluene.

There are glaring exceptions to any rule on orientation. For instance the mercuration of nitrobenzene gives over 50% *o*- and about 40% *m*- and 10% *p*-products.[15] The bromination of bromobenzene at 500° gives mainly *m*-dibromobenzene.[16]

The meta-directing power of groups has come to be associated with their multiple linkages. Almost the only exception to this relation is the meta-directing effect of the $-CCl_3$ group. This follows the Crum Brown and Gibson Rule, however, inasmuch as

$$H(CCl_3) \rightarrow HOCCl_3 \rightarrow COCl_2$$

takes place readily. The meta directing power of the CCl_3 group is approached by the $CHCl_2$ group. Thus benzal chloride, on nitration, gives *o*-, *m*-, and *p*-compounds in 23, 39 and 43% yields. The nitration of benzyl chloride gives about 15% *m*-compound as compared with 4% *m*-compound obtained from toluene.

The relative proportions of *ortho* and *para* products are influenced by conditions and by the nature of the entering group. Thus bromobenzene on chlorination gives nearly as much *ortho* as *para* compound but on sulfonation gives essentially the pure *para* product. A fairly complete list of the orienting effects of groups has been worked out.[17]

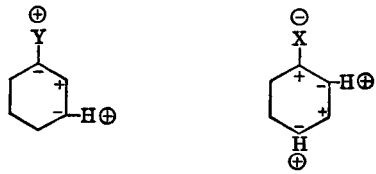
1. *Meta*-directing: SO_3H, NO_2, CHO, CO_2H, CO_2R, $CONH_2$, COR, $COCO_2H$, CN, CCl_3, NH_3X, NR_3X.

2. *Ortho-para*-directing: OH, OR, OAc, NH_2, NHR, NR_2, NHAc, N=N, CH_3, CH_2Cl, CH_2ONO_2, CH_2SO_3H, CH_2NH_2, CH_2CN, CH_2CO_2H, $CH_2CH_2CO_2H$, $CH{=}CHCO_2H$, $CH{=}CHNO_2$, $C{\equiv}CCO_2H$, C_6H_5, Na, K.

The polar nature of the atom attached to the benzene ring is probably the

[15] Coffey. *J. Chem. Soc.* 127, 1029 (1925).
[16] Wibaut, Van Loon. *Nature* 139, 151 (1937).
[17] Vorlander. *Ber.* 52B, 263, 283, 308, 309, 311 (1919).

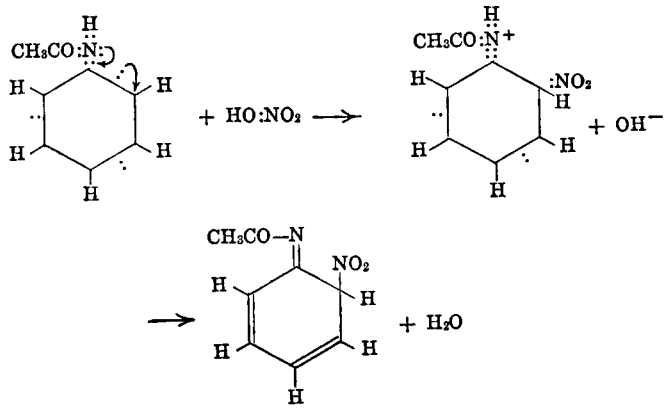
deciding factor in orientation. A positive "pole" directs to the meta position. This effect, sometimes known as the *inductive* or *I* effect, also slows down the velocity of substitution as compared with that in compounds containing *o-p*-directing groups. The effect of "positive" and "negative" groups on benzene substitution has been expressed as follows.[18]



The H atoms marked + are the ones removed on further substitution. The significance of the sign of the "pole" attached to the ring is seen in the action of nitric acid on aniline in concentrated sulfuric acid and on acetanilide. The first gives meta and the second gives ortho and para compounds. The aniline sulfate solution contains the strongly positive group $-NH_3^{\oplus}$ and consequently gives *m*-substitution.

In the case of acetanilide the unbonded pair of electrons on nitrogen probably are drawn into conjugation with the ring giving a resonance form with a free electron pair in the *ortho* carbon atom. To this adds the positive NO_2 group.

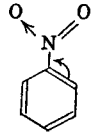
Thus,



and the addition product, shown partially in electronic notation, loses water to give a product which, by a tautomeric shift, yields the ortho substitution product. This effect is called a *tautomeric* effect or *T* effect.[19] An opposite

[18] Fry. *J. Am. Chem. Soc.* **36**, 248, 1035 (1914); **37**, 855 (1915).
[19] Ingold. *Rec. trav. chim.* **48**, 806 (1929).

effect explains the meta directing effect of such groups as the nitro group.



The shift of the electron pair is indicated by the arrows in the above formula.

The "metalation" of benzene apparently offers an exception to this generalization. Thus phenylpotassium reacts with EtK to give mainly the *p*-K_2-compound.[20]

$$C_6H_5K + EtK \rightarrow p\text{-}C_6H_4K_2$$

The relation of electrical properties of groups in relation to their orienting power has been extensively studied.[21]

D. Individual Aromatic Halides

Fluorobenzene, C_6H_5F, b. 85°, is made from aniline by diazotization. It is completely inert. The nearness of its boiling point to that of the corresponding hydrogen compound, benzene (80°) is characteristic of fluorine compounds.

Chlorobenzene, phenyl chloride, C_6H_5Cl, b. 132°, is obtained by the chlorination of benzene using various catalysts such as $FeCl_3$, I_2, etc.[22] Since it is an important intermediate for phenol, aniline and the nitrated chlorobenzenes, it is made in large amounts. The yield of chlorobenzene and its by-products varies with the conditions.[23] If 65% of the benzene is chlorinated, the yield of products is about as follows: chlorobenzene 58%, *p*-Cl_2-benzenes 6%, *o*-Cl_2-2%, *m*-Cl_2- less than 1%, 1,2,3-Cl_3- and 1,2,4-Cl_3-benzenes about 0.5% each. The nitration and sulfonation of chlorobenzene take place mainly in the *o*- and *p*-positions. Chlorobenzene gives a Grignard reagent on heating with Mg without any solvent.

Bromobenzene, phenyl bromide, C_6H_5Br, b. 157°, is readily made by adding Br_2 to benzene in presence of Fe filings. It is of special value in organic chemistry in the form of the Grignard reagent, C_6H_5MgBr. Similarly it is a source of sodium phenyl for synthetic reactions.[24]

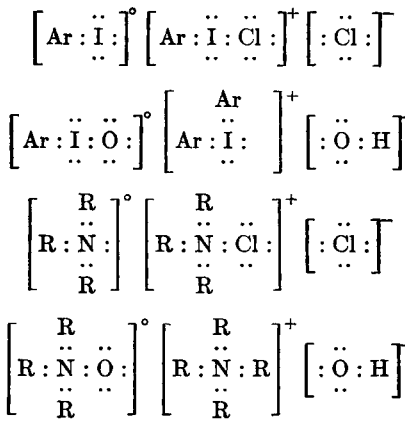
Iodobenzene, phenyl iodide, C_6H_5I, b. 188°, is best made from benzene, iodine and nitric acid.[25] It is chiefly interesting because of the polyvalency of its iodine atom. With dry Cl_2 in anhydrous inert solvents, it gives a yellow

[20] Gilman, Kirby. *J. Am. Chem. Soc.* **58**, 2074 (1936).
[21] *Ann. Rep. Chem. Soc.* (London) **1926**, 129; **1927**, 148; **1928**, 137; **1930**, 130.
[22] Ellis. "Chemistry of Petroleum Derivatives." Reinhold, 1934. p. 755.
[23] Bourion. *Compt. rend.* **170**, 1319 (1920).
[24] Morton, Stevens. *J. Am. Chem. Soc.* **53**, 2244 (1931).
[25] Datta, Chatterjee. *J. Am. Chem. Soc.* **39**, 435 (1917).

crystalline compound, $C_6H_5ICl_2$, *phenyl iodide chloride*. Bases change this to *iodosobenzene*, C_6H_5IO, a yellow substance which explodes at 210° and can form salts with acids. HCl gives the dichloride while HOAc gives a diacetate. On standing or warming, it undergoes disproportionation to give phenyl iodide and *iodoxybenzene*, $C_6H_5IO_2$. This is a crystalline, neutral compound which explodes at 230°. Iodosobenzene can be made directly from iodobenzene by oxidation with ozone or peracetic acid. Iodoxybenzene can be made from iodosobenzene and Caro's acid, H_2SO_5, or from iodobenzene and perbenzoic acid. Treatment of iodosobenzene with phenylmagnesium bromide gives *diphenyliodonium hydroxide*, a strong base.

$$ArIO + ArMgX \rightarrow Ar_2I-OMgX \rightarrow Ar_2I-OH$$

This can also be obtained by treating a mixture of iodoso- and iodoxy-benzene with AgOH. Diphenyliodonium iodide, $Ph_2I.I$, m. 176°, is a salt like Me_4NI. Heat decomposes it to 2 PhI. The nature of these polyvalent compounds of iodine is better expressed electronically than by ordinary bonds. Analogous nitrogen compounds are given for comparison



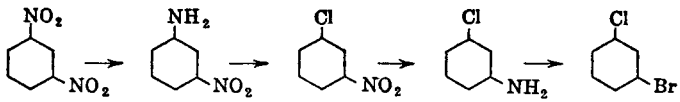
Halides of Benzene Homologs

These resemble phenyl or benzyl halides depending on the position of the halogen in the ring or the side chain. Certain exceptional reactions occur. Thus the fusion of ortho and para chlorotoluenes with NaOH and Cu powder at 315° gives about 25 and 35 per cent *meta* cresol respectively.[26] Similar results were obtained with *o*-Cl-ethylbenzene. Yields as high as 70% *m*-cresol have been obtained from *o*-Cl-toluene. The normal hydrolysis products are obtained if a copper reactor is used instead of one of iron.

[26] Meharg, Allen. *J. Am. Chem. Soc.* **54**, 2920 (1932).

Aromatic Polyhalides

These are obtained by direct halogenation or by diazotization of suitable amines. Further substitution in a phenyl halide takes place almost exclusively in the *ortho* and *para* positions. The *meta*-disubstituted product is formed in very small amounts. Thus chlorination or nitration of chlorobenzene gives mainly *o*- and *p*-dichlorobenzene and *o*- and *p*-nitrochlorobenzene. Further action gives mainly the unsymmetrical or 1,2,4-trichloro- and chlorodinitrobenzenes. In chlorination, all three possible tetrachlorobenzenes are formed while in nitration the final product is 1,2,4,6-chlorotrinitrobenzene because of the *meta*-orienting effect of the nitro groups. *m*-Dihalogenated benzenes are best obtained by alternate reduction and diazotization of *m*-dinitrobenzene. For instance



p-Dichlorobenzene (Para, Paradow), m. 53°, b. 173°, is obtained as a by-product in the chlorination of benzene. It is extensively used as a moth and caterpillar repellant. It is also an intermediate for making *p*-chlorophenol and hydroquinone. *o-Dichlorobenzene*, m. −17.6°, b. 179°, is a cheap by-product of the para compound because it has to be removed in order to raise the m.p. and prevent the latter from caking. It is used as a high-boiling solvent, for an insecticide and in making *o*-chlorophenol and pyrocatechol. A curious preparation of *o*-Cl_2-benzene is by heating *o*-Br-nitrobenzene with NH_4Cl at 320°.[27]

The *trichlorobenzenes* are the *sym-*, m. 63°, b. 208°, the *vic-*, m. 53°, b. 219°, and the *unsym-*, m. 17°, b. 213°. These properties illustrate the effect of symmetry in raising the solidification point and the vapor pressure. The 1,2,4-compound is obtained exclusively by the action of bases with benzene hexachloride. It is also the chief product of the trichlorination of benzene. *Hexachlorobenzene*, m. 227°, b. 326°, is readily obtained by exhaustive chlorination.

***p*-Dibromobenzene,** m. 87°, b. 219°, is a by-product of the bromination of benzene. It readily gives a Grignard reagent and less readily gives a di-Grignard reagent. The meta compound is obtained by bromination at about 500°.[28]

Hexaiodobenzene, C_6I_6, m. 350°, is obtained from benzene heated at 180° with I_2 and 60% oleum.[29]

Arylsubstituted unsaturated halides are known in great numbers. *β*- or *ω-Bromostyrene*, $C_6H_5CH=CHBr$, is readily obtained by boiling cinnamic acid

[27] *Ann. Rep. Chem. Soc.* (London) **1904**, 94.
[28] Wibaut, Van Loon. *Nature* **139**, 151 (1937).
[29] Durand, Mancet. *Bull. soc. chim.* [5] **2**, 665 (1935).

dibromide with sodium carbonate.

$$PhCHBrCHBrCO_2Na \rightarrow NaBr + CO_2 + PhCH=CHBr$$

With fused KOH it gives phenylacetylene. With alcoholic KOH the chief product is PhCH=CHOEt.

V. AROMATIC SULFONIC ACIDS

One of the most notable characteristics of aromatic hydrocarbons and their derivatives is the ease with which they can be sulfonated by treatment with concentrated or fuming sulfuric acid or chlorosulfonic acid, $ClSO_3H$.

Sulfonic acids are strong acids, intermediate between HCl and H_2SO_4. Their salts, even those of Ca and Ba, are readily soluble. With water these salts give *hydrotropic solutions* which act as good solvents for materials insoluble in water.[1] Sodium xylenesulfonate and sodium cymenesulfonate are very effective. Substances like nitrobenzene, benzaldehyde, and diphenylamine dissolve readily in these solutions.

Benzenesulfonic acid, $C_6H_5SO_3H$, m. 51°, is readily obtained from benzene and sulfuric acid on heating.

$$C_6H_6 + H_2SO_4 \rightarrow H_2O + C_6H_5SO_3H$$

The C−S linkage is very stable. It can be broken by heating at about 150° with hydrochloric acid or superheated steam or by fusion with strong alkalies.

$$PhSO_3H + H_2O \rightarrow C_6H_6 + H_2SO_4$$
$$PhSO_3Na + 2\ NaOH \rightarrow PhONa + Na_2SO_3 + H_2O$$

In one of these processes the phenyl appears to be "negative" and in the other "positive." Another important replacement of the sulfonic acid group gives benzonitrile on fusion with alkali cyanide.

$$PhSO_3Na + NaCN \rightarrow Na_2SO_3 + PhCN$$

Benzenesulfonic acid as a strong acid forms salts. It forms esters with primary alcohols. These, on heating alone, give olefins while heating with excess alcohol gives ethers. Thus aromatic sulfonic acids are useful catalysts for the preparation of olefins and ethers. They have the advantage of not causing charring as does sulfuric acid. Sulfonic esters react fairly smoothly with Grignard reagents to form hydrocarbons.[2]

$$ArSO_3R + R'MgX \rightarrow R-R' + ArSO_3MgX$$

If the ester of a halogenated alcohol is so used, this method can be employed to make higher alkyl halides. Thus the carbon chain of an alkyl halide can be increased by three carbons by converting it to the Grignard reagent and heating

[1] McKee. *Ind. Eng. Chem.* **38**, 382 (1946).
[2] Gilman. *J. Am. Chem. Soc.* **47**, 523 (1925).

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[1] McKee. *Ind. Eng. Chem.* **38**, 382 (1946).
[2] Gilman. *J. Am. Chem. Soc.* **47**, 523 (1925).

with a sulfonic ester of 3-chloropropyl alcohol.[3]

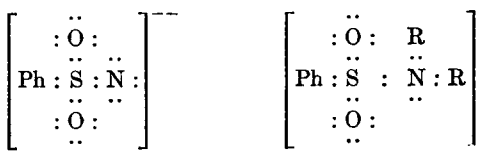
$$RMgX + ArSO_3(CH_2)_3Cl \rightarrow R(CH_2)_3Cl$$

Inorganic acid chlorides such as PCl_5 replace the hydroxyl with chlorine forming *benzenesulfonyl chloride*, $PhSO_2Cl$, m. 14.5°, b. 246°.

$$PhSO_3H + PCl_5 \rightarrow PhSO_2Cl + POCl_3 + HCl$$

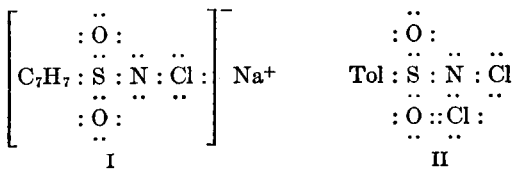
This behaves as an acid chloride. It is only slightly reactive with cold water but reacts in the usual way with hot water, bases and ammonia. The product of the last reaction, *benzenesulfonamide*, m. 150°, is representative of the aromatic sulfonamides which are useful in identifying sulfonic acids because they are easily purified crystalline substances of definite melting points.

The sulfonamides differ from the amides of carboxylic acids in being soluble in alkalies. This solubility is due to the H attached to nitrogen since $PhSO_2NH_2$ and $PhSO_2NHR$ are soluble in alkali while $PhSO_2NR_2$ is not.



The Hinsberg method of separating primary, secondary and tertiary amines is based on this property (p. 170). The N-chloro-derivatives of the sulfonamides obtained by the action of HOCl have antiseptic properties.

Chloramine T (Tolamine) is the sodium salt of N-chloro-*p*-toluenesulfonamide obtained from the amide and NaOCl solution (I). *Dichloroamine-T* is the N-dichloro compound (II). It is used as a water disinfectant. Chloramine B is the sodium salt of N-chlorobenzenesulfonamide. *Halozone* is the corresponding carboxylic acid obtained by oxidizing *p*-toluenesulfonamide with chromic acid mixture and treating the product with alkali and chlorine.



I II

The ortho sulfonic acid of toluene is important as related to saccharin. Toluene on treatment with excess of chlorosulfonic acid gives a considerable amount of *o*-toluenesulfonyl chloride with the *p*- and *m*-compounds as by-products.

[3] Rossander. *J. Am. Chem. Soc.* 50, 1491 (1928).

In this process the chlorosulfonic acid acts both as a sulfonating agent and an acid chloride

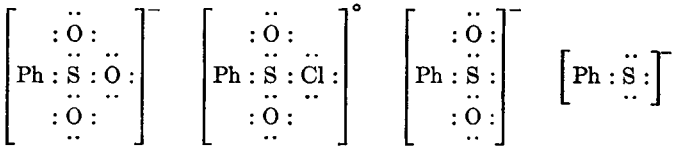
$$C_7H_8 \rightarrow C_7H_7SO_3H \rightarrow C_7H_7SO_2Cl$$

The *p*-toluenesulfonyl chloride is an important by-product.

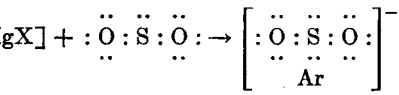
Aryl sulfonyl chlorides on vigorous acid reduction, as with Zn dust and acid, give thiophenols. The acids themselves cannot be thus reduced. The chlorides with neutral or basic reducing agents give sulfinic acids, $ArSO_2H$, or their salts. Thus *p*-toluenesulfonyl chloride with water and zinc dust gives zinc *p*-toluenesulfinate which gives the sodium salt with sodium carbonate solution.[4]

$$2\ TolSO_2Cl + 2\ Zn \rightarrow ZnCl_2 + (TolSO_2)_2Zn \rightarrow 2\ TolSO_2Na$$

The sulfinic acids are readily oxidized to sulfonic acids. They differ from the latter in being reducible to thiophenols by acid and metals. The sulfinic acid group is replaced by the HgCl group on boiling with $HgCl_2$ solution.



Sulfinic acids can also be prepared from Grignard reagents and SO_2.



Sulfonic acids of the homologs of benzene are known in great numbers. Those containing at least four substituent groups have been extensively studied because of the *Jacobsen reaction*, a peculiar process in which groups like alkyl, halogen or sulfonic acid shift intermolecularly under the influence of concentrated sulfuric acid. The peculiar action of sulfuric acid on durene is an example (p. 616).

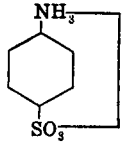
Nitration, sulfonation, and halogenation of benzenesulfonic acid give mainly the meta compounds. The *o*- and *p*-nitrobenzenesulfonic acids are made by oxidizing the corresponding disulfides with dilute nitric acid.

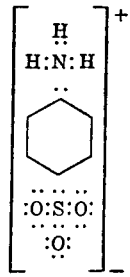
$$O_2NC_6H_4Cl \xrightarrow{Na_2S_2} (O_2NC_6H_4S)_2 \xrightarrow{HNO_3} O_2NC_6H_4SO_3H$$

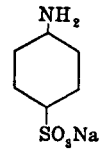
Sulfanilic acid, *p*-aminobenzenesulfonic acid, is obtained by "baking" aniline sulfate to about 200°. It exists as an internal salt or "Zwitterion." With strong bases it gives salts but does not do so with acids. This is because of the strongly acid nature of the sulfonic acid group. These relations are

[4] "Org. Syntheses."

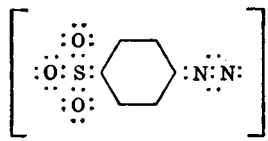
shown in the following formulas:







The "bond" between the active groups in the first formula is probably entirely imaginary. The Zwitterion formula better represents the facts. Sulfanilic acid has been used in colorimetric determination of nitrites.[5] The *m*-isomer, *metanilic acid*, is obtained by reducing the *m*-nitrobenzenesulfonic acid obtained by sulfonating nitrobenzene. Diazobenzenesulfonic acid is a relatively stable diazonium salt.



The *o*- and *p*-phenolsulfonic acids are readily obtained by direct sulfonation of phenol. The ortho compound is used as an antiseptic, Aseptol or Sozolic acid. 2,6-Diiodophenol-4-sulfonic acid is Sozoiodol, a substitute for iodoform.

A new cation exchange resin is made by the condensation of phenolsulfonic acids with formaldehyde.

Just as the NH_2 and OH groups activate the *o*- and *p*-H atoms, so do they loosen the sulfonic acid groups in these positions. Thus the sulfonic acids of aniline and phenol are much more readily hydrolyzed than those of benzene. An example of this is the conversion of *o*-phenolsulfonic acid to the *p*-compound by boiling water. This represents the results of two equilibrium reactions rather than a true rearrangement.

$$o\text{-acid} + H_2O \rightleftharpoons \text{phenol} + H_2SO_4 \rightleftharpoons p\text{-acid} + H_2O$$

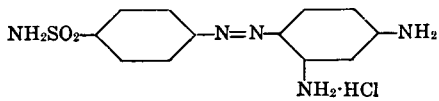
The *p*-acid is less readily hydrolyzed and is formed predominantly during sulfonation.

Sulfanilamide, *p*-aminobenzenesulfonamide, m. 166°, is prepared by reacting acetanilide with chlorsulfonic acid, treating with ammonia to form the sulfonamide, followed by acid hydrolysis of the acetyl group:

[5] Rider, Mellon. *Ind. Eng. Chem., Anal. Ed.* 18, 96 (1946).

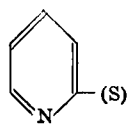
$$MeCONHC_6H_5 \xrightarrow{ClSO_3H} MeCONHC_6H_4SO_2Cl \xrightarrow{NH_3} MeCONHC_6H_4SO_2NH_2 \xrightarrow[H_2O]{H} NH_2C_6H_4SO_2NH_2$$

Sulfanilamide and some of its derivatives have specific action on streptococci.[6] The bacterial diseases cured or remedied are streptococci infections, pneumonia, meningitis, gonorrhea, dysentery, paratyphoid and typhoid. Antistreptococci action was first noted in 1932 with Prontosil Red, m. 250°, an azo dye.[7]

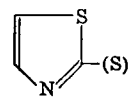


Since then more than 2500 derivatives of sulfanilamide have been described. Among the more important are the following:

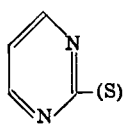
(S) = [−NHSO$_2$C$_6$H$_4$NH$_2$]



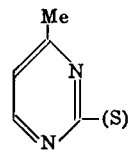
Sulfapyridine



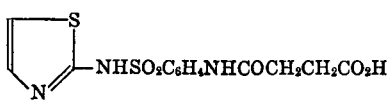
Sulfathiazole



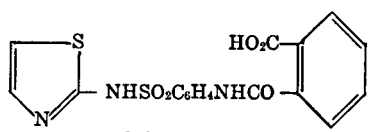
Sulfadiazine



Sulfamerazine



Sulfasuxidine
(succinylsulfathiazole)

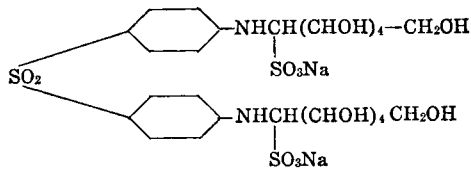


Sulfathalidine
(phthalylsulfathiazole)

[6] Domagk. *Deut. med. Wochschr.* 61, 250 (1935).
[7] Mietzsch, Klarer. Ger. patent No. 607,537 (1935); 610,320 (1935).

The curative powers of the sulfanilamides are believed due to their structural similarity to *p*-aminobenzoic acid.[8,9] The latter is essential in the enzymatic systems of growth and reproduction of many bacteria. Thus the bacteria absorb the sulfa drug as a substitute for *p*-aminobenzoic acid, are unable to multiply, and are destroyed by the normal defenses of the body.

Promin is sodium 4,4′-diaminodiphenylsulfone-N,N′-didextrose sulfonate or



It appears capable of inhibiting the progress of leprosy.[10] It is useful in the treatment of tuberculosis.

VI. NITRO COMPOUNDS OF BENZENE HYDROCARBONS

A. True Aryl Nitro Compounds

These have the $-NO_2$ group attached directly to a benzene ring. Treatment of benzene and especially its homologs with concentrated nitric acid readily gives mononitro derivatives

$$C_6H_6 + HONO_2 \rightarrow H_2O + C_6H_5NO_2$$

The use of mixtures of nitric acid with sulfuric acid, of fuming nitric acid (d. > 1.4) and of mixtures with fuming sulfuric acid increases the intensity of the nitration process. Thus, whereas, concentrated nitric acid will give only the mononitro compound, a mixture with concentrated sulfuric acid will form *m*-dinitrobenzene (with traces of the *o*- and *p*-isomers). Mixtures of the two fuming acids give finally 1,3,5-trinitrobenzene which is resistant to further nitration.

Nitrobenzene, Oil of Mirbane, Essence of Mirbane, $C_6H_5NO_2$, m. 5°, b. 208°, is a very pale yellow liquid of the odor of bitter almonds. It is made by the nitration of benzene with nitrating acid, mixed acid, a mixture of concentrated nitric and sulfuric acid. On a large scale, very careful cooling is necessary because of the exothermic reaction. On the laboratory scale the relation of surface to volume of the small flasks used readily gives the necessary cooling. The value of the parachor for nitro benzene indicates that the nitro group

[8] Woods. *Brit. J. Ex. Path.* 21, 74 (1940).
[9] Bell, Roblin. *J. Am. Chem. Soc.* 64, 2905 (1942).
[10] Faget. *U. S. Pub. Health Repts.* 58, 1729 (1943).

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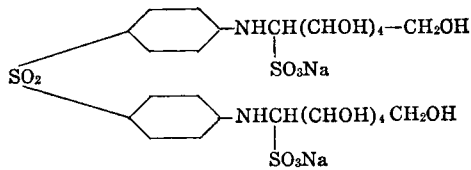

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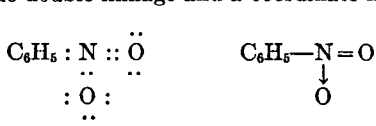
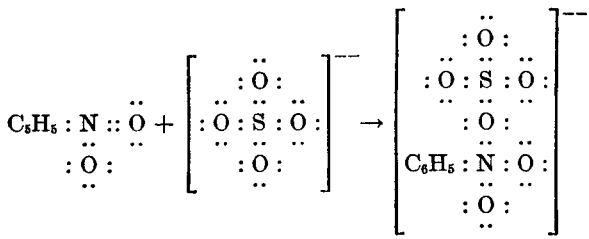
contains only one true double linkage and a coordinate linkage.



Nitrobenzene forms a crystalline "sulfate," $PhNO_2 . H_2SO_4$, m. 11°, which can be crystallized from ether.[1] The formation of such a product may be pictured electronically

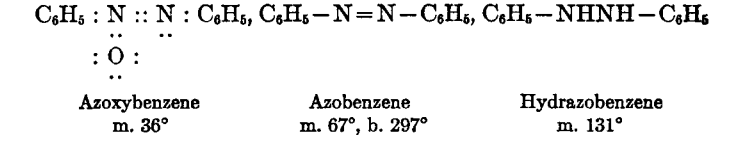


It would thus be analogous to the nitric acid compound of a sulfoxide. The C—N linkage in nitrobenzene is very stable. No reaction is known by which it can be split without complete decomposition of the molecule.

Reduction of nitrobenzene gives a variety of products. With acids and active metals, the oxygen atoms are removed and replaced by 2 H to give aniline

$$C_6H_5NO_2 + 6\,[H] \rightarrow 2\,H_2O + C_6H_5{-}NH_2$$

Under other conditions only one O is removed and replaced by 2 H to give phenylhydroxylamine, C_6H_5NHOH, which readily undergoes rearrangement to *p*-aminophenol, $HOC_6H_4NH_2$. Various alkaline reductions give bimolecular reduction products.



Azoxybenzene	Azobenzene	Hydrazobenzene
m. 36°	m. 67°, b. 297°	m. 131°

The older formulas for azoxybenzene, containing the O attached to both N atoms or the O attached by a double bond to one N, are less accurate than the unsymmetrical formula with coordinately linked oxygen. According to this formulation, azoxybenzene is related to the amine oxides.

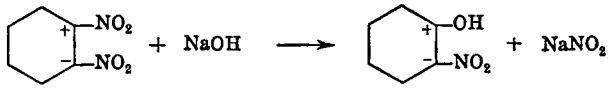
All three bimolecular reduction products of nitrobenzene give aniline on vigorous acid reduction.

[1] *Ann. Rep. Chem. Soc.* (London) **1923**, 94.

Nitrobenzene gives the *Piria Reaction* when heated with a sulfite and then with mineral acid to give aniline and sulfanilic acid.[2] This reaction is given by practically all aromatic nitro compounds.

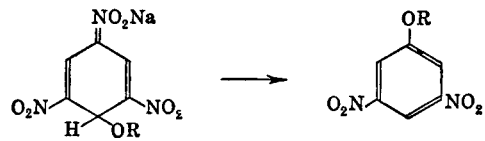
m-Dinitrobenzene, m. 90.8°, b. 303°, is readily obtained by nitrating nitrobenzene. Each of the nitro groups shows the properties of that in nitrobenzene. The H atoms which are *o-* or *o,p-* to the two nitro groups are more sensitive to oxidation than those in benzene. Thus potassium ferricyanide converts *m*-dinitrobenzene to 2,6- and 2,4-dinitrophenols. This reactivity of the *o,p*-H atoms does not extend to ordinary substitution reactions which take place with difficulty and then mainly in the *m*-position.

o-Dinitrobenzene, m. 118°, b. 319°, and *p-dinitrobenzene,* m. 172°, b. 299°, are formed in only minute amounts by direct nitration. They are prepared from the corresponding nitroanilines by replacing the NH_2 by NO_2 on diazotization and treatment with excess nitrous acid and Cu_2O. A nitro group in the *o-* or *p*-position to another nitro group does not exhibit the stable C—N linkage found in nitro- and *m*-dinitrobenzenes. Treatment with alkali or ammonia replaces one of the NO_2 groups by OH or NH_2 respectively. This behavior has been regarded as indicating an alternating polarity in the benzene carbon atoms.[3]



The activating effect of a nitro group on another nitro group in the *o-* and *p*-position but not on one in the *m*-position is similar to the effect on H and halogen atoms in these positions.

1,3,5-Trinitrobenzene, *sym*-trinitrobenzene, m. 122°, can be made directly by vigorous nitration of the *m*-dinitro compound with a mixture of fuming nitric and sulfuric acids but is more conveniently prepared from trinitrotoluene.[4] It resembles the dinitro compound, including the ease of oxidation of the H atoms each of which is *o,o,p-* to nitro groups. Substitution reactions are unknown, however. While one nitro group does not activate another one in the *m*-position, two such groups have an activating effect on a third, as is shown by the action of *sym*-trinitrobenzene with sodium alcoholates to give replacement of one NO_2 by alkoxyl. The intermediate product is a highly colored compound probably of quinoid structure.



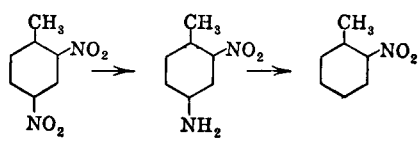
[2] Hunter. *J. Am. Chem. Soc.*, **53**, 1432 (1931).
[3] Fry. *J. Am. Chem. Soc.* **36**, 248 (1914).
[4] "Org. Syntheses."

Trinitrobenzene forms stable molecular addition products with various aromatic and unsaturated hydrocarbons. These compounds often have melting points higher than either component. Thus the compounds with naphthalene (m. 80°) and with acenaphthene (m. 97°) melt at 152° and 168° respectively. The compound with 2 C_6H_6 melts at 71°.

1,2,4-Trinitrobenzene, *asym*-trinitrobenzene, m. 57°, is made from dinitroaniline. The 1-NO_2 is readily replaced by OH or NH_2 because of the activating influence of the *o*- and *p*-NO_2 groups.

Nitrotoluenes are obtained by nitrating toluene. As is usual, the *o*- and *p*-H atoms in toluene are more easily replaced than the H atoms in benzene. Nitration of toluene under mild conditions gives mainly *o*- and *p*-NO_2-toluenes with less than 5% *m*-. The relative proportions of *o*- and *p*- depend somewhat on conditions although the *o*-compound usually predominates. On a large scale, the finished products are obtained in the ratio 61:35.5:3.5 for *o*-, *p*- and *m*-. More vigorous nitration gives 2,4-dinitrotoluene and 2,4,6-trinitrotoluene with only small amounts of isomers.

***o*-Nitrotoluene,** $CH_3C_6H_4NO_2$, m. −10°, n. 218°, is separated from its isomers by means of alternate freezing and distillation, thus taking advantage of its lower freezing and boiling points. It can be freed from traces of the *p*-compound by long boiling with alcoholic NaOH which reduces the latter. On acidification and steam distillation, the pure *o*-compound distills. The pure *o*-compound can also be made from 2,4-dinitrotoluene by partial reduction to convert the *p*-NO_2 group to amino which can be replaced by H by diazotization in presence of alcohol.

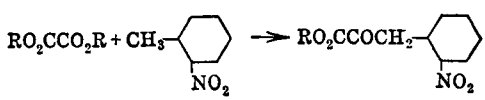


Its chemical properties resemble those of nitrobenzene except that the methyl group may react like that in nitromethane. This is an important example of Vinylogy.

$$CH_3-NO_2,\ CH_3-C=C-NO_2,\ CH_3-C=C-C=C-NO_2.$$

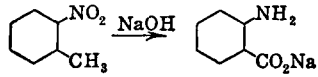
The last grouping is found in *p*-nitrotoluene, in which the methyl hydrogens also show alpha-H reactions.

o-Nitrotoluene reacts with ethyl oxalate and sodium ethylate to give a Claisen or aldol type condensation.

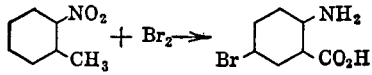


On treatment with alkali, *o*-nitrotoluene undergoes internal oxidation and

reduction to give *o*-aminobenzoic acid.

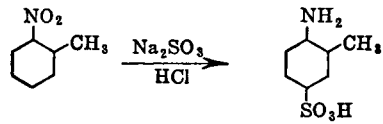


A similar process takes place when bromine is dropped into *o*-nitrotoluene heated to 170°.



In spite of these internal oxidations of the methyl group it is not as easily converted to carboxyl by ordinary oxidizing agents as in the *m*- and *p*-isomers. Thus dilute nitric acid and chromic acid mixture do not give *o*-nitrobenzoic acid but permanganate does.

o-Nitrotoluene gives a 34% yield of 2-toluidine-5-sulfonic acid by the Piria reaction.

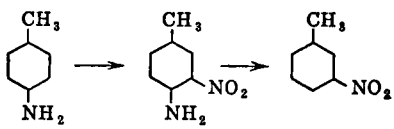


***m*-Nitrotoluene,** m. 16°, b. 230°, is formed in small amounts in the commercial nitration of toluene (4%). In order to improve the quality of the *o*- and *p*-compounds it is removed and is available in about 90% purity. The impurities can be eliminated by their reaction with Et oxalate and NaOEt (p. 636). *m*-Nitrotoluene does not react because the groupings

$$CH_3-C-C=C-NO_2$$

and $CH_3-C=C-C-NO_2$ give no vinylogy effect. The reaction mixture is acidified and steam distilled. The unchanged pure *m*-nitrotoluene distills over leaving the substituted pyruvic esters behind.

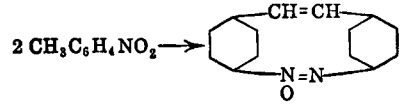
m-Nitrotoluene can be synthesized from *p*-toluidine by nitration and elimination of the NH_2 group. The nitro group enters almost entirely *o*- to the NH_2 group because of its greater orienting influence.



***p*-Nitrotoluene,** m. 51°, b. 234°, is readily separated from the nitration mixture obtained from toluene. Its reactions are like those of the *o*-isomer. The H atoms *o*- to the methyl are *m*- to the nitro group and are consequently more active than the H atoms in nitrobenzene or in *m*-nitrotoluene. Boiling with dilute nitric acid oxidizes the methyl group to form *p*-nitrobenzoic acid.

A similar reaction takes place with the *m*-compound but not with the *o*-compound.

Hot aqueous KOH produces an oxidation-reduction process with *p*-nitrotoluene which involves two molecules with the possible formation of a 12-member ring.[5]



2,4-Dinitrotoluene, m. 70°, is readily obtained by nitrating toluene or the *o*- or *p*-mononitro derivatives. It gives the expected reactions and, in addition, reacts readily with aldehydes, the methyl H atoms behaving as α-H.[5a]

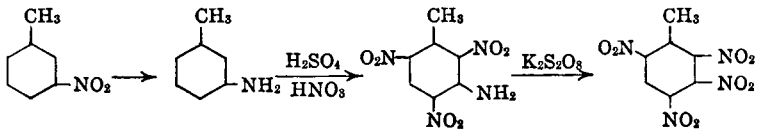
$$CH_3C_6H_3(NO_2)_2 + RCHO \rightarrow H_2O + RCH{=}CHC_6H_3(NO_2)_2$$

The reactivity of the methyl group is like that found in crotonic aldehyde (p. 225).

2,4,6-Trinitrotoluene, T.N.T., Trotyl, Tolite, m. 81.5°, obtained by exhaustive nitration of toluene, is an important high explosive. It is relatively safe because of its difficulty of detonation. In fact it will burn without exploding. Attempts to further nitrate trinitrotoluene give oxidation of the methyl to carboxyl and splitting to give tetranitromethane.[5b] Oxidation of T.N.T. with chromic acid mixture converts the methyl to carboxyl (OS). The resulting trinitrobenzoic acid loses CO_2 on merely boiling with water and gives *sym*-trinitrobenzene (OS). The isomers of T.N.T. have been carefully studied because their presence decreases the stability of the explosive. Thus while T.N.T. is stable to moisture, an isomer having two nitro groups ortho to each other would react with moisture to give nitrous acid and a nitrated cresol. The absence of such isomers is assured by careful insistence on the correct melting point for T.N.T.

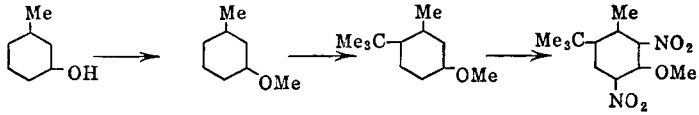
All six possible trinitrotoluenes have been made.[5c]

2,3,4,6-Tetranitrotoluene has been made as an explosive but has the disadvantage of lower stability both to shock and to the action of water. The fourth nitro group cannot be introduced by nitration but is obtained by oxidizing an amino group with a persulfate. The steps for its preparation follow.



[5] *Ann. Rep. Chem. Soc.* (London) 1917, 117.
[5a] *Ann. Rep. Chem. Soc.* (London) 1904, 98.
[5b] *ibid.* 1914, 99.
[5c] *ibid.* 1915, 88.

Artificial musks. Several nitro groups in an aromatic compound containing a tertiary butyl group give an odor resembling natural musk. Toluene or xylene treated with an isobutyl or tertiary butyl halide and aluminum chloride gives considerable amounts of *m-t*-butyl compounds. Three nitro groups can be introduced into these to give *toluene musk* and *xylene musk*. Musk Ambrette is made from *m*-cresol.



B. Aryl Substituted Aliphatic Nitro Compounds

Phenylnitromethane, ω-nitrotoluene, $C_6H_5CH_2NO_2$, b. 226°,

$$C_6H_5CH = NO_2H,$$

m. 84°, can be made from toluene in several ways.

1. Heating with dilute nitric acid in a sealed tube.
2. Treatment of benzyl chloride with silver nitrite.
3. From benzyl cyanide, an alkyl nitrate and NaOEt. While this appears the most difficult method, it is actually the best. The conversion of toluene to benzyl chloride and the latter to the cyanide gives no trouble

$$C_6H_5CH_2CN + EtONO_2 + EtONa \rightarrow C_6H_5C(CN)=NO_2Na$$

Hydrolysis of the nitrile group and elimination of the resulting carboxyl proceed smoothly.

$$C_6H_5C(CN)=NO_2Na \xrightarrow{NaOH} C_6H_5C(CO_2Na)=NO_2Na \xrightarrow{acid} CO_2 + C_6H_5CH_2NO_2$$

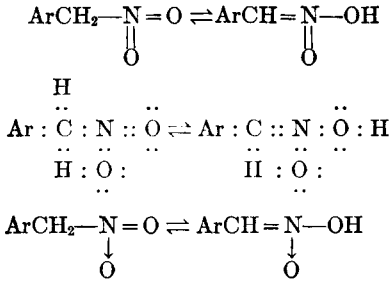
The structure is proved by reduction to benzylamine, $C_6H_5CH_2NH_2$. The Na compound on heating gives stilbene.[6]

$$2\ PhCH=NO_2Na \rightarrow PhCH=CHPh + 2\ NaNO_2$$

Phenylnitromethane is a typical pseudo acid. It dissolves slowly in alkali to give a true salt. Acidification of the salt gives the solid *acinitro* form which is rapidly soluble in bases and gives a conducting solution in water, whereas the liquid form does not. On standing, the solid acinitro form changes to the liquid true nitro compound. The former gives a color with ferric chloride while the latter does not. The structures of the two forms may be represented

[6] *Ann. Rep. Chem. Soc.* (London) 1905, 103.

in a variety of ways.[7]



Aromatic nitro compounds with unsaturated side chains may be illustrated by the nitrostyrenes.

ω-Nitrostyrene, $C_6H_5CH=CHNO_2$, is obtained by the direct action of styrene with nitric acid by a process resembling the action of chlorine with isobutylene (p. 40). *o-Nitrostyrene,* $O_2NC_6H_4CH=CH_2$, and its isomers are obtained from the corresponding nitrocinnamic acids by adding HBr and hydrolyzing with elimination of CO_2. *o-Nitrophenylacetylene,*

$$O_2NC_6H_4C\equiv CH,$$

and its isomers are similarly obtained by adding Br_2 to the cinnamic acid, removing 2 HBr and decarboxylating.

C. Nitro Compounds of the Aromatic Halides

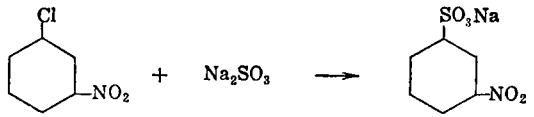
o- and *p*-Nitro-halogen-benzenes, in a ratio of about 3:7, are obtained by nitrating the phenyl halides. The isomers are readily separated because of the higher melting points and lower solubilities of the *p*-isomers. The *o*-isomer is obtained in a eutectic mixture with the *p*-compound. The mixture can be separated by alternate distillation and freezing or recrystallization. Further nitration gives 2,4- and 2,4,6-polynitro compounds. The halogen atoms which are ortho or para to a nitro group readily give metathetical reactions with reagents like bases, ammonia and alkali sulfides to give nitrophenols, nitroanilines and nitrophenyl sulfides and disulfides. This reactivity is in sharp contrast to the usual inactivity of aromatic halides (p. 619). The presence of two or three nitro groups in *o-* and *p*-positions further increases the activity of the halogen. Thus 2,4,6-trinitrochlorobenzene acts as an acid chloride and is called *picryl chloride.* Picryl iodide is a stable yellow crystalline product obtainable from the chloride and KI.[8]

2,4-Dinitrochlorobenzene is an important intermediate for various *sulfur dyes.* It is also used in making picric acid, first being hydrolyzed to dinitrophenol which can be easily converted to the trinitro compound.

[7] *Ann. Rep. Chem. Soc.* (London) **1927**, 107.
[8] Hepp. *Ann.* **215**, 361 (1882).

A single nitro group will not render an aromatic halogen atom active enough to react with sodium malonic ester. If the positions *o*- and *p*- to the halogen contain *also* a MeCO or CN grouping, then reaction is possible.

m-Nitro-halogen-benzenes may be obtained by the vigorous chlorination or bromination of nitrobenzene. A more convenient method, suitable also for the iodo compound, is the replacement of the amino group in *m*-nitroaniline which is easily made by the partial reduction of *m*-dinitrobenzene or by the nitration of aniline in conc. sulfuric acid. The halogen meta to the nitro group is not activated as is that ortho or para to such a group. An exception is found in the action with alkali sulfite solutions which takes place with the *m*- as well as with the *o*- and *p*-compounds.[9]



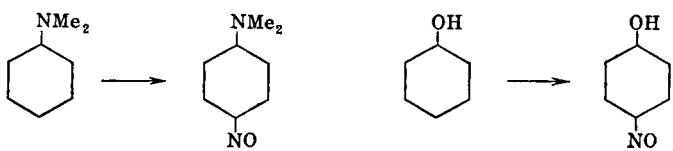
D. Nitroso and Hydroxylamino Derivatives of Aromatic Hydrocarbons

Nitrosobenzene, C_6H_5NO, m. 68°, is a colorless crystalline substance which gives green solutions. The solid is a dimer while the colored solutions contain the monomer. Nitrosobenzene is most readily obtained by the oxidation of phenylhydroxylamine, C_6H_5NHOH, by ferric chloride or chromic acid solution. It can also be made by the action of nitrosyl chloride, NOCl, on diphenylmercury. Its structure is indicated by its reduction to aniline and its oxidation to nitrobenzene. It condenses with amines much as carbonyl compounds do but the intermediate addition compound of the aldol type loses water spontaneously to give an azo compound.

$$C_6H_5N{=}O + H_2NC_6H_5 \rightarrow [C_6H_5N(OH)NHC_6H_5] \rightarrow C_6H_5N{=}NC_6H_5$$

In CS_2 solution it is bimolecular. In such a solution Br_2 or HNO_3 gives *para* substitution.[10] *p*-Bromonitrosobenzene has a more reactive halogen than the Cl in picryl chloride.

Nitroso compounds of aromatic substances containing activating groups like dialkylamino and hydroxyl can be made directly by treatment with nitrous acid.



[9] Sprung. *J. Am. Chem. Soc.* 52, 1650 (1930).
[10] Ingold. *J. Chem. Soc.* 1925, 513.

β-Phenylhydroxylamine, or simply phenylhydroxylamine, C_6H_5NHOH, m. 81°, is made from nitrobenzene by neutral reduction either catalytically or by Zn dust and water in presence of a salt like $CaCl_2$. Oxidation gives nitrosobenzene or azoxybenzene, a product of the action of nitrosobenzene with unchanged material. Fehling's solution oxidizes phenylhydroxylamine. It is a strong base in contrast to aniline. Conc. H_2SO_4 converts it to the sulfate of *p*-aminophenol, the parent substance of the photographic developer Metol. Air and mild oxidizing agents like Fehling's solution convert it to azoxybenzene while chromic acid mixture gives nitrosobenzene.

A test for an aromatic nitro compound is treatment with Zn dust and water to give a phenylhydroxylamine which is capable of reducing Fehling's solution.

VII. ARYLAMINES

A. Phenyl Amine and its Homologs

These are known in great numbers and variety and are of the greatest practical and theoretical importance. Those with the NH_2 in the side chain are made by the ordinary aliphatic reactions. The true aromatic amines with the NH_2 attached directly to an aromatic nucleus are made in various ways.

1. By reduction of the corresponding nitro compound. A great variety of reducing agents may be used including active metals and acids, stannous chloride, ammonium sulfide and ferrous hydroxide.

2. By reaction of a chloro compound with NH_3 either alone or with catalysts such as copper salts. Chloro derivatives of aromatic hydrocarbons require temperatures around 200° but the presence of nitro and similar groups lowers the reaction temperature to around 100°.

3. By the reaction of phenols with NH_3 and zinc chloride at about 300°.

4. By Hofmann's amide reaction with a hypohalite or a halogen and a base.

The aromatic primary amines are extraordinarily weak bases. Thus the basic dissociation constants for $C_6H_5NH_2$, CH_3NH_2 and NH_3 in water solution are about 3×10^{-10}, 5×10^{-4} and 2×10^{-5} respectively.

Aniline, aminobenzene, phenylamine, $C_6H_5NH_2$, colorless, m. 6°, b. 182°, is typical of the aromatic amines. It was discovered by various workers and appears in the early literature as "Krystallin," "cyanol" ("Kyanol"), and "benzidam." Aniline is prepared commercially in two ways:

1. By reduction of nitrobenzene with iron and water and a small amount of acid. The cycle of changes is probably

$$2\ HCl + Fe \rightarrow 2\ [H] + FeCl_2$$

$$6\ [H] + C_6H_5NO_2 \rightarrow C_6H_5NH_2 + 2\ H_2O$$

$$6\ FeCl_2 + 16\ H_2O + C_6H_5NO_2 \rightarrow C_6H_5NH_2 + 6\ Fe(OH)_3 + 12\ HCl$$

The net result is expressed as follows, the HCl behaving in a sense as a catalyst.

$$2\ Fe + 4\ H_2O + C_6H_5NO_2 \rightarrow C_6H_5NH_2 + 2\ Fe(OH)_3$$

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The net result is expressed as follows, the HCl behaving in a sense as a catalyst.

$$2\ Fe + 4\ H_2O + C_6H_5NO_2 \rightarrow C_6H_5NH_2 + 2\ Fe(OH)_3$$

2. By heating ammonia and chlorobenzene at about 200° with a mixture of cuprous oxide and chloride. The latter is the catalyst and the former prevents the formation of NH_4Cl which tends to reverse the reaction. The net reaction is as follows:

$$2\ C_6H_5Cl + 2\ NH_3 + Cu_2O \rightarrow 2\ C_6H_5NH_2 + Cu_2Cl_2 + H_2O$$

Without the Cu_2O the reaction would be

$$C_6H_5Cl + 2\ NH_3 \leftrightharpoons C_6H_5NH_2 + NH_4Cl$$

The cuprous chloride is treated with enough alkali to change most of it to the oxide and the mixture is used for the next charge. Thus the overall change is

$$C_6H_5Cl + NH_3 + NaOH \rightarrow C_6H_5NH_2 + NaCl + H_2O$$

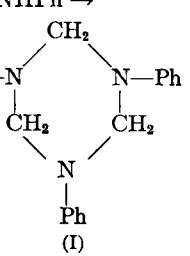
Properties. The properties of aniline are characteristic of aromatic amines in general. It is a weaker base than ammonia. Its salts readily hydrolyze. The temperatures at which it is completely miscible with various hydrocarbons are characteristic of the latter. Thus the C.T.S. (critical solution temperatures) for aniline of the heptanes vary from 66.3° for triethylmethane to 78.8° for diisopropylmethane.[1] The C.T.S. for cycloparaffins are lower than for the open chain compounds, the values for cyclohexane being 31°, for Me-cyclohexane 41° and for decahydronaphthalene 34°. The values for olefins are lower than for saturated compounds, 26° for octene-1, 68° for cetene and −20° for cyclohexene. The values for aromatic compounds are too low to be useful.

Reactions. Aniline *resembles the aliphatic primary amines* in many ways. It forms crystalline salts with strong acids, substituted ammonium salts of chloroauric and chloroplatinic acids, and double salts with $ZnCl_2$ $HgCl_2$ etc. The H atoms of the NH_2 are replaceable by alkali metals. They are also replaceable by halogens on treatment with hypohalous acids. It adds alkyl halides and can finally be converted to a quaternary ammonium compound. It reacts with aldehydes. With formaldehyde it gives crystalline anhydroformaldehyde-aniline, m. 141° (I). This action is another example of a process which continues until a stable 6-ring can be formed.

$$PhNH_2 + CH_2O \rightarrow PhNHCH_2OH \rightarrow PhNHCH_2NHPh \rightarrow$$

$$PhNHCH_2N(Ph)CH_2OH \rightarrow PhNHCH_2N(Ph)CH_2NHPh \rightarrow$$

$$PhNHCH_2N(Ph)CH_2N(Ph)CH_2OH \rightarrow$$



(I)

[1] Edgar. *J. Am. Chem. Soc.* **51**, 1540 (1929).

With chloroform and alcoholic KOH aniline gives the carbylamine test forming phenyl isocyanide, C_6H_5NC, of characteristic odor. With CS_2 it forms a thiourea, *thiocarbanilide*, which reacts with acids to give *phenyl mustard oil*. These properties are illustrated by the following formulas and equations:

$ArNH_3Cl$.	$(ArNH_3)_2SO_4$.	$(ArNH_3)AuCl_4$.	$(ArNH_3)_2PtCl_4$.
$(ArNH_2)_2.HgCl_2$.	$ArNHNa$.	$ArNHBr$.	
$ArMeNH_2I$.	$ArMe_2NHI$.	$ArMe_3NI$.	
$(ArNH)_2CHR$.	$ArN=CHAr$ (Schiff's bases).		

The latter occur as amorphous polymers.

$$ArNH_2 + CHCl_3 + 3\ KOH \rightarrow ArNC + 3\ KCl + 3\ H_2O$$
$$2\ ArNH_2 + CS_2 \rightarrow (ArNH)_2CS + H_2S$$
$$(ArNH)_2CS + HCl \rightarrow ArNCS + ArNH_3Cl$$

Aniline reacts with an excess of phosgene to give *phenylisocyanate*, C_6H_5NCO.

$$PhNH_2 + COCl_2 \rightarrow PhNCO + 2\ HCl$$

Phenylisocyanate is valuable for the identification of alcohols and primary and secondary amines by converting them to phenyl urethans and substituted ureas of definite melting points.

$$PhNCO + ROH \rightarrow PhNHCO_2R$$
$$PhNCO + RNH_2 \rightarrow PhNHCONHR$$
$$PhNCO + R_2NH \rightarrow PhNHCONR_2$$

Naphthylisocyanate, made from naphthylamine, is similarly used. An excess of aniline with phosgene gives *sym*-diphenylurea.

The presence of an aromatic ring in aniline causes it to *differ from aliphatic amines*:

1. It is much weaker as a base. This is presumably related to the attachment of the NH_2 to an unsaturated system. The salts of aniline are more readily hydrolyzed than those of the aliphatic amines or NH_3.

2. Its oxidation is much more complex, resulting in azobenzene, aniline black,[2] *p*-aminophenol, phenols, quinones, and various resinous products. The practically important products are quinone, $O=C_6H_4=O$, formed by vigorous oxidation and aniline black,

$$C_6H_5N=(C_6H_4=N-C_6H_4-N)_3=C_6H_4=NH,$$

formed under milder conditions.[3] Aniline ordinarily darkens rapidly on standing, due to oxidation. This can be retarded if the aniline is entirely free from nitrobenzene and is stored in aluminum containers.

[2] *Ann. Rep. Chem. Soc.* (London) **1909**, 99.
[3] Green. *Chem. Zentr.* **1914**, I, 535.

3. Substitution readily takes place in the *o*- and *p*-positions. This may take place by an initial attack on the nitrogen atom. Thus bromination probably involves the steps

$$C_6H_5NH_2 \rightarrow C_6H_5NHBr \rightarrow BrC_6H_4NH_2$$

The migration from N to the ring always takes place in the *p*- or *o*-position. No *m*-compound is formed. The migration may be intra- or intermolecular. The ready substitutions include nitration, sulfonation, halogenation and mercuration.

A peculiar type of substitution is involved in the rearrangement of an alkyl group from N to the *p*- or *o*-position on heating the hydrochlorides of N-alkyl anilines.

An exception to the usual *o*- and *p*-substitution of aniline is its nitration in conc. sulfuric acid solution to give a considerable amount of *meta*-nitroaniline.[4]

4. The most important difference is in its action with nitrous acid. Whereas aliphatic primary amines react with nitrous acid and HCl to give nitrogen and alcohols, chlorides and olefins both without and with rearrangement, the aromatic primary amines give *diazonium salts* which are moderately stable and can be used in a great variety of reactions. This process of *diazotization* is of great practical and theoretical importance.

$$ArNH_2 + HCl + HNO_2 \rightarrow ArN_2Cl + 2\ H_2O$$

The arylammonium ion apparently reacts with nitrous acid with the elimination of two molecules of water to form an aryldiazonium ion.

$$[ArNH_3]^+ + HONO \rightarrow 2\ H_2O + [ArN{\equiv}N]^+$$

The latter ion probably has an electronic structure resembling those of the cyanide ion and of carbon monoxide, nitrogen and acetylene (p. 409).

$$[Ar{:}\overset{\cdot\cdot}{N}{:}\overset{\cdot\cdot}{N}{:}]^+$$

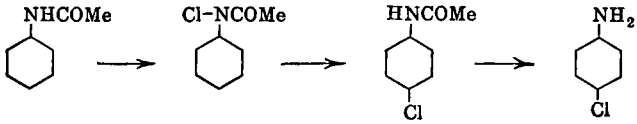
The solution of benzene diazonium chloride is stable while cold.

5. Aniline readily undergoes catalytic hydrogenation to form cyclohexylamine.[5]

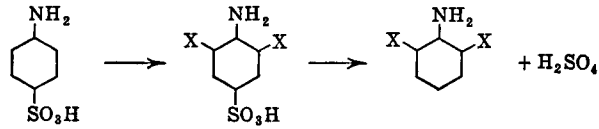
Halogenated anilines. The amino group activates the *o*- and *p*-H atoms to a high degree. The treatment of aniline with chlorine in presence of water gives oxidation products due to the action of hypochlorous acid. Treatment in solvents, like glacial acetic acid, converts aniline to *sym*-trichloroaniline. To introduce only one chlorine, it is necessary to lower the activating effect of the amino group by acetylation. Treatment with chlorine then gives *p*-chloroacetanilide with very little of the ortho isomer. The first step is probably the formation of N-chloroacetanilide which rearranges in presence of acid to

[4] *Ann. Rep. Chem. Soc.* (London) 1915, 89.
[5] *Ann. Rep. Chem. Soc.* (London) 1920, 87.

the *p*-compound. Vigorous hydrolysis of the anilide gives *p*-chloroaniline, m. 71°, b. 231°.



It is also readily obtained by the acid reduction of *p*-nitrochlorobenzene. Its *o*- and *m*-isomers are similarly prepared from the nitro compounds. The presence of the halogen decreases the basic properties of the amine. The bromoanilines are obtained similarly. *sym-Tribromoaniline*, m. 119°, is readily obtained by passing air through bromine and into an aqueous solution of aniline hydrochloride. It can also be made by simply mixing solutions of bromine and aniline hydrochloride. Its great insolubility was utilized in the first method for extracting bromine from sea water for use in Ethyl fluid in gasoline (p. 88). The sea water was treated with amounts of aniline and chlorine corresponding to the bromine content. Insoluble Br_3-aniline was precipitated, one pound being obtained from about 2500 gallons of sea water. Now the liberated bromine is simply blown out by means of air and absorbed in a carbonate solution. Monobromoaniline is obtained like the monochloro compound. *Triiodoaniline*, m. 185°, is made by using iodine monochloride, ICl, much as bromine is used. 2,4-Dihalogenated anilines are made by the halogenation of acetanilide. 2,6-Dihalogenated anilines are made by the careful halogenation of sulfanilic acid followed by the removal of the sulfonic acid group by steam at about 200°.



If excess of halogen is used, the sulfonic acid group is replaced by halogen.

It should be remembered that halogenated anilines are even more dangerously toxic than aniline itself.

Nitroanilines. The direct treatment of aniline with nitric acid results in a complex mixture of mono-, di- and tri-nitro-compounds together with oxidation products. Similar treatment of acetanilide, however, gives mainly the *p*-nitro compound with very little of the *o*-compound. Hydrolysis gives *p*-nitroaniline. Nitration of aniline in concentrated sulfuric acid gives mainly *m*-nitroaniline.

Nitroanilines are better prepared from nitro derivatives than from aniline, the *o*- and *p* compounds by treating *o*- and *p*-nitrochlorobenzenes with NH_3 and the *m*-compound by partial reduction of *m*-dinitrobenzene.

In the nitroanilines, the amino group has practically completely lost its basic nature. The nitro group has the same effect on the *o*- and *p*-positions

as in the chloro compounds. Thus *o*- and *p*-nitroanilines can readily be hydrolyzed to the nitrophenols by bases. *sym-Trinitroaniline, picramide*, $C_6H_2(NH_2)(NO_2)_3$, m. 188°, is readily obtained from the chloro compound and NH_3. Hydrolysis gives picric acid, trinitrophenol. 2,3,4,6-Tetranitroaniline, the explosive T.N.A., is made from *m*-nitroaniline with mixed sulfuric and nitric acids.

***o*-, *m*-, and *p*-Toluidines,** aminotoluenes, $CH_3C_6H_4NH_2$, b. 199.8°, 202.9°, and 200.3° respectively,[6] are obtained by reducing the nitrotoluenes. *p*-Toluidine melts at 43°, and the three acetyl derivatives, the *acetotoluidides*, melt at 110°, 65° and 153° respectively. The basic properties of the NH_2 group are not greatly changed by the methyl group in the ring. The acetotoluidides can be oxidized to acetaminobenzoic acids.

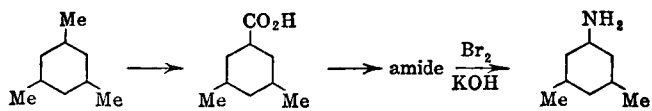
All six possible *xylidines*, aminoxylenes or C-dimethylanilines,

$$(CH_3)_2C_6H_3NH_2,$$

are known. They are obtained from the corresponding nitro compounds. Names, melting points and boiling points are as follows:

(1) 1,2,3-xylidine, *v*-*o*-xylidine, liq., 223°; (2) 1,2,4-xylidine, *u*-*o*-xylidine, 49°, 226°; (3) 1,3,2-xylidine, *v*-*m*-xylidine, liq., 216°; (4) 1,3,4-xylidine, *u*-*m*-xylidine, liq., 212°; (5) 1,3,5-xylidine, *s*-*m*-xylidine, liq., 220°; 1,4,2-xylidine, *p*-xylidine, 15°, 213°. The 1,3,4-compound is made by rearranging N-Me_2-aniline by heat.

Commercial xylidine contains all the isomers except the 1,3,5-compound, which can be obtained from 1,3,5-xylenol with ammonium chloride and pressure at 350–360°.[7] It can also be obtained by the Hofmann reaction on the amide of mesitylenic acid.



Mesidine and pseudocumidine are 2,4,6- and 2,4,5-Me_3-anilines respectively. Higher anilines are tetramethylaniline (isoduridine), m. 64°, b. 260°, and pentamethylaniline, m. 151°, b. 278°.[8]

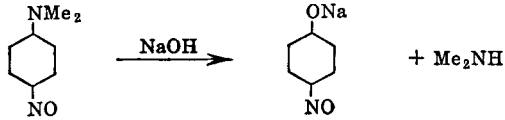
Aromatic primary amines can be identified by means of a great variety of derivatives including the acetyl compounds and the *p*-toluene sulfonates.

B. N-Alkylanilines

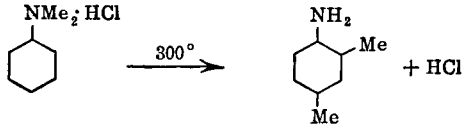
These are obtained by treating aniline with alkylating agents. Monomethylaniline and dimethylaniline are made by heating aniline, MeOH and HCl or H_2SO_4 under pressure. They cannot be separated by distillation (boil-

[6] *J. Am. Chem. Soc.* 49, 1009 (1927).
[7] *J. Soc. Chem. Ind.* 51, 283 (1932).
[8] Limpach. *Ber.* 21, 648 (1888).

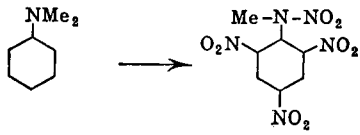
ing points 195.7°, 193.5°). The addition of a methyl would be expected to raise the boiling point by increasing the molecular weight but it also lowers the boiling point by increasing the symmetry of the molecule. They can be separated by acetylation of the monomethylaniline and distillation. Separation by acid is not possible because C_6H_5NMeAc dissolves in acid. The introduction of methyl groups decreases the basicity of the nitrogen, the basic ionization constants $\times 10^{-10}$ of $PhNH_2$, PhNHMe and $PhNMe_2$ being about 3.5, 2.6 and 2.4. The reactions of mono- and di-methylanilines are those typical of secondary and tertiary amines except that the benzene ring gives the possibility of substitution reactions. As with aniline, substitution by halogen, nitro, sulfonic and similar groups takes place readily in the *o*- and *p*-positions. Moreover a nitroso group is readily introduced. Monomethylaniline with nitrous acid gives the expected nitrosamine, PhN(NO)Me. Under the influence of alcoholic HCl, the nitroso group rearranges to the *p*-position to give $ON-C_6H_4-NHMe$. When dimethylaniline is treated with nitrous acid, *p*-nitrosodimethylaniline, m. 85°, results. The NO group can be oxidized to NO_2 or reduced to NH_2. Moreover the NO group in the *p*-position activates the dimethylamino group so that boiling with bases gives *p*-nitrosophenol and dimethylamine.



This reaction is useful in making pure higher secondary amines such as di-*n*-butylamine from N-di-*n*-butylaniline. The activity of the *p*-H in dimethylaniline is also shown by its easy condensation with phosgene to give Michler's ketone, $(Me_2NC_6H_4)_2CO$, an important dye intermediate, and with aromatic aldehydes to give triphenylmethane dyes such as Malachite Green. Further evidence of the activity of the ring is shown in the action of heat on the hydrochlorides of the methylanilines, methyl groups migrating to *p*- and *o*-positions. This process is used commercially to make 2,4-xylidine.



Vigorous nitration of dimethylaniline in presence of H_2SO_4 gives N-Me-2,4,6,N-tetranitroaniline, the explosive *Tetryl*.



Diethylaniline, $C_6H_5N(C_2H_5)_2$, b. 216°, prepared from aniline and EtBr, is used for certain rhodamine dyes.

Higher N-alkylanilines are obtained by means of alcohols or alkyl halides. The possibility of rearrangement of the reagents should be kept in mind. The migration of a higher alkyl group to the *p*-position may involve rearrangement within the group. Thus N-isoamylaniline on heating with HCl gives *p-t*-amylaniline hydrochloride, whereas heating with $CdSO_4$ as a catalyst gives *p*-isoamylaniline.

Benzylaniline, $C_6H_5NHCH_2C_6H_5$, m. 38°, b. 306°, readily obtained from aniline and benzyl chloride, is an important dye intermediate as is also *methylbenzylaniline,* $C_6H_5N(CH_3)CH_2C_6H_5$, m. 9°, b. 306°.

Quaternary ammonium compounds of the type $(ArNR_3)X$ are obtainable if the alkyl groups are not too complex and if the aryl group is not substituted in both ortho positions. Examples of these limitations are the inactivity of *sym*-Br_3-aniline with MeI and the fact that PhNMeEt reacts readily with MeI but $PhNMe_2$ reacts very incompletely with EtI. Correspondingly greater difficulties are obtained with larger and with branched groups.

Prostigmin is the dimethylcarbamic ester of 3-hydroxyphenyl-trimethylammonium bromide, useful in the treatment of muscle spasm (NNR).

Phenyltrimethylammonium hydroxide, $(C_6H_5NMe_3)OH$, is a colorless soluble strong base which can be made from its chloride by alcoholic NaOH with the precipitation of NaCl. Heat decomposes it to MeOH and $PhNMe_2$.

An isomer of monomethylaniline and the toluidines is *benzylamine,* $C_6H_5CH_2NH_2$, b. 185°, which is readily prepared from benzyl chloride and NH_3. The formation of secondary and tertiary amines may be avoided by using acetamide in place of ammonia.

$$PhCH_2Cl + NH_2COMe \rightarrow PhCH_2NHCOMe \xrightarrow{H_2O} PhCH_2NH_2$$

It is more basic than its isomers. The N-alkyl derivatives are still more basic. A substance apparently related to benzylamine is $PhCH_2NMe_4$, a red powder obtained by treating Me_4NCl with $PhCH_2Na$, in an attempt to prepare a "pentavalent" nitrogen organic compound. The true nature of this substance is shown by the fact that it is instantly hydrolyzed by cold water to give toluene and Me_4NOH. Thus it is merely a special quaternary ammonium salt in which the benzyl group serves as the negative ion, $(Me_4N)^+(CH_2Ph)^-$.[9]

Benzyl dialkyl amines, $PhCH_2NR_2$, with acetic anhydride give benzyl acetate and R_2NCOMe.

Benzyltrimethylammonium hydroxide, $(PhCH_2NMe_3)OH$, as would be expected, is a strong base.

Benzyl cetyl dimethyl ammonium chloride is Triton X-400.

The next homolog, *phenylethylamine,* $C_6H_5CH_2CH_2NH_2$, is formed from *phenylalanine* during the decay of certain proteins. It is also related to physiologically active substances like adrenalin, ephedrin and tyramine.

[9] Schlenk. *Ber.* **50,** 274 (1917).

Several aminopropyl benzenes have physiological activity (vasoconstrictors). Benzedrine is $PhCH_2CH(NH_2)CH_3$.

C. Acyl Arylamines

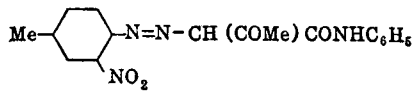
Just as ammonium acetate on heating gives acetamide, so the salts of organic acids and aryl amines readily give acyl derivatives of the amines. The resulting compounds are *anilides*, *toluidides*, *xylidides*, etc. The acetyl derivatives of most arylamines are crystalline solids of definite melting points.

Acetanilide, $C_6H_5NHCOCH_3$, m. 115°, b. 304°, is readily formed by refluxing aniline and acetic acid. In glacial acetic acid, it shows slight basic properties forming a salt with HCl. Acetanilide was formerly used in medicine as "antifebrine." Treatment with P_2S_5 gives thioacetanilide, $PhNHCSMe$. *Diacetanilide*, $PhN(COMe)_2$, m. 37°, is formed by vigorous treatment of acetanilide with acetyl chloride or acetic anhydride. Strange to say, *o*-substituted anilines give diacetyl derivatives with great ease. This is true even of *sym*-tribromoaniline in which both *o*-positions are occupied. As will be recalled, this substance has almost no basic properties.

Acetoacetanilide, $CH_3COCH_2CONHC_6H_5$, is readily available from the action of aniline with acetoacetic ester or with the dimer of ketene (acetylketene).

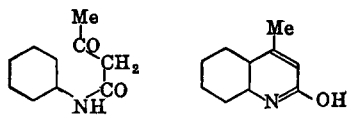
$$MeCOCH=C=O + PhNH_2 \rightarrow PhNHCOCH_2COMe$$

It is an important dye intermediate, giving the stable Hansa Yellows by action with suitable diazonium salts. These are more readily available because of lowered costs of ethyl acetate, sodium and acetoacetic ester on one hand and of acetone, ketene and its dimer on the other.

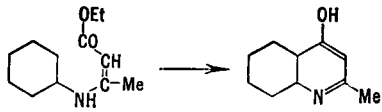


Hansa Yellow G,

Dehydration of acetoacetanilide gives ring-closure to form γ-Me-α-OH-quinoline.



At lower temperatures aniline gives a derivative of the enol form of acetoacetic ester, $PhNHC(Me)=CHCO_2Et$, β-phenylaminocrotonic ester. This on heating gives γ-OH-α-Me-quinoline.



Dibasic acids react with aniline in all possible ways. Thus oxalic acid gives *oxanilic acid*, $PhNHCOCO_2H$, m. 150°, and oxanilide, $(PhNHCO)_2$, m. 252°. Carbonic acid is related to carbanilide, diphenylurea, $(PhNH)_2CO$, m. 235°, b. 260°, and *phenylisocyanate*, phenylcarbimide, C_6H_5NCO. The former is obtained by passing phosgene, $COCl_2$, into excess aniline while the latter is formed by heating aniline hydrochloride and passing in an excess of phosgene. Phenylisocyanate is valuable for the identification of primary and secondary alcohols with which it forms crystalline *phenylurethans*, $PhNHCO_2CH_2R$ and $PhNHCO_2CHRR'$. It dehydrates tertiary alcohols with the formation of diphenylurea. *Thiocarbanilide*, diphenylthiourea, $(PhNH)_2CS$, m. 154°, a derivative of thiocarbonic acid, is readily made by boiling aniline with CS_2. With HCl it gives *phenyl mustard oil*, phenylisothiocyanate, PhNCS, b. 222°. This gives crystalline mixed thioureas with primary and secondary amines, PhNHCSNHR, PhNHCSNRR'. α-Naphthylthiourea (ANTU) is a powerful rat poison.

Phenylglycine, $C_6H_5NHCH_2CO_2H$, and related compounds are readily obtained from aniline and α-halogen acids.

D. Di- and Tri-aryl Amines

Diarylamines are obtained by heating an arylamine with its hydrochloride or that of another amine.

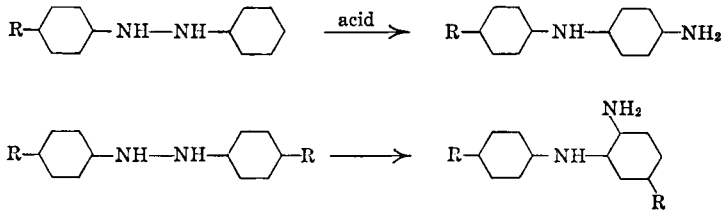
$$ArNH_2 + ArNH_3Cl \rightarrow Ar_2NH + NH_4Cl$$

Diphenylamine, $(C_6H_5)_2NH$, m. 54°, b. 302°, is an even weaker base than aniline. Its salts are hydrolyzed completely by cold water. As a secondary amine, it gives a nitrosamine, m. 66°, and an acetyl derivative, m. 103°. In sulfuric acid it gives a blue color with a trace of nitrous acid. Its nitrosamine undergoes rearrangement with alcoholic HCl to form *p*-nitrosodiphenylamine, $ON-C_6H_4NHC_6H_5$ (Fischer-Hepp Rearrangement).

Diphenylamine gives N-metal compounds more readily than aniline or ammonia.

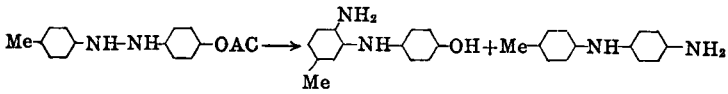
Diphenylamine is used in making certain dyes and as a stabilizer for explosives.

Many substituted diphenylamines are available by the *semidine rearrangement*. This is of two types, the para and the ortho, which can be illustrated as follows.[10]



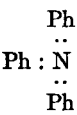
[10] *Ann. Rep. Chem. Soc.* (London) 1922, 97.

A more complex example involving both types follows.



The elimination of the OH group in the latter product is unusual (ibid.).

Triphenylamine, $(C_6H_5)_3N$, m. 127°, is made by dissolving Na in boiling diphenylamine and adding phenyl bromide. Triphenylamine does not react with acids. Evidently the electron pair cannot be combined with a proton.



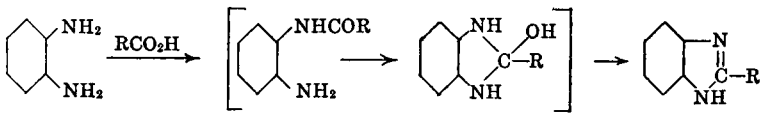
E. Aryl Diamines

These are obtained by reduction of suitable dinitro, amino nitro, amino nitroso and amino azo compounds. The *o*-, *m*-, and *p*-compounds can be considered separately.

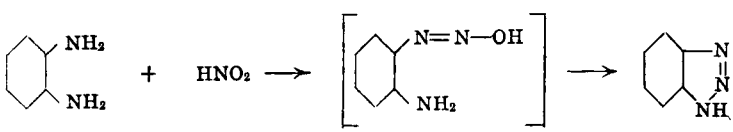
Ortho diamines are best prepared by reducing *o*-nitroanilines. Thus *o*-phenylene diamine involves the steps chlorobenzene, *o*-nitrochlorobenzene, *o*-nitroaniline and *o*-phenylene diamine. Similarly a toluylene-*o*-diamine can be made; *p*-toluidine, *p*-acet-toluidine, nitro-*p*-acet-toluidine, nitro-*p*-toluidine, toluylene-*o*-diamine.

The *o*-diamines contain active groups in the 1,4-position to each other and are consequently in a position to form 5- and 6-membered rings with suitable reagents.

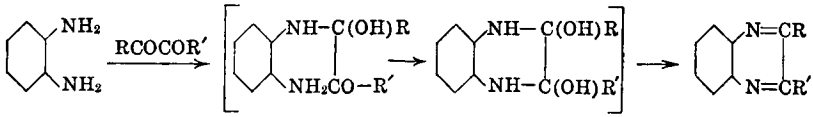
1. With organic acids they give benzimidazoles instead of giving ordinary acyl derivatives. The latter are probably first formed but then undergo ring closure.



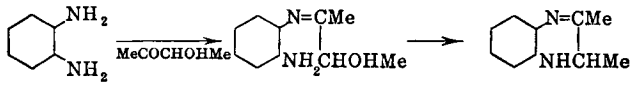
2. Nitrous acid gives azoimino (benzotriazole p. 776) compounds. The diazonium compound formed from one NH_2 group reacts with the other to give a 5-ring.



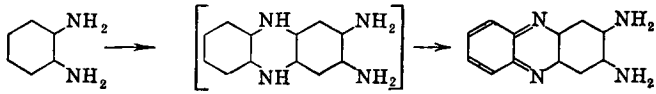
3. With α-diketones and α-ketoalcohols they give *quinoxalines* and dihydroquinoxalines respectively. Again the reaction is undoubtedly initiated at one amino group to produce a product containing active groups in the 1,6-position to each other.



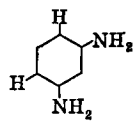
Thus glyoxal and *o*-phenylenediamine give *quinoxaline* itself. Acetoin gives dimethyldihydroquinoxaline.



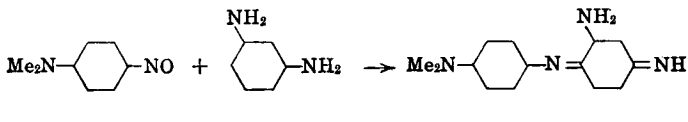
4. Careful oxidation, as with $FeCl_3$, gives diaminophenazines. The *p*-position to each NH_2 group reacts with an NH_2 from another molecule.



***m*-Diamines** are best prepared by reduction of *m*-dinitro compounds formed by direct nitration. Nitrous acid, even in traces, converts the *m*-diamines to brown dyes. The ease of this reaction is due to the activation of two of the H atoms by the *o*- and *p*-NH_2 groups.



One of these reacts with a molecule of diazotized amine. Thus, with excess of amine, the product is 3′,2,4-triaminoazobenzene. Other examples of the activation of these H atoms is the ready formation of indamines from *m*-diamines with *p*-nitrosodimethylaniline or with *p*-diamines on oxidation.



Indamines

***p*-Diamines** are made by reduction of a variety of compounds:

1. *p*-Nitroanilines obtained either by nitration of acetanilides or from *p*-nitrochloro derivatives.
2. *p*-Nitroso derivatives.
3. Amino azo compounds.

$$C_6H_5N{=}NC_6H_4NH_2 \rightarrow C_6H_5NH_2 + H_2NC_6H_4NH_2$$

Vigorous oxidation converts *p*-diamines to quinones. Oxidation of mixtures with *m*-diamines gives indamines.

VIII. DIAZONIUM SALTS AND RELATED COMPOUNDS

A. Diazonium Salts

As has been seen, primary aromatic amines can be diazotized with nitrous acid to give moderately stable solutions which lose N_2 only on standing, heating or by action of light. These solutions contain *diazonium salts* to which are assigned the structures

$$\left[Ar{-}N{\equiv}N\right]^{+}Cl^{-} \qquad \left[Ar : \overset{\cdot\cdot}{N} : \overset{\cdot\cdot}{N} :\right]^{+}Cl^{-}$$

Water insoluble amines can be diazotized in conc. H_2SO_4, glacial acetic acid, by conversion with chlorosulfonic acid to soluble sulfamic acids ($ArNHSO_3H$) and also by reduction of the particle size of the compound.

Reactions of Diazonium Salts

A. ***Replacement reactions.*** These involve the formation of nitrogen gas and the replacement of the diazonium group by another univalent group.

1. Replacement by H. Treatment by means of alcohols and other reducing agents such as hypophosphorous acid, alkaline formaldehyde, sodium stannite, hydrazine and the like has been studied in a multitude of cases.[1]

An alcohol-benzene solution of *sym*-Br_3-aniline treated with concentrated sulfuric acid and sodium nitrite gives *sym*-Br_3-benzene[1a] (OS).

$$Br_3C_6H_2NH_2 + H_2SO_4 + NaNO_2 + C_2H_5OH \rightarrow C_6H_3Br_3 + N_2 + CH_3CHO + NaHSO_4 + 2\,H_2O$$

In other cases the diazonium group is replaced by OC_2H_5 instead of by H.

2. Replacement by OH. This is the common decomposition of diazonium salts, especially on warming with dilute sulfuric acid.

$$ArN_2X + H_2O \rightarrow ArOH + N_2 + HX$$

3. Replacement by halogen. Treatment with KI or HI usually gives an iodo compound smoothly. Replacement by Cl or Br is usually best achieved

[1] "Org. Reactions," Vol. II, p. 262.
[1a] "Org. Synthesis."

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[1] "Org. Reactions," Vol. II, p. 262.
[1a] "Org. Synthesis."

in presence of the proper acid and copper powder (Gattermann) or the proper cuprous halide dissolved in the corresponding acid (Sandmeyer). Heating the diazonium fluoroborate gives replacement by F. Fluorobenzene can be prepared by the use of anhydrous HF in the diazotization of aniline and subsequent decomposition.

4. Replacement by CN. This is a special case of the Sandmeyer-Gattermann reaction taking place with $KCu(CN)_2$.

5. Replacement by aryl residues takes place when a dry diazonium salt is heated with an aromatic hydrocarbon and $AlCl_3$. In the Gomberg reaction[1b] an aryl diazonium compound reacts with an aryl hydrocarbon under neutral or alkaline conditions with elimination of N to give a diaryl compound.

6. Miscellaneous replacements give aryl thiocyanates, sulfides (diazonium compounds react with sulfides of sodium with *explosive violence*[2]) sulfinic acids and nitro, fluoro, and mercury compounds. An addition reaction of an aryl diazonium chloride in the presence of acetone and a cupric salt is as follows:

$$ArN_2Cl + CH_2{=}CHCN \rightarrow ArCH_2CHClCN + N_2$$

B. Reactions which retain the nitrogen atoms.

1. Reduction gives arylhydrazines. In this way phenylhydrazine is prepared.[3]

$$PhN_2Cl + 2\ Na_2SO_3 + 2\ H_2O \rightarrow PhNHNH_2.HCl + 2\ Na_2SO_4$$

2. Alkaline oxidation gives nitramines among other products.

$$ArN_2Cl + 2\ NaOH + [O] \rightarrow ArN{=}NO_2Na + NaCl + H_2O$$ [3a]

3. Active hydrogen compounds of various kinds give coupling reactions in which the *azo group*, $-N{=}N-$, appears in the product.

a. Active methylene compounds like acetoacetic ester give azo compounds and the tautomeric arylhydrazones.

$$MeCOCH_2CO_2R + ArN_2Cl \rightarrow \begin{matrix} MeCOCH(CO_2R)\text{—}N{=}N\text{—}Ar \\ \downarrow\uparrow \\ MeCOC(CO_2R){=}N\text{—}NH\text{—}Ar \end{matrix}$$

b. Arylamines give *diazoamino compounds.*

$$ArN_2Cl + ArNH_2 \rightarrow ArN{=}N{-}NHAr$$

c. Aromatic compounds with highly activated ring H atoms such as phenols, naphthols and N-dialkylanilines couple in the active position

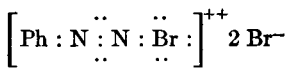
$$ArN_2Cl + C_6H_5NMe_2 \rightarrow ArN{=}N{-}C_6H_4NMe_2$$
$$ArN_2Cl + C_6H_5OH \rightarrow ArN{=}N{-}C_6H_4OH$$

These compounds are typical azo dyes.

[1b] Gomberg, Bachmann, *J. Am. Chem. Soc.* **46**, 2339 (1924).
[2] Nawiasky, Ebersole, Werner. *Chem. Eng. News.* **23**, 1247 (1945).
[3] "Org. Syntheses."
[3a] Bamberger and Landsteiner, Ber. **26**, 482-95 (1893).

While simple diazonium salts have to be prepared in solution as used, some of the more complex ones can be prepared as *solid stabilized diazonium compounds* (*explosive!*) usually as double salts with zinc chloride mixed with drying agents such as aluminum sulfate and also with certain stabilizing agents such as disulfonic acids of naphthalene, particularly the 1,5.

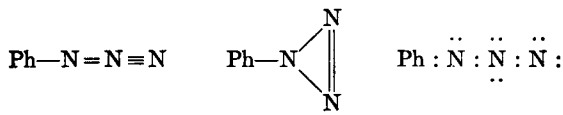
Benzenediazonium perbromide, $C_6H_5N_2BrBr_2$, is a crystalline solid obtained by adding Br_2 and HBr to a diazonium salt. It liberates I_2 from KI. Its constitution may be as follows:



With NH_3 it gives phenylazoimide, the phenyl ester of hydrazoic acid

$$PhN_2Br_3 + 4\ NH_3 \rightarrow PhN_3 + 3\ NH_4Br$$

The structure of phenylazoimide is written variously.



X-Ray measurements indicate a linear structure.

B. Diazo Compounds

Benzene diazonium salts with KOH give a precipitate of *potassium benzene normal diazotate* which can also be prepared from nitrosobenzene and hydroxylamine.

$$PhNO + H_2NOH + KOH \rightarrow PhN{=}NOK + 2\ H_2O$$

It gives the following reactions.

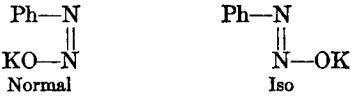
1. HCl gives benzene diazonium chloride.
2. With alkaline solutions of phenols, it gives azo dyes.
3. Alkaline reduction gives phenylhydrazine.
4. Oxidation gives potassium benzenediazoate, $PhN{=}NO_2K$.
5. With benzoyl chloride and alkali it gives a benzoyl derivative,

$$PhN{=}NOCOPh.$$

6. Heating with KOH at 130° gives an isomeric isodiazotate which shows reactions 1 to 5 and thus is a stereoisomer rather than a structural isomer.[4] The isomerism is like that of the oximes. The *syn* form has been assigned to the normal diazotates which lose N_2 more readily than do the isodiazotates

[4] Hantzsch. *Ber.* **38**, 2056 (1905).

which are given the *anti* structure.



The free acids corresponding to these salts are very unstable, either losing N to give phenol or isomerizing to a nitrosamine

$$PhOH + N_2 \leftarrow PhN{=}N{-}OH \rightarrow PhNH{-}N{=}O$$

Diazotized *p*-nitroaniline with NaOH gives a stable isodiazotate,

$$O_2NC_6H_4N_2ONa,$$

which is used in making Para Red by acidifying with HCl and coupling with *β*-naphthol.

Diazosulfonates and cyanides are also known. The latter may occur in three forms one of which is an electrolyte. The forms from diazotized *p*-anisidine are assigned the structures

C. Diazoamino Compounds

The following types are possible:

1. $ArN{=}N{-}NHAr$
2. $ArN{=}N{-}NHAr'$
3. $ArN{=}N{-}NRAr$
4. $ArN{=}N{-}NHR$
5. $RN{=}N{-}NHR$
6. $RN{=}N{-}NHR'$

The unsymmetrical types 2,4, and 6 exist in equilibrium with their tautomers having H at the other end of the nitrogen chain. They are pale yellow crystalline neutral compounds of fair stability. Thus *diazoaminobenzene*, $PhN{=}N{-}NHPh$, m. 98°, crystallizes in bright yellow plates or prisms and is moderately stable.[6]

Preparation. 1. From a diazonium salt and an amine. The tautomeric nature of the product from a primary amine is shown by the production of the same product from benzenediazonium chloride and *p*-toluidine and from *p*-toluene diazonium chloride and aniline. This character is further shown by the reaction of the product with hot sulfuric acid to give phenol, *p*-cresol, aniline and *p*-toluidine.

2. From a primary arylamine and insufficient nitrous acid in absence of excess mineral acid. Under these conditions as soon as a molecule is diazotized it couples with another molecule.

[6] "Org. Syntheses."

3. From esters of hydrazoic acid and Grignard reagents

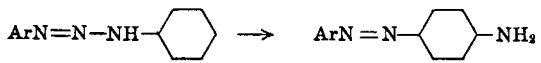
$$ArN_3 \xrightarrow{ArMgX} \xrightarrow{acid} ArN=N-NHAr$$

Alkyl groups can also be used.

Reactions. 1. The imino nitrogen does not form salts with acids. The H is replaceable by metals and by acetyl however.

2. They behave like their components. Thus boiling diazoaminobenzene with sulfuric acid gives N_2, phenol and aniline while with HBr it gives bromobenzene and aniline. Nitrous acid and HCl convert a diazoamino compound to two molecules of a diazonium chloride.

3. They rearrange to aminoazo compounds under the catalytic influence of an amine salt such as aniline hydrochloride.



If the *p*-position is occupied and the *o*-position is open the rearrangement takes place more slowly to that position.

D. Azo, Hydrazo and Azoxy Compounds

It has been seen that the alkaline reduction of nitrobenzene to aniline can be made to go through the steps of azoxybenzene, azobenzene and hydrazobenzene.

Azo compounds, ArN=NAr, ArN=NAr′, and ArN=NR are neutral colored substances which are insoluble in water but soluble in organic solvents.

Preparation. 1. By controlled reduction of nitro or azoxy compounds with alkaline reducing agents such as NaOH and Zn dust, sodium amalgam or sodium stannite solution.

2. By distilling azoxybenzene with Fe.

3. By oxidation of hydrazobenzene or of amino compounds by $KMnO_4$. The reaction is likely to go partly to the azoxy stage.

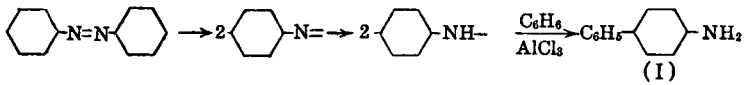
4. By condensation of an aromatic nitroso compound with an amine.

$$ArNH_2 + ArNO \rightarrow \left[\begin{array}{c} OH \\ | \\ ArN-NHAr \end{array}\right] \rightarrow ArN=NAr$$

5. Substituted azo compounds containing activating groups such as NH_2, either free or alkylated, and OH are obtained by coupling aromatic amines or phenols with diazonium salts. These products form the important class of azo dyes.

Reactions. Oxidation gives azoxy compounds while reduction gives hydrazo and amino compounds. A very striking reaction is that of aromatic azo compounds with aromatic hydrocarbons and $AlCl_3$. The azo compound, under the influence of the $AlCl_3$, apparently splits into free radicals. The

action of benzene and azobenzene to give a 70% yield of *p*-xenylamine (I) may be illustrated as follows:

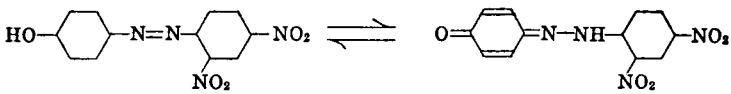


(I)

Azobenzene and diphenyl in this reaction give a fair yield of

$$C_6H_5C_6H_4C_6H_4NH_2.$$

Azobenzene, $C_6H_5N=NC_6H_5$, *cis*, m. 71.4°; *trans* (ordinary form), m. 68°, b. 293°, crystallizes in red plates. It is readily obtained by adding the calculated amount of Zn dust to an alcoholic NaOH solution of nitrobenzene.[7] Certain hydroxyazobenzenes act as quinone monohydrazones while others do not.[8]



The quinone structure is evidenced by the addition of cyclopentadiene according to the Diels-Alder reaction.

Hydrazo compounds, ArNHNHAr, etc. are colorless crystalline compounds which do not form salts with acids. They are readily *produced* by reduction of nitro compounds with zinc dust and alkali, by electrolytic or catalytic reduction.

Reactions. 1. While acids do not form salts the imino-H atoms are replaceable by alkali metals and by acetyl and nitroso groups.

2. Vigorous reduction, as with Na_xHg, gives the amine.

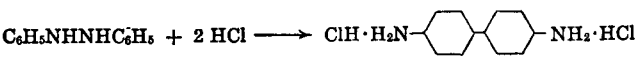
3. Mild oxidizing agents like air or ferric chloride give azo compounds.

4. Heat, or even long standing, results in disproportionation to an azo compound and an amine.

$$2\ ArNHNHAr \rightarrow ArN=NAr + 2\ ArNH_2$$

As a matter of fact this is a monomolecular reaction and probably involves a primary disproportionation into aniline and ArN=, a nitrogen radical, which dimerizes to azobenzene.[9]

5. Mineral acids cause the benzidine rearrangement which gives diaminodiphenyls.



Benzidine dihydrochloride

[7] "Org. Syntheses."

[8] Lauer, Miller. *J. Am. Chem. Soc.* **57**, 520 (1935).

[9] Stieglitz, Curme. *Ber.* **46**, 911 (1913).

This change involves the interchange of a group attached to nitrogen and a *p*-hydrogen analogous to the rearrangement of a nitroso group from N to the *p*-C. In this case the changes occur twice concurrently for the most part. If the *p*-position in one ring is blocked, only one change is possible and the *semidine rearrangement* takes place to give amino diphenylamines.

$$p\text{-}MeC_6H_4NHNHC_6H_5 \rightarrow p\text{-}MeC_6H_4NHC_6H_4NH_2\text{-}p.$$

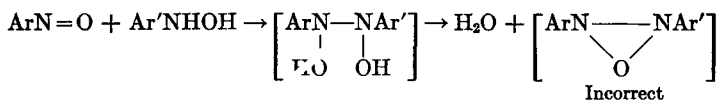
Hydrazobenzene, $C_6H_5NHNHC_6H_5$, m. 131°.[10]

Azoxy compounds, $ArN{=}N(O)Ar$, $ArN{=}N(O)Ar'$ and $Ar'N{=}N(O)Ar$, are colored crystalline compounds.

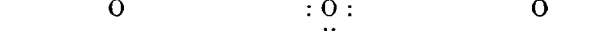
Preparation. 1. The symmetrical compounds are best made by reduction of nitro compounds with alcoholic KOH.

2. By careful oxidation of simple or mixed azo compounds.

3. By condensation of a nitroso compound and an arylhydroxylamine. This reaction was the basis of the older erroneous symmetrical formulation of the azoxy grouping.



The unsymmetrical character of the azoxy group is shown by the formation of two isomeric azoxy compounds by the oxidation of an unsymmetrical azo compound.[11] The formula usually assigned to the azoxy compounds having a "pentavalent" N is probably less accurate than the electronic formula.



Reactions. 1. Reduction gives azo compounds.

2. Conc. H_2SO_4 causes a rearrangement to a *p*-hydroxyazo compound.

$$ArN{=}N(O)C_6H_5 \rightarrow ArN{=}NC_6H_4OH\text{-}p$$

Azoxybenzene, $C_6H_5N{=}N(O)C_6H_5$, m. 36°, pale-yellow crystals, insoluble in organic solvents, is prepared from nitrobenzene and sodium arsenite.[12]

Hydrazines, derivatives of H_2NNH_2, of all possible types are known. The most important is *phenylhydrazine*, $C_6H_5NHNH_2$, m. 23°, prepared by reduction of benzenediazonium chloride with Na_2SO_3.[13] It is strongly basic, a powerful reducing agent and toxic. Its sulfate, on treatment with HgO, gives benzenediazonium sulfate. Vigorous reduction converts it to aniline and

[10] "Org. Syntheses."
[11] Angeli, Valori. *Atti accad. Lincei* (1910–1915).
[12] "Org. Syntheses."
[13] "Org. Syntheses."

ammonia. Alkylation of the base or its metal derivatives takes place on the N next to the phenyl giving unsymmetrical derivatives such as *methylphenylhydrazine*, $PhMeNNH_2$, which is an important reagent for sugars. The most important reaction of phenylhydrazine is that with ketones and aldehydes and with simple sugars. The crystalline character, ease of purification and definite melting points make the resulting *phenylhydrazones* and *osazones* valuable for purposes of isolation and identification. The discovery of phenylhydrazine by Emil Fischer gave him the key with which he later unlocked the problems of the monosaccharides. With carbonyl compounds which do not give crystalline phenylhydrazones, the *p*-substituted phenylhydrazines are valuable. The most important of these are the *p*-bromo-, *p*-nitro-, and *p*-phenyl-compounds. *unsym-Diphenylhydrazine*, $(C_6H_5)_2NNH_2$, m. 34°, is obtained by reducing the nitroso compound of diphenylamine with Zn and acid. It reacts with carbonyl compounds like phenylhydrazine. 2,4-Dinitrophenylhydrazine is a valuable reagent for carbonyl compounds which give liquid or low-melting derivatives with phenylhydrazine itself.

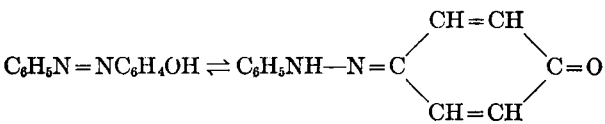
Completely substituted hydrazines, Ar_2NNAr_2, are obtained by oxidizing Ar_2NH with PbO_2. On standing, these change to Ar_3N and $ArN=NAr$. In benzene they give colored solutions presumably containing free ArN radicals.[14]

E. Azo Dyes

These contain in addition to the *chromophore* group, $-N=N-$, an *auxochrome* group which is either basic like NH_2 or NMe_2 or acidic like OH. These or other active groups either hold the dye to the fiber in the *direct dyeing* of silk or wool or to the *mordant* such as the hydroxides of various heavy metals to give the colored *lakes* formed in the *indirect dyeing* of cotton. The structure of an azo dye is readily found by vigorous reduction with Sn and HCl or alkaline sodium hydrosulfite to give two amines which can then be identified.

$$ArN=NArX + 4\,[H] \rightarrow ArNH_2 + XArNH_2$$

Hydroxyazo compounds are probably tautomeric.



The *chrysoidines* are a group of yellow to brown dyes including *p*-aminoazobenzene, Aniline Yellow, and its derivatives. Butter Yellow is the corresponding N-dimethyl compound. These dyes are obtained by coupling a suitable diazonium salt with a suitable aryl amine. If a primary amine is used, the first product is a diazoamino compound which can be rearranged to the

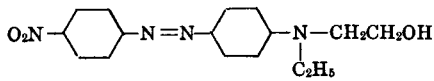
[14] Wieland. *Ber.* 48, 1078 (1915).

desired product by warming with an amine hydrochloride as a catalyst.

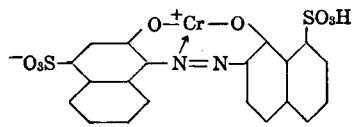
$$ArN_2Cl + ArNH_2 \rightarrow ArN_2NHAr \rightarrow ArN_2ArNH_2$$

The aryldiazo group always shifts to the *p*-position if possible. If that is occupied, it shifts more slowly to the *o*-position. *Chrysoidine* itself, the hydrochloride of 2,4-diaminoazobenzene, is obtained from benzenediazonium chloride and *m*-phenylenediamine. Both NH_2 groups in the latter activate the same H. *Bismarck Brown* is the hydrochloride of 2,4,3′-triaminoazobenzene obtained by the treatment of 2 mols of *m*-phenylene diamine in acid with 1 mol of nitrous acid. Thus, as soon as an amino group reacts, the resulting diazonium salt couples with another molecule of diamine. *Methyl Orange* is the Na salt of helianthine, 4-dimethylaminoazobenzene-4′-sulfonic acid, obtained by diazotizing sulfanilic acid and coupling with dimethylaniline. *Methyl Red* is the Na salt of 4-Me_2N-azobenzene-2′-carboxylic acid, similarly prepared from anthranilic acid and dimethylaniline.[15]

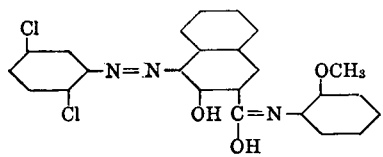
A scarlet dispersed dye for cellulose acetate and nylon is made by coupling 4-nitraniline to 2-(N-ethylanilino)ethanol.



A greenish-blue dye which contains metal in complex union dyes wool from a dilute sulfuric acid bath:



Cotton is dyed fast shades by formation of the color in the fiber by use of a diazonium compound and an arylamide of 2-hydroxy-3-naphthoic acid. The following is scarlet:



Bis-azo dyes having two azo groups can be obtained in a variety of ways:

1. A diamine can be treated with an excess of nitrous acid or "tetrazotized" to give two diazonium salt groups in the molecule. These can then be coupled with two molecules of a suitable phenyl- or arylamine. A modification of *Bismarck Brown* is obtained by coupling tetrazotized *m*-phenylenediamine with 2 mols of the diamine.

[15] "Org. Syntheses."

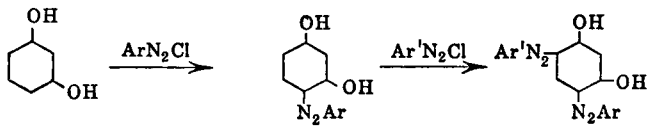
2. An amino derivative of an azo compound can be diazotized and coupled. *Sudan III* is thus obtained from aminoazobenzene and β-naphthol; it is an oil soluble red.

3. A nitro-amine can be diazotized and coupled, the nitro group reduced with sulfide to amino which in turn can be diazotized and coupled to give an unsymmetrical dye:

$$O_2N-Ar-NH_2 \rightarrow O_2N-Ar-N_2Cl \xrightarrow{Ar'H} O_2N-Ar-N_2-Ar' \xrightarrow{Ar''H}$$
$$H_2N-Ar-N_2-Ar' \rightarrow ClN_2-Ar-N_2Ar' \longrightarrow Ar''-N_2-Ar-N_2-Ar'$$

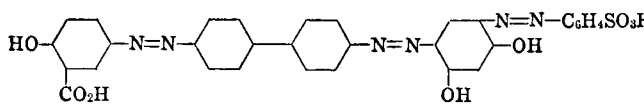
In the above scheme the NO_2 group can be replaced by $NHCOCH_3$ whereby hydrolysis replaces the reduction.

4. A diamine or a dihydric phenol can be coupled with 2 mols of a diazonium salt or successively with one mol of each of two different diazonium salts. This procedure is possible because after one such coupling has taken place a second coupling takes place much more slowly.



If Ar is the radical of *m*-xylidine and Ar′ that of sulfanilic acid the product is *Resorcinol Brown.*

Tris-azo and tetrakis-azo dyes are obtained by applications of the same principles. *Congo Brown G* is the product of coupling diazotized sulfanilic acid with the bis-azo dye from benzidine, salicylic acid and resorcinol.



Hessian Brown BB is obtained by coupling 2 mols of diazotized sulfanilic acid with the bis-azo dye from the coupling of tetrazotized benzidine with 2 mols of resorcinol.

"The Aromatic Diazo-Compounds and Their Technical Applications." K. H. Saunders, 1949.

Kirk, Othmer. "Encyclopedia of Chemical Technology," Vol. II, 1948. Chapter on Azo Dyes.

IX. PHENOLS

Phenols have at least one hydroxyl group attached directly to the benzene ring. They are characterized by more strongly acidic properties than those of the alcohols. Practically all phenols have antiseptic properties.

A. Monohydric Phenols

Phenol, carbolic acid, C_6H_5OH, m. 42°, b. 181°, occurs in coal tar along with many homologs (*tar acids*). The pure white crystalline substance turns red due to partial oxidation. A small amount of water dissolves in it to give a liquid. Phenol is soluble in 15 parts of water at room temperature and is readily soluble in alcohol and ether. It is poisonous and gives dangerous burns on the skin. The best treatment is immediate application of a dilute solution of bromine in glycerol which converts the phenol to the very insoluble tribromophenol. Treatment with alcohol is also effective.

Preparation. The methods used to obtain phenol apply to its homologs in general.

1. From coal tar. Extraction by a base followed by acidification, usually by CO_2 in the form of flue gases, gives a mixture of phenols (tar acids) which can be fractionally distilled.

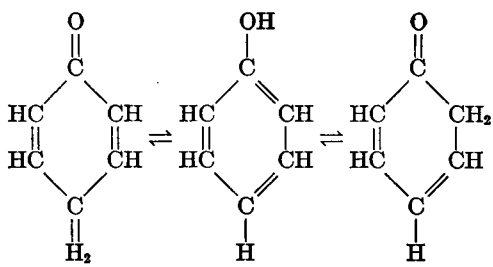
2. Fusion of an alkali sulfonate with alkali gives the phenate and a bisulfite.

3. Heating chlorobenzene and NaOH in presence of diphenyl oxide under pressure gives sodium phenate.[1]

4. A diazonium sulfate solution on heating gives a phenol.

5. While the direct oxidation of benzene to phenol has not yet been achieved commercially the Raschig Process virtually accomplishes this. Chlorobenzene is produced by a vapor phase reaction of benzene, HCl and O_2 over a copper catalyst at 230°. Hydrolysis with steam, using a silica gel catalyst, yields phenol and HCl. The HCl is recovered. Oxygen is the only reagent not regenerated.

Reactions. A consideration of the formula of phenol shows several relations of its hydroxyl to the rest of the molecule. It can be regarded as a tertiary alcohol but the acidic properties do not correspond to such a classification since tertiary alcohols are less acidic than primary and secondary alcohols. Moreover tertiary alcohols are hard to oxidize whereas phenols are very sensitive to oxidation. Phenol may also be regarded as a vinyl alcohol and an allyl alcohol. Moreover there is evidence that a tendency to tautomerism also exists in the phenols.



[1] Hale. *Ind. Eng. Chem.* **20**, 114 (1928).

This process probably involves the addition of H^+ ion at the 2,4, or 6 position followed by the expulsion of H^+ ion from the hydroxyl and a corresponding shift of bonds. The tautomerism of phenol probably accounts for its easy oxidation. It undoubtedly accounts for its easy hydrogenation to hexahydrophenol (cyclohexanol, hexalin).

The reactions of phenol are typical of this class of compounds. They may be divided into three groups: those involving (*A*) the H of the hydroxyl group, (*B*) the hydroxyl group itself and (*C*) the *o*- and *p*-H atoms of the ring.

A. Reactions involving the replacement of the hydroxyl hydrogen.

1. The hydrogen is replaceable by means of strong bases to give phenolates, phenates or phenoxides, ArONa, etc. These are readily hydrolyzed but not to the same extent as the alcoholates. Since phenol is a very weak acid, it is liberated from its salts by CO_2.

$$C_6H_5ONa + CO_2 + H_2O \rightarrow C_6H_5OH + NaHCO_3$$

Claisen's alkali, a mixture of KOH, H_2O and CH_3OH, is used to isolate weakly acidic phenols. Phenol forms crystalline compounds with amines which are probably salt-like in nature.

2. Replacement of the H of the hydroxyl group by acid groups gives esters. This process takes place less readily than with primary and secondary alcohols. *Phenyl acetate*, $C_6H_5OCOCH_3$, b. 193°, obtained by heating phenol, acetic anhydride and anhydrous sodium acetate is much more readily hydrolyzed than ordinary acetates. Salts of phenyl hydrogen sulfate such as $C_6H_5OSO_3K$ occur normally in the urine of the herbivora and in that of other animals after ingestion of phenol.

3. Ethers of phenol are readily obtained by treating a phenolate or a phenol in alkaline solution with an alkylating agent such as MeI or Me_2SO_4. *Anisole*, $C_6H_5OCH_3$, b. 154° and *phenetole*, $C_6H_5OC_2H_5$, b. 170°, are the best known phenyl ethers. *Diphenyl ether*, diphenyl oxide, $(C_6H_5)_2O$, m. 28°, b. 259°, is obtained by heating chlorobenzene and NaOH under high pressure (Dow). A mixture with diphenyl forms a valuable high temperature transfer medium (Dowtherm).

4. *Phenolates*, phenates, PhONa, give metathetical reactions with alkyl halides with unusual smoothness apparently because of the great activity of the phenolate ion, PhO^-.

For the identification of phenols 2,4-dinitrochlorobenzene has been found to be an excellent reagent. The procedure is simple and the ethers formed are highly crystalline, stable solids which are easily purified and possess sharp melting points. The presence of water in the phenol does not interfere. The reagent has the advantage of being quite stable.[2]

[2] Bost. *J. Am. Chem. Soc.* **57**, 2368 (1935).

The melting points of the ether derivatives of typical phenols appear in the following table.

Phenol	*m.p.*	*Phenol*	*m.p.*
Phenol	69°	*m*-Nitrophenol	138°
o-Cresol	90	*p*-Nitrophenol	120
m-Cresol	74	2-Chloro-5-hydroxytoluene	112
p-Cresol	93.5	*o*-Iodophenol	95
Thymol	67	*o*-Chlorophenol	99
Guaiacol	97	*m*-Chlorophenol	75
α-Naphthol	96	*p*-Chlorophenol	126
β-Naphthol	122	2,4-Dichlorophenol	119
p-Hydroxydiphenyl	118	2,4,6-Trichlorophenol	136
Resorcinol	194	*o*-Bromophenol	89
Eugenol	114	*p*-Bromophenol	141
Isoeugenol	130	2,4-Dibromophenol	135
Vanillin	131	2,4,6-Tribromophenol	135
o-Nitrophenol	142	*p*-Iodophenol	156

5. Phenol gives a violet color with dry ferric chloride. Many phenols give characteristic colors with this reagent.

B. Replacement of the hydroxyl group.

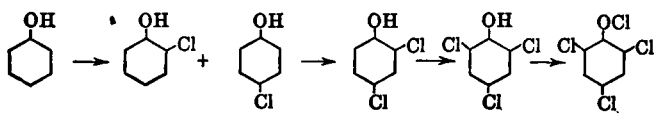
1. Reduction or replacement by H is achieved by distillation with zinc dust. This process is valuable in studying the structure of complex phenols.

2. The replacement of the OH by halogen on treatment with halides of phosphorus, etc. takes place only to a limited extent, the chief products being esters of phosphorus acids, etc.

3. Replacement of the OH by NH_2 is obtained by heating with the addition compound of NH_3 and zinc chloride or calcium chloride.

C. Reactions of the o- and p-H atoms of the ring.

1. Ordinary substitutions such as halogenation, nitration and sulfonation are very easy. The ease of oxidation is so great, however, that care has to be used to avoid complex oxidation products. Careful chlorination gives trichlorophenol and finally trichlorophenyl hypochlorite.



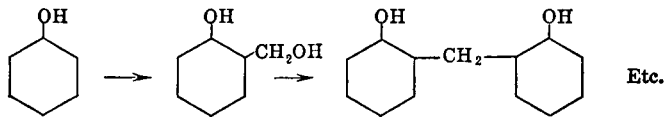
Phenol can be nitrated by dilute nitric acid in the cold. More vigorous treatment gives tarry oxidation products. Nitrated phenols are better prepared by hydrolysis of the nitrated chlorobenzenes.

2. Coupling with diazonium salts takes place readily, mainly in the para position.

3. A replacement of ring H takes place in the Kolbe synthesis of phenolic acids from phenates and CO_2.

4. Similarly the Reimer-Tiemann synthesis of phenolic aldehydes from phenates and chloroform involves an *o-* or *p-H*.

5. The most important use of phenol is based on the reactions of its *o-* and and *p-H* atoms with formaldehyde to give resins of the bakelite type (amberlite, durez, resinox, etc.). Steps such as the following are involved.



Such reactions can take place at three places in each phenol molecule. The resulting large molecules are too complex to crystallize and consequently form resins.[3] Modified phenol formaldehyde resins made by the condensation of sulfonic acids of aromatic OH compounds are useful as ion exchange materials (Amberlite IR-100).

6. Alkylation reactions readily yield alkylphenols. The higher alkyl substituted phenols, wax phenols, are multifunctional oil additives, combining properties of pour-point depressant action, improved viscosity index and antioxidant value. Metaloxy derivatives of such compounds have exceptional antioxidant value for lubricating oils.[4]

7. A special reaction of one of the ortho positions is shown by the conversion of allyl phenyl ether at 200° to *o*-allylphenol. This is a typical case of the Claisen Rearrangement.[5,6]

8. Various complex reactions, such as oxidation, involve the ring hydrogen atoms. Liebermann's reaction consists of mixing the phenol with concentrated sulfuric acid and adding a little nitrite or a nitrosamine to produce a colored solution which turns blue or green on addition of alkali.

Thiophenol, mercaptobenzene, phenyl mercaptan, phenyl hydrosulfide, C_6H_5SH, b. 172°, is made by acid reduction of benzenesulfonyl chloride or by treating phenol with phosphorus pentasulfide. It has a vile odor. It gives ordinary mercaptan reactions such as the formation of $(PhS)_2Hg$ and PhSHgCl and ready oxidation to $(PhS)_2$. With benzenediazonium salts it gives Ph_2S.

Substituted Phenols

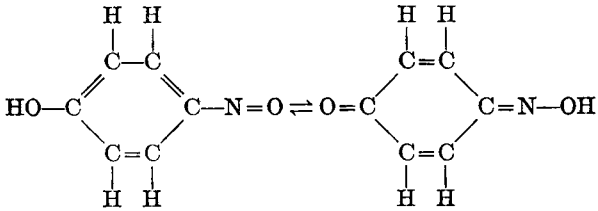
Many ortho and para compounds are obtained by direct substitution. They can usually be separated by taking advantage of the greater volatility of the ortho compound and the higher melting point of the para compound. The meta compounds are usually made from the corresponding nitro compound by reduction to the amine and diazotization of the latter.

[3] Wanscheidt. *Ber.* 69, 1900 (1936).
[4] Reiff. U. S. Pat. Nos. 2,197,833; 2,253,811 (1940).
[5] Tarbell. *Chem. Rev.* 27, 495 (1940).
[6] "Org. Reactions," II. p. 1.

p-Bromophenol is readily obtained by brominating phenol in a solvent such as CS_2 (OS).[7a] *p*-Chlorophenol is obtained by the action of *p*-dichlorobenzene with NaOH under pressure. The *o*-compound is prepared similarly. *o*-Bromo- and *o*-iodo-phenol can be obtained by diazotizing the *o*-halogenated aniline or from *o*-chloromercuriphenol. Phenol can be directly iodinated by treatment with iodine and HgO in water suspension. Excess halogen converts phenol to the 2,4,6-trihalogenated products. Aqueous phenol with bromine water gives a precipitate of *sym*-tribromophenol, m. 92°.

2,4-Dichlorophenoxyacetic acid (2,4-D) a derivative of 2,4-dichlorophenol is used to destroy weeds.

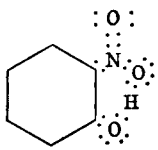
***p*-Nitrosophenol,** HOC_6H_4NO, is readily obtained from phenol and nitrous acid, from any *p*-nitroso-N-dialkylaniline and aqueous alkali, or from the controlled action of hydroxylamine with *p*-benzoquinone. It is identical with the monoxime of quinone.

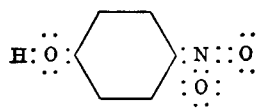


It forms colorless needles or greenish plates. It detonates on heating.

Nitrophenols

Treatment of phenol with cold dilute nitric acid gives a mixture of the *o*- and *p*-nitrophenols which can be separated by steam distillation, the ortho compound being volatile. This marked difference in volatility is believed to indicate the existence of a chelate ring and the consequent absence of a simple hydroxyl group in the *o*-compound.

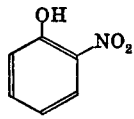


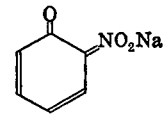


A better method for preparing these substances is by the action of bases on the readily available *o*- and *p*-nitrochlorobenzenes (p. 640). The nitro group activates the chlorine in *o*- or *p*-position so that high temperatures and pressures are not necessary. The *o*- and *p*-nitrophenols form highly colored salts with bases or even alkali carbonates. These salts probably have quinoidal

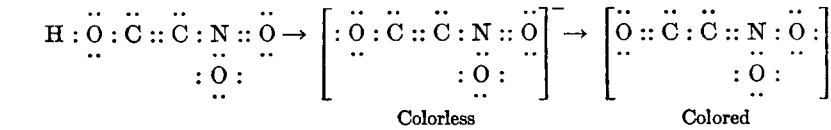
[7a] "Org. Syntheses."

structures.



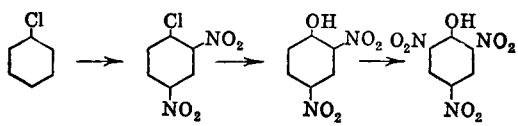


The systems $HO-C=C-NO_2$ and $HOC=C-C=C-NO_2$ found in *o*- and *p*-nitro phenols are not greatly ionized. Moreover, it is highly improbable that a hydrogen migrates along the chain to give an acid $C=NO_2H$. The base simply removes the hydrogen ions and causes the further ionization of the hydroxyl hydrogen. This makes possible an electron shift to form the more stable colored quinoidal ion.



Acidification supplies H^+ ions to the carbonyl oxygen and reverses the process. In a phenol not containing a nitro group in the *o*- or *p*-position, the removal of H^+ ion by the base leaves merely the phenate ion. The quinoid structure of the salts of the *o*- and *p*-nitrophenols is supported by measurements of the absorption spectra and by the fact that the sodium salts do not react readily with chloroacetic ester to give derivatives of phenoxyacetic acid as do the true phenates, including the sodium compound of *m*-nitrophenol which cannot form a quinoid structure.

The 2,4- and, less readily, the 2,6-dinitrophenols are obtained by further nitration. In presence of sulfuric acid, the nitration can be carried to the final step of *sym*-trinitrophenol or *picric acid*, m. 122°. This substance is a fairly strong acid. When the hydroxyl hydrogen is removed there are three different possible shifts to give a stable quinoidal ion. While it can be made from phenol it is better prepared in the following steps:



Picric acid is an explosive and a dye for silk and wool. The salts of picric acid, even those with the alkali metals, are much more explosive than the acid itself. Consequently picric acid cannot be used as an explosive in shells except with a non-metal liner. It has been largely replaced by safer explosives such as trinitrotoluene, and by better dyes. It retains its use as a treatment for burns. Picric acid forms crystalline compounds with aromatic amines and

phenols and even with aromatic hydrocarbons. Treatment of picric acid with PCl_5 gives *picryl chloride*, *sym*-trinitrochlorobenzene, m. 81°, in which the Cl is activated by all three nitro groups.

Aminophenols

They are made by reduction of nitrophenols. The *o*- and *p*-compounds can also be made from the nitrochlorobenzenes and ammonia. They do not form phenates but give salts with strong acids. The free *o*- and *p*-bases are readily oxidized while the *m*- is not. Thus the first two and their derivatives are used as photographic developers.

***p*-Aminophenol,** m. 184°, rodinol, is obtained by the electrolytic reduction of nitrobenzene in sulfuric acid, the first product being β-phenylhydroxylamine which rearranges to the aminophenol. Oxidation converts it to quinone and treatment with chlorine gives quinone chlorimide, $O=C_6H_4=NCl$. *Amidol* is a salt of 2,4-diaminophenol. One of the commonest developers is *metol*, pictol, N-methyl-*p*-aminophenol, which can be made from hydroquinone and monomethylamine or by heating *p*-hydroxyphenylglycine in solution in a phenol.

$$HOC_6H_4NHCH_2CO_2H \rightarrow CO_2 + HOC_6H_4NHCH_3$$

***m*-Aminophenol** is best made by the alkali fusion of *m*-aminobenzenesulfonic acid.

Anisidines, $CH_3OC_6H_4NH_2$, and **phenetidines,** $C_2H_5OC_6H_4NH_2$, are used in making azo dyes. Two preparations of these substances are given in the following steps:

1. $ClC_6H_4NO_2 \rightarrow ROC_6H_4NO_2 \rightarrow ROC_6H_4NH_2$
2. $ROC_6H_4NH_2 \rightarrow ROC_6H_4N_2Cl \xrightarrow{\text{Phenol}}$
   $RQC_6H_4N=NC_6H_4OH \rightarrow ROC_6H_4N=NC_6H_4OR \rightarrow 2\ ROC_6H_4NH_2$

The second preparation is no longer of practical value.

Aceto-*p*-phenetidine, phenacetine, $EtOC_6H_4NHCOMe$, is an antipyretic.

Homologs of Phenol

Many of these are found in coal tar, wood tar, cracked petroleum products, and in certain essential oils. Commercial *cresylic acid* contains a small amount of phenol, the three cresols and considerable amounts of higher phenols including several xylenols. These mixtures of phenol homologs are largely used to make resins with formaldehyde; for this purpose fractions of fairly definite composition are in demand. Various higher *tar acid* fractions are also available; these are used chiefly in disinfectants.

The three *cresols*, m. 31°, 12°, and 35° are available commercially; they may also be obtained pure by diazotization of the three toluidines. By fractionation of crude coal tar acid mixture *o*-cresol, b. 191°, is obtained; *m*-

and *p*-cresols b. 203° and 202°, are obtained as a mixture. Pure *m*-cresol is separated from the mixture through complex with 2,6-lutidine and *p*-cresol through complex with quinaldine.[9] A mixture of cresols with various soaps gives a soluble disinfectant, lysol, cresoline, etc. Dinitro-orthocresol is used as a weed killer. Tricresyl phosphate is a lubricating oil additive which reduces abrasion. The corresponding phosphite is an antioxidant. The *o*- and *m*-cresols can be obtained by heating phosphorus pentoxide with carvacrol and thymol respectively. The six *xylenols* ("Xenols") have the following melting and boiling points: *ortho*-xylenols, 1,2,3-, 72°, 217°; 1,2,4-, 65°, 227°; *meta*-xylenols, 1,3,2-, 49°, 212°; 1,3,4-, 24°, 211°; 1,3,5-, *sym*-, 63°, 222°; *para*-xylenol, 1,4,2-, 75°, 211.5°. The 1,2,4-, 1,3,5-, and 1,3,4-xylenols are available commercially (Reilly). The *symmetrical Xylenol* is most abundant in coal tar acid and is most readily separated.[10] Also available commercially are *m*-ethylphenol, b. 219°, and *p*-ethylphenol, b. 218° (Reilly).

Carvacrol is 2-hydroxy-4-isopropyltoluene. It occurs in certain essential oils but is best prepared by heating camphor with iodine. This remarkable change in structure involves the elimination of only two H atoms.

$$C_{10}H_{16}O + I_2 \rightarrow 2\ HI + C_{10}H_{14}O$$

Carvacrol when heated with P_2S_5 gives *p*-cymene (*p*-isopropyl-toluene). With P_2O_5 it gives propylene and *o*-cresol.

Thymol is an isomer of carvacrol having the OH in the 3-position. It is readily available from oil of thyme and by alkylation of *m*-cresol. Its reactions are like those of its isomers except that P_2O_5 gives propylene and *m*-cresol. Thymol iodide, $[C_6H_2(CH_3)(C_3H_7)OI]_2$, is used as an antiseptic dusting powder in treating wounds.

B. Dihydric Phenols

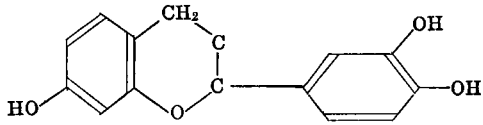
These resemble the monohydric phenols in most chemical properties. Those with the hydroxyls in the ortho or para position are especially sensitive to oxidation and are valuable reducing agents and serve as developers in photography.

Pyrocatechol, pyrocatechin, brenzcatechin, *o*-dihydroxybenzene, *o*-$C_6H_4(OH)_2$, m. 105°, b. 240°, can be made by alkaline fusion of *o*-phenol sulfonic acid or *o*-dichlorobenzene. It has also been prepared by the action of HI on its monomethyl ether, *guaiacol*, found in beechwood tar. It is a powerful reducing agent, precipitating silver even from cold silver nitrate. Cautious oxidation with silver oxide gives orthobenzoquinone.[11] It is used as an additive to inhibit deterioration of cracked gasoline.

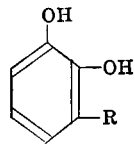
[9] Cislak. U. S. Pat. Nos. 2,432,062; 2,432,063 (1947).
[10] Kester. *Ind. Eng. Chem.* 24, 770 (1932).
[11] Willstätter. *Ber.* 41, 2580 (1908).

Its alkaline solution absorbs oxygen readily. Ferric chloride gives a green color. Bromination readily introduces 4 Br atoms. The product is oxidized by nitric acid to give dark red tetrabromo-*o*-benzoquinone.

Catechol, often misused as the name for pyrocatechol, is the compound.



Long chain substituted catechols are the principle toxic constituents of poison ivy and other related plants. The alkyl side chains are unsaturated, contributing to their absorption by the skin, while the catechol nucleus provides the irritant action. The general structure is



in which R may be $C_{15}H_{27}$ (urushiol-poison ivy) $C_{15}H_{29}$ (bhilawanol-marking nut tree), $C_{17}H_{31}$ (laccol-lac trees).[12]

Veratrole, m. 22°, b. 207°, is the dimethyl ether of pyrocatechol.

Creosol, b. 222°, 2-methoxy-4-methylphenol, a homolog of guaiacol, is also found in beechwood tar.

Resorcinol, resorcin, *m*-dihydroxybenzene, m. 119°, b. 276°, is prepared by the potash fusion of both *m*- and *p*-disulfonic acids of benzene. It is also obtained by similar fusion of all three of the bromobenzenesulfonic acids and of *m*-phenolsulfonic acid. It gives a dark violet color with $FeCl_3$. Although a less vigorous reducer than its *o*- and *p*-isomers it reduces silver nitrate solution on warming and an ammoniacal silver solution even in the cold. On being heated with a solution of sodium bicarbonate, resorcinol gives *beta*-resorcylic acid which, in turn, is readily decarboxylated.[13] A similar reaction of resorcinol is with sodium bisulfite giving the 4-sulfonic acid, with one of the hydroxyls covered by a sulfate group. Its chief uses are in the preparation of fluorescein by action with phthalic anhydride and of hexylresorcinol. Because of the positions rendered very active by the *op*-hydroxyl groups it is a valuable coupling component of azo dyes. Nitration gives *styphnic acid*, *sym*-trinitroresorcinol, which gives *styphnates* which are used for identification purposes much like picrates.

[12] Wasserman. *J. Chem. Education* 20, 448 (1943).

[13] "Org. Reactions," Vol. II.

Orcinol, *sym*-dihydroxytoluene, (1,3,5), m. 108°, b. 290°, is found in various lichens. With phthalic anhydride it gives no compound analogous to fluorescein.

Hydroquinone, quinol, *p*-dihydroxybenzene, m. 170°, b. 286°, is prepared by the reduction of quinone, usually with sulfurous acid. Most oxidizing agents first change it to quinhydrone and then to quinone. Its strong reducing properties make it the most valuable photographic developer. Fusion with KOH in presence of air gives 1,2,4-trihydroxybenzene.

C. Trihydric Phenols

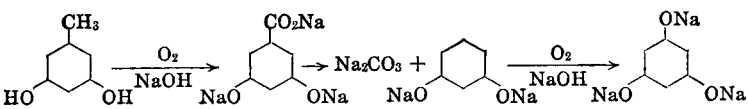
Pyrogallol, pyrogallic acid, 1,2,3-trihydroxybenzene, m. 134°, b. 309°, is made by thermal decarboxylation of gallic acid. It is a powerful reducing agent, especially in alkaline solution, as in its common use for absorbing oxygen in gas analysis. It differs from its symmetrical isomer in not reacting as a ketone with hydroxylamine. Pyrogallol and its derivatives are used as gasolene antioxidants.

Phloroglucinol, *sym*-trihydroxybenzene, m. 219°, occurs in various natural resins and in the glucoside *phloridzin*. The preparations of phloroglucinol involve a variety of principles.

1. By fusion of benzene-1,3,5-trisulfonic acid with alkali.

2. By similar fusion of resorcinol in presence of air. Thus benzene-*m*-disulfonic acid can be converted to phloroglucinol in much the way that anthraquinone *mono*sulfonic acid is converted to the *dihydroxyl* compound, alizarin.

3. A related although apparently remarkable preparation is by the fusion of *orcinol*, 3,5-$(OH)_2$-toluene, with NaOH in presence of air. The following changes probably occur



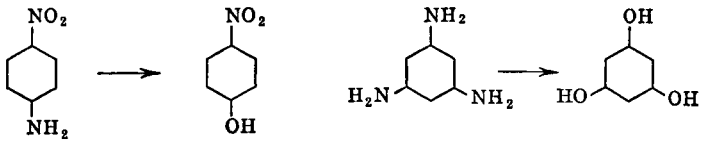
4. *sym*-Triaminobenzene is hydrolyzed to the trihydroxy compound by merely boiling its hydrochloride with water. The same product is obtained from the corresponding benzoic acid. The steps involved in the preparation of phloroglucinol from commercial trinitrotoluene would be as follows:

$$\text{T.N.T.} \xrightarrow[(OS)]{[O]} C_6H_2(NO_2)_3CO_2H \xrightarrow{[H]} C_6H_2(NH_2)_3CO_2H \xrightarrow[H_2O]{HCl}$$

$$CO_2 + 3\,NH_3 + C_6H_3(OH)_3$$

This ready hydrolysis of *negative* groups in the *meta* position to each other is interesting in view of the ready hydrolysis of such groups when *ortho* or *para*

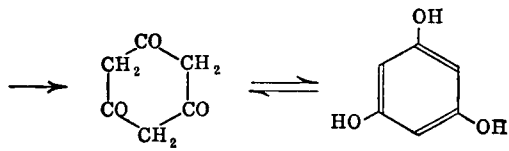
to *positive* groups like the nitro group. Thus the following changes take place readily.



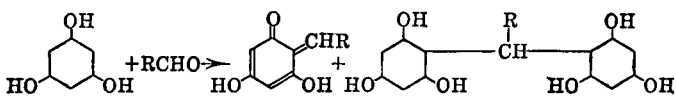
On the other hand the hydrolysis of *m*-nitroaniline and of *p*-phenylene diamine is not easy.

5. Acetone and malonyl chloride in presence of $CaCO_3$ form phloroglucinol.[14] In this reaction the carbonyl groups of the acid chloride give an aldol condensation with the α-H atoms of the acetone

$$ClCOCH_2COCl + CH_3COCH_3 \rightarrow$$
$$ClCOCH_2C(OH)(Cl)CH_2COCH_3 \rightarrow ClCOCH_2COCH_2COCH_3 \rightarrow$$



The tautomeric reactions of phloroglucinol have been studied extensively. It gives ordinary phenolic reactions but also acts as triketocyclohexane. The *trioxime*, $C_6H_6(=NOH)_3$, decomposes at 140°. The condensation with aldehydes[15] involves both forms.



A similar process is responsible for its use in determining pentosans. The latter are converted by HCl to furfural which forms an insoluble compound with phloroglucinol.

Hydroxyquinol, hydroxyhydroquinone, 1,2,4-$(OH)_3$-benzene, can be made by alkaline fusion of hydroquinone in presence of air. Its triacetate is formed by the action of glacial acetic acid with quinone. It does not react with hydroxylamine.

Hexahydroxybenzene, $C_6(OH)_6$, is obtained as the explosive potassium compound from metallic potassium and carbon monoxide. It can be oxidized to a hydrated form of the corresponding tri-quinone, triquinoyl.

[14] Komninos. *Bull. soc. chim.* **23**, 449 (1918).
[15] *Ann. Rep. Chem. Soc.* (London) 1914, 129.

X. AROMATIC ALCOHOLS

These compounds have hydroxyl attached to a side chain or aliphatic portion of a mixed aliphatic aromatic compound such as toluene or diphenylmethane. They may be regarded and are often named as aryl derivatives of carbinol. Their reactions are analogous to those of the corresponding classes of aliphatic alcohols. The activity of OH on a carbon attached directly to an aryl group is increased. Similarly, the activity of H in a like position is increased toward oxidation and removal in dehydration. In other words, *H and OH when alpha to a benzene ring are unusually active.*

Benzyl alcohol, phenylcarbinol, $C_6H_5CH_2OH$, b. 205°, is readily made from benzyl chloride and a base. It is only slightly soluble in water. Substituted benzyl alcohols are obtainable by reduction of the corresponding benzamides with sodium amalgam.

$$XC_6H_4CONH_2 + 4\,[H] \rightarrow XC_6H_4CH_2OH + NH_3$$

Benzhydrol, diphenylcarbinol, $(C_6H_5)_2CHOH$, m. 69°, b. 299°, is a typical secondary alcohol both in its preparations and its reactions. The presence of the two phenyl groups attached to a single carbon excludes the possibility of rearrangements. Benadryl, the dimethylaminoethyl ether hydrochloride of benzhydrol, $(C_6H_5)_2CHOCH_2CH_2N(CH_3)_2.HCl$, is an antihistamine agent which relieves the spasm of smooth muscle. It is used for all kinds of allergies and is particularly effective in relieving persons suffering from hay fever.

Triphenylcarbinol, $(C_6H_5)_3COH$, m. 159°, can be made from diphenylketone and PhMgBr and by the hydrolysis of the corresponding halides. The effect of the three phenyl groups is shown by its preparation by the oxidation of triphenylmethane and by its ready reduction to triphenylmethane by zinc and acetic acid. Some reducing agents like titanous chloride convert the carbinol to triphenylmethyl.

Phenylethyl alcohol, β-phenylethyl alcohol, benzylcarbinol,

$$C_6H_5CH_2CH_2OH,$$

b. 221°, occurs in rose oil and is much used in perfumes. It is best prepared by the reduction of ethyl phenylacetate, $PhCH_2CO_2Et$. This process is best carried out by means of absolute alcohol and sodium.[1,2] Catalytic reduction is likely to cause dehydration of the carbinol because of the activating effect of the phenyl group on the alpha H atoms. Phenylethyl alcohol has also been prepared by the action of phenylmagnesium chloride with ethylene oxide. This is one of the few commercial uses of the Grignard reagent.

Phenylmethylcarbinol, α-phenylethyl alcohol, $C_6H_5CHOHCH_3$, b. 203°, is best prepared from acetaldehyde and PhMgBr. Since it is readily dehydrated, all traces of acid must be eliminated before its distillation.

[1] Bouveault, Blanc. *Compt. rend.* 136, 1676 (1903).
[2] Hansley. *Ind. Eng. Chem.* 39, 55 (1947).

ω-Phenylpropyl alcohol, $C_6H_5(CH_2)_3OH$, b. 235°, is obtained by reducing *cinnamyl alcohol*, styryl carbinol, "styrone," $C_6H_5CH=CHCH_2OH$, m. 33°, b. 258°, which occurs as a cinnamic ester (styracin) in storax. Cinnamyl alcohol gives typical allylic rearrangements. Thus treatment with PBr_3 gives both $PhCH=CHCH_2Br$ and $PhCHBrCH=CH_2$.

XI. AROMATIC ALDEHYDES

The direct attachment of the aldehyde group to an aromatic ring gives substances resembling trimethylacetaldehyde in having no alpha hydrogen and thus giving neither aldol condensations nor polymerizations. On the other hand the carbonyl group is very reactive.

Benzaldehyde, oil of bitter almonds, C_6H_5CHO, b. 179°, is typical of aromatic aldehydes. It occurs as the glucoside, *amygdalin*.

Preparation. 1. It is made starting from toluene by a variety of processes.

a. Benzyl chloride, $C_6H_5CH_2Cl$, is hydrolyzed and oxidized by heating with water and a mild oxidizing agent such as a nitrate of lead or copper. Benzyl chloride can also be converted to benzaldehyde by heating with alkali and the calculated amount of chromate, the aldehyde being distilled out as fast as formed. Hexamine-benzyl chloride when hydrolyzed with boiling water gives benzaldehyde (Sommelet Reaction).[1]

b. Benzal chloride, $C_6H_5CHCl_2$, can be hydrolyzed either with acid or lime to give benzaldehyde.

c. Benzoic acid can be converted to benzoyl chloride which can be converted to benzaldehyde by hydrogen in presence of a palladium catalyst.[2]

$$PhCOCl + H_2 \rightarrow HCl + PhCHO$$

Benzoyl chloride can be converted to its cyanide and then to phenylglyoxylic acid which loses CO_2 on distillation.

$$PhCOCl \rightarrow PhCOCN \rightarrow PhCOCO_2H \rightarrow CO_2 + PhCHO$$

These last two methods are specially applicable to complex aldehydes and give a method for going from an aromatic amine through the nitrile and acid to the aldehyde.

d. Etard's reagent, CrO_2Cl_2, converts an aromatic methyl group to an aldehyde group. The mechanism of this process involves the formation of intermediate compounds such as $C_6H_5CH_3.2\ CrO_2Cl_2$.

2. Benzaldehyde can be made from benzene.

a. By the action of carbon monoxide at high pressure.

b. By the treatment of benzene with CO in presence of HCl and anhydrous aluminum chloride. In this process it may be assumed that formyl chloride, HCOCl, is the active agent.

[1] Sommelet. *Compt. rend.* 157, 852 (1913).

[2] Rosenmund, Zetsche. *Ber.* 54B, 425 (1921).

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c. The Grignard reagent from chloro- or bromo-benzene reacts with an excess of an alkyl formate at low temperature to give benzaldehyde.

$$PhMgBr + HCO_2R \rightarrow PhCH(OR)OMgBr \rightarrow ROMgBr + PhCHO$$

An alkyl orthoformate similarly gives the acetal of benzaldehyde which can readily be hydrolyzed by dilute acid.

$$PhMgBr + CH(OR)_3 \rightarrow ROMgBr + PhCH(OR)_2$$

The *reactions* of benzaldehydes may be divided into those of (I) the aldehyde hydrogen, (II) the carbonyl group and (III) the benzene nucleus.

I. The H of the aldehyde group has the usual reactivity, being readily oxidized to OH. Thus benzaldehyde which has been exposed to air always contains benzoic acid. The absence of alpha H atoms makes possible reactions not observed in their presence.

a. Chlorine replaces the H to give benzoyl chloride whereas in ordinary aldehydes it gives an alpha chloro aldehyde.

b. Alkalies bring about an oxidation and reduction, the Cannizzaro reaction.[3]

$$2\ PhCHO + KOH \rightarrow PhCO_2K + PhCH_2OH$$

If the aldehyde is freed from all but the merest traces of peroxides, the reaction takes place only about 1/25 as rapidly as with the usual "purified" benzaldehyde.[4]

c. A related reaction is that of Tischenko in which a sodium or aluminum alcoholate condenses two molecules to form benzyl benzoate (OS).

$$2\ PhCHO \rightarrow PhCO_2CH_2Ph$$

d. Alkali cyanides give the *benzoin condensation* in which the H plays the part of the active H in the aldol condensation.

$$2\ PhCHO \rightarrow PhCHOHCOPh$$

II. *A.* The carbonyl group gives the usual *addition* reactions.

a. Reducing agents and catalytic hydrogenation give benzyl alcohol.

b. Hydrocyanic acid gives mandelonitrile, PhCHOHCN.

c. Sodium bisulfite gives a crystalline addition compound which has been shown to be a hydroxy sulfonate, $PhCHOHSO_3Na$.

B. The condensation reactions of the carbonyl group probably take place by way of initial addition.

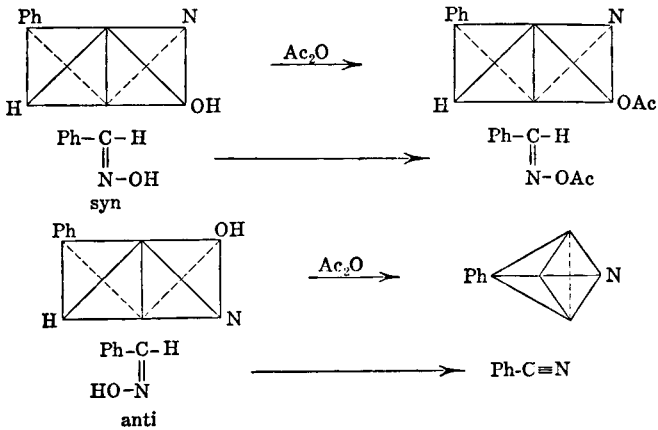
a. Primary amines first give addition products and then benzal (benzylidene) amines or *Schiff's bases.*

$$PhCHO + PhNH_2 \rightarrow [PhCHOHNHPh] \rightarrow PhCH{=}NPh$$

[3] "Org. Reactions," II, p. 94.

[4] Kharasch, Foy. *J. Am. Chem. Soc.* **57**, 1510 (1935).

b. Hydroxylamine gives *syn* or *alpha* benzaldoxime, m. 35°. Acids convert this to the *anti* or *beta* benzaldoxime, m. 125°. The latter reacts with acetic anhydride to give benzonitrile. This reaction was formerly thought to indicate the *syn* form. The stereochemistry of the oximes has been studied in great detail by means of substituted benzaldehydes.[5–7]



Obviously the models used are inadequate to show the mechanism by which *trans* elimination takes place.

c. Hydrazine gives benzalazine, $PhCH=N-N=CHPh$, m. 93°. High temperatures convert it to N_2 and stilbene.

d. Phenyl hydrazine gives benzaldehyde phenyl hydrazone,

$$PhCH=NNHPh,$$

m. 152°.

e. It gives the aldol condensation with the alpha H of suitable aldehydes and ketones. The influence of the phenyl group on an $\alpha-OH$ causes the spontaneous dehydration of the aldol first formed. Thus benzaldehyde and acetaldehyde in presence of dilute base or a trace of HCl give cinnamic aldehyde readily.

$$PhCHO + CH_3CHO \rightarrow [PhCHOHCH_2CHO] \rightarrow PhCH=CHCHO$$

Acetone gives benzalacetone, $PhCH=CHCOMe$, m. 42°, and dibenzalacetone, $(PhCH=CH)_2CO$, m. 112°. The latter is valuable as an identifying derivative of both acetone and benzaldehyde.

f. A reaction related to the aldol condensation is the *Perkin synthesis* of unsaturated acids from aromatic aldehydes, sodium salts of aliphatic acids and

[5] Meisenheimer. *Ber.* **54B**, 3206 (1921).
[6] *Ann. Rep. Chem. Soc.* (London) **1925**, 105; **1926**, 126.
[7] Hauser, Vermillion. *J. Am. Chem. Soc.* **63**, 1224 (1941).

their anhydrides. Thus cinnamic acid is prepared by heating benzaldehyde, anhydrous sodium acetate and acetic anhydride.[8]

$$PhCHO + CH_3CO_2Na + Ac_2O \rightarrow [PhCHOHCH_2CO_2Na] \rightarrow PhCH{=}CHCO_2Na + 2\ AcOH$$

Hydrogen which is alpha to a carboxyl group or to a conjugated system containing a carboxyl takes part in this reaction. Thus sodium propionate gives α-methylcinnamic acid while sodium crotonate gives $PhCH{=}CHCH{=}CHCO_2H$ (Vinylogy).

g. Aromatic compounds containing active ring H such as dimethylaniline condense with benzaldehyde in presence of zinc chloride. This is an important preparation for triphenylmethane dyes.

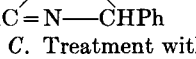
$$PhCHO \rightarrow [PhCHOHC_6H_4NMe_2] \rightarrow PhCH(C_6H_4NMe_2)_2$$

The failure to obtain the intermediate product is another example of the activity of OH alpha to phenyl.

h. The reaction of benzaldehyde with NH_3 illustrates again the activating effect of an aryl group on an alpha OH. The steps may include the following:

$$PhCHO \rightarrow PhCH(OH)NH_2 \rightarrow PhCH{=}NH \rightarrow PhCH(NH_2)_2 \rightarrow PhCH(NHCHOHPh)_2 \rightarrow \underset{\text{Hydrobenzamide}}{PhCH(N{=}CHPh)_2}$$

Acids convert hydrobenzamide to a dihydroglyoxaline derivative, *amarin*,



C. Treatment with PCl_5 gives benzal chloride, $PhCHCl_2$. Once again the absence of alpha H precludes side reactions.

III. Sulfonation and nitration give ring substitution mainly in the meta position.

***m*-Nitrobenzaldehyde**, m. 58°, is obtained with about 20% of the *o*-compound by direct nitration of benzaldehyde. Reduction of its bisulfite compound gives a solution of *m-aminobenzaldehyde* useful in making triphenylmethane dyes.

***o*-Nitrobenzaldehyde,** m. 40°, and its *p*-isomer, m. 106°, are prepared by the controlled oxidation of *o*- and *p*-nitrocinnamic acids obtained by direct nitration. *o*-Nitrobenzaldehyde in sunlight or in presence of alkali undergoes intramolecular oxidation and reduction to give *o*-nitrosobenzoic acid.[9]

Phenyl acetaldehyde, α-tolualdehyde, $C_6H_5CH_2CHO$, b. 194°, is best prepared from cinnamic acid by first adding HOCl and then rearranging and decarboxylating the product.

$$PhCH{=}CHCO_2H \rightarrow PhCHOHCHClCO_2H \rightarrow [PhCH_2C(OH)ClCO_2H] \rightarrow [PhCH_2COCO_2H] \rightarrow PhCH_2CHO$$

[8] "Org. Reactions," I, p. 210.

[9] Ciamician, Silber. *Ber.* **34**, 2040 (1901).

Cinnamic aldehyde, $C_6H_5CH=CHCHO$, b. 246°, is readily obtained from cinnamon oil through the bisulfite compound. It is a typical alpha beta unsaturated carbonyl compound. Reducing agents readily saturate the double bond, presumably by a process of 1,4-addition. Further reduction gives $Ph(CH_2)_3OH$. Treatment with aluminum alkoxides gives cinnamyl alcohol.[10]

$$3\ PhCH=CHCHO + Al(OCHMe_2)_3 \rightarrow (PhCH=CHCH_2O)_3Al + 3\ Me_2CO$$

The action of cinnamic aldehyde with bisulfites is characteristic of alpha beta unsaturated aldehydes. Three types of compounds are possible:

(I) $PhCH=CHCH(OH)SO_3Na$,
(II) $PhCH(SO_3Na)CH_2CH(OH)SO_3Na$,
and (III) $PhCH(SO_3Na)CH_2CHO$.

(I) is obtained by the action of cold bisulfite solution on the aldehyde. Boiling with water converts (I) to (II) and free aldehyde. (II) can also be made from the aldehyde and an excess of hot conc. bisulfite solution. Boiling (II) with dilute sulfuric acid gives (III). Dry distillation or treatment with hot dilute NaOH solution converts all three to the free aldehyde.

The use of cinnamic aldehyde in aldol condensations gives substances with complex conjugated systems of double bonds. Thus, with acetaldehyde it gives $PhCH=CHCH=CHCH=O$.

XII. AROMATIC KETONES

These show typical ketone reactions except to the extent that an aryl group attached directly to a carbonyl group provides no alpha H and offers a greater amount of steric hindrance to certain addition reactions than do simple aliphatic groups.

Acetophenone, methyl phenyl ketone, acetylbenzene, Hypnone,

$$C_6H_5COCH_3,$$

m. 20°, b. 202°, is best *prepared* by the Friedel-Crafts reaction from benzene, acetyl chloride and aluminum chloride. Molecular amounts of the latter must be used because it forms a stable addition compound with the product of the reaction. This is generally true of carbonyl compounds.

Reactions. Acetophenone gives typical ketone reactions. It forms an oxime, m. 59°, and a phenylhydrazone, m. 105°. These are not known in stereoisomeric forms. This may be due to the much greater stability of one form because of the wide difference in the phenyl and methyl groups or, more probably, to the possibility of tautomeric change.

$$Ph{-}C(=N{-}OH){-}CH_3 \rightleftharpoons Ph{-}C(-NHOH)=CH_2 \rightleftharpoons Ph{-}C(=N{-}OH){-}CH_3$$

[10] Meerwein et al. *J. Prakt. Chem.* **147**, 211 (1936).

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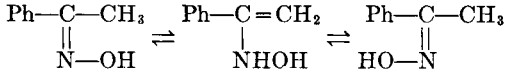

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Acetophenone is readily reduced and adds HCN in the usual way. The effect of the phenyl group is shown by the failure to form compounds with bisulfites. Halogenation readily gives *phenacyl halides*, $PhCOCH_2X$. *Phenacyl chloride*, ω-chloroacetophenone, is a widely used relatively harmless lachrymator ("CN") used for controlling mobs and the like. It is best made from chloroacetyl chloride, benzene and aluminum chloride. Tribromoacetophenone reacts with alkali very slowly to give the haloform reaction whereas dibromoacetophenone, NaOBr and NaOH react instantly. Vigorous oxidation converts acetophenone to benzoic acid. Controlled oxidation with cold alkaline $KMnO_4$ attacks only the methyl group giving $PhCOCO_2H$, phenylglyoxylic acid (benzoylformic acid).

Reaction of acetophenone with ammonium polysulfide at 200–220° C. yields phenylacetamide. This is an example of the Willgerodt reaction.[1]

The alpha H atoms of acetophenone readily take part in aldol condensations. Thus benzaldehyde and a trace of dilute base give $PhCH=CHCOPh$, *benzalacetophenone, chalcone*, m. 58°. Mild treatment of acetophenone with HCl gives *dypnone*, $MePhC=CHCOPh$. Longer treatment continues the condensation process to give *sym*-triphenylbenzene. Polyhydroxychalcones are used in the synthesis of flavones.

Treatment of acetophenone with cold fuming nitric acid gives mainly the *m*-nitro compound with a smaller amount of the *o*-compound. Warming with conc. nitric acid gives

$$PhCOC(NO{:}C(NO)COPh.$$

Substituted acetophenones have been made in great variety. Direct nitration of acetophenone gives mainly *m*-nitroacetophenone, m. 81°. The chief by-product is the oily *o*-compound but the latter is best prepared by the action of 30% sulfuric acid on the product of *o*-nitrobenzoyl chloride and sodioacetoacetic ester. Both carboxyl and acetyl are removed.

$$O_2NC_6H_4COCH(CO_2R)COCH_3 \rightarrow O_2NC_6H_4COCH_3$$

p-Nitroacetophenone, m. 81°, can be prepared similarly from *p*-nitrobenzoyl chloride but a better method starts with the nitration of cinnamic acid which readily gives the *p*-compound

$$O_2NC_6H_4CH=CHCO_2H \xrightarrow{Br_2} \xrightarrow{HOK}$$

$$O_2NC_6H_4C\equiv CCO_2K \xrightarrow[H_2SO_4]{70\%} CO_2 + O_2NC_6H_4COCH_3$$

The last step involves the hydration of the triple bond and the splitting of the resulting keto acid. It is a general process for producing the acetyl group.

$$RC\equiv CCO_2H \rightarrow RCOCH_2CO_2H \rightarrow RCOCH_3$$

[1] "Org. Reactions," III. p. 83.

Reduction of the nitroacetophenones with Sn and HCl gives the three *amino-acetophenones*, *o*-, oil, *m*-, m. 93°, *p*-, m. 106°, b. 294°. The *p*-compound can also be made by heating aniline or acetanilide with an excess of acetic anhydride and zinc chloride. The aminoacetophenones can be diazotized in the usual way.

In some cases substituted acetophenones are made by the Friedel-Crafts reaction of acetyl chloride with a substituted aromatic compound such as chlorobenzene or the phenyl ethers like anisole. This is not possible with compounds containing groups like carboxyl and hydroxyl which react with aluminum chloride. Nitrobenzene does not react and can thus be used as a solvent in the Friedel-Crafts reaction.[2]

p-Hydroxyacetophenone can be prepared by heating phenyl acetate with $AlCl_3$. This is the Fries Reaction.[3]

Benzophenone, diphenyl ketone, $(C_6H_5)_2CO$, m. α-49°, β-26°, b. 306°, is best prepared by the Friedel-Crafts reaction on benzoyl chloride and benzene. It can also be made by oxidizing diphenylmethane. It forms an oxime, m. 140°, and a phenylhydrazone, m. 105°. Reduction gives benzhydrol (I) and benzpinacol (II) m. 186° dec.

$$\underset{}{Ph_2CO} \rightarrow \underset{I}{Ph_2CHOH} + \underset{II}{Ph_2C(OH)C(OH)Ph_2}$$

The formation of the latter, and especially its ready rearrangement on dehydration to give benzpinacolone, Ph_3CCOPh, m. 182°, show the danger of considering too literally the term steric hindrance.

Vinyl phenyl ketone, $CH_2=CHCOPh$, adds PhMgBr entirely 1,4- to give only $PhCH_2CH_2COPh$.[4] A similar result is obtained with propenyl phenyl ketone, $MeCH=CHCOPh$. By contrast, the isomeric methyl cinnamyl ketone, $MeCOCH=CHPh$, adds mainly to the carbonyl group giving only about 10% 1,4-addition.

XIII. PHENOLIC ALCOHOLS, ALDEHYDES AND KETONES

Many of these either occur in nature or are readily prepared from natural products. *Saligenin* and *anisyl alcohol* are *o*-hydroxy- and *p*-methoxybenzyl alcohols. *Coniferyl alcohol*, obtained from the glucoside *coniferin*, is

$$3\text{-MeO-4-HO-}C_6H_3CH=CHCH_2OH.$$

The *o*- and *p*-hydroxybenzyl alcohols are very sensitive to acid, readily undergoing complex condensation reactions. This peculiarity is the basis of resin formation from phenols and formaldehyde (Bakelite). The first step is an aldol-type condensation involving the carbonyl of the formaldehyde and an

[2] Groggins. "Unit Processes in Organic Synthesis," 3rd Ed. McGraw-Hill, 1947. p. 769.
[3] "Org. Reactions," I. p. 342.
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H which is *o*- or *p*- to the hydroxyl to form a hydroxybenzyl alcohol. *o*- and *p*-Aminobenzyl alcohols are even more sensitive to acid. Thus *p*-NH_2-benzyl alcohol with acid gives $(C_7H_7N)_x$. This product presumably is a long chain polymer $HOCH_2C_6H_4NH(CH_2C_6H_4NH)_yCH_2C_6H_4NH_2$. A similar product is obtained when attempts are made to prepare *p*-aminobenzyl halides from the corresponding nitro compounds.

Salicylaldehyde and **anisaldehyde** are *o*-OH and *p*-OMe-benzaldehydes. 3,4-Dihydroxybenzaldehyde is *protocatechuic aldehyde* while the 3-methyl ether of the latter is *vanillin* and the 3,4-methylene ether is *piperonal.*

Derivatives of piperonal, especially piperonyl butoxide, butylcarbityl 6-propylpiperonyl ether, when combined with pyretheum give excellent insecticides[1] (see pyretheum).

Salicylaldehyde is obtained by the Reimer-Tiemann reaction (see below) using carefully controlled conditions. The other aldehydes of this group are made from naturally occurring allyl or propenyl phenol ethers. The former are rearranged to the latter by means of alkali and the $\alpha\beta$-double bond is broken by oxidation to give an aldehyde group. *Anethole,*

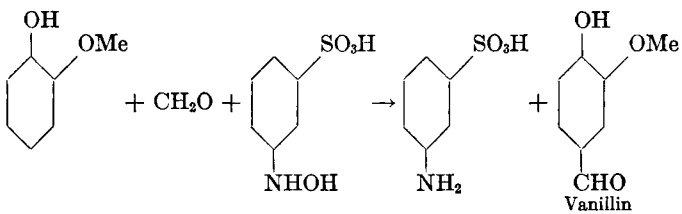
$$p\text{-MeOC}_6\text{H}_4\text{CH}=\text{CHMe}$$

gives anisaldehyde.

Eugenol, 4-OH-3-OMe-$C_6H_3CH_2CH=CH_2$, gives *isoeugenol* and then vanillin. Acetyl isoeugenol obtained by isomerizing eugenol with a base and acetylating with acetic anhydride is oxidized to vanillin.

$$\text{3-MeO-4-OH-C}_6\text{H}_3\text{CH}_2\text{CH}=\text{CH}_2 \xrightarrow{\text{KOH}} \text{ArCH}=\text{CH}\text{—}\text{CH}_3 \xrightarrow{\text{Ac}_2\text{O}} \xrightarrow{[\text{O}]} \text{Vanillin.}$$

Vanillin is made commercially from the lignin byproducts of the paper industry.[2] A common preparation of vanillin is from guaiacol in the following steps:

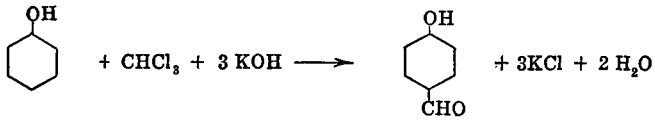


Vanillin

Safrole, 3,4-$CH_2O_2C_6H_3CH_2CH=CH_2$, through *isosafrole* gives piperonal. The splitting of the methylene group to give protocatechuic aldehyde is not easy. It can be achieved by treatment with cold PCl_5 to change the $=CH_2$ to $=CCl_2$. Hydrolysis gives $=C=O$ forming a carbonate which on further hydrolysis gives the free dihydroxy compound.

[1] Mail. *Chem. Inds.* 61, 218 (1947).
[2] Howard. *Chem. Inds.* 48, 724 (1941).

Phenols treated with alkali and chloroform (*Reimer-Tiemann*) are converted to the corresponding *o*- and *p*-hydroxyaldehydes.



In the Duff reaction phenols are treated with hexamethylenetetramine in anhydrous glycerol in the presence of glyceroboric acid. Hydrolysis with sulfuric acid produces *o*-hydroxy aldehydes. Similarly phenols react with HCN and HCl in presence of zinc chloride to give formimides which can be hydrolyzed to hydroxy aldehydes (Gattermann). If RCN is used in place of HCN the final product is a ketone. For the HCN process, a convenient method is to treat a suspension of $Zn(CN)_2$ in dry ether with dry HCl and then add the phenolic compound.[3]

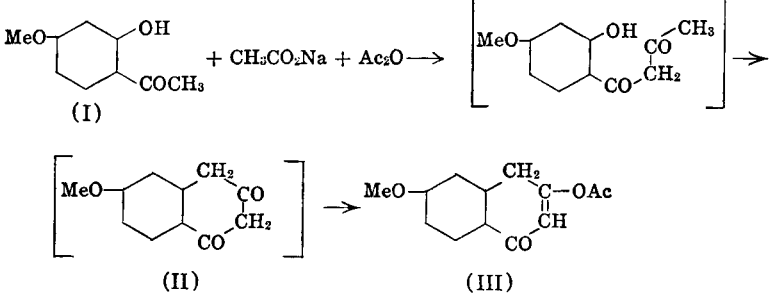
$$Zn(CN)_2 + 2\,HCl \rightarrow ZnCl_2 + 2\,HCN$$

$$C_6H_5OH + HCN + HCl \rightarrow HOC_6H_4CH{=}NH.HCl \xrightarrow{H_2O} HOC_6H_4CHO + NH_4Cl$$

The most important member of this group is vanillin, the active flavoring material of the vanilla bean.

The three *hydroxyacetophenones* or *acetylphenols* are known. The *p*-compound, m. 108°, can be made directly from phenol, acetic anhydride and $ZnCl_2$. The *o*-, liquid, and the *m*-compound, m. 93°, can be made from the nitroacetophenones by reduction with Sn and HCl followed by diazotization. They are also available from the methyl ethers of the corresponding substituted benzoylacetic esters and phenylpropiolic acids.

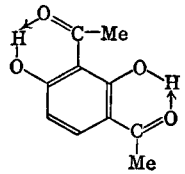
Resacetophenone, acetoresorcinol, $2,4\text{-}(OH)_2\text{-}C_6H_3COCH_3$, m. 142°, is readily obtained by heating resorcin with acetic acid and zinc chloride. Its monomethyl ether is *peonol*, m. 50°. Peonol (I) gives an interesting modification of the Perkin synthesis to give dehydrodiacetylpeonol (III).



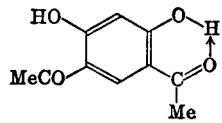
[3] Adams, Levine. *J. Am. Chem. Soc.* **45**, 2373 (1923).

Treatment of III with a carbonate gives II, which is tautomeric with the 6-Me ether of 1,3,6-$(OH)_3$-naphthalene.

The *2,4-* and *4,6-diacetylresorcinols* differ widely in properties. The first m. 91° and is volatile with steam while the second m. 182° and is non-volatile with steam. These differences are explained on the basis of chelate rings.



2,4-



4,6-

Alternating unsaturation may be necessary for such a stable 6-chelate ring.

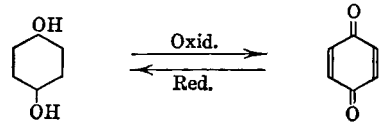
Quinacetophenone, C-acetylhydroquinone, 2,5-$(OH)_2C_6H_3COCH_3$, m. 202°, is made from hydroquinone, acetic acid and zinc chloride. Similarly prepared, is *4-acetylpyrocatechol,* m. 116°.

XIV. QUINONES AND RELATED COMPOUNDS

A. Benzoquinones

The simple quinones are conjugated diketocyclohexadienes closely related to ortho and para dihydroxy benzene derivatives.

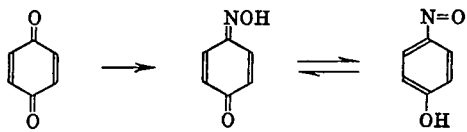
Benzoquinone, quinone, $C_6H_4O_2$, m. 116°, yellow pungent crystals, is readily obtained by oxidizing aniline with chromic acid. Its constitution is shown by its formation by the oxidation of hydroquinone and its easy conversion to the latter by reduction.



Hydroquinone Quinone

Quinhydrone is a crystalline green compound of these two substances in equimolecular proportions. It is the first product of the oxidation and reduction of the two substances.

Quinone reacts with 1 mol of hydroxylamine hydrochloride to give a monoxime which is identical with *p*-nitrosophenol.



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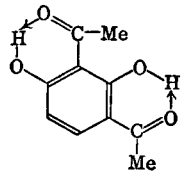
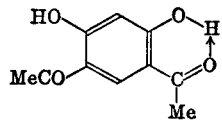


2,4-



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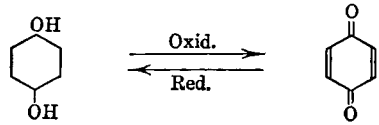

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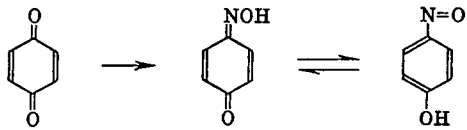
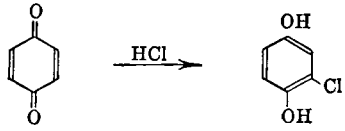
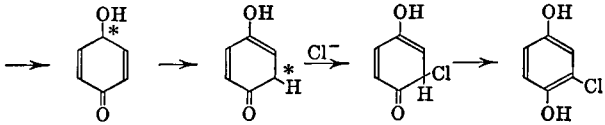


The change to the latter may be regarded as involving the addition of a hydrogen ion to the carbonyl oxygen with the expulsion of one from the NOH group.

Quinone can give either addition or substitution reactions with halogens depending on conditions. It adds halogen acids in a peculiar way to give mono-halogen hydroquinones.



This process probably involves two 1:3 shifts as follows (the * indicating a C with only 6 electrons):

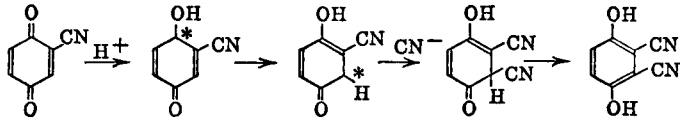


The first of these corresponds to the older conception of 1,4-addition and the second to enolization. The last step gives the completely conjugated benzene derivative. The action of HBr is more complex, the products being quinhydrone, a reduction product of quinone and both mono- and dibromohydroquinones.

Quinone reacts with aniline in hot alcoholic solution to give *2,5-dianilinoquinone and hydroquinone*. Apparently a molecule of aniline adds to give 2-anilinohydroquinone much as HCl adds to quinone. This is then oxidized by a molecule of quinone which is thus reduced to hydroquinone. The resulting 2-anilinoquinone can then add another molecule of aniline to give *2,5-dianilinohydroquinone* which is oxidized to the final product. There is no evidence of any addition to give a 2,3- or a 2,6-product. Primary alcohols react with quinone in presence of $ZnCl_2$ to give 2,5-dialkoxyquinones and hydroquinone. Changes of this type indicate that quinone is a stronger oxidizing agent than substituted quinones. Another addition of this type is that of benzene sulfinic acid to give phenyl-2,5-dihydroxyphenyl sulfone.

The one reaction in which two molecules add *unsymmetrically* to quinone is the action of a cyanide and a mineral acid in which the products are 2,3-dicyanohydroquinone and hydroquinone. The first part of the process may be the formation of cyanohydroquinone in the same way that HCl adds to quinone. Oxidation of this by quinone would give hydroquinone and cyanoquinone. The latter might be expected to add HCN to form the 2,5-dicyano derivative. Apparently the course of the reaction is as follows (* indicating

a carbon with only 6 electrons)



I.

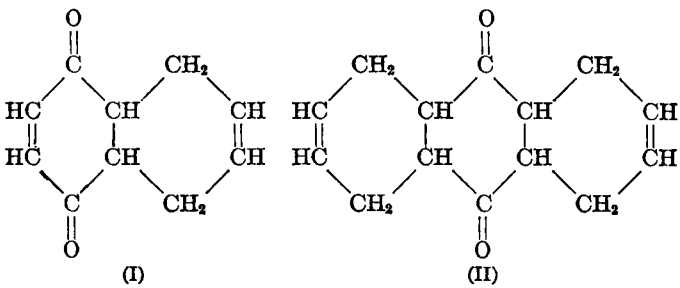
By analogy to other addition reactions of quinone the intermediate (I) might have been expected to undergo the allylic shift with carbons 5 and 6 with the entry of the second CN at 5. This apparently is prevented by the strong tendency to form a *double bond alpha beta to the CN group* in (I).

Quinone undergoes internal oxidation and reduction when treated with acetic anhydride and sulfuric acid, giving the acetate of hydroxyhydroquinone.

$$C_6H_4O_2 + 2\ Ac_2O \rightarrow C_6H_3(OAc)_3 + AcOH$$

This peculiar change is merely an addition analogous to that of HCl to quinone, followed by the formation of the stable triacetate.

The formula of benzoquinone indicates it to be an alpha beta unsaturated ketone. This is confirmed by its participation in the Diels-Alder reaction with conjugated dienes. Thus it reacts with butadiene to give 5,8,9,10-H_4-1,4-naphthoquinone (I) and 1,4,5,8,11,12,13,14-H_8-anthraquinone (II).



(I) (II)

With cyclopentadiene, quinone gives similar products having *endomethylene* groups, $-CH_2-$ connecting the 5,8-positions in (I) and the 1,4- and 5,8-positions in (II).

Chloranil, tetrachloroquinone, $C_6Cl_4O_2$, m. 290° (sealed tube), is formed by chlorinating quinone but is better prepared from *p*-nitroaniline by chlorination, reduction to dichloro-*p*-phenylene diamine and then simultaneous chlorination and oxidation by potassium chlorate and HCl. A still cheaper method for large scale manufacture is the oxidation of trichlorophenol with chromic acid. It forms yellow crystals which readily sublime. It is used commercially as an oxidizing agent in the preparation of dyes such as methyl violet. It oxidizes

halogen acids to the halogens with the formation of Cl_4-hydroquinone. It is stable to strong oxidizing agents such as aqua regia, nitric acid and concentrated sulfuric acid. In contrast to its stability to acid reagents, is its ready reactivity with various alkaline reagents. The usual result is the replacement of the 2- and 5-Cl atoms. The ease of replacement of the Cl atoms recalls the reactivity of acid chlorides. Dilute KOH gives *potassium chloranilate*, $C_6Cl_2O_2(OK)_2.H_2O$, dark red needles. An even more surprising change is the action of $NaNO_2$ solution to give sodium nitranilate, $C_6(NO_2)_2O_2(ONa)_2$. Both the Na and K salts are only sparingly soluble. Aniline and sodium phenolate react with chloranil with the replacement of two Cl atoms by PhNH and PhO groups respectively. Dilute $KHSO_3$ replaces two Cl by 2 SO_3K groups and reduces the quinone to a hydroquinone. Conc. K_2SO_3 gives insoluble *potassium thiochronate*, $C_6(OH)(OSO_3K)(SO_3K)_4.4\,H_2O$. Heating this with 2 KOH gives *potassium euthiochronate*, $C_6(SO_3K)_2O_2(OK)_2$ and 3 $KHSO_3$.

Aqueous ammonia replaces two Cl in chloranil by NH_2 and OH giving $C_6Cl_2(NH_2)(OH)O_2$ while alcoholic NH_3 gives $C_6Cl_2(NH_2)_2O_2$, chloranilamide.

Ortho-Benzoquinone, 1,2-diketocyclohexadiene-3,5, $C_6H_4O_2$, is obtained by oxidation of an ether solution of pyrocatechol with Ag_2O.[1] The corresponding Cl_4- and Br_4-compounds are readily obtainable by halogenating pyrocatechol and oxidizing the products with nitric acid. Orthoquinones are red.

B. N-Analogs of Quinones

Compounds in which $=N-$ takes the place of one or both $=O$ groups are known in great variety. These include:

1. **Chloroimides** containing the $=NCl$ group and formed by the oxidation by hypochlorite of suitable amino compounds. Thus *p*-aminophenol hydrochloride gives quinone chloroimide, $O=C_6H_4=NCl$ while *p*-phenylenediamine hydrochloride gives the dichloroimide, $ClN=C_6H_4=NCl$. The $=NCl$ group is readily reduced to $-NH_2$ or hydrolyzed to $=O$.

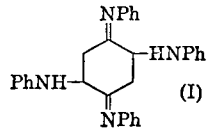
2. **Quinone diimide,** $HN=C_6H_4=NH$, is obtained as bright yellow crystals which explode on heating and can be reduced to *p*-phenylenediamine or hydrolyzed to quinone.

3. **Quinone monoxime,** $O=C_6H_4=NOH$, has already been mentioned as the stable tautomeric form of *p*-nitrosophenol just as $MeCOCH=NOH$ is related to $MeCOCH_2NO$. In both cases the $-N=O$ group tends to take a hydrogen ion and become $=NOH$, thus causing the expulsion of H^+ from another part of the molecule. *Quinone dioxime,* $HON=C_6H_4=NOH$, dec. 240°, is best made from "*p*-nitrosophenol" and hydroxylamine hydrochloride. It gives a *syn*- and an *anti*-diacetate, m. 147° and 190° dec.

[1] Willstätter, Pfannenstiel. *Ber.* **37**, 4744 (1904).

4. **Quinone monoanil,** $O=C_6H_4=NC_6H_5$, m. 97°, red crystals and *quinone dianil*, $C_6H_5N=C_6H_4=NC_6H_5$, m. 180°, are obtained by oxidizing *p*-OH-diphenylamine and diphenyl-*p*-phenylenediamine, $C_6H_4(NHC_6H_5)_2$.

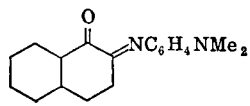
Azophenin (I), the dianil of 2,5-dianilinoquinone, is obtained by a variety of processes including the action of heat on a mixture of *p*-nitrosodiphenylamine, aniline and aniline hydrochloride.



(I)

It is also formed by the action of aniline with quinone dianil. The fact that neither the mono- nor the di-anil can be made from quinone and aniline indicates the ease with which aniline adds 1:4 to the system $O=C-C=C$ rather than 1:2 to the carbonyl group.

Indamines and **indophenols** are dyes related to the quinone anils. *Phenylene Blue* is made by oxidizing a mixture of aniline and *p*-phenylene diamine. The dye is the hydrochloride of $NH_2C_6H_4N=C_6H_4=NH$. Other indamine dyes are *Bindschedler's Green* and *Toluylene Blue*. *p*-Nitrosodimethylaniline can be substituted for the *p*-diamine in the preparation of indamines. *Indophenols* are similarly made by oxidizing a mixture of a phenol or a naphthol with a *p*-diamine or *p*-nitrosodimethylaniline. *Indophenol Blue* is made from the latter and α-naphthol. It has the structure

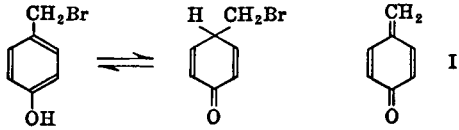


C. Pseudophenols, Methylene Quinones and Semibenzenes

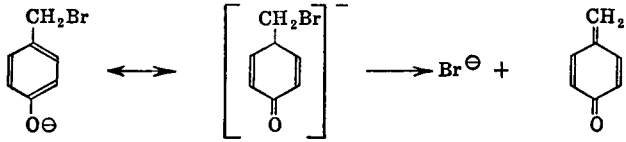
A phenol having an *o*- or *p*-side chain with a halogen alpha to the ring behaves abnormally with bases. Instead of dissolving to give a phenolate the halogen is removed and a methylene quinone is obtained. Many such *pseudo phenols* have been studied.[2] Most of these have been very complex but the principles involved may be illustrated by the unknown *p*-hydroxybenzyl bromide. They show well the difference between the older conservative conception that a structure formula was purely a "reaction" formula and did not necessarily indicate the actual structure of the molecule and the more modern conviction of the literal truth of most structural formulas. As the ordinary formula for a substance like *p*-OH-benzyl bromide would not explain

[2] Auwers, Zincke. For references see Richter-Anschütz. "The Chemistry of Carbon Compounds," Vol. III. Elsevier Publishing Co., New York, 1946.

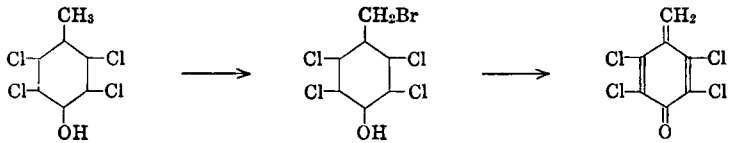
its insolubility in alkali, a quinoidal or pseudophenol structure was proposed.



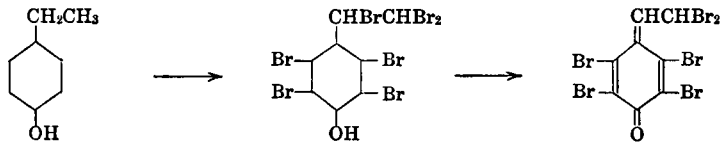
The first formula corresponds to the formation of an acetate in the ordinary way while the second gives a ready interpretation of the formation of the methylene quinone (I) by the action of alkali. It is more probable that the substance has the true phenol formula and that the presence of the halogen alpha to the ring makes possible the formation of the methylene quinone from the phenolate ion formed by the action of the base.

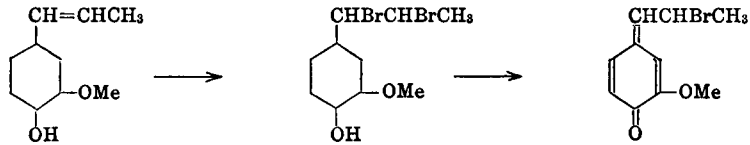


The net result is that a normal reaction, started in one part of the molecule, causes a change in another reactive part of the molecule before the first change has reached its ordinary conclusion. Some of the "pseudophenols" and related methylene quinones which have been prepared follow:



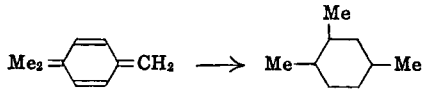
m. 160°



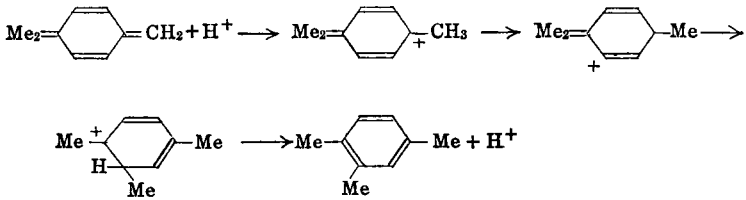


The methylene quinones usually undergo condensation to very complex products.

The **semibenzenes** resemble the quinones in many ways. A trace of acid transforms these to the isomeric aromatic compounds.[3]



This is a combination of an allylic shift and a pinacolone rearrangement caused by the addition of a proton



A more complex reaction but one involving the same types of change is the formation of pentamethylbenzene by the action of a trace of acid on 1,1,2,6-Me_4-4-methylene-cyclohexadiene-2,5.

XV. AROMATIC CARBOXYLIC ACIDS

These are known in great variety. In general they resemble the aliphatic acids in chemical properties. Those having the carboxyl attached directly to the aromatic ring have no alpha H and so resemble more closely the tri-substituted acetic acids. Like them they are usually solids. The most characteristic preparation of such acids is by the oxidation of side chains which removes all of the latter except the carbon attached to the ring. The product is stable to oxidation unless it contains some strongly *o,p*-orienting group such as OH or NH_2. When the carboxyl is attached to a side chain the properties are more nearly like those of the analogous aliphatic acids. Aromatic acids are known with practically all types of substituents in the nucleus or side chains. In general, the carboxyl derivatives of the aromatic series are slightly stronger acids than those of the aliphatic series.

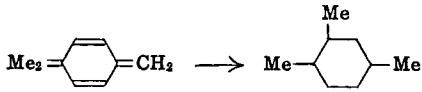
A. Benzoic Acid and Its Derivatives

Benzoic acid, carboxybenzene, benzene carboxylic acid, $C_6H_5CO_2H$, m. 121°, b. 250°, is found in many natural gums and balsams. It occurs characteristically in the urine of the herbivora as hippuric acid, $PhCONHCH_2CO_2H$. The preparation and reactions of benzoic acid are typical of acids having the carboxyl attached directly to the aromatic nucleus.

[3] *Ann Rep. Chem. Soc.* (London) **1922**, 96.

The methylene quinones usually undergo condensation to very complex products.

The **semibenzenes** resemble the quinones in many ways. A trace of acid transforms these to the isomeric aromatic compounds.[3]



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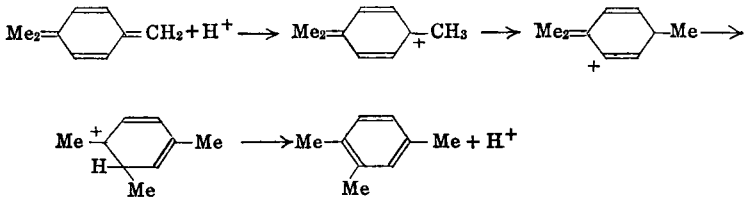

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[3] *Ann Rep. Chem. Soc.* (London) **1922**, 96.

Preparation. 1. The most typical method is by the conversion of the methyl group of toluene to carboxyl by direct or indirect oxidation. This preparation is possible because of the stability of the benzene ring to any but the most vigorous oxidation.

a. Toluene can be oxidized to benzoic acid by refluxing with dilute nitric acid, chromic acid mixture, or alkaline permanganate. The process is slow because of the insolubility of the toluene in the aqueous reagents and its relative inactivity. The most commonly used oxidant is chromic acid which can be regenerated electrolytically from the chromic salts formed.

$$PhCH_3 + Na_2Cr_2O_7 + 4\ H_2SO_4 \rightarrow PhCO_2H + Na_2SO_4 + Cr_2(SO_4)_3 + 5\ H_2O$$

b. When benzaldehyde is made from benzyl chloride by hydrolysis and oxidation or by the hydrolysis of benzal chloride, benzoic acid is always obtained as a by-product which can be separated by distillation and by washing with bicarbonate solution.

c. Benzotrichloride, $C_6H_5CCl_3$, obtained by chlorinating boiling toluene without a catalyst, can be hydrolyzed to benzoic acid

$$C_6H_5CCl_3 + 2\ H_2O \rightarrow 3\ HCl + C_6H_5CO_2H$$

Formerly this process offered the difficulty due to the presence of a small but toxic impurity of *p*-chlorobenzoic acid which rendered the product unsuitable for use as a food preservative in the common use of "one tenth of one percent of benzoate of soda." This difficulty is overcome by purifying the benzotrichloride by careful fractional distillation.

2. An increasingly important preparation is by the catalytic decarboxylation of phthalic anhydride.[1]

3. The hydrolysis of benzonitrile, C_6H_5CN, which can be obtained in a variety of ways.

$$C_6H_5CN + 2\ H_2O \rightarrow C_6H_5CO_2H + NH_3$$

In general, aromatic nitriles are much more difficult to hydrolyze than their aliphatic analogs. In some cases the hydrolysis proceeds to the acid amide and then stops. Treatment with concentrated sulfuric acid, with a mixture of concentrated sulfuric acid and glacial acetic acid or with sulfuric acid and sodium nitrite, will usually complete the process.

4. Phenylmagnesium halides with CO_2 give benzoic acid. A similar method involves the action of CO_2 on phenyl bromide and sodium or the action of sodium on a mixture of phenyl bromide and ethyl chlorocarbonate. Treatment of benzene with ethylpotassium (EtK) and then with CO_2 gives benzoic and terephthalic acids.[2]

5. The Friedel-Crafts reaction between benzene and phosgene or carbamic chloride in presence of $AlCl_3$ gives benzoyl chloride or benzamide which can be hydrolyzed to the acid.

[1] Conover. U. S. Patent No. 2,063,365 (1937).

[2] Gilman, Kirby. *J. Am. Chem. Soc.* 58, 2074 (1936).

The *reactions* of benzoic acid can be divided into those of the carboxyl group and of the benzene ring.

I. *Carboxyl reactions.*

a. Salts are formed in the usual way. Sodium benzoate is used as a food preservative. Calcium benzoate crystallizes with 3 H_2O in glistening prisms. The addition of 2% calcium benzoate to greases made from fatty acid soaps increases their water resistance. Sodium benzoate solution, with halogens, gives mixtures of *o-*, *m-*, and *p*-halogen-benzoic acids. Silver benzoate with iodine gives CO_2, phenyl benzoate and AgI. In presence of benzene, the organic products are iodobenzene (31%) and phenyl benzoate (32%). The Ag salt of *p*-toluic acid similarly gives 18% iodobenzene and 52% phenyl toluate.[3]

b. Esters are best prepared by refluxing benzoic acid in the required alcohol with a trace of HCl gas or conc. H_2SO_4. The Me, Et and *n*-Pr esters b. 199.6°, 212.6° and 231°. Higher aliphatic esters, when distilled at atmospheric pressure, decompose to benzoic acid and the olefin. *Benzyl benzoate*, m. 21°, b. 324°, used as an antispasmodic and miticide, is usually prepared from benzaldehyde by the catalytic action of sodium benzylate, $PhCH_2ONa$, or $Al(OEt)_3$.[4] Another preparation is from dry sodium benzoate and benzoyl chloride. This reaction is catalyzed by a small amount of tertiary amines. Aromatic esters are less reactive than aliphatic esters in hydrolysis and ammonolysis. This is not surprising as they are "tertiary" acids. Thus the reactivity of Et_3CCO_2Et would probably be even less than that of $C_6H_5CO_2Et$.

Benzoyl chloride, C_6H_5COCl, b. 198°, can be made in the usual ways. Commercially it is made by the partial hydrolysis of benzotrichloride. It is made in large amounts for the preparation of benzoyl peroxide. It is less reactive than ordinary aliphatic acyl halides. Benzoylation of OH and NH_2 compounds is usually carried out by the *Schotten-Baumann* method of using benzoyl chloride and a *base.*

$$ROH + PhCOCl + NaOH \rightarrow PhCO_2R + NaCl + H_2O$$

Benzoyl bromide, b. 219°, can be made by PBr_3 and benzoic acid. **Benzoyl iodide,** m. 3°, b. 135° (25 mm), is best made by passing HI gas through benzoyl chloride until no more HCl is displaced. It is very reactive. **Benzoyl fluoride,** b. 155°, is formed from the chloride and KHF_2. **Benzoyl cyanide,** C_6H_5COCN, m. 33°, b. 206°, is formed by distilling the chloride with CuCN[5] or by the successive action of nitrous acid and acetic anhydride on acetophenone.

$$PhCOCH_3 \xrightarrow{HNO_2} PhCOCH{=}NOH \xrightarrow{Ac_2O} PhCOCN.$$

[3] Birckenbach, Meisenheimer. *Ber.* **69B**, 723 (1936).
[4] "Org. Syntheses."
[5] "Org. Syntheses."

It behaves like an acyl halide rather than a keto nitrile. With NH_3, aniline, diethylzinc and Zn and HCl it gives benzamide, benzanilide, phenyl ethyl ketone and benzaldehyde. With metallic sodium it gives a polymer, m. 95°, which reacts with NaOH to give sodium benzoate, NaCN and NH_3. Only with cold fuming HCl does it react like a nitrile to give benzoylformic acid, $PhCOCO_2H$.

Benzoic anhydride, $(C_6H_5CO)_2O$, m. 42°, b. 360°, is prepared by heating benzoyl chloride with anhydrous oxalic acid. Its reactions are like those of acetic anhydride.

Benzoyl peroxide, (Lucidol) $(C_6H_5CO)_2O_2$, m. 108°, made by benzoyl chloride and sodium peroxide, is relatively stable. It is used as a bleaching agent for wheat flour. *Perbenzoic acid,* $HO-O-COC_6H_5$, is obtained from the peroxide.[6]

$$(PhCO)_2O_2 + EtONa \rightarrow PhCO_2Et + PhCO_3Na$$

Its chloroform solution is an oxidizing agent.[7]

Benzamide, $C_6H_5CONH_2$, m. 130°, b. 290°, is readily made from benzoyl chloride and ammonium carbonate. Silver compounds are known of the forms PhCONHAg, orange, and PhC(OAg)NH, colorless.

Benzanilide, $C_6H_5CONHC_6H_5$, m. 161°, b. 119° (10 mm), is made by heating benzoic acid and aniline (OS).

Benzoylhydrazine, benzhydrazide, $C_6H_5CONHNH_2$, m. 112°, is easily made from hydrazine and ethyl benzoate.

Benzazide, benzoyl azoimide, $C_6H_5CON_3$, m. 30°, is formed from the hydrazide by nitrous acid. It is explosive on heating alone. When heated with water, it gives N_2, $PhNHCO_2H$ (unstable) and $(PhNH)_2CO$. With alcohol it gives $PhNHCO_2R$. These are Curtius rearrangements (p. 186) in which the intermediate isocyanate has added a molecule of solvent. With NaOEt it gives NaN_3 and Et benzoate.

Benzonitrile, phenyl cyanide, C_6H_5CN, b. 191°, is obtained from

a. Benzamide with PCl_5 or P_2O_5.

b. Sodium benzene sulfonate fused with NaCN.

c. Benzene diazonium chloride and cuprous cyanide (Sandmeyer).

d. Benzoic acid distilled with NH_4SCN.

Its reactions are typical nitrile reactions. Thus with HCl, NH_3 and amines, and H_2O it gives benzimino chloride, amidines and benzamide respectively. Reduction gives benzyl amine and hydrolysis gives benzoic acid. Ammonium sulfide gives *thiobenzamide,* $C_6H_5CSNH_2$, m. 116°.

B. Substituted Benzoic Acids

These are known in great number. Some of the meta derivatives can be made by direct substitution. The three isomers of a monosubstituted benzoic acid can often be made in three general ways:

[6] "Org. Syntheses."

[7] *ibid.*

1. By oxidation of a substituted toluene by means of dilute nitric acid which converts the methyl to carboxyl.

2. By diazotizing an aminobenzoic acid and introducing the desired group.

3. By diazotizing a substituted aniline, replacing the diazonium group by CN, and hydrolyzing the resulting nitrile.

The *halogen benzoic acids* illustrate the first two methods and a few special ones in addition. The four *o-halogenbenzoic acids* are usually obtained by diazotizing anthranilic acid (prepared from naphthalene) and replacing the diazonium group by treatment with HF, Cu_2Cl_2, Cu_2Br_2 or KI. *o-Iodobenzoic acid*, m. 162°, is of special interest because of its ready conversion by treatment with chlorine in $CHCl_3$ solution and then with water to *o-iodosobenzoic acid*, $C_6H_4(IO)CO_2H$, m. 244° dec., which is converted by alkaline permanganate to *o-iodoxybenzoic acid*, $C_6H_4(IO_2)CO_2H$, which explodes at 233°. If *o-iodobenzoic acid* is needed in large amounts it will probably be made from phthalic anhydride through anhydro-*o*-hydroxymercuribenzoic acid.[8]

$$C_6H_4(CO)_2O \xrightarrow{HgCl_2} \xrightarrow{heat}$$

$$CO_2 + C_6H_4(HgO)CO \xrightarrow[ICl]{NaCl} HgCl_2 + C_6H_4ICO_2Na$$

A remarkable formation of *o*-halogenbenzoic acids is by the action of alcoholic KCN at 200°, on the *meta*-nitrohalogen benzenes.[9]

The four *m-halogenbenzoic acids* can be made by diazotizing *m*-aminobenzoic acid obtained by reducing the nitro compound formed by the direct nitration of benzoic acid. *m*-Chlorobenzoic acid can be made by direct chlorination by heating benzoic acid, MnO_2 and conc. HCl at 150°. *m*-Bromobenzoic acid is obtained by heating benzoic acid, bromine and water at 150°. *m*-Iodobenzoic acid can be made by heating benzoic acid with KIO_3 and H_2SO_4 or by heating silver benzoate with iodine at 150°. The difficulty of these direct halogenations of benzoic acid well illustrates the fact that *meta directing groups make substitution in the benzene ring more difficult.*

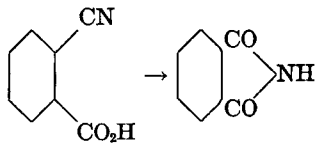
The *m*-halogenbenzoic acids can also be made by the action of alcoholic KCN at 200° on the *para*-nitrohalogen benzenes.[10]

While the four *p-halogenbenzoic acids* can be made by diazotization of *p*-aminobenzoic acid prepared from the *p*-NO_2-compound obtained by oxidizing *p*-NO_2-toluene, it is better to make them by oxidizing with dil. nitric acid the *p*-halogentoluenes prepared either by direct halogenation or by diazotizing *p*-toluidine. *p*-Iodobenzoic acid has been made by the action of iodine on *p*-chloromercuribenzoic acid.[11]

[8] "Org. Syntheses."
[9] Richter. *Ber.* 4, 21 (1871).
[10] Richter. *Ber.* 4, 21 (1871).
[11] "Org. Syntheses."

Polyhalogenbenzoic acids are available. Thus 2,4-*dibromobenzoic* acid, m. 167°, is obtained by oxidizing 2,4-Br_2-toluene with nitric acid while 2,4,6-Br_3-benzoic acid, m. 187°, is made by brominating *m*-aminobenzoic acid and then removing the NH_2 group by diazotization. *Pentabromobenzoic acid*, m. 252°, is made by heating with Br_2 at 200°, *3,4,5-Br_3-benzoic acid*, m. 239°, obtained by carefully brominating *p*-aminobenzoic acid and replacing the NH_2 by diazotization.

The three *cyanobenzoic acids*, $C_6H_4(CN)CO_2H$, are made by diazotizing the aminobenzoic acids and treating with $Cu_2(CN)_2$ made from KCN and $CuSO_4$. The *o*-acid melts about 180°, changing to phthalimide.



Of the three *nitrobenzoic acids*, the *m*-acid is available by direct nitration of benzoic acid with fuming nitric acid. About 20 and 2% of the *o*- and *p*-acids are formed at the same time. The *o*- and *p*-acids are best prepared by oxidizing *o*- and *p*-nitrotoluenes with permanganate or dilute nitric acid. With *m*-nitrotoluene commercially available, the *m*-acid could perhaps be made more cheaply by oxidizing it than by nitrating benzoic acid.

Di- and *tri-nitrobenzoic acids* are available by the standard reactions. *3,5-Dinitrobenzoic acid*, m. 205°, is easily made by nitrating benzoic acid with a mixture of fuming nitric acid and sulfuric acid. This acid is valuable in identifying primary and secondary alcohols because of the relatively high melting points of its esters. *2,4-Dinitrobenzoic acid*, m. 183°, and *2,4,6-trinitrobenzoic acid*, m. 228°, are made by oxidizing the corresponding nitrotoluenes with chromic acid mixture.[12]

Sulfobenzoic Acids, Sulfonic Acids of Benzoic Acid

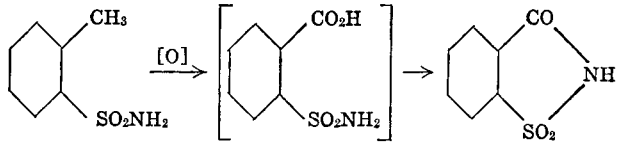
The **m-acid** is obtainable by direct sulfonation of benzoic acid with fuming sulfuric acid. The acid sodium salt is relatively insoluble in NaCl solution.

o-Sulfobenzoic acid is important because its imide is *saccharin*, large amounts of which are made to be used as a sweetening agent in place of carbohydrates. A solution of one part in three thousand of water is about as sweet as a one percent sucrose solution. The steps for its preparation follow:

Toluene is treated with chlorosulfonic acid to give a mixture of *o*- and *p*-toluene sulfonyl chlorides. The latter is a solid and most of it can be separated readily from the liquid *o*-compound. The latter is carefully purified

[12] "Org. Syntheses."

and then converted to the amide. This is oxidized with chromic acid. The resulting acid forms the internal benzosulfimide, *saccharin.*



The hydrolysis of saccharin with HCl gives acid ammonium *o*-sulfobenzoate[13] which, with $SOCl_2$, gives the anhydride[14] which can be converted to the free acid or used to make sulfonephthaleins just as phthalic anhydride is used.

***p*-Sulfobenzoic acid,** m. 200° dec., is made by sulfonating toluene and oxidizing the product with chromic acid mixture or permanganate. It is purified as the acid barium salt and then converted to the free acid by the calculated amount of H_2SO_4.

Aminobenzoic Acids

They are obtained by reducing the nitro compounds with such reagents as zinc and acid, ammonium sulfide, and alkaline ferrous hydroxide. Their reduction in alkaline solution is very easy because of the solubilizing effect of the carboxyl group. The aminobenzoic acids, as amphoteric substances, are soluble in either acid or basic solution.

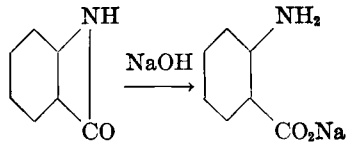
$$H_2NC_6H_4CO_2^{\ominus} \xleftarrow{OH^{\ominus}} {}^{\oplus}H_3NC_6H_4CO_2^{\ominus} \xrightarrow{H^{\oplus}} {}^{\oplus}H_3NC_6H_4CO_2H$$

Diazotization gives internal diazonium salts, ${}^{\oplus}N_2C_6H_4CO_2^{\ominus}$, similar to those formed by the aminosulfonic acids. The NH_2-benzoic acids give the reactions of both their reactive groups including ready substitution *o*- and *p*- to the NH_2 group. When the carboxyl is *o*- or *p*- to the NH_2, it may be replaced during such a change. Thus the careful bromination of *p*-NH_2-benzoic acid gives the 2,6-Br_2 compound but vigorous treatment with an excess of Br_2 gives CO_2 and Br_3-aniline.

Anthranilic acid, *o*-aminobenzoic acid, m. 145°, is best made by the Hofmann reaction through the action of hypochlorite and alkali on phthalimide. It is the starting point for the preparation of indigo using naphthalene as the ultimate raw material. When diazotized and coupled with Me_2-aniline it gives the indicator Methyl Red.[15] The anhydride or inner amide, *anthranil* (I), is obtained by reducing *o*-NO_2-benzaldehyde with Sn and acetic acid. With

[13] *ibid.*
[14] *ibid.*
[15] "Org. Syntheses."

NaOH it gives Na anthranilate.



(I)

Methyl anthranilate is used in perfumes.

***p*-Aminobenzoic acid** is important because its esters have local anesthetic properties. *Anesthesin*, *Butesin*, *Novocaine* (*Procaine*), and *Butyn* are salts of its ethyl, *n*-butyl, β-diethylaminoethyl, and γ-di-*n*-butylaminopropyl esters.

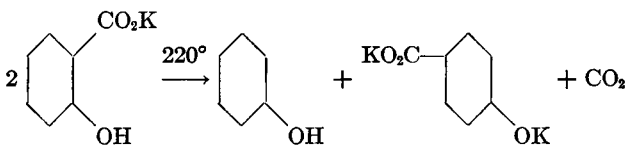
Phenolic Acids

These have the properties of a phenol and a substituted benzoic acid. Thus with NaOH they give di-sodium salts but with carbonates they give mono-sodium salts, only the carboxyl reacting. The positions *o*- and *p*- to the hydrozyl have the usual reactivity toward substituting reagents. If the carboxyl is on one of these positions it also may be displaced. Thus treatment of salicylic acid with excess bromine water gives CO_2 and Br_3-phenylhypobromite.

Salicylic acid, *o*-hydroxybenzoic acid, m. 155°, is prepared by heating Na phenate with CO_2 under pressure at 130° (Kolbe) if K phenate is used below 150° the same result is obtained but at higher temperatures the *p*-compound results

$$C_6H_5ONa + CO_2 \rightarrow C_6H_5OCO_2Na \rightarrow C_6H_4(OH)CO_2Na$$

The mechanism of the reaction is indicated by the fact that K salicylate at 220° gives phenol and the di-K salt of *p*-OH-benzoic acid.



Salicylic acid and its compounds have antiseptic properties. The ubiquitous drug, Aspirin, is acetylsalicylic acid.

Methyl salicylate, $C_6H_4(OH)CO_2CH_3$, b. 223°, is artificial oil of wintergreen.

Phenyl salicylate, $C_6H_4(OH)CO_2C_6H_5$, m. 43°, is used as *Salol* in medicine. Because of its stability to acid, it passes unchanged through the stomach and undergoes alkaline hydrolysis in the intestine to give phenol and Na salicylate. It is prepared from salicylic acid, phenol and $POCl_3$. It is used in sun-tan creams.

***m*-Hydroxybenzoic acid,** m. 201°, is made by alkali fusion of sodium *m*-sulfobenzoate or by diazotization of *m*-aminobenzoic acid or its methyl ester. The reactions of the NH_2 and CO_2H groups are independent of each other. The carboxyl is not easily removed as it is when *o*- and *p*- to the OH group.

***p*-Hydroxybenzoic acid,** m. 213°, is made by the action of CO under pressure on K phenoxide at 200° or by the action of carbon tetrachloride on phenol in presence of NaOH (Reimer, Tiemann). Its reactions are typical of its two reactive groups. Its methyl ether is *anisic acid*, $CH_3OC_6H_4CO_2H$, m. 184°, b. 280°.

Protocatechuic acid, 3,4-dihydroxybenzoic acid, m. 199°, is obtained by the alkaline fusion of various natural resins which probably contain depsides of this acid. It is obtained along with *pyrocatechuic acid*, 2,3-$(OH)_2$-benzoic acid, m. 204°, when pyrocatechol is heated with ammonium carbonate. Its 3-Me ether is *vanillic acid*, m. 207°, which is formed by oxidizing the related aldehyde, vanillin. Its dimethyl ether is *veratric acid*, m. 181°, while its 3,4-methylene ether is *piperonylic acid*, m. 228°, which is related to piperic acid. Capsaicin is a vanillyl amide,[16]

$$Me_2CHCH=CH(CH_2)_4CONHCH_2C_6H_3(OH)OMe.$$

Gentisic acid, 2,5-dihydroxybenzoic acid, m. 197°, is made by heating hydroquinone and $KHCO_3$ solution at 130°. Heating resorcinol with ammonium carbonate gives mainly *β-resorcylic acid*, 2,4-$(OH)_2$-benzoic acid, m. 213°, with a smaller amount of the 2,6-acid, *γ-resorcylic acid*, m. 167° dec. *α-Resorcylic acid*, 3,5-$(OH)_2$-benzoic acid, m. 237°, is made by fusing disulfobenzoic acid with KOH. It is more stable than its isomers which have the carboxyl *o*- or *p*- to hydroxyl. The local anesthetic, *orthoform*, is the methyl ester of 3-amino-4-hydroxybenzoic acid.

Gallic acid, 3,4,5-trihydroxybenzoic acid, m. 220° dec., occurs in nut galls, in tea, and as glucosides in tannins. It is obtained by hydrolysis of nut galls and certain tannins. On heating, it gives CO_2 and pyrogallol. Its chief use is in ink. Propyl gallate is a non-injurious food antioxidant of high activity. Its reactions have been extensively studied because of its relation to the natural *depsides*. These are esters formed from two or more molecules of the same or different phenolic acids. Thus the simplest di-depside is *p*-hydroxybenzoyl-*p*-hydroxybenzoic acid, $HOC_6H_4CO_2C_6H_4CO_2H$, m. 261°. The secret of success in these studies is the protection of the hydroxyl groups so that they will not interfere with the reactions of the carboxyl groups. At first this was done by acetylation but later it was more successfully achieved by means of the carbethoxy group, $-CO_2Et$, introduced by means of chloroformic ester. The superiority of the latter group is due to its easier removal. Whereas the acetyl group can be removed only by vigorous treatment with HCl, the carbethoxy group can be removed by mild treatment with alcoholic ammonia. A means of protecting two adjacent hydroxyls is the action of phosgene which

[16] *Ann. Rep. Chem. Soc.* (London) **1923**, 98.

forms a carbonate. *m-Digallic acid*, *m*-galloyl-gallic acid, m. 285° can be made by the following steps which show its structure:

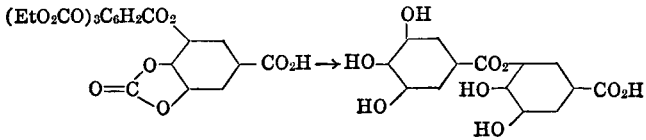
1. Gallic acid is treated with NaOH and $ClCO_2Et$ to give

$$(EtO_2CO)_3C_6H_2CO_2H$$

which can then be converted to the acid chloride by cold PCl_5.

2. Gallic acid, NaOH, and $COCl_2$ give a carbonate involving the 3- and 4-hydroxyls but leaving the 5-OH free.

3. The acid chloride can be condensed with the free OH. The protecting groups can then be removed by treatment with alcoholic NH_3 without breaking the phenol ester linkage.



m-Digallic acid

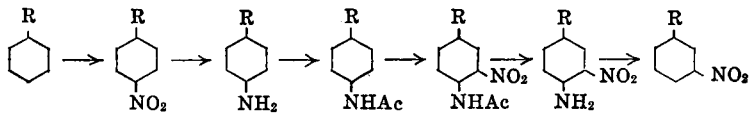
If the pentamethyl ether of this acid is converted to the acid chloride which is then condensed with glucose it is possible to obtain a methylated pentadigalloyl glucose which is identical with a methyl *tannin* obtained by methylating Chinese tannin with diazomethane.

The technique of Bergmann (p. 513) for protecting a group by the action of $PhCH_2OCOCl$ and removal of the protecting group by mild hydrogenation could undoubtedly be used in depside studies.

Simpler depsides occur in various lichens. For instance *lecanoric acid* is the di-depside of *orsellinic acid*, 4,6-dihydroxy-*o*-toluic acid, m. 176°. *Evernic acid*, m. 169°, is the monomethyl ether of this di-depside.

Alkyl Benzoic Acids

The three *toluic acids* or methylbenzoic acids can be made by oxidation of the three xylenes with dilute nitric acid. In the case of the *p*-compound, *p*-cymene is more available than *p*-xylene and the oxidation removes mainly the isopropyl group because of the point of attack presented by its tertiary H. The toluic acids can also be made from the nitriles obtained by diazotizing the three toluidines and applying the Sandmeyer reaction. Higher *alkylated benzoic acids* can be made through the steps: hydrocarbon, nitro compound, amine, nitrile, acid. This gives only the *o*- and *p*-series. The *m*-series is harder to make.



This can then be converted to the amine, nitrile and acid of the *m*-series.

The six possible *xylic acids* or dimethylbenzoic acids are known. *Hemellitic acid*, 2,3-Me_2-benzoic acid, 2,3-xylic acid, m. 144°, is made by oxidizing hemimellitene with dilute nitric acid. *3,4-Xylic acid*, m. 166°, can be made by oxidizing pseudocumene (along with smaller amounts of the 2,4-acid) or from the nitrile obtained by fusing a cyanide with a salt of *o*-xylene-4-sulfonic acid. *2,6-Xylic acid*, m. 116°, is made by fusing a salt of the difficultly obtainable *m*-xylene-2-sulfonic acid with a formate. *2,4-Xylic acid*, m. 126°, is the most readily available of these acids. Probably the best preparation is by the action of phosgene and $AlCl_3$ on *m*-xylene. *Mesitylenic acid*, 3,5-xylic acid, m. 166°, is made by oxidizing mesitylene with dilute nitric acid. *2,5-Xylic acid*, isoxylic acid, m. 132°, is made from the amide obtained from *p*-xylene, NH_2COCl and $AlCl_3$ in CS_2 solution.

The six possible *trimethylbenzoic acids* are made by oxidation of the three tetramethylbenzenes with dilute nitric acid. Prehnitene gives mainly *prehnitylic acid*, 2,3,4-Me_3-benzoic acid, m. 167°. From its mother liquors is obtained the isomeric *2,3,6-Me_3-benzoic acid*, m. 106°. Durene can give only one acid of this series, *durylic acid* (cumylic acid), 2,4,5-Me_3-benzoic acid, m. 150°. Isodurene gives the three possible monobasic acids in nearly equal amounts. When the barium salts are crystallized the first to separate is that of *α-isodurylic acid*, 3,4,5-Me_3-benzoic acid, m. 215°. The acids are liberated from the mother liquors and are crystallized from ligroin. The first to separate is *β-isodurylic acid*, 2,4,6-Me_3-benzoic acid, m. 152°. From the mother liquors is obtained *γ-isodurylic acid*, 2,3,5-Me_3-benzoic acid, m. 127°.

The three possible *tetramethylbenzoic acids* have been made. The 2,3,4,5-Me_4-acid, m. 165° is made by oxidizing Me_5-benzene. The *2,3,4,6-acid*, m. 140°, is made by oxidizing the corresponding methyl ketone obtained from isodurene, acetyl chloride and $AlCl_3$ in CS_2, at low temperature. The *2,3,5,6-acid*, m. 179°, is similarly made from phosgene and durene.

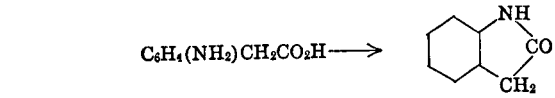
The complex relationships of symmetry and melting points are well illustrated by the polymethylbenzoic acids.

C. Aryl-substituted Aliphatic Acids

These are known in nearly as large numbers as the substituted benzoic acids. Because they usually have one or two alpha H atoms and may have reactive groups both in the side chain and the ring, their chemistry is very complex.

Phenylacetic acid, α-toluic acid, $C_6H_5CH_2CO_2H$, m. 77°, b. 265°, is available from benzyl cyanide, $C_6H_5CH_2CN$, b. 232°, which is readily formed from benzyl chloride and a cyanide. The expected substitution products involving the α- and aryl hydrogens are known. They give the normal reactions. An exception is *o*-amino-phenylacetic acid which cannot exist in the free form but

becomes oxindole, m. 120°.



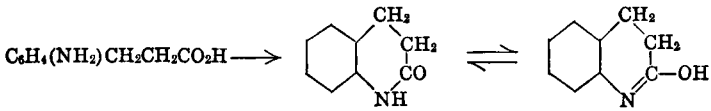
This is another example of the ease of ring closure when two mutually reactive groups are in the 1,5-position. *Phenylacetamide*, $C_6H_5CH_2CONH_2$, may be prepared from benzoyl chloride by the *Arndt-Eistert synthesis.*[17]

$$C_6H_5COCl \xrightarrow{CH_2N_2} C_6H_5COCHN_2 \xrightarrow[Ag_2O]{NH_3,\ EtOH} C_6H_5CH_2CONH_2$$

A convenient preparation from acetophenone is by the *Willgerodt reaction.*[18]

$$C_6H_5COCH_3 \xrightarrow{(NH_4)_2S_x} C_6H_5CH_2CONH_2$$

β-Phenylpropionic acid, hydrocinnamic acid, $C_6H_5CH_2CH_2CO_2H$, m. 48°, b. 280°, is obtained by the easy reduction of cinnamic acid either by nascent or catalytic hydrogen. Its α-amino derivative is phenylalanine, a protein decomposition product. When the NH_2 group is in the *o*-position, the free acid changes spontaneously to *hydrocarbostyril*, a dihydroquinoline derivative.



α-Phenylpropionic acid, hydratropic acid, $C_6H_5CH(CH_3)CO_2H$, b. 265°, is obtained by reducing atropic acid formed by dehydrating tropic acid.

Since phenyl halides do not react with substances like Na-malonic ester, *phenylethylmalonic ester*, $C_6H_5(Et)C(CO_2R)_2$, the intermediate for the important soporific Luminal cannot be made from malonic ester. Several methods have been devised for its preparation.

1. Phenylacetic and oxalic esters are condensed and the phenyloxaloacetic ester is decomposed by heat.

$$EtO_2C(Ph)CH_2 + EtOCOCO_2Et \rightarrow$$
$$EtO_2C(Ph)CHCOCO_2Et \rightarrow CO + PhCH(CO_2Et)_2$$

Treatment with Na and EtBr gives the desired product although the yield is not good.

[17] "Org. Reactions."
[18] *ibid.*

2. Benzylcyanide with sodamide in ether gives a sodium derivative which reacts with ethyl carbonate.[19]

$$PhCH_2CN \xrightarrow{NaNH_2} \xrightarrow{Et_2CO_3} PhCH(CN)CO_2Et \xrightarrow[EtOH]{HCl} PhCH(CO_2Et)_2, \text{ etc.}$$

3. Benzyl cyanide can be ethylated by Na and EtBr.[20]

$$PhCH_2CN \xrightarrow[EtBr]{Na} PhEtCHCN \xrightarrow[ClCO_2Me]{Na}$$

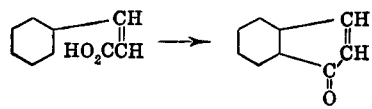
$$PhEtC(CN)CO_2Me \xrightarrow[MeOH]{HCl} PhEtC(CO_2Me)_2$$

The phenylethylacetonitrile does not condense with ethyl carbonate.

Cinnamic acid, *trans*-β-phenylacrylic acid, $C_6H_5CH=CHCO_2H$, m. 133°, b. 300°, occurs in natural balsams and resins and can be readily prepared by the Perkin reaction by heating benzaldehyde, sodium acetate and acetic anhydride. It gives the reactions of an alpha beta unsaturated acid and of a benzene compound. Nitration gives *o*- and *p*-nitro compounds. Fusion with KOH gives acetic and benzoic acids.

Allocinnamic acid, the *cis*-form, m. 68°, is prepared in a variety of ways but most readily by the catalytic reduction of phenylpropiolic acid. It exists in polymorphic forms as various isocinnamic acids, m. 59°, 38°, 80°, and possibly 131°.

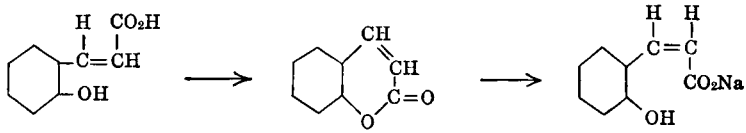
Two **α-bromocinnamic acids,** m. 120° and 131°, are obtained from cinnamic acid dibromide. Two β-bromocinnamic acids, m. 135° and 159°, are obtained by adding HBr to phenyl propiolic acid. The *cis* forms yield indenones with sulfuric acid.



***o*-Aminocinnamic acid,** obtained by the reduction of the *o*-NO_2 acid from the direct nitration of allocinnamic acid, spontaneously changes to carbostyril, α-OH-quinoline, an example of the ease of 6-ring closure. This change also indicates the *cis* nature of the acid. The stereoisomeric *o*-NH_2-cinnamic acid does not change to a ring compound but gives ordinary cinnamic acid when its NH_2 group is replaced by H.[21]

[19] Nelson, Cretcher. *J. Am. Chem. Soc.* **50**, 2758 (1928).
[20] Rising, Tsoh-Wu Zee. *J. Am. Chem. Soc.* **50**, 1208 (1928).
[21] Stoermer, Heymann. *Ber.* **45**, 3099 (1912).

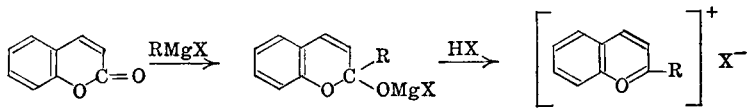
trans-o-Hydroxycinnamic acid, *coumaric* acid, is made by diazotizing the *o*-NH_2-acid or by the Perkin synthesis from salicylaldehyde. Vigorous dehydration with acetic anhydride gives *coumarin*, m. 67°, b. 290°, an inner anhydride. This dissolves in NaOH to give the salt of *coumarinic acid* the *cis-o*-OH-cinnamic acid.



Coumaric acid Coumarin Coumarinic acid

Coumarin is an important natural and artificial perfume and flavoring material. It is used with vanillin in artificial vanilla extract and in fixing odors in perfumes.

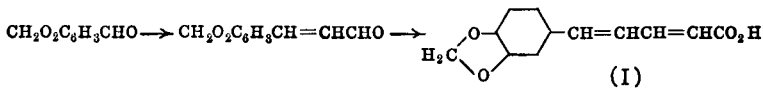
Coumarin, with Grignard reagents, gives a peculiar type of pseudo base.



A benzopyrilium salt

Caffeic acid, 3,4-$(OH)_2$-cinnamic acid, m. 220°, occurs in plant products, notably in coffee as *chlorogenic acid*, a di-depside in which it is esterified with the 3-OH of quinic acid. The 3-Me-ether of caffeic acid is *ferulic acid*, m. 168°, while the 4-Me-ether is *hesperitinic acid*, or isoferulic acid, m. 228°. *Umbellic acid*, 2,4-$(OH)_2$-cinnamic acid, readily changes to *umbelliferone*, m. 224°, a hydroxycoumarin. *Aesculetin*, *daphnetin*, *scopoletin*, *limettin*, and *fraxetin* are coumarins related respectively to the following cinnamic acids, 3,4-$(OH)_2$-, 2,3,4-$(OH)_3$-, 3-MeO-4-OH-, 2,4-$(MeO)_2$-, 2,3,4-$(OH)_3$-5-MeO-.

Piperic acid (I), m. 217°, b. 220° dec., as the piperidide *piperine*, is the chief constituent of pepper. Its synthesis from piperonal well illustrates the value of the aldol condensation and its modifications. The first step is a condensation with acetaldehyde and the second with Na acetate and Ac_2O.



(I)

Atropic acid, α-phenylacrylic acid, $CH_2=C(C_6H_5)CO_2H$, m. 107°, b. 267° dec., is made by dehydrating tropic acid. Fusion with KOH gives formic and phenylacetic acids.

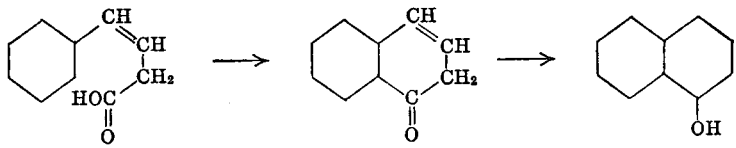
β-Benzalpropionic acid, γ-phenylisocrotonic acid, γ-phenylvinylacetic acid, $C_6H_5CH=CH-CH_2CO_2H$, m. 86°, b. 302°, is readily obtained by a modified Perkin reaction using benzaldehyde, Na succinate and Ac_2O at 110°. The steps are probably as follows:

$$PhCHO + \begin{matrix} CH_2CO_2Na \\ | \\ CH_2CO_2Na \end{matrix} \rightarrow \begin{matrix} PhCHOH-CH-CO_2Na \\ | \\ CH_2CO_2Na \end{matrix} \rightarrow$$

$$\begin{matrix} PhCH-CHCO_2Na \\ | \quad | \\ OCOCH_2 \end{matrix} \rightarrow PhCH=CH-CH_2CO_2Na$$

(I)

Phenylparaconic acid, m. 99°, corresponding to (I) is a byproduct. Further heating converts it to the unsaturated acid. The latter on refluxing for some time gives α-naphthol.



Phenylpropiolic acid, $C_6H_5C\equiv CCO_2H$, m. 137°, is made by eliminating 2 HBr from cinnamic acid dibromide or its ester. With H_2O at 120° it gives CO_2 and $PhC\equiv CH$ while with sulfuric acid it gives $PhCOCH_2CO_2H$.

Aryl Substituted Aliphatic Hydroxy and Keto Acids

Mandelic acid, phenylglycollic acid, $C_6H_5CHOHCO_2H$, m. 118°, occurs in amygdalin and is made from benzaldehyde cyanohydrin (*mandelonitrile*), dec. 170°.

Phthalide, m. 73°, b. 290°, is the inner ester of *o*-hydroxymethyl-benzoic acid obtained by the reduction of phthalic anhydride or phthalyl chloride with Zn and HCl.

Tropic acid, α-phenyl-β-hydroxypropionic acid, $HOCH_2CH(C_6H_5)CO_2H$, m. 118°, obtained by the hydrolysis of its tropine ester, atropine, has been synthesized by reducing the condensation product of ethyl phenylacetate and ethyl formate.

$$PhCH_2CO_2Et + HCO_2Et \rightarrow HCOCHPhCO_2Et \rightarrow$$
$$HOCH=CPhCO_2Et \rightarrow HOCH_2CHPhCO_2Et$$

Atrolactic acid, α-phenyl-α-hydroxypropionic acid, m. 93°.

Benzoylformic acid, phenylglyoxylic acid, $C_6H_5COCO_2H$, is a typical ketonic acid obtained by hydrolyzing benzoyl cyanide with cold conc. HCl.[22]

[22] Oakwood, Weisgerber. *Org. Syntheses* **24**, 16 (1944).

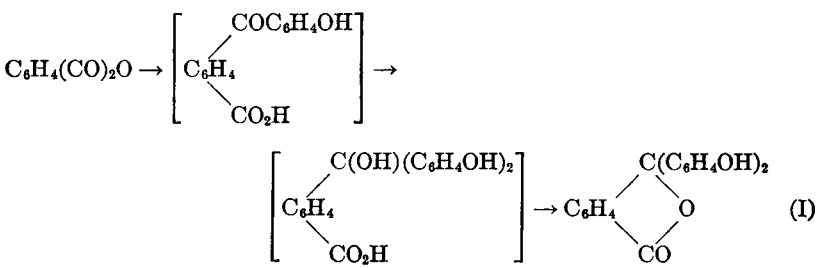
Benzoylacetic acid, $C_6H_5COCH_2CO_2H$, m. 103°, is obtained as its ester like acetoacetic ester by the condensation of Et benzoate and Et acetate by means of NaOEt. It and its ester resemble the other beta keto acids and their esters.

D. Dibasic Aromatic Acids

These have been made in great number and variety. Their properties depend on the position of the two carboxyl groups in relation to the aromatic ring, the side chain, if any, and to each other.

Phthalic acid, benzene-*o*-dicarboxylic acid, $C_6H_4(CO_2H)_2$, m. 213°, is formed by the oxidation of any benzene derivative having only two carbon substituents, these being in the ortho position. Naphthalene can be oxidized to phthalic acid in a variety of ways, including the famous method of oxidizing with concentrated sulfuric acid in presence of mercuric sulfate, supposedly discovered by the accidental breaking of a thermometer during a sulfonation experiment. Sodium amalgam converts it to di-, tetra- and hexahydrophthalic acids which are known in all the theoretically possible stereoisomeric forms.

Phthalic anhydride, m. 130°, b. 284°, is made cheaply in large quantities by the catalytic oxidation of naphthalene vapor with air under carefully controlled conditions. In addition to the ordinary reactions of an acid anhydride, it reacts with the *p*-H of phenols. The formation of phenolphthalein (I) is typical

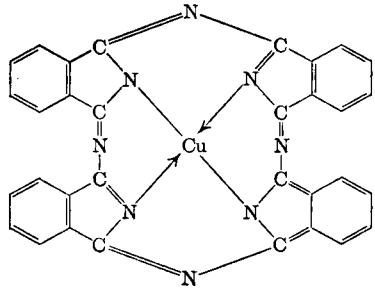


Similarly fluorescein is made from resorcinol. With aromatic hydrocarbons, phthalic anhydride condenses readily in presence of $AlCl_3$ to give substituted *o*-benzoylbenzoic acids which are important intermediates for making anthraquinones.

Phthalic anhydride reacts with alcoholic NH_3 to give ammonium phthalamate, $NH_2COC_6H_4CO_2NH_4$. Treatment of this substance or the free acid with hypohalites gives anthranilic acid. Phthalic anhydride can be catalytically decarboxylated to benzoic acid (p. 692).

Phthalic anhydride also reacts with copper salts and urea to give copper phthalocyanine which is a blue pigment of extreme stability. Exhaustive

chlorination of copper phthalocyanine gives a bright green, very stable pigment.



Copper phthalocyanine

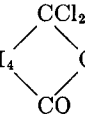
Normal and acid esters of phthalic acid are known. The former are obtained in the usual way from the acid or anhydride and excess of alcohol refluxed with a small amount of HCl or H_2SO_4. These esters are stable and very high boiling. They are extremely important as plasticizers. The dibutyl and di-2-ethylhexyl esters are used in place of mercury in high vacuum pumps of the vapor diffusion type. The latter ester has vapor pressures considerably less than the corresponding ones for mercury. The acid esters are obtained by the direct action of the anhydride and an alcohol. These are still acids and form salts. The salts with optically active bases like brucine can be used for separating *d*- and *l*- forms of optically active alcohols (p. 115).

Nitration and sulfonation of phthalic anhydride give the *3*- and *4-nitro*- and *3*- and *4-sulfo-phthalic acids*. The *3*- and *4*-isomers can be separated by differences in solubility, the former being less soluble. *3*- and *4-aminophthalic acids* can exist only as certain complex salts and as esters. Both free acids spontaneously lose CO_2 and give *m*-aminobenzoic acid. This is an unusual example of the activating effect of NH_2 on the *o*- and *p*-positions. *Luminol* is the hydrazide of 3-aminophthalic acid.

Heating the mercuric salt of phthalic acid gives CO_2 and anhydro-*o*-hydroxymercuribenzoic acid.[23] Similarly 3-nitrophthalic acid gives the 2-mercuri-3-NO_2-benzoic acid derivative (OS) in which the 2-Hg can be replaced by halogen to give 2-halogen-3-NO_2-benzoic acids.

Phthalimide, $C_6H_4(CO)_2NH$, m. 238°, is made by passing NH_3 gas over hot phthalic anhydride. Its potassium compound is readily formed by adding conc. KOH to alcoholic phthalimide. It is the intermediate for the *Gabriel synthesis of primary amines*. Potassium 3-nitrophthalimide is a convenient reagent for the identification of organic halogen compounds.

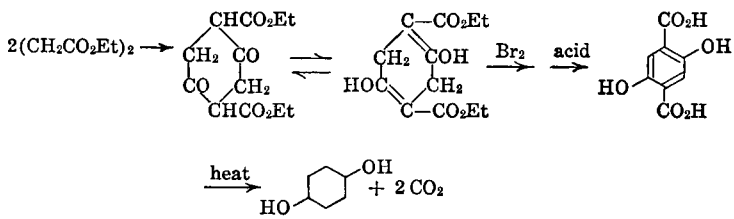
[23] "Org Syntheses."

Phthalyl chloride exists in both the symmetrical form, $C_6H_4(COCl)_2$, m. 16°, and the unsymmetrical form,  , m. 89°.

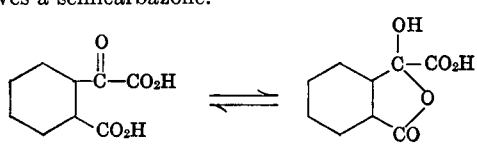
Phthalic anhydride and PCl_5 give the first which is converted to the second by heating with pure $AlCl_3$.[24] Apparently the $AlCl_3$ forms a more stable compound with the carbonyl group of the *unsym*-form than with either carbonyl of the true acid chloride form.

Isophthalic acid, benzene-1,3-dicarboxylic acid, m. 330°, is made by oxidizing *m*-xylene. It forms no anhydride. Its barium salt is readily soluble while those of the *o*- and *p*-phthalic acids are difficultly soluble. Its methyl ester melts at 68°. *Uvitic acid*, toluene-3,5-dicarboxylic acid, m. 290°, is obtained by oxidizing mesitylene.

Terephthalic acid, benzene-1,4-dicarboxylic acid, sublimes without melting. It is made by oxidizing *p*-toluic acid or *p*-cymene from spruce turpentine. Its Me and Et esters melt at 140° and 44° respectively. The theoretically possible stereoisomers of the di-, tetra- and hexahydroterephthalic acids have been made. Succinylosuccinic ester, obtained by the action of NaOEt on ethyl succinate, is a derivative of dihydroterephthalic acid.



Phthalonic acid, *o*-carboxybenzoylformic acid, is a good example of ring-chain tautomerism.[25] For instance it gives two dimethyl derivatives, only one of which gives a semicarbazone.



E. Polybasic Aromatic Acids

All the theoretically possible acids are known.

Benzenetricarboxylic acids. Hemimellitic acid, the 1,2,3-acid, m. 203° dec., is made by permanganate oxidation of acenaphthene. On heating the

[24] "Org. Syntheses."

[25] *Ann. Rep. Chem. Soc.* (London) **1927**, 114.

Hg salt, the 2-carboxyl is lost to give anhydro-2-hydroxymercuri-isophthalic acid. The Hg can be replaced by halogen to give 2-derivatives of isophthalic acid. *Trimellitic acid*, the 1,2,4-acid, m. 216° dec., is made by oxidizing abietic acid or colophony (rosin) with dilute nitric acid. The isopropyl group and the aliphatic part of the molecule are oxidized leaving three carboxyl groups. *Trimesic acid*, 1,3,5-, m. 350°, is available by a great variety of reactions including the oxidation of mesitylene, the hydrolysis of the nitrile from *sym*-benzenetrisulfonates and NaCN, and the hydrolysis of the ester from the action of NaOEt on ethyl formate and acetate. This is another example of successive aldol condensations which finally lead to a stable unreactive product.

$$HCO_2Et + CH_3CO_2Et \rightarrow HCOCH_2CO_2Et$$

$$2\ HCOCH_2CO_2Et \rightarrow EtO_2CCH_2CHOHCH(CO_2Et)CHO \rightarrow EtO_2CCH_2CHOHCH(CO_2Et)CHOHCH(CO_2Et)CHO$$

The active carbonyl group is now in the 1,6-position to an α-H. Their reaction closes the ring. The loss of $3\ H_2O$ from the secondary OH groups and the adjacent H atoms which are α- to carbethoxyl groups gives *sym*-$C_6H_3(CO_2Et)_3$. In trimesic acid, the carboxyl groups have little influence on each other.

Benzene tetracarboxylic acids are obtained by oxidizing the Me_4-benzenes. The melting points given are taken in sealed tubes as heat causes anhydride formation with greater or less ease. *Prehnitic acid*, 1,2,3,5-, m. 237°; *mellophanic acid*, 1,2,3,4-, m. 238°, Me_4 ester, m. 130°; *pyromellitic acid*, 1,2,4,5, m. 270°, Me_4 ester, m. 141°.

Benzene pentacarboxylic acid, m. 230°, is made by cold permanganate oxidation of pentamethylbenzene. *Mellitic acid*, benzene hexacarboxylic acid, $C_6(CO_2H)_6$, m. 288°, occurs as its aluminum salt in honey stone, brown coal and peat. It can be made from this salt or by oxidizing Me_6-benzene with cold permanganate. It is also formed in the oxidation of graphite and willow charcoal with nitric acid. Heat removes one or more carboxyl groups. Powdered coal in aqueous alkali reacts with oxygen at 200–300° and 500–1200 psi to convert about 50% of the carbon to mellitic acids, largely tri- and tetracarboxylic.[26]

XVI. HYDROCARBONS WITH TWO OR MORE SEPARATE BENZENE NUCLEI AND THEIR DERIVATIVES

A. Diphenyl and Its Derivatives

Diphenyl, biphenyl, phenylbenzene, $C_6H_5C_6H_5$, m. 71°, b. 255°, is made commercially by heating benzene to a high temperature with the elimination of H_2. The by-products include *p*- and *m*-diphenylbenzenes, *sym*-triphenyl-

[26] Franke, Kiebler. *Chem. Ind.* 58, 580 (1946).

Hg salt, the 2-carboxyl is lost to give anhydro-2-hydroxymercuri-isophthalic acid. The Hg can be replaced by halogen to give 2-derivatives of isophthalic acid. *Trimellitic acid*, the 1,2,4-acid, m. 216° dec., is made by oxidizing abietic acid or colophony (rosin) with dilute nitric acid. The isopropyl group and the aliphatic part of the molecule are oxidized leaving three carboxyl groups. *Trimesic acid*, 1,3,5-, m. 350°, is available by a great variety of reactions including the oxidation of mesitylene, the hydrolysis of the nitrile from *sym*-benzenetrisulfonates and NaCN, and the hydrolysis of the ester from the action of NaOEt on ethyl formate and acetate. This is another example of successive aldol condensations which finally lead to a stable unreactive product.

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[26] Franke, Kiebler. *Chem. Ind.* 58, 580 (1946).

benzene, 4,4′-diphenyl-diphenyl, and a little triphenylene (1,2,3,4-dibenzonaphthalene).[1]

In the laboratory, diphenyl is obtained by passing benzene vapor through hot iron tubes (Berthelot). Commercially the heating is made more effective by using melted lead containing various catalysts.

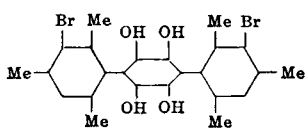
Diphenyl can also be made in the following ways, among others:

$$2\ PhBr + 2\ Na \rightarrow Ph-Ph \quad \text{(Fittig)}$$
$$2\ PhI + 2\ Cu \rightarrow Ph-Ph + Cu_2I_2 \quad \text{(Ullmann)}$$
$$2\ PhMgBr + 2\ CuCl_2 \rightarrow Ph-Ph + MgBr_2 + MgCl_2 + Cu_2Cl_2$$

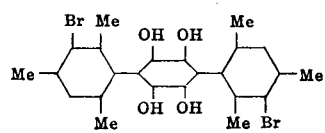
An ether solution of $FeCl_3$ gives a 90% yield of diphenyl from PhMgBr. Because of its stability, diphenyl is used as a high temperature heat transfer medium, as in Dowtherm, a eutectic mixture of diphenyl and diphenyl oxide.

Great numbers of derivatives of diphenyl have been studied because of (1) its cheapness as an intermediate and (2) the peculiar isomerism of many of its *o,o′*-substitution products. Although these contain no asymmetric carbon, certain of them were early resolved into optical isomers. A simple example of such a resolvable substance is 6-NO_2-diphenyl-2,2′-dicarboxylic acid. At first it was believed that the isomerism indicated the existence of the two phenyl groups in two parallel planes. The isomerism is actually due to a restricted rotation about the 1,1′-bond in compounds in which the substituents in the 2,2′, 6,6′ positions are large enough to prevent free rotation.[2] The work of Adams and his co-workers has shown this hypothesis to be correct. A typical preparation of a resolvable diphenyl derivative is that of 6,6′-dinitro-diphenyl-2,2′-dicarboxylic acid from the action of Cu on 2-iodo-3-nitrobenzoic acid obtained from the mercuration product of 3-nitrophthalic acid.

In terphenyl compounds having the middle ring completely substituted a peculiar type of *cis-trans* isomerism is possible.[3] Complete ortho substitution by suitable groups in the end rings restricts rotation and makes isomerism possible as in the following pair of compounds



cis



trans

The *interference* of the Me and OH groups in the *o*-positions prevents free rotation and tends to hold the end rings in a plane at right angles to that of the middle ring.

[1] Bachman. *J. Am. Chem. Soc.* **49**, 2089 (1927).
[2] Turner, Kenyon, Mills. *Ann. Rep. Chem. Soc.* (London) **1926**, 119.
[3] Adams, Shidneck. *J. Am. Chem. Soc.* **53**, 2203 (1931).

Two chief methods are available for making unsymmetrical biaryls.[4] These may be illustrated by the following examples:

$$BrC_6H_4N_2Cl + C_6H_6 + NaOH \rightarrow BrC_6H_4C_6H_5$$

and

$$BrC_6H_4N(NO)COCH_3 + C_6H_6 \rightarrow BrC_6H_4C_6H_5 + N_2 + CH_3CO_2H$$

Many higher analogs of diphenyl are known. For instance, sexiphenyl, $C_6H_5(C_6H_4)_4C_6H_5$, has been made as follows:

$$2\ PhN{=}NPh + Ph{-}Ph \xrightarrow[AlCl_3]{HCl} 2\ Ph{-}C_6H_4C_6H_4NH_2 \rightarrow 2\ ArI \xrightarrow[330°]{Ag} Ar{-}Ar$$

Diphenyl can be halogenated, nitrated and sulfonated in the usual way. Substitution takes place first in the 4- and 4′-positions and then in the positions ortho to the bond between the phenyl groups.

Derivatives of Diphenyl

The univalent group, $C_6H_5{-}C_6H_4{-}$ is called *xenyl.* All the ordinary derivatives are known. Their chemistry closely parallels that of the phenyl compounds.

4-Aminodiphenyl, p-xenylamine, $C_6H_5C_6H_4NH_2$, can be made by nitration and reduction from diphenyl in the usual way or by the Friedel-Crafts reaction on azobenzene and benzene.

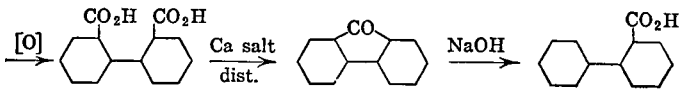
Benzidine, 4,4′-diaminodiphenyl, m. 128°, b. 400°, is obtained by the action of acids on hydrazobenzene. It forms a sparingly soluble sulfate which may be used in the determination of sulfur.[5] It and related substances such as *tolidine,* 3,3′-Me_2-benzidine, m. 128°, and *dianisidine,* 3,3′-$(MeO)_2$-benzidine, m. 138°, made from *o*-nitrotoluene and *o*-nitrophenol, are useful in making complex azo dyes. Benzidine is a dangerous carcinogenic compound causing malignant tumors in the bladder. Contact with the skin must be avoided. *Diphenyline,* 2,4′-diaminodiphenyl, m. 45°, is obtained in small amounts in the preparation of benzidine. Its sulfate is soluble as contrasted with that of benzidine. *N-Me₄-benzidine,* $Me_2NC_6H_4C_6H_4NMe_2$, is formed by the action of 1 mol of dimethylaniline hydrochloride with 1 mol of $NaNO_2$.

Diphenic acid, diphenyl-2,2′-dicarboxylic acid, m. 229°, is readily prepared by the oxidation of phenanthrene. It readily forms diphenic anhydride, m. 217°. Distillation of its calcium salt gives *fluorenone* (I).

The other carboxylic acids of diphenyl are made by the usual processes for aromatic acids. The three monobasic acids are *o*-, *m*-, and *p*-phenylbenzoic acids, m. 114°, 162°, and 219°. The ortho acid can best be made by fusing

[4] "Org. Reactions," II. p. 224.
[5] Platner. *Ind. Eng. Chem., Anal Ed.* **18**, 334 (1946).

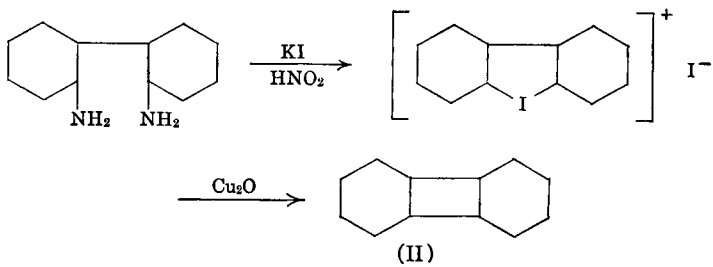
fluorenone with a base. The preparation from phenanthrene takes the following steps:



(I)

The chemistry and stereochemistry of diphenyls.[6,7]

Diphenylene, $(C_6H_4)_2$, (II) has been made from 1,1′-diaminodiphenyl by the following series of reactions:[8]



(II)

Its nature is shown by molecular weight, oxidation to phthalic acid, and hydrogenation to diphenyl.

***p*-Diphenylbenzene**, $C_6H_5C_6H_4C_6H_5$, m. 215°, is obtained among other products from *p*-Br_2-benzene, bromobenzene and Na. *sym*-Triphenylbenzene, $C_6H_3(C_6H_5)_3$, m. 170°, can be made by the action of HCl gas on acetophenone.

B. Diphenylmethane

$(C_6H_5)_2CH_2$, m. 26°, b. 262°, is made from benzyl chloride, benzene and $AlCl_3$. It can similarly be made from benzene and CH_2Cl_2, and by the action of sulfuric acid on a mixture of benzene and methylal, $H_2C(OMe)_2$, or benzene and benzyl alcohol. The methylene H atoms are highly reactive as would be expected from their being α- to two phenyl groups. Replacement by bromine is easy. The resulting monobromide is hydrolyzed to benzhydrol,

$$(C_6H_5)_2CHOH,$$

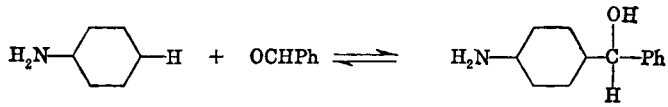
m. 69°, b. 299°. When benzhydrol is substituted in the para position by *o,p*-orienting groups such as NH_2, NMe_2, OH, OMe, etc., substituting reagents such as bromine, nitric acid, nitrous acid, etc. cause a splitting at the carbinol

[6] *Chem. Rev.* 12, 261 (1933).
[7] *Ann. Rep. Chem. Soc.* (London) 1933, 255.
[8] Lothrop. *J. Am. Chem. Soc.* 63, 1187 (1941).

group.[9–11]

$$\mathrm{PhCHOHC_6H_4NH_2} \xrightarrow{\mathrm{Br_2}} \mathrm{PhCHO} + \mathrm{C_6H_2Br_3NH_2}$$

This change can be regarded as the removal of a product of the reversal of an aldol condensation by which the benzhydrol could be formed from benzaldehyde and the amine or phenol.



The dye intermediate, Michler's hydrol, is p,p'-$(Me_2N)_2$-benzhydrol.

***p,p'*-Diaminodiphenylmethane,** $(H_2NC_6H_4)_2CH_2$, and its $N-Me_4$ derivative are readily obtained from formaldehyde with aniline or Me_2-aniline. In the first case intermediate steps can be distinguished.

$$\mathrm{PhNH_2} + \mathrm{H_2CO} \rightarrow \mathrm{PhN{=}CH_2} \xrightarrow[\mathrm{PhNH_3Cl}]{\mathrm{PhNH_2}} \mathrm{(H_2NC_6H_4)_2CH_2}$$

Diamides are formed readily on heating with monobasic aliphatic acids. They have been suggested as derivatives for identification.[12]

Diphenylmethane-*o*-carboxylic acids are important intermediates in making anthraquinones. ***o*-Benzylbenzoic acid,** m. 114°, is readily obtained by Na_xHg reduction of *o*-benzoylbenzoic acid. Sulfuric acid readily closes a 6-ring to form anthrone which gives anthraquinone on oxidation. *2,2'-Dihydroxy-5,5'-dichlorodiphenylmethane, DDM,* is an important mildew-proofing agent.

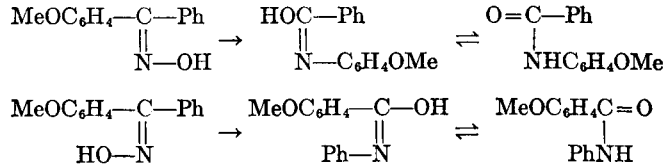
Oxidation of diphenylmethane gives *benzophenone,* $(C_6H_5)_2CO$, b. 305°, which exists in polymorphic forms m. 48°, 26°, and 51°. It is better prepared from the hydrolysis of Ph_2CCl_2 prepared from benzene, CCl_4 and $AlCl_3$.[13] Its oxime melts at 142°.[14] The reactions of benzophenone and its substitution products are those which would be expected of a ketone with no α-H. Thus it is split by sodamide.

$$\mathrm{Ph_2CO} + \mathrm{NaNH_2} \rightarrow \mathrm{PhCONH_2} + \mathrm{C_6H_6}$$

Unsymmetrically substituted benzophenones may form isomeric oximes. Thus anisylphenyl ketone gives two oximes, one of which on Beckmann rearrangement with PCl_5 or AcCl gives PhCONHAn and the other AnCONHPh. These can be identified by hydrolysis to benzoic acid and anisidine and to

[9] Clarke. *J. Am. Chem. Soc.* **33**, 1135 (1911).
[10] Esselen. *J. Am. Chem. Soc.* **36**, 308 (1914).
[11] Kohler. *J. Am. Chem. Soc.* **38**, 1205 (1916).
[12] Ralston. *J. Am. Chem. Soc.* **61**, 1604 (1939).
[13] "Org. Syntheses."
[14] *ibid.*

anisic acid and aniline respectively.

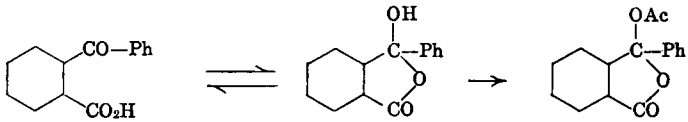


Regardless of the mechanism of the process, the net change can be regarded as an interchange of the OH with the group *trans* to it.[15]

Michler's ketone, an important dye intermediate, is made by phosgene and dimethylaniline. No $AlCl_3$ is needed.

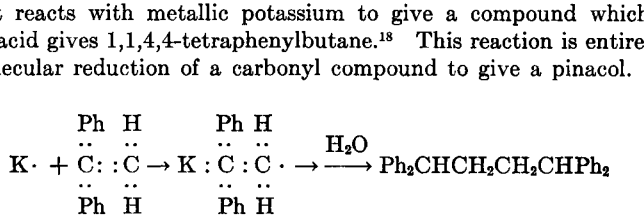
$$2\ PhNMe_2 + COCl_2 \rightarrow CO(C_6H_4NMe_2)_2$$

Benzophenone carboxylic acids can be made by oxidizing the homologs of benzophenone. The *o*-compound, ***o*-benzoylbenzoic acid,** m. 127°, is readily available as an intermediate in anthraquinone manufacture from benzene, phthalic anhydride and $AlCl_3$. As a gamma keto acid it exists in equilibrium with a lactone-hemiacetal form as is evidenced by its acetylation.



Reduction by Na_xHg changes benzoylbenzoic acids to benzylbenzoic acids. The most important reaction of *o*-benzoylbenzoic acid is its easy ring closure with H_2SO_4 or P_2O_5 at 180° to give anthraquinone.[16]

1,1-Diphenylethane, $(C_6H_5)_2CHCH_3$, b. 286°, is made from paraldehyde, benzene and H_2SO_4 or from benzene, a cuprous chloride catalyst and acetylene (Nieuwland). 1,1-Diphenylethylene, $(C_6H_5)_2C{=}CH_2$, b. 277°, is made from PhMgBr and ethyl acetate.[17] It polymerizes very readily in the presence of acids. It reacts with metallic potassium to give a compound which with water or acid gives 1,1,4,4-tetraphenylbutane.[18] This reaction is entirely like the bimolecular reduction of a carbonyl compound to give a pinacol. Electronically



The potassium first adds to give a "free radical," two of which unite.

[15] *Ann. Rep. Chem. Soc.* (London) **1922**, 95.
[16] Gleason. *J. Am. Chem. Soc.* **51**, 310 (1929).
[17] "Org. Syntheses."
[18] Schlenk. *Ber.* **47**, 473 (1914).

Benzilic acid, diphenylglycollic acid, $(C_6H_5)_2C(OH)CO_2H$, m. 150°, is obtained by the action of benzil and a base. The oxidation of benzoin to benzil and the rearrangement of the latter can be carried out in one operation.[19]

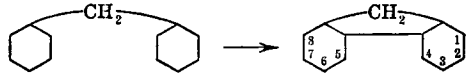
$$3\ PhCHOHCOPh + NaBrO_3 + 3\ NaOH \rightarrow 3\ Ph_2C(OH)CO_2Na + NaBr + 3\ H_2O$$

Benzilic acid is readily reduced to diphenylacetic acid, $(C_6H_5)_2CHCO_2H$, m. 145°, by HI formed by red P, I_2 in glacial acetic acid.[20] The hydrochloride of the diethylaminoethyl ester of diphenylacetic acid,

$$(C_6H_5)_2CHCO_2CH_2CH_2NEt_2.HCl$$

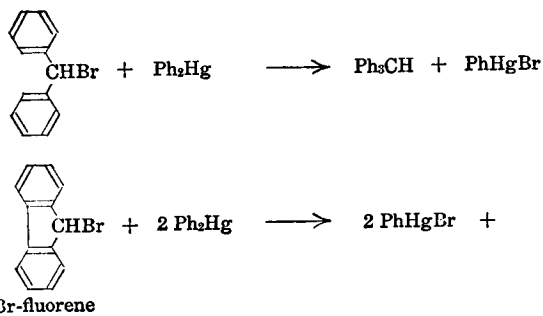
is used for anesthesia of the lower intestinal tract.

Related to diphenylmethane and to diphenyl is *fluorene* (I), diphenylenemethane, m. 116°, b. 295°, found in coal tar and formed from diphenylmethane by passage through a red hot Fe tube.



(I)

It is readily oxidized to fluorenone, diphenylene ketone, m. 84°, which can be educed to *fluorenyl alcohol,* 9-fluorenol, m. 153°. Fusion of the ketone with KOH gives diphenyl-2-carboxylic acid. 9-Bromofluorene shows a marked contrast to the analogous diphenylbromomethane. While the latter reacts with alcoholic KOH and with diphenylmercury to give metatheses producing diphenylmethyl ethyl ether and triphenylmethane, the former with both reagents gives bis-diphenyleneethylene (II), red crystals, m. 188°.



9-Br-fluorene

(II)

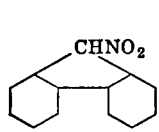
Thus this bromide acts as a bromide of a dibenzocyclopentadiene rather than a phenylated methyl bromide. The red hydrocarbon is also formed by the action of PbO_2 on fluorene at 330°. Fluorene with SeO_2 gives only 5% fluorenone

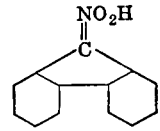
[19] "Org. Syntheses."
[20] "Org. Syntheses."

whereas diphenylmethane under identical conditions gives 87% benzophenone.[21] With hypochlorite solution, fluorene gives a small yield of fluorenone.[22]

Certain Grignard reagents have been found to react with bidiphenyleneethylene to give the corresponding substituted ethanes. This is the first time a Grignard reagent has been successfully added to an olefin.[23]

Phenanthraquinone, with alkali, gives the benzilic acid rearrangement to give *diphenyleneglycolic acid*, (9-hydroxyfluorene-9-carboxylic acid), m. 162°. 9-Nitrofluorene has been prepared in the true and acinitro forms from fluorene, ethyl nitrite and KOEt.[24]

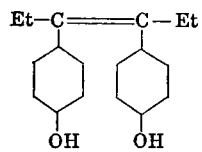




C. Dibenzyl and Its Derivatives

Dibenzyl, 1,2-diphenylethane, $C_6H_5CH_2CH_2C_6H_5$, m. 53°, b. 284°, is best made by ethylene chloride, benzene and $AlCl_3$. It can be oxidized catalytically to benzaldehyde. *Stilbene*, trans-1,2-diphenylethylene, $C_6H_5CH=CHC_6H_5$, m. 125°, b. 307°, can be made in a variety of ways including the action of toluene on PbO at a red heat and by the action of benzylmagnesium chloride with benzaldehyde. The alcohol first formed is dehydrated with great ease because both the OH and H are α- to phenyl. *Isostilbene*, b. 143° (20 mm) is the *cis* form.

Diethylstilbestrol, stilbestrol, m. 171°, is a completely synthetic estrogen which has the action of estrone and is claimed to be capable of replacing the natural hormone in every way (NNR 436). It is several times as potent as estrone.



In *hexestrol* (NNR 442), which has similar physiological action, the double bond is absent.

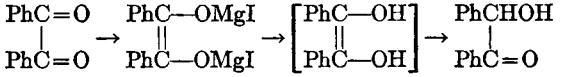
Stilbene dibromide, $C_6H_5CHBrCHBrC_6H_5$, m. 237°, reacts with alcoholic KOH to give first bromostilbene and then *tolan*, diphenylacetylene, $C_6H_5C\equiv CC_6H_5$, m. 62°, b. 300°. With some reagents, which might be expected to give replacement of the Br atoms, stilbene dibromide instead gives

[21] Postovskii. *Ber.* **68B**, 852 (1935).
[22] Schiessler. *J. Am. Chem. Soc.* **70**, 3958 (1948).
[23] Fuson, Porter. *J. Am. Chem. Soc.* **70**, 895 (1948).
[24] *Ann. Rep. Chem. Soc.* (London) **1908**, 91.

up bromine. Thus with KSH it gives stilbene. Similarly with di-*p*-tolylmercury it gives stilbene and tolyl bromide. With silver acetate, stilbene dibromide gives two isomeric diacetates which on hydrolysis form *hydrobenzoin* and *isohydrobenzoin*, the *meso* and *racemic* forms respectively of 1,2-Ph_2-glycol, $C_6H_5CHOHCHOHC_6H_5$, m. 138° and 119°. The latter has been resolved by manual sorting of the enantiomorphic crystals.[25] Tolan on reduction gives *sym*-diphenylethane. Oxidation with SeO_2 gives a 35% yield of benzil.[26] *Benzoin*, phenylbenzoylcarbinol, $C_6H_5CHOHCOC_6H_5$, m. 134°, is made from benzaldehyde and NaCN solution.[27] Its great ease of reduction is probably due to an enediol form, PhC(OH)=C(OH)Ph. It has been suggested as a qualitative reagent for Zn^{++}, with which a green fluorescence is produced.[28]

Benzil, dibenzoyl, $C_6H_5COCOC_6H_5$, yellow crystals, m. 95°, is obtained by oxidizing benzoin with nitric acid or with an alkaline copper solution.[29]

Reduction of benzil gives all the theoretically possible compounds, namely, benzoin, PhCOCHOHPh, hydrobenzoin, PhCHOHCHOHPh, desoxybenzoin, $PhCH_2COPh$, diphenylethane, etc. The last two products are obtained by reduction with HI. The ready production of benzoin is not an indication that one carbonyl group is unusually susceptible to reduction. The mechanism of the process is indicated by the action of alkali metals or of the equivalent (MgI_2 + Mg) combination.[30]



Thus the reaction is initiated by a 1,4-addition to the system, O=C−C=O.

Heating benzil with alcoholic KOH gives the *benzilic acid rearrangement* to form potassium benzilate, $Ph_2C(OH)CO_2K$. The conversion of benzoin to benzil and then to benzilic acid can be combined by heating the former with $NaBrO_3$ + NaOH.[31]

Ammonium cyanide (NaCN + NH_4Cl) splits benzil to give benzamide and benzaldehyde cyanohydrin.

Benzil monoxime exists in two forms, α-, m. 134°, β-, m. 113°. The following are the configurations

[25] Erlenmeyer. *Ber.* **30**, 1531 (1897).
[26] Postovskii. *Ber.* **68B**, 852 (1935).
[27] "Org. Syntheses."
[28] White. *Ind. Eng. Chem., Anal. Ed.* **15**, 599 (1943).
[29] "Org. Syntheses."
[30] Gomberg. *J. Am. Chem. Soc.* **49**, 2584 (1927).
[31] "Org. Syntheses."

These are based on a variety of evidence including the formation of metallic derivatives of the α-form, the greater volatility of the β-form (due to a chelate ring),[32] and the formation of the benzoyl derivative of the β-oxime from triphenylisoxazole and O_3.[33,34] Three forms of *benzildioxime* are definitely known: α-, m. 237°, β-, m. 207°, γ-, m. 163°.[35,36] A δ-form has been reported but not confirmed.[37,38]

Various substituted benzils have been prepared in colorless as well as in the ordinary yellow forms.[39,40] The colorless forms react only slowly with 1,2-diamines while the yellow forms react rapidly to give quinoxalines. The condition may be a peculiar bond tautomerism

$$\underset{\text{Yellow}}{\mathrm{ArC(=O)-C(=O)Ar}} \rightleftharpoons \underset{\text{Colorless}}{\mathrm{ArC(-O-)=C(-O-)Ar}}$$

Desoxybenzoin, phenyl benzyl ketone, $C_6H_5COCH_2C_6H_5$, m. 55°, is best made from benzene, phenylacetyl chloride and $AlCl_3$.[41] PhCOCHPh is the *desyl group*. The CH_2 group in desoxybenzoin shows the same reactions as that group in 1,3-dicarbonyl compounds such as malonic and acetoacetic esters. Thus it gives a sodium compound and condenses with aldehydes in presence of catalysts such as piperidine (Knoevenagel) and adds to the conjugated system in $\alpha\beta$-unsaturated carbonyl compounds.[42]

D. Triphenylmethane and Its Derivatives

Triphenylmethane compounds are readily formed. Just as one phenyl group activates an α-carbon group, so two phenyl groups on the same carbon have an even more pronounced effect on α-groups. This may be illustrated by the stepwise action of CCl_4 with benzene in presence of $AlCl_3$

$$CCl_4 \rightarrow PhCCl_3 \rightarrow Ph_2CCl_2 \rightarrow Ph_3CCl$$

Each chloride is much more reactive than the preceding one. The last chloride forms a very stable compound with $AlCl_3$ (p. 719). The introduction of another phenyl group is not possible by any ordinary process. A similar result is found with benzaldehyde and benzene in presence of acid condensing agents.

$$PhCHO \rightarrow PhCHOHPh \rightarrow Ph_3CH$$

[32] Sidgwick. *J. Chem. Soc.* **127**, 907 (1925).
[33] Meisenheimer. *Ber.* **54B**, 3195 (1921).
[34] *Ann. Rep. Chem. Soc.* (London) **1922**, 8; **1925**, 106; **1926**, 127.
[35] *ibid.* **1921**, 88; **1922**, 95; **1924**, 111.
[36] Ponzio. *Gazz. chim. ital.* **62**, 415 (1932).
[37] Atack. *J. Chem. Soc.* **119**, 1175 (1921).
[38] Meisenheimer. *Ber.* **57B**, 276 (1924).
[39] Irvine. *Proc. Chem. Soc.* **23**, 62 (1907).
[40] *Ann. Rep. Chem. Soc.* (London) **1922**, 109.
[41] "Org. Syntheses."
[42] Ionescu. *Bull. soc. chim.* **51**, 171 (1932).

Groups like OH, NH_2 NR_2, etc. which activate *p*-H make such triphenylmethane condensations even easier.

Triphenylmethane, tritane, $(C_6H_5)_3CH$, m. 93°, b. 360°, can be made from $CHCl_3$ and benzene by the Friedel-Crafts reaction but is better made from carbon tetrachloride.[43] The reaction mixture is decomposed with ether.

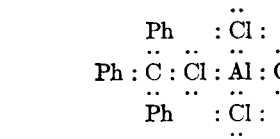
$$Ph_3CCl.AlCl_3 + Et_2O \rightarrow Ph_3CH + EtCl + MeCHO + AlCl_3$$

The tertiary H is easily replaced by halogen, by OH by means of oxidizing agents, and by metallic potassium on heating. In contrast to this reactivity of the tertiary H is the conversion by cold fuming nitric acid to the trinitro compound, $HC(C_6H_4NO_2)_3$, m. 207°. Reduction gives the *p*-triamino compound, paraleucaniline which, on oxidation, gives pararosaniline. Oxidation of the trinitro compound with chromic acid gives the corresponding carbinol.

A peculiar formation of tritane which shows the inadequacy of the simpler conception of steric hindrance is by the action of sodium diphenylmethyl with diphenyl sulfoxide.

Triphenylchloromethane, trityl chloride, $(C_6H_5)_3CCl$, m. 112°, b. 310°, is readily prepared from triphenylcarbinol. It gives the reactions of a tertiary chloride. In addition, it reacts on boiling with alcohol to give triphenylmethyl ethyl ether. The ease of introducing the *trityl* group in place of a primary alcoholic hydroxyl is utilized in making trityl derivatives of carbohydrates. Introduction of one such group in place of the H of the terminal $-CH_2OH$ often gives a fairly high melting solid. The process is carried on in cold pyridine solution.

Trityl chloride forms a very stable compound with $AlCl_3$ which is interesting electronically.



This compound is the main product of the action of CCl_4 with benzene and $AlCl_3$. It reacts with ether to give triphenylmethane.[44]

Trityl chloride acts like an inorganic chloride with silver nitrate and conc. H_2SO_4 to give AgCl and HCl gas respectively. Tritylmagnesium chloride can be obtained in excellent yields under carefully controlled conditions.[45]

Trityl bromide, $(C_6H_5)_3CBr$, m. 152°, is best made by the action of bromine on Ph_3CH.

Triphenylcarbinol, trityl alcohol, $(C_6H_5)_3COH$, m. 159°, is readily available from benzophenone and PhMgBr. It is a typical tertiary alcohol except that

[43] "Org. Syntheses."
[44] *ibid.*
[45] Gilman, Zoellner. *J. Am. Chem. Soc.* **51**, 3493 (1929).

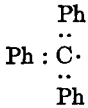
of course, olefin formation is not possible. Dehydration readily gives the ether. The reactivity of the OH is seen from the ready reaction with formic acid to give tritane and CO_2.

Triphenylmethylamine, tritylamine, $(C_6H_5)_3CNH_2$, m. 105° is made from NH_3 and a trityl halide. The NH_2 is easily removed by hydrolysis. Boiling with alcohol replaces it by OEt.

Triphenylmethyl, $(C_6H_5)_3C-$,[46] is obtained by the action of metals on trityl halides in absence of air or by reducing agents like vanadous chloride[47] with the halides or the carbinol. It absorbs oxygen to give a peroxide, $Ph_3C-O-O-CPh_3$. The *free radical* exists in equilibrium with hexaphenylethane.

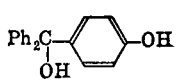
$$2\ Ph_3C \rightleftharpoons Ph_3C-CPh_3$$

Electronically, the free radical is neutral but unstable because it has an *odd* electron.

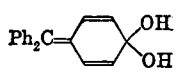


Since 1900 a tremendous mass of information has been developed about *tervalent* carbon and *free radicals* as illustrated by triphenylmethyl and related substances. ("Atomic and Free Radical Reactions," Steacie, ACS Monograph, Reinhold, N.Y.C., 1946.)

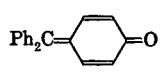
Hydroxytriarylcarbinols present a type of tautomerism which is of the utmost importance in the triphenylmethane dyes. Thus *p*-hydroxytriphenylcarbinol can be obtained in a yellow form, m. 140°, which loses water readily to give fuchsone or in a colorless form, m. 159°, which loses water only slowly.[48]



colorless

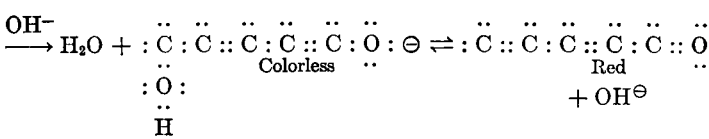


colored



Fuchsone

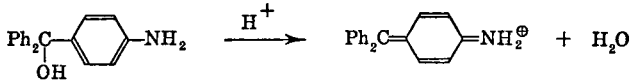
Bases turn the colorless form red at once. The OH^- ion removes the H^+ from the phenolic hydroxyl. This causes a shift of electrons in the 6-atom chain to liberate the tertiary hydroxyl.



[46] Gomberg. *J. Am. Chem. Soc.* **22**, 757 (1900).
[47] Conant, Sloan. *J. Am. Chem. Soc.* **45**, 2466 (1923).
[48] Anderson, Gomberg. *J. Am. Chem. Soc.* **50**, 203 (1928).

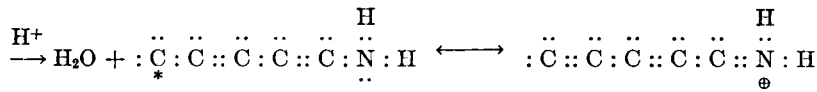
H^+ ions add to the $:\underset{\cdot\cdot}{C}::\underset{\cdot\cdot}{O}$ system to give $:\underset{\cdot\cdot}{C}:\underset{\cdot\cdot}{O}:H$ thus reversing the change. This series of changes shows that the hydroxytrityl alcohol, in common with the related acid tritane dyes, is a pseudo acid.

***p*-Aminotriphenylcarbinol** is a colorless compound which turns red with acids. The difference in the two compounds is that between the benzenoid and quinoid structures.



colorless colored

The colored compounds are salts of *fuchsonimine*. The electronic shift in the 6-atom chain is entirely analogous to that in the corresponding phenolic compound except that in this case the change is initiated by H^+ instead of by OH^-. The tertiary hydroxyl is removed by the H^+ ion and the electron shift follows



Hydroxyl ions reverse the change by adding to the C*. Thus aminotrityl alcohol and the related basic tritane dyes are *pseudo-bases*.

E. Triphenylmethane Dyes

The colored compounds of the monohydroxy- and monoaminotriphenylcarbinols are not useful as dyes because they contain no *auxochrome groups*. This lack can be overcome by additional acidic or basic groups such as OH, NH_2, NMe_2 etc. These not only fix the dye to the mordant or the fiber but modify its shade as well.

The dyes are closely related to colorless tritane derivatives. These are called *leuco-compounds*. Oxidation converts them to the corresponding tertiary alcohols which readily change from the colorless benzenoid forms to the quinoid dyes. These colorless alcohols are *pseudo acids* or *pseudo bases* because with bases or acids *they give salts of different structure from the parent substances*.

The triphenylmethane dyes fall in two main groups, the acid and the basic types.

1. Acid dyes. These contain a *quinone* grouping with additional acid groups. They are used with mordants to give colored *lakes*.

a. Aurins are related to hydroxytriphenylmethane.

b. Phthaleins have a carboxyl or sulfonic acid group in one of the rings ortho to the methane carbon.

2. Basic dyes. These contain a *quinonimine* grouping with additional basic groups. These dye silk and wool directly.

a. Malachite green and related dyes have two of the phenyl groups substituted with basic groups.

b. Rosaniline or magenta dyes have basic groups in all three phenyls.

Aurin Dyes.

These are hydroxy derivatives of fuchsone (p. 720).

Benzaurin, *p*-hydroxyfuchsone, is made by condensing benzaldehyde with phenol and oxidizing the leuco compound (I).

$$PhCHO + 2\ C_6H_5OH \rightarrow \underset{(I)}{PhCH(C_6H_4OH)_2} \rightarrow$$

$$[PhC(OH)(C_6H_4OH)_2] \rightarrow C(C_6H_5)(C_6H_4OH)=C_6H_4=O$$

Aurin, pararosolic acid, is the corresponding dihydroxy compound. It can be made in a variety of ways, the commonest of which is the heating of phenol with oxalic acid and H_2SO_4

$$3\ C_6H_5OH + H_2C_2O_4 \rightarrow$$

$$CO_2 + 2\ H_2O + \underset{\text{Leucaurin}}{CH(C_6H_4OH)_3} \rightarrow \underset{\text{Aurin}}{(HOC_6H_4)_2C=C_6H_4=O}$$

The first step may be an aldol condensation involving a *p*-H and "nascent" carbon monoxide or, more probably, a similar condensation with one carbonyl group of the oxalic acid.

$$\begin{matrix} O \\ \| \\ C\text{—}OH \\ | \\ CO_2H \end{matrix} + C_6H_5OH \rightarrow \left[\begin{matrix} (HO)_2C\text{—}C_6H_4OH \\ | \\ CO_2H \end{matrix}\right] \rightarrow CO_2 + H_2O + HOC_6H_4CHO$$

Corallin yellow is sodium aurin. Heating aurin with water under pressure gives phenol and 4,4′-$(OH)_2$-benzophenone, a reversal of the aldol condensation.

Rosolic acid is aurin with a methyl *o*- to one hydroxyl. It was discovered by the oxidation of a mixture of phenol and *o*- and *p*-cresols, the methyl of the latter forming the methane carbon. A common oxidizing mixture is arsenic acid dissolved in sulfuric acid.

Chrome violet is the sodium salt of aurin-tricarboxylic acid obtained from salicylic acid, formaldehyde, $NaNO_2$ and H_2SO_4.[49] The corresponding NH_4 salt is *aluminon*, a delicate colorimetric reagent for aluminum in presence of elements which usually interfere in its detection.[50, 51]

The reduction of the aurins gives the *leuco* compounds, hydroxytritanes.

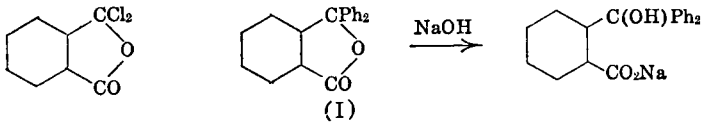
[49] "Org. Syntheses."

[50] Winter, Thrun, Bird. *J. Am. Chem. Soc.* **51**, 2721 (1929).

[51] Yoe. *J. Am. Chem. Soc.* **54**, 1022 (1932).

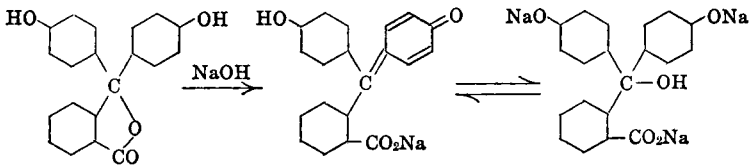
Phthalein or Eosin Dyes.

The parent substance is tritane-*o*-carboxylic acid, $Ph_2CHC_6H_4CO_2H$, m. 162°, which can be made by reducing *phthalophenone*, m. 115°, the lactone of the corresponding tertiary carbinol. Phthalophenone (I) is made from phthalyl chloride and benzene in presence of $AlCl_3$. The symmetrical chloride is converted to the unsymmetrical by the action of the $AlCl_3$.[52]



(I)

Phenolphthalein is the corresponding di-*p*-OH compound formed by condensing phthalic anhydride with phenol in presence of sulfuric acid, oxalic acid or tannic chloride. It is colorless but gives characteristic purple-red salts with bases. With excess of strong conc. base it becomes colorless again.



Colorless Colored Colorless

The change is due to OH^- as illustrated with *p*-hydroxytritane (p. 720).

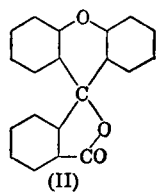
Concentrated sulfuric acid turns phenolphthalein red, probably through the formation of an oxonium salt.

Phenolphthalein gives an oxime, m. 212°, a diacetyl compound, m. 143°, and colorless and red alkyl derivatives. With Zn dust and a base, it is reduced to *phenolphthalin* (the leuco compound), the alkaline solution of which is colorless but is readily oxidized to a red solution of a phenolphthalein salt.

The laxative properties of phenolphthalein are increased by the presence of anthraquinone derivatives in the yellow material.

Salts of phenolphthalein.[53]

Fluoran (II) is a by-product of the preparation of phenolphthalein. It forms oxonium salts.



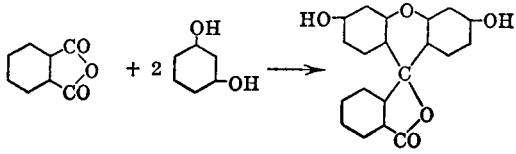
(II)

[52] "Org. Syntheses."

[53] Dehn. *J. Am. Chem. Soc.* **54**, 2947 (1932).

Phenolsulfonephthalein, Phenol Red, is obtained from sulfobenzoic anhydride[54] and phenol. Its chemistry is like that of phenolphthalein except that it is colored even when acid. It thus exists as the quinoid free acid instead of the benzenoid lactone. Its tetrabromo compound, *Bromophenol Blue*, exists in a colorless lactoid form as well as the blue quinoid form.

Fluorescein, dihydroxyfluoran, resorcinolphthalein, is formed from phthalic anhydride and resorcinol heated at 200°.



The fluorescent properties of the alkaline solutions of fluorescein and related dyes derived from *m*-dihydroxy benzenes may be related to the following interchange

This change consists merely in the removal of H^+ from the phenolic hydroxyl and its addition to the carbonyl oxygen of the quinoid system with the resulting shift of electrons along the 11-atom system terminated by the 2 oxygen atoms. Uranine is the Na salt.

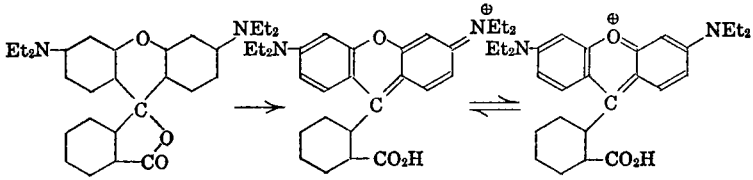
Fluorescence, Ahr. 1906, 102 pp.

Four Br atoms can be introduced into the positions ortho to the hydroxyls of fluorescein. The K or the Na salt of this compound is Eosin. Halogenated phthalic anhydrides can be used to give fluoresceins. Thus a variety of dyes containing up to 8 atoms of halogen can be prepared. Such dyes include Erythrosin, Rose Bengal, Phloxin, etc.

Mercurochrome is the sodium salt of hydroxymercuridibromofluorescein. Since the Hg is ortho to a phenolic OH it is readily removed by acid.

Gallein is tetrahydroxyfluoran obtained from pyrogallol and phthalic anhydride.

Rhodamines are fluoran derivatives having two R_2N groups in place of the hydroxyls of fluorescein. *Rhodamine B* is typical as a chloride with a combination of quinoid and oxonium groupings.



[54] "Org. Syntheses."

Diaminotritane Dyes Related to Malachite Green.

***p*-Diaminotriphenylmethane** is made from benzaldehyde and an aniline salt in presence of $ZnCl_2$ or HCl. Oxidation of this leuco compound and formation of the chloride gives a dye, *Döbner's Violet.* Its chemistry is entirely analogous to that of the aurin dyes, the C=NH group taking the place of the C=O group of the quinoid system. In the case of the amino compounds, salts are formed with acids by the production of an ion containing the $C=NH_2^+$ or $C=NR_2^+$ grouping.

$$PhCHO + 2\,C_6H_5NH_2 \rightarrow PhCH(C_6H_4NH_2)_2 \rightarrow PhC(OH)(C_6H_4NH_2)_2 \rightarrow$$

Leuco base — Color base

$$PhC(C_6H_4NH_2)=C_6H_4=NH \rightarrow PhC(C_6H_4NH_2)=C_6H_4=NH_2^{\oplus}Cl^{\ominus}$$

Dye

The change from color base to dye by H^+ ions and the reverse change by OH^- ions is as illustrated by *p*-aminotritane (p. 720).

The corresponding N-tetramethyl derivative is *Malachite Green*, prepared by heating benzaldehyde with dimethylaniline and $ZnCl_2$ or H_2SO_4 and oxidizing the resulting leuco compound and converting it to the chloride. It is used as a double compound with $ZnCl_2$ or oxalic acid. *Brilliant Green* is the corresponding tetraethyl compound. *Acid Green* is a sulfonic acid of the analogous compound from benzaldehyde and ethylbenzylaniline.

The *leuco* base of Malachite Green is a *colorless* crystalline compound, m. 94°. Oxidation with PbO_2 gives the *colorless* tertiary carbinol, m. 132°. This dissolves in cold acid to give a *colorless* solution. Only on heating is the green dye formed.

$$=C(OH)-C_6H_4NMe_2.HCl \rightarrow =C=C_6H_4=NMe_2Cl + H_2O$$

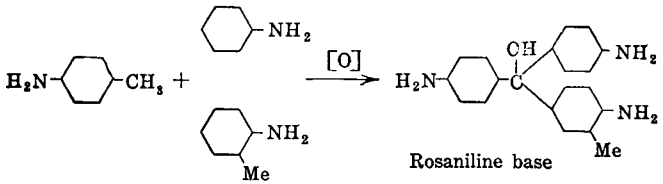
Colorless — Green

The colorless salt is the ordinary amine hydrochloride while the green quinoid salt is the salt of the stable cation obtained by rearrangement of the pseudo base, the tertiary carbinol.

Triaminotritane Dyes Related to Rosaniline.

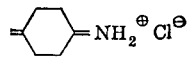
These were the original "aniline dyes" obtained by oxidizing crude aniline with arsenic acid. The *p*-toluidine in the mixture supplied the tritane carbon for union by condensation with *p*-H in the aniline and *o*-toluidine present. The result was *fuchsine* or *magenta*, a salt of rosaniline, *p*-triaminodiphenyl-*m*-tolylmethane. This was originally obtained as *Mauve* or *Mauvein* by Perkin in 1856 as the first artificial dye. He obtained it in an attempt to make

quinine by the action of chromic acid on crude aniline.



Rosaniline base

The chief improvement in the original process has been the use of milder oxidizing agents, notably nitrobenzene and nitrotoluenes. "Aniline for Red" is crude aniline containing toluidines and consequently suitable for making magenta. Reduction of the color base converts the C(OH) to CH giving leucaniline. Treatment of the color base with HCl gives the dye which contains the quinoid grouping



Diazotization can be used to convert rosaniline to rosolic acid.

A solution of fuchsine is decolorized by sulfurous acid with formation of a rather unstable addition product. Addition of an aldehyde causes the transfer of the sulfurous acid to the latter with the regeneration of the violet-red color of the dye (Schiff's Reagent for aldehydes).

Parafuchsine, (I), is the hydrochloride of *pararosaniline,* the quinonimine form of tri-*p*-aminophenylcarbinol, obtained by oxidizing a mixture of *p*-toluidine and aniline. Nitrobenzene or nitrotoluene can be used as the oxidizing agent.

$$2\ C_6H_5NO_2 + 4\ C_6H_5NH_2 + 3\ CH_3C_6H_4NH_2 + 3\ HCl \rightarrow 4\ H_2O + 3\ \underset{\text{(I)}}{(H_2NC_6H_4)_2C{=}C_6H_4{=}NH.HCl}$$

Pararosaniline and rosaniline can also be made by oxidizing mixtures of *p*-diaminodiphenylmethane and aniline and *o*-toluidine respectively.

Methyl violets are N-methylated rosaniline dyes made by methylating the dyes or by preparing them from Me_2N-compounds in place of aniline and the toluidines. Michler's Ketone, Michler's Hydrol and the related di-*p*-dimethylaminophenylmethane are valuable in making these dyes. *Crystal Violet* is the hydrochloride of the hexamethyl compound,

$$(Me_2NC_6H_4)_2C{=}C_6H_4{=}NMe_2{\oplus}Cl{\ominus}.$$

The methyl chloride addition product is *Methyl Green* or *Light Green. Ethyl Green* is the corresponding EtCl addition product. *Methyl Violet* is Me_6-pararosaniline hydrochloride formed by oxidizing dimethylaniline with cupric chloride. One of the six methyl groups in three molecules of the Me_2-aniline

supplies the methane carbon of the dye. It is probably the most important tritane dye.

Phenylated rosanilines shift in color to violet and then blue. *Triphenyl fuchsine, Aniline Blue, Diphenylamine Blue, Spirit Blue,* is obtained in a variety of ways including the action of diphenylamine with oxalic acid or formaldehyde. Sulfonic acids of the rosanilines are water-soluble dyes such as *Water Blue* and *Patent Blue.*

("Colour Index," F. M. Rowe, Society of Dyers and Colourists.) ("Synthetic Dyestuffs," Thorpe and Linstead. Giffin & Co. Ltd.)

Tetraphenylmethane, $C(C_6H_5)_4$, m. 285°, b. 431°, can be made from trityl chloride and phenylmagnesium bromide in about 5% yield or by the following steps from the action of phenylhydrazine and trityl bromide.[55]

$$\rightarrow Ph_3CNHNHPh \xrightarrow{\text{Air}} Ph_3CN{=}NPh \xrightarrow{130^\circ} N_2 + Ph_4C$$

The attempt to prepare the analogous completely phenylated ethane led to the discovery of triphenylmethyl by Gomberg and the opening up of the whole chapter of free radical chemistry. The great stability of tetraphenylmethane is noteworthy.

Phenylated ethanes. All possible ones have been prepared. The hexa compound dissociates into free radicals at 20°.

Tetraphenylethylene, $(C_6H_5)_2C{=}C(C_6H_5)_2$, m. 221°, b. 425°, is readily obtained from benzophenone dichloride heated with zinc or with diphenylmethane. It adds H_2[56] and Cl_2 normally but does not add HX or bromine. With the latter it gives 9,10-diphenylphenanthrene in 25% yield.[57]

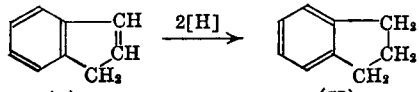
XVII. AROMATIC COMPOUNDS WITH CONDENSED RINGS

The simplest of these is indene, a fusion of a benzene and a cyclopentadiene ring.

Indene (I), b. 180°, is obtained from coal tar. It adds bromine readily to give a dibromide. Mild oxidation gives *homophthalic acid*

$$o\text{-}C_6H_4(COOH)CH_2COOH,$$

while oxidation with nitric acid gives phthalic acid. Sulfuric acid gives a polymer. Treatment with Na and alcohol gives *hydrindene* (II), b. 177°. The reduction of the C=C by this means is made possible by the presence of the benzene ring.



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[55] Gomberg. *Ber.* **30**, 2043 (1897).
[56] Zartman, Adkins. *J. Am. Chem. Soc.* **54**, 1668 (1932).
[57] Schoepfle, Ryan. *J. Am. Chem. Soc.* **54**, 3687 (1932).

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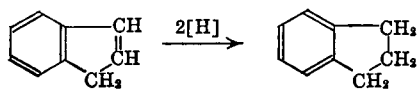

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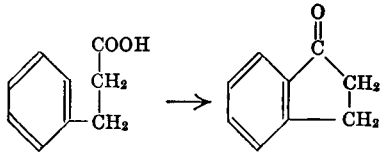
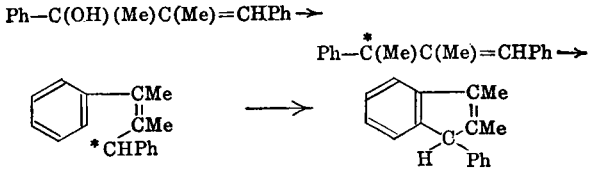
[55] Gomberg. *Ber.* **30**, 2043 (1897).
[56] Zartman, Adkins. *J. Am. Chem. Soc.* **54**, 1668 (1932).
[57] Schoepfle, Ryan. *J. Am. Chem. Soc.* **54**, 3687 (1932).

Catalytic hydrogenation at high pressure with copper chromite catalyst also gives hydrindene.

One of the most prolific synthetic methods for *hydrindone*-1 and substituted compounds is the intramolecular acylation of cyclic compounds having suitable side chains. A typical example is the conversion of β-phenylpropionic acid to hydrindone-1.



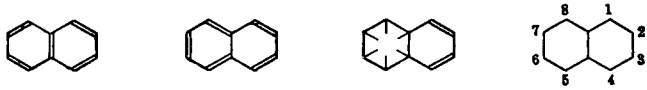
Literally hundreds of such ring closures have been achieved.[1] (Cf. pp. 729–30.) The formation of substituted indenes is very easy from substances containing the grouping $Ph-CR=CR-C(OH)R_2$ in which R may be alkyl, aryl or H. Often a rearrangement takes place before the ring closure. Thus the product of the action of MeMgX with benzalpropiophenone readily gives 1-Ph-2,3-Me_2-indene with acids.



A. Naphthalene and Its Derivatives

Just as an open chain of at least six carbon atoms tends to form a six-membered ring under suitable conditions, a compound with at least ten carbon atoms may form a substance having two six-membered rings, two of the carbons forming part of both rings.

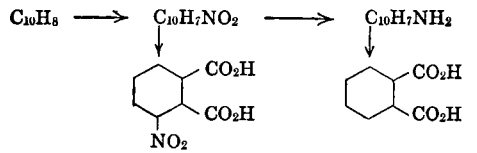
Naphthalene, $C_{10}H_8$, m. 80°, b. 218°, is the largest single constituent of coal tar, occurring up to 6% in it. The structure of naphthalene involves the same uncertainty as to the fourth valence of carbon as is presented by benzene.



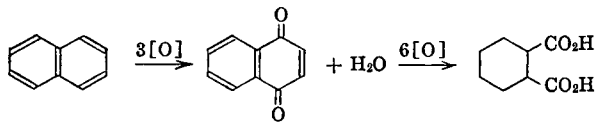
Much study has been given to the problem.[2–4] Usually the non-committal double hexagon formula is used. The presence of a benzene ring with two

[1] Johnson. "Org. Reactions," II, p. 114.
[2] Kohlrausch. *Ber.* **68B**, 893 (1935).
[3] Fieser. *J. Am. Chem. Soc.* **57**, 1459 (1935).
[4] Fries. *Ber.* **69B**, 715 (1936).

carbons in the *o*-position is shown by the ready oxidation of naphthalene to *o*-phthalic acid. That the other ring is either a benzene ring or can become one is indicated by the following changes.

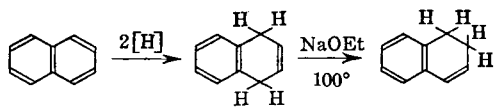


Thus, in one case the part not containing the N substituent was oxidized leaving the other part as a benzene ring while in the other case the part containing the N group was destroyed leaving the unsubstituted part also as a benzene ring. Naphthalene forms a yellow crystalline compound with picric acid, m. 149°. Naphthalene is more readily oxidized than benzene. The first step in the oxidation can be achieved by CrO_3 in acetic acid to give α-naphthoquinone. Further oxidation gives phthalic acid.



Air oxidation gives phthalic anhydride which is used to make plastics and as an important intermediate for the production of xanthene and vat dyes.

Naphthalene is more easily hydrogenated than benzene. Addition of Na to an alcoholic solution of naphthalene gives 1,4-dihydronaphthalene, m. 25°, b. 212°, a result of 1,4-addition. Heating with NaOEt at 100° gives the 1,2-compound.

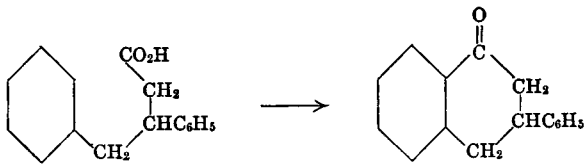


The 1,4-compound is a typical benzene with an unsaturated side chain. One mol of Br_2 adds readily to give a dibromide, m. 74°, which easily loses 2 HBr to give naphthalene again. Cautious oxidation converts 1,4-H_2-naphthalene to *o*-phenylenediacetic acid, $C_6H_4(CH_2CO_2H)_2$, m. 150. More vigorous oxidation gives phthalic acid. In the same way careful oxidation of the 1,2-H_2 naphthalene gives *o*-$C_6H_4(CO_2H)CH_2CH_2CO_2H$. It is not possible to go beyond the dihydro stage with Na and an alcohol. Thus this peculiar hydrogenation in the case of naphthalene is possible only because the ends of a conjugated system are both α- to a benzene ring.

Hydrogenation with a nickel catalyst gives 1,2,3,4-*tetrahydronaphthalene, tetralin*, m. −30°, b. 207°, an important cheap solvent. This substance

contains a true benzene ring with four alicyclic CH_2 groups forming another ring attached in the *o*-positions. Oxidation gives phthalic acid. Bromine substitutes in the alicyclic ring. The monobromide and dibromide lose 1 and 2 HBr giving dihydronaphthalene and naphthalene readily. These processes take place so easily that a good way to convert bromine to HBr is to drop it into an excess of boiling tetralin. The aromatic ring of tetralin can be nitrated and sulfonated. Thus the monosodium sulfonate is "Alkanol"-S, a wetting agent. Tetralin is easily oxidized by air to α-tetralone,[5] but the intramolecular acylation of cyclic compounds having suitable side chains leads to many substituted α-tetralones.

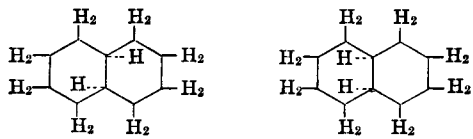
An example is the cyclization of *β, γ-diphenylbutyric acid* to 3-phenyl 1-tetralone.[6]



Thus the usefulness of this prolific synthetic process is again illustrated (see page 728).

β-Tetralone is made by the addition of Na to an alcoholic solution of β-methoxynaphthalene.

Ordinarily the catalytic hydrogenation of naphthalene stops at the H_4 stage. More vigorous treatment gives *decahydronaphthalene, decalin,* bicyclo-(4.4.0)decane, *cis,* b. 193°, d. 0.895; *trans,* b. 185°, d. 0.870. Pt black gives mainly the *cis* form while Ni gives mainly the *trans* form.[6a]



trans *cis*

Synthetic decalin derivatives are usually *trans* while the natural di-cyclic sesquiterpenes are usually related to the *cis* form.[7] Decalin cannot be nitrated or sulfonated. Oxidation gives deep seated changes ending in CO_2 and H_2O. Naphthalene can also *add* Cl_2 or 2 Cl_2 more readily than can benzene. Dry chlorine gas acts on solid naphthalene to give *naphthalene tetrachloride,* $C_{10}H_8Cl_4$, m. 182°. Bases convert it to a mixture of dichloronaphthalenes. In dimethylether naphthalene adds sodium.[8]

[5] *Ann. Rep. Chem. Soc.* (London) **1937,** 236.
[6] Johnson. "Org. Reactions," II, p. 114.
[6a] *Ann. Rep. Chem. Soc.* (London) **1924,** 92.
[7] *Ann. Rep. Chem. Soc.* (London) **1932,** 153.
[8] Scott. *J. Am. Chem. Soc.* **58,** 2442 (1936).

Naphthalene gives all the *substitution reactions* of which benzene is capable. In general it resembles toluene in ease of substitution. Whereas benzene gives only one monosubstitution product naphthalene can give two. The 1,4,5, and 8 positions are like each other as are the 2,3,6, and 7 positions but the two sets of four are different from each other. The first four are called α- as they are in that position to the other ring while the other four are β-. Considering one ring of naphthalene as the ring in which substitution is to take place, it is found to have side chains $-CH=CH-$ much like the side chain in cinnamic acid which gives only *o*- and *p*-substitution. Thus it is not surprising that the direct introduction of a group into naphthalene takes place in one of the α-positions which are *ortho* to the side chain rather than in a β-position which is *meta*. Some exceptions are the sulfonation of naphthalene at high temperatures and the Friedel-Crafts reaction both of which give β-substitution.

Of disubstituted naphthalenes, *ten* isomers are possible when the groups are alike and *fourteen* when they are different. The 1:8-position is the *peri* position and resembles the *o*-position in making possible anhydride formation and other changes involving the formation of 5- and 6-membered rings including carbons 1,9, and 8.

The methylnaphthalenes are obtained from coal tar and some cyclization processes in the petroleum industry. *α-Methylnaphthalene*, m. − 22°, b. 243°, can be made from α-bromonaphthalene, MeI and Na (Wurtz-Fittig), or more easily by the chloromethylation of naphthalene with formaldehyde and HCl followed by H_2 reduction of the α-chloromethylnaphthalene.[9] No satisfactory synthesis has been devised for *β-methylnaphthalene* m. 35°, b. 245°. However it has been made by the Friedel-Crafts reaction.[10] The reason for the failure of β-Br-naphthalene and MeI to give the β-Me-compound is probably due to too great a difference in the reactivity of the two halides. Thus β-Br-naphthalene, ethyl bromide and Na give β-ethyl-naphthalene, b. 251°. The failure of the Friedel-Crafts reaction may be from a similar reason. Naphthalene alone acts readily with $AlCl_3$ to form dinaphthyls and other compounds. With ethyl chloride and $AlCl_3$ it gives β-Et-naphthalene. Methylnaphthalenes are used as a standard high knocking fuel for Diesel engines.

Other alkylated naphthalenes are made from the alcohol, naphthalene and either $AlCl_3$, BF_3 or HF as catalysts.[11]

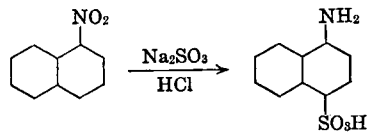
Agathalene is 1,2,5-trimethylnaphthalene. **Sapotalene** is the 1,2,6-compound. Because of their relation to the terpenes, all the possible trimethylnaphthalenes have been synthesized.[12] 1,2,5,6-Tetramethylnaphthalene is made by the dehydrogenation of pentacyclic triterpenes.[13] 1-Methyl-7-

[9] "Org. Reactions," I, p. 70.
[10] Tchéou, Young. *C. A.* **31**, 6646 (1937).
[11] "Org. Reactions," III. p. 1.
[12] Ruzicka. *Helv. Chim. Acta* **15**, 140 (1932).
[13] *Ann. Rep. Chem. Soc.* (London) **1937**, 329.

ethylnaphthalene has been made from artemisin.[14] *Cadalene*, 1,6-dimethyl-4-isopropylnaphthalene, and *eudalene*, 1-methyl-7-isopropylnaphthalene, are related to the terpenes.

All ten possible *dichloronaphthalenes* have been made. In most cases they have been obtained by replacing NH_2 by Cl or H and SO_2Cl by Cl in suitable naphthalene intermediates of the dye industry. The melting points of the isomers follow: 1,2-, 37°; 1,3-, 61°; 1,4-, 68°; 1,5-, 107°; 1,6-, 49°; 1,7-, 64°; 1,8-, 88°; 2,3-, 120°; 2,6-, 136°; 2,7-, 114°. They well illustrate the complex relations of constitution and melting points. The chlorination of naphthalene gives nearly pure *α-chloronaphthalene*, b. 259°. About 5% of the β-compound, m. 57°, b. 266°, is also formed and can be separated by suitable crystallization.[15] It is best obtained from β-naphthylamine through diazotization. Further chlorination gives polychloro compounds, first oils and then waxes (Halowax). When free of HCl these waxes have valuable dielectric properties.

α-Nitronaphthalene, $C_{10}H_7NO_2$, m. 57°, b. 304°, is readily obtained by direct nitration which gives a mixture of about 94% α- and 6% β-nitronaphthalene.[16] The β-isomer can easily be removed by recrystallization from alcohol, or by sweating.[17] It gives the usual reactions of nitro compounds. In addition, it reacts with PCl_5 to give α-chloronaphthalene. In this reaction nitronaphthalenes differ from nitrobenzene. α-Nitronaphthalene gives naphthionic acid by the Piria reaction.



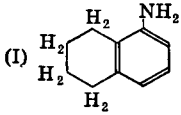
Further nitration gives 1,5- and 1,8-$(NO_2)_2$-naphthalene, m. 217° and 173°. 1,3-$(NO_2)_2$-Naphthalene, m. 145°, is made by acetylating α-naphthylamine, dinitrating, hydrolyzing and treating a sulfuric acid solution of the resulting 2,4-$(NO_2)_2$-naphthylamine with ethyl nitrite to replace the NH_2 by H. *β-Nitronaphthalene*, m. 77°, b. 165° (15 mm.), is readily obtained indirectly by treating diazotized β-naphthylamine with $NaNO_2$ and cuprous oxide. It can also be obtained in low yields by the direct nitration of naphthalene.

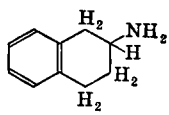
α-Naphthylamine, $C_{10}H_7NH_2$, m. 50°, b. 301°, is made by reducing the nitro compound. Its reactions are like those of aniline. Commercial α-naphthylamine has a very vile odor. It is easily phenylated by heating with excess aniline to *phenyl-α-naphthylamine*, an important rubber antioxidant. The catalysts in this phenylation are sulfanilic acid, $ZnCl_2$, and even traces of HCl. NH_3 is formed.

[14] *ibid.* **1932**, 156.
[15] Britton. U. S. Patent No. 1,917,822 (1933).
[16] Fierz-David. *Helv. Chim. Acta* **26**, 99 (1943).
[17] Wieland, Gubelmann. U. S. Patent No. 1,836,211.

β-Naphthylamine, m. 112°, b. 294°, is made from β-naphthol through the Bucherer reaction by heating with NH_3 and ammonium bisulfite. The replacement of OH by NH_2 is easier than in the benzene series. In fact, naphthols and naphthylamines, especially as their sulfonic acids, are interconvertible by the Bucherer reaction by treatment with ammonium sulfite and with sodium bisulfite respectively.[18] β-Naphthylamine differs from the α-compound in being odorless and more stable to oxidation. It is a very dangerous carcinogenic compound causing malignant tumors in the bladder. Breathing the vapors and contact with the skin must be avoided as the introduction of even traces into the system may produce serious tumors which sometimes do not appear until years after the exposure.

The two naphthylamines behave quite differently with Na and an alcohol. The α-compound adds 4 H on the ring not containing the NH_2 group to give *ar-tetrahydro-α-naphthylamine*, b. 273°, (I), so-called because it is an aromatic amine capable of diazotization and other typical aromatic amine reactions. It resembles aniline closely, including its weak basic properties. The β-compound adds 4 H mainly on the ring containing the NH_2 to give *ac-tetrahydro-β-naphthylamine*, b. 246°, (II), so-called because it is a typical alicylic amine. Instead of giving a diazonium salt it gives a stable nitrite which melts at 140° and decomposes at 190° to N_2, H_2O, and dihydronaphthalene. It is a strong enough base to absorb CO_2.

(I) 

(II) 

***ac*-H_4-α-naphthylamine,** b. 243°, and ***ar*-H_4-β-naphthylamine,** b. 274°, have also been made, the first indirectly and the latter as a by-product of the *ac*-compound.

The naphthylamines give practically the same reactions as does aniline. Bromination and nitration of the acetnaphthalides proceed as with acetanilide. The α-compound is substituted in the 4-position ("*p*-") while the β-compound is substituted in the 1-position ("*o*-"). Heating α-naphthylamine sulfate gives the normal aniline rearrangement (see page 742). Direct sulfonation of β-naphthylamine gives a mixture of *2-naphthylamine-6,8-disulfonic acid* (Amino G) and *2-naphthylamine-1,5,7-trisulfonic acid.*

The *sulfonation* of naphthalene is easier than that of benzene and always gives a mixture of isomers. Concentrated acid at 40–80° gives a mixture of about 96% α- and 4% β-sulfonic acid. The separation is easily made by means of the Ca or Ba salts, those of the α-acid being more soluble. The sulfonic acid group is more readily replaced in fusion reactions than with benzenesulfonic acid. For instance, the sulfonyl chlorides on fusion with

[18] "Org. Reactions, I, p. 105.

PCl_5 have the SO_2Cl group replaced by Cl. The α-acid when heated with conc. sulfuric acid gives the β-acid. The equilibrium mixture at 155–160° contains about 85% β- and 15% α-sulfonic acid which is the mixture obtained by sulfonating naphthalene with conc. sulfuric acid at 155–160°.[19] This is the usual process since the α-substitution products of naphthalene are available by a variety of processes whereas the β-compounds are practically all made through the β-sulfonic acid. The conversion of the α- to the β-acid is not a true rearrangement but rather a result of hydrolysis, the β-acid being less readily hydrolyzed.

$$2\ C_{10}H_8 + 2\ H_2SO_4 \underset{160°}{\overset{40°}{\rightleftharpoons}} \underset{15\%}{\overset{96\%}{\alpha\text{-}C_{10}H_7SO_3H}} + \underset{85\%}{\overset{4\%}{\beta\text{-}C_{10}H_7SO_3H}} + 2\ H_2O$$

$$\alpha\text{-}C_{10}H_7SO_3H + H_2O \rightleftharpoons H_2SO_4 + C_{10}H_8 \rightleftharpoons \beta\text{-}C_{10}H_7SO_3H + H_2O$$

Four *naphthalenedisulfonic acids* are readily available. Sulfonation with oleum at 40° gives a mixture containing about 70% of the *1,5-* and about 20–25% of the *1,6-* with some of the *2,7-disulfonic acid.*[20] Sulfonation with sulfuric acid at 165° and then adding oleum at 165° gives a mixture containing about 24% *2,6-* and about 65% of the *2,7-* with some *1,6-disulfonic acid.*[21] Five other disulfonic acids of naphthalene have been made. The only missing member of the ten theoretically possible isomers is the 2,3-acid.

Of the fourteen possible *naphthalenetrisulfonic acids*, the *1,3,6-* and *1,3,7-acids* are obtained by direct sulfonation of naphthalene which is the first step in the manufacture of *H Acid.* The *1,3,5-*, *1,4,5-*, and *2,3,6-acids* are made indirectly.

Of the twenty-two theoretically possible *tetrasulfonic acids* of naphthalene, the *1,3,5,7-* and *1,3,6,8-acids* are known.

The appearance of a sulfonic acid group in the 1-position in most of the polyacids indicates the high activity of the α-position even after several groups have entered the molecule. The predominance of β-groups is because of the greater stability of the β-sulfonic acids under the necessarily drastic conditions required to introduce several groups. The wetting agent, Nekal, or "Aquarex" BBX, is isopropylated naphthalene β-sodium sulfonate, made by treating the β-sulfonic acid with isopropyl alcohol. Daxad 11, a dispersing agent, is naphthalene β-sulfonic acid treated with formaldehyde. The action of naphthalene sulfonic acids with formaldehyde gives various complex synthetic tanning materials (syntans, Leukanol, etc.).

Six *nitronaphthalene sulfonic acids* are obtainable by nitrating the sulfonic acids of naphthalene, the α-acid giving the *1,4-*, *1,5-*, and *1,8-acids* and the β-acid giving the *1,3-*, *1,6-*, and *1,7-acids*, the NO_2 group being 1- in each case. The 1,2-acid is not formed, apparently, because the meta-directing influence of the sulfonic acid group overbalances the reactivity of an α-position *ortho* to it.

[19] "Org. Reactions," III, p. 156.
[20] "Org. Reactions," III, p. 158.
[21] Fierz-David. *Helv. Chim. Acta* 6, 1133 (1923).

Six *nitronaphthalene disulfonic acids* are obtained by nitration of the following disulfonic acids to give the indicated products, the NO_2 group being numbered first:

2,6- → 1,3,7-; 2,7- → 1,3,6-;
1,4- → 1,5,8-; 1,6- → 1,3,8-;
1,5- → 1,4,8- and 2,4,8-.

The last product is remarkable as involving the entrance of a group other than SO_3H into a beta position. Evidently the *meta*-effect of the sulfonic acid group partly counterbalances the reactivity of the α-positions. Of course, the 1,5-disulfonic acid necessitates the entrance of a nitro group either para to the sulfonic acid (in an α-position) or meta (in a β-position).

1-Nitronaphthalene-3,6,8-trisulfonic acid is made by the nitration of 1,3,6-naphthalene trisulfonic acid, the second step in the manufacture of H acid.

1,8-Dinitronaphthalene-3-sulfonic acid is obtained by nitrating 1-nitronaphthalene-6-sulfonic acid. The dinitration of naphthalene-2,7- and -1,5-disulfonic acids illustrates the principles of orientation in naphthalene compounds. In the first case two α-positions are meta to the two sulfonic groups. The result is *1,8-dinitronaphthalene-3,6-disulfonic acid,* the parent substance of the important intermediate, *H acid.* In the second case one nitro group occupies an α-position *para* to the sulfonic acid group and the other takes the β-position *meta* to the other group, the product being *1,6-dinitronaphthalene-4,8-disulfonic acid.*

Naphthylamine monosulfonic acids are known corresponding to 13 of the 14 possible isomers, the missing one being the 2,3-acid. Six of them can be made by reducing the nitro acids. The 1,2-acid can be made by heating Na naphthionate to 250°. The most important of these acids are the Cleve's acids, α-naphthylamine-6-and-7-monosulfonic acids, *Peri acid,* α-naphthylamine-8-sulfonic, and Laurent's acid, α-naphthylamine-5-sulfonic acid. The less important is *Broenner's acid,* 2,6-. *Naphthionic acid α-naphthylamine-4-sulfonic acid* is easily made by baking the amine sulfate. Thus the HSO_3 group takes the *para* position just as in the baking of aniline sulfate to give sulfanilic acid. The *naphthylamine disulfonic* acids are made by reducing the nitro compounds and by sulfonating the naphthylamines. The important α-naphthylamine derivatives are the 3,8- (*Epsilon acid*) and the 4,8-disulfonic acids. The β-naphthylamine compounds in order of importance are the 5,7-, (Amino J), the 6,8-, (Amino G), and the 4,8-disulfonic acids. Amino G and J are important dye intermediates. The important *trisulfonic acids* are *α-naphthylamine-3,6,8-trisulfonic acid, Koch acid,* made by reducing the corresponding nitro compound (third step in the manufacture of H acid) and *β-naphthylamine-1,5,7-trisulfonic acid* which is easily hydrolyzed in dilute H_2SO_4 to Amino J. There are no amino tetrasulfonic acids known probably because the two known acids do not nitrate.

Both *naphthols,* $C_{10}H_7OH$, are found in coal tar and can be made by fusion

of the naphthalene sulfonates with NaOH. *α-Naphthol*, m. 96°, b. 288°, and *β-naphthol*, m. 122°, b. 294°, resemble the phenols but have their OH groups more readily replaceable by treatment with NH_3 and PCl_5. Pure α-naphthol free from any trace of the β-compound can be made by heating α-naphthylamine with dil. H_2SO_4 in an autoclave. *ar-Tetrahydro-α-naphthol*, m. 69°, b. 263°, can be made by diazotizing the corresponding amine or from the action of Na and alcohol on α-napththol, or simply hydrogenating α-naphthol with a nickel catalyst. The corresponding *ac*-compound is a liquid made by hydrogenating α-naphthol with a copper chromite catalyst. β-Naphthol with amyl alcohol and Na gives mainly *ac-H_4-β-naphthol*, b. 262° with a smaller amount of the *ar*-compound, m. 59°, b. 276°. In both cases the *ar*-compounds are true phenols and the *ac*-compounds true alcohols. Both naphthols are oxidized to dinaphthols by $FeCl_3$. *β-Naphthyl methyl ether, nerolin*,

$$C_{10}H_7OCH_3,$$

m. 72°, b. 274°, is a perfume material.

The naphthols give nitroso compounds with nitrous acid. As with phenol, these are really mono-oximes of quinones. α-Naphthol gives mainly the 2-oxime of β-naphthoquinone, m. 164° dec., with a lesser amount of the 4-oxime of α-naphthoquinone, m. 152°. *Nitroso-β-naphthol*, m. 109°, the 1-oxime of β-naphthoquinone, is used in determining Fe and Co because it does not give precipitates with Al, Cr, Mn and Ni.

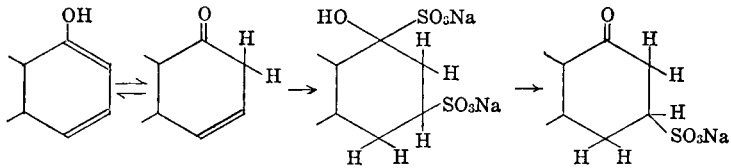
The *nitration* of α- and β-naphthol gives respectively the 4- and 1-nitro-compounds. 2,4-Dinitro-α-naphthol is *Martius Yellow* or *Naphthalene Yellow* while its 7-sulfonic acid obtained from α-naphthol-2,4,7-trisulfonic acid and nitric acid is *Naphthol Yellow S* or *Fast Yellow*. It cannot be made by sulfonating the dinitro compound.

The direct *sulfonation* of *α-naphthol* under various conditions gives the *2-* and *4-* (Nevile-Winther acid) *sulfonic acids*, the *2,4-* and 4,7-*disulfonic acids*, and the *2,4,7-trisulfonic acid*. The latter loses the 4-group on treatment with sodium amalgam and acid to give the *2,7-disulfonic acid*. The Nevile-Winther's acid is also easily made by the Bucherer reaction on naphthionic acid. The *5*-sulfonic acid and the 3,6-disulfonic acid of α-naphthol are obtained by the action of NaOH at high temperature on naphthalene-1,5-disulfonic and 1,3,6-trisulfonic acids respectively. Many other α-naphthol sulfonic acids have been made by diazotizing the corresponding NH_2 acids. Thus the *1,8-acid* is obtained. It readily gives an anhydride 1,8-naphthol-sulfone, "naphsultone," m. 154°, b. 360°. With cold fuming sulfuric acid this compound gives *α-naphthol-2,4,8-trisulfonic acid*. With nitric acid, this gives 2,4-dinitro-α-naphthol-8-sulfonic acid. The direct sulfonation of *β-naphthol* gives the 6-sulfonic acid (Schaeffer's acid)[22], the *8-sulfonic acid* (*Crocein acid*), the *1-sulfonic acid*, the *3,6-disulfonic acid* (*R acid*) and the *6,8-disulfonic acid* (G acid).

[22] Engel. *J. Am. Chem. Soc.* 52, 2835 (1930).

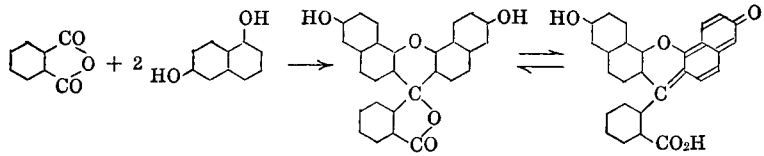
Phenyl β-naphthylamine is an important rubber antioxidant. It is made by heating β-naphthol with an excess of aniline and a small amount of $ZnCl_2$ as a catalyst.

The tautomerism of naphthols is shown by the action of $NaHSO_3$ with 1,5- and 2,7-$(OH)_2$-naphthalenes.[23] The α-compound adds 2 $NaHSO_3$. Boiling with water removes 1 $NaHSO_3$ and gives sodium 5-OH-1-ketotetrahydronaphthalene-3-sulfonate.



The β-compound adds only 1 $NaHSO_3$. This can be converted by NH_3 and heat to 2-NH_2-7-OH-naphthalene.

1,6-Dihydroxynaphthalene gives a fluorescein with phthalic anhydride.[24] The colorless and colored forms are as follows:



Even the free acid exists in the colored quinoid form when free of solvent.

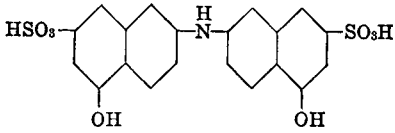
Chromotropic acid, 1,8-$(OH)_2$-naphthalene-3,6-disulfonic acid, is obtained by diazotizing Koch acid to replace the NH_2 by OH. The 8-SO_3H is then replaced by OH by a regular caustic fusion.

Aminonaphthols are like the amino phenols in preparation and properties. The commonest are the 1,4-; 1,8-; 2,1-; and 2,7-compounds, the OH being numbered first. Various mono and disulfonic acids of the aminonaphthols are important dye intermediates. The most important of these is *H acid, 8-amino-α-naphthol-3,6-disulfonic acid* which is made by the caustic fusion of Koch acid (fourth step in the manufacture of H acid) replacing the 8-sulfonic acid group by OH. Other important dye intermediates are *Gamma acid,* 1-OH-7-NH_2-3-SO_3H-, *J acid,* 1-OH-6-NH_2-3-SO_3H-, *Chicago acid,* 8-OH-1-NH_2-2,4$(SO_3H)_2$-, and the 2-OH-1-NH_2-4-SO_3H acid. The last acid is made by treating nitroso β-naphthol with $NaHSO_3$.

Phenyl J acid, 1-OH-6-NHC_6H_5-3-SO_3H, is made by heating J acid with an excess of aniline and sodium bisulfite. Here the Bucherer reaction is used to introduce the $-NHC_6H_5$ group. Similarly in the presence of even traces of

[23] *Ann. Rep. Chem. Soc.* (London) **1922**, 108.
[24] Koenigs. *Ann. Rep. Chem. Soc.* (London) **1914**, 114.

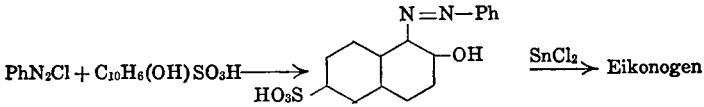
sodium bisulfite J acid forms *di*-J *acid* or *Rhoduline acid* by the loss of ammonia.



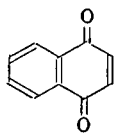
Rhoduline acid

Phenyl J acid and Rhoduline acid are dye intermediates.

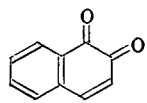
An important photographic developer is sodium 1-amino-2-naphthol-6-sulfonate, *Eikonogen*. One method of preparation is from Schaeffer's acid and benzene diazonium chloride.



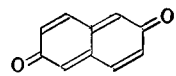
Naphthoquinones. Three are known, the α- or *1,4*- the β- or *1,2*- and the *amphi*- or 2,6-naphthoquinones. They are yellow or red crystalline compounds resembling the benzoquinones.



Alpha



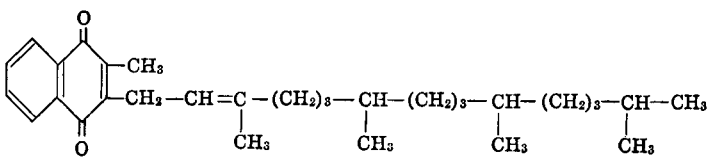
Beta



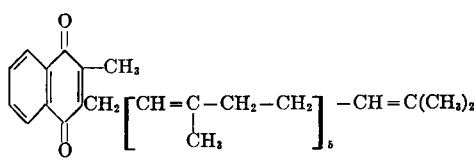
Amphi

They are made by oxidizing the corresponding amino hydroxy or dihydroxy compounds. They are readily reduced to the dihydroxy compounds.

The α-naphthoquinones occur in nature as vitamin K_1 and K_2.

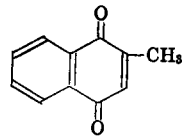


Vitamin K_1



Vitamin K_2

Vitamin K_1 was isolated from alfalfa and K_2 from sardine meal.[25–27] K_1 has been synthesized and compared with the natural product. During the intensive investigation of 1,4-naphthoquinones for antibleeding activity, *Menadione, 2-methyl-1,4-naphthoquinone,*



Menadione

was found to have about twice the activity of the natural vitamin K_2. It is easily made by the chromic anhydride oxidation of 2-methylnaphthalene[28] and is used in medicine in place of the more expensive natural product. The hydroquinone as well as the hydroquinone diacetate of Menadione are very active and are used in medicine.

Several *hydroxy-α*-naphthoquinones occur in nature. *Lawsone* and *juglone* are the 2- and 5-compounds respectively. *Plumbagin* is the 5-OH-2-Me-compound. *Naphthazarine* is the 5,6-$(OH)_2$-compound. *Lapachol*[29] is related to naphthoquinone.[30] β-Naphthoquinone-4-sulfonic acid is used to estimate amino acid nitrogen in blood.[31] An example of an amphi-naphthoquinoid compound is the fluorescein from phthalic anhydride and 1,6-$(OH)_2$-naphthalene (p. 737).

Naphthalenecarboxylic Acids

α- and β-Naphthoic acids, m. 161° and 184°, are made by the usual methods. *β-Hydroxy naphthoic acid, 2-hydroxy-3-naphthoic acid,* is made by the action of CO_2 on sodium β-naphtholate. Many insoluble colored pigments are made by coupling diazo compounds to β-hydroxy naphthoic acid. The anilide, *p*-toluide, etc. are also important dye intermediates.

α- and β-Naphthalene acetic acid are prepared by the Willgerodt reaction and the Kindler modification of the Willgerodt Reaction.[32] α-Naphthalene acetic acid is an important growth promoting plant hormone.

The best known of the dibasic acids is *naphthalic acid,* the peri acid, naphthalene-1,8-dicarboxylic acid, m. 270°, made by oxidizing acenaphthene.

[25] Dam et al. *Helv. Chim. Acta* **22**, 310 (1939).
[26] Doisy et al. *J. Am. Chem. Soc.* **61**, 1295 (1939).
[27] Almquist, Doisy, Fieser. *J. Am. Chem. Soc.* **61**, 2557 (1939).
[28] Fieser. *J. Biol. Chem.* **133**, 391 (1940).
[29] Hooker. *J. Am. Chem. Soc.* **58**, 1190 (1936).
[30] Fieser. *J. Am. Chem. Soc.* **58**, 572 (1936).
[31] Folin. *J. Biol. Chem.* **51**, 377 (1922).
[32] "Org. Reactions," III, p. 83.

It behaves like phthalic acid in many ways. It forms a cyclic anhydride and imide and reacts with mercuric acetate with replacement of one carboxyl by HOHg- which forms an inner salt with the other carboxyl.

3-Nitronaphthalic acid can be obtained by direct nitration of the anhydride in cold conc. H_2SO_4 by the calculated amount of KNO_3. It is to be observed that this is the nitration of a naphthalene compound in the *beta* position. The 4-nitro-compound is obtained by oxidizing 4-NO_2-acenaphthene.

Naphthalene-1,2-dicarboxylic acid, m. 178° dec., can be made by heating Na naphthionate in refluxing naphthalene to give the 1,2-isomer, diazotizing and replacing the NH_2 by Cl, fusing the 1-Cl-2-SO_3Na-compound with potassium ferrocyanide in presence of copper to give the 1,2-$(CN)_2$-naphthalene and hydrolyzing the latter with KOH. The *1,4-dicarboxylic acid*, m. 240°+, can be made similarly from naphthionic acid. The *2,3-dicarboxylic acid*, m. 235° dec., is made from diethylnaphth-2,3-indandione, $C_{10}H_6(CO)_2CEt_2$, prepared by the Friedel-Crafts reaction on naphthalene and diethylmalonyl chloride. It is colorless and less soluble than the yellow 1,2-compound which is formed in small amounts. Treatment with KOH opens the indandione ring and oxidation with nitric acid converts the resulting Et_2-acetyl-naphthoic acid to the 2,3-dibasic acid. These dibasic acids resemble phthalic acid in forming anhydrides and in having the carboxyl readily replaceable by Hg. This is also true of their nitro derivatives. Replacement of the Hg by H, halogen and other groups gives many synthetic possibilities.

1,4,5-Naphthalenetricarboxylic acid is readily made by oxidizing an acyl derivative of acenaphthene. Its anhydride melts at 274°. Treatment of this with MeOH and H_2SO_4 gives the monomethyl ester, m. 222°, without changing the anhydride grouping.

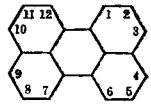
1,4,5,8-Naphthalenetetracarboxylic acid is obtained by oxidizing *peri*-succinoylacenaphthene.[33] It gives a diimide which forms a characteristic yellow Na salt.

αα-, *ββ-*, and *αβ-dinaphthyls*, $(C_{10}H_7)_2$, are known. The first two melt at 160° and 187°. They can be obtained in good yield by the action of ethereal $FeCl_3$ solution on the naphthyl Grignard reagents.

[33] Fieser. *J. Am. Chem. Soc.* **54**, 4347 (1932).

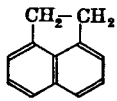
Compounds with More Than Two Condensed Rings

Perylene is a di-naphthylene many derivatives of which have been made.

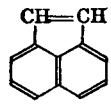


B. Acenaphthene and Related Compounds

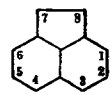
Acenaphthene, (I), m. 95°, b. 277°, found in coal tar, is a naphthalene with a bridge of two CH_2 groups in the *peri* position. At red heat it loses 2 H to form acenaphthylene (II), m. 93°. The latter has been isolated from the solid products of the pyrolysis of natural gas[34]



(I)

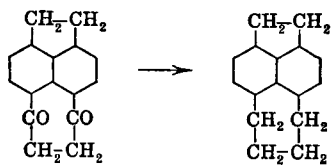


(II)



The fact that II is bright yellow while I is colorless illustrates the effect of an accumulation of conjugated double linkages. Oxidation of acenaphthene gives acenaphthoquinone which is really not a quinone but a 7,8-diketo compound. Further oxidation gives naphthalic acid and then hemimellitic acid.

The reactivity of the 3- and 4-positions in acenaphthene is shown by the condensation with succinic anhydride to give a seven-membered ring in *peri*-succinoylacenaphthene (III), m. 208°, and the corresponding hydrocarbon, *peri*-tetramethyleneacenaphthene (IV), m. 138°.[35]



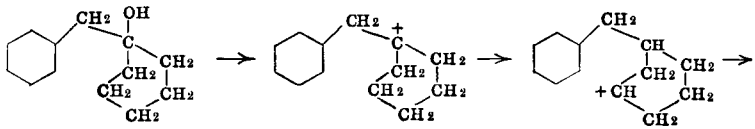
III IV

The reduction is by the Wolff-Kishner procedure using hydrazine hydrate and NaOEt at 160°.

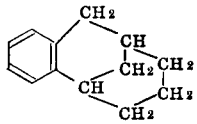
A tetralin derivative with a 3-C bridge across the meta positions in the *ac*-ring is obtained by dehydrating 1-benzylcyclohexanol (V).[36] Its formation is another example of the shift of a reactive spot in a molecule to a position

[34] Campbell. *J. Am. Chem. Soc.* **58**, 1051 (1936).
[35] Fieser. *J. Am. Chem. Soc.* **54**, 4347 (1932).
[36] Cook. *J. Chem. Soc.* **1936**, 62.

which makes possible the closure of a 6-ring.



(V)

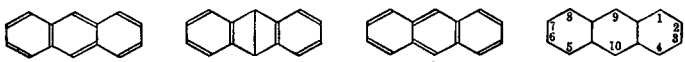


(VI)

(VI) is 2,3-benzo-(1.3.3)-bicyclo-2-nonene.

C. Anthracene

Anthracene is found in coal tar up to about one per cent. It is readily separated in a fraction containing carbazole and phenanthrene. Distillation with KOH retains the first as its nonvolatile N-K derivative. Phenanthrene can be removed by CS_2 from the distillate.



A. B. C. D.

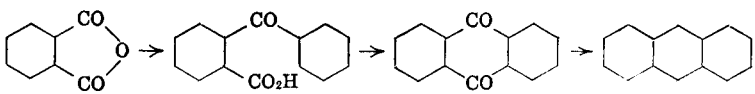
No one of the formulas A, B, and C expresses completely the peculiar properties of anthracene but all of them taken together seem to do so. This is probably a perfect case of *resonance* between several electronic formulas.[37] Anthracene is so peculiar that it is worthwhile to give various syntheses which have a bearing on its structure and properties.

1. Benzyl chloride heated with water at 200° gives it, dibenzyl and other products $4\ PhCH_2Cl \rightarrow C_{14}H_{10} + PhCH_2CH_2Ph + 4\ HCl$. Probably the first product is 9,10-dihydroanthracene which readily loses its two extra H atoms.

2. *o*-Bromobenzyl bromide with Na gives H_2-anthracene which is changed to anthracene on mild oxidation.

3. *o*-Tolyl phenyl ketone heated with zinc dust gives anthracene.

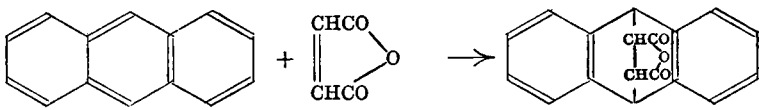
4. Phthalic anhydride and benzene with $AlCl_3$ give *o*-benzoylbenzoic acid. Treatment with P_2O_5 or sulfuric acid at 180° gives anthraquinone which on distillation with Zn dust forms anthracene.



[37] Pauling. *J. Chem. Phys.* **4**, 673 (1936).

5. The formation of anthracene from acetylene tetrabromide, benzene and $AlCl_3$ has been used as evidence for the existence of a para bond in the middle ring. It should be remembered, however, that $AlCl_3$ is very effective in breaking bonds and establishing new ones.

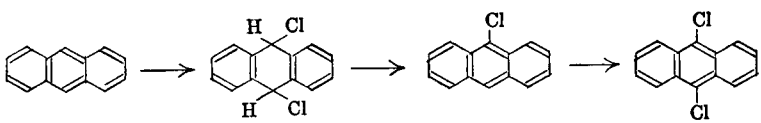
Properties. Anthracene, $C_{14}H_{10}$, m. 215°, b. 342°, forms colorless crystals which have a remarkable blue fluorescence. This probably depends on the excitation of a transformation between forms A and C possibly through B. Reduction readily gives 9,10-dihydroanthracene, m. 107°, in which the end rings are definitely like benzene. It is not fluorescent. High temperatures or treatment with oxidizing agents removes the 9,10-H atoms. The easy addition and removal of 2 H in positions 9,10 is reminiscent of the corresponding processes with quinone. Hence form B is called the quinone form. Addition takes place at 9,10- rather than at 1,4 in A or at 5,8 in B because the 9,10-positions are alpha to a true benzene ring in both cases. The best argument for the existence of a conjugated system between 9 and 10 as in A and C rather than of a para bond as in B is the fact that anthracene acts as the conjugated diene in the Diels-Alder reaction with maleic anhydride giving a bridge in the 9,10 position to form a new six-membered ring in the usual way.



Further hydrogenation of H_2-anthracene gives $C_{14}H_{16}$ and $C_{14}H_{24}$. Mild oxidation also attacks the 9,10-positions giving anthraquinone.

Sunlight converts a solution of anthracene to the less soluble *para-anthracene*, $(C_{14}H_{10})_2$, m. 244°, which is more stable in many ways than anthracene. It is relatively difficult to oxidize it to anthraquinone. On melting, it reverts to anthracene.

Derivatives of Anthracene. Three mono-substitution products are possible, the α-(1,4,5 or 8), the β-(2,3,6 or 7) and the γ-(9, or 10). The structures of such products are determined by oxidation, a γ-derivative giving anthraquinone, and the α- and β-derivatives giving the corresponding α- and β-substituted anthraquinones and then 3- and 4-substituted phthalic acids respectively unless the nature of the group is such as to favor the destruction of the ring to which it is attached (OH, NH_2). Anthracene adds Cl_2 in the 9,10-position. Bases remove 1 HCl giving 9-Cl-anthracene. Further chlorination gives the 9,10-Cl_2-compound.



Bromination in CS_2, solution gives 9,10-Br_2-anthracene, m. 221°. Alcoholic KOH reduces it to anthracene with the formation of MeCHO. Anthracene with pure Br_2 gives dibromoanthracene tetrabromide, m. 180° dec., which changes on heating to tribromoanthracene, m. 169°, and on treatment with alcoholic KOH to *Br_4-anthracene*, m. 254°. That 2 Br in each of these last compounds occupy the 9,10-positions is shown by their conversion respectively to monobromo and dibromoanthraquinone.

Cautious *sulfonation*, avoiding oxidation to anthraquinone, gives *α-* and *β-anthracenesulfonic acids*, the former predominating. It and its salts are more soluble than the *β*-compounds. Anthracenedisulfonic acids are also available.

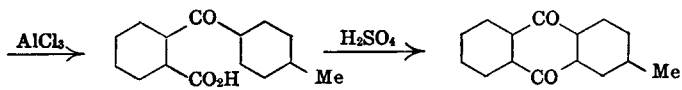
All attempts at the *nitration* of anthracene result in its oxidation to anthraquinone. The first step in the process may be the addition of nitric acid to the 9,10-system to give "*anthracene nitrate*," m. 127° dec.

Hydroxyanthracenes. The *α-* and *β-anthrols*, m. 153° and dec. 200° respectively, are obtained from the sulfonic acids by alkaline fusion. 9-Hydroxy- and 9,10-dihydroxyanthracenes are obtained from anthraquinone.

Anthraquinone, 9,10-diketo-9,10-dihydroanthracene, $C_{14}H_8O_2$, m. 285°, b. 380°, occurs repeatedly in anthracene chemistry because of the ease of its formation and its great stability. Commercially it is made in large amounts as a dye intermediate.

1. By oxidizing anthracene with chromic acid or catalytically by air.

2. From phthalic anhydrides.[38] This method has been used for making a great variety of substituted anthraquinones from suitably substituted phthalic anhydrides and aromatic hydrocarbons. Thus *β*-Me-anthraquinone is readily obtained from toluene and phthalic anhydride.



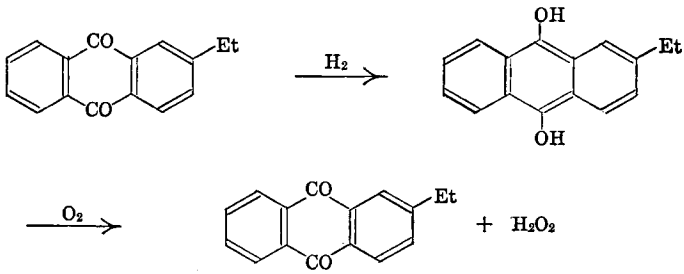
Sometimes the ring closure of the substituted *o*-benzoylbenzoic acid is difficult. It can then be reduced to the corresponding benzylbenzoic acid in which the ring can be closed more readily. The resulting anthrone can then be oxidized to the desired anthraquinone.

3. A preparation which indicates its ketonic nature is by the distillation of calcium phthalate.

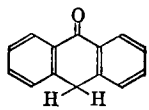
[38] Gleason. *J. Am. Chem. Soc.* **51**, 310 (1929).

Anthraquinone can be split by fusion with alkali to give two molecules of a benzoate. This is like the splitting of benzophenone by NaOH to give benzene and Na benzoate.

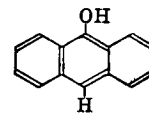
β-Et-anthraquinone has been suggested for use in a novel synthesis of hydrogen peroxide:



Reduction of anthraquinone by HI gives anthracene and its 9,10-H_2-compound. Treatment with Sn and HCl in glacial acetic acid reduces one CO to CH_2 to give *anthrone* (I), 9-keto-9, 10-H_2-anthracene, m. 155°.[39] It can also be obtained from *o*-benzylbenzoic acid and H_2SO_4 at 80°. Anthrone dissolves in hot dilute bases. Acidification precipitates the enol form anthranol (II), γ-OH-anthracene, 9-OH-anthracene, m. 120°. This gives a yellow solution in glacial acetic acid. Boiling gives colorless anthrone.

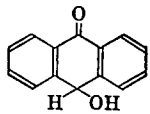


(I)

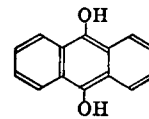


(II)

Solutions of (II) are fluorescent while those of (I) are not. Bromination of (I) followed by hydrolysis gives *oxyanthranol* (III), m. 167°, which is converted almost completely by alcoholic HCl to 9,10-$(OH)_2$-anthracene, *anthrahydroquinol* (IV), m. 180°, which can also be made by reducing anthraquinone with Zn and NaOH or by heating anthracene in HOAc with PbO_2.



(III)



(IV)

As would be expected, (IV) gives fluorescent solutions while (III) does not. (IV) is readily oxidized, even by air, to anthraquinone.

[39] "Org. Syntheses."

Monohalogen anthraquinones are not obtainable by direct halogenation. The β-compounds can be made from phenyl halides and phthalic anhydride.

Two *dibromoanthraquinones*, m. 245° and 275°, are obtainable, one by direct bromination at 160° and the other by the oxidation of Br_4-anthracene.

Nitration of anthraquinone gives *mono-* and *di-nitro*-derivatives, m. 230° and 260°.

Sulfonation is difficult, requiring 40% oleum at 160°. The product is *anthraquinone-β-sulfonic acid*, with the 2,6- and 2,7-disulfonic acids and about 5% of the α-acid. Mercuric sulfate catalyzes the formation of the α-acid and makes sulfonation possible under milder conditions. The by-products are then the *1,5-* and *1,8-disulfonic acids*. The sulfonic acid group is readily hydrolyzed from the α-position of anthraquinone. Alkaline fusion of the sulfonic acids is accompanied by air oxidation to give an extra hydroxyl group. This ease of oxidation is utilized in preparing *alizarin*, 1,2-dihydroxyanthraquinone, m. 289°, by fusing anthraquinone-β-sulfonic acid with alkali and the calculated amount of chlorate. Alizarin occurs in madder root as the glucoside, ruberythric acid, $C_{26}H_{28}O_{14}$. Its alkaline solution is used with mordants to give colored *lakes*, Al and Sn giving red, Ca blue, and Fe violet black. *Anthrarubin* is the anthranol obtained by reducing alizarin. Many other dihydroxyanthraquinones are known. The most important are the following: (1,3-) *xanthopurpurin*, m. 264°, (1,4-) *quinizarin*, m. 195°, (1,5-) *anthrarufin*, *rufol* m. 265°, dec., (1,8-) *chrysazin*, *chrysazol*, m. 225° dec., (2,3-) *hystazin*, *hystazarin*, m. 280°, (2,6-) anthraflavinic acid, m. 330°+, (2,7-) isoanthraflavinic acid, m. 330°+.

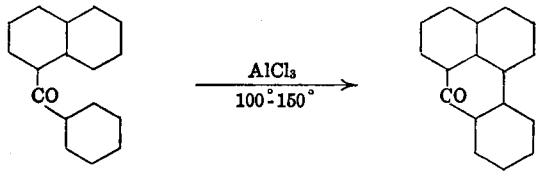
Many important dyes are related to alizarin and are similarly used with mordants to form insoluble lakes. The following are polyhydroxy derivatives of anthraquinone: (1,2,3-) *anthragallol*, Anthracene Brown, (1,2,4-) *purpurin*, (1,2,6-) *flavopurpurin*, (1,2,7-) *anthrapurpurin*, (1,2,6,8-) *Alizarin Bordeaux B*, (1,2,3,5,6,7-) *Anthracene Brown SW*, (1,2,4,5,6,8-) Anthracene Blue WR. Many more complex alizarin dyes, especially those containing sulfonic acid groups, are known. Certain dyes are identified by the alizarin name without being related to it. Thus *Alizarin Yellow C* is gallacetophenone, 2,3,4-$(OH)_3$-acetophenone, obtained from pyrogallol and acetic acid, *Alizarin Yellow A* is 2,3,4-$(OH)_3$-benzophenone, Alizarin Black S or naphthazarin is 3,4-$(OH)_2$-α-naphthoquinone, and *Alizarin Green G* and *B* are oxazin dyes formed from sulfonic acids of β-naphthoquinone and aminonaphthols.

Tectoquinone is β-Me-anthraquinone. *Rubiadin* is 2-Me-1,3-$(OH)_2$-anthraquinone and *munjistin* is the same with Me oxidized to carboxyl.

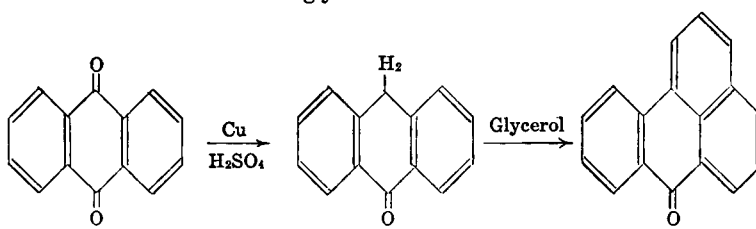
Das Anthracen und die Anthrachinone, J. Houben, 890 pp., Thieme, Leipzig 1929.

Benzanthrone, m. 170°, can be made by heating α-benzoylnaphthalene

with $AlCl_3$.



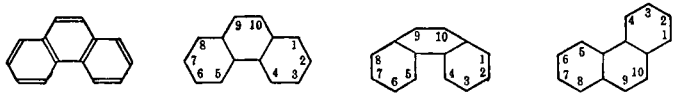
Benzanthrone is also prepared by heating a reduction product of anthraquinone with sulfuric acid and glycerol.[40]



It is an important intermediate for vat dyes.

D. Phenanthrene

Phenanthrene, $C_{14}H_{10}$, m. 99°, b. 340°, an isomer of anthracene, occurs with that substance in coal tar. It is a diphenyl with the 2,2′-positions bridged by a $-CH=CH-$ group thus forming three condensed benzene rings.



Like anthracene it gives fluorescent solutions. It is more difficult to oxidize and to reduce than anthracene. The first product of hydrogenation with copper chromite catalyst is *9,10-dihydrophenanthrene*, m. 35°. Oxidation with chromic acid yields *phenanthrene quinone*, 9,10-diketo-9,10-dihydrophenanthrene, m. 206. Further oxidation of the latter with hydrogen peroxide in acetic acid solution gives *diphenic acid*, diphenyl-2,2′-dicarboxylic acid, m. 229°. The quinone can be reduced with sulfurous acid to *phenanthraquinol*, 9,10-$(OH)_2$-phenanthrene.

Bromination of phenanthrene yields *9,10-dibromophenanthrene*; in the presence of a catalyst such as ferric bromide, however, *9-bromophenanthrene*, m. 63°, is produced in good yield.[41] The latter readily forms a Grignard reagent with magnesium, carbonation of which gives the *9-carboxylic acid*, m. 252°. Reaction with conc. sulfuric acid at 60° yields a mixture of the 2-,

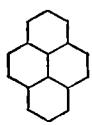
[40] "Org. Syntheses," II.

[41] Price. *J. Am. Chem. Soc.* **58**, 1838 (1936).

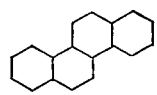
3- and 9- *monosulfonic acids*, together with a trace of the 1-isomer, illustrating the reactivity of the *beta* positions. Disulfonic acids are also formed. At 120°, conc. sulfuric acid gives mainly the 2- and 3-phenanthrene sulfonic acids. Fusion of the latter with KOH yields the corresponding *phenanthrols*. Acetylation with acetyl chloride and $AlCl_3$ in nitrobenzene solution results in the formation of *2-* and *3-acetophenanthrene* in 1:4 ratio. With oxalyl chloride, phenanthrene produces primarily the *3-carboxylic acid*, m. 269°, Me ester, m. 95°, with smaller amounts of the *2-carboxylic acid*, m. 258°, Me ester, m. 96°, and still less of the *9-carboxylic acid*, m. 252°, Me ester, m. 115°.[42]

Phenanthrene assumes added importance because of its relation to such widely diverse and essential groups of substances as the sterols, bile acids, morphine and sex hormones. (Phenanthrene and its Derivatives. Fieser, A.C.S. Monograph, 1936.)

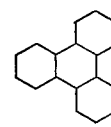
More complex hydrocarbons having condensed benzene nuclei are known in large numbers. Some of these come from coal-tar, others from the stupp-fat obtained in the working up of mercury ores at Idria and many more by synthetic methods which have been stimulated by the discovery of carcinogenic hydrocarbons (Cook).



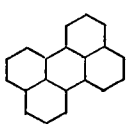
Pyrene
$C_{16}H_{10}$
m. 150°



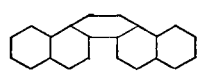
Chrysene
$C_{18}H_{12}$
m. 251°



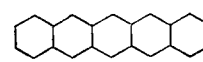
Triphenylene
$C_{18}H_{12}$
m. 198°



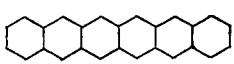
Perylene
$C_{22}H_{14}$
m. 269°



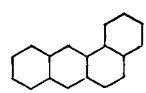
Picene
$C_{22}H_{14}$
m. 364°, b. 520°



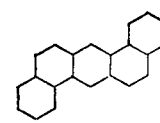
Pentacene
$C_{22}H_{14}$
m. 271°



Hexacene
$C_{22}H_{16}$
dec. 300°

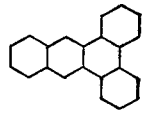


Benz(a)anthracene
$C_{18}H_{12}$
m. 159°

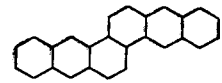


Dibenz(a,h)
anthracene
$C_{22}H_{14}$ m. 262°

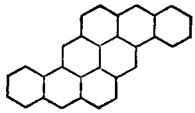
[42] Mosettig. *J. Am. Chem. Soc.* 54, 3328 (1932).



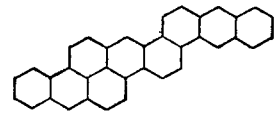
Dibenzanthracene-$\alpha\gamma$
Dibenz (a,c) anthracene
$C_{22}H_{14}$
m. 202°



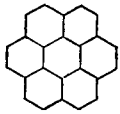
Dibenzochrysene (bk)
Dibenzo (b,k) chrysene
$C_{26}H_{16}$
m. 400°



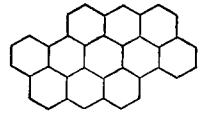
Pyranthrene
$C_{30}H_{16}$
sublimes



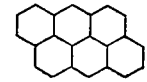
Dinaphthoperylene (3,2,1-cd,lm)
Dinaphtho (1,2,3-cd,1′,2′,3′-lm)
perylene
$C_{34}H_{18}$
subl. 400°



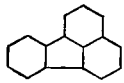
Coronene
$C_{24}H_{12}$
m. 430°
(Scholl 1932)



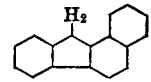
Dinaphthocoronene
dinaphtho (abc, jkl)
coronene
$C_{36}H_{16}$
subl. 500°



Anthanthrene
$C_{22}H_{12}$
m. 262°



Fluoranthene
idryl, $C_{16}H_{10}$
m. 110°

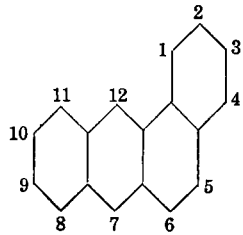


Chrysofluorene
$C_{17}H_{12}$
m. 188°, b. 413°

Everest, "Higher Coal-Tar Hydrocarbons," Longmans, Green and Co., 1927. Clar, "Aromatische Kohlenwasserstoffe," Edwards Brothers, Inc., 1944.

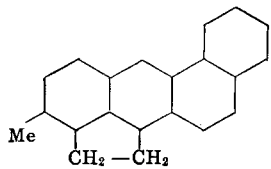
E. Carcinogenic Hydrocarbons

Certain polynuclear aromatic hydrocarbons have specific action in producing cancer in animals.[43–45] With few exceptions, e.g., benzo(c)phenanthrene, they are all derivatives of benz(a)anthracene:

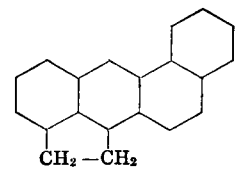


(I)

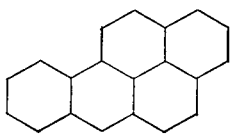
Only those derivatives having substituents at the 7, 8, or 12 positions are strong carcinogens, as tested with mice. Several of the most potent cancer-producing hydrocarbons are listed:



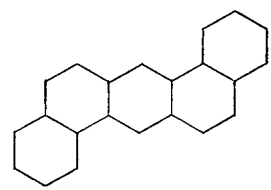
20-Me-cholanthrene
$C_{21}H_{14}$
(II)



Cholanthrene
$C_{20}H_{12}$
(III)



Benzo(a)pyrene
$C_{20}H_{12}$
(IV)



Dibenz(a,h)anthracene
$C_{22}H_{14}$
(V)

In order of decreasing carcogenicity, these are II > III > IV > V. Benzo(a)-pyrene (IV) was isolated originally from coal tar and shown to be the active carcinogen in that substance.

[43] Kennaway. *Brit. Med. J.* **1930**, 1044; *Biochem. J.* **24**, 497 (1930).
[44] Cook. *J. Chem. Soc.* **1930**, 1087.
[45] Fieser. *J. Am. Chem. Soc.* **59**, 2561 (1937).

PART IV

HETEROCYCLIC COMPOUNDS

Heterocyclic compounds have one or more atoms of elements other than carbon as members of their ring structures. The commonest element so occurring is nitrogen. Next to it comes oxygen and then sulfur. Many other elements are less commonly found as members of rings.

I. CLASSIFICATION

The heterocyclic compounds fall in two main classes.

1. Those resembling the alicyclic compounds, in which the properties of the atoms and groups involved are much as they would be in an open chain structure.

2. Those containing a conjugation of unsaturated groups or atoms which give an effect like that in benzene. Such compounds as pyridine, pyrrole, thiophene and furan show many aromatic properties which are destroyed on partial or complete hydrogenation much as happens with benzene.

Many heterocyclic compounds have condensed rings, that is, pairs of rings having two atoms in common. Sometimes both rings are heterocyclic but very often one is a benzene ring.

The most important 5-membered *heterocyclic systems* are listed below. In each case an angle represents a CH group

Furan

C_4H_4O

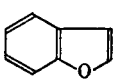
Thiophene

C_4H_4S

Pyrrole

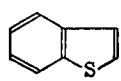
C_4H_5N

The positions in the above compounds and their derivatives are numbered counter-clockwise with the hetero atom as 1-.



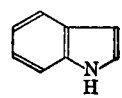
Coumarone

C_8H_6O



Benzothiophene

C_8H_6S



Indole

C_8H_7N

Pyrazole

$C_3H_4N_2$

Imidazole
Glyoxalin

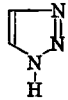
$C_3H_4N_2$

Thiazole

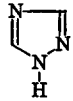
C_3H_3NS

Oxazole

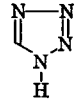
C_3H_3ON



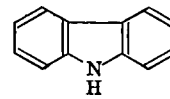
1,2,3-Triazole
$C_2H_3N_3$



1,2,4-Triazole
$C_2H_3N_3$



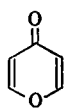
Tetrazole
CH_2N_4



Carbazole
Dibenzopyrrole

In each of these 5-membered rings there are three points of unsaturation, the two double bonds and an atom capable of an -onium valence. These are conjugated as in benzene. This conjugation obscures the individual unsaturation much as in benzene. Thus the double bonds in these compounds have about the same inactivity as those in benzene. Moreover, the "unsaturation" of the hetero-atom has largely disappeared. Thus pyrrole is a very weak base. Thiophene fails to give the addition compounds with substances like MeI and $HgCl_2$ which are characteristic of open chain sulfides. This failure is not due to the presence of the isolated double bonds, for vinyl sulfide readily gives the compound $(CH_2=CH)_2S.HgCl_2$. In accordance with these analogies to benzene, all these heterocyclic compounds show aromatic properties in varying degrees.[1]

Among the important *6-membered heterocyclic systems* are the following:



γ-Pyrone
$C_5H_4O_2$

α-Pyrone
$C_5H_4O_2$

Pyridine
C_5H_5N

Pyridazine
$C_4H_4N_2$

Pyrimidine
$C_4H_4N_2$

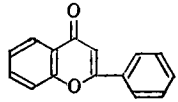
Pyrazine
$C_4H_4N_2$

Penthiophene
C_5H_6S

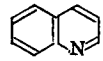
Dioxane
$C_4H_8O_2$

[1] Gilman, Towne. *Rec. trav. Chim.* 51, 1054 (1932).

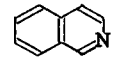
Chromone
$C_9H_6O_2$



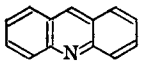
Flavone
2-Phenylchromone



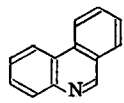
Quinoline
C_9H_7N



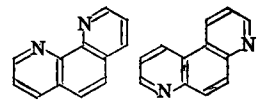
Isoquinoline
C_9H_7N



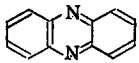
Acridine
Dibenzopyridine
$C_{13}H_9N$



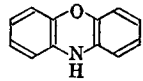
Phenanthridine
3,4-Benzoquinoline



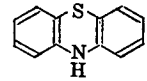
Phenanthrolines
1,10- "ortho"
4,7- "para"



Phenazine
$C_{12}H_8N_2$



Phenoxazine
$C_{12}H_9ON$



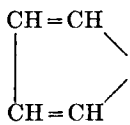
Phenothiazine
$C_{12}H_9NS$

An inspection of these heterocyclic formulas shows that some have the characteristic conjugated unsaturation of benzene while others have that of quinone and still others have neither. The analogy of acridine and phenazine to anthracene is confirmed by the reactions of these substances.

In the naming of the heterocyclic compounds, the -ole ending is used to designate a five-membered ring, the -ine ending, a six-membered ring, and the presence of nitrogen, sulfur or oxygen in the ring by the abbreviations -az-, -thi-, -ox- respectively. Many compounds which were named before these conventions were generally accepted, do not conform. In numbering the positions in heterocyclic compounds, the hetero atom is usually No. 1 even though substitution on it may be impossible. Exceptions are carbazole in which the N is No. 9 and the analogs of anthracene in which the atoms of the middle ring are No. 9 and No. 10.

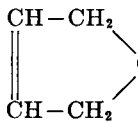
II. FIVE-MEMBERED RINGS

A. Furan and Derivatives

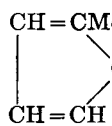
Furan, furfurane,  , b. 32°, is obtained in various thermal decompositions as in wood distillation. It is readily prepared by heating furan-

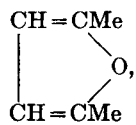
2-carboxylic acid,[1] or by the catalytic cracking of furfural (du Pont). It is stable to sodium and sodium hydroxide but is resinified by strong acids. Gaseous chlorination at 50° under conditions which permit the rapid removal of HCl gives 2-chloro-furan.[2] The diene character of furan is shown by the addition of maleic anhydride.[3] It is converted into *tetrahydrofuran*, C_4H_2O, b. 66°, by catalytic reduction. Tetrahydrofuran shows the properties of a cyclic ether. It is converted into tetramethylene chlorohydrin with dilute hydrochloric acid, into 1,4-dichlorobutane with concentrated hydrochloric acid, into 1,4-butanediol diacetate with acetic anhydride and into butadiene upon dehydration. At 0° it can be chlorinated to 2,3-dichloro-tetrahydrofuran which reacts with Grignard reagents to give 2-alkyl-3-chlorotetrahydrofuran. These compounds may be converted to alcohols of the type

$$HO-C-C-C=C-R.$$[4]

2,5-Dihydrofuran,  , b. 67°, is made by heating erythritol with

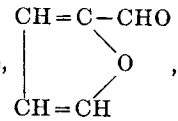
formic acid, a process analogous to the production of allyl alcohol from glycerol.

2-Methylfuran, sylvane,  , b. 65°, and *2,5-Me_2-furan*,

 ,

b. 94°, are contained in wood tar and in the products from distilling sucrose with lime. The former can be made by copper chromite catalyzed reduction of furfural[5] (cf. furfural). Sylvane is hydrolytically reduced over nickel on Celite at 150° to 1,4-pentanediol.[6] 2,5-Dimethylfuran can also be made from acetonylacetone with $ZnCl_2$ or P_2O_5 (C and C). This change may be regarded as a simple dehydration of the dienol. Dilute HCl at 270° changes Me_2-furan to acetonylacetone.[7]

[1] "Org. Syntheses."
[2] Cass, Capelin. *C. A.* **42**, 7340 (1948).
[3] Woodward, Baur. *J. Am. Chem. Soc.* **70**, 1161 (1948).
[4] Normant. *Ind. Parfum.* **3**, 156 (1948).
[5] Hixon et al. *Ind. Eng. Chem.* **40**, 502 (1948).
[6] Schnilpp et al., *J. Am. Chem. Soc.* **69**, 672 (1947).
[7] "Org. Syntheses."

Furfural, furfurol, furol, α-furaldehyde, α-furfuraldehyde,  ,

b. 162°, is obtained by the action of mineral acids on pentoses and pentosans which occur in large amounts in vegetable products such as oat hulls, cornstalks, corn cobs, bran and the like. Commercially it is made in large amounts by the action of sulfuric acid with oat hulls (Quaker Oats Company).[8] The chemical industry based on furfural is of tremendous importance. Among the many products available from furfural are: 1,4-butandiol, dihydropyran, tetrahydropyran, 1,5-pentandiol, 2-methylfuran, cyclopentanones, adipic acid and Nylon[9] (cf. adipic acid). Thus furfural is converted to 2-methylfuran in 95% yields over a special Cu Cr Ca catalyst at 200–225°.[10] With nickel and hydrogen at temperatures below 100° it is converted to 2-methyltetrahydrofuran, while above 100° it rearranges to 2-pentanone.[11] It is used as a selective solvent for petroleum refining. The aldehyde reactions of furfural are almost exactly like those of benzaldehyde. Thus KCN gives *furoin*,

$$C_4H_3O.CHOHCO.C_4H_3O,$$

m. 135°, analogous to benzoin. From a mixture of benzaldehyde and furfural KCN gives *benzfuroin*, $C_4H_3O.CHOHCO.C_6H_5$, m. 139°. These on oxidation give *furil*, $(C_4H_3O.CO)_2$, m. 162°, and *benzfuril*, $C_4H_3O.COCOC_6H_5$, m. 41°. *Furil* with alkali gives *furilic acid*, difurylglycollic acid, $(C_4H_3O)_2C(OH)CO_2H$, which decomposes below 100°. Ammonia gives *furfuramide*, $(C_4H_3O.CH)_3N_2$, m. 117°, which is converted by alkalis or heat to the isomeric furfurin, m. 116°, corresponding to hydrobenzamide and amarin.

Tetrahydrofurfuryl alcohol, $C_5H_{10}O_2$, b. 177°, is formed by the nickel catalyzed reduction of furfural. Its higher esters such as the oleate are used as plasticizers for polyvinyl chloride. By use of a copper-chromium oxide catalyst, the reduction of furfural can be controlled to give *furfuryl* alcohol, $C_5H_6O_2$, b. 170°.[12]

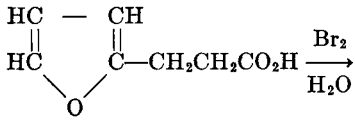
Furylacrylic acid, *trans* $C_4H_3O.CH=CHCO_2H$, m. 141°, (ICI) is made by the Perkin reaction from furfural, NaOAc and Ac_2O at 170°. This and the *allo* or *cis* form, m. 103°, are obtained by heating furalmalonic acid,

$$C_4H_3O.CH=C(CO_2H)_2,$$

m. 205° dec. obtained by warming furfural, malonic acid and HOAc. Reduction of furylacrylic acid readily gives β-furylpropionic acid. This with Br_2 water followed by oxidation with Ag_2O gives *furonic acid*, a keto unsaturated

[8] Dunlop. *Ind. Eng. Chem.* **40**, 204 (1948).
[9] Cass. *Chem. Ind.* **60**, 612 (1948).
[10] Holdren. *C. A.* **42**, 8214 (1948).
[11] Wilson. *J. Am. Chem. Soc.* **70**, 1313 (1948).
[12] Wojcik. *Ind. Eng. Chem.* **40**, 210 (1948).

dibasic acid which is reduced by HI to pimelic acid.[13]

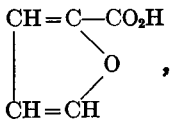


$$OCH{-}CH{=}CH{-}CO{-}CH_2CH_2CO_2H \xrightarrow[HI]{Ag_2O} HO_2CCH{=}CHCOCH_2CH_2CO_2H \longrightarrow HO_2C(CH_2)_5CO_2H$$

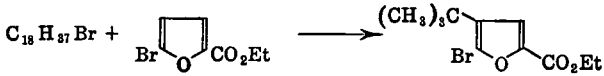
The first step consists in 1,4-addition of bromine, followed by hydrolysis to give the 1,4-keto-aldehyde. Furylacrylic acid with alcoholic HCl gives acetone diacetic ester, $CO(CH_2CH_2CO_2Et)_2$.[14]

Furfural, through the Perkin reaction with *n*-butyric anhydride and salts, gives *α*-ethyl-*β*-furylacrylic acid incorrectly called furylangelic acid.[15]

Furoic acid, pyromucic acid, furan-2-carboxylic acid,



m. 133°, was originally made by heating mucic acid but is now prepared from the readily available furfural either by cautious oxidation or by the Cannizzaro reaction. While many of its reactions resemble those of benzoic acid it differs in being readily oxidized, for instance, by permanganate. With dry bromine it gives a *tetrabromide,* m. 160° dec., which with alcoholic KOH gives *3,4-* and *3,5-dibromofuroic acids,* m. 192° and 168°. Mono- and tri-bromofuroic acids have also been made. 5-Bromo-furoic ester gives a remarkable reaction with $AlCl_3$ and alkyl halide. Thus *n*-AmCl, *n*-Hex-Br and *n*-octadecyl bromide all give the same product, ethyl 4-*tert*-bu-5-Br-2-furoate.[16] A yield of 46% was obtained from the C_{18} bromide.

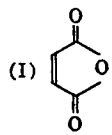


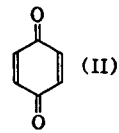
Substitution reactions such as nitration, bromination and sulfonation are usually successful only on substituted furans in which a group such as carboxyl or carbethoxy reduces the tendency to tar formation. The great ease of substitution in the Friedel-Crafts reaction is such that benzene can often be used as the solvent. The diene character of furan is shown by the addition of maleic anhydride (Diels and Alder).

[13] Baeyer. *Ber.* **10**, 1358 (1877).
[14] Marckwald. *Ber.* **20**, 2811 (1887).
[15] Carter. *J. Am. Chem. Soc.* **50**, 2299 (1928).
[16] Gilman, Burtner. *J. Am. Chem. Soc.* **57**, 909 (1935).

The semicarbazone of 5-nitro-2-furfuraldehyde, *Furacin*,[17] is an effective surface antiseptic.

Maleic anhydride (I) may be regarded as the quinone of furan. This relation is indicated by its formation of colored addition compounds with phenols, amines, etc. similar to those formed by quinone (II).

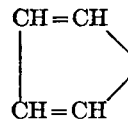

(I)


(II)

The oxidation of 5-hydroxymethylfurfural is in part responsible for the browning of fruits.[18]

Orientation in the furan series has been studied intensively.[19]

B. Pyrrole


b. 131°

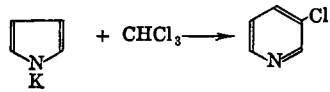
This is found in coal tar and the oil from the preparation of bone black. It is best obtained from this bone oil. Succinimide on distillation with zinc dust gives pyrrole (p. 382). It does not form salts with acids. With ethereal HCl in the cold it gives a trimer, $(C_4H_5N)_3.HCl$;[20] in cold aqueous acid a polymeric amorphous material, "pyrrole red," is formed.

The imino H of pyrrole is replaceable by metals, alkyl and acyl radicals. At pH of 1, all five hydrogens of pyrrole undergo deuterium exchange; at a pH of 2 or greater only the imino hydrogen is exchanged. Pyrrole can be purified by heating with solid KOH and distilling the other bases from the residue of the solid potassium compound. NaOH does not act on it and even metallic Na acts very slowly. Pyrrole can be synthesized by heating ammonium mucate with glycerol at 200° and by heating furoic acid with $ZnCl_2$-2 NH_3 and CaO. An interesting preparation is by passing diethyl amine through a red-hot tube. With hydroxylamine, the pyrrole ring opens and forms the dioxime of succinic dialdehyde, $HON=CH(CH_2)_2CH=NOH$.

Treatment of potassium pyrrole with alkyl and acyl halides gives both N- and C-(α) substitution products. Pyrrole reacts in many cases like phenol. Thus with HCN and HCl 2-pyrrole aldehyde is formed in a reaction comparable to the Gattermann aldehyde synthesis. It couples with diazonium salts in the alpha position to give azo dyes and reacts with formaldehyde and

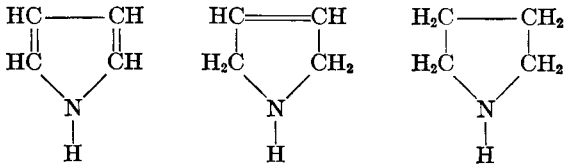
[17] Dodds. *J. Pharmacol.* **86**, 311 (1946).
[18] MacKinney et al. *J. Am. Chem. Soc.* **70**, 3577 (1948).
[19] Gilman. *Chem. Rev.* **11**, 327 (1932).
[20] *Ann. Rep. Chem. Soc.* (London) **1927**, 159.

diethylamine in a Mannich condensation to give 2,5-di(diethylaminomethyl)-pyrrole. A peculiar change occurs with chloroform and KOH to give 3-chloropyridine by a ring enlargement.



It is interesting that benzotrichloride and pyrrole give 3-phenylpyridine in an analogous reaction. Iodine and a base give *tetraiodopyrrole*, iodole, dec. 150°, which has been used as an antiseptic of the iodoform type.

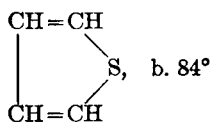
Pyrrole with zinc and acetic acid gives dihydropyrrole or *pyrroline*, b. 91°. Further reduction with HI gives tetrahydropyrrole or *pyrrolidine*, b. 86°. The effect of conjugation in masking the basic properties of the N in pyrrole is shown by the fact that its H_2- and H_4-derivatives are strong bases.



Pyrrolidine is best prepared by the catalytic hydrogenation of pyrrole. The central unit in the coloring matters of hemoglobin and chlorophyll is a giant, sixteen-membered, planar ring in which four pyrrole nuclei are joined through carbon atoms.

Polyvinylpyrrolodine, Periston, a blood plasma substitute, is obtained from the action of acetylene and ammonia with butyrolactone.

C. Thiophene



b. 84°

This occurs with benzene (b. 80.5°) in coal tar. It can be removed from benzene by repeated shakings with conc. sulfuric acid which sulfonates the thiophene more easily than it does the benzene. It can also be removed by refluxing with mercuric acetate which mercurates the thiophene with great ease and the benzene slowly, if at all, under these conditions. Thiophene is made on a laboratory scale by heating sodium succinate with P_2S_3.[21] It is now available in any required amount from the reaction of *n*-butane with sulfur

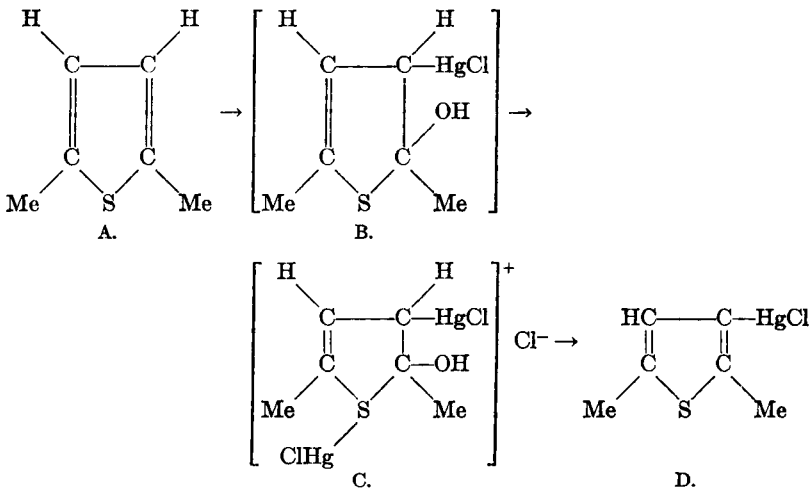
[21] "Org. Syntheses."

at 600°.[22] The reaction products include *n*-butenes, butadiene, and thiophene. By recycling the unchanged butane and other products boiling below thiophene, the latter can be obtained in 50% yields. *n*-Pentane and isopentane give 2-methylthiophene and 3-methylthiophene respectively under similar conditions.

Thiophene undergoes nitration, halogenation, sulfonation, alkylation, acylation, chloromethylation, and mercuration in the alpha position. These reactions take place with greater ease than with benzene and milder conditions are necessary to avoid side reactions. In addition to these reactions which are characteristic of benzene itself, thiophene reacts with formaldehyde and ammonia in a Mannich-type reaction, yielding 2-aminomethylthiophene and di-(2-thenyl)amine,[23] and condenses with formaldehyde under mildly acidic conditions to give resins.[24]

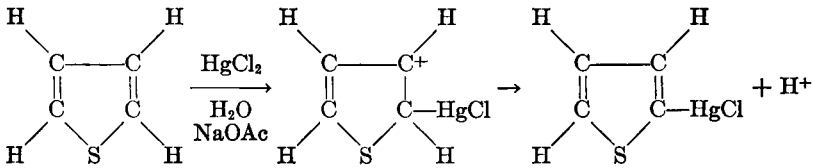
Contrary to the behavior of most C-Hg compounds, α-chloromercurithiophene reacts metathetically with acetyl chloride to give α-acetylthiophene, *acetthienone*.

The behavior of αα′-disubstituted thiophenes with mercuric chloride and sodium acetate throws light on the mechanism of mercuration and the effect of ring conjugation. The first product analyzes for an addition product of one molecule each of thiophene, basic mercuric chloride and mercuric chloride. Boiling with alcohol gives $HgCl_2$ and a 3-ClHg-compound. The steps are probably as follows:



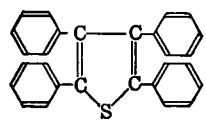
[22] Rosmussen et al. *Ind. Eng. Chem.* **38**, 376 (1946).
[23] Hartough et al. *J. Am. Chem. Soc.* **70**, 1146 (1948).
[24] Caesar, Sachanen. *Ind. Eng. Chem.* **40**, 922 (1948).

The S atom in A is incapable of forming an addition compound with $HgCl_2$ because its unsaturation is inactivated by conjugation with the two double bonds. As soon as a molecule of B has formed, its sulfur no longer is conjugated as part of the cyclic unsaturation and can add a molecule of mercuric chloride. Long boiling removes H_2O from C giving D in which the S is again part of the ring conjugation and so incapable of holding the $HgCl_2$. With thiophene itself, the process probably takes place much like the action of chlorine with isobutylene (p. 40).



The $^+$ indicates a carbon with only 6 electrons. If Cl^- or OH^- should add to this carbon the S could then add $HgCl_2$ to give a stable product. The loss of the α-H as a proton or H^+ ion with regeneration of the conjugated unsaturation makes the process seem one of simple substitution. In the case of the 2,5-disubstituted thiophenes, such as A, the less active β-H is not expelled quickly enough to prevent the two bimolecular processes which produce B and C.

Whereas open chain and saturated cyclic sulfides are easily oxidized to sulfones the sulfur in thiophene and its ordinary homologs is not attacked by oxidizing agents unless the ring is broken. A notable exception is the ready formation of a sulfone by the action of H_2O_2 on *tetraphenylthiophene, thionessal,* m. 184°, formed by the action of sulfur on stilbene.



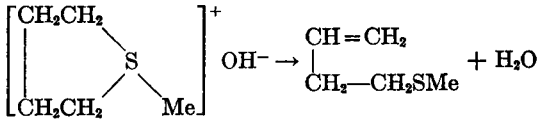
It would seem that the double bonds in the thiophene ring have become conjugated with those of the four phenyl groups to such an extent that they leave the unsaturation of the sulfur free for action with the H_2O_2.

The chemistry of thiophene and its homologs has been studied extensively. The physical properties of these substances closely resemble those of the corresponding benzene compounds. Apparently the grouping C—S—C is very nearly equivalent to C—C=C—C.[25]

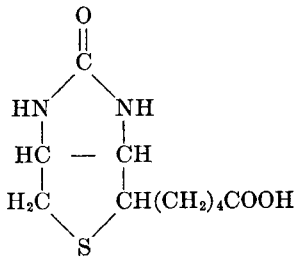
Tetrahydrothiophene, tetramethylene sulfide, $(CH_2)_4S$, b. 118°, is readily made from $Br(CH_2)_4Br$ and Na_2S. It acts as an ordinary sulfide giving a

[25] Erlenmeyer, Leo. *Helv. Chim. Acta* **16**, 1381 (1933).

sulfone, and addition products with MeI, $HgCl_2$, etc. Treatment of the sulfonium iodide with a base and heat opens the ring as in the exhaustive methylation of cyclic amines.

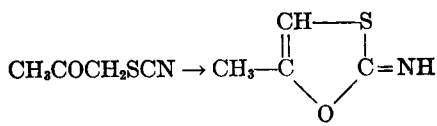


Biotin, vitamin H, coenzyme R, is a tetrahydrothiophene derivative.



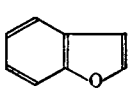
It was originally isolated from egg yolk and subsequently from milk, yeast, and liver. Biotin is a growth factor for yeast and its deficiency causes a dermatitis in rats. Its role in human nutrition is not yet fully known. A factor in egg white, *avidin*, inactivates biotin either *in vivo* or *in vitro* and thus an egg white-rich diet causes the symptoms of a biotin deficiency even in the presence of an abundance of the vitamin. The structure of biotin was deduced by brilliant degradative studies[26] and its structure was confirmed by its total synthesis.[27] The analog of biotin in which the sulfur is replaced with oxygen, *oxybiotin*, shows approximately one-half of the microbiological activity of biotin itself.[28] The thiophene analog of biotin, *2,3,4,5-tetradehydrobiotin*, has been made, but shows none of the activity of biotin.[29] Synthetic biotin is now produced in quantity (Merck).

A substance related to both furan and thiophene is α-methylrhodim obtained from thiocyanoacetone and NH_3.[30]

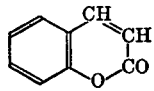


[26] du Vigneaud et al. *J. Biol. Chem.* **146**, 495 (1942).
[27] Harris et al. *J. Am. Chem. Soc.* **67**, 2096 (1945).
[28] Hofmann. *J. Am. Chem. Soc.* **67**, 1459 (1945).
[29] Cheney, Piening. *J. Am. Chem. Soc.* **67**, 731 (1945).
[30] *Ann. Rep. Chem. Soc.* (London) **1919**, 105.

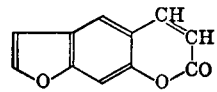
Coumarone, benzofuran, b. 170°, occurs in coal-tar and has been synthesized in various ways. Many coumarone derivatives occur in plants. Thus *xanthotoxin* is a combination of coumarone and coumarin structures.[31]



Coumarone

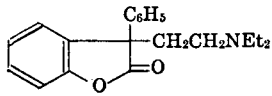


Coumarin

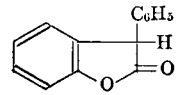


Xanthotoxin

3-Phenyl-2-benzofuranone (II) is made by heating mandelic acid and phenol. Alkylation with β-diethylaminoethyl chloride gives the antispasmatic amethone (I) 3-β-diethylaminoethyl-3-phenyl-2-benzofuranone hydrochloride.

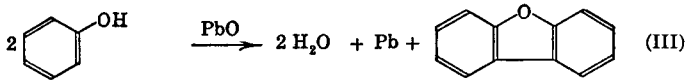


(I)



(II)

Diphenylene oxide, dibenzofuran (III), m. 82°, b. 283°, is made by heating phenol with PbO.



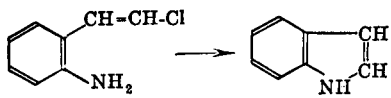
(III)

Because of the occurrence of the dibenzofuran grouping in morphine many of its derivatives have been prepared.[32, 33]

Benzothiophene, m. 31°, b. 221°, resembles naphthalene much as thiophene resembles benzene.

D. Indole and Its Derivatives

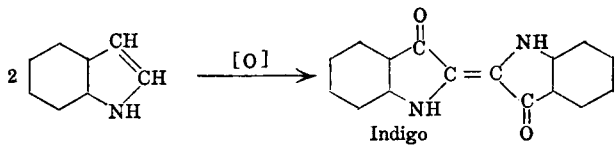
Indole, benzopyrrole, (IV), m. 52°, is of great importance as the parent substance of indigo. It has been synthesized in many ways, one of the simplest of which is the action of NaOEt on *o*-amino-ω-chlorostyrene.[34]



(IV)

[31] Späth. *Monatsh.* 69, 75 (1936).
[32] Mosettig, Robinson. *J. Am. Chem. Soc.* 57, 2186 (1935); 58, 688 (1936); 61, 1148 (1939).
[33] Gilman. *J. Am. Chem. Soc.* 61, 951, 1365 (1939).
[34] "Org. Syntheses."

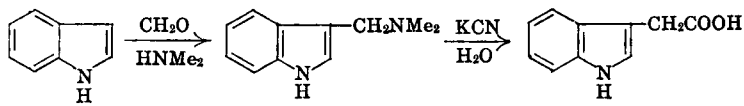
Like pyrrole, it is very feebly basic and can have its imino H replaced by alkyl, acyl and K. Direct oxidation gives indigo in small yields.



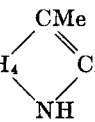
Indigo

This is a bimolecular oxidation analogous to the bimolecular reductions which give pinacols from ketones.

Indole condenses with formaldehyde and dimethylamine to give *gramine*, 3-dimethylaminomethyl-indole, which reacts with potassium cyanide under hydrolytic conditions to give indol-3-acetic acid.[35]

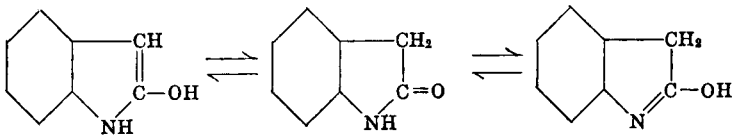


Gramine and related heterocyclic compounds also undergo alkylation in the malonic ester synthesis.[36]

Skatole, 3-methylindole, 

m. 95°, is formed by decay of albumen, the precursor being the amino acid tryptophan. It has an overpowering fecal odor and is used in minute amounts in perfumes.

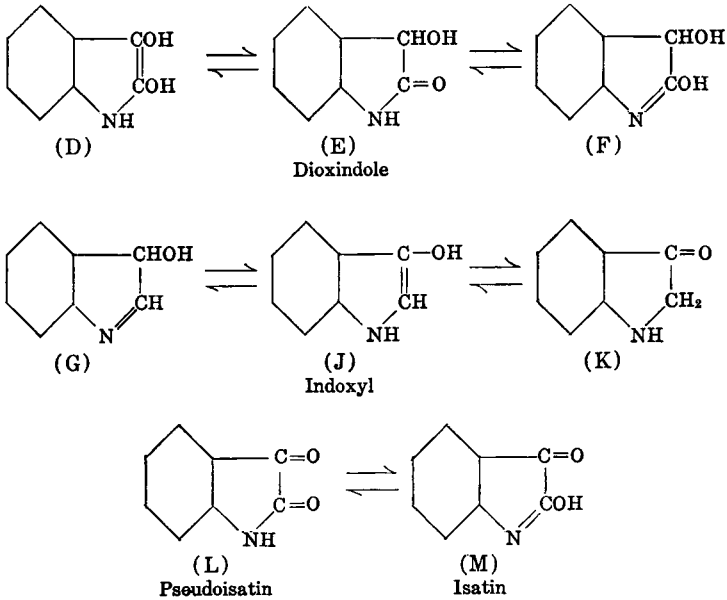
Indole-3-acetic acid has been identified as the plant growth-hormone, hetero-auxin,[37] and probably acts by intensifying the photosynthetic activity. Many analogous substances have been tested for their growth-promoting activity.[38] Oxygen derivatives of indole are widely known.



(A) (B) (C)

Oxindole

[35] Snyder, Pilgrim. *J. Am. Chem. Soc.* **70**, 3770 (1948).
[36] Albertson. *J. Am. Chem. Soc.* **70**, 669 (1948).
[37] Kögl et al. *Z. physiol. Chem.* **214**, 241; **216**, 31 (1933); **225**, 215; **228**, 90 (1934).
[38] *Ann. Rep. Chem. Soc.* (London) **1935**, 425.

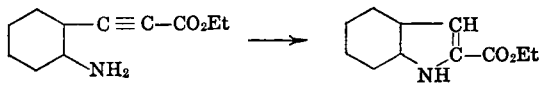


Whereas indole is not soluble in acids, oxindole (form A), dioxindole (form D) and indoxyl are soluble. Oxindole (form C), dioxindole (form F) and indoxyl (form J) are also soluble in bases while isatin is soluble only in bases. Forms B, E and L are ordinary acid amide forms while forms C, F and M are tautomeric acidic forms of the amides in which the grouping C = NPh plays the part of the C = O of a carboxyl group. The solubility of indoxyl in bases is surprising. Apparently the grouping C = C in the aromatic pyrrole ring acts like the C = O in a carbonyl group. This is the same as saying that the hydroxyl is phenolic in nature. Form G of indoxyl is readily subject to hydrolysis to give an amino hydroxyaldehyde which probably accounts for the great instability of indoxyl. The presence of OH in forms A, D and J apparently interferes with the conjugation of the nitrogen unsaturation in the pyrrole ring and thus restores its basic properties.

Oxindole, 2-hydroxyindole, (A, B, C, p. 763), m. 120°, the lactam of *o*-aminophenylacetic acid, is made by reducing *o*-nitrophenylacetic acid or dioxindole. It can be easily oxidized to dioxindole. This easy oxidation is due to the enol form A which can be changed to form E by the addition of a positive hydroxyl at the 3-position and the expulsion of H^+ from the 2-OH. As has been noted above, oxindole is amphoteric.

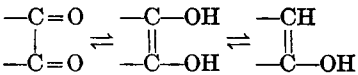
Indoxyl, 3-hydroxyindole, (G, J, K, p. 764), m. 85°, while isomeric with oxindole differs radically from it in being very unstable. It is readily oxidized

to indigo by air in basic solution and by ferric chloride in acid solution. Derivatives of both J and K are known. *Indoxylic acid*, 3-hydroxyindole-2-carboxylic acid, subl. 123°, can be obtained as the ethyl ester by reducing ethyl *o*-NO_2-phenylpropiolate, the amino group adding internally to the triple bond.



The acid loses CO_2 to give indoxyl which is readily oxidized to indigo. Indoxylic acid is also formed by the alkali fusion of phenylglycine-*o*-carboxylic acid. Since this latter compound is readily available from chloroacetic acid and anthranilic acid, this is the basis of one of the successful commercial syntheses of indigo.

Dioxindole, 2,3-dihydroxyindole, (D, E, F, p. 764), m. 180° can be made by reducing isatin. Further reduction gives oxindole. It is also formed by oxidizing oxindole. The reactive groups in the oxidation-reduction series of isatin ⇌ dioxindole ⇌ oxindole are



Isatin, diketodihydroindole, m. 201°, exists in form M (p. 764). It is readily made by oxidizing indigo, oxindole, dioxindole or indoxyl. Reduction gives dioxindole and then oxindole rather than the isomeric indoxyl. Isatin has been synthesized in many ways. Treatment with PCl_5 gives *isatin chloride*,  , m. 180° dec. O-Ethers of isatin and N-alkyl derivatives of pseudoisatin (L, p. 764) are known.

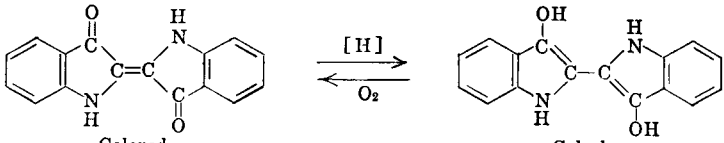
E. Indigo and Related Compounds

Indigo (I) is the oldest known dye and is still one of the most important. The indigo plant contains the colorless glucoside, *indican*, which on hydrolysis (enzymatic) breaks down into glucose and indoxyl. This is immediately oxidized by air to the very insoluble indigo dye. Indigo is changed by reduction to the alkali-soluble *indigo white* (II). This was originally accomplished in "fermentation vats" by bacterial action, but is now accomplished with sodium hydrosulfite, $Na_2S_2O_4$, or sodium formaldehyde sulfoxylate,

$$NaSO_2CH_2OH.$$

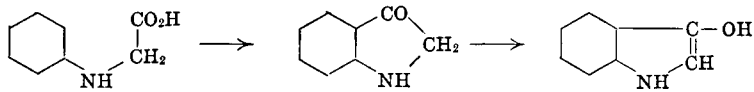
The indigo white (leuco-compound) is oxidized back to the insoluble indigo by air. These reactions are the basis of the process of vat dyeing whereby the

insoluble dye is fixed within the fiber. X-ray diffraction shows that the dye molecule has the symmetrical *trans* structure.

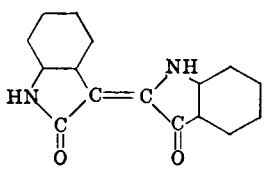


Colored (I) Colorless (II)

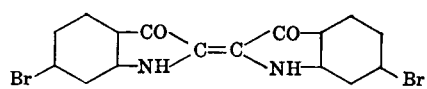
Mono- and disulfonic acids of indigo are readily formed. The Na salt of the latter is *indigo carmine*. Many syntheses of indigo have been developed. The most important of these is the *phenylglycine process* which involves the fusion with $NaNH_2$ and NaOH of phenylglycine made from aniline and chloroacetic acid. The product is indoxyl which is oxidized to indigo by air.



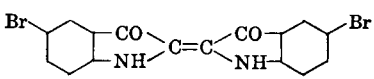
Many dyes involving modifications of the indigo molecule are known. *Indirubin* (III) is made by alkaline condensation of isatin and indoxyl, the 3-carbon of the former becoming attached to the 2-carbon of the latter. Imperial purple, royal purple, or Tyrian purple was obtained from a species of Mediterranean shellfish. It has been shown to be a dibromo indigo (IV), which along with thyroxine and the recently discovered antibiotics, chloromycetin, geodin, and erdin, is one of the few naturally occurring organic compounds containing non-ionic halogen. The direct bromination of indigo gives (V). Thioindigo has S in place of the NH groups in indigo (VI).



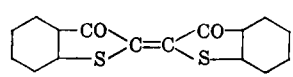
(III)



(IV)



(V)



(VI)

F. Carbazole (VII), m. 245°, b. 355°

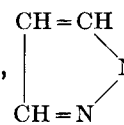
This is dibenzopyrrole or the 2,2′-imide of diphenyl. It occurs in coal tar. It can be made by heating diphenylamine in a red hot tube.

(VII)

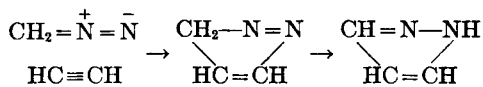
The conjugation of the nitrogen with the two benzene rings increases the stability of the compound, decreases the ability of the N to unite with H^+ and increases its tendency to lose H^+. Its formation of a K compound with KOH is used in separating it from crude anthracene. Oxidation of carbazole gives a variety of products.[39] Silver oxide gives N-N-dicarbazyl, a colorless compound which gives colored solutions containing considerable amounts of the bivalent nitrogen free radical.[40] Nitration gives 1- and 3-nitro compounds. A partly hydrogenated carbazole grouping is found in strychnine. The carbazole ring system is present in some of the fastest blue vat dyes which in many cases have replaced the indigos. *Hydrone Blue,* one of the most important of these, is made by condensing carbazole with nitrosophenol in sulfuric acid and submitting the product to a sulfur melt.

N-Vinylcarbazole is prepared from carbazole and acetylene and polymerizes to a highly effective heat-resistant and insulating polymer, Polectron, Luvican, which resembles mica especially in its dielectric properties.[41]

G. Pyrazole and Related Compounds

Pyrazole, 

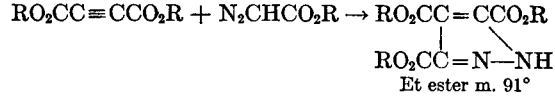
m. 70°, b. 188°, is a stable weak base. As in the case of pyrrole and its analogs, the unsaturation of the nitrogen is masked by the ring conjugation. It has aromatic properties as shown by its nitration to give *4-nitropyrazole,* m. 162°, b. 323°. Pyrazole can be made from diazomethane and acetylene in cold ether solution. This involves a peculiar addition of a 1,3-type if ordinary formulas are used.



It can also be made from pyrazole-3,4,5-tricarboxylic ester prepared either by

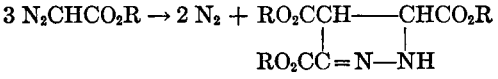
[39] *Ann. Rep. Chem. Soc.* (London) **1921**, 126.
[40] Branch, Smith. *J. Am. Chem. Soc.* **42**, 2405 (1920).
[41] Busse et al. *Ind. Eng. Chem.* **40**, 2271 (1948).

addition of diazoacetic ester to acetylenedicarboxylic ester,



Et ester m. 91°

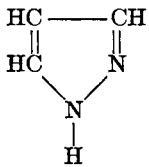
or by the action of Br_2 on the corresponding pyrazoline ester obtained by heating diazoacetic ester alone



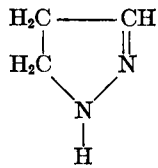
Pyrazoline-tricarboxylic ester
Et ester m. 99°

The action of Br_2 in producing a double bond is typical of a dihydroaromatic compound. The ester is hydrolyzed to *pyrazole-3,4,5-tricarboxylic acid*, m. 233°, which on higher heating gives pyrazole. The aromatic nature of the pyrazole ring is further shown by the production of this acid by the permanganate oxidation of 3,4,5-Me_3-pyrazole, the three methyl groups being oxidized to carboxyl groups without changing the nucleus.

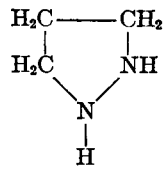
The hydrogenation products of pyrazole are no longer aromatic but show basic properties.



Pyrazole



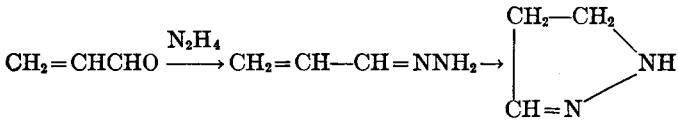
Pyrazoline
b. 144°



Pyrazolidine

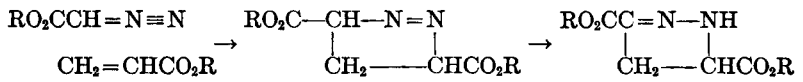
Pyrazolines are obtainable by a variety of reactions including:

1. The action of hydrazine or one of its derivatives with an $\alpha\beta$-unsaturated aldehyde or ketone. Thus acrolein and hydrazine give *pyrazoline*.

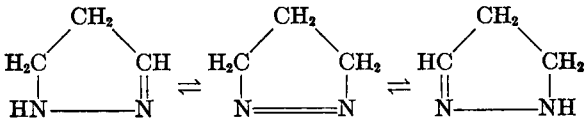


The last step consists in the usual ring closure when an active H is in the 1,5-relation to a double bond.

2. The addition of aliphatic diazo compounds to $\alpha\beta$-unsaturated esters. The *3,5-dicarboxylic ester*, Me ester, m. 94°, is formed from diazoacetic ester and acrylic ester while the *4,5-dicarboxylic ester*, Me ester, m. 97°, is formed from diazomethane and maleic or fumaric ester. The former process shows that the N adds to the α-carbon.

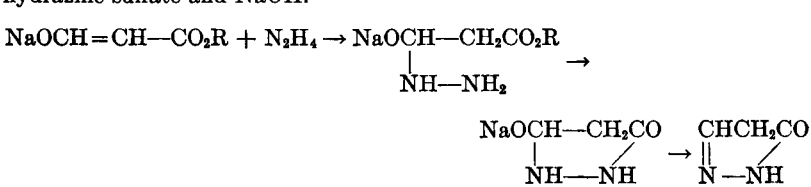


The 3- and 5-positions in pyrazolines are identical, because of the peculiar tautomerism which is possible.

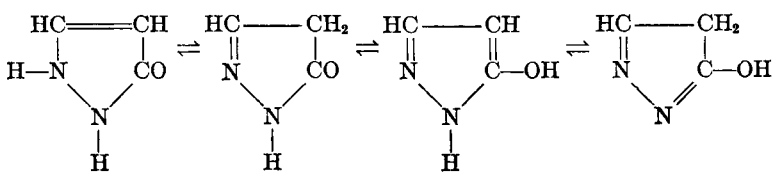


Many pyrazoline derivatives lose N_2 on heating to form cyclopropane derivatives.

Pyrazolone, 3-ketopyrazoline, m. 165°, is made from Na formylacetic ester, hydrazine sulfate and NaOH.



The CH_2 group can be alkylated like that in 1,3-diketones, the CH=N group evidently playing the part of C=O or C≡N. The CH_2 also forms an isonitroso compound, C=NOH, with nitrous acid. Pyrazolone is amphoteric, being soluble in acids and also in bases.



The first form is evidently responsible for the basic properties. The enol form is a hydroxyl derivative of pyrazole, an aromatic compound, and so has phenolic properties. *1-Phenyl-3-methylpyrazolone*, m. 127°, is made from phenylhydrazine and ethyl acetoacetate. Methylation gives *1-phenyl-2,3-dimethylpyrazolone* or *antipyrine*, m. 113°, an important febrifuge. *Pyramidon*,

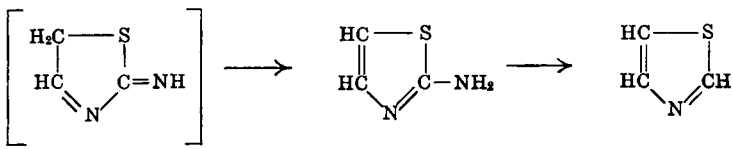
Aminopyrine, 1-phenyl-2,3-dimethyl-4-dimethylaminopyrazolone is a stronger and longer lasting antipyretic and has important analgesic properties. It has been the cause of fatal agranulocytosis. It is made by the nitration, reduction, and methylation of antipyrine.

Thiazole (I) b. 117°, closely resembles pyridine in much the way that thiophene resembles benzene.

(I)

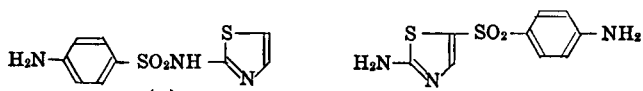
In each case the S plays the same part as $-CH=CH-$ in determining physical and chemical properties. It is made by heating with alcohol the diazonium salt of *2-aminothiazole*, m. 90°, obtained from chloroacetaldehyde and thiourea.

$$ClCH_2CHO + H_2NC(SH)=NH \rightarrow ClCH_2CH=NC(SH)=NH \rightarrow$$



In actual practice, α,β-dichloroethyl ether, which decomposes into chloroacetaldehyde and ethanol *in situ*, is used instead of the unstable and lachrymatory chloroacetaldehyde. Chloroacetone and thiourea give 2-amino-5-methylthiazole.[42]

The sulfanilamide derivative *sulfathiazole*,[43] N^1-(2-thiazolyl)sulfanilamide (I), is one of the most important of the sulfa drugs. It is obtained from 2-aminothiazole by reaction with *p*-acetylaminobenzenesulfonyl chloride followed by hydrolysis of the acetyl group. The N^2-succinyl derivative is known as *sulfasuxidine*. *Promizole*[44] (II), a thiazole analog of *p,p'*-diaminodiphenylsulfone, has shown limited success in the treatment of leprosy.

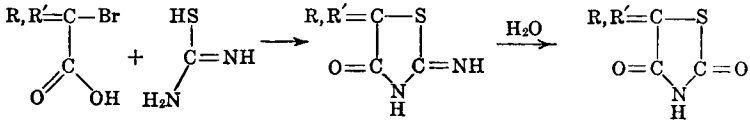


(I) (II)

[42] "Org. Syntheses."
[43] Northey. *Chem. Rev.* **27**, 85 (1940).
[44] Bambas. *J. Am. Chem. Soc.* **67**, 671 (1945).

2-Mercaptobenzothiazole (*Captax*) is an important rubber accelerator made from aniline, carbon disulfide, and sulfur.

Thiazolidones are made by heating a mixture of thiourea, an α-bromoacid and sodium acetate in alcohol or dioxane. The intermediate imine readily hydrolyzes.[45]

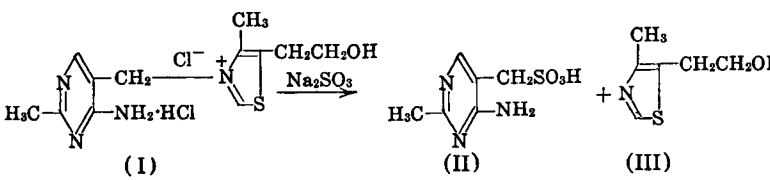


The product has the same fundamental structural unit, R,R′=C−CO−NH−, as the corresponding barbiturates, hydantoins, etc., and shows the same hypnotic properties.[46]

Vitamin B_1, *thiamine, aneurin,* (I), the component of the vitamin B complex whose deficiency is responsible for beriberi, was first isolated in a pure crystalline state from rice polishings in which it is present to the extent of about 1 gram per 100 pounds. The degradation reaction which proved to be the key to the elucidation of its structure was the remarkable cleavage with sodium bisulfite at room temperature into two approximately equal parts.

$$\underset{\text{I}}{C_{12}H_{18}N_4OSCl_2} + Na_2SO_3 \rightarrow \underset{\text{II}}{C_6H_9N_3O_3S} + \underset{\text{III}}{C_6H_9NOS} + 2\ NaCl$$

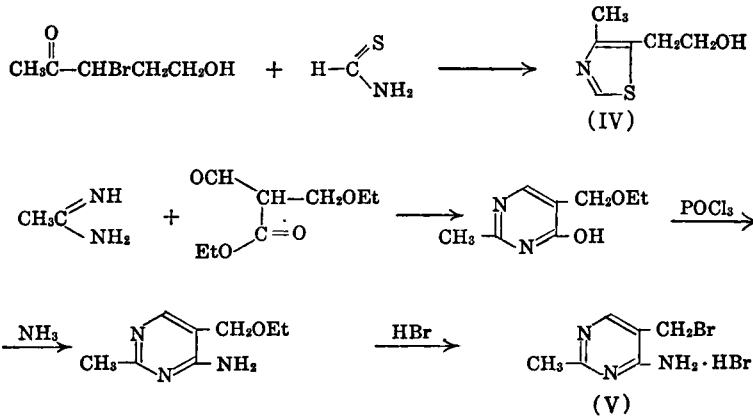
The first of these products (II) was proven to be a pyrimidine sulfonic acid. The second (III) was shown to be a thiazole derivative by its oxidation to 4-methylthiazole-5-carboxylic acid. The degradation reaction was interpreted as follows.



The correctness of this formulation was shown by its total synthesis and the identity of the natural and synthetic products.[47] The pyrimidine and thiazole portions of the molecule were prepared separately from aliphatic components

[45] Jones et al. *J. Chem. Soc.* **1946**, 91.
[46] Shonle. *J. Org. Chem.* **3**, 193 (1938).
[47] Williams et al. *J. Am. Chem. Soc.* **57**, 229, 517, 536, 1093, 1856 (1935).

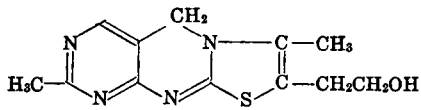
as indicated in the following equations.



(IV)

(V)

The final step is the reaction of the bromomethylpyrimidine (V) with the thiazole (IV) to give the bromide derivative of the vitamin. Synthetic thiamine is now available in any required amount. In the form of its pyrophosphoric acid ester, thiamine functions as a co-carboxylase. It is probably essential in the fermentation process for the conversion of pyruvic acid to acetaldehyde and carbon dioxide. Oxidizing agents such as potassium ferricyanide convert thiamine into thiochrome (VI), a yellow pigment which shows a strong blue fluorescence, the intensity of which is used as the basis for the chemical assay of the vitamin.



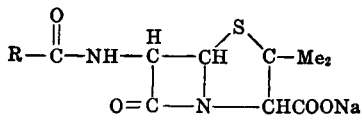
(VI)

Several analogs of thiamine have been prepared. The thiamine molecule is very specific, however, and only in one case where an ethyl group replaces the 2-methyl group in the pyrimidine ring has the analog retained any vitamin activity.[48] *Pyrithiamine*, in which an analogous pyridine portion replaced the thiazole moiety of thiamine molecule,[49] was found to be antagonistic to the true vitamin.[50]

The discovery and development of the antibiotic *penicillin* which is obtained commercially from the mold *Penicillin chrysogenum* has revolutionized chemotherapy. Its structure has been worked on by a large number of

[48] Stein, Sampson, Cline, Stevens. *J. Am. Chem. Soc.* **63**, 2059 (1941).
[49] Wooley, White. *J. Biol. Chem.* **149**, 285 (1943).
[50] Roblin. *Chem. Rev.* (1946).

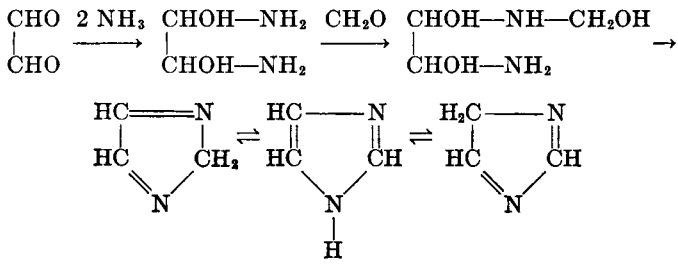
American and British workers in a cooperative effort and is generally accepted as the following thiazolidine with fused β-lactam ring.



Penicillin	
n-Pentenyl	F
n-Amyl	K
Benzyl	G
p-Hydroxybenzyl	X

The nature of the R group determines the type of penicillin. The biosynthesis of the different types can be controlled to a certain extent; thus the addition of phenylacetamide to the nutrient media on which the mold grows, increases the production of penicillin G greatly. Penicillin in a moist state and especially under acid conditions is rapidly inactivated as a result of the cleavage of the β-lactam ring. The β-lactam ring has also been the limiting factor in the synthetic studies. Very small amounts of penicillin have been prepared synthetically but by a method which does not conclusively confirm the above structure.

Imidazole, glyoxaline, (A, B, C), m. 90°, b. 256°, is made from glyoxal, formaldehyde and NH_3.



A. B. C.

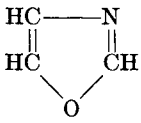
It can exist in the tautomeric forms A, B, and C, derivatives of all three forms of which are known. Imidazole is strongly basic but acetyl chloride and acetic anhydride have no action on it. MeI and alkali give *1-methylglyoxaline, b. 199°*. The methyl derivatives of imidazole, pyrazole, and pyrrole show interesting differences in volatility. The boiling points are as follows:

	Imidazole 256°			Pyrazole 188°			Pyrrole 131°	
N-Me	"	199°	N-Me	"	127°	N-Me	"	113°
5-Me	"	263°	5-Me	"	205°	2-Me	"	148°
2-Me	"	267°				3-Me	"	143°

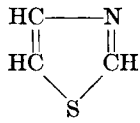
In the case of imidazole and pyrazole, a methyl attached to C raises the b.p. 7–17° while in pyrrole the increase is 17–22°. On the other hand a methyl group attached to N in imidazole and pyrazole *lowers* the b.p. 57° and 61°

respectively whereas in pyrrole it lowers it only 13°. These differences are explainable in a large part by association which is possible in the compounds which contain two nitrogen atoms in the ring and have a hydrogen atom on one of these.

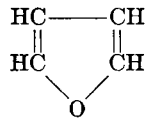
Hydrobenzamide on heating above 360° loses hydrogen with the formation of *lophine*, 2,4,5-triphenylimidazole. This is probably formed through the intermediate *amarin*, 2,4,5-triphenyldihydroimidazole.



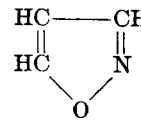
Oxazole
(I)



Thiazole



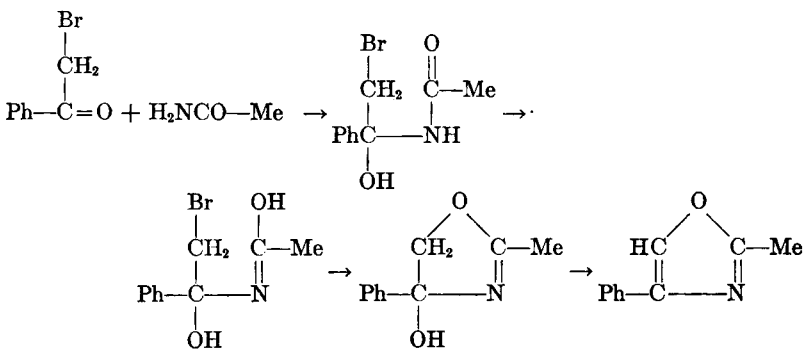
Furan



Isoxazole
(II)

H. Oxazoles and Related Compounds

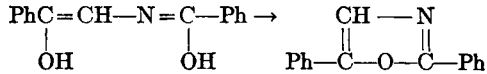
Oxazole (I), corresponding to thiazole and furan, is known only in certain derivatives containing aromatic groups. *2-Methyl-4-phenyloxazole*, m. 45°, b. 242°, is readily made by heating acetamide and bromoacetophenone at 130°.



The stability of the oxazole ring is shown by the fact that it is not broken when the phenyl group is nitrated and the nitro group is reduced to amino. On the other hand boiling with water decomposes it to form acetic acid and probably diphenyldihydropyrazine. 2,5-Diaryloxazoles are obtained from aromatic aldehydes and their cyanohydrins in presence of ethereal HCl. *2,5-Diphenyloxazole*, m. 74°, b. 360°+, is thus made from benzaldehyde. The reaction involves two peculiar steps, the addition of the aldehyde H to the C of the CN group and an unusual tautomeric shift which makes possible the

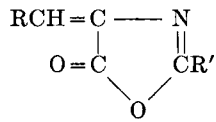
ring closure.

$$PhCH(OH)CN + PhCHO \rightarrow PhCH(OH)CH{=}N{-}CO{-}Ph \rightarrow$$

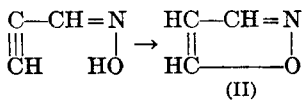


4,5-Diphenyloxazole, m. 44°, is obtained from benzoin, KCN and H_2SO_4.

Azlactones, obtained by a modification of the Perkin reaction using aldehydes and alpha acylamino acids, contain the 5-oxazolone ring and are important intermediates in the synthesis of α-amino acids.[51]

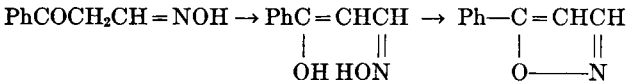


Isoxazoles have been studied extensively. Isoxazole, (II), b. 95°, is made from propargylic aldehyde and hydroxylamine. The oxime, having an active H in the 1,5-relation to a triple bond, undergoes ring closure.

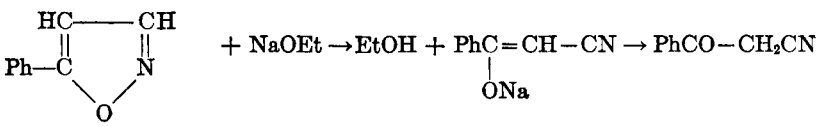


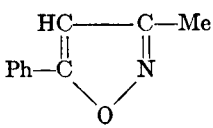
(II)

NaOEt opens the ring to give $NaOCH{=}CH{-}C{\equiv}N$. The monoximes of β-ketoaldehydes and β-diketones give 5- and 3,5-substituted isoxazoles.



When the 3-position is free, the ring is readily split by bases as in the case of isoxazole itself. If the 3-position is occupied, the ring is stable to bases.



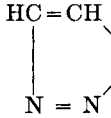


$+ NaOEt \rightarrow$ no action.

The 3-H evidently makes possible an unusual tautomeric change to give the α-cyanoketone which is removed by the alkali as an enolate.

[51] "Org. Reactions," III.

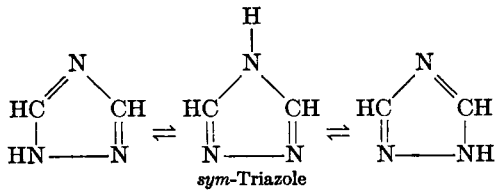
Thiodiazole,



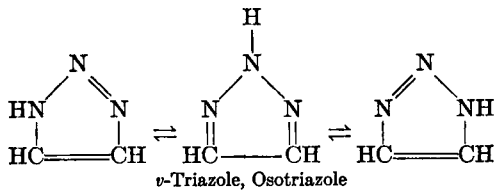
S, b. 158°, does not have a disagreeable odor, is stable to acids but is decomposed by bases. It is very weakly basic.

I. Triazoles

Two types are known, each of which may exist in three tautomeric forms as shown.



sym-Triazole

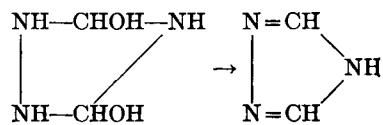


v-Triazole, Osotriazole

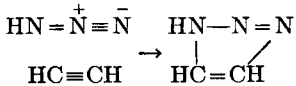
The two changes are probably bimolecular involving a trace of H^+ ion.

***sym*-Triazole,** 1,2,4-triazole, m. 121°, b. 260°, can be made from formamide and formyl hydrazide at 260°

$$HCO{-}NHNH_2 + HCO{-}NH_2 \rightarrow HCO{-}NHNH{-}CHOH{-}NH_2 \rightarrow$$

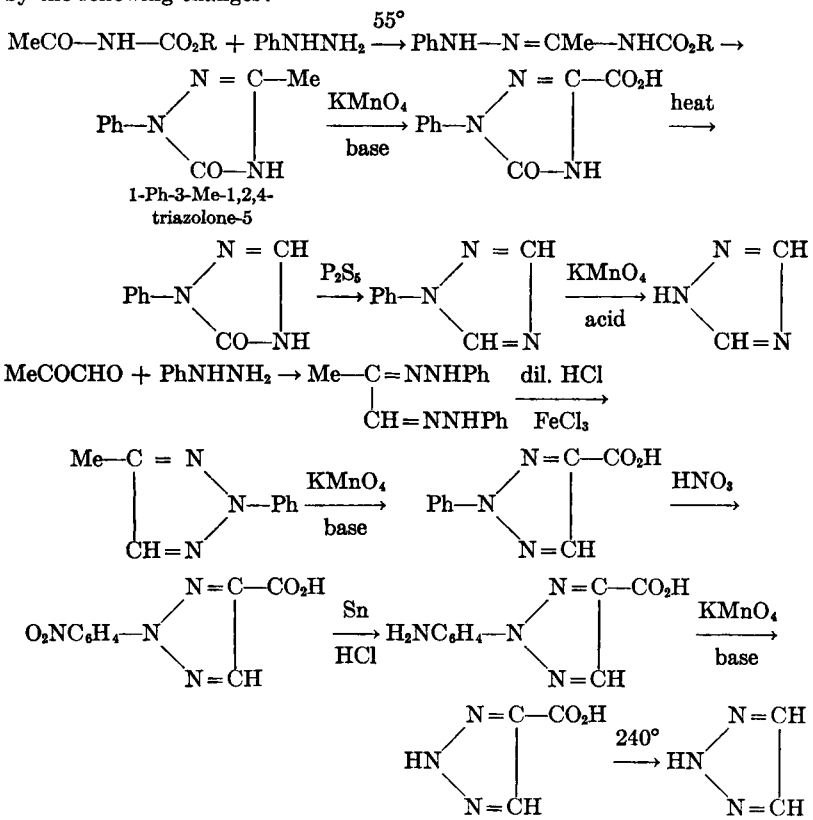


***v*-Triazole,** osotriazole, 1,2,3-triazole, b. 206°, can be made from acetylene and hydrazoic acid.

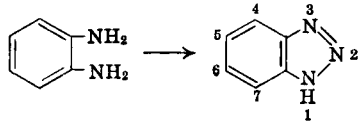


The name osotriazole is derived from the synthesis of these compounds from

the osazones of 1,2-dicarbonyl compounds. Boiling copper sulfate solution converts the sugar osazones (p. 480) to osatriazole derivatives.[52] The chemistry of the triazoles, especially the stability of the conjugated rings, is shown by the following changes:



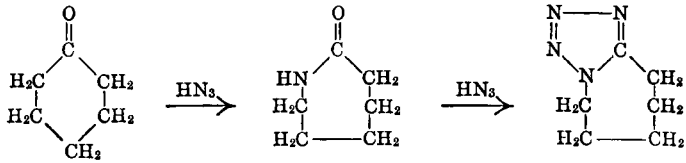
Benztriazoles are formed by the action of nitrous acid on orthodiamines.



All the experimental evidence indicates the complete equivalence of the 5 and 6 positions. This is explainable on the basis of an extremely facile tautomerism as shown for *v*-triazole.

[52] Haskins, Hann, Hudson. *J. Am. Chem. Soc.* **68**, 1766 (1946).

Tetrazoles. Pentamethylene tetrazole, *metrazole, cardiazole,* is made by the action of excess hydrazoic acid on cyclohexanone in sulfuric acid.[53] The probable intermediate, ϵ-aminocaprolactam, is formed by a rearrangement analogous to the Beckmann rearrangement of oximes.



The product is a cardiac stimulant and is used in shock therapy of schizophrenia.

III. SIX-MEMBERED HETEROCYCLIC RINGS

These fall into two groups, the saturated rings which show no properties different from their aliphatic analogs, and the unsaturated rings, especially those with ring conjugation resembling that of benzene and related compounds. Among the former are glutaric anhydride, δ-valerolactone, piperidine

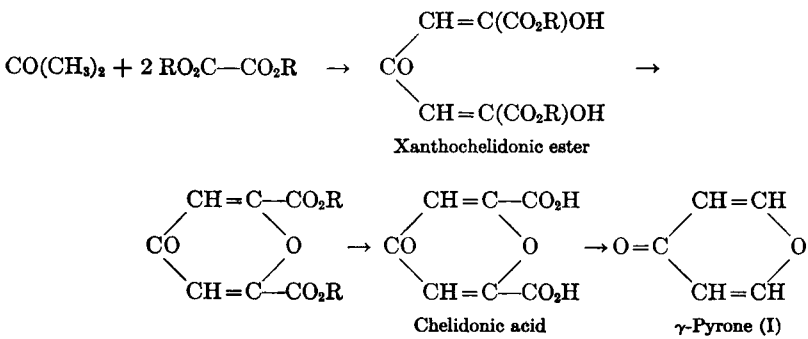
$$CH_2(CH_2CH_2)_2NH,$$

and morpholine, $O(CH_2CH_2)_2NH$.

A. Pyrones

Although tetrahydropyrane and dihydropyrane are well known, pyrane itself is known only in the form of its derivatives, the pyrones.

γ-Pyrone, (I) m. 32°, b. 315°, is made by heating its dicarboxylic acid, *chelidonic acid,* m. 262° dec., which is synthesized from acetone and ethyl oxalate in presence of NaOEt.[1]



[53] Wolff. "Org. Reactions," III.

[1] "Org. Syntheses."

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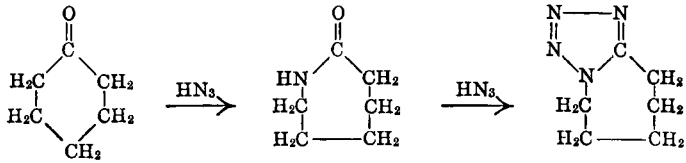

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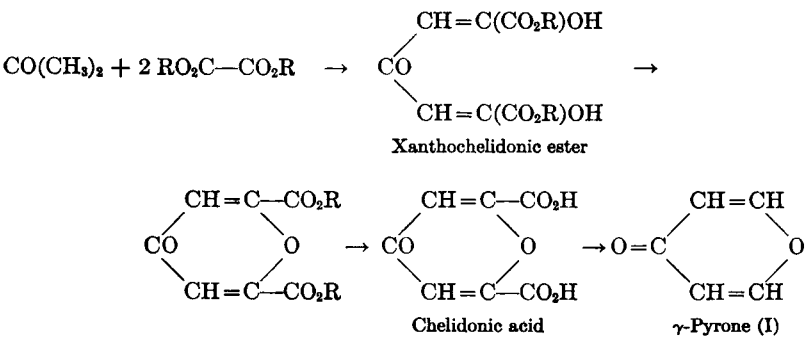
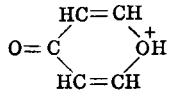


[53] Wolff. "Org. Reactions," III.
[1] "Org. Syntheses."

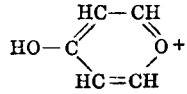
The γ-pyrones form definite crystalline salts with acids. These were the first definitely established *oxonium salts*. These salts are analogous to ammonium salts.

$(Me_3NH)^+Cl^-$ $(C_5H_4O_2H)^+Cl^-$

The proton can become attached to either the ring oxygen atom as in (I) or the carbonyl oxygen as in (II).

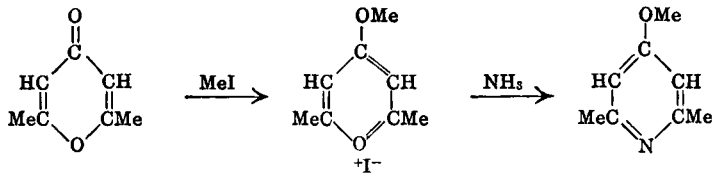


(I)



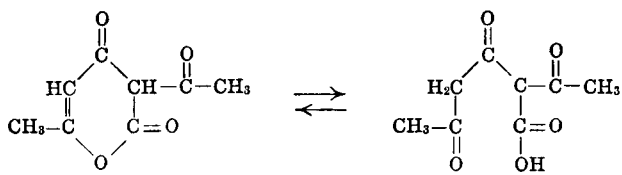
(II)

α,α′-Dimethyl-γ-pyrone reacts with methyl iodide giving an addition compound which on treatment with ammonia forms α,α′-dimethyl-γ-methoxy pyridine.



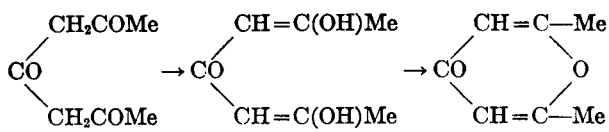
The oxonium compounds must therefore have the structure represented by formula II. The greater stability of the acid salts of the γ-pyrones results from the resonance between the equivalent Kekulé-like structures.

Dehydroacetic acid, Dehydranone[2] (C and C), III, is the lactone of α,γ-diacetyl-acetoacetic acid (IV).



(III) (IV)

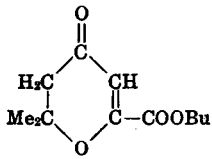
αα′-Dimethyl-γ-pyrone, m. 132°, b. 250°, is made by heating diacetylacetone obtained from phosgene and Cu acetoacetic ester.



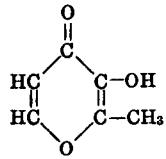
[2] "Org. Syntheses."

The same product is formed by heating dehydroacetic acid (III) with HCl. In this reaction the lactone ring is opened to IV which then decarboxylates to diacetylacetone.

Indalone, α,α'-dimethyl-α'-carbobutoxy-dihydro-γ-pyrone (USI), the condensation product from dibutyl oxalate and mesityl oxide with sodium methylate, is an effective insect repellent.



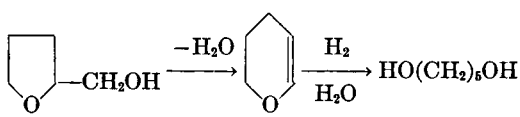
Indalone



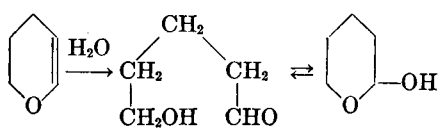
Maltol

Maltol, 3-hydroxy-2-methyl-4-pyrone, m. 159°, is present in the bark of the larch and in pine needles. It is obtained from hardwood tars and tar oils, and also from the alkali degradation of streptomycin. The brilliant purple color it gives with ferric chloride forms the basis for a convenient test for this antibiotic. Its lower homolog, *pyromeconic acid*, 3-hydroxy-4-pyrone, is obtained from the decarboxylation of *meconic acid*, 2,6-dicarboxy-3-hydroxy-4-pyrone, which is present in opium.

Dihydropyran, b. 86°, is formed by passing tetrahydrofurfuryl alcohol over aluminum oxide at 150–350°.[2] It is hydrogenated in anhydrous media to tetrahydropyrane and with copper chromite in aqueous solution to pentamethylene glycol.[2a] Mild hydrolysis gives δ-hydroxyvaleraldehyde which is



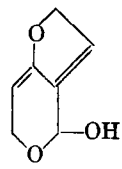
in equilibrium with its cyclic hemiacetal.[2b] This constitutes a simple model



of the ring system in the pyranose sugars. It is a valuable intermediate for many pentamethylene derivatives. Dihydropyran adds bromine to give 2,3-Br_2-tetrahydropyrane, hydrogen bromide to give 2-Br-tetrahydropyrane,[2c] and methanol with H^+ to give 2-methoxytetrahydropyrane. 2-Br-Tetrahydropyrane couples with Grignard reagents to give 2-alkyl-tetrahydropyranes.

[2a] Brenner and Starky. *C. A.* **42**, 5466 (1948).
[2b] Schniepp and Geller. *J. Am. Chem. Soc.* **68**, 1646 (1946).
[2c] Paul. *Compt. rend.* **198**, 375 (1934).

Patulin, clavicin, an antibiotic obtained from *Penicillium patulin*, is a dihydropyran derivative.[2d]

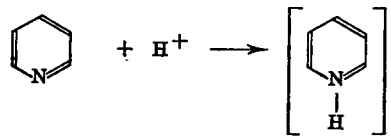


Patulin

B. Pyridine and Its Derivatives

Pyridine, C_5H_5N, b. 115.3°, m. −42°, occurs in coal tar in a mixture with its homologs. It has a disagreeable odor, particularly in the crude state, which makes it valuable as a constituent of mixtures for denaturing alcohol. In contrast to benzene, pyridine is completely miscible with water. It possesses unique solvent properties, combining the characteristics of an aromatic, hydrophyllic, and basic substance. Pyridine can be successfully dried only by standing over BaO. The mixture should not be boiled.

The conjugated system of three double bonds gives the ring aromatic properties and the stability characteristic of such rings. Since the salt forming ability of the N is not involved in the ring unsaturation as it is in pyrrole and related substances, pyridine is a base and forms pyridinium ions, but its basic strength ($K_b = 2.3 \times 10^{-9}$) is very much less than that of the saturated compound piperidine ($K_b = 1.6 \times 10^{-3}$).



Pyridine is even more stable to oxidation than is benzene. Its homologs are oxidized to pyridine carboxylic acids.

Lauryl pyridinium chloride is a cationic detergent which is effective both as a cleaning agent and a germicide. *Ceepryn*, cetyl pyridinium chloride, m. 83°, is reported to be the most effective of the alkyl pyridinium halides as an antiseptic. The Karl Fischer reagent, a solution of SO_2, MeOH, and I_2 in pyridine, is the most effective reagent for the determination of moisture in an organic solvent. The dark color of this solution is destroyed by water. The reagent is standardized against pure water or a standard solution of water in some organic solvent. The primary reaction is:

$$I_2 + SO_2 + 3\ C_5H_5N + H_2O \rightarrow 2\ C_5H_5N \cdot HI + C_5H_5N \cdot SO_3$$

[2d] Woodward and Singh. *J. Am. Chem. Soc.* **72**, 1428 (1950).

Nitration, halogenation, and sulfonation reactions of pyridine are very difficult. When such substitution does occur, the nitro-, halo- or sulfonic acid group enters the beta position. This is presumably because the reagent, instead of attacking one of the double bonds as in benzene, attaches itself to the highly reactive nitrogen and forms a relatively stable compound without substitution. For instance, pyridine reacts with fuming sulfuric acid to give pyridinium sulfate which only sulfonates with excess fuming sulfuric acid above 300°. On the other hand, pyridine is aminated with sodium amide in liquid ammonia to give 2-aminopyridine.[3]

The number of isomers of substituted pyridines corresponds to its ring structure. Thus there are three mono- and six di-substitution products. With the N as 1, the 2 and 6 positions are called *alpha*, the 3 and 5 *beta* and the 4 *gamma*. In the same way that benzene derivatives show a difference in reactivity between the *o*- and *p*-derivatives on one hand and the *m*-derivatives on the other, the α- and γ-derivatives of pyridine show marked similarties to each other but differ markedly from the β-derivatives.

Many of the substitution reactions of pyridine and pyridine derivatives show great similarity to the reactions of nitrobenzene or the corresponding substituted nitrobenzene. For example, neither pyridine nor nitrobenzene is substituted in the Friedel-Crafts reaction and both *p*-chloronitrobenzene and 4-chloropyridine react with ammonia, the first to give *p*-nitroaniline, and the second to give 4-aminopyridine.

Reactions of Pyridine

A. Those of the N atom.

1. H^+ ions unite with it to give pyridinium ions. Concentrated nitric and sulfuric acids merely form salts without any substituting action even at fairly elevated temperatures.

2. Methyl iodide and many other alkyl halides react to form N-alkyl pyridinium ions, and halide ions.

3. Halogens add in the cold to pyridine to form stable perhalides, $C_5H_5NX_2$, and these give stable salts with HX, $C_5H_5NX_2 \cdot HX$.

B. Reactions of the ring.

1. Oxidation is fairly difficult and pyridine may even be used as solvent for certain oxidations.

2. Reduction is very easy. Alcohol and Na, catalytic hydrogenation, or electrolytic reduction give hexahydropyridine, *piperidine*.

3. Hydrolysis of the reaction mixture from sodium and pyridine at 80° gives a mixture of bipyridyls in which the γ,γ-isomer predominates.

4. Nitration goes only with difficulty, typical conditions being the addition of KNO_3 to a solution of pyridine in fuming sulfuric acid at 300° (15% yield).

[3] "Org. Reactions," I.

The polyalkyl homologues of pyridine are somewhat easier to nitrate.[4] Nitrogen dioxide (NO_2), however, at 120° gives a 10% yield of beta-NO_2-pyridine.[5] 2-Nitro pyridine is obtained from 2-aminopyridine by oxidation with hydrogen peroxide.[6]

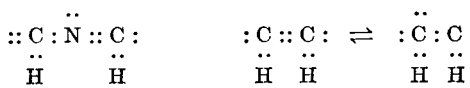
5. Sulfonation with fuming sulfuric acid in the presence of mercuric sulfate gives pyridine-beta-sulfonic acid.[7] This is like the sulfonation of aniline in concentrated sulfuric acid solution to give the *m*-acid. The sulfonic acid group can be replaced by OH or CN by the usual fusion reactions.

6. Chlorine and water simply give the hypochlorite of pyridine. In presence of bases, chlorine destroys the ring with the formation of N_2, $CHCl_3$ etc.

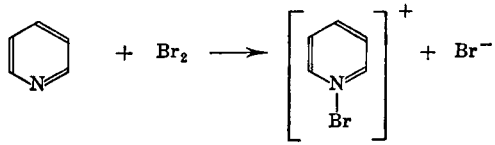
Vapor phase halogenation of pyridine has been studied extensively.[8,9] Bromination at 300° gives a mixture of 3-bromo- and 3,5-dibromo-pyridine, but at 500° the orientation is changed and 2-bromo- and 2,6-dibromopyridine are formed. The reaction presumably changes from that of an attack by positive bromine at 300° to that of attack by bromine atoms at 500°. A fair yield of 3-bromopyridine may be had by heating pyridine perbromide hydrochloride to 200°.[10] The vapor phase chlorination of pyridine at 270° gives a mixture of 2-chloropyridine, 2,6-dichloropyridine, and 3,5-dichloropyridine.[11]

7. Heating with $NaNH_2$ gives 2-amino- and 2,6-diaminopyridine along with a trace of 4-amino pyridine.[12]

Halogenated pyridines. As has been seen, the activity of the N atom in combining with halogen interferes with the halogenation of the ring. The situation can best be shown electronically. The N and the C=C unsaturation may be shown as follows:

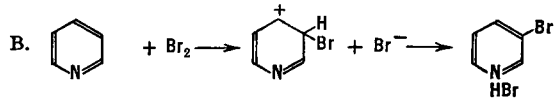


The bromine reacts with the nitrogen unsaturation in pyridine at ordinary temperatures as shown in *A*.

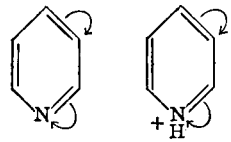
A. 

[4] Plazek. *Ber.* **72B**, 577 (1939).
[5] Shorigin, Topchiev. *Ber.* **69B**, 1874 (1936).
[6] Kirpal, Böhm. *Ber.* **67B**, 767 (1931).
[7] McElvain, Goese. *J. Am. Chem. Soc.* **65**, 2233 (1943).
[8] Wibaut et al. *Rec. trav. chim.* **51**, 940 (1932); **58**, 994 (1939); **60**, 22 (1941); **64**, 55 (1945).
[9] McElvain, Goese. *J. Am. Chem. Soc.* **65**, 2227 (1943).
[10] Englent, McElvain. *J. Am. Chem. Soc.* **51**, 863 (1929).
[11] Wibaut, Nicolai. *Rec. trav. chim.* **58**, 709 (1939).
[12] Leffler. "Org. Reactions," I.

Only at temperatures of 300° does the bromine react with the C=C unsaturation.



Substitution occurs at the beta position because of the electron attraction of the ring nitrogen which leaves a residual positive character to the α- and γ- carbon atoms. This is greatly increased in acid solution in which pyridine exists as the pyridinium ion.



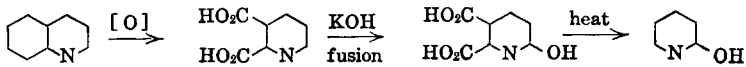
α- and γ-Chloropyridines, b. 168° and 148°, are best made from PCl_5 or $POCl_3$ and the corresponding hydroxypyridines. The chlorine resembles that in the *o*- and *p*-chloro-nitrobenzenes in being replaceable by OH, NH_2, OR, SH, *etc.*

β-Chloropyridine, b. 149°, is obtained by the remarkable action of pyrrole potassium with $CHCl_3$, CCl_4, chloral, *etc.* (p. 758), or by the conventional Sandmeyer diazo reaction on 3-aminopyridine. The —Cl is not ordinarily replaced. Reduction with Na_xHg or Zn and HCl gives 3-chloropiperidine whereas the reduction of the 2- and 4-isomers removes the Cl, giving mainly piperidine.

Pyridine-3-sulfonic acid is obtained by sulfonation at 330–350°. It shows the expected properties, including amphoteric reactions, and replacement of the sulfonic group on potassium cyanide fusion to give 3-cyanopyridine.

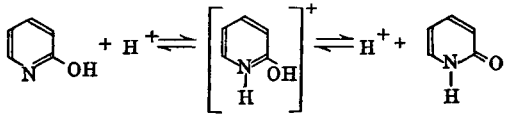
Hydroxypyridines

Only 3-hydroxypyridine and its derivatives are typically phenolic. Although 2-, 3-, and 4-hydroxypyridines all give colors with ferric chloride, the coloration with the 2- and 4-isomers is very weak. The 2-, 3-, and 4-hydroxypyridines are readily nitrated in contrast to pyridine itself, giving 2-hydroxy-5-nitro-, 3-hydroxy-2-nitro- and 4-hydroxy-3-nitro-pyridine respectively. 3-Hydroxypyridine, m. 128°, is best formed by the alkali fusion of the 3-pyridine sulfonic acid. 2-Hydroxypyridine, m. 107°, b. 281°, is best obtained from 2-aminopyridine by treatment with nitrous acid. A unique synthesis starts with quinoline.

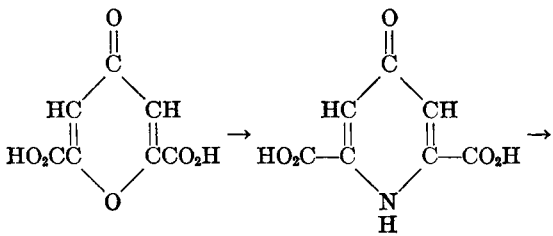


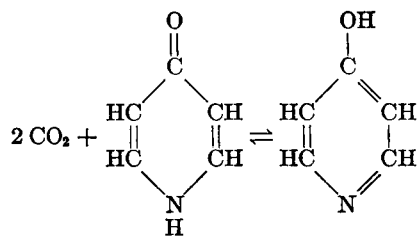
Quinolinic acid

It probably exists mainly as *α-pyridone*, 2-keto-1,2-dihydropyridine. This is indicated by the very similar ultraviolet absorption spectra of 2-hydroxypyridine and N-methyl-2-pyridone in neutral solution, but the greatly different absorption spectra of 2-methoxypyridine. The ready change to this keto form is due to the tendency of the N to unite with H^+ ion and is a good illustration of the bimolecular nature of tautomerization.



Treatment with MeI and a base gives 1-Me-α-pyridone, b. 250°. This reacts with PCl_5 to give 2-Cl-pyridine, with the elimination of methyl chloride. *γ-Hydroxypyridine*, *γ-pyridone*, m. 148°, b. 350°+, is made by heating *chelidamic acid*, 4-hydroxypyridine-2,6-dicarboxylic acid, pyridone-2,6-dicarboxylic acid, m. 220° dec. which is readily obtained from NH_3 and chelidonic acid.[13]





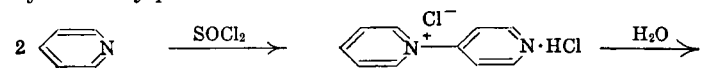
As in the case of α-hydroxypyridine, γ-hydroxypyridine probably exists in neutral solution primarily as the pyridone. It is impossible for 3-hydroxypyridine to assume the pyridone structure just as it is impossible to have a *meta*-quinone.

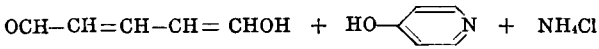
4-Hydroxypyridine may also be prepared in fair yield from pyridine *via* pyridylpyridinium chloride hydrochloride[14] by the very interesting reaction in

[13] "Org. Syntheses."

[14] Koenigs, Greiner. *Ber.* 64B, 1049 (1931).

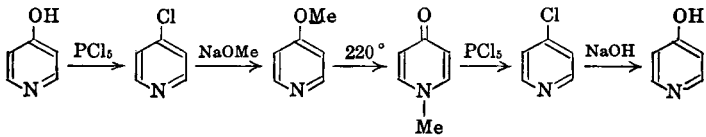
which one pyridine ring is opened at the nitrogen atom giving glutaconic dialdehyde as a by-product.



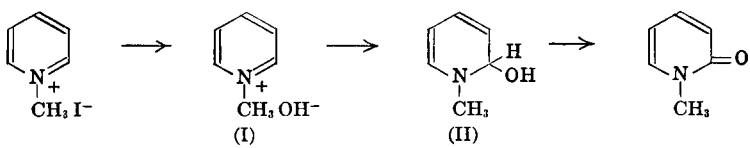


Several non-toxic, soluble, iodinated derivatives of pyridones are relatively opaque to X-rays and have therefore found use for intravenous urography. *Diodone* is the N-(β-carboxymethyl) derivative of 3,5-diiodo-4-pyridone. *Neoselectan B* (*Iodoxyl, Neoiopax*) is the sodium salt of 1-methyl-3,5-diiodo-4-pyridone-2,6-dicarboxylic acid.

N-Methyl-γ-pyridone, a low melting solid, is obtained by treating γ-pyridone with methyl iodide in basic solution. It may also be prepared by rearrangement at 220° of γ-methoxypyridine, b. 191°, obtained from γ-chloropyridine and sodium methylate by heating to 220°.



N-Methyl-α-pyridone, m. 30°, b. 250°, may be obtained in a similar way by the rearrangement of 2-methoxypyridine or more directly by the potassium ferricyanide oxidation of pyridine methiodide in basic solution.[15]



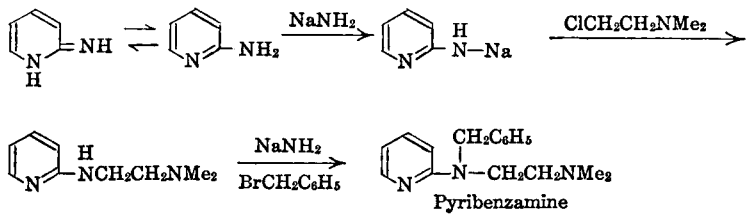
The equilibrium between the pyridinium hydroxide (I) and the carbinol base (II) greatly favors the former.[16] The action of PCl_5 with pyridone is much like that with acetone in which the chief product is $MeCCl=CH_2$ or with N-substituted amides such as benzanilide in which the product has the imidochloride structure, $C_6H_5CCl=N-C_6H_5$. In each case, the reaction may be due to the "enol" form or to the loss of HCl from a dichloride. In the case of the N-Me-pyridone, a mechanism like the latter process is indicated.

Aminopyridines, α- m. 56°, b. 204°; β- m. 64°, b. 252°; γ- m. 158°, can all be made by the Hofmann reaction on the amides of the acids which are readily

[15] "Org. Syntheses."
[16] Aston. *J. Am. Chem. Soc.* **53**, 1448 (1931).

obtained by the oxidation of the respective methylpyridines (picolines). This is the method of choice for the laboratory preparation of the β- and γ-isomers but α-aminopyridine is prepared commercially by the reaction of sodium amide on pyridine.[17] With excess sodium amide at higher temperatures, 2,6-diaminopyridine is the main product.[18] Although the amino group in α-aminopyridine cannot be diazotized in the usual manner, it can be replaced by halogen in good yield by a modified procedure in which pyridine perbromide hydrobromide is treated with sodium nitrite in HBr solution.[19,20] β-Aminopyridine shows all of the reactions of an aromatic amine.

Sulfapyridine, 2-(*p*-aminobenzenesulfonamido)-pyridine, is made by reactions completely analogous to the preparation of sulfathiazole. α-Aminopyridine is also the intermediate in the synthesis of the antihistamine drug *Pyribenzamine*[21] used in the treatment of allergic conditions. The 2-NH_2-pyridine is first treated with sodium amide in order to prevent substitution on the ring nitrogen atom *via* the imino form.



2,6-$(NH_2)_2$-pyridine couples with phenyldiazonium chloride to give an azo dye 2,6-$(NH_2)_2$-3-phenylazopyridine, *Pyridium*, which is used as an urinary antiseptic.

Pyridine homologs can be obtained in great variety from coal tar and bone oil. Picolines, methylpyridines, α-, b. 129°; β-, b. 144°; γ-, b. 145°, resemble pyridine in general; all are commercially available. The α-isomer can be separated from the other pyridine bases by efficient fractionation, but β-picoline, γ-picoline, and 2,6-Me_2-picoline, *2,6-lutidine*, b. 144.5°, all boil within one degree. They are successfully separated by azeotropic distillation with water.[22,23] α-Picoline is formed in small yield (6%) when acetaldehyde-ammonia is heated with acetaldehyde.[24] Presumably crotonaldehyde or its

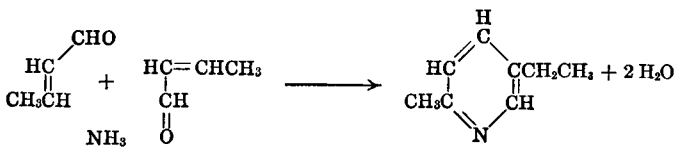
[17] "Org. Reactions," I.
[18] Shreve et al. *Ind. Eng. Chem.* **32**, 173 (1940).
[19] Craige. *J. Am. Chem. Soc.* **56**, 231 (1933).
[20] "Org. Syntheses."
[21] Hutterer et al. *J. Am. Chem. Soc.* 68, 1999 (1946).
[22] Cislak, Karnatz. *C. A.* 41, 2447 (1947).
[23] Cislak, Karnatz. Brit. Patent No. 580,048, Aug. 26, 1946.
[24] Frank et al. *J. Am. Chem. Soc.* 68, 1368 (1946).

equivalent is first formed.

$$CH_3CH{=}CHCHO + H_2NCHOHCH_3 \rightarrow$$

$$CH_3CH{=}CH{-}CH{=}NCHOHCH_3 \rightarrow \begin{matrix} CH{-}CH_2{-}CHCH_3 \\ \| \quad\quad | \\ CH{-}CH{=}N \end{matrix}$$

The intermediate dihydropicoline is dehydrogenated to α-picoline, excess acetaldehyde acting as the hydrogen acceptor. The major product in this reaction is 2-methyl-5-ethylpyridine, *aldehyde collidine* (50–70%). This must be formed by the condensation of two moles of crotonaldehyde or their equivalent, with ammonia. This amounts to a Diels-Alder type condensation with subsequent rearrangement of the unsaturation to give the completely conjugated pyridine system.



β-Picoline is obtained by various reactions.

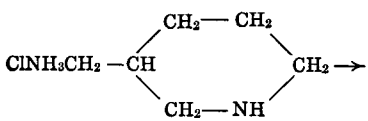
1. Dry distillation of strychnine and certain other alkaloids with lime.

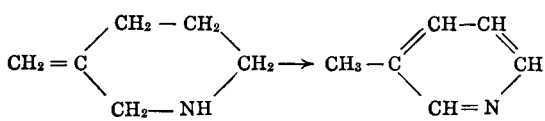
2. Reaction of acrolein and ammonia over a catalyst at elevated temperatures.

3. From glycerol in the presence of ammonium phosphate and P_2O_5. This reaction is probably equivalent to the process whereby β-picoline is formed in the dry distillation of bones.

4. From trimethylenediamine hydrochloride. An 8-membered ring may form first and then undergo ring-narrowing as happens in the change of cyclohexane to methylcyclopentane or the ring may close in the 1,6-position by the following steps;

$$2\,NH_2(CH_2)_3NH_2 \xrightarrow{HCl} ClNH_3(CH_2)_3NH(CH_2)_3NH_3Cl \xrightarrow{HCl}$$





The methyl group of α- and γ-*picoline* differs from that of the β-isomer by giving α-H reactions in condensing with aldehydes and ketones. Thus the

grouping $N=C-CH_3$ resembles $O=C-CH_3$. The stability given by the pyridine ring makes possible reactions which could not take place with this grouping in simpler compounds. Thus α-picoline and formaldehyde at 150° undergo an aldol-type condensation to give first 2-(β-hydroxyethyl)-pyridine which readily dehydrates to the commercially available 2-vinylpyridine. This product is remarkable not only because it shows properties comparable to styrene in polymerization with butadiene, but also because it shows the addition reactions characteristic of an α,β-unsaturated substance such as acrylonitrile. α-Picoline reacts with sodium amide to liberate ammonia and give α-picolyl sodium. This can be carbonated to α-(2-pyridyl)-acetic acid or treated with alkyl halides to give a variety of picoline homologs such as 2-*n*-amylpyridine and 2-*n*-hexylpyridine (Reilly Tar) in good yield.

α- and γ-Picolines are also formed by rearrangement when pyridinemethiodide is heated to 300°. This is closely analogous to the formation of *o*- and *p*-toluidines from N-Me-anilines. α- and γ-Ethylpyridines, b. 148° and 166°, are similarly prepared. When pyridinium compounds with higher alkyl halides are decomposed, rearrangements may occur within the alkyl group. Thus the *n*-propyl iodide compound gives isopropylpyridines. α-*n*-Propylpyridine, *conyrine*, is obtained by dehydrogenating its hexahydroderivative, the alkaloid *coniine*. It is synthesized from 1-(2-pyridyl)-2-propanol, made from α-picoline and acetaldehyde.[25]

Dimethylpyridines, lutidines: 2,3-, b. 161°; 2,4-, b. 158°; 2,5-, b. 156°; 2,6-, b. 144°; 3,4-, b. 179°, are found in coal tar and bone oil. 2,6-Lutidine is synthesized by decarboxylation of 3,5-dicarboxy-2,6-dimethylpyridine, obtained by the Hantzsch synthesis.[26] *Trimethylpyridines, collidines*, are known. The 2,4,6- or *sym*-collidine, b. 172°, is made from acetoacetic ester and aldehyde-ammonia or from acetamide and acetone at 250°. In both cases the aldol condensation produces molecules capable of 1,6-ring closure. The second case gives a pyridine directly without any dehydrogenation. The mesityl oxide formed from the acetone reacts with the acetamide in the simplest possible way.

$$(CH_3)_2C=CH-CO-CH_3 \rightarrow$$

$$CH_3-\underset{\displaystyle CH_3}{\underset{|}{C}}=CH-\underset{\displaystyle CH_3}{\underset{|}{C}}=N-CO-CH_3 \rightarrow \quad CH_3-\underset{|}{C}=CH-\overset{\displaystyle CH=C(CH_3)N}{\overset{\|}{C}}-CH_3$$

The final ring closure is a cyclic aldol condensation involving H which is α- to the conjugated system $C=C-C=N$ instead of merely α- to $C=O$.

2,4-Lutidine and 2,4,6-collidine are useful in the identification of amino-acids.

[25] "Org. Syntheses."
[26] *ibid.*

Pyridine carboxylic acids are made in general by:

1. Oxidation of alkylpyridines. In some cases more complex side chains are removed leaving one or more carboxyl groups. Thus nicotine and quinoline give nicotinic and quinolinic acids respectively.

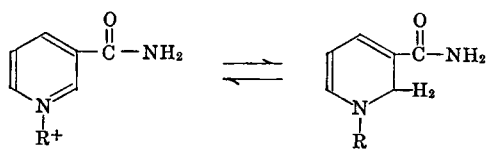
2. By partial decarboxylation of dibasic acids. The ease of decarboxylation decreases in the order α-, γ-, and β-. This is the same order as the decreasing dissociation constants.

The *monobasic acids* are *picolinic*, α-, m. 135°, *nicotinic*, β- m. 231°, and *isonicotinic*, γ- m. 309° (sealed tube).

All six possible pyridine dicarboxylic acids are known: *quinolinic*, 2,3- m. 190°, *lutidinic*, 2,4- m. 235°, *dipicolinic*, 2,6- m. 226°, *isocinchomeronic*, 2,5- m. 236°, *dinicotinic*, 3,5- m. 323°, and *cinchomeronic*, 3,4- m. 266°.

Vinylpyridines, the 2- and the 4-vinylpyridines, are best made from 2-picoline, and 4-picoline, the 3-vinylpyridine, may be prepared from 3-acetylpyridine. The 2-vinylpyridine (Reilly) is commercially important in the synthesis of special elastomers.[27] 2-Vinylpyridine reacts with ammonium hydroxide and sulfur to give 2-pyridine acetamide.[28] beta-(2-Pyridyl)-ethyl sulfonic acid and beta-(4-pyridyl)-ethyl sulfonic acid are made in high yields by the action of sodium bisulfite on 2- and 4-vinylpyridine.[29]

Nicotinic acid, *Niacin,* was recognized in 1937 as a member of the vitamin B complex (Elvehjem). Either the acid or its amide, *niacinamide*, will cure human pellagra. Nicotinic acid functions in metabolism as a portion of coenzymes I and II (diphosphopyridine nucleotide and triphosphopyridine nucleotide) promoting cellular oxidation through a reversible oxidation-reduction system. Presumably this is accomplished as indicated in the following equation by addition of hydrogen to give a dihydropyridine derivative. The probable structure for R is -ribose-OPO_2H-OPO_2H-O-ribose-adenine.



Coramine, *niketha*mide, N,N-diethylnicotinamide, is a powerful central nervous system stimulant with properties similar to metrazole. It is used as an antidote for an overdose of a central nervous system depressant such as the barbiturates.

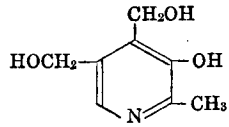
Pyroxidine, *adermine, vitamin* B_6, is another member of the water-soluble B-complex. Its deficiency is responsible for a dermatitis in rats. A phosphoric acid ester has been prepared from pyridoxine which has all of the activity of

[27] Frank et al. *Ind. Eng. Chem.* **40**, 879 (1948).

[28] Pattison, Carmack. *J. Am. Chem. Soc.* **68**, 2033 (1946).

[29] Doering, Weil. *J. Am. Chem. Soc.* **69**, 2461 (1947).

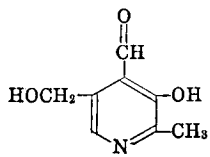
natural codecarboxylase. Its role in human nutrition has not yet been clarified. The structure of pyridoxine has been established by synthesis[30] as 2-methyl-3-hydroxy-4,5-di-(hydroxymethyl)-pyridine.



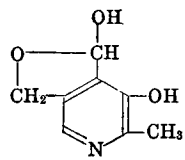
Recent work[31] has shown that there are associated with pyridoxine two distinct pyridoxine-like substances which have high growth promoting properties for certain bacteria. It was deduced by microbiological experiments that these substances were an aldehyde (named *pyridoxal*) and an amine (*pyridoxamine*) which were interconvertible by a transamination reaction as indicated in the following equation where glutamic acid acts as the source for the transfer of the amine group.

Pyridoxal + Glutamic Acid → Pyridoxamine + α-Ketoglutaric Acid

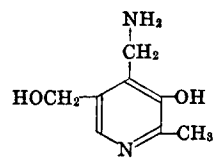
It has been confirmed by synthesis[32] that pyridoxal is the oxidation product of pyridoxine in which the aldehyde group is in the 4 position (I). The aldehyde may have the inner hemi-acetal structure (II). Pyridoxamine is the corresponding amine (III).



(I)



(II)



(III)

Hydrogenated Pyridines

The di-, tetra-, and hexa-hydro compounds of pyridine and its derivatives are known. They all readily revert to pyridine. Their dehydrogenation is extraordinarily easy as compared with that of hydro-benzene derivatives.

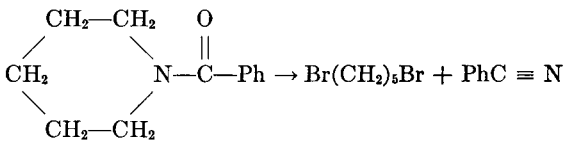
Piperidine, hexahydropyridine, pentamethyleneimine, $(CH_2)_5NH$, b. 106°, is a strong base made by reducing pyridine in a variety of ways. Piperidine occurs in the alkaloid of pepper, *piperine*, which is the piperidide of piperic acid. Large scale manufacture is by the nickel catalyzed hydrogenation of pyridine. Substituted piperidines are most frequently made by reduction of the corresponding pyridine compound using platinum catalyst in acid solution.

[30] Harris, Folkers. *J. Am. Chem. Soc.* 61, 1245 (1939).
[31] Snell. *J. Am. Chem. Soc.* 66, 2082 (1944).
[32] Harris, Heyl, Folkers. *J. Am. Chem. Soc.* 66, 2088 (1944).

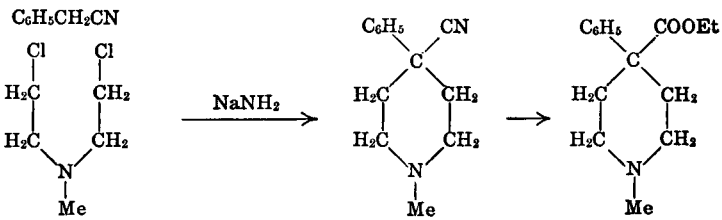
Piperidine gives the reactions of a secondary aliphatic amine. Exhaustive methylation gives first $CH_2=CH(CH_2)_3NMe_2$ and then

$$CH_3CH=CHCH=CH_2,$$

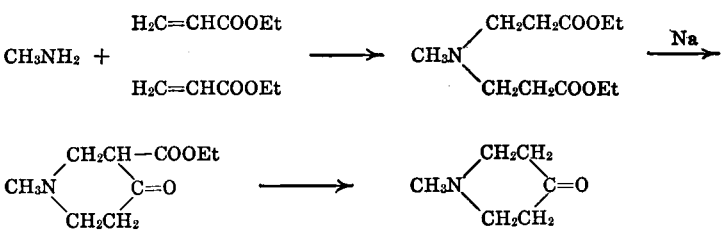
the latter being a rearrangement product of the expected 1,4-diene. Piperidine is a source of pentamethylene compounds (v. Braun). The benzoyl compound is treated with PBr_5 and distilled.[32a]



Demerol, 1-Me-4-Ph-4-COOEt-piperidine, is a potent analgesic which resembles morphine both in this respect and also in its addiction properties. It is prepared by an interesting and general ring synthesis.[33]



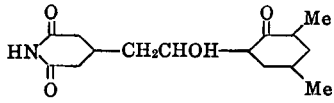
Piperidones are formed by a Dieckmann condensation of a suitable basic ester (or nitrile) which is readily obtained from acrylic ester (or nitrile) by the addition to a secondary amine.[34]



Actidione, $C_{15}H_{23}NO_4$, an antibiotic from *Streptomyces griseus*, is a 4-substituted

[32a] Leonard, Nommensen. *J. Am. Chem. Soc.* **71**, 1809 (1949).
[33] Eisleb. *Ber.* **74**, 1433 (1941).
[34] McElvain, Kuettel. *J. Am. Chem. Soc.* **53**, 2692 (1931).

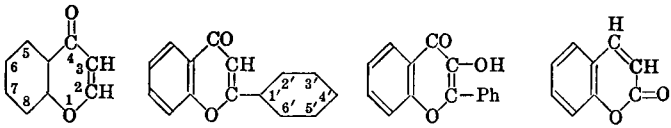
glutarimide derivative.[35]



It is active against yeast and other fungi and has been used to control powdery mildew in concentrations as low as 5 parts per million.

C. Chromone and Derivatives

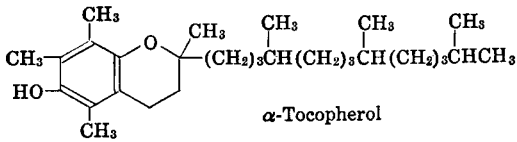
Chromone, benzpyrone, m. 59°, and **flavone,** 2-phenylbenzpyrone, m. 97°, are parent substances of many natural vegetable colors and dyes. *Coumarin* is the isomer of chromone related to α-pyrone.



Chromone Flavone Flavanol Coumarin

1. Related to chromane. *Chromane,* the parent compound of the series, is made from PhONa and $Br(CH_2)_3Br$ or $Cl(CH_2)_3OH$. First an ether is formed and then the ring is closed by heating with $ZnCl_2$.

Vitamin E, the *tocopherols,* are food factors necessary to normal reproduction in young rats and mice. They do not seem to be required food factors for sheep, goats and rabbits and their role in human nutrition is still unknown. Vitamin E is a mixture, of which α-tocopherol is the most potent constituent.

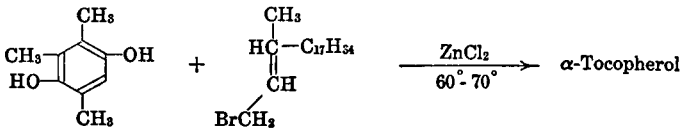


α-Tocopherol

β- and γ-Tocopherol differ only in having two methyl groups in the benzene ring in the 5,8- and 7,8-positions respectively. The synthesis of α-tocopherol[36] was accomplished by condensing 2,3,5-trimethylhydroquinone and phytyl bromide, prepared from the naturally occurring alcohol, phytol, which is

[35] Kornfield et al. *J. Am. Chem. Soc.* 71, 150 (1949).
[36] Karrer et al. *Helv. Chim. Acta* 21, 520, 820, 939 (1938).

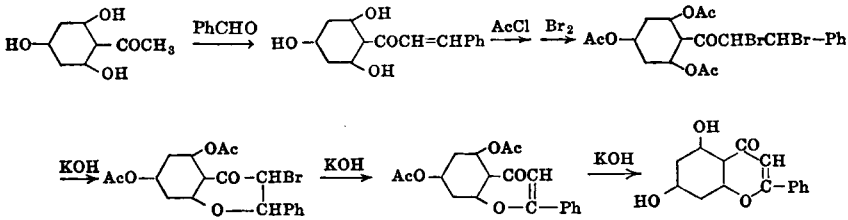
obtained from the saponification of chlorophyll.



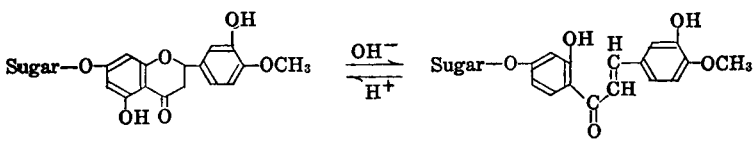
Many other related compounds show vitamin E activity.[37]

2. Related to flavone. *Chrysin*, 5,7-$(OH)_2$-flavone and *luteolin*, 5,7,3′,4′-$(OH)_4$-flavone.

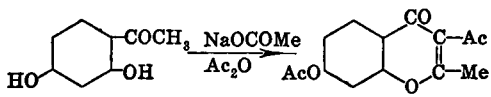
A general method of synthesis for many flavones is from polyhydroxychalcones obtained from suitably substituted benzaldehydes and acetophenones by the Claisen reaction. One OH must be ortho to the CO so as to make possible the closing of the pyrone ring. The synthesis of chrysin would involve the following steps:



Hesperidine, the glucoside of *hesperitin*, 5,7,3′-$(OH)_3$-4′-OMe-2,3-H_2-flavone, is found in lemon peel, citrus fruit, and red pepper; it has been synthesized. An equilibrium exists between hesperidine and its corresponding chalcone, the chalcone being favored in alkaline media and the flavanone in acid.[37a]



Hydroxyacetophenones can take part in a Perkin type reaction with acid anhydrides and Na salts of aliphatic and aromatic acids to give chromones and flavones respectively. With aliphatic acids an acyl group appears in the 3-position but not with the aromatic acids[38]

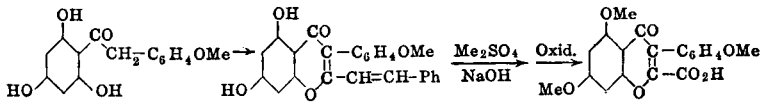


2-Me-3-acetyl-7-acetoxychromone

[37] Smith. *Chem. Rev.* 27, 287 (1940).
[37a] Warner, Webb. *Science* 96, 302 (1942).
[38] Wittig et al. *Ann.* 446, 155 (1925).

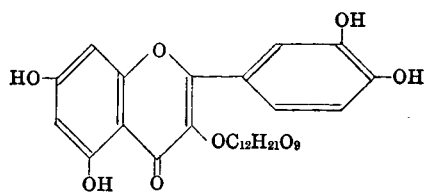
Similarly resacetophenone, with sodium anisate and anisic anhydride, gives 7-OH-4′-MeO-flavone, *pratol.*

3. Related to flavanol (3-OH-flavone). If suitable ω-methoxyacetophenones are used, the products have MeO- in the 3-position and on demethylation give *flavanols.* The following naturally occurring substances have been made in this way: *galingin,* 5,7-$(OH)_2$-; *datiscetin,* 5,7,2′-$(OH)_3$-; *kaempherol,* 5,7,4′-$(OH)_3$-; *fisetin,* 7,3′,4′-$(OH)_3$-; *quercitin,* 5,7,3′,4′-$(OH)_4$-; *morin,* 5,7,2′,4′-$(OH)_4$-; *quercetazetin,* 5,6,7,3′,4′-$(OH)_5$-; *gossypetin,* 5,7,8,3′,4′-$(OH)_5$-; *myricetin,* 5,7,3′,4′,5′-$(OH)_5$-flavanol. A further modification of the Perkin reaction is used to give *isoflavones* (3-phenylchromones, p. 793). A polyhydroxyphenyl benzyl ketone, having OH ortho to the CO, is heated with Na cinnamate and cinnamic anhydride. The methylene group supplies the α-H atoms while the cinnamic compounds supply the carbonyl group.



Decarboxylation and demethylation give *5,7,4′-(OH)$_3$-3-phenylchromone,* 5,7,4′-$(OH)_3$-isoflavone, *genista.*

Rutin, m. 214° dec., is the closely related 3-rhamnoglucoside of quercetin.



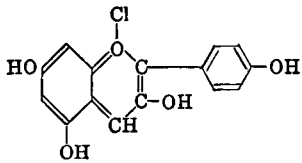
It is found widely distributed in plants and occurs most abundantly in green buckwheat. Both hesperidin and rutin have been shown to have a beneficial effect on abnormally fragile capillaries. Rutin is available in substantial quantity for the treatment of capillary fragility associated with hypertension.[39,40]

Anthocyanidins are related to the *flavanes* and are obtained by hydrolysis of the glucosidic *anthocyanins* of plant coloring matters. There has been much controversy concerning the structure of these benzopyrylium salts. They were originally considered exclusively oxonium salts as indicated in the follow-

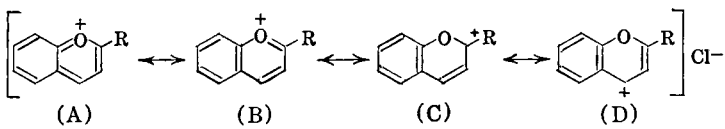
[39] *Chem. Ind.* 59, 74 (1948).

[40] Couch, Lindauer. *Proc. Soc. Exptl. Biol. Med.* 55, 228 (1944).

ing structure of *pelargonidin chloride,* the simplest of the anthocyanidins.



The chlorine is ionic. Recent evidence indicates a resonating ion with contributions from the various electronic structures A, B, C, and D.



(A) (B) (C) (D)

Cyanidin chloride and **delphinidin chloride** are the 3′,4′-$(OH)_2$- and 3′,4′,5′-$(OH)_3$-compounds corresponding to pelargonidin. *Oenidin* (*syringidin*) *chloride* is the 3′,5′-dimethyl ether of delphinidin chloride. *Myrtillidin chloride* is a mixture of the last two chlorides.

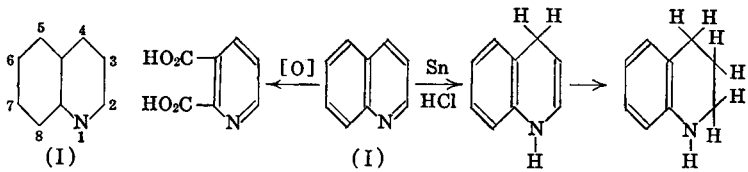
Coumarin itself is made from *o*-hydroxycinnamic acid (p. 703). Many coumarin derivatives are found in nature; two of the simpler are *umbelliferone,* 7-hydroxycoumarin, and *esculetin,* 6,7-dihydroxy-coumarin. *3,3′-Methylene-bis-(4-hydroxycoumarin)* is found in sweet clover and spoiling hay. Cattle feeding on it develop the "sweet clover disease" which is characterized by a progressive diminution of the clotting ability of the blood.[41] It is used as an anticoagulant having the opposite effect of vitamin K to which it is antagonistic.

Quinoline and Related Compounds

Quinoline, C_9H_7N, (I) b. 239°, occurs in coal-tar and bone-oil, is obtained by alkaline decomposition of certain alkaloids and can be synthesized in a great variety of ways from aniline and from aniline derivatives. Substituted quinoline compounds show the properties expected of a benzene or pyridine derivative depending upon whether the substituent is in the benzene or pyridine portion of the molecule. In line with the fact that nitration and sulfonation of pyridine are much more difficult than benzene, these reactions introduce a nitro or sulfonic acid group into the benzene portion (positions 6 and 8). On the other hand, amination of quinoline with sodium amide gives 2-aminoquinoline. The pyridine ring is more readily reduced but the benzene

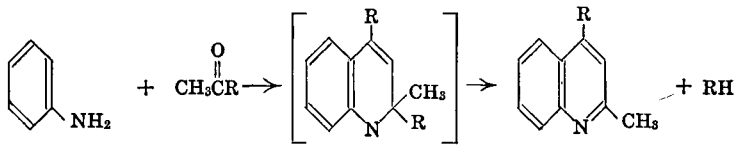
[41] Link et al. *J. Am. Chem. Soc.* 65, 2285 (1943).

ring is the more readily oxidized.



Seven mono-substituted quinolines are possible because of its unsymmetrical structure. The positions numbered 2 to 8 are also known as α-, β-, γ-, a-(ana-), p-, m-, and o-. The position of side chains is determined by oxidation to carboxylic acids or by synthesis.

The most important synthesis of quinoline is that of Skraup which employs aniline and glycerol heated with sulfuric acid and an oxidizing agent like nitrobenzene or arsenic acid.[42] The process probably involves the formation of acrolein or its equivalent from the glycerol, subsequent reaction with aniline to give the Schiff's base of the 1,4-addition product, ring closure with loss of the second molecule of aniline, and oxidation of the resulting dihydroquinoline by the nitrobenzene (or other oxidizing agent such as arsenic pentoxide) to quinoline. Acrolein may be used directly in the reaction.[43] Crotonaldehyde gives α-methylquinoline. Almost any substituted aniline can be used in the Skraup synthesis. A remarkable quinoline synthesis is the formation of 2,4-dialkylquinoline from the heating (180–200°) of aniline hydrochloride with a ketone.



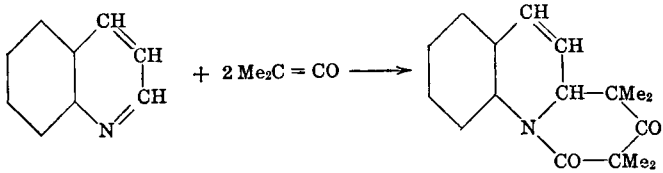
The tendency for formation of the conjugated quinoline structure is so great that a hydrocarbon is formed by the elimination of the larger group from the α-position of the intermediate dihydroquinoline.

Quinolinium salts are analogous to pyridinium salts. Quinoline is readily reduced to *dihydroquinoline*, m. 161°, by metals and acids. The process is readily continued to give *tetrahydroquinoline*, b. 245°. Its N-ethyl derivative is *cairolin*, a febrifuge. Further reduction involving the benzene ring to give decahydroquinoline, m. 48°, b. 204°, is possible only by vigorous hydrogenation with HI or catalysts.

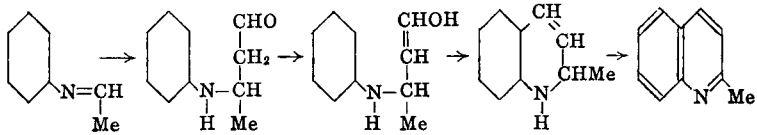
[42] "Org. Syntheses."

[43] Yale, Bernstein. *J. Am. Chem. Soc.* **70**, 254 (1948).

Quinoline forms a remarkable compound with 2 mols of dimethyl ketene.

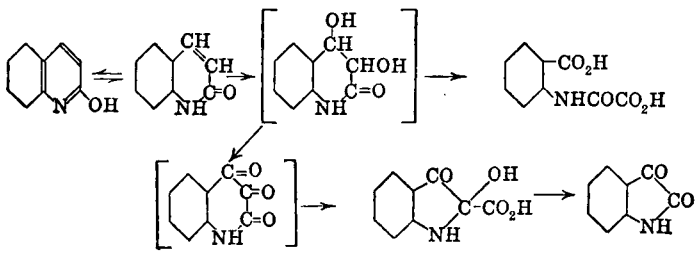


The most important methylquinoline is the α- or 2-isomer, *quinaldine*, b. 246°, which occurs in coal-tar and can be synthesized by heating aniline and paraldehyde with HCl. The ethylidineaniline first formed undergoes an aldol condensation with another molecule of aldehyde. Enolization, ring closure and air-oxidation give the *quinaldine*.



Quinaldine shows the reactions noted with α- and γ-Me-pyridines, the H atoms of the Me group having α-H properties and consequently giving condensation reactions with aldehydes, ketones and other active carbonyl compounds. Thus phthalic anhydride gives *Quinoline Yellow*, $C_9H_6NCH(CO)_2C_6H_4$, the disulfonic acid of which is *Quinoline Yellow* S. CrO_3 and H_2SO_4 convert quinaldine to quinoline-α-carboxylic acid while permanganate gives pyridine-2,3,6-tricarboxylic acid. The cyanine dyes are obtained from quinaldine and similar substances. An extraordinary number of derivatives of the cyanine dyes have been studied as sensitizers for photographic emulsions.[44]

Carbostyril, 2-hydroxyquinoline, m. 200°, is obtained from *o*-aminocinnamic acid and 50% H_2SO_4. It has phenolic properties. Oxidation with alkaline $KMnO_4$ gives isatin and oxalylanthranilic acid.



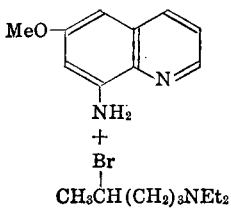
[44] Brooker et al. *J. Am. Chem. Soc.* **67**, 1896 (1945).

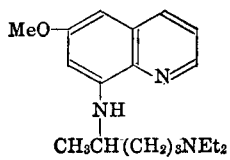
8-*Hydroxyquinoline*, oxyquinoline, is prepared by the Skraup reaction on *o*-aminophenol. It forms characteristic complexes with various metallic ions and its insoluble copper salt is a valuable fungicide for impregnation of fabrics, leather, etc. The sulfonic acid salt, $(C_9H_{10}N)_2H_2SO_4$, Chinosol, is a bactericidal agent.[45]

All seven quinoline moncarboxylic acids are known. The 2-acid, *quinaldinic* acid, m. 156°, and the 4-acid, *cinchoninic* acid, m. 254°, are made by oxidizing quinaldine and cinchonine. The *3-acid*, m. 275°, is obtained by a remarkable series of reactions starting with the condensation of aniline with *n*-butyraldehyde in presence of HCl to give *2-Pr-3-Et-quinoline*, b. 293°. This reaction is exactly analogous to the formation of quinaldine from aniline and paraldehyde. Oxidation attacks the 2-group first, giving 3-Et-quinoline-2-carboxylic acid which is readily decarboxylated to 3-Et-quinoline, b. 267°, which gives the 3-acid on oxidation. The *7-acid*, m. 247°, is made by oxidizing 7-Me-quinoline obtained by the Skraup synthesis from *m*-toluidine and *m*-nitrotoluene. The 5-, 6-, and 8-acids, m. 320°+, 292°, and 187°, can be made by the Skraup synthesis using amino- and nitrobenzoic acids with glycerol and sulfuric acid.

Quinic acid, 6-methoxyquinoline-4-carboxylic acid, m. 280°, is obtained by oxidizing quinine. *Acridinic acid*, quinoline-2,3-dicarboxylic acid, from the oxidation of acridine, loses CO_2 at 130° to give quinoline-3-carboxylic acid.

Plasmochin, pamaquin, the first of the synthetic antimalarial drugs, is made by the reaction of 1-NEt_2-4-Br-pentane, *Noval Bromide*, on 8-NH_2-6-MeO-quinoline.

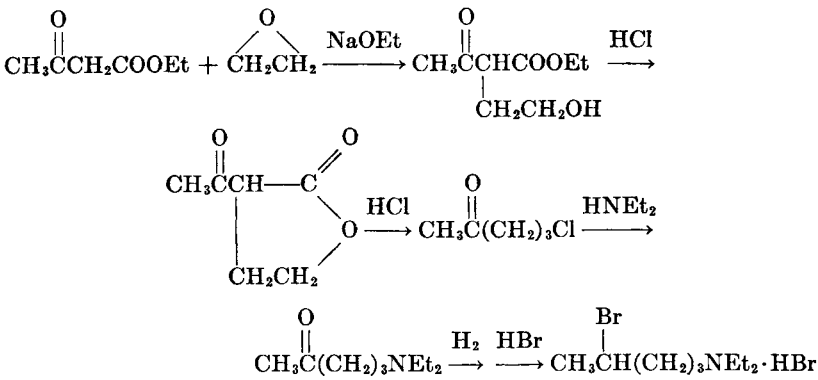




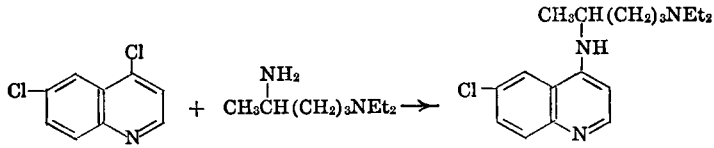
By using 1-isopropylamino-5-Cl-pentane instead of *Noval Bromide*, *pentaquine*,[46] SN 13276, a compound which is more active and less toxic than Plasmochin is obtained. 8-NH_2-6-MeO-quinoline is obtained by reduction of the nitro compound which is formed in the Skraup reaction on 2-NO_2-MeO-aniline.[47] The aliphatic aminohalide is obtained from acetoacetic ester *via* α-acetyl-

[45] Benignus. *Ind. Eng. Chem.* **40**, 1426 (1948).
[46] Drake et al. *J. Am. Chem. Soc.* **68**, 1529 (1946).
[47] "Org. Syntheses."

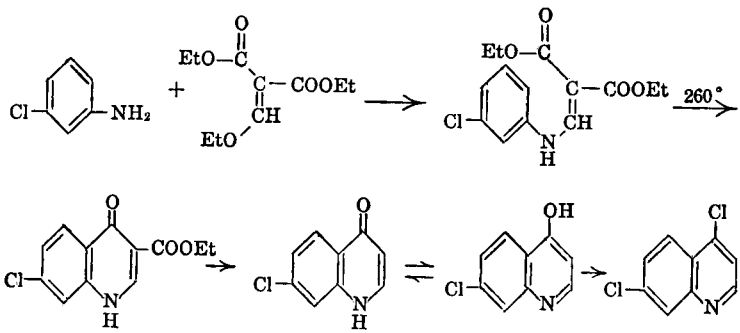
butyrolactone (USI).



A certain amount of rearrangement occurs in the formation of the secondary bromide. This is minimized by the use of thionyl bromide.[48] Reductive amination of 1-NEt_2-4-pentanone, *Noval Ketone*, gives 1-NEt_2-4-NH_2-pentanone, *Noval Diamine*. This is used in the synthesis of *chloroquine* (SN 7618).



4,7-Cl_2-quinoline is made by the condensation of ethoxymethylenemalonic ester, *EMME*, with *m*-Cl-aniline followed by ring closure upon heating to 260° in boiling diphenyl ether, hydrolyzing, decarboxylating, and treating with $POCl_3$.[49]

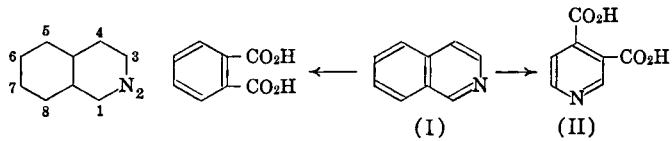


[48] Elderfield et al. *J. Am. Chem. Soc.* **68**, 1516, 1579 (1946).
[49] Price, Roberts. *J. Am. Chem. Soc.* **68**, 1204 (1946).

This reaction is adaptable to the preparation of a great variety of quinoline compounds. In the reaction of the 4,7-Cl_2-quinoline with the aliphatic diamine, only the 4-Cl is replaced since it is reactive, just as is 2- or 4-Cl-pyridine while the 7-Cl is inert just as in chlorobenzene.

Nupercaine is the β-diethylaminoethyl amide of 2-butoxyquinoline-4-carboxylic acid. It is a local anesthetic and has found special use in spinal anesthesia. *Cincophen* or *Atophan*, 2-phenylquinoline-4-carboxylic acid, is an analgesic and antipyretic with action similar to the salicylates. It has been used in the treatment of rheumatic fever and gout but is known to cause liver damage. *Chinosol, 8-OH-quinoline*, is an analytical reagent for several metal ions and is commonly used for the determination of magnesium. It is also an antiseptic. Iodination and sulfonation gives 8-OH-7-I-5-SO_3H-quinoline, *Chinofon* or *Yatren*, which is also an antiseptic and is used in the treatment of ameobic dysentery. Treatment with iodine chloride gives 5-Cl-7-I-8-OH-quinoline, *Vioform*.

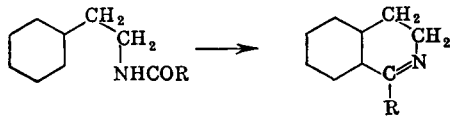
Isoquinoline, (I) m. 24°, b. 240°, is βγ-benzopyridine while quinoline is αβ-benzopyridine. Its structure is proved by its oxidation to give phthalic acid and cinchomeronic acid (II).



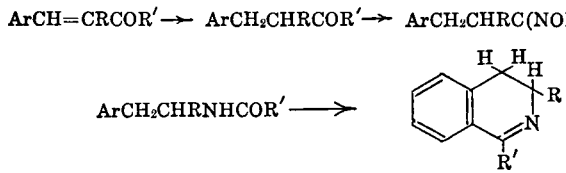
(I) (II)

It is best separated from crude quinoline from coal tar by alternate crystallization of the sulfates and fractional distillation of the bases.

The N-acyl derivatives of β-arylethylamines undergo ring closure to give 3,4-dihydro-isoquinolines.

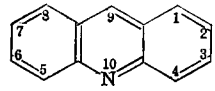


A method of making a variety of such acylamines starts with the unsaturated ketones readily obtained by condensing an aromatic aldehyde and a ketone.



These reactions are of great importance in alkaloid syntheses.

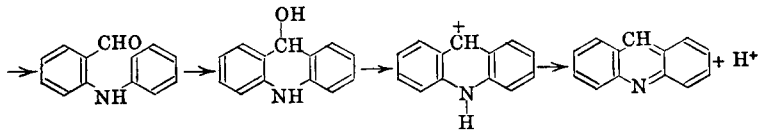
Acridine, m. 108°, b. 346°, 2,3,5,6-dibenzopyridine, occurs in crude anthracene from coal tar. It shows analogies to pyridine and to anthracene. The evidence for a para bond in the middle ring is about like that for one in anthracene.



A different numbering system is employed in the British literature. It can be oxidized to quinoline-2,3-dicarboxylic acid and to pyridine-2,3,5,6-tetracarboxylic acid. It has been synthesized in a variety of ways including:

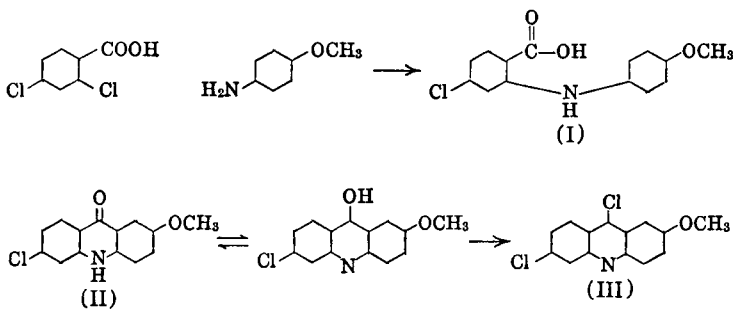
1. The action of formyldiphenylamine with $ZnCl_2$. This has been assumed to indicate a para bond.

2. The action of Cu and Na_2CO_3 on a mixture of iodobenzene and *o*-aminobenzaldehyde. The steps involved may be the following:



The removal of the OH group leaves the C^+ with only six electrons which induces an allylic shift to give a pyridine ring. Acridine is a tertiary base, weaker than quinoline. It gives *acridinium compounds.* Its dihydro derivative, m. 169°, is not basic. In structure, the latter is related to diphenylamine.

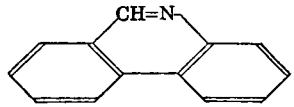
3. The method of Ullmann. An N-phenylanthranilic acid derivative such as I is treated with H_2SO_4. An internal cyclic dehydration takes place with the formation of an acridine, in this case 2-MeO-6-Cl-9-acridone (II).



If $POCl_3$ is used instead of H_2SO_4, the 9-Cl compound, III, is formed directly. *Atabrine, Atebrin, mepacrine, quinacrine,* 2-Meo-6-Cl-9-(δ-diethylamino-α-methylbutylamino)acridine, the antimalarial drug, is formed by the reaction of III with 1-diethylamino-4-aminopentane.

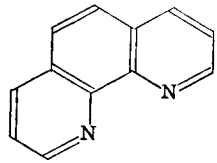
Aminoacridines are used as dyes and antiseptics; metaphenylene diamine and formaldehyde react in the presence of $ZnCl_2$ to give 3,6-$(NH_2)_2$-acridine, the monohydrogen sulfate of which is *Proflavin*. The quaternary methochloride derivative is *Acriflavin*. *Acridine Yellow*, 2,8-$(NH_2)_2$-3,7-Me_2-acridine hydrochloride, is obtained in an analogous manner; *m*-aminodimethylaniline similarly gives *Acridine Orange*. By using benzaldehyde in place of formaldehyde, the 9-phenyl derivatives, *Benzoflavine* and *Acridine Orange R Extra*, respectively, are obtained.

Phenanthridine bears the same relation to phenanthrene that acridine does



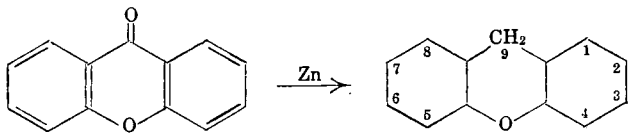
to anthracene. It occurs in coal tar and can be made by heating formaminodiphenyl, benzylidene aniline or N-Me-carbazole. The tendency to form the conjugated pyridine ring is notable.

1,10-Phenanthroline, *ortho-phenanthroline*, m. 117°, is prepared by heating

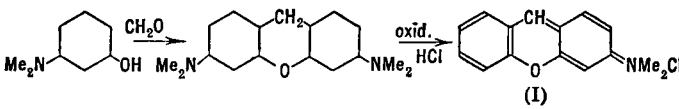


either 8-aminoquinoline or *o*-phenylenediamine with glycerol, nitrobenzene, and sulfuric acid.[50] It is used as an oxidation-reduction indicator.

Xanthone, dibenzo-γ-pyrone, 9-ketoxanthene, m. 174°, b. 355°, is obtained by heating salicylic acid with acetic anhydride. Distillation with zinc dust gives the parent substance *xanthene*, m. 100°, b. 315°.



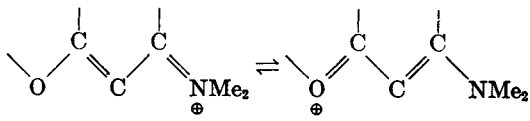
Treatment of xanthone with NaOH and Zn gives xanthydrol, the 9-OH compound. *Euxanthone*, 1,7-dihydroxyxanthone, occurs as a glucoside in mango leaves. *Pyronine*, formorhodamine, (I), is made from formaldehyde and *m*-dimethylaminophenol.



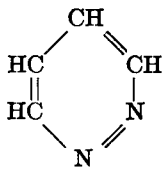
(I)

[50] Smith, Getz. *Chem. Rev.* 16, 113 (1935).

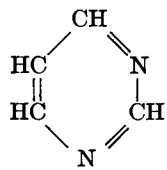
It is in equilibrium with the corresponding oxonium salt



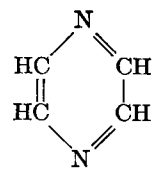
D. THE DIAZINES



Pyridazine
b. 208°

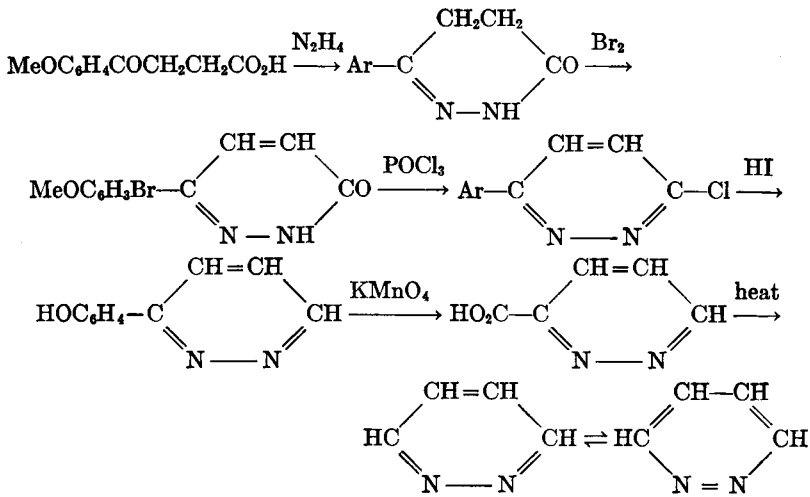


Pyrimidine
m. 22°, b. 124°



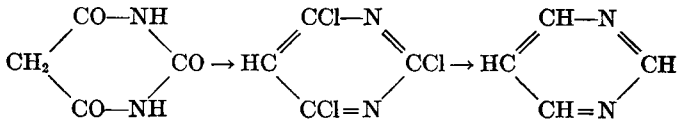
Pyrazine
m. 47°, b. 118°

The preparation of *pyridazine* involves the following steps starting with anisole, succinic anhydride and $AlCl_3$ to give *β-p*-anisoylpropionic acid.

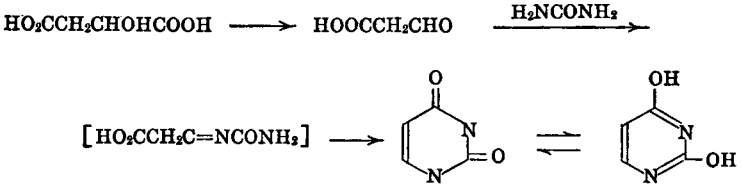


Many of these reactions serve to emphasize the analogy of pyridazine to pyridine and to illustrate its aromatic nature. Its surprisingly high boiling point is like those of pyrazole (188°) and imidazole (256°) rather than those of its isomers. Benzopyridiazines, such as *phthalhydrazide*, 1,4-dihydroxyphthalazine, are made by the reaction of phthalic acid or its derivatives with hydrazine.

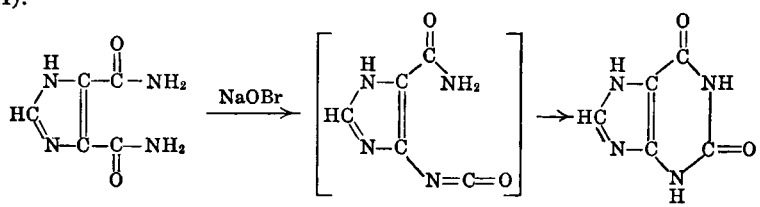
Pyrimidine is the parent member of a very large group of compounds including the barbiturates (page 434), the purines (pg. 438–44), and other natural products. It can be made by the action of zinc dust and water on the 2,4,6-Cl_3-derivative obtained from barbituric acid and $POCl_3$.



Pyrimidine itself is very difficult to obtain in contrast to pyridine and quinoline. *Uracil*, 2,4-dihydroxypyrimidine, is obtained as one of the hydrolytic cleavage products of the nucleic acids, and is formed by treating a fuming sulfuric acid solution of urea with malic acid. The malic acid acts like a typical α-OH acid, losing CO and H_2O to form an aldehyde, formylacetic acid, which then reacts with the urea.



Thiouracil, 2-thio-4-hydroxypyrimidine, which is made in the same manner with the substitution of thiourea for urea, decreases the metabolic rate in humans and is used in the treatment of hyperthyroidism. 6-*n*-Propylthiouracil is a superior drug in thyroid therapy since the incidence of agranulocytosis is materially less. Various fused ring derivatives of uracil have been formed *via* the Hofmann rearrangement of ortho dicarboxyamides. Thus methyl glyoxaline-4,5-dicarboxyamine (I) gives the purine derivative xanthine (II).

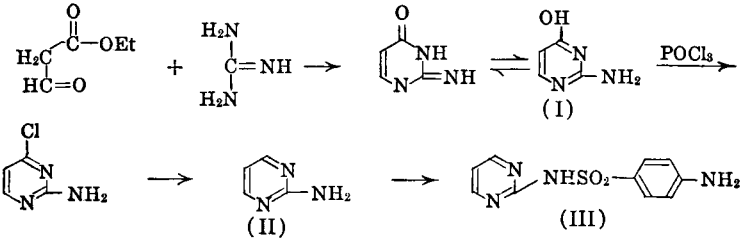


This is a general reaction and has been used for the synthesis of purine nucleosides.[51]

2-Aminopyrimidine (II), which is used for the synthesis of *sulfadiazine* (III), is prepared from isocytosine (I), 2-amino-4-hydroxypyrimidine. *Isocytosine* may be made as indicated for uracil by substitution of guanidine for

[51] Baxter, McKean, Spring. *J. Chem. Soc.* 1948, 523.

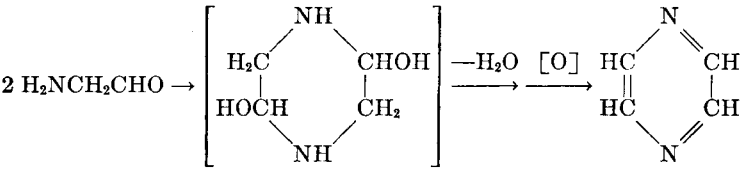
urea, but it is made commercially by condensing formylacetic ester with guanidine.



By using acetoacetic ester instead of formyl acetic ester in the same series of reactions [51a], 2-amino-6-methylpyrimidine and *sulfamerazine* are formed.

Quinazoline derivatives, benzopyrimidines, are readily obtained from anthranilic acid and related compounds. *2,4-Dihydroxyquinazoline*, benzoylene urea, is prepared from anthranilic acid and urea or potassium cyanate.[51b]

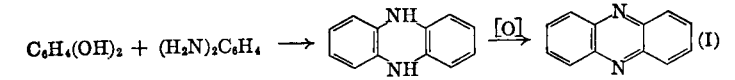
Pyrazine can be made from its carboxylic acids and by oxidation of aminoacetaldehyde with $HgCl_2$ and a base.



The last step is like that of the oxidation of dihydro derivatives of acridine and anthracene. Quinoxaline on oxidation gives *pyrazine-2,3-dicarboxylic acid.* This can be either totally or partially decarboxylated to pyrazine or pyrazine-2-carboxylic acid. This latter compound can be converted through the amide and a Hofmann degradation into *2-aminopyrazine*, the intermediate in the synthesis of *sulfapyrazine.*

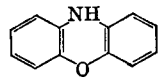
Piperazine, diethylenediimine, hexahydropyrazine, m. 104°, b. 145°, is made from ethylene dichloride and ammonia.

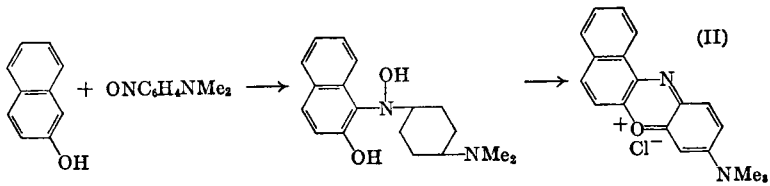
Quinoxaline, 2,3-benzopyrazine, m. 30°, b. 226°, can be made from *o*-phenylene diamine and glyoxal. *Phenazine*, (I) 2,3,5,6-dibenzpyrazine, m. 171°, is obtained as yellow crystals by heating nitrobenzene, aniline and NaOH at 140° or by oxidizing the colorless dihydro compound obtained by heating pyrocatechol and *o*-phenylenediamine.



Phenazine dyes contain OH or NH_2 groups.

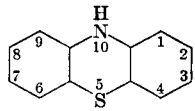
[51a] Organic Syntheses.
[51b] Organic Syntheses.

Phenoxazine, $C_{12}H_9ON$, m. 156°  can be regarded as the parent substance of the leuco bases of the *phenoxazine dyes* such as *Meldola's Blue* (II) obtained from β-naphthol and *p*-nitrosodimethylaniline.



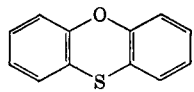
The Cl is, of course, ionic and the oxonium salt is in equilibrium with the corresponding ammonium salt (p. 804).

Phenothiazine, m. 185°, is a valuable anthelminic.

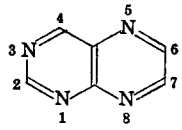


It is formed by the fusion of diphenylamine with sulfur. The dye *methylene blue*, 3,7-$(NMe_2)_2$-phenothiazine chloride, is the best known derivative.

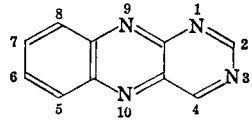
Phenothioxin, b. 180° (10 mm.), m. 55°, is the oxygen, sulfur analog of phenothiazine.



Several fused heterocyclic ring systems are of special interest. Pyrimidopyrazines [52] constitute the nucleus of pterin coloring materials that form the pigments of certain butterfly wings, and are also found in the scales of certain fish, the hypodermis of crab, in various insects, and in the vitamin, folic acid. A fused benzopyrazino-pyrimidine forms the alloxazine nucleus which is found in lumiflavin, lumichrome and riboflavin.



Pterin

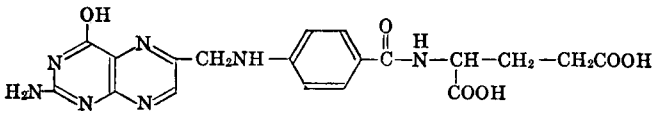


Alloxazine

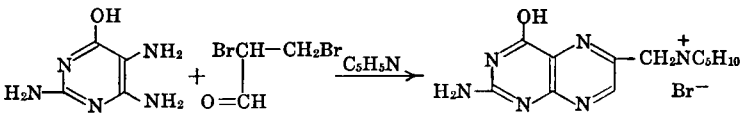
Folic acid, vitamin B_c, norite eluate factor, liver *L. casei* factor, is a vitamin found in green foliage, yeast, liver, *etc.* It is necessary for growth of

[52] Gates. *Chem. Rev.* 41, 63 (1947).

certain bacteria and yeast and is also necessary for normal growth and hemoglobin formation in chicks. It is successfully used to treat certain forms of anemia in man. It gives three substances on degradation, 2-amino-4-hydroxypteridine-6-carboxylic acid, *p*-aminobenzoic acid, and glutamic acid. These are joined as shown in the formulas.[53]

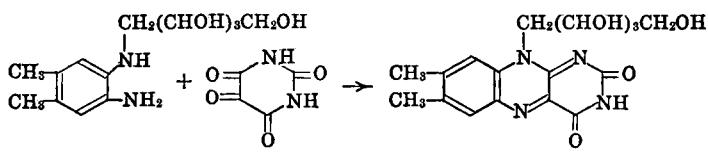


The pteridine portion of the molecule has been synthesized by the following condensation.



The treatment of this product with *p*-aminobenzoyl-L(-)-glutamic acid gives folic acid. Adequate quantities of the synthetic vitamin are commercially available.

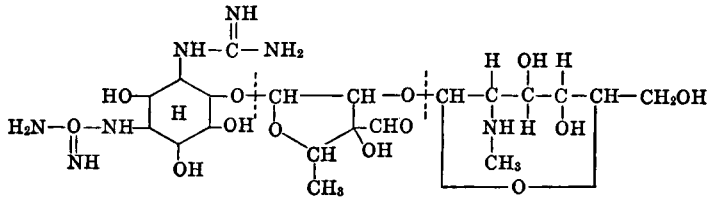
Riboflavin, vitamin B_2, lactoflavin, 6,7-dimethyl-9-D-ribityl-isoalloxazine, is a water-soluble substance found in milk whey and is responsible for the yellow-green fluorescence of the latter. It is obtained in substantial quantity as the by-product in certain fermentations and is also produced synthetically. Riboflavin is necessary in the human diet to prevent certain conditions including keritits and corneal vascularization. In the form of its phosphoric acid ester, it serves as a coenzyme important in cell respiration. Riboflavin has been synthesized by the condensation of alloxan with 4,5-dimethyl-2-aminophenylribamine.[54]



The alloxan may be replaced by its equivalent, 5,5-dichlorobarbituric acid.[55] The difficulties in the commercial adaptation of this synthesis have been in obtaining sufficiently large quantities of relatively pure *o*-xylene and of ribose. Riboflavin is very sensitive to sunlight, being converted quantitatively into *lumichrome*, 6,7-dimethylalloxazine, in neutral solution and primarily into *lumiflavin*, 6,7,9-trimethylisoalloxazine, in alkaline solution.

[53] SybbaRow et al. *J. Am. Chem. Soc.* **70**, 14 (1948).
[54] Kuhn, Weygard. *Ber.* **68**, 1282 (1935).
[55] Tishler et al. *J. Am. Chem. Soc.* **67**, 2165 (1945).

Streptomycin, $C_{21}H_{39}O_{12}N_7$, is an antibiotic extracted from the culture broths of *Actinomyces griseus*, which shows strong bactericidal power, especially against Gram-negative bacilli. Degradation studies have shown that it is split into three fragments, designated *streptidine*, *streptanose*, and *N-methyl-L-glucosamine*. The results of intensive study indicate that these units are joined as shown in the following molecular formula. Hydrolysis at the dotted lines gives the indicated fragments.



It has not been synthesized. It is noteworthy that the sugar unit belongs to the L family, the unnatural form. In a similar manner, the β,β-dimethylcysteine obtained from the antibiotic penicillin belongs to the unnatural D series of amino acids.

Alkaloids

Originally all nitrogenous compounds related to plants were classed as alkaloids. The group has been gradually limited as more information has become available as to the structure of the individual compounds. The alkaloids are mainly complex basic compounds which occur in plants as salts with organic hydroxy acids such as malic, citric, tannic and quinic acids. Isolation of alkaloids is often accomplished by means of extraction with immiscible solvents, crystallization of salts, chromatographic adsorption or ion exchange media.

Simple alkaloids such as coniine and nicotine contain only C, H and N and are volatile. The majority also contain oxygen and are crystalline. Most of them are tertiary amines. All are optically active.

The alkaloids are apparently built up by relatively simple reactions involving α-H atoms, carbonyl, amino and hydroxyl groups, including ring formation.[56]

Alkaloids give precipitates with reagents such as phosphomolybdic acid, potassium mercuric iodide solution, KI_3 solution and tannin. Much knowledge on the structure of individual alkaloids has been achieved by a great variety of processes including the following:—

1. Acetylation to give the number of *hydroxyl* groups.

[56] Robinson. *J. Chem. Soc.* 111, 876 (1917). *Ann. Rep. Chem. Soc.* (London) **1917**, 135; **1919**, 155.

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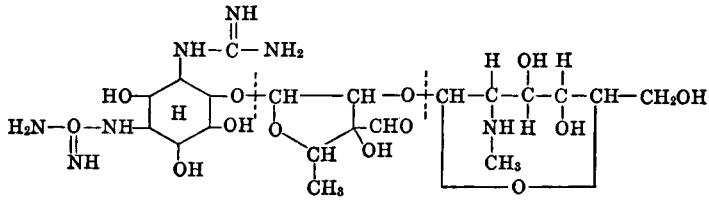

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2. Suitable treatment with HI to give the number of *methoxyl* groups (Zeisel)[57] and *NMe* groups.

3. Determination of $-NH_2$ and $=NH$ groups.

4. Hydrolysis.

5. Oxidation or dehydrogenation as by Se.

6. Exhaustive methylation.

7. Degradation to more stable substances by heating with alkalies or with zinc dust.

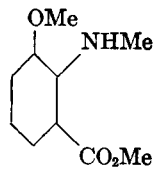
8. Ultraviolet and infrared absorption spectra.

Formulas and physical properties of the alkaloids, Lange's Handbook; classification, Thorpe's Dictionary; chemistry, Henry, "The Plant Alkaloids;" analytical methods, Allen, "Commercial Organic Analysis," vol. 7; Manske and Holmes, "The Alkaloids."

The simpler alkaloids consist of one ring or of two rings attached as in diphenyl. In a few cases the N is external to the ring but usually it forms part of a ring as in pyrrole and pyridine.

A. Derivatives of Aryl Substituted Amines

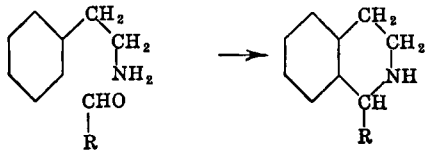
The simplest alkaloid of this type is *damascenine*, a derivative of anthranilic acid.[58, 59]



A benzyl amine derivative is *capsaicin*, the active principle of paprika. It is the vanillyl amide of a decylenic acid,

$$4\text{-}(OH)\text{-}3(OMe)\text{-}C_6H_3CH_2NHCO(CH_2)_4CH=CHCHMe_2.$$

β-Phenylethylamine derivatives occur as such in important alkaloids and serve as building units for the numerous isoquinoline alkaloids.



[57] Niederl, Niederl. "Organic Quantitative Microanalysis." John Wiley and Sons Inc., 1942, p. 239.

[58] Ewins. *J. Chem. Soc.* **101**, 544 (1912).

[59] Kaufmann, Rothlin. *Ber.* **49**, 578 (1916).

The mold *penicillium notatum* can utilize β-phenylethylamine to synthesize the potent antibiotic *penicillin*.

Tyramine, β-*p*-hydroxyphenylethylamine, $HOC_6H_4CH_2CH_2NH_2$, m. 161°, occurs in ergot and is formed in the putrefaction of proteins by decarboxylation of tyrosine. It has been synthesized. *Hordenine* (anhaline), m. 118°, is its NMe_2 derivative. *Mescaline* is 3,4,5-trimethoxyphenylethylamine,

$$(MeO)_3C_6H_2CH_2CH_2NH_2.$$

α-Fagarine is believed to belong to this group but its exact structure is in doubt.[60]

Ephedrine has been used medicinally for 5000 years. The naturally occuring levo form is the most active physiologically. An ingenious synthesis of the optically active base starts with the fermentation of sugar in the presence of benzaldehyde to give levo-phenylacetylcarbinol. The active ketoalcohol is then condensed with methylamine and reduced.

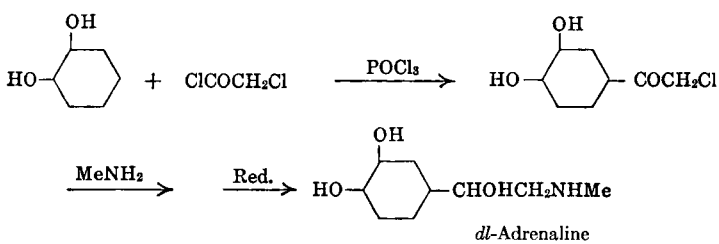
$$C_6H_5CHOHCOCH_3 + MeNH_2 \xrightarrow{H_2} \underset{\text{Ephedrine}}{C_6H_5CHOHCH(NHMe)CH_3}$$

Pseudoephedrine, m. 118°, differs from its stereoisomer in the configuration of the α-carbon. Isomerization of *l*-ephedrine by acids gives an equilibrium mixture with *d*-pseudoephedrine.

Propadrine is nor-ephedrine. It is made synthetically as follows from propiophenone.

$$C_6H_5COCH_2Me \xrightarrow[HCl]{RONO} C_6H_5COCMe \underset{\|}{} NOH \xrightarrow{H_2} C_6H_5CHOHCHNH_2Me$$

Adrenaline, epinephrine, from the suprarenal glands, was the first hormone to be isolated. It has been synthesized as follows, starting with pyrocatechol and chloroacetyl chloride.



dl-Adrenaline

d-Tartaric acid is used to separate the *d*- and *l*-forms. The latter is the natural form and is some twenty times as effective in raising the blood pressure. The

[60] Surrey. *J. Am. Chem. Soc.* **70**, 2887 (1948).

d-form is racemized by heating with acid and the resulting *dl*-mixture is further separated.

Many derivatives of β-phenylethylamine have been synthesized and a number are used in medicine. They usually increase the blood pressure and stimulate the sympathetic nervous system. In this series is found one of the best known correlations of the effect of chemical structure on physiological activity.

Benzedrine, 1-phenyl-2-aminopropane, is prepared from phenylacetone by the Leuckart reaction.

$$C_6H_5CH_2COCH_3 \xrightarrow[\text{or } HCONH_2]{HCOONH_4} C_6H_5CH_2CH(NHCHO)CH_3 \xrightarrow{HCl} C_6H_5CH_2CH(NH_2)CH_3$$

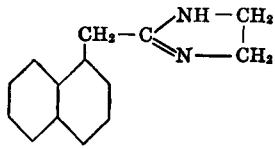
Neosynephrine, *m*-$HOC_6H_4CHOHCH_2NHCH_3$, is prepared by a modification of the adrenaline synthesis.

Cobefrine, (nor-homo-adrenaline), 3,4-$(HO)_2C_6H_3$-$CHOHCHNH_2CH_3$, is synthesized by the method used for propadrine.

Vonedrine is synthesized from 2-phenylpropylchloride and methylamine.

$$C_6H_5CH(CH_3)CH_2Cl + MeNH_2 \rightarrow C_6H_5CH(CH_3)CH_2NHMe$$

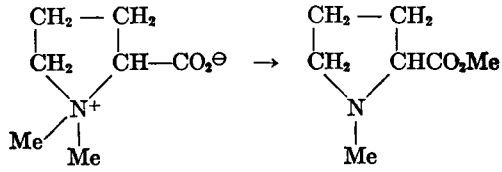
The presence of the β-methyl group is significant in that it is similar pharmacologically to a hydroxyl group. The characteristic effects of β-phenylethylamine derivatives are retained in *Privine,* 2-(1-naphthylmethyl)-2-imidazoline,



and occur also in *Tuamine,* 2-aminoheptane.

B. Derivatives of Pyrrole

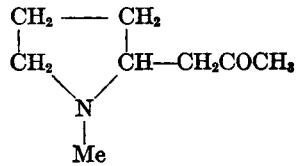
Stachydrine (I), m. 235°, is the betaine of *hygric acid,* N-methylpyrrolidine-α-carboxylic acid. Distillation gives the methyl ester.



(I)

Betonicine, dec. 244°, and *turicine,* m. 249°, are stereoisomers of 4-OH-stachydrine.

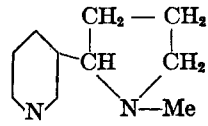
Hygrine, $C_8H_{15}ON$, is N-Me-α-pyrrolidylacetone



Oxidation gives hygric acid.

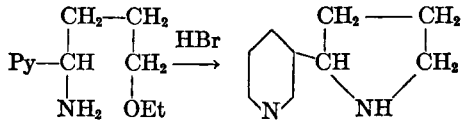
Cuscohygrine, $C_{13}H_{24}ON_2$, occurs with hygrine but is readily separated by means of its difficultly soluble nitrate. It is a symmetrically disubstituted acetone containing two N-Me-α-pyrrolidyl groups instead of one as in hygrine.

Nicotine, $C_{10}H_{14}N_2$, the chief alkaloid of tobacco, is α-(β-pyridyl)-N-Me-pyrrolidine, (II), b. 247°. Suitable oxidative degradations give pyridine-β-carboxylic acid (nicotinic acid) and N-Me-pyrrolidine-α-carboxylic acid, (hygric acid).



(II)

Of several nicotine syntheses only one will be given. This is from pyridine through its β-sulfonic acid and β-cyano compound.[61] The latter is converted by $EtO(CH_2)_3MgBr$ to a ketone which is changed to its oxime. Reduction and ring closure give nornicotine (III) which is methylated to give *r*-nicotine.



(III)

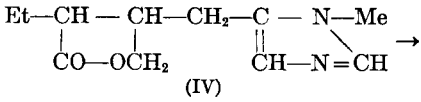
Myosmine is (III) with two less H in the pyrrolidine ring.[62]

Carpaine, $C_{14}H_{25}O_2N$, is a pyrrolidine with an α-side chain of 10 carbons including a lactone grouping. Oxidation gives suberic acid.

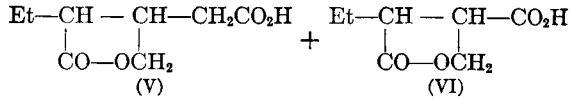
[61] Craig. *J. Am. Chem. Soc.* **55**, 2854 (1933).
[62] Späth, Wenush, Zajic. *Ber.* **69B**, 393 (1936).

C. Imidazole Derivatives

The fundamental grouping in *pilocarpine* (IV), $C_{11}H_{16}N_2O_2$, m. 34°, is shown by distillation with Zn dust to form 1-Me- and 1,5-Me_2-imidazole. Oxidation gives homopilopic (V) and pilopic acids (VI)



(IV)

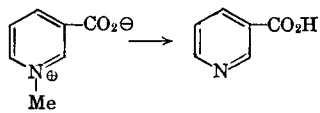


(V) (VI)

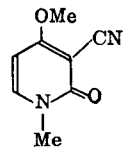
Pilocarpine has been synthesized.[63]

D. Derivatives of Pyridine and Piperidine

Trigonelline is the betaine of pyridine-β-carboxylic acid. It is cleaved by heating with pyridine hydrochloride.

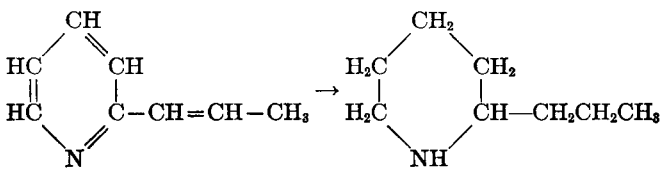


Ricinine of the castor bean is N-Me-3-cyano-4-methoxy-2-pyridone.[64, 65]



Poison hemlock contains various alkaloids including coniine, its N−Me derivative, γ-coniceine, δ-coniceine, conhydrine and pseudoconhydrine.

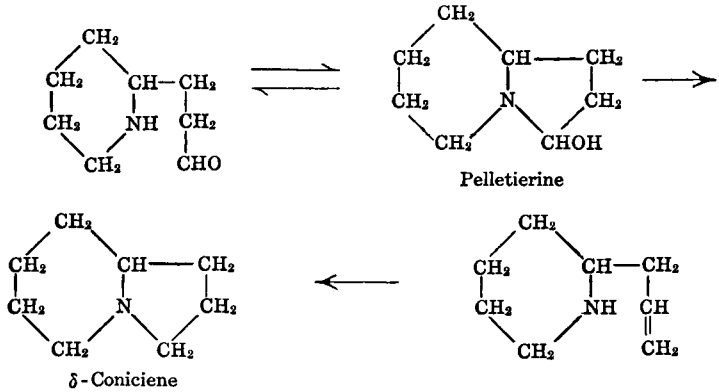
Coniine is α-*n*-propylpiperidine, b. 167°. Reduction by HI at high temperature gives *n*-octane and oxidation gives pyridine-α-carboxylic acid. The synthesis is easy by the action of Na and alcohol on α-propenylpyridine obtained from α-Me-pyridine and MeCHO.



Coniine

[63] Preobrashenski et al. *Ber.* **66B**, 1187 (1933); **69B**, 1835 (1936).
[64] Späth, Koller. *Ber.* **56B**, 880 (1923).
[65] *Ann. Rep. Chem. Soc.* (London) **1923**, 153.

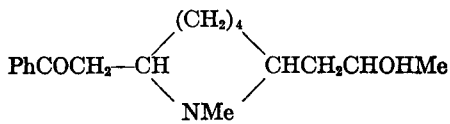
The ready reduction of even the side chain is a good example of the activating effect of the N. Heating with zinc dust gives α-propylpyridine or *conyrine*. Synthetic *dl*-coniine can be resolved by means of *d*-tartaric acid. *γ-Coniceine*, b. 174°, is Δ2-2-propyl-tetrahydropyridine. *δ-Coniceine* (I) is a fusion of a piperidine and a pyrrolidine ring.[66,67] It can be regarded as the reduction product of the cyclic form of the aldehyde pelletierine or the cyclization product of an allylpiperidine.



Conhydrine has an α-hydroxyl group in the side chain of coniine whereas *pseudoconhydrine* is 5-OH-coniine.

Pelletierine and **isopelletierine** have $-CH_2CH_2CHO$ and $-CH_2COCH_3$ respectively in place of the propyl group of coniine. Since pelletierine does not react with nitrous acid it is believed to exist in a cyclic form.[68] *Pseudopelletierine* (p. 824) has a $-CH_2COCH_2-$ bridge between the α-positions of N-Me-piperidine and thus contains a fusion of a piperidine and a γ-piperidone ring.

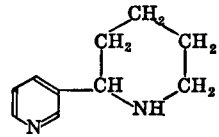
Lobeline (lobelidine) is an N-Me-piperidine substituted in one α-position by $PhCOCH_2-$ and in the other by $PhCHOHCH_2-$. Related are *lobelanine* and *lobelanidine* which have respectively 2 $PhCOCH_2-$ and 2 $PhCHOHCH_2-$ in the α-positions. The corresponding *nor*-compounds contain a free NH group.[69] *Lobinine* is related to these alkaloids but has a 7-membered ring.[70]



[66] Chattaway, Wünsch. *J. Chem. Soc.* **95**, 129 (1909).
[67] *Ann. Rep. Chem. Soc.* (London) **1909**, 102.
[68] *Ann. Rep. Chem. Soc.* (London) **1918**, 109.
[69] *ibid.* **1929**, 169.
[70] *Ann. Rep. Chem. Soc.* (London) **1931**, 165.

The betel nut (areca-nut) contains *guvacine*, 1,2,5,6-H_4-pyridine-3-carboxylic acid, m. 293°, *arecaine* or *arecaidine*, its NMe compound, m. 232°, and their methyl esters, *guwacoline* and *arecoline* respectively.

Anabasine is β-(α-piperidyl)-pyridine.[71]



Piperine, m. 128°, the piperidide of piperic acid, occurs in pepper, 3,4-$(CH_2O_2)C_6H_3CH=CHCH=CHCONC_5H_{10}$. Other pungent materials such as *capsaicin*, *spilanthol* and *pellitorine* have also been shown to be substituted amides of unsaturated acids.[72]

E. Complex Alkaloids

These contain condensed or fused ring systems. In some, the N appears in only one ring, while in others it functions as part of two or three heterocyclic rings. The following formal (not preparative) relationships are of interest.

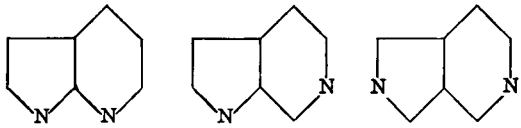
I. Nitrogen in one ring.

1. Rings with 2 C atoms in common.

a. Benzene and pyrrole give indole and isoindole. Strychnine and brucine are related to the former. A benzene ring and two pyrrolidine rings form the parent substance of eserine.

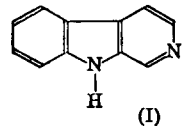
b. Benzene and pyridine give quinoline and isoquinoline. The former is found in the cinchona alkaloids and to the latter are related many important groups of alkaloids including the anhalonium group, papaverine, narcotine, berberine and even morphine.

c. A pyrrole and a pyridine ring may be fused with 2 C atoms in common in six ways. The following three fusions are found in calycanthine.



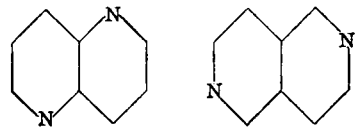
[71] Orekhov. *Ber.* **67B**, 1606 (1934).
[72] *Ann. Rep. Chem. Soc.* (London) **1930**, 202.

The former is found in harman (I), the parent substance of harmine and harmaline.



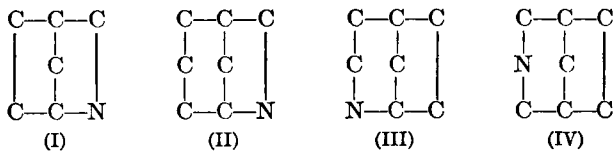
(I)

d. The following two fusions of two pyridine rings are also found in calycanthine.

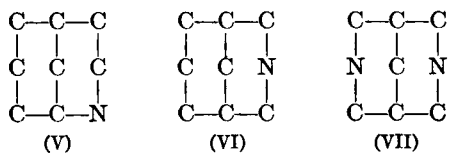


There are four other possible fusions of two such rings.

2. Rings with 3 C atoms in common. Using 5- and 6-membered rings the following might be possible.



(I) (II) (III) (IV)

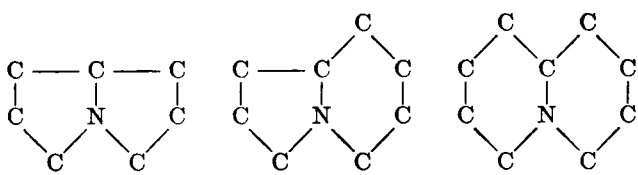


(V) (VI) (VII)

Only (I) involves any considerable strain. In (V) and (VI) there is no strain. System (V) as related to morphine and thebaine is called *mornuclidine*. In (VII) two pyridine rings have the γ- and both β-carbons in common. This grouping is found in sparteine, cytisine and anagyrine.

II. Nitrogen common to two or three rings.

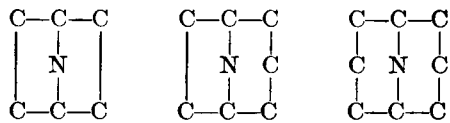
1. Fusion with N and 1 C common to both rings.



The first is pyrrolizidine which occurs in retronecine, the nitrogenous part of a number of senecio alkaloids. The second is found in δ-coniceine, lycorine, calycanthine and some of the erythrina alkaloids. Related to the last grouping are lupinine, berberine, corydaline, sparteine, and julolidine. The first involves considerable strain and the last none at all. The fusion of *two* N-rings in similar ways gives the combinations found in vasicine and in rutaecarpine and evodiamine respectively.

2. Fusion with N and 2 C common to both rings. This can happen in two ways, the N having either two or three of its valences involved in ring formation.

a. Two valences of N in ring combination.

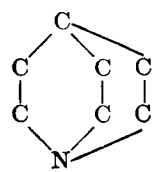


Again, a condensation of two pyrrolidine rings is apparently impossible but a combination of a pyrrolidine and a piperidine ring involves little strain and gives such important alkaloids as atropine and cocaine. Two piperidine rings can be fused without any strain giving the parent substance of pseudopelletierine.

b. Three valences of N in ring combination. None of the possibilities is found in known alkaloids. The N in such a system would be under serious strain.

3. Fusion with N and 3 C common to two rings.

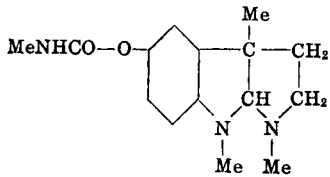
In the *quinuclidine* portion of such important alkaloids as cinchonine and quinine the N forms part of three condensed piperidine rings which have it and the γ-C in common. This structure is entirely strainless.



F. Alkaloids Containing Pyrrole Rings Fused with Other Rings

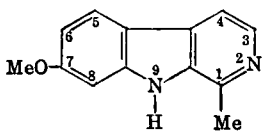
The strychnine alkaloids belong to this class since they are related to indole. Because of their importance they will be considered separately.

Physostigmine, eserine, $C_{15}H_{21}O_2N_3$ (I), contains a pyrrolidine ring condensed with dihydroindole. It is the N-Me-carbamate of the phenol, *eseroline*, and it has been synthesized.[73]

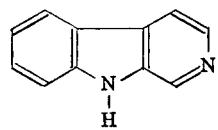


(I)

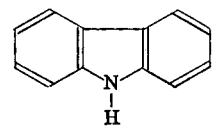
Harmine (II) is related to a carbazole (IV) with the 2-CH replaced by N.[74]



(II)

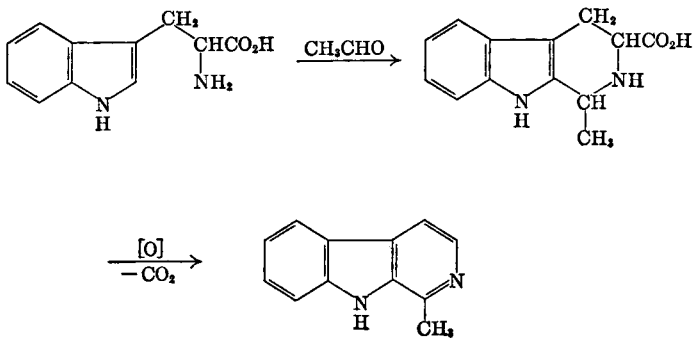


(III)



(IV)

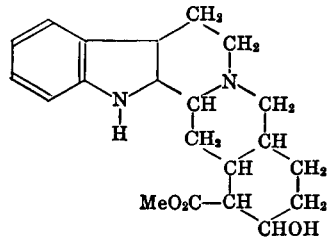
The parent substance is β-carboline or 2,9-pyrindole (III). *Harmaline* is 3,4-dihydroharmine. *Harman*, 1-Me-β-carboline, is conveniently made by condensing *dl*-tryptophan with acetaldehyde and oxidizing the product.[75]



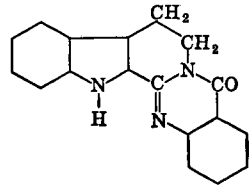
[73] Julian, Pikl, Boggess. *J. Am. Chem. Soc.* **56**, 1797 (1934).
[74] Kermack, Perkin, Robinson. *J. Chem. Soc.* **121**, 1872 (1922).
[75] Snyder et al. *J. Am. Chem. Soc.* **70**, 222 (1948).

Tetrahydroharman can be prepared readily from acetaldehyde and 3-β-aminoethylindole at room temperature at pH 5–7.[76,77]

Yohimbine, $C_{21}H_{26}O_3N_2$, is related to harmine and probably has the following structure.[78]

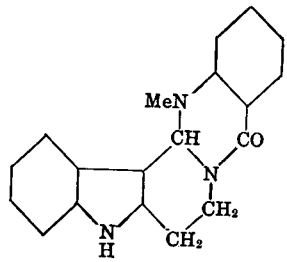


Rutaecarpine combines a pyrrole, a pyridine and a pyrimidine ring with two benzene rings.



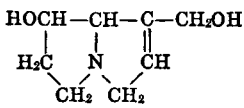
Hydrolysis gives anthranilic acid and 1-keto-1,2,3,4-H_4-carboline. The latter has been synthesized.[79]

Evodiamine is similarly related to N-Me-anthranilic acid and 3,9-pyrindole[80] (cf. III, p. 819).

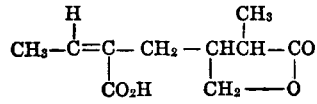


[76] Hahn, Ludewig. *Ber.* **67B**, 2031 (1934).
[77] *Ann. Rep. Chem. Soc.* (London) **1934**, 267.
[78] Witkop. *Ann.* **554**, 83 (1943).
[79] *Ann. Rep. Chem. Soc.* (London) **1927**, 161.
[80] *ibid.* **1921**, 142.

Retronecine, $C_8H_{13}O_2N$(I), is the basic portion of *senecionine* in which it is esterified with senecic acid, probably (II).



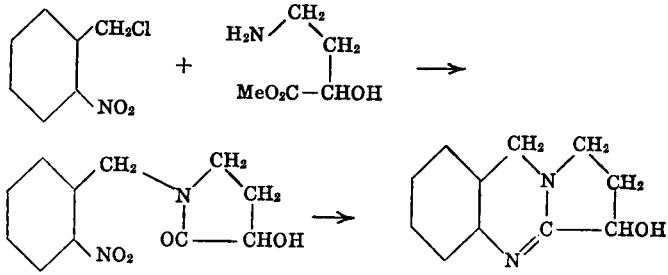
(I)



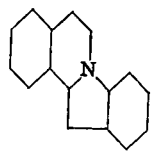
(II)

Other senecio alkaloids are esters of retronecine or related pyrrolizidine bases and a variety of acids believed to be derived from monoterpenes.[81]

Vasicine, peganine, $C_{11}H_{12}ON_2$, contains a benzpyrimidine nucleus fused through C_2 and N_3 with a pyrrolidine ring. It has been synthesized from *o*-nitrobenzyl chloride and methyl 4-amino-2-hydroxybutyrate. Reduction of the nitro group was accompanied by ring closure.[82]



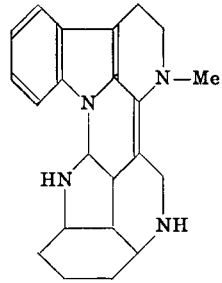
Erythrina alkaloids[83] have fused isoquinoline and indole systems. The parent ring structure is common to erythramine, erythraline and erythratine.



Calycanthine, $C_{22}H_{26}N_4$,[84, 85] is believed to have the following formula in-

[81] *Ann. Rev. Biochem.* 1942 (1944).
[82] Späth, Kuffner, Platzer. *Ber.* 68, 699 (1935).
[83] Folkers, Koniuszy, Shavel. *J. Am. Chem. Soc.* 64, 2146 (1942).
[84] Manske, Marion. *Can. J. Research* 17B, 293 (1939).
[85] Chen, Powell, Chen. *J. Am. Pharm. Assoc.* 31, 513 (1942).

volving seven rings.



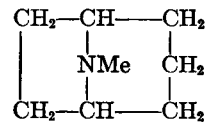
These include two benzene, two pyrrole, and three pyridine rings, all except one of which are partially or completely hydrogenated. Considering adjacent fused pairs of rings, the formula contains nine combinations including two indoles, one quinoline, two combinations of fused pyridine rings, three fusions of a pyridine and a pyrrole ring and a combination in which one N and one C serve in common in a pyridine and a pyrrole ring (pp. 817–818).

Gelsemine, $C_{20}H_{22}O_2N_2$, belongs to this group since it can be degraded to skatole and a base $C_{11}H_{11}N$ which is probably a dimethylisoquinoline.[86]

Aspidospermine, $C_{22}H_{30}O_2N_2$, is a new type of indole alkaloid which can be degraded to an alkyl indole and 3,5-dimethyl-3-ethylpyridine.[87]

G. Tropine Alkaloids

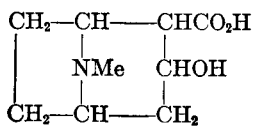
These contain fused pyrrolidine and piperidine rings with the N serving as a bridge across a 7-C ring. They can also be regarded as piperidine derivatives with a $-CH_2CH_2-$ bridge between the alpha positions.



Tropane

Tropine is the $\gamma-OH$ derivative of tropane.

Coca leaves contain cocaine, cinnamoyl cocaine, benzoyl ecgonin, and α- and β-truxilline, all related to ecgonine (tropine carboxylic acid) and also *tropacocaine*, the benzoic ester of pseudotropine.

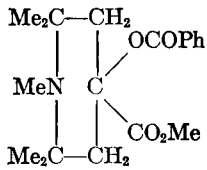


Ecgonine

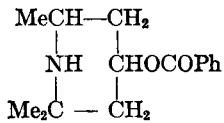
[86] Witkop. *J. Am. Chem. Soc.* **70**, 1424 (1948).
[87] *ibid.* **70**, 3712 (1948).

In *cocaine* the carboxyl group of ecgonine is methylated and the hydroxyl group is benzoylated. Because of its value as a local anesthetic and in the hope of producing a substitute which is not habit-forming, many modifications of the cocaine molecule have been made. α-Cocaine, which has no anesthetic action, is made from tropinone by the cyanohydrin synthesis and thus has the $-OCOPh$ and $-CO_2Me$ groups both on the $\gamma-C$ of the piperidine ring. Putting other alkyl groups in place of methyl in cocaine has little effect on its action. Very few acids besides benzoic acid give anesthetic compounds when esterified with ecgonine.

Alpha Eucaine (I) and Beta Eucaine (II) are made from triacetoneamine and from diacetoneamine respectively.



(I)

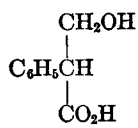


(II)

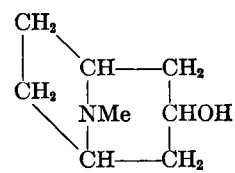
Useful substitutes for cocaine in local anesthesia are the *p*-aminobenzoates of the alkamines such as novocaine (procaine) and Butyn.

Cinnamoyl cocaine has the cinnamoyl group in place of the benzoyl group in cocaine. α- and β-Truxilline are esters of ecgonine methyl ester with α- and β-truxillic acids.

Atropine, m. 115°, is the ester of *dl-tropic acid,* α-phenylhydracrylic acid, m. 118°, (III) and tropine (IV).



(III)



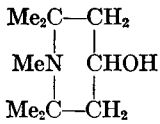
(IV)

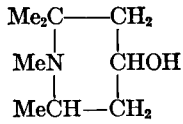
Tropine (IV), m. 63°, b. 233°, and *pseudotropine,* m. 108°, b. 241°, are stereoisomers, differing in the configuration of the OH group. Both are optically inactive.

Tropinone is the ketone corresponding to (IV). It has been synthesized from succinic dialdehyde, acetone dicarboxylic ester and methylamine, a remarkable example of ring closure. *Tropeines* are esters of tropine. Certain of these have mydriatic action (dilation of pupil of the eye) similar to that of atropine. *Homatropine* and *pseudoatropine* are synthetic tropine esters of

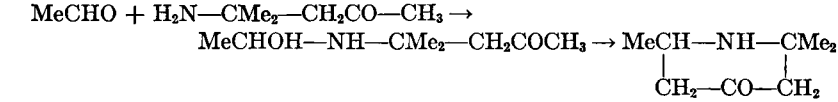
mandelic acid and atrolactic acid respectively. *Hyoscyamine*, m. 108°, is the tropine ester of *l*-tropic acid.

Substitutes for atropine have been made not only from tropine but from synthetic substances containing somewhat similar groupings. Thus the mandelic esters of the following two substances have mydriatic action, the second combination being used as *Euphthalmine*.

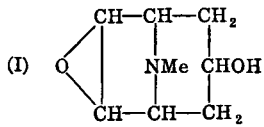




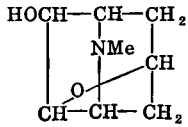
The first is made by methylating and reducing triacetoneamine while the second is made by similar processes on the condensation product of acetaldehyde and diacetoneamine.



Scopolamine, hyoscine, is the tropic ester of *scopine*, (I) a tropine molecule with an epoxy group between the two β-positions of the pyrrolidine ring. On treatment with acids, bases or heat, this rearranges to *scopoline* (II) which has an oxygen bridge between the γ-position of the piperidine ring and a β-position in the pyrrolidine ring thus forming a tetrahydrofuran ring.[88]



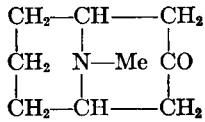
(I)



(II)

H. Alkaloids Containing a Fusion of Two Piperidine Rings

Pseudopelletierine (III), N-methylgranatonine, may be regarded as a cyclooctanone ring with a symmetrical N-Me bridge or as a fused structure combining an N-Me-piperidine and an N-Me-γ-piperidone, the N-Me and the two $\alpha-$C atoms being common to both rings.



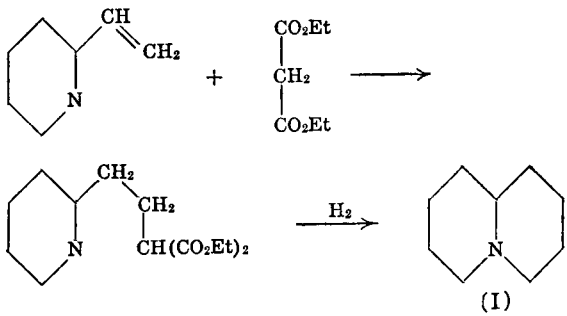
(III)

[88] *Ann. Rep. Chem. Soc.* (London) 1922, 160.

It has been synthesized by condensing glutaric dialdehyde, acetonedicarboxylic ester and methylamine at 25° in a solution buffered to pH 7.[89] *Isopelletierine*, instead of having a $-CH_2COCH_2-$ bridge across the α-positions of an N-Me piperidine, simply has the group $-CH_2COCH_3$ in one α-position of piperidine and is thus related closely to coniine.

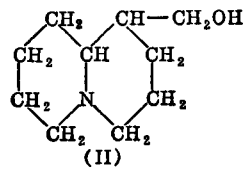
I. Lupine Alkaloids

These contain two piperidine rings with the N and one $\alpha-C$ in common. The parent substance, *norlupinane* (quinolizidine) (I), can be made by hydrogenation of diethyl β-(2-pyridyl)-ethylmalonate, prepared by the Michael addition of 2-vinylpyridine to diethyl malonate.[90]



(I)

Lupinine (II), m. 69°, has not been synthesized.

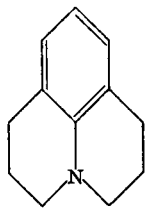


(II)

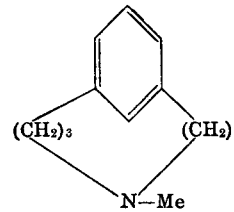
Julolidine (III) can be synthesized from tetrahydroquinoline and trimethylene chlorobromide.[90a] It forms a MeCl compound which can be reduced by NaHg with opening of the bond between the N and the benzene ring to give a compound containing a 10-membered ring across the meta

[89] Schöpf, Lehmann. *Ann.* 518, 1 (1935).
[90] Boekelheide, Rothchild. *J. Am. Chem. Soc.* 69, 3149 (1947).
[90a] Organic Syntheses.

positions in a benzene ring (IV).[91,92]

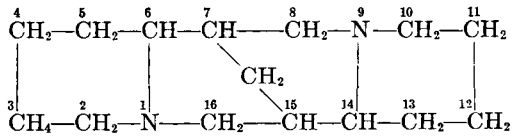


(III)

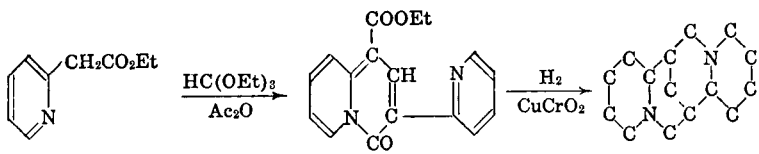


(IV)

Sparteine and related alkaloids contain the lupinane system (II).[93–98] Sparteine, $C_{15}H_{26}N_2$, (V), consists of a four-ring system each half of which contains a lupinane grouping. The middle of the system contains two piperidine rings with the γ- and both β-carbons in common.



Sparteine has been synthesized in two steps from ethyl-2-pyridylacetate.[99]

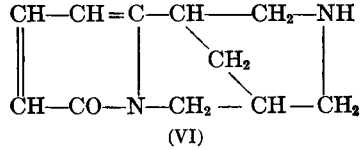


(V)

Lupanine, $C_{15}H_{24}ON_2$, is 2-ketosparteine and *anagyrine*, $C_{15}H_{20}ON_2$, is 2-keto-3,4,5,6-tetra*de*hydrosparteine. Catalytic reduction of anagyrine gives lupanine while further reduction gives sparteine. *Monolupine*, $C_{16}H_{22}ON_2$, and *rhombinine* are identical with anagyrine.[100] *Cytisine*, $C_{11}H_{14}ON_2$

[91] v. Braun, Heider, Wyczatkowska. *Ber.* **51**, 1215 (1918).
[92] v. Braun, Neumann. *Ber.* **52**, 2015 (1919).
[93] Ing. *J. Chem. Soc.* **1933**, 504.
[94] Clemo, Raper. *J. Chem. Soc.* **1933**, 644.
[95] Winterfeld, Rauch. *Arch. Pharm.* **272**, 273 (1934).
[96] *Ann. Rep. Chem. Soc.* (London) **1934**, 279.
[97] Robinson. *Biol. Rev.* **1935**, 498.
[98] Couch. *J. Am. Chem. Soc.* **58**, 688 (1936).
[99] Leonard, Beyler. *J. Am. Chem. Soc.* **70**, 2298 (1948).
[100] Marion, Ouelett. *J. Am. Chem. Soc.* **70**, 3076 (1948).

(VI),[101–103] differs from anagyrine by not having carbons 10–13.

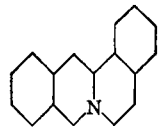


(VI)

Matrine is related to cytisine.

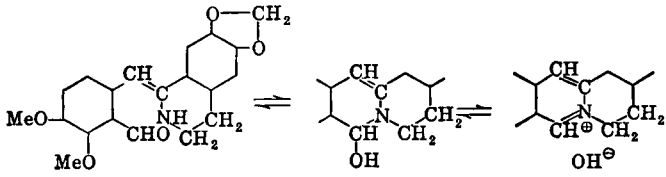
J. Berberine Alkaloids

These contain the lupinane system (p. 825, I) fused with two benzene rings, one in linear and the other in angular combination. The skeleton is as follows:



They can also be regarded as di-isoquinoline combinations in which the N is common to both isoquinoline groups and one carbon serves as C_1 and C_3 respectively in the two systems. The corresponding *paraberberine* compounds in which the four rings are linearly combined do not occur in nature and are very difficultly prepared.[104]

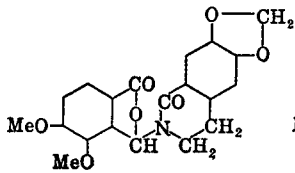
Berberine, $C_{20}H_{19}O_5N$, m. 145°, shows a peculiar tautomerism found also in cryptopine and protopine. Since it contains the grouping O–C–N–C it can also react in an aldehyde form. It moreover acts as a quaternary ammonium compound. These relations are shown in the following formulas for berberine



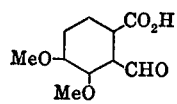
Mild oxidation converts the CHOH to CO giving oxyberberine. Another product involves the breaking of the double bond to give a carboxyl and a ketone. The former gives a lactone with the OH forming *berberal* (I). This on

[101] Ing. *J. Chem. Soc.* **1932**, 2778.
[102] *Ann. Rep. Chem. Soc.* (London) **1933**, 235.
[103] Späth, Galinovsky. *Ber.* **69**, 761 (1936).
[104] *Ann. Rep. Chem. Soc.* (London) **1926**, 170.

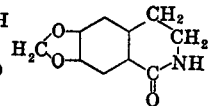
hydrolysis gives *pseudo-opianic acid* (II) and *noroxyhydrastinine* (III)



(I)

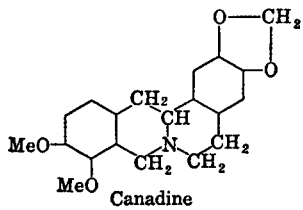


(II)



(III)

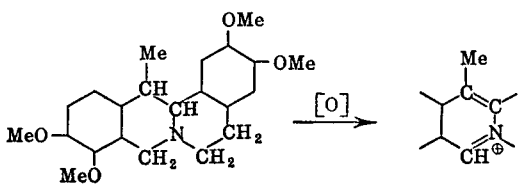
Protoberberine is the berberine molecule without substituents in the aromatic rings. *Coptisine* is 2,3,9,10-bismethylenedioxyprotoberberine.[105] *Palmatine* similarly has four $-$OMe groups.[106] *Canadine*, $C_{20}H_{21}O_4N$, can be made by reduction of berberine and is called tetrahydroberberine. It contains no double bond or hydroxyl in the lupinane system. Oxidation gives berberine.



Canadine

Capaurimine has the same skeleton as canadine but has 2 HO and 3 MeO groups.[107]

Isocorypalmine, sinactine and **H_4-berberrubine** are related to canadine.[108] *Corydaline*, $C_{22}H_{27}NO_4$, (IV) is structurally related to canadine but has 2 MeO groups in place of the O_2CH_2 grouping and has a Me in the 7-position of the lupinane system (N = 1). Mild oxidation gives *dehydrocorydaline*, $C_{22}H_{25}NO_5$, (V) corresponding to berberine.



(IV) (V)

Oxidation of corydaline gives *hemipinic* and *metahemipinic acids*, 3,4- and 4,5-dimethoxyphthalic acids respectively, and *corydaldine*, 1-keto-6,7(MeO)$_2$-

[105] *ibid.* 1926, 167.
[106] *ibid.* 1927, 168; 1929, 178.
[107] Manske. *J. Am. Chem. Soc.* 69, 1800 (1947).
[108] *Ann. Rep. Chem. Soc.* (London) 1928, 192; 1931, 173.

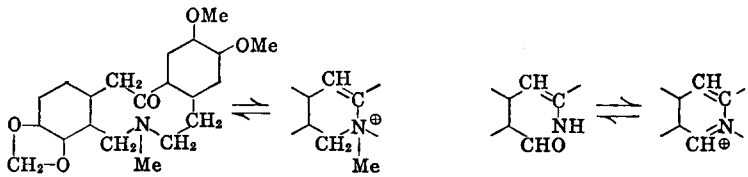
1,2,3,4-H_4-isoquinoline.[109] *Corybulbine*, $C_{21}H_{25}O_4N$, *isocorybulbine*, $C_{21}H_{25}O_4N$, and *bulbocapnine*, $C_{20}H_{19}O_4N$, are related to corydaline.[110]

Emetine, $C_{29}H_{40}O_4N$, is believed to have the corydaline system fused with isoquinoline. It may be prepared by methylation of *cephaeline*, $C_{28}H_{38}O_4N$, with phenyltrimethylammonium hydroxide.

K. Cryptopine Alkaloids

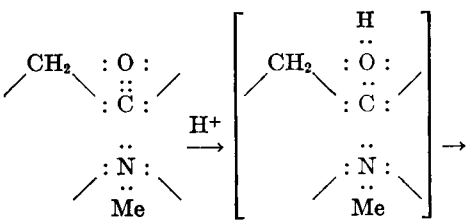
These contain a 10-membered ring such as would be obtained by breaking the bond between N and C in the middle of the lupinane section of the berberine molecule.[111]

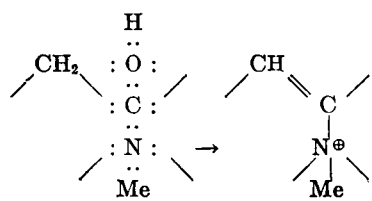
Cryptopine, $C_{21}H_{23}NO_5$, m. 219°, has formula (I) while *protopine*, $C_{20}H_{19}NO_5$, m. 208°, differs from it only in having a methylene ether grouping in place of the two MeO groups. Acids cause ring closure to give salts of (II). This change is entirely analogous to the conversion of the aldehyde form of berberine (III) to a salt of (IV).



(I) (II) (III) (IV)

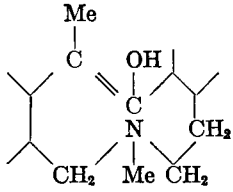
The mechanism of the action of H^+ ion is readily illustrated electronically. The addition of the proton to the oxygen of the carbonyl group leaves its

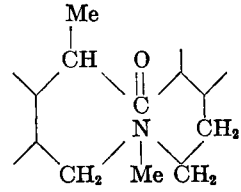




[109] *ibid.* 1934, 276.
[110] *ibid.* 1925, 149.
[111] *Ann. Rep. Chem. Soc.* (London) 1926, 168.

carbon with only 6 electrons. Since this carbon can readily approach the N in space it shares the open electron pair of the latter forming a new C—N linkage and leaving the N as a positive quaternary ammonium ion. *Corycavidine* is like cryptopine but with the O_2CH_2 and two OMe in opposite rings and a Me on the carbon between the ring and the CO group. *Corycavine* and *corycavamine* are enol and keto forms of a similar homolog of protopine. The central portions of their molecules have the following structures:

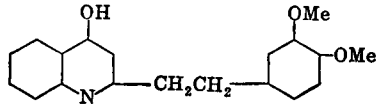




L. Quinoline Alkaloids

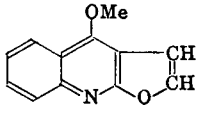
A few simple derivatives have been found in natural products such as angostura bark which gives 2-*n*-amylquinoline, the corresponding 4-methoxy compound and even small amounts of quinoline and 2-Me-quinoline as well as the N-Me-2-keto-dihydro compound.[112]

Galipoline contains a homoveratryl group attached in the 2-position of 4-HO-quinoline.

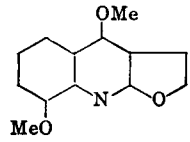


The methyl ether is *galipine* and *cusparine* has OCH_2O in place of the *o*-methoxyl groups.

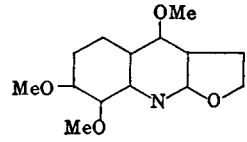
Dictamine (I) contains a quinoline condensed with a furan ring. *γ-Fagarine* (II) and *skimmianine* (III) are methoxyl derivatives.



(I)



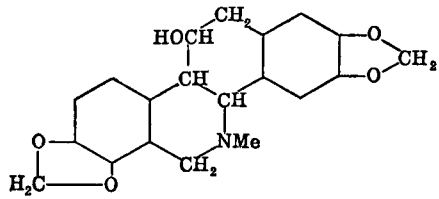
(II)



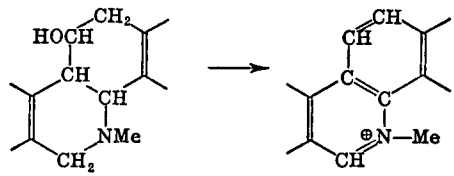
(III)

[112] *Ann. Rep. Chem. Soc.* (London) 1930, 190.

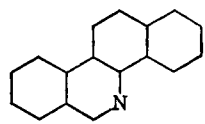
Chelidonine is related to both quinoline and isoquinoline since it contains a phenanthridine skeleton.[113]



Sanguinarine is the quaternary base related to it. The change in the central portion of the molecule is as follows:

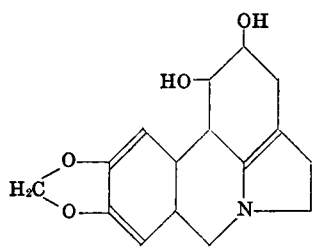


Distillation with Zn dust converts them to α-naphthaphenanthridine



Homochelidonine and **chelerythrine** are a similarly related pair having two OMe groups in the isoquinoline ring in place of the O_2CH_2 group.

Lycorine is a phenanthridine nucleus fused with a pyrrole ring.[114]

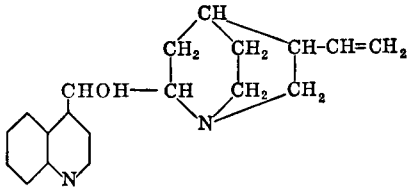


M. Cinchona Alkaloids

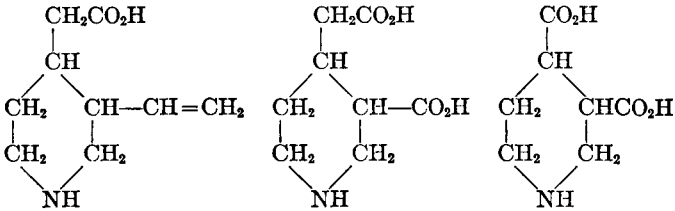
These are the most important quinoline alkaloids although their properties are more dependent on the *quinuclidine* part of the molecule, a fusion of three piperidine rings, than on the quinoline portion.

[113] *Ann. Rep. Chem. Soc.* (London) **1931**, 168.
[114] Kondo, Ikeda. *Ber.* **73B**, 867 (1940).

Cinchonine, $C_{19}H_{22}N_2O$, m. 264°, consists of a secondary alcohol group, —CHOH, attached to the 4-position of quinoline and the 2-position of 5-vinylquinuclidine.



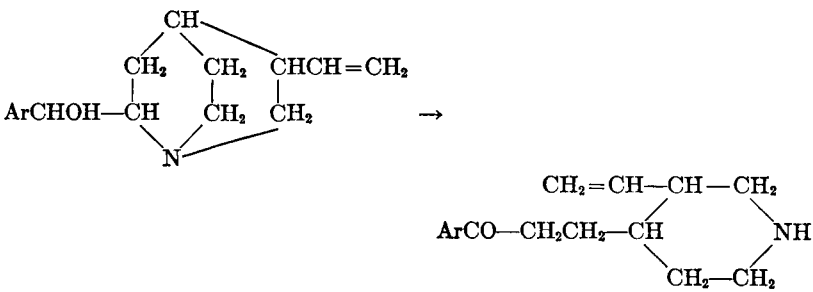
Mild oxidation converts the CHOH to CO to form *cinchoninone.* Oxidation with chromic acid gives cinchoninic acid (quinoline-4-carboxylic acid) and *meroquinene* (I) which on further oxidation gives *cincholoiponic acid* (II), then loiponic acid (III) and finally *cinchomeronic acid* (pyridine-3,4-dicarboxylic acid).



(I) (II) (III)

The quinuclidine part of the molecule can also be removed by treating cinchoninone with amyl nitrite to form cinchoninic acid and the oxime of 5-vinyl-2-quinuclidone. The same product is obtained from cinchonine and from quinine.[115] It is really an amide of an hydroxamic acid and is hydrolyzed readily to give meroquinene (I).

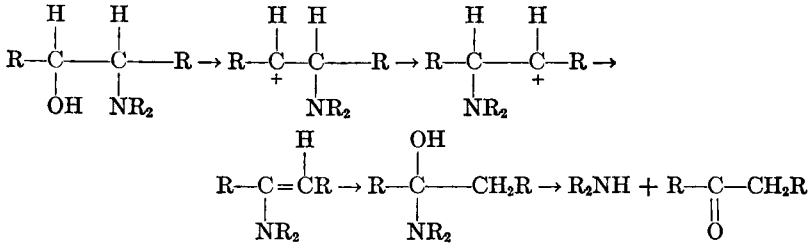
Heating cinchonine with acid causes a splitting between the N and C_2 of the quinuclidine group.



Cinchotoxine (Cinchonicine)

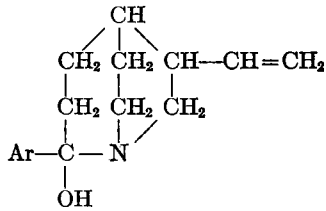
[115] *Ann. Rep. Chem. Soc.* (London) 1910, 136.

This breaking of the HO−C−C−N grouping to give O=C−C+HN fragments is characteristic. It probably goes by the same mechanism as the pinacolone rearrangement, the N shifting instead of the CH_3.



Cinchonidine, m. 207°, is a stereoisomer of cinchonine differing in the configuration of the α−C in the quinuclidine group and perhaps in the carbinol grouping.

Hydrocinchonine, m. 277°, and **hydrocinchonidine,** m. 229°, occur with cinchonine and are readily prepared by catalytic reduction in which the vinyl group is changed to ethyl. *hetero-Cinchonine* is the result of the transfer of the linkage of C_2 from the quinuclidine N to the carbinol C with the widening of one piperidine to form a 7-ring.[116]



This change is like that which gives cinchotoxine except that the primary shift is that of a C instead of N.

Quinine, $C_{20}H_{24}O_2N_2$, m. 177°, is 6-methoxycinchonine. Oxidation converts the CHOH to CO giving *quininone*, the vinyl group to carboxyl, giving *quitenine*. Further oxidation of the ketone or treatment with nitrous acid and hydrolysis gives meroquinene (I) (p. 832) and *quininic acid*, 6-methoxy-4-quinoline carboxylic acid.

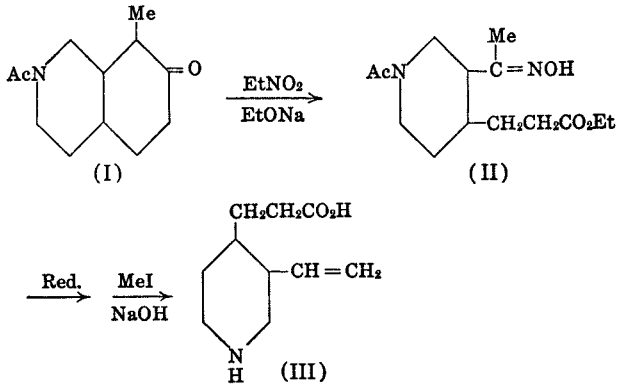
Treatment of quinine with acid opens one of the piperidine rings in the quinuclidine part of the molecule and forms *quinotoxine* entirely analogous to cinchotoxine.

The total synthesis of quinine has been accomplished.[117] 7-OH-isoquinoline was converted by the Mannich reaction and reduction to the 8-Me-derivative.

[116] *ibid.* 1934, 273.

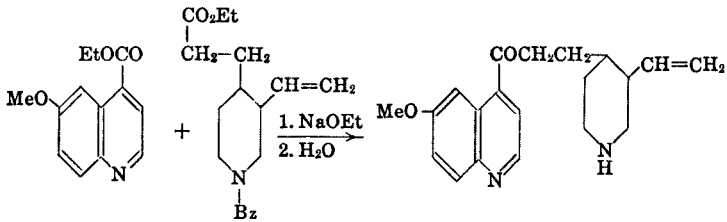
[117] Woodward, Doering. *J. Am. Chem. Soc.* **67**, 860 (1945).

Hydrogenation and oxidation of the N-acetyl derivative gave N-acetyl-7-keto-8-Me-decahydroisoquinoline (I). $EtNO_2$ and EtONa converted the latter to a derivative of dihydrohomomeroquinene (II) which by reduction and the Hofmann degradation gave homomeroquinene (III).



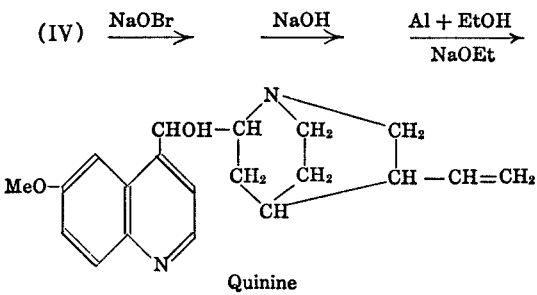
(I) (II) (III)

This was esterified and the benzoyl derivative was condensed with 6-MeO-4-carbethoxyquinoline. Hydrolysis of the benzoyl group gave quinotoxine (IV).



(IV)

The latter had been converted to quinine.[118]



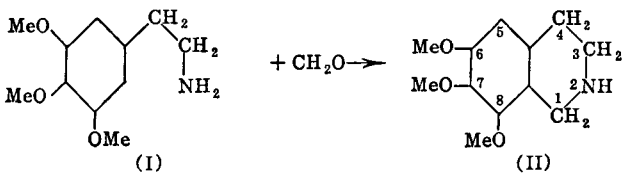
Quinine

[118] Rabe, Kinder. *Ber.* 51, 466 (1918).

Quinidine, m. 171°, **hydroquinine,** m. 172°, and **hydroquinidine,** m. 167°, are related to quinine as are the corresponding compounds to cinchonine (p. 832). *Cupreine,* m. 202°, is 6-hydroxycinchonine. Methylation converts it to quinine. *Hydrocupreine* is best made by demethylating hydroquinine with HCl at 150°. From it are prepared ethers, homologs of hydroquinine which are valuable disinfectants. *Optoquin,* the ethyl ether, has specificity for the *pneumococcus.* The $HOCH_2CH_2-$ ether is as effective and safer. *Eucupine* and *Vuzine* are the isoamyl and *sec*-octyl ethers.

N. Isoquinoline Alkaloids

The simplest type is obtainable by condensing aldehydes with hydroxy derivatives of β-phenylethyl amines, the aldehyde carbon forming C_1 of the isoquinoline. The first step is the ordinary addition of an amine to a carbonyl compound. The next is 1,6-ring closure involving the H para to the activating OH or OMe group. Thus mescaline (I) and formaldehyde react readily to give O-Me-anhalamine (II).



(I) (II)

Pellotine Me ether can be made by methylating the product of ring closure of acetyl mescaline.[119] Some of the important simple *tetrahydroisoquinolines* follow:

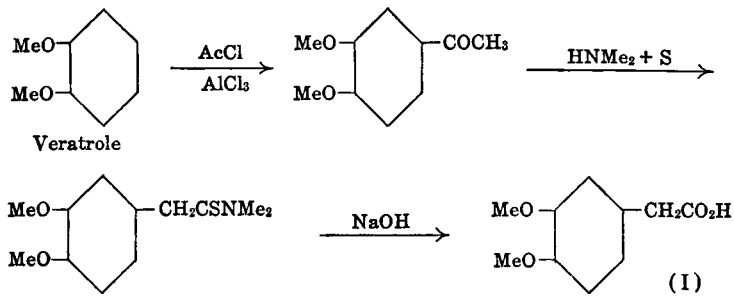
Name	Substituents, Position				
	1-	2 (N)-	6-	7-	8-
Norsalsoline	Me		OH	OH	
Salsoline	Me		OH	OMe	
Carnegine	Me	Me	OMe	OMe	
Pellotine	Me	Me	OMe	OMe	OH
Anhalonidine	Me		OMe	OMe	OH
Anhalamine			OMe	OMe	OH
Anhalidine		Me	OMe	OMe	OH
Anhalonine	Me		OMe	O—CH_2—O	
Lophophorine	Me	Me	OMe	O—CH_2—O	

O. Papaverine Alkaloids

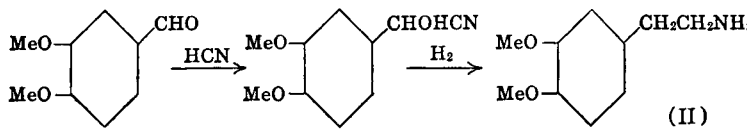
These have a benzyl group attached to the 1-position of isoquinoline. **Papaverine,** $C_{20}H_{21}O_4N_2$, m. 147°, 1-(3′,4′-dimethoxybenzyl)-6,7-dimethoxy-

[119] *Ann. Rep. Chem. Soc.* (London) **1922,** 162.

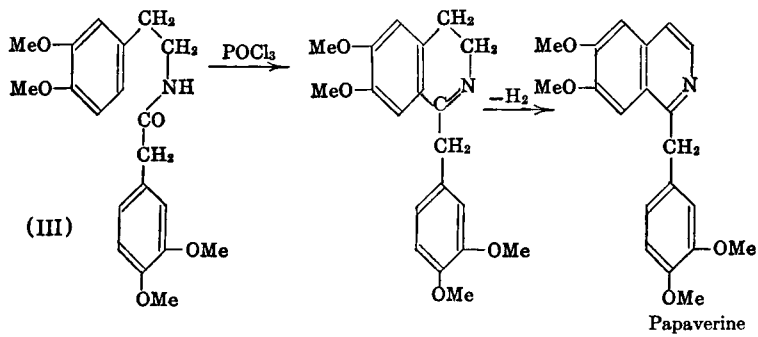
isoquinoline, and its 1,2- and 3,4-dihydro and 1,2,3,4-tetrahydroderivatives have been synthesized in a variety of ways. One of the best starts with veratrole and veratraldehyde.[120] *Homoveratric* acid (I) was prepared by means of the Willgerodt reaction.



Homoveratrylamine (II) was made from veratraldehyde.



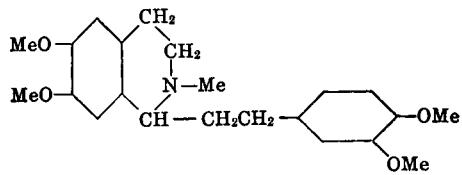
The salt of (I) and (II) on heating yielded the amide (III). Ring closure with $POCl_3$ gave dihydropapaverine which was dehydrogenated.



Papaveraldine has the CH_2 of papaverine oxidized to CO. Thus it is a 1-benzoylisoquinoline derivative. *Pavine* is 1,2-H_2-papaverine. *Laudanosine*, m. 89°, is N-Me-1,2,3,4-H_4-papaverine. *Laudanine* (laudanidine, tritopine), m. 166° is *dl*-laudanosine with the 3′-OH unmethylated. *Laudanidine* is its *l*-form.

[120] Kindler, Peschke. *Arch. Pharm.* **272**, 236 (1934).

Homolaudanosine is like laudanosine but has $-CH_2CH_2$ between the rings instead of CH_2[121]

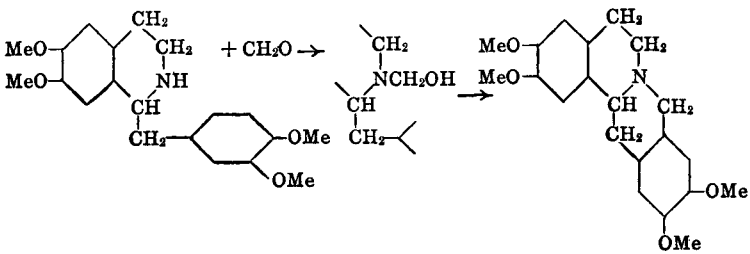


Removal of the methyls from the MeO groups gives *homolaudanosoline.*

Coclaurine has 7,4′-$(OH)_2$-6-MeO instead of the 4 MeO groups in H_4-papaverine and an N-Me group. Combination of two molecules by ether linkages in various ways gives oxycanthine, trilobine, bebeerine and related alkaloids.[122]

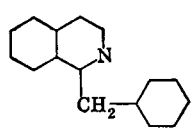
Codamine is laudanosine with a free 7-OH group.[123]

The *relation of papaverine alkaloids to those of the berberine type* may be shown by the action of formaldehyde with H_4-papaverine to give norpseudocorydaline.

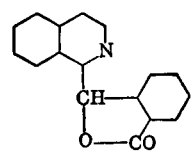


P. Phthalide Isoquinoline Alkaloids, Narcotine Alkaloids

These have a phthalide grouping attached to C_1 of isoquinoline in place of the benzyl group of papaverine.



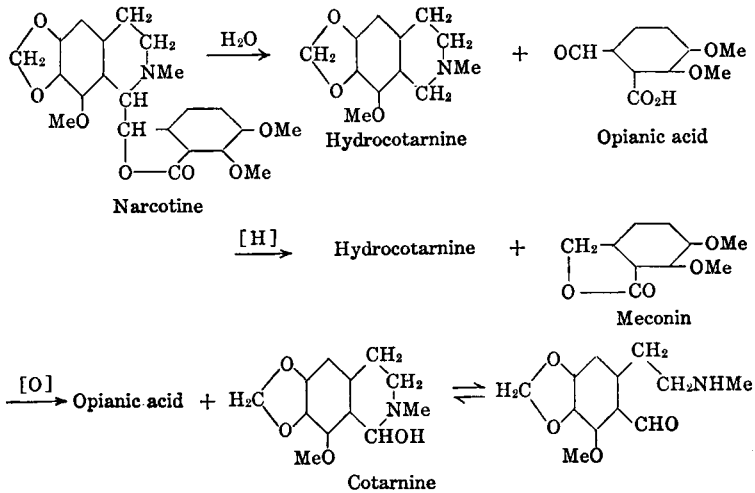
Papaverine type



Narcotine type

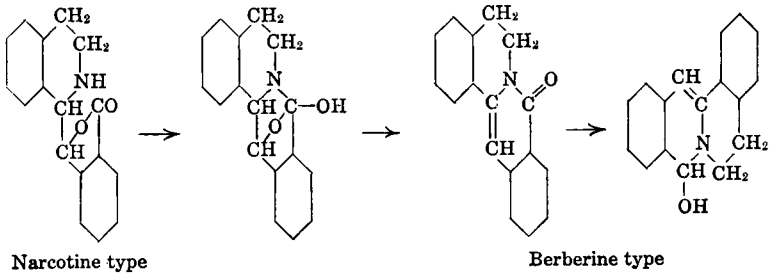
[121] *Ann. Rep. Chem. Soc.* (London) 1934, 276.
[122] *ibid.* 1942, 204.
[123] *ibid.* 1926, 165.

Narcotine, $C_{22}H_{23}O_7N$, m. 176°, one of the abundant opium alkaloids, is related to laudanosine but has a methylene ether grouping in place of the 6,7-$(MeO)_2$ and has an additional OMe in the 8-position and a lactone ring between the 2′-position and the benzyl carbon. Its hydrolysis at 140°, and its oxidation and reduction indicate its constitution.



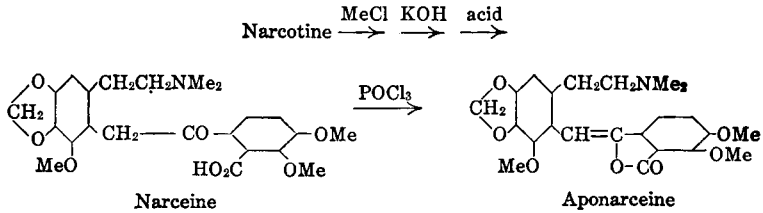
Cotarnine gives open chain compounds with hydroxylamine, acetone, etc., and ring compounds with HCl, HCN, etc. *Gnoscopine, dl*-narcotine, has been made by the condensation of meconin and cotarnine.

Meconin, m. 101°, is 5,6-dimethoxyphthalide or the lactone of 2-hydroxymethyl-5,6-dimethoxybenzoic acid. The relation of the narcotine and berberine types of alkaloids is shown schematically as follows:



Narceine, $C_{23}H_{27}NO_8.3H_2O$, m. 171°, is made by the action of alkalies on the MeCl compound of narcotine. The $-O-C-C-N$ grouping is broken at the $C-N$ linkage as in the splitting of ephedrine (p. 811) and in the con-

version of the cinchona alkaloids to toxines (p. 832). Narceine with $POCl_3$ gives *aponarceine*

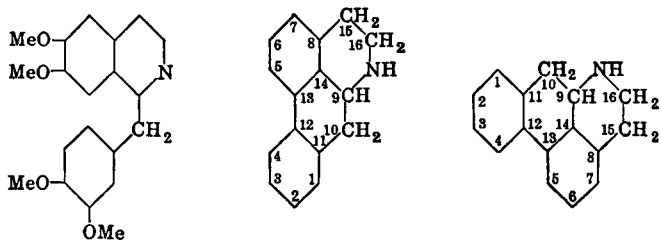


Hydrastine, $C_{21}H_{21}NO_6$, m. 132°, differs structurally from narcotine only in not having the 8-MeO group. It is not found in opium and differs from narcotine in being even less narcotic. Its oxidation gives opianic acid and *hydrastinine*, m. 117°, which is cotarnine without the 8-MeO group.[124]

Other phthalide isoquinoline alkaloids related to narcotine are *adlumine* and *bicuculline* and the free hydroxy acid of the latter, *bicucine*.[125]

Q. Aporphine Alkaloids

The parent substance, aporphine, a phenanthrene isoquinoline type, is closely related to tetrahydropapaverine.[126]



The relation to morphine is also close, C_{15} being attached through a bridge to C_{13} in the latter substance. The relation is shown by the ready conversion of morphine to apomorphine on boiling with dilute HCl (p. 840). This type of change is apparently very easy as many plants produce aporphine alkaloids whereas fewer produce the morphine and papaverine types. The aporphines contain combinations of hydroxy, methoxyl and methylenedioxy groups.

[124] *Ann. Rep. Chem. Soc.* (London) **1931**, 166.
[125] Manske. *Can. J. Research* **8**, 142, 404 (1933).
[126] *Ann. Rep. Chem. Soc.* **1924**, 136; **1927**, 173.

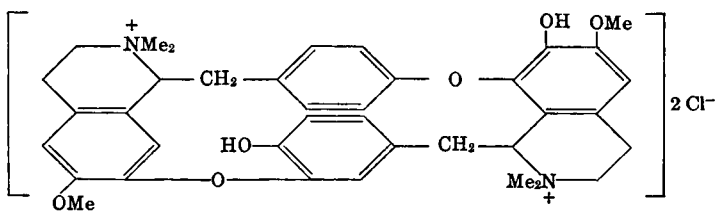
Some of the more important follow: (all have N—Me)

Aporphine alkaloid	Position of groups		
	—OH	—OMe	—OCH_2O—
Apomorphine	3,4-		
Morphothebaine	4,6-	3-	
Isothebaine	4-	3,5-	5,6-
Pukateine	4-		
Laureline		3-	5,6-
Boldine	2,6-	3,5-	
Corytuberine	4,5-	3,6-	
Laurepukine (?)	5,6		3,4-
Actinodaphnine (Domesticine)	2-	3-	5,6
Dicentrine (Isodomesticine)	3-	2-	5,6
Epidicentrine		5,6-	2,3-
Bulbocapnine	4-	3-	5,6-
Isocorydine	4-	3,5,6-	
Corydine	5-	3,4,6-	
Glaucine		2,3,5,6-	

Laurotetanine has a free NH group, being 2-OH-3,5,6-$(OMe)_3$-aporphine.

R. Bis-benzylisoquinoline Alkaloids

These involve combinations of two molecules of the papaverine type by means of ether linkages in large strainless rings.[127] The curare alkaloids belong to this group. *d-Tubocurarine chloride* is an example in which the N's are quaternary.[128] It is used in anesthesia to give muscular relaxation.

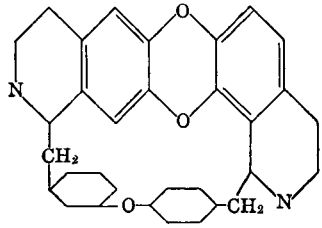


Bebeerine, chondocurine and related alkaloids have similar skeletons with the N's tertiary.

Trilobine, isotriloline and **menisarine** have two benzylisoquinoline groups

[127] *Ann. Rep. Chem. Soc.* (London) **1933**, 242.
[128] King. *Chemistry & Industry*, 739 (1935).

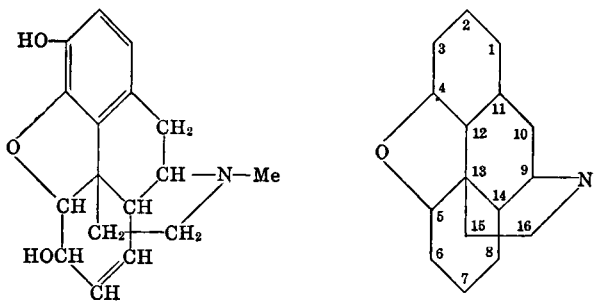
joined in a different way. They differ from each other in MeO substituents.



In **berbamine, oxycanthine** and **phaeanthine** the isoquinoline groups are joined by one O-bridge, while in **dauricine** only the benzyl groups are connected.

S. Morphine and Related Alkaloids

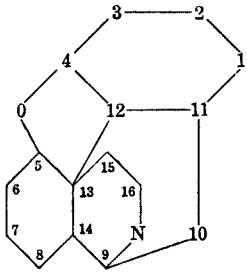
Morphine, $C_{17}H_{19}NO_3$, m. 253°, is the most important of about 25 alkaloids found in opium. The relation of the N to the rest of the molecule is less simple than in the other alkaloids. The accepted structure[129] as ordinarily written emphasizes its relation to a partially hydrogenated phenanthrene



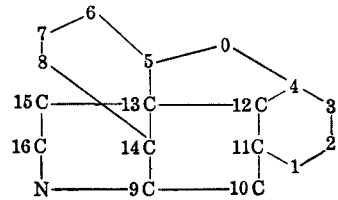
While such a formula appears awkward in two dimensions, scale models show that the $-CH_2CH_2NMe-$ bridge between the 9- and 13-positions in the phenanthrene nucleus is without strain. The molecule thus consists of the fusion of the following five rings, benzene, cyclohexane, cyclohexene, tetrahydrofuran, and piperidine. Other ways to consider the molecule are as an isoquinoline system fused with a naphthalene system across positions 9 and 13 (I) or as a mornuclidine system fused with two benzene rings in the 11,12- and 13,14-positions (II). The carbons of the supplementary rings are represented

[129] *Ann. Rep. Chem. Soc.* (London) 1926, 173.

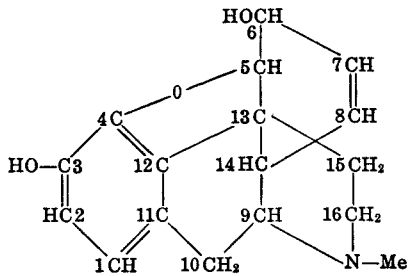
by their numbers.



(I)



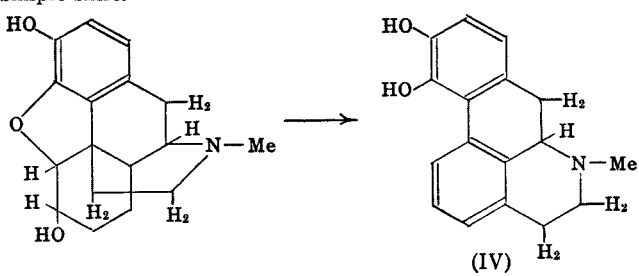
(II)



(III)

Morphine contains five asymmetric carbon atoms 6,5,13,14 and 9 which are attached in succession in an unbranched chain. This relation is shown in (III).[130]

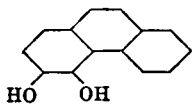
Among the many conversions of morphine, one of the easiest to produce is its conversion to *apomorphine* (IV) on warming with acids. This consists in dehydration at positions 5 and 6 with formation of a new benzene ring and the consequent shift of the N bridge from the quaternary C_{13} to C_8 thus forming a different isoquinoline ring. On scale models this change is seen to be an entirely simple shift.



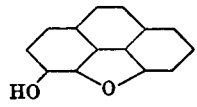
(IV)

[130] Emde. *Naturwissenschaften* 18, 539 (1930).

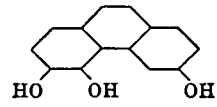
Distillation of morphine with Zn dust gives phenanthrene. The position of the oxygen atoms is shown by conversion to the phenanthrene derivatives, the 3-Me ethers of morphol (V), morphenol (VI), and 3,4,6-trihydroxyphenanthrene (VII)



(V)



(VI)

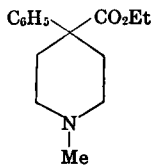


(VII)

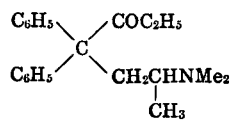
The C−C−N bridge is readily removed by any change which makes the middle ring aromatic. As shown by models the mornuclidine system can exist only because of the polyplanar nature of the cyclohexane ring. As soon as the latter is flattened by becoming aromatic, the meta bridge from C_9 to C_{13} becomes impossible.

Codeine, m. 155°, is the 3-methyl ether of morphine. It is prepared by heating the morphine salt of phenyltrimethylammonium hydroxide. *Dihydromorphinone* and *dihydrocodeinone* are the corresponding ketones at C-6. The latter undergoes an unusual nuclear methylation and opening of the O-bridge by reaction with MeMgI. The product is an intermediate for the preparation of methyldihydromorphinone (Metopon).[131] Morphine and the above mentioned derivatives are used as analgesics. Those having free phenolic groups are more potent than the corresponding Me-ethers.

Demerol (I) and **Methadon** (Amidone) (II) are synthetic compounds having analgesic action.

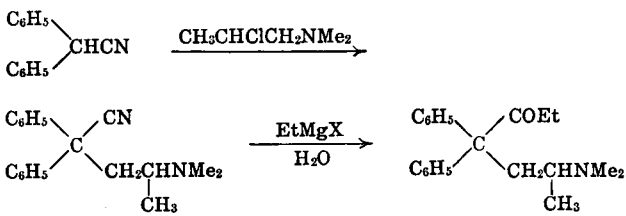


(I)



(II)

The latter is prepared from diphenylacetonitrile. Introduction of the side-chain involves an interesting rearrangement.

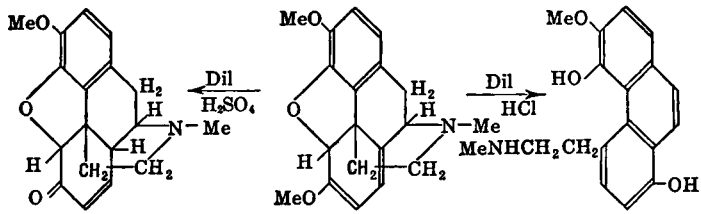


[131] Small, Fitch, Smith. *J. Am. Chem. Soc.* **58**, 1457 (1936).

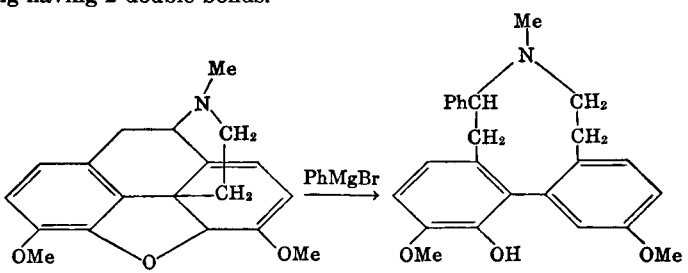
α-Isomorphine, m. 247° is an epimer of morphine differing only in the configuration of the CHOH. It gives *isocodeine*, m. 172°. Both codeine and isocodeine on oxidation give the ketone, *codeinone*, m. 187°. **β-Isomorphine,** m. 183°, and **γ-isomorphine,** m. 278° are epimers with the alcoholic hydroxyl on C_8 instead of C_6. They give *allopseudo-codeine*, liq. and *pseudocodeine*, m. 181° both of which form *pseudocodeinone*, m. 174°, on oxidation.

Ethyl morphine, Dionine, is next to codeine in importance in the United States as a morphine derivative. Diacetyl morphine, Heroin, is prohibited in the United States but is still produced elsewhere.

Thebaine, $C_{19}H_{21}NO_3$, m. 193°, is the methyl ether of the enol form of codeinone as shown by its conversion to that substance and MeOH by action of dilute sulfuric acid. In general, its conversions correspond to those of morphine except that dilute HCl gives *thebenine*, a phenanthrene derivative in which the OH has shifted from C_6 to C_8 and the C−C−N bridge has broken loose and been attached as a methylaminoethyl group to C_6.



The action of Grignard reagents on thebaine leads to a remarkable change. It has been shown by Small[132] that the product occurs in two pairs of stereoisomeric forms and that C-9 is asymmetric. The reaction with PhMgBr is believed by Robinson[133] to involve addition at C-9 and the O-bridge resulting in breaking of the 9–14 bond, opening of the O-bridge and aromatization of the ring having 2 double bonds.

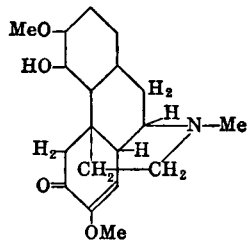


The resulting phenyldihydrothebaine exists in two pairs of stereoisomeric

[132] Small, Sargent, Bralley. *J. Org. Chem.* 12, 839 (1947).
[133] Robinson. *Nature* 160, 815 (1947); *Proc. Roy. Soc.* (London) **B135**, v (1947).

molecular forms because of the restricted rotation of the biphenyl rings. The isomers of each pair are interconvertible by inversion of the optical center at C-9.

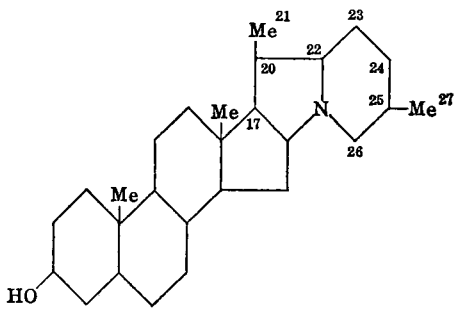
Sinomenine is related to morphine and thebaine and probably has the formula



(II)

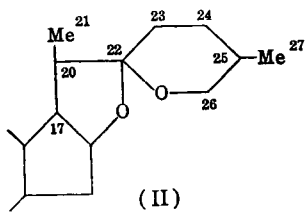
T. Other Alkoloids

Solanidine, $C_{27}H_{43}ON$, contains the cyclopentanohydrophenanthrene nucleus which is characteristic of so many biologically important substances such as the sterols, bile acids, sex hormones, heart aglucones, toad poisons and the like. It has been assigned formula (I) combining this nucleus and an octahydropyrrocoline system.[134] It will be seen that the number of carbon



(I)

atoms attached at C-17 is the same as in cholesterol. The arrangement of the nitrogenous part retains the cholesterol chain as it is retained in tigogenin (II).



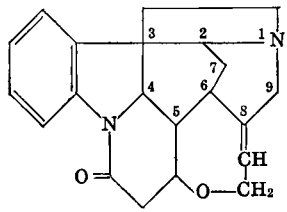
(II)

[134] Prelog, Szpilfogel. *Helv. Chim. Acta* **25**, 1306 (1942).

This formula (I) has been proven by a partial synthesis of the saturated compound from sarsasapogenin.[135]

The veratrine alkaloids **jervine, subijervine, germine** and **cevine** are C_{27} compounds and are related to solanidine and the sterols. On dehydrogenation they give 2-ethyl-5-methylpyridine but differ in that they do not yield the Diels' hydrocarbon.

Strychnine, $C_{21}H_{22}O_2N_2$, contains groupings not found in other classes of alkaloids. An enormous amount of study has lead to the proposal of various formulae. The following is considered as best representing its structure.[136]



Neostrychnine differs only in having the double bond shifted to 8–9, and *pseudostrychnine* is 2-hydroxystrychnine. *α*- and *β*-**Colubrines** are methoxy derivatives while **brucine** is dimethoxy strychnine. **Vomicine** is less closely related to strychnine.

[135] *Bio. Rev.* **1946**, 186.
[136] Woodward, Brehm. *J. Am. Chem. Soc.* **70**, 2107 (1948).

PART V

ORGANOPHOSPHORUS AND ORGANOMETALLIC COMPOUNDS

I. ALIPHATIC COMPOUNDS

A. ALKYL COMPOUNDS OF MEMBERS OF THE PHOSPHORUS FAMILY

Alkyl compounds of phosphorus resemble those of nitrogen in many ways but differ in being less basic and more subject to oxidation, properties which would be predicted from a comparison of the parent substances ammonia and phosphine, PH_3, the latter being very weakly basic and highly inflammable. There are primary, secondary, and tertiary phosphines and quaternary phosphonium compounds. Each additional alkyl group increases the basic properties from the primary phosphines RPH_2 whose hydrochlorides are decomposed by water to R_4POH which is a strong base comparable with R_4NOH and KOH.

The action of phosphine with alkyl halides does not give primary and secondary phosphines but gives directly the tertiary and quaternary compounds. This is because of the rapidly increasing basicity accompanying the introduction of the alkyl groups, the ease of addition of RX being strongly in the order $R_3P > R_2PH > RPH_2 > PH_3$. Treatment of the resulting mixture with alkali and distillation gives the volatile tertiary phosphine leaving the stable phosphonium salt in solution.

Phosphonium iodide, PH_4I, heated with an alkyl halide and zinc oxide, gives a mixture of primary and secondary phosphines. These can be converted to their hydrochlorides of which R_2PH_2Cl is stable in water while RPH_3Cl is hydrolyzed completely to RPH_2 by cold water.

Tertiary phosphines can be made from Grignard reagents or dialkyl zinc compounds and PCl_3.

Phosphorus, heated with alkyl iodides at 180°, gives a mixture of polyiodides from which the quaternary phosphonium iodide can be prepared by treatment with hydrogen sulfides.[1] The reaction resembles the dismutation which takes place when phosphorus is heated with water under pressure

$$8\ P + 12\ H_2O \rightarrow 5\ PH_3 + 3\ H_3PO_4$$
$$2\ P + 7\ RI \rightarrow R_4PI_3 + R_3PI_4$$

Of the two organic products, the first is changed by H_2S solution to R_4PI and the latter to the phosphine oxide, R_3PO which is more soluble than the phosphonium compound.

[1] Masson. *J. Am. Chem. Soc.* **55**, 139 (1889).

Phosphine with formaldehyde and HCl gives crystalline tetrahydroxymethylphosphonium chloride $(HOCH_2)_4PCl$.[2]

The boiling points of the methyl- and ethyl phosphines (°C.) are −14, 25, 41 and 25, 85, 128 respectively.

Oxidation of primary phosphines gives monoalkylphosphonic acids, $RPO(OH)_2$, (phosphinsäure), analogous to arsonic and sulfonic acids. Related monoalkylphosphinous acids RPHO(OH) are obtained by the action of water with an alkylphosphine dichloride, $RPCl_2$, obtainable from dialkylmercury and PCl_3. The latter acids resemble phosphorous acid in being disproportionated by heat.

$$4\ H_3PO_3 \rightarrow PH_3 + 3\ H_3PO_4$$
$$3\ RPHO_2H \rightarrow RPH_2 + 2\ RPO_3H_2$$

$MePO_3H_2$, m. 105°.

Secondary phosphines on oxidation give dialkylphosphinic acids, R_2PO_2H. Me_2PO_2H, m. 76°.

Tertiary phosphines give phosphine oxides, R_3PO, which differ from the corresponding nitrogen compounds in stability to heat and reducing agents. Thus they are formed when quaternary phosphonium hydroxides are heated

$$R_4POH \rightarrow R_3PO + RH$$

This is in marked contrast to the behavior of R_4NOH. Triethylphosphine undergoes autoxidation in air much as phosphorus does. Thus a substance which can be oxidized but which does not ordinarily react rapidly with oxygen gas undergoes rapid oxidation in the presence of such a substance. Probably a peroxide is first formed. Thus the process involved in the oxidation of indigo white by air in presence of Et_3P are probably as follows:

$$Et_3P \rightarrow Et_3PO_2 \rightarrow \text{Indigo blue} + Et_3PO.$$

Characteristically, half of the oxygen goes to the readily oxidizable substance and half to the less readily oxidizable substance, the "acceptor." Me_3PO, m. 138°, b. 215°.

Tertiary phosphines react exothermally with sulfur giving R_3PS. They also add halogens to form R_3PX_2. R_3P also reacts violently with CS_2.

Et_3PS, m. 94°. Et_3PSe, m. 112°. $Et_3P.CS_2$, m. 95°.

Alkyl compounds of arsenic. These differ from the corresponding nitrogen compounds even more than do those of phosphorus. The primary, secondary and tertiary arsines have practically no basic properties. Like the phosphines they are readily oxidized. The quaternary compounds resemble those of nitrogen. The hydroxides are strong bases.

The arsines are prepared very differently from the amines. Thus the best preparations for *methylarsine*, $MeAsH_2$, b. +2° are:

[2] *Ann. Rep. Chem. Soc.* (London) 1922, 67.

1. By reduction of methylarsenic dichloride, b. 133°, obtained from $HgMe_2$ and $AsCl_3$.

2. By reduction of sodium methylarsonate, $MeAsO_3Na_2$, prepared from MeI and sodium arsenite. A barely alkaline solution of As_2O_3 in NaOH is used in this reaction. NaI is formed and the methyl carbon with only six electrons attaches itself to the free electron pair of the arsenite ion.[3] This is similar to the action of a sulfite to give a sulfonate with an alkyl halide. Sodium methylarsenate is used medicinally as Arrhenal. *n*-Propylarsonic acid is used in determining small amounts of zirconium in steel.[4]

Like all arsenic compounds, especially the volatile ones, methylarsine is poisonous.

Dimethylarsine, cacodyl hydride, Me_2AsH, b. 37° is an extremely poisonous, spontaneously inflammable liquid of terrible odor. The corresponding oxide, cacodyl oxide, $(Me_2As)_2O$, is obtained by heating As_2O_3 and potassium acetate.[5,6] Many compounds of the cacodyl radical (Me_2As-) have been studied. Its chloride, with zinc, gives cacodyl, $Me_2AsAsMe_2$, b. 170°, spontaneously inflammable. It reacts with limited amounts of oxygen, sulfur and halogens to give cacodyl compounds. With MeI it gives cacodyl iodide and tetramethylarsonium iodide. Cacodylic acid is dimethylarsinic acid, Me_2AsO_2H.

Trimethylarsine, Me_3As, b. 53°, is the poisonous volatile material formed by biological methylation of arsenic compounds in wall-papers containing either arsenical pigments or "aniline dyes" at a time when the oxidation step in their preparation was by means of arsenic acid[7] (p. 848).

Tertiary arsines are made from $AsCl_3$ with Grignard reagents or alkyl zinc compounds.

The arsines are readily oxidized to arsonic acids, $RAsO_3H_2$, arsinic acids, $RR'AsO_2H$, and arsine oxides, RR'R''AsO. The acids can be reduced by H_2SO_3 to the trivalent form of arsenic and converted to the related sodium salts which react with alkyl halides in the same way as sodium arsenite. The final product is the tertiary arsine oxide.

The arsines readily unite with oxygen, sulfur and halogens to give pentavalent compounds. When the pentavalent chlorides R_nAsCl_{5-n} ($n=1$ to 4) are heated, RCl separates leaving $R_{n-1}AsCl_{4-n}$. This, with chlorine, gives $R_{n-1}AsCl_{6-n}$, etc., until all alkyl groups are removed and $AsCl_3$ is left. This is a remarkable difference from the behavior of nitrogen compounds. Another important difference is the reaction of the arsines with arsenic chloride.

$$R_3As + AsCl_3 \rightarrow R_2AsCl \text{ and } RAsCl_2$$

Methyldichloroarsine, CH_3AsCl_2, was used as a war gas. It was ineffective compared with mustard gas. It can be prepared according to the last equation

[3] "Org. Reactions," II, p. 431.
[4] Geist. *Ind. Eng. Chem., Anal. Ed.* **9**, 169 (1937).
[5] Cadet. *Mém. Math. phys.* **3**, 363 (1760).
[6] Bunsen. *Ann.* **46**, 1 (1843).
[7] Challenger. *Chemistry & Industry* **54**, 657 (1935).

or by the action of SO_2 and HCl on $MeAsO_3Na_2$ obtained from sodium arsenite and Me_2SO_4 or MeCl.

A penta-alkyl compound of arsenic can be made, Me_5As, from zinc dimethyl and Me_4AsI. It is a volatile liquid.

The war gas, Lewisite, is chlorovinyldichloroarsine.

$$ClCH=CHAsCl_2.$$

When prepared from $AsCl_3$ and acetylene, much of the secondary and tertiary arsines are obtained. These can be changed to Lewisite by heating with $AsCl_3$.

Organic Arsenical Compounds, Raiziss and Gavron, A.C.S. Monograph, Chemical Catalog Company, New York, 1923.

Alkyl compounds of antimony, Stibines. In these, the increasing metallic nature of antimony makes marked changes from the amines. $SbCl_3$ with zinc alkyls gives *trialkylstibines*. They are spontaneously inflammable liquids. With halogens, oxygen and sulfur they form R_3SbX_2, R_3SbO and R_3SbS. A remarkable reaction is that with HCl which generates hydrogen as though a free metal were involved.

$$R_3Sb + 2\ HCl \rightarrow H_2 + R_3SbCl_2$$

Just as a free metal discharges hydrogen ions by means of its valence electrons the antimony, when attached to three alkyl groups acquires metallic properties in the sense that its free electron pair acts like a free metal.

$$Ca : + \ 2\ H : \ddot{\underset{\cdot\cdot}{Cl}} : \rightarrow Ca^{++} + 2\ Cl^- + H : H$$

$$\begin{matrix} R \\ \cdot\cdot \\ R : Sb : \\ \cdot\cdot \\ R \end{matrix} + 2\ H : \ddot{\underset{\cdot\cdot}{Cl}} : \rightarrow \left[\begin{matrix} R \\ \cdot\cdot \\ R : Sb : \ddot{\underset{\cdot\cdot}{Cl}} : \\ \cdot\cdot \\ R \end{matrix} \right]^+ + Cl^- + H : H$$

Another example of the metallic tendencies of antimony is the existence of salts such as R_3SbSO_4.

Me_3Sb, b. 81°. Et_3Sb, b, 159°. Me_5Sb, b. 100°.

Alkyl iodides add to tertiary stibines giving quaternary stibonium compounds of properties like the corresponding ammonium compounds. The hydroxide, R_4SbOH, is also a strong base.

Organic Derivatives of Antimony, Christiansen, A.C.S. Monograph, Chemical Catalog Company, New York, 1925.

Alkyl compounds of bismuth. These behave as metallo-organic compounds in contrast to the compounds of N, P, As and Sb. They are prepared from $BiCl_3$ and Grignard reagents. The bismuth trialkyls react with acids to give bismuth salts and hydrocarbons.

$$Me_3Bi + 3\ HCl \rightarrow BiCl_3 + 3\ CH_4$$

With halogens and sulfur they show no tendency to form pentavalent compounds but suffer the usual splitting of the C-metal linkage.

$$Me_3Bi + 3\ I_2 \rightarrow BiI_3 + 3\ MeI$$
$$2\ Me_3Bi + 6\ S \rightarrow Bi_2S_3 + 3\ Me_2S$$

No quaternary compounds are formed.

Me_3Bi, b. 110°. It explodes when heated in air.

B. METAL ALKYLS

Alkyls of the alkali metals are obtained from the metals and mercury alkyls in the absence of air.[8] Sodium added to dimethylzinc precipitates metallic zinc. While the zinc compound does not act with CO_2 the resulting product gives sodium acetate.

$$MeNa + CO_2 \rightarrow MeCO_2Na$$

The alkali alkyls are generally non-volatile solids, insoluble in inert organic solvents. Their solutions in diethylzinc conduct electricity.[9] These properties are in sharp contrast to those of substances like the volatile, soluble, non-conducting arsines. One type of substance is polar and the other is non-polar.[10]

Lithium alkyls are best prepared in a pentane solvent from Li and RCl or RBr in N_2 atmosphere.[11, 12] Unlike the RNa and RK compounds, the lithium alkyls are soluble in organic solvents and conduct poorly in diethylzinc. They are useful in certain synthetic processes in which Grignard reagents fail.

Sodium ethyl reacts with ether to give NaOEt, ethane and ethylene.[13] This reaction introduces complications into Wurtz reactions run in ether solution since RNa is probably an intermediate.

NaEt when heated below 150° gives ethane, ethylene, hydrogen and sodium acetylide. NaMe gives CH_4, sodium and Na_2C_2.[14]

Organo-alkali compounds.[15, 17]

Organo-metals.[16]

Alkyl derivatives of magnesium. The Grignard reagent, RMgX, is the most important reagent ever introduced into organic chemistry.[18] It is formed from the alkyl halides with metallic magnesium, usually in the presence

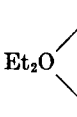
[8] Schlenk. *Ann.* **463**, 1 (1928).
[9] Hein. *Z. anorg. allgem. Chem.* **141**, 161 (1924).
[10] Carothers. *J. Am. Chem. Soc.* **51**, 588 (1929).
[11] Ziegler. *Ann.* **479**, 135 (1930).
[12] Gilman. *J. Am. Chem. Soc.* **54**, 1957 (1932); **62**, 2327 (1940).
[13] *Ann. Rep. Chem. Soc.* (London) **1923**, 58.
[14] Carothers, Coffman. *J. Am. Chem. Soc.* **52**, 1254 (1930).
[15] Wooster. *Chem. Rev.* **1932**, II, 1 (1928).
[16] Ahrens. *Sammlung Chemische-Technischen Vortrage* **1927**, 320.
[17] Schlenk, Bergmann. *Ann.* **463**, 1; **464**, 1.
[18] Grignard. *Compt. rend.* **130**, 1322 (1900).

of anhydrous ethyl ether but other solvents such as higher ethers,[19] tertiary amines and even hydrocarbons may be used. In special cases no solvent is used. In the solution obtained there is an equilibrium

$$2\ RMgX \rightleftharpoons R_2Mg + MgX_2.$$

Of the three substances only R_2Mg is soluble in dioxan.[20]

The nature of the oxonium complex of the Grignard reagent with ether has never been settled. It has been proved *not* to be of the type originally proposed



by Grignard.[21]

Grignard reagents can be prepared from alkyl halides of all classes.[22] No rearrangements take place in the action of alkyl halides with magnesium. However, Grignard reagents derived from allylic systems often give rearrangement products in their reactions.[23]

The Grignard reagent has several types of reactions.

1. With compounds having hydrogen attached to a non-metal other than carbon (*active H compounds*) it gives hydrocarbons and a compound having $-MgX$ in place of the H.

$$RMgX + HOH \rightarrow RH + HOMgX$$

In this reaction it is acting as a very sensitive hydrocarbo base. Ammonia, primary and secondary amines and all acids give compounds of the types NH_2MgX, $RNHMgX$, R_2NMgX and $Q-MgX$(HQ as acid). Even H attached to C acts in the grouping $-C\equiv CH$ to give $-C\equiv CMgX$ which is a true Grignard reagent usable in the usual syntheses.

The action of methyl Grignard reagent in a high boiling ether is used as a quantitative test for active hydrogen compounds ($-OH$, $-NH$, $-SH$ etc.) by measuring the methane evolved.[24]

2. With multiple linkages between carbon and another element it adds with the MgX on the other element and the alkyl group on the carbon.

$$=C=O + RMgX \rightarrow =C(R)OMgX \rightarrow =C(R)OH$$

The last step is one of hydrolysis to form the organic compound and magnesium hydroxide. The latter is dissolved by acid or by ammonium salts

[19] Marvel. *J. Am. Chem. Soc.* **50**, 2810 (1928).
[20] Schlenk. *Ber.* **64**, 734 (1931).
[21] Thorpe, Kamm. *J. Am. Chem. Soc.* **36**, 1022 (1914).
[22] Gilman. *J. Am. Chem. Soc.* **51**, 1576 (1929).
[23] Young. *J. Am. Chem. Soc.* **68**, 1472 (1946).
[24] Kohler. *J. Am. Chem. Soc.* **52**, 3736 (1930).

if the organic product is sensitive to acids.

$$=C=S \rightarrow =C(R)SMgX \rightarrow =C(R)SH$$
$$-C\equiv N + RMgX \rightarrow -C(R)=NMgX \rightarrow -C(R)=NH \rightarrow -C(R)=O$$

Besides the normal reactions with esters to produce ketones and *t*-alcohols, Grignard reagents also react to remove the hydrogens of the carboxy and alkoxy portion of certain type esters.[25]

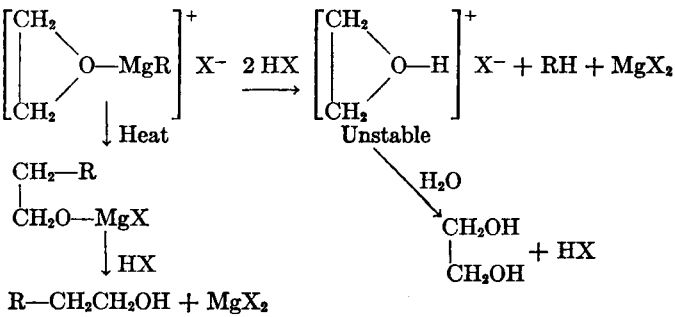
3. With elements such as the halogens, oxygen and sulfur, Grignard reagents form alkyl halides, alcohols and mercaptans.

$$2\ RMgX + O_2 \rightarrow RX + MgO + ROMgX \rightarrow ROH$$

These reactions have not been adequately studied.[26] Hydrogen peroxide (30%) gives alcohols.

4. With halides such as PCl_3 and $HgCl_2$, to introduce alkyl groups in place of halogen atoms.

5. With ethylene oxides. The first product is an oxonium salt which, when treated with water or acid, gives RH and the glycol related to the oxide. If the first addition product is heated to about 150° (danger of explosion), it changes to RCH_2CH_2OMgX:



6. With alkyl halides to give hydrocarbons.

$$RX + R'MgX \rightarrow MgX_2 + RR'$$

The yields are poor, especially so, with tertiary halides. A better modification involves the use of alkyl esters of aromatic sulfonic acids.

$$Tol\text{-}SO_3R + R'MgX \rightarrow RR' + Tol\text{-}SO_3MgX$$

Esters of aliphatic sulfonic acids give sulfones

$$RSO_3R' + R''MgX \rightarrow RR''SO_2 + R'OMgX$$

[25] Hauser. *J. Am. Chem. Soc.* 70, 606 (1948).
[26] Goebel, Marvel. *J. Am. Chem. Soc.* 55, 1693 (1933).

Allyl halides react well with Grignard reagents to give 1-olefins.

7. Silver bromide produces a peculiar coupling to give hydrocarbon, R—R.[27]

$$2\ RMgBr + 2\ AgBr \rightarrow R{-}R + 2\ MgBr_2 + 2\ Ag$$

8. The Grignard reagent is said to act "abnormally" with carbonyl compounds in three ways, by acting as a reducing agent, by acting as a base in causing enolization and condensation. These reactions appear when the normal reactions are cut down by branching of the chain in the carbonyl compound or the reagent or both.

a. Reduction. A good example is the conversion of Me_3CCOCl to Me_3CCH_2OH by the action of *t*-BuMgCl.[28] The aldehyde is an intermediate.

b. Enolization. The recovery of an unchanged carbonyl compound after treatment with a Grignard reagent was first taken as indicating the inactivity of the former but was later recognized as due to the formation of an enolate —C=COMgX which gives back the original carbonyl compound on acidification. Recognition of this process resulted in much work on the measurement of the "degree of enolization" of carbonyl compounds by treatment with MeMgX and measurement of the evolved CH_4.[29] Contrary to the earlier conception, the amount of enolization depends on the branching of *both* the carbonyl compound and the reagent. Thus diisopropyl ketone with MeMgBr gives 95% addition with no detectable enolization or reduction; with isobutylmagnesium bromide it gives 11% enolization, 78% reduction to diisopropylcarbinol and 8% addition to form the *t*-alcohol; and with neopentylmagnesium chloride it gives 90% enolization, 4% addition and no reduction.[30]

c. Condensation. A good example is the action of acetone with iso-BuMgBr (p. 214).

9. Grignard Reagents give a characteristic color with iodine and Michler's ketone.[31, 32]

Magnesium in Organic Chemistry.[33]

Grignard reagent.[34]

Alkyl compounds of beryllium and calcium resembling the Grignard reagent have been prepared.[35]

Alkyl compounds of zinc are typical metallo-organic compounds.[36] They are completely decomposed by all compounds containing hydrogen attached to elements other than singly or doubly linked carbon. Thus they react with

[27] Gardner. *J. Am. Chem. Soc.* **51**, 3375 (1929).
[28] Whitmore. *J. Am. Chem. Soc.* **63**, 643 (1941).
[29] Smith, Guss. *J. Am. Chem. Soc.* **59**, 804 (1937).
[30] Whitmore, George. *J. Am. Chem. Soc.* **64**, 1239 (1942).
[31] Gilman, Schulze. *J. Am. Chem. Soc.* **47**, 2002 (1925).
[32] Gilman, Heck. *J. Am. Chem. Soc.* **52**, 4949 (1930).
[33] "Magnesium in Organic Chemistry." Cortot, 1925.
[34] Grignard reagent. Ahrens *Sammlung Chemische-Technischen Vortrage* 1905, 89; 1908, 90.
[35] Gilman. *J. Am. Chem. Soc.* **49**, 2904 (1927).
[36] Frankland. *Ann.* **71**, 213 (1849).

active hydrogen compounds such as water, ammonia, acids, and acetylene.

$$R_2Zn + HQ \rightarrow RH + RZnQ \rightarrow RH + ZnQ_2$$

The dialkylzincs are spontaneously inflammable liquids which must be handled in a CO_2 atmosphere. The alkylzinc halides are salt-like materials which give the dialkylzinc compounds on heating. A zinc copper alloy reacts with alkyl iodides to give RZnI. Distillation gives R_2Zn and ZnI_2.[37]

Historically, the dialkylzincs are very important. Their ability to react with carbonyl groups made available many new types of compounds.

$$RCHO + R_2'Zn \rightarrow RR'CHOZnR' \rightarrow RR'CHOH$$

At present their most important use is in replacing a halogen by an alkyl group when the result cannot be achieved in any other way. Thus:

$$Me_3CCl + R_2Zn \rightarrow Me_3CR.$$[38]

For this purpose they are better than Grignard reagents although the yields are still poor.

The zinc compounds are sometimes useful in making ketones from acid chlorides since they react only slowly with the products whereas Grignard reagents act rapidly with ketones.

Dialkylzinc compounds react readily only with tertiary halides and with acid halides. Other types of halides are not sufficiently reactive to give the full yield.

Zinc diethyl in ether solution is a poor conductor but can be electrolyzed to give zinc at the cathode and ethyl radicals at the anode.[39]

Me_2Zn, b. 46°, Et_2Zn, b. 118°.

Organocadmium compounds are much used in the synthesis of ketones and deserve mention.[40]

Alkyl compounds of mercury. These show properties of both the non-metallic and metallic derivatives of organic compounds. They are not attacked by water but are split by acids. The dialkyl mercury compounds, R_2Hg, are poisonous liquids. The organomercuric salts, RHgX, are crystalline solids.

General methods of preparation.

1. Sodium amalgam with alkyl bromides in presence of a catalyst such as ethyl acetate, gives R_2Hg.

2. Grignard reagents, with mercuric or mercurous halides, give RHgX or R_2Hg depending on the proportions used.

Reactions: 1. Mercury dialkyls react with mercuric salts.

$$R_2Hg + HgX_2 \rightarrow 2\ RHgX$$

[37] Noller. *J. Am. Chem. Soc.* **51**, 594 (1929).
[38] *ibid.*
[39] Rodebush. *J. Am. Chem. Soc.* **51**, 638 (1929).
[40] Cason. *Chem. Rev.* **40**, 15 (1947).

2. Alkylmercuric salts can be converted to dialkyl mercury compounds by treatment with a Grignard reagent or with any reagent which removes mercuric ions from solution more completely than does NaOH

$$RHgCl + RMgCl \rightarrow R_2Hg + MgCl_2$$
$$2\ RHgCl + 4\ NaCN \rightarrow R_2Hg + Na_2Hg(CN)_4 + 2\ NaCl$$

3. Both types of mercury compound react with acids, especially halogen acids, with splitting of the C—Hg linkage and formation of a hydrocarbon.

$$R_2Hg \rightarrow RH + RHgCl \rightarrow RH + HgCl_2$$

In common with other organometallic compounds, these alkyl compounds of mercury are thus *hydrocarbo bases*[41] in the same sense that NaOH and $NaNH_2$ are aquo and ammono bases respectively.

4. The C—Hg linkage is split by halogens.

$$R_2Hg + X_2 \rightarrow RX + RHgX \rightarrow RX + HgX_2$$

This method is of preparative value as in the case of bromides and iodides of neopentyl and pinacolyl (pp. 75–6) which cannot be made by other methods.

5. It might be expected that alkyl mercury compounds would react with alkyl halides to give HgX_2 and higher paraffins. This is not possible. Either there is no reaction or the C—Hg compound merely removes HX from the halide, thus acting as a hydrocarbo base.

Me_2Hg, b. 95°.	MeHgI, m. 143°.
Et_2Hg, b. 160°.	EtHgCl, m. 193°.

Methylmercuric iodide can be made from MeI and Hg in sunlight. The change is catalyzed by mercurous iodide.

Ethylmercuric chloride is important industrially as a fungicide in treating seeds, lumber, etc. It is used in high dilution either in solution or in dusting powders. It is made from $HgCl_2$ and lead tetraethyl.

Alkylmercuric hydroxides, RHgOH, contrary to older reports, are very weak bases. They can be prepared from RHgCl by alcoholic KOH which precipitates KCl. The impression that MeHgOH was a strong base came from the fact that it liberates NH_3 from ammonium salts and has a caustic effect on the skin. It is actually a weaker base than aniline. It forms an insoluble carbonate and a soluble bicarbonate. Boiling either with water expels CO_2 *completely* leaving the free base. An aqueous solution of the base reacts quantitatively with NaCl solution precipitating RHgCl and leaving NaOH in the solution. Thus NaCl can be causticized by this peculiar base in the same way that sodium carbonate is converted to NaOH by lime. The compounds, RHgOH, are unique in being *weak, soluble, stable bases.* All other weak bases are either insoluble or unstable.

Mercuric salts react with olefins and acetylenes.

[41] Jones. *J. Am. Chem. Soc.* **40**, 1257 (1918).

It is possible to attach several mercury atoms to a carbon. Thus the organic compound containing the smallest percentage of carbon is the iodide of ethane hexamercarbide, $(IHg)_3CC(HgI)_3$.

Organic Compounds of Mercury, Whitmore, A.C.S. Monograph, Chemical Catalog Company, New York, 1921.

Alkyl compounds of boron are made from Grignard or zinc compounds with BCl_3 and with boric acid esters such as $(MeO)_3B$. *Trimethylborane* is a gas, and BEt_3 boils at 95°. They are spontaneously inflammable and are decomposed by acids to give hydrocarbons. Alkyl boric acids, R_2BOH and $RB(OH)_2$, are obtained by replacing part of the chlorine atoms in BCl_3 and hydrolyzing the products. They thus have properties of both metal and non-metal alkyl compounds.

Aluminum trialkyls can be made from RMgX and $AlCl_3$ or from the mercury alkyls with metallic aluminum. Aluminum powder with ethyl iodide gives Et_2AlI and $EtAlI_2$, b. 120° and 160°. Both are spontaneously inflammable and are decomposed by water as are the trialkyl compounds.

Me_3Al, b. 130°.

Gallium triethyl, b. 142°, is made from gallium and $HgEt_2$. It is spontaneously inflammable.[42] $GaMe_3$, b. 55.7°, is prepared from the chloride and Me_2Zn. The solid even at −76° catches fire spontaneously.[43]

Thallium triethyl, b. 51° (1.5 mm.), is obtained from lithium ethyl and thallous chloride.[44]

Alkyl compounds of silicon are made like those of bismuth or boron. A more recent method involves the action of organic halides on silicon in the presence of a copper or silver catalyst at elevated temperatures.[45]

The "silicones" or organopolysiloxanes are by far the most important class of organosilicon compounds. These consist of an arrangement of alternate silicon and oxygen atoms in which the silicon atoms are linked to organic groups. They are prepared by the hydrolysis of organochlorosilanes, $RSiCl_3$, R_2SiCl_2 and R_3SiCl. In the form of fluids, greases and resins, these new polymers are important because of their remarkable heat stability, low rate of viscosity change with temperature, water-repellent properties, chemical inertness, and excellent electrical properties for insulation.

The chemical behavior of organosilicon monomers containing functional groups attached to carbon is of special interest because the introduction of the silicon atom leaves the compounds as true organic substances in many respects. An interesting example is the occurrence of a typical "neopentyl" rearrangement on treatment of silico-neopentyl chloride, Me_3SiCH_2Cl, with aluminum

[42] Dennis. *J. Am. Chem. Soc.* **54**, 182 (1932).
[43] Kraus. *J. Am. Chem. Soc.* **55**, 3547 (1933).
[44] Birch. *J. Am. Chem. Soc.* **56**, 1132 (1934).
[45] Rochow. *J. Am. Chem. Soc.* **67**, 963 (1945).

chloride to give $Me_2EtSiCl$.[46] Me_4Si, b. 26°. Me_3SiCl, b. 57°. Me_3SiOH, b. 97°. $Me_3SiOSiMe_3$, b. 100°. Me_3SiCH_2Cl, b. 97°.

Germanium alkyls have been made and studied extensively.[47–49] Et_4Ge, b. 163.5°, d. 0.99, pleasant odor.

Alkyl compounds of tin have been extensively studied. They are made from alkyl iodides with alloys of tin with sodium or zinc. Mixed compounds R_nSnI_{4-n} are obtainable.

Treatment of the alkyl tin compounds with halogen acids or halogens replaces alkyl groups by halogens forming paraffins or alkyl halides. They do not act with water.

Me_3SnCl with Na gives Me_6-stanno-ethane, $Me_3Sn\text{-}SnMe_3$, which dissociates into free radicals in solution. Dimethyltin, made from Me_2SnCl_2 and Na, readily unites with oxygen to form Me_2SnO.

Me_4Sn, b. 78°, Me_3SnI, b. 170°, Me_2SnI_2, m. 30°, b. 228°.

Et_4Sn, b. 181°. $Et_3SnSnEt_3$, b. 270°.

Asymmetric tin compounds of the type MeEtPrSnI have been obtained in optically active forms.[50]

Alkyl compounds of lead have been studied very extensively especially in recent years because of the interest in lead tetraethyl as an anti-knock for gasoline. The lead tetra-alkyls resemble the mercury dialkyls in general properties and reactions.

The lead dialkyls are unstable. Lead chloride heated with a Grignard reagent gives the tetra-alkyl.

$$2\ PbCl_2 + 4\ RMgCl \rightarrow R_4Pb + 4\ MgCl_2 + Pb$$

Free methyl and ethyl radicals were first prepared by heating the lead alkyls.[51] Their half life is about 0.006 sec. Higher alkyl radicals decompose even more rapidly into olefins and methyl or ethyl radicals. The free radicals attack metallic mercury forming Me_2Hg which can be identified as MeHgBr.[52]

Lead tetraethyl is made commercially by heating ethyl chloride under pressure with sodium lead alloy. The amount produced per year is of the order of a quarter of a billion pounds.

Many simple and mixed lead tetra-alkyls have been prepared.[53]

Mixed compounds R_nPbCl_{4-n} and diplumbic compounds R_3PbPbR_3 are known. Trivalent and bivalent lead alkyls have been prepared.

Me_3PbOH is a strong base.

Organic Compounds of Lead. Calingaert, Rev. 1925, 43–84.

[46] Whitmore, Sommer, Gold. *J. Am. Chem. Soc.* **69**, 1976 (1947).
[47] Dennis. *J. Phys. Chem.* **30**, 1055 (1926).
[48] Kraus. *J. Am. Chem. Soc.* **54**, 1635 (1932).
[49] Rochow. *J. Am. Chem. Soc.* **69**, 1729 (1947).
[50] Pope, Peachey. *Proc. Roy. Soc.* (London) **1900**, 16, 42, 116.
[51] Paneth. *Ber.* **62**, 1335 (1929).
[52] Rice. *J. Am. Chem. Soc.* **54**, 3529 (1932).
[53] Grüttner. *Ber.* **51**, 1293 (1918).

The metallo-organic compounds of Cu, Ag, Au, Cr, Th, Fe, Pt etc. are available.

II. AROMATIC COMPOUNDS

A. AROMATIC COMPOUNDS OF MEMBERS OF THE PHOSPHORUS FAMILY

Many such compounds are known. In formulas they resemble the compounds of nitrogen. In general they can be made by treating the inorganic halides with aromatic mercury compounds.[1] Thus

$$PCl_3 + Ph_2Hg \rightarrow PhPCl_2 + PhHgCl$$

Because of their use in the treatment of protozoal diseases such as syphilis and African sleeping sickness, the aromatic compounds of arsenic have been studied most extensively.

The most important aromatic compounds of arsenic are the arsonic acids (arsinic acids), $ArAsO_3H_2$. These are most generally prepared from a diazotized amine and sodium arsenite (Bart Reaction).[2]

$$ArN_2Cl + Na_2HAsO_3 \rightarrow ArAsO_3HNa + NaCl + N_2$$

The process resembles the formation of a sulfonate from sodium sulfite and an alkyl halide (p. 152). In each case a "carbonium ion" adds to the free electron pair in the -ite ion.

Another preparation is by the combined oxidation and hydrolysis of an aryldichloroarsine by chlorine water

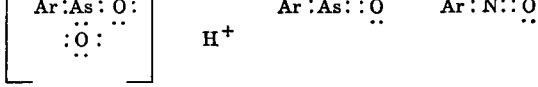
$$ArAsCl_2 + Cl_2 + 3\ H_2O \rightarrow ArAsO_3H_2 + 4\ HCl$$

If an activating group such as OH or NH_2 is present, direct arsonation with sirupy arsenic acid is possible (Bechamp Reaction).[3]

$$HOC_6H_5 + H_3AsO_4 \rightarrow H_2O + HOC_6H_4AsO_3H_2$$

The reaction requires a higher temperature than does nitration. This causes a greater amount of oxidation by the arsenic acid to give various complex colored oxidation products of the phenol or the amine. Thus the arsonation of aniline gives only about a 15% yield of *arsanilic acid*.[4]

The arsonic acids can be dehydrated to give anhydrides, $ArAsO_2$, analogous to the nitro compounds. The relation may be shown electronically:



[1] Michaelis. *Ann.* **293**, 196, 248, 257, 291, 303, 313 (1896).
[2] "Org. Reactions," II, p. 417.
[3] "Org. Reactions," II, p. 428.
[4] "Org. Syntheses."

The inability of the nitrogen to assume a hydrated form corresponding to the arsonic acids is probably due to the smallness of its kernel as compared with that of arsenic and corresponds to the non-existence of orthonitric acid, H_3NO_4.

The aryl arsonic acids are crystalline solids.

The arsonic acid group is attached firmly to the aromatic nucleus and can be removed only by heating with HI.

The aryl arsonic acids give soluble alkali and insoluble heavy metal salts.

Reduction converts the arsonic acids to *arsenoxides*, ArAsO, corresponding to nitroso compounds, to arseno compounds, ArAs=AsAr, analogous to azo compounds, and to primary arsines, $ArAsH_2$, related to aniline as AsH_3 is to NH_3.

Arsanilic acid, *p*-aminophenyl arsonic acid, $H_2NC_6H_4AsO_3H_2$, readily obtained by the direct arsonation of aniline (OS) shows all the properties of an aromatic amine and an arsonic acid. Its sodium salt is *Atoxyl* formerly used in protozoal diseases but abandoned because of its toxicity, especially to the optic nerve.

Phenolarsonic acid, *p*-hydroxyphenylarsonic acid, $HOC_6H_4AsO_3H_2$, from the direct arsonation of phenol,[5] is the main intermediate for Salvarsan.

Tryparsamide, N-phenylglycineamide-4-arsonic acid,

$$H_2NCOCH_2NHC_6H_4AsO_3H_2,$$

made from arsanilic acid and chloroacetamide[6] is valuable in African sleeping sickness and has been proposed for use in paresis.

Arsenobenzene, $C_6H_5As=AsC_6H_5$, m. 196°, pale yellow crystals, can be made from phenylarsine and phenylarsenoxide or by the reduction of phenylarsonic acid.

The *arseno group* is much less stable than the azo group. Thus heat converts arsenobenzene to *triphenylarsine*, $(C_6H_5)_3As$, and arsenic. Chlorine, oxygen and sulfur break the As—As bond to give $ArAsCl_2$, ArAsO and ArAsS.

Substituted arsenobenzenes containing hydroxyl or amino groups or combinations of them are less toxic than the arsonic acids and have replaced them in therapy.

When an arsonic acid containing a nitro group is reduced, either or both groups may be attacked depending on the reducing agent used.

1. Both groups can be reduced completely by an active metal and a strong acid to give aminoarylarsines such as $H_2NC_6H_4AsH_2$.

2. The nitro group can be reduced to amino and the arsonic acid group to arsenoxide by sulfurous acid with catalysts like HI, $SOCl_2$ etc. to give aminoarsenoxides, $H_2NC_6H_4AsO$.

3. The nitro group can be reduced by ferrous hydroxide without changing the arsonic acid group to give $H_2NC_6H_4AsO_3H_2$.

[5] Conant. *J. Am. Chem. Soc.* 41, 431 (1919).
[6] Jacobs. *J. Am. Chem. Soc.* 41, 1587 (1919).

4. The arsonic acid group can be reduced to give an arseno compound without changing the nitro group by means of phosphorous acid, H_3PO_3, or hypophosphorous acid, H_3PO_2.

5. The most important reduction gives the aminoarseno compounds. This is best given by sodium hydrosulfite, $Na_2S_2O_4$.

Salvarsan, Arsphenamine, "606," Kharsivan, Arsenobillon, 3,3'-diamino-4,4'-dihydroxyarsenobenzene hydrochloride,[7] was the first important arsenical drug and is still made and used in large amounts. Several preparations are known. *p*-Hydroxyphenylarsonic acid, obtained by direct arsonation of phenol or by diazotization of arsanilic acid, is nitrated ortho to the hydroxyl group. Reduction of this product with sodium hydrosulfite gives the base of salvarsan. Salvarsan is kept free from air because of its ready conversion to the more toxic arsenoxide. It is probable that the latter is the actual therapeutic agent in the body since salvarsan does not kill protozoa *in vitro* whereas the arsenoxide does. The latter has been introduced into therapy as Mapharsen, 3-amino-4-hydroxyphenylarsenoxide.

Neosalvarsan, neoarsphenamine, "914," is the sodium salt of the formaldehyde sulfoxylate of salvarsan base. The grouping $-NHCH_2OSONa$ renders it soluble in water to give a neutral solution whereas salvarsan gives a strongly acid solution which has to be exactly neutralized just before its use. Many modifications of the salvarsan structure have been prepared and tested.

Compounds have been prepared containing arsenic as a member of a heterocyclic ring. The best known of these is 10-chloro-5,10-dihydrophenarsazine, Adamsite, "DM," obtained from diphenylamine and $AsCl_3$. It was prepared during World War I as a toxic sternutatory.

"Organic Arsenical Compounds." Raiziss and Gavron. A.C.S. Monograph No. 15.

Organic compounds of antimony have been prepared in great numbers by reactions much like those used for arsenicals.

"Organic Derivatives of Antimony." Christiansen, A.C.S. Monograph No. 24.

B. AROMATIC COMPOUNDS OF MERCURY AND OTHER METALS

These have been studied in great variety. Mercury derivatives especially are known for every type of aromatic hydrocarbon and their derivatives.

Mercury diphenyl, diphenylmercury, $(C_6H_5)_2Hg$, m. 121°, is typical of the aromatic *mercuri-bis* compounds in which both valences of mercury are attached to carbon.

Preparation. 1. From bromobenzene and dilute sodium amalgam in presence of catalysts such as ethyl acetate.

2. From mercuric chloride or phenylmercuric chloride and excess phenylmagnesium bromide.

[7] Ehrlich, Bertheim. *Ber.* **45**, 763 (1912).

3. From phenylmercuric halides and various reagents which remove mercuric ions from solution more completely than does a base. The reaction

$$2\ ArHgX \rightleftharpoons Ar_2Hg + HgX_2$$

usually goes to the left. Removal of Hg ions causes it to go to the right. Alkali sulfides give insoluble HgS and leave diphenylmercury. Iodides, thiosulfates and similar compounds give stable complex ions of mercury. Alkaline reducing agents such as sodium stannite, copper and pyridine, and hydrazine[8] give metallic mercury and the diarylmercury.

4. From the double salt of benzenediazonium chloride and $HgCl_2$ heated with copper.[9]

$$2\ PhN_2Cl.HgCl_2 + 6\ Cu \rightarrow Ph_2Hg + Hg + 2\ N_2 + 6\ CuCl$$

This is the most general preparation of aromatic mercuri-bis compounds and gives substances otherwise not readily available. Thus di-β-naphthylmercury is easily made from β-naphthylamine.[10]

Reactions. 1. Diphenylmercury is *stable* to water, alcohols, ammonia, hydrogen sulfide and other active hydrogen compounds which decompose C—Mg linkages.

2. With strong acids, the C—Hg linkages are split stepwise, the first one being much more easily split than the second.

$$Ph_2Hg \xrightarrow{HX} C_6H_6 + PhHgX \xrightarrow{HX} HgX_2 + C_6H_6$$

3. Halogens also break the C—Hg linkages stepwise

$$Ph_2Hg \xrightarrow{X_2} PhX + PhHgX \xrightarrow{X_2} HgX_2 + PhX$$

In this respect thiocyanogen, $(SCN)_2$, acts like a halogen.[11]

4. Active metals replace the mercury. In this way phenyl compounds of Na, Mg, Zn, Cd, Al and Bi have been obtained.

5. Halides of non-metals such as boron, silicon, phosphorus, arsenic and antimony react with mercury diphenyl to give phenyl compounds of the non-metal. One or more of the halogen atoms are replaced by phenyl, depending on conditions.

6. Mercuric salts give a reaction characteristic of mercuri-bis compounds to form the half organic mercury derivatives

$$Ar_2Hg + HgX_2 \rightarrow 2\ ArHgX$$

7. Reactions which might be expected but which fail are ones analogous to certain Grignard reactions. Thus there is no action with carbonyl compounds

[8] Gilman. *Rec. trav. chem.* **55**, 563 (1936).
[9] Nesmejanov. *Ber.* **62B**, 1018 (1929).
[10] "Org. Syntheses."
[11] Söderbäck. *Ann.* **419**, 217 (1919).

and no metathesis with alkyl halides. In the latter case the organic mercury compound acts at high temperature as a *hydrocarbo base.*[12]

$$Me_2CHCH_2Br + Ph_2Hg \rightarrow PhHgBr + C_6H_6 + Me_2C{=}CH_2$$

Phenylmercuric salts are obtainable in a variety of ways:

1. By direct mercuration of benzene by mercuric acetate in alcohol solution.

$$C_6H_6 + Hg(OAc)_2 \rightarrow C_6H_5HgOAc + HOAc$$

Mercuration is a general process and follows the same course as bromination but is less vigorous than the latter process. Treatment of the phenylmercuric acetate with halide solutions gives phenylmercuric halides.

2. From benzenesulfinic acid and mercuric chloride.

$$PhSO_2H + HgCl_2 \rightarrow PhHgCl + SO_2 + HCl$$

This gives a very general process for introducing mercury into a specific position in an aromatic nucleus. The process can start with a known amine and go to the sulfinic acid by diazotization or can start with a known sulfonic acid and go through the sulfonyl chloride to the sulfinic acid. The most readily available aromatic mercurial is *p*-tolylmercuric chloride made in this way from the by-product, *p*-toluenesulfonyl chloride, of saccharin manufacture.[13]

3. By diazotization of aniline through the double salt with mercuric chloride.[14]

4. By the action of mercuric salts on various substances such as phenylmagnesium bromide, phenylboric acid, $PhB(OH)_2$, or phenylarsenoxide, PhAsO.

The *reactions* of the phenylmercuric salts resemble those of diphenylmercury.

Mercury derivatives of aromatic compounds containing activating groups such as hydroxyl and amino are readily available by direct mercuration in positions para and ortho to these groups. Just as the NH_2 and OH groups render the *o*- and *p*-H atoms more readily replaceable they weaken a C—Hg bond in the *o*- or *p*-position. Such compounds react more readily with acids than do phenylmercuric derivatives.

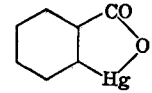
The ease of mercuration of such compounds can be illustrated by phenol. Thus if dry mercuric acetate is added to an excess of hot phenol the chief products are *o*- and *p*-acetoxymercuriphenol and 2,4-di-acetoxymercuriphenol. When the mixture is poured into hot water, the first two and the excess of phenol dissolve. Thus the more highly mercurated products can be removed by filtration while hot. Treatment of the filtrate with hot NaCl solution precipitates *p*-chloromercuriphenol. Another filtration while hot gives a

[12] Jones. *J. Am. Chem. Soc.* **40**, 1257 (1918).
[13] "Org. Syntheses."
[14] Nesmejanov. *Ber.* **62B**, 1010 (1929).

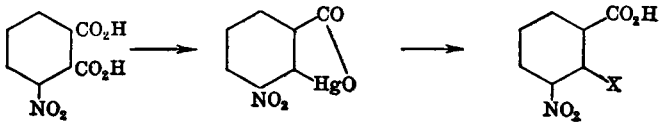
filtrate which deposits *o*-chloromercuriphenol in a high state of purity on cooling.[15] The careful treatment of this compound with 1 mol of halogen or thiocyanogen gives the corresponding *o*-substituted phenol very satisfactorily.[16]

Mercury derivatives of aromatic compounds containing *meta*-directing substituents can also be obtained by direct mercuration. Usually a mixture of all possible compounds is obtained with the *ortho* predominating. Consequently an indirect method of preparation is usually employed to obtain a pure product. Thus the three mercuribenzoic acids are best obtained respectively by oxidation of *p*-chloromercuritoluene,[17] from diazotized *m*-aminobenzoic acid and from phthalic anhydride by heating with mercuric acetate to give anhydro-*o*-hydroxymercuribenzoic acid.[18]

$$C_6H_4(CO)_2O \rightarrow C_6H_4(CO_2Na)_2 \rightarrow C_6H_4(CO_2)_2Hg \rightarrow CO_2 +$$



This reaction is general for aromatic dibasic acids which form internal anhydrides. In the case of 3-nitrophthalic acid, the 2-carboxyl is eliminated exclusively.[19] This gives a method of making such substances as 2-bromo-3-nitrobenzoic acid which would not otherwise be available.[20] The corresponding iodo compound has been invaluable in preparing ortho substituted diphenyls by the action of Cu.



Merthiolate, sodium ethylmercuri thiosalicylate, and Metaphen, the anhydride of 4-nitro-3-hydroxy-mercuri ortho cresol, are finding wide use as germicides (NRR, 144–146, 1946).

Organic Compounds of Mercury. Whitmore, A.C.S. Monograph No. 3, 1921.

[15] "Org. Syntheses."
[16] *ibid.*
[17] *ibid.*
[18] *ibid.*
[19] *ibid.*
[20] *ibid.*

ADDENDA AND COMMENTS

Addition reactions are probably the most important processes in organic chemistry. A typical organic reaction may be said to consist of a primary addition followed by further addition or by a splitting to give the final products.

A carbon atom with only six electrons or an open sextet (C*) represents a reactive system which may be responsible for many of the peculiar rearrangements of organic chemistry (Whitmore 1932–). It should be noted that such a system is not formed by any simple process of ionization but is a result of some more complex change usually preceded by an addition reaction. A good example is the formation of an oxonium salt from an alcohol and its decomposition to give H_2O and other products.

$$R:\ddot{O}:H + H:\ddot{X}: \rightarrow \left[R:\underset{\underset{H}{\ddot{}}}{\ddot{O}}:H\right]^{+} + \left[:\ddot{X}:\right]^{-} \rightarrow H_2O + R^{*}$$

The resulting electronically deficient fragment can then undergo a variety of changes including olefin formation, rearrangement and reaction with negative ions in the solution.

The carbonyl group is the most important single group in organic chemistry. This is related to its extraordinary ability to add a great variety of groups. Still very much of a mystery is its participation in condensations of the aldol type.

Catalysis is of increasing importance in organic chemistry. It is not recognized sufficiently in this book. Nature with her catalytic reactions taking place at ordinary temperature is far ahead of the organic chemist in this field.

The term condensation covers a multitude of reactions in which organic molecules unite either by direct addition or by direct addition followed by the elimination of a simple molecule like water or alcohol.

The importance of conjugation and conjugated systems is increasingly recognized.

The Diels-Alder reaction still remains the only important new general reaction developed in over a decade.

Dismutation or disproportionation is an old process which has now achieved general recognition. In its commonest form it consists of mutual oxidation and reduction by two similar molecules or groups which exist in an intermediate stage of oxidation, making possible action either as oxidizer or reducer. A classical example is that of the Cannizzaro reaction in which one molecule of benzaldehyde acts as a reducing agent and is oxidized to a benzoate and

another molecule of benzaldehyde acts as an oxidizing agent and is reduced to benzyl alcohol.

The importance of the Grignard reagent in organic chemistry is indicated by the two pages which it occupies in the Index.

General processes such as decarboxylation, dehydration, dehydrogenation, hydrogenation and hydrolysis can best be studied by reference to their occurrence in widely varying types of organic molecules.

The study of a subject like isomerism can well be supplemented by reference to Gilman's large two-volume advanced treatise, "Organic Chemistry" (1938).

The importance of oxidation as a general tool in organic chemistry is only partly indicated by the half page devoted to it in the Index.

The increasing importance of plant and animal products of known structure is only inadequately mirrored by their treatment in this volume.

Reduction is an even more universal process of organic chemistry than is oxidation. Its control has also been more thoroughly mastered.

Of course, a book of this limited scope cannot do more than touch on the important field of resins. A multitude of details will be found in works like Ellis "Synthetic Resins and Their Plastics."

There is a difference of opinion concerning the phenomenon of resonance. Some workers feel that it is a phenomenon of the utmost importance while others rather doubt its existence. Certainly there are many properties of conjugated systems which cannot be expressed by our ordinary single and multiple bonds. If these are not properly expressed in terms of the present conception of resonance, a more adequate conception will have to be developed because the phenomena certainly exist.

The closing of rings and their properties is of the widest significance.

The problem of the splitting of a C–C linkage is more important than the space devoted to it would indicate. Unfortunately, the facts are relatively meagre and widely scattered. It is, of course, intimately related to the problem of molecular rearrangements which necessarily involve the splitting of such a linkage and the formation of a new C–C linkage.

The important subject of tautomerism is covered rather extensively. The probability that it is an intermolecular rather than an intramolecular process is emphasized.

INDEX

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This comprehensive index covers both volumes of the work.
Volume One contains pages 1 through 596 and Volume Two contains pages 597 through 866.

A

a-, Ana-position

α-, Alpha position or angle of rotation of plane polarized light

[*α*], Specific rotation

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Ac, acetyl, CH_3CO (not acetate gp.)

Ac alicylic

ACC, American Cyanamid Co. 417

Accelerator 188

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