CHAPTER XXVI

PHENOLS

PHENOLS are aromatic compounds containing hydroxyl groups directly attached to the nucleus, and they are classified as monohydric, dihydric, trihydric phenols, etc. according as they contain one, two, three, etc., hydroxyl groups.

MONOHYDRIC PHENOLS

General methods of preparation. 1. A number of monohydric phenols occur in coal-tar and their extraction from this source is very important commercially.

(i) *Middle oil* (p. 499) is cooled, whereupon naphthalene crystallises out (43 per cent.). The oil is pressed free from the naphthalene and then treated with aqueous sodium hydroxide, which dissolves the phenols. The alkaline liquor is drawn off, boiled, and air is blown through; this removes naphthalene (that remained after cooling the oil), pyridine, etc. The liquid is allowed to cool and then carbon dioxide is blown through, thereby decomposing the sodium phenoxides into the free phenols and sodium carbonate, the latter dissolving in the aqueous layer. This aqueous layer is drawn off, and the crude phenols (the yield of which is about 12 per cent. of the middle oil) are fractionated. Three fractions are collected: *phenol*, b.p. 182° (20 per cent.), *cresols*, b.p. 190–203° (43 per cent.) and *xylenols*, b.p. 211–225° (26 per cent.); the residue is *pitch*.

(ii) *Heavy oil* is treated in the same manner as above. After being pressed to remove naphthalene, the residual oil contains cresols, higher phenols, naphthol, etc. (heavy oil contains about 7 per cent. of the phenols).

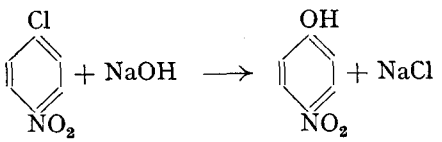
2. Phenols may be prepared by fusion of sodium sulphonates with sodium hydroxide:

$$Ar{\cdot}SO_3Na + NaOH \longrightarrow ArOH + Na_2SO_3$$

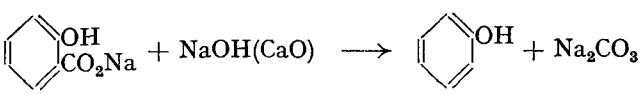
3. When a diazonium sulphate solution is steam distilled, a phenol is produced:

$$Ar{\cdot}N_2HSO_4 + H_2O \longrightarrow ArOH + N_2 + H_2SO_4$$

4. Phenols are formed when compounds containing an "activated" halogen atom are heated with aqueous sodium hydroxide; *e.g.*, *p*-nitrophenol from *p*-chloronitrobenzene:



5. Distillation of phenolic acids with soda-lime produces phenols; *e.g.*, sodium salicylate gives phenol:



6. Phenols may be prepared by means of a Grignard reagent:

$$Ar{\cdot}MgBr \xrightarrow{O_2} Ar{\cdot}O{\cdot}MgBr \xrightarrow{acid} ArOH$$

Alternatively, the Grignard reagent may be converted into a phenol via a boronic or borinic acid (these need not be isolated; Hawthorne, 1957):

$$ArMgX \xrightarrow[(ii)\ H_2O]{(i)\ B(OMe)_3} ArB(OH)_2 \textit{ or } Ar_2BOH \xrightarrow{H_2O_2} ArOH \quad (60\text{–}70\%)$$

Phenol (*carbolic acid, hydroxybenzene*), C_6H_5OH, may be prepared by any of the general methods; commercially, it is prepared from coal tar (see above). The supply from this source is now insufficient to give the amount of phenol required for industry, and so it is also prepared synthetically. Various methods are used. The oldest synthetic method is the fusion of sodium benzenesulphonate with soldium hydroxide:

$$C_6H_5{\cdot}SO_3Na \xrightarrow{NaOH} C_6H_5ONa \xrightarrow{HCl} C_6H_5OH$$

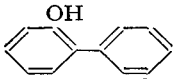
A more recent method is to heat chlorobenzene with 10 per cent. solution of sodium carbonate or sodium hydroxide under pressure at about 300°:

(i) $C_6H_5Cl + Na_2CO_3 + H_2O \longrightarrow C_6H_5OH + NaCl + NaHCO_3$

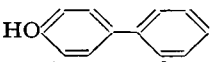
(ii) $C_6H_5Cl + C_6H_5OH + Na_2CO_3 \longrightarrow (C_6H_5)_2O + NaCl + NaHCO_3$

By adding about 10 per cent. of diphenyl ether to the reaction mixture, the further formation of this ether is prevented in reaction (ii).

In addition to diphenyl ether, some *o*- and *p*-hydroxydiphenyls are obtained:



o-compound



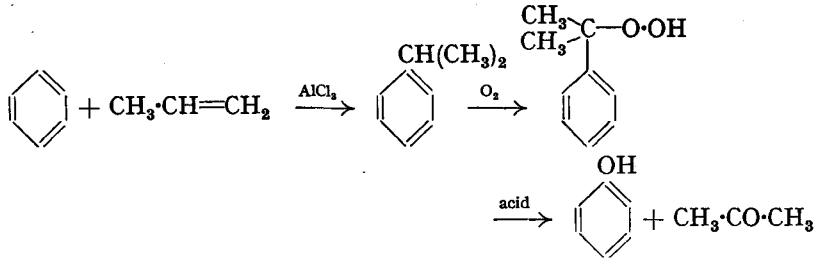
p-compound

The *o*-compound is used as an antiseptic, and the *p*- for making resins.

One of the newest methods of preparing phenol synthetically is to heat chlorobenzene (prepared by the Raschig method, p. 548) with steam at 425° in the presence of a catalyst:

$$C_6H_6 + HCl + \tfrac{1}{2}O_2 \longrightarrow C_6H_5Cl + H_2O$$
$$C_6H_5Cl + H_2O \longrightarrow C_6H_5OH + HCl$$

The hydrochloric acid formed in the second reaction is returned for use in the first. Another new method is the oxidation of cumene to the hydroperoxide which is then decomposed into phenol and acetone by means of acid:



Properties of phenol—these are characteristic of monohydric phenols. Phenol is a colourless crystalline solid, m.p. 43°, b.p. 182°, which turns pink on exposure to air and light. It is moderately soluble in cold water, but is readily soluble in ethanol and ether. Phenol undergoes the *Liebermann reaction* (*cf.* p. 317); when phenol is dissolved in concentrated sulphuric

acid and a few drops of aqueous sodium nitrite added, a red colour is obtained on dilution, and turns green when made alkaline with aqueous sodium hydroxide.

Phenol is used as an antiseptic and disinfectant, and in the preparation of dyes, drugs, bakelite, etc.

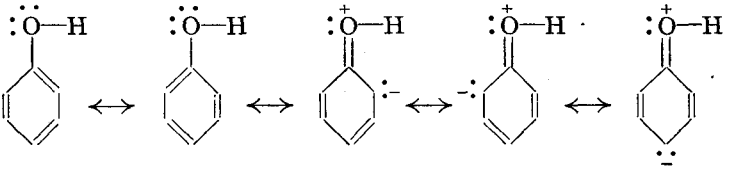
Reactions. 1. Phenol gives a violet colour with ferric chloride; this reaction is characteristic of all compounds containing the grouping —C(OH)=C< (*cf.* enols, p. 220).

2. Phenol behaves as a weak acid, forming *phenoxides* with strong alkalis:

$$C_6H_5OH + NaOH \longrightarrow C_6H_5ONa + H_2O$$

Since phenol is a weaker acid than carbonic acid, it may be separated from carboxylic acids by making the solution alkaline with sodium hydroxide, and then passing in carbon dioxide. Phenol is liberated from its sodium salt and so may be extracted with ether; the carboxylic acid salts are *not* decomposed by carbon dioxide.

Phenols are stronger acids than the alcohols, one possible explanation being that the former exist as resonance hybrids whereas the latter do not:



Thus the oxygen atom acquires a positive charge, and so attracts the electron pair of the O—H bond, thereby facilitating the release of a proton. Since resonance is impossible in alcohols, the hydrogen atom is more firmly linked to the oxygen. Support for this argument is to be found in the fact that the resonance energy of phenol is greater than that of the benzene ring (this indicates that the presence of the hydroxyl group has given rise to a larger number of resonating structures); and it has also been shown that the C—OH bond has about 16 per cent. double bond character. Puttnam (1960), from spectroscopic studies, has shown that in all phenols the hydroxyl group is coplanar with the aromatic ring. This is in keeping with the partial double-bond character of the C—O bond.

3. Phenol can be halogenated, nitrated, and sulphonated to give *o*- and *p*-derivatives (the hydroxyl group is *o*-*p*-orienting; *cf.* 2 above).

4. Phenol reacts with phosphorus pentachloride to form only a very small amount of chlorobenzene, the main product being triphenyl phosphate, $(C_6H_5O)_3PO$ (see p. 545). Phenol does *not* react with hydrogen chloride.

5. When distilled with zinc dust, phenol is converted into benzene:

$$C_6H_5OH + Zn \longrightarrow C_6H_6 + ZnO$$

Phenol may also be converted into benzene by treating with hydrogen at atmospheric pressure in the presence of molybdenum oxide as catalyst (Fischer *et al.*, 1932):

$$C_6H_5OH + H_2 \longrightarrow C_6H_6 + H_2O$$

6. When heated with the double compounds of ammonia and zinc or calcium chloride, phenol forms aniline:

$$C_6H_5OH + NH_3 \xrightarrow{ZnCl_2} C_6H_5{\cdot}NH_2 + H_2O$$

Aniline is also produced when phenol is heated with ammonia under pressure.

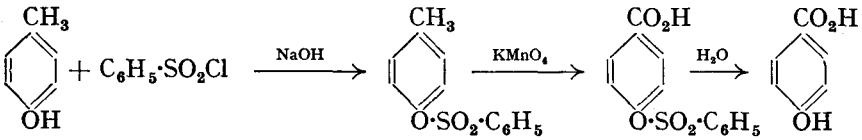
7. The alkali phenoxides react with alkyl halides to form phenolic ethers; *e.g.*, sodium phenoxide and methyl iodide form *anisole*:

$$C_6H_5ONa + CH_3I \longrightarrow C_6H_5{\cdot}O{\cdot}CH_3 + NaI$$

8. Phenol can be hydrogenated in the presence of a nickel catalyst at 160° to *cyclo*hexanol (*cf.* reaction 5, above):

$$C_6H_5OH + 3H_2 \xrightarrow{Ni} C_6H_{11}OH \quad (ex.)$$

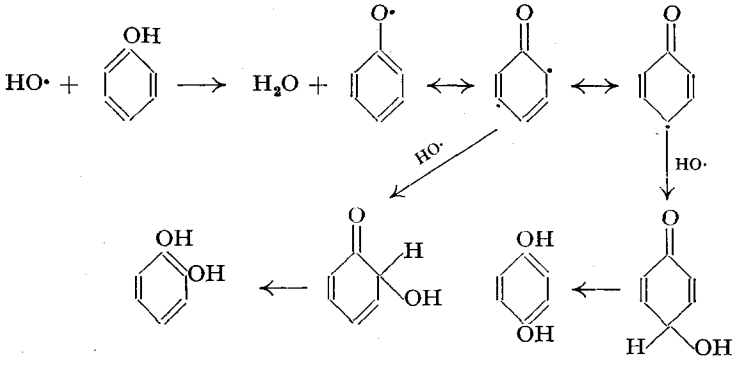
When phenol is oxidised with potassium permanganate, the ring is broken down (most phenols behave in a similar manner). Homologues of phenol can, however, be oxidised to the corresponding phenolic acid *provided the hydroxyl group is protected by alkylation or acylation.* The best means of protection is the formation of the benzenesulphonate, *e.g.*,



Phenol also undergoes the **Elbs persulphate oxidation** (1893). In this reaction, monohydric phenols are oxidised to dihydric phenols with potassium persulphate in alkaline solution. If the *p*-position to the hydroxyl group is free, the quinol is formed; if the *p*-position is occupied, the catechol derivative is formed. The yields of dihydric phenol are often low, but the products can readily be isolated pure.

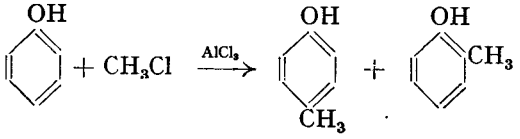
Phenols, as a group, appear to undergo homolytic substitution by the mechanism of *transfer substitution*, *e.g.*, hydroxylation of phenol by hydrogen peroxide in the presence of ferrous ions gives a mixture of catechol and quinol (Weiss *et al.*, 1951):

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + HO^- + HO\cdot$$



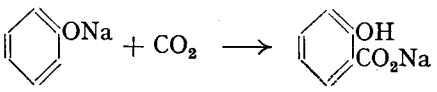
Other products are also obtained, *e.g.*, *o*-benzoquinone. Phenols also react with lead tetra-acetate by transfer substitution. The initial products are *o*- and *p*-acetoxyl derivatives (replace HO· by Me·COO· in the above equations). These derivatives, however, are usually attacked further (Cavill *et al.*, 1954).

9. Phenol undergoes the Friedel–Crafts reaction to form mainly the *p*-derivative and a small amount of the *o*-:



10. Phenol couples in the *p*-position with diazonium salts in alkaline solution to form hydroxyazo-compounds (p. 601).

11. When sodium or potassium phenoxide is heated with carbon dioxide, a phenolic acid is formed (see p. 681), *e.g.*, salicylic acid:

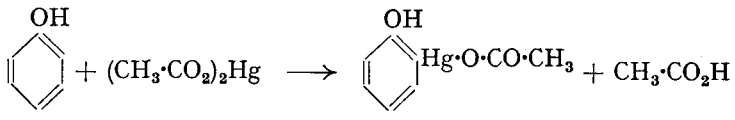


12. Phenol is chloromethylated (p. 535) so readily that usually polymers are obtained.

The presence of a negative group, however, decreases the activating effect of the hydroxyl group; *e.g.*, *p*-nitrophenol may be successfully chloromethylated to give 2-hydroxy-5-nitrobenzyl chloride.

On the other hand, phenol may be chloromethylated successfully by first converting it into an ester (usually the ethyl phenyl carbonate by means of chloroformic ester), and chloromethylating this.

13. Phenol can be readily mercurated, *e.g.*, when refluxed with aqueous mercuric acetate, *o*-acetoxymercuriphenol is formed (together with some dimercurated compound):

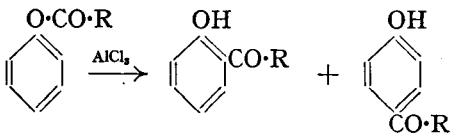


14. Phenol undergoes the *Reimer–Tiemann reaction* (p. 655), and the *Gattermann reaction* (p. 646).

15. When treated with acid chlorides, phenol forms phenyl esters:

$$C_6H_5OH + R{\cdot}COCl \longrightarrow R{\cdot}CO_2C_6H_5 + HCl$$

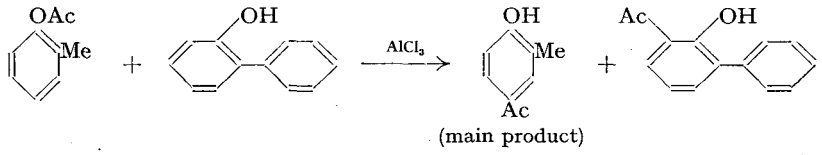
These phenyl esters, under suitable conditions, undergo the **Fries rearrangement** (1908). This consists of the conversion of a phenyl ester into an *o*- or *p*-hydroxyketone, or a mixture of both, by treatment with anhydrous aluminium chloride:



Generally low temperatures (60° or less) favour the formation of the *p*-isomer, whereas high temperatures (above 160°), favour the *o*-isomer. In either case, the yield of phenolic ketone is better than that obtained by means of a Friedel–Crafts reaction.

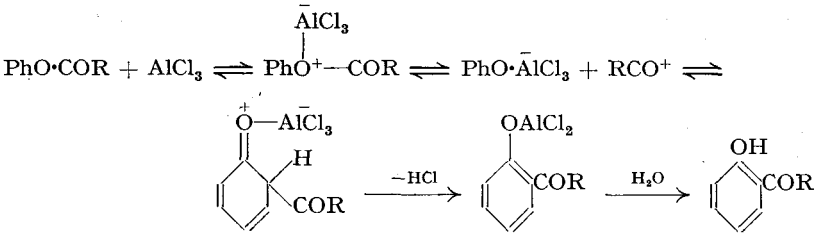
Many theories have been proposed for the Fries rearrangement, but none is certain. There is evidence for an intermolecular mechanism, since, when a

mixture of esters is rearranged, cross products are obtained, *e.g.* (Baltzly *et al.*, 1948):



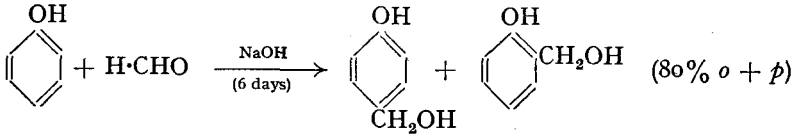
(main product)

A highly favoured mechanism is the following intermolecular one based on the Friedel–Crafts acylation with acid chlorides (p. 533):



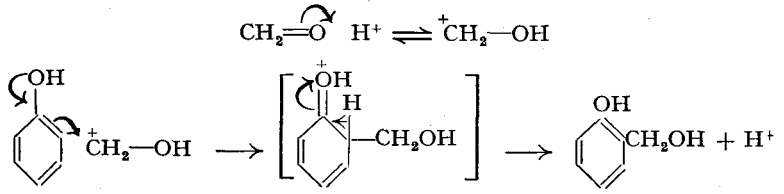
Ralston *et al.* (1940–) showed that variations in the amount of aluminium chloride and in the solvent influence the *o*/*p* ratio in the Fries rearrangement in the same way as they do in the Friedel–Crafts reaction; this supports the analogy between the two reactions.

16. Phenol condenses with aliphatic and aromatic aldehydes in the *o*- and *p*-positions, the most important example being the condensation with formaldehyde. At low temperature, in the presence of dilute acid or alkali, and using formalin (40 per cent. aqueous formaldehyde), the main product is *p*-hydroxybenzyl alcohol, together with a small amount of the *o*-isomer.

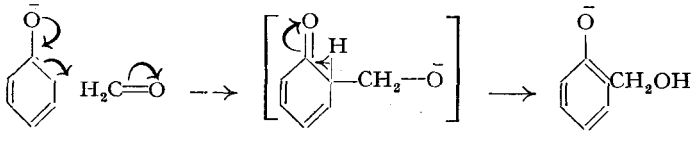


This is known as the **Lederer–Manasse reaction** (1894); its mechanism may be:

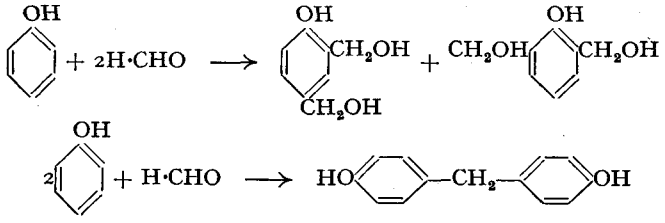
Acid catalysis



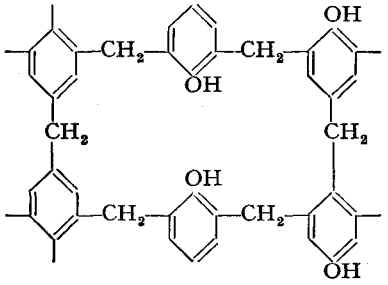
Base catalysis



When larger amounts of formaldehyde are used, bishydroxymethylphenol and *p*:*p*′-dihydroxydiphenylmethane are obtained:

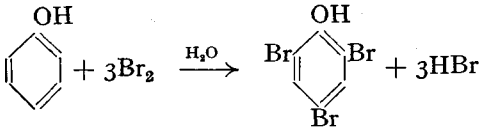


These condensations are the basis of the preparation of phenol-formaldehyde resins; phenol and excess formaldehyde, in the presence of dilute sodium hydroxide, slowly form a three-dimensional polymer of the possible structure:



Substituted Phenols

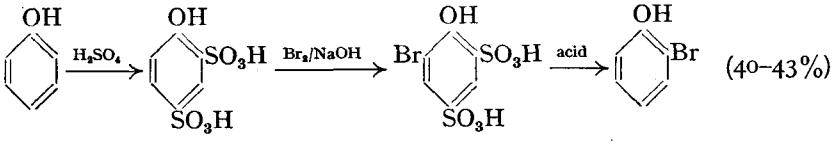
Halogenated Phenols. The presence of the hydroxyl group activates the *o*- and *p*-positions to such an extent that phenol, on treatment with chlorine or bromine water, gives an immediate precipitate of the 2 : 4 : 6-trihalogen derivative:



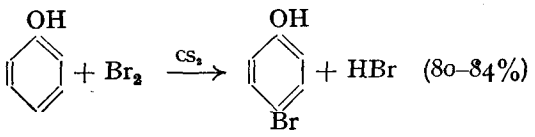
This reaction may be used to estimate phenol quantitatively.

Gaseous chlorine or bromine at 150–180° attacks phenol to give mainly the *o*-halogen derivative and a small amount of the *p*-isomer. If phenol is halogenated in glacial acetic acid or in carbon tetrachloride solution, the mono-, di- or trihalogen derivative is produced according to the amount of halogen used. Phenol can also be chlorinated with sulphuryl chloride, the reaction being less vigorous and more easily controlled than with chlorine.

o-Bromophenol may be obtained in a high state of purity by first sulphonating phenol to give the disulphonic acid derivative, which is then treated with sodium hydroxide and bromine. The mixture is acidified and steam distilled, whereupon the sulphonic acid groups are eliminated, the resulting *o*-bromophenol distilling over:

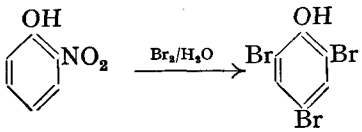


p-*Bromophenol* may be prepared by adding bromine dissolved in carbon disulphide to a cooled solution of phenol in carbon disulphide:

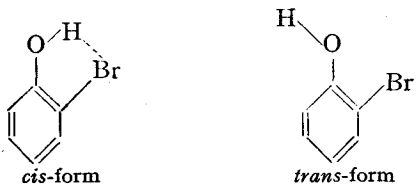


o- and *p*-Halogeno-phenols may be prepared pure from the corresponding halogeno-anilines.

If the hydroxyl group is in the *o*- or *p*-position to a negative group such as NO_2, CO_2H, or SO_3H, then on treatment with *aqueous* halogen, the negative group is often displaced, the product being the trihalogen derivative of phenol; *e.g.*,

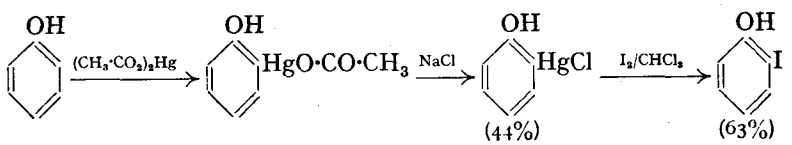


o-*Bromophenol* shows two absorption bands in the infrared; this has been explained by suggesting the existence of two isomers due to hydrogen bonding. *o*-Iodophenol behaves similarly, but it appears that *o*-chlorophenol exists almost entirely in the *cis* form (hydrogen bonding is much stronger for chlorine than for bromine or iodine).

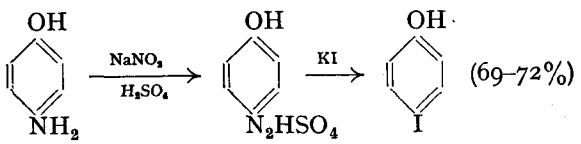


cis-form *trans*-form

o-*Iodophenol* is best prepared by heating phenol with mercuric acetate, converting the *o*-acetoxymercuriphenol into the corresponding chloromercuri-derivative by heating with aqueous sodium chloride, and replacing the chloromercuri-group by treatment with iodine in chloroform solution:



p-*Iodophenol* may be prepared as follows:

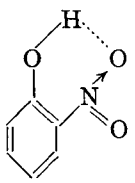


The halogenated phenols, particularly the *o*- and *p*-derivatives, are stronger acids than phenol itself, *e.g.*, tribromophenol decomposes carbonates. This may be due to the inductive effect of the halogen atom which enhances

resonance, thereby increasing the tendency for proton release in the hydroxyl group.

When the halogenated phenols are fused with potassium hydroxide, halogen is replaced by hydroxyl, but the positions do not always remain the same, *e.g.*, all three isomeric chlorophenols give resorcinol (*m*-dihydroxy benzene).

Nitrophenols. Treatment of phenol with cold dilute nitric acid gives a mixture of *o*- and *p*-nitrophenols, the latter predominating; oxidation products are also obtained. These isomers may be separated by steam distillation. As we have seen (p. 53), solubility in hydroxylic solvents depends on, among other things, the power to form hydrogen bonds with the solvent. Phenol can form these bonds and hence a certain solubility in water can be expected. This argument also applies to substituted phenols since the hydroxyl group is still present, but in the *o*-compounds, however, because chelation is possible, hydrogen bonding with the solvent water molecules is hindered and hence the solubility is lowered. Furthermore, since chelation causes the *o*-compound to behave as a "monomer," this isomer will be more volatile than the corresponding *m*- and *p*-isomers. Thus the effects of chelation are lower solubility and greater volatility in the *o*-compounds, thereby enabling these to be separated from their *m*- and *p*-isomers by steam distillation. The *o*-isomer may also be separated from the *p*- by crystallisation or by chromatography.

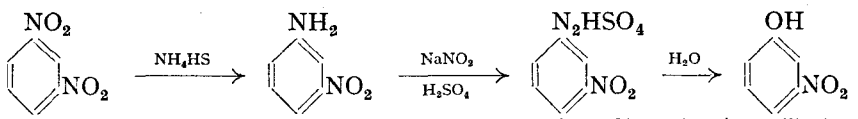


It has been found that the nitration of phenol (and of aniline) is accelerated by the presence of nitrous acid, and it appears that the mechanism of the reaction is different from that of ordinary nitration. Evidence for this is based on the observation that when phenol is nitrated in the presence of very little nitrous acid, *o*- and *p*-nitrophenols are formed in the ratio of 7 : 3. When nitrated in the presence of a large amount of nitrous acid, the ratio becomes 1 : 9, which is the ratio in which *o*- and *p*-nitrosophenols are formed if the nitric acid is omitted. It is therefore believed that the nitroso-compound is formed first, and this is then oxidised to the nitro-compound (Hughes *et al.*, 1946). This scheme may be used to prepare pure *p*-nitrophenol in very good yield; phenol is treated with nitrous acid and the product, *p*-nitrosophenol, is oxidised to *p*-nitrophenol.

o- and *p*-Nitrophenols are prepared commercially by direct nitration of phenol, and by hydrolysis of *o*- and *p*-chloronitrobenzenes with aqueous sodium hydroxide.

o- and *p*-Nitrophenols are also formed when nitrobenzene is heated with solid potassium hydroxide (*cf.* p. 525).

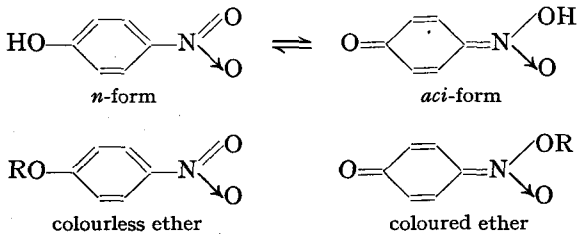
m-Nitrophenol may be prepared from *m*-dinitrobenzene:



(81–86% on the nitroaniline)

o-Nitrophenol is a yellow solid, m.p. 45°; the *m*- and *p*-isomers are colourless solids, m.ps. 97° and 114°, respectively. The *o*- and *p*-derivatives are stronger acids than the *m*-, and all are stronger acids than phenol (*cf.* chlorophenols, above). All three are readily reduced to the corresponding aminophenols, and the nitro-group in the *o*- and *p*-compounds is displaced on treatment with bromine water, 2 : 4 : 6-tribromophenol being formed. The salts of the three nitrophenols are highly coloured (yellow to red), and *o*- and *p*-nitrophenols give rise to two series of ethers, one colourless and the

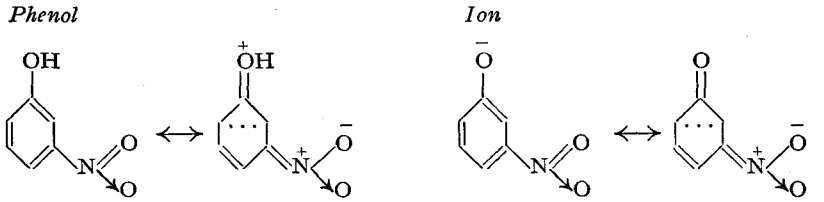
other coloured. The colour of the latter series is believed to be due to the presence of the *quinonoid* structure:



Only one form of the nitrophenols is known, but the existence of two series of ethers suggests that the nitrophenols are tautomeric. The colourless ethers are stable, and are only very slowly hydrolysed to the nitrophenol: the coloured ethers are unstable, and are easily hydrolysed. The *n*-ethers are produced by alkylating the nitrophenol in the usual way (*e.g.*, with alkyl halide and alkali). If, however, the silver salt of the nitrophenol is treated with alkyl iodide, a mixture of the *n*- and *aci*-ethers is obtained.

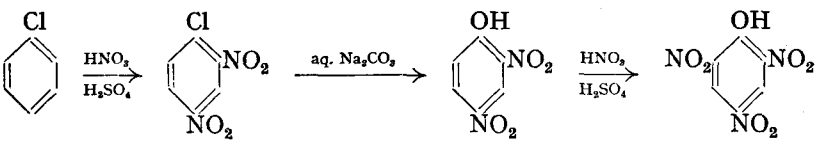
The ethers of *m*-nitrophenol exist only in one form—colourless. This agrees with the fact that the *m*-compound cannot form the quinonoid structure.

On the other hand, it is difficult to explain the colour of the salts of *m*-nitrophenol on this theory. One suggestion is that the ion can resonate more than the undissociated phenol, and this gives rise to colour.



Owing to the negative charge on the oxygen atom, more of the other resonating structure is present. This also explains why *m*-nitrophenol is a stronger acid than phenol.

When *o*- and *p*-nitrophenols are nitrated, 2 : 4-dinitrophenol is formed, and this, in turn, can be further nitrated to 2 : 4 : 6-trinitrophenol (*picric acid*). The yield of picric acid is poor due to large losses by oxidation. Picric acid is prepared commercially by first sulphonating phenol and then nitrating the product (see p. 609). Another commercial method is as follows:

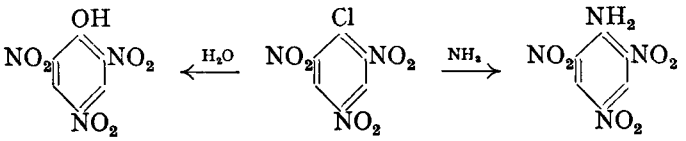


The interesting point to note about this method is that the presence of the negative nitro-group protects, to a large extent, the hydroxyl group from oxidation. It is in the nitration of phenol to the *o*- and *p*-nitrophenols that the loss by oxidation is greatest.

Picric acid may be obtained in the laboratory by oxidising *s*-trinitrobenzene with potassium ferricyanide.

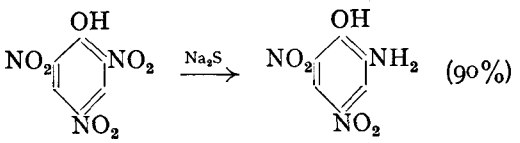
When benzene is subjected to *oxynitration, i.e.*, simultaneous oxidation and nitration by means of a solution of mercuric nitrate in nitric acid, 2 : 4-dinitrophenol and picric acid are formed. This is often referred to as the **Wolffenstein-Böters reaction** (1906).

Picric acid is a yellow crystalline solid, m.p. 122°, with a bitter taste (Greek: *pikros*, bitter). It is almost insoluble in cold water, but is soluble in hot water and in ether. It is a fairly strong acid, decomposing carbonates; the three nitro-groups in the *p*- and two *o*-positions create the maximum enhancement of resonance. The yellow colour is probably due to the presence of a large amount of the quinonoid structure. Picric acid forms crystalline molecular compounds known as *picrates*, with aromatic hydrocarbons, amines and phenols; their picrates are frequently used to identify these classes of compounds. When treated with bleaching powder, picric acid forms chloropicrin (p. 117) as one of the products. Picric acid forms *picryl chloride* when treated with phosphorus pentachloride. Although phenol gives a very poor yield of chlorobenzenes with phosphorus pentachloride, the nitrophenols (*o*-, *p*-, and *o* : *p*-derivatives) give fairly good yields of chloro-compound (the nitrophenols are relatively strongly acidic). The chlorine atom in picryl chloride is very reactive (owing to the presence of the three nitro-groups in the *p*- and two *o*-positions); *e.g.*, when boiled with water, picryl chloride forms picric acid, and when shaken with concentrated ammonia, *picramide*:



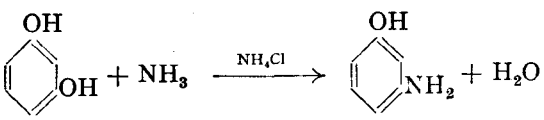
The chlorine atom is also readily replaced by hydrogen when picryl chloride is treated with hydrogen iodide (see p. 557).

Picramic acid (*2-amino-4 : 6-dinitrophenol*) is formed when picric acid is reduced with sodium sulphide (*cf.* p. 564):



Picric acid is used in the manufacture of explosives, and is a dye for wool and silk.

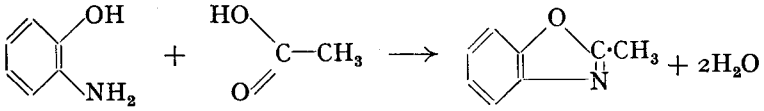
Aminophenols. These may be prepared by reducing the corresponding nitrophenols with metal and acid, or catalytically. *m*-Aminophenol (used in the manufacture of dyes) is prepared commercially by heating resorcinol with ammonia and ammonium chloride under pressure at 200°:



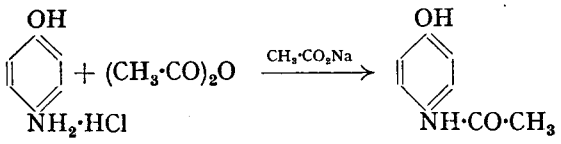
This replacement reaction is only satisfactory for the preparation of the *m*-isomer.

o- and *p*-Aminophenols are more weakly acidic than phenol, possibly

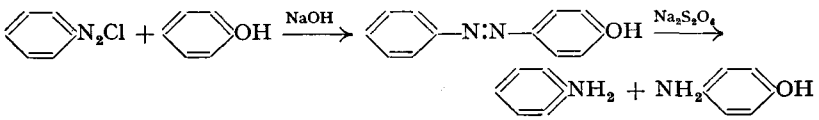
due to the amino-group inhibiting resonance of the hydroxyl group with the benzene ring; thus they do not form phenoxides with alkalis. On the other hand, they form salts with strong inorganic acids. The *o*- and *p*-derivatives are readily oxidised to the corresponding quinones; the *m*-compound is not easily oxidised (and does not give a quinone). *o*-Aminophenol has a marked tendency to form cyclic compounds (*cf.* *o*-phenylenediamines, p. 579); *e.g.*, with acetic acid it forms 2-methylbenzoxazole:



The amino-group in aminophenols is more readily acetylated than the hydroxyl group; *e.g.*, when *p*-aminophenol hydrochloride is acetylated with one equivalent of acetic anhydride in the presence of aqueous sodium acetate, *p*-acetamidophenol is formed:



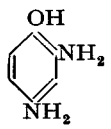
p-*Aminophenol*, m.p. 186°, is very important as a photographic developer. It may be prepared by boiling phenylhydroxylamine with sulphuric acid (see p. 561), or by reducing hydroxyazobenzene with sodium hyposulphite:



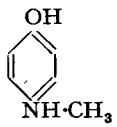
It is prepared industrially by the electrolytic reduction of nitrobenzene in sulphuric acid (see p. 561).

p-Aminophenol is readily oxidised to *p*-benzoquinone (p. 669).

Two other important photographic developers are *amidol*, m.p. 78°, and *metol*, m.p. 87°:

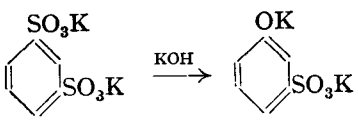


amidol

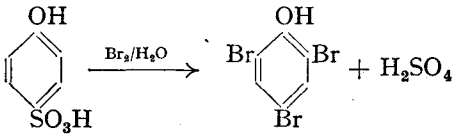


metol

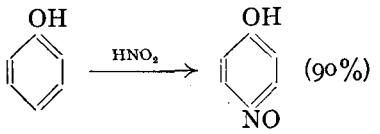
Phenolsulphonic acids. When phenol is treated with concentrated sulphuric acid, *o*- and *p*-phenolsulphonic acids are formed, the former being the main product at ordinary temperatures, and the latter at higher temperatures (110°); the *o*-compound rearranges to the *p*- on heating. *m*-Phenolsulphonic may be obtained by the controlled potassium hydroxide fusion of benzene-*m*-disulphonic acid at about 180°:



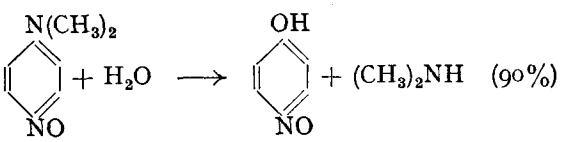
When *o*- or *p*- to a hydroxyl group (or an amino-group), a sulphonic acid group is often displaced by halogen when the sulphonic acid is halogenated in aqueous solution (*cf.* nitrophenols):



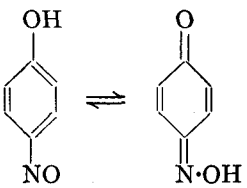
Nitrosophenols. When treated with nitrous acid, phenol forms mainly *p*-nitrosophenol, and a small amount of the *o*-compound:



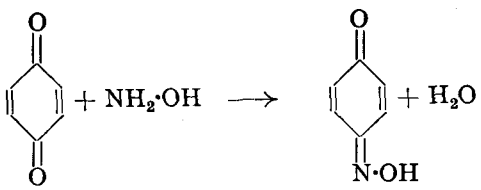
p-Nitrosophenol is also formed when *p*-nitrosodimethylaniline is boiled with alkali (p. 573):



***p*-Nitrosophenol** crystallises from hot water in pale yellow needles which readily turn brown. On the other hand, it crystallises from ether in brownish-green flakes. This colour suggests that *p*-nitrosophenol may have a quinonoid structure, *i.e.*, the following tautomeric system is present (*cf.* nitrophenols):



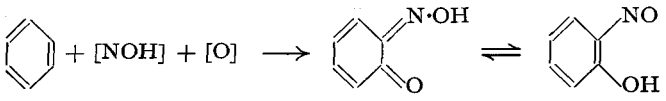
This is supported by the fact that *p*-nitrosophenol has been shown to be identical with the monoxime of *p*-benzoquinone, which may be prepared by the action of hydroxylamine on *p*-benzoquinone:



Havinga *et al.* (1955) have shown, from a study of ultraviolet spectra, that *p*-nitrosophenol exists in solution as the phenol together with the quinone oxime, but in the solid state it appears that only the latter form is present. Hadži (1956), from an examination of the infrared spectrum of the mon-

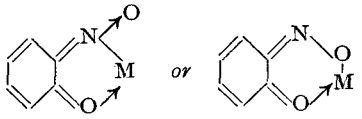
oxime of benzoquinone, concludes that the oxime structure is correct for the compound in the solid state, and that this form predominates in chloroform solution.

o-*Nitrosophenol* may be prepared by the **Baudisch reaction** (1913), which uses the *nitrosyl radical* NOH and an oxidising agent; a nitroso- and a hydroxyl group are introduced into the ring (*cf.* oxynitration, p. 628):



The nitrosyl radical is formed by the reduction of nitrous acid or the oxidation of hydroxylamine; the presence of a copper salt is essential, both to stabilise the nitrosyl radical and to ensure that *o*-, and not *p*-nitrosophenol, is formed.

The characteristic property of *o*-nitrosophenol is its ability to form highly-coloured chelated compounds with heavy metals; the complex has the quinone–monoxime structure (which is necessary for colour):



M = metal

Homologues of Phenol

Cresols (*hydroxytoluenes*), $CH_3 \cdot C_6H_4OH$. The cresols occur in the middle and heavy oil fractions of coal-tar (p. 499). The mixture of the three cresols (together with a little phenol) is known as *cresylic acid* or *creosote*, and is used for preserving purposes, *e.g.*, timber, railway sleepers, etc. A solution of cresols in soapy water is known as *lysol*, which is used as a disinfectant.

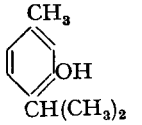
The boiling points of the cresols are: *o*-, 191°; *m*-, 201°; *p*-, 202·5°. By means of a very good fractionating column it is possible to separate the *o*-isomer from the other two. Each isomer can be obtained pure from the corresponding toluidine.

When either *o*- or *m*-chlorotoluene is heated with aqueous sodium hydroxide at about 300–320° under pressure, a certain amount of *m*-cresol is obtained.

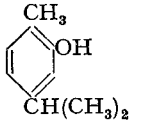
The methyl group in the cresols is *not* oxidised to a carboxyl group by chromic acid; nor is the ring attacked (*cf.* p. 512). If, however, the hydroxyl group is acetylated or alkylated, the methyl group can then be oxidised.

m- and *p*-Cresols are used in the manufacture of resins, plasticisers, etc.

Two higher homologues of phenol are the isomers *thymol* (3-hydroxy-4-*iso*-propyltoluene), and *carvacrol* (2-hydroxy-4-*iso*propyltoluene):



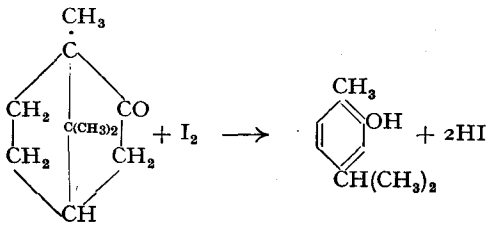
thymol, m.p. 51°



carvacrol, b.p. 237°

Thymol occurs in the essential oil, oil of thyme, but is prepared commercially by heating *m*-cresol and *iso*propanol with sulphuric acid; it is used in perfumery

and as an antiseptic. Carvacrol also occurs in some essential oils, but is prepared by heating camphor with iodine:

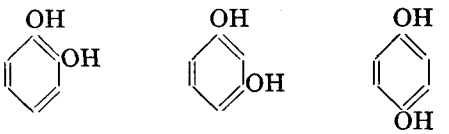


It is used in perfumery and as an antiseptic.

A number of monochloro-derivatives of monohydric phenols are also very good disinfectants, *e.g.*, 2-chloro-5-hydroxytoluene.

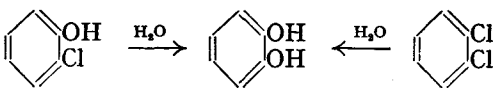
DIHYDRIC PHENOLS

There are three possible dihydroxybenzenes, and all are known:

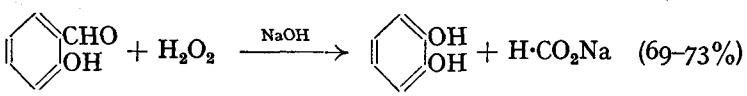


catechol resorcinol quinol

Catechol (*o-dihydroxybenzene*) occurs in certain plants. It may be prepared by the alkaline fusion of *o*-phenolsulphonic acid; commercially, it is prepared by heating *o*-chlorophenol or *o*-dichlorobenzene with 20 per cent. aqueous sodium hydroxide and a trace of copper sulphate at 190° under pressure:



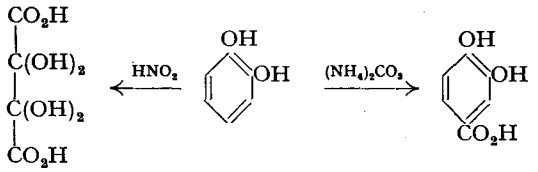
Catechol may be conveniently prepared in the laboratory by the action of alkaline hydrogen peroxide on salicylaldehyde:



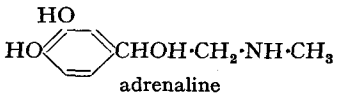
This reaction is characteristic of *o*- and *p*-hydroxyaldehydes; it is known as the **Dakin reaction** (1909).

Catechol is a colourless solid, m.p. 105°, soluble in water, ethanol and ether. With ferric chloride it gives a green coloration which turns red on the addition of sodium carbonate. Catechol is a powerful reducing agent: its aqueous solution darkens on exposure to air due to oxidation; it reduces cold silver nitrate and warm Fehling's solution. It is used as a photographic developer. Catechol is oxidised by silver oxide in ether solution to *o*-benzoquinone, and it condenses with many compounds, *e.g.*, with phthalic anhydride in the presence of sulphuric acid to form alizarin (p. 806).

Two curious reactions of catechol are its oxidation with nitrous acid in ether solution to dihydroxytartaric acid, and its easy carboxylation to protocatechuic acid by heating with aqueous ammonium carbonate at 140° under pressure:



Important derivatives of catechol are *guaiacol* and *adrenaline* (the hormone secreted by the adrenal glands):

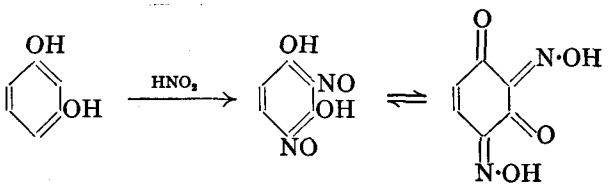


adrenaline

Resorcinol (m-*dihydroxybenzene*) is prepared industrially by the alkaline fusion of benzene-*m*-disulphonic acid.

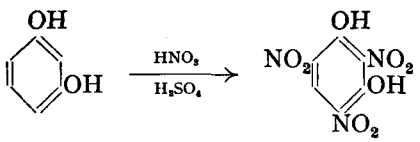
Resorcinol is also formed when benzene-*p*-disulphonic acid or all three bromobenzenesulphonic acids are fused with alkali.

Resorcinol is a colourless crystalline solid, m.p. 110°, very soluble in water, ethanol and ether. Its aqueous solution gives a violet coloration with ferric chloride. It is not so powerful a reducing agent as the *o*- and *p*-isomers, but it will reduce silver nitrate and Fehling's solution on warming. With nitrous acid it forms dinitrosoresorcinol:



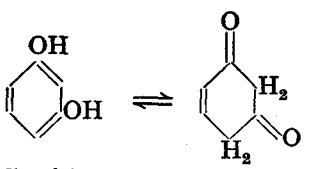
This is known as *Fast Green* O, and is used as a dye.

When nitrated, resorcinol forms **styphnic acid** (2 : 4 : 6-*trinitroresorcinol*), m.p. 180°:



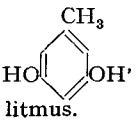
Styphnates are used to identify certain compounds by molecular complex formation (*cf.* picrates, p. 628; see also p. 557).

A number of reactions of resorcinol are best explained on the assumption that resorcinol behaves as a tautomeric substance:

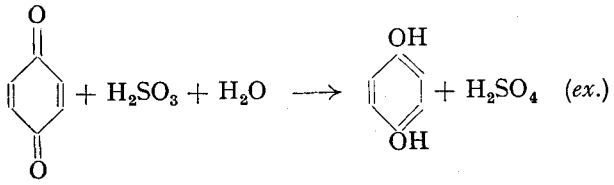


dienol form diketo form

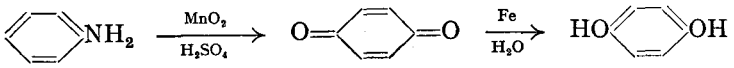
Resorcinol is used for making dyes.

Orcinol (3 : 5-*dihydroxytoluene*),  , m.p. 290°, is found in many lichens, and is chemically related to litmus.

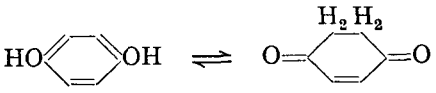
Quinol (*hydroquinone*, p-*dihydroxybenzene*) occurs in the glucoside *arbutin*. It may be prepared by diazotising *p*-aminophenol (yield 30 per cent)., or by reducing *p*-benzoquinone with sulphurous acid:



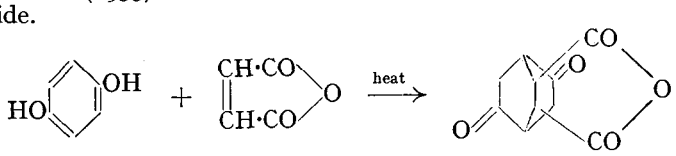
It is made commercially as follows:



Quinol is a colourless solid, m.p. 170°, very soluble in water, ethanol and ether. It is a powerful reducing agent and hence is used as a photographic developer. It is oxidised by ferric chloride to *p*-benzoquinone; it is also oxidised by diazonium salts, no coupling taking place at all. In both cases, the oxidation takes place via the intermediate formation of *quinhydrone* (p. 670). Quinol behaves as a tautomeric compound.



Cookson *et al.* (1955) have shown that quinol forms an adduct with maleic anhydride.



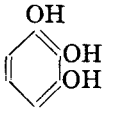
This is particularly interesting since it is the first example of an adduct being formed from a *monocyclic* hydrocarbon (see Diels–Alder reaction, p. 472.)

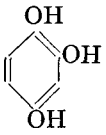
Clathrates. When quinol is crystallised from a solution in water saturated with sulphur dioxide, a quinol-sulphur dioxide complex is obtained. These inclusion complexes are also formed with hydrogen sulphide, methanol, etc., and have a molecular formula of the type $3C_6H_4(OH)_2{\cdot}Z$ (where Z is one molecule of the second component). Powell *et al.* (1948), using X-ray analysis, found that in these complexes the quinol molecules were linked together through hydrogen bonds to form giant molecules the cavities in which enclosed the second component. Powell named these complexes **clathrates,** and showed that the " cages " must be large enough to contain the molecule of the second component and that they must be so arranged that the enclosed molecules do not escape. These clathrates are stable, but the imprisoned molecules may be released either by melting or by means of an organic solvent which dissolves quinol.

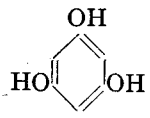
Clathrates differ from channel complexes (p. 387) in that each molecule of the second component is enclosed in a separate molecular cage of limited size, and thus the possible variations of this second component depend on *molecular size*. Hence clathrates may be used to separate certain homologues, *e.g.*, quinol forms a clathrate with methanol but not with any other homologue of this alcohol series.

TRIHYDRIC PHENOLS

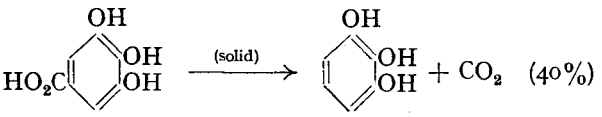
There are three possible trihydroxybenzenes, and all are known:


pyrogallol


hydroxyquinol

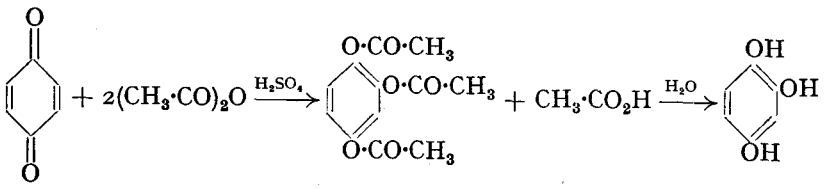

phloroglucinol

Pyrogallol (vic-*trihydroxybenzene*) may be prepared by heating solid gallic acid in a stream of carbon dioxide, or by heating an aqueous solution of gallic acid at 210° under pressure:

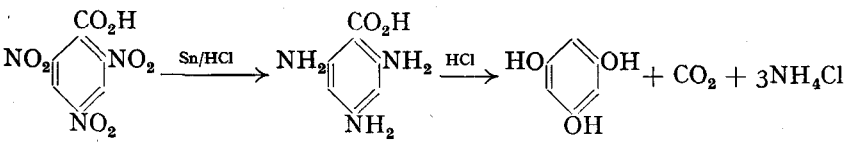


Pyrogallol is a colourless solid, m.p. 133°, soluble in water, ethanol and ether; its aqueous solution gives a red coloration with ferric chloride. Alkaline solutions of pyrogallol oxidise very rapidly on exposure to air, and hence are used in gas analysis for the absorption of oxygen (and carbon dioxide); the pyrogallol is oxidised to a complex mixture containing, among other things, carbon monoxide, carbon dioxide, acetic and oxalic acids. Pyrogallol also reduces the salts of silver, gold, platinum and mercury to their metals. It is used as a photographic developer.

Hydroxyquinol (as-*trihydroxybenzene*), m.p. 140°, may be prepared by the alkaline fusion of quinol in air. It is best prepared by hydrolysing its triacetate, which is obtained by heating *p*-benzoquinone with acetic anhydride and concentrated sulphuric acid:

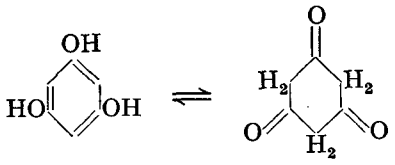


Phloroglucinol (s-*trihydroxybenzene*) is obtained when many plant resins are fused with alkalis. It may be prepared by fusing resorcinol with sodium hydroxide in the air, but a convenient laboratory method is to reduce *s*-trinitrobenzoic acid, and heat the resulting amino-derivative with hydrochloric acid (yield: 46–53 per cent. as dihydrate):



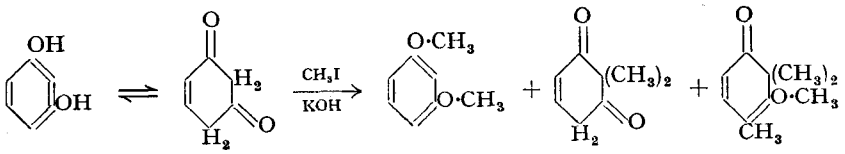
It should be noted that this decarboxylation and replacement of amino-groups by hydroxyl merely by boiling with hydrochloric acid is *not* a general reaction.

Phloroglucinol is a colourless solid, m.p. 218°, fairly soluble in water, its aqueous solution giving a bluish-violet coloration with ferric chloride. Its alkaline solutions rapidly darken on exposure to air due to oxidation. Phloroglucinol behaves as a tautomeric compound; *e.g.*, when warmed with acetic anhydride, it forms the triacetate, and when treated with hydroxylamine, the trioxime:

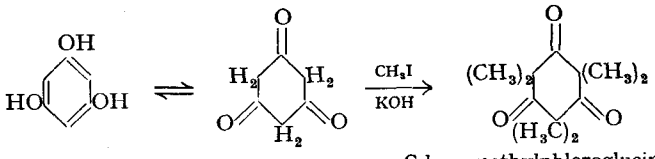


This tautomeric system was formerly supported by the statement that phloroglucinol could be prepared from acetone and malonyl chloride, but according to Elvidge *et al.* (1952), these two compounds do *not* give phloroglucinol.

Infrared spectra studies have shown that *all* phenols are entirely enolic in the solid state and also in solution. Of all the phenols mentioned in the foregoing account, the tendency to react as a ketone is most pronounced in phloroglucinol. Further evidence for the existence of tautomerism in phenols is the formation of two types of alkyl derivatives when alkylated with alkyl halide in the presence of alkali, *viz.*, *O*- and *C*-alkyl derivatives; *e.g.*, resorcinol gives a mixture of three methylated products:

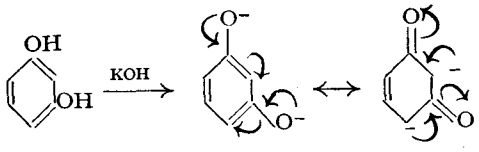


Phloroglucinol forms only the *C*-alkyl derivatives:



C-hexamethylphloroglucinol

These alkylations, however, may be explained, not by the existence of a keto-enol system, but by attack of alkyl carbonium ions at negative points in the system. This is a reasonable assumption since alkylations are always carried out in alkaline solution, and so one can expect the presence of a resonance hybrid ion (Thomson, 1956), *e.g.*,



In addition to the phenols described above, three tetrahydric, one pentahydric, and one hexahydric phenol are known.

AROMATIC ETHERS

The aromatic ethers may be divided into two groups, the *phenolic ethers*, which are of the type Ar·O·R, and the ethers of the type Ar_2O (the diaryl ethers).

Phenolic ethers. These may be prepared by heating sodium phenoxide with alkyl halide in ethanol solution, or by treating an alkaline solution of a phenol with alkyl sulphate:

$$ArONa + RX \longrightarrow Ar{\cdot}O{\cdot}R + NaX \quad (v.g.)$$
$$ArONa + R_2SO_4 \longrightarrow Ar{\cdot}O{\cdot}R + RNaSO_4 \quad (v.g.\text{–}ex.)$$

Phenolic methyl ethers may be obtained in excellent yield by the action of diazomethane on a phenol:

$$ArOH + CH_2N_2 \longrightarrow Ar{\cdot}O{\cdot}CH_3 + N_2 \quad (ex.)$$

Two important phenolic ethers are **anisole** (*methyl phenyl ether, methoxybenzene*), $C_6H_5{\cdot}O{\cdot}CH_3$, b.p. 155°, and **phenetole** (*ethyl phenyl ether, ethoxybenzene*), $C_6H_5{\cdot}O{\cdot}C_2H_5$, b.p. 172°. These ethers are prepared industrially by the alkylation of phenol with methyl or ethyl sulphate, or with the methyl and ethyl esters of *p*-toluenesulphonic acid.

Anisole and phenetole are used as the starting point for the preparation of various derivatives. They are stable liquids; they are unaffected by most acids and alkalis, but are decomposed by concentrated hydriodic acid (or hydrobromic acid) into phenol and alkyl iodide (or bromide):

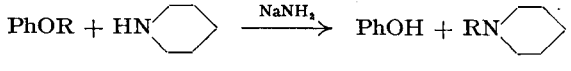
$$C_6H_5{\cdot}O{\cdot}CH_3 + HI \longrightarrow C_6H_5OH + CH_3I$$

The alkyl iodide can be absorbed by an ethanolic solution of silver nitrate, and the silver iodide so formed, weighed. This is the basis of the **Zeisel method** for the estimation of methoxyl and ethoxyl groups.

Phenolic ethers may be decomposed by refluxing with aluminium chloride, or better, with aluminium bromide, in benzene solution, using one equivalent of aluminium halide for each alkoxyl group present. The mechanism of the reaction is uncertain; according to Pfeiffer and Loewe (1936), the reaction takes place as follows:

$$C_6H_5{\cdot}O{\cdot}R + AlCl_3 \longrightarrow \left[C_6H_5{-}\overset{\overset{-}{AlCl_3}}{\underset{+}{O}}{-}R\right] \longrightarrow RCl + C_6H_5{\cdot}O{\cdot}AlCl_2 \xrightarrow{H_2O} C_6H_5OH + HOAlCl_2$$

On the other hand, this conversion of phenolic ethers into phenols is very conveniently carried out by boiling the ether in piperidine containing sodamide (Brotherton *et al.*, 1957):



Phenolic ethers may also be decomposed by refluxing in pyridine solution with sodium:

$$C_6H_5{\cdot}O{\cdot}R + 2Na \longrightarrow C_6H_5Na + RONa \xrightarrow{H_2O} C_6H_6 + ROH$$

Formation of an ether provides a means of protecting the hydroxyl group in many reactions; *e.g.*, in the Friedel–Crafts reaction, due to acidic character of the hydroxyl group, aluminium chloride is attacked with the liberation of hydrogen chloride:

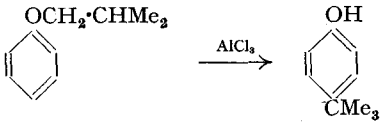
$$C_6H_5OH + AlCl_3 \longrightarrow C_6H_5{\cdot}OAlCl_2 + HCl$$

Thus to carry out a successful Friedel–Crafts reaction with phenol, it is necessary to use a large amount of aluminium chloride. This, however, may be avoided by carrying out the reaction with the methyl ether, but the temperature must be kept as low as possible to prevent the catalyst decomposing the ether.

In certain cases, phenolic ethers rearrange to the *o*- or *p*-alkyl compound:

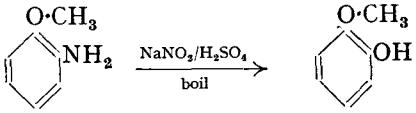
$$C_6H_5OR \xrightarrow{AlCl_3} o\text{- or } p\text{-}R{\cdot}C_6H_4OH$$

This rearrangement occurs fairly readily when the alkyl group is tertiary; secondary alkyl groups migrate less easily, and primary groups with great difficulty, if at all, *e.g.*, aluminium chloride dealkylates anisole and phenetole, but Smith (1933) showed:



Dewar *et al.* (1959) have examined the rearrangement of *n*- and *sec.*-butyl phenyl ether, and conclude from their experiments that the rearrangement occurs by intramolecular and intermolecular mechanisms operating independently.

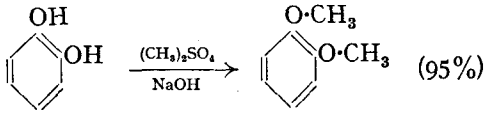
Catechol ethers. Guaiacol (*o-hydroxyanisole*), m.p. 32°, b.p. 205°, occurs in beech-wood tar from which it may be obtained by fractional distillation. Guaiacol is prepared synthetically from *o*-anisidine:



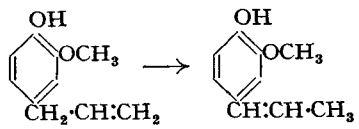
When refluxed with constant boiling hydrobromic acid, or heated with hydriodic acid at 130°, guaiacol is converted into catechol.

Guaiacol is used in medicine, and as the starting material in the preparation of vanillin (see p. 659).

Veratrole (1 : 2-*dimethoxybenzene*), b.p. 207°, may be prepared by methylating catechol with methyl sulphate in alkaline solution:



Eugenol (4-*allylguaiacol*), b.p. 254°, occurs in oil of cloves and in many other essential oils. When heated with ethanolic potassium hydroxide, or better, with potassium hydroxide in diethyleneglycol at 180°, eugenol isomerises to ***iso*-eugenol** (4-*propenylguaiacol*):

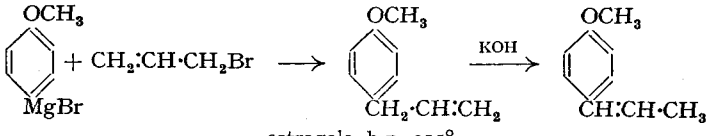


eugenol *iso*eugenol

This migration of the double bond in the allyl side-chain, under the influence of alkali, is general; this is an example of prototropy.

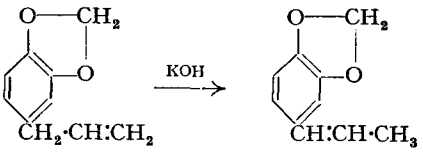
*iso*Eugenol, b.p. 267·5°, also occurs naturally, and gives vanillin on gentle oxidation.

Anethole (p-*methoxypropenylbenzene*), m.p. 22–23°, b.p. 235°, is one of the chief constituents of aniseed oil, from which it is obtained. It is also prepared synthetically by the interaction of *p*-methoxyphenylmagnesium bromide and allyl bromide, and isomerising the product, **estragole** (*methyl-chavicol*), with alkali:



estragole, b.p. 215°

Safrole (4-*allyl*-1 : 2-*methylenedioxybenzene*), b.p. 232°, occurs in camphor oil and sassafras oil. When heated in ethanolic potassium hydroxide solution, or better, in a concentrated solution of potassium hydroxide in cellosolve, safrole isomerises to ***iso*safrole**:



safrole *iso*safrole

*iso*Safrole, b.p. 252°, also occurs naturally, and gives piperonal on gentle oxidation (p. 660).

Aromatic ethers of the type Ar_2O. These are most conveniently prepared by means of the *Ullmann reaction* (*cf.* p. 576); *eg.*, **diphenyl ether** may be prepared by refluxing a mixture of bromobenzene, phenol, potassium hydroxide with a small amount of copper as catalyst:

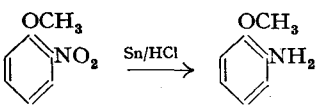
$$C_6H_5Br + C_6H_5OH + KOH \xrightarrow{Cu} (C_6H_5)_2O + KBr + H_2O \quad (90\%)$$

Diphenyl ether may also be prepared by heating phenol with aluminium chloride:

$$2C_6H_5OH \xrightarrow{AlCl_3} (C_6H_5)_2O + H_2O$$

Diphenyl ether is a solid, m.p. 28°, with a geranium odour. It is *not* decomposed by hydriodic acid, and is valuable as a high temperature heat transfer medium.

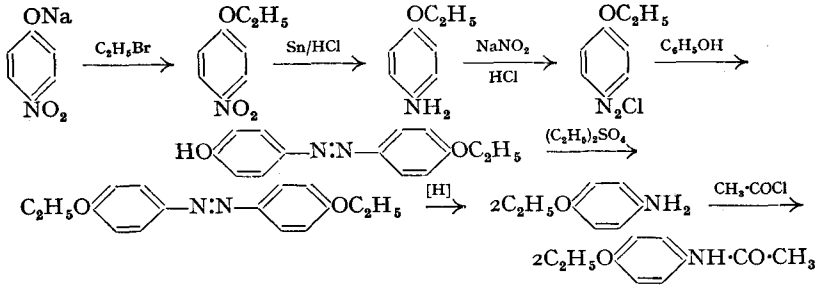
Ethers of aminophenols. The methyl ethers of *o*- and *p*-aminophenol are known as *o*-anisidine and *p*-anisidine, respectively, and each may be prepared by reducing its corresponding nitroanisole, *e.g.*, *o*-anisidine from *o*-nitroanisole:



The anisidines are used in the preparation of azo-dyes.

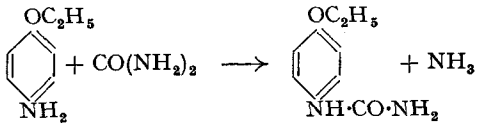
The ethyl ethers of the aminophenols are known as **phenetidines**; these are also

used in the preparation of azo-dyes. The acetyl derivative of *p*-phenetidine is known as **phenacetin,** and is prepared commercially as follows:



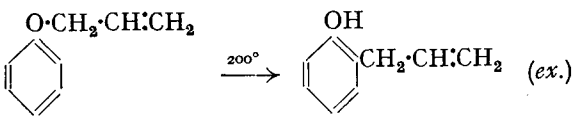
Phenacetin is replacing acetanilide in medicine; it is a very good analgesic (*i.e.*, promotes relief from pain) and antipyretic (*i.e.*, fever-reducing).

Dulcin is the carbamyl derivative of *p*-phenetidine, and is prepared by heating *p*-phenetidine with urea:

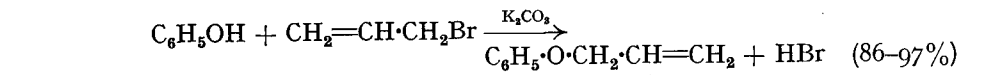


Dulcin is a solid, m.p. 171°, and is about 200 times as sweet as sugar; it is used commercially as a sweetening agent.

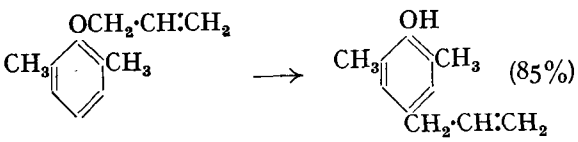
Claisen rearrangement. When heated to about 200°, allyl ethers of phenols rearrange to form the corresponding *o*-allylphenols, *e.g.*,



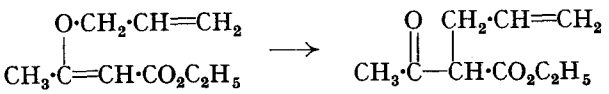
This is known as the *Claisen rearrangement.* The starting material may be readily prepared by heating phenol with allyl bromide in acetone solution in the presence of potassium carbonate:



In the Claisen rearrangement the allyl group migrates to the *o*-position preferably, but if both *o*-positions are occupied, it migrates to the *p*-position:

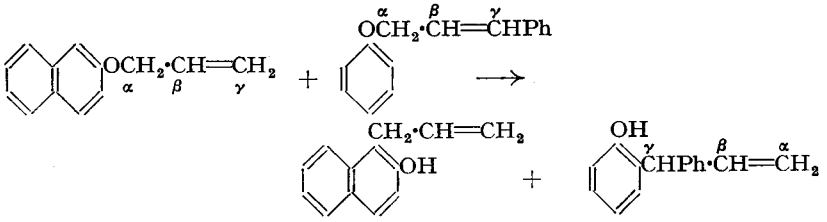


The Claisen rearrangement also takes place with allyl ethers of enols; actually, the rearrangement was originally discovered by Claisen (1912), while working on *O*-allylacetoacetic ester:

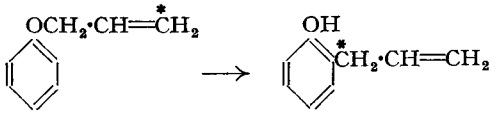


This reaction further shows the resemblance between phenols and enols.

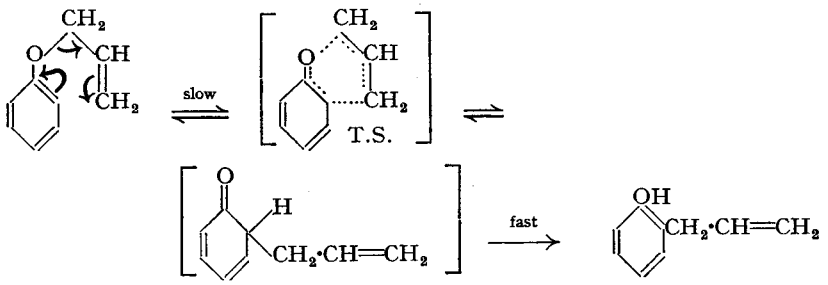
The mechanism of the Claisen rearrangement has been the subject of a great deal of work. The intramolecular nature of the rearrangement has been demonstrated by the fact that if two different ethers are heated together, they rearrange independently, *e.g.*, Hurd *et al.* (1937) heated a mixture of allyl 2-naphthyl ether and cinnamyl phenyl ether and did *not* obtain cross products:



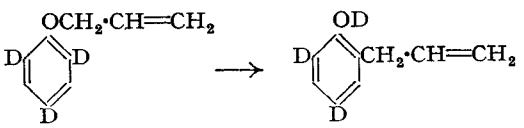
Kincaid *et al.* (1939) showed the rearrangement was of the first order, and other workers have shown that when the allyl group migrates to the ring in the *o*-rearrangement, the α,γ-bonding is reversed (see above example). Schmid *et al.* (1953), using the allyl radical labelled with ^{14}C at the γ-carbon atom, also showed that the rearranged product contained the tracer atom attached to the nucleus:



These examples suggest that the reversal of the bonding in the allyl group is a necessary requirement in the rearrangement. The following intramolecular *cyclic* mechanism is in agreement with the foregoing facts:

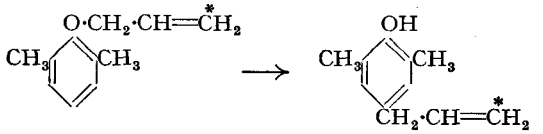


A point of interest here is that the electron-flow has been drawn in a clockwise direction. White *et al.* (1958) have obtained evidence to show that this is so. It will also be noted that the formation of a dienone is postulated in this mechanism; evidence for its existence has been obtained in the *para* rearrangement (see below). Support for the migration of the *o*-hydrogen in the dienone is given by the following experiment of Kistiakowsky *et al.* (1942):

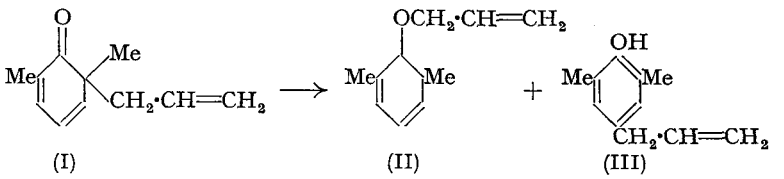


The mechanism of the *p*-rearrangement is believed to occur in two stages, each one with " inversion ", and thus the final product will *not* be " inverted ".

Schmid *et al.* (1953) showed the following rearrangement occurred with labelled allyl 2 : 6-dimethylphenyl ether:

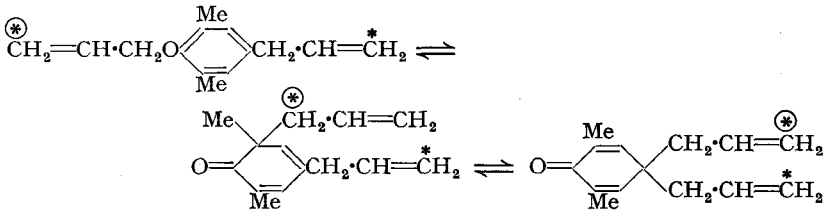


The existence of the dienone and the *reversibility* of the steps (as shown in the *o*-rearrangement) have been demonstrated by Curtin *et al.* (1954, 1956). Curtin *et al.* (1957) also prepared (I) and showed it rearranged above 70° to give a mixture of (II) and (III):



(I) (II) (III)

Conroy *et al.* (1954, 1956) also have demonstrated the existence of the dienone by rearranging allyl 2 : 6-dimethylphenyl ether in the presence of maleic anhydride; a small amount of adduct was isolated. Thus a Diels–Alder reaction has occurred, and this is powerful evidence for the formation of the dienone (the dienophile in this system). The reversibility of both stages in the *p*-arrangement has also been demonstrated by Schmid *et al.* (1956) using allyl radicals labelled with ^{14}C:



(IV)

Compound (IV), in which labelling was only in the *C*-allyl group (Ċ), was recovered *chemically* unchanged after being heated to 160°, but was now also labelled in the *O*-allyl group (C), the isotope being equally distributed between the terminal methylene groups.

A two-stage mechanism for this *p*-rearrangement, each stage involving a cyclic transition state, accounts for all of the facts. In the second stage, *o*- to *p*-, the cyclic transition state will be highly deformed.

QUESTIONS

1. Describe how each of the following compounds is prepared commercially:—(*a*) Phenol, (*b*) *o*- and *p*-nitrophenols, (*c*) picric acid, (*d*) *m*- and *p*-aminophenols, (*e*) catechol, (*f*) resorcinol, (*g*) anisole, (*h*) phenetole, (*i*) phenacetin, (*j*) dulcin.

2. Name the compounds and state under what conditions they are formed when phenol is treated with:—(*a*) $FeCl_3$, (*b*) NaOH, (*c*) Na_2CO_3, (*d*) Br_2, (*e*) HNO_3, (*f*) H_2SO_4, (*g*) Zn, (*h*) NH_3, (*i*) H_2, (*j*) EtI, (*k*) $KMnO_4$, (*l*) $Ph{\cdot}N_2Cl$, (*m*) CO_2, (*n*) AcCl, (*o*) $H{\cdot}CHO$, (*p*) SO_2Cl_2, (*q*) PCl_5, (*r*) HNO_2, (*s*) $AlCl_3$.

3. Discuss the *differences* between the properties of PhOH and EtOH and attempt to account for them.

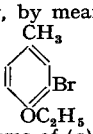
4. Starting with benzene or toluene, show how you would prepare:—(*a*) phenol, (*b*) 5-nitro-2-hydroxybenzyl alcohol, (*c*) *o*-nitrosophenol, (*d*) *p*-hydroxyacetophenone, (*e*) *p*-hydroxybenzyl chloride, (*f*) *o*-, *m*- and *p*-bromophenols, (*g*) *o*- and *p*-iodophenols, (*h*) *m*-nitrophenol, (*i*) picramide, (*j*) picramic acid, (*k*) *N*-acetylaminophenol, (*l*) *m*-phenolsulphonic acid, (*m*) *o*-, *m*- and *p*-cresols, (*n*) thymol, (*o*) *s*-trinitrobenzoic acid.

5. Write an account of:—(*a*) displacement of groups in phenol derivatives, (*b*) hydrogen bonding in phenol derivatives, (*c*) acid or basic strengths of phenol derivatives, (*d*) nitration of phenol, (*e*) the colour of nitrophenol ethers.

6. Describe the preparation and the more important properties of:—(*a*) the three dihydroxybenzenes, (*b*) the three trihydroxybenzenes.

7. Starting with any phenol you like, show how you would synthesise:—(*a*) guaiacol, (*b*) veratrole, (*c*) eugenol, (*d*) anethole, (*e*) diphenyl ether, (*f*) *o*-anisidine, (*g*) *p*-phenetidine.

8. Define and give examples of:—(*a*) Chloromethylation, (*b*) mercuration, (*c*) Fries reaction, (*d*) Lederer–Manasse reaction, (*e*) oxynitration, (*f*) Baudisch reaction, (*g*) Zeisel method, (*h*) Ullmann reaction, (*i*) Claisen rearrangement, (*j*) Elbs persulphate oxidation.

9. How would you show, by means of analytical and synthetic evidence, that the structure of a compound is  ?

10. Discuss the mechanisms of (*a*) the Fries reaction, (*b*) the Claisen rearrangement.

11. Give an account of the principles involved in the separation of isomeric substituted phenols.

12. Write an essay on clathrates.

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CHAPTER XXVII

ALCOHOLS, ALDEHYDES, KETONES AND QUINONES

AROMATIC ALCOHOLS

AROMATIC alcohols are compounds containing a hydroxyl group in a *side-chain*, and may be regarded as aryl derivatives of the aliphatic alcohols. Aromatic alcohols may be classified as primary, secondary, or tertiary alcohols, and their methods of preparation are similar to those used for aliphatic alcohols (p. 124). Only primary alcohols will be discussed in this section; secondary and tertiary aromatic alcohols are dealt with in the chapter on polynuclear hydrocarbons.

Benzyl alcohol (*phenylcarbinol*), $C_6H_5{\cdot}CH_2OH$, may be prepared:

(i) By hydrolysing benzyl chloride with aqueous sodium hydroxide:

$$C_6H_5{\cdot}CH_2Cl + NaOH \longrightarrow C_6H_5{\cdot}CH_2OH + NaCl \quad (70\%)$$

This method is used commercially:

(ii) By reducing benzaldehyde with zinc and hydrochloric acid:

$$C_6H_5{\cdot}CHO + 2[H] \longrightarrow C_6H_5{\cdot}CH_2OH$$

(iii) By means of the Cannizzaro reaction:

$$2C_6H_5{\cdot}CHO + NaOH \longrightarrow C_6H_5{\cdot}CH_2OH + C_6H_5{\cdot}CO_2Na \quad (90\%)$$

It may also be prepared by means of a crossed Cannizzaro reaction (p. 165):

$$C_6H_5{\cdot}CHO + H{\cdot}CHO + NaOH \longrightarrow C_6H_5{\cdot}CH_2OH + H{\cdot}CO_2Na$$

Benzyl alcohol (which is isomeric with the cresols) is a colourless liquid, b.p. 205°, sparingly soluble in water but readily soluble in organic solvents. Its reactions are similar to those of the primary aliphatic alcohols; *e.g.*, on oxidation, it forms benzaldehyde and finally benzoic acid:

$$C_6H_5{\cdot}CH_2OH \xrightarrow{[O]} C_6H_5{\cdot}CHO \xrightarrow{[O]} C_6H_5{\cdot}CO_2H$$

Benzyl alcohol forms esters, many of which are used in perfumery, *e.g.*, benzyl acetate (prepared from benzyl alcohol and acetic anhydride) occurs in oil of jasmine. Benzyl alcohol reacts with sodium to form sodium benzyl oxide.

In addition to the above reactions, benzyl alcohol exhibits aromatic properties due to the presence of the ring, *e.g.*, it can be nitrated, sulphonated, etc. Care, however, must be taken to avoid reaction with the hydroxyl group; it is therefore generally better, when preparing nuclear-substituted derivatives of benzyl alcohol, to use benzyl chloride (the CH_2Cl and CH_2OH groups are both *o-p*-orienting), and then hydrolyse to the alcohol.

Benzyl alcohol may be catalytically (palladium) reduced to toluene:

$$C_6H_5{\cdot}CH_2OH + H_2 \xrightarrow{Pd} C_6H_5{\cdot}CH_3 + H_2O$$

This reaction occurs when the benzyl group is attached to O, N, or S, and may also be effected by sodium amalgam or lithium aluminium hydride. *Debenzylation* is a very useful reaction since a benzyl group may be introduced into a compound to protect a sensitive group and then removed at the end of the reaction.

Hydroxybenzyl alcohols may be prepared by the Lederer–Manasse reaction (p. 623). ***o*-Hydroxybenzyl alcohol, salicyl alcohol** (*saligenin*), *o*-$HO{\cdot}C_6H_4{\cdot}CH_2OH$, occurs in the glucoside *salicin*. It is a crystalline solid, m.p. 87°, and is used in medicine as an antipyretic.

2-Phenylethanol (*β-phenylethyl alcohol*), $C_6H_5{\cdot}CH_2{\cdot}CH_2OH$, may be prepared by reducing phenylacetic ester with sodium and ethanol:

$$C_6H_5{\cdot}CH_2{\cdot}CO_2C_2H_5 + 4[H] \longrightarrow C_6H_5{\cdot}CH_2{\cdot}CH_2OH + C_2H_5OH$$

It is prepared industrially by the action of ethylene oxide on phenylmagnesium bromide:

$$C_6H_5{\cdot}MgBr + \overset{O}{\diagup\diagdown}CH_2{\cdot}CH_2 \longrightarrow C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}OMgBr \xrightarrow{H_2O} C_6H_5{\cdot}CH_2{\cdot}CH_2OH$$

2-Phenylethanol is a colourless oil, b.p. 220°, and is the chief consitutent of rose oil. When heated with alkali, it forms styrene.

2-Phenylethanol and its esters are used in perfumery.

AROMATIC ALDEHYDES

Aromatic aldehydes fall into two groups: those in which the aldehyde group is directly attached to the nucleus, and those in which it is attached to the side-chain. The former group comprises the aromatic aldehydes; the latter, which behave as aliphatic aldehydes, are best regarded as aryl-substituted aliphatic aldehydes.

Benzaldehyde (*benzenecarbonal*), $C_6H_5{\cdot}CHO$, is also known as *oil of bitter almonds*, since it is found in the glucoside *amygdalin* which occurs in bitter almonds. Amygdalin may be hydrolysed by dilute acids or the enzyme emulsin to benzaldehyde, glucose and hydrogen cyanide:

$$C_{20}H_{27}O_{11}N + 2H_2O \longrightarrow C_6H_5{\cdot}CHO + 2C_6H_{12}O_6 + HCN$$

Benzaldehyde may be prepared by any of the following methods, which are general for its homologues as well.

1. By the hydrolysis of benzylidene chloride with water at 100°, in the presence of iron powder as catalyst:

$$C_6H_5{\cdot}CHCl_2 + H_2O \longrightarrow C_6H_5{\cdot}CHO + 2HCl \quad (76\%)$$

Benzylidene chloride usually contains benzyl chloride and benzotrichloride, and consequently the product of hydrolysis is contaminated with benzyl alcohol and benzoic acid. If, however, hydrolysis is carried out with boric acid, then only benzylidene chloride is hydrolysed, the other two being unaffected under these conditions (the Makarov–Zemlianskii–Prokin method, 1936).

2. By boiling benzyl chloride with aqueous copper or lead nitrate in a current of carbon dioxide. The mechanism of the reaction is unknown; the equation usually given is:

$$2C_6H_5{\cdot}CH_2Cl + Pb(NO_3)_2 \longrightarrow 2C_6H_5{\cdot}CHO + PbCl_2 + 2HNO_2 \quad (40\%)$$

3. *By the oxidation of toluene.* This may be done in the vapour phase or in the liquid phase. In *vapour-phase oxidation*, toluene is catalytically oxidised with air diluted with nitrogen to prevent complete oxidation of the hydrocarbon. The temperature may be as high as 500°, and the catalyst is the oxide of metals such as manganese, molybdenum, zirconium, etc.:

$$C_6H_5{\cdot}CH_3 + O_2 \longrightarrow C_6H_5{\cdot}CHO + H_2O$$

Oxidation of hydrocarbons containing a side-chain of two or more carbon atoms gives mainly a ketone since only the α-carbon atom is readily oxidised, *e.g.*, ethylbenzene forms acetophenone:

$$C_6H_5{\cdot}CH_2{\cdot}CH_3 \xrightarrow[ZrO_2]{O_2} C_6H_5{\cdot}CO{\cdot}CH_3$$

In *liquid phase oxidation*, toluene is oxidised with manganese dioxide and 65 per cent. sulphuric acid at 40°. This method is used commercially.

Benzaldehyde may be conveniently prepared in the laboratory by oxidising toluene with chromium trioxide in acetic anhydride. As the benzaldehyde is formed, it is converted into benzylidene acetate, thereby preventing further oxidation of the benzaldehyde. Hydrolysis of the acetate with dilute sulphuric or hydrochloric acid gives benzaldehyde:

$$C_6H_5{\cdot}CH_3 \xrightarrow[(CH_3{\cdot}CO)_2O]{CrO_3} C_6H_5{\cdot}CH(O{\cdot}CO{\cdot}CH_3)_2 \xrightarrow{H_2O} C_6H_5{\cdot}CHO + CH_3{\cdot}CO_2H \quad (40\text{–}50\%)$$

A better yield of benzaldehyde may be obtained by oxidising benzyl alcohol with chromium trioxide in acetic anhydride (yield 90 per cent.) or with acid dichromate (yield 80–95 per cent.).

An interesting oxidising agent is chromyl chloride (**Étard's reaction,** 1877). In this method the hydrocarbon is treated with chromyl chloride in carbon tetrachloride solution and the complex, which is precipitated, is decomposed with water:

$$C_6H_5{\cdot}CH_3 + 2CrO_2Cl_2 \longrightarrow C_6H_5{\cdot}CH_3{\cdot}2CrO_2Cl_2 \xrightarrow{H_2O} C_6H_5{\cdot}CHO \quad (80\%)$$

Side-chains larger than methyl are oxidised at the *terminal* carbon atom, *e.g.*, ethylbenzene gives phenylacetaldehyde:

$$C_6H_5{\cdot}CH_2{\cdot}CH_3 \longrightarrow C_6H_5{\cdot}CH_2{\cdot}CHO$$

4. **Gattermann–Koch aldehyde synthesis** (1897). Benzaldehyde may be synthesised by bubbling a mixture of carbon monoxide and hydrogen chloride through a solution of nitrobenzene or ether containing benzene and a catalyst consisting of aluminium chloride and a small amount of cuprous chloride:

$$C_6H_6 + CO + HCl \xrightarrow{AlCl_3} C_6H_5{\cdot}CHO + HCl$$

In the absence of cuprous chloride the yield is very poor: in its presence, and under normal pressure, the yield is 30–50 per cent.; under high pressure, the yield is 80–90 per cent. Benzaldehyde can also be prepared from benzene and carbon monoxide under a pressure of 90 atmospheres in the presence of aluminium chloride. The reaction, however, must be carried out in the presence of a small amount of water which, presumably, produces hydrogen chloride by hydrolysis of aluminium chloride:

$$C_6H_6 + CO \xrightarrow[H_2O]{AlCl_3} C_6H_5{\cdot}CHO \quad (g.)$$

This method is used commercially.

When there are substituents in the ring, *e.g.*, a methyl group, the aldehyde group is introduced into the *p*-position only. The Gattermann–Koch aldehyde synthesis is not applicable to phenols and their ethers.

5. **Gattermann aldehyde synthesis** (1906). When benzene is treated with a mixture of hydrogen cyanide and hydrogen chloride in the presence of

aluminium chloride, and the complex so produced decomposed with water, benzaldehyde is produced (in low yield).

Two mechanisms have been proposed for this reaction:

(i) *Formamidine hydrochloride* (*iminoformyl chloride*) is formed as an intermediate:

$$HCl + HCN \xrightarrow{AlCl_3} HN{=}CHCl$$

$$C_6H_6 + HN{:}CHCl \xrightarrow{AlCl_3} HCl + \underset{\text{aryl imine}}{C_6H_5{\cdot}CH{:}NH} \xrightarrow{H_2O} C_6H_5{\cdot}CHO + NH_3$$

(ii) *Chloromethyleneformamidine* is formed as an intermediate (Hinkel *et al.*, 1935):

$$2HCN + HCl \xrightarrow{AlCl_3} ClCH{:}N{\cdot}CH{:}NH$$

$$C_6H_6 + ClCH{:}N{\cdot}CH{:}NH \xrightarrow{AlCl_3} HCl + \underset{\text{aryl methyleneformamidine}}{C_6H_5{\cdot}CH{:}N{\cdot}CH{:}NH} \xrightarrow{H_2O}$$

$$C_6H_5{\cdot}CH{:}NH + NH_3 + H{\cdot}CO_2H \xrightarrow{H_2O} C_6H_5{\cdot}CHO + NH_3$$

There is evidence in support of each of these mechanisms, but it appears that (i) is more widely accepted.

The Gattermann reaction is applicable to phenols and phenolic ethers (see also phenolic aldehydes, p. 655).

6. **Sommelet's Reaction** (1913). Benzaldehyde is produced when benzyl chloride is refluxed with hexamethylenetetramine in aqueous ethanolic solution, followed by acidification and steam distillation:

$$C_6H_5{\cdot}CH_2Cl + (CH_2)_6N_4 \longrightarrow C_6H_5{\cdot}CHO \quad (60\text{–}70\%)$$

The mechanism of this reaction is uncertain. According to Angyal *et al.* (1953), the mechanism is:

(i) $C_6H_5{\cdot}CH_2Cl + C_6H_{12}N_4 \longrightarrow [C_6H_5{\cdot}CH_2{\cdot}C_6H_{12}N_4]^+Cl^- \longrightarrow$

$$C_6H_5{\cdot}CH_2{\cdot}N{=}CH_2 \overset{H^+}{\rightleftharpoons} C_6H_5{\cdot}CH_2{\cdot}\overset{+}{N}H{=}CH_2$$

(ii) $C_6H_5{\cdot}CH_2{\cdot}\overset{+}{N}H{=}CH_2 + C_6H_5{\cdot}\underset{H}{CH}{-}\overset{+}{N}H_2 \rightleftharpoons$

$$C_6H_5{\cdot}CH_2{\cdot}NH{\cdot}CH_3 + C_6H_5{\cdot}CH{=}\overset{+}{N}H_2 \xrightleftharpoons{H_2O} C_6H_5{\cdot}CHO + NH_3$$

Methylenebenzylamine, formed by hydrolysis of the quaternary compound, adds on a proton, and the ion thus formed reacts with benzylamine (formed as an intermediate) with transfer of a *hydride* ion from the latter to the former.

7. **Rosenmund reduction** (1918). Benzaldehyde is produced by bubbling hydrogen through benzoyl chloride in xylene solution in the presence of a palladium catalyst until the theoretical amount of hydrogen chloride has been evolved. The liquid is then acidified and steam distilled. To stop the reaction at the aldehyde stage, a quinoline-sulphur poison is added:

$$C_6H_5{\cdot}COCl + H_2 \xrightarrow{Pd} C_6H_5{\cdot}CHO + HCl \quad (v.g.)$$

This method may be used to prepare hydroxybenzaldehydes, provided the hydroxyl group is protected, *e.g.*, by acetylation.

8. **Stephen's method** (1925). When phenyl cyanide is reduced with stannous chloride and hydrochloric acid in ethereal solution, and then the product hydrolysed with water, benzaldehyde is formed (*cf.* p. 148):

$$C_6H_5{\cdot}CN \xrightarrow[(ii)\ H_2O]{(i)\ SnCl_2/HCl} C_6H_5{\cdot}CHO \quad (v.g.)$$

This method is a general one except for *o*-substituted cyanides, *e.g.*, *o*-tolyl cyanide, in which the yields are negligible due, possibly, to steric hindrance.

Sodium triethoxyaluminium hydride, $Na(EtO)_3AlH$, converts aromatic (and heterocyclic) cyanides via the imines, into aldehydes in excellent yield (Hesse *et al.*, 1957). The reagent is prepared from aluminium ethoxide and sodium hydride in ether or tetrahydrofuran.

9. Benzaldehyde may be prepared by the reaction between phenylmagnesium bromide and ethyl formate:

$$C_6H_5{\cdot}MgBr + H{\cdot}CO_2C_2H_5 \longrightarrow C_6H_5{\cdot}CHO + MgBr(OC_2H_5)$$

10. Benzaldehyde may be obtained from aniline via the diazonium salt and formaldoxime (Beech, 1954):

$$C_6H_5{\cdot}N_2Cl \xrightarrow{CH_2{=}NOH} C_6H_5{\cdot}CH{=}NOH \xrightarrow{H_2O} C_6H_5{\cdot}CHO \quad (40\%)$$

Benzaldehyde is a colourless liquid, b.p. 179°, with a smell of almonds. It is only slightly soluble in water, but is readily soluble in ethanol and ether; it is steam-volatile. It is used for flavouring purposes, in perfumery and in the dye industry.

Benzaldehyde (and aromatic aldehydes in general) resembles aliphatic aldehydes in the following reactions:

(i) It gives the Schiff's reaction.

(ii) It is readily oxidised, *i.e.*, it is a strong reducing agent; *e.g.*, it reduces ammoniacal silver nitrate to silver, itself being oxidised to benzoic acid. Benzaldehyde oxidises to benzoic acid when exposed to air. Baeyer and Villiger (1900) suggested that this oxidation took place by autoxidation via the formation of perbenzoic acid:

$$C_6H_5{\cdot}\overset{\overset{O}{\|}}{C}{-}H + O_2 \longrightarrow C_6H_5{\cdot}\overset{\overset{O}{\|}}{C}{-}O{-}OH \xrightarrow{C_6H_5{\cdot}CHO} 2C_6H_5{\cdot}CO_2H$$

Later work, however, has indicated that this mechanism is incomplete, and that autoxidation proceeds first via the free peroxide radical.

According to Bäckström (1934), the mechanism of the reaction is:

$$C_6H_5{\cdot}CHO \xrightarrow{h\nu} C_6H_5{\cdot}\dot{C}H{-}\dot{O}$$

$$C_6H_5{\cdot}\dot{C}H{-}\dot{O} + C_6H_5{\cdot}CHO \longrightarrow C_6H_5{\cdot}\dot{C}{=}O + C_6H_5{\cdot}\dot{C}HOH$$

$$C_6H_5{\cdot}\dot{C}{=}O + O_2 \longrightarrow C_6H_5{\cdot}C(=O){-}O{-}O\cdot$$

$$C_6H_5{\cdot}C(=O){-}O{-}O\cdot + C_6H_5{\cdot}CHO \longrightarrow C_6H_5{\cdot}C(=O){-}O{-}OH + C_6H_5{\cdot}\dot{C}{=}O$$

$$C_6H_5{\cdot}C(=O){-}O{-}OH + C_6H_5{\cdot}CHO \longrightarrow 2C_6H_5{\cdot}CO_2H$$

(iii) Benzaldehyde forms a bisulphite compound, and may be prepared pure via this compound:

$$C_6H_5{\cdot}CHO + NaHSO_3 \longrightarrow C_6H_5{\cdot}CH(OH){\cdot}SO_3Na$$

(iv) Benzaldehyde forms a cyanohydrin (*mandelonitrile*), $C_6H_5{\cdot}CH(OH){\cdot}CN$, with hydrogen cyanide, and an oxime (and phenylhydrazone) with hydroxylamine (and phenylhydrazine). The latter compounds exist in two geometrical isomeric forms, *e.g.*, benzaldoxime:

With hydrazine, benzaldehyde forms benzylideneazine, $C_6H_5{\cdot}CH{:}N{\cdot}N{:}CH{\cdot}C_6H_5$.

(v) Benzaldehyde reacts with phosphorus pentachloride to form benzylidene chloride:

$$C_6H_5{\cdot}CHO + PCl_5 \longrightarrow C_6H_5{\cdot}CHCl_2 + POCl_3$$

(vi) Benzaldehyde readily undergoes condensation with many aromatic and aliphatic compounds (see below).

Benzaldehyde (and other aromatic aldehydes) differs from aliphatic aldehydes in the following ways:

(i) It does not reduce Fehling's solution.

(ii) It does not readily polymerise; *e.g.*, it does not resinify with sodium hydroxide, but undergoes the Cannizzaro reaction due to its not having an α-hydrogen atom:

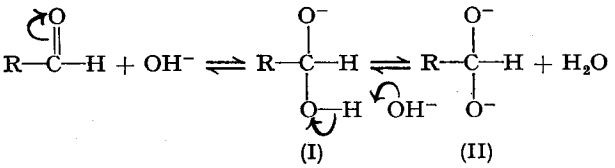
$$2C_6H_5{\cdot}CHO + NaOH \longrightarrow C_6H_5{\cdot}CH_2OH + C_6H_5{\cdot}CO_2Na$$

The reaction may be carried out in two ways: (i) in homogeneous alkaline solution; (ii) in heterogeneous systems (an organic phase and a strongly alkaline aqueous phase). It is usual to carry out the reaction by method (i).

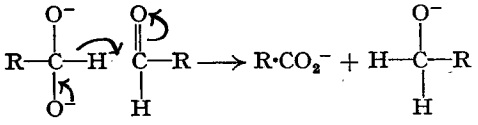
The mechanism of the Cannizzaro reaction in the homogeneous phase is uncertain. Fredenhagen *et al.* (1938) showed that when benzaldehyde undergoes the Cannizzaro reaction in D_2O, the benzyl alcohol produced contained no C—D bonds. Thus hydrogen must be transferred directly from one molecule to the other. A difficulty in arriving at a mechanism is that the order of the reaction varies with the nature of the solvent; it may be third- or fourth-order, *i.e.*,

$$\text{rate} \propto [RCHO]^2[OH^-] \quad \textit{or} \quad [RCHO]^2[OH^-]^2$$

Hammett (1940), on the evidence available at that time, proposed the following mechanism:



Then *hydride ion* transfer occurs:



If (I) is the active species, then have rate $\propto[OH^-]$; if (II), then have rate $\propto[OH^-]^2$. Also, if neither (I) nor (II) can eliminate a hydride ion as such, but requires an acceptor, then in both cases have rate $\propto[RCHO]^2$. Thus when (I) is the active species, the reaction is third-order; when (II) is the active species, the reaction is fourth-order.

The mechanism in the heterogeneous phase is believed to be a free-radical one.

(iii) Benzaldehyde does not yield a simple addition product with ammonia, but forms a complex product, *hydrobenzamide.*

$$3C_6H_5{\cdot}CHO + 2NH_3 \longrightarrow C_6H_5{\cdot}CH(—N{:}CH{\cdot}C_6H_5)_2 + 3H_2O \quad (90\%)$$

Benzaldehyde also reacts with primary aromatic amines to form *anils* or *Schiff bases*; *e.g.*, with aniline it forms benzylideneaniline:

$$C_6H_5{\cdot}CHO + C_6H_5{\cdot}NH_2 \longrightarrow C_6H_5{\cdot}CH{:}N{\cdot}C_6H_5 + H_2O \quad (85\%)$$

Aliphatic aldehydes tend to form compounds of the type.

$$R{\cdot}CH(NH{\cdot}C_6H_5)_2.$$

(iv) Reduction of benzaldehyde with zinc and hydrochloric acid or with sodium amalgam gives *hydrobenzoin* as well as benzyl alcohol (*cf.* pinacol, p. 253):

$$2C_6H_5{\cdot}CHO + 2[H] \longrightarrow C_6H_5{\cdot}CHOH{\cdot}CHOH{\cdot}C_6H_5$$

(v) When chlorinated in the absence of a halogen carrier, benzaldehyde forms benzoyl chloride (no α-hydrogen present):

$$C_6H_5{\cdot}CHO + Cl_2 \longrightarrow C_6H_5{\cdot}COCl + HCl$$

(vi) Benzaldehyde behaves as a base in concentrated sulphuric acid (see p. 662).

Condensation Reactions of Benzaldehyde

1. **Claisen reaction** (see also p. 158). Benzaldehyde, in the presence of dilute alkali, condenses with aliphatic aldehydes or ketones containing α-hydrogen; *e.g.*, with acetaldehyde it forms *cinnamaldehyde*:

$$C_6H_5{\cdot}CHO + CH_3{\cdot}CHO \xrightarrow{NaOH} C_6H_5{\cdot}CH{:}CH{\cdot}CHO + H_2O$$

With acetone, benzaldehyde forms benzylideneacetone (m.p. 42°; used in perfumery):

$$C_6H_5{\cdot}CHO + CH_3{\cdot}CO{\cdot}CH_3 \xrightarrow{NaOH} C_6H_5{\cdot}CH{:}CH{\cdot}CO{\cdot}CH_3 + H_2O \quad (65\text{–}78\%)$$

If the reaction is carried out in aqueous ethanolic sodium hydroxide, *dibenzylideneacetone* (m.p. 112°) is produced by interaction of benzylideneacetone and another molecule of benzaldehyde:

$$C_6H_5{\cdot}CH{:}CH{\cdot}CO{\cdot}CH_3 + C_6H_5{\cdot}CHO \longrightarrow C_6H_5{\cdot}CH{:}CH{\cdot}CO{\cdot}CH{:}CH{\cdot}C_6H_5 + H_2O \quad (90\text{–}94\%)$$

Benzaldehyde also condenses with acetophenone to form *phenyl styryl ketone* (*benzylideneacetophenone*):

$$C_6H_5{\cdot}CHO + CH_3{\cdot}CO{\cdot}C_6H_5 \xrightarrow{NaOH} C_6H_5{\cdot}CH{:}CH{\cdot}CO{\cdot}C_6H_5 + H_2O \quad (85\%)$$

Derivatives of phenyl styryl ketone are known as *chalkones*. Phenyl styryl ketone may be reduced catalytically (platinum) in ethyl acetate solution to *benzylacetophenone*:

$$C_6H_5{\cdot}CH{:}CH{\cdot}CO{\cdot}C_6H_5 + H_2 \xrightarrow{Pt} C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}C_6H_5 \quad (81\text{–}95\%)$$

The above condensation reactions, apart from their synthetic value, illustrate the use of benzaldehyde to detect the presence of a $—CH_2·CO-$ group in carbonyl compounds (*cf.* p. 163).

Benzaldehyde condenses with crotonaldehyde, in the presence of pyridine acetate, to form 5-phenylpentadienal:

$$C_6H_5·CHO + CH_3·CH{:}CH·CHO \longrightarrow C_6H_5·CH{:}CH·CH{:}CH·CHO + H_2O$$

This reaction is an example of vinylogy (p. 287), and was introduced by Kuhn (1929).

Benzaldehyde also condenses with nitromethane to form ω-nitrostyrene; the methylene group is made " active " by the adjacent nitro-group:

$$C_6H_5·CHO + CH_3·NO_2 \xrightarrow{NaOH} C_6H_5·CH{:}CH·NO_2 + H_2O \quad (80–83\%)$$

2. **Perkin reaction** (1877). When benzaldehyde (or any other aromatic aldehyde) is heated with the anhydride of an aliphatic acid (containing two α-hydrogen atoms) in the presence of its sodium salt, condensation takes place to form a β-arylacrylic acid; *e.g.*, with acetic anhydride and sodium acetate, cinnamic acid is formed:

$$C_6H_5·CHO + (CH_3·CO)_2O \xrightarrow{CH_3·CO_2Na} C_6H_5·CH{:}CH·CO_2H$$

With propionic anhydride and sodium propionate, α-methylcinnamic acid is formed:

$$C_6H_5·CHO + (CH_3·CH_2·CO)_2O \xrightarrow{CH_3·CH_2·CO_2Na} C_6H_5·CH{:}C(CH_3)·CO_2H$$

The mechanism of the Perkin reaction has been the subject of much discussion. Perkin believed that the anhydride was involved, whereas Fittig believed it was the salt. The general feeling now is that it is the anhydride that is the addendum; the actual steps involved, however, are uncertain. The mechanism may be as follows (*cf.* the aldol condensation):

$$CH_3·CO·O·CO·CH_3 + CH_3·CO_2^- \rightleftharpoons \bar{C}H_2·CO·O·CO·CH_3 + CH_3·CO_2H$$

$$C_6H_5·\overset{\overset{O}{\|}}{C}H + \bar{C}H_2·CO·O·CO·CH_3 \rightleftharpoons C_6H_5·\overset{\overset{\bar{O}}{|}}{C}H·CH_2·CO·O·CO·CH_3 \overset{H^+}{\rightleftharpoons}$$

$$C_6H_5·\overset{\overset{OH}{|}}{C}H·CH_2·CO·O·CO·CH_3 \xrightarrow{-H_2O} C_6H_5·CH{:}CH·CO·O·CO·CH_3$$

$$\xrightarrow{H_2O} C_6H_5·CH{:}CH·CO_2H + CH_3·CO_2H$$

It should be noted that only the α-hydrogen atoms of the anhydride are involved in the condensation.

Experiment has shown that the Perkin reaction proceeds more readily when the aldehyde contains a halogen atom or a nitro-group in the ring.

The Perkin reaction does not usually take place with aliphatic aldehydes, but does occur if the anhydride is *p*-nitrophenylacetic anhydride (*inter alia*, Crawford *et al.*, 1959).

Benzaldehyde undergoes the Knoevenagel reaction with malonic acid in ethanolic ammonia to form cinnamic acid:

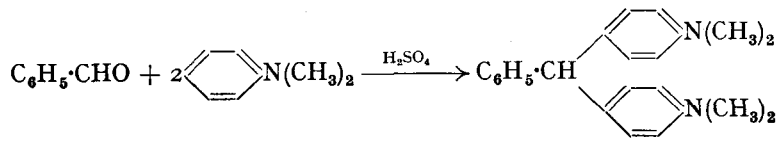
$$C_6H_5·CHO + CH_2(CO_2H)_2 \longrightarrow C_6H_5·CH{:}CH·CO_2H + CO_2 + H_2O$$

A special case of the Perkin reaction is the condensation of benzaldehyde with cyclic anhydrides, *e.g.*, succinic anhydride (see p. 281).

3. **Benzoin condensation.** When refluxed with aqueous ethanolic potassium cyanide, benzaldehyde forms benzoin (see also p. 706):

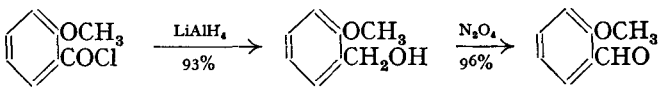
$$2C_6H_5{\cdot}CHO \xrightarrow{KCN} C_6H_5{\cdot}CHOH{\cdot}CO{\cdot}C_6H_5 \quad (83\%)$$

4. Benzaldehyde condenses with phenols and tertiary aromatic amines in the presence of sulphuric acid or zinc chloride to form triphenylmethane derivatives; *e.g.*, with dimethylaniline it forms *malachite green*:

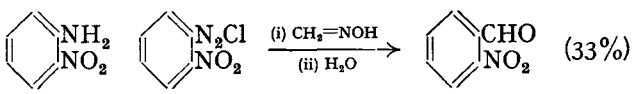


Derivatives of benzaldehyde

A large variety of substituted benzyl alcohols can be oxidised to the corresponding aldehydes by means of dinitrogen tetroxide solutions (yields: 91–98 per cent.). The benzyl alcohols (except the nitro-compounds) may be obtained by reduction of acid chloride or methyl esters with lithium aluminium hydride (Field *et al.*, 1955), *e.g.*,

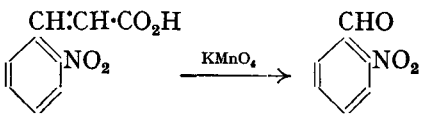


Various substituted benzaldehydes may also be obtained via diazonium salts (Beech, 1954), *e.g.*,

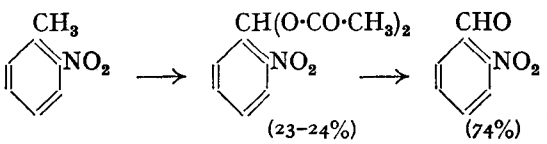


Nitrobenzaldehydes. Curiously enough, nitrating mixture nitrates benzaldehyde to a large extent instead of oxidising it (as might have been expected). The main product is the *m*-isomer, m.p. 58° (about 50 per cent.), together with the *o*-isomer (about 20 per cent.).

o-Nitrobenzaldehyde may be prepared by oxidising *o*-nitrocinnamic acid with cold aqueous potassium permanganate:

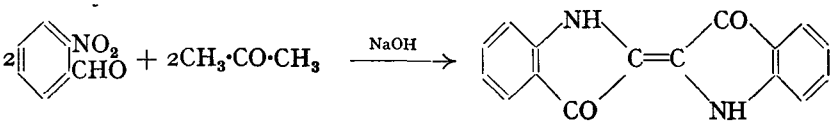


Alternatively, it may be prepared by dissolving *o*-nitrotoluene in glacial acetic acid containing acetic anhydride, and adding chromium trioxide and sulphuric acid. The product is the diacetate and this, on hydrolysis, gives the aldehyde:



A better yield may be obtained by oxidising the *o*-nitrotoluene with manganese dioxide and sulphuric acid.

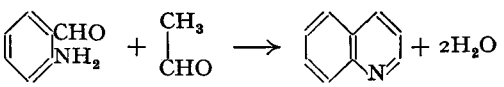
o-Nitrobenzaldehyde is a yellow solid, m.p. 44°. Its most important reaction is its conversion into indigotin when heated with acetone and sodium hydroxide:



p-*Nitrobenzaldehyde* (m.p. 106°) may be prepared by oxidising *p*-nitrocinnamic acid or *p*-nitrotoluene; it may also be prepared by oxidising *p*-nitrobenzyl chloride with aqueous lead nitrate.

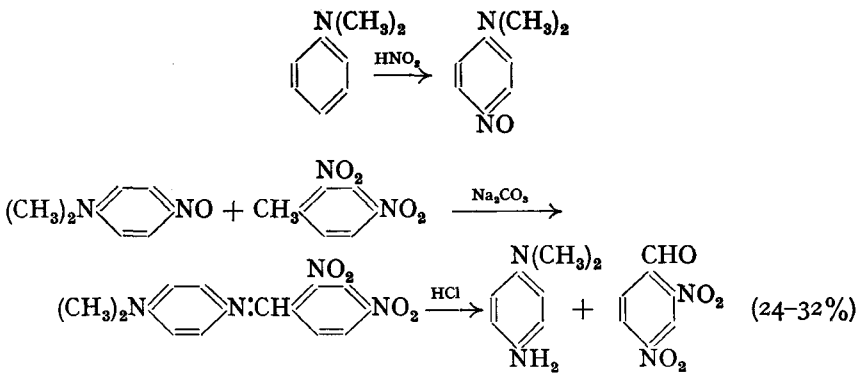
All three nitrobenzaldehydes may be reduced to the corresponding aminobenzaldehydes by shaking a mixture of nitrobenzaldehyde and solid sodium carbonate with ferrous sulphate solution (*cf.* p. 565). The reduction may also be effected by stannous chloride and hydrochloric acid. On the other hand, sodium borohydride reduces nitrobenzaldehydes to the corresponding nitrobenzyl alcohols. This reduction (yield: 75 per cent.) may also be effected with 1 : 1 mixture of lithium aluminium hydride and aluminium chloride (Nystrom, 1955).

o-*Aminobenzaldehyde* readily condenses with compounds containing a —CH_2·CO—group to form quinoline compounds; *e.g.*, with acetaldehyde it forms *quinoline*:



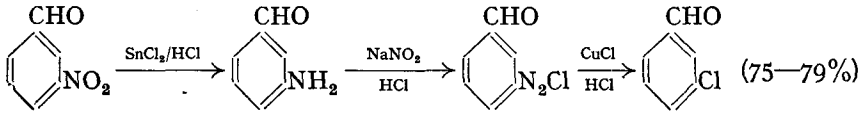
m- and p-*Aminobenzaldehydes* are used in the preparation of dyes. *o*- and *p*-Aminobenzaldehydes are prepared commercially by the oxidation of the corresponding aminobenzyl alcohols (see method 3, p. 656).

2 : 4-*Dinitrobenzaldehyde* (m.p. 72°) may be prepared by dissolving dimethylaniline in concentrated hydrochloric acid and adding sodium nitrite. The *p*-nitroso-compound so produced is heated with 2 : 4-dinitrotoluene in the presence of sodium carbonate, and the condensation product is then heated with hydrochloric acid (*cf.* p. 559):

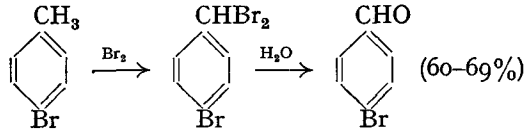


Halogen derivatives of benzaldehyde. *m*-Halogenobenzaldehydes may be prepared from *m*-nitrobenzaldehyde by reduction and subsequent

replacement of the diazo-group by halogen (Sandmeyer reaction), *e.g.*, *m*-chlorobenzaldehyde:

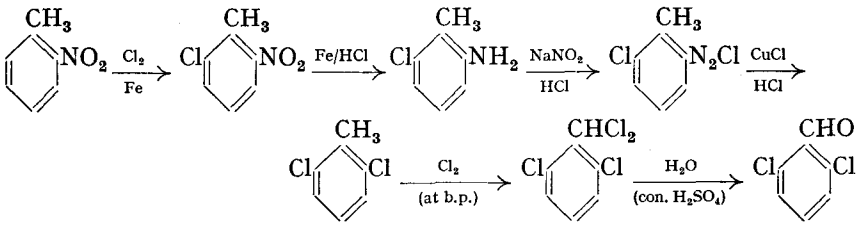


o- and *p*-Halogeno-benzaldehydes may be prepared by brominating the corresponding halogeno-toluenes at their boiling points in the presence of light to give the benzylidene bromide derivative, and hydrolysing this with calcium hydroxide; *e.g.*, *p*-bromobenzaldehyde from *p*-bromotoluene:



Alternatively, the halogeno-toluene may be oxidised with manganese dioxide and sulphuric acid.

2 : 6-*Dichlorobenzaldehyde* (m.p. 72°) is important in the preparation of triphenylmethane dyes; it may be prepared as follows:



Concentrated sulphuric acid must be used to hydrolyse the *o* : *o'*-dichlorobenzylidene chloride; alkali has very little effect (this is an example of steric hindrance). The overall yield of 2 : 6-dichlorobenzaldehyde is very small; this is to be expected from the large number of steps involved. This method illustrates the important point that although a particular method gives a small yield of the desired product, it may be the only worthwhile method to use. It is therefore important that the reader should realise that many syntheses, although very complicated, may nevertheless be the best in practice (*cf.* 2 : 4-dinitrobenzaldehyde, above).

Benzaldehydesulphonic acids. Sulphonation of benzaldehyde gives mainly the *m*-derivative. The *o*- and *p*-isomers are prepared indirectly.

Cinnamaldehyde (3-*phenylpropenal*), $C_6H_5{\cdot}CH{:}CH{\cdot}CHO$, is the chief constituent of cinnamon oil, from which it may be isolated by means of its bisulphite compound. It may be prepared synthetically by the Claisen reaction between benzaldehyde and acetaldehyde:

$$C_6H_5{\cdot}CHO + CH_3{\cdot}CHO \xrightarrow{NaOH} C_6H_5{\cdot}CH{:}CH{\cdot}CHO + H_2O$$

Cinnamaldehyde is an oil, b.p. 252°, which slowly oxidises in air to cinnamic acid. This acid may also be obtained by oxidising cinnamaldehyde with ammoniacal silver nitrate:

$$C_6H_5{\cdot}CH{:}CH{\cdot}CHO + [O] \longrightarrow C_6H_5{\cdot}CH{:}CH{\cdot}CO_2H$$

Vigorous oxidising agents, *e.g.*, acid permanganate, convert cinnamaldehyde into benzoic acid.

Cinnamaldehyde forms the normal bisulphite compound with sodium hydrogen sulphite, but on prolonged treatment with this reagent, the sodium salt of a disulphonic acid is formed, possibly as follows (*cf.* p. 278):

$$C_6H_5{\cdot}CH{:}CH{\cdot}CHO + NaHSO_3 \rightleftharpoons C_6H_5{\cdot}CH{:}CH(OH){\cdot}SO_3Na$$

$$\downarrow$$

$$C_6H_5{\cdot}\underset{\displaystyle SO_3Na}{\underset{|}{CH}}{\cdot}CH_2{\cdot}CHO \overset{NaHSO_3}{\rightleftharpoons} C_6H_5{\cdot}\underset{\displaystyle SO_3Na}{\underset{|}{CH}}{\cdot}CH_2{\cdot}CH(OH){\cdot}SO_3Na$$

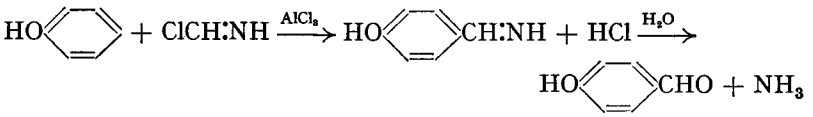
(1 : 4-addition)

The normal addition is reversible; the 1 : 4-addition is irreversible, and hence all the cinnamaldehyde is gradually converted into the disulphonic acid. Cinnamaldehyde adds on bromine to the double bond to form the dibromide, $C_6H_5{\cdot}CHBr{\cdot}CHBr{\cdot}CHO$, and is reduced by aluminium *iso*propoxide to cinnamyl alcohol, $C_6H_5{\cdot}CH{:}CH{\cdot}CH_2OH$.

PHENOLIC ALDEHYDES

Phenolic aldehydes (*hydroxyaldehydes*) are very important compounds, and contain an aldehyde group and one or more hydroxyl groups directly attached to the nucleus.

General methods of preparation. 1. **Gattermann's aldehyde synthesis** (*cf.* benzaldehyde, p. 646). When phenol or a phenolic ether is treated with a mixture of hydrogen cyanide and hydrogen chloride in the presence of aluminium chloride, and the complex produced then decomposed with water, *p*-hydroxy-(or alkoxy)benzaldehyde is the main product:

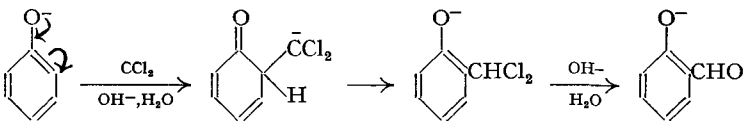


When one hydroxyl group is present in the ring, aluminium chloride is used as catalyst; but with *m*-substituted di- or trihydric phenols, zinc chloride is a better catalyst.

Instead of a mixture of hydrogen cyanide and hydrogen chloride, zinc cyanide and hydrogen chloride may be used (Adams *et al.*, 1923). Pure zinc cyanide, however, is ineffective; a trace of potassium or sodium chloride is necessary. Hinkel (1937) has shown that zinc cyanide may be used for hydrocarbons, and Niedzielski and Nord (1941) have found that sodium cyanide may be used for any aromatic hydrocarbon except benzene.

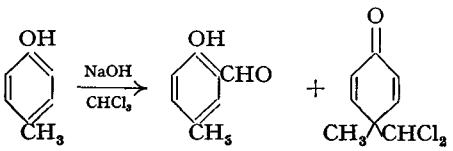
2. **Reimer–Tiemann reaction** (1876). This reaction is carried out by refluxing an alkaline solution of phenol with chloroform at 60°, distilling off the excess chloroform, acidifying the residual liquid with sulphuric acid, and then steam-distilling it. Unchanged phenol and *o*-hydroxybenzaldehyde distil over, leaving behind *p*-hydroxybenzaldehyde.

The mechanism of the Reimer–Tiemann reaction is uncertain. According to Wynberg (1954) it proceeds via the formation of dichloromethylene (produced from the chloroform; see p. 117):

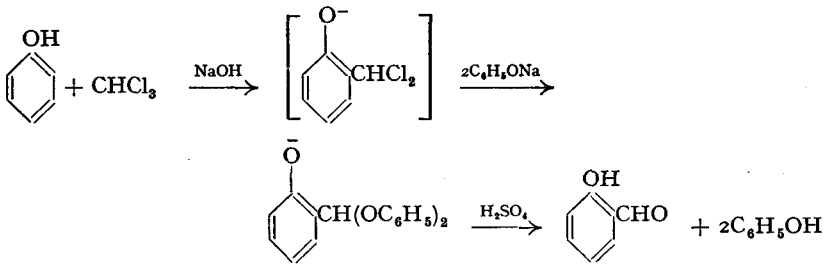


Kinetic work by Robinson (1961) supports this mechanism.

When *o*- or *p*-cresol is used instead of phenol, a ketonic by-product containing the dichloromethyl group is always obtained, *e.g.*,

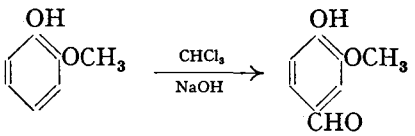


A large amount of phenol always remains unreacted in the Reimer–Tiemann reaction. To account for this, Armstrong and Richardson (1933) suggested:



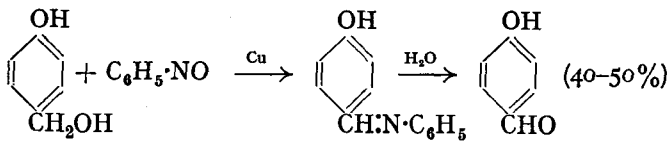
These authors obtained evidence for the existence of the diphenylacetal derivative in the alkaline solution. Another interesting point about the Reimer–Tiemann reaction is that the nature of the *cation* affects the *o*/*p* ratio, *e.g.*, with sodium hydroxide, the ratio is 2 : 1; with cæsium hydroxide, 1 : 1 (Brady *et al.*, 1950).

In the Reimer–Tiemann reaction, phenols react with chloroform and alkali to give *o*- and *p*-phenolic aldehydes, the *o*-isomer predominating. The yields are not usually above 50 per cent., and the presence of a negative group such as NO_2, CN, CO_2H, or SO_3H (*m*-orienting) decreases the yield to less than 25 per cent. If one of the *o*-positions is occupied, the aldehyde group tends to go to the *p*-position; *e.g.*, guaiacol forms vanillin:

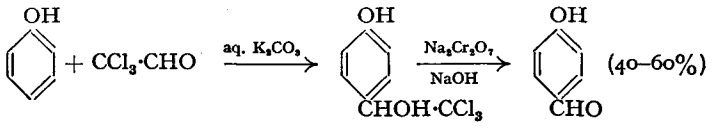


If carbon tetrachloride is used instead of chloroform, the product of the reaction is a phenolic acid (see p. 681).

3. *o*- and *p*-Hydroxybenzyl alcohols may be prepared by the Lederer-Manasse reaction (p. 623). These alcohols may be oxidised to the corresponding hydroxyaldehydes (aminobenzaldehydes may be prepared similarly from aniline). This method is used industrially, the oxidation being carried out with nitrosobenzene or phenylhydroxylamine, in the presence of copper as catalyst:

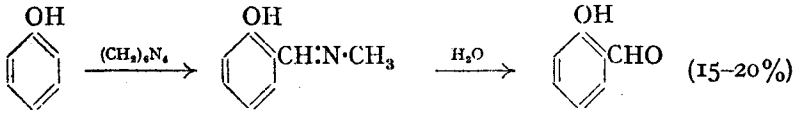


An extension of the above method is the *chloral condensation.* This is a modified Lederer–Manasse reaction, chloral being used instead of formaldehyde, *e.g.*,



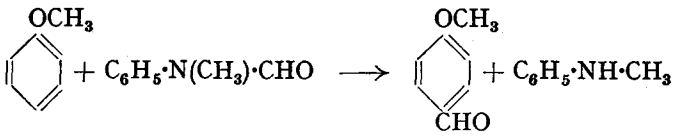
In this reaction, the chloral always enters the *p*-position unless it is occupied, in which case *o*-substitution takes place, but to a lesser extent.

4. **Duff's reaction** (1932). When phenol is heated with a mixture of hexamethylenetetramine, glycerol and boric acid, the mixture then acidified with sulphuric acid and steam distilled, *o*-hydroxybenzaldehyde is formed:



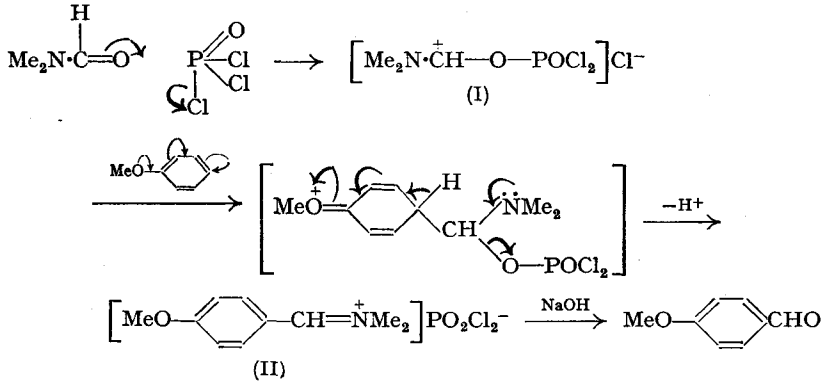
This method gives only the *o*-compound, and is hindered by the presence of a negative group in the ring.

5. **Formylation with *N*-methylformanilide** (Vilsmeier and Haack, 1927). Provided the aromatic compound has a labile hydrogen atom in the nucleus it can be formylated, *i.e.*, an aldehyde group can be introduced, by means of *N*-methylformanilide. The method works well for the *o*- and *p*-positions of phenolic ethers (and dialkyl anilines); it does not work with hydrocarbons, except with anthracene, in which case the aldehyde group enters the 9-position (see p. 731). The formylation is carried out by treating the compound with *N*-methylformanilide and phosphoryl chloride, and when the reaction is complete, adding aqueous sodium acetate and steam distilling:



Dimethylformamide, $H{\cdot}CO{\cdot}N(CH_3)_2$, may be used instead of *N*-methylformanilide.

A possible mechanism for formylation with phosphoryl chloride and dimethylformamide is:



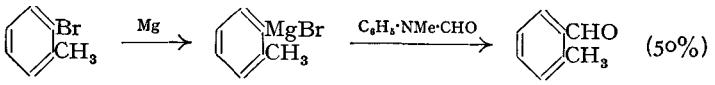
This mechanism is a combination of proposals by various workers, and evidence obtained to support it is:

(i) Silverstein *et al.* (1955) suggested the preliminary formation of the 1 : 1-complex (I), and Bosshard *et al.* (1959) prepared this complex and showed it formylated *N* : *N*-dimethylaniline.

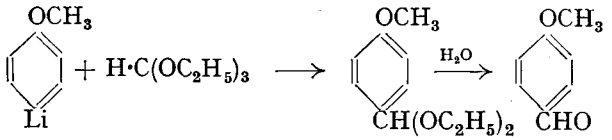
(ii) Smith (1954) isolated the free base of (II) when the substrate was indole.

(iii) Finar *et al.* (1961) have isolated the dichlorophosphates (II) using various pyrazoles as substrates, and their infrared studies showed the absence of the C—O—P bond and the presence of the C=N bond.

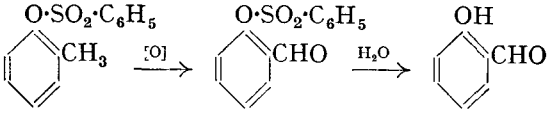
N-Methylformanilide (and, in general, disubstituted formamides) reacts with Grignard reagents to form aldehydes (Bouveault, 1904; Smith *et al.*, 1941), *e.g.*,



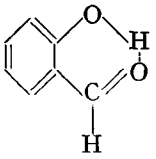
6. **By means of organo-lithium compounds.** When a substituted phenyllithium compound is heated with ethyl orthoformate or *N*-methylformanilide, an intermediate compound is obtained which, on hydrolysis with acid, gives a substituted benzaldehyde in 70 per cent. yield, *e.g.*,



Salicylaldehyde (*o-hydroxybenzaldehyde*) occurs in certain essential oils. It may be prepared by any of the general methods applicable to *o*-hydroxyaldehydes. It is manufactured by the oxidation of *o*-hydroxybenzyl alcohol (obtained by method 3, above), and by the oxidation of *o*-cresylbenzenesulphonate with manganese dioxide and sulphuric acid:

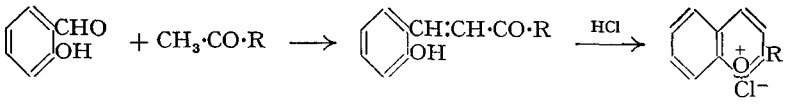


Salicylaldehyde is an oil, b.p. 197°, soluble in water and alkalis to give a yellow solution. The aqueous solution gives a violet coloration with ferric chloride. Salicylaldehyde may be oxidised to salicylic acid and reduced to *o*-hydroxybenzyl alcohol. Oxidation with alkaline hydrogen peroxide converts it into catechol (see p. 632).

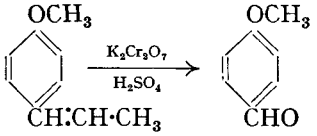


The hydroxyl group of salicylaldehyde is not so reactive as that in the *m*- and *p*-isomers. This is probably due to hydrogen bonding, which also accounts for the high volatility of salicylaldehyde (compared with the *m*- and *p*-compounds).

Salicylaldehyde (and other *o*-hydroxy-aldehydes) condenses with ketones to unsaturated ketones which, under the form influence of hydrochloric acid, form ring compounds known as **pyrylium compounds**, in which the oxygen is tercovalent unielectrovalent:



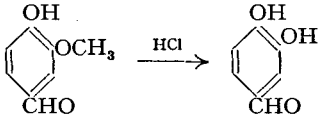
Anisaldehyde (p-*methoxybenzaldehyde*) occurs in various essential oils. It is prepared industrially by oxidising anethole (by ozonolysis or with acid dichromate):



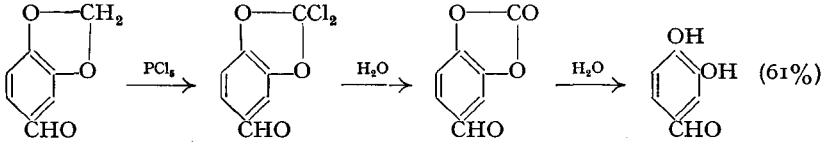
Anisaldehyde may be prepared synthetically by methylating *p*-hydroxybenzaldehyde with methyl sulphate and aqueous sodium hydroxide or with methyl iodide and ethanolic potassium hydroxide. It may also be prepared synthetically by introducing an aldehyde group into the *p*-position of anisole (*e.g.*, methods 1, 5 and 6), or by oxidation of the corresponding alcohols (*cf.* p. 652, derivatives of benzaldehyde).

Anisaldehyde is an oil, b.p. 248°, which may be oxidised to anisic acid and reduced to anisyl alcohol.

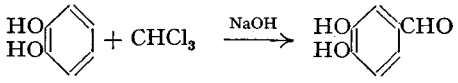
Protocatechualdehyde (3 : 4-*dihydroxybenzaldehyde*) may be prepared by heating vanillin with hydrochloric acid:



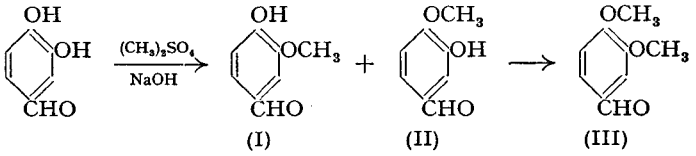
It may also be prepared by adding phosphorus pentachloride to piperonal, then treating the product with cold water, and finally boiling the solution:



Protocatechualdehyde may be prepared synthetically by means of the Reimer–Tiemann reaction using catechol:

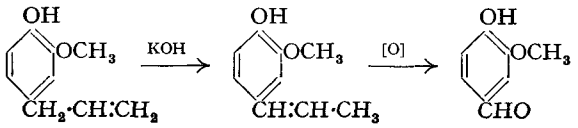


Protocatechualdehyde is a crystalline solid, m.p. 153°, soluble in water. Its aqueous solution gives a green coloration with ferric chloride, and reduces ammoniacal silver nitrate. When methylated with approximately one equivalent of methyl sulphate, protocatechualdehyde gives a mixture of vanillin (I), and *iso*vanillin (II); excess methyl sulphate gives veratraldehyde (III):



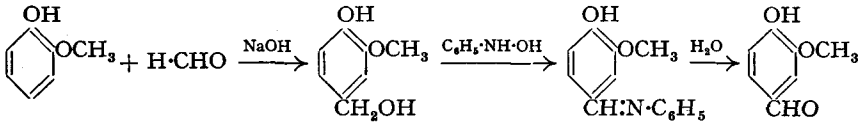
Vanillin (***m*-methoxy-*p*-hydroxybenzaldehyde**) occurs in many substances of plant origin, *e.g.*, the vanilla bean. It may be prepared synthetically from guaiacol (p. 638) by means of the Reimer–Tiemann or the Gattermann reaction. Industrially, it is prepared:

(i) By oxidising *iso*eugenol (from eugenol) with nitrobenzene:



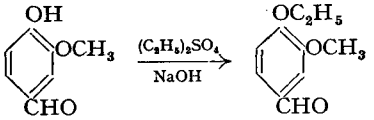
If the oxidation is carried out with acid dichromate, it is necessary to protect the hydroxyl group (by acetylation, etc.). On the other hand, ozonolysis may be used without protecting the hydroxyl group.

(ii) By the Lederer–Manasse reaction as follows:

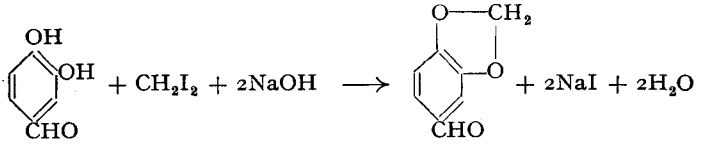


(iii) The liquors from the extraction of lignin from wood-pulp contain vanillin, and are now used as a source of vanillin.

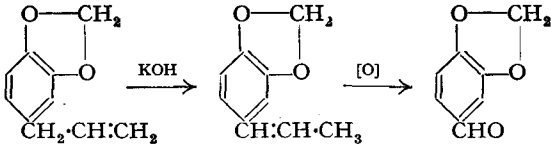
Vanillin is a crystalline solid, m.p. 81°. When heated with hydrochloric acid, it forms protocatechualdehyde; with methyl sulphate it forms veratraldehyde. Ethylation converts vanillin into ethylvanillin (a synthetic compound), which is three times as strong as vanillin:



Piperonal (*heliotropin*, 3 : 4-*methylenedioxybenzaldehyde*) is the methylene ether of protocatechualdehyde, and is obtained when piperic acid (from the alkaloid piperine) is oxidised. It may be prepared synthetically by treating protocatechualdehyde with methylene iodide and sodium hydroxide:



It is manufactured by the oxidation of *iso*safrole (from safrole) by ozonolysis or with acid dichromate:



Piperonal is a solid, m.p. 37°, with the smell of heliotrope. It may be oxidised to piperonylic acid and reduced to piperonyl alcohol. When treated with phosphorus pentachloride and then with water, piperonal forms protocatechualdehyde (see above). This aldehyde is also obtained, together with formaldehyde or methanol, when piperonal is heated with dilute hydrochloric acid at 200° under pressure.

AROMATIC KETONES

Aromatic ketones may be either arylalkyl ketones or diaryl ketones.

Acetophenone (*methyl phenyl ketone, acetylbenzene*), $C_6H_5{\cdot}CO{\cdot}CH_3$, may be prepared by distilling a mixture of calcium benzoate and calcium acetate:

$$(C_6H_5{\cdot}CO_2)_2Ca + (CH_3{\cdot}CO_2)_2Ca \longrightarrow 2C_6H_5{\cdot}CO{\cdot}CH_3 + 2CaCO_3$$

It may also be prepared by the catalytic oxidation of ethylbenzene (p. 646), but it is best prepared by means of the Friedel–Crafts reaction:

$$C_6H_6 + CH_3{\cdot}COCl \xrightarrow{AlCl_3} C_6H_5{\cdot}CO{\cdot}CH_3 + HCl \quad (50\%)$$

The yield is improved (to 60 per cent.) by using a mixture of aluminium and mercury chlorides as catalyst.

Alkyl aryl ketones may be prepared from diazonium salts and aldoximes other than formaldoxime (see p. 588), and by the phenylation of ketones (see p. 542).

Acetophenone is a solid, m.p. 20°; it is used as an hypnotic (under the name of hypnone) and in perfumery. When reduced with sodium and ethanol, acetophenone gives *phenylmethylmethanol*, $C_6H_5{\cdot}CHOH{\cdot}CH_3$; reduction by Clemmensen's method gives ethylbenzene. Ethylbenzene is also produced when the reducing agent is lithium aluminium hydride containing aluminium chloride. Oxidation with cold potassium permanganate gives *phenylglyoxylic acid* (*benzoylformic acid*) which, on further oxidation, is converted into benzoic acid:

$$C_6H_5{\cdot}CO{\cdot}CH_3 \xrightarrow{[O]} C_6H_5{\cdot}CO{\cdot}CO_2H \xrightarrow{[O]} C_6H_5{\cdot}CO_2H$$

Acetophenone is oxidised by selenium dioxide to *phenylglyoxal*:

$$C_6H_5{\cdot}CO{\cdot}CH_3 + SeO_2 \longrightarrow C_6H_5{\cdot}CO{\cdot}CHO + Se + H_2O \quad (69\text{–}72\%)$$

Acetophenone can be chloromethylated (p. 535), and it is readily halogenated in the ω-position; *e.g.*, *phenacyl bromide* (ω-bromoacetophenone) is formed when acetophenone is treated with bromine in ether at 0° in the presence of a small amount of aluminium chloride:

$$C_6H_5{\cdot}CO{\cdot}CH_3 + Br_2 \longrightarrow C_6H_5{\cdot}CO{\cdot}CH_2Br + HBr \quad (64\text{–}66\%)$$

Phenacyl bromide (m.p. 51°) is used to identify acids, with which it forms well-defined crystalline esters. It is oxidised to phenylglyoxal by dissolving it in a large excess of dimethyl sulphoxide (Kornblum *et al.*, 1957).

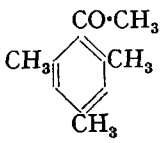
When treated with two equivalents of bromine, acetophenone forms ω : ω-dibromoacetophenone (*phenacylidene bromide*). This compound undergoes rearrangement on treatment with alkali to form *mandelic acid*:

$$C_6H_5{\cdot}CO{\cdot}CHBr_2 \xrightarrow[\text{(ii) HCl}]{\text{(i) KOH}} [C_6H_5{\cdot}CO{\cdot}CH(OH)_2] \longrightarrow C_6H_5{\cdot}CHOH{\cdot}CO_2H$$

This rearrangement does not take place if both *o*-positions are occupied, *e.g.*, in the ω : ω-dibromo-derivative of acetomesitylene.

Phenacyl chloride, m.p. 59°, may be conveniently prepared by the Friedel–Crafts condensation between chloroacetyl chloride and benzene:

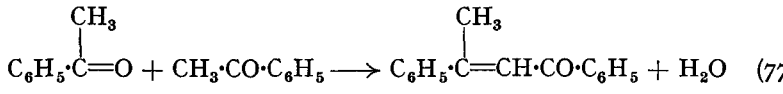
$$C_6H_6 + CH_2Cl{\cdot}COCl \xrightarrow{AlCl_3} C_6H_5{\cdot}CO{\cdot}CH_2Cl + HCl$$



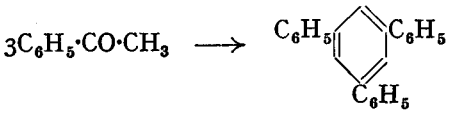
Acetophenone forms an oxime, phenylhydrazone and cyanohydrin, but does not form a bisulphite compound (*cf.* p. 151). It reacts with ammonia to form acetophenone-ammonia, $(C_6H_5{\cdot}C{\cdot}CH_3)_3N_2$ (*cf.* benzaldehyde and ammonia), and with Grignard reagents in the usual way. When, however, both *o*-positions in acetophenone are occupied, the compound exhibits steric hindrance; *e.g.*, acetomesitylene does not form an oxime, and does not react with Grignard reagents in the usual way.

The acetyl group is *m*-orienting, and so when acetophenone undergoes nuclear substitution, the main product is the *m*-derivative.

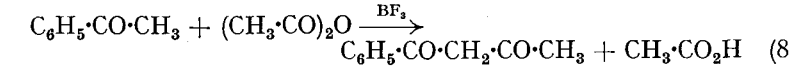
In the presence of aluminium *tert.*-butoxide, acetophenone undergoes condensation to form **dypnone** (b.p. 340–345°):



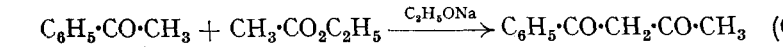
In the presence of hydrochloric acid, *s*-triphenylbenzene (m.p. 172°) is formed:



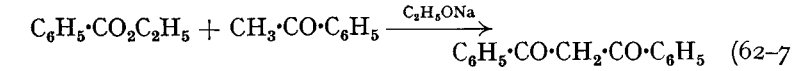
Acetophenone condenses with acetic anhydride in the presence of boron trifluoride to form *benzoylacetone*, m.p. 61° (Meerwein *et al.*, 1934):



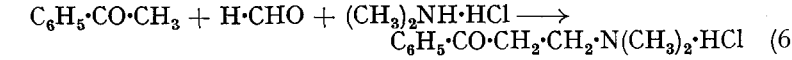
This is also formed by the condensation of acetophenone with ethyl acetate in the presence of sodium ethoxide:



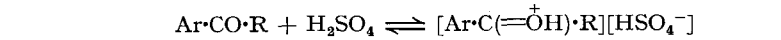
Acetophenone condenses with ethyl benzoate in the presence of sodium ethoxide to form *dibenzoylmethane*, m.p. 77°.



Acetophenone undergoes the Mannich reaction (see p. 306):

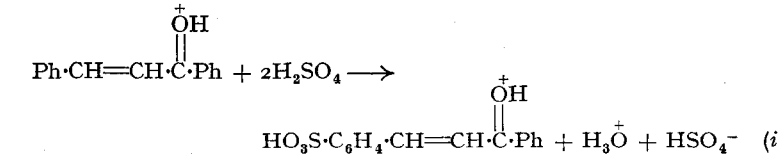


Aromatic aldehydes and ketones generally behave as bases in concentrated sulphuric acid; cryoscopic experiments show that i (van't Hoff factor) is 2, and this value agrees with the following equation (R = H or R):



The carbonyl compound may be recovered by dilution with water.

On the other hand, certain *unsaturated* ketones behave differently. Gillespie *et al.* (1954) found that all but two of the fourteen unsaturated carbonyl compounds investigated by them gave freezing point depressions in sulphuric acid which increase with time and only reach a constant limiting value after a long period. These stable values varied up to 6. These results have been attributed to sulphonation, and sulphonic acids have been isolated in certain cases, *e.g.*, benzylideneacetophenone gives first a value of $i = 2$, and finally $i = 4$.



The solutions of these oxonium salts are much deeper in colour than the ketone or the solution of the ketone in an organic solvent, *e.g.*, benzylideneacetophenone is a very pale yellow solid, and its solution in ethanol is also pale yellow, but its solution in concentrated sulphuric acid is deep yellow. These deep-coloured oxonium salts have therefore been named *halochromic* salts.

Willgerodt reaction (1887). This is the name given to those reactions in which a carbonyl compound is converted into an amide with the same number of carbon atoms. The Willgerodt reaction was originally carried out by heating an aryl alkyl ketone with an aqueous solution of yellow ammonium polysulphide; *e.g.*, acetophenone forms the amide of phenylacetic acid, together with a small amount of the ammonium salt:

$$C_6H_5{\cdot}CO{\cdot}CH_3 \xrightarrow{(NH_4)_2S_x} C_6H_5{\cdot}CH_2{\cdot}CO{\cdot}NH_2 + C_6H_5{\cdot}CH_2{\cdot}CO_2NH_4$$

The amido-group is always formed at the end of the chain whatever the size of the R group in $C_6H_5{\cdot}CO{\cdot}R$; *e.g.*, butyrophenone forms γ-phenylbutyramide:

$$C_6H_5{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3 \longrightarrow C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}NH_2$$

The Willgerodt reaction is very useful for preparing aryl-substituted aliphatic acids.

A modified technique of carrying out the Willgerodt reaction is to heat the ketone with approximately equimolecular amounts of sulphur and a dry amine (Kindler, 1923, 1927); a particularly useful amine is morpholine,  . The final product is a thioamide and this, on acid or alkaline hydrolysis, gives an acid; or alternatively, on electrolytic reduction, the thioamide gives an amine, *e.g.*,

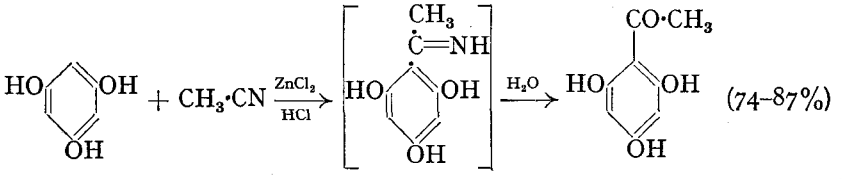
$$C_6H_5{\cdot}CO{\cdot}CH_3 + (CH_3)_2NH + S \longrightarrow C_6H_5{\cdot}CH_2{\cdot}C(=S){\cdot}N(CH_3)_2$$

$$C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}N(CH_3)_2 \xleftarrow{[H]} C_6H_5{\cdot}CH_2{\cdot}C(=S){\cdot}N(CH_3)_2 \xrightarrow{\text{acid}} C_6H_5{\cdot}CH_2{\cdot}CO_2H$$

Thus, by means of the Kindler procedure, bases containing the nitrogen atom on the terminal carbon atom of the side-chain can be synthesised.

The Willgerodt reaction was originally limited to ketones, but it has now been shown to be applicable to olefins, acetylenes, alcohols, halides, amines, etc.

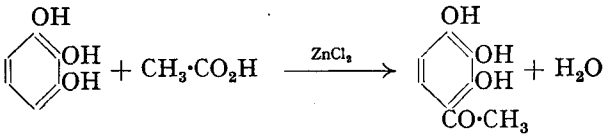
Phenolic ketones may be prepared by the **Houben–Hoesch synthesis** (1927). This is the condensation of cyanides with polyhydric phenols, particularly *m*-compounds, in the presence of zinc chloride and hydrogen chloride; *e.g.*, phloroglucinol condenses with methyl cyanide to form *phloroacetophenone* (m.p. 219°):



This method is really an extension of Gattermann's phenolic aldehyde synthesis. It is not applicable to phenol itself.

Phenolic ketones may also be prepared by the Fries rearrangement

(p. 622), and by heating polyhydric phenols with aliphatic acids in the presence of fused zinc chloride; *e.g.*, pyrogallol and acetic acid form *gallacetophenone* (m.p. 173°):



Many phenolic ketones occur naturally, free or as glycosides.

Benzophenone (*diphenyl ketone*), $C_6H_5{\cdot}CO{\cdot}C_6H_5$, may be prepared in a similar manner to acetophenone, *e.g.*,

(i) By heating calcium benzoate:

$$(C_6H_5{\cdot}CO_2)_2Ca \longrightarrow C_6H_5{\cdot}CO{\cdot}C_6H_5 + CaCO_3 \quad (30\%)$$

(ii) By the Friedel–Crafts condensation between benzoyl chloride and benzene:

$$C_6H_6 + C_6H_5{\cdot}COCl \xrightarrow{AlCl_3} C_6H_5{\cdot}CO{\cdot}C_6H_5 + HCl \quad (80\%)$$

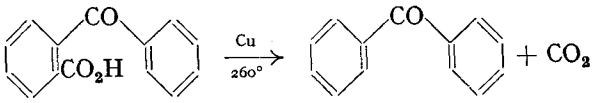
Carbonyl chloride may be used instead of benzoyl chloride:

$$2C_6H_6 + COCl_2 \xrightarrow{AlCl_3} C_6H_5{\cdot}CO{\cdot}C_6H_5 + 2HCl$$

The Friedel–Crafts reaction may also be carried out with carbon tetrachloride, followed by steam distillation of the dichloro-compound produced:

$$2C_6H_6 + CCl_4 \xrightarrow{AlCl_3} (C_6H_5)_2CCl_2 \xrightarrow{H_2O} (C_6H_5)_2CO \quad (80\text{–}89\%)$$

(iii) By heating *o*-benzoylbenzoic acid with copper powder at 260°:



Benzophenone exists in two solid forms, a stable, m.p. 49°, and an unstable form, m.p. 26°. It cannot be chloromethylated (*cf.* acetophenone). It is reduced by zinc and ethanolic potassium hydroxide to **benzhydrol** (*diphenylcarbinol*, m.p. 68°) and by zinc and acetic acid to **benzopinacol** (m.p. 188°):

$$(C_6H_5)_2C(OH){\cdot}C(OH)(C_6H_5)_2 \underset{(90\%)}{\xleftarrow[CH_3{\cdot}CO_2H]{Zn}} (C_6H_5)_2CO \xrightarrow[(90\%)]{Zn/KOH} (C_6H_5)_2CHOH$$

When benzophenone, dissolved in *iso*propanol to which a drop of acetic acid has been added, is exposed to bright sunlight, benzopinacol is formed:

$$2(C_6H_5)_2CO + (CH_3)_2CHOH \xrightarrow{h\nu} (C_6H_5)_2C(OH){\cdot}C(OH)(C_6H_5)_2 + (CH_3)_2CO \quad (93\text{–}94\%)$$

When benzophenone is dissolved in *iso*propanol and a small amount of sodium added, benzhydrol is formed. This compound is believed to be formed via benzopinacol which is first produced and then decomposed by sodium *iso*propoxide to benzophenone and benzhydrol. Evidence in favour

of this mechanism is afforded by the fact that benzopinacol is decomposed into benzophenone and benzhydrol by sodium hydroxide:

$$(C_6H_5)_2C(OH)\cdot C(OH)(C_6H_5)_2 \xrightarrow{NaOH} (C_6H_5)_2CO + (C_6H_5)_2CHOH$$

Benzopinacol is also obtained by the reduction of benzophenone with a mixture of magnesium and magnesium iodide, which appears to behave as magnesious iodide, MgI (Gomberg and Bachmann, 1927):

$$2(C_6H_5)_2CO + 2MgI \longrightarrow (C_6H_5)_2C(IMgO)-C(OMgI)(C_6H_5)_2 \xrightarrow{-MgI_2} (C_6H_5)_2C(O-Mg-O)C(C_6H_5)_2$$

$$\xrightarrow{H_2O} (C_6H_5)_2C(OH)\cdot C(OH)(C_6H_5)_2$$

When heated in acetic acid solution in the presence of iodine as catalyst, benzopinacol undergoes the pinacol–pinacolone rearrangement (p. 171) to form *benzopinacolone* (m.p. 179°):

$$(C_6H_5)_2C(OH)\cdot C(OH)(C_6H_5)_2 \longrightarrow (C_6H_5)_3C\cdot CO\cdot C_6H_5 + H_2O \quad (98\text{–}99\%)$$

When distilled with zinc dust, or reduced with a mixture of lithium aluminium hydride and aluminium chloride, benzophenone forms diphenylmethane, and when fused with potassium hydroxide, benzene and potassium benzoate:

$$(C_6H_5)_2CO + KOH \longrightarrow C_6H_6 + C_6H_5\cdot CO_2K$$

Benzophenone forms an oxime, but does not form a cyanohydrin or a bisulphite compound. The explanation for the latter is not clear; it may be due entirely to the steric effect.

Benzophenone dissolves sodium without the evolution of hydrogen, forming a compound (blue or green) which reacts rapidly with iodine or oxygen, and consequently is believed to be a free radical:

$$(C_6H_5)_2CO + Na \longrightarrow (C_6H_5)_2\dot{C}-\bar{O}Na^+$$

There is also present the following equilibrium (*cf.* acyloins, p. 194):

$$2(C_6H_5)_2\dot{C}-\bar{O}Na^+ \rightleftharpoons \begin{matrix}(C_6H_5)_2C-\bar{O}Na^+\\ |\\ (C_6H_5)_2C-\bar{O}Na^+\end{matrix}$$

The sodium salts of the free radicals are known as **metallic ketyls.** They are decomposed by water into benzophenone and benzhydrol (possibly via the dimer; *cf.* benzopinacol above). Aromatic ketones with a primary or secondary alkyl group evolve hydrogen when treated with sodium; *i.e.*, they enolise, and so will not form a metallic ketyl.

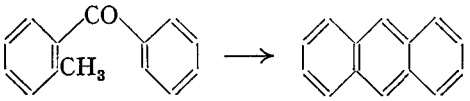
A very important derivative of benzophenone is **Michler's ketone,** which may be prepared by treating dimethylaniline with carbonyl chloride:

$$COCl_2 + 2C_6H_4N(CH_3)_2 \longrightarrow (CH_3)_2NC_6H_4-CO-C_6H_4N(CH_3)_2 + 2HCl$$

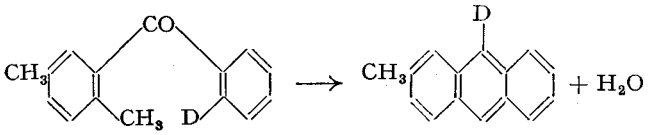
Michler's ketone is used in the preparation of certain triphenylmethane dyes (p. 788).

Elbs reaction (1884). This is the reaction whereby a polynuclear hydrocarbon is formed by the pyrolysis of a diaryl ketone containing a methyl

or a methylene group in the *o*-position to the carbonyl group; *e.g.*, *o*-methylbenzophenone forms anthracene (see also p. 727):



The mechanism of the Elbs reaction is uncertain; according to Badger *et al.* (1953) it proceeds via free radicals. Hurd *et al.* (1951), using deuterium as tracer, have shown that hydrogen in the 9-position (in anthracene) does not come from the *o*-methyl group but from the *o*-hydrogen of the benzene ring, *e.g.*,



STEREOCHEMISTRY OF ALDOXIMES AND KETOXIMES

Many aromatic aldoximes and ketoximes exist in two isomeric forms, and this was explained by Hantzsch and Werner (1890) as being due to geometrical isomerism. According to these authors, nitrogen is tervalent (in oximes) and is situated at one corner of a tetrahedron with its three valencies directed towards the other three corners; consequently the three valencies are not coplanar. These authors also assumed that there is no free rotation about the C=N bond, and therefore proposed configurations (I) and (II) for the two isomers:

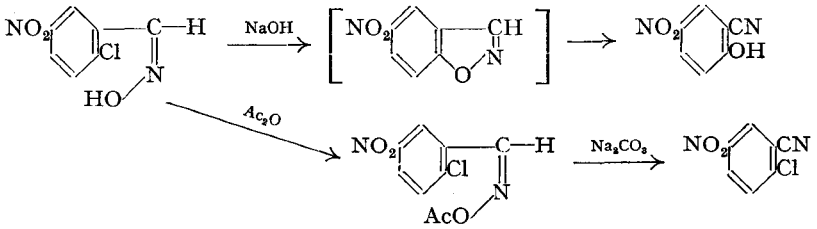
(I) (II)

Many facts are in favour of geometrical isomerism, *e.g.*, (i) if Ar = R, then isomerism disappears; (ii) the absorption spectra show that both have identical structures.

Determination of Configuration

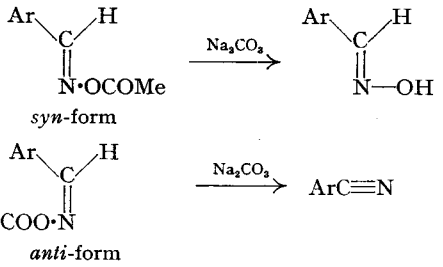
Aldoximes. The two isomeric aldoximes may be distinguished by the behaviour of their acetyl derivatives towards aqueous sodium carbonate; one gives the oxime back again, and the other forms the cyanide Ar·CN.

Brady *et al.* (1925) showed that the cyanide is formed by *anti*-elimination. These authors found that only one of the two isomers of 2-chloro-5-nitrobenzaldoxime readily gave ring closure on treatment with sodium hydroxide; this isomer is therefore the *anti*- (*trans*-) isomer. Furthermore, it was this isomer that gave the cyanide, thus showing that *anti*-elimination must have occurred.



Actually, the ring compound produced, the 5-nitrobenz*iso*oxazole, is unstable, and rearranges to nitrosalicylonitrile.

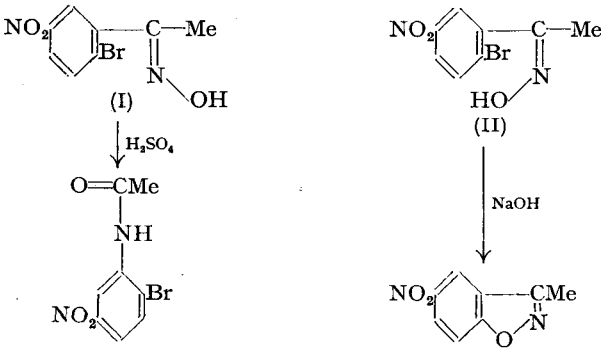
Thus the general reaction may be formulated as follows, the *anti*-oxime giving the cyanide and the *syn*-(*cis*-)oxime regenerating the oxime:



Ketoximes. Beckmann rearrangement (1886). When treated with reagents such as phosphorus pentachloride, sulphuric acid, polyphosphoric acid, etc., aromatic ketoximes undergo the Beckmann rearrangement to form an acid amide:

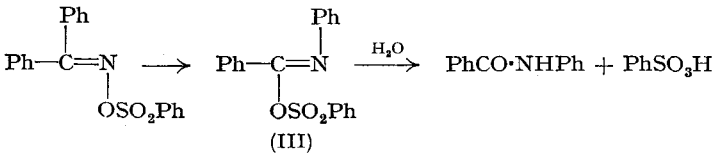
$$Ar_2C{=}NOH \longrightarrow Ar{\cdot}CO{\cdot}NHAr$$

Meisenheimer (1921, 1925) showed that the rearrangement occurs by *anti*-rearrangement, *e.g.*, he (1925) showed that the α-oxime of 2-bromo-5-nitroacetophenone is unaffected by sodium hydroxide, whereas the β-isomer undergoes ring closure to form 3-methyl-5-nitrobenz*iso*-oxazole; thus the α-oxime is the *syn*-methyl isomer (I), and the β-oxime the *anti*-methyl isomer (II). When treated with sulphuric acid or phosphorus pentachloride, the α-oxime underwent the Beckmann rearrangement to give the *N*-substituted acetamide; thus the exchange occurs in the *anti*-positions.



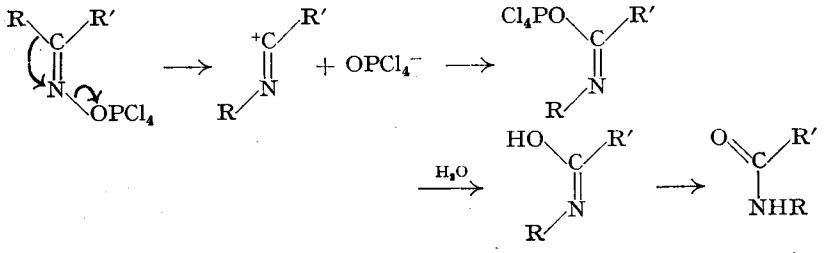
Thus by identifying the amide and using the fact that the rearrangement occurs in the *anti*-position, the configuration of the ketoxime can be determined.

The mechanism of the Beckmann rearrangement is still the subject of much discussion. Since the oxime itself does not rearrange, it is reasonable to suppose that some intermediate is formed between oxime and reagent, and it is this intermediate which rearranges. Kuhara *et al.* (1914, 1916) prepared the benzenesulphonate of benzophenone oxime and showed this readily underwent rearrangement in neutral solvents to give an isomeric compound (III) which gave benzanilide on hydrolysis; thus:

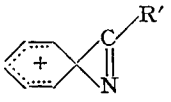


The structure of (III) was assigned to it on the basis of the similarity of its absorption spectrum with that of synthetic compounds of similar structure.

Chapman (1934–) showed the rate of rearrangement of benzophenone oxime picryl ester is more rapid in polar solvents than in non-polar. This is strong evidence that the rate-determining step is the ionisation of the intermediate. Furthermore, Kenyon *et al.* (1946) found that when (+)-α-phenylethyl methyl ketoxime is rearranged with sulphuric acid, the product is almost 100 per cent. optically pure (retention). Thus the rearrangement is intramolecular. A mechanism which fits these facts is the 1,2-shift as follows (for PCl_5):



(When sulphuric acid is used, replace $OPCl_4$ in the above equation by OH_2^+.)



When the migrating group is aryl and contains an electron-releasing group in the *p*-position, the rearrangement is accelerated. This may be cited as evidence for the formation of a bridged ion (*cf.* p. 101).

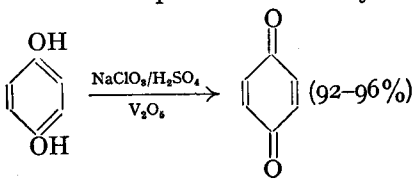
Other mechanisms have also been suggested (Stephen *et al.*, 1956).

QUINONES

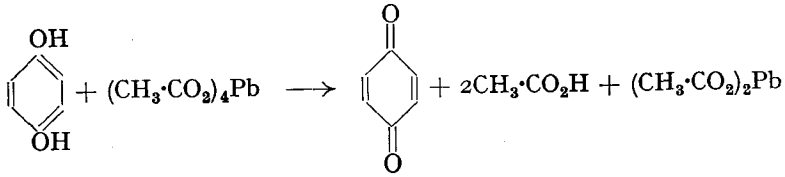
Quinones are compounds which are formed by the replacement of two hydrogen atoms in the nucleus by two oxygen atoms. Two quinones of benzene are possible: *o*-benzoquinone and *p*-benzoquinone:

m-Benzoquinone has not been prepared; it is impossible to arrange two carbonyl oxygen atoms in the ring in the *m*-position and still maintain a valency of four for carbon (*cf.*, however, *m*-nitrophenol, p. 627).

***p*-Benzoquinone** (p-*quinone*) may be prepared by the oxidation of quinol with ferric chloride, manganese dioxide and sulphuric acid, or acid dichromate; the best oxidising agent is sodium chlorate in dilute sulphuric acid in the presence of vanadium pentoxide as catalyst:

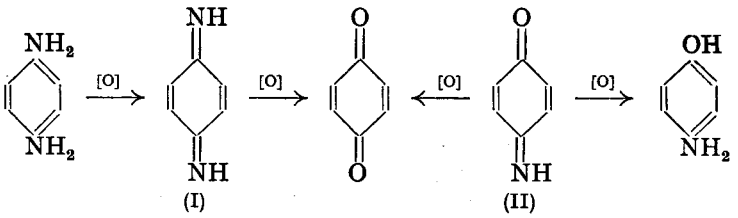


Quinol may also be oxidised to quinone by lead tetra-acetate.



p-Benzoquinone is usually prepared in the laboratory by the oxidation of aniline with potassium dichromate and sulphuric acid.

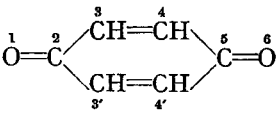
In general, *p*-quinones may be prepared by the oxidation (using dichromate-sulphuric acid) of *p*-dihydroxy-, *p*-diamino- or *p*-aminohydroxy-compounds, *e.g.*,

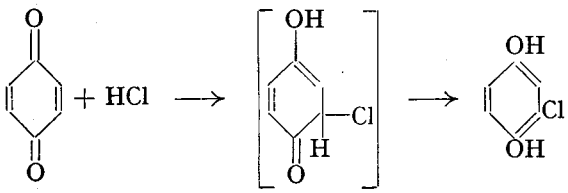


The intermediate products I (p-*benzoquinonedi-imine*) and II (p-*benzoquinoneimine*) can be isolated under certain conditions (see p. 672).

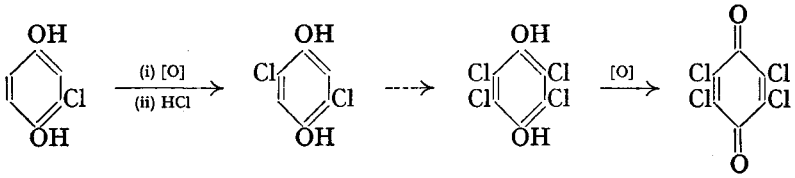
p-Benzoquinone crystallises in yellow prisms, m.p. 116°; it has a sharp smell, sublimes when heated, is slightly soluble in water, and is steam-volatile. On exposure to light, *p*-benzoquinone turns brown.

The yellow colour of *p*-benzoquinone is due to the presence of the quinonoid structure  . This structure is also known as a *crossed conjugated system*; it contains three (or more) conjugated double bonds which are not arranged in a continuous chain. *p*-Benzoquinone behaves in many ways as an αβ-unsaturated ketone rather than as an aromatic compound; *e.g.*, it adds on bromine in the 3 : 4-positions to give the dibromo-derivative; with excess bromine, it adds on two more bromine atoms in the 3′ : 4′-positions to give the tetrabromo-derivative. It also adds on hydrogen chloride to form mainly *chloroquinol* (*chlorohydroquinone*), m.p. 106°; the mechanism of this addition is possibly 1 : 4-addition first, followed by enolisation:





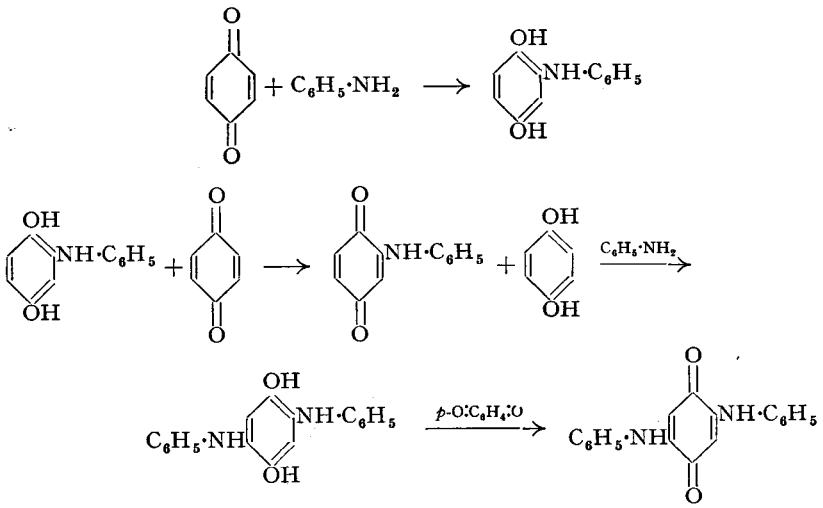
Chloroquinol, on oxidation, gives chloro-*p*-benzoquinone. By repeating the process of adding hydrogen chloride and then oxidising, the final product obtained is *tetrachloro*-p-*benzoquinone* (*chloranil*):



Chloranil is used as a fungicide and as an oxidising agent (see below).

As can be seen from the above equation, chloro-*p*-benzoquinone adds on hydrogen chloride to form 2 : 5-dichloroquinol; this is to be expected by 1 : 4-addition (other dichloro-derivatives, however, are also possible by 1 : 4-addition,

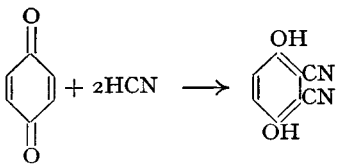
but only the 2 : 5-appears to be formed). In the same way, *p*-benzoquinone forms 2 : 5-addition compounds with primary or secondary amines in ethanolic solution, but in this case the quinone, and not the quinol derivative, is obtained. This is believed to be formed as follows (via 1 : 4-addition), *e.g.*, with aniline, the final product is 2 : 5-dianilino-*p*-benzoquinone:



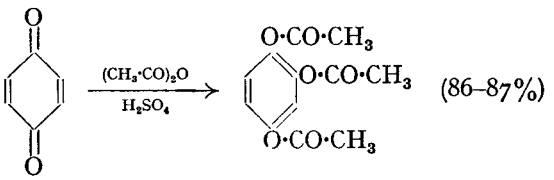
p-Benzoquinone is a fairly strong oxidising agent, but although it is not strong enough to oxidise chloroquinol, it can oxidise anilino-compounds (itself being reduced to quinol).

In a similar way, primary alcohols, in the presence of zinc chloride, form 2 : 5-dialkoxy-*p*-benzoquinones with *p*-benzoquinone.

The addition of hydrogen cyanide to *p*-benzoquinone is exceptional in that 2 : 3-dicyanoquinol is formed:



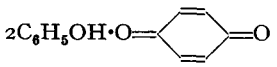
When treated with acetic anhydride in the presence of sulphuric acid, *p*-benzoquinone forms hydroxyquinol triacetate; this is known as the **Thiele acetylation** (1898).



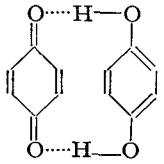
p-Benzoquinone is easily reduced to quinol (1 : 6-addition) by sulphurous acid, hydrogen sulphide, or sodium hyposulphite (yield: 80 per cent.).

An intermediate in this reduction is quinhydrone (green prisms, m.p. 171°). **Quinhydrones** are a group of coloured substances formed from quinones and another aromatic compound. Some are believed to be charge-transfer complexes (p. 557), *e.g.*, *phenoquinone* (I; red); phenol acts as the electron donor and the

quinone as the electron acceptor. Another type of quinhydrone is the one formed between one molecule of benzoquinone and one molecule of quinol. The structure of this type is uncertain, but it is believed that the rings of the two molecules are parallel and held together by hydrogen bonds at both ends (II).



(I)

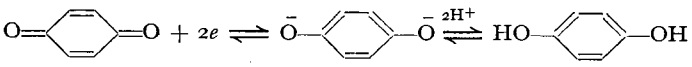


(II)

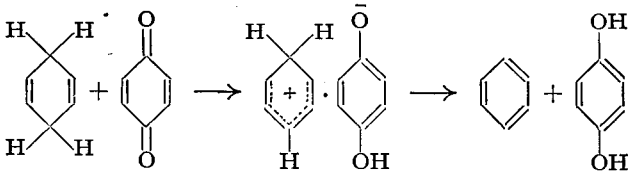
Since the compounds are coloured, this suggests that the complexes are resonance hybrids produced by charge-transfer " bonding " (see p. 775).

p-Benzoquinone is so easily reduced that it is used as an oxidising agent—generally chloranil is more satisfactory—in reactions where inorganic oxidising agents must be avoided. It liberates iodine from acidified potassium iodide solution, and is oxidised by silver oxide to maleic acid (and other products). It forms a monoxime and a dioxime (see below), and can act as a dienophile in the Diels–Alder reaction, *e.g.*, with butadiene it forms a hydrogenated anthraquinone derivative (see p. 728).

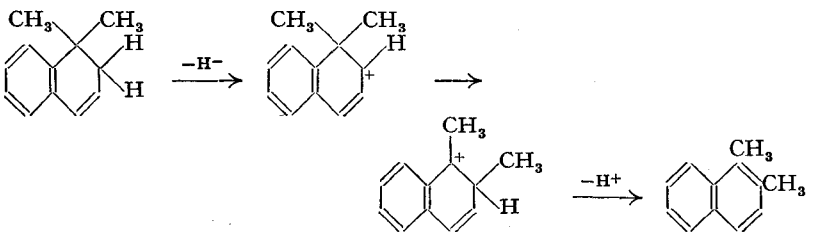
It has been suggested that the oxidising property of benzoquinone is due to the fact that when the quinone adds on two electrons, the benzenoid structure (with a large resonance energy) is obtained:



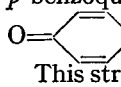
Benzoquinone dehydrogenates many hydroaromatic compounds, and the hydrogen transfer has been shown to take place with the transfer of hydride ions:



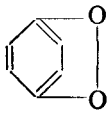
An interesting point about this dehydrogenation is that, on the basis of this mechanism, it might be anticipated that *gem.*-dialkylhydroaromatic compounds would be converted into aromatic compounds with a migration of the " blocking " group (*cf.* the Wagner rearrangement, p. 131). Such reactions have been effected in practice by using high-potential quinones, *e.g.*,



Structure of *p*-benzoquinone. Analysis and molecular-weight determinations show that the molecular formula of *p*-benzoquinone is $C_6H_4O_2$. On

reduction, *p*-benzoquinone gives quinol, which is known to be *p*-dihydroxybenzene. Thus *p*-benzoquinone contains two oxygen atoms in the *p*-positions; this is supported by the fact that on mild oxidation, quinol forms *p*-benzoquinone. Using these facts Fittig (1863) proposed the formula  for *p*-benzoquinone.

This structure, however, did not appear to agree with certain other properties of *p*-benzoquinone; *e.g.*, on treatment with phosphorus pentachloride, *p*-dichlorobenzene is formed. This reaction appears to indicate that oxygen is linked to carbon by a *single* bond. Graebe (1867) therefore suggested

 *or (writing this in another way)* 

Many other properties of *p*-benzoquinone, however, do not agree with Graebe's formula, but do agree with Fittig's; *e.g.*,

(i) *p*-Benzoquinone forms a monoxime and a dioxime. This indicates the presence of two carbonyl groups.

(ii) *p*-Benzoquinone behaves as an unsaturated cyclic ketone rather than as an aromatic compound; *e.g.*, its addition of halogens, halogen acids, etc., is not characteristic of aromatic compounds.

(iii) *p*-Benzoquinone behaves as a dienophile in the Diels–Alder reaction; this indicates the presence of the grouping O=C—C=C.

(iv) Infrared measurements of benzoquinone have shown that a carbonyl group is present.

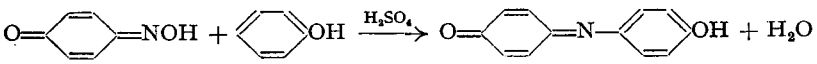
(v) If Graebe's formula were correct, there appears to be no reason why *m*-benzoquinone should not exist.

It can therefore be seen from the foregoing that Fittig's formula agrees better with the properties of *p*-benzoquinone and consequently is the accepted one.

***p*-Benzoquinone oximes.** *p*-Benzoquinone forms two oximes with hydroxylamine. With one equivalent of hydroxylamine the monoxime is formed, and this is tautomeric with *p*-nitrosophenol (p. 630). The dioxime is a yellow crystalline solid.

***p*-Benzoquinoneimine,** $NH{:}C_6H_4{:}O$, and ***p*-benzoquinonedi-imine,** $NH{:}C_6H_4{:}NH$, may be prepared by the careful oxidation of *p*-aminophenol and *p*-phenylenediamine, respectively, with silver oxide in ethereal solution. The mono-imine is a bright yellow crystalline solid; the di-imine is colourless and unstable. When warmed with inorganic acids, both compounds form *p*-benzoquinone and ammonia.

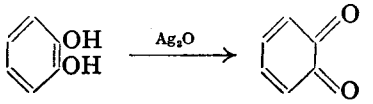
Indophenol may be prepared by condensing *p*-nitrosophenol with phenol in the presence of 70 per cent. sulphuric acid or concentrated hydrochloric acid:



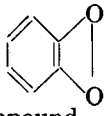
It is a brown solid, m.p. 160°, giving a red solution in ethanol; it was formerly used as a dye.

* ***o*-Benzoquinone** may be prepared by the oxidation of catechol with silver oxide in dry ethereal solution in the presence of anhydrous sodium sulphate. The latter is necessary to remove the water formed during the reaction,

since *o*-benzoquinone is readily oxidised by silver oxide in the presence of water:

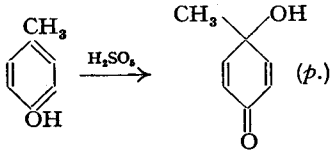


o-Benzoquinone exists in two forms, one as unstable green needles, and the other, stable light-red crystalline plates. It is odourless, not steam volatile, and is reduced to catechol by sulphurous acid. It is a strong oxidising agent, *e.g.*, it liberates iodine from acidified potassium iodide.

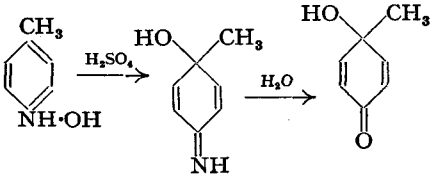
The alternative structure  has been rejected on grounds similar to those used for the *p*-compound.

Many benzoquinone compounds occur naturally, and are the cause of the colour in the pigments in which they are found.

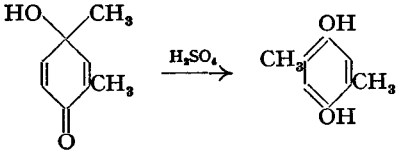
Quinols may be prepared by oxidising *p*-alkylphenols with Caro's acid; *e.g.*, *p*-cresol gives p-*toluquinol* (4-*methylquinol*):



Quinols may also be prepared by treating *p*-alkylphenylhydroxylamines with dilute sulphuric acid. Rearrangement to the imine first takes place (*cf.* phenylhydroxylamine, p. 561), and this is then hydrolysed to the quinol; *e.g.*, *p*-tolylhydroxylamine gives first iminotoluquinone and then *p*-toluquinol:



Quinols are colourless solids, soluble in alkalis, readily acetylated and readily reduced to the *p*-alkyl-phenol. Their most characteristic reaction is their great tendency to rearrange to the aromatic structure; *e.g.*, 2 : 4-dimethylquinol, under the influence of dilute sulphuric acid, rearranges to 2 : 5-dimethylquinol:



QUESTIONS

1. Starting with benzene or toluene, show how you would prepare:—(*a*) $Ph{\cdot}CH_2OH$, (*b*) $Ph{\cdot}CH_2{\cdot}CH_2OH$, (*c*) $Ph{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2OH$, (*d*) m-$HO{\cdot}C_6H_4{\cdot}CH_2OH$, (*e*) o-$NO_2{\cdot}C_6H_4{\cdot}CH_2OH$, (*f*) p-$ClC_6H_4{\cdot}CH_2OH$, (*g*) p-$BrC_6H_4{\cdot}CO{\cdot}CH_2Br$, (*h*) $Ph{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_2$, (*i*) 2 : 3′ : 4-trinitrostilbene.

2. Describe, in detail, methods for preparing benzaldehyde. Name the compounds and state the conditions under which they are formed when benzaldehyde is treated with:—(*a*) O_2, (*b*) $AgNO_3$, (*c*) Fehling's solution, (*d*) $NaHSO_3$, (*e*) HCN, (*f*) $NH_2{\cdot}OH$, (*g*) NH_3, (*h*) PCl_5, (*i*) NaOH, (*j*) N_2H_4, (*k*) $Ph{\cdot}NH_2$, (*l*) H, (*m*) Cl_2, (*n*) $CH_3{\cdot}CHO$, (*o*) Me_2CO, (*p*) $H{\cdot}CHO$, (*q*) $MeNO_2$, (*r*) $Ph{\cdot}CO{\cdot}CH_3$, (*s*) Ac_2O, (*t*) succinic anhydride, (*u*) PhOH, (*v*) $Ph{\cdot}NMe_2$, (*w*) HNO_3, (*x*) H_2SO_4.

3. Describe how each of the following compounds may be prepared:—(*a*) *o*-, *m*- and *p*-nitrobenzaldehydes, (*b*) 2 : 4-dinitrobenzaldehyde, (*c*) *m*- and *p*-chlorobenzaldehydes, (*d*) 2 : 6-dichlorobenzaldehyde, (*e*) anisaldehyde, (*f*) protocatechualdehyde, (*g*) vanillin, (*h*) veratraldehyde, (*i*) piperonal, (*j*) benzoylacetone, (*k*) 4-*n*-hexyl-resorcinol, (*l*) benzhydrol, (*m*) benzopinacol, (*n*) chloranil, (*o*) quinhydrone.

4. Write a detailed account of the general methods of preparing phenolic aldehydes. Discuss the properties of salicylaldehyde.

5. How may cinnamaldehyde, acetophenone and benzophenone be prepared? Name the compounds and state the conditions under which they are formed when each of these compounds is treated with:—(*a*) oxidising agents, (*b*) reducing agents, (*c*) Br_2, (*d*) HCN, (*e*) $NH_2{\cdot}OH$, (*f*) $NaHSO_3$, (*g*) NH_3, (*h*) HNO_3, (*i*) HCl, (*j*) Ac_2O, (*k*) EtOAc, (*l*) $(NH_4)_2S_x$, (*m*) Me_2NH + S.

6. Write an account of the isomerism of the aromatic aldoximes and ketoximes.

7. Describe the preparation and properties of *o*- and *p*-benzoquinones. Outline the evidence for the accepted structures of these compounds.

8. A compound has the molecular formula C_7H_8O. Write out all the possible isomers and show how you would distinguish between them.

9. Define and give examples of:—(*a*) Étard's reaction, (*b*) Gattermann–Koch aldehyde synthesis, (*c*) Gattermann aldehyde synthesis, (*d*) Sommelet's reaction, (*e*) Rosenmund reduction, (*f*) Stephen's method, (*g*) Cannizzaro reaction, (*h*) Claisen reaction, (*i*) Perkin reaction, (*j*) vinylogy, (*k*) Knoevenagel reaction, (*l*) Reimer–Tiemann reaction, (*m*) Duff's reaction, (*n*) Mannich reaction, (*o*) Willgerodt reaction, (*p*) Houben–Hoesch synthesis, (*q*) Elbs reaction, (*r*) Beckmann rearrangement.

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CHAPTER XXVIII

AROMATIC ACIDS

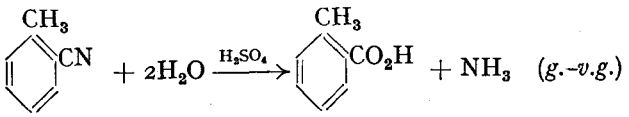
AROMATIC acids are compounds containing one or more carboxyl groups which are directly attached to the nucleus. Those acids in which the carboxyl group occurs in the side-chain may be regarded as aryl-substituted aliphatic acids, but they are also classified as aromatic acids, since they exhibit aromatic properties due to the presence of a benzene ring.

MONOBASIC ACIDS WITH THE CARBOXYL GROUP ATTACHED TO THE RING

General methods of preparation. 1. By the oxidation of the corresponding alcohol or aldehyde; *e.g.*, benzaldehyde gives benzoic acid:

$$C_6H_5{\cdot}CHO \xrightarrow{KMnO_4} C_6H_5{\cdot}CO_2H \quad (v.g.)$$

2. By the hydrolysis of the corresponding cyanide, *e.g.*, *o*-tolyl cyanide gives *o*-toluic acid:



(*g.*–*v.g.*)

3. By means of a Grignard reagent, *e.g.*,

$$C_6H_5{\cdot}MgBr + CO_2 \longrightarrow C_6H_5{\cdot}CO_2MgBr \xrightarrow{HCl} C_6H_5{\cdot}CO_2H \quad (90\%)$$

4. By means of the Friedel–Crafts reaction; *e.g.*, treatment of benzene with carbonyl chloride in the presence of anhydrous aluminium chloride gives benzoyl chloride which, on hydrolysis, forms benzoic acid:

$$C_6H_6 + COCl_2 \xrightarrow{AlCl_3} C_6H_5{\cdot}COCl \longrightarrow C_6H_5{\cdot}CO_2H \quad (55\text{–}58\%)$$

Excess of carbonyl chloride must be used in this method; otherwise benzophenone will be the main product (p. 664).

5. By the oxidation of benzene homologues with dilute nitric acid, dichromate and sulphuric acid, alkaline permanganate, or chromium trioxide in glacial acetic acid. In some cases it may be more convenient to chlorinate the hydrocarbon, and then oxidise the chloro-derivative, *e.g.*,

$$C_6H_5{\cdot}CH_3 \xrightarrow{Cl_2} C_6H_5{\cdot}CH_2Cl \xrightarrow[KMnO_4]{Na_2CO_3} [C_6H_5{\cdot}CH_2OH] \xrightarrow{[O]} C_6H_5{\cdot}CO_2H \quad (80\%)$$

In this way the oxidation of the side-chain is much easier, since the intermediate alcohol is much more readily oxidised than the hydrocarbon itself.

General properties. In general, the aromatic acids are slightly stronger acids than the aliphatic, less soluble in water, and less volatile. They are fairly easily soluble in hot water, and are readily decarboxylated by heating with soda-lime.

Benzoic acid (*benzenecarboxylic acid*), $C_6H_5{\cdot}CO_2H$, is present in certain resins, particularly gum-benzoin; it is also present in balsams. Benzoic acid is also found as *hippuric acid* (*benzoylglycine*) in the urine of horses.

Benzoic acid may be prepared in the laboratory by any of the general methods. Commercially, it is prepared as follows:

(i) By the hydrolysis of benzotrichloride with aqueous calcium hydroxide in the presence of iron powder as catalyst (this is an example of indirect oxidation):

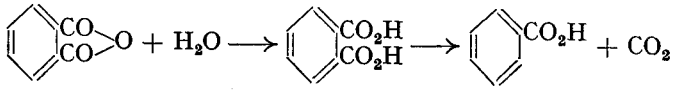
$$C_6H_5{\cdot}CCl_3 + 2H_2O \xrightarrow[Fe]{Ca(OH)_2} C_6H_5{\cdot}CO_2H + 3HCl$$

(ii) By the catalytic oxidation of toluene with air and stannic vanadate as catalyst:

$$2C_6H_5{\cdot}CH_3 + 3O_2 \longrightarrow 2C_6H_5{\cdot}CO_2H + 2H_2O$$

(iii) By the hydrolysis of benzoyl chloride prepared from benzene and carbonyl chloride (see method 4 above).

(iv) When phthalic anhydride and steam are passed over a metal phthalate catalyst, *e.g.*, zinc, chromium or nickel salt at 200–300°, some of the resulting phthalic acid is decarboxylated to benzoic acid:



Benzoic acid is a white crystalline solid, m.p. 122°, sparingly soluble in cold water but readily soluble in hot water, ethanol and ether. It is steam-volatile. It forms salts in the usual way; the silver salt (white) and the ferric salt (buff-coloured) are insoluble. Benzoic acid readily forms esters when it is refluxed with an alcohol in the presence of a small amount of concentrated sulphuric acid or hydrogen chloride. Benzoic esters are pleasant-smelling liquids which are denser than water. Phenyl benzoate, which may be prepared by the action of benzoyl chloride on an alkaline solution of phenol, is a solid, m.p. 71°. In general, it has been found that benzoic acid containing a substituent in the *o*-position does not esterify as easily as the *m*- or *p*-isomer. If both *o*-positions (with respect to the carboxyl group) are occupied, then esterification occurs with the greatest difficulty, if at all. Furthermore, once the ester is formed from these di-*ortho*-substituted benzoic acids, it is very difficult to hydrolyse them. The explanation for these abnormal reactions is not yet complete (see the *ortho*-effect, p. 686, for further details).

Benzoyl chloride (*benzenecarbonyl chloride*), $C_6H_5{\cdot}COCl$, was the first acid chloride to be discovered. It may be readily prepared by distilling benzoic acid with phosphorus pentachloride or with thionyl chloride:

$$C_6H_5{\cdot}CO_2H + SOCl_2 \longrightarrow C_6H_5{\cdot}COCl + HCl + SO_2 \quad (75\text{–}80\%)$$

It is prepared commercially by chlorinating benzaldehyde in the cold (benzaldehyde contains no α-hydrogen atom):

$$C_6H_5{\cdot}CHO + Cl_2 \longrightarrow C_6H_5{\cdot}COCl + HCl \quad (ex.)$$

Another commercial method is to heat benzoic acid with benzotrichloride:

$$C_6H_5{\cdot}CO_2H + C_6H_5{\cdot}CCl_3 \longrightarrow 2C_6H_5{\cdot}COCl + HCl$$

Benzoyl chloride is a colourless fuming liquid, b.p. 197°, with an irritating odour. It is only very slowly decomposed by water or by dilute sodium hydroxide (*cf.* acetyl chloride), and because of this, compounds containing an active hydrogen atom can be benzoylated in the presence of dilute aqueous sodium hydroxide. This method of benzoylation is known as the **Schotten–Baumann reaction.** *e.g.*,

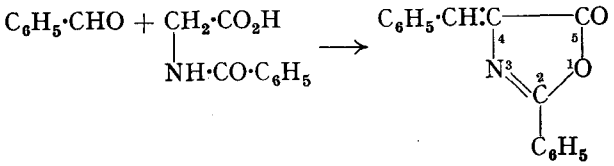
$$C_6H_5{\cdot}COCl + C_6H_5{\cdot}NH_2 + NaOH \longrightarrow C_6H_5{\cdot}CO{\cdot}NH{\cdot}C_6H_5 + NaCl + H_2O$$

p-Nitrobenzoyl and 3 : 5-dinitrobenzoyl derivatives of the alcohols are usually well-defined crystalline substances, and so are used to characterise the alcohols.

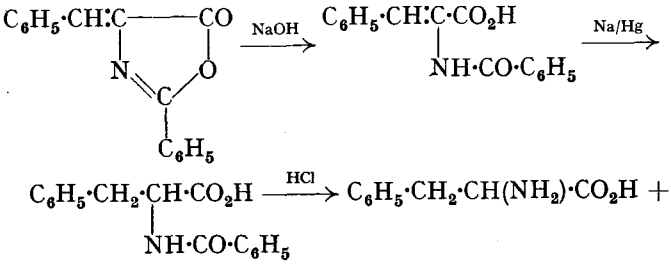
Hippuric acid (*benzoylglycine*) may be readily prepared by the action of benzoyl chloride on glycine:

$$C_6H_5{\cdot}COCl + NH_2{\cdot}CH_2{\cdot}CO_2H \longrightarrow C_6H_5{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CO_2H + HCl$$

It is a white solid, m.p. 188°, almost insoluble in water. Its most important reaction is its condensation with aromatic aldehydes to form **azlactones**; *e.g.*, when heated with benzaldehyde, acetic anhydride and sodium acetate, hippuric acid forms benzoyl-α-aminocinnamic azlactone (*2-phenyl-4-benzylideneoxazol-5-one*):



This reaction is usually referred to as the **Erlenmeyer azlactone synthesis** (1893). Azlactones are very important as intermediates in the preparation of amino- and ketoacids; *e.g.*, *phenylalanine* may be prepared from the above azlactone as follows:



See also p. 685 for another synthetic use of azlactones.

Benzamide (*benzenecarbonamide*), $C_6H_5{\cdot}CO{\cdot}NH_2$, may be prepared by the action of concentrated aqueous ammonia on benzoyl chloride or by hydrolysing phenyl cyanide with warm alkaline 3 per cent. hydrogen peroxide:

$$C_6H_5{\cdot}COCl + 2NH_3 \longrightarrow C_6H_5{\cdot}CO{\cdot}NH_2 + NH_4Cl \quad (v.g.)$$

$$C_6H_5{\cdot}CN \xrightarrow{H_2O_2} C_6H_5{\cdot}CO{\cdot}NH_2 \quad (ex.)$$

Benzamide is a white crystalline solid, m.p. 130°. It undergoes most of the usual reactions of an aliphatic acid amide; *e.g.*, it is readily hydrolysed by dilute acids or alkalis to benzoic acid and ammonia; it forms mercury benzamide, $(C_6H_5{\cdot}CO{\cdot}NH)_2Hg$, with mercuric oxide. Benzamide forms two types of ethers, *N*- and *O*- (*cf.* p. 205); *e.g.*, when the *silver salt* of benzamide is treated with ethyl iodide, *O*-ethylbenzamide, $C_6H_5{\cdot}C(OC_2H_5){:}NH$, is formed (hydrolysis gives benzoic acid, ethanol and ammonia). On the other hand, when the *sodium salt* is treated with ethyl iodide, *N*-ethylbenzamide, $C_6H_5{\cdot}CO{\cdot}NH{\cdot}C_2H_5$, is formed (hydrolysis gives benzoic acid and ethylamine).

Benzoic anhydride, $(C_6H_5{\cdot}CO)_2O$, may be prepared by heating a mixture of sodium benzoate and benzoyl chloride:

$$C_6H_5{\cdot}CO_2Na + C_6H_5{\cdot}COCl \longrightarrow (C_6H_5{\cdot}CO)_2O + NaCl \quad (g.)$$

A better method is to slowly distil a mixture of benzoic acid and acetic anhydride (*cf.* p. 201):

$$2C_6H_5{\cdot}CO_2H + (CH_3{\cdot}CO)_2O \longrightarrow (C_6H_5{\cdot}CO)_2O + 2CH_3{\cdot}CO_2H \quad (72\text{–}74\%)$$

McGookin *et al.* (1951) have prepared benzoic anhydride by the action of dry silver oxide or yellow mercuric oxide on benzoyl chloride in benzene:

$$2C_6H_5{\cdot}COCl + Ag_2O \longrightarrow (C_6H_5{\cdot}CO)_2O + 2AgCl$$

Benzoic anhydride is a white solid, m.p. 42°. It is only very slowly decomposed by water (*cf.* acetic anhydride); it may be used in the Schotten–Baumann reaction, but is not so convenient as benzoyl chloride.

Benzoyl peroxide, $C_6H_5{\cdot}CO{\cdot}O{\cdot}O{\cdot}CO{\cdot}C_6H_5$, may be prepared by the action of sodium peroxide on benzoyl chloride:

$$2C_6H_5{\cdot}COCl + Na_2O_2 \longrightarrow (C_6H_5{\cdot}CO)_2O_2 + 2NaCl$$

A more convenient method is to add a mixture of benzoyl chloride and aqueous sodium hydroxide to cool hydrogen peroxide with vigorous shaking:

$$2C_6H_5{\cdot}COCl + 2NaOH + H_2O_2 \longrightarrow (C_6H_5{\cdot}CO)_2O_2 + 2NaCl + 2H_2O \quad (80\text{–}95\%)$$

Benzoyl peroxide is a fairly stable solid, m.p. 104°. It is used as a bleaching agent for white flour.

Perbenzoic acid, $C_6H_5{\cdot}CO{\cdot}O{\cdot}OH$, may be prepared by adding a solution of benzoyl peroxide in chloroform to a cooled solution of sodium methoxide in methanol and extracting the product, sodium perbenzoate, with ice-cold water. When the aqueous solution is acidified with cold concentrated sulphuric acid, extracted with chloroform, and then the chloroform removed under reduced pressure, perbenzoic acid (m.p. 41°) remains:

$$(C_6H_5{\cdot}CO)_2O_2 + CH_3ONa \longrightarrow C_6H_5{\cdot}CO{\cdot}O_2Na + C_6H_5{\cdot}CO_2CH_3 \quad (82\%)$$

Kergomard *et al.* (1956) have prepared perbenzoic acid by reaction between benzoyl chloride and an aqueous ethanolic solution of sodium peroxide, or better, hydrogen peroxide and sodium carbonate.

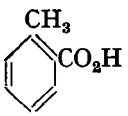
Perbenzoic acid is a fairly active oxidising agent; *e.g.*, it converts the ethylenic bond quantitatively into the ethylene oxide derivative:

$$>C{=}C< + C_6H_5{\cdot}CO{\cdot}O_2H \longrightarrow >C\overset{O}{\frown}C< + C_6H_5{\cdot}CO_2H$$

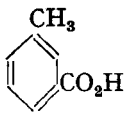
Perbenzoic acid is therefore used for the detection and estimation of ethylenic bonds (Prileschaiev reaction; *cf.* p. 74). It is far less troublesome to handle than peracetic acid, and so is used preferably (often as its sodium salt).

Phenyl cyanide (*benzonitrile, benzenecarbonitrile*) may be prepared by heating benzamide with phosphorus pentoxide, by means of the Sandmeyer reaction with benzenediazonium chloride (p. 586), or by fusing sodium benzenesulphonate with sodium cyanide (p. 609). It is a colourless oil, b.p. 191°, and behaves similarly to the aliphatic cyanides.

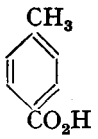
There are many homologues of benzoic acid, but only the **toluic acids** need be mentioned:



o-toluic acid, m.p. 105°



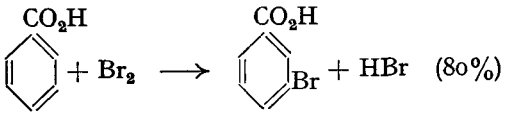
m-toluic acid, m.p. 111°



p-toluic acid, m.p. 180°

Each may be prepared by oxidising the corresponding xylene with dilute nitric acid, or from the corresponding toluidine (via the cyanide).

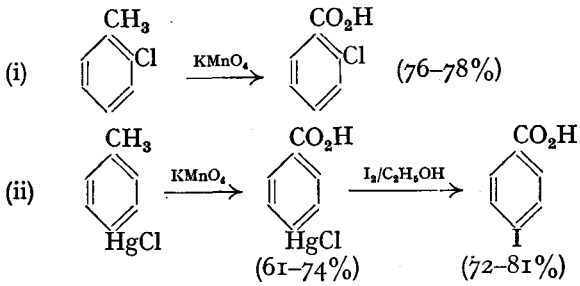
Substituted derivatives of benzoic acid. Benzoic acid is attacked by the usual electrophilic reagents chlorine, bromine, nitric and sulphuric acids, to give mainly the *m*-derivatives; *e.g.*, *m*-bromobenzoic acid may be obtained by heating benzoic acid, bromine and water under pressure:



Waters *et al.* (1950) have prepared *m*-iodobenzoic acid (75% yield) by adding iodine to a solution of benzoic acid in concentrated sulphuric acid containing silver sulphate. The active species in this case is the iodinium ion (*cf.* p. 69):

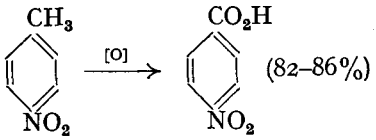
$$I_2 + H_2O \rightleftharpoons HOI + H^+ + I^-$$
$$Ag_2SO_4 + 2I^- \longrightarrow 2AgI + SO_4^{2-}$$
$$HOI + H^+ \rightleftharpoons H_2OI^+ \rightleftharpoons H_2O + I^+$$

o- and *p*-Substituted benzoic acids may be obtained by oxidising the corresponding toluene derivatives, *e.g.*,

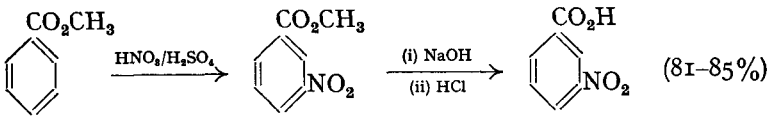


Many substituted benzoic acids may also be prepared from the corresponding aminobenzoic acids (via the diazonium salts). *o*- and *p*-Substituted benzoic acids may be obtained directly by using, *e.g.*, the sodium salt of benzoic acid (see p. 520).

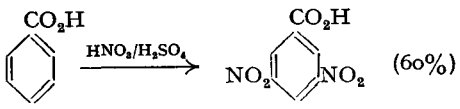
Nitrobenzoic acids. *o*- and *p*-Nitrobenzoic acids may be prepared by oxidising the corresponding nitrotoluenes with acid dichromate:



m-Nitrobenzoic acid may be prepared by direct nitration of methyl benzoate:

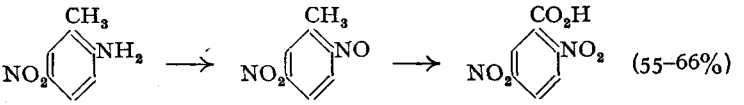


3:5-Dinitrobenzoic acid, m.p. 204°, is formed when benzoic acid is nitrated with a mixture of fuming nitric and sulphuric acids:



It is used to characterise alcohols.

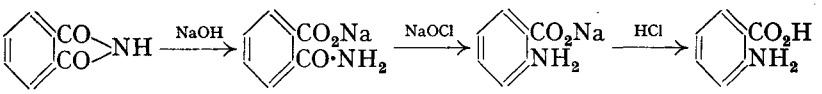
2 : 5-Dinitrobenzoic acid may be prepared by treating 2-amino-5-nitrotoluene with potassium persulphate and sulphuric acid (*i.e.*, Caro's acid) and further oxidising the product, 5 nitro-2-nitrosotoluene, with potassium dichromate and sulphuric acid:



Aminobenzoic acids. All three aminobenzoic acids may be obtained by reduction of the corresponding nitrobenzoic acids.

Anthranilic acid (*o-aminobenzoic acid*) may be prepared by reducing *o*-nitrobenzoic acid. An interesting preparation is by the internal oxidation of *o*-nitrotoluene (p. 558).

Commercially, anthranilic acid is prepared by oxidising phthalimide with aqueous sodium hydroxide and sodium hypochlorite (the Hofmann reaction):

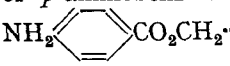


Anthranilic acid is a white solid, m.p. 145°, soluble in water, ethanol and ether; it behaves as an acid and as an amine; it does not exist as an inner salt in the solid state (*cf.* sulphanilic acid). When distilled, anthranilic acid is decarboxylated to aniline.

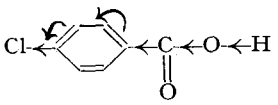
Methyl anthranilate is used in perfumery, since it is the characteristic constituent of jasmine and orange blossoms. Anthranilic acid is used in the industrial preparation of indigotin (p. 802).

***m*-Aminobenzoic acid,** m.p. 174°, is used in the preparation of azo-dyes.

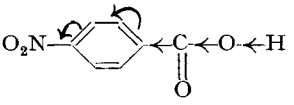
***p*-Aminobenzoic acid,** m.p. 186°, is one of the substances comprising the vitamin B complex. It has been claimed that it is an anti-grey hair factor; it is also said to be essential for the growth of chicks. Certain derivatives of *p*-aminobenzoic acid are used as local anaesthetics, *e.g.*, *novocaine*,



All the halogeno- and nitro-benzoic acids are stronger acids than benzoic acid itself. Both halogen and the nitro-group behave as electron-withdrawing groups, and thereby facilitate the release of the proton in the carboxyl group, *e.g.*,

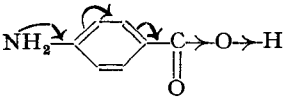


(−I effect)



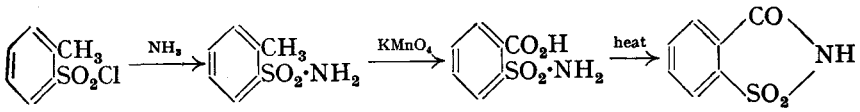
(−R effect)

The aminobenzoic acids are all weaker acids than benzoic acid because of the electron-donating property of the amino group (+R effect).



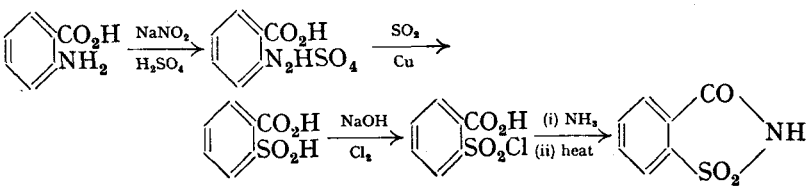
Sulphobenzoic acids. Sulphonation of benzoic acid gives *m*-sulphobenzoic acid. The *o*- and *p*-isomers may be prepared by oxidising the corresponding toluenesulphonic acids,

Saccharin (*o-sulphobenzoic imide*) may be prepared by treating toluene with chlorosulphonic acid and separating the *o*- and *p*-toluenesulphonyl chlorides (p. 612). The *o*-compound is then treated with ammonia, and the resulting amide oxidised with permanganate to *o*-sulphamide benzoic acid; this, on heating, forms saccharin:



Pure saccharin, in high yield, may be obtained by oxidising *o*-toluenesulphonamide with dichromate and sulphuric acid (Matveev, 1946).

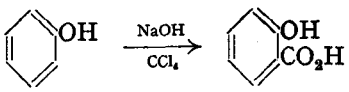
The method described above was one of the first to be used industrially. Many other industrial methods are now employed; *e.g.*, one starts with anthranilic acid; this is diazotised and treated with liquid sulphur dioxide in the presence of copper as catalyst. The sulphinic acid derivative thereby obtained is treated with chlorine in alkaline solution, and the sulphonyl chloride so produced is treated with ammonia and heated:



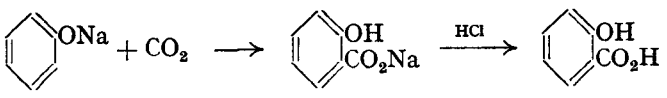
Saccharin is a crystalline solid, m.p. 224°, and 550 times as sweet as sugar. It is almost insoluble in water, and hence is sold as its sodium salt, which is very soluble. Saccharin is very sweet in dilute but is bitter in concentrated solutions. It is used instead of sugar for many purposes, *e.g.*, sweetening preserves, drinks, etc. It is also used by diabetics and obese persons.

Phenolic Acids. There are three hydroxybenzoic acids; only the *o*-isomer, *salicylic acid*, is important.

Salicylic acid (*o-hydroxybenzoic acid*) occurs as its methyl ester in many essential oils. It may be obtained by the oxidation of salicylaldehyde or salicyl alcohol; or fusing *o*-sulphobenzoic acid with sodium hydroxide. Salicylic acid may be prepared by replacing the amino-group in anthranilic acid by hydroxyl (via the diazonium salt), and also by the Reimer–Tiemann reaction using an alkaline solution of phenol and carbon tetrachloride (*cf.* p. 655):

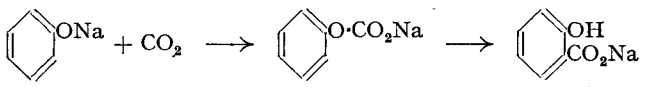


The original industrial method of preparing salicylic acid was the **Kolbe synthesis** (1859), and this was slightly modified by Schmitt (1885) to give the method (the **Kolbe–Schmitt reaction**) used now. This process is carried out by heating sodium phenoxide with carbon dioxide at 120–140° under pressure.

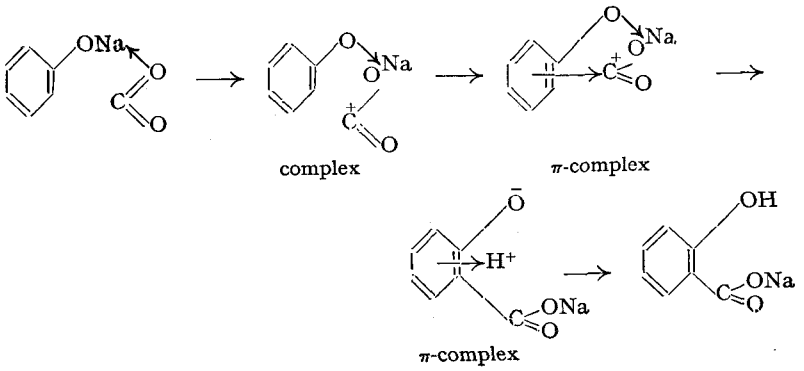


A small amount of the *p*-derivative is formed at the same time, and if the temperature rises above 140°, the *p*-isomer is the main product. A by-product in the Kolbe–Schmitt reaction is 4-hydroxy*iso*phthalic acid (3–5 per cent.).

The mechanism of the Kolbe–Schmitt reaction is uncertain. Schmitt believed that sodium phenyl carbonate was formed as an intermediate and that this rearranged to salicylic acid:

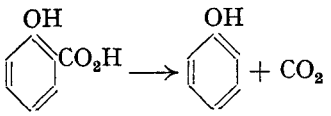


There is, however, much experimental evidence against this mechanism. Jones *et al.* (1954), by an examination of the infrared absorption spectrum of the product obtained in the Kolbe–Schmitt reaction, have been led to suggest ths following intramolecular mechanism involving a sodium phenoxide-carbon dioxide complex and a π-complex:

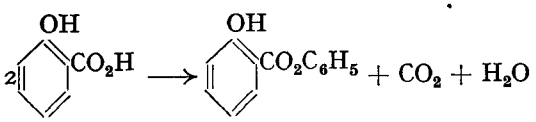


Salicylic acid is a white crystalline solid, m.p. 159°, sparingly soluble in cold water but readily soluble in hot water, ethanol and ether. It is used as an antiseptic, in medicine, and in the preparation of azo-dyes.

Salicylic acid behaves as a phenol and as an acid. Its aqueous solutions give a violet coloration with ferric chloride. When heated quickly, salicylic acid sublimes; but when heated slowly, it undergoes decarboxylation:



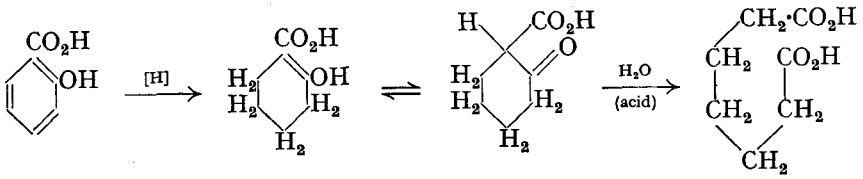
On the other hand, when heated to about 200°, it forms phenyl salicylate:



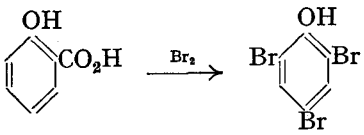
This is possibly formed by combination of phenol (the first decomposition product) with unchanged salicylic acid.

It has been found that as the number of hydroxyl groups in the *o*- and *p*-positions with respect to the carboxyl group increases, so the ease of decarboxylation (and carboxylation) increases. In any case, decarboxylation is always readily effected by heating with soda-lime. When the potassium salt of salicylic acid is heated at 230°, *p*-hydroxybenzoic acid is formed (see

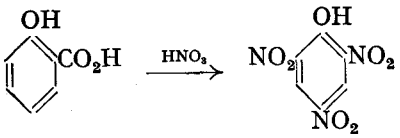
below). When reduced with sodium and *iso*pentanol, salicylic acid is converted into pimelic acid. The mechanism of this reaction is uncertain; one that has been proposed is:



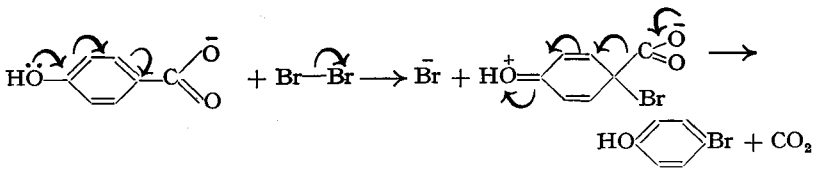
When treated with bromine water, salicylic acid forms s-tribromophenol, the carboxyl group being displaced by bromine:



This reaction is characteristic of the carboxyl group when it is *o*- or *p*- to a hydroxyl or an amino-group (*cf.* p. 616). Similarly, the carboxyl group is displaced by a nitro-group when salicylic acid is treated with fuming nitric acid:



The reason for this ready displacement of the carboxyl group by bromine or by the nitro-group is not certain, but it may possibly occur by the following mechanism:

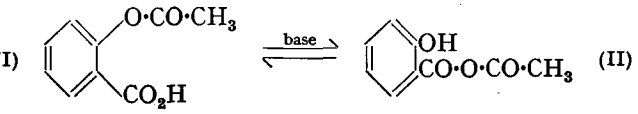


Decarboxylation in alkaline solution may be explained similarly (a proton is the attacking agent instead of Br^+).

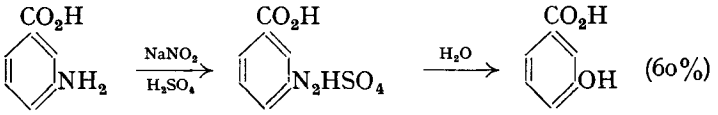
When treated with carbonates, only the carboxyl group in salicylic acid forms salts; with alkali, both the carboxyl and hydroxyl groups form salts. Sodium salicylate is used in the treatment of rheumatism. Salicylic acid is a stronger acid than its *m*- and *p*-isomers (see the *ortho*-effect, below).

Methyl salicylate, *o*-$HO{\cdot}C_6H_4{\cdot}CO_2CH_3$, b.p. 224°, is the principal constituent of oil of wintergreen. It may be prepared by direct esterification, and is used in perfumery and as a flavouring material *Salol* (*phenyl salicylate*), *o*-$HO{\cdot}C_6H_4{\cdot}CO_2C_6H_5$, m.p. 43°, may be prepared by heating salicylic acid with phenol in the presence of phosphoryl chloride. It is used as an internal antiseptic. *Aspirin* (*acetylsalicylic acid*), *o*-$CH_3{\cdot}CO{\cdot}O{\cdot}C_6H_4{\cdot}CO_2H$, m.p. 135°, may be prepared by acetylating salicylic acid with a mixture of acetic anhydride and glacial acetic acid. Aspirin behaves in a number of unusual ways, and Davidson *et al.* (1953) have suggested that the assumption of an equilibrium between aspirin (I) and salicyloylacetic anhydride (II)

offers an explanation for several of the unusual properties of aspirin as well as its pronounced acetylating action.

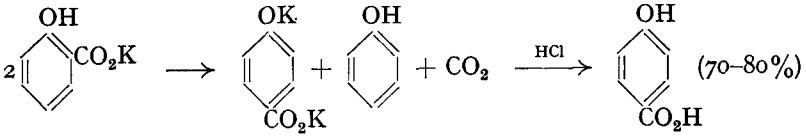


***m*-Hydroxybenzoic acid,** m.p. 201°, may be prepared from *m*-aminobenzoic acid:

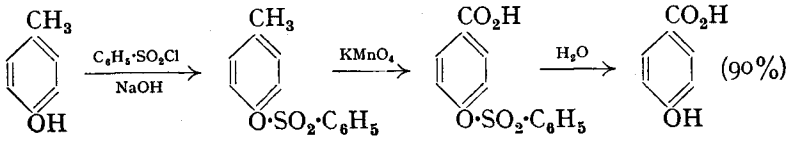


It does *not* give a coloration with ferric chloride.

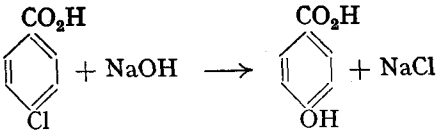
***p*-Hydroxybenzoic acid,** m.p. 214°, may be prepared by heating potassium salicylate at 230°:



It may also be prepared by oxidising the methyl group in *p*-cresol (with protection of the hydroxyl group during the oxidation):



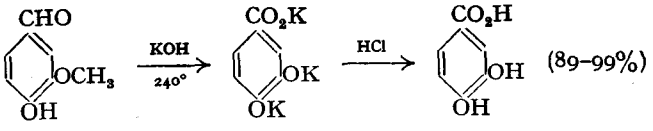
p-Hydroxybenzoic acid is formed when *p*-chlorobenzoic acid is heated with aqueous sodium hydroxide:



Many esters of *p*-hydroxybenzoic acid have antiseptic properties. The acid gives a red coloration with ferric chloride.

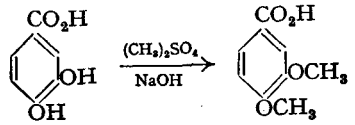
Anisic acid (*p-methoxybenzoic acid*), *p*-$CH_3O{\cdot}C_6H_4{\cdot}CO_2H$, m.p. 184°, may be prepared by the oxidation of anethole (p. 639). When heated with concentrated hydriodic acid, anisic acid forms *p*-hydroxybenzoic acid and methyl iodide, and on distillation with calcium oxide it forms anisole (p. 637).

Protocatechuic acid (3 : 4-*dihydroxybenzoic acid*) occurs in various plants, and is formed when certain resins (catechin, gum-benzoin, etc.) are fused with alkali. It may be prepared by heating catechol with aqueous ammonium carbonate at 140° under pressure (p. 632), or from vanillin as follows (note the demethylation):

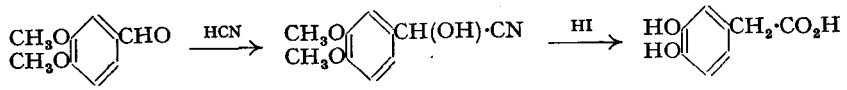


Protocatechuic acid crystallises with one molecule of water of crystallisation; the anhydrous acid melts at 199° with decomposition into catechol and carbon dioxide.

Veratric acid (3 : 4-*dimethoxybenzoic acid*), m.p. 181°, may be prepared by methylating protocatechuic acid with methyl sulphate in the presence of aqueous sodium hydroxide:

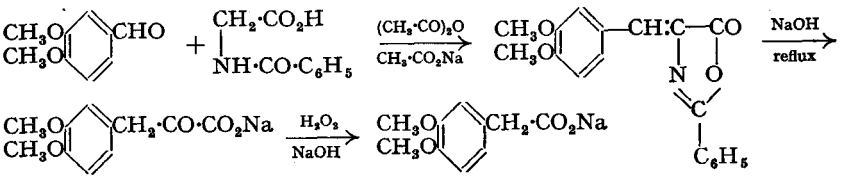


Homoprotocatechuic acid (3 : 4-*dihydroxyphenylacetic acid*), m.p. 127°, may be prepared by treating veratraldehyde with hydrogen cyanide and boiling the product, 3 : 4-dimethoxymandelonitrile, with hydriodic acid (Pictet and Gams, 1909):

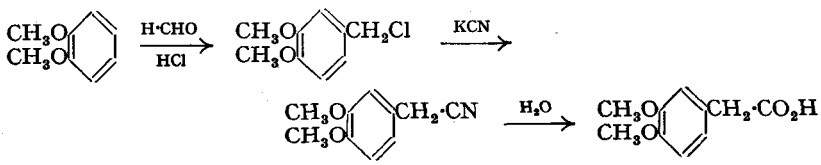


It should be noted that the prefix *homo* indicates that the compound contains one more carbon atom than the parent substance.

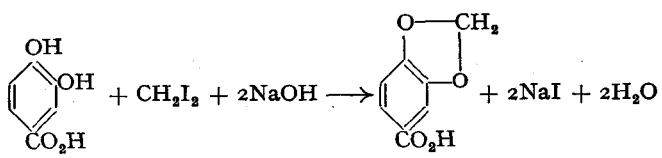
Homoveratric acid (3 : 4-*dimethoxyphenylacetic acid*), m.p. 99°, may be prepared by methylating homoprotocatechuic acid with methyl sulphate in the presence of aqueous sodium hydroxide. It may be prepared via the azlactone synthesis as follows:



Homoveratric acid may also be prepared by chloromethylating veratrole, treating the product with potassium cyanide, and hydrolysing the homoveratronitrile so produced (Bide and Wilkinson, 1945):

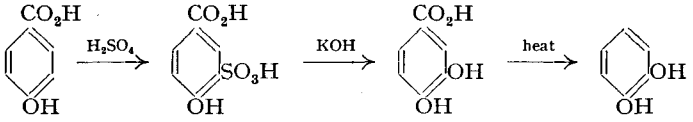


Piperonylic acid (3 : 4-*methylenedioxybenzoic acid*), m.p. 229°, may be prepared by the oxidation of piperonal (p. 660), or by heating protocatechuic acid with methylene iodide and aqueous sodium hydroxide:



Piperonal and piperonylic acid are oxidation products of piperic acid, which occurs in the alkaloid piperine. Veratric acid is one of the products of oxidation of the alkaloid papaverine. The orientation of the groups in these acids (and in

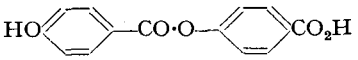
the corresponding homo-acids) may be shown as follows. Sulphonation of *p*-hydroxybenzoic acid (the orientation of which is known) produces a sulphonic acid derivative in which, according to the rules of directing power, the sulphonic acid group is *o*- to the hydroxyl group. This derivative, on fusion with potassium hydroxide, produces the dihydroxybenzoic acid in which the two hydroxyl groups are *o*- to each other. This is confirmed by the fact that the acid, *viz.*, protocatechuic acid, gives catechol (orientation known) when heated to its melting point:



Thus protocatechuic acid must be 3 : 4-dihydroxybenzoic acid. Hence the dimethoxy-derivative, veratric acid, must be 3 : 4-dimethoxybenzoic acid. At the same time, the orientations of the corresponding aldehydes, protocatechualdehyde and veratraldehyde, are established. Similarly, since piperonylic acid is the methylene ether of protocatechuic acid (shown by analytical and synthetic evidence), its orientation is also established. Finally, since homoprotocatechuic acid (and its methylated derivative, homoveratric acid) can be synthesised from veratraldehyde (see above), its orientation is thus ascertained.

Gallic acid (3 : 4 : 5-*trihydroxybenzoic acid*), m.p. 253°, occurs in the free state in tea and in many plants. It is best prepared by boiling tannin (tannic acid) with dilute acids. When heated at its melting point, it forms pyrogallol and carbon dioxide (p. 635). It is a powerful reducing agent and hence is used as a photographic developer. It is readily soluble in water, and its aqueous solution gives a bluish-black precipitate with ferric chloride. This property is used in the manufacture of ink.

Depsides. These are esters of aromatic hydroxyacids with hydroxyacids. They are known as di-depsides, tri-depsides, etc., according to the number of molecules in the ester; *e.g.*, the simplest di-depside is that formed from two molecules of *p*-hydroxybenzoic acid:



Depsides are related to certain types of tannins.

The *ortho*-effect. As we have already seen, the properties of *o*-compounds usually differ very much from those of the corresponding *m*- and *p*-isomers. The effect of *o*-substituents was first observed in 1872 when Hofmann found that aminopentamethylbenzene gave little or no quaternary ammonium compound on heating with methyl iodide. This was soon followed by many other cases in which reaction was slowed down, or completely inhibited by the presence of substituents in the *o*-positions; *e.g.*,

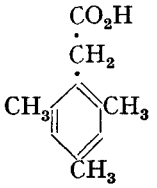
(i) Benzamide is readily hydrolysed, whereas pentamethylbenzamide cannot be hydrolysed.

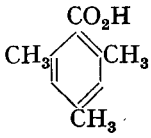
(ii) Benzaldehyde forms an anil with aniline but not with *s*-tribromoaniline.

(iii) Benzoic acid and *o*-substituted benzoic acids form methyl esters with methanol and hydrogen chloride (Fischer–Speier method), but di-*ortho*-substituted benzoic acids do not form methyl esters under the same conditions (Victor Meyer, 1874).

Victor Meyer (1894) attempted to explain these abnormalities by **steric hindrance**, *i.e.*, the *o*-groups mechanically interfered in the reaction of the carboxyl group, tending to shield it from the attacking reagent. This seemed to be supported by the fact that if the carboxyl group was removed from the ring by one carbon atom, esterification was normal; *e.g.*, mesityl-

acetic acid, (I), esterifies readily, whereas mesitoic acid, (II), does not esterify at all (by the Fischer–Speier method):

(I) 

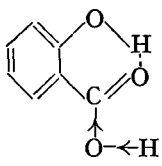
 (II)

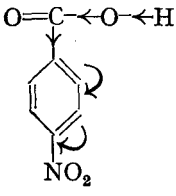
On the other hand, Kellas (1897) found that esterification of *o*-substituted benzoic acids is slower than that of the *m*- and *p*-isomers, and that the *m*-isomer is esterified more rapidly than the *p*-. This latter observation is contrary to Victor Meyer's explanation. On the basis of a purely spatial effect, the *m*- and *p*-substituted benzoic acids would have been expected to have esterified at the same rate, since in both acids the substituent groups do not mechanically interfere. Kellas also found that the nitro-group hindered esterification more effectively than the iodine atom, and since the former group has a smaller volume than the latter, the reverse results would have been expected.

A detailed study of the reactivity and strength of *o*-substituted benzoic acids and *o*-substituted amines, and the abnormal effects of *o*-substituents on the hydrolysis of esters, amides and cyanides, has shown that the effects cannot be explained by mechanical interference alone. In fact, in many cases, it is doubtful whether the *spatial factor* (*i.e.*, mechanical interference) operates at all. It is the polar influence of the substituents (and other factors) which usually plays a prominent part in the abnormal reactions of these *o*-substituted compounds. Thus the term steric hindrance, originally intended by Victor Meyer to denote a spatial effect, is misleading. Hence many chemists prefer to call the general phenomenon (of abnormal behaviour) the **proximity effect**, a term which denotes the special influence of groups near the reacting group. The ***ortho*-effect** is a special case of the proximity effect, being used only in connection with *nuclear* substituents. The term steric hindrance is, however, still used to denote the proximity effect (as defined above).

Steric factors play a part in the *ortho*-effect, but other contributing factors are chelation and the steric inhibition of resonance. These factors, particularly chelation, are also partly responsible for a number of proximity effects in general.

The *ortho*-effect due to chelation is exhibited by the *o*-nitro-, halogeno- and hydroxy-benzoic acids; *e.g.*, salicylic acid is stronger than its corresponding *m*- and *p*-isomers. Owing to chelation there is an increased inductive effect (as shown), thereby facilitating the release of the proton. As already pointed

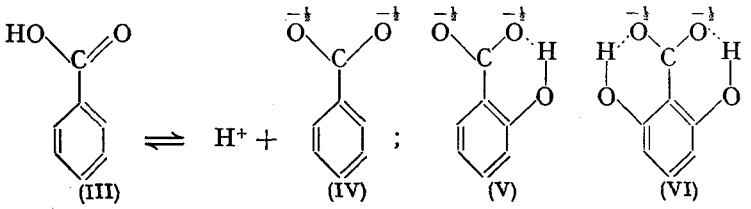




out, *p*-nitrobenzoic acid is stronger than benzoic acid due to the polar influence of the nitro-group transmitted through the ring. The nitro-group, however, behaves in the same way in the *o*-position, but the *o*-derivative is a stronger acid than the *p*-. Hence some other factor operates in the case of

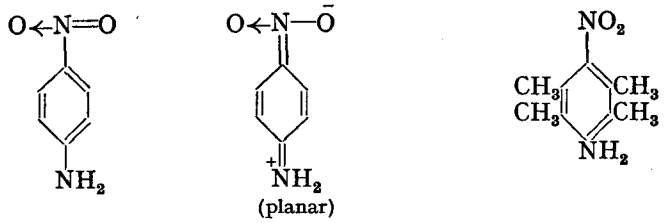
the *o*-compound, and is absent in the *p*-. Chelation may also be used to explain the volatility of *o*-halogenophenols (p. 625), *o*-nitrophenol (p. 626), etc.

An alternative explanation for this *ortho*-effect in *o*-hydroxybenzoic acids is as follows. The carboxylate ion (IV), because of the equivalence of its



two resonating structures, has a greater resonance energy than the undissociated acid (III) and so is more stable (p. 184). Any structural change in the molecule that will stabilise the anion *i.e.*, increases its contribution, will therefore increase the strength of the acid. An *o*-hydroxyl group can stabilise the anion by intramolecular hydrogen bonding (V), and so this *o*-hydroxyacid is stronger than the corresponding *m*- and *p*-isomers (where chelation is not possible). Furthermore, *two* *o*-hydroxyl groups should stabilise the anion even more (VI) and so 2 : 6-dihydroxybenzoic acid should be a much stronger acid than *o*-hydroxybenzoic acid; this has been found to be so in practice.

The dipole moment of *p*-nitroaniline is greater than the sum of the dipoles of the nitro- and amino-groups. This is attributed to increased resonance of both of these groups:



On the other hand, the dipole moment of nitroaminodurene is the sum of the dipoles of the nitro- and amino-groups (Birtles and Hampson, 1937). This may be explained by the non-existence of any charged structures. These must be planar, and this is impossible in nitroaminodurene due to the steric effect of the methyl groups. This is an example of the *steric inhibition of resonance.*

The actual geometry of these highly substituted benzenes is an interesting problem. In benzene the ring is flat and the hydrogen atoms are coplanar with this ring. Electron-diffraction investigations of polyhalogenobenzenes suggest that such molecules are non-planar (Hassel *et al.*, 1947), whereas X-ray studies indicate that in the solid state such molecules are very closely or even exactly planar (Tulinsky *et al.*, 1958; Gafner *et al.*, 1960). Ferguson *et al.* (1959, 1961) have examined, by X-ray analysis, various substituted benzoic acids, *e.g.*, *o*-chloro- and bromo-benzoic acid, and 2-chloro-5-nitrobenzoic acid. In all three molecules the steric strain is relieved by small out-of-plane displacements of the exocyclic valency bonds in addition to the larger in-plane displacement of these bonds away from one another. This type of deformation is referred to as *molecular overcrowding* (see also p. 739).

MONOBASIC ACIDS WITH THE CARBOXYL GROUP IN THE SIDE-CHAIN

Phenylacetic acid (*α-toluic acid*), $C_6H_5{\cdot}CH_2{\cdot}CO_2H$, occurs in certain esters; it may be prepared from benzyl chloride as follows:

$$C_6H_5{\cdot}CH_2Cl \xrightarrow{KCN} C_6H_5{\cdot}CH_2{\cdot}CN \xrightarrow[(H_2SO_4)]{H_2O} C_6H_5{\cdot}CH_2{\cdot}CO_2H \quad (60\text{–}70\%)$$

It may also be prepared by reducing mandelonitrile with hydriodic acid and red phosphorus:

$$C_6H_5{\cdot}CH(OH){\cdot}CN \xrightarrow{HI/P} C_6H_5{\cdot}CH_2{\cdot}CO_2H \quad (90\%)$$

Phenylacetic acid is a white crystalline solid, m.p. 77°, soluble in hot water. Since it contains two α-hydrogen atoms, it is reactive in the side-chain as well as in the ring, *e.g.*, chlorination in the cold in the presence of a halogen carrier, gives *o*- and *p*-nuclear substitution; chlorination at the boiling point of the acid, in the absence of a halogen carrier, gives replacement of the α-hydrogen (*cf.* toluene, p. 549). When oxidised with chromic acid, phenylacetic acid is converted into benzoic acid.

Mandelic acid (*phenylglycollic acid*), $C_6H_5{\cdot}CHOH{\cdot}CO_2H$, may be obtained from the glucoside amygdalin by regulated hydrolysis (*cf.* benzaldehyde, p. 645). It may be prepared by adding a saturated solution of sodium hydrogen sulphite to a mixture of aqueous sodium cyanide and benzaldehyde, separating the layer of mandelonitrile, and hydrolysing this with cold concentrated hydrochloric acid:

$$C_6H_5{\cdot}CHO \xrightarrow{NaHSO_3} C_6H_5{\cdot}CH(OH){\cdot}SO_3Na \xrightarrow{NaCN}$$
$$C_6H_5{\cdot}CH(OH){\cdot}CN \xrightarrow[(HCl)]{H_2O} C_6H_5{\cdot}CH(OH){\cdot}CO_2H \quad (50\text{–}52\%)$$

Mandelic acid may also be prepared by the hydrolysis of phenacylidene chloride (*cf.* p. 661):

$$C_6H_5{\cdot}CO{\cdot}CH_3 \xrightarrow[(CH_3{\cdot}CO_2H)]{Cl_2} C_6H_5{\cdot}CO{\cdot}CHCl_2 \xrightarrow[(ii)\ HCl]{(i)\ NaOH}$$
$$C_6H_5{\cdot}CHOH{\cdot}CO_2H \quad (76\text{–}87\%)$$

Mandelic acid is a white crystalline solid, fairly soluble in water. It behaves as a hydroxyacid, and is optically active. The acid obtained from amygdalin is lævorotatory, m.p. 133°; the m.p. of the DL-acid is 118°. On vigorous oxidation, mandelic acid gives benzoic acid.

Hydratropic acid (*α-phenylpropionic acid*), $C_6H_5{\cdot}CH(CH_3){\cdot}CO_2H$, b.p. 265°, may be prepared by the reduction of *atropic acid*, $C_6H_5{\cdot}C(:CH_2){\cdot}CO_2H$, obtained by heating *tropic acid*, $C_6H_5{\cdot}CH(CH_2OH){\cdot}CO_2H$, which occurs in the alkaloid atropine.

β-Phenylpropionic acid (*hydrocinnamic acid*), $C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$, may be prepared by reducing cinnamic acid with sodium amalgam:

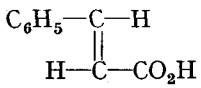
$$C_6H_5{\cdot}CH{:}CH{\cdot}CO_2H + 2[H] \longrightarrow C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H \quad (85\%)$$

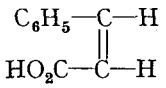
The reduction may also be carried out electrolytically, using a lead anode (yield: 80–90 per cent.). β-Phenylpropionic acid may be synthesised from benzyl chloride and malonic ester:

$$C_6H_5{\cdot}CH_2Cl + [CH(CO_2C_2H_5)_2]^-Na^+ \longrightarrow C_6H_5{\cdot}CH_2{\cdot}CH(CO_2C_2H_5)_2 + NaCl$$
$$\xrightarrow[(ii)\ boil]{(i)\ acid} C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H + CO_2 + 2C_2H_5OH$$

β-Phenylpropionic acid is a white crystalline solid, m.p. 47°, soluble in hot water. It is oxidised by chromic acid to benzoic acid.

Cinnamic acid, $C_6H_5{\cdot}CH{:}CH{\cdot}CO_2H$, is the *trans*-isomer, and hence is also known as **trans-β-phenylacrylic acid.** The *cis*-isomer (cis-β-*phenylacrylic acid*) is usually called **allocinnamic acid:**


cinnamic acid


allocinnamic acid

Cinnamic acid is the form that occurs naturally (free and as esters) in balsams and resins. It may be prepared:

(i) *By Perkin's reaction* (p. 651):

$$C_6H_5{\cdot}CHO + (CH_3{\cdot}CO)_2O \xrightarrow{CH_3{\cdot}CO_2Na} C_6H_5{\cdot}CH{:}CH{\cdot}CO_2H \quad (85\%)$$

(ii) *By Knoevenagel's reaction* (p. 280):

$$C_6H_5{\cdot}CHO + CH_2(CO_2H)_2 \xrightarrow[\text{heat}]{NH_3/C_2H_5OH} C_6H_5{\cdot}CH{:}CH{\cdot}CO_2H \quad (80\%)$$

(iii) By the *Claisen condensation* between benzaldehyde and ethyl acetate in the presence of sodium ethoxide (since benzaldehyde is one of the reactants, this is also referred to as a *Claisen reaction*; see p. 158):

$$C_6H_5{\cdot}CHO + CH_3{\cdot}CO_2C_2H_5 \xrightarrow{C_2H_5ONa} C_6H_5{\cdot}CH{:}CH{\cdot}CO_2C_2H_5 \xrightarrow[(acid)]{H_2O} C_6H_5{\cdot}CH{:}CH{\cdot}CO_2H + C_2H_5OH \quad (68\text{–}74\%)$$

(iv) By heating benzylidene chloride with sodium acetate:

$$C_6H_5{\cdot}CHCl_2 + CH_3{\cdot}CO_2Na \longrightarrow C_6H_5{\cdot}CH{:}CH{\cdot}CO_2Na + 2HCl$$

(v) By the oxidation of benzylideneacetone with sodium hypochlorite (*cf.* the haloform reaction):

$$C_6H_5{\cdot}CH{:}CH{\cdot}CO{\cdot}CH_3 \xrightarrow{NaOCl} C_6H_5{\cdot}CH{:}CH{\cdot}CO_2H$$

Methods (iv) and (v) are used industrially.

Cinnamic acid is a crystalline solid, m.p. 133°. It behaves as an αβ-unsaturated acid, and as a benzene derivative. It is reduced by sodium amalgam to γ-phenylpropionic acid; reduction of its ethyl ester, however, leads to the formation of the bimolecular product, ethyl β : β′-diphenyladipate (*cf.* p. 278):

$$2C_6H_5{\cdot}CH{:}CH{\cdot}CO_2C_2H_5 \xrightarrow{[H]} \begin{matrix} C_6H_5{\cdot}CH{\cdot}CH_2{\cdot}CO_2C_2H_5 \\ | \\ C_6H_5{\cdot}CH{\cdot}CH_2{\cdot}CO_2C_2H_5 \end{matrix}$$

When a phenyl group is attached to the β-carbon atom of an α : β-unsaturated carbonyl compound, both the double bond and carbonyl group are reduced by lithium aluminium hydride (*cf.* p. 276):

$$C_6H_5{\cdot}CH{=}CH{\cdot}CO_2H \xrightarrow{LiAlH_4} C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2OH$$

By using the inverse addition at −10°, the double bond is left intact, *e.g.*,

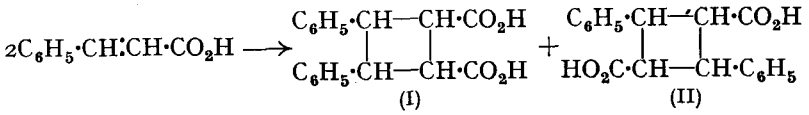
$$C_6H_5{\cdot}CH{=}CH{\cdot}CO_2C_2H_5 \xrightarrow[-10°]{LiAlH_4} C_6H_5{\cdot}CH{=}CH{\cdot}CH_2OH$$

When oxidised with chromic acid, cinnamic acid forms a mixture of benzaldehyde and benzoic acid. Concentrated nitric acid nitrates it to a mixture of *o*- and *p*-nitrocinnamic acids, the latter predominating.

When distilled with soda-lime, cinnamic acid forms styrene:

$$C_6H_5{\cdot}CH{:}CH{\cdot}CO_2Na + NaOH \longrightarrow C_6H_5{\cdot}CH{:}CH_2 + Na_2CO_3$$

Styrene is also obtained when cinnamic acid is heated for some time just above its melting point. When exposed to sunlight, cinnamic acid dimerises to a mixture of *truxinic acid* (3 : 4-*diphenyl*cyclo*butane*-1 : 2-*dicarboxylic acid*), (I), and *truxillic acid* (2 : 4-*diphenyl*cyclo*butane*-1 : 3-*dicarboxylic acid*), (II):



Allocinnamic acid is believed to occur in four allotropic forms, m.ps 32°, 42°, 58°, and 68°; all are unstable, the form melting at 32° being the least stable. Allocinnamic acid may be prepared in one or other of its forms by exposing cinnamic acid to ultraviolet light, or by the partial reduction of phenylpropiolic acid with hydrogen and colloidal platinum as catalyst:

$$C_6H_5{\cdot}C{:}C{\cdot}CO_2H + H_2 \xrightarrow{Pt} C_6H_5{\cdot}CH{:}CH{\cdot}CO_2H$$

Allocinnamic acid readily changes into cinnamic acid, and under the influence of light dimerises to truxinic acid.

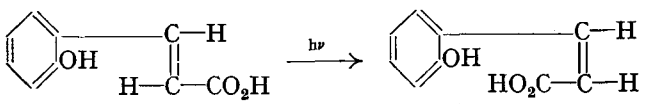
Phenylpropiolic acid (*phenylpropynoic acid*), $C_6H_5{\cdot}C{:}C{\cdot}CO_2H$, may be prepared by boiling the ethyl ester of cinnamic acid dibromide with ethanolic potassium hydroxide:

$$C_6H_5{\cdot}CH{:}CH{\cdot}CO_2C_2H_5 \xrightarrow[(CCl_4)]{Br_2} C_6H_5{\cdot}CHBr{\cdot}CHBr{\cdot}CO_2C_2H_5 \xrightarrow[\text{(ii) acid}]{\text{(i) KOH/}C_2H_5OH} C_6H_5{\cdot}C{:}C{\cdot}CO_2H \quad (77\text{–}81\%)$$

Phenylpropiolic acid is a crystalline solid, m.p. 136°. On catalytic reduction (using colloidal platinum), phenylpropiolic acid forms allocinnamic acid. Reduction with zinc and acetic acid gives cinnamic acid, and with sodium amalgam, β-phenylpropionic acid. When refluxed with barium hydroxide solution, phenylpropiolic acid is converted into phenylacetylene:

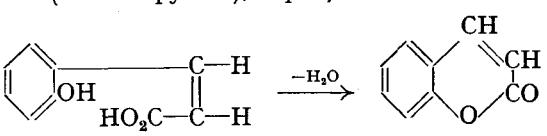
$$C_6H_5{\cdot}C{:}C{\cdot}CO_2H \longrightarrow C_6H_5{\cdot}C{:}CH + CO_2$$

***o*-Coumaric acid** (o-*hydroxycinnamic acid*), m.p. 108°, may be prepared by boiling coumarin (see below) with sodium ethoxide, or by diazotising *o*-aminocinnamic acid and then heating the diazonium sulphate solution. When exposed to ultraviolet light, *o*-coumaric acid (the stable *trans*-form) is converted into *coumarinic acid* (the unstable *cis*-form):

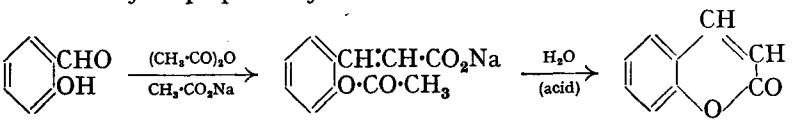


coumaric acid coumarinic acid

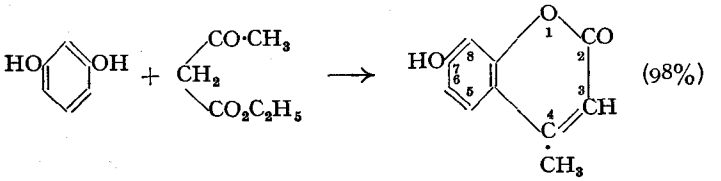
Coumarinic acid (o-*hydroxyallocinnamic acid*) is unstable, spontaneously forming its δ-lactone as soon as it is set free from its salts; the lactone is known as *coumarin* (benzo-α-pyrone), m.p. 67°:



Coumarin may be prepared by the Perkin reaction.

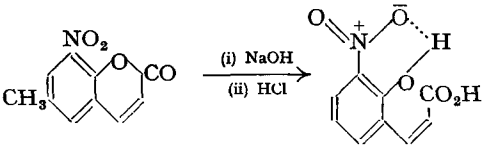


One of the most convenient methods for synthesising coumarins is the **Pechmann reaction** (1883) which is the condensation of a phenol with a β-keto-ester. The usual condensing reagents are sulphuric acid, phosphorus pentoxide, etc., but Koo (1955) has shown that polyphosphoric acid is very effective, *e.g.*, resorcinol and ethyl acetoacetate give 7-hydroxy-4-methylcoumarin:



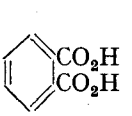
Coumarin is a natural perfume, and is also used as an artificial flavour. When heated with sodium ethoxide, it is converted into coumaric acid.

Crawford *et al.* (1956) have shown that *free* coumarinic acids can be isolated from 8-nitrocoumarins but not from other nitrocoumarins. The stability of these acids is attributed to chelation of the nitro-group with the neighbouring hydroxyl group, *e.g.*,

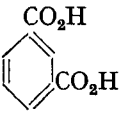


DIBASIC AROMATIC ACIDS

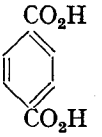
There are three benzenedicarboxylic acids possible, and all are known:



phthalic acid

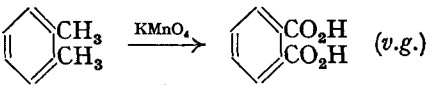


*iso*phthalic acid



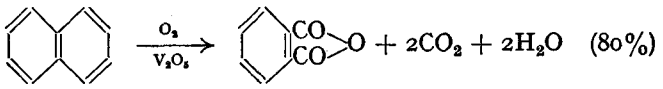
terephthalic acid

Phthalic acid (*benzene*-1 : 2-*dicarboxylic acid*) may be prepared by the oxidation of any benzene derivative having only two side-chains in the *o*-positions; permanganate or dilute nitric acid is used as the oxidising agent (chromic acid brings about ring rupture; see p. 538):



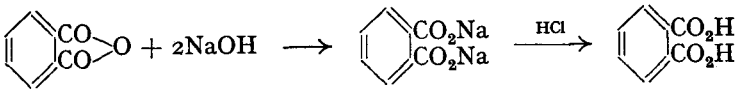
Industrially, phthalic acid is prepared by the oxidation of naphthalene with concentrated sulphuric acid and mercuric sulphate as a catalyst at a temperature of 200° (the yield varies between 25–60 per cent.). This method is almost obsolete, the oxidation being now carried out by passing

naphthalene vapour mixed with air over vanadium pentoxide as catalyst at 400–500°:

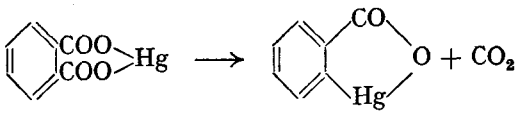


Maleic acid is obtained as a by-product. A more recent method is to use *o*-xylene as the starting material instead of naphthalene.

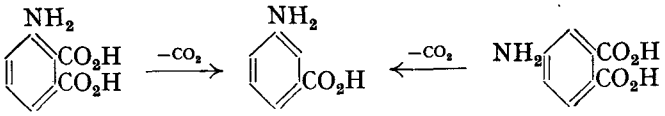
In all the above methods, the product of oxidation is phthalic anhydride. This is readily converted into the acid by heating it with alkali, and then acidifying:



Phthalic acid is a white crystalline solid, m.p. 231° (rapid heating), with conversion into its anhydride. It is almost insoluble in cold water, but is fairly readily soluble in hot water. It undergoes most of the typical reactions of a dicarboxylic acid. When heated with potassium hydroxide, it is decarboxylated to benzene. It is reduced by sodium amalgam to di-, tetra- and hexahydrophthalic acids. Mercuration of phthalic acid is usually carried out by refluxing the sodium salt with aqueous mercuric acetate containing sodium acetate, until no ionic mercury remains in the solution. Phthalic acid may also be mercurated by fusing it with mercuric acetate, or by heating the mercury salt of phthalic acid until the mercury has been transferred to the nucleus:



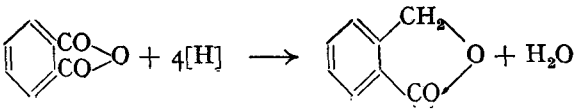
Phthalic anhydride is prepared industrially by the oxidation of naphthalene or *o*-xylene (see above). It is a white solid, m.p. 128°, slowly hydrolysed by water but rapidly by alkalis or acids. When nitrated, phthalic anhydride forms a mixture of 3- and 4-nitrophthalic acids. When these are reduced, their corresponding aminophthalic acids spontaneously decarboxylate to form *m*-aminobenzoic acid:



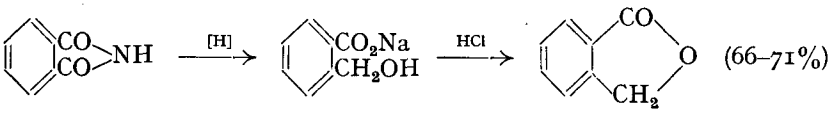
It is the carboxyl group *o*- or *p*- to the amino-group that is lost. The esters of these aminophthalic acids are quite stable.

Phthalic anhydride undergoes a large number of condensation reactions (see text). Phthalic anhydride and phthalic acid are used industrially in the preparation of dyes, plastics (glyptals), plasticisers, benzoic acid, etc.

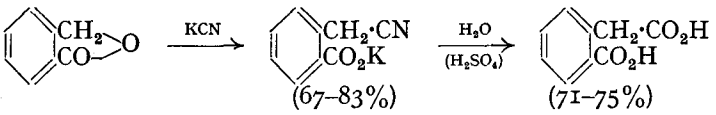
Phthalide may be prepared by reducing phthalic anhydride with zinc dust and aqueous sodium hydroxide:



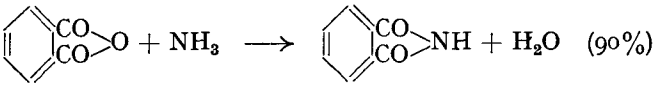
It is also formed when the anhydride is reduced catalytically with nickel at 200°, but is accompanied by varying amounts of toluic acid and ring-hydrogenated compounds, *e.g.*, hexahydrophthalic acid. Phthalide may also be prepared by reducing phthalimide with a zinc-copper alloy and aqueous sodium hydroxide:



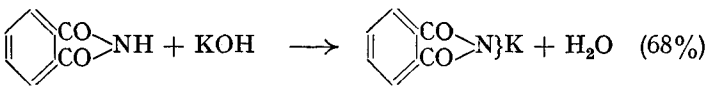
Phthalide is a white crystalline solid, m.p. 75°. It may be converted into *homophthalic acid*, m.p. 175°, by fusing it with potassium cyanide at 180° and hydrolysing the product with boiling 50 per cent. sulphuric acid:



Phthalimide may be prepared by heating phthalic anhydride with dry ammonia at about 200° under pressure:

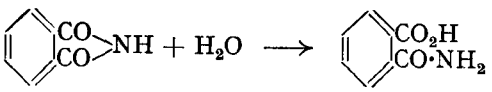


It is a white solid, m.p. 238°. It is weakly acidic; *e.g.*, with ethanolic potassium hydroxide it forms potassio-phthalimide:

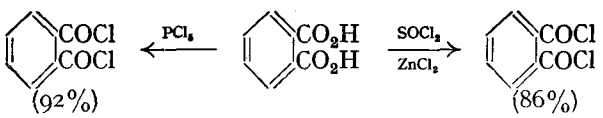


This salt is used in Gabriel's synthesis of primary amines (p. 311), and for preparing many α-aminoacids. The salt is decomposed into phthalimide by carbon dioxide.

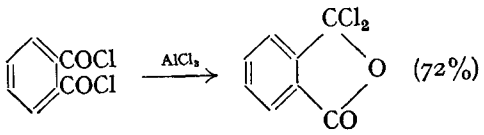
Treatment of phthalimide with alkaline sodium hypochlorite results in the formation of anthranilic acid (p. 680). When hydrolysed with warm aqueous sodium hydroxide, phthalimide forms phthalic acid. If, however, phthalimide is allowed to stand in cold aqueous potassium hydroxide, or if warmed with barium hydroxide solution, it is converted into *phthalamic acid*:



Phthaloyl chloride (phthalyl chloride) may be prepared by heating phthalic acid or phthalic anhydride with phosphorus pentachloride at 150°. It may also be prepared by heating phthalic acid with thionyl chloride in the presence of zinc chloride at 220° (*cf.* p. 377):

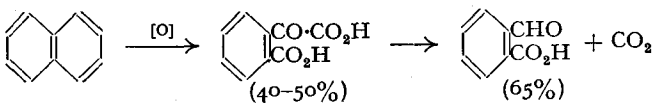


Phthaloyl chloride is a colourless oily liquid, m.p. 15–16°. When heated with aluminium chloride for some time, it is converted into *as*-phthaloyl chloride, m.p. 89° (*cf.* succinyl chloride):

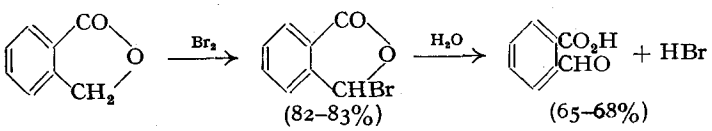


When reduced with zinc and hydrochloric acid, phthaloyl chloride is converted into phthalide.

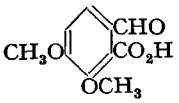
Phthalaldehydic acid (*o-formylbenzoic acid*), m.p. 100·5°, may be prepared by oxidising naphthalene with alkaline permanganate and decomposing the product, *phthalonic acid*, by boiling it in xylene solution:



Phthalaldehydic acid may be prepared by passing bromine vapour into phthalide and heating the product, 2-bromophthalide, with water:

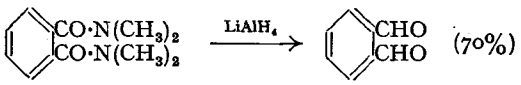


Opianic acid (5 : 6-*dimethoxyphthalaldehydic acid*), m.p. 150°, is one of the

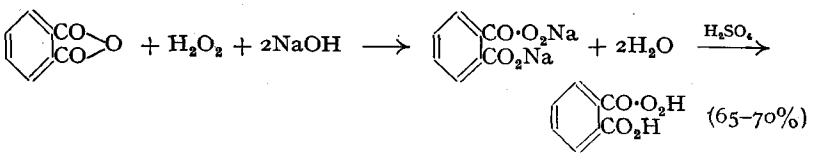


products obtained by heating *narcotine* (an alkaloid of opium) with water.

Phthalaldehyde, m.p. 56°, may be prepared by ozonolysis of naphthalene (p. 713), or by the reduction of phthalobisdimethylamide with lithium aluminium hydride (Weygand *et al.*, 1951).



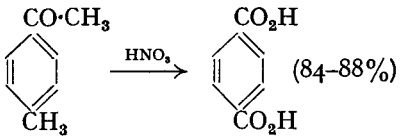
Monoperphthalic acid may be prepared by adding phthalic acid to a cooled alkaline solution of hydrogen peroxide, acidifying, and extracting with ether:



Monoperphthalic acid resembles perbenzoic acid in its properties, but is more stable.

***iso*Phthalic acid** (*benzene-1 : 3-dicarboxylic acid*) may be prepared by oxidising *m*-xylene with permanganate. It is a crystalline solid, m.p. 346°. It does *not* form an anhydride.

Terephthalic acid (*benzene*-1 : 4-*dicarboxylic acid*) may be prepared by oxidising *p*-xylene with permanganate, or by oxidising *p*-methylacetophenone with concentrated nitric acid at about 300°:



It is white powder which sublimes without melting when heated. It does *not* form an anhydride. It forms polyesters with glycol, and the plastic so obtained is known as *terylene*.

Polycarboxylic acids. Three isomeric tri- and three isomeric tetracarboxylic acids are known; one penta- and one hexacarboxylic acid are also known.

Mellitic acid (*benzenehexacarboxylic acid*) may be prepared by oxidising hexamethylbenzene with permanganate. It is also formed when graphite or wood-charcoal is oxidised with fuming nitric acid.

Mellitic acid is a stable solid, m.p. 288° (with decomposition). It occurs as its aluminium salt in peat and lignite.

QUESTIONS

1. Describe the methods for preparing benzoic acid in the laboratory and industrially.
2. How may each of the following compounds be prepared:—(*a*) Ph·COCl, (*b*) Ph·CO·NH_2, (*c*) Ph·CO·NH·CH_2·CO_2H, (*d*) $(Ph·CO)_2O$, (*e*) $(Ph·CO)_2O_2$, (*f*) PhCO·O_2H, (*g*) *o*-, *m*- and *p*-CH_3·C_6H_4·CO_2H, (*h*) *m*-BrC_6H_4·CO_2H, (*i*) *o*-, *m*- and *p*-NO_2·C_6H_4·CO_2H, (*j*) *p*-IC_6H_4·CO_2H, (*k*) *o*-HO_3S·C_6H_4·CO_2H, (*l*) 3 : 5-$(NO_2)_2C_6H_3$·CO_2H, (*m*) 2 : 5-$(NO_2)_2C_6H_3$·CO_2H, (*n*) *o*-NH_2·C_6H_4·CO_2H, (*o*) novocaine, (*p*) saccharin?
3. Write an account of the laboratory and industrial methods of preparing salicylic acid. Name the compounds and state the conditions under which they are formed when salicylic acid is treated with:—(*a*) heat, (*b*) NaOH/CaO, (*c*) H, (*d*) Br_2, (*e*) Na_2CO_3, (*f*) NaOH, (*g*) HNO_3, (*h*) MeOH, (*i*) PhOH, (*j*) Ac_2O.
4. Starting with benzene or toluene, show how you would prepare:—(*a*) *m*- and *p*-HOC_6H_4·CO_2H, (*b*) anisic acid, (*c*) protocatechuic acid, (*d*) veratric acid, (*e*) homoprotocatechuic acid, (*f*) homoveratric acid, (*g*) piperonylic acid, (*h*) gallic acid, (*i*) $PhCH_2$·CO_2H, (*j*) PhCH(OH)·CO_2H, (*k*) hydratropic acid, (*l*) $PhCH_2$·CH_2·CO_2H, (*m*) PhC:C·CO_2H, (*n*) coumaric acid, (*o*) coumarinic acid, (*p*) coumarin.
5. Discuss the methods for determining the orientation of the groups in the acids (*a*)–(*h*) in question 4.
6. Write an essay on the ortho-effect.
7. Write an account of the preparation and properties of cinnamic and allocinnamic acids.
8. Define and give examples of:—(*a*) the Schotten–Baumann reaction, (*b*) Erlenmeyer's azlactone synthesis, (*c*) the Prileschaiev reaction, (*d*) Kolbe–Schmitt reaction, (*e*) Pechmann reaction.
9. Describe the preparation and some important reactions of:—(*a*) phthalic acid, (*b*) phthalic anhydride, (*c*) phthalide, (*d*) phthalimide, (*e*) homophthalic acid, (*f*) phthaloyl chloride, (*g*) phthalaldehydic acid, (*h*) monoperphthalic acid, (*i*) *iso*phthalic acid, (*j*) terephthalic acid.
10. Write an account of the analytical and synthetic evidence (i) for the structure of opianic acid, (ii) for the orientation of 3- and 4-nitrophthalic acids.

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CHAPTER XXIX

POLYNUCLEAR HYDROCARBONS AND THEIR DERIVATIVES

POLYNUCLEAR hydrocarbons may be divided into two groups, those in which the rings are isolated, *e.g.*, diphenyl, diphenylmethane, etc; and those in which two or more rings are fused together in the *o*-positions, *e.g.*, naphthalene, anthracene, etc.

ISOLATED SYSTEMS

Diphenyl (*biphenyl*), $C_6H_5{\cdot}C_6H_5$, occurs in small quantities in coal-tar. It may be prepared:

(i) **By Fittig's reaction** (1863). This is carried out by treating bromobenzene with sodium in ethereal solution:

$$2C_6H_5Br + 2Na \longrightarrow C_6H_5{\cdot}C_6H_5 + 2NaBr \quad (20\text{–}30\%)$$

Benzene, *o*-diphenylbenzene and triphenylene are obtained as by-products (*cf.* p. 534). It should be noted that the Fittig reaction is analogous to the Wurtz reaction. The former, however, involves the use of aryl halide only, the latter, alkyl halide. The Wurtz–Fittig reaction involves the use of both alkyl and aryl halides.

(ii) When bromobenzene in ethanolic solution is made alkaline and refluxed with hydrazine in the presence of a palladium catalyst on a calcium carbonate support, diphenyl is obtained (Busch *et al.*, 1936):

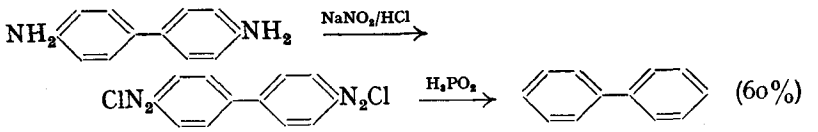
$$2C_6H_5Br + 2[H] \longrightarrow C_6H_5{\cdot}C_6H_5 + 2HBr \quad (80\%)$$

(It is the hydrazine which supplies the hydrogen.)

(iii) (*a*) By warming benzenediazonium sulphate in ethanol with copper powder:

$$2C_6H_5{\cdot}N_2HSO_4 \xrightarrow[C_2H_5OH]{Cu} C_6H_5{\cdot}C_6H_5 + 2N_2 + 2H_2SO_4 \quad (25\%)$$

(*b*) By diazotising benzidine and allowing the diazonium salt solution to stand in contact with hypophosphorous acid:

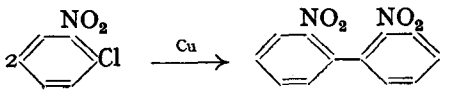


(60%)

(iv) By the **Ullmann diaryl synthesis** (1903). Iodobenzene is heated with copper powder in a sealed tube:

$$2C_6H_5I + 2Cu \longrightarrow C_6H_5{\cdot}C_6H_5 + 2CuI \quad (80\%)$$

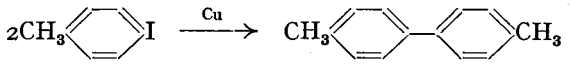
Aryl chlorides and bromides do not usually react unless there is a negative group *o*- or *p*- to the halogen atom, *e.g.*, *o*-chloronitrobenzene forms 2 : 2′-dinitrodiphenyl:



(52–61%)

Aryl iodides react readily, but aryl fluorides are not sufficiently reactive for the Ullmann diaryl synthesis.

By choosing suitable starting materials, it is possible to prepare many diphenyl derivatives by the Ullmann synthesis, *e.g.*, 4 : 4′-dimethyldiphenyl from *p*-iodotoluene:



Kornblum *et al.* (1952) have shown that dimethylformamide is a good solvent for this synthesis, and the yields obtained are higher.

There is a large amount of evidence to support a free-radical mechanism for the Ullmann diaryl synthesis (Rapson, 1941; Bell, 1954; Nursten, 1955).

(v) Arylmagnesium halides do not react with aryl halides. Reaction, however, will take place in the presence of small quantities of metal halides such as $CoCl_2$, $NiCl_2$, $FeCl_3$, etc. (Kharasch and Fields, 1941); *e.g.*, diphenyl is formed by reaction between phenylmagnesium bromide and bromobenzene in the presence of a small amount of cobaltous chloride:

$$C_6H_5{\cdot}MgBr + C_6H_5Br \xrightarrow{CoCl_2} C_6H_5{\cdot}C_6H_5 + MgBr_2 \quad (g.)$$

Traces of benzene, terphenyl, etc. are also formed. The mechanism of the reaction is uncertain; Kharasch believes it takes place via free radicals:

$$C_6H_5{\cdot}MgBr + CoCl_2 \longrightarrow C_6H_5{\cdot}CoCl + MgClBr$$
$$2C_6H_5{\cdot}CoCl \longrightarrow C_6H_5{\cdot}C_6H_5 + 2{\cdot}CoCl$$
$${\cdot}CoCl + C_6H_5Br \longrightarrow CoClBr + C_6H_5{\cdot}$$
$$C_6H_5{\cdot} \longrightarrow C_6H_6,\ C_6H_5{\cdot}C_6H_5, \text{ etc.}$$

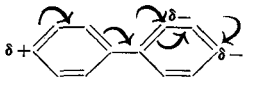
Industrially, diphenyl is prepared by passing benzene vapour through a red-hot tube, preferably packed with pumice (600–800°):

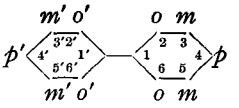
$$2C_6H_6 \longrightarrow C_6H_5{\cdot}C_6H_5 + H_2$$

A more recent method is to mix benzene vapour (preheated to 650°) with superheated steam (1000–1100°), and passing the mixture into steel vessels coated internally with a film of Fe_3O_4.

Diphenyl is a colourless crystalline solid, m.p. 71°, insoluble in water but soluble in ethanol and ether. It is increasing in use as a heat transfer medium; chlorinated diphenyls are used as plasticisers.

Diphenyl undergoes the usual nuclear substitution reactions, the phenyl group being *o*- and *p*-orienting (one phenyl group behaving as an electron-releasing group and the other as an electron-acceptor). The first substituent enters mainly the 4-position, and to a lesser extent the 2-position. Introduction of a second substituent usually takes place in the *unsubstituted* ring; *e.g.*, on nitration, the main product is 4-nitrodiphenyl, together with

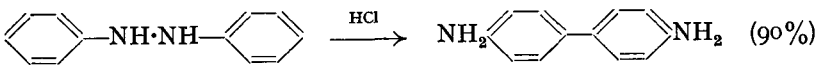




a small amount of 2-nitrodiphenyl. Further nitration gives 4 : 4′-dinitrodiphenyl (and some 2 : 4′- and 2 : 2′-dinitrodiphenyls). Diphenyl behaves similarly on halogenation and sulphonation.

When oxidised with chromic acid, diphenyl forms a small amount of benzoic acid, most of the hydrocarbon being oxidised completely to carbon dioxide and water.

Benzidine (4 : 4′-*diaminodiphenyl*) may be prepared by the *benzidine transformation* (p. 603); hydrazobenzene, on warming with hydrochloric acid, rearranges to benzidine:

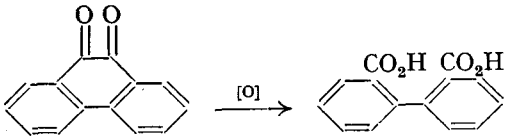


The structure of benzidine may be shown by its formation on the reduction of 4 : 4′-dinitrodiphenyl (which may be prepared by the Ullmann synthesis starting with *p*-bromonitrobenzene).

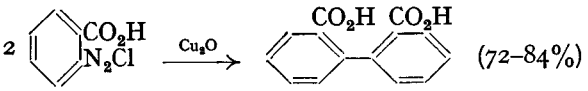
Benzidine is a colourless solid, m.p. 127°. Its hydrochloride is soluble, but its sulphate is sparingly soluble in water. It is very important commercially since it is used in the preparation of azo-dyes, *e.g.*, congo red (p. 783).

***o*-Tolidine** (4 : 4′-*diamino*-3 : 3′-*dimethyldiphenyl*), m.p. 129°, and **dianisidine** (4 : 4′-*diamino*-3 : 3′-*dimethoxydiphenyl*), m.p. 138°, are manufactured on a large scale as intermediates in the preparation of azo-dyes.

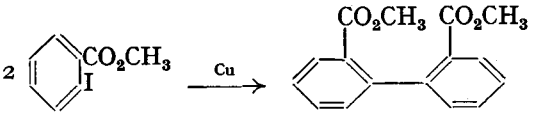
Diphenic acid (*diphenyl*-2 : 2′-*dicarboxylic acid*) may be readily prepared by oxidising phenanthraquinone with potassium dichromate and sulphuric acid, or by the direct oxidation of phenanthrene with 50 per cent. hydrogen peroxide in glacial acetic (68% yield; O'Connor *et al.*, 1951).



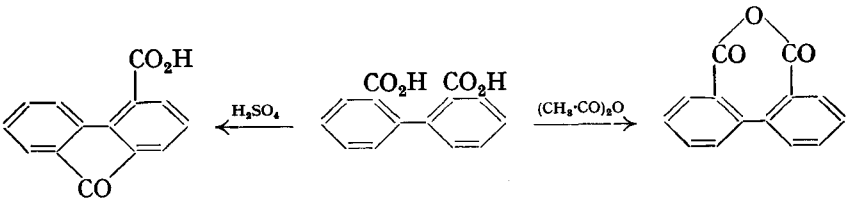
It may also be prepared by the action of ammoniacal cuprous oxide on diazotised anthranilic acid:



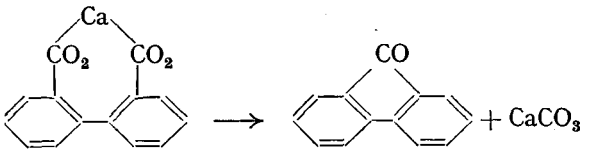
The methyl ester may be obtained by heating methyl *o*-iodobenzoate with copper powder (Ullmann synthesis):



Diphenic acid is a solid, m.p. 229°. When heated with acetic anhydride, it forms diphenic anhydride, and when heated with concentrated sulphuric acid, fluorenone-4-carboxylic acid:

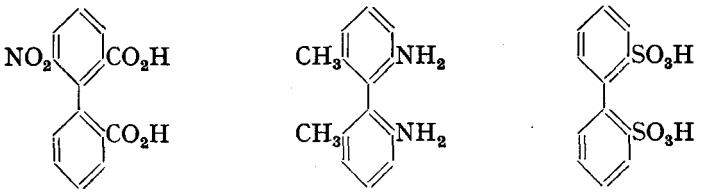


When the calcium salt of diphenic acid is distilled, fluorenone is obtained:



When oxidised with potassium permanganate, diphenic acid forms phthalic acid. Distillation with soda-lime gives diphenyl.

If at least three of the positions 2, 2′, 6 and 6′ are occupied by sufficiently large groups, free rotation about the single bond joining the two phenyl groups is no longer possible. Provided each ring has not a vertical plane of symmetry, this restricted rotation gives rise to optical activity due to the molecule being *asymmetric as a whole* (p. 403); *e.g.*, *6-nitrodiphenyl-2 : 2′-dicarboxylic acid* (I), and *6 : 6′-diamino-2 : 2′-dimethyldiphenyl*, (II), have been resolved. If the substituent group is large enough, then only two groups



(I) (II) (III)

in the *o*- and *o*′-positions will cause restricted rotation, *e.g.*, *diphenyl-2 : 2′-disulphonic* acid, (III), has been resolved.

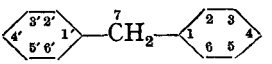
The cause of the restricted rotation is believed to be due mainly to the steric effects of the groups in the *o*- and *o*′-positions.

Since the optical activity of diphenyl compounds arises from restricted rotation, it might be expected that racemisation would not be possible. In practice, however, many optically active diphenyls can be racemised, *e.g.*, by boiling in solution. The general theory of these racemisations is that heating increases the amplitude of vibrations of the substituents and also the amplitude of vibration of the interannular bond. In addition to these bond stretchings, the various valency angles between ring and substituents are also deformed. Thus the nuclei will pass through a common plane, and hence, when the molecule returns to its restricted state, it will do so equally in the (+)- and (−)-forms, *i.e.*, the molecules are racemised.

o-Substituted diphenyls exhibit the phenomenon of molecular overcrowding, but in this type of molecule the strain can be relieved by rotation about the interannular bond (see also p. 739).

A number of polyphenyls and some of their derivatives have been prepared, *e.g.*, *terphenyl*, *quaterphenyl*, *quinquephenyl*, and *sexiphenyl*.

Diphenylmethane. Some related compounds of diphenylmethane have



already been discussed, *e.g.*, benzophenone (p. 664). Diphenylmethane may be prepared:

(i) By the Friedel–Crafts condensation between benzyl chloride and benzene:

$$C_6H_5{\cdot}CH_2Cl + C_6H_6 \xrightarrow{AlCl_3} C_6H_5{\cdot}CH_2{\cdot}C_6H_5 + HCl \quad (50\%)$$

(ii) By the condensation between one molecule of formaldehyde and two molecules of benzene in the presence of concentrated sulphuric acid:

$$2C_6H_6 + CH_2O \xrightarrow{H_2SO_4} C_6H_5{\cdot}CH_2{\cdot}C_6H_5 + H_2O$$

(iii) By heating benzophenone with hydriodic acid and red phosphorus at 160° under pressure:

$$C_6H_5{\cdot}CO{\cdot}C_6H_5 \xrightarrow{HI/P} C_6H_5{\cdot}CH_2{\cdot}C_6H_5 \quad (95\%)$$

(iv) By allowing a mixture of benzyl alcohol, benzene, acetic and sulphuric acids to stand for 6 hours:

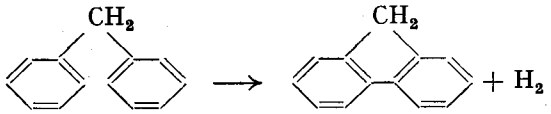
$$C_6H_5{\cdot}CH_2OH + C_6H_6 \longrightarrow C_6H_5{\cdot}CH_2{\cdot}C_6H_5 + H_2O \quad (25\%)$$

(v) By reducing benzophenone with a mixture of lithium aluminium hydride and aluminium chloride.

Diphenylmethane is a crystalline solid, m.p. 26°. Its reactions are similar to those of diphenyl, *e.g.*, on nitration, the nitro-group enters mainly the 4-position; the second nitro-group then enters the 4′-position (the benzyl group is *o-p*-orienting). Since the hydrogen of the methylene group is very active (due to each ring being electron-attracting, *i.e.*, each ring behaves as a negative group), bromination of diphenylmethane gives rise to substitution at the methylene carbon atom, and not in the ring, to form, *e.g.*, diphenylmethyl bromide:

$$C_6H_5{\cdot}CH_2{\cdot}C_6H_5 + Br_2 \longrightarrow C_6H_5{\cdot}CHBr{\cdot}C_6H_5 + HBr$$

When oxidised with chromic acid, diphenylmethane forms benzophenone. When its vapour is passed through a red hot tube, diphenylmethane forms fluorene:



Triphenylmethane may be prepared by the Friedel–Crafts condensation between benzene and either benzylidene chloride or chloroform:

$$2C_6H_6 + C_6H_5{\cdot}CHCl_2 \xrightarrow{AlCl_3} (C_6H_5)_3CH + 2HCl$$

$$3C_6H_6 + CHCl_3 \xrightarrow{AlCl_3} (C_6H_5)_3CH + 3HCl \quad (33\%)$$

It may also be prepared by condensing benzaldehyde with benzene in the presence of zinc chloride:

$$C_6H_5{\cdot}CHO + 2C_6H_6 \xrightarrow{ZnCl_2} (C_6H_5)_3CH + H_2O$$

Triphenylmethane is a colourless crystalline solid, m.p. 93°. It is the parent substance of the triphenylmethane dyes (p. 786). When brominated, it forms triphenylmethyl bromide, $(C_6H_5)_3CBr$ (*cf.* diphenylmethane, above). Oxidation with chromium trioxide in acetic acid converts triphenylmethane into *triphenylcarbinol*, m.p. 165°:

$$(C_6H_5)_3CH + [O] \longrightarrow (C_6H_5)_3COH \quad (85\%)$$

This compound may also be prepared by reaction between phenylmagnesium bromide and benzophenone or ethyl benzoate:

$$(C_6H_5)_2CO + C_6H_5{\cdot}MgBr \longrightarrow (C_6H_5)_3COMgBr \xrightarrow{H_2O} (C_6H_5)_3COH \quad (75\%)$$

$$C_6H_5{\cdot}CO_2C_2H_5 + 2C_6H_5{\cdot}MgBr \longrightarrow (C_6H_5)_3COMgBr \xrightarrow{H_2O} (C_6H_5)_3COH \quad (89\text{–}93\%)$$

Triphenylcarbinol reacts almost instantaneously with hydrochloric acid in acetic acid or with acetyl chloride to form triphenylmethyl chloride (*cf.* tertiary alcohols, p. 130):

$$(C_6H_5)_3COH + CH_3{\cdot}COCl \longrightarrow (C_6H_5)_3CCl + CH_3{\cdot}CO_2H \quad (93\text{–}95\%)$$

In the presence of hydrochloric acid, triphenylcarbinol forms ethers with alcohols, *e.g.*,

$$(C_6H_5)_3COH + CH_3OH \xrightarrow{HCl} (C_6H_5)_3C{\cdot}O{\cdot}CH_3 + H_2O$$

It condenses with aniline hydrochloride to form *p*-aminotetraphenylmethane, and when refluxed with formic acid, it forms triphenylmethane.

Triphenylcarbinol is reduced to triphenylmethane by lithium aluminium hydride containing aluminium chloride.

When treated with sodium in ethereal solution (or in liquid ammonia), triphenylmethane forms triphenylmethylsodium:

$$(C_6H_5)_3CH + Na \longrightarrow (C_6H_5)_3\bar{C}Na^+ + \tfrac{1}{2}H_2$$

This compound forms the sodium salt of triphenylacetic acid when heated with carbon dioxide.

Derivatives of triphenylmethane are best prepared synthetically (see, *e.g.*, p. 786).

Triphenylmethyl chloride may be prepared from triphenylcarbinol and acetyl chloride (see above), or by the Friedel–Crafts condensation between benzene and carbon tetrachloride; tetraphenylmethane is *not* formed:

$$3C_6H_6 + CCl_4 \xrightarrow{AlCl_3} (C_6H_5)_3CCl + 3HCl \quad (68\text{–}84\%)$$

Triphenylmethyl chloride is a crystalline solid, m.p. 112°. The halogen atom is extremely reactive, *e.g.*, when boiled with water, triphenylmethyl chloride forms the corresponding alcohol, and with ethanol it forms the ethyl ether:

$$(C_6H_5)_3C{\cdot}O{\cdot}C_2H_5 \xleftarrow{C_2H_5OH} (C_6H_5)_3CCl \xrightarrow{H_2O} (C_6H_5)_3COH$$

Triphenylmethyl chloride may be converted into triphenylmethane as follows:

$$(C_6H_5)_3CCl \xrightarrow{Mg} (C_6H_5)_3C{\cdot}MgCl \xrightarrow{H_2O} (C_6H_5)_3CH$$

This reaction is particularly interesting since the preparation of the Grignard reagent from triphenylmethyl bromide was shown to be via a free-radical mechanism (Gomberg and Bachmann, 1930). These authors showed that when half the total amount of magnesium had reacted, the solution contained triphenylmethyl and hexaphenylethane, *but no Grignard reagent*:

$$2(C_6H_5)_3CBr + Mg \longrightarrow 2(C_6H_5)_3C{\cdot} + MgBr_2$$

$$Mg + MgBr_2 \rightleftharpoons 2{\cdot}MgBr$$

$$(C_6H_5)_3C{\cdot} + {\cdot}MgBr \longrightarrow (C_6H_5)_3C{\cdot}MgBr$$

Conductivity measurements of triphenylmethyl chloride in liquid sulphur dioxide indicate that this compound is only partly ionised and that the conductance data can be analysed in terms of two processes, ionisation to ion pairs and dissociation of the ion pairs to free ions (Lichtin *et al.*, 1951).

$$Ph_3CCl \rightleftharpoons Ph_3C^+Cl^- \rightleftharpoons Ph_3C^+ + Cl^-$$

This is supported by spectroscopic evidence (Pocker, 1959).

Tetraphenylmethane may be prepared by the action of phenylmagnesium bromide on triphenylmethyl chloride:

$$(C_6H_5)_3CCl + C_6H_5{\cdot}MgBr \longrightarrow (C_6H_5)_4C + MgClBr \quad (v.p.)$$

It may also be prepared by diazotising *p*-aminotetraphenylmethane in ethanolic solution and then boiling (see also triphenylcarbinol, above):

$$(C_6H_5)_3COH + C_6H_5{\cdot}NH_2{\cdot}HCl \longrightarrow (C_6H_5)_3C{\cdot}C_6H_4{\cdot}NH_2{\cdot}HCl \xrightarrow[C_2H_5OH]{NaNO_2} (C_6H_5)_4C$$

Tetraphenylmethane *cannot* be prepared by reaction between benzene and carbon tetrachloride in the presence of aluminium chloride (see triphenylmethyl chloride, above). The reason for this is not certain, but it is likely that the steric effect plays a large part in hindering the reaction.

Tetraphenylmethane is a very stable crystalline solid, m.p. 282°.

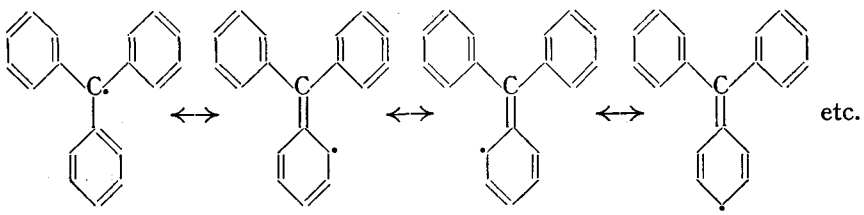
Hexaphenylethane may be prepared by the action of silver, zinc or mercury on triphenylmethyl chloride in benzene solution *in the absence of air*:

$$2(C_6H_5)_3CCl \xrightarrow{Ag} (C_6H_5)_3C{\cdot}C(C_6H_5)_3 + 2AgCl$$

It is a colourless solid, m.p. 145–147°, but when dissolved in a non-ionising solvent such as benzene or *cyclo*hexane, it forms a *yellow* solution. This yellow colour is due to the dissociation of hexaphenylethane into the free radical triphenylmethyl (Gomberg, 1900):

$$(C_6H_5)_3C{-}C(C_6H_5)_3 \rightleftharpoons 2(C_6H_5)_3C\cdot$$

The stability of this free radical is attributed to resonance, a large number of resonating structures contributing to the resonance hybrid:



The reason for the colour of this free radical is uncertain.

Triphenylmethyl reacts immediately with a number of reagents to form triphenylmethyl derivatives, *e.g.*, with oxygen, it forms a colourless peroxide:

$$2(C_6H_5)_3C\cdot + O_2 \longrightarrow (C_6H_5)_3C{\cdot}O{\cdot}O{\cdot}C(C_6H_5)_3$$

With iodine it forms triphenylmethyl iodide, and with nitric oxide, nitrosotriphenylmethane:

$$2(C_6H_5)_3C\cdot + I_2 \rightleftharpoons 2(C_6H_5)_3CI$$
$$(C_6H_5)_3C\cdot + NO \longrightarrow (C_6H_5)_3C{\cdot}NO$$

It also combines with sodium to form triphenylmethylsodium, a brick-red solid and an electrical conductor:

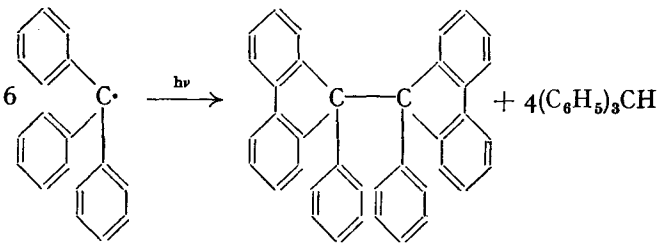
$$(C_6H_5)_3C\cdot + Na \longrightarrow (C_6H_5)_3\bar{C}Na^+$$

None of these reactions is typical of a hydrocarbon, and the dissociation of hexaphenylethane was finally proved by molecular weight determinations (freezing point and elevation of boiling point). Triphenylmethyl was the first free radical to be discovered.

In addition to the above reactions, triphenylmethyl can act as a powerful reducing agent, and will reduce the salts of silver, gold and mercury to the metals, *e.g.*,

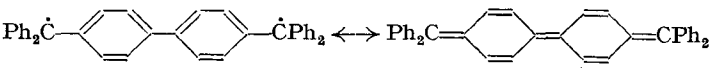
$$(C_6H_5)_3C\cdot + AgCl \longrightarrow (C_6H_5)_3CCl + Ag$$

It will also reduce ferric chloride to ferrous chloride, and this reaction may be used as a test for the presence of a free radical. Yellow solutions of triphenylmethyl are slowly decolorised on exposure to sunlight, triphenylmethane and diphenyl-bisdiphenylene-ethane being formed due to disproportionation:



This hexa-arylethane can also dissociate into free radicals, but does so to a much smaller extent than hexaphenylethane.

The triphenylmethyl radical is an example of a long-life free radical (see also p. 365). The problem here is why does hexaphenylethane dissociate so readily (as compared to ethane)? The answer is believed to be as follows. The free radical is stabilised by resonance, which therefore acts as a " driving force " in the dissociation. At the same time, steric factors also operate. In hexaphenylethane (sp^3 hybridisation) there is steric strain due to crowding, and this is relieved by dissociation to form a planar or almost planar free radical (sp^2 hybridisation; resonance requires complete or almost complete planarity). That the steric effect is operating is supported by the fact that methyl groups in the *o*-positions increase the dissociation. Further support for the steric effect is the case of Tschitschibabin's hydrocarbon:



This compound contains about 4·5 per cent. free radical, but when all four *o*-positions are occupied by chlorine the free-radical content is almost 100 per cent. In the chlorinated compound coplanarity of the two benzene rings is prevented, *i.e.*, this is an example of steric inhibition of resonance (*cf.* the diphenyls).

When dissolved in liquid sulphur dioxide, the solution shows a high conductivity (Walden, 1903), and this was explained by assuming that the hexaphenylethane dissociates into positive and negative ions:

$$(C_6H_5)_3C{\frown}C(C_6H_5)_3 \rightleftharpoons (C_6H_5)_3C^+ + (C_6H_5)_3C^-$$

According to Anderson (1935), however, the dissociation is probably:

$$(C_6H_5)_6C_2 + 2SO_2 \rightleftharpoons 2(C_6H_5)_3C^+ + 2\dot{S}O_2^-$$

The existence of the triphenylmethyl carbonium ion has definitely been established by Dauben *et al.* (1960), who prepared the crystalline perchlorate, $Ph_3C^+ClO_4^-$, and the borofluoride, $Ph_3C^+BF_4^-$. These carbonium ions have been shown to have the property of abstracting hydride ions from hydrocarbons of low nucleophilic power:

$$Ph_3C^+ClO_4^- + RH \rightleftharpoons Ph_3CH + R^+ClO_4^-$$

This property thus affords a means of preparing new carbonium salts.

Dibenzyl (1 : 2-*diphenylethane*), $C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}C_6H_5$, may be prepared by the Friedel–Crafts condensation between benzene and ethylene chloride:

$$2C_6H_6 + ClCH_2{\cdot}CH_2Cl \xrightarrow{AlCl_3} C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}C_6H_5 + 2HCl$$

Another method of preparation is by the action of sodium or copper on benzyl bromide:

$$2C_6H_5{\cdot}CH_2Br \xrightarrow{Na} C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}C_6H_5$$

Dibenzyl is a white solid, m.p. 52°. It is oxidised by permanganate or chromic acid to benzoic acid.

Stilbene (*trans*-s-diphenylethylene), $C_6H_5{\cdot}CH{:}CH{\cdot}C_6H_5$, may be prepared:

(i) By heating benzylidene chloride with sodium:

$$2C_6H_5{\cdot}CHCl_2 + 4Na \longrightarrow C_6H_5{\cdot}CH{=}CH{\cdot}C_6H_5 + 4NaCl$$

(ii) By treating benzylmagnesium bromide with benzaldehyde and dehydrating the product, benzylphenylmethanol:

$$C_6H_5{\cdot}CHO + C_6H_5{\cdot}CH_2{\cdot}MgBr \longrightarrow C_6H_5{\cdot}CH\begin{matrix}\diagup OMgBr \\ \diagdown CH_2{\cdot}C_6H_5\end{matrix} \xrightarrow{H_2O}$$

$$C_6H_5{\cdot}CHOH{\cdot}CH_2{\cdot}C_6H_5 \xrightarrow[(heat)]{-H_2O} C_6H_5{\cdot}CH{=}CH{\cdot}C_6H_5$$

(iii) By reducing benzoin with amalgamated zinc and an ethanolic solution of hydrogen chloride:

$$C_6H_5{\cdot}CHOH{\cdot}CO{\cdot}C_6H_5 \longrightarrow C_6H_5{\cdot}CH{=}CH{\cdot}C_6H_5 \quad (53\text{–}57\%)$$

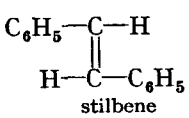
(iv) By heating α-phenylcinnamic acid in quinoline in the presence of copper chromite:

$$C_6H_5{\cdot}CHO + C_6H_5{\cdot}CH_2{\cdot}CO_2K \xrightarrow{(CH_3{\cdot}CO)_2O}$$

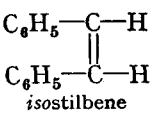
$$C_6H_5{\cdot}CH{=}C(C_6H_5){\cdot}CO_2H \longrightarrow C_6H_5{\cdot}CH{=}CH{\cdot}C_6H_5$$

(v) Stilbene may also be prepared by the Meerwein reaction (p. 588).

Stilbene, m.p. 124°, is the stable *trans*-isomer; *iso*stilbene, b.p. 145° (13 mm.), is the unstable *cis*-isomer:



stilbene



*iso*stilbene

iso*Stilbene* may be prepared by reducing tolan with zinc dust and ethanol:

$$C_6H_5{\cdot}C{\equiv}C{\cdot}C_6H_5 + 2[H] \longrightarrow C_6H_5{\cdot}CH{=}CH{\cdot}C_6H_5$$

*iso*Stilbene may also be prepared by irradiating stilbene with ultraviolet light.

*iso*Stilbene is readily converted into stilbene under the catalytic influence of traces of hydrogen bromide and peroxides.

Stilbene is reduced by sodium and ethanol to dibenzyl. It adds on bromine to form stilbene bromide which, on heating with ethanolic potassium hydroxide, forms **tolan** (*diphenylacetylene*), m.p. 62°;

$$C_6H_5{\cdot}CH{=}CH{\cdot}C_6H_5 \xrightarrow{Br_2} C_6H_5{\cdot}CHBr{\cdot}CHBr{\cdot}C_6H_5 \xrightarrow{KOH} C_6H_5{\cdot}C{:}C{\cdot}C_6H_5$$

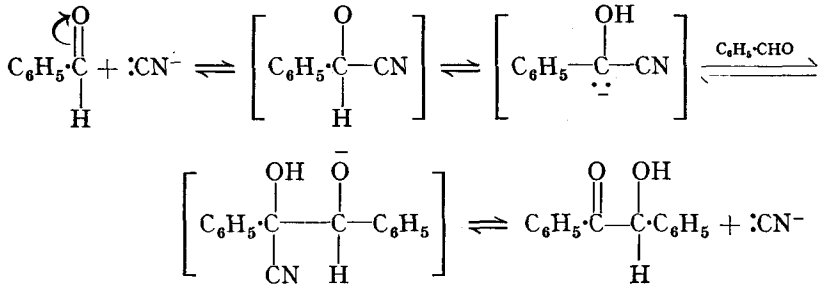
Stilbene bromide reacts with silver acetate to form two isomeric diacetates. These, on hydrolysis, form hydrobenzoin and *iso*hydrobenzoin (see later):

$$C_6H_5{\cdot}CH(O{\cdot}CO{\cdot}CH_3){\cdot}CH(O{\cdot}CO{\cdot}CH_3){\cdot}C_6H_5 \xrightarrow{H_2O} C_6H_5{\cdot}CHOH{\cdot}CHOH{\cdot}C_6H_5$$

Benzoin, $C_6H_5{\cdot}CHOH{\cdot}CO{\cdot}C_6H_5$, is usually prepared by the *benzoin condensation*, this reaction being carried out by refluxing benzaldehyde with aqueous ethanolic potassium cyanide:

$$2C_6H_5{\cdot}CHO \xrightarrow{KCN} C_6H_5{\cdot}CHOH{\cdot}CO{\cdot}C_6H_5 \quad (83\%)$$

Weiss (1941) has proposed a chain mechanism. On the other hand, Lapworth (1903) proposed an ionic mechanism:



Recently it has been shown that some thiazole and imidazole salts may also bring about the benzoin condensation (Breslow, 1958).

When a mixture of aldehydes is treated with aqueous ethanolic potassium cyanide, " mixed " benzoins (as well as the " single " benzoins) are obtained:

$$Ar{\cdot}CHO + Ar'{\cdot}CHO \xrightarrow{KCN} Ar{\cdot}CHOH{\cdot}CO{\cdot}Ar' + Ar'{\cdot}CHOH{\cdot}CO{\cdot}Ar$$

Furthermore, the reversibility of the benzoin condensation is indicated by the fact that when the benzoin $Ar{\cdot}CHOH{\cdot}CO{\cdot}Ar$ is heated with the aldehyde $Ar'{\cdot}CHO$ in the presence of potassium cyanide, a mixed benzoin is obtained (Buck and Ide, 1933):

$$Ar{\cdot}CHOH{\cdot}CO{\cdot}Ar + 2Ar'{\cdot}CHO \rightleftharpoons 2Ar{\cdot}CHOH{\cdot}CO{\cdot}Ar'$$

Aliphatic aldehydes do not undergo the benzoin condensation.

Benzoin is a colourless solid, m.p. 137°. It contains an asymmetric carbon atom and both the (+)- and (−)-forms have been prepared (Mackenzie and Wren, 1908, 1913). Benzoin is reduced to **deoxybenzoin** (*desoxy-*

benzoin), $C_6H_5{\cdot}CH_2{\cdot}CO{\cdot}C_6H_5$, m.p. 60°, which may also be prepared by the following Friedel–Crafts reaction:

$$C_6H_5{\cdot}CH_2{\cdot}COCl + C_6H_6 \xrightarrow{AlCl_3} C_6H_5{\cdot}CH_2{\cdot}CO{\cdot}C_6H_5 + HCl \quad (82\text{–}83\%)$$

The prefix *deoxy-* (formerly *desoxy-*) indicates the replacement of a hydroxyl group by hydrogen. Deoxybenzoin contains an active methylene group; *e.g.*, it forms a sodio-derivative, condenses with aldehydes in the presence of piperidine, and adds on to αβ-unsaturated carbonyl compounds (*cf.* ethyl malonate).

Benzoin is an α-hydroxyketone; hence it reduces Fehling's solution and forms an osazone. When reduced by sodium amalgam, benzoin forms mainly **hydrobenzoin,** and a small amount of ***iso*hydrobenzoin:**

$$C_6H_5{\cdot}CHOH{\cdot}CO{\cdot}C_6H_5 + 2[H] \longrightarrow C_6H_5{\cdot}CHOH{\cdot}CHOH{\cdot}C_6H_5$$

This formula (tolylene glycol) contains two identical asymmetric carbon atoms, and hence the compound can exist in the *dextro, laevo,* and *meso*-forms (*cf.* tartaric acid). The racemic modification is known as hydrobenzoin (m.p. 139°), and the *meso*-form as *iso*hydrobenzoin (m.p. 121°). Both forms give benzoic acid on oxidation.

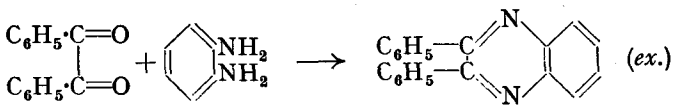
Benzoin is oxidised by chromic acid to a mixture of benzaldehyde and benzoic acid, and by nitric acid to **benzil**:

$$C_6H_5{\cdot}CHOH{\cdot}CO{\cdot}C_6H_5 \xrightarrow[HNO_3]{[O]} C_6H_5{\cdot}CO{\cdot}CO{\cdot}C_6H_5 \quad (96\%)$$

Benzil is a yellow crystalline solid, m.p. 95°. It behaves as a typical α-diketone, *e.g.*, it is oxidised by hydrogen peroxide in acetic acid to benzoic acid, forms a monoxime and dioxime, etc.

Two monoximes of benzil are known: α-(*cis*-), m.p. 134°, and β-(*trans*-), m.p. 113°. Three dioximes are possible and all are known: α-(*cis–cis*-), m.p. 237°, β-(*trans–trans*-) m.p. 207°, and γ- or *amphi*-(*cis–trans*-), m.p. 166° (*cf.* p. 667).

Benzil condenses with *o*-phenylenediamine to form 2 : 3-*diphenylquinoxaline*:



(*ex.*)

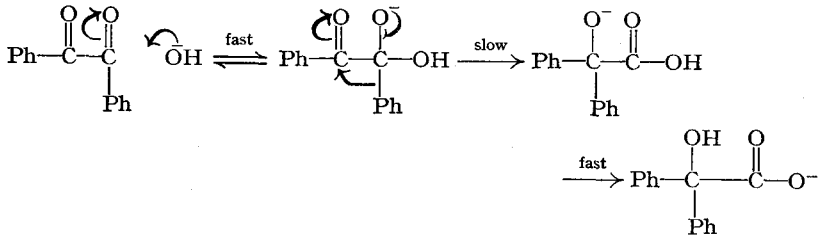
The nature of the reduction products of benzil depends on the reducing agent used. Thus reduction with sodium amalgam gives hydrobenzoin (and some *iso*hydrobenzoin); amalgamated zinc and hydrogen chloride in ethanol, stilbene; sodium hyposulphite in ethanol, benzoin; amalgamated tin and hydrogen chloride in ethanol, deoxybenzoin; and catalytic reduction using nickel at 230°, dibenzyl.

When heated with ethanolic potassium hydroxide, benzil undergoes the **benzilic acid rearrangement:**

$$C_6H_5{\cdot}CO{\cdot}CO{\cdot}C_6H_5 + KOH \longrightarrow (C_6H_5)_2C(OH){\cdot}CO_2K \quad (77\text{–}79\%)$$

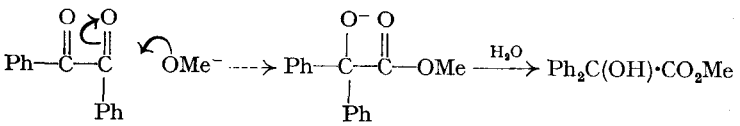
The mechanism of this rearrangement is uncertain. The rearrangement has been shown to be of the first order with respect to both benzil and hydroxide ion (Westheimer, 1936), and it has also been shown that when benzil is heated for a very short time with methanolic sodium hydroxide in water containing ^{18}O, the benzil recovered contained ^{18}O (Roberts and Urey, 1938). This is in keeping with the assumption that the first step is the rapid *reversible* addition of hydroxide

ion to benzil. All of these results are accounted for by the following mechanism that was proposed by Ingold in 1928:



This is an example of the 1,2-shift, and since a phenyl radical is involved, it is possible that a phenonium ion is formed as an intermediate. A prediction that can be made from the above mechanism is that when the two aryl groups are different, the one that is more electron-releasing (due to the presence of a suitable substituent, *e.g.*, *p*-MeO) will tend to neutralise the positive charge on the carbon atom to which it is attached when the C=O bond is polarised. Thus it will be the *other* CO group that will link with the hydroxide ion, and consequently it will be the aryl group attached to this " other " CO group that migrates preferentially. This prediction is borne out in practice, *e.g.*, in *p*-methoxybenzil, the methoxyphenyl group migration was about 32 per cent. (Roberts *et al.*, 1951).

Pfeil *et al.* (1956) have shown that barium and thallous hydroxide are more effective reagents than sodium or potassium hydroxide. Furthermore, it has also been shown that the hydroxide ion is *not* a specific catalyst; sodium methoxide and potassium *t*-butoxide produce the corresponding esters of benzilic acid (Doering *et al.*, 1956). Formation of these esters is strong evidence that the first step in the rearrangement is the addition of the nucleophilic reagent.



Benzilic acid (m.p. 150°) forms diphenylacetic acid when refluxed in acetic acid solution with hydriodic acid and red phosphorus:

$$(C_6H_5)_2C(OH)\cdot CO_2H + 2[H] \longrightarrow (C_6H_5)_2CH\cdot CO_2H + H_2O \quad (94\text{–}97\%)$$

When oxidised with chromic acid, benzilic acid forms benzophenone.

CONDENSED SYSTEMS

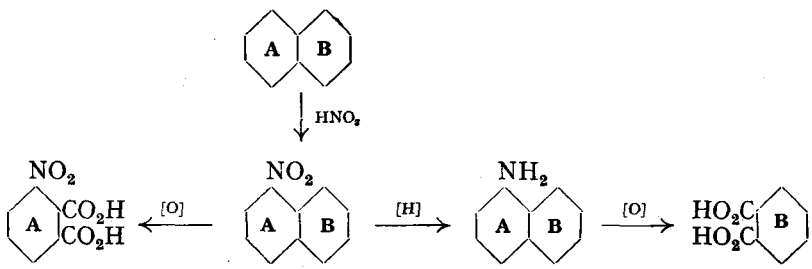
NAPHTHALENE

Naphthalene, $C_{10}H_8$, is the largest single constituent of coal-tar (6 per cent.). It is obtained by cooling the middle and heavy oils (p. 499), whereupon naphthalene crystallises out. The oil is pressed free from the naphthalene, the crude naphthalene cake melted, treated with concentrated sulphuric acid (to remove basic impurities), washed with water, and then treated with aqueous sodium hydroxide (to remove acidic impurities). Finally the naphthalene is distilled to give the pure product. It is interesting to note that naphthalene does *not* occur in low-temperature carbonisation tar.

The modern tendency for isolating naphthalene is to replace the " hot-pressing process " by the continuous washing or distillation processes. Naphthalene is also now being made synthetically from petroleum. Petro-

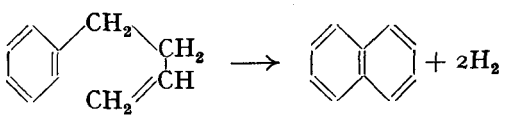
leum fractions are passed over a heated catalyst, *e.g.*, copper, at 680° at atmospheric pressure; naphthalene and higher aromatics are obtained.

Structure of naphthalene. Erlenmeyer (1866) proposed the symmetrical formula, (I), for naphthalene, and Graebe (1869) proved that it did consist of two benzene rings fused together in the *o*-positions. He used several methods, but the line of approach was the same, *e.g.*, he found that on oxidation, naphthalene gave phthalic acid. Thus naphthalene contains the group (II), *i.e.*, a benzene ring with two side-chains in the *o*-positions. When nitrated, naphthalene gave nitronaphthalene which, on oxidation, gave *o*-nitrophthalic acid. This indicates that the nitro-group is in the benzene ring, and that it is the side-chains which are oxidised. When nitronaphthalene was reduced and the corresponding aminonaphthalene oxidised, phthalic acid was obtained. As we have seen (p. 539), an amino-group attached to the nucleus renders the latter extremely sensitive to oxidation. Hence the inference is that the benzene ring in phthalic acid obtained by oxidation of aminonaphthalene is not the same ring as that originally containing the nitro-group in nitronaphthalene, *i.e.*, contains *two* benzene naphthalene rings. The above facts fit the following scheme:

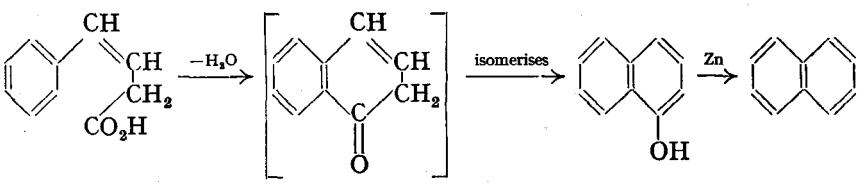


This structure for naphthalene has been confirmed by many syntheses, *e.g.*,

(i) When 4-phenylbut-1-ene is passed over red-hot calcium oxide, naphthalene is formed:

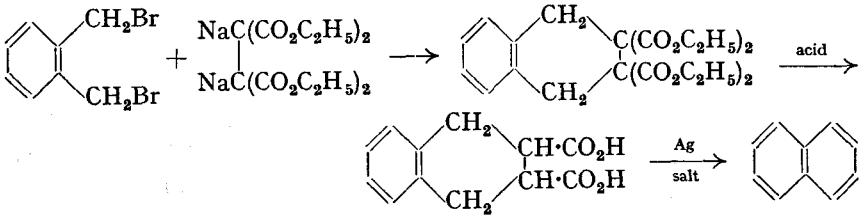


(ii) When 4-phenylbut-3-enoic acid is heated, 1-naphthol is formed and this, on distillation with zinc dust, gives naphthalene:

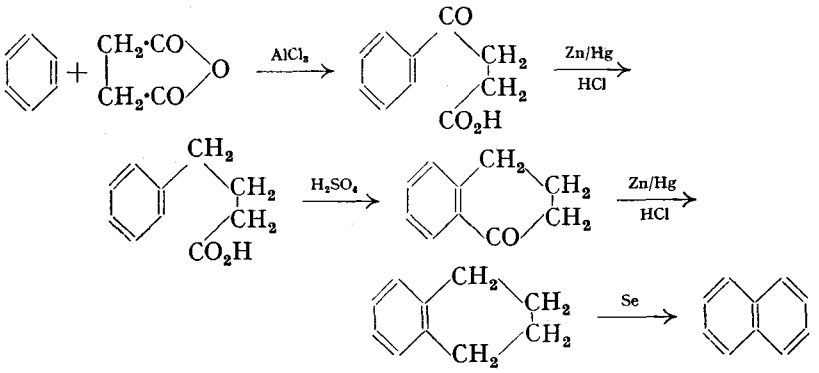


(iii) *o*-Xylylene bromide combines with disodioethanetetracarboxylic ester to form tetrahydronaphthalenetetracarboxylic ester and this, when

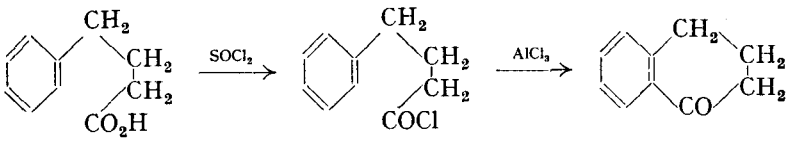
refluxed in acid solution, gives tetrahydronaphthalenedicarboxylic acid. When the silver salt of this acid is heated, naphthalene is formed:



(iv) **Haworth synthesis** (1932). Benzene is treated with succinic anhydride in the presence of aluminium chloride, and the ketonic acid produced (Burcker, 1882) is reduced by the Clemmensen method. The ring is closed by heating with concentrated sulphuric acid and the product, α-tetralone, reduced to tetrahydronaphthalene by the Clemmensen method. This compound is then dehydrogenated to naphthalene by distilling it with selenium:

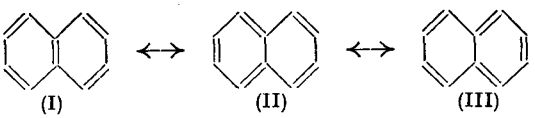


It should be noted that ring closure may also be effected by means of a Friedel–Crafts reaction on the acid chloride as follows:



It should be noted here that the formation of cyclic ketones by *intramolecular* acylation is a very important synthetic process. Sulphuric, phosphoric, hydrofluoric acid, and especially polyphosphoric acid (PPA), are commonly used as catalysts for ring-closure of acids, and aluminium or stannic chlorides for acid chlorides.

Positions of the double bonds in naphthalene. Many suggestions have been made regarding the fourth valency of each carbon atom in naphthalene, but only two formulæ need be considered, the symmetrical formula (I), and the unsymmetrical, (II) (and III). Physico-chemical evidence, *e.g.*, heat of combustion, etc., points towards naphthalene being a resonance hybrid of mainly three resonating structures, (I), (II) and (III):

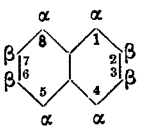


It should be noted that there are $n + 1$ principal resonating structures for a polynuclear hydrocarbon containing n benzene rings fused together in a *linear* manner.

The resonance energy of naphthalene is 75 k. cal./mole. This value is larger than that for benzene and is to be expected, since in the case of the latter only two resonating structures contribute to the resonance hybrid

Fries rule (1935). Fries compared the possible arrangements of double bonds in polynuclear compounds with benzoquinones. Structures (II) and (III) have arrangements corresponding to *o*-benzoquinone. Since quinones are far more reactive than a purely aromatic compound, Fries believed that the *stable* form of a polynuclear compound did not contain this quinonoid arrangement. He therefore formulated the following rule: *the most stable arrangement of a polynuclear compound is that form which has the maximum number of rings in the benzenoid condition*, i.e., *three double bonds in each individual ring*. Thus, according to the Fries rule, naphthalene tends to behave as structure (I) (with two benzenoid rings) rather than as (II) or (III) (with one benzenoid ring).

Isomerism and nomenclature of naphthalene derivatives. Positions 1, 4, 5 and 8 are identical (α- positions), as are positions 2, 3, 6 and 7 (β- positions). In the old literature, the positions 1 : 2- were known as *o*-; 1 : 3-, *m*-; 1 : 4-,



p-; 1 : 5-, *ana*; 1 : 6-, *epi*; 1 : 7-, *kata*; 1 : 8-, *peri*; 2 : 6-, *amphi*; and 2 : 7-, *pros*. Some of these prefixes are still used, but it is best to use numbers; the Greek letters α- and β- are still frequently used to indicate the position of a single substituent.

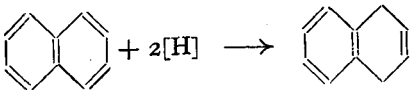
Monosubstitution products.	$C_{10}H_7X$	Two: 1- and 2-
Disubstitution products.	$C_{10}H_6X_2$	10 isomers
	$C_{10}H_6XY$	14 isomers

There are 14 possible isomers for $C_{10}H_5X_3$, 22 for $C_{10}H_4X_4$, 14 for $C_{10}H_3X_5$, 10 for $C_{10}H_2X_6$, 2 for $C_{10}HX_7$, and 1 for $C_{10}X_8$.

Properties of naphthalene. Naphthalene exists as lustrous plates, m.p. 80°, insoluble in water but very soluble in hot ethanol, cold ether, benzene, etc. It has a characteristic odour and is very volatile. It is used as an insecticide and in the preparation of phthalic anhydride and dyes.

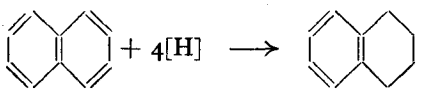
Naphthalene resembles benzene in many of its reactions but is more reactive, forming addition and substitution products more readily than benzene and is more readily oxidised and reduced (especially in the 1 : 4- positions).

Addition compounds of naphthalene. A number of reduction products of naphthalene can be isolated, the nature of the product depending on the reducing agent used. When reduced with sodium and ethanol, naphthalene gives 1 : 4-*dihydronaphthalene* (1 : 4-*dialin*), m.p. 25°:



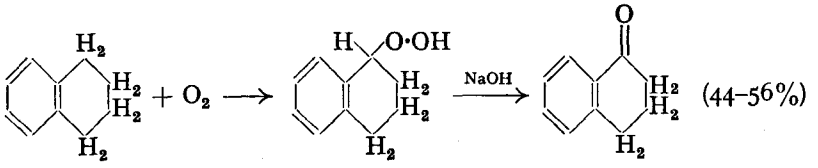
1 : 4-dialin is unstable, readily isomerising to 1 : 2-dialin (m.p. −8°) when heated with ethanolic sodium ethoxide. 1 : 2-Dialin is also unstable, fairly readily eliminating hydrogen to form naphthalene.

When reduced with sodium and *iso*pentanol, naphthalene gives 1 : 2 : 3 : 4-*tetrahydronaphthalene* (*tetralin*), b.p. 206–208°:

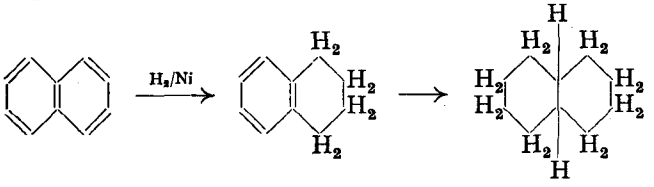


Tetralin is used as a solvent for varnishes, lacquers, etc. When treated with bromine in the presence of light, tetralin forms the mono- and dibromo-derivatives, substitution occurring in the *alicyclic* ring. When these bromo-derivatives are heated, hydrogen bromide is eliminated, the monobromo-compound forming dialin, and the dibromo-, naphthalene. In the absence of light and in the presence of iron as halogen carrier, tetralin undergoes substitution in the aromatic ring to form 5- and 6-bromo-1 : 2 : 3 : 4-tetrahydronaphthalenes.

α-**Tetralone,** b.p. 129·4°/12 mm., may be prepared by synthesis (iv), p. 710, or by heating tetralin with air for 50 hours at 70° and decomposing the peroxide with dilute sodium hydroxide:



When naphthalene is catalytically reduced using nickel, tetralin and then *decahydronaphthalene* (*decalin*) are obtained:



Decalin exists in two geometrical isomeric forms, *cis*- (b.p. 193°) and *trans*- (b.p. 185°). With nickel as catalyst, the main product is the *trans*-isomer; with platinum, *cis*- (see also p. 492). The commercial product is a mixture of the two forms, and is used as a solvent for varnishes, lacquers, etc.

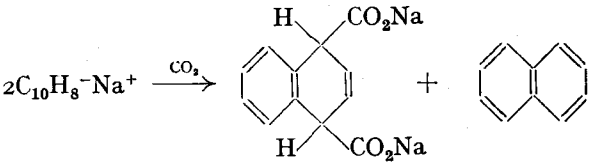
Dry chlorine adds on to solid naphthalene to give naphthalene di- and tetrachlorides, $C_{10}H_8Cl_2$ and $C_{10}H_8Cl_4$. In both of these compounds the chlorine atoms are in the same ring (shown by the fact that on oxidation, both form phthalic acid). When naphthalene dichloride is heated at 40°, hydrogen chloride is eliminated and 1-chloronaphthalene is produced. When naphthalene tetrachloride is treated with alkali, a mixture of dichloronaphthalenes is formed, the 1 : 3-isomer predominating.

Naphthalene reacts with sodium *without* loss of hydrogen to give a highly coloured addition compound. It appears that this compound contains only *one* sodium atom, and is formed by the transfer of one electron to the naphthalene.

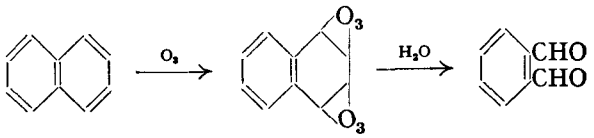
$$C_{10}H_8 + Na \longrightarrow C_{10}H_8^-Na^+$$

Sodium-naphthalene reacts with water to give 1 : 4-dihydronaphthalene, and reacts with carbon dioxide to form mainly the sodium salt of 1 : 4-

dihydronaphthalene-1 : 4-dicarboxylic acid; half of the sodium naphthalene is converted into naphthalene.



Oxidation of naphthalene. Naphthalene is oxidised by concentrated sulphuric acid and mercuric sulphate or by air in the presence of vanadium pentoxide, to phthalic anhydride (p. 692). It is oxidised by acid permanganate to phthalic acid, and by alkaline permanganate to phthalonic acid (p. 695). Chromic acid oxidises it to 1 : 4-naphthaquinone (p. 772). When treated with ozone, naphthalene forms the *diozonide* and this, on treatment with water, gives *phthalaldehyde*:



Substitution products of naphthalene. Orientation in the naphthalene nucleus is more complicated than in the benzene nucleus, due to the presence of two rings in the former. The first group always enters the 1-position in naphthalene except in two cases, when the 2-derivative is the main product: (i) sulphonation at high temperature, and (ii) in the Friedel–Crafts reaction. Introduction of a second substituent can give rise to *homonuclear* (*isonuclear*) substitution (the second substituent entering the *same* ring as the first), or to *heteronuclear* substitution (the second substituent entering the *other* ring). The following empirical generalisations are useful for predicting the position taken up by the second substituent:

(*a*) When Cl, Br, OH, CH_3, NH·R or NH·CO·CH_3 is in the 1-position, homonuclear substitution takes place mainly in position 4, and to a lesser extent in 2.

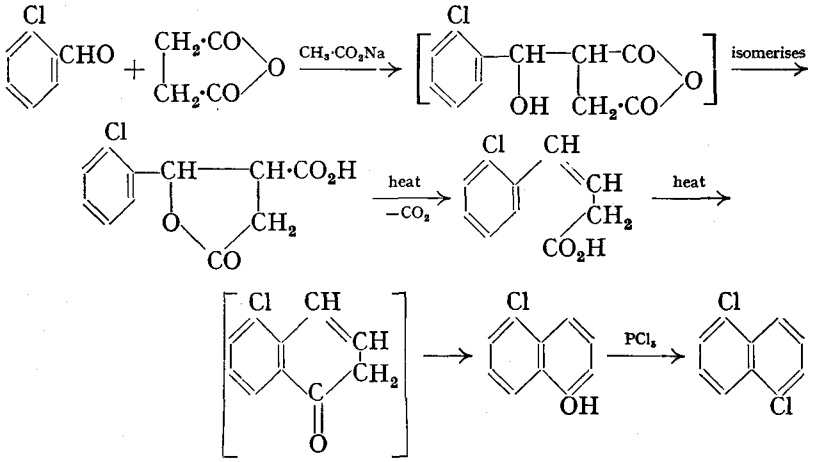
(*b*) When OH, CH_3, NH·R or NH·CO·CH_3 is in the 2-position, homonuclear substitution usually takes place in the 1-position (the introduction of the SO_3H group is an exception; this group enters position 6).

It is worth noting that homonuclear substitution usually occurs when the group already present is *o-p*-orienting.

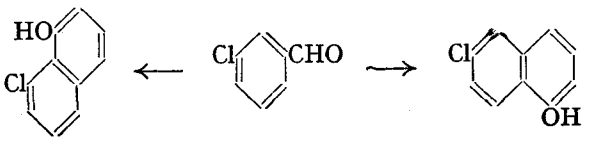
(*c*) When NO_2 or SO_3H is in the 1- or 2-position, heteronuclear substitution occurs in position 5 or 8; if halogen or NH_2 is in the 2-position, heteronuclear substitution also occurs in position 5 or 8.

It is relatively easy to determine the orientation of monosubstitution products of naphthalene by oxidation to the phthalic acid derivative or by synthesis. It is, however, not always easy for disubstituted derivatives. It can be readily ascertained by means of oxidation (to phthalic acid derivatives) whether both substituents are in the same ring or not. 1 : 8-Compounds, if the substituents are of the right type, *e.g.*, carboxyl groups, readily form cyclic derivatives, and hence these positions (1 : 8-) may be determined. In some cases it is possible to synthesise disubstituted derivatives by *unambiguous syntheses*; *e.g.*, 1 : 5-dichloronaphthalene may

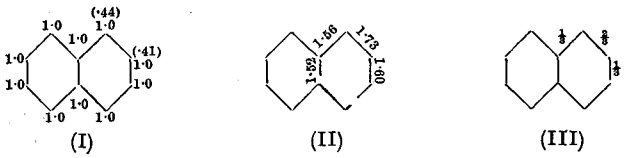
be synthesised from *o*-chlorobenzaldehyde and succinic anhydride as follows (*cf.*, p. 281):



Similarly, *p*-chlorobenzaldehyde gives 1 : 7-dichloronaphthalene. On the other hand, *m*-chlorobenzaldehyde gives rise to an *ambiguous* synthesis, since two chloronaphthols are obtained and there is no means (from the synthesis) of ascertaining which is which:



Naphthalene is an *alternant hydrocarbon* (p. 528), and the π-electron densities are unity at all positions. Hence, at first sight, it might be expected that positions 1 and 2 would be attacked equally well by the usual electrophilic



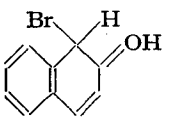
(I) (II) (III)

reagents. There is, however, another factor which must be considered when the charge densities are equal at various positions. This is the *self-polarisability* of the position, and the larger the magnitude of this self-polarisability, the more reactive will that point be to electrophilic (or nucleophilic) reagents. In benzene all the carbon atoms carry a charge of unity, and the self-polarisabilities are also equal (as shown by calculation). Hence no particular carbon atom in benzene is preferentially attacked. The case of naphthalene, however, is different. The self-polarisability is greater at position 1 than 2 (figures in parentheses in I), and hence the former is more readily attacked than the latter; this is the case in practice.

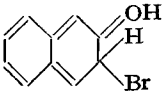
Bond order (or double-bond character) may also be used to study the reactivities of the various positions of the naphthalene molecule (*cf.* p. 529). (II) shows the bond orders obtained by calculation. (III) shows the double-bond character of the various bonds, and is obtained by taking the average of the three resonating structures of naphthalene given on p. 710. This average has been obtained on the *assumption* that each resonating structure contributes *equally* to the

resonance hybrid. The problem that always arises in polynuclear hydrocarbons is the weighting of the various possible valency structures. The usual practice is to omit Dewar structures (*i.e.*, structures with formal bonds) and also polar structures, and to take the Kekulé structures as being of equal weights. On this basis, it can be seen that the π-electron density is greater in the 1 : 2- than in the 2 : 3-bond. It might therefore be expected that the former would be more reactive than the latter, since, although neither is a double bond, both can function as double bonds, the 1 : 2-bond being " nearer " to a double bond than the 2 : 3-. Badger (1948–50) has shown that double-bond reagents add to the bond having the highest order (*cf.* the ozonide of naphthalene, p. 713). It might also be noted that these bonds with the highest orders are those which were supposed to be " fixed " double bonds, *i.e.*, in naphthalene the 1 : 2-bond was a " fixed " double bond, in accordance with the Fries rule (p. 711).

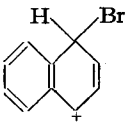
Still another way of studying organic reactions has been to calculate the energy of activation for the various positions in a molecule. When the attacking reagent forms the transition state, two of the delocalised π-electrons in the naphthalene molecule must be polarised to form a σ-bond with the attacking electrophilic reagent (p. 516). The lower the bond localisation energy, the more readily will the transition state be formed. Furthermore, the higher the bond order, *i.e.*, the greater the π-electron density in that bond, the smaller will be the bond localisation energy. This accounts for substitution of 2-naphthol in



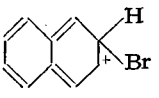
(IV)



(V)



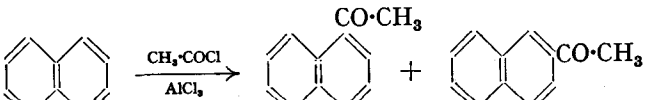
(VI)



(VII)

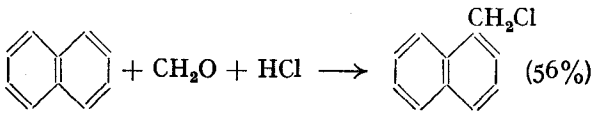
position 1 and not in 3. In (IV), the intermediate is formed by localisation of the 1 : 2-bond; in (V), by that of the 2 : 3-bond. Since the former has the higher bond order, this one will be more readily localised, *i.e.*, the energy of activation of (IV) is lower than that of (V), and so the reaction proceeds via (IV) and not via (V). In the substitution of naphthalene itself, two intermediates are possible, (VI) and (VII); the former is the more stable, and so 1-substitution occurs rather than 2- (*cf.* self-polarisabilities, above).

The Friedel–Crafts reaction with naphthalene. Naphthalene is attacked by aluminium chloride when vigorous conditions are used (dinaphthyls and compounds with one of the naphthalene rings opened are formed). Hence to carry out the Friedel–Crafts reaction successfully, mild conditions (low temperatures) must be used, and even then the maximum yield is about 60 per cent. With methyl iodide, 1- and 2-methylnaphthalenes are formed; with ethyl bromide, only 2-ethylnaphthalene; and with *n*-propyl bromide, 2-*iso*propylnaphthalene. With alcohols and aluminium chloride, 2 : 6-dialkylnaphthalenes are obtained but with alcohols and boron trifluoride, 1 : 4-dialkylnaphthalenes (Price, 1943). Introduction of an acyl group in the presence of aluminium chloride gives a mixture of 1- and 2-ketones, the nature of the solvent affecting the percentage of each; *e.g.*, with acetyl chloride in carbon disulphide as solvent, 1- and 2-naphthyl methyl ketone are formed in a ratio of 3 : 1; in nitrobenzene, 1 : 9:



Chloromethylation of naphthalene using a mixture of paraformaldehyde, hydrochloric acid, glacial acetic acid and phosphoric acid gives

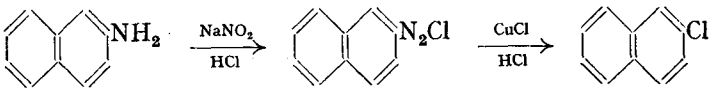
mainly the 1-derivative and a small amount of the 1 : 5-bischloromethyl-derivative:



When naphthalene is chloromethylated with boiling aqueous formaldehyde and concentrated hydrochloric acid, a mixture of compounds is obtained from which 1 : 4- and 1 : 5-bischloromethylnaphthalenes have been isolated (Badger *et al.*, 1947).

Halogen derivatives. Naphthalene is very easily halogenated, *e.g.*, when brominated in boiling carbon tetrachloride solution, naphthalene forms 1-bromonaphthalene (yield 72–75 per cent.). Further bromination gives mainly the 1 : 4-dibromo-derivative, and some 1 : 2-. Sulphuryl chloride (1 equivalent) in the presence of aluminium chloride at 25° chlorinates naphthalene to give the 1-chloro-derivative; with 2 equivalents of sulphuryl chloride (at 100–140°), 1 : 4-dichloronaphthalene is formed.

2-Halogeno-naphthalenes are conveniently prepared from 2-naphthylamine by diazotisation, etc. *e.g.*,



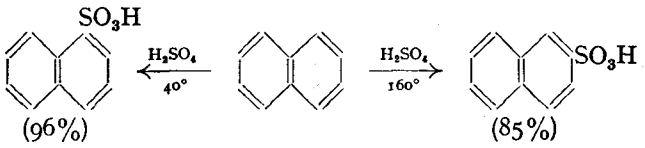
Chlorination of naphthalene at 250°, in the presence of iodine, gives 1- and 2-monochloronaphthalenes in the proportion of 9 : 1; above 340°, the proportion is 1 : 1 (Wibaut *et al.*, 1950). The halogen atom in naphthalene behaves similarly as in the benzene ring, but is more reactive.

Nitronaphthalenes. Nitric acid attacks naphthalene at room temperature to form 1-nitronaphthalene. This is a yellow solid, m.p. 60°, which behaves like nitrobenzene, but differs in that it forms 1-chloronaphthalene when treated with phosphorus pentachloride (nitrobenzene does not react).

Nitration of naphthalene at high temperature gives a mixture of 1 : 5- and 1 : 8-dinitronaphthalenes. Other dinitro-derivatives are prepared by special means.

2-Nitronaphthalene (m.p. 79°) may be prepared by heating 2-naphthalene-diazonium borofluoride with sodium nitrite and copper powder.

Naphthalenesulphonic acids. When naphthalene is treated with concentrated sulphuric acid at 40°, the main product is the 1-derivative (m.p. 91°); at 160°, the main product is the 2-derivative (m.p. 102°):



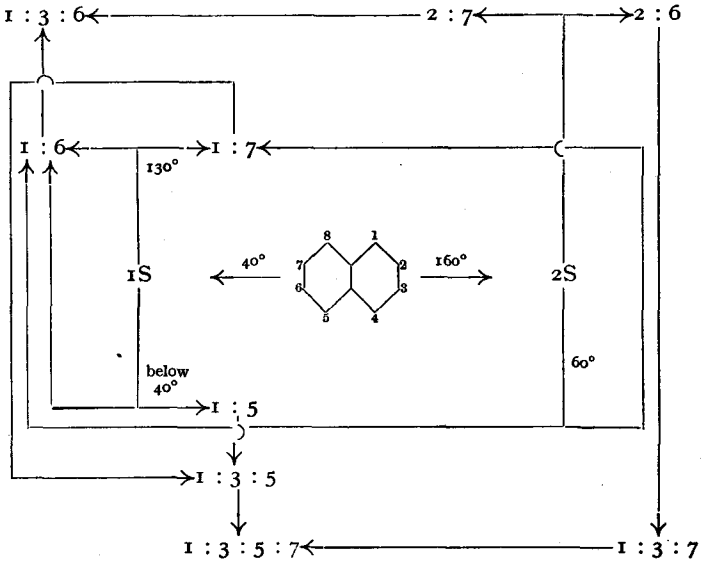
The two isomeric acids may be separated by means of their calcium or lead salts, those of the 1-acid being more soluble than the 2-. The 2-acid may be obtained pure by treating the mixture of 1- and 2-naphthalenesulphonic acids with superheated steam; the 1-acid is decomposed into naphthalene, the 2-acid being practically unaffected.

1- and 2-Naphthalenesulphonic acids behave similarly to benzenesulphonic acid, but the sulphonic acid group in the former is more easily replaced;

e.g., when fused with phosphorus pentachloride, both acids give the corresponding chloronaphthalenes. Both acids are oxidised to phthalic acid by acid permanganate. When heated with concentrated sulphuric acid, the 1-acid is converted into the 2-isomer. Thus the former is the kinetically controlled product and the latter the thermodynamically controlled one.

β-Naphthalenesulphonic acid is the starting point of practically all β-naphthalene derivatives.

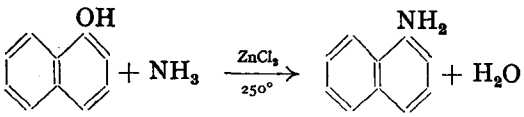
Sulphonation of the 1-sulphonic acid with concentrated sulphuric acid below 40° gives 1 : 5- (70 per cent.) and 1 : 6-disulphonic acids (25 per cent.); at 130°, the main products are 1 : 6- and 1 : 7-disulphonic acids. Sulphonation of the 2-acid at 60° gives 1 : 6- (80 per cent.) and 1 : 7-disulphonic acid (20 per cent.); above 140°, the main product is 2 : 7-disulphonic acid, and a small amount of 2 : 6-. Armstrong and Wynne's rule (1890) for the orientation of naphthalene-



polysulphonic acids is useful: two sulpho-groups never occupy positions *o*, *p* or *peri* to each other. This rule limits the number of isomers that can be formed by direct sulphonation of naphthalene to two mono-, six di-, three tri-, and one tetra-sulphonic acid. The table above summarises the products obtained by the sulphonation of naphthalene with concentrated sulphuric acid (note the various migrations).

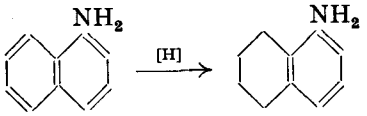
Many of these sulphonic acids are very important dye-intermediates.

Naphthylamines. 1-Naphthylamine (**α-naphthylamine**) may be prepared by reducing 1-nitronaphthalene with iron and hydrochloric acid (yield 80–85 per cent.). This method is used industrially. 1-Naphthylamine may also be prepared by the Bucherer reaction (see below) or by heating 1-naphthol with the double compound of zinc chloride and ammonia (this amination occurs more easily than with phenol):



1-Naphthylamine has recently been prepared by heating 1-naphthoic acid with hydroxylamine and polyphosphoric acid (Snyder *et al.*, 1953).

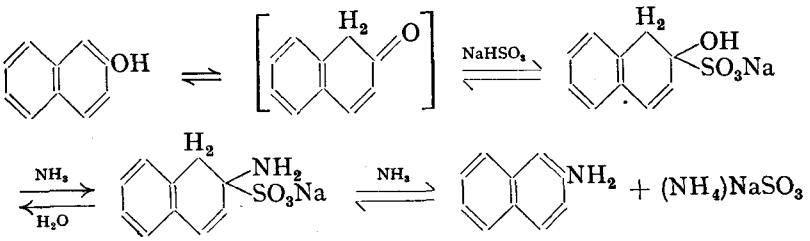
1-Naphthylamine is a colourless solid, m.p. 50°, almost insoluble in water but very soluble in ethanol and ether. It has an unpleasant odour, and turns red on exposure to air. It reduces ammoniacal silver nitrate, and solutions of its salts give a blue precipitate with ferric chloride. Oxidation with boiling chromic acid gives β-naphthaquinone; with permanganate, phthalic acid is obtained. 1-Naphthylamine is reduced by sodium and *iso*pentanol to *ar*-tetrahydro-1-naphthylamine; the prefix *ar*- is the abbreviation of *aromatic* and indicates that the four hydrogen atoms are *not* in the ring containing the amino-group:



The systematic name is 5 : 6 : 7 : 8-tetrahydro-1-naphthylamine.

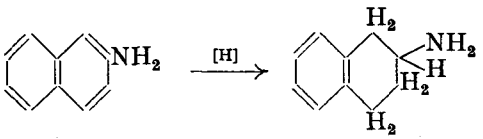
1-Naphthylamine couples with diazonium salts in the 4-position.

2-Naphthylamine (**β-naphthylamine**) is prepared industrially from 2-naphthol by the **Bucherer reaction** (1904). This is the reversible conversion of a naphthol into a naphthylamine in the presence of an aqueous sulphite or hydrogen sulphite. The mechanism of the formation of 2-naphthylamine from 2-naphthol, sodium hydrogen sulphite and ammonia is believed to be as follows:



2-Naphthylamine is prepared commercially by heating 2-naphthol with aqueous ammonium hydrogen sulphite at 150° under pressure (yield: 94–96 per cent.). 2-Naphthylamine has also been prepared from 2-naphthoic acid (*cf.* the 1-isomer above).

2-Naphthylamine is a colourless solid, m.p. 112°, insoluble in water but soluble in ethanol and ether. It is odourless, reduces ammoniacal silver nitrate, but gives *no* coloration with ferric chloride. It is oxidised by permanganate to phthalic acid and reduced by sodium and *iso*pentanol to *ac*-tetrahydro-2-naphthylamine (1 : 2 : 3 : 4-tetrahydro-2-naphthylamine); the prefix *ac*- is the abbreviation of *alicyclic* and indicates that the four hydrogen atoms are in the ring containing the amino-group (*cf.* above):

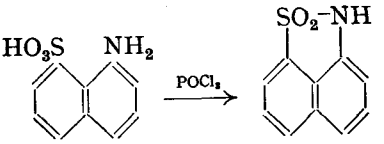


2-Naphthylamine couples with diazonium salts only in the 1-position; if this is occupied, no coupling occurs.

Naphthylaminesulphonic acids. These are very important industrially for making dyes. When heated with excess concentrated sulphuric acid at 130°, 1-naphthylamine forms 1-naphthylamine-4-sulphonic acid (*naphthionic*

acid). This is used in the preparation of Congo red (p. 783), and is manufactured by the baking process of naphthylamine hydrogen sulphate (*cf.* sulphanilic acid). Prolonged action of sulphuric acid at 130° converts 1-naphthylamine into 1-naphthylamine-5-sulphonic acid (*Laurent's acid*). If the heating is prolonged still further, Laurent's acid rearranges to 1-naphthylamine-6-sulphonic acid (*Cleve's acid*).

1-Naphthylamine-8-sulphonic acid (*Schollkopf's acid*) may be prepared by reduction of the corresponding nitro-sulphonic acid. When heated with phosphoryl chloride, 1-naphthylamine-8-sulphonic acid forms *naphthsultam*:



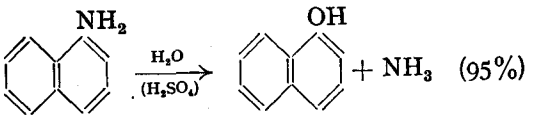
Sultams may be regarded as *inner* sulphonamides.

When heated with concentrated sulphuric acid, 2-naphthylamine gives four different sulphonic acids according to the temperature: 2-naphthylamine-5-sulphonic acid (*Dahl's acid*), 2-naphthylamine-6-sulphonic acid (*Bronner's acid*), 2-naphthylamine-7-sulphonic acid (F-*acid*), and 2-naphthylamine-8-sulphonic acid (*Badische's acid*).

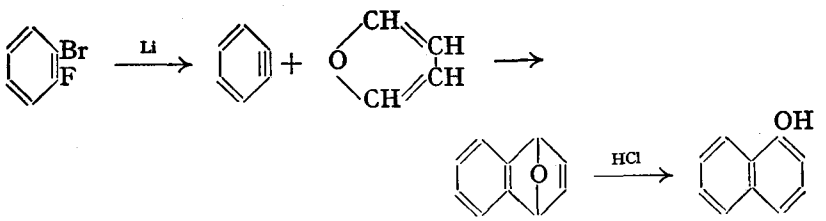
Naphthols. Both 1- and 2-naphthols are present in coal-tar. They are prepared industrially by fusing the corresponding naphthalenesulphonic acid with sodium hydroxide:

$$C_{10}H_7{\cdot}SO_3Na + NaOH \xrightarrow{300^\circ} C_{10}H_7OH + Na_2SO_3 \quad (70\text{–}80\%)$$

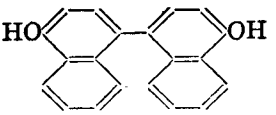
Pure 1-naphthol may be prepared by heating 1-naphthylamine with dilute sulphuric acid at 290° under pressure:



A most interesting preparation of 1-naphthol is by the reaction between *o*-bromofluorobenzene and lithium amalgam in the presence of furan (Wittig *et al.*, 1955). The reaction proceeds via a benzyne intermediate (p. 547):



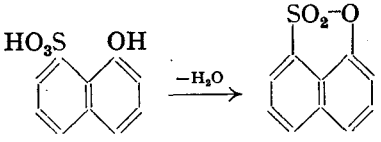
1-Naphthol (**α-naphthol**) is a colourless crystalline solid, m.p. 94°, with a faint phenolic odour. It is sparingly soluble in water, but is readily soluble in alkalis to form naphthoxides, *e.g.*, $C_{10}H_7ONa$. With ferric chloride it gives a violet-blue precipitate of *α-dinaphthol* (4 : 4′-bis-1-naphthol):



1-Naphthol reduces ammoniacal silver nitrate, is oxidised by alkaline permanganate to phthalonic acid and by chromic acid to α-naphthaquinone. It is reduced by sodium and *iso*pentanol or *ar*-tetrahydro-1-naphthol (*ar-1-tetralol*).

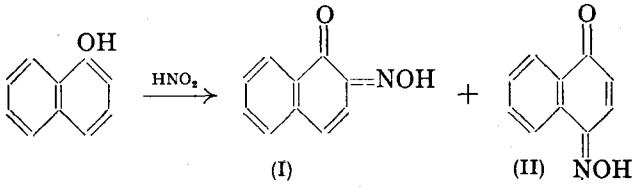
Direct sulphonation of 1-naphthol under mild conditions gives a mixture of 1-naphthol-2-sulphonic acid (*Schaeffer's acid*) and 1-naphthol-4-sulphonic acid (*Nevile-Winther's acid*). More vigorous conditions result in the formation of 1-naphthol-2 : 4-disulphonic acid and finally 1-naphthol-2 : 4 : 7-trisulphonic acid.

1-Naphthol-8-sulphonic acid forms an *inner* ester when heated:



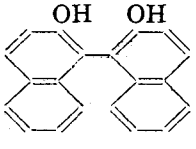
This is known as *naphthsultone*.

Treatment of 1-naphthol with nitrous acid gives mainly the 2-oxime of β-naphthaquinone, (I), and a small amount of the 4-oxime of α-naphthaquinone, (II) (*cf.* nitrosophenol):

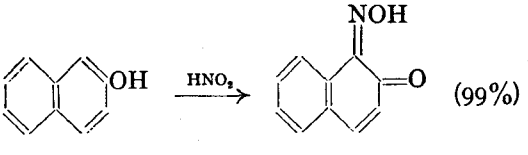


1-Naphthol couples with diazonium salts in the 4-position.

2-Naphthol (**β-naphthol**) is a colourless crystalline solid, m.p. 123°, with a faint phenolic odour. It resembles 1-naphthol in most of its properties, but is more reactive. With ferric chloride it gives a green precipitate of β-*dinaphthol* (1 : 1'-bis-2-naphthol). It reduces ammoniacal silver nitrate, and is oxidised by alkaline permangante to phthalonic acid. It is reduced



by sodium and *iso*pentanol to mainly *ac*-tetrahydro-2-naphthol (*ac-2-tetralol*). With nitrous acid it forms the 1-oxime of β-naphthaquinone (nitroso-β-naphthol):

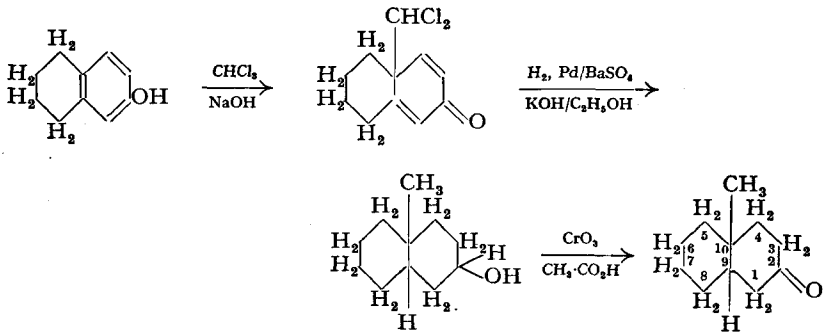


This is used for the detection and estimation of cobalt. 2-Naphthol couples with diazonium salts only in the adjacent 1-position; if this is occupied, no coupling takes place. Only the oxime form exists in the solid state, but

in solution only the other tautomer (nitrosonaphthol) is present (Burawoy *et al.*, 1955).

Some 2-naphthol ethers (methyl and ethyl), known as *nerolins*, are used in perfumery. When 2-naphthol is sulphonated, the original product is 2-naphthol-1-sulphonic acid, but this is unstable and rearranges to 2-naphthol-8-sulphonic acid (*croceic acid*) at low temperature. Croceic acid, at 100°, rearranges to 2-naphthol-6-sulphonic acid (*Schaeffer's β-acid*). When sulphonated with larger amounts of concentrated sulphuric acid, 2-naphthol gives disulphonic acids. At low temperature the main product is 2-naphthol-6 : 8-disulphonic acid (G-*acid*); at higher temperatures, mainly 2-naphthol-3 : 6-disulphonic acid (R-*acid*). G- and R-acids are used in the manufacture of dyes.

Woodward (1940) prepared 10-methyldecal-2-one from *ar*-2-tetralol by means of the Reimer–Tiemann reaction as follows:



This synthesis is based on the fact that the intermediate product in the Reimer–Tiemann reaction can be isolated when the *p*-position to the hydroxyl group is occupied by, *e.g.*, a methyl group (p. 656).

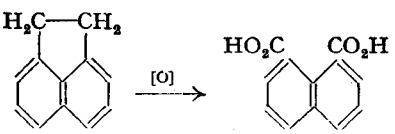
Naphthalenecarboxylic acids. **1-Naphthoic acid** (*naphthalene-1-carboxylic acid*), m.p. 161°, may be prepared by the hydrolysis of the corresponding cyanide, or by the oxidation of 1-acetylnaphthalene with sodium hypochlorite. It may also be prepared from 1-naphthylmagnesium bromide as follows:

$$1\text{-}C_{10}H_7\cdot MgBr + (C_2H_5O)_2CO \xrightarrow{\text{ether}} 1\text{-}C_{10}H_7\cdot CO_2C_2H_5 + C_2H_5OMgBr \quad (68\text{–}73\%)$$

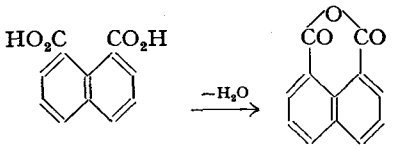
2-Naphthoic acid, m.p. 184°, may be prepared by methods similar to those used for the 1-isomer.

1- and 2-Naphthoic acids are insoluble in cold or hot water, and both readily eliminate carbon dioxide to form naphthalene when heated with soda–lime. Both undergo most of the usual reactions of a carboxylic acid, but 1-naphthoic acid shows the proximity effect due to the carbon atom in position 8; *e.g.*, 2-chloro-1-naphthoic acid is not esterified by the Fischer–Speier method, whereas the isomeric 1-chloro-2-naphthoic acid gives the ester under the same conditions.

Naphthalic acid (*naphthalene-1 : 8-dicarboxylic acid*) may be prepared by oxidising acenaphthene with acid dichromate:



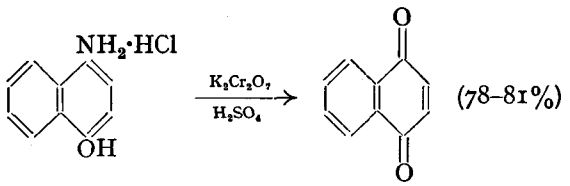
It is a solid, and when heated at 180° forms naphthalic anhydride:



This is in keeping with the fact that all *peri*-(1 : 8)-substituents interact if possible (*cf.* sultams and sultones).

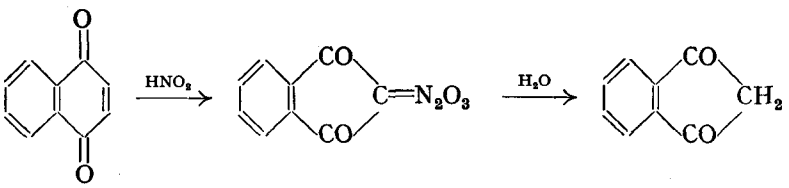
Naphthaquinones. Theoretically, six naphthaquinones are possible: 1 : 2-, 1 : 4-, 1 : 5-, 1 : 7-, 2 : 3- and 2 : 6-. Only three are known, the 1 : 2-, 1 : 4- and 2 : 6-, but it appears that derivatives of 2 : 3-naphthaquinone have been prepared.

1 : 4-Naphthaquinone (**β-naphthaquinone,** 1 : 4-*dihydronaphthalene*-1 : 4-*dione*) may be prepared by the oxidation of 1 : 4-diamino-, dihydroxy- or aminohydroxynaphthalene, *e.g.*,



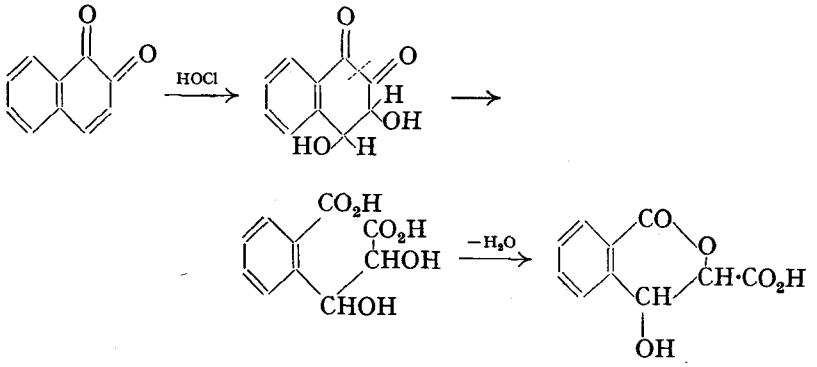
It may also be prepared by the direct oxidation of naphthalene with dichromate and sulphuric acid, or chromium trioxide in glacial acetic acid (yield 40 per cent.).

1 : 4-Naphthaquinone is a volatile yellow solid, m.p. 125°, with a pronounced odour. It resembles *p*-benzoquinone in many ways chemically, but it is not reduced by sulphurous acid. It is reduced by metal and acid to 1 : 4-*dihydroxynaphthalene* (*naphthalene*-1 : 4-*diol*) and oxidised by nitric acid to phthalic acid. It forms a monoxime; this is tautomeric, and in the solid state it exists as the oxime, and in solution this form predominates in equilibrium with the nitrosophenol form (Havinga *et al.*, 1955; Hadži, 1956). A most remarkable reaction is its conversion into *indane*-1 : 3-*dione* (1 : 3-*diketohydrindene*) on treatment with nitrous acid:

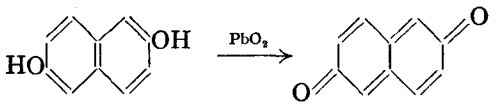


Vitamin K (the antihaemorrhagic factor) is a derivative of 1 : 4-naphthaquinone.

1 : 2-Naphthaquinone (**β-naphthaquinone,** 1 : 2-*dihydronaphthalene*-1 : 2-*dione*) may be prepared by oxidising 1-amino-2-naphthol with dichromate and sulphuric acid (yield 75 per cent.). It is a non-volatile, odourless, red solid which decomposes at 115–120°. A most remarkable reaction is the fission of the quinone ring with simultaneous hydroxylation when 1 : 2-naphthaquinone is treated with chlorine-water (or with hypochlorous acid); phenylglyceric-*o*-carboxylic lactone is the final product:

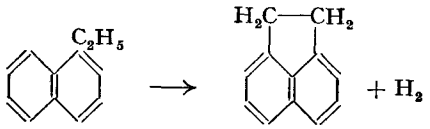


2 : 6-Naphthaquinone (***amphi*-naphthaquinone**, 2 : 6-*dihydronaphthalene*-2 : 6-*dione*) may be prepared by oxidising 2 : 6-dihydroxynaphthalene in benzene solution with " active " lead dioxide (this may be prepared by decomposing lead tetra-acetate with water; Kuhn *et al.*, 1950):

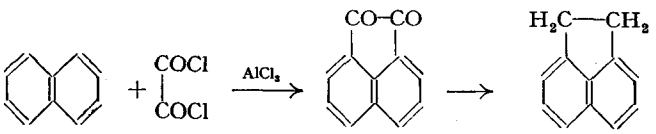


It is an orange, non-volatile, odourless solid, m.p. 135°.

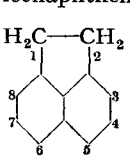
Acenaphthene, $C_{12}H_{10}$, occurs in coal-tar; it may be prepared by passing 1-ethylnaphthalene through a red-hot tube:

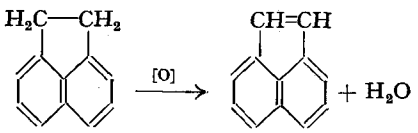


It may also be prepared by a Friedel–Crafts reaction using naphthalene and oxalyl chloride and reducing the product, 1 : 2-*acenaphthaquinone*, by the Wolff–Kishner method (p. 153):



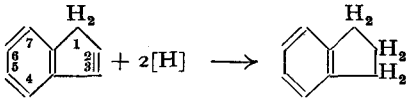
Acenaphthene is a colourless solid, m.p. 96°. On oxidation with dichromate and sulphuric acid, acenaphthene is converted into 1 : 2-acenaphthaquinone which, by further action of the oxidising agent, gives naphthalic acid. This shows that the ethylene group occupies the 1 : 8- positions of naphthalene. Substitution in acenaphthene occurs most readily in the 5- and 6-positions, *e.g.*, bromination, nitration and sulphonation give the corresponding 5-derivatives. When oxidised with lead peroxide or passed through a red-hot tube, acenaphthene forms *acenaphthylene*:



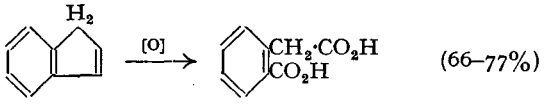


Indene (benzo*cyclo*pentadiene), C_9H_8, occurs in the coal-tar fraction boiling at 175–185°. It may be obtained from this fraction by precipitating with picric acid and purifying the picrate by recrystallisation. When the picrate is steam-distilled, it is decomposed, the indene passing over in the distillate. Alternatively, indene may be obtained from the coal-tar fraction by heating the latter with sodium, separating the sodioindene formed (solid) and steam-distilling it, whereupon indene distils over.

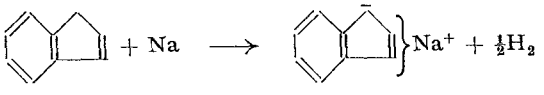
Indene is a colourless liquid, b.p. 182°, which readily polymerises (*cf. cyclo*pentadiene). It is reduced by sodium and ethanol to 2 : 3-*dihydroindene* (*indane* or *hydrindene*):



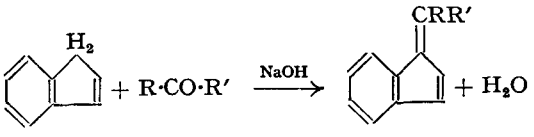
Oxidation of indene with acid dichromate gives homophthalic acid.



Indane, b.p. 177°, occurs in coal-tar. Indene combines with halogen to form 2 : 3-dihalogeno-indane. The methylene group in indene is very reactive, *e.g.*, indene forms a sodio-derivative:

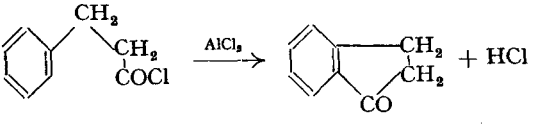


It liberates paraffins from alkyl-magnesium halides, condenses with ethyl oxalate in the presence of sodium ethoxide to form indene-oxalic ester, and with aldehydes or ketones in the presence of alkali to form benzofulvenes:

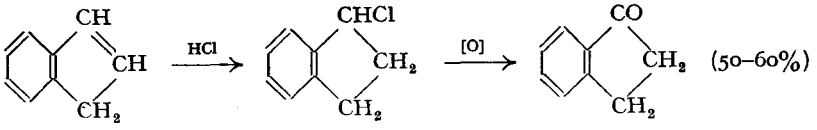


These benzofulvenes are highly coloured; *benzofulvene* has been prepared (R = R′ = H). All the foregoing reactions are characteristic of the methylene group in *cyclo*pentadiene.

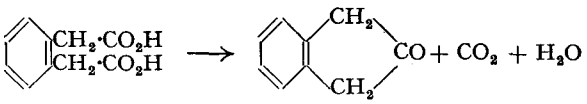
Indan-1-one (*α-hydrindone*), m.p. 42°, may be synthesised by an internal Friedel–Crafts reaction on β-phenylpropionyl chloride:



It may also be prepared by treating indene with hydrochloric acid and oxidising the product, 1-chloroindane, with chromium trioxide in acetic acid:



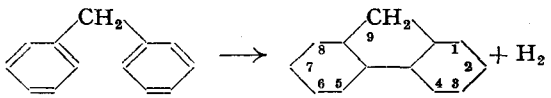
Indan-2-one (β-*hydrindone*), m.p. 61°, may be prepared by heating xylylene-*o*-dicarboxylic acid:



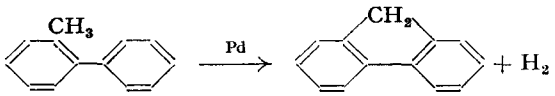
Indane-1 : 3-dione may be prepared by the action of nitrous acid on 1 : 4-naphthaquinone (p. 722).

Fluorene (*diphenylenemethane*), $C_{13}H_{10}$, occurs in coal-tar (fraction 270–300°) and can be separated from the other compounds by means of its sodio-derivative (*cf.* indene). It may be prepared:

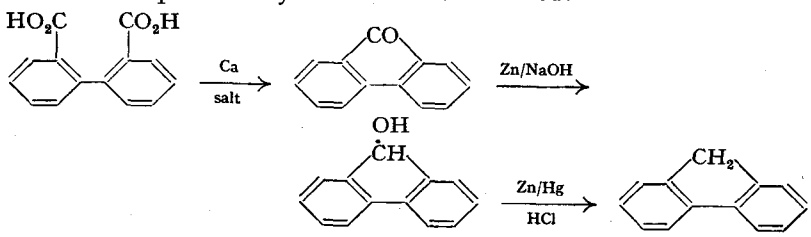
(i) By passing diphenylmethane through a red-hot tube:



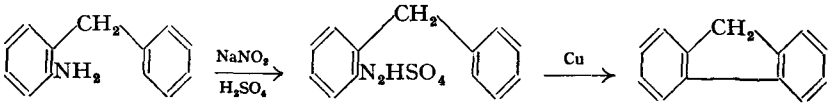
(ii) By passing *o*-methyldiphenyl over palladium at 450°:



(iii) By heating the calcium salt of diphenic acid, reducing the product, fluorenone, with zinc dust and ethanolic sodium hydroxide, and then reducing the fluorenol so produced by the Clemmensen method:



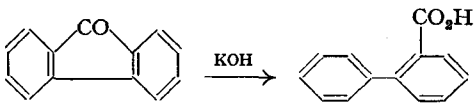
(iv) Fluorene may be prepared by means of the Pschorr synthesis (p. 735), starting with *o*-aminodiphenylmethane.



Alternatively, *o*-aminobenzophenone may be used as the starting material and the product, fluorenone, reduced to fluorene as in (iii).

Methods (iii) and (iv) are useful for preparing substituted fluorenes with the substituents in known positions.

Fluorene is a colourless solid, m.p. 116°, with a blue fluorescence. The methylene group is active (*cf. cyclo*pentadiene), *e.g.*, fluorene forms a sodio-derivative, liberates hydrocarbons from Grignard reagents, and condenses with aldehydes and ketones in the presence of alkali. These condensation products are colourless or slightly coloured (*cf.* indene). When fluorene is halogenated, nitrated or sulphonated, the first substituent enters the 2-position, and the second the 7-position. Fluorene is oxidised by chromium trioxide in glacial acetic acid to *fluorenone* (m.p. 84°). This is oxidised by permanganate to phthalic acid. When fused with potassium hydroxide, fluorenone is converted into diphenyl-2-carboxylic acid:



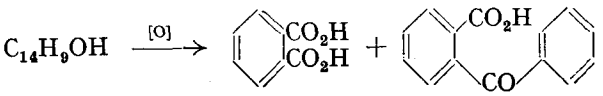
This acid is also formed when fluorenone is heated with potassium hydroxide in diphenyl ether at 180° (Huntress and Seikel, 1939). The opening of the five-membered ring in this manner offers a means of determining the orientation of substituted fluorenones (and fluorenes).

ANTHRACENE

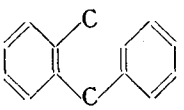
Anthracene, $C_{14}H_{10}$, is obtained from the anthracene oil fraction of coal-tar by cooling the latter and pressing the solid (which crystallises out) free from liquid. The crude anthracene contains phenanthrene and carbazole. The anthracene cake is powdered and washed with "solvent naphtha" which dissolves the phenanthrene, and the remaining solid is then washed with pyridine which dissolves the carbazole. The anthracene is purified by sublimation. Alternatively, after removal of phenanthrene, the remaining solid is fused with potassium hydroxide, whereby potassio-carbazole is formed; unreacted anthracene is sublimed out of the melt and recovered.

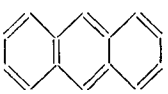
Until recently, there has been very little use for carbazole, and thus the recovery of anthracene was expensive. Since anthracene is mainly used as the starting point of anthraquinone, a cheaper method of isolating anthracene from coal-tar is to remove the phenanthrene first, and then catalytically oxidise the remaining mixture of anthracene and carbazole by air and vanadium pentoxide at 300–500°. Under these conditions, anthracene is oxidised to anthraquinone and carbazole is completely oxidised (to carbon dioxide, etc.).

Structure of anthracene. Bromination of anthracene gives bromo-anthracene, $C_{14}H_9Br$, which, on fusion with potassium hydroxide, forms hydroxyanthracene, $C_{14}H_9{\cdot}OH$, and this, on vigorous oxidation, gives phthalic acid and a small amount of *o*-benzoylbenzoic acid (Anschutz and Japp, 1878):

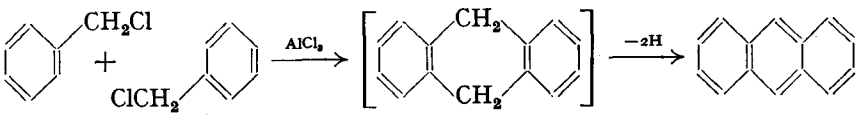


This suggests that anthracene contains at least two benzene rings, and that its skeleton is as shown. The presence of two benzene rings is confirmed by the fact that on fusion with potassium hydroxide at 250°, anthraquinone (which may be obtained from anthracene by direct oxidation) gives *two* molecules of benzoic acid. The above skeleton contains 14 carbon atoms, and to fit in 10 hydrogen atoms and retain the quadrivalency of carbon, the middle ring must be closed, *i.e.*, a structure of anthracene which is consistent with the foregoing reactions is three benzene rings fused together in a linear manner. This structure has been amply confirmed by many syntheses.

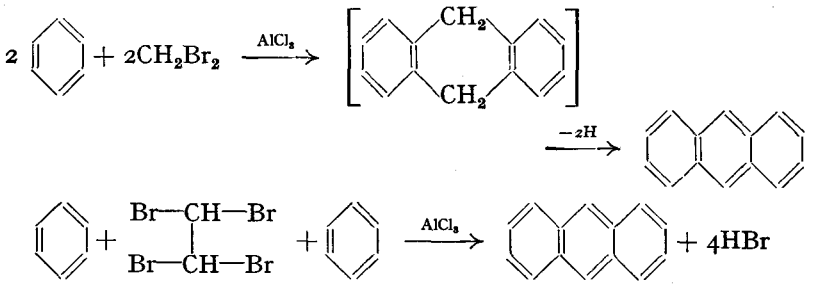




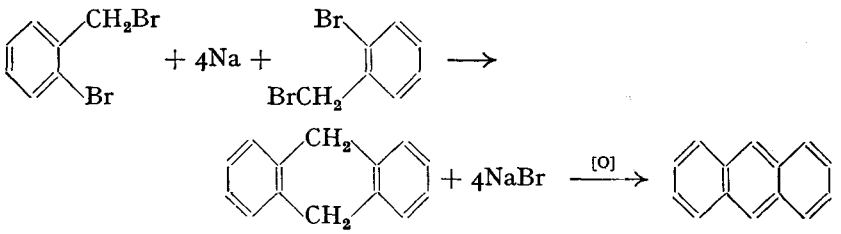
Synthesis of anthracene. (i) By a Friedel–Crafts reaction using benzyl chloride; 9 : 10-*dihydroanthracene*, which is first formed, readily eliminates two hydrogen atoms under the conditions of the experiment to form anthracene:



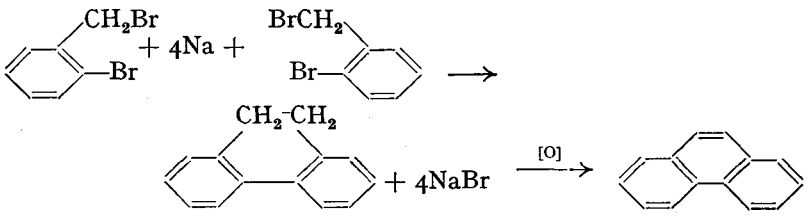
Anthracene is also formed by the Friedel–Crafts condensation between benzene and methylene bromide, or between benzene and acetylene tetrabromide:



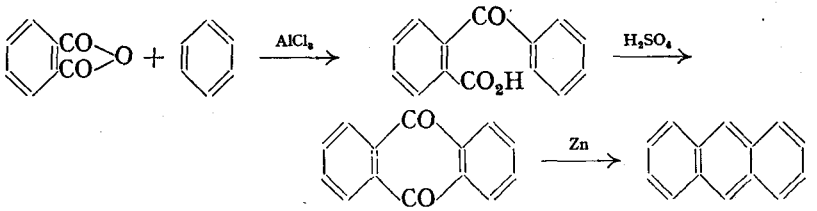
(ii) By heating *o*-bromobenzyl bromide with sodium; the product, dihydroanthracene, is converted into anthracene by mild oxidation:



Some phenanthrene is formed at the same time:

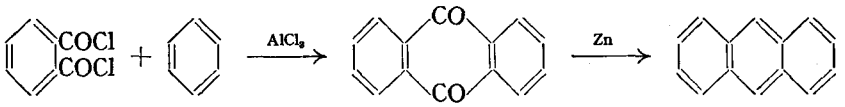


(iii) When phthalic anhydride in benzene solution is treated with aluminium chloride, *o*-benzoylbenzoic acid is formed. This, on heating with concentrated sulphuric acid at 100°, forms anthraquinone, which, on distillation with zinc dust, gives anthracene:

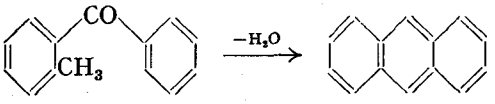


According to Koo (1953), polyphosphoric acid is the best reagent for cyclising *o*-benzoylbenzoic acid.

Alternatively, anthraquinone may be prepared by the action of aluminium chloride on phthaloyl chloride in benzene solution:



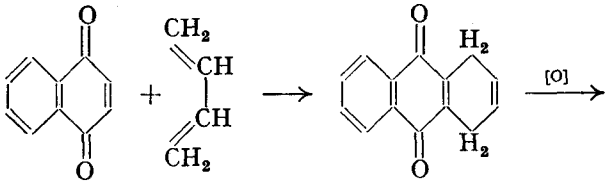
(iv) Anthracene may be prepared by means of the **Elbs reaction** (see also p. 665):

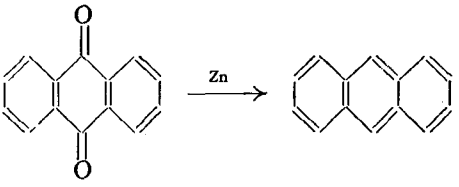


This reaction is usually carried out by heating the ketone under reflux or at 400–450° until water is no longer evolved. The yield of hydrocarbon is usually low, but often the Elbs reaction is the only means of preparing certain polynuclear hydrocarbons.

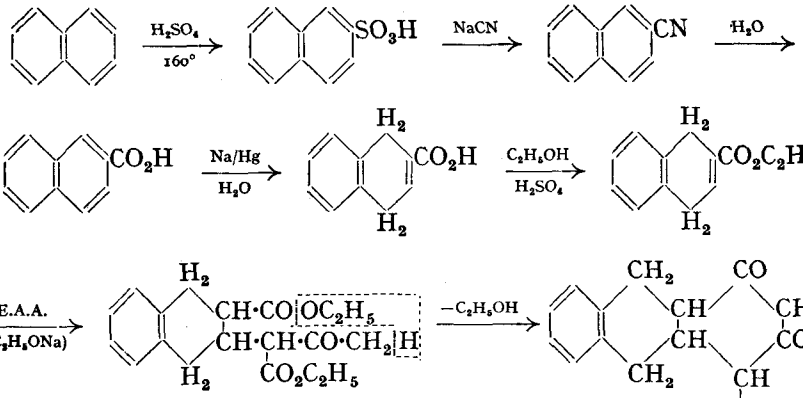
(v) Anthracene may be synthesised in the following ways starting with naphthalene (thereby showing the presence of the naphthalene nucleus in anthracene):

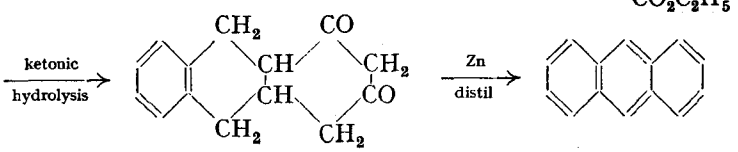
(*a*) 1 : 4-Naphthaquinone undergoes the Diels–Alder reaction with butadiene to form 1 : 4-dihydroanthraquinone. This, on oxidation with chromium trioxide in glacial acetic acid, gives anthraquinone:





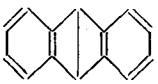
(*b*) In this method, naphthalene is converted into 1 : 4-dihydronaphthalene-2-carboxylic ester, and this is then made to undergo the Michael condensation (p. 279) with acetoacetic ester, etc.:



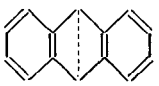


Positions of the double bonds in anthracene. Many structures have been proposed for anthracene.

Structure (I) was accepted by many because of the synthesis of anthracene from benzene and acetylene tetrabromide (see method (i)). This structure,



(I)

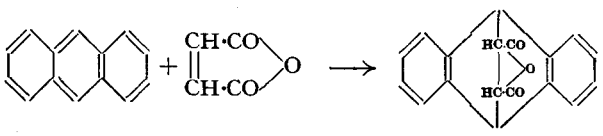


(Ia)

however, has been considered unlikely for various reasons, *e.g.*,

(i) The synthesis of anthracene from naphthalene (and other syntheses) indicates the absence of a *para*-bond.

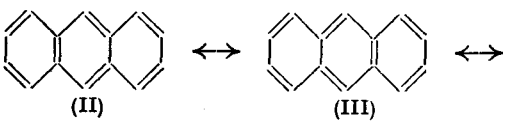
(ii) Anthracene adds on maleic anhydride to form *endoanthracenemaleic anhydride*, the addition occurring in the middle ring:



Since the middle ring behaves as a diene, this indicates it contains conjugated double bonds (*cf.* Diels–Alder reaction).

(iii) X-Ray analysis studies have shown that all the carbon atoms of anthracene lie in a plane, and that the distance between the *para*-carbon atoms in each ring is the same as in benzene. According to calculations of Oakley *et al.* (1949), however, (I) is a contributing structure to the resonance hybrid, *i.e.*, one of the resonating structures has a 9: 10 formal bond, (Ia) (*cf.* the Dewar structures of benzene, p. 507).

All the evidence points towards anthracene being a resonance hydrid of the four resonating structures (II–V):

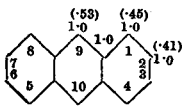


(II) (III)

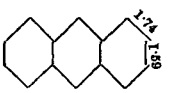
(IV) (V)

The resonance energy of anthracene is 105 k. cal./mole.

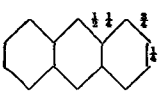
Anthracene is an *alternant hydrocarbon* (p. 528), and the π-electron densities are unity at all positions. The self-polarisabilities are in the following order: $9 > 1 > 2$ (I). Consequently position 9 will be the most reactive, then 1 and



(I)



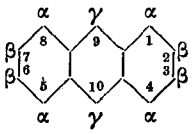
(II)



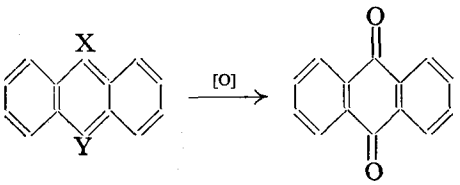
(III)

finally 2. (II) shows bond orders (obtained by calculation), and (III) shows double-bond characters (obtained by taking the average of the four resonating structures of anthracene; *cf.* naphthalene, p. 714).

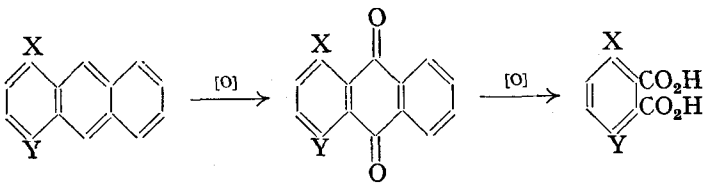
Isomerism of anthracene derivatives. There are three possible mono-substitution products: 1- or α-, 2- or β- and 9- or γ- (or *meso*-). There are 15 possible disubstitution products if both substituents are identical; if the substituents are not identical, the number of isomers is larger.



Orientation of anthracene derivatives. It is usually difficult to determine the orientation of anthracene derivatives except in the case where the substituents occupy the 9- and 10-positions. When a mono- or di-substituted anthracene is oxidised with dichromate and sulphuric acid, an *unsubstituted anthraquinone* is generally obtained if the substituents were in the 9 : 10-positions:

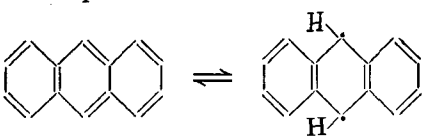


A *substituted anthraquinone* results if the substituents were not in the 9 : 10-positions, and on further oxidation phthalic acid or substituted phthalic acids are obtained, *e.g.*,

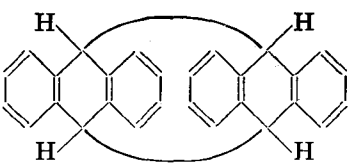


Orientation of anthracene derivatives may also be ascertained by unambiguous syntheses using method (iii).

Properties of anthracene. Anthracene is a colourless solid, m.p. 216°, with a blue fluorescence. It is insoluble in water and sparingly soluble in organic solvents. Anthracene is very reactive in the 9 : 10-positions. The reason for this is not clear, but it has been suggested that anthracene is in equilibrium with a free diradical (Clar, 1932). This may possibly account for the reactivity at these positions:

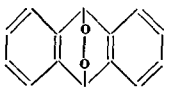


A saturated solution of anthracene in xylene, on exposure to light, forms crystals of the dimer, dianthracene (para-anthracene). X-Ray analysis studies led to the suggestion that the two anthracene molecules are linked in the 9 : 9′ : 10 : 10′-positions to give the structure shown (Hengstenberg, *et al.*, 1932). For this structure to be possible, each anthracene molecule must be folded about the line joining the 9 : 10-carbon atoms (since this dimer is actually a derivative of 9 : 10-hydroanthracene; the 9 : 10-carbon atoms are *tetrahedrally*



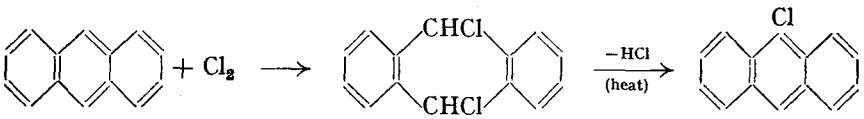
hybridised). This structure has been confirmed by ultraviolet spectrum studies of dianthracene (Weiss *et al.*, 1955). When dianthracene is melted, it reforms anthracene.

Anthracene adds on one molecule of oxygen in the presence of light to form a colourless photo-oxide (anthracene peroxide), the structure of which is also believed to be folded, since this oxide is also actually a derivative of 9 : 10-dihydroanthracene. Anthracene forms a red picrate (m.p. 138°) which dissociates into its constituents when treated with a large amount of ethanol; phenanthrene picrate is stable under these conditions.



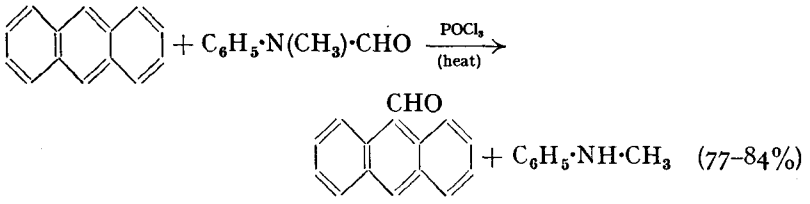
Anthracene undergoes the Diels–Alder reaction in the 9 : 10-positions (see above); phenanthrene does not give the Diels–Alder reaction. When reduced with sodium and *iso*pentanol, anthracene forms 9 : 10-dihydroanthracene, m.p. 107°, which is not fluorescent and which, on heating or on treatment with concentrated sulphuric acid, loses the two hydrogen atoms to reform anthracene. Catalytic reduction of anthracene using nickel at 200–250° gives, according to the amount of hydrogen used, tetra-, hexa- and octahydroanthracene, and finally perhydro-anthracene, $C_{14}H_{24}$ (the prefix *per* is often used to denote complete hydrogenation of a ring system).

When chlorine is passed into a cold solution of anthracene in carbon disulphide, anthracene dichloride is formed:



If this is heated or treated with alkali, hydrogen chloride is eliminated with the formation of 9-chloroanthracene. This is also obtained by chlorinating anthracene at 100°, together with some 9 : 10-dichloroanthracene. Bromine reacts similarly, *e.g.*, bromination of anthracene in boiling carbon tetrachloride solution gives 9 : 10-dibromoanthracene (yield: 83–88 per cent.). Sulphuryl chloride, at room temperature, converts anthracene into 9 : 10-dichloroanthracene. Oxidation of all these halogeno-anthracenes converts them into anthraquinone (thereby indicating the positions of the halogen atoms; *cf.* above).

Anthracene can be chloromethylated in the 9- and 9 : 10-positions, and can be formylated in the 9-position:

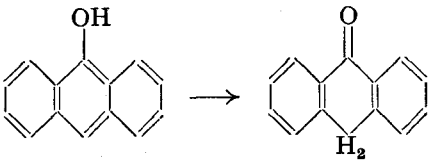


Attempts to nitrate anthracene with aqueous nitric acid lead to the formation of anthraquinone by oxidation. If, however, the nitration is carried out in acetic anhydride at 15–20°, 9-nitroanthracene (m.p. 145°) and 9 : 10-dinitroanthracene (m.p. 294°) can be isolated. Anthracene is readily sulphonated to a mixture of the 1- and 2-sulphonic acids, some disulphonic acids also always being obtained; the 2-position is favoured at high temperature. If the sulphonation of anthracene is carried out in glacial acetic acid, a mixture of about equal amounts of 1- and 2-anthracenesulphonic acid is obtained; these acids may be separated by means of their barium salts, that of the

former acid being more soluble. The 1-sulphonic acid shows no tendency to rearrange to the 2-acid (*cf.* naphthalenesulphonic acids, p. 716). With excess concentrated sulphuric acid, anthracene gives disulphonic acids, the 1 : 8- at low temperatures, and the 2 : 7- at high temperatures.

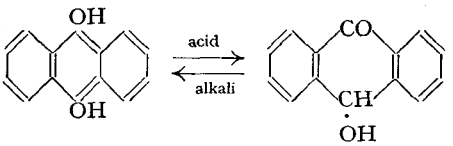
Hydroxyanthracenes. 1- and 2-*Hydroxyanthracenes* are known as **anthrols.** Each may be obtained from the corresponding anthracenesulphonic acid by alkaline fusion. 1-Anthrol is a yellow solid, m.p. 152°; 2-anthrol is a brownish solid which decomposes at 200°.

10-*Hydroxyanthracene*, also known as **anthranol,** is an unstable yellow solid, m.p. 120°, and when quickly heated, forms **anthrone** (10-*keto*-9 : 10-*dihydroanthracene*—the keto-group is numbered last and consequently its isomer is known as 10- and *not* 9-hydroxyanthracene). Anthrone is the stable form and is a colourless solid, m.p. 154°.



Since the hydrogen atom migrates across the ring, this type of tautomerism is called *trans-annular tautomerism.* Infrared spectroscopy studies by Flett (1948) indicate that solid anthrone does not exist in equilibrium with the enol form (anthranol). Anthrone may be prepared by heating *o*-benzylbenzoic acid with concentrated sulphuric acid, or by reducing anthraquinone with tin and hydrochloric acid in glacial acetic acid. Anthrone dissolves in warm dilute alkalis, and these solutions, on acidification, precipitate the enol form.

Reduction of anthraquinone with zinc dust and aqueous sodium hydroxide gives *anthracene*-9 : 10-*diol* or *anthraquinol* (*anthrahydroquinone*). This is a brown solid, m.p. 180°; its alkaline solutions (deep red) oxidise in air to give anthraquinone. When anthraquinol in alkaline solution is immediately acidified, it partly tautomerises to *oxanthranol*, m.p. 167° (*trans*-annular tautomerism):

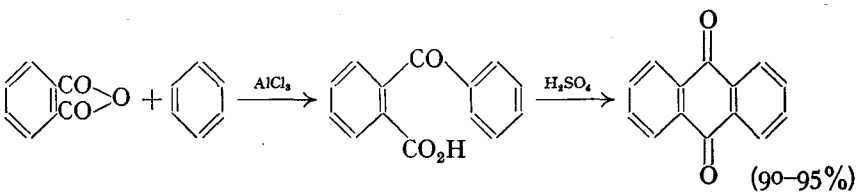


Anthracenecarboxylic acids. **1-** and **2-Anthroic acids** may be prepared by the hydrolysis of the corresponding cyanides (prepared by fusion of the sodium sulphonate with sodium cyanide). **9-Anthroic acid** may be prepared by hydrolysing its acid chloride which may be prepared by heating anthracene with oxalyl chloride at 160°. 9-Anthroic acid exhibits steric hindrance.

Anthraquinone (9 : 10-*dihydroanthracene*-9 : 10-*dione*). There are nine possible isomeric quinones of anthracene, but only three are known: 1 : 2-, 1 : 4- and 9 : 10-. The most important one is the 9 : 10-compound, and this is referred to simply as anthraquinone.

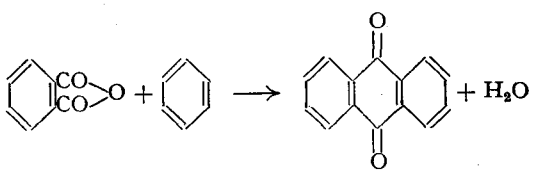
Before 1914, anthraquinone was made by oxidising anthracene with sodium dichromate and sulphuric acid (yield: 90 per cent.). Later, instead of isolating anthracene free from carbazole, the mixture of these two compounds was oxidised under conditions whereby anthracene was converted into anthraquinone and the carbazole completely oxidised. This method is

cheaper than the original, but the cheapest method to-day is a synthetic one:

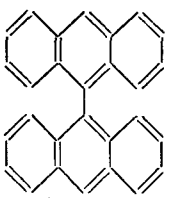


By using chlorobenzene or toluene instead of benzene, chloro- or methyl-anthraquinone is obtained; these are used in the manufacture of dyes.

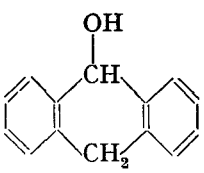
A possible future industrial method may be that of Sachanen and Caesar (1946), who showed that anthraquinone can be obtained in one step from phthalic anhydride and benzene by using a silica–alumina catalyst at 370°:



Anthraquinone is a pale yellow compound which sublimes in needles that melt at 268°. When distilled with zinc dust, or heated with hydriodic acid at 150°, anthraquinone forms anthracene. Anthraquinone is very stable and shows very little resemblance to *p*-benzoquinone, *e.g.*, it has no smell, is not very volatile, and is not reduced by sulphurous acid. When anthraquinone is reduced, the nature of the reduction product depends on the reducing agent used, *e.g.*, with tin and hydrochloric acid in acetic acid, anthrone is formed; using zinc instead of tin, the main product is *dianthryl*, (I); with zinc dust and aqueous sodium hydroxide, anthraquinol; and with zinc dust and aqueous ammonium hydroxide, 9 : 10-dihydroanthranol, (II):



(I)



(II)

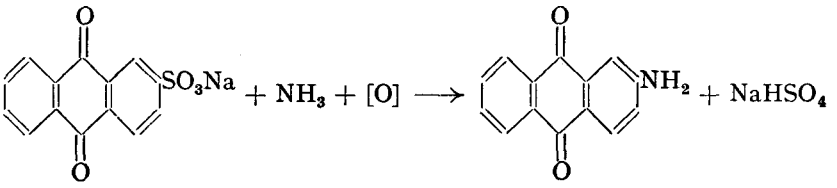
Nitration of anthraquinone with mixed acid gives 1-nitroanthraquinone; further nitration gives mainly 1 : 5- and 1 : 8-dinitroanthraquinones, and small amounts of the 1 : 6- and 1 : 7-dinitro-compounds. The nitro-group in the 1-position is very reactive, *e.g.*, it is replaced by an amino-group when 1-nitroanthraquinone is heated with ammonia.

Anthraquinone is very difficult to sulphonate with concentrated sulphuric acid, but it is readily sulphonated with oleum at 160°. The first product is the 2-sulphonic acid and a small amount of the 1-isomer; prolonged heating gives a mixture of 2 : 6- and 2 : 7-anthraquinonedisulphonic acids in about equal amounts. If mercuric sulphate is used as a catalyst, the sulphonation takes an entirely different course. The first product now is the 1-sulphonic acid, and then a mixture of the 1 : 5- and 1 : 8-disulphonic acids. The sulphonic acid group in the 1- or 2-positions is easily displaced;

e.g., when 1- or 2-anthraquinonesulphonic acid is treated with chlorine, the corresponding chloroanthraquinone is obtained.

Anthraquinone does not undergo the Friedel–Crafts reaction, and is halogenated with very great difficulty; in fact, monohalogeno-anthraquinone cannot be obtained directly.

2-Aminoanthraquinone, m.p. 304°, is very important as an intermediate in the preparation of indanthrene dyes. It is prepared industrially by heating the sodium salt of anthraquinone-2-sulphonic acid with a solution of ammonia, ammonium chloride and sodium arsenate under pressure at 200°. The sodium arsenate oxidises the liberated sulphite which otherwise would attack the amine produced.:

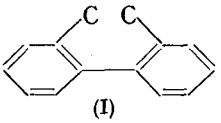


Alizarin (1 : 2-*dihydroxyanthraquinone*) is the most important dihydroxy-derivative of anthraquinone, and is used as a mordant dye (p. 806).

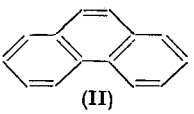
PHENANTHRENE

Phenanthrene, $C_{14}H_{10}$, is isomeric with anthracene; it is an example of an *angular* polynuclear hydrocarbon. It occurs in the anthracene oil fraction of coal-tar, and is separated from anthracene by means of solution in solvent naphtha (see p. 726). Phenanthrene is structurally related to certain alkaloids, *e.g.*, morphine, and to the steroids, *e.g.*, cholesterol.

Structure of phenanthrene. When oxidised with sodium dichromate and acetic acid, phenanthrene forms phenanthraquinone which, on further oxidation with dichromate and sulphuric acid, gives diphenic acid. This, on distillation with soda-lime, gives diphenyl. The structures of the last two compounds are known. Therefore phenanthrene contains the skeleton (I).



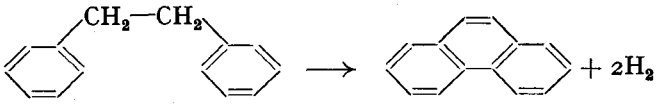
(I)



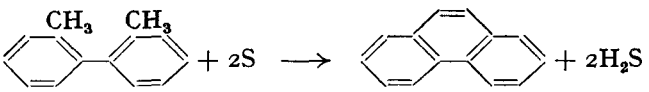
(II)

This is equivalent to $C_{14}H_8$. Thus two hydrogen atoms are missing; these may be fitted in by closing the middle ring, *i.e.*, a possible structure for phenanthrene is (II). This structure has been amply confirmed by many syntheses.

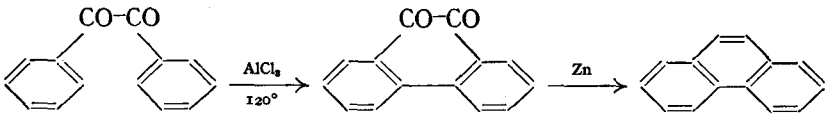
Synthesis of phenanthrene. (i) By passing 2 : 2′-dimethyldiphenyl, dibenzyl or stilbene through a red-hot tube; the yields are poor in each case:



An interesting preparation is the *cyclo*dehydrogenation of 2 : 2′-dimethyldiphenyl by means of sulphur:

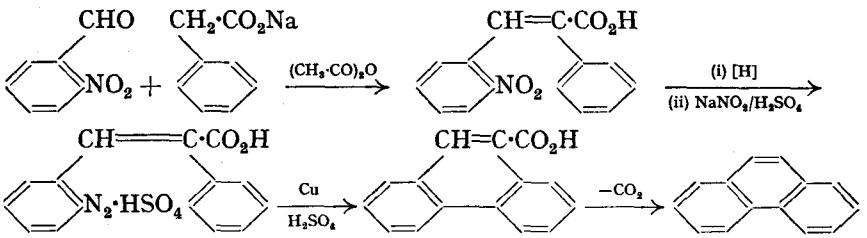


(ii) By treating benzil with aluminium chloride at 120° and then heating the product, phenanthraquinone, with zinc dust:



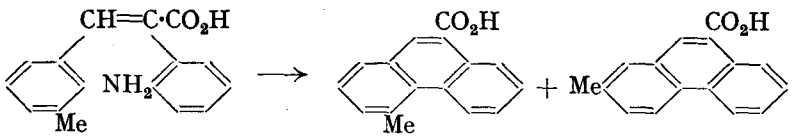
(iii) By treating *o*-bromobenzyl bromide with sodium; anthracene is also formed (see method ii, p. 727).

(iv) **Pschorr synthesis** (1896). This is carried out by heating *o*-nitrobenzaldehyde with sodium β-phenylacetate in the presence of acetic anhydride (Perkin's reaction), reducing and diazotising the product, α-phenyl-*o*-nitrocinnamic acid, and treating the diazonium salt with sulphuric acid and copper powder. Phenanthrene-9-carboxylic acid is produced and this, on strong heating, forms phenanthrene:

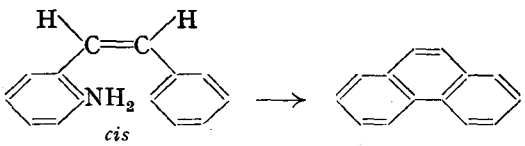


In some cases ring closure of the diazonium salt occurs spontaneously without the addition of copper powder.

The Pschorr synthesis offers a means of preparing substituted phenanthrenes with the substituents in known positions. In those cases, however, where isomerism in the cyclised product is possible, it is usual to obtain both isomers, *e.g.*,

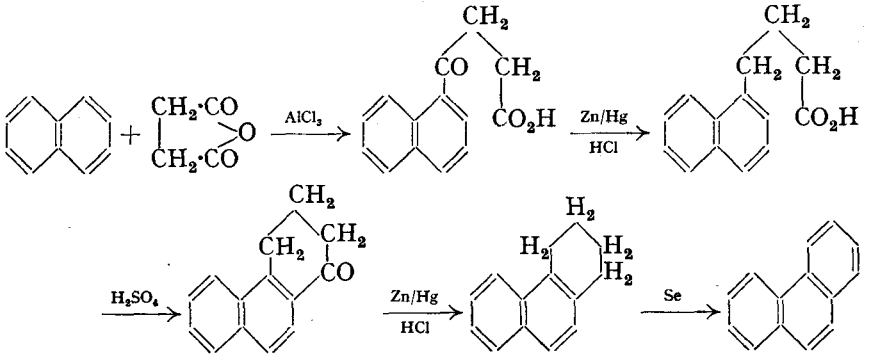


A further point to note is that since ring closure is effected between two rings, these rings must be in the *cis* position, *e.g.*, *cis*-*o*-aminostilbene gives phenanthrene, but the ***trans*** isomer does not.



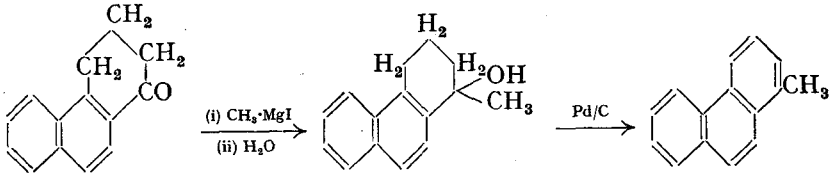
The Pschorr synthesis is really an example of intramolecular phenylation. The uncatalysed decomposition is believed to proceed by the nucleophilic unimolecular mechanism (see p. 524). In the presence of copper, however, there is much evidence to show that the decomposition occurs by a homolytic mechanism (*cf.* p. 585).

(v) **Haworth synthesis** (*cf.* naphthalene):

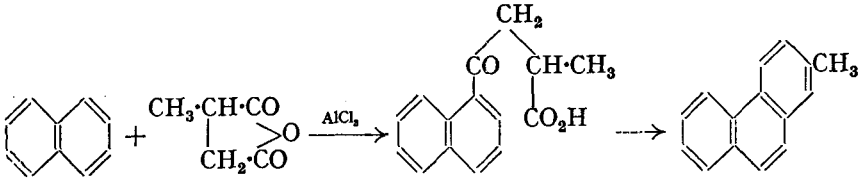


Naphthalene also condenses with succinic anhydride in the 2-position, but this also gives phenanthrene when treated as above; no anthracene is formed since ring closure in only the 1-position of naphthalene, and not in 3.

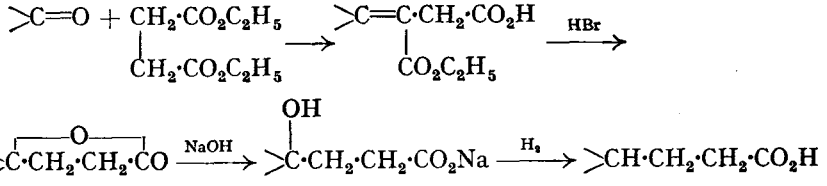
The Haworth synthesis is very useful for preparing alkylphenanthrenes with the alkyl groups in known positions; *e.g.*, after ring closure, 1-methylphenanthrene may be obtained by the action of methylmagnesium iodide on the ketone, etc.:



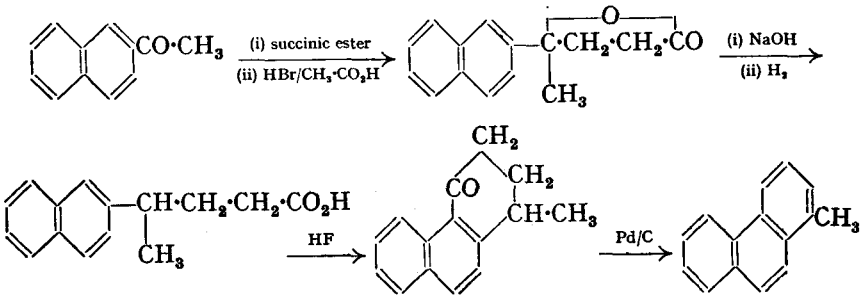
By using methylsuccinic anhydride instead of succinic anhydride, a methyl group can be introduced into the 2-position:



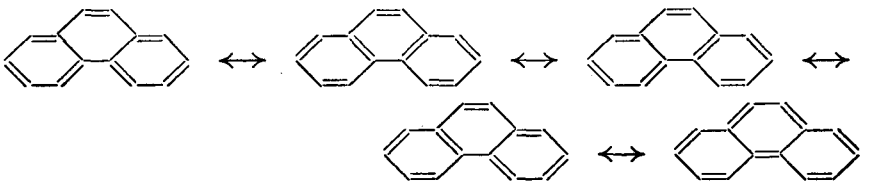
(vi) **Stobbe condensation** (1893). This is the condensation between succinic ester and a carbonyl compound in the presence of sodium ethoxide. Johnson (1944) has improved the yield by using potassium *tert.*-butoxide in *tert.*-butanol as the condensating agent, and has used this method to introduce a propionic acid residue at the site of the carbonyl group in an aromatic ketone. The condensation product is refluxed with concentrated hydrobromic acid in glacial acetic acid and the γ-lactone formed is catalytically reduced (using copper oxide-chromic oxide) via the sodium salt:



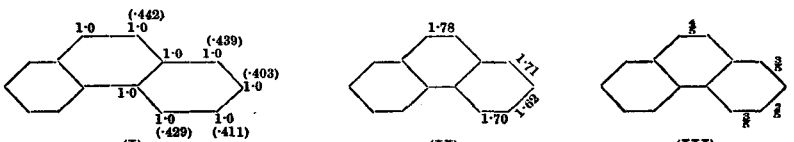
Johnson has used this procedure to prepare polynuclear compounds, *e.g.*, 1-methylphenanthrene from 2-acetylnaphthalene. After introduction of the propionic acid residue at the site of the carbonyl group, the ring is closed by means of anhydrous hydrogen fluoride, and the product dehydrogenated over heated palladium on charcoal:



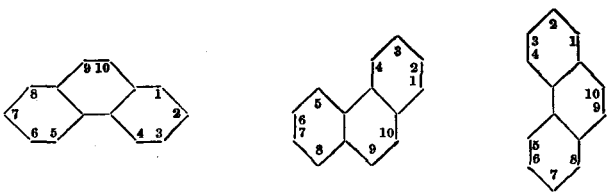
Positions of the double bonds in phenanthrene. Phenanthrene is best represented as a resonance hybrid of 5 resonating structures (its resonance energy is 105 k. cal./mole):



(I) shows the charge densities and self-polarisabilities, (II) the bond orders, and (III) the double-bond character in phenanthrene (*cf.* naphthalene, p. 714).



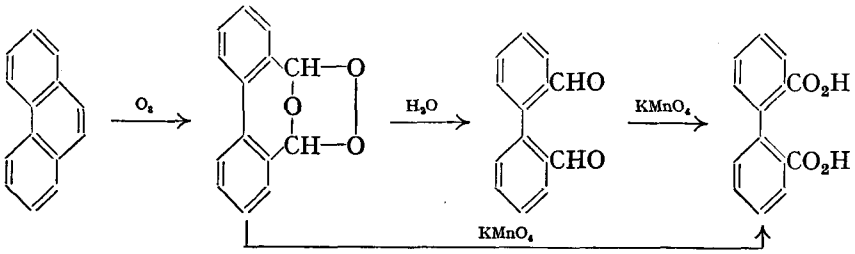
Isomerism of phenanthrene derivatives.



The formula of phenanthrene may be written in the three ways shown. There are 5 monosubstitution products possible: 1, 2, 3, 4 and 9. If the two substituents are identical, then 25 disubstitution products are possible. Due to the great number of isomers, derivatives of phenanthrene are usually prepared synthetically and not by direct substitution in the phenanthrene nucleus.

Properties of phenanthrene. Phenanthrene is a white solid, m.p. 99°; its solution in benzene shows a blue fluorescence. It is very reactive in

the 9 : 10-positions, and this reactivity may possibly be due to the large amount ($\frac{4}{5}$) of double bond character; *e.g.*, phenanthrene is readily catalytically reduced (using copper oxide-chromic oxide) to 9 : 10-dihydrophenanthrene, and it adds on bromine to form 9 : 10-phenanthrene dibromide. These addition reactions occur almost as easily as with a pure ethylenic bond. Dichromate in glacial acetic acid oxidises phenanthrene to phenanthraquinone. Schmitt *et al.* (1955) have prepared a stable monoozonide of phenanthrene. This has been shown to be the 9 : 10-compound by conversion into diphenic acid.



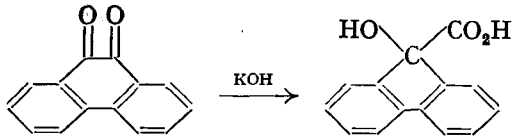
When treated with bromine in the presence of iron as halogen carrier, phenanthrene forms 9-bromophenanthrene. This is the starting point of 9-substituted phenanthrenes, *e.g.*, when heated with cuprous cyanide at 260°, 9-bromophenanthrene forms the corresponding cyano-compound; this may be hydrolysed to phenanthrene-9-carboxylic acid. Phenanthrene undergoes the Friedel–Crafts reaction mainly in the 3-, and to a small extent, in the 2-position. It is chloromethylated in the 9-position. When nitrated phenanthrene gives a mixture of three mononitro-derivatives, the 3-isomer predominating. Sulphonation of phenanthrene gives a mixture of 1-, 2-, 3- and 9-phenanthrenesulphonic acids, and the ratio of these isomers depends on the temperature.

Hydroxyphenanthrenes. Five *phenanthrols* are known: 1 , 2-, 3-, 4- and 9-, 3 : 4-Dihydroxyphenanthrene is a degradation product of morphine (an alkaloid).

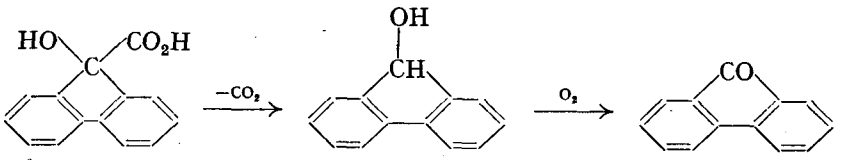
Phenanthraquinone (9 : 10-*dihydrophenanthrene*-9 : 10-*dione*) may be synthesised from benzil (method ii, p. 735), but it is conveniently prepared by oxidising phenanthrene with sodium dichromate or chromium trioxide in glacial acetic acid (yield is excellent).

Phenanthraquinone is an orange solid, m.p. 208°, which is odourless and not steam-volatile. It combines with one or two molecules of hydroxylamine to form phenanthraquinone monoxime and dioxime, respectively, and it is reduced by sulphurous acid to **phenanthrene-9 : 10-diol** (*phenanthraquinol*). In all of these reactions phenanthraquinone resembles *o*-benzoquinone.

When nitrated, phenanthraquinone gives a mixture of 2- and 4-nitrophenanthraquinones; more vigorous nitration produces a mixture of the 2 : 7- and 4 : 5-dinitro-compounds. Oxidation with sodium dichromate and sulphuric acid converts phenanthraquinone into diphenic acid. When warmed with alkali, phenanthraquinone undergoes the benzilic acid rearrangement (p. 707) to form 9-hydroxyfluorene-9-carboxylic acid:



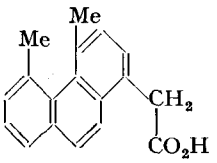
This, on heating in air, eliminates carbon dioxide and the product, fluorenol, is oxidised to fluorenone:



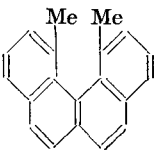
Phenanthraquinone readily reacts with *o*-phenylenediamines to form phenazines which, since they are insoluble in many organic solvents, are very useful for characterising *o*-phenylenediamines (see also p. 579).

1 : 2-, 1 : 4- and 3 : 4-Phenanthraquinones have also been prepared.

Molecular overcrowding. Optical activity can arise from restricted rotation about a single bond, but it is also possible that, because of steric repulsion between groups, the molecule may become distorted due to molecular overcrowding in which the strain cannot be relieved by rotation as in the diphenyls. One example of this is the phenanthrene derivative (I). The



(I)



(II)

phenanthrene nucleus is planar, and substituents lie in this plane. If, however, fairly large groups are in positions 4 and 5, there will not be enough room to accommodate both groups in the plane of the nucleus. This leads to strain due to molecular overcrowding, and this strain is relieved by bending of substituents out of the plane of the nucleus and/or buckling of the aromatic rings. Such a molecule will not be planar, and hence is asymmetric and consequently should be resolvable. Newman *et al.* (1940, 1947) have partially resolved (I), and also (in 1955) prepared the optically active forms of (II) (see also p. 688).

QUESTIONS

1. Discuss the preparation and properties of diphenyl and diphenic acid.
2. Starting with benzene or toluene, show how you would synthesise:—(*a*) 4 : 4′-dimethyldiphenyl, (*b*) 2 : 2′-aminodiphenyl, (*c*) benzidine, (*d*) dibenzyl, (*e*) stilbene, (*f*) benzoin, (*g*) deoxybenzoin, (*h*) hydrobenzoin, (*i*) benzil, (*j*) benzilic acid, (*k*) diphenylacetic acid, (*l*) 2 : 4 : 6-trinitrostilbene.
3. How may each of the following compounds be prepared:—(*a*) CH_2Ph_2, (*b*) $CHPh_3$, (*c*) CPh_4, (*d*) C_2Ph_6?

Name the compounds and state the conditions under which they are formed when each of the above hydrocarbons is treated with:—(*a*) HNO_3, (*b*) H_2SO_4, (*c*) Br_2, (*d*) I_2, (*e*) oxidising agents, (*f*) NO, (*g*) Na.

4. Write an essay on the preparation and properties of free radicals.
5. Formulate the course of the reaction when each of the two benzil monoximes and three benzil dioximes undergoes the Beckmann transformation.
6. Write an account of the analytical and synthetic evidence for the structure of:—(*a*) naphthalene, (*b*) anthracene, (*c*) phenanthrene.
7. Name the compounds and state the conditions under which they are formed when naphthalene, anthracene and phenanthrene are each treated with:—(*a*) reducing agents, (*b*) oxidising agents, (*c*) Br_2, (*d*) MeI, (*e*) HCHO, (*f*) HNO_3, (*g*) H_2SO_4, (*h*) Na, (*i*) AcCl, (*j*) SO_2Cl_2.
8. Describe the preparation and properties of:—(*a*) 1-, 2- and 10-hydroxyanthracenes, (*b*) anthrone, (*c*) anthraquinone, (*d*) phenanthraquinone.

9. Starting with any aromatic hydrocarbon you like, show how you would synthesise:—1 : 5-dichloronaphthalene, (*b*) 7-chloro-1-naphthylamine, (*c*) 2-naphthoic acid, (*d*) 1-naphthylacetic acid, (*e*) 2-bromonaphthalene, (*f*) 2 : 6-dihydroxynaphthalene, (*g*) indene, (*h*) acenaphthene, (*i*) 2-chlorofluorene, (*j*) 2-nitroanthracene, (*k*) 9-anthroic acid, (*l*) 2-chloroanthraquinone, (*m*) 3-chlorophenanthrene, (*n*) 1 : 2-dimethylphenanthrene, (*o*) 9-phenanthroic acid.

10. Define and give examples of:—(*a*) Fittig's reaction, (*b*) Ullmann's synthesis, (*c*) benzoin condensation, (*d*) benzilic acid rearrangement, (*e*) Haworth synthesis, (*f*) Fries rule, (*g*) Alternant hydrocarbon, (*h*) Elbs reaction, (*i*) Pschorr synthesis, (*j*) Stobbe condensation, (*k*) molecular overcrowding.

11. Discuss the optical activity of diphenyl compounds.

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CHAPTER XXX

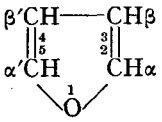
HETEROCYCLIC COMPOUNDS

HETEROCYCLIC compounds are cyclic compounds with the ring containing carbon and other elements, the commonest being oxygen, nitrogen and sulphur. There are a number of heterocyclic rings which are easily opened and do not possess any aromatic properties, *e.g.*, ethylene oxide, γ- and δ-lactones, etc. These are not considered to be heterocyclic compounds. Heterocycles are those compounds with five- or six-membered heterocyclic rings which are stable, contain conjugated double bonds, and exhibit aromatic character.

FIVE-MEMBERED RINGS

FURAN AND ITS DERIVATIVES

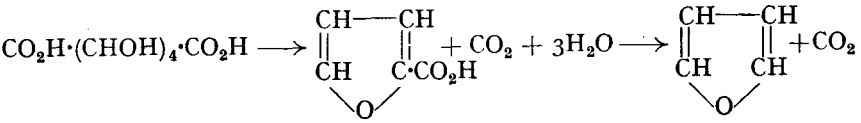
Furan (*furfuran*) contains one oxygen atom in its ring, and its structure is as shown. The position of side-chains or substituents is indicated by numbers (or by Greek letters), number 1 being given to the oxygen atom:



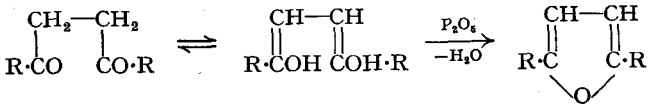
When a heterocyclic compound contains only one hetero-atom, this atom is always given the number 1. If the heterocyclic ring is part of a condensed system, the number given to the hetero-atom depends on the type of compound in question (see later).

There are two monosubstituted derivatives of furan, 2 (or α) and 3 (or β); there are four disubstitution products: 2 : 3 (α : β), 2 : 4 (α : β'), 2 : 5 (α : α') and 3 : 4 (β : β').

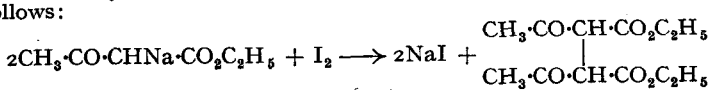
Furan is obtained when wood, especially pine-wood, is distilled. It may be prepared by the dry distillation of mucic acid, and heating the product, *furoic acid*, at its b.p.:



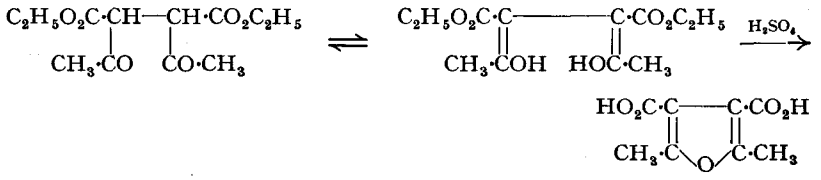
A general method of preparing furan derivatives is to dehydrate 1 : 4-diketones or dialdehydes with, *e.g.*, phosphorus pentoxide:



Alternatively, furan derivatives may be prepared from ethyl acetoacetate as follows:

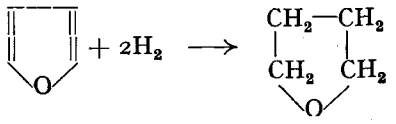


When diacetosuccinic ester is heated with dilute sulphuric acid, 2 : 5-dimethylfuran-3 : 4-dicarboxylic acid is formed:

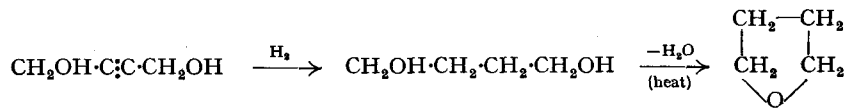


If ammonia is used instead of sulphuric acid, 2 : 5-dimethylpyrrole-3 : 4-dicarboxylic ester is obtained.

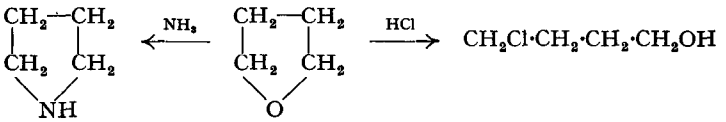
Furan is a colourless liquid, b.p. 32°, which turns green a pine splint moistened with hydrochloric acid. It is catalytically reduced (palladium-palladium oxide) to *tetrahydrofuran*:



Tetrahydrofuran may be manufactured synthetically from butyne-1 : 4-diol (*cf.* p. 274):

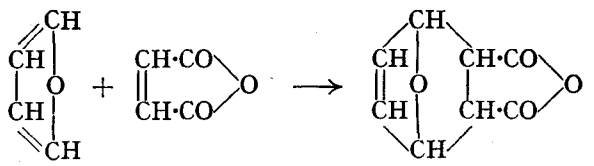


Tetrahydrofuran is a valuable solvent, and it can be made to react with carbon monoxide and water to give adipic acid. With ammonia it forms pyrrolidine, and with hydrogen chloride, tetramethylene chlorohydrin:



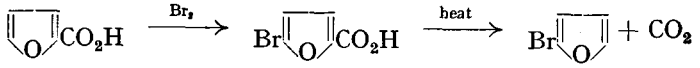
Kaluszyner (1957) has converted tetrahydrofuran into tetramethylene dibromide by reaction with sodium bromide and concentrated sulphuric acid. Bailey *et al.* (1960) have reduced tetrahydrofuran to *n*-butanol with a mixture of lithium aluminium hydride and aluminium chloride.

Furan undergoes the Diels–Alder reaction, and can be easily mercurated:



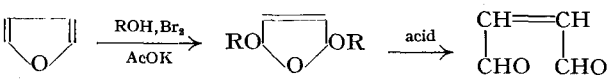
Substituents usually enter the 2- or 5-position if one is unoccupied, even though a *m*-orienting group, *e.g.*, NO_2 or SO_3H, is already present in one of these positions (some Friedel–Crafts reactions are exceptional, the alkyl radical entering the 3-position). When the 2- and 5-positions are both occupied, the substituent enters the 3-position. Furan is very readily attacked by oxidising agents, *e.g.*, it cannot be directly nitrated with nitric acid; the furan nucleus is completely oxidised. 2-Nitrofuran may be pre-

pared by nitrating furan with acetyl nitrate. Similarly, furan cannot be directly sulphonated (resinified products are obtained), but the 2-sulphonic acid may be prepared by the action of pyridine-sulphur trioxide on furan. If a negative group is present in the ring, then sulphonation can be carried out directly, *e.g.*, furoic acid gives furoic-5-sulphonic acid. The direct halogenation of furan is also not possible (the ring is destroyed), but if a negative group is present, halogenation can be carried out, *e.g.*, furoic acid gives 5-bromofuroic acid.



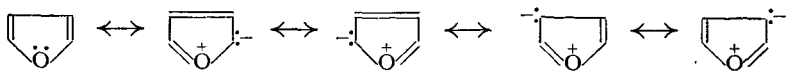
Furan undergoes the Gattermann reaction (p. 646) to form furfural. Since aluminium chloride attacks the ring, Friedel–Crafts reactions are best carried out with stannic chloride as catalyst. If, however, a negative group is present in the ring, then alkylation may be carried out using aluminium chloride.

The action of an alcoholic solution of bromine on furan in the presence of potassium acetate, sodium carbonate, etc., produces 2 : 5-dialkoxy-2 : 5-dihydrofuran (Jones, 1947). The most important reaction of these compounds is their conversion into unsaturated 1 : 4-dicarbonyl compounds on acid hydrolysis:



Reduction of the dialkoxy-compound followed by hydrolysis gives saturated 1 : 4-dicarbonyl compounds.

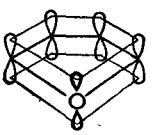
Furan behaves as a resonance hybrid. It appears that (I), (II) and (III) are



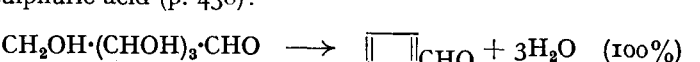
(I) (II) (III) (IV) (V)

the main contributing structures, since, as pointed out above, 2- (or 5-) substitution (with electrophilic reagents) occurs most readily. At the same time, (IV) and (V) would account for 3-substitution when the 2- and 5-positions are both occupied. Calculations of the bond lengths and comparison with the measured values show that (I) contributes about 85 per cent. to the resonance hybrid.

It should be noted that one of the lone pairs of the oxygen atom enters into resonance with the ring; we now have six electrons involved as in benzene. From the M.O. point of view, one lone pair of the oxygen atom conjugates with the four p_z electrons of the ring, thereby producing a " closed circuit " of six π-electrons (these will be in three M.O.s; *cf.* benzene, p. 509). Furan and all other *five-membered* rings are *non-alternant* compounds (p. 528), and since the oxygen atom has supplied *two* electrons to form the closed circuit, the π-electron densities at each carbon atom will be *greater* than unity, and are greatest at the 2- and 5-positions (see pyrrole, p. 750). Thus electrophilic attack will occur most readily at position 2 (or 5), but if these are occupied, and provided the substituent groups leave the ring π-electron distribution very little affected, electrophilic attack can now occur at position 3 (or 4), since the charge density here is also greater than unity.

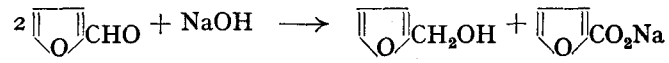


Furfural (*furfuraldehyde*) may be prepared by distilling pentoses with dilute sulphuric acid (p. 438):

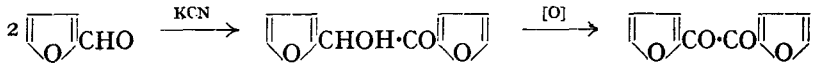


It is manufactured by treating oat husks, cotton-seed hulls or maize cobs with dilute sulphuric acid followed by steam distillation (the starting materials are rich in pentoses).

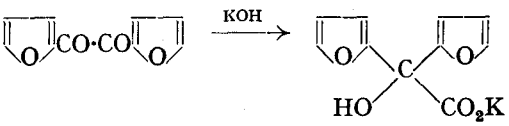
Furfural is a colourless liquid, b.p. 162°. Chemically it is very similar to benzaldehyde, *e.g.*, with aqueous sodium hydroxide furfural forms *furfuryl alcohol* and *furoic acid*:



With ethanolic potassium cyanide *furoin* is formed and this, on oxidation, gives *furil*:



When heated with aqueous potassium hydroxide, furil gives *furilic acid*:



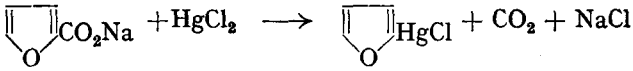
Furfural reacts with ammonia to form *furfuramide*, $(C_5H_4O)_3N_2$, and can undergo the Perkin reaction and the Claisen reaction. It is easily oxidised by silver oxide to the corresponding acid; it is oxidised by sodium chlorate to maleic acid, and Salchinkin *et al.* (1955) have shown that 30 per cent. hydrogen peroxide oxidises furfural to succinic acid. Furfural condenses with dimethylaniline in the presence of zinc chloride to form *furfuraldehyde green* (analogous to malachite green, p. 786). A characteristic reaction of furfural is the red coloration it gives with aniline and hydrochloric acid; it also turns green a pine splint moistened with hydrochloric acid (*cf.* furan, above).

Furfural is used for the preparation of dyes, plastics and maleic acid. It is also used as a solvent in synthetic rubber manufacture, and as an extraction liquid in petroleum refining.

Furfuryl alcohol, b.p. 170°, may be prepared by reducing furfural, or by means of the Cannizzaro reaction on furfural (see above).

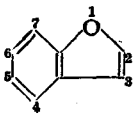
Furoic acid (**furan-2-carboxylic acid,** *pyromucic acid*) may be prepared by the dry disillation of mucic acid, or by the oxidation of furfural with acid dichromate.

It is a solid, m.p. 133°, and behaves more like an unsaturated aliphatic acid rather than benzoic acid (*cf.* furfural); *e.g.*, furoic acid is readily oxidised by alkaline permanganate, brominated by bromine vapour (it adds on four bromine atoms), and oxidised by bromine-water to fumaric acid. The sodium salt of furoic acid is decarboxylated by mercuric chloride to give the mercuri-chloride (this does not occur with furan-3-carboxylic acid):

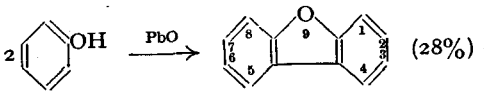


Furan-3-carboxylic acid occurs naturally.

Benzofuran (**benzfuran,** *coumarone*) occurs in coal-tar. It is a liquid, b.p. 174°, and is used in the manufacture of plastics.



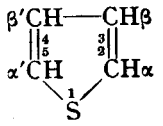
Dibenzofuran (**dibenzfuran,** *diphenylene oxide*) may be prepared by heating phenol with lead oxide at 150°:



It may also be prepared by passing diphenyl ether through a red-hot tube. It is a white solid, m.p. 87°.

THIOPHEN AND ITS DERIVATIVES

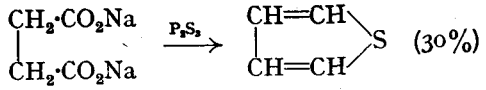
Thiophen occurs in coal-tar and shale oils. Its b.p. (84°) is close to that of benzene and hence it is difficult to separate from the benzene fraction obtained from coal-tar. Thiophen can be sulphonated more readily than benzene, and this property is used to separate the two compounds by repeatedly shaking benzene (from coal-tar) with cold concentrated sulphuric acid, whereby the water-soluble thiophensulphonic acid is formed. A better means of separation is to reflux the benzene with aqueous mercuric acetate whereupon thiophen is mercurated and benzene is not. Thiophen may be recovered from its mercurated derivative by distilling the latter with hydrochloric acid. The presence of thiophen in benzene may be detected by the *indophenin reaction.* This is the development of a blue colour when benzene is treated with isatin and sulphuric acid.



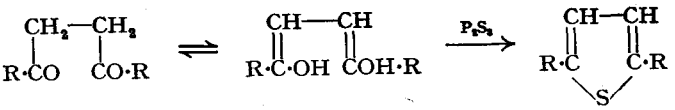
Thiophen may be prepared by passing a mixture of acetylene and hydrogen sulphide through a tube containing alumina at 400°.

$$2C_2H_2 + H_2S \longrightarrow C_4H_4S + H_2$$

This method is used commercially. It is also manufactured by reaction between *n*-butane and sulphur in the vapour phase. Since butadiene also forms thiophen under these conditions, and since sulphur is a dehydrogenating agent, the reaction with *n*-butane probably proceeds via butadiene as an intermediate. Thiophen may also be prepared by heating sodium succinate with phosphorus trisulphide:



Derivatives of thiophen may be prepared by heating 1 : 4-diketones with phosphorus trisulphide (*cf.* furan derivatives):



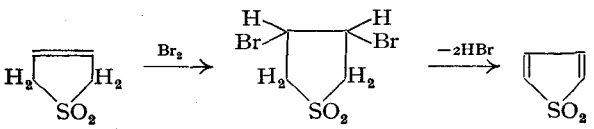
Thiophen is a liquid which is easily sulphonated, nitrated or chlorinated in the α-position. It was this close chemical similarity to benzene that masked the presence of thiophen in benzene from coal-tar. V. Meyer (1882) found that a sample of benzene prepared by heating sodium benzoate with soda-lime did not give the indophenin test. Subsequently he showed that it was a sulphur-containing compound, which he called *thiophene,* that was responsible for the indophenin reaction.

Thiophen undergoes substitution mainly in the 2-position; some substitution may also occur in the 3-position, particularly when alkylated. Thiophen is

fairly readily polymerised by acids, and stannic chloride is better than aluminium chloride for Friedel–Crafts reactions (*cf.* furan). It can be nitrated by fuming nitric acid in acetic anhydride to give mainly 2-nitrothiophen, and is readily sulphonated in the 2-position with *cold* concentrated sulphuric acid. 2-Halogenothiophens may be prepared by direct action between the halogen and thiophen under suitable conditions, *e.g.*, chlorination at 100° gives almost 100 per cent. 2-chlorothiophen. Thiophen may be catalytically hydrogenated to *thiophan* (tetrahydrothiophen), provided a very large amount of the catalyst (palladium) is used to overcome the poisoning effect of the sulphur (Mozingo *et al.*, 1945). On the other hand, reduction of thiophen with sodium in liquid ammonia gives 2 : 3- and 2 : 5-dihydrothiophen (Birch *et al.*, 1951).

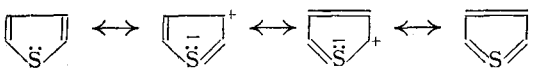
Various derivatives of thiophen may be prepared from the monobromo-derivative, *e.g.*,

Thiophen does not form sulphonium salts and cannot be oxidised to a sulphoxide or sulphone; hydrogen peroxide *opens* the thiophen ring, the sulphur being oxidised to sulphuric acid. Thiophensulphone (thiophen-1 : 1-dioxide) has, however, been prepared indirectly as follows (Melles *et al.*, 1953):



Many thiophen *derivatives* may be directly oxidised to the sulphone by perbenzoic acid.

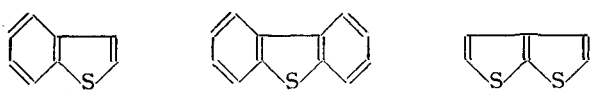
Thiophen is a resonance hybrid (V.B. method), or forms a " closed circuit ", the sulphur atom contributing *two* electrons (see furan, p. 743; replace the oxygen atom by sulphur). The problem of thiophen, however, appears to be more complicated than this because of the fact that sulphur can use a 3*d* orbital (oxygen cannot). The valency angle of C–S–C in thiophen is about 91°, and not the expected value of about 105°. Schomaker *et al.* (1939) explained this by assuming that some of the sulphur 3*d* orbitals are used in the V.B. structures (II–IV).



(I) (II) (III) (IV)

This has been supported and extended by calculations using the M.O. method (Longuet–Higgins, 1949).

A number of condensed thiophen systems are known, *e.g.*, *benzothiophen* (V) (also known as *thionaphthen* because it closely resembles naphthalene), *dibenzothiophen* (VI), and *thiophthen* (VII).

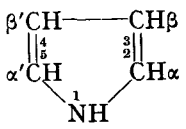


(V) (VI) (VII)

PYRROLE AND ITS DERIVATIVES

Pyrrole is a very important five-membered heterocyclic ring because its nucleus occurs in many natural compounds, *e.g.*, alkaloids, chlorophyll, hæmatin, etc. In addition to the 2- and 3-derivatives, pyrrole can form 1- or *N*-derivatives in which imino hydrogen is replaced.

Pyrrole occurs in coal-tar and bone oil. It may be isolated from bone oil by washing the latter with dilute alkali to remove acidic substances, then with acid to remove strongly basic substances, and finally fractionating. Pyrrole distils over in the fraction boiling between 100° and 150°, and may be purified by fusing with potassium hydroxide. Solid potassiopyrrole is formed and this, on steam distillation, gives pure pyrrole.



Pyrrole may be synthesised by passing a mixture of acetylene and ammonia through a red-hot tube:

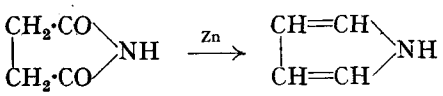
$$2C_2H_2 + NH_3 \longrightarrow C_4H_5N + H_2$$

It is conveniently prepared by distilling a mixture of ammonium mucate and glycerol at 200°:

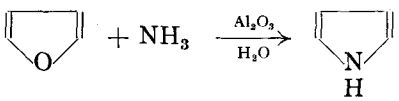
$$CO_2NH_4\cdot(CHOH)_4\cdot CO_2NH_4 \longrightarrow C_4H_5N + 2CO_2 + NH_3 + 4H_2O \quad (37\text{–}40\%)$$

If salts of mucic acid with primary amines are decomposed as above, then *N*-substituted pyrroles are obtained, *e.g.*, aniline mucate gives *N*-phenylpyrrole.

Pyrrole is also formed when succinimide is distilled with zinc dust:

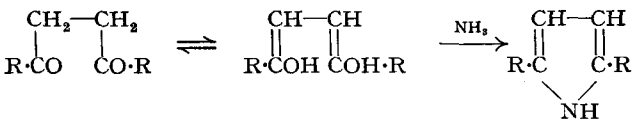


Pyrrole is manufactured by passing a mixture of furan, ammonia and steam over heated alumina as catalyst:

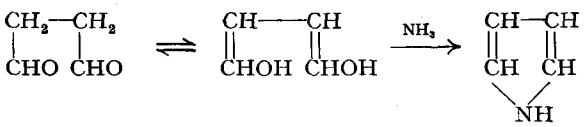


Many methods are available for synthesising pyrrole derivatives, *e.g.*,

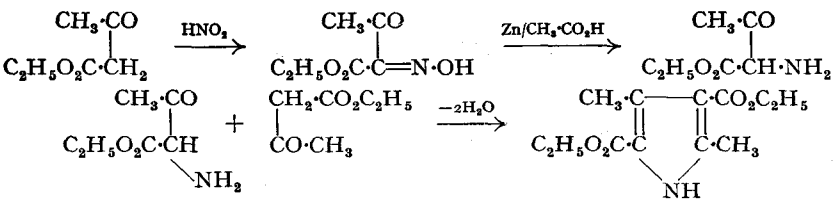
(i) **Paal–Knorr synthesis** (1885). This is carried out by treating a 1 : 4-diketone with ammonia, primary amines, hydrazines, etc., *e.g.*,



If succinaldehyde is used as the 1 : 4-dicarbonyl compound, pyrrole itself is obtained

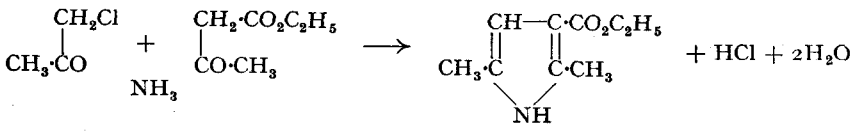


(ii) **Knorr synthesis** (1884; 1886). This is the most general method, and involves the condensation between an α-aminoketone and a β-diketone or β-keto-ester; *e.g.*, 3 : 5-dimethylpyrrole-2 : 4-dicarboxylic ester may be prepared from acetoacetic ester as follows:



Since α-aminoketones generally undergo self-condensation, they are best prepared *in situ* (as illustrated above).

(iii) **Hantzsch synthesis** (1890). This is the condensation between chloroacetone, a β-ketoester, and a primary amine, *e.g.*,



Some furan derivative is also formed.

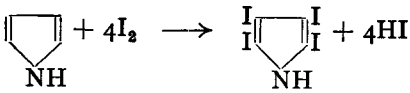
Properties of pyrrole. Pyrrole is a colourless liquid, b.p. 131°, which rapidly darkens on exposure to air. It is sparingly soluble in water but readily soluble in ethanol and ether. A characteristic reaction is the turning red of a pine splint moistened with hydrochloric acid when exposed to the vapour of pyrrole (and many of its derivatives). Pyrrole is a very weak secondary base, dissolving very slowly in cold dilute acids, and these solutions, on warming, form pyrrole-red (pyrrole polymers); concentrated acids resinify pyrrole rapidly. Pyrrole, however, gives 2-nitropyrrole (21 per cent. yield) when nitrated with nitric acid in acetic anhydride at −10° (Rinkes, 1934). Sulphonation of pyrrole with pyridine-sulphur trioxide in ethylene chloride gives the 2-sulphonic acid (Terentyev, 1949).

Pyrrole shows a number of resemblances to phenols and aromatic amines. The imino-hydrogen of pyrrole is replaceable by potassium, alkyl or acyl radicals. When pyrrole is heated with solid potassium hydroxide, potassiopyrrole is formed:

$$C_4H_4NH + KOH \longrightarrow C_4H_4\bar{N}K^+ + H_2O$$

Potassiopyrrole reacts with carbon dioxide and with chloroform as do phenols in the Kolbe–Schmitt and Reimer–Tiemann reactions, to form 2- and 3-pyrrolecarboxylic acids and pyrrole-2-aldehyde, respectively. It reacts with acetyl chloride at about 80° to form *N*-acetylpyrrole, and with methyl iodide at about 60° to give *N*-methylpyrrole. When these last two reactions are carried out at higher temperatures (150–220°), the 2- or 3-substituted product is obtained instead of the *N*-compound; this may be due to rearrangement of the *N*-compound (*cf.* Hofmann–Martius rearrangement, p. 574).

Pyrrole may be readily halogenated, the most important halogeno-pyrrole being tetraiodopyrrole, formed by the action of potassium iodide-iodine solution on pyrrole:

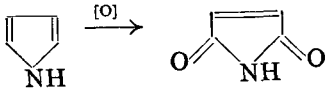


This is often used as a substitute (under the name of *iodole*) for iodoform, but is much more expensive. Pyrrole couples with diazonium salts in the 2-position in weakly acid solution, and in the 2- and 5-positions (to give the bisazo-compound) in alkaline solution. If the 2- and 5-positions are occupied by, *e.g.*, methyl groups, coupling takes place in the 3-position. When pyrrole is treated with methylmagnesium iodide, *N*-pyrrylmagnesium iodide is formed and this, on treatment with methyl iodide, gives mainly 3-methylpyrrole, and a little of the 2-isomer.

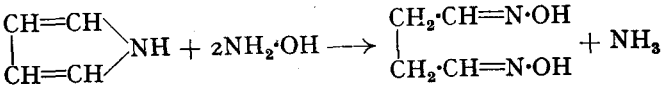
Pyrrole is mercurated with great difficulty. Experience has shown that the ease of mercuration of heterocyclic compounds varies considerably with the nature of the hetero-atom. Generally, those containing oxygen or

sulphur are easily mercurated (*cf.* thiophen), whereas those containing nitrogen are mercurated with great difficulty.

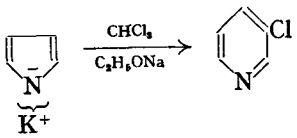
Pyrrole is oxidised by chromium trioxide in sulphuric acid to maleic-imide:



Alkaline hypochlorite (or hypobromite) converts pyrrole into dichloro- (or dibromo-) maleic-imide. When pyrrole is treated with hydroxylamine, *the ring is opened* and succinaldehyde dioxime is formed:



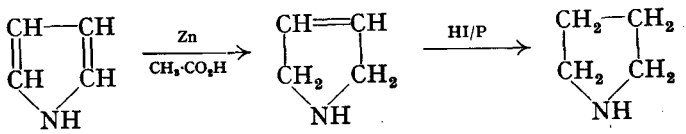
When potassiopyrrole is heated with chloroform and sodium ethoxide, *ring expansion* takes place, the product being 3-chloropyridine (*cf.* p. 117):



The yields are better if lithiopyrrole is used instead of potassiopyrrole (Alexander *et al.*, 1950).

The same result may be achieved by passing a mixture of pyrrole and chloroform through a glass tube at 550° (Rice *et al.*, 1955).

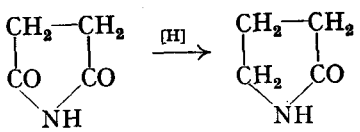
Reduction products of pyrrole. Pyrrole is reduced by zinc and acetic acid to **pyrroline** (2 : 5-*dihydropyrrole*), b.p. 91°. This, on heating with hydriodic acid and red phosphorus, gives **pyrrolidine** (*tetrahydropyrrole*), b.p. 88°:



Pyrrolidine may also be prepared by catalytically reducing pyrrole using nickel at 200°, or by the electrolytic reduction of succinimide. A potential source of pyrrolidine is its preparation by the action of ammonia on tetrahydrofuran (p. 742).

Pyrroline and pyrrolidine are both strong bases, and do not show any tendency to polymerise.

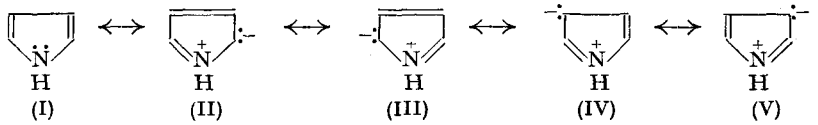
2-Pyrrolidone, m.p. 25°, may be prepared by the electrolytic reduction of succinimide:



2-Pyrrolidone is the *lactam* (*cf.* lactones) of γ-aminobutyric acid.

3-*Pyrrolidone* is also known.

Pyrrole behaves as a resonance hybrid, the main contributing structures being (I), (II) and (III). From the M.O. point of view, the lone pair on the nitrogen



(I) (II) (III) (IV) (V)

atom conjugates with the four p_z electrons of the ring, thereby producing a "closed circuit" of six π-electrons (which are accommodated in three M.O.s). Like all odd-membered rings, pyrrole is *non-alternant* (p. 528), and the charge densities will not be unity at each position in the molecule. Since the nitrogen atom has supplied *two* electrons to form the closed circuit, the charge density at each carbon atom is *greater* than unity, being greater at the α-positions than the β- (as shown by calculation). Hence electrophilic attack occurs most readily at the α-position. Had the nitrogen atom retained its lone pair, its charge density would have been 2, but owing to conjugation, it is less than this, and so acquires a small positive charge.

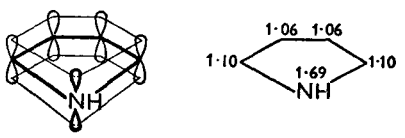
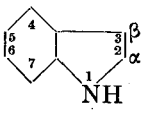
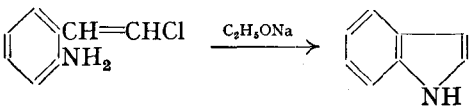


FIG. 30.1.

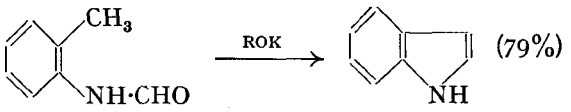
Indole (*benzopyrrole*) occurs in coal-tar, jasmine flowers and orange blossoms. Some indole derivatives, *e.g.*, indole-3-acetic acid, indole-3-propionic acid, etc., have great growth-promoting action on plants (and are known as *heteroauxins*). Indole is the parent substance of indigotin (p. 800). It may be synthesised in many ways, *e.g.*,



(i) **Lipp synthesis** (1884). This is carried out by heating *o*-amino-ω-chlorostyrene with sodium ethoxide.

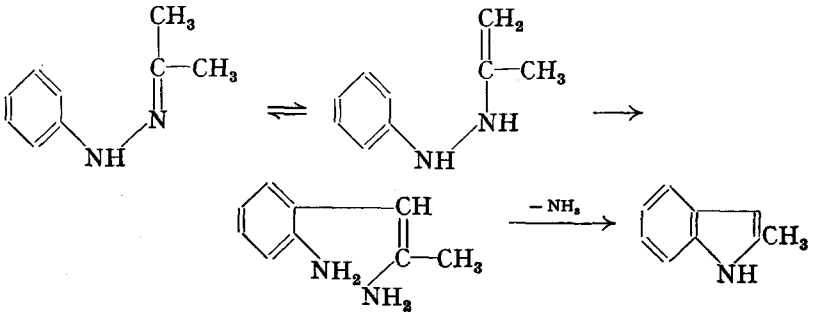


(ii) When heated with potassium alkoxides, formyl-*o*-toluidide gives indole (Friedman, 1948).



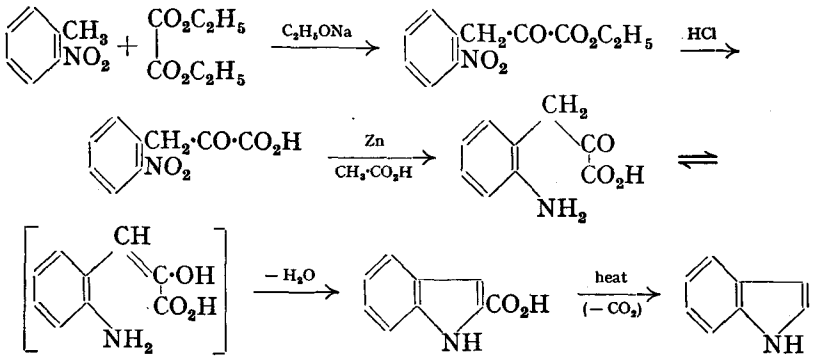
(iii) **Fischer's indole synthesis** (1886). This is the most important method of preparing indole derivatives, and is carried out by heating the phenylhydrazone or substituted phenylhydrazone of an appropriate aldehyde, ketone, or ketonic acid with zinc chloride as catalyst. Boron trifluoride has been found to be a very good reagent for converting phenylhydrazones into indole derivatives.

The mechanism of the reaction is uncertain, but a highly favoured one is that of Robinson (1918). According to him acetone phenylhydrazone forms 2-methylindole by first tautomerising, the tautomer then undergoing the *o*-benzidine rearrangement, and the diamino-compound so produced eliminating a molecule of ammonia with ring closure:



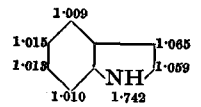
Allen *et al.* (1943) and Clusius *et al.* (1952), using ^{15}N, have shown that it is the nitrogen atom attached to the aromatic ring that is retained in the product, the other nitrogen atom being eliminated as ammonia.

(iv) **Reissert synthesis** (1897). This is a very good method, and is carried out with *o*-nitrotoluene (or its substituted derivatives) and ethyl oxalate as follows:

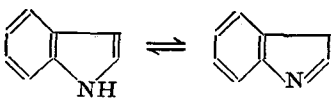


Indole is a crystalline solid, m.p. 52°. It resembles pyrrole in many of its properties, and is oxidised by ozone to indigotin.

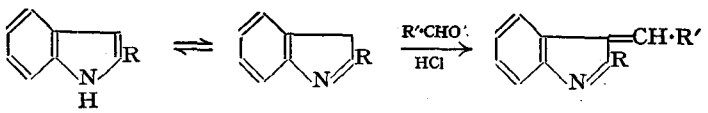
Indole is most readily substituted in the 3-position, *e.g.*, treatment with iodine gives 3-iodoindole; the Reimer–Tiemann reaction produces indole-3-aldehyde; the rearrangement of, for example, *N*-acetylindole gives 3-acetylindole. The calculated charge densities for indole are as shown.



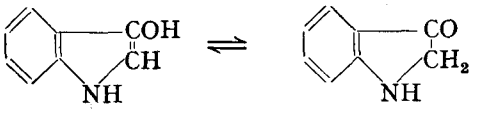
Indole behaves in some ways as a tautomeric substance, the tautomer being known as *indolenine*. Indolenine itself has never yet been isolated, but its



derivatives are known, and these may be prepared, *e.g.*, by condensation between indoles and aldehydes.

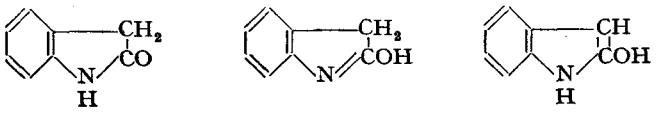


Indoxyl is the term usually applied to the keto-form of **3-hydroxyindole** (the enolic form):



Derivatives of both are known (see p. 802 for its preparation). Indoxyl is a bright yellow solid, m.p. 85°, and is readily oxidised in alkaline solution by air to indigotin.

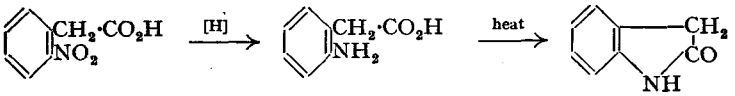
Oxindole. There are three possible formulæ for oxindole:



(I) (II) (III)

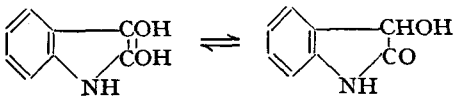
Chemical evidence was assumed to favour the *lactam* form (I), but (II) and (III) were also considered to be present (Julian *et al.*, 1935). This has been supported by infrared measurements (Bergmann, 1955), but O'Sullivan *et al.* (1956), from infrared measurements of oxindole in chloroform solution, believe that only (I) is present.

Oxindole may be prepared by reducing *o*-nitrophenylacetic acid with tin and hydrochloric acid.

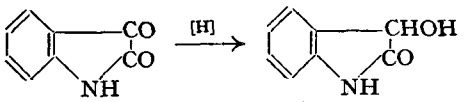


It is a colourless solid, m.p. 120°.

Dioxindole (3-*hydroxyoxindole*) is tautomeric with **2 : 3-dihydroxyindole:**

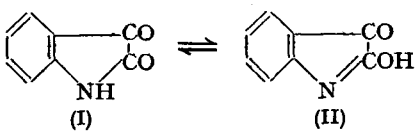


It may be prepared by reducing isatin with zinc and hydrochloric acid:



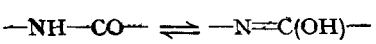
It is a colourless solid, m.p. 180°.

Isatin exists in two forms, the term *ψ*-isatin being applied to the *lactam* form (I), and isatin to the *lactim* form (II) (both are derivatives of 2 : 3-dihydroindole; and the name isatin is often applied to I):



(I) (II)

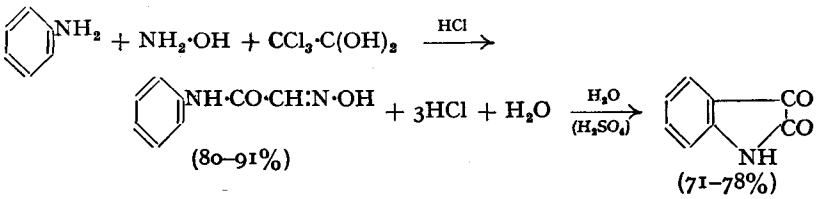
This is an example of the *amido–imidol* tautomeric system:



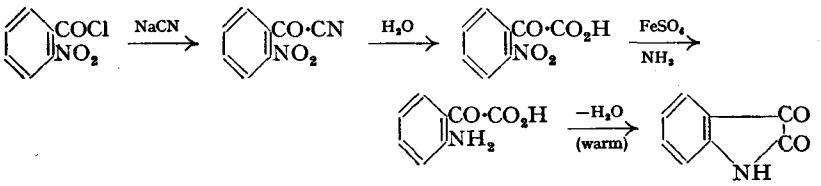
It appears to be the first case of tautomerism to be recognised. Isatin reacts as the lactam form towards most reagents, *e.g.*, the N atom is readily acetylated by

heating with acetic anhydride, and when the sodium salt is heated with methyl iodide, the *N*-methyl is formed. On the other hand, when the silver salt is heated with methyl iodide, the *O*-ether is obtained (*cf.* amides). Infrared measurements of isatin (and a series of substituted isatins), however, provide no support for the existence of a classical lactim structure in the solid state or in dilute chloroform solution (O'Sullivan *et al.*, 1956).

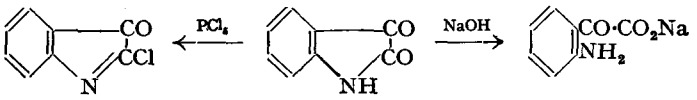
Isatin was first obtained by the oxidation of indigotin with nitric acid. It is best prepared by heating a solution of concentrated hydrochloric acid containing aniline, chloral hydrate, hydroxylamine and sodium sulphate. "*iso*Nitroso-acetanilide" (oximinoacetanilide) crystallises out and this, on treatment with concentrated sulphuric acid, forms isatin:



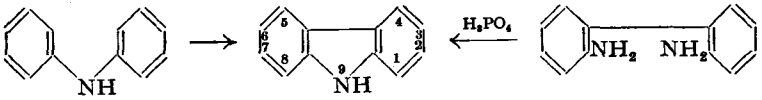
The following synthesis from *o*-nitrobenzoyl chloride clearly shows the structure of isatin (Claisen *et al.*, 1879):



Isatin is a red solid, m.p. 200°. With phosphorus pentachloride it forms *isatin chloride*, and with warm sodium hydroxide, *isatic acid*:



Carbazole (*dibenzopyrrole*) may be isolated from the anthracene fraction of coal-tar (see p. 726). It may be synthesised by passing diphenylamine through a red-hot tube, or better, by heating 2 : 2′-diaminodiphenyl at 200° with concentrated phosphoric acid (the yield is almost quantitative; Leditschke, 1953).



Carbazole is a colourless solid, m.p. 245°. Silver oxide converts it into N : N′-*dicarbazyl*, which is a colourless compound but gives coloured solutions due to its dissociation into free carbazyl radical (*cf.* p. 577). Carbazole is used in the preparation of polyvinylcarbazole plastics.

AZOLES

Azole is the suffix used for five-membered rings containing two or more hetero-atoms, at least one of which is nitrogen.

Nomenclature. (i) When the heterocyclic compound contains two or more hetero-atoms, the starting point is the hetero-atom of as high a group in the periodic table and as low an atomic number in that group. Thus the order of naming will be O, S, N.

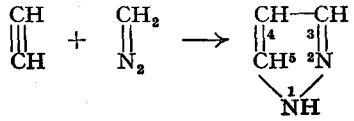
(ii) With the atom of the preferred kind as number 1, the ring is numbered in such a way that the hetero-atoms are given the lowest numbers possible.

(iii) Of two or more numberings conforming to rules (i) and (ii), the one that is chosen is that which assigns low numbers most nearly in the order of precedence established by rule (i).

(iv) Of two or more numberings conforming to rules (i)–(iii), the one that is chosen is that which gives hydrogen atoms the lowest numbers possible.

Hetero-atoms are indicated by prefixes: **O** by **oxa, S** by **thia** and **N** by **aza.**

Pyrazoles. Pyrazole may be prepared by passing acetylene into a cold ethereal solution of diazomethane.



Pyrazole is a colourless solid, m.p. 70°. It has aromatic properties, readily undergoing substitution (with the usual electrophilic reagents) in the 4-position.

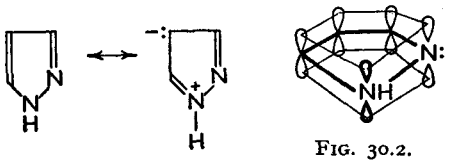
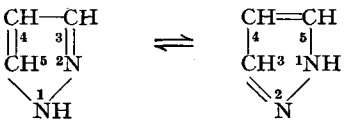
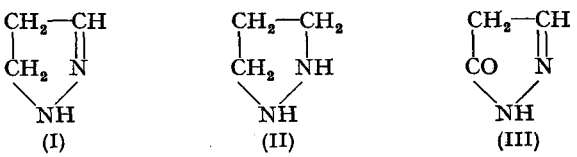


FIG. 30.2.

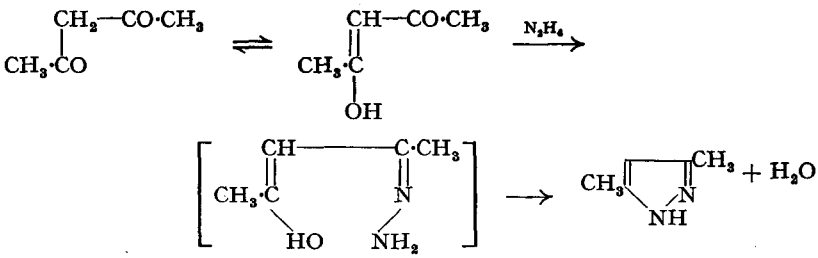
Pyrazole is a tautomeric substance; this cannot be demonstrated in pyrazole itself, but may be shown as follows. If pyrazole is tautomeric, then positions 3 and 5 are identical; if not tautomeric, these positions are different. When the phenyl group in 3-methyl-1-phenyl- and 5-methyl-1-phenylpyrazole is removed, *both* compounds give the *same* methylpyrazole. Hence positions 3 and 5 are equivalent, and this can only be explained by assuming that pyrazole is tautomeric.



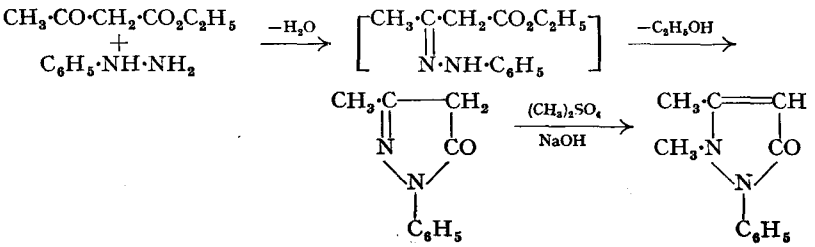
Pyrazole may be catalytically reduced to pyrazoline (I) and then to pyrazolidine (II). Both are stronger bases than pyrazole. 5-Ketopyrazoline or *pyrazol-5-one* is (III) (see below).



Pyrazole derivatives. One of the chief methods for preparing these is by reaction between hydrazines and 1 : 3-dicarbonyl compounds, *e.g.*, hydrazine and acetylacetone form 3 : 5-dimethylpyrazole.

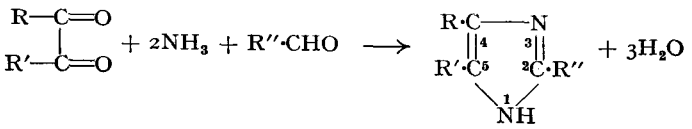


5-Pyrazolones are formed by reaction between hydrazines and β-ketonic esters, *e.g.*, 3-methyl-1-phenylpyrazolone from phenylhydrazine and ethyl acetoacetate. This, on methylation, gives *antipyrine* (*phenazone*, 2 : 3-dimethyl-1-phenyl-pyrazol-5-one), which is used in medicine as a febrifuge.

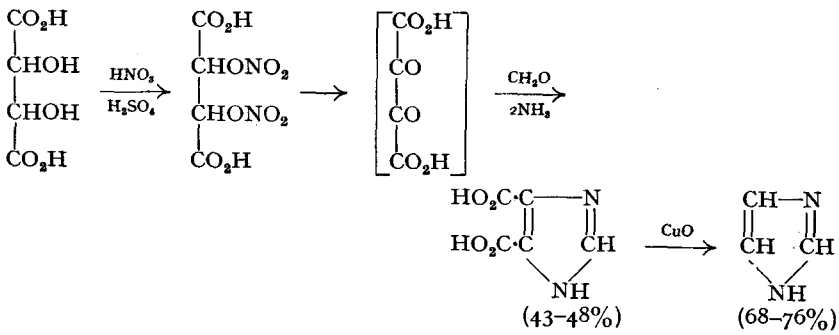


Glyoxalines (iminazoles, imidazoles). Imidazole is isomeric with pyrazole, and occurs in the purine nucleus (p. 387) and in histidine (p. 323).

A general method for preparing imidazoles is by reaction between α-dicarbonyl compounds, ammonia and an aldehyde.

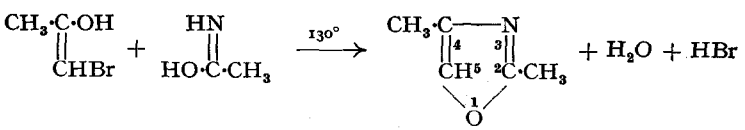


Glyoxal, ammonia and formaldehyde produce imidazole itself. This, however, is best prepared as follows: tartaric acid is treated with a mixture of concentrated nitric and sulphuric acids, the product, tartaric acid dinitrate (" dinitrotartaric acid "), then treated with formalin and ammonia solution, and the imidazole-4 : 5-dicarboxylic acid formed is then decarboxylated by heating with copper oxide.



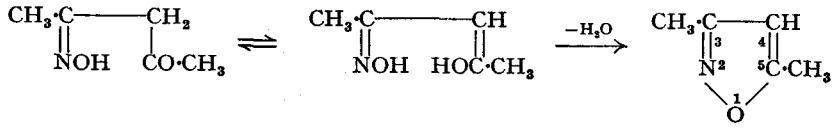
Imidazole is a solid, m.p. 90°. It appears to be tautomeric (positions 4 and 5 are identical).

Oxazoles are formed by reaction between acid amides and α-halogeno-ketones, *e.g.*, acetamide and bromoacetone form 2 : 4-dimethyloxazole (the enol forms have been written to simplify the equation).

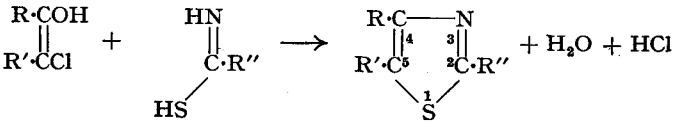


Only derivatives of oxazole are known.

***iso*-Oxazoles.** These are formed by warming the mono-oximes of 1 : 3-diketones, *e.g.*, 3 : 5-dimethyl*iso*oxazole from acetylacetonemonoxime.

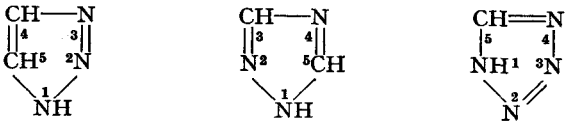


Thiazoles may be prepared by reaction between an α-chloro-carbonyl compound and a thioacid amide (enol forms have been written in the equation).



Thiazole itself may be prepared from chloroacetaldehyde and thioformamide. Thiazole is a liquid, b.p. 117°. Vitamin B_1 contains the thiazole nucleus.

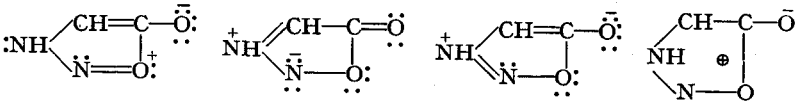
Triazoles and **tetrazoles** are also known.



osotriazole triazole tetrazole

All are tautomeric substances. Osotriazoles may be prepared by oxidising osazones (p. 444).

A very remarkable five-membered ring is that in **sydnones**. These were prepared by Earl and Mackney (1935), and the peculiar feature of these compounds is that it is not possible to give them a structure which represents covalent bonds by the usual paired electrons, *e.g.*, sydnone (I, II, III). Dipole and infrared studies indicate this compound is a resonance hybrid; it has been named a



(I) (II) (III) (IV)

meso-ionic structure and may be written as (IV) (Baker *et al.*, 1955). Sydnones possess an aromatic sextet; they undergo halogenation and nitration at the CH carbon atom.

SIX-MEMBERED RINGS

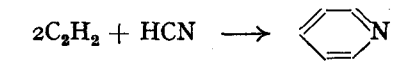
PYRIDINE AND ITS DERIVATIVES

Pyridine occurs in the light oil fraction of coal-tar and in bone oil, and is a decomposition product of several alkaloids. Pyridine is obtained from light oil by treating the latter with dilute sulphuric acid. This dissolves pyridine and other basic substances. The acid layer is neutralised with sodium hydroxide and the liquid repeatedly fractionated.

Pyridine is a colourless liquid, b.p. 115°, with a disagreeable odour. It is completely miscible with water and is hygroscopic. It is basic, and is only very slowly attacked by boiling concentrated nitric acid or chromic acid. It resembles benzene in many of its properties and this partly led Körner (1864) to adopt the ring structure for pyridine, a structure which is confirmed by synthesis.

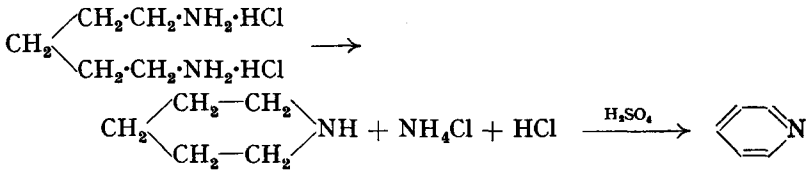
Synthesis of pyridine. There are many methods available for the synthesis of pyridine, *e.g.*,

(i) By passing a mixture of acetylene and hydrogen cyanide through a red-hot tube:

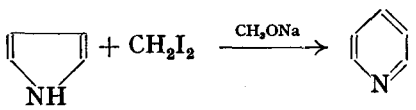


(ii) By passing a mixture of formaldehyde (1 part by volume), acetaldehyde (2 parts) and ammonia (1 part) over heated alumina (other compounds are also formed).

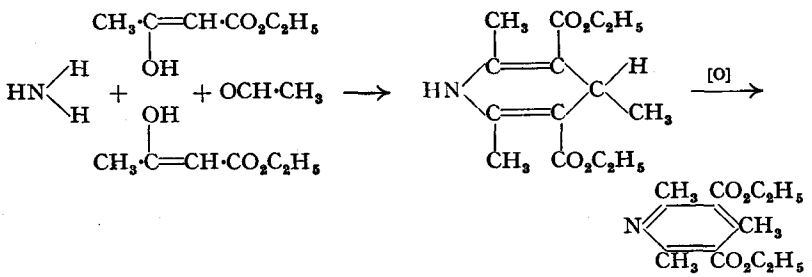
(iii) By heating the hydrochloride of pentamethylenediamine and oxidising the product, *piperidine*, with concentrated sulphuric acid at 300°:



(iv) By heating pyrrole with methylene iodide and sodium methoxide at 200° (*cf.* p. 475):

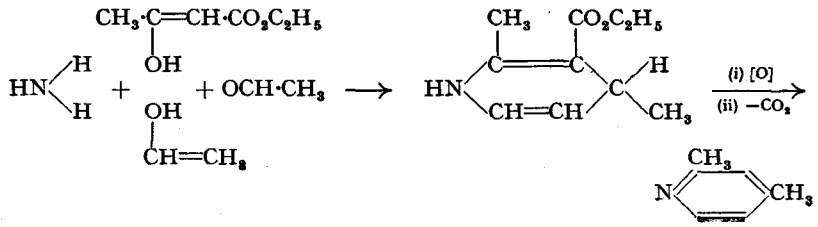


Pyridine derivatives may be prepared by various methods. One important method is the *Hantzsch pyridine synthesis* (1882). A β-dicarbonyl compound (2 mol.) is condensed with an aldehyde (1 mol.) and ammonia (1 mol.). The dihydropyridine derivative is obtained, and this gives the pyridine derivative on oxidation with nitric acid, *e.g.*,



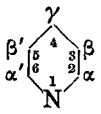
This ester can be hydrolysed and then decarboxylated to 2 : 4 : 6-trimethylpyridine.

If one molecule of ethyl acetoacetate and two molecules of acetaldehyde are used, the *dimethyl* derivative is obtained.



Reactions of pyridine. Pyridine can undergo substitution just as does benzene, but less easily than the latter. There are three possible mono-substitution products, and six disubstitution products if the two substituent groups are identical.

(i) At ordinary temperatures, pyridine adds on halogen to form dihalides, *e.g.*, $C_6H_5\overset{+}{N}Br\}Br^-$. If, however, pyridine and bromine (or chlorine) are passed over a catalyst of pumice or charcoal at 300°, a mixture of 3-bromo-pyridine and 3 : 5-dibromopyridine is obtained; at 500° a mixture of the 2- and 2 : 6-bromo-derivatives is obtained. At 300° the reaction is probably electrophilic in character, whereas at 500° the mechanism is probably via free radicals. 3-Chloropyridine may be obtained by heating potassiopyrrole with chloroform and sodium ethoxide (see p. 749). 2- and 4-Chloropyridines may be obtained by diazotising the corresponding amino-compounds in concentrated hydrochloric acid and treating with cuprous chloride.

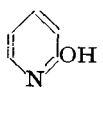


Halogen in the 2- or 4-position is reactive, being fairly readily replaced by OH, CN, NH_2, etc. In this respect these halogeno-pyridines resemble *o*- and *p*-chloronitrobenzenes (see later).

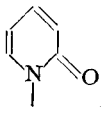
(ii) Pyridine reacts with nitric acid fairly readily only if a hydroxyl or an amino-group is present in the ring. Pyridine itself is nitrated to 3-nitro-pyridine by heating with concentrated sulphuric acid and potassium nitrate at 300°. 2- and 4-Nitropyridines may be obtained by oxidising the corresponding amino-compounds with hydrogen peroxide in sulphuric acid.

(iii) Sulphonation of pyridine is difficult, but when heated with concentrated sulphuric acid at 350° for some hours, pyridine gives pyridine-3-sulphonic acid. 2- and 4-Pyridinesulphonic acids may be prepared by oxidation of the corresponding thiols (prepared by the action of potassium hydrogen sulphide on the chloropyridine).

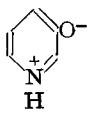
The sulphonic acid group can be replaced by hydroxyl or by the cyano-group. Fusion of pyridinesulphonic acid with potassium hydroxide is one method of preparing the monohydroxypyridines (*pyridols*). The structures of 2- and 4-hydroxypyridine have been the subject of much work. Originally, the hydroxy-structure, (I), was proposed, but it soon became apparent that this was unsatisfactory and so the ketonic formula (2-pyridone), (II), was proposed. X-Ray studies (Penfold, 1953) and infrared work (Gibson *et al.*, 1955) have shown that, in the solid state, the structure is predominantly the amide form (II), and Mason (1957) has shown this is also the case in chloroform or carbon tetrachloride solution. On the other hand, 3-hydroxypyridine exhibits phenolic properties, but its structure contains a large proportion of the zwitterion (III).



(I)



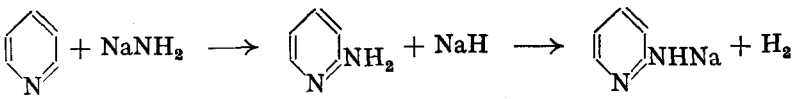
(II)



(III)

(iv) Pyridine may be fairly easily mercurated in the 3-position with aqueous mercuric acetate.

(v) When heated with sodamide in toluene solution, pyridine forms 2-aminopyridine; excess of sodamide produces 2 : 6-diaminopyridine (**Tschitschibabin (Chichibabin) reaction,** 1914). Actually, the sodium salts are formed, but on treatment with water, are hydrolysed to the amine.



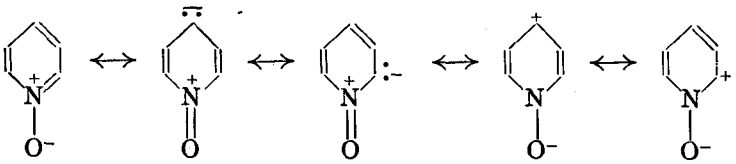
The three monoaminopyridines can be obtained by means of the Hofmann reaction on the amides of the pyridine monocarboxylic acids.

3-Aminopyridine can be diazotised easily; 2- and 4-aminopyridines are difficult to diazotise. Angyal *et al.* (1952), from an examination of the infrared absorption spectra, have concluded that 2- and 4-aminopyridine (and aminoquinolines) are mainly in the amino form (*cf.* the corresponding hydroxy compounds).

(vi) Pyridine is a strong tertiary base, forming salts with inorganic acids, *e.g., pyridine hydrochloride* or *pyridinium chloride*, $C_5H_5\overset{+}{N}HCl^-$. Pyridine forms quaternary salts when heated with alkyl halides, *e.g., pyridine methiodide* or *N-methylpyridinium iodide*, $C_5H_5\overset{+}{N}\cdot CH_3I^-$. This, when heated at 300°, gives 2- and 4-methylpyridines (*cf.* alkylanilines, p. 574).

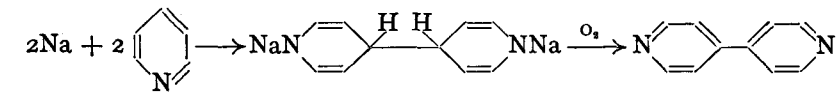
(vii) Sodium and ethanol, electrolytic reduction, or catalytic reduction using nickel convert pyridine into piperidine (see later). On the other hand, when pyridine is heated with hydriodic acid at 300°, the ring is opened with the formation of *n*-pentane and ammonia.

(viii) Pyridine is oxidised by perbenzoic acid to pyridine-1-oxide. Dipole moment studies have shown it to be a resonance hybrid of the following resonating structures (Linton, 1940; Ochiai, 1953):

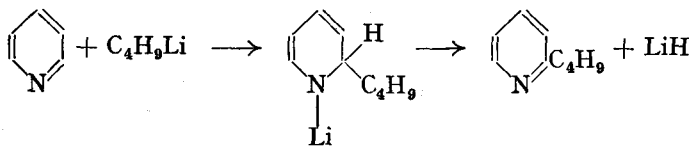


In general, *N*-oxides may be prepared by direct oxidation with peracetic acid, but in a number of cases perbenzoic or monoperphthalic acid may be used.

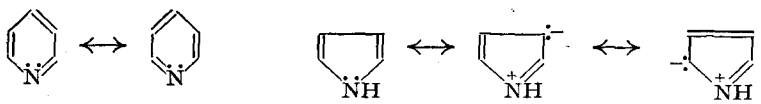
(ix) When pyridine is treated with sodium, and the disodio-derivative so produced is exposed to the air, 4 : 4′-dipyridyl is formed:



(x) When heated with *n*-butyl-lithium, pyridine forms 2-*n*-butylpyridine (Ziegler *et al.*, 1930).

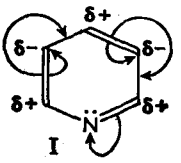


Pyridine is a resonance hybrid of two Kekulé structures (the resonance energy is 31 k. cal./mole), and this leaves the lone pair of the nitrogen atom free to unite with a proton:

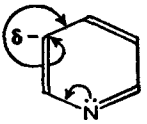


In pyrrole the lone pair takes part in the resonance, and consequently is not so free to unite with a proton. Hence pyrrole is a much weaker base than pyridine.

Two types of electromeric effects are possible in pyridine, (I) and (II):



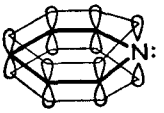
I



II

In (I) the 2, 4 and 6 positions are points of electron-deficiency, and hence attack at these positions is easy for nucleophilic reagents and difficult for electrophilic, and vice versa at positions 3 and 5; *e.g.*, nitration and sulphonation (electrophilic reagents) give 3-substitution, whereas sodamide (the $\ddot{N}H_2^-$ ion is the attacking reagent, and is nucleophilic) gives 2-substitution. In (II), the 3- and 5-positions are points of high electron-density, and consequently will be attacked by electrophilic reagents as in (I). Positions 2, 4 and 6 are unaffected and hence attack at these points is difficult. In any case, substitution in pyridine is not so easy as in benzene, thereby resembling nitrobenzene rather than benzene. This may be due to the fact that since electrophilic reagents are used in acid solution, pyridine is converted into the pyridinium ion, thereby preventing the lone pair of the nitrogen atom from participating in the electromeric effect.

In pyridine each carbon atom supplies one p_z electron, and the nitrogen atom (in the trigonal state) also one p_z electron to form the " closed circuit ". Pyridine is an even-membered ring, and so is an *alternant* compound (p. 528). The nitrogen atom, however, is strongly electron-attracting, and so the electron cloud



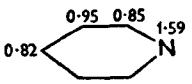
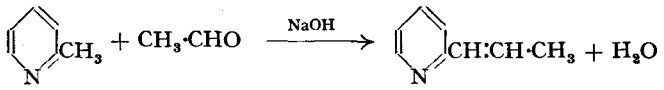


FIG. 30.3.

is concentrated round the nitrogen atom, thereby decreasing *below unity* all charge densities on the carbon atoms. Position 3 has the highest π-electron density, and so *electrophilic* substitution will occur here most easily. *Nucleophilic* substitution will occur most readily at position 4 and almost as easily at position 2; actually substitution in the latter position usually takes place in practice. Some other factors, *e.g.*, bond order, polarisability, must therefore operate.

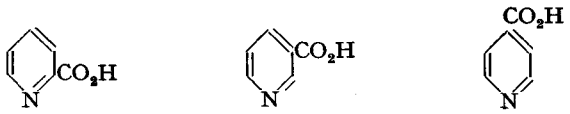
Pyridine finds great use in organic chemistry due mainly to its strong basic property and solvent properties. Because of its basic property, pyridine is used in many reactions where halogen acid is produced, or where it is desired to remove a molecule of halogen acid to form an unsaturated compound; *e.g.*, acetylation (with acetyl chloride), benzoylation (with benzoyl chloride), removal of hydrogen bromide from bromosuccinic ester to form the unsaturated ester (ethanolic potassium hydroxide would saponify the ester at the same time). Pyridine is used as a halogen carrier in Dam's solution (pyridine, bromine and sulphuric acid dissolved in glacial acetic acid) which is used for the determination of the iodine number (p. 261) of unsaturated compounds. Pyridine is used as a catalyst in the formation of Grignard reagents, and also as a solvent in the estimation of active hydrogen (see p. 350); it may be used in epimerisation (p. 446). Pyridine dissolves copper oxide (to give a modified Fehling's solution) and potassium permanganate, and these solutions may be used for oxidation purposes where aqueous solutions fail or are undesirable. Pyridine acts as a catalyst in the Perkin and Knoevenagel reactions, and forms complexes with many metallic salts and so may be used for their identification.

Pyridine homologues occur in coal-tar and bone oil. There are three methylpyridines and these are known as **picolines.** The methyl group in 2- and 4-picolines is reactive (*cf.* nitrotoluenes, p. 559); *e.g.*, 2-picoline condenses with acetaldehyde in the presence of warm aqueous sodium hydroxide to form 2-propenylpyridine:



Oxidation of gaseous picolines with air at 380° over mixed vanadium–molybdenum oxides gives mainly the pyridine–aldehydes (Mathes *et al.*, 1955). There are six *dimethylpyridines* (**lutidines**) and six *trimethylpyridines* (**collidines**).

Pyridinecarboxylic acids. There are three monocarboxylic acids, and each may be obtained by oxidising the corresponding picoline:

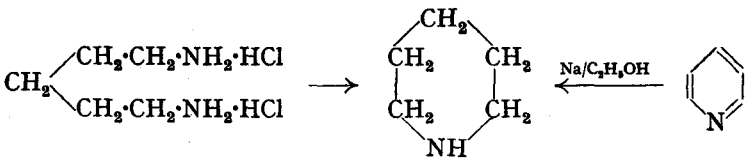


picolinic acid nicotinic acid *iso*nicotinic acid

All three acids may be reduced to the corresponding piperidinecarboxylic acids by means of sodium and ethanol, or better, catalytically.

There are six pyridinedicarboxylic acids, but only two are important: **quinolinic acid** (*pyridine*-2 : 3-*dicarboxylic acid*), which is an oxidation product of quinoline, and **cinchomeronic acid** (*pyridine*-3 : 4-*dicarboxylic acid*), an oxidation product of *iso*quinoline.

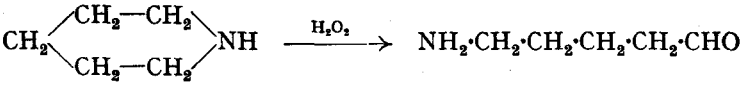
Piperidine occurs in the alkaloid piperine. It may be prepared by reducing pyridine (see reaction vii), or by heating the hydrochloride of pentamethylenediamine:



It is a colourless liquid, b.p. 106°, and gives the reactions of a secondary aliphatic amine. It is oxidised by concentrated sulphuric acid at 300° to pyridine.

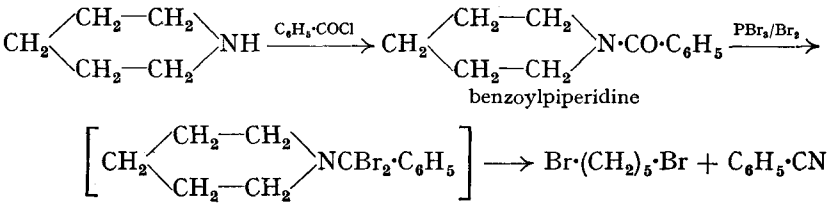
Methods of ring fission. Many heterocyclic compounds (containing nitrogen) occur naturally, and an extremely important step in the determination of their structure is to ascertain the disposition of the carbon atoms. A common procedure is to first reduce the heterocyclic compounds, and then open the ring of the product by the following methods (in which piperidine is used as the example):

(i) *Secondary* cyclic amines may be opened by treatment with 3 per cent. hydrogen peroxide, *e.g.*, piperidine gives δ-aminovaleraldehyde:



(ii) *Von Braun's method* (1910) may be used to open *secondary* cyclic amines by treating them with benzoyl chloride in the presence of aqueous

sodium hydroxide, adding phosphorus tribromide and cooled bromine to the product, and then distilling under reduced pressure, *e.g.*,

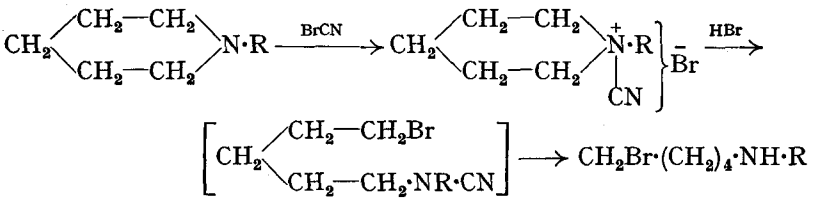


It might be noted that this provides a good method of preparing 1 : 5-dibromopentane.

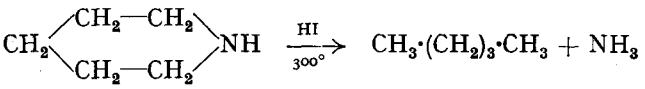
(iii) *von Braun cyanogen bromide reaction* (1900). This is the reaction of a tertiary amine with cyanogen bromide to form an alkyl bromide and a disubstituted cyanamide:

$$R_3N + BrCN \longrightarrow RBr + R_2N{\cdot}CN$$

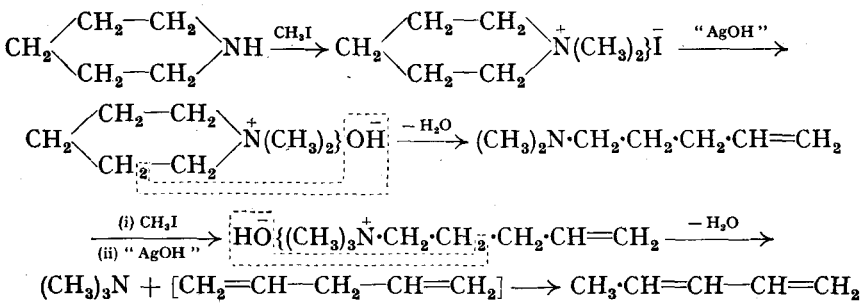
This reaction has been used in alkaloid chemistry for opening tertiary *cyclic* amines. The tertiary amine is treated with cyanogen bromide, and the product is then heated with constant boiling hydrobromic acid, *e.g.*, an *N*-alkylpiperidine:



(iv) Piperidine may be converted into *n*-pentane by heating with hydriodic acid at 300°:

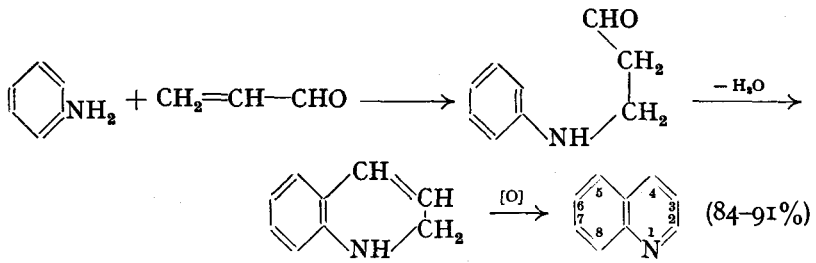


(v) **Hofmann's exhaustive methylation method** (1881) is the most important method of opening heterocyclic rings, but it fails with unhydrogenated pyridine, quinoline and *iso*quinoline derivatives, and with hydrogenated quinolines. Consider piperidine as our example. This is heated with methyl iodide and the quaternary salt produced, dimethylpiperidinium iodide, is converted into the corresponding hydroxide by moist silver oxide. When this is heated, water is eliminated, a hydrogen atom in the β-*position* with respect to the nitrogen atom being eliminated, and the ring opened at the nitrogen atom on the *same* side as the β-hydrogen atom eliminated. The product is dimethyl-4-pentenylamine and this, when the above treatment is repeated, eliminates water (the β-hydrogen atom being removed) and trimethylamine, forming penta-1 : 4-diene. This, however, isomerises to *piperylene* (penta-1 : 3-diene). This isomerisation is general, an isolated double bond system always rearranging, if possible, to form a conjugated system (the double bond moving to the middle of the chain; see also p. 319 for mechanism):

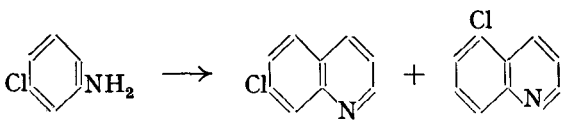


Quinoline is present in coal-tar and bone oil, and was first obtained from the alkaloid *quinine* by alkaline decomposition. It is obtained commercially from coal-tar, or prepared synthetically.

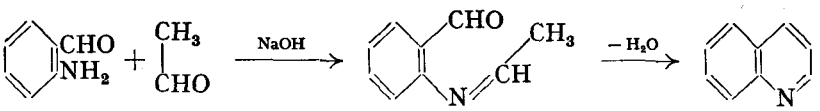
(i) **Skraup synthesis** (1880) is a very important method, and may be carried out by heating a mixture of aniline, nitrobenzene, glycerol, concentrated sulphuric acid and ferrous sulphate. Nitrobenzene acts as an oxidising agent, and ferrous sulphate makes the reaction less violent. Arsenic acid may be used instead of nitrobenzene and the former is better since the reaction is less violent. The mechanism of the Skraup synthesis is not certain. It is generally believed that the glycerol is converted into acraldehyde, and that the aniline adds on to this in the 3 : 4-positions (*cf.* p. 278):



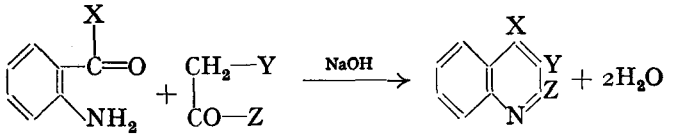
In general, the Skraup synthesis may be carried out with any primary aromatic amine in which at least one position *ortho* to the amino-group is vacant. If both *o*-positions are vacant, then both quinolines are usually formed *e.g.*,



(ii) **Friedländer's synthesis** (1882) is another important method for synthesising quinoline and many of its derivatives; *e.g.*, quinoline is formed when *o*-aminobenzaldehyde is condensed with acetaldehyde in aqueous sodium hydroxide:



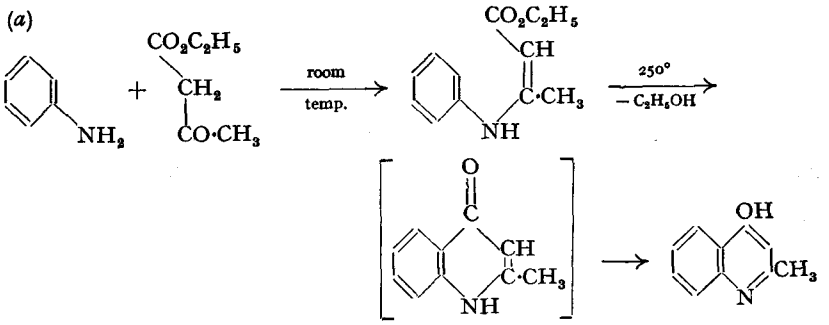
Derivatives of quinoline may be prepared by condensing *o*-aminoaldehydes or ketones with any aliphatic aldehyde or ketone containing the grouping $-CH_2 \cdot CO-$:



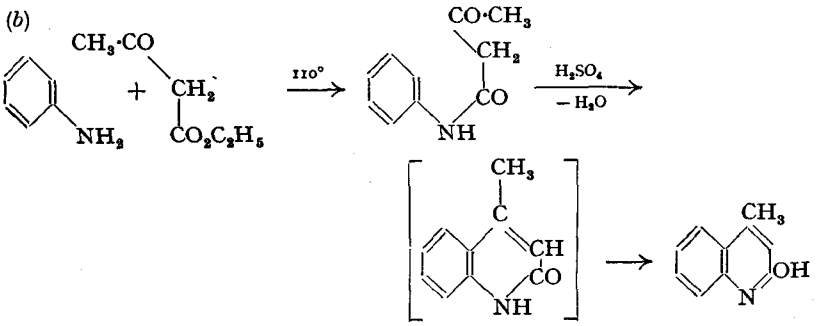
e.g., if X is CH_3, Y $CO_2C_2H_5$, and Z CH_3 (*i.e.*, the compound $YCH_2 \cdot COZ$ is ethyl acetoacetate), the product is 2 : 4-dimethylquinoline-3-carboxylic ester.

(iii) Condensation between β-ketonic esters and primary aromatic amines produces quinolines, the nature of the product depending on the conditions, *e.g.*, aniline and E.A.A.

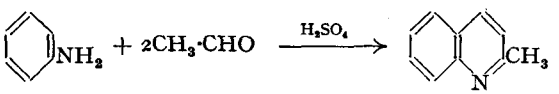
(*a*)



(*b*)

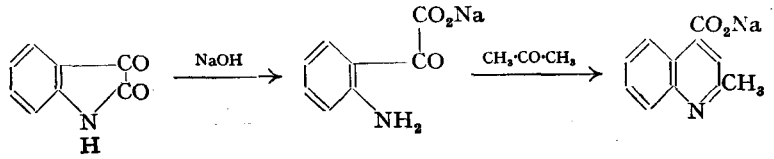


(iv) Homologues of quinoline may be prepared by the **Doebner–Miller synthesis** (1881); *e.g.*, aniline and paraldehyde heated with sulphuric acid form *quinaldine* (2-methylquinoline).

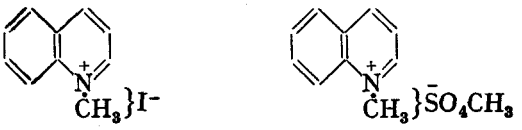


The Doebner–Miller synthesis is applicable to almost any aromatic primary amine, and the aldehyde may also be any α : β-unsaturated aldehyde (*cf.* mechanism of Skraup reaction):

(v) **Pfitzinger reaction** (1886). This is carried out by heating isatin with alkali in the presence of a ketone, *e.g.*,



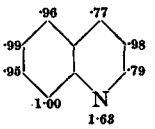
Quinoline is a colourless oil, b.p. 238°, sparingly soluble in water but completely miscible with ethanol and ether. It is a tertiary base and forms salts with inorganic acids; with alkyl halides it forms *quinolinium salts* (quaternary salts), *e.g.*, with methyl iodide it forms *quinoline methiodide* or N-*methylquinolinium iodide*, (I); with methyl sulphate it forms *quinoline methylmethosulphate* or N-*methylquinolinium methyl sulphate*, (II):



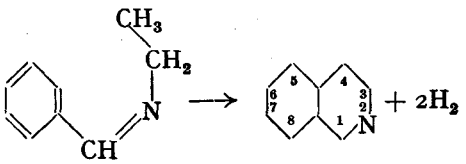
(I) (II)

Quinoline is oxidised by permanganate to quinolinic acid (p. 761). The methyl group in the 2-position (quinaldine) and in the 4-position (lepidine) is very active and undergoes many condensation reactions (see cyanine dyes, p. 796).

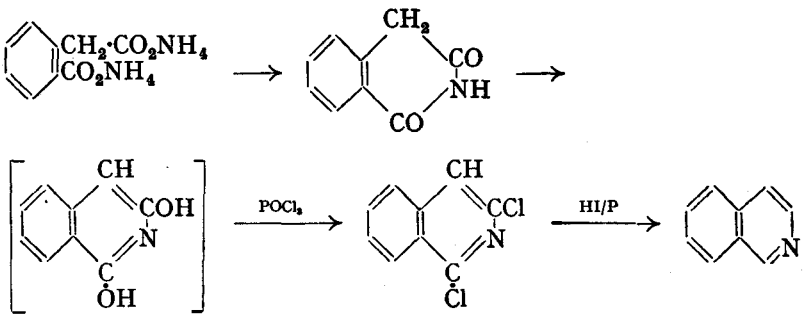
The nitrogen atom deactivates the pyridine ring, and so substituents enter the benzene ring. Calculation of charge densities shows that position 8 will be attacked preferentially by electrophilic reagents, and position 2 by nucleophilic reagents. In practice, nitration gives a mixture of 5- and 8-nitroquinolines; bromination also occurs in the 5- and 8-position under conditions of high acidity (de la Mare *et al.*, 1958).



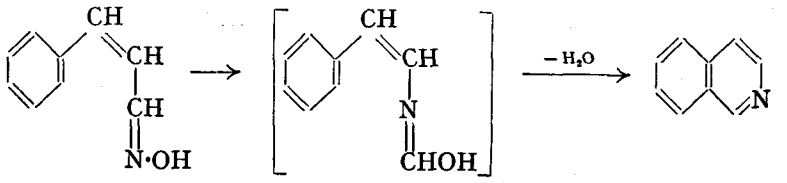
***iso*Quinoline** is always present with quinoline, and it may be separated from the latter by converting both compounds into their sulphates; these are separated by fractional crystallisation from ethanol in which *iso*quinoline sulphate is only sparingly soluble. *iso*Quinoline is a decomposition product of many alkaloids. It may be synthesised in many ways, *e.g.*, (i) By passing benzylidene-ethylamine vapour through a red-hot tube:



(ii) By heating ammonium homophthalate, treating the product, homophthalimide, with phosphoryl chloride, and reducing the dichloro-compound so produced with hydriodic acid and red phosphorus:



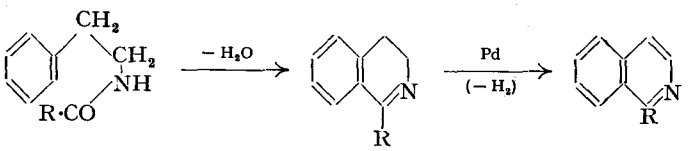
(iii) By heating the oxime of cinnamaldehyde with phosphorus pentoxide:



The formation of *iso*quinoline, and not quinoline, can only be explained by assuming that the oxime first undergoes the Beckmann transformation (p. 667), which is then followed by ring closure.

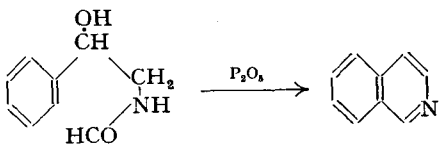
In addition to the above methods for *iso*quinoline itself, there are also three important methods which have a wide application. In the first two, partially reduced *iso*quinolines are obtained, but these may be readily dehydrogenated to the corresponding *iso*quinolines.

Bischler–Napieralski reaction (1893). In this method a β-phenylethylamide is made to undergo cyclodehydration to a 3 : 4-dihydro*iso*quinoline by heating with phosphorus pentoxide or anhydrous zinc chloride at high temperature; or better still, with phosphoryl chloride, phosphorus pentachloride, etc., at lower temperatures (about 140°).

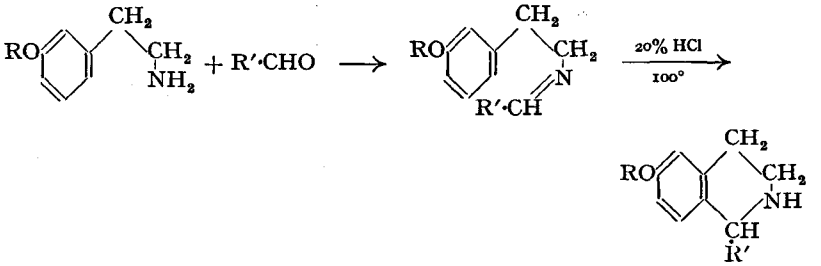


Dehydrogenation to the *iso*quinoline may be effected by heating the dihydro-compound with sulphur or selenium, or catalytically with, *e.g.*, palladium black.

*iso*Quinolines can be obtained directly by using β-hydroxyethylamides, *e.g.*,



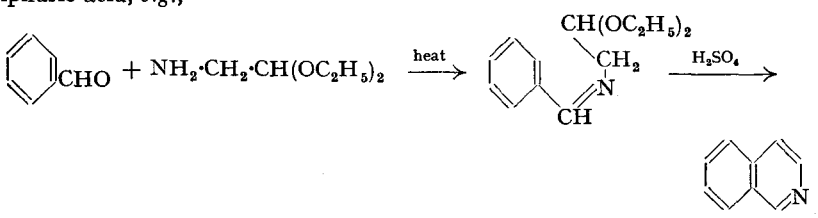
Pictet–Spengler reaction (1911). Condensation between a β-arylethylamine and an aldehyde in the presence of a large excess of hydrochloric acid at 100° produces a 1 : 2 : 3 : 4-tetrahydro*iso*quinoline. This reaction, however, is successful only if the aromatic nucleus contains a hydroxyl or an alkoxyl group *para* to the position of ring closure. The tetrahydro-compound may be



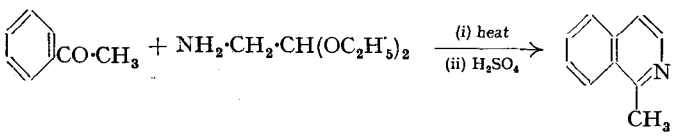
converted into the *iso*quinoline by catalytic dehydrogenation, or by heating with an ethanolic solution of iodine containing sodium acetate, or by heating with mercuric acetate.

Pomeranz–Fritsch reaction (1893). This is carried out by condensing an

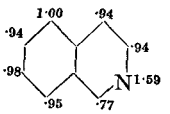
aromatic aldehyde with an aminoacetal and then cyclising the product with sulphuric acid, *e.g.*,



If an aromatic ketone is used instead of the aldehyde, then the product is a 1-substituted *iso*quinoline, *e.g.*,

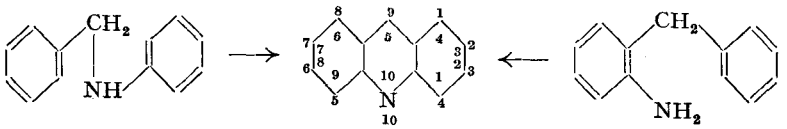


*iso*Quinoline is a colourless solid (or liquid), m.p. 23°, and resembles quinoline in many of its properties. It is oxidised by permanganate to a mixture of phthalic and cinchomeronic acids (p. 761).



Nitration occurs at positions 5 and 8 in *iso*quinoline; the former agrees with expectations from charge densities, but position 7 would have been expected to be the next position to be attacked (*cf.* quinoline).

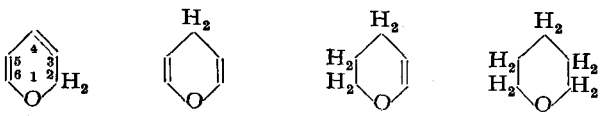
Acridine occurs in the anthracene fraction of coal-tar. It may be synthesised by passing the vapour of benzylaniline or *o*-aminodiphenylmethane through a red-hot tube (the outside numbering is to be used now):



Acridine is a colourless solid, m.p. 110°; it is a tertiary base, but weaker than quinoline. It is the parent substance of a number of dyes and antiseptics (p. 795).

SIX-MEMBERED RINGS WITH ONE OXYGEN ATOM

The simplest six-membered rings with one oxygen are **1:2-** (or α-) **pyran,** (I), and **1:4-** (or γ) **pyran,** (II). These, however, are unknown, but *dihydro-*

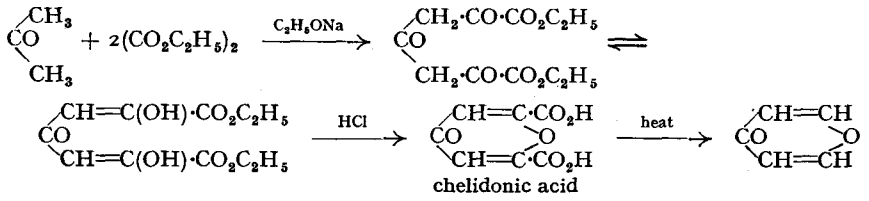


(III) and *tetrahydropyran* (IV) have been prepared. The pyranose sugars (p. 452) are derivatives of tetrahydropyran.

The corresponding keto-derivatives of the pyrans are known as **pyrones**:

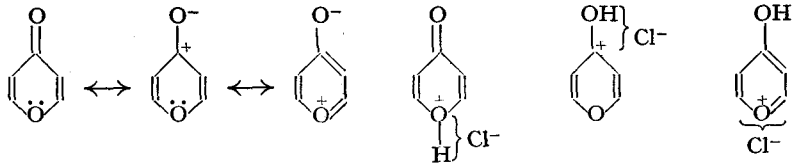
α-pyrone γ-pyrone

γ-Pyrone may be prepared by heating *chelidonic acid* just above its m.p. (262°). Chelidonic acid (a naturally occurring substance) may be prepared from acetone and ethyl oxalate.



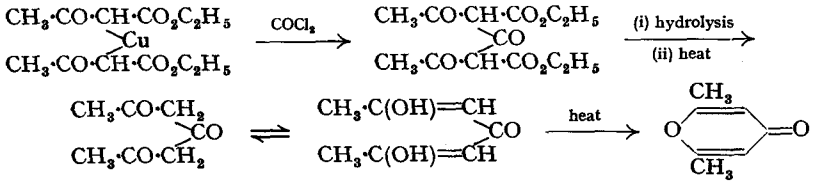
chelidonic acid

γ-Pyrone, m.p. 32·5°, is basic and shows some aromatic properties, and so it is possibly a resonance hybrid with contributing structures such as (III). γ-Pyrone does *not* form an oxime or phenylhydrazone. Similarly, the structure of γ-pyrone salts may be (VI) rather than (IV). According to Brown (1951), however, calculation of general charge distribution suggests (V) as the structure of the oxonium salts (this corresponds to (II) for γ-pyrone itself).

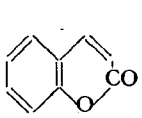


(I) (II) (III) (IV) (V) (VI)

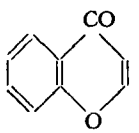
2:6-Dimethyl-γ-pyrone is a very important derivative of γ-pyrone from the theoretical point of view, since its salt with hydrochloric acid was the first *oxonium* salt to be prepared (Collie and Tickle, 1890); the structure of this salt corresponds to that of (V) or (VI). The dimethyl-γ-pyrone may be prepared from the copper salt of ethyl acetoacetate as follows:



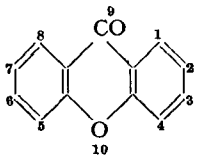
Condensed pyrone systems are important since many occur naturally:



α-benzopyrone
or coumarin
(α-chromone)

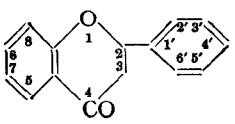


γ-benzopyrone
(γ-chromone)



xanthone

α-Flavone is 2-phenyl-γ-chromone, and many of its derivatives are the colouring matter of flowers:



SIX-MEMBERED RINGS WITH TWO NITROGEN ATOMS

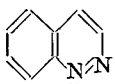
These are known collectively as the *diazines*, and the *o*-, *m*- and *p*-isomers are called *pyridazines* (*oiazines*), *pyrimidines* (*miazines*) and *pyrazines* (*piazines*), respectively:

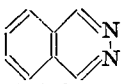

pyridazine
b.p. 208°

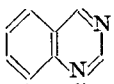

pyrimidine
m.p. 22°

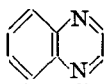

pyrazine
m.p. 53°

The corresponding *benzodiazines* are:

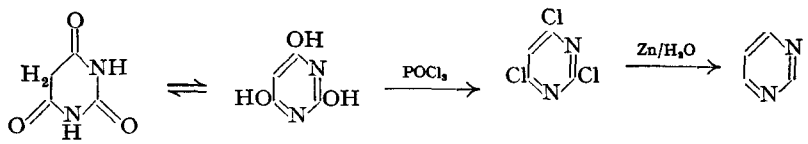

cinnoline


phthalazine

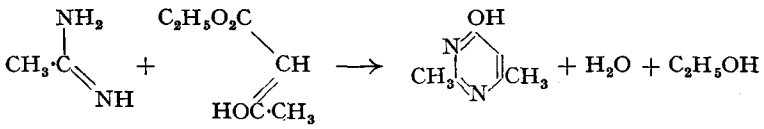

quinazoline


quinoxaline

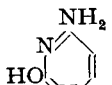
The pyrimidines are a particularly important group of compounds, since the pyrimidine nucleus occurs in purines, nucleic acids and synthetic barbiturates (p. 387). Barbituric acid may be regarded as 2 : 4 : 6-trihydroxypyrimidine, and pyrimidine may be prepared from barbituric acid as follows:

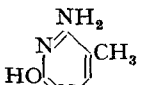


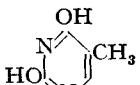
A very important general method for preparing pyrimidines is the condensation between a β-dicarbonyl compound and a compound which has the amidine structure, *e.g.*, 6-hydroxy-2 : 4-dimethylpyrimidine from ethyl acetoacetate and acetamidine.

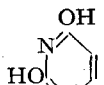


Some pyrimidines found in nucleic acids are:


cytosine


5-methylcytosine


thymine


uracil

QUESTIONS

1. Discuss the preparation and properties of furan, furfural and furoic acid.
2. Describe the preparation of thiophen, and compare and contrast the behaviour of the sulphur atom in thiophen with that in the alkyl sulphides.
3. Describe the preparation of pyrrole and compare and contrast its reactions with phenol and aniline.
4. Name the compounds and state the conditions under which they are formed when pyridine is treated with:—(*a*) reducing agents, (*b*) oxidising agents, (*c*) Br_2, (*d*) HNO_3, (*e*) H_2SO_4, (*f*) $(AcO)_2Hg$, (*g*) $NaNH_2$, (*h*) MeI, (*i*) Na.
5. Write an essay on the methods of opening heterocyclic rings containing one nitrogen atom.

6. Suggest a synthesis for each of the following compounds:—(*a*) furan-3 : 4-dicarboxylic acid, (*b*) 6-nitroquinoline, (*c*) 7-methylquinoline, (*d*) 2 : 3 : 4-trimethylquinoline, (*e*) 7-nitro-2 : 3-dimethylquinoline, (*f*) 1-methyl*iso*quinoline.

7. Write an account of the analytical and synthetic evidence for the structure of:—(*a*) quinoline, (*b*) *iso*quinoline.

8. Discuss the use of E.A.A. in the synthesis of heterocyclic compounds.

9. Define and give examples of:—(*a*) Paal–Knorr synthesis, (*b*) Knorr synthesis, (*c*) Hantzsch synthesis, (*d*) Fischer's indole synthesis, (*e*) Hofmann's exhaustive methylation method, (*f*) Skraup's synthesis, (*g*) Friedländer's quinoline synthesis, (*h*) Hantzsch pyridine synthesis, (*i*) Doebner–Miller synthesis, (*j*) Lipp synthesis, (*k*) Reissert synthesis, (*l*) Chichibabin reaction, (*m*) Pfitzinger reaction, (*n*) Bischler–Napieralski reaction, (*o*) Pictet–Spengler reaction, (*p*) Pomeranz–Fritsch reaction.

10. Discuss the procedure and results of the exhaustive methylation of:—(*a*) 3-methylpyrrole, (*b*) indole, (*c*) quinoline, (*d*) *iso*quinoline.

11. Describe the preparation and properties of:—(*a*) pyrazole, (*b*) imidazole, (*c*) oxazoles, (*d*) *iso*-oxazoles, (*e*) thiazole, (*f*) sydnones, (*g*) pyrones, (*h*) pyrimidine, (*i*) antipyrine.

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CHAPTER XXXI

DYES

FOR a substance to act as a dye, certain conditions must be fulfilled, *viz.*,

(i) It must have a suitable colour.

(ii) It must be able to " fix " itself or be capable of being " fixed " to the fabric.

(iii) When fixed, it must not be fugitive, *i.e.*, it must be fast to light; and it must be resistant to the action of water and, to a certain extent (the more the better), to dilute acids and alkalis (particularly the latter on account of the alkaline nature of " washing soda ").

Many natural dyes have been known for a long time. These were obtained from animal and vegetable sources. Today, however, practically all dyes are synthetic and are prepared from aromatic compounds, the only source of which, until recently, was coal-tar; hence the name *coal-tar dyes.*

Colour. When white light (7,500–4,000 A) falls on a substance, the light may be totally reflected or totally absorbed. In the former case, the substance appears white; in the latter, black. If a certain proportion of the light is absorbed and the rest reflected, the substance has the colour of the *reflected* light. If only a *single* band is absorbed, the substance has the *complementary* colour (of the absorbed band).

TABLE IX

(A)	Colour absorbed	Visible (complementary) colour
4000–4350	violet	yellow-green
4350–4800	blue	yellow
4800–4900	green-blue	orange
4900–5000	blue-green	red
5000–5600	green	purple
5600–5800	yellow-green	violet
5800–5950	yellow	blue
5950–6050	orange	green-blue
6050–7500	red	blue-green

If a substance absorbs all visible light except one band, which it reflects, the substance will have the colour of that reflected band. Thus a substance can appear blue because it absorbs the yellow portion of the spectrum only; or because it absorbs *all the visible spectrum except blue.* The shades, however, will be different. Apparently no dye gives a pure shade, *i.e.*, does not reflect only one band of wave-lengths; *e.g.*, malachite green reflects green light, but also, to a small extent, red, blue and violet.

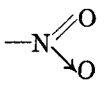
Many substances which appear to be colourless nevertheless have absorption spectra, but in these cases, absorption takes place in the infrared or ultraviolet, and not in the region of the visible spectrum.

RELATION BETWEEN COLOUR AND CONSTITUTION

Graebe and Liebermann (1868) observed that organic colouring matter could be reduced to colourless compounds, and that when the hydrogen atoms (added by the reduction) were removed by oxidation, the original

colour was regenerated. It was Witt (1876), however, who was the first to point out that colour usually appeared in an organic compound when that compound contained certain "unsaturated groups". Consider, for example, diazomethane and glyoxal. These are the simplest coloured organic compounds. Both contain "unsaturated groups", and on reduction diazomethane gives methylhydrazine, and glyoxal, glycol; both reduction products are colourless. It is important to note that the carbonyl group is referred to as an *unsaturated group* (by Witt). Its presence in a compound, however, does not give rise to unsaturation (see definition of unsaturation, p. 8). As will be seen subsequently, a more appropriate term than unsaturated group would have been a *group with multiple bonds*.

Witt called these groups with multiple bonds **chromophores**; some of the more important chromophoric groups are:

Nitro  nitroso —N=O; azo —N=N—

azoxy —N=N→O azoamino —N=N—NH—

carbonyl C=O thiocarbonyl C=S

Witt named the compound containing the chromophoric group, a **chromogen.** Experience has shown that if the chromogen contains only one chromophore, it is usually coloured (yellow), and that the depth of colour (see later) generally increases with the number of chromophores. A single C=C group is not sufficient to produce colour, but if a number of them are present in conjugation, colour may develop, *e.g.*, $CH_2{=}CH_2$ is colourless; $CH_3{\cdot}(CH{=}CH)_6{\cdot}CH_3$ is yellow.

Witt also pointed out that the presence of certain groups in the chromogen deepen colour, although these groups are *not* chromophores. These he called **auxochromes.** Auxochromes are acidic (phenolic) or basic, the most important being: OH, NH_2, NH·R and NR_2.

Radicals which bring about deepening of colour are known as **bathochromic groups,** and those which bring about the opposite effect, **hypsochromic groups.** Deepening of colour (in colour chemistry) means the change in colour as follows: yellow→orange→red→purple→violet→blue→green→black. Since visible colour is the complementary colour of the absorbed band, bathochromic groups shift the absorption maxima from the violet towards the red (*i.e.*, they *lower* the frequency of the light absorbed). Conversely, hypsochromic groups shift the absorption maxima from the red to the violet (*i.e.*, they *raise* the frequency of the light absorbed). Experience has shown that auxochromes are usually bathochromic, and that replacement of hydrogen in the NH_2 group by R or Ar generally has a bathochromic effect. On the other hand, acetylation of OH or NH_2 (*i.e.*, replacement of hydrogen by an acetyl group) generally has a hypsochromic effect.

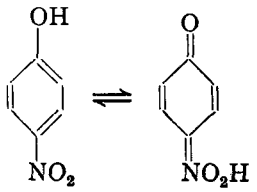
Nietzki (1879) stated that increase in molecular weight deepened colour; *e.g.*, substitution of a naphthalene nucleus for benzene in azo-dyes, deepens the colour from yellow to red. Schütze (1892) showed that there were many exceptions to Nietzki's rule (it was Schütze who introduced the terms bathochrome and hypsochrome). Piccard (1913) also found that Nietzki's rule was not always true, and showed that in these cases the introduction of the heavier group introduced a second absorption band at the blue end of the spectrum.

It has already been pointed out that in order to act as a dye, a substance must be capable of fixing itself or being fixed to the fabric. No chromogens act as a dye; the presence of a salt-forming group is necessary. Auxo-

chromes are such groups and so, apart from their auxochromic properties (of deepening colour), they are also necessary to make the chromogen a dye. Thus auxochromes perform two functions. The sulphonic acid and carboxyl groups possess very little auxochromic properties; their presence, however, makes a chromogen a dye, the sulphonic acid group making the dye soluble in water, and the carboxyl group usually enabling the dye to form lakes (see later).

Armstrong (1885) pointed out that quinones (*o*- and *p*-) are coloured, and suggested that all colouring matters of known structure could generally be represented by a quinonoid structure. This meant that if the quinonoid structure was present, the substance would be coloured; if absent, colourless. This view was accepted quickly, but before long it was shown that the quinonoid formula could not be given to some coloured compounds, *e.g.*, fulvenes. It is important to note, however, that these compounds all contain conjugated double bonds (see later).

Armstrong's quinonoid theory was very useful since it stimulated further work on this problem of the relation between colour and constitution. Armstrong believed that the quinonoid structure accounted for the colour of nitrophenols but no proof of this belief was forthcoming until Hantzsch (1906) prepared the two kinds of ethers (p. 627). Hantzsch was thus led to believe that change in colour involved a change in structure, and he also thought that the quinonoid structure was essential for the production of colour in compounds containing benzene rings. As time went on, however, Hantzsch changed his views about the significance of conjugation with respect to colour, and by 1919, he believed that some other factor played a part, *viz.*, the state of the mloecule as a whole, and that it cannot be represented by a static formula (inset).



The relation between colour and constitution discussed above is empirical, and it is only recently that some headway has been made on the theoretical side of the problem. When light (this term will be used for electromagnetic waves of any wavelength) is absorbed by a molecule, the molecule undergoes transition from a state of lower to a state of higher energy. If E_1 is the original energy content of the molecule and E_2 the higher energy content, then $h\nu = E_2 - E_1 = \Delta E$, where h is Planck's constant and ν the frequency of the absorbed light. If the molecule is monatomic, the energy absorbed can only be used to raise the energy levels of the electrons, thereby changing the atom from its *ground* state to some *excited* state. If, however, the molecule consists of more than one atom, the light absorbed may bring about changes in electronic, rotational or vibrational energy. Since electronic transitions are associated with large amounts of energy relative to rotational and vibrational transitions, ΔE is large for the former, *i.e.*, ν is large (and consequently the wavelength is short); for the latter, ΔE is small, *i.e.*, ν is small (and consequently the wavelength is long). Thus changes in electronic states give absorption (or emission) in the visible and ultraviolet parts of the spectrum, whereas changes in rotational and vibrational energies give absorption (or emission) respectively in the far and near infrared. Since we are concerned with colour, we shall deal mainly with the visible part of the spectrum.

As we have seen (p. 23) an electron must occupy some *particular* orbital. Thus ΔE must have *definite* values (for physically stable molecules, *i.e.*, molecules not undergoing any type of dissociation), and hence the frequency of the light absorbed (or emitted) will have definite values, *i.e.*, each value will be associated with a particular line in the spectrum. In complex molecules there will be a very large number of possible excited states, and since, when we examine the absorption spectrum of a compound, we are dealing with very large numbers of molecules, all these excited states will be produced (under the right conditions), *i.e.*, the spectrum will consist of a very large number of lines, and where these

lines are very close together (owing to the values of ΔE being very close), bands will appear in the spectrum (see also later). Thus the absorption spectra of complex molecules will appear as bands, these bands appearing in *definite* regions. It is the existence of these bands in definite parts of the spectrum that gives rise to colour. In practice the *first* absorption band of a compound is the most important, *i.e.*, the band which occurs at the *lowest* frequency (ΔE smallest), and is due to transition from the ground state to the lowest (first) excited state.

Not only must the *frequency* of the light be considered, but also whether transitions between different energy levels in the molecule can occur, *i.e.*, whether they are " permitted " or " forbidden " transitions. The *probability of transition* is related to the *dipole moment of transition* or *transition dipole* of the molecule. Light absorption by a molecule can occur only when the dipole moment changes in that molecule. The more symmetrical the molecule, the smaller is the possibility of a transition dipole, and therefore the less likely is the molecule to absorb light. Calculation has also shown that the greater is the transition dipole, the greater is the *intensity* of the absorption. If the *electric* dipole is zero, absorption may still occur if the transition *magnetic* dipole is not zero, but absorption of light in this case is usually weak. The introduction of any group into a molecule which decreases symmetry will thus increase the transition dipole and consequently increase the intensity of absorption. At the same time, however, new " resonance paths " may be introduced, and hence not only is there a change in intensity of absorption (due to an increase in the transition dipole), but there is also a shift of the band to longer wavelengths (see below).

As pointed out on p. 31, an important difference between V.B. and M.O. theories is that in the former electrons are dealt with in *pairs*, whereas in the latter they can be dealt with *singly*. This has produced some differences in the theory of light absorption, but nevertheless there is a large amount of ground common to both theories (V.B. and M.O.).

According to the V.B. theory, oscillating (vibrating) electrons in a molecule permit absorption of light by the substance. When light is absorbed by a molecule, there is an *induced* oscillation of the electron pairs (in bonds) throughout the length of the molecule. Lewis and Calvin, and Mulliken have assumed that the electrons are oscillating in the ground state of the molecule, the character of these oscillations being the same as that of the induced oscillation in the excited state. When the molecule is raised to its first excited state, the absorption spectrum corresponding to this will have the lowest frequency. If the molecule is raised to its second excited state, *i.e.*, the amplitude of vibration of the oscillating electrons is increased, then the second absorption band will appear. For a *long* molecule which has an absorption band of low frequency, the electron displacements must be small compared to the dimensions of the molecule, and so the first two excited states occur close together. If the frequency of the absorption band is relatively high for a *short* molecule, the electronic displacements are effectively those in the resonating structures (see later), and so the two excited states are widely separated.

Absorption of light raises the molecule from its ground state to an (electronically) excited state, and the difference in energy between the two states will determine the frequency of the light absorbed. Whether the molecule is symmetrical or not, oscillation of electron pairs produces a changing dipole moment, since they become associated with one or other of the bonded pair of atoms. Thus a changing dipole moment is present in both ground and excited states. It has been shown experimentally that the ease of excitation of the following groups is:

$$N{=}O > C{=}S > N{=}N > C{=}O > C{=}N > C{=}C$$

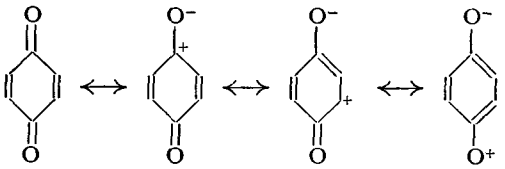
Thus colour (due to the presence of one of these groups) will *deepen from right to left.*

The smaller the difference in energy between ground and excited states, the lower is the frequency, or longer the wavelength, of the light absorbed. Anything that decreases ΔE will therefore displace the bands to the longer wavelengths. It has been shown that resonance among *charged* structures lowers the energies of both ground and excited states, and since charged structures contribute more to the excited than to the ground state, the energy of the former will be

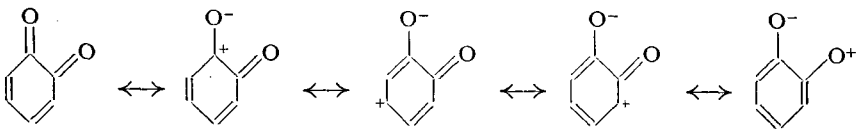
lowered more than that of the latter. Thus, in general, *colour is deeper the greater is the resonance among the various charged forms*. It was Bury (1935) who first pointed out that many dyes could be represented as resonance hybrids.

All the above unsaturated groups (N=O, etc.) are easily polarised, *i.e.*, readily produce charged structures in the excited state; hence their presence in a molecule tends to produce colour. Let us now consider benzene. Its charged structures contribute relatively little to the ground or excited states, and so benzene absorbs only in the ultraviolet, and the absorption is weak due to the symmetry of the molecule. In nitrobenzene the contribution of charged structures is larger than in benzene, and consequently the absorption band is shifted to the longer wavelengths (blue), thereby producing a pale yellow colour (which is the complementary colour of the blue band); the intensity of absorption is also increased because of the loss of symmetry. In *p*-nitroaniline there is a still larger contribution of charged structures, and hence the colour is deeper (orange-red) and still more intense.

The colour of quinones may be explained by resonance among charged structures:

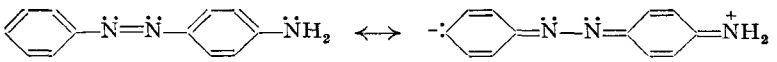


There are similar resonating structures for *o*-benzoquinone:

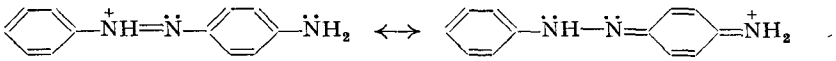


Thus all compounds which can be represented as a quinonoid structure (*ortho* or *para*) will probably be coloured. Moreover, since the number of resonating structures is greater for the *o*-compound than for the *p*-, the former will be deeper in colour (*o*-quinone is red and *p*-quinone is yellow).

Let us now consider aminoazobenzene. This is a resonance hybrid of a number of resonating structures of which only the following two will be considered:



Aminoazobenzene is yellow, only one charged structure contributing to the resonance. In acid solution, aminoazobenzene exists as the following resonance hybrid:

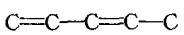


This is violet, and the deepening of colour is due to the fact that only *charged* structures contribute to the resonance hybrid. Here is an example where the addition of acid produces a greater bathochromic effect than is caused by adding an auxochrome.

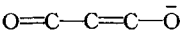
From the foregoing it can be seen that chromophores give rise to the potentiality of colour by introducing the possibility of resonance involving *charged* structures. Auxochromes (the " key atoms " of which have a lone pair of electrons) change the colour of the chromogen by enhancing resonance, or by producing new forms involving separation of charge.

The longer the conjugation in a molecule, the deeper will be the colour. Conjugation of chromophores also deepens colour. Lewis and Calvin showed that the effect of conjugation is due to the increase in the number of electrons involved in the oscillation. When the conjugated system also contains atoms

such as N, S, O, etc., then the absorption frequency is much lower than that of the corresponding conjugated carbon compound, *e.g.*, the absorption frequency of (II) is lower than that of (I) because (II) has a charge and is less symmetrical than (I). Furthermore, the more the charge can be made to reside on the *terminal* atoms, the longer will be the wavelength of the absorbed light.

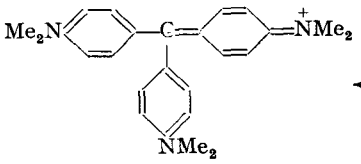


(I)

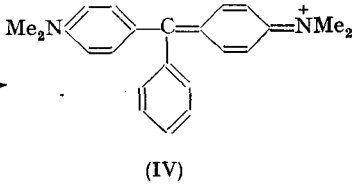


(II)

From the foregoing account it might have been expected that resonance among an increasingly larger number of resonating structures would deepen colour. Consider crystal violet (III), and malachite green (IV).



(III)

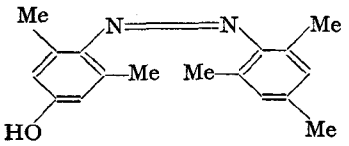


(IV)

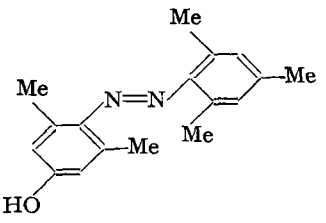
(III) has a larger number of resonating structures than (IV), yet the colour of the latter is deeper than that of the former. In (III) the charge on each N atom is approximately two-thirds that on each N in (IV). Therefore the charge that migrates in (III) is smaller than that in (IV), and so the absorption frequency of (III) is higher (or the wavelength is shorter) than that of (IV).

There is, however, another factor introduced. When a molecule has a conjugated system extending in two directions, there may be two optical axes, *i.e.*, absorption will give rise to excited states of different energies and therefore to absorption bands of *different* frequencies. Lewis and Calvin associated the band of *lowest* frequency with the *longest* axis in the molecule. This is called the *x*-band, and the band corresponding to the axis at right angles to this *major axis* is the *y*-band. Generally the *x*-axis of a molecule can readily be determined from the structural formula. (IV) has *x*- and *y*-bands, but (III) has only *one* band (the *x*- and *y*-axes in (III) are identical). Furthermore, if each axis acts independently, the *x*-bands of both (III) and (IV) should be about the same wavelength. This has been found to be so in practice. (IV), however, also has a *y*-absorption band, and it is the presence of this that makes the colour of (IV) different from that of (III).

Another factor that plays a part in colour is the steric factor. Brode *et al.* (1952) prepared the *cis* and *trans* forms of the following hydroxyazo compound (azophenol):



cis



trans

The *trans* form is coloured, whereas the *cis* is colourless; the former can undergo resonance, but in the latter a planar configuration is prevented by the spatial effect of the *o*-methyl groups, and consequently resonance is inhibited and there is therefore no colour (this is an example of steric inhibition of resonance, p. 688). The colourless *cis* form, on standing, changes to the coloured *trans* form. It is of interest to note, in this connection, that fading, with azo-dyes, may be due, at least partly, to the conversion of the *trans* form into the *cis*.

In general, when two conjugated fragments R and S are joined by a single bond, the electronic spectrum depends largely on the coplanarity between the

two fragments. If R and S lie in mutually perpendicular planes, the spectrum of the molecule is very similar to the superimposed spectra of RH and SH. Furthermore, in such a molecule the intensity of the absorption band usually decreases with increasing steric distortion from the coplanar configuration. There are, however, many cases where the frequency of a band remains unchanged or is shifted in either direction as the molecule is distorted.

Now let us consider the problem of light absorption from the M.O. point of view. In M.O. theory, an atom or a molecule is excited when *one* electron is transferred from an orbital of lower to one of higher energy. Such transitions can occur only between " permitted " orbitals. In *atoms*, allowable transitions are $s \longleftrightarrow p$, $p \longleftrightarrow d$, etc.; $s \longrightarrow s$ is forbidden (p. 24). In *molecules*, a g state must go to a u state, or vice versa; transitions $u \longrightarrow u$, and $g \longrightarrow g$ are forbidden (p. 31).

An unsymmetrical molecule in the ground state has a dipole moment, and the dipole moment will generally change if the internuclear distances change. Absorption of light increases the amplitude of vibration. On the other hand, a symmetrical molecule will not have a dipole moment, but one may be produced in an excited state. In a diatomic molecule, transition of an electron from a bonding to the corresponding anti-bonding orbital is always an allowed transition.

Let us first consider the hydrogen molecule. The electron pair in the σ-bond can be excited, and excitation can be effected by absorption of light, *e.g.*, the hydrogen molecule in the ground state (Fig. 1*a*) can be raised to its first excited state (Fig. 1*b*). In the ground state we have a σ_g orbital (*bonding* orbital), and

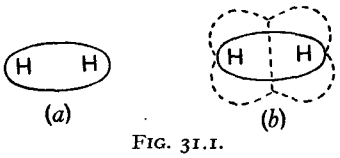


FIG. 31.1.

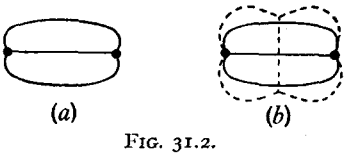


FIG. 31.2.

in the first excited state we have *one* electron in the σ_g orbital and the *other* electron in a σ_u orbital (*antibonding* orbital; see p. 30). Absorption of light of the *requisite* amount of energy can transfer one electron from a σ_g to a σ_u orbital (this is an allowable transition). Now the amount of energy required to raise one electron from a σ_g to a σ_u orbital is large, *i.e.*, the frequency of the incident light must be high, and so the wavelength is very short. Thus the hydrogen molecule absorbs in the ultraviolet (we are not considering rotational and vibrational spectra).

The ethylene molecule in its ground state has, in addition to a σ-bond, a π_u (bonding) orbital (Fig. 2*a*), and in the first excited state a π_g (antibonding) orbital (Fig. 2*b*) in which *one* electron has been excited (this is an allowable transition; see p. 31). Since it requires less energy to excite a π-electron than a σ-electron, the wavelength of the absorbed light necessary to raise one electron from a π_u to a π_g orbital will therefore be longer, *i.e.*, the absorption spectrum of ethylene will be in the longer wavelength region (than that of hydrogen).

In a compound containing two *isolated* double bonds (p. 83), the absorption band has about the same frequency as that of one double bond, but the intensity is greater. In a compound containing two bonds in conjugation we now have delocalised bonds. Let us consider the simple case of butadiene (p. 88, Fig. 4.1). (*d*) represents the molecule in the ground state; (*e*) and (*f*) represent excited states, that of (*f*) being a higher state. Excitation of butadiene can therefore cause the transfer of *one* electron from (*b*) to (*e*) or (*f*), or *one* from (*c*) to (*e*) or (*f*). If all these occurred, *four* absorption bands would be produced. Calculation has shown that the energy difference between (*c*) and (*e*) is lower than that of any other transition; (it should be noted that this transition is from the highest level of the ground state to the lowest level of the excited state; see also below). Thus when butadiene absorbs light (of requisite wavelength), the absorption band of *longest* wavelength corresponds to excitation of one electron from (*c*) to (*e*), and other bands of *shorter* wavelength correspond to the other transitions.

As we have seen (p. 88), in a conjugated system containing $2n$ π-electrons, there are n bonding and n antibonding orbitals. Calculation and experimental

work have shown that as conjugation increases, the energy difference between the highest occupied and the lowest unoccupied π-orbitals decreases. Thus, as conjugation extends, the wavelength of the absorption band increases. When it reaches the *visible* part of the spectrum, colour will appear in the compound, *e.g.*, in the polyenes, $CH_3{\cdot}(CH{=}CH)_n{\cdot}CH_3$, when $n = 6$, the absorption band occurs in the blue region, and so the compound is yellow (complementary colour). Thus increased conjugation deepens colour, and this effect offers an explanation for Nietzki's rule (p. 772); *e.g.*, when benzene rings are replaced by naphthalene, conjugation is extended.

Although it always requires less energy to transfer π-electrons than σ-electrons from one orbital to another, nevertheless all π-electrons are not transferred with equal ease. The energy required depends on the nature of the atoms embraced in the M.O.

Now let us consider benzene. This is a symmetrical molecule, all the carbon atoms carrying equal charges of unity. Thus benzene has no transition dipole, and so would not be expected to absorb light. In practice, however, it shows *weak* absorption in the ultraviolet (one electron passes from (II) or (III) to (IV) or (V), p. 509; also see p. 775). When a nitro-group is introduced into the benzene ring, the molecule is no longer symmetrical; the nitro-group is conjugated with the rest of the molecule, and the carbon atoms are no longer equally charged (p. 528). Nitrobenzene therefore has a dipole moment and consequently a large transition dipole, and so strong absorption bands can be expected. Furthermore, because of the extended conjugation, the energy difference between the highest occupied and the lowest unoccupied orbitals is decreased, and so the absorption band will have a longer wavelength than that of benzene. It actually occurs in the blue region, and so nitrobenzene is yellow.

In aniline, the lone pair on the nitrogen atom becomes conjugated with the ring (p. 528), and the molecule now has a dipole moment and therefore a transition dipole. At the same time the absorption band of aniline has a longer wavelength than that of benzene. The absorption spectrum of aniline in *acid* solution, however, is almost the same as that of benzene. This is because the lone pair (on the " key atom ", p. 518) has been removed from conjugation by co-ordination with a proton.

In *p*-nitroaniline, the conjugation is more extended than in either nitrobenzene or aniline, the separation of charge is greater, and so the wavelength of the absorbed light is longer. In general, any group which conjugates with the benzene ring will shift the frequency of the absorbed light to longer wavelengths (auxochromes behave like chromophores in this respect). Thus, for a compound to act as a dye (as far as *colour* is concerned), it is necessary for the molecule to have as large a changing dipole moment as possible, and this may be achieved by the presence of two or more polar groups as far apart as possible but connected by a conjugated system.

Free radicals are usually coloured, and this is because ΔE is small.

The V.B. resonance approach to colour is satisfactory from a qualitative point of view, but the M.O. method appears to be more promising from a quantitative point of view. It has now been possible to calculate the light absorption of many molecules, and good agreement has been obtained between calculated and observed values. A simplified version of the M.O. method has now been developed (Coulson *et al.*, 1947; Dewar, 1952).

NOMENCLATURE OF DYES. There is no systematic nomenclature of dyes. Many have names that have been given to them by the manufacturers, and so it is not unusual to find a given dye having several names. Generally, each dye has a trade name (or names), and the shade is indicated by a letter, *e.g.*, Y or G = yellow (*gelb*); O = orange; R = red; B = blue. Sometimes the letter is repeated, the number of letters indicating roughly the intensity of the colour, *e.g.*, methyl violet 6B is a very deep purple (close to blue). Sometimes the letters have other meanings, *e.g.*, alizarin blue D; here the D means that this dye is a *direct* cotton colour; fuchsine S, the S indicating that the dye is an *acid* (*sauer*) colour. The letter F is often used to indicate that the dye is fast to light.

To avoid difficulties, the Society of Dyers and Colourists have compiled a Colour Index in which each dye is assigned its individual colour number (**C.I. no.**).

Classification of Dyes. Dyes are classified according to their chemical constitution or by their application to the fibre. The former is of theoretical value to the chemist but of little importance to the dyer who is mainly concerned with the reaction of dyes towards the fibre being dyed.

Chemical Classification. The chemical constitutions of dyes are so varied that it is difficult to classify them into distinct groups. The following classification is used in this book; in some cases a particular dye could be placed in one or other group.

(1) Nitro-dyes; (2) Nitroso-dyes; (3) Azo-dyes; (4) Diphenylmethane dyes; (5) Triphenylmethane dyes; (6) Xanthen dyes; (7) Diphenylamine dyes; (8) Heterocyclic dyes: (i) *acridine group*, (ii) *quinoline group*, (iii) *azine group*, (iv) *thiazine group*, (v) *oxazine group*; (9) Vat dyes: (i) *indigoid group*, (ii) *anthraquinone group*; (10) Anthraquinoid dyes (not vat dyes); (11) Sulphur dyes; (12) Phthalocyanine dyes.

Classification according to application

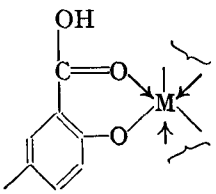
1. **Acid dyes** are the sodium salts of sulphonic acids and nitrophenols. They dye animal fibres directly, but not vegetable; they are mostly applied to wool and silk.

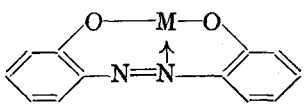
2. **Basic dyes** are mostly the salts of colour bases (p. 786) with hydrochloric acid or zinc chloride. They dye animal fibres directly, and vegetable fibres which have been mordanted with tannin. Basic dyes are mostly applied to cotton and silk.

3. **Direct dyes** (*substantive dyes*) dye animal and vegetable fibres directly.

4. **Mordant dyes** (*adjective dyes*) dye neither animal nor vegetable fibres directly, but require a mordant. If the dye is acidic, the mordant must be basic; if the dye is basic, then the mordant must be acidic. For acidic dyes the mordants are metallic hydroxides; for basic dyes the mordant generally used is tannin (tannic acid). For metal mordanting, the fabric is dipped into a solution of the metallic salt and the " padded " fibre is then dipped into the solution of the dye; this produces an insoluble coloured lake which is fast to washing. For tannin mordanting, the fabric is dipped into a tannin bath, but since the lakes are dull and tend to be fugitive, potassium antimonyl tartrate (tartar emetic) is added to the tannin bath; this produces brighter and more insoluble lakes.

The colour of the lake depends on the metal used; the commonest metals are chromium, aluminium, iron and tin. Lakes are believed to be chelate compounds formed between the metal and the dye. The majority of mordant dyes owe their special properties to the presence of hydroxyl groups, and it appears that dyes containing one hydroxyl group will be mordanted if this hydroxyl group is *ortho* to a carboxyl, nitroso-, azo- or imino-group, *e.g.*,





Chromium, aluminium and iron usually form chelate compounds containing *three* dye molecules. It is important to note that the sulphonic acid group cannot form lakes.

5. **Vat dyes** are insoluble in water, but are reduced by alkaline sodium hyposulphite (dithionite) to alkali-soluble compounds which are readily

reoxidised to the dye. These reduced compounds are often white or colourless, and so are called **leuco-compounds.** Dyes in the leuco-condition dye both animal and vegetable fibres directly. Vat dyes are used mostly on cotton.

6. **Ingrain** or **developed dyes** are dyes which are produced in the fibre. They are divided into three broad groups:

(i) *Ice-colours.* These are produced generally on cotton by soaking the fibre (" padding ") in the secondary component (phenol or amine) of the azo-dye, and developing the colour by immersion in the diazonium salt solution. The name *ice-colours* was given because diazotisation and coupling are carried out at *low* temperatures.

(ii) A direct cotton-dye containing a free amino-group is applied to the fibre and diazotised by dipping into a nitrous acid solution, followed by dipping into a solution of the secondary component (phenol or amine), whereupon the azo-dye is produced.

(iii) *Aniline-black.* This is produced by the oxidation of aniline hydrochloride either by oxidising the fibre impregnated with the amine salt, or by heating the fibre with a solution of aniline hydrochloride containing the oxidising agent (potassium chlorate, and vanadium salts as catalyst).

7. **Sulphur dyes** are dyes containing sulphur, and are soluble in aqueous sodium sulphide. Sulphur dyes are used exclusively for vegetable fibres, the dye being regenerated in the fabric by oxidation in the atmosphere, or by oxidation with dilute aqueous potassium dichromate.

8. **Rayon dyes.** Viscose rayon and *cupra silk* (p. 465) can be dyed in the usual way; acetate rayon, however, requires special dyes and techniques.

9. **Organic pigments.** These are not dyes in the sense that they dye fibres, but are solids which are generally insoluble in water, and are used for colouring paints, varnishes, etc. Some pigments have been made water soluble and then are used as dyes, *e.g.*, phthalocyanine dyes.

Theory of Dyeing. It appears that the mechanism of dyeing depends on the nature of both the dye and the fibre. Textile fibres fall into two main groups, vegetable and animal. *Vegetable fibres* are cellulose fibres, *e.g.*, cotton, linen, flax, hemp and jute. *Animal fibres* are protein fibres, *e.g.*, wool, silk and leather. There is also a third type of fibres, the *artificial* and *synthetic fibres*, *e.g.*, rayons (cellulose-type) and nylons (protein-type).

X-Ray photographs show that textile fibres are built up from long-chain molecules which are present as amorphous material containing crystalline regions which are known as *crystallites* or *micelles*. In these micelles the long-chain molecules are arranged parallel to one another, and are held together by the usual crystal forces, and in the case of wool, by cross-linkages between the chains. The edges of the micelles are not clearly defined but merge into amorphous material of the same chemical structure as the micelles, though not arranged in a definite oriented pattern. Thus a fibre consists of a number of micelles linked by amorphous parts.

When a fibre is placed in water, it swells owing to the osmotic pressure developed internally. It has been shown (by X-ray studies) that swelling takes place in the amorphous parts, producing open pores large enough to permit the passage of dye molecules. According to one theory of dyeing, the dye molecules enter the fibre by diffusing through these pores and then along the parallel channels in the micellar portions.

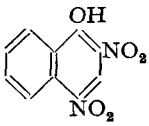
In cellulose fibres, it has been suggested that the dye molecule is oriented parallel to the micellar chains, and is attached by hydrogen bonding. Since hydrogen bonding is not very strong, it is necessary to have a *long* dye molecule in order to get a number of points of attachment by hydrogen bonding. As the dye molecule becomes longer (bigger), however, it becomes less soluble and so less easily dissolved out, *i.e.*, it becomes faster to washing. On the other hand, if the dye molecule becomes too large, it becomes too insoluble to be applied. In such cases it can be made soluble by reduction and then regenerated by oxidation, thereby giving a very fast dye since it is so highly insoluble. Furthermore, as

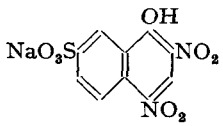
far as cellulose is concerned, the shape of the dye must be linear and planar. Thus, with azo-dyes the *cis* form, which is neither linear nor planar, cannot align itself parallel to the micellar chains (see p. 776).

Protein fibres contain free amino- and carboxyl groups. In acid solution the carboxyl group is undissociated, and the charged $-\overset{+}{N}H_3$ ion is produced. These ions are capable of attracting dye anions to form salts. In alkaline solution it is the carboxylate ion, $-CO_2^-$, which is present, and this is capable of attracting a dye cation to form a salt.

Nitro-dyes. These contain the nitro-group as the chromophore, and hydroxyl group usually as the auxochrome. The simplest nitro-dye is picric acid and was first prepared by Woulfe (1771), who noted its capacity to dye silk bright yellow; the colour, however, is fugitive. Picric acid is really the first synthetic dye, but it was Perkin (1856) who founded the synthetic coal-tar dye industry (see p. 798).

Martius Yellow (*Manchester Yellow*) is 2 : 4-dinitro-1-naphthol (I; Martius, 1864), and is prepared by nitrating 1-naphthol-2 : 4-disulphonic acid (*cf.* picric acid, p. 610). It has been used as the sodium, calcium or ammonium salt, but it


(I)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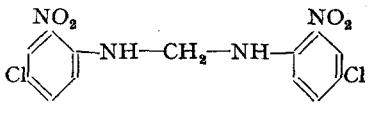
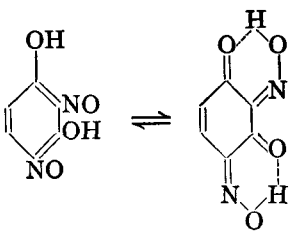
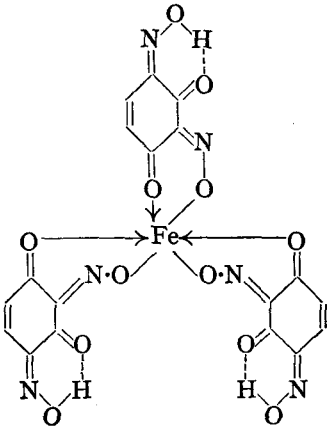

(III)

is fugitive and readily sublimes off the fibre. It has therefore been replaced by **Naphthol Yellow S** (Caro, 1879), 2 : 4-dinitro-1-naphthol-7-sulphonic acid (sodium or potassium salt; II). This is the most important nitro-dyestuff, and is now made by nitrating 1-naphthol-2 : 4 : 7-trisulphonic acid or 4-nitroso-1-naphthol-2 : 7-disulphonic acid. This dye has been very much used as an acid dye for wool and silk.

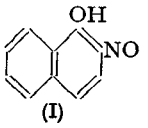
Lithol Fast Yellow GG (III) is a pigment, and is used as a non-poisonous substitute for *Chrome Yellow* (lead chromate). It is prepared by condensing *p*-chloro-*o*-nitroaniline with formaldehyde.

Nitroso-dyes. In these the chromophore is the nitroso-group, and the auxochrome the hydroxyl group. Nitroso-dyes are prepared by the action of nitrous acid on phenols and naphthols. Only the *o*-nitroso-compounds are useful, and these are used mainly in the form of their green iron lakes in dyeing and printing; *e.g.*, **Fast Green O** (Fitz, 1875) is prepared by the action of nitrous acid on resorcinol, and it is the oxime form which produces the lakes (the oxime form is stabilised by intramolecualr hydrogen bonding):

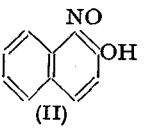




Two other nitroso-dyes are **Gambine R** (2-nitroso-1-naphthol, I) and **Gambine Y** (1-nitroso-2-naphthol, II).



(I)



(II)

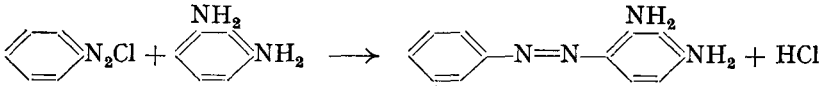
AZO-DYES

In azo-dyes the chromophore is the azo-group, and the common auxochromes are NH_2, NR_2 and OH. Azo-dyes, as far as application is concerned, are classified as *basic, acid, direct, ingrain* and *mordant dyes.*

The structure of an azo-dye is readily found by reduction with stannous chloride and hydrochloric acid, or with sodium hyposulphite (dithionite), whereupon the azo-group is ruptured with the formation of primary amines which are then identified:

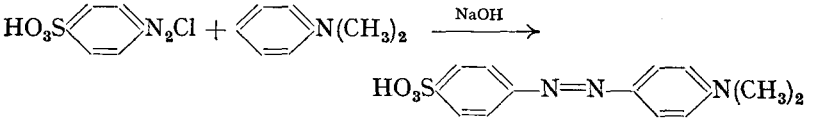
$$Ar{\cdot}N{=}N{\cdot}Ar' \xrightarrow{[H]} Ar{\cdot}NH_2 + Ar'{\cdot}NH_2$$

Basic Azo-dyes contain NH_2 or NR_2 as the auxochrome. **Aniline Yellow** (*aminoazobenzene,* p. 597) and **Butter Yellow** (p-*dimethylaminoazobenzene,* p. 598) are the simplest basic azo-dyes, but are of very little value as dyes since they are sensitive to acids. **Phenylene Brown** or **Bismarck Brown G** (Martius, 1863) was the first commercially important azo-dye, and was manufactured by the action of nitrous acid on excess of *m*-phenylenediamine. It consists of a mixture of the hydrochlorides of mono- and bisazo-derivatives (see p. 579). **Chrysoidine G** (Caro, 1875; Witt, 1876) is prepared by coupling diazotised aniline with *m*-phenylenediamine:

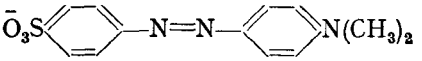


It is an orange dye, and is still used for dyeing cotton on a tannin mordant.

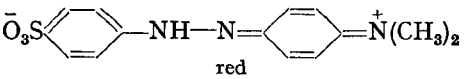
Acid Azo-dyes contain a sulphonic acid group. **Methyl Orange** (*helianthin*) is prepared by coupling diazotised sulphanilic acid with dimethylaniline:



It dyes only in fugitive shades; it is used as an indicator, being orange in alkaline solution and red in acid solution (*cf.* Congo red, below):

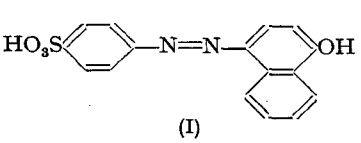


orange

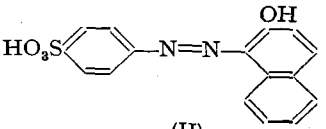


red

Coupling diazotised sulphanilic acid with 1-naphthol gives **Orange I** (Griess, 1876), and with 2-naphthol it gives **Orange II** (Roussin, 1876). These Orange dyes were the first acidic azo-dyes to be put on the market.

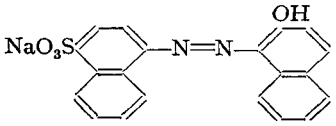


(I)

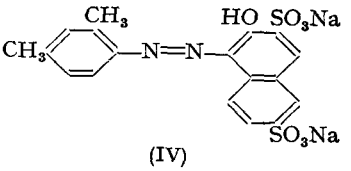


(II)

Fast Red AV, (III), (Caro, 1877) is made by coupling diazotised naphthionic acid (p. 718) with 2-naphthol. **Ponceau 2R,** (IV), is prepared by coupling diazotised *m*-xylidine with the sodium salt of R-acid (p. 721).

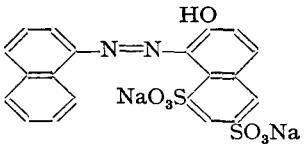


(III)

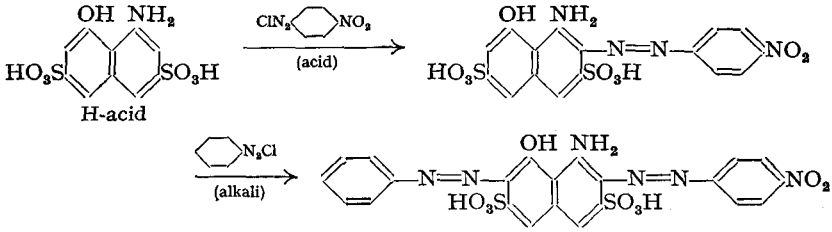


(IV)

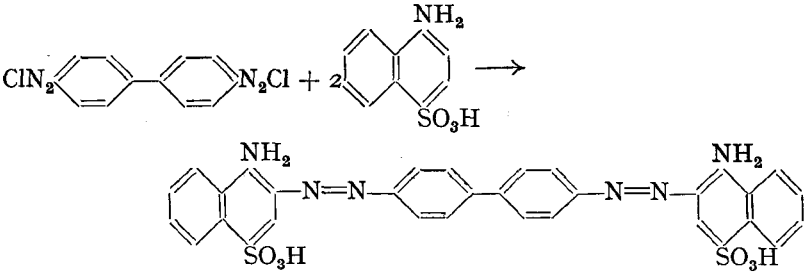
Crystal Ponceau 6R is prepared by coupling diazotised 1-naphthylamine with the sodium salt of G-acid (p. 721).



Naphthol Blue Black B (Hofmann, 1891) is one of the most largely used black acid dyes. It is made by coupling H-acid with one molecule of diazotised *p*-nitroaniline in *acid* solution (coupling occurs in the 2-position), and then coupling the product, in alkaline solution, with one molecule of diazotised aniline (coupling occurs in the 7-position):

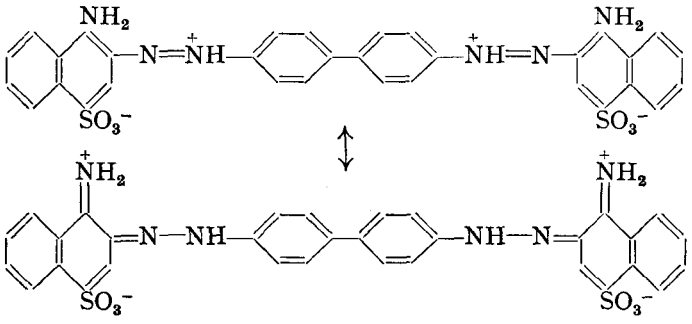


Direct Azo-dyes. Congo Red (Bottiger, 1885) is a bisazo-dye which is prepared by coupling tetrazotised benzidine with two molecules of 1-naphthylamine-4-sulphonic acid:

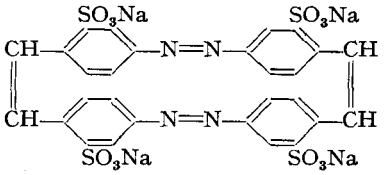


This is red in alkaline solution, and its sodium salt dyes cotton a full red. Congo red was the first synthetic dye produced that was capable of dying cotton directly. It is very sensitive to acids, the colour changing from red

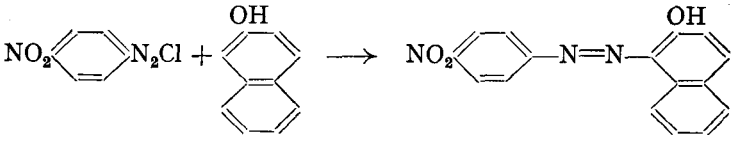
to blue in the presence of inorganic acids. This blue colour, *i.e.*, the deepening of colour, may be attributed to the formation of new structures similar to those of aminoazobenzene (see p. 775):



Stilbene dyes. These are examples of direct azo-dyes without the use of diazotisation and coupling, *e.g.*, **Sun Yellow** (Walter, 1883) is made by heating 4-aminotoluene-2-sulphonic acid with sodium hydroxide solution. The structures of these stilbene dyes were elucidated by Green, Wahl *et al.* (1897–1908).



Ingrain Azo-dyes. These insoluble azo-dyes are known as **azoic dyes.** Dyeing with **Para Red** is carried out by " padding " the fibre with an alkaline solution of 2-naphthol containing Turkey-red oil, drying the cloth, and then immersing it in an ice-cold bath of diazotised *p*-nitroaniline:

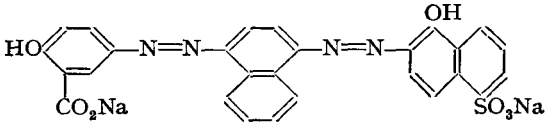


The colour of ingrain azo-dyes can be varied from orange to blue by varying the amine component (diazotised), *e.g.*,

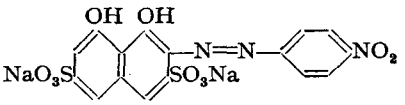
2-naphthol + *m*-nitroaniline = *Nitroaniline Orange*
,, + 2 : 4-dinitroaniline = *Permanent Red 2G*
,, + dianisidine = *Dianisine Blue*

Mordant Azo-dyes. Chromium is the most important metal used in mordanting azo-dyes, producing the so-called *azo-chrome mordant dyes.* The fibre is mordanted by boiling with potassium dichromate solution, usually with a reducing agent such as formic, lactic, or oxalic acid (the dichromate is converted into chromic hydroxide).

Diamond Black F (Lauch and Krekeler, 1889) is one of the earliest chrome dyes, and is produced by coupling diazotised 5-aminosalicylic acid with 1-naphthylamine, and diazotising the product with 1-naphthol-4- or 5-sulphonic acid, *e.g.*,

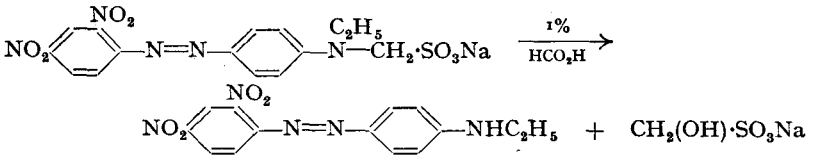


Instead of mordanting the fibre first, the azo-dye may be applied to the fibre first, and then the dye " chromed " by boiling with sodium dichromate and a reducing agent. By this procedure the colour may be changed completely. Most of the azo-dyes that are " after-chromed " on the fibre are derived from *chromotropic acid* (1 : 8-dihydroxynaphthalene-3 : 6-disulphonic acid); *e.g.*, **Chromotrope 2B** (Kuzel, 1890) is prepared by coupling *p*-nitroaniline with chromotropic acid:



This dyes wool a bluish-red; the colour is changed into blue to black by " after-chroming ".

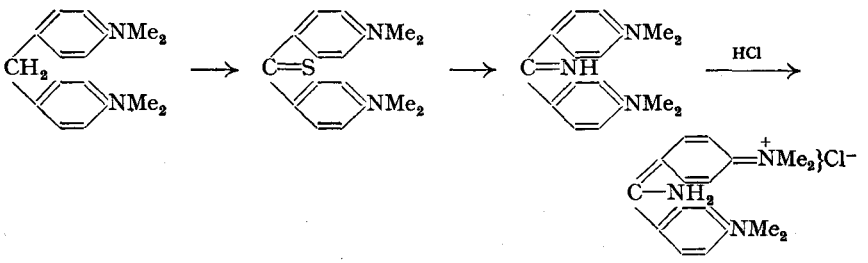
Cellulose acetate rayon dyes. It was found to be very difficult to dye rayon by the usual dyestuffs, since the dyeings were not fast. The first dyes specially designed for dyeing rayon were the *Ionamine dyes* (Green and Saunders, 1922). These are methyl-ω-sulphonates of insoluble aminoazo-compounds which are slowly hydrolysed in the hot dye bath (65–75°), giving formaldehyde bisulphite and the aminoazo-compound in a form readily absorbed by the fibre, *e.g.*, **Ionamine Red KA.**



A more general method is one discovered independently by Shepherdson and Ellis (1923). The insoluble dye, by means of dispersing agents—originally sulphoricinoleic acid, but now replaced by more effective reagents—is prepared in a state of uniform fine dispersions in the dye bath. These dispersions are not satisfactory for all purposes.

DIPHENYLMETHANE DYES

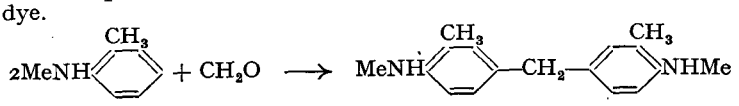
Auramine O was discovered independently by Kern and Caro (1883). They prepared it by fusing Michler's ketone (p. 665) with ammonium and zinc chlorides at 150–160°. It is now prepared by heating *p* : *p'*-tetramethyldiaminodiphenylmethane with sulphur, ammonium chloride and a large excess of sodium chloride



in a current of ammonia at about 200° (Sandmeyer, 1889); this produces *Auramine Base*. This, with hydrochloric acid forms the hydrochloride, *Auramine O*, a yellow basic dye. It has a low fastness, being readily hydrolysed to the corresponding ketone. Nevertheless, it is largely used for dyeing cotton, paper, leather, wool, silk and jute; it is also used for lake-making.

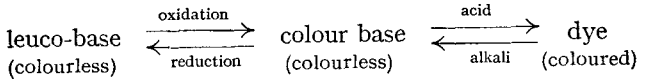
Auramine G (Grehn and Schmid, 1892) is made in a similar way from the condensation product of monomethyl-*o*-toluidine and formaldehyde, which is

heated with sulphur in a current of ammonia. Auramine G is a greenish-yellow basic dye.

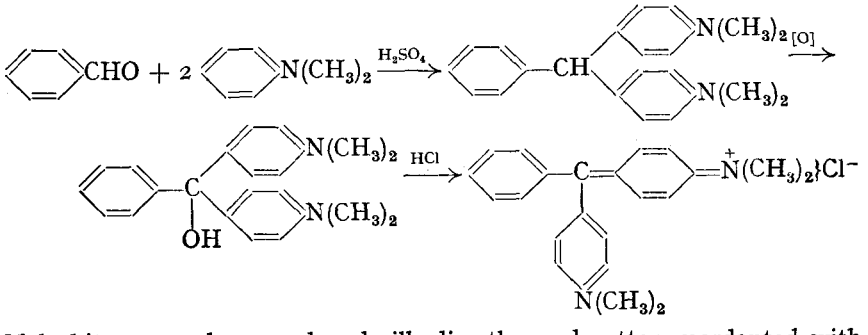


TRIPHENYLMETHANE DYES

Triphenylmethane dyes are obtained by the introduction of NH_2, NR_2 or OH groups into the rings of triphenylmethane. The compounds so obtained are colourless—the **leuco-compounds**—and these, on oxidation, are converted into the corresponding tertiary alcohols, the **colour bases,** which readily change from the colourless benzenoid forms to the quinonoid dyes in the presence of acid, due to salt formation. The salts are easily reconverted into the leuco-base:

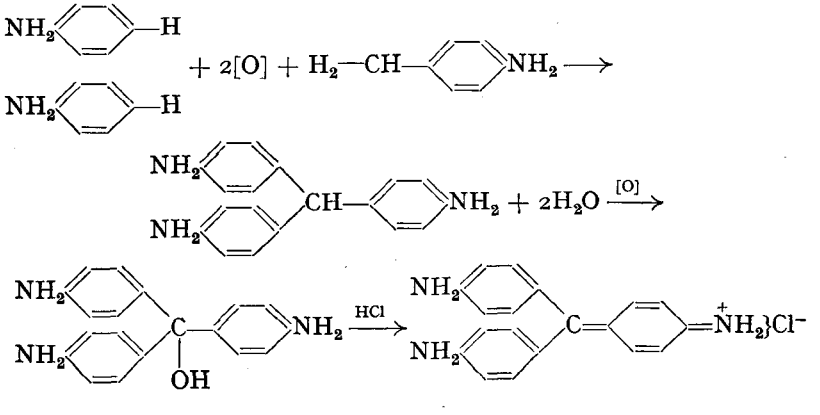


Malachite Green (O. Fischer, 1877) is prepared by condensing dimethylaniline (2 molecules) with benzaldehyde (1 molecule) at 100° in the presence of concentrated sulphuric acid. The leuco-base produced is oxidised with lead dioxide in a solution of acetic acid containing hydrochloric acid; the resulting colour base gives malachite green with excess hydrochloric acid:



Malachite green dyes wool and silk directly, and cotton mordanted with tannin. **Fast Green** or **Brilliant Green** (Bindschedler and Busch, 1879) is the sulphate of the corresponding ethyl derivative; it gives a more yellow shade than malachite green, and is also a powerful antiseptic.

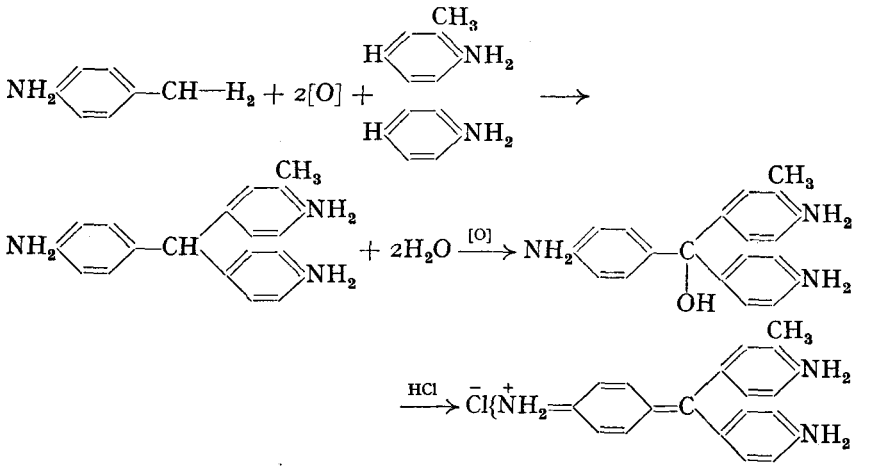
Pararosaniline is prepared by oxidising a mixture of *p*-toluidine (1 molecule) and aniline (2 molecules) with arsenic acid or nitrobenzene:



In the newer process, pararosaniline hydrochloride is prepared by starting with aniline (2 molecules) and formaldehyde (1 molecule), and treating the product, 4 : 4′-diaminodiphenylmethane, with aniline hydrochloride in the presence of an oxidising agent:

$$2C_6H_5{\cdot}NH_2 + CH_2O \longrightarrow NH_2{\cdot}C_6H_4{-}CH_2{-}C_6H_4{\cdot}NH_2 \xrightarrow[[O]]{C_6H_5{\cdot}NH_2{\cdot}HCl} (NH_2{\cdot}C_6H_4{-})_2C{=}C_6H_4{=}\overset{+}{N}H_2\}Cl^-$$

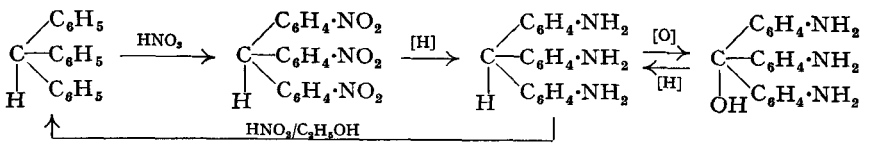
Rosaniline, Magenta, Fuchsine (Verguin, 1859) is the *o*-methyl derivative of pararosaniline. It is produced by oxidising an equimolecular mixture of aniline, *o*- and *p*-toluidines, and their hydrochlorides, with nitrobenzene in the presence of iron filings. The product is a mixture of rosaniline and pararosaniline, in which the former predominates:



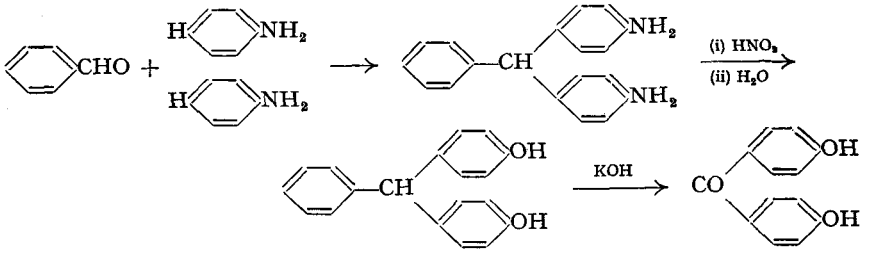
Crystals of rosaniline show a green metallic lustre, and dissolve in water to form a deep-red solution. This solution is decolorised by sulphur dioxide and is then known as Schiff's reagent, which is used as a test for aldehydes (see p. 160). The chemical changes involved in the preparation of Schiff's reagent are still uncertain.

Rosaniline (and pararosaniline) dyes wool and silk directly, producing a violet-red colour; cotton must first be mordanted with tannin.

Structure of rosaniline dyes. Determination of the structures of the rosaniline dyes was carried out by E. and O. Fischer (1878, 1880) as follows. Pararosaniline, on reduction, gives *leucaniline* (the leuco-base). This was shown to be a primary triamine which, on treatment with nitrous acid and subsequent boiling with ethanol, gave triphenylmethane ($C_{19}H_{16}$). Triphenylmethane, on treatment with fuming nitric acid, gave a trinitro-derivative which, on reduction, gave leucaniline, and this, on oxidation, gave pararosaniline base (the colour base):



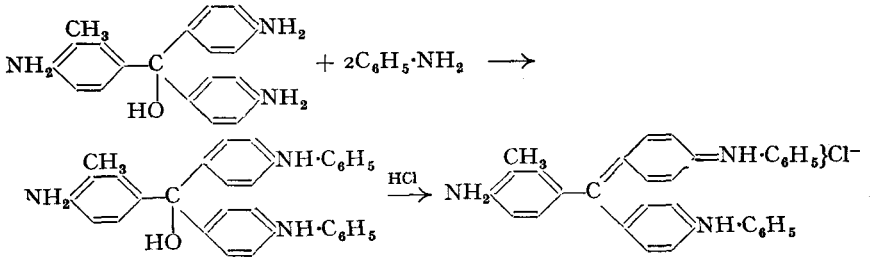
Thus pararosaniline base is a triaminotriphenylcarbinol. Each benzene ring probably contains one amino-group since the colour base is synthesised from 2 molecules of aniline and one of *p*-toluidine. Also, nitration of triphenylmethane is likely to introduce one nitro-group into each ring, and furthermore, it is probable that each nitro-group is in the *p*-position (*cf.* diphenyl and diphenylmethane). The positions of the three amino-groups, however, were found as follows. Condensation of benzaldehyde with aniline in the presence of zinc chloride gives diaminotriphenylmethane. This, on treatment with nitrous acid and followed by boiling with water, gives dihydroxytriphenylmethane which, on fusion with potassium hydroxide, gives *p* : *p'*-dihydroxybenzophenone. These reactions may be formulated as follows:



The two amino-groups in diaminotriphenylmethane are therefore in the *p*-positions. Since *p*-nitrobenzaldehyde condenses with aniline to give a product which, on reduction, gives leucaniline, it follows that all three amino-groups are in the *p*-positions to the methane carbon atom.

The structure of rosaniline was found in a similar manner. The hydrocarbon obtained was $C_{20}H_{18}$, and one structure that agrees with this is diphenyltolylmethane. The position of the methyl group in the tolyl ring is indicated by the fact that, in order to obtain rosaniline, *o*-toluidine must be used as one of the starting materials (see above). This position (*ortho* to the *p*-amino-group) is confirmed by condensing 4-nitro-3-methylbenzaldehyde with aniline, and reducing the product; leucorosaniline is obtained.

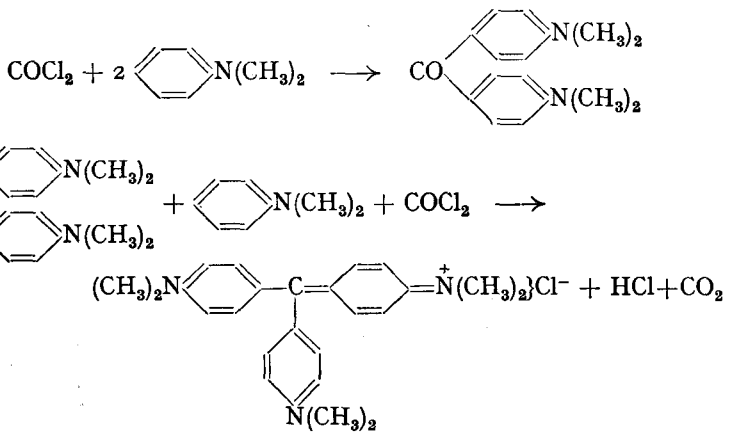
Aniline Blue (Girard and de Laire, 1861) is the diphenyl derivative of rosaniline, and is prepared by heating the latter with aniline and benzoic acid (the function of the acid in this reaction is obscure). The *o*-methyl group prevents phenylation of the amino-group in this ring (steric effect). If pararosaniline is used, the *triphenyl* derivative is obtained.



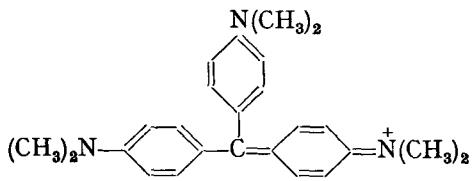
Aniline Blue is readily sulphonated, the sulphonic acid group entering the *substituted phenyl radicals*. Nicholson (1862) thus prepared **Alkali Blue** (the monosulphonic acid) and **Soluble Blue** (the trisulphonic acid). These compounds dye wool and silk directly.

Crystal Violet (Kern, 1883) may be prepared by heating *Michler's ketone* with dimethylaniline in the presence of phosphoryl chloride or carbonyl

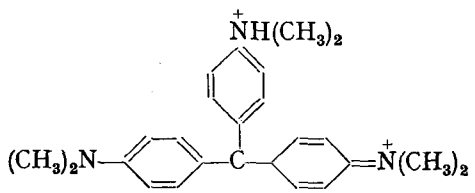
chloride. If the latter compound is used, then crystal violet may be prepared directly by heating carbonyl chloride and dimethylaniline:



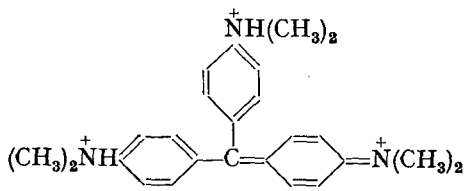
A weakly acid solution of crystal violet is purple. In *strongly* acid solution the colour is green, and in still more strongly acid solution, the colour is yellow. The explanation of these colour changes may be as follows (*cf.* p. 775). In weakly acid solution crystal violet exists as the singly charged ion (I). In this state two-thirds of the charge can oscillate in the horizontal direction. In strongly acid solution, if crystal violet exists as the *doubly* charged ion (II), the whole unit of charge can oscillate in the horizontal



(I)



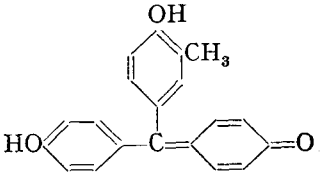
(II)



(III)

direction, and consequently the colour *deepens* (the vertical direction of oscillation is inhibited due to the fixation of the lone pair by proton addition). In very strongly acid solution another proton is added to form the ion (III) with three charges. In this ion relatively little resonance (with oscillation of charge) is possible, and consequently the colour lightens.

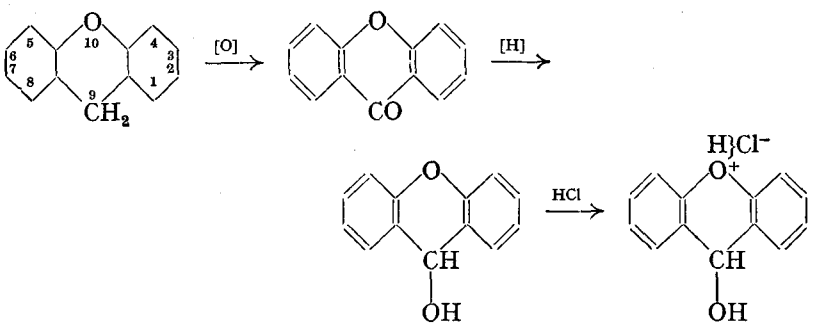
Rosolic acid, Aurin is prepared by diazotising rosaniline and boiling the diazonium compound with water. It crystallises in red prisms, which are soluble in alkalis to form intense red solutions. It is used as an indicator,



and has been used in the form of lakes for the printing of wall-papers. **Para-aurin** is the corresponding hydroxy-compound of pararosaniline.

XANTHEN DYES

The parent substance of this group of dyes is **xanthen** (*dibenzo*-1 : 4-*pyran*). This, on oxidation, yields **xanthone** (9-*ketoxanthen*) which, on reduction, yields **xanth-hydrol** (9-*hydroxyanthen*). This forms *oxonium salts* with inorganic acids (*cf.* p. 768):

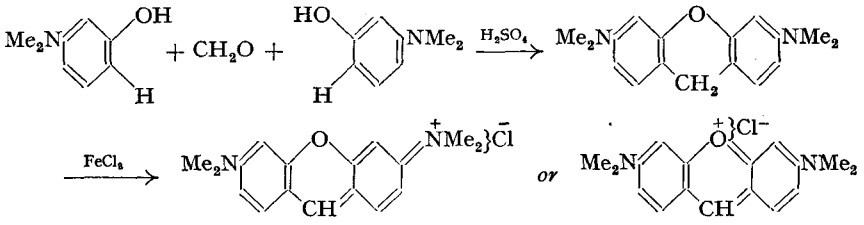


Dyes are obtained from xanthen by the introduction of auxochromes into positions 3 and 6 (*i.e.*, the *p*-positions with respect to the carbon atom linking the two benzene nuclei).

Pyronines. *Pyronine G* (Bender, 1889) is prepared by condensing formaldehyde (1 mol.) with *m*-dimethylaminophenol (2 mols.) in the presence of concentrated sulphuric acid, and then oxidising the leuco-compound with ferric chloride.

Pyronine G dyes silk and cotton mordanted with tannin a crimson red.

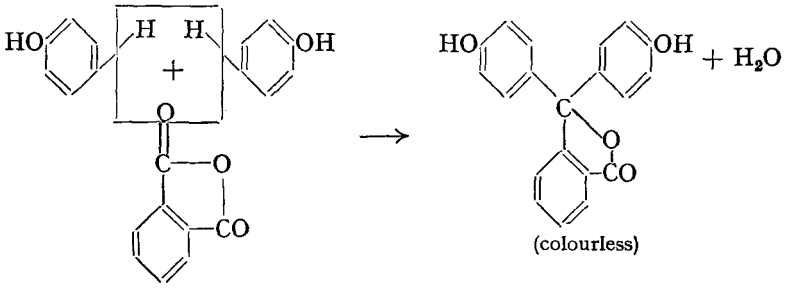
Since two electronic structures are possible in which the conjugation is totally different, more information is necessary to say which form predominates, or even whether both forms are present.



Phthaleins. A sub-group of the xanthen dyes is the **phthaleins.** These are obtained by condensing phenols with phthalic anhydride in the presence

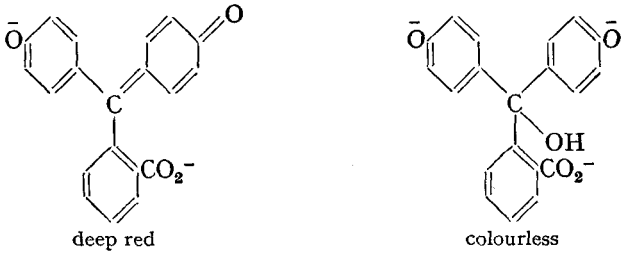
of certain dehydrating agents, *viz.*, concentrated sulphuric acid, zinc chloride or anhydrous oxalic acid.

Phenolphthalein (Baeyer, 1871) is not a xanthen derivative but a triphenylmethane derivative. Since, however, it is prepared from phenol and phthalic anhydride, it is more closely allied to the phthaleins in (preparation and properties), and hence is here considered in the phthalein group. Phenolphthalein is prepared by heating phthalic anhydride (1 molecule) with phenol (2 molecules) in the presence of concentrated sulphuric acid:



(colourless)

It is a white crystalline solid, insoluble in water, but soluble in alkalis to form deep red solutions:

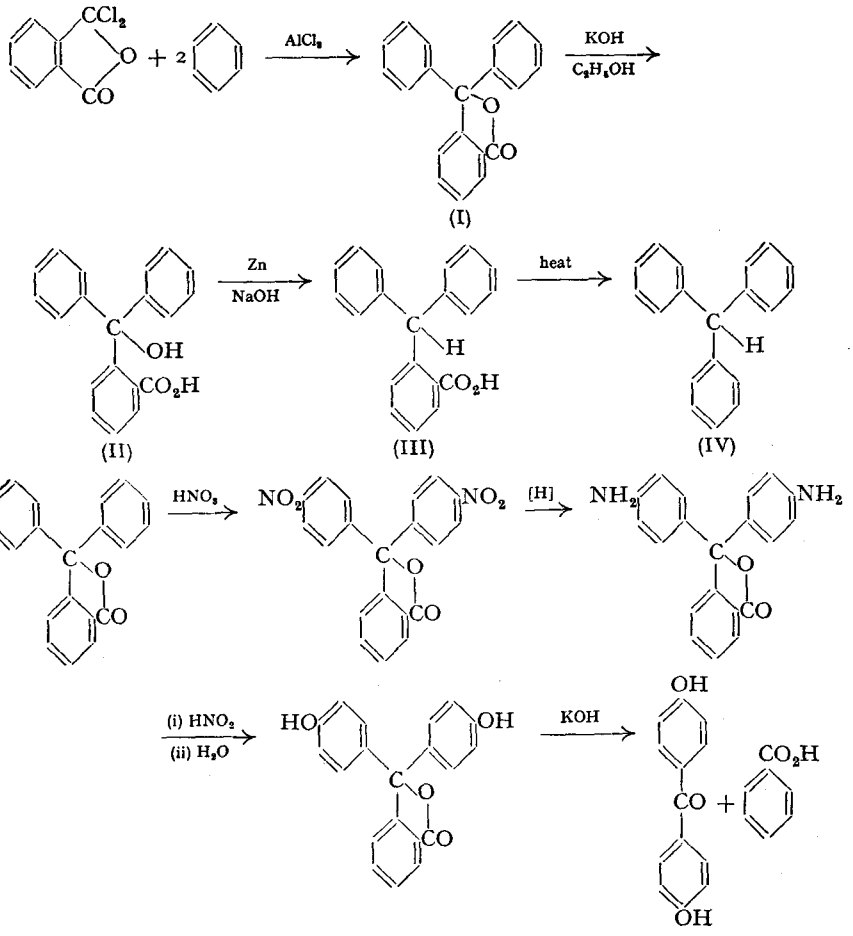


deep red colourless

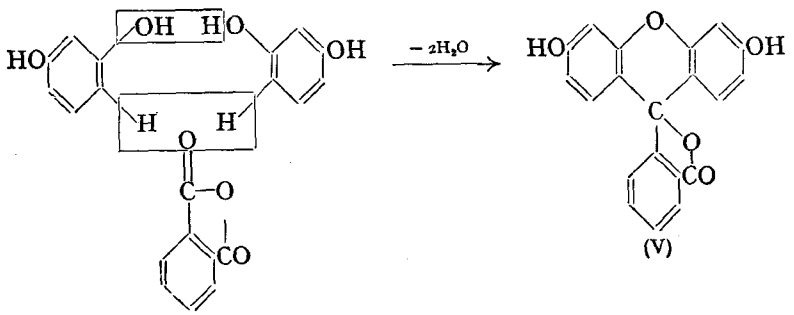
In the presence of *excess* strong alkali, the solution of phenolphthalein becomes colourless again due to the loss of the quinonoid structure and resonance (but see fluorescein, below).

Structure of phenolphthalein. Phthaloyl chloride condenses with benzene in the presence of aluminium chloride to form 3 : 3-diphenylphthalide (phthalophenone), (I). This, on heating with ethanolic potassium hydroxide, gives triphenylcarbinol-*o*-carboxylic acid, (II), which, on treatment with zinc dust and ethanolic sodium hydroxide, gives triphenylmethane-*o*-carboxylic acid, (III). This on dry distillation gives triphenylmethane, (IV). When 3 : 3-diphenylphthalide is nitrated, a mixture of two dinitro-derivatives is obtained. Reduction of these two dinitro-compounds results in the formation of two diamino-compounds, one of which, being much less soluble than the other, crystallises out first. This less soluble diamino-compound gives phenolphthalein when treated with nitrous acid. These reactions show that phenolphthalein contains the triphenylmethane nucleus, and that it is a dihydroxy-derivative of 3 : 3-diphenylphthalide. The problem now is to ascertain the positions of the two hydroxyl groups. That they are in different rings is indicated by the fact that phenolphthalein is formed when phthalic anhydride (1 molecule) is heated with phenol (2 molecules). Thus, when 3 : 3-diphenylphthalide is nitrated, we may assume that the dinitro-compound produced contains one nitro-group in each benzene ring, the phthalic acid ring remaining unsubstituted (this ring may be regarded as already substituted, and hence the nitro-groups will enter the *unsubstituted* rings, and probably in the *p*-positions; *cf.* diphenyl). When phenolphthalein is fused with potassium hydroxide, it gives benzoic acid and

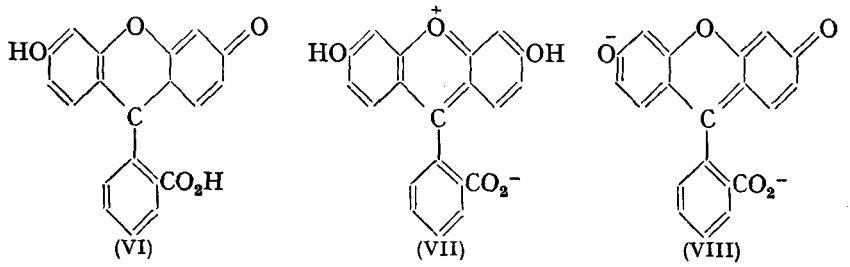
p : *p*′-dihydroxybenzophenone. Thus each hydroxyl group occupies a *p*-position with respect to the methane carbon atom. The foregoing reactions may therefore be formulated:



Fluorescein is a xanthen derivative, and is prepared by heating phthalic anhydride (1 molecule) with resorcinol (2 molecules) at 200°, or at 110–120° with anhydrous oxalic acid:



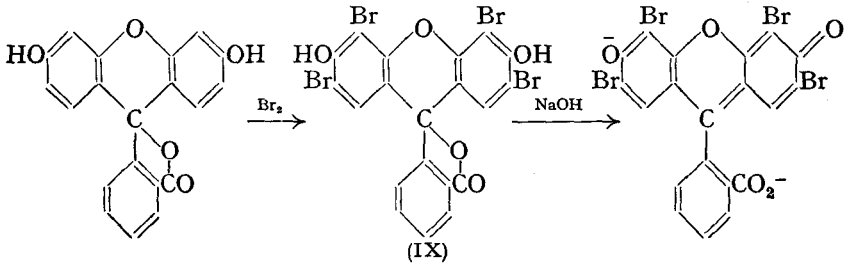
Fluorescein is a red powder insoluble in water. Since it is coloured, the non-quinonoid uncharged structure V has been considered unsatisfactory. Two quinonoid structures are possible in which the conjugation is totally different, one having the *p*-quinonoid structure, VI, and the other the *o*-quinonoid, VII (which contains tercovalent oxygen):



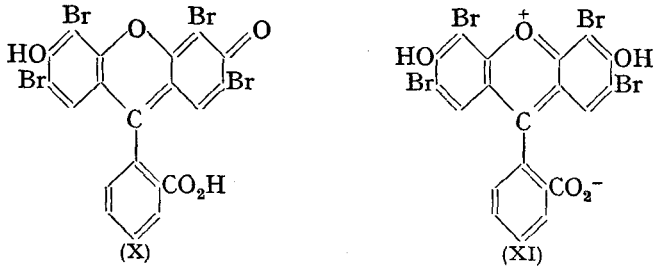
Davies *et al.* (1954) have examined the infrared absorptions of phenol, phenolphthalein, fluorescein, and some of their alkali derivatives, and have concluded that the classical representation of fluorescein (V) is to be preferred. (VI) is eliminated because of the absence of the characteristic absorption of the carboxyl group, and similarly, the frequencies of the carboxylate ion (in VII) are also absent.

Fluorescein dissolves in alkalis to give a reddish-brown solution which, on dilution, gives a strong yellowish-green fluorescence. The structure of the fluorescein anion is (VIII) (oxygen becomes tercovalent unielectrovalent only in acid solution). The sodium salt of fluorescein is known as **Uranine,** and dyes wool and silk yellow from an acid bath; the colours are fugitive.

Eosin (Caro, 1871) is tetrabromofluorescein, and is prepared by the action of bromine on fluorescein in glacial acetic acid solution:

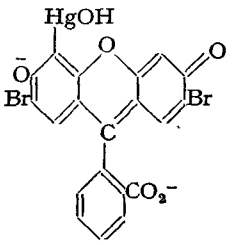


Eosin itself is a red powder and so its structure may not be (IX), but may be (X) or (XI) (*cf.* fluorescein):

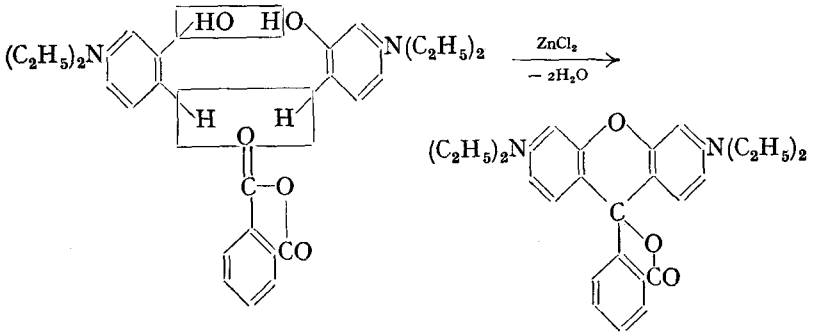


Eosin dyes wool and silk a pure red, with a yellow fluorescence in the case of silk. Eosin is also used as the lead lake *Vermilionette* for poster printing. Most red inks are dilute solutions of eosin.

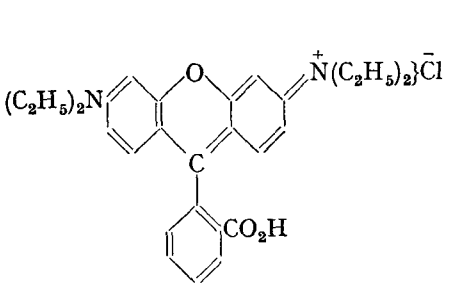
Mercurochrome 220 is a derivative of fluorescein, and is used as an antiseptic.



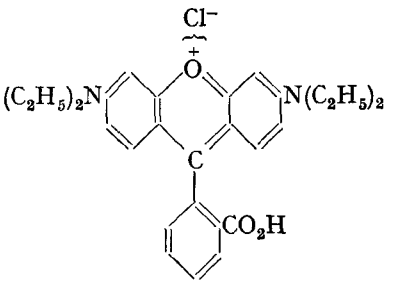
Rhodamines are prepared by condensing phthalic anhydride (1 molecule) with *m*-aminophenol (2 molecules) or its derivatives, *e.g.*, **Rhodamine B**:



The hydrochloride of Rhodamine B may be (XII) or (XIII) (*cf.* above):

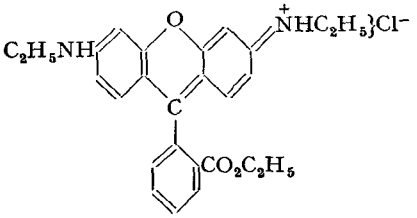


(XII)



(XIII)

Rhodamine 6G is the ethyl ester of diethylrhodamine.

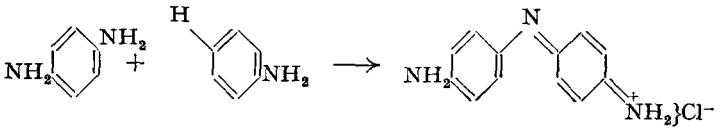


or the *o*-form

The rhodamines are red basic dyes, the *N*-alklyated derivatives being more highly coloured than the unsubstituted compounds. They dye wool and silk directly, and cotton mordanted with tannin.

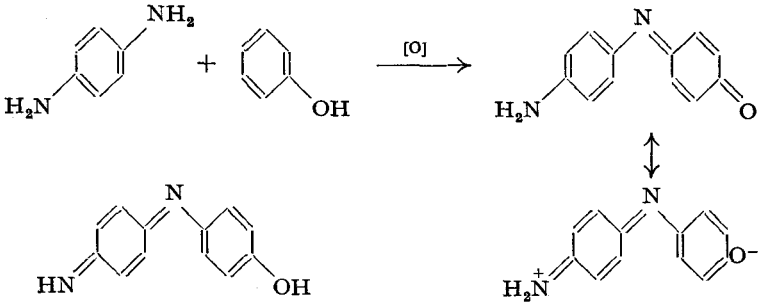
DIPHENYLAMINE (QUINONE-IMINE) DYES

One group of these dyes is the **Indamines** (Nietzki, 1877). The simplest indamine is **Phenylene Blue,** and is prepared by oxidising a solution of a mixture of *p*-phenylenediamine and aniline with potassium dichromate in acetic acid–concentrated hydrochloric acid.



The indamines (which form blue or green salts) are very sensitive to the action of acids, which hydrolyse them to quinones. Hence they are not used as dyes but mainly as starting materials for the manufacture of azines, thiazines and oxazines.

The **Indophenols** are another group of diphenylamine dyes. The simplest is **Indophenol** (Blue), and is prepared by oxidising a mixture of *p*-phenylenediamine and phenol with alkaline hypochlorite solution:



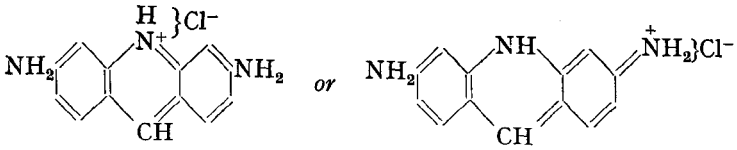
Indophenol is usually given the amino-structure and not the imino-structure because it is insoluble in alkalis but soluble in acids which hydrolyse them to quinones.

The indophenols are blue in colour, and owing to their sensitivity to acids, are not used now as dyestuffs, but only as the starting materials for various sulphur dyes.

HETEROCYCLIC DYES

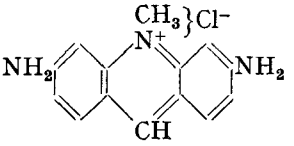
Acridine Group. Acridine dyes are all yellow to orange and brown, basic dyes; they are used in calico printing, dyeing cotton, silk and particularly leather. Some acridine dyes have medicinal and antiseptic properties.

3 : 6-Diaminoacridine is made by heating a mixture of *m*-phenylenediamine, glycerol, oxalic acid and zinc chloride, and oxidising the leuco-compound (see p. 767 for numbering):

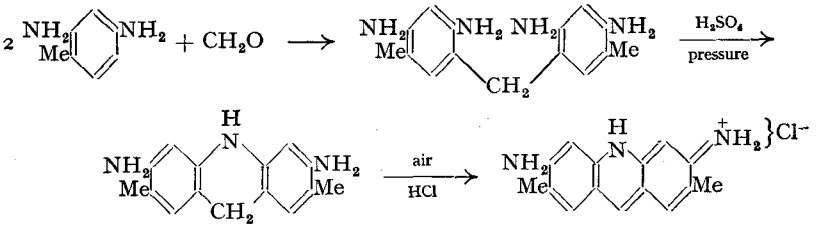


The corresponding sulphate is the antiseptic **proflavine**. On acetylating 3 : 6-diaminoacridine, methylating the 10-N atom by means of methyl

p-toluenesulphonate, and then hydrolysing the product with dilute hydrochloric acid, 3 : 6-diamino-10-methylacridinium chloride is produced. This is known as **acriflavine,** and possesses trypanocidal action (*i.e.*, the power to kill trypanosomes which are micro-organisms causing sleeping sickness and other diseases). It has now been replaced by more potent trypanocides, but it is still used as an antiseptic:

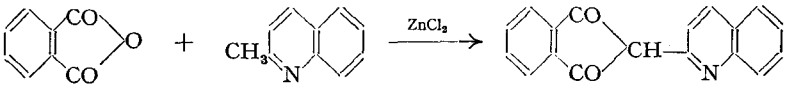


Acridine Yellow is one of the more important acridine dyes, and is prepared from 2 : 4-diaminotoluene and formaldehyde:

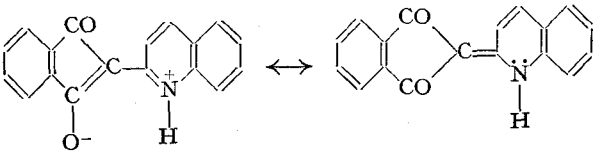


Quinoline group. Most of these dyes are more important as photographic sensitisers than as dyes for fabrics.

Quinoline Yellow (Jacobsen, 1882) is the most important quinoline compound used as a dyestuff for textiles. It is prepared by condensing phthalic anhydride with quinaldine in the presence of zinc chloride.

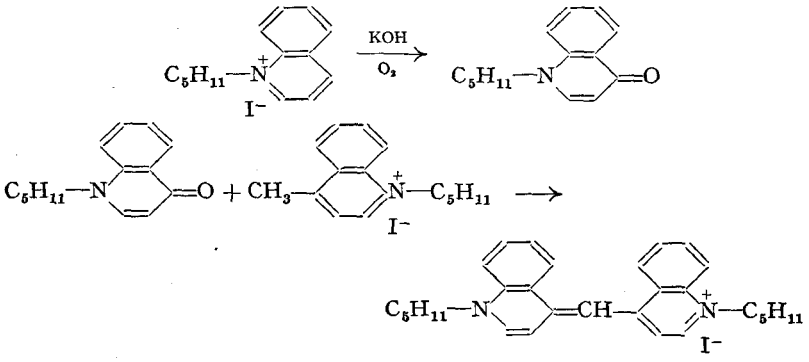


This structure is probably incorrect, since the dye is coloured and so requires a charged structure; it also forms an *N*-methyl derivative which has almost the same absorption spectrum as Quinoline Yellow, thereby indicating a similarity in structure. Hence Quinoline Yellow is considered to be the following resonance hybrid (the *extended* conjugation in the dipolar ion should be noted).

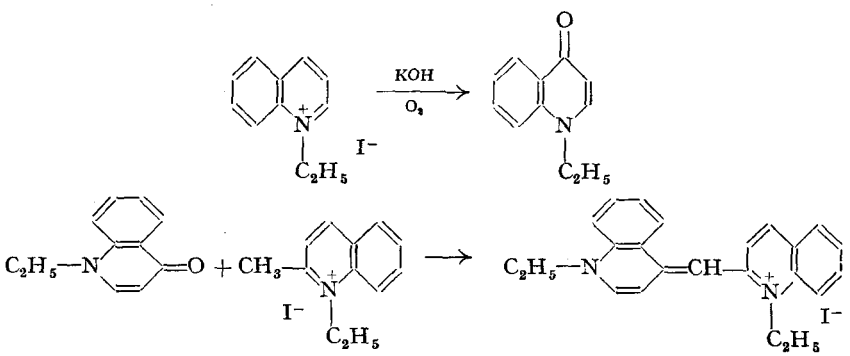


Cyanine (*Quinoline Blue*). The cyanine dyes contain two quinoline nuclei linked in the 4 : 4′-positions by a =CH— group. They were discovered by Williams (1856). They are too fugitive and apparently too expensive to be used as dyes. Vogel (1873) first discovered the photographic sensitising properties of cyanine. Ordinary silver halide photographic plates are sensitive only to the blue and violet regions of the spectrum. By adding a suitable cyanine compound the plates are made sensitive to other regions of the spectrum: yellow, orange, red or green. Plates can also be made sensitive to *all* parts of the spectrum; they are then said to be *panchromatic*.

Cyanine is formed by the air oxidation of a mixture of amylquinolinium and amyllepidinium iodides in the presence of aqueous alkali.

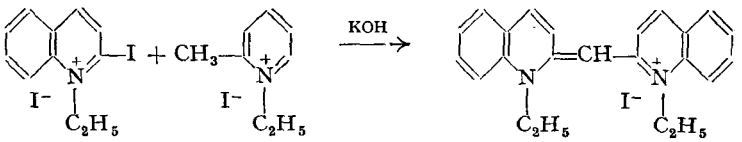


***iso*Cyanine dyes** contain two quinoline nuclei linked in the 2 : 4′-positions by a =CH— group. The first *iso*cyanine was **Ethyl Red** (Hoogewerff and van Dorp, 1883), and is prepared from quinoline and quinaldine ethiodides by air oxidation in the presence of alkali.



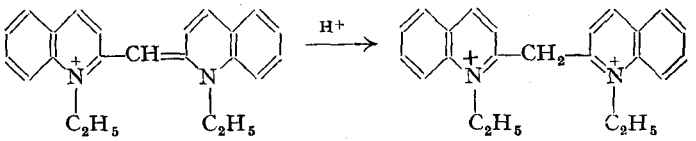
Ethyl Red sensitises plates evenly from orange to the ultraviolet.

Pseudocyanine dyes contain two quinoline nuclei linked in the 2 : 2′-positions by a =CH— group. They are prepared by the action of ethanolic potassium hydroxide on a mixture of a 2-iodoquinoline alkiodide and a quinaldine alkiodide, *e.g.*,

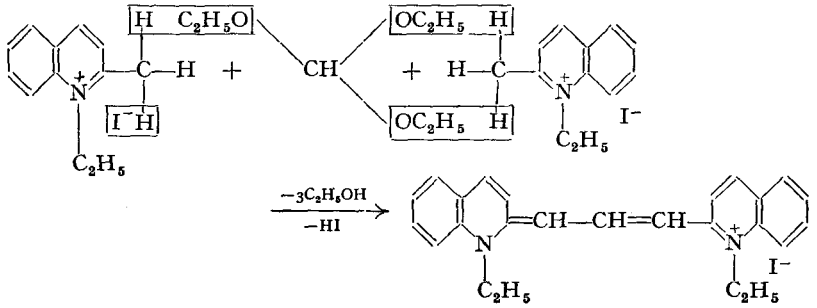


The pseudocyanines are sensitisers for the blue to the green part of the spectrum.

Acidification destroys the colour of cyanine dyes. This is due to the fact that *both* nitrogen atoms become charged, a proton is taken into the chain, and so resonance is prevented between the two nitrogen atoms (see p. 775).



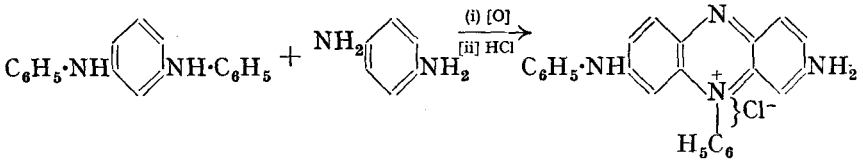
Sensitol Red or **Pinacyanole** (König, 1905) is a *carbocyanine*, and sensitises in the red-to-orange region. Carbocyanines are compounds containing two quinoline nuclei linked in the 2 : 2′-positions by =CH—CH=CH—. *Sensitol Red* is prepared by the action of excess ethyl orthoformate on quinaldine ethiodide in boiling pyridine solution.



The isomeric 4 : 4′-carbocyanines are known as *kryptocyanines*, and are sensitisers for the red and infrared regions. 2 : 4′-Carbocyanines are known as *dicyanines*.

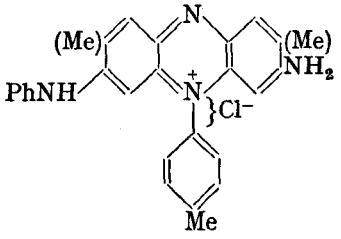
Azine Dyes. Perkin (1856), in search for the synthesis of the alkaloid quinine, oxidised crude aniline sulphate with potassium dichromate, and obtained a black precipitate from which he extracted a mauve colouring matter with methylated spirit. Perkin found that this material had the properties of a dye. This was the first synthetic dye to be used, and was used for dyeing silk under the name of *Aniline Purple* or *Tyrian Purple*. Aniline Purple was the first basic dye to be used, but no method was known (when it was discovered) for applying it to cotton. Perkin and Pullar, independently in 1857, discovered the general method of applying basic dyes to cotton mordanted with insoluble inorganic compounds of tannin. Aniline Purple was used in France under the name of *mauve*, and the dye afterwards became known by this name; it is also known as *mauveine*.

Perkin found that his material contained two products, one from pure aniline—*pseudo-mauveine*, and the other from aniline and *o*-toluidine (the latter was an impurity in crude aniline)—*mauveine*. The structure of pseudomauveine was established by Nietzki who prepared it by oxidising a mixture of *p*-phenylenediamine and diphenyl-*m*-phenylenediamine:

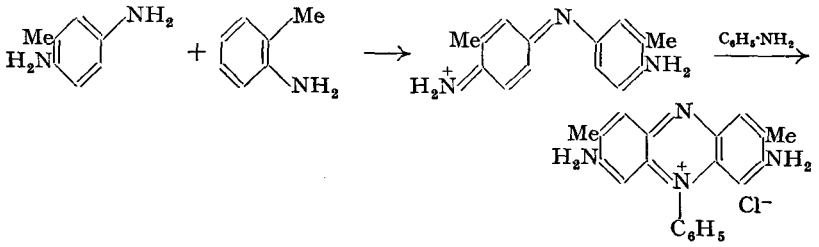


The structure may be the *p*-quinonoid instead of the *o*- shown above (*cf.* fluorescein, etc.).

Mauveine is a mixture of compounds of the type



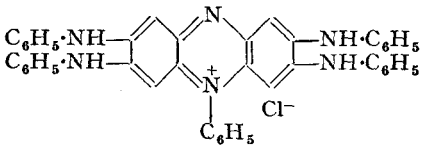
More useful dyes than Mauveine are the **Safranines**—these are more strongly basic than the mauveines. **Safranine T** (Williams, 1859) is prepared by oxidising a mixture of 2 : 5-diaminotoluene, *o*-toluidine and aniline with sodium dichromate and hydrochloric acid (an indamine is formed as an intermediate).



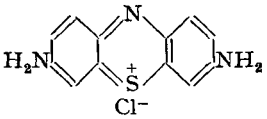
It is a red basic dye, dyeing wool, silk and " tanned " cotton red shades.

Indulines (Caro, 1863) are phenylamino-derivatives of the mauveines, and are prepared by heating a mixture of aminoazobenzene, aniline and its hydrochloride under pressure. They are very much used for colouring leather polishes, for printing cotton and for newspapers.

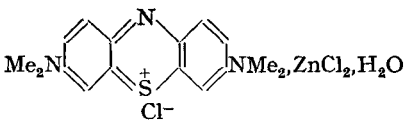
Induline Blue 6B is insoluble in water (as are other indulines), but is made water soluble by sulphonation; the alkaline solutions are used as dyes and for making lakes and inks.



Thiazine dyes. *Lauth's Violet* (1876) was the first thiazine dye to be prepared; it is made by oxidising with ferric chloride in hydrochloric acid a hydrochloric acid solution of *p*-phenylenediamine saturated with hydrogen sulphide.

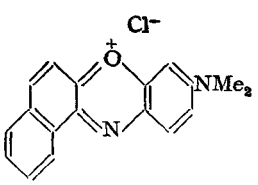


Methylene Blue (Caro, 1876) may be prepared in a similar way to Lauth's violet, but *p*-aminodimethylaniline is used instead of *p*-phenylenediamine. A better preparation is to oxidise a mixture of *p*-aminodimethylaniline and



dimethylaniline with potassium dichromate in the presence of sodium thiosulphate and aluminium sulphate (Bernthsen). The zinc double chloride is used in dyeing, and is largely used for dyeing cotton mordanted with tannin. Methylene Blue, free from the zinc, is used in calico printing, as an indicator and in medicine.

Oxazine dyes. Meldola's Blue or **Naphthol Blue** (1879) is prepared by the

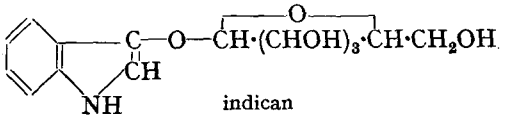


action of excess *p*-nitrosodimethylaniline hydrochloride on 2-naphthol in hot methanol solution.

It is used commercially as the zinc double chloride for dyeing cotton mordanted with tannin; it dyes the fabric an indigo blue. It is also used as a leather dye.

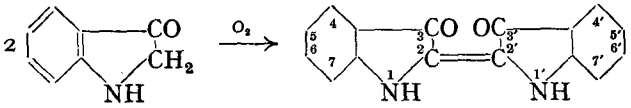
VAT DYES

Indigoid Group. India appears to be the birth-place of **indigo—indigotin** is its official name. It is the oldest known dye—mummy cloths, 5000 years old, have been found that were dyed with indigotin. *Woad*, which is an impure form of indigotin (and is obtained from the plant *Isatis tinctoria*), contains a small amount of *indican* which is the glucoside of indoxyl:

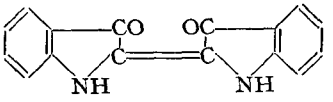


indican

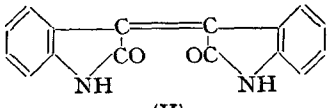
Indigotin used to be obtained from plants of the *indigofera* group, but is now prepared synthetically. These plants do not contain indigotin but indican which, on hydrolysis with hydrochloric acid or by enzymes which occur in the crushed plant, is converted into indoxyl and this, on oxidation by atmospheric oxygen, gives indigotin:



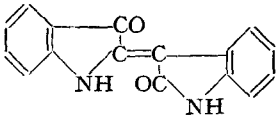
Structure of indigotin. Vapour density determination shows that the molecular formula of indigotin is $C_{16}H_{10}O_2N_2$. Oxidation of indigotin with nitric acid gives two molecules of isatin only, two oxygen atoms being added on in the process. This implies that the indigotin molecule contains two identical units joined together, and that each unit, when indigotin is oxidised, gives a molecule of isatin. There are three possible structures of indigotin which meet these requirements:



(I)

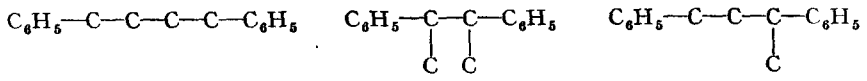


(II)



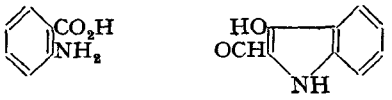
(III)

The carbon skeletons of these are different, *viz.*,



(I) (II) (III)

Synthesis (iv) below, in particular, indicates (I), and this structure is supported by the fact that on hydrolysis with dilute alkali, indigotin gives anthranilic

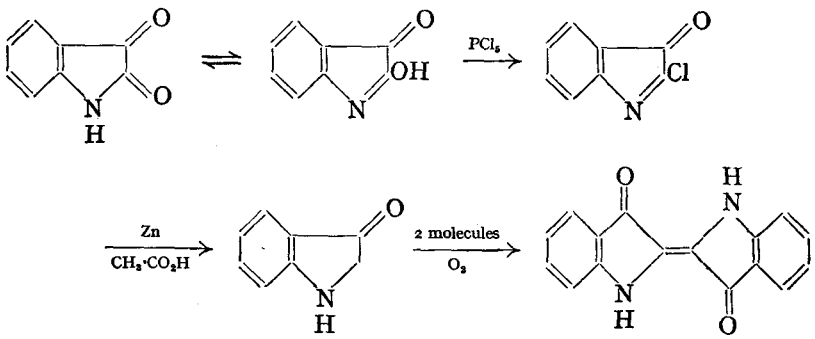


acid and indoxyl-2-aldehyde. Only structure (I) can give rise to these two products. Actually, all three compounds (I), (II) and (III), are known: (I) is indigotin, (II) *iso*indigotin, and (III) indirubin. Furthermore, indigotin is the *trans*-isomer of (I) (see below).

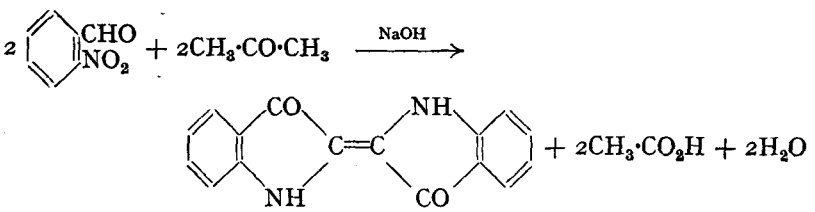
Synthesis of indigotin. Many syntheses of indigotin are known, and they may be divided into two groups:

A. *Syntheses of historical and theoretical interest* (*these show the structure of indigotin.*) All are due to Baeyer.

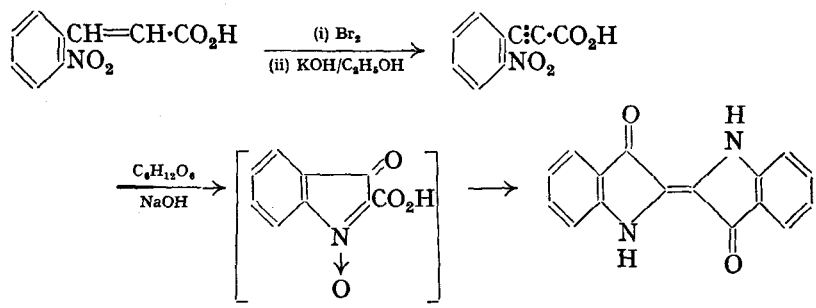
(i) When isatin is treated with phosphorus pentachloride and the product, isatin chloride, reduced with zinc dust in glacial acetic acid, indoxyl is formed and this, on atmospheric oxidation, gives indigotin (Baeyer, 1878):



(ii) When *o*-nitrobenzaldehyde is warmed with acetone in the presence of a little sodium hydroxide, indigotin is formed (Baeyer, 1882):

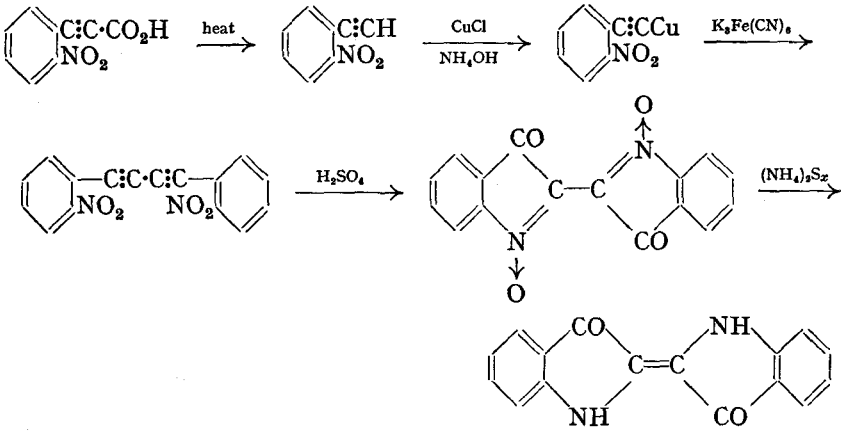


(iii) Bromination of *o*-nitrocinnamic acid, followed by treatment with ethanolic potassium hydroxide, produces *o*-nitrophenylpropiolic acid. This, on heating with glucose and aqueous sodium hydroxide, gives indigotin, possibly via *isatogenic acid* (Baeyer, 1880):



(iv) *o*-Nitrophenylacetylene, produced by heating *o*-nitrophenylpropiolic acid, forms the copper salt when treated with ammoniacal cuprous chloride. On treatment with potassium ferricyanide, this salt is converted into a diyne

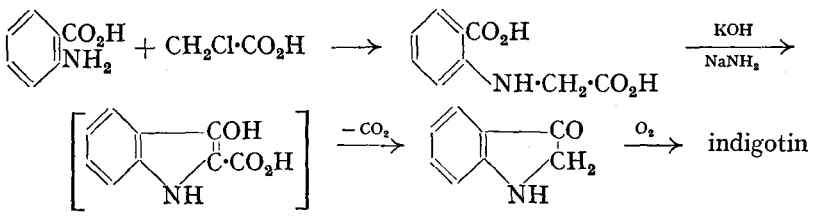
derivative which, by means of concentrated sulphuric acid, is converted into *di-isatogen* and this, on reduction with aqueous ammonium polysulphide, gives indigotin (Baeyer, 1882):



This synthesis shows clearly that the carbon skeleton of indigotin is C_6H_5—C—C—C—C—C_6H_5 (*cf.* above).

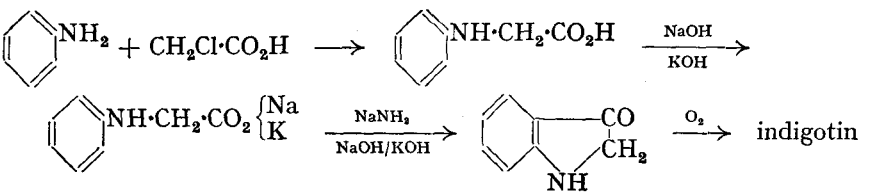
B. *Commercial syntheses of indigotin.* Natural indigotin is now produced only on a very small scale. It is interesting to note that Noelting (1886) expressed the opinion that although Baeyer had synthesised indigotin (in 1878), he (Noelting) did not think it was possible to manufacture synthetic indigotin on a scale large enough to compete with natural indigotin:

(i) Anthranilic acid (prepared from naphthalene as the starting material) is heated with chloroacetic acid and the product, phenylglycine-*o*-carboxylic acid, is heated with a mixture of potassium hydroxide and sodamide. Indoxylic acid is thereby produced, and this decarboxylates into indoxyl which, on exposure to air, is oxidised to indigotin:



This method is due to Heumann (1896).

(ii) Aniline is heated with chloroacetic acid, the product, phenylglycine, converted into a mixture of its sodium and potassium salts, and these fused with sodamide and a mixture of sodium and potassium hydroxides at 220–240°. Indoxyl which is thereby obtained is converted into indigotin by atmospheric oxygen (the "mixed salt" requires a lower temperature of fusion, and consequently the yield of indoxyl is better):

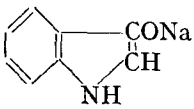


This method was first used in 1890, the fusion, however, being carried out with potassium hydroxide alone (Heumann). In 1896 this method was abandoned, and method (i) was used due to the cheap cost of phthalic anhydride from naphthalene. This oxidation was successful due to the accidental breaking of a thermometer, an accident which led to the discovery in 1893 that mercury catalyses the oxidation of naphthalene with sulphuric acid. Furthermore, method (i) gave better yields than (ii). About 1898, however, it was found that the addition of sodamide in the fusion in method (ii) increased the yield, and so (ii) was used again. Still later the preparation of phenylglycine was modified as follows. Formaldehyde is converted into its bisulphite compound on treatment with an aqueous saturated solution of sodium hydrogen sulphite at 50–80°. This compound is then warmed with aniline at 50–70°, then treated with aqueous sodium cyanide, and the product hydrolysed with water at 70°:

$$CH_2O + NaHSO_3 \longrightarrow CH_2(OH)\cdot SO_3Na \xrightarrow{C_6H_5\cdot NH_2} C_6H_5\cdot NH\cdot CH_2\cdot SO_3Na$$
$$\xrightarrow{NaCN} C_6H_5\cdot NH\cdot CH_2\cdot CN \xrightarrow{H_2O} C_6H_5\cdot NH\cdot CH_2\cdot CO_2H$$

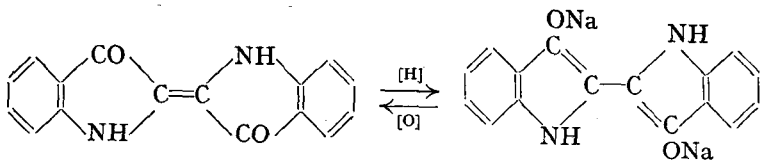
(iii) Aniline, on treatment with ethylene oxide, forms *N*-phenyl-2-hydroxyethylamine and this, on fusion with a mixture of sodium and potassium hydroxides at 200°, gives the sodium (and potassium) alkoxide. When this sodium salt is heated with sodamide and a mixture of sodium and potassium hydroxides at 200°, the *N*-sodio-derivative is produced. This is dehydrogenated on heating rapidly to 300°, and on rapid cooling to 235°, ring closure takes place with the formation of the sodium salt of indoxyl. This, when treated with water and allowed to stand exposed to the air, gives indigotin:

$$C_6H_5\cdot NH_2 + \underset{CH_2-CH_2}{\overset{O}{\diagup\diagdown}} \longrightarrow C_6H_5\cdot NH\cdot CH_2\cdot CH_2OH \xrightarrow[200°]{NaOH/KOH}$$
$$C_6H_5\cdot NH\cdot CH_2\cdot CH_2ONa \xrightarrow[NaNH_2]{NaOH/KOH} C_6H_5\cdot N(Na)\cdot CH_2\cdot CH_2ONa \xrightarrow[(ii)\ 235°]{(i)\ 300°}$$



$\xrightarrow{air/H_2O}$ indigotin

Properties of indigotin. Indigotin is a dark blue powder with a coppered lustre. It is insoluble in water, but when its paste is agitated with alkaline sodium hyposulphite in large vats, the insoluble indigotin is reduced to the soluble leuco-compound, *indigotin-white*:

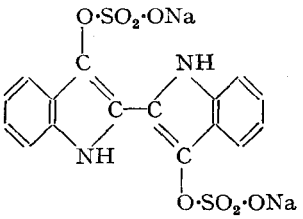


The material to be dyed is soaked in this alkaline solution and then exposed to the air, whereupon the original blue dye is regenerated in the cloth.

In vat-colour printing (of calico), " local dyeing " is achieved by making the dye pigment into a thick paste (by means of a " thickener ", *e.g.*, starch), and applying this locally in the presence of alkali and a reducing agent, *e.g.*, sodium formaldehyde-sulphoxylate (*Rongalite, formosul*), $CH_2(OH)\cdot SO_2Na$, which is

prepared by reducing formaldehyde bisulphite with zinc and acetic acid. The colour is finally developed by means of an oxidising agent, *e.g.*, sodium nitrite.

In textile printing, *e.g.*, shirtings, dress materials, etc., indigotin-white is not sufficiently stable to be used. Hence textile printing (and ordinary dyeing) may be effected by first converting indigotin into **indigosol O** by treating indigotin-white with chlorosulphonic acid in the presence of pyridine. This produces the disulphuric ester which, by means of sodium hydroxide, is converted into its sodium salt, indigosol O. This is readily applied to animal or vegetable fibres

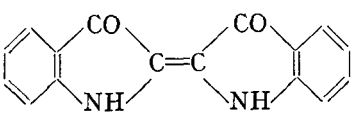


by soaking the fabric in the solution, and then oxidising the indigosol O in *acid* solution (with sodium nitrite) to the original insoluble vat dye. Here we have an example of a vat dye being applied without the vatting process. Indigosol O is stable in neutral or alkaline solution, but is hydrolysed to indigotin-white in acid solution.

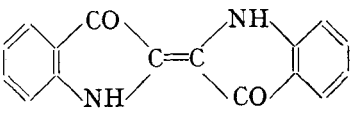
When heated with concentrated alkali, indigotin gives a brownish-red solid which, on distillation, gives aniline. Aniline was actually first obtained this way (Fritzsche, 1840). When refluxed first with dilute alkali and then with sulphuric acid, indigotin gives anthranilic acid. If the acid stage is omitted, indoxyl-2-aldehyde can be isolated, but this tends to condense with the anthranilic acid; the acid decomposes this complex and also any free aldehyde.

With metals indigotin forms complexes, the structure of which is not certain, but is probably chelate.

Two geometrical isomers are possible for indigotin:



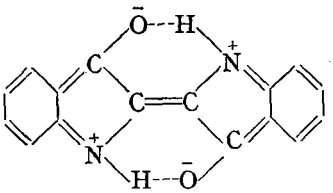
cis-form



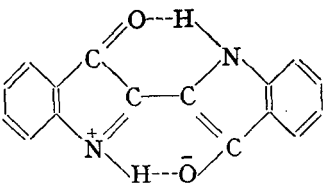
trans-form

Derivatives of both are known, but the stable form is the *trans*-; X-ray analysis shows that the indigotin molecule contains a centre of symmetry. There is, however, some evidence to show that it is the *cis*-form which is produced in the cloth, and that it slowly changes into the stable *trans*-form.

The colour of indigotin requires explanation by charged structures, *e.g.*, the *o*-quinonoid charged structure (IV) is a possibility; at the same time, this structure would be stabilised by hydrogen bonding:



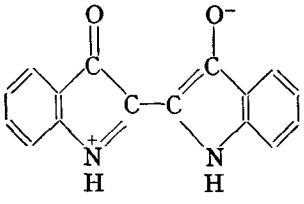
(IV)



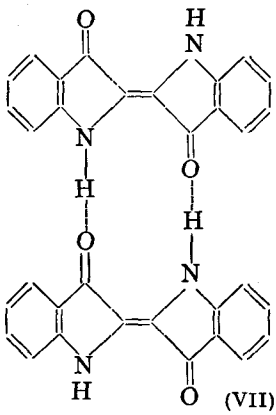
(V)

An alternative charged structure for indigotin is V; this does not involve any quinonoid structures, but it is again stabilised by hydrogen bonding. Furthermore, the presence of this resonating structure may be used to explain the

conversion of the labile *cis*-form into the stable *trans*-form since it contains a *single* bond linking the two units together. If we imagine that the *cis* form is formed first, and that (VI) is the main contributing resonating structure, then due to the repulsion between the strongly electron-attracting oxygen atoms, and the attraction between the negatively charged oxygen atom and the positively charged nitrogen atom, rotation will take place about the



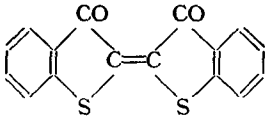
(VI)



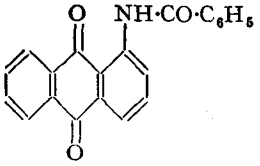
(VII)

C—C *single* bond to give the stable *trans*-form V. This form is so stabilised by intramolecular hydrogen bonding that it cannot be isomerised to the *cis* form by the action of light (Brode *et al.*, 1954). The problem, however, cannot be regarded as settled. According to Holt *et al.* (1956), the hydrogen bonding in indigotin is intermolecular and *not* intramolecular; thus (VII) represents the molecule. Furthermore, indigotin has been shown to be dimeric in *p*-toluidine solution.

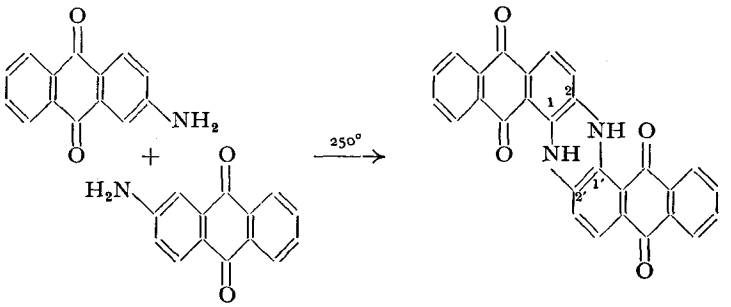
Derivatives of indigotin. Indigotin can be chlorinated or brominated directly in the 5, 5′, 7 and 7′ positions. The tetrachloro-derivative, **Brilliant Indigo B,** and the tetrabromo-derivative, **Brilliant Indigo 2B,** are both used commercially; both are brighter than indigotin. **Tyrian Purple** (" *Purple of the Ancients* ") is 6 : 6′-dibromoindigotin, and was originally obtained from a species of molluscs in the Mediterranean. It is not commercially important since much cheaper dyes of similar colour are available. **Indigo Carmine** is the sodium salt of indigotin 5 : 5′-disulphonic acid. **Thioindigo Red** (Friedländer, 1905) is an important vat dye. An interesting point about this compound is that, as in the case of indigotin, two geometrical isomers are possible, but since hydrogen bonding is not possible in the sulphur compound, neither form is stabilised, and in solution both forms appear to exist in equilibrium (Wyman *et al.*, 1951).



Anthraquinone type of vat dyes. The *algol colours* are acylaminoanthraquinones, *e.g.*, **Algol Yellow W.G.** This dyes cotton in yellow shades, and is readily prepared by heating the corresponding amino-compound with benzoic acid.



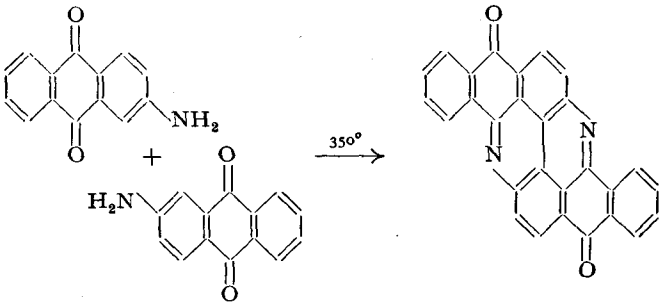
Indanthrone (*Indanthrene Blue R*; Bohn, 1901) is prepared by fusing 2-aminoanthraquinone with potassium hydroxide in the presence of potassium chlorate or nitrate at 250°.



It is reduced by alkaline sodium hyposulphite to the alkali-soluble form (leuco-compound; brown) which is oxidised to the dye by exposure to air.

Substituted indanthrones are also very important vat dyes, *e.g.*, 4 : 4′-dichloro- and dibromo-derivatives give greener blues than the parent compound.

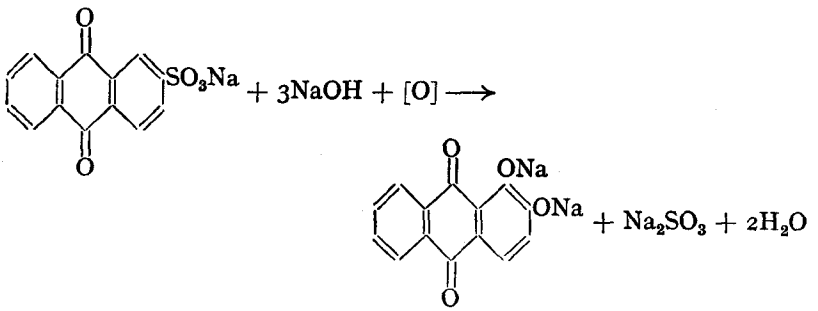
Flavanthrone (*Flavanthrene, Indanthrene Yellow G.*; Bohn, 1901) is formed by fusing 2-aminoanthraquinone with potassium hydroxide at 350° (*cf.* above).



It is now made by the action of antimony pentachloride on 2-aminoanthraquinone in boiling nitrobenzene solution.

ANTHRAQUINOID DYES

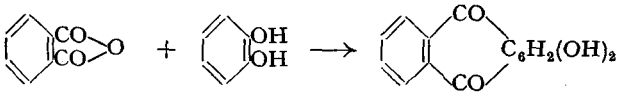
Alizarin is one of the most important anthraquinoid dyes; it is the chief constituent of the madder root. Alizarin is 1 : 2-dihydroxyanthraquinone, and is now manufactured synthetically by sulphonating anthraquinone with fuming sulphuric acid at high temperatures, and fusing the sodium salt of the product, anthraquinone-2-sulphonic acid, with sodium hydroxide and the calculated quantity of potassium chlorate at 180–200° under pressure:



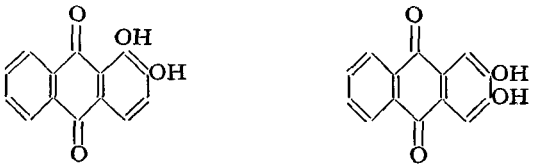
The function of the potassium chlorate is to provide oxygen for the oxidation of the 1-carbon atom to COH.

Structure of alizarin. Analysis and molecular weight determinations show that the molecular formula of alizarin is $C_{14}H_8O_4$. When distilled with zinc dust, alizarin gives anthracene; this shows that it is an anthracene derivative. When heated with the calculated quantity of bromine, anthraquinone forms dibromoanthraquinone and this, on fusion with potassium hydroxide, gives alizarin; this indicates that alizarin is dihydroxyanthraquinone. Actually this was the method used by Graebe and Liebermann, who were the first to synthesise alizarin. A most interesting feature of this synthesis is that these authors thought they had obtained 1 : 2-dibromoanthraquinone. Much later work has shown that they were actually working with 2 : 3-dibromoanthraquinone, and that rearrangement had therefore taken place during the fusion with alkali.

Vigorous oxidation of alizarin gives phthalic acid, thereby indicating that the two hydroxyl groups are in the same ring; otherwise an hydroxyphthalic acid would have been obtained, or the whole molecule broken down completely. Thus alizarin must be the 1 : 2-, 1 : 3-, 1 : 4- or 2 : 3-dihydroxy-derivative of anthraquinone. Since alizarin may be obtained by heating a mixture of phthalic anhydride and catechol with a little sulphuric acid at 130°, the two hydroxyl groups must be in the *o*-positions in alizarin:

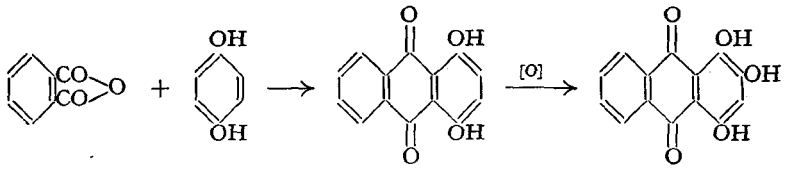


There are two possibilities, *viz.*, 1 : 2- (I) and 2 : 3- (II):



(I) (II)

When oxidised with manganese dioxide and sulphuric acid, alizarin forms *purpurin*, a trihydroxy-derivative of anthraquinone in which the three hydroxyl groups are in the *same* ring (as shown by oxidation to phthalic acid). (I) can give rise to two trihydroxy-derivatives, 1 : 2 : 3- and 1 : 2 : 4-; (II), only one, 1 : 2 : 3-. Purpurin has been shown to be 1 : 2 : 4-trihydroxyanthraquinone by condensing phthalic anhydride with quinol, and oxidising the product, *quinizarin*:



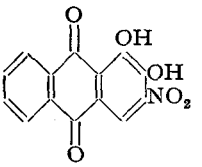
Thus structure (I) is alizarin, and this is supported by the facts (i) that nitration of alizarin under different conditions gives *two* isomeric mononitro-derivatives in both of which the nitro-group is in the same ring as the hydroxyl groups (oxidation gives no nitrophthalic acid), and (ii) that alizarin forms *two* monoacyl derivatives (1- and 2-).

Properties of alizarin. Alizarin forms ruby red crystals, m.p. 290°, almost insoluble in water but fairly soluble in ethanol. It dissolves in alkalis to give purple solutions. It is a mordant dye, and the colour of

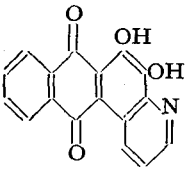
the lake depends on the metal used. Aluminium gives a red lake (*Turkey Red*), iron (ferric) a violet-black and chromium a brown-violet. Aluminium and iron lakes are usually employed for cotton dyeing and for printing, and aluminium and chromium lakes for wood dyeing.

In addition to the aluminium compound, the lake contains calcium salts, Turkey-red oil and sodium phosphate. These additional compounds affect the brightness of the lake and increase its stability towards acids and alkalis. It appears that aluminium hydroxide alone does not yield a lake with alizarin, but only after the addition of a calcium salt.

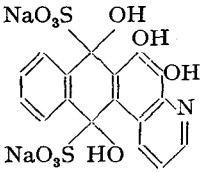
Alizarin Orange (Rosenstiehl, 1876) is prepared by nitrating alizarin in sulphuric acid solution in the presence of boric acid. It forms orange lakes with aluminium. **Alizarin Blue** (Prud'homme, 1877) may be prepared by first reducing Alizarin Orange to the corresponding amino-compound and then heating this with glycerol, sulphuric acid and nitrobenzene (Skraup's synthesis). It dyes



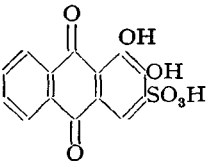
Alizarin Orange



Alizarin Blue



Alizarin Blue S



Alizarin Red S

wool mordanted with chromium a blue colour. **Alizarin Blue S** (Brunck, 1881) is the soluble bisulphite compound of Alizarin Blue. It gives a reddish-blue lake with chromium. **Alizarin Red S** (Graebe and Liebermann, 1871) is prepared by sulphonating alizarin with fuming sulphuric acid. It dyes wool mordanted with aluminium a scarlet red, and a bordeaux when mordanted with chromium.

SULPHUR DYES

Sulphur dyes are prepared by heating various organic compounds such as amines, aminophenols and nitrophenols, with sodium polysulphide. Sulphur dyes are coloured solids, insoluble in water and acids, but soluble in cold alkaline solutions of sodium sulphide, in which the dyes are reduced to the leuco-compound. Cotton is dipped and then exposed to the air, whereupon the leuco-compound is oxidised to the dye. Oxidation may also be effected by immersion in a warm bath of dilute potassium dichromate.

Sulphur dyes have complex structures, many of which are uncertain or unknown.

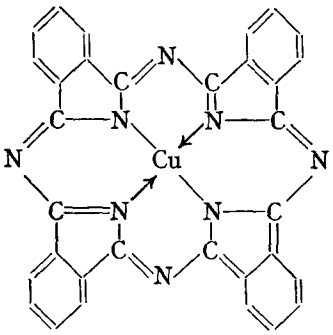
A largely used sulphur dye is that for dyeing cloth khaki. This dye is made by heating *p*-phenylenediamine, *p*-aminoacetanilide and sulphur, with or without benzidine, and then heating the product with sodium sulphide.

PHTHALOCYANINE PIGMENTS AND DYES

The **phthalocyanines** are a very important new class of organic dyes and pigments; they are coloured blue to green. They are very fast to light, heat, acids and alkalis, and are very useful for paints, printing inks, synthetic plastics and fibres, rubber, etc.

The phthalocyanine dyes were discovered by accident at the works of Scottish Dyes Ltd. in 1928. It was there observed that some lots of phthalimide, manufactured by the action of ammonia on molten phthalic anhydride in an iron vessel, were contaminated with a blue pigment. The structure and method of formation of this iron compound were established by Linstead and his co-workers (1934).

The first commercial phthalocyanine dye was **Monastral Fast Blue BS.** This is copper phthalocyanine, the copper atom taking place of the hydrogen



atoms in the two NH groups of phthalocyanine itself and being co-ordinated with the other two nitrogen atoms. The colour depends on the metal (copper, magnesium, lead, etc.), and the greener shades are obtained by direct chlorination or bromination.

Metal phthalocyanines may be prepared:

(i) By passing ammonia into molten phthalic anhydride or phthalimide in the presence of a metal salt.

(ii) By heating *o*-cyanoarylamides or phthalonitriles with metals or metallic salts.

(iii) By heating phthalic anhydride or phthalimide with urea and a metallic salt, preferably in the presence of a catalyst such as boric acid.

Phthalocyanine may be prepared by heating phthalonitrile with a little triethanolamine.

Phthalocyanines are made water soluble by sulphonation, and these soluble salts are used as direct dyes.

QUESTIONS

1. Write an essay on the relation between colour and constitution.
2. Discuss the classification of dyes according to their application.
3. Write an essay on the azo-dyes.
4. Discuss the analytical and synthetic evidence for the structure of:—(*a*) triphenylmethane dyes, (*b*) indigotin, (*c*) alizarin.
5. Describe the preparation of:—(*a*) Bismarck Brown G, (*b*) Methyl Orange, (*c*) Congo Red, (*d*) Chromotrope 2B, (*e*) Malachite Green, (*f*) Pararosaniline, (*g*) Rosaniline, (*h*) Crystal Violet, (*i*) Phenolphthalein, (*j*) Fluorescein, (*k*) Rhodamine B, (*l*) Indigotin, (*m*) Alizarin, (*n*) Copper phthalocyanine, (*o*) Naphthol Yellow S, (*p*) Aniline Blue, (*q*) Pyronine G, (*r*) Quinoline Yellow, (*s*) Methylene Blue, (*t*) Meldola's Blue.
6. Write an essay on the Cyanine dyes.
7. Write an account of the Vat Dyes.

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EXAMINATION QUESTIONS

1. By means of equations and short notes indicate some typical examples of the use of (*a*) malonic ester in the synthesis of homocyclic compounds, and (*b*) acetoacetic ester in the synthesis of heterocyclic compounds (B.Sc. Special, U.L., 1948).

2. A hydrocarbon of molecular formula $C_{12}H_{10}$ is nitrated to a substance $C_{12}H_9NO_2$ which is converted by the action of chromic acid mixture into a dicarboxylic acid $C_{13}H_7NO_6$. Further oxidation of this acid yields 4-nitrobenzene-1 : 2 : 3-tricarboxylic acid, whereas reduction of the nitro-group followed by drastic oxidation produces benzene-1 : 2 : 3-tricarboxylic acid.

Explain these facts and give the structural formula of the original hydrocarbon (A.R.I.C., 1948).

3. Write an essay on *one* of the following topics:—

(*a*) The concept of resonance (mesomerism) in relation to the structure of molecules.

(*b*) The influence of substituents on the strengths of organic acids and bases.

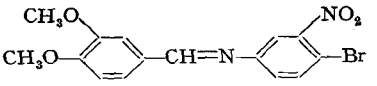
(*c*) Keto-enol tautomerism—including methods for the estimation of the proportions of tautomerides in such equilibrium mixtures (B.Sc. Special, U.L., 1948).

4. Outline the methods of preparation and the characteristic reactions of *five* of the following compounds:—(*a*) urea, (*b*) ethyl chloroformate, (*c*) keten, (*d*) chloroform, (*e*) diacetyl, (*f*) acetonylacetone, (*g*) phenyl *iso*cyanate (phenylcarbimide) (B.Sc. Special, U.L., 1945).

5. Indicate briefly by means of formulæ and equations how each of the following substances may be prepared from nitrobenzene:—nitrosobenzene, diphenyl, phenacetin, quinoline, phenylhydrazine, azoxybenzene, Bismarck Brown, *p*-aminoacetophenone (A.R.I.C., 1946).

6. Classify the different types of isomerism which are known and give formulæ illustrating one example of each type (A.R.I.C., 1948).

7. A substance is believed to possess the following structure:



Suggest reactions you would carry out in order to confirm it. Indicate a method of synthesising this compound (B.Sc. Special, U.L., 1945).

8. Describe methods for the preparation of aromatic sulphonic acids, and indicate the most important reactions of these compounds (B.Sc. General, U.L., 1939).

9. Write an account of the preparation of aromatic aldehydes, and give three condensation reactions of benzaldehyde (B.Sc. General, U.L., 1946).

10. Give an account of methods which have been used to convert aldohexoses into aldopentoses and aldoheptoses. Outline the essential proof of the structure of glucose (B.Sc. General, U.L., 1944).

11. Discuss the work which has been carried out in investigating the kinetics of any *one* organic reaction or class of reactions (F.R.I.C., *Branch C*, 1948).

12. Describe and explain the reactions which have been observed in aromatic compounds where substitution or displacement is effected by an anionoid (nucleophilic) reagent (F.R.I.C., *Branch C*, 1948).

13. State briefly how any *five* of the following substances could be conveniently prepared in the laboratory, ethyl alcohol and acetic acid being available as starting materials:—

Methyldiethylcarbinol, diethylacetic acid, dichloroacetic acid, methyl ethyl ketone, sulphonal, methylamine (A.R.I.C., 1947).

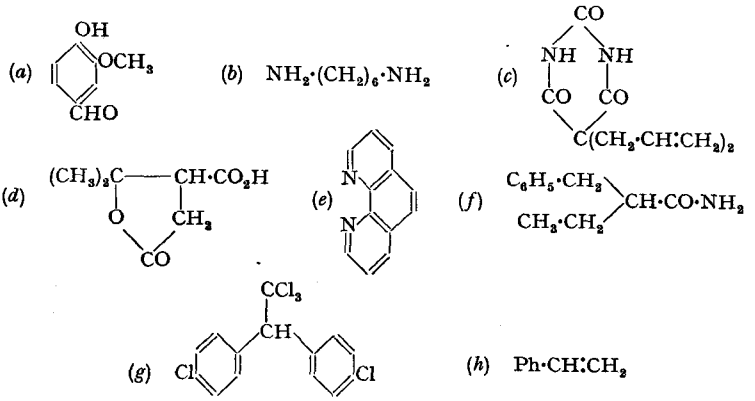
14. Give the approximate conditions under which phenol (or a simple derivative of phenol) may be caused to react with (*a*) carbon dioxide, (*b*) chloroform, (*c*) a diazo solution, (*d*) hydrogen and (*e*) methylating agent. Indicate the products in each case and give any necessary explanation of the process involved (B.Sc. General, U.L., 1943).

15. Mention *six* general reactions used in organic chemistry by which a new carbon–carbon bond is formed. Give one example of each, indicate any essential experimental conditions and explain the range of applicability of the reaction (A.R.I.C., 1945).

16. Give an account of the ways in which acetylene has been used for synthetic purposes (F.R.I.C., *Branch C*, 1947).

17. Classify the more important reactions of the diazo-compounds, differentiating between reactions in which nitrogen is eliminated and reactions in which it is not (B.Sc. General, U.L., 1943).

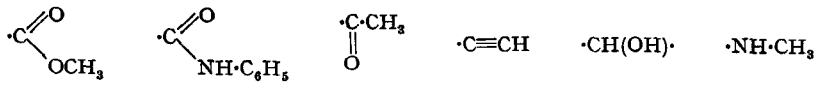
18. Suggest methods by which *five* of the following compounds can be obtained from easily accessible materials. Write notes on any points of interest in connection with the substances you select:



(B.Sc. Special, U.L., 1945).

19. Discuss any four of the following terms: Centre of symmetry; optical (Walden) inversion; asymmetric synthesis; restricted rotation; racemisation. Give clear examples to illustrate your answer (B.Sc. General, U.L., 1943).

20. Give a brief account of methods which have been used to prove the presence in a molecule of the following groups:



(B.Sc. General, U.L., 1939).

21. Explain, giving examples, the use of any *six* of the following substances in organic chemistry: selenium, maleic anhydride, diazoacetic ester, periodic acid, sodamide, thoria, copper powder, phenyl *isocyanate* (F.R.I.C., *Branch C*, 1946).

22. Indicate briefly by means of formulæ and equations how the following substances may be conveniently prepared from phenol:—(*a*) chloropicrin, (*b*) *p*-hydroxyacetophenone, (*c*) pimelic acid, (*d*) *p*-dinitrobenzene, (*e*) adipic acid, (*f*) aurin, (*g*) *p*-hydroxybenzene-azo-naphthalene (A.R.I.C., 1946).

23. Give the more important methods available for the synthesis of pyrrole and its derivatives. Describe the characteristic properties and behaviour of these compounds. In which respects do they show resemblance to aromatic substances?

How can pyrrole be converted into (*a*) an open-chain compound, (*b*) a pyridine derivative, (*c*) a strong cyclic base? (A.R.I.C., 1946).

24. Indicate the methods available for the preparation of the aliphatic amines. In what ways do primary, secondary and tertiary amines differ in their chemical behaviour? (B.Sc. General, 1937).

25. Write a general account of the use of organo-metallic compounds for synthetic purposes, giving examples.

In which circumstances is zinc used in preference to magnesium? (A.R.I.C., 1945).

26. What are the main classes of dye-stuffs? Give an example of each class, referring to its mode of manufacture and its use in dyeing (B.Sc. Special, U.L., 1947).

27. Write a concise essay on *one* of the following subjects:—(*a*) Free radicals, (*b*) alcoholic fermentation, (*c*) " aromatic character " (B.Sc. Special, U.L., 1943).

28. Write a full account of the formation and properties of formaldehyde and its polymeric modifications (B.Sc. Special, U.L., 1948).

29. What methods are available for the preparation of ketones of the aliphatic and aromatic series, including aromatic hydroxy-ketones?

What is Michler's ketone? How is it prepared, and how may it be used in the preparation of dyes? (A.R.I.C., 1945).

30. Review the methods by which cyclic polymethylene compounds have been obtained, with special reference to the methods of Ruzicka and of Ziegler (B.Sc. Special, U.L., 1945).

31. Indicate *three* methods of synthesising aliphatic monocarboxylic acids, and *three* methods of introducing the carboxyl group into an aromatic nucleus. In each case give examples, and mention the reagents employed and the essential conditions for reaction (B.Sc. Special, U.L., 1944).

32. Discuss the influence of neighbouring groups or atoms on the reactivity of hydrogen which is in combination with carbon (B.Sc. Special, U.L., 1943).

33. Write notes on *three* of the following:—Hofmann's conversion of amides into primary amines, (*b*) Perkin's reaction, (*c*) the benzidine change, (*d*) Sandmeyer's reaction, (*e*) catalytic hydrogenation (B.Sc. Special, U.L., 1943).

34. Outline the important advances which have been made in recent years in the utilisation of petroleum as an initial material for the preparation of organic compounds (B.Sc. Special, U.L., 1943).

35. Write notes on *two* of the following:—(*a*) Friedel–Crafts' reaction, (*b*) the reduction of nitrobenzene, (*c*) hydroxy-azo-dyestuffs, (*d*) quinones (B.Sc. Special, U.L., 1944).

36. Write a general account of the industrially important esters of glycerol (B.Sc. Special, U.L., 1946).

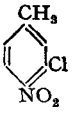
37. Discuss *one* of the following physical properties in relation to molecular structure:—(*a*) dipole moment, (*b*) molecular refraction, (*c*) diamagnetic susceptibility, (*d*) colour (*i.e.*, the electronic absorption spectrum) (B.Sc. Special, U.L., 1946).

38. Discuss the significance of the terms " electrophilic reagent " and " nucleophilic reagent " with reference to:—(*a*) addition to the carbonyl double bond, (*b*) addition to the ethylenic double bond, (*c*) substitution in the benzene nucleus (B.Sc. Special, U.L., 1946).

39. Discuss the structure of any three of the following substances: urea, glycine, glucose, anthraquinone, phenolphthalein, sulphanilic acid (B.Sc. General, U.L., 1939).

40. Compare and contrast the reactions of (*a*) acetaldehyde and acetone, (*b*) ethyl nitrite and nitroethane (B.Sc. General, U.L., 1936).

41. Describe briefly the experiments you would carry out in order to confirm the constitution of substances which are stated to have the following formulæ:

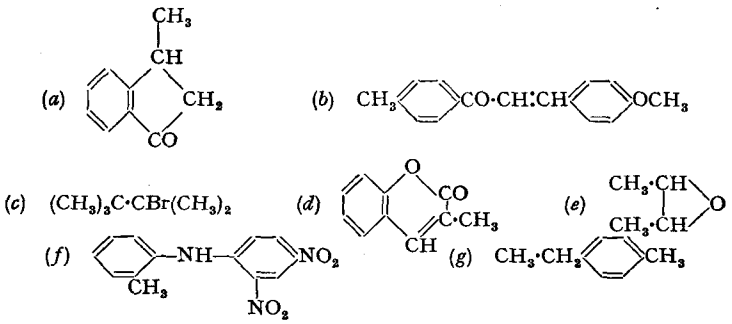
(*a*) $CN{\cdot}CH(NH_2){\cdot}CO_2H$; (*b*) $CH_3{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH_2{\cdot}O{\cdot}CH_3$; (*c*) 

(B.Sc. Special, U.L., 1943).

42. Review both direct and indirect methods which are available for the introduction of halogen atoms into an aromatic nucleus. Include a brief statement indicating the causes of the known results of the direct chlorination and dichlorination of benzene (B.Sc. General, U.L., 1944).

43. Review the methods which are available for methylating hydroxylic compounds (B.Sc. Special, U.L., 1939).

44. Suggest practicable syntheses, from readily accessible materials, of any five of the following:



(B.Sc. Special, U.L., 1942).

45. Describe (*a*) a method of manufacture, and (*b*) an alternative small scale method of preparation of each of the following: acetaldehyde; phenol; benzoic acid (B.Sc. Special, U.L., 1939).

46. Describe the main uses of any five of the following in the organic chemical laboratory:—Aluminium tri-*iso*propoxide; selenium dioxide; perbenzoic acid; pyridine; maleic anhydride; picric acid; metallic palladium (B.Sc. Special, U.L., 1940).

47. To what uses have metals been put as catalysts in organic chemistry? (B.Sc. Special, U.L., 1938).

48. Compare and contrast the reactions of (*a*) acetaldehyde and benzaldehyde, (*b*) ethyl alcohol and phenol, (*c*) ethyl iodide and iodobenzene (B.Sc. General, U.L., 1935).

49. By means of suitable examples show how the electronic theory of valency has proved helpful in explaining the reactivity of organic compounds (A.R.I.C., 1940).

50. Give an account of the structure and synthesis of *either* alizarin *or* indigotin (A.R.I.C., 1945).

APPENDIX

NOMENCLATURE

In dealing with the systematic methods of nomenclature, no attempt has been made to indicate whether a particular system is described in the Geneva system, or whether it is described in the I.U.P.A.C. rules. Irrespective of its origin the method of nomenclature has been referred to in the text as the I.U.P.A.C. system. In any case, the reader should appreciate that organic nomenclature is in a state of flux. This is unfortunate, but inevitable. What is more unfortunate is that there is no complete agreement among the various publishing societies.

Many of the I.U.P.A.C. rules have been given in the text. The reader should find the following remarks of some assistance in nomenclature.

Order of radicals. In British usage, the following order was adopted for naming radicals prior to April, 1950: Cl, Br, I, F, NO_2, NO, NH_2, $NH{\cdot}CO{\cdot}CH_3$, NH, OH, CHO, CO, CN, CNS, CO_2H, $R{\cdot}CO_2$, RO, R·CO, R, H. R is an alkyl or aryl radical, and these radicals were named in the following order:

(i) Cyclic precede acyclic radicals.
(ii) More saturated precede less saturated radicals.
(iii) Less complex precede more complex radicals.
(iv) Univalent precede bivalent radicals.

Since April, 1950 (but see also below) the *Chemical Society* has adopted an order for prefixes denoting substituents, which, in general, follows American usage, except for differences in nomenclature, spelling, italicising or punctuation.

(i) The names of substituents cited as prefixes are arranged alphabetically, regardless of the number of each (see list above); *e.g.*,

3-**a**mino-4-**c**hloro-2-naphthol
ethyl **m**ethyl ketone
5-**n**itro-1 : 4-di**ph**enylnaphthalene
1-**a**cetyl-2-**a**mino-4-**h**ydroxy-3 : 5 : 6-tri**m**ethylanthracene
methyl **p**ropyl succinate

N.B. **m**ethyl **h**ydrogen phthalate

(ii) Compound radical names are treated as *units*, and when several prefixes begin with the same letter, short names precede longer ones, *e.g.*,

1-(2 : 4-**d**initrophenyl)-3-**m**ethylnaphthalene
1-**methyl**-4-**methylamino**anthracene
1-**d**imethylamino-2-**e**thylnaphthalene

(iii) Italicised prefixes are neglected when assembling substituents; but isomeric substituents are arranged in alphabetical order of the italicised prefixes, except that *iso* follows directly after *n*, and *o* precedes *m*. The following are some of the more important italicised prefixes: *aci, allo, amphi, anti, as, cis, cyclo, endo, gem, iso, meso, neo, peri, sec, spiro, syn, tert, trans, vic.*

1-**f**luoro-4-*cyclo***p**entylbenzene
n-**p**ropyl *iso***p**ropyl ether
o-**n**itrophenyl-*m*-**n**itrophenylacetic acid

(iv) When a compound contains one principal function, then this is expressed in the ending of the name, *e.g.*,

3-ethyl-2-methyl*cyclo*hexane-1-carboxylic acid

This rule also applies to aromatic compounds.

(v) When a compound contains more than one functional group, the compound is named by using the suffix of the principal function and the prefixes of all the other functions (p. 235). This rule also applies to aromatic compounds.

(vi) In some cases the order may be changed to avoid ambiguity, *e.g.*, phenyldichloroarsine is used for $C_6H_5{\cdot}AsCl_2$, as dichlorophenylarsine might be taken as $C_6H_3Cl_2{\cdot}AsH_2$.

The *Chemical Society* now follows the I.U.P.A.C. rules (1957), according to which prefixes are to be italicised when they define the positions of named substitutents or which are used to define stereoisomers. Furthermore, prefixes are to be arranged alphabetically, and of the above-mentioned italicised prefixes (section iii), those which retain their italics are *anti*, *cis*, *endo*, *meso*, *peri*, *syn*, *trans*. Thus:

4-cyclopentyl-1-fluorobenzene; isopropyl propyl ether

Also, commas are to be used to separate numerals:

1,2,3-tribromobenzene

Use of Greek letters. The Greek alphabet is:

α	alpha
β	beta
γ	gamma
δ (Δ)	delta
ε	epsilon
ζ	zeta
η	eta
θ	theta
ι	iota
κ	kappa
λ	lambda
μ	mu
ν	nu
ξ	xi
ο	omicron
π	pi
ρ	rho
σ	sigma
τ	tau
υ	upsilon
φ	phi
χ	chi
ψ	psi
ω	omega

The use of Greek letters to indicate the positions of substituents in a chain is to be avoided; numerals should be used. Greek letters, however, may be used (and are preferable) to indicate positions of substituents in compounds described by trivial names, *e.g.*, α-hydroxypropionic acid (lactic acid). Greek letters are also used to indicate the *class* of compound, *e.g.*, α, β, γ-, . . . diketones; γ- and δ-lactones, etc.

Writing of names. The general practice is to " run on " the names of radicals replacing hydrogen atoms in a compound, *e.g.*, chlorobenzene, 1-nitropropane, ethylmethylcarbinol, etc. If the compound is named by any general term, then each part of the name is written separately, *e.g.*, ethyl alcohol, ethyl methyl ether, acetic acid, methyl propyl ketone, butyraldehyde oxime (but butyraldoxime), acetaldehyde phenylhydrazone, etc.

ORGANIC CHEMISTRY PUBLICATIONS

Before using any book, consult the preface for information about the contents. The preface usually gives all the information necessary. Also note the date of the publication.

Chemical Dictionaries

Thorpe's Dictionary of Applied Chemistry. This contains short articles on a very wide field of subjects, and also contains a large bibliography of original literature.

Heilbron's Dictionary of Organic Compounds. This gives a concise account of the physical and chemical properties of organic compounds, and references to good methods of preparation.

Physical Constants

Heilbron's Dictionary of Organic Compounds.
International Critical Tables.
Kaye and Laby, *Tables of Physical and Chemical Constants.*
Landolt and Bornstein, *Physikalisch-Chemische Tabellen.*
Chemist's Year Book (British).
Handbook of Chemistry and Physics (American).
Lange's *Handbook of Chemistry.*

Reference Books

There are many excellent single volume texts available on Organic Chemistry. The following, however, are of a more specialised character:

Sidgwick, *The Organic Chemistry of Nitrogen.*
Morton, *The Chemistry of Heterocyclic Compounds.*
Cohen, *Organic Chemistry for Advanced Students* (3 vols.).
Gilman, *Advanced Organic Chemistry* (4 vols.).
Richter's Organic Chemistry (4 vols.).
Huckel, *Theoretical Principles of Organic Chemistry* (two volumes; translated by Rathmann).
Stewart, *Recent Advances in Organic Chemistry* (3 vols.).
Elderfield (Ed.), *Heterocyclic Compounds* (1950—).
Chemistry of the Carbon Compounds (Edited by Rodd), Elsevier (1951—).
Radt (Ed.), *Elsevier's Encyclopædia of Organic Chemistry* (1940—).
Gowan and Wheeler, *Name Index of Organic Reactions,* Longmans, Green (1960).
Progress in Organic Chemistry, Butterworths (1952—).
Progress in Stereochemistry, Butterworths (1954—).
Beilstein's Handbuch der Organischen Chemie.

In addition to the above reference books which are mainly theoretical in character, there are also a number of reference books on practical organic chemistry, *e.g.*,

Houben-Weyl, *Die Methoden der Organischen Chemie.*

Organic Syntheses. These are published annually (1921—). There are now also three collected volumes.

Organic Reactions (1942—). These contain detailed discussions of a large number of organic reactions, and also include an account of the practical methods.

Weissberger, *Physical Methods of Organic Chemistry.*
Theilheimer, *Synthetic Methods of Organic Chemistry* (1947—).

Migrdichian, *Organic Synthesis*, Reinhold (Vol. I and II, 1957).
Hickinbottom, *Reactions of Organic Compounds*, Longmans, Green (3rd ed., 1957).
Weygand, *Organic Preparations*, Interscience publishers (1945).

LITERATURE

The more important periodicals are:

American: **Journal of the American Chemical Society** (*J. Amer. Chem. Soc.*). It was first issued in 1879, and was incorporated with the American Chemical Journal since 1913. It is now issued twice a month.
Belgian: **Bulletin de la Société chimique de Belgique** (*Bull. Soc. chim. Belg.*). It was first issued in 1887. Monthly.
British: **Journal of the Chemical Society** (*J.C.S.*). Issued since 1848. Monthly.
Dutch: **Recueil des travaux chimiques des Pays-Bas** (*Rev. trav. chim.*). Issued since 1882. Monthly.
French: **Bulletin de la Société chimique de France** (*Bull. Soc. chim.*). Issued since 1858. Monthly.
German: **Berichte der deutschen chemischen Gesellschaft** (*Ber.*). Issued since 1868. Monthly.
Italian: **Gazzetta chimica italiana** (*Gazzetta*). Issued since 1871. Monthly.
Russian: **Journal of General Chemistry** (U.S.S.R.) (*J. Gen. Chem.* (*U.S.S.R.*).) This is a U.S. translation of *Zhurnal obschei Khimii*.
Swiss: **Helvetica Chimica Acta** (*Helv. Chim. Acta*). Issued since 1918. Intermittent.

The above journals are general in that they publish research on all branches of chemistry. Besides these, however, are a large number of specialised journals which deal with only Organic, Physical, Analytical, Biological, Industrial chemistry, etc.

Other useful sources of Organic Chemistry are:

Justus Leibig's Annalen der Chemie (*Annalen*).
Journal of Organic Chemistry (*J. Org. Chem.*)
Journal für praktische Chemie (*J. pr. Chem.*).
Monatshefte für Chemie und verwandte Teile anderer Wissenschaften (*Monatsh.*).
Tetrahedron (*The International Journal of Organic Chemistry*).
Transactions of the Faraday Society (*Trans. Faraday Soc.*).

Owing to the large number of journals, it is impossible to read everything published. Hence abstracting journals have appeared for the benefit of the chemist. The most important abstracting journals are:

Chemical Abstracts. These are American, were begun in 1907, and are issued twice a month. Four decennial indexes have appeared: 1917, 1927, 1937 and 1947.

British Chemical Abstracts. These began in 1871 and were issued monthly until January, 1954, when the publication of the abstracts in "Pure Chemistry" was discontinued.

Current Chemical Papers. This is a new publication of the Chemical Society, and began January 1954. It is issued monthly, and its aim is to inform chemists of new work as quickly as possible. Since only the titles of papers are given, this periodical does not replace abstracts.

Chemisches Zentrallblatt. This began in 1830 (under the name of Pharmaceutisches Zentrallblatt, and subsequently modified several times). It is issued weekly.

Index Chemicus. This is a service of the *Institute for Scientific Information* (American). It is a twice-monthly register and index of *new* chemical compounds. It reports and indexes new chemical compounds within 30 days after their appearance in the primary journals. It was begun in 1960.

All good abstracts have the following three indexes: author, subject and formula.

Author index. This is arranged alphabetically. To search the author index it is necessary to know the name of the author and also how to spell it; care must be exercised with some surnames, *e.g.*, Tschitschibabin or Chichibabin.

Subject index. This is arranged alphabetically. When searching the literature about a particular subject, the word (name) and related words (names) should be looked up, *e.g.*, suppose we wish to ascertain the work that has been done on *fats*. The procedure would be to look up:

(i) Fats.
(ii) Oils.
(iii) Esters.
(iv) Individuals, *e.g.*, olein, palmitin, etc.
(v) Saponification.
(vi) Soaps.
(vii) Hydrolysis.
(viii) Edible fats and oils.
(ix) The author index of the various papers, since it is quite likely that the author has published more than one paper on the subject.

When using the subject index, it is advisable to work backwards chronologically, since recent papers will give references to earlier ones.

When searching for a particular compound, the reader should bear in mind alternative names for that particular compound, and also the possibility of alternative methods of numbering.

Formula Index should offer no difficulties. It is probably best to search this.

In addition to journals containing original papers, there are reviews published by various societies. These are critical surveys of literature published during a certain period, and are extremely valuable sources of information, *e.g.*,

Annual Reports of the Chemical Society (published annually). There is now a cumulative (subject) index for volumes **1–46** (1904–1949).

Quarterly Reviews (Chem. Soc).. These began in 1947.

Chemical Reviews (six a year).

Journal of Chemical Education (monthly).

Many journals also give critical surveys, or publish lectures that have been given by specialists, *e.g.*, **Journal of the Chemical Society, Journal of Industrial and Engineering Chemistry, Journal of the Society of Chemical Industry.** The periodicals **Nature** and **Chemistry and Industry** are used as a means of correspondence as well as for publications. The Chemical Society also now issues monthly the (new) **Proceedings of the Chemical Society** (1957—) in which communications and lectures are printed. There are also the **Tetrahedron Letters** (begun 1959).

SEARCHING THE LITERATURE

Some indication of searching the literature has already been given in the foregoing.

Finding a paper given the reference. Original papers are given as author, name of periodical, year of publication, volume number (in heavy print, or underlined in written work), and page, *e.g.*,

E. F. Armstrong, *J.C.S.*, 1903, **83**, 1305. This is British practice. American practice is slightly different, *viz.*

E. F. Armstrong, *J.C.S.*, **83**, 1305 (1903).

Sometimes mistakes are made in giving a reference.

Wrong author. No difficulty will be encountered here, provided the nature of the article is known.

Wrong Journal. In this case it is best to consult the author or subject indexes of the abstracting journals.

Wrong year. If the volume number is correct, there should be no difficulty.

Wrong volume. If the year is correct, there should be no difficulty.

Wrong page. In this case one should look up the annual index of the authors or subjects, or both.

When consulting a reference in an abstracting journal, the reader should look up the same year and at least two years afterwards. The more efficient the abstracting journal, the sooner will an abstract of a publication appear.

Finding information about a compound of known formula (and structure). This is usually done by looking up Beilstein, and then the Chemical Abstracts.

Beilstein's Handbuch. There is now a fourth edition, and this is intended to give a complete survey of organic chemistry up to Jan. 1st, 1910. The plan of the arrangement is described in volume I, pp. 1–46 and pp. 939–944. The subject matter is divided into four main divisions:

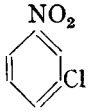
(i) *Acyclic compounds.*	Volumes I–IV.
(ii) *Isocyclic compounds.*	Volumes V–XVI.
(iii) *Heterocyclic compounds.*	Volumes XVII–XXVII.
(iv) *Natural products.*	Volumes XXX and XXXI.

Volume XXVIII is the general names index: part 1, A–G; part 2, H–Z. Volume XXIX is the general formulæ index: part 1, C_1–C_{13}; part 2, C_{14}–C_{195}.

The names index is arranged alphabetically. To look up the formulæ index, the molecular formula of the compound is written down with the elements in the following order:

C H O N Cl Br I F S P

After P the elements appear in alphabetical order. Each page is marked at the top by (*a*) an arabic number which gives the number of carbon atoms in the compound listed on that page, and (*b*) a Roman number which gives the number of other elements present in the compounds listed *e.g.*, *m*-chloronitrobenzene:



≡ $C_6H_4O_2NCl$

This contains six carbon atoms and four other elements. Therefore the page marked 6IV is found, and looking down the pages marked in this way, the desired compound will soon be found.

There is now a new Index which covers the main work and the first and second supplements (volumes I–XXVII). In the formula index, the compounds are listed by the number of carbon atoms, the number of hydrogen atoms, and according to the alphabetical order of the other elements, *e.g.*, $CBrCl_3O_2S$, $C_2H_5NO_2S$. Alongside the compound will be found various numbers, *e.g.*, **18**, 548 (this is the main work, Vol. 18, p. 548); **19**, 402, II 413 (this is the main work, Vol. 19, p. 402; and the second supplement, Vol. 19 (this is not repeated, p. 413); **5**, I 357; **3**, 69, I 31, II 55.

There is a first supplement to Beilstein's fourth edition, in most cases one to each volume; otherwise, the supplements may be combined, *e.g.*, the supplements for volumes III and IV are combined into one volume. The literature survey of the first supplement is from Jan. 1st, 1910 to Jan. 1st, 1920. There is also a second supplement giving the literature survey from Jan. 1st, 1920 to Jan. 1st, 1930. A third supplement has now been begun.

How to use Beilstein. Each volume and supplement has a table of contents and an index consisting partly of names and partly of formulæ. The simplest way to find a compound is to look up the collected indexes of names and formulæ. Having found the compound in the main volumes, the searcher will then find later information (if any) in the corresponding supplements. System numbers are used for cross-reference purposes.

In Beilstein will be found an account of methods of preparation, properties, derivatives, etc.

Each main division of Beilstein is subdivided into functional group compounds in the following order:

Acyclic and Isocyclic. Hydrocarbons, hydroxy-compounds, carbonyl compounds, hydroxy-carbonyl compounds, carboxylic acids, hydroxy-acids, carbonyl acids, hydroxy-carbonyl acids, sulphinic acids, sulphonic acids, hydroxy-sulphonic acids, carbonyl-sulphonic acids, carboxy-sulphonic acids, amines, hydroxyamines, carbonyl-amines, hydroxy-carbonyl-amines, aminoacids, hydroxylamines, hydrazines, azo-compounds, diazo-compounds, azoxy-compounds, metallic compounds.

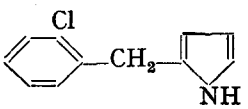
Heterocyclic. 1 cyclic oxygen (S, Se, Te); 2 cyclic oxygen; 3 cyclic oxygen; 4 cyclic oxygen; 5 cyclic oxygen.

1 cyclic nitrogen; 2 cyclic nitrogen; . . . . 8 cyclic nitrogen.

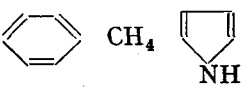
Natural products. Hydrocarbons (petroleum), ethereal oils, sterols, fats, waxes, carbohydrates, alkaloids, proteins.

The division of a particular compound is determined by its *stem-nucleus*. This is obtained by replacing in the formula all the atoms or groups attached to carbon by the equivalent number of hydrogen atoms, except where replacement involves the breaking of a cyclic chain. When the stem-nucleus has been obtained, the following general rule is applied: when the compound is derived from two or more compounds, or contains two or more functional groups, that compound is discussed under the parent compound to be found *last* in the classification.

Example 1.



The stem nuclei are:



Since pyrrole is described last in the classification of these three compounds, the compound under consideration will be found under pyrrole.

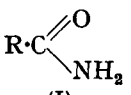
Example 2.

$$ClCH_2{\cdot}CH_2OH$$

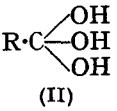
This is a derivative of ethanol, and will therefore be found under the substitution products of ethanol (described immediately after ethanol).

It is important to note that X, NO, NO_2 and N_3 are *not* functional groups, and that their order (of discussion) is F, Cl, Br, I, NO, NO_2, N_3 (immediately after the parent compound).

Difficulty may be encountered when more than one functional group, or one functional group and one or more *apparent* functional groups are attached to the *same* carbon atom. The following examples show how to find the compound:

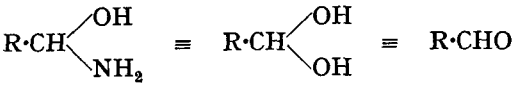
(i) 

(I)



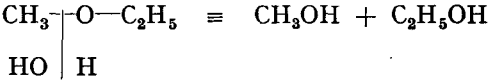
(II)

Replace the functional groups in (I) by hydroxyl groups. This gives (II), which is an acid (ortho-acid). (I) will therefore be found under the derivatives of the acid $R{\cdot}CO_2H$:

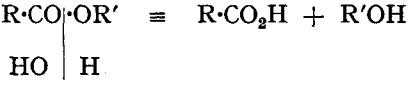
(ii) 

(iii) $NH_2{\cdot}C(:NH){\cdot}NH_2 \equiv HO{\cdot}C(OH)_2{\cdot}OH \equiv H_2CO_3$

(iv) $R{\cdot}CCl_3$. Since there is no functional group present, this compound will be found under $R{\cdot}CH_3$:

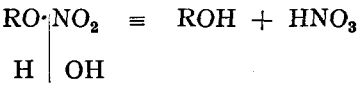
(v) 

This compound will be found under the derivatives of ethanol (ethanol occurs later than methanol):

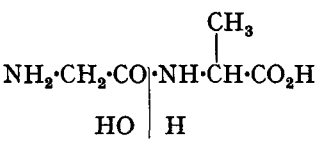
(vi) 

This will be found under $R{\cdot}CO_2H$, since this is discussed later than R'OH.

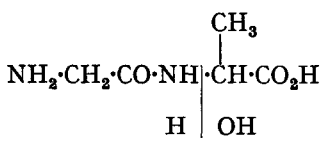
Note however:



This compound will be described under ROH, since HNO_3 is inorganic. Inorganic acid derivatives are discussed in the following order: hydrogen peroxide, halogen-oxyacids, sulphur-oxyacids, nitrogen-oxyacids, phosphorus oxyacids, arsenic-oxyacids, silicon-oxyacids, halogen acids, . . .

(vii) 

(III)

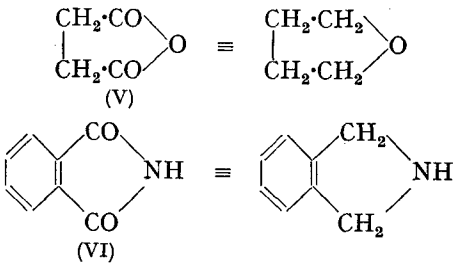


(IV)

This is an example where a compound may be broken up in two (or more) ways. In such cases, the decomposition is carried out in the way which gives the stem-nucleus described later than any obtained in any other way. (III) gives glycine and alanine; (IV) gives glycine (amide derivative) and

lactic acid. Since alanine is described later than any other decomposition product, the compound will be found under alanine:

(viii)



(V)

(VI)

(V) and (VI) are both to be found under *heterocyclic* compounds, the former under the division of 1 cyclic oxygen atom, and the latter, 1 cyclic nitrogen atom.

READING REFERENCES

Huntress, *A Brief Introduction to the Use of Beilstein's Handbuch der Organischen Chemie*, Wiley (1930).
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