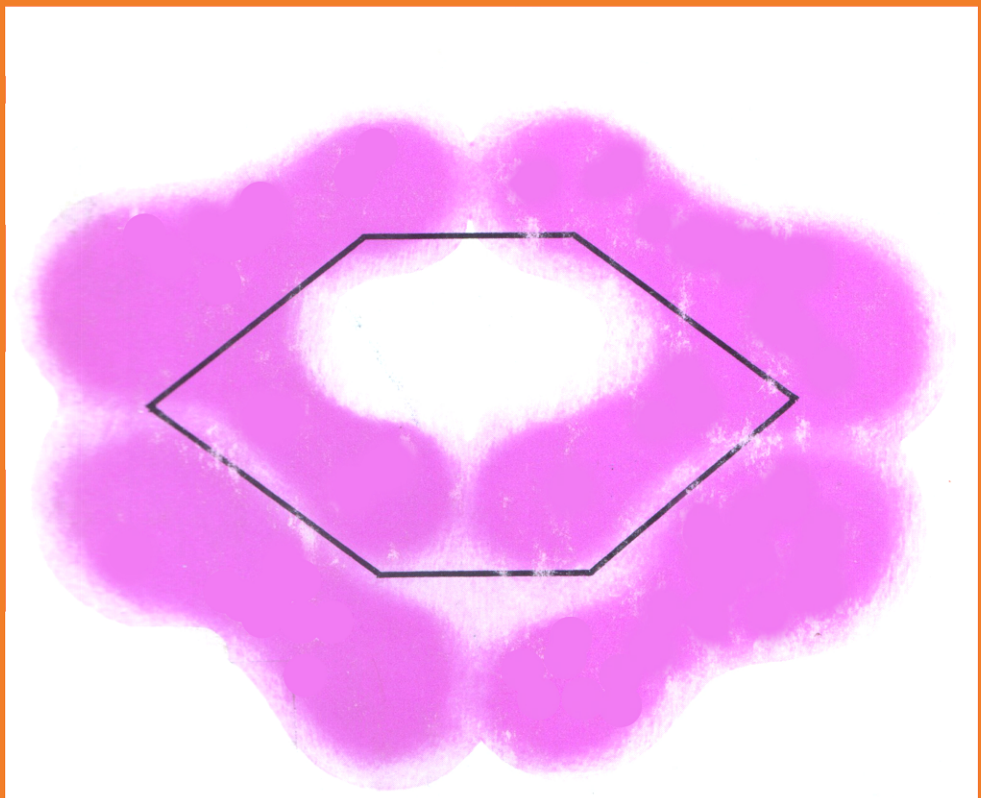
FUNDAMENTALS OF ORGANIC CHEMISTRY

A.N. NESMEYANOV, N.A. NESMEYANOV



VOLUME 3

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FUNDAMENTALS OF ORGANIC CHEMISTRY

by

A.N. Nesmeyanov

and

N.A. Nesmeyanov

This is Volume III of a four-volume textbook designed for a systematic study of organic chemistry. The material covered in the book is divided into two parts and covers a considerably wider field than does the normal university treatment of the subject. Part One (the first three volumes) is constructed along "classical" lines. Part Two (volume IV) is intended for attentive reading rather than for close study. Volume III is devoted to aromatic and heterocyclic compounds. The material is presented in order of increasing sophistication – first, rather simply and in detail, and then in more and more concise form.

This book has been translated from the second revised Russian edition published in two volumes in 1974. The first Russian edition (in two volumes) was published in 1969.

The book may be used for self-study and for reading the course of organic chemistry at universities and chemical higher schools. It will undoubtedly be of interest to post-graduates, teachers, scientists and engineers working in the field of organic chemistry.

FUNDAMENTALS OF ORGANIC CHEMISTRY

Volume III

А. Н. Несмеянов, Н. А. Несмеянов

НАЧАЛА ОРГАНИЧЕСКОЙ ХИМИИ

Издательство «Химия» Москва

A. N. NESMEYANOV and N. A. NESMEYANOV

FUNDAMENTALS OF ORGANIC CHEMISTRY

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AROMATIC COMPOUNDS

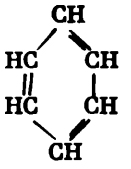
Chapter 7

Benzene and its derivatives

7.1. Benzene and Its Structure

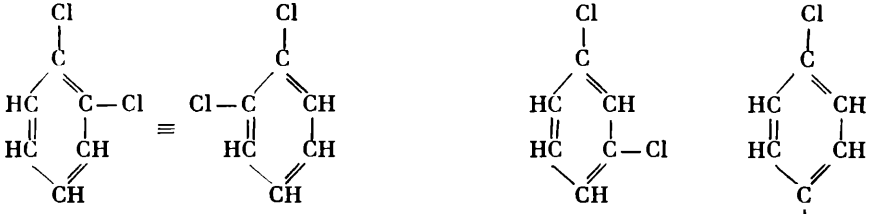
We have already said (see Volume I, Chapter 1) about the purely chance origin of the term **aromatic compounds** which was given at the beginning of the XIXth century to benzene, its derivatives and compounds based on hydrocarbons with condensed benzene rings (naphthalene, anthracene, etc.). The first compounds of this series known to chemists (benzaldehyde, benzoic acid, toluene, and others) were either pleasant-smelling compounds or compounds derived from fragrant balsams (toluene from Balsam of Tolu) or from other fragrant exotic products (benzoic acid from gum benzoin, a naturally occurring resin). The parent hydrocarbon of the aromatic series, **benzene**, was discovered in 1825 by Faraday in an illuminating gas from which it crystallized on cooling. The structure of benzene was largely established by Kekulé in 1865, five years after the enunciation of the theory of chemical structure by Butlerov. In spite of this, the constitution of benzene and its derivatives remained to be a puzzle, on which chemists fixed their attention during all the subsequent history of chemical science and which has been resolved only relatively recently. The facts which were known to Kekulé and which served as the basis for the Kekulé formula of benzene were as follows.

Benzene



and its homologues may be represented by the formula C_nH_{2n-6}, which, because of the obvious monocyclic structure for benzene, must signify the presence in it of three double bonds (or one triple and one double bond).

In benzene, all the carbon atoms are equivalent, just as all the hydrogen atoms are, which is consistent only with the assumption of a cyclic structure. Thus, the replacement of any hydrogen atom of benzene gives rise to the same monosubstituted product. On the other hand, there always exist three isomeric disubstituted derivatives of benzene, namely, *ortho-* (abbreviated to *o-*), *meta-* (*m-*), and *para-* (*p-*) isomers. The Kekulé formula given above satisfies all these facts, except for the number of *ortho*-disubstituted benzenes, which was recognized by Kekulé.



I ≡ II

o-Dichlorobenzene

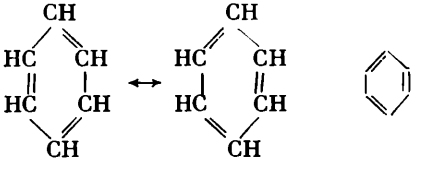
III

m-Isomer

IV

p-Isomer

Indeed, if one is guided by the knowledge of the chemistry of the aliphatic series, formulas I and II must correspond to two different structurally isomeric compounds. In actual fact, no such two *ortho*-isomers exist and *ortho*-disubstituted benzenes always exist in the form of only a single compound, just as the *meta-* and *para*-isomers. Kekulé had to introduce a special hypothesis of the rapid "oscillation" of the double bonds in benzene in order to maintain his formula, which is expressed by the double-headed arrow placed between formulas V and VI. For the sake of brevity, one formula is usually written, implying however that the double bonds of the ring are not fixed in certain definite positions. Ordinarily, in writing the formulas of benzene and other aromatic compounds the symbols for carbon and hydrogen atoms are omitted in a hexagon (formula VII):

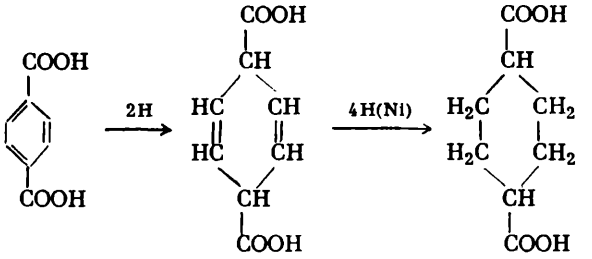


V VI VII

The subsequent development of chemistry provided numerous confirmations of the Kekulé structure.

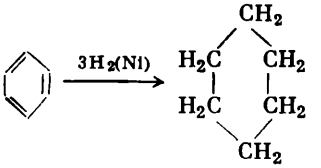
Baeyer established that terephthalic acid (*p*-benzenedicarboxylic acid) could be reduced with nascent hydrogen to cyclohexadienedicarboxylic acid, and that the latter could be hydrogenated to cyclo-

hexanedicarboxylic acid:

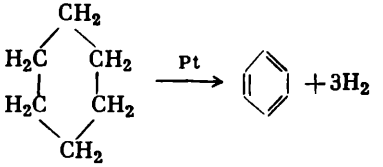


Thus, in this way the benzene and cyclohexane series were for the first time related to each other and the presence of a six-membered ring in benzene was conclusively proved.

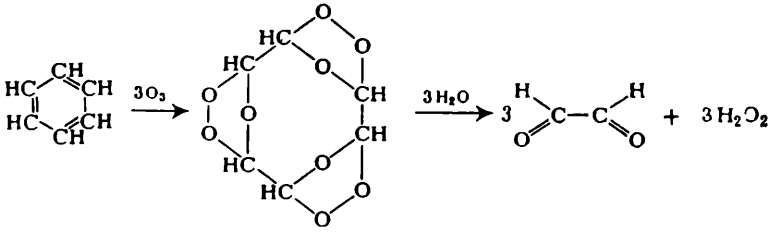
About 1900, Sabatier showed, by using his method of hydrogenation of unsaturated compounds with molecular hydrogen over nickel, that the same interrelationships exist between benzene itself and cyclohexane:



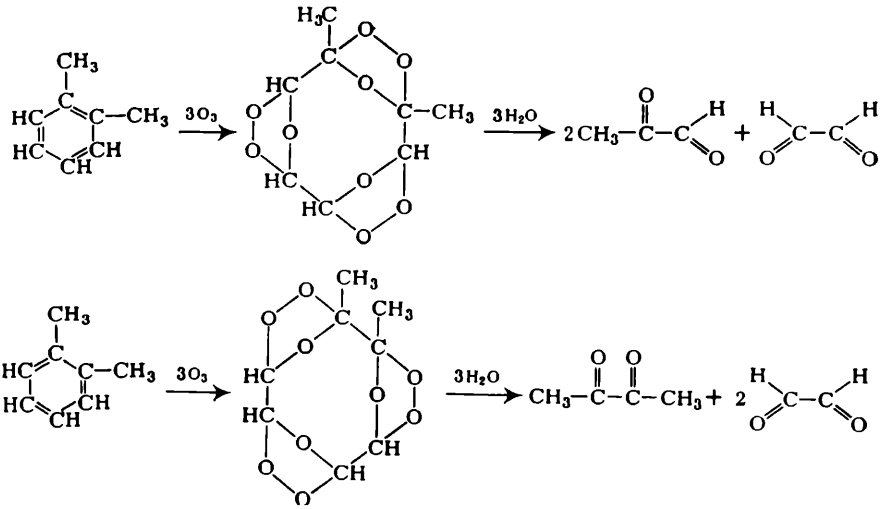
In 1912, Zelinsky accomplished the reverse reaction—the **aromatization** of cyclohexane to benzene over a platinum or palladium catalyst:



In 1904, Harries effected the ozonolysis of benzene, the course of the reaction being similar to that of the ozonolysis of olefins. This proves that all the carbon atoms of benzene are olefinic in valence state; the benzene ozonide on hydrolysis is converted to glyoxal and hydrogen peroxide:

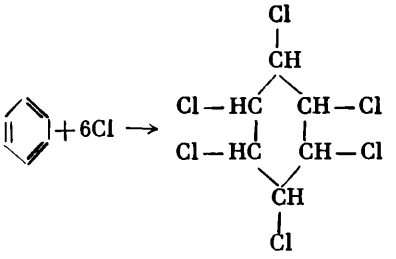


The ozonolysis of *o*-xylene (*o*-dimethylbenzene) leads to glyoxal, methylglyoxal and diacetyl in the molecular ratio 3 : 2 : 1 (Wibaut, 1941):



which clearly proves the complete equivalence of all the carbon-carbon bonds in the ring of *o*-xylene with respect to ozonolysis and hence the oscillation of the double bonds.

Benzene has been found to be capable of adding, in the presence of light, six chlorine atoms and of being converted, as a result, into a mixture of the geometric isomers of hexachlorocyclohexane (benzene hexachloride), including the *gamma*-isomer which is a very powerful insecticide known as **gammexane** or **lindane**:

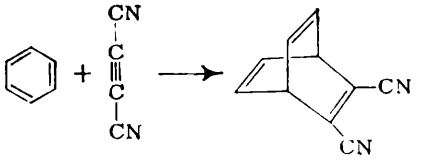


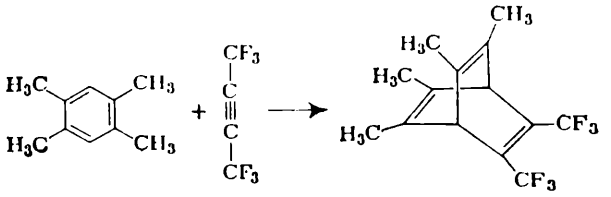
Molecular chlorine dissolves in benzene without entering into reaction with it.

It has recently been established that benzene, and even better its homologues, can also react as dienes, by way of adding very active dienophiles under vigorous reaction conditions. This addition reaction is strongly favoured by aluminium chloride which improves the

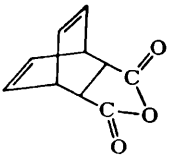
yield and reduces the temperature down to room temperature (instead of 150-480°C).

The following are examples of such syntheses, leading to derivatives of bicyclo [2.2] octatriene (Ciganek, 1967; Krespan *et al.*, 1968):





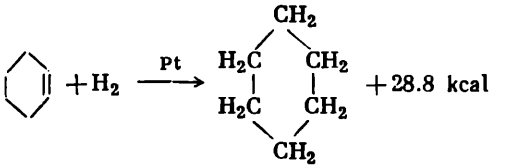
When the reaction mixture is irradiated, maleic anhydride too adds to benzene in the same way as it adds to a diene, to give the following compound

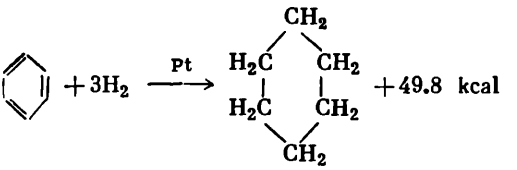


The structure of benzene suggested by Kekulé is confirmed by numerous syntheses of benzene, its homologues and derivatives from compounds of the aliphatic series, which will be given on page 21.

In spite of the seemingly excellent agreement between the Kekulé formula and the experimental facts, many outstanding chemists turned again and again to the re-examination of the structure of benzene and proposed other formulas (Claus, Ladenburg, Baeyer), which are now of only historical interest. Such objections to the formulation of benzene by Kekulé were based on the fact that benzene (and all aromatic compounds) is incomparably more inert in addition reactions than olefins. Only a few addition reactions ($3H_2$/Ni; O_3; 6Cl) take place, and many of the reagents that add to olefins lead to the replacement of hydrogens in the aromatic series. Especially characteristic is the stability of benzene towards oxidizing agents ($KMnO_4$, $H_2Cr_2O_7$).

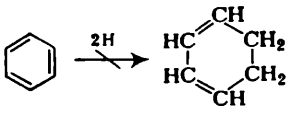
The greater chemical inertness of benzene, as compared with olefins (cycloolefins which are closest to benzene) becomes clear from the following energy comparison:

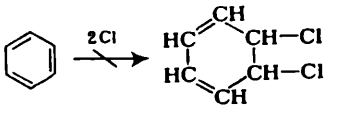




If each of the double bonds of benzene were energetically equivalent to the double bond of cyclohexene, the hydrogenation of benzene to cyclohexane should liberate $28.8 \times 3 = 86.4$ kcal/mole, i.e., 36.6 kcal/mole greater than the observed heat of hydrogenation. Benzene is energetically poorer by this amount (and, hence, more stable) than could be expected from a cycloolefin with the fixed Kekulé structure—cyclohexatriene.

Any disturbance of the benzenoid character of an aromatic compound, say, by way of addition of at least a pair of atoms due to the removal of two electrons from the sextet, would lead to an additional loss of the "resonance energy" (36.6 kcal/mole), which is exactly one of the causes why such reactions are rare.





From the molecular-orbital diagrams given earlier (see the MO method in Volume I, page 307 *et seq.*) it is seen that in the case of butadiene one may speak, with certain reservations, of the double bonds between carbon atoms 1 and 2 or 3 and 4, though the π-bonds in butadiene are not localized to such an extent as they are localized in ethylene. This is evidenced by the bond order between carbon atoms 2 and 3, which is significantly different from 2 (ca. 1.45), the

values of the delocalization energy (in the MO method) or the resonance energy (in terms of the resonance theory) which are different from zero, though being small, and finally, by the somewhat reduced length of the bond between carbon atoms 2 and 3 (1.48 Å instead of 1.54 Å for a single carbon-carbon linkage). Thus, the representation of butadiene by the structural formula $CH_2=CH-CH=CH_2$ is not unambiguous.

As regards benzene, one cannot speak of localized bicentric π-bonds. All the six bonds in the benzene molecule are equivalent, just as all the six carbon atoms, which has been conclusively proved by the experimental data: the molecule is coplanar, the length of each of the six bonds is 1.40 Å, all the bond angles are equal to 120°, and the symmetry of the molecule is hexagonal. The results of the quantum-mechanical calculations are in agreement with the experimental data.

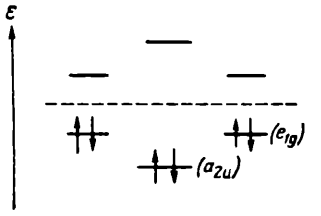


Fig. 7.1.
Diagram of orbital-energy levels for the benzene molecule.

The calculation made by the LCAO-MO method in the Hückel π-electron approximation is based on the assumption of the six atomic p_z-orbitals of carbon. The energy-level diagram and the delocalization of electrons over the energy levels for the ground state are shown qualitatively in Fig. 7.1.

The dashed horizontal line signifies the energy of the electron on the atomic p_z-orbital of carbon, which is assumed to be the reference point on the orbital-energy scale; the heavy horizontal lines are the orbital-energy levels. The levels situated below the dashed line represent the bonding molecular orbitals, and those lying above, the antibonding orbitals; the arrows indicate the π-electrons (with opposite spins) on the bonding orbitals.

All the molecular orbitals are of the π-type (Fig. 7.2).

In the ground state of the molecule, two electrons occupy the lowest-lying orbital (a_{2u}), which belongs to the lower nondegenerate value of the orbital energy. The remaining four electrons occupy two bonding molecular orbitals (e_{1g}), which belong to the next (in increasing order) doubly degenerate energy level. The three antibonding molecular orbitals $(\pi_1^*, \pi_2^*, \pi_3^*)$ are disposed symmetrically to the bonding ones relative to the reference point on the orbital-energy scale (see Fig. 7.1). The π-electrons of benzene move to these orbitals upon excitation by absorption in the near ultraviolet region (the $\pi \rightarrow \pi^*$ transition). The first absorption maximum in the electronic spectrum of benzene corresponds to the lowest light quantum and, hence, to the greatest maximum wavelength $\lambda \approx 250$ mμ (2500 Å).

Figure 7.2 shows the boundary surfaces of the molecular π-orbitals of benzene, and Fig. 7.3 is an approximate representation of the boundary surface of the three-dimensional π-electron density in the benzene molecule.

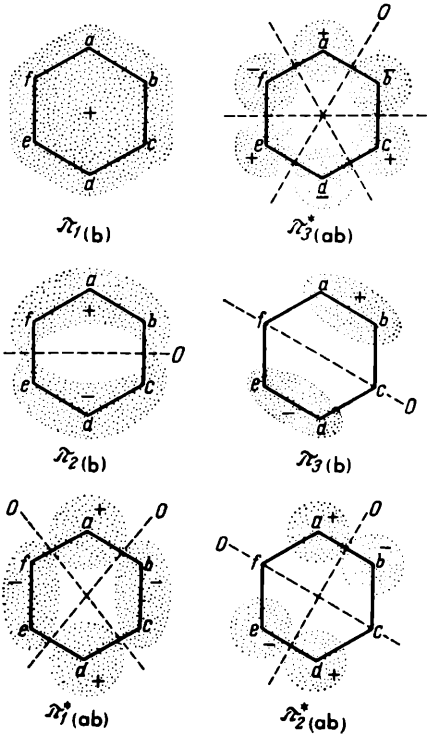
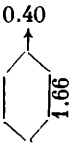


Fig. 7.2.

Boundary surfaces of the molecular π-orbitals of benzene (top view): π_1, π_2, π_3 — bonding orbitals (a_{2u}, e_{1g}, e_{1g}, respectively); π_1^*, π_2^*, π_3^* — antibonding orbitals; the dashed lines 0 are the nodal planes.

The molecular diagram of benzene, as established in the Hückel π-electron approximation, has the following form:



The effective charges on the atoms are equal to zero; the symmetry permits one to indicate only the order of one bond (1.66) and the free-valency number (0.40) of one atom; the orders of the σ-bonds are assumed to be equal to unity (see Volume I, page 315).

The diagram of benzene reflects well the equilibration of the bonds and the equivalence of the atoms.

The delocalization energy, as compared with a system of three localized bicentric π-bonds of the Kekulé formula in β units is equal to 2 (ca. 36 kcal/mole).

In 1931, Hückel formulated and substantiated, within the framework of his π-electron approximation in the LCAO-MO method, the so-called $(4n + 2)$ rule.

According to this rule, flat monocyclic systems consisting of atoms that supply $4n + 2$ p-electrons to the π-electron system of the molecule, are, like benzene, aromatic rings with closed electron shells (all the bonding and only bonding orbitals are occupied by electrons) which are stabilized by the considerable delocalization energy.

Hückel predicted, however, the possibility of the destabilizing effect of the strain of the σ-skeleton.

Systems of this kind will also be discussed in Volume IV under "Nonbenzenoid Aromatic Systems".

It is interesting to note that cyclooctatetraene, which does not satisfy the Hückel rule, is absolutely devoid of the aromatic na-

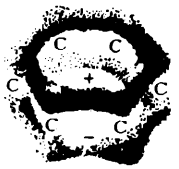
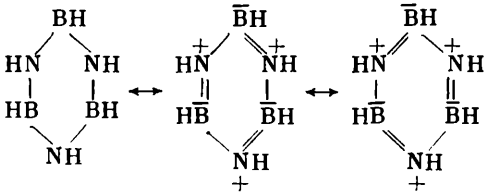


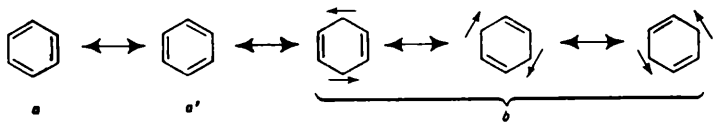
Fig. 7.3.

The boundary surface of the three-dimensional π-electron density in the benzene molecule (approximate representation).

ture*. There also exist heterocyclic aromatic systems (see under "Heterocyclic Compounds"), including "inorganic benzene"—**borazole**:



Passing over to the description of the π-electronic structure of benzene from the viewpoint of the resonance theory, we may represent it as a resonance hybrid of five "canonical" structures—two Kekulé structures (*a* and *a'*) and three Dewar structures (*b*)**:



It will be recalled that the concept of resonance comes from the tendency to make use, as much as possible, of the conventional methods of representation of molecular structure in classical chemistry. Resonating forms are not considered to exist individually even as the excited states of the molecule.

* Under the action of an alkali metal, however, cyclooctatetraene captures two electrons and is converted into the aromatic binegative anion $C_8H_8^{2-}$ which satisfies the Hückel rule ($4 \times 2 + 2 = 10$).

** This representation of the Dewar structures is legitimate since the π-bonds between the carbon atoms in the *para*-position are of formal character and importance here is attached, on the one hand, to the antiparallelism of the spins of *p*-electrons on the atomic p_z-orbitals of these atoms and, on the other hand, to the completeness of the set of canonical structures. It should, of course, be kept in mind that the arrows do not imply the absolute orientation of the spins.

The main contributing forms are the Kekulé structures (*a* and *a'*). In the resonance of the five canonical structures the contributions* of structures *a* and *a'* are much greater than that of any of structures *b*. The contribution of one Dewar structure and that of one Kekulé structure is in the ratio 0.19:1; in percentage terms, the contribution of one of the Kekulé structures is 39 per cent, while the contribution of one Dewar structure is only 7 per cent. The hybrid of the five canonical contributing structures is energetically poorer than the Kekulé structure** by the amount of the resonance energy, namely by 36.6 kcal/mole, and the Kekulé structure is considerably poorer than the Dewar structure.

In spite of the absence in benzene of localized double bonds, its structure is still commonly represented by the Kekulé formula. Along with this formula, use is also made of other formulas which have been suggested to express the high symmetry of the molecule. In what follows we shall use the first and the last of the formulas given:

The Dewar structures *b* which contribute little to the resonance hybrid, are better represented by formula I rather than by formula II which Dewar himself used to represent the benzene structure to avoid the use of one formula to designate different compounds.

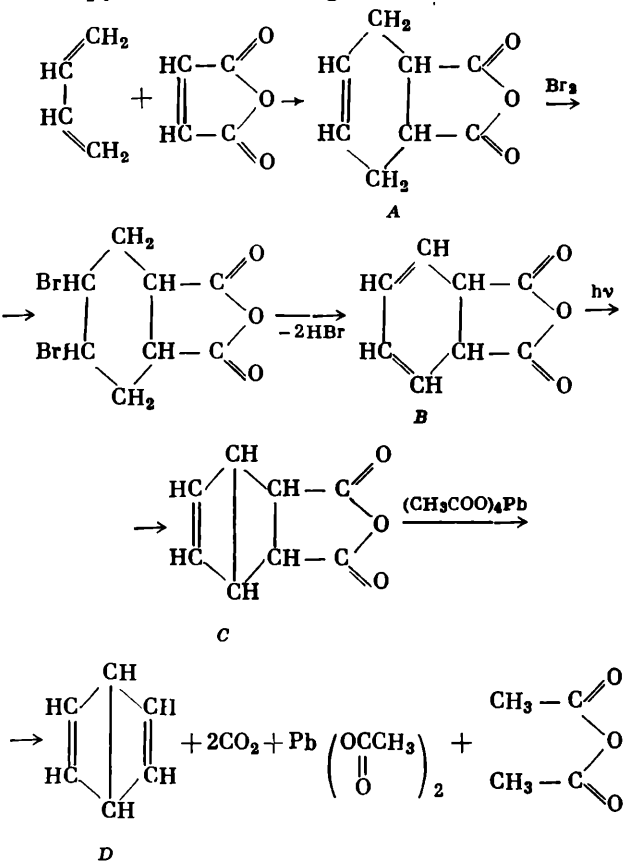
I II

The point is that the so-called *Dewar benzene* II has been recently obtained as a chemical entity, whose molecule contains only four π-electrons; the geometry of its nuclear configuration differs from that of benzene, and the linkage between atoms 1 and 4 is not a π-bond. This Dewar benzene, or bicyclo[2.2.0]hexa-2,5-diene, was obtained in 1963 by Van Tamelen and Pappas in the following way: the adduct of 1,3-butadiene and maleic anhydride (*A*) was converted into the anhydride of 3,5-cyclohexadiene-1,2-dicarboxylic acid (*B*)

* The contribution of a resonating structure is defined as the square of the absolute value of the coefficient for the corresponding structure in the linear combination representing the resonance. In the case of real wave functions and coefficients this is the square of the coefficient. The greater the contribution of the structure, the closer it is, in a certain, strictly mathematically determinable sense, to the linear combination representing the resonance.

** The energy of the Kekulé structure is calculated according to the additivity rule from thermochemical data.

which underwent rearrangement under the influence of ultraviolet light to the product *C*; the decarboxylation of *C* with lead tetraacetate at 45°C in pyridine solution gave the Dewar benzene *D*:



A *B* *C* *D*

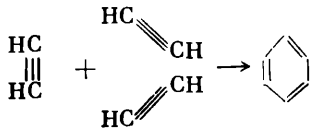
Bicyclo[2.2.0]hexa-2,5-diene (Dewar benzene) is a valence isomer and not a resonating structure of benzene and differs from the latter in spectral characteristics, NMR spectrum and chemical properties (its pyrolysis leads to diallyl). Heated up to 90°C for half an hour the hydrocarbon *D* isomerizes to benzene.

A. Synthesis of Benzene and Its Derivatives from Aliphatic and Alicyclic Hydrocarbons

Of industrial importance at present are the aromatization of paraffins and the dehydrogenation of cyclohexanes (reactions 3 and 4). Reactions 1 and 2 are only of instructive interest; in particular,

they confirm the above conclusions about the structure of benzene. Only in certain cases, say, for mesitylene, triphenylbenzene, hexaphenylbenzene, are such syntheses of preparative value.

1. Berthelot obtained small amounts of benzene by passing electric sparks through acetylene. At 450-500°C over activated charcoal (used by N. D. Zelinsky for filling a gas mask) acetylene is converted in good yield into a mixture of aromatic hydrocarbons containing benzene (N. D. Zelinsky, B. A. Kazansky, 1922):

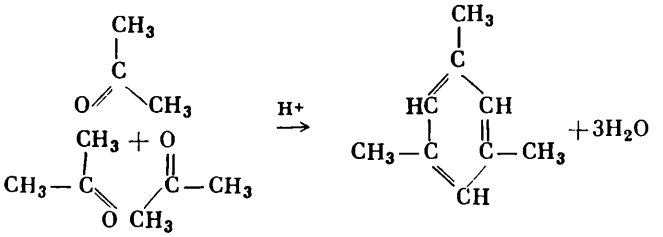


The same reaction can be effected by the Reppe method (1948)—the wet method using the action of dicarbonyl-ditriphenylphosphine-nickel $[(C_6H_5)_3P]_2Ni(CO)_2$, which is obtained from triphenylphosphine and nickel tetracarbonyl. The same catalyst trimerizes monosubstituted acetylenes into 1,3,5-substituted benzenes (see Volume IV, "Organoelement Compounds") and into structurally isomeric 1,3,4-derivatives of benzene. It has been found since the Reppe discovery that the same effect is exerted by a number of complex catalysts. For example, according to M. E. Volpin, $[(C_2H_5O)_3P]_4CoCl$ also catalyzes the trimerization of acetylenes into benzenes.

Ziegler catalysts [$Al(C_2H_5)_3 + TiCl_4$, see Volume II, page 55] which cause the polymerization of ethylene and its homologues, trimerize both mono- and disubstituted acetylenes into 1,3,5-trisubstituted and hexasubstituted benzenes, respectively (Franzus; Lutz). According to the data obtained by V. O. Reikhsfeld and K. L. Makovetsky, this trimerization is best effected with a mixture of triisobutylaluminium and titanium tetrachloride in the ratio of Al:Ti = 3:1.

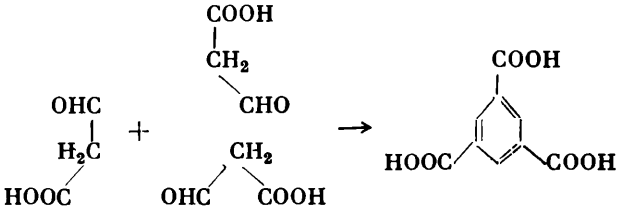
Diphenylacetylene is converted into hexaphenylbenzene in the presence of the various catalysts, in particular, by the action of $CrCl_3$ at the moment of its reduction by a Grignard reagent (Zeiss).

2. Acetone when acted on by concentrated sulphuric acid forms 1,3,5-trimethylbenzene (mesitylene). The reaction is a case of cyclic croton condensation of three molecules of a ketone:

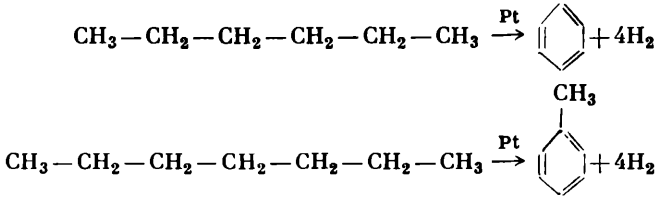


All ketones of the type $R—CO—CH_3$ behave in a similar way. For instance, from acetophenone, $C_6H_5COCH_3$, there can be produced 1,3,5-triphenylbenzene.

This type of cyclization reaction is in general rather widespread; if the starting compound contains an aldehyde group linked to a very mobile methylene group, the reaction takes place spontaneously, often in a quantitative yield. For example, reactions that should have resulted in the formation of a semi-aldehyde of malonic acid, $HOOC—CH_2—CHO$, in fact lead to the croton condensation of the latter into trimesic acid:



3. A remarkable reaction of aromatization of paraffins was discovered by N. D. Zelinsky, B. A. Kazansky, and A. F. Plate. When *n*-hexane, *n*-heptane and other paraffins having a chain of at least six carbon atoms are passed over a platinum catalyst at about 300°C, benzene is formed (in the first case), toluene (in the second) or their homologues, and hydrogen is evolved:

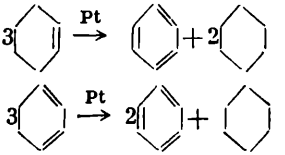


It has been found that the same effect can be achieved by using, as a catalyst, chromium oxide on aluminium oxide (B. L. Moldavsky) at a higher temperature (> 400°C). These reactions are widely employed in the aromatization of petroleum fractions.

4. As pointed out above, by passing vapours of cyclohexane (or of its homologues) over a platinum or palladium catalyst at about 300°C it is possible to convert it quantitatively into benzene (or its homologues) (N. D. Zelinsky, 1912). Later it was found that such a dehydrogenation of cyclohexanes can be accomplished by heating them with sulphur up to about 400°C (Ruzicka) or with selenium (up to about 500-600°C), hydrogen being evolved as hydrogen sulphide or hydrogen selenide.

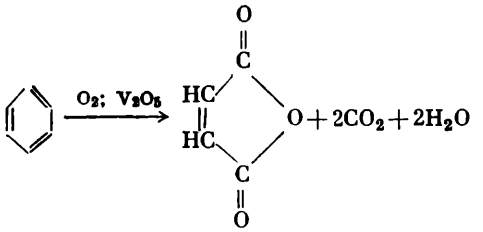
5. Cyclohexene, cyclohexadiene and their homologues disproportionate in the presence of platinum or palladium into benzene and

cyclohexane (or their homologues) even at room temperature (the Zelinsky "irreversible catalysis" reaction):



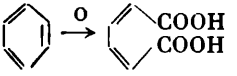
B. Conversion of Benzene into Aliphatic and Alicyclic Hydrocarbons

However stable benzene is, its aromatic system is destroyed under vigorous conditions. This happens when, for example, benzene is subjected to vigorous oxidation with air over V_2O_5 as a catalyst, the reaction leading to maleic anhydride:



The process is utilized on an industrial scale.

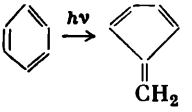
In the organism (of rabbits), benzene is oxidized to muconic acid and is thus removed from the body. When this reaction is taking place, the carbon skeleton of six carbon atoms and the two double bonds of benzene are retained:



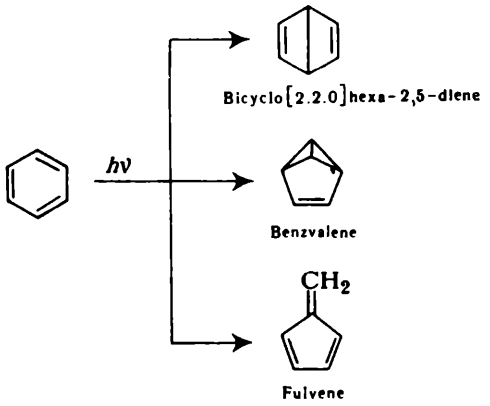
The hydrogenation of benzene to cyclohexane has already been considered (see page 13).

The reduction of benzene by HI proceeds with isomerization and leads to methylcyclopentane (N. M. Kishner).

By acting on benzene with ultrasound, Zechmeister (1957) obtained acetylene which he isolated in the form of copper acetylenide; he isomerized benzene to fulvene by the action of ultraviolet radiation:



In 1968, Ward and Wishnok irradiated benzene in the liquid state by far ultraviolet light (1650-2000 Å) and obtained a valence isomer of benzene—Dewar benzene (bicyclo[2.2.0]hexa-2,5-diene) along with two other valence isomers of benzene—benzvalene and fulvene:



C. Sources of Aromatic Hydrocarbons

Benzene and its nearest homologues, naphthalene and other condensed aromatic hydrocarbons in the form of their numerous derivatives find the various applications in industry—in the production of plastics, synthetic rubbers, dyes. They are also used as drugs, solvents, and intermediates for the various branches of the organic chemicals industry. Many million tons of these products are consumed every year in the world. One of the principal (and until recently the sole) source of these products was coal tar produced by coking coal to meet the demands of metallurgy (formerly, with the purpose of producing illuminating gas). When the coking coal is heated in a closed vessel up to 1000°C, pyrolysis takes place, as a result of which coke is left, coke gases are removed and coal tar is distilled off, which is a heavy viscous black mass (the yield is about 3 per cent of the amount of coal).

The yield and composition of coal tar are strongly dependent on the temperature and rate of the coking process. The higher they are, the lower the yield of coal tar and the content of valuable phenols in it. In this sense, the interests of the metallurgical and chemical industries do not coincide. The greater portion of volatile hydrocarbons is contained in the coke-oven gas the amount of which evolved per 1 ton of coal is 250 m^3. In 1 m^3 of this gas there is about 40 g of benzene and toluene; the benzene-to-toluene ratio in the mixture is from 3:1 to 5:1. The hydrocarbons are isolated from the gas through

absorption by the heavier fractions of coal tar. The remaining portion of these hydrocarbons is isolated from coal tar which is first subjected to distillation into rough fractions (see Table 7.1).

TABLE 7.1. **Fractions of Coal Tar**

Fraction	Composition
Light oil (fraction 80-170°C; yield 3-5 per cent)	Contains cyclopentadiene and aromatic hydrocarbons — benzene, toluene, *o*-, *m*-, and *p*-xylenes, small amounts of polymethylbenzenes and ethylbenzene, and also nitrogen- and sulphur-containing heterocyclic compounds
Middle (or *carbolic*) *oil* (fraction 170-240°C; yield about 10 per cent)	Contains mainly naphthalene, both methylnaphthalenes, phenol, and *o*-, *m*-, and *p*-cresols
Heavy (or *creosote*) *oil* (fraction 240-270°C; yield 10-15 per cent)	Naphthalene, cresols, homologues of naphthalene and naphthols, diphenyl, acenaphthene, partly quinoline
Green (or *anthracene*) *oil* (fraction up to 360°C; yield ca. 20 per cent)	Anthracene, phenanthrene, fluorene, indole, carbazole
Pitch (residue from distillation; yield up to 60 per cent)	Coal, higher condensed aromatic hydrocarbons

The fractionation gives the crude benzene-toluene fraction (about 1 per cent of the amount of coal tar), naphthalene (about 6 per cent), from which phenol and cresols (totalling 1.5 per cent) are separated by taking advantage of their solubility in aqueous alkali; about 1 per cent of anthracene is also isolated.

A source of aromatic hydrocarbons which is constantly increasing in importance is petroleum refining. More than half of the total amount of aromatics is produced from petroleum.

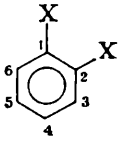
Certain types of crude oil (for example, Maikop oil, Rumanian oil, the Borneo oil) contain appreciable amounts of benzene and its homologues. Aromatic hydrocarbons can be isolated from the corresponding fractions by using selective solvents, say, liquid sulphuric anhydride and furfural, or by adsorption on silica gel, with the aid of which the readily adsorbable aromatic hydrocarbons are separated.

In this way, however, only a small portion of aromatic hydrocarbons is produced. The bulk of aromatic hydrocarbons is obtained by pyrolysis or catalytic aromatization of the hydrocarbons contained in petroleum. *Pyrolysis* carried out at about 800°C in pipe stills converts the alicyclic and aliphatic hydrocarbons of petroleum into aromatic hydrocarbons, fragment olefins and the lower alkanes. The principal route for production of the aromatics is *catalytic aromatization* based on the reactions described above. In this process, use is made of a platinum catalyst which functions at lower temperatures (platforming) and of chromium oxide on alumina, and also of oxides of other metals (Mo, V) at 450-500°C. In petroleum refining, the benzene-toluene-xylene ratio is 1:4:5, whereas the coking process yields a preponderance of benzene: it is five times as much as toluene and 15 times as much as the xylenes.

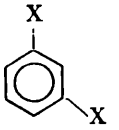
D. Isomerism of Substituted Benzenes

We have already mentioned that monosubstituted benzenes have no isomers; for example, there exists only one monomethylbenzene—toluene. It has been proved, through a special series of reactions, that if each of the remaining hydrogen atoms in a monosubstituted benzene is replaced successively and the first substituent is eliminated (i.e., replaced by hydrogen), the same monosubstituted benzene will be produced.

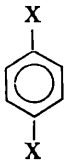
Disubstituted benzenes with identical substituents exist in three and only three isomeric forms (position isomers):



ortho- or 1,2-
-Di-X-benzene



meta- or 1,3-Di-
X-benzene

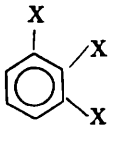


para- or 1,4-Di-
X-benzene

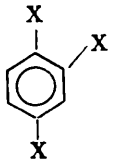
The positions of substituents in the benzene ring are usually indicated by the numeral designations of the carbon atoms in benzene. The designations *ortho*-, *meta*-, and *para*- were introduced by

Körner. Usually these are contracted to *o*-, *m*-, and *p*-, or 1,2,-1,3-, and 1,4-.

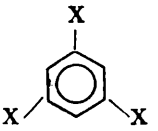
Trisubstituted (with identical substituents) benzenes also exist in the form of three isomers:



Vicinal or 1,2,3-tri-X-benzene

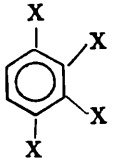


Asymmetrical or 1,2,4-tri-X-benzene

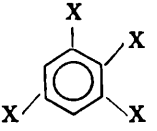


Symmetrical or 1,3,5-tri-X-benzene

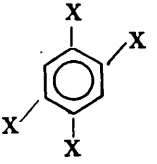
The number of tetrasubstituted benzenes is evidently 3 too (the two hydrogen atoms that have not been replaced are in the *ortho*-, *para*-, or *meta*-position relative to each other):



1,2,3,4-Tetra-X-benzene



1,2,3,5-Tetra-X-benzene

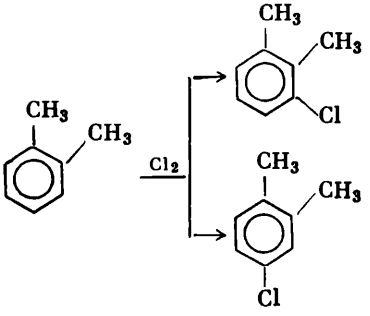


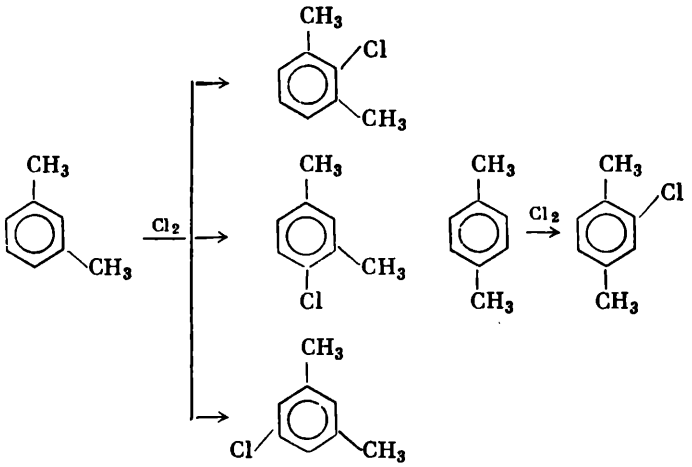
1,2,4,5-Tetra-X-benzene

And, finally, there is one pentasubstituted benzene (and again provided that the substituents are the same).

A considerably larger number of combinations is obtained in the case of different substituents. For instance, 10 position isomers are possible if there are three different substituents.

The identity of each of the three isomeric disubstituted benzenes formed was originally established by **Körner's absolute method:** the introduction of a new substituent by direct replacement of hydrogen by halogen, nitro group, etc. (see below), gives two isomeric compounds for the *ortho*-isomer, three for the *meta*-isomer, and only one compound for the *para*-isomer:

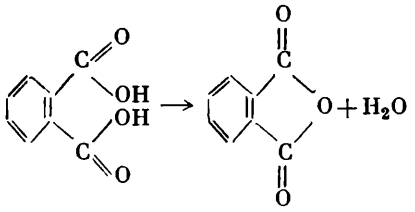




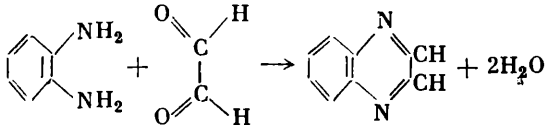
By separating the reaction products and establishing the number of isomers formed one can solve the problem.

This method, however, is difficult to apply since it is not easy, for example, to isolate each of the three isomers present in a mixture because they may be present in greatly unequal amounts and the isomer contained in a very small amount (a few per cent or fractions of a per cent) must not be lost.

Another method of establishing the position of substituents, especially suitable for *ortho*-derivatives, is based on the ability of isomers to form cyclic derivatives. For instance, phthalic acid is *o*-benzenedicarboxylic acid since it is the only one of its isomers that forms a cyclic anhydride:

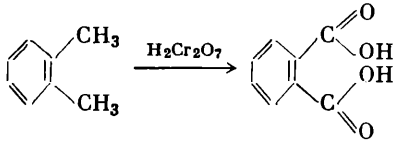


o-Phenylenediamine is the only one among its isomers that forms heterocycles with a number of dialdehydes and diketones:

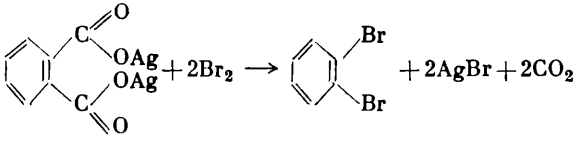


At present there is no need to resort to the determination of the positions of substituents by any of the primary methods since we

know the positions of substituents in numerous derivatives to which any new compound can be reduced by a series of appropriate reactions. For example, knowing that the carboxyl groups in phthalic acid are in the *ortho*-position relative to each other, we can establish the correspondence of the positions in phthalic acid and in *o*-xylene by oxidizing the latter by chromic acid to phthalic acid



or through the action of bromine on silver phthalate, as a result of which the carboxyls are replaced by bromine and *o*-dibromobenzene is obtained:



XXVI. Physical Methods of Determination of the Structure of Organic Molecules* III

The method of measuring the *dipole moments* of molecules, which was worked out by Debye in 1912, provided chemists with the absolute method of establishing the position of substituents in the benzene ring. This method, however, appeared at the time when there was almost no need to apply it for this purpose.

If we know the dipole moments of two monosubstituted benzene derivatives, μ_1 and μ_2, then we can calculate the dipole moment μ of a disubstituted benzene with two such substituents by using the formula of vectorial addition:

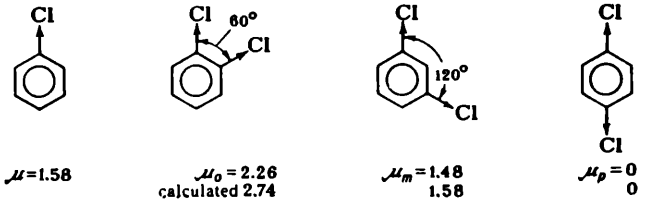
$$\mu = \sqrt{\mu_1^2 + \mu_2^2 + 2\mu_1\mu_2 \cos \alpha}$$

Here α is the angle between the vectors of the dipole moments of two substituents in one benzene ring. For the *ortho*-position, $\alpha = 60°$, $\cos \alpha = \frac{1}{2}$; for the *meta*-position, $\alpha = 120°$, $\cos \alpha = -\frac{1}{2}$; for the *para*-position, $\alpha = 180°$, $\cos \alpha = -1$.

In the case of identical substituents, the electric moments of which are directed along the diagonals of the benzene hexagon, the dipole moments of disubstituted benzenes will be expressed, as

* See also Volume I, page 430, and Volume II, page 283.

compared with the dipole moment of a monosubstituted benzene, by the following values (in Debye units), chlorobenzenes being taken as examples:



$\mu = 1.58$ $\mu_o = 2.26$ calculated 2.74 $\mu_m = 1.48$ 1.58 $\mu_p = 0$ 0

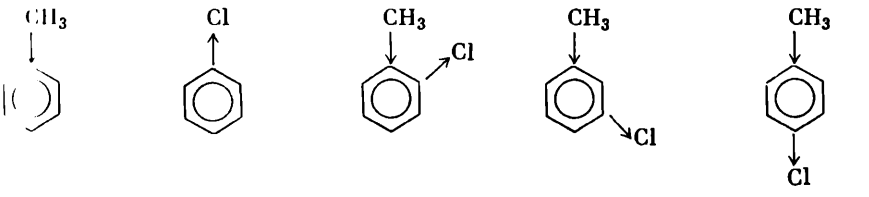
The overall formula transforms in such cases to the following:

$$\mu_o = \mu\sqrt{3} \qquad \mu_m = \mu \qquad \mu_p = 0.$$

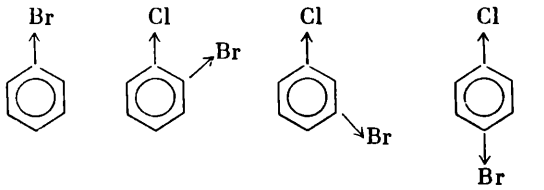
The agreement between the calculated dipole moment and the one experimentally found is not ideal, especially for *ortho*-isomers, where the substituents exert a strong mutual effect which violates the additivity. There are cases where the additivity is disturbed much more strongly. In spite of this, all the three isomers can be differentiated with certainty by the values of the dipole moments.

In case the substituents are different, even if the dipole moments of the monosubstituted benzenes are unknown and their direction does not coincide with the diagonal of the hexagon but their signs* are known, we can still differentiate with certainty between all the three isomers by their dipole moments.

Examples are the following:



Toluene 0.4D | Chlorobenzene 1.58D | *o*-Chlorotoluene 1.56D | *m*-Chlorotoluene 1.79D | *p*-Chlorotoluene 2.19D



Bromobenzene 1.54D | *o*-Chlorobromobenzene 2.21D | *m*-Chlorobromobenzene 1.53D | *p*-Chlorobromobenzene 0.1D

* Whether the negative end of the dipole is pointing to or from the benzene ring can easily be deduced if one knows the electrical nature of the constituent atoms of the substituent group.

For the above formulas to be used quantitatively it is necessary, however, that the vector direction of the dipole of the substituent coincides with the diagonal of the benzene hexagon, which is always fulfilled only for monoatomic substituents (halogens), for linearly built substituents ($C \equiv N$, $-C \equiv C-R$) and for substituents with a symmetric arrangement of atoms, i.e., such substituents in which the "centre of gravity" of the charged atoms lies on the diagonal of the benzene hexagon (CH_3, CCl_3, NO_2). This condition is not fulfilled even for carboxyl groups and, say, the ethyl ester of terephthalic acid has $\mu = 2.3D$.

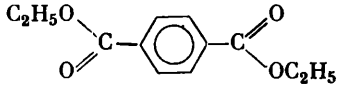


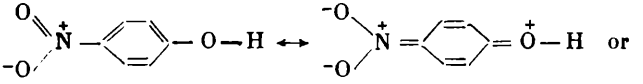
Table 7.2 lists a number of examples in which the additivity of the dipole moments of benzenes with the simplest substituents is retained.

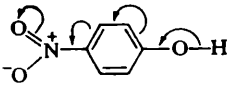
TABLE 7.2. **The Additivity of the Dipole Moments (in Debye Units) of Substituted Benzenes**

Monosubstituted benzene		Disubstituted Benzenes						
Substituent	μ	Substituent	*ortho-*		*meta-*		*para-*	
			μ_{obs}	μ_{cal}	μ_{obs}	μ_{cal}	μ_{obs}	μ_{cal}
Cl	1.58	Cl, Cl	2.27	2.74	1.48	1.58	0	0
Br	1.54	Br, Br	2.1	2.67	1.46	1.54	0	0
NO_2	3.98	NO_2, NO_2	6.00	6.90	3.89	3.98	0	0
NH_2	1.53	NH_2, NH_2	1.45	—	1.79	1.80	1.5	—
OH	1.6	NO_2, Cl	4.1	4.97	3.4	3.47	2.50	2.40
		NO_2, NH_2	4.24	3.66	4.94	4.72	6.2	5.17
		Cl, NH_2	1.77	1.71	—	—	2.27	2.30
		NO_2, OH	—	—	—	—	5.07	4.34

As seen from Table 7.2, the additivity for *para-* and *meta*-derivatives of benzenes is fulfilled better than for *ortho*-substituted derivatives. Deviations of this kind are accounted for by the geometric distortion of the molecule—by the withdrawal of the substituents out of the plane of the ring, and by the departure of the angle of the benzene hexagon from 120°. Additivity disturbances of an absolutely different kind are observed if the entering groups (this is best illustrated for *para*-arranged substituents) possess opposite mesomeric effects ($+M$ and $-M$) and, hence, being in the opposite positions

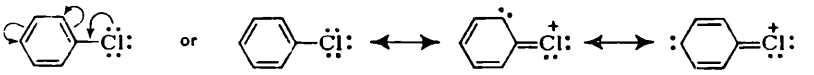
of the benzene ring, act concertedly. The increase of μ as compared with the calculated value is a consequence of conjugation (resonance). This is particularly clear in the case of *p*-nitrophenol (see Table 7.2), whose constitution may be represented by the following structures:





This effect is associated with a deepening of the original colour of a compound (page 122), on the basis of which it was discovered by Izmailsky in 1913 (he gave the name *mesotropy* to this phenomenon). Ingold who studied this effect extensively, introduced the term **mesomerism** which has come to be widely used in the literature; later the term **resonance** was introduced by Pauling. From the viewpoint of the non-additivity of dipole moments the mesomeric effect can be traced for *p*-nitroaniline (page 106) and *p*-dimethylaminonitroaniline.

A phenomenon of the same kind can be traced out for monosubstituted benzenes as well. As pointed out above, the dipole moment of halobenzenes is considerably lower than the dipole moments of the corresponding alkyl halides. This is accounted for by the following type of mesomerism:



In the presence of electron-attracting substituents the dipole moments of aromatic compounds are higher than those of aliphatic compounds:

$\mu = 4.03$ D $\mu = 3.15$ D $\mu = 3.94$ D $\mu = 3.51$ D

In all the cases, the benzene nucleus shows its "pliability" to the "requirements" of the entering group.

Thus, the dipole moments provide much information not only about the disposition of substituents in the benzene ring but also about their interaction with the benzene ring and with one another through the benzene ring.

E. The Nomenclature of Benzene Derivatives

For hydrocarbons of the benzene series and their derivatives use is made of trivial (common), radicofunctional and Geneva (systematic) names. Trivial names require no comment. Radicofunctional names (which are little used) are based on the names of radicals:

C_nH_{2n-6} . . . Arene (ArH)
C_nH_{2n-7} . . . Aryl (Ar)
C_nH_{2n-8} . . . Arylene

C_6H_5 . . . . . Phenyl (from the original old name of benzene — "phene")
C_6H_4 . . . . . Phenylene (*o*-, *m*-, or *p*-)
$CH_3C_6H_4$ . . . Tolyl (*o*-, *m*-, or *p*-)
$C_6H_5CH_2$ . . . Benzyl
C_6H_5CH . . . Benzylidene

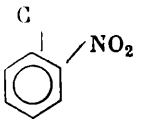
The halogen derivatives are named by this nomenclature as follows: C_6H_5Cl—phenyl chloride (a little-used name); $ClC_6H_4CH_3$—

TABLE 7.3. **Aromatic Hydrocarbons**

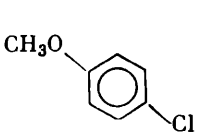
Formula	Name	Position of substituent group
C_6H_6	Benzene	—
$C_6H_5CH_3$	Toluene or methylbenzene	1
$C_6H_4(CH_3)_2$	Xylene or dimethylbenzene:	
	ortho-	1,2-
	meta-	1,3-
	para-	1,4-
$C_6H_3(CH_3)_3$	Trimethylbenzene	
	vicinal or hemimellitene	1,2,3-
	asymmetrical or pseudocumene	1,2,4-
	symmetrical or mesitylene	1,3,5-
$C_6H_2(CH_3)_4$	Tetramethylbenzene	
	vicinal or prehnitene	1,2,3,4-
	durene	1,2,4,5-
	isodurene	1,2,3,5-
$C_6H(CH_3)_5$	Pentamethylbenzene	—
$C_6(CH_3)_6$	Hexamethylbenzene	—
$C_6H_5C_2H_5$	Ethylbenzene	1
$C_6H_5C_3H_7$	*n*-Propylbenzene	1
$C_6H_5CH(CH_3)_2$	Isopropylbenzene or cumene	1
$CH_3C_6H_4CH(CH_3)_2$	*p*-Methylisopropylbenzene or *p*-cymene	1,4-

tolyl chloride (also a little-used name); $C_6H_5CH_2Cl$—benzyl chloride; $C_6H_5CHCl_2$—benzylidene chloride.

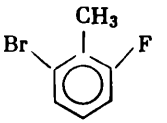
According to the Geneva nomenclature (the IUPAC system), the names of aromatic hydrocarbons are preceded by the names of substituent groups with numerals for carbon atoms bearing the substituents; for example,



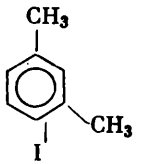
1-Chloro-2-nitrobenzene



1-Methoxy-4-chlorobenzene



2-Fluoro-6-bromotoluene or 2-fluoro-6-bromo-1-methylbenzene



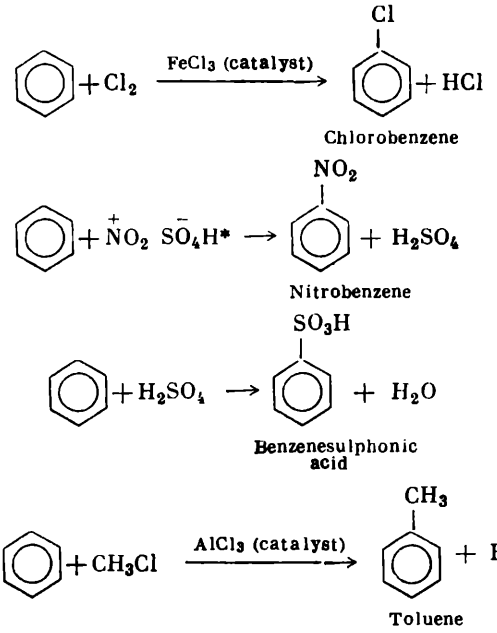
4-Iodo-*m*-xylene or 4-iodo-1,3-dimethylbenzene

of the Benzene Series

m. p., °C	b. p., °C	Density d_4^{20}	Refractive index n_D^{20}	Dipole moment μ in benzene at 20°C, D
5.51	80.10	0.8790	1.5011	0
95.0	110.63	0.8669	1.4969	0.4
29.0	144.41	0.8802	1.5054	0.53
53.6	139.10	0.8641	1.4972	0.37
13.2	138.4	0.8610	1.4958	0.12
15	176.1	0.8945	1.5139	—
57.4	169.35	0.8758	1.5048	—
52.7	164.7	0.8651	1.4993	0.0
-4	204.0	0.9012	1.5203	—
80.0	195.0	0.838 (at 81°C)	1.6150	0
24.0	197.0	0.8960 (at 0°C)	1.5130	—
53.0	230.0	0.847 (at 107°C)	1.5049 (at 73°C)	—
166.0	265.0	—	1.8012	0
94.0	136.2	0.8669	1.4982 (at 14.5°C)	0.39 (at 25°C)
101.6	159.2	0.8620	1.4920	0.42
96.9	152.4	0.8618	1.4914	0.43
73.5	176.0	0.8570	1.49 (at 15°C)	0.0

F. Electrophilic Substitution in the Benzene Series

Benzene and, even more readily, its homologues enter into reaction with many electrophilic reagents in such a manner that one or more hydrogen atoms of the benzene ring are replaced by the electrophilic groups of the attacking reagent. Let us write, as an example, four overall equations for reactions of this kind for benzene itself:



All these reactions will be discussed in detail in the appropriate sections. At this point it is important to note that substitution reactions of this kind, which proceed easily at room temperature, constitute the most characteristic property of aromatic compounds, which differentiates them sharply from saturated compounds. As regards olefins, under the influence of the same reagents they undergo other reactions under ordinary conditions—electrophilic addition across the double bond or polymerization, so that the possibility of a substitution reaction remains unrevealed.

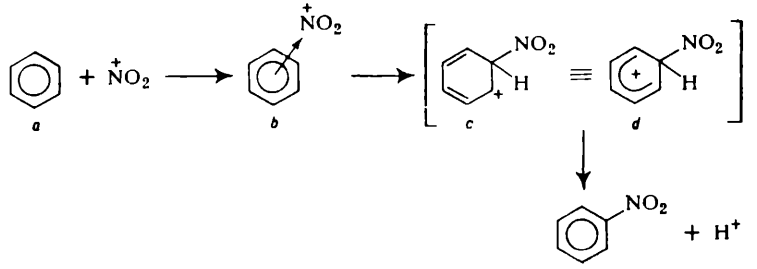
In all probability, the first stage of the attack of an electrophilic reagent is the formation of a π-complex (Dewar), in which the elect-

---

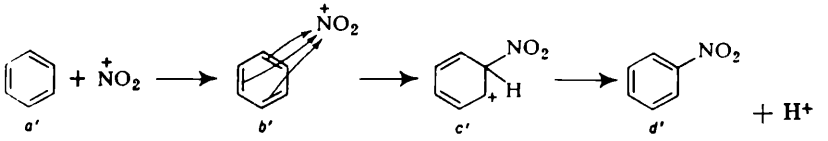
* The nitronium sulphate resulting from the dissolution of nitric acid in sulphuric acid:

$$HNO_3 + 2H_2SO_4 \rightleftarrows \overset{+}{N}O_2\ \overset{-}{S}O_4H + H_3O^+ + HSO_4^-$$

rophilic species (Cl^+, NO_2^+, SO_3H^+, CH_3^+ in our examples) becomes attached to the benzene molecule at the expense of all its π-electrons (as we shall see later, stable isolable π-complexes may also sometimes be formed). Then the electrophilic particle pulls a pair of electrons from the benzene ring (from the aromatic sextet), the other four π-electrons being arranged into two conjugated double bonds

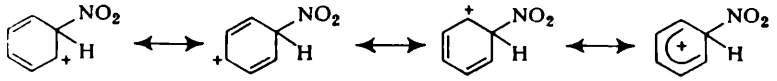


or, using the Kekulé formulas,



Of course, these π-electrons are shared, as we have seen for butadiene. But, besides, the positive centre (the carbonium ion) adjacent to the site being attacked (formula *c*) does not remain indifferent to the neighbouring system of π-electrons, and in fact the π-electrons are spread over all the five carbon atoms left in the second valence state, and the carbon atom being attacked becomes a tetrahedral carbon (in the first valence state). It is for this reason that formula *c* is often replaced by formula *d* (the σ-complex) with the positive charge being spread over all the five carbon atoms.

In principle, this transition-state complex is more correctly represented as a resonance hybrid of the following structures:



From this representation it becomes clear that the distribution of the positive charge is unequal, the maximum being in positions 2, 4, and 6 relative to the carbon atom attacked. Then the carbon atom that has been attacked and has become tetrahedral loses a proton and the electron pair, from which this proton has been expelled,

becomes a part of the newly formed aromatic sextet of π-electrons ($c' \rightarrow e$).

In what follows we shall use formulas of the types *c* and *d*, neglecting any differences between them. Structures of the type *c* or *d*, to which the initially formed π-complex is transformed, are called σ-complexes by analogy. For simplicity, these σ-complexes will occasionally be called (though not quite correctly) reaction complexes or transition states; for the moment we shall explain the difference between a true transition state and a σ-complex.

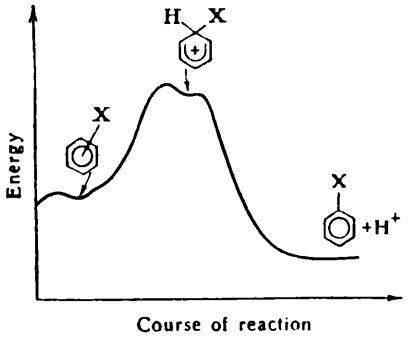


Fig. 7.4.

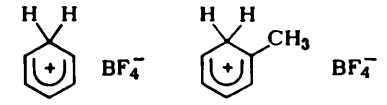
Energy diagram for the electrophilic substitution reaction in the benzene ring.

The intermediate stage of a reaction (see Volume I, page 120) equivalent to the peak of the energy barrier and higher in energy than reactants and products, is usually referred to as the **transition state.** A reaction may pass over several such barriers. This is shown schematically in Fig. 7.4. The first low peak is the transition state leading to an unstable π-complex, and the first minimum is a π-complex. The second peak is the transition state leading to a σ-complex, and the following low minimum is a σ-complex. Lastly, the third low peak corresponds to the transition state from the σ-complex to the reaction products. Energetically the second peak, the low minimum of the σ-complex, and the third peak differ insignificantly from one another—their ordinates are almost equal. According to Hammond's postulate (see Volume IV, "Mechanisms of Chemical Reactions"), by this condition and by the geometry the σ-complex is close to both neighbouring transition states, which justifies the above simplification.

1. Protonation and Deuteration of Benzene. The simplest and therefore instructive reaction of electrophilic substitution in benzene and, in general, in the aromatic series is the protonation and deuteration. Benzene is soluble in strong anhydrous acids, and in deuterated acids it exchanges, one after another, all its hydrogens for deuterium*. With hydrogen halide in the presence of aluminium halide (i.e., with acid $HAlCl_4$) benzene and its homologues form complexes which are solid at low temperatures. Analogous complexes are formed with HBF_4 (e.g., the toluene complex with m.p. —65°C). As eviden-

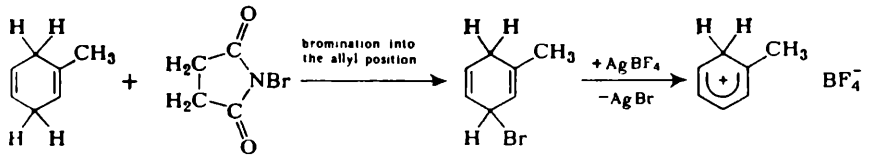
* Of course, the exchange of the hydrogen atoms of benzene for those of the acid takes place in an analogous manner.

ced by the detailed spectroscopic study of such substances carried out by Perkampus, they have the following structure:



Protonated benzene — Protonated toluene

Indeed, Olah synthesized such a complex by the following reaction:



The reaction product turned out to be identical with the product of direct protonation of toluene. Structures of this type, postulated by Ingold as intermediates in electrophilic substitution reactions in aromatic rings, will be discussed later (see page 43).

Mackor, Hofstra and van der Waals determined directly the basicity of a number of aromatic hydrocarbons, including benzene and its homologues by measuring their distribution between hexane and anhydrous hydrogen fluoride. The basicity constant K_b is equal in this case to

$$K_b = \frac{[ArH_2^+][F^-]}{[ArH]} = \frac{f_\pm^2}{f_{ArH}}$$

where the expressions in square brackets are the concentrations of the corresponding ions or molecule; f are the activity coefficients of the ions (f_+ and f_-) and the molecule.

Below are given the basicity constants of some aromatic hydrocarbons:

	log K_b		log K_b
Benzene	−9.4	*m*-Xylene	−3.2
Toluene	−6.3	Mesitylene	−0.4
p-Xylene	−5.7	Hexamethylbenzene	+1.4

As seen from these data, benzene is a very weak base, which captures a proton by the mechanism indicated above. As the alkylation proceeds the basic strength of aromatic hydrocarbons increases by many orders of magnitude.

2. **Electron Capture Reactions.** Under the action of strong electron donors all aromatic hydrocarbons are capable of capturing one

electron and forming a radical-anion which gives an EPR signal (see Volume IV, "Electron Paramagnetic Resonance"). Benzene captures an electron more difficultly than other aromatic hydrocarbons; it accepts an electron only from potassium but not from sodium, and forms an undissociated ion pair $\bar{C}_6H_6\overset{+}{K}$. This electron occupies the lowest-lying of the unoccupied benzene orbitals.

3. **Metalation.** As discovered by P. P. Shorygin, benzene enters into the following exchange reaction with sodium and potassium alkyls:

$$C_6H_6 + \bar{C}H_3\overset{+}{Na} \longrightarrow C_6H_5\bar{}\overset{+}{Na} + CH_4$$

This reaction has hardly any analogy among the reactions of electrophilic and nucleophilic substitution into the aromatic ring and should probably be regarded as the attack of an alkyl anion on a hydrogen of benzene. It is analogous to the action of a Grignard reagent on acetylene.

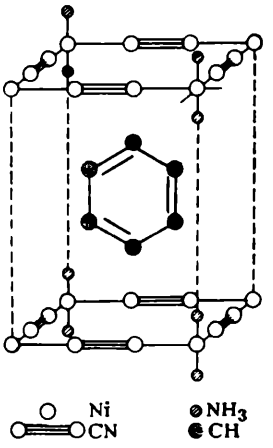


Fig. 7.5.

Schematic representation of the clathrate complex $C_6H_6 \cdot Ni(CN)_2NH_3$.

4. **Clathrate Compounds of Benzene.** Hofmann discovered a "molecular compound" of benzene, $C_6H_6 \cdot Ni(CN)_2NH_3$, which remained to be a puzzle for a long time. Powell and Reiner obtained a number of analogous compounds for derivatives of benzene and aromatic heterocyclic compounds (thiophene, etc.). X-ray studies have revealed the clathrate (page 148) nature of these compounds: benzene is trapped in the vacancies of the lattice formed by the inorganic ingredients of the compound (Fig. 7.5).

5. **Synthesis of Benzene Homologues.** The homologues of benzene can be synthesized by the action of sodium on a mixture of an alkyl halide and a halogenobenzene (Wurtz-Fittig reaction), e.g.,

$$C_6H_5Br + C_2H_5Br + 2Na \longrightarrow C_6H_5C_2H_5 + 2NaBr$$

This reaction, however, only partly proceeds in the desired direction. Along with the end desired products, there are formed a diaryl (the diphenyl $C_6H_5C_6H_5$ in the above example) and the products of the interaction of two aliphatic radicals, $2C_2H_5\cdot$, i.e., an alkane, alkene, and dialkyl (C_2H_6, C_2H_4 and C_4H_{10} in this particular case). Therefore, more extensive use is made of the alkylation of benzene by

alkyl halides or olefins by the Friedel-Crafts reaction, i.e., in the presence of anhydrous aluminium chloride as a catalyst*. The reaction proceeds even at room temperature:

$$C_6H_6 + ClCH_3 \xrightarrow{AlCl_3} C_6H_5CH_3 + HCl$$

$$C_6H_6 + nClCH_3 \xrightarrow{AlCl_3} C_6H_{6-n}(CH_3)_n + nHCl$$

$$C_6H_6 + 6ClCH_3 \xrightarrow{AlCl_3} C_6(CH_3)_6 + 6HCl$$

$$C_6H_6 + ClCH_2CH_3 \xrightarrow{AlCl_3} C_6H_5CH_2CH_3 + HCl$$

$$C_6H_6 + CH_2 = CH_2 \xrightarrow{AlCl_3} C_6H_5CH_2CH_3$$

$$C_6H_6 + CH_2 = CHCH_3 \xrightarrow{AlCl_3} C_6H_5CH(CH_3)_2$$

$$C_6H_6 + CH_2 = C(CH_3)_2 \xrightarrow{AlCl_3} C_6H_5C(CH_3)_3$$

The interaction of very active olefins with benzene can be induced not only by the action of aluminium chloride but also by acids (concentrated sulphuric acid, hydrogen fluoride, and phosphoric acid). As seen from the examples given, asymmetrically built olefins introduce secondary or tertiary alkyl radicals into benzene. Primary alkyl radicals, with the exception of methyl and ethyl, cannot be introduced in this way. Basically, the version of the Friedel-Crafts reaction with olefins may in principle be regarded as the addition of benzene to olefins taking place in accordance with Markovnikov's rule (the hydrogen of benzene adds on to the "more hydrogenated" olefinic carbon, and the phenyl radical adds on to its partner). Aluminium bromide and alkyl bromides may also be used. Apart from an aluminium halide, the following compounds may be used as catalysts for the Friedel-Crafts reaction (given in order of diminishing catalytic action): BF_3 (only for alkyl fluorides), $GaCl_3$, $SnCl_4$, $FeCl_3$. These catalysts are used only for alkylation of aromatic compounds more nucleophilic than benzene. The alkylation by olefins is preferably carried out by using phosphoric acid as a catalyst.

Friedel-Crafts reactions are typical reactions of electrophilic substitution into the aromatic ring. The action of a Friedel-Crafts catalyst (which is always a Lewis base) on an alkyl halide and an olefin can be illustrated by the following scheme:

$$RCl + AlCl_3 \longrightarrow \overset{\delta+}{R}\left[\begin{matrix} Cl & Cl \\ & Al \\ Cl & Cl \end{matrix}\right]^{\delta-}$$

* The application of this remarkable catalyst in organic chemistry is due to G. G. Gustavson (1878), Professor of the Forest Academy (the present Timiryazev Agricultural Academy).

The activation by aluminium chloride may be reduced to the simple polarization of the alkyl halide $\overset{\delta+\delta-}{RCl} \ldots AlCl_3$ without its complete ionization:

$$R'CH=CH_2+AlCl_3 \longrightarrow \overset{\delta+}{R'CH}-\overset{\delta-}{CH_2}-Al(Cl)Cl$$

The resulting carbonium ions or complexes with a charge of $\delta+$ on carbon are strong electrophilic reagents which attack the aromatic ring by their positive carbon. The aluminium halide, however, is not inert to the benzene nucleus and exerts an activating effect on it. This is confirmed by the fact that in the presence of aluminium chloride benzene forms sandwich-like π-complexes with metals (see Volume IV), which are not formed in the absence of aluminium chloride. The attempts made by B. N. Menshutkin to prove the formation of compounds of aluminium chloride and benzene by physicochemical analysis, however, failed to give a positive result, whereas aluminium bromide (also a catalyst for the Friedel-Crafts reaction) is known to form such compounds.

According to V. V. Korshak and N. N. Lebedev, the reaction between an alkyl halide and an aromatic hydrocarbon takes place in such a way that the breaking of the C—Cl bond and the formation of a C—C bond in the complex $RCl \cdot AlCl_3$ occur concurrently. In nitrobenzene, an ordinary medium for these reactions (nitrobenzene itself does not enter into Friedel-Crafts reactions), there is first formed a complex whose cationic part becomes attached to the alkyl halide, polarizing it and catalysing the reaction:

$$2C_6H_5NO_2+Al_2Cl_6 \longrightarrow \underset{K^+}{\left[(C_6H_5NO_2)_2Al(Cl)_2\right]^+}\underset{A^-}{[AlCl_4]^-}$$

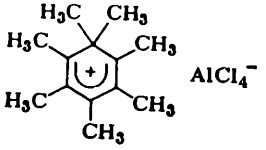
$$\left[(C_6H_5NO_2)_2Al(Cl)_2\right]^+ + RCl \longrightarrow \left[(C_6H_5NO_2)_2Al(Cl)_2\right]^+ \overset{\delta-}{Cl}-\overset{\delta+}{R}$$

In a medium with a lower dielectric constant, the complex formed acts now as an ion pair, $\overset{-}{A}\overset{+}{K}$, and has a weaker polarizing effect on RCl. Therefore, in this case, benzene too must be activated, so that the entire reaction is expressed by the following scheme:

$$\overset{-+}{AK} \ldots \overset{\delta-}{Cl}-\overset{\delta+}{R}+ArH \ldots \overset{-+}{AK} \longrightarrow ArR+HCl+\overset{+-}{2KA}$$

It is highly interesting that the alkylation of benzene by a methyl halide does not end with the formation of hexamethylbenzene. As

the reaction proceeds further, a σ-complex is formed, which has the following structure and composition (of course, with the anion $AlCl_4^-$)

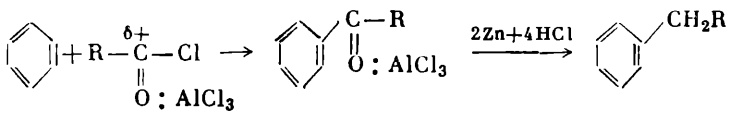


which is the prototype of σ-complexes formed in electrophilic substitution in the benzene ring and is similar to the σ-complexes of benzene and toluene with a proton or deuteron (see page 39).

A distinctive feature of syntheses with aluminium chloride is that it catalyses not only the alkylation but also the dealkylation of benzene homologues since it is capable of rupturing carbon-carbon bonds. Besides, under more vigorous conditions aluminium chloride favours the isomerization of the carbon chain of an alkyl halide or an olefin. Thus, complications may arise in alkylation reactions involving the use of $AlCl_3$.

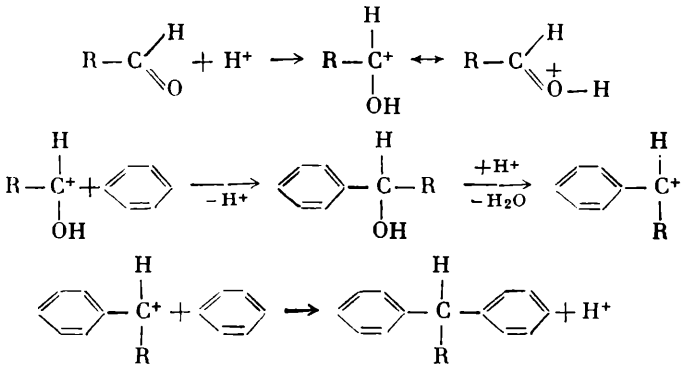
Tsukervanik worked out a reaction of alkylation of aromatic hydrocarbons by alcohols in the presence of aluminium chloride and showed that in this case an alcohol ROH is converted into an alkylating agent $ROAlCl_2$. Such an alkylation by alcohols proceeds in the presence of boron trifluoride as well. Olefins alkylate aromatic compounds also in the presence of acids—sulphuric, phosphoric, etc. Industrial processes of this kind, say, the production of ethylbenzene and isopropylbenzene, have been developed in the USSR by M. A. Dalin and Yu. G. Mamedaliev.

Benzene homologues can also be synthesized by the Friedel-Crafts acylation reaction with subsequent reduction of the acylbenzene (a ketone) to an alkylbenzene by the Clemmensen method. The acylation of benzene proceeds only up to the monoacylbenzene stage and is not accompanied by isomerization:



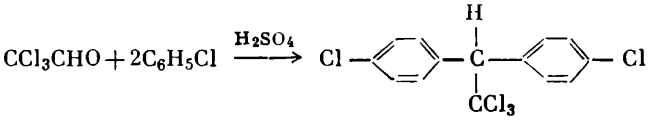
6. **Synthesis of Diaryl- and Triarylmethanes.** Aldehydes in a strongly acid medium react vigorously with aromatic hydrocarbons and even with their less reactive halogen derivatives at a low temperature. The end products of this reaction are diarylalkanes or, in the case of aromatic aldehydes, triarylmethanes. The reaction proceeds, of course, through the stage of formation of a secondary alcohol

(which is not usually isolated) by the following scheme:



Thus, the reaction occurs as an electrophilic substitution in the aromatic ring upon the attack of a carbonium ion.

In a solution of hydrogen fluoride, aldehydes react analogously with toluene at as low a temperature as —70°C. Chloral at room temperature in concentrated sulphuric acid enters into the above-described reaction with chlorobenzene, forming the well-known insecticide DDT:



Condensations of this kind will also be considered later (see pages 246 and 252).

XXVII. Orientation in Electrophilic Substitution

Electrophilic substitution reactions in the benzene series obey the following regularities established in an empirical way (Holleman).

1. The place of entry of an incoming electrophilic substituent is determined (largely) by the nature of one or more substituents already present in the benzene ring.

2. Substituents (directing groups) are subdivided into the following two classes:

(a) **substituents of the first kind,** or *ortho-para* directing groups which direct the incoming substituent (the second entrant) into the *ortho-* and *para*-positions relative to itself (here and further directing groups are given in order of diminishing orienting effect or directive

power; R is an alkyl):

$-\bar{O}$, $-NR_2$, $-NHR$, $-NH_2$, $-OH$, $-OR$, $-NH-\overset{O}{\overset{\|}{C}}-R$, $-O-\overset{O}{\overset{\|}{C}}-R$,
$-CH_3$ and other alkyls, alkenyls, I, Br, Cl, F

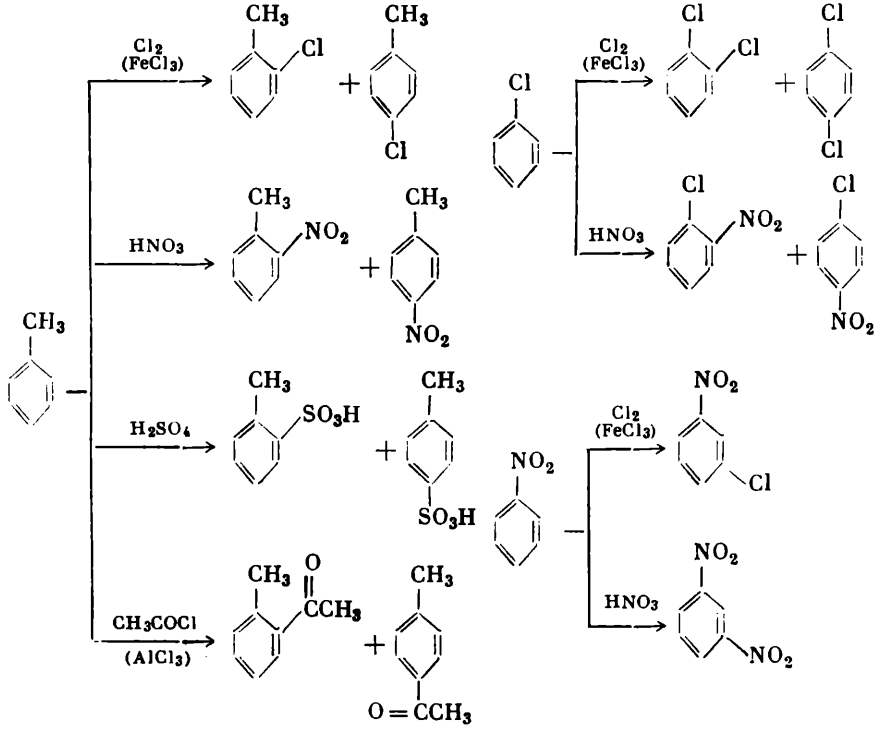
(b) **substituents of the second kind** or *meta* directing groups which orient the incoming substituent to the *meta*-position:

$-\overset{+}{N}R_3$, $-\overset{+}{N}\overset{O}{\diagup\!\!\diagdown}\overset{O^-}{}$, $-CN$, $-SO_3H$, $-CF_3$, $-CCl_3$, $-C\overset{H}{\diagup\!\!\diagdown}\overset{O}{}$, $-C\overset{R}{\diagup\!\!\diagdown}\overset{O}{}$,

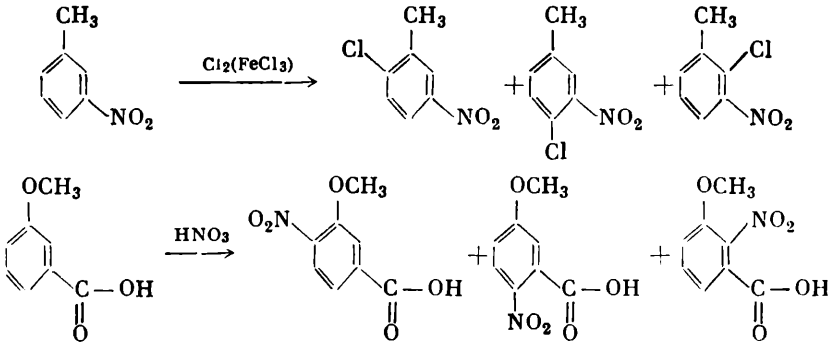
$-C\overset{O}{\diagup\!\!\diagdown}\overset{OH}{}$, $-C\overset{O}{\diagup\!\!\diagdown}\overset{OR}{}$

3. *o,p*-Substituents facilitate (accelerate) the entry of an electrophilic substituent, while *m*-substituents hinder (retard) the process. There is an exception to this rule: though the halogens are *ortho-para* directors, they nevertheless impede the entry of a further substituent. Another exception will be encountered in the discussion of diphenyl oxide and triphenyloxonium.

The following scheme illustrates the first two rules of orientation:



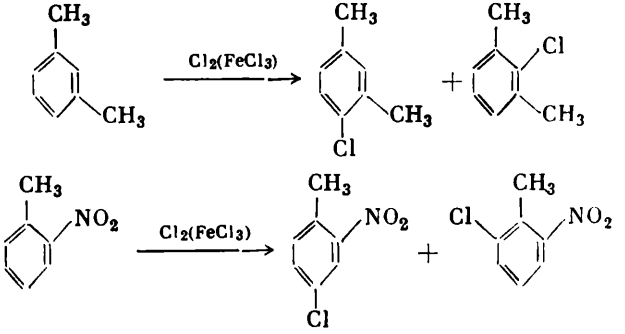
When there are two substituents of different types, the place to be occupied by a third electrophilic substituent is determined by the *ortho-para* directing group since it activates the benzene ring towards electrophilic attack. For example,



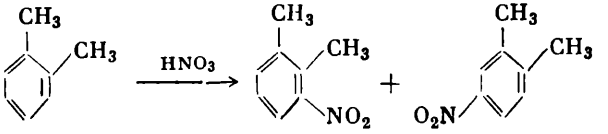
If the two substituents already present in the benzene ring are of the same directive type, then the place of entry of a further group is determined by the stronger one, and if the orienting effects of the groups present do not differ too strongly, all isomers (*meta-*, *ortho-* and *para* isomers) are obtained.

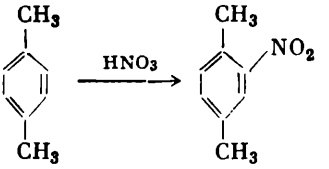
Orientation may be concerted when the two substituents present in the ring direct a new entrant into one position (in which case the place of entry of the incoming substituent is obvious) and disconcerted. Examples of these orientations are the following:

1. *Concerted orientation*:

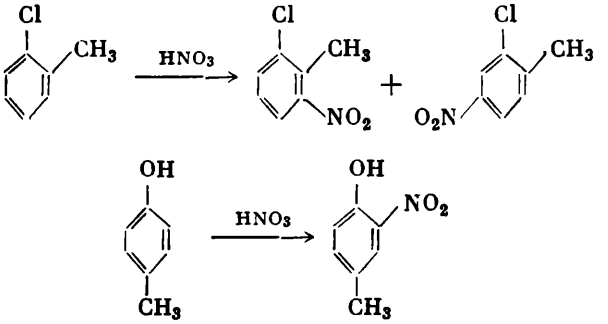


2. *Non-concerted orientation with directing groups of equal orienting effect*:





3. *Non-concerted orientation with directing groups of different orienting effect*:



There arises a question: How could all that has been said above be related to the Körner rule (see page 28) concerning the establishment of the positions of the substituents in disubstituted benzenes? In other words, which of these is the *para*-, which the *meta*-, and which the *ortho*-isomer? The Körner method is based on the possibility of formation of all the isomers possible when a third substituent enters the nucleus on further substitution, and the orientation rules impose restrictions on the number of possible isomers. The point is that the orientation rules determine the principal directions of the reaction, those isomers which are obtained in very small amounts (fractions of a per cent or a few per cent) being neglected, while the Körner method of orientation is based on taking account of all the products of the reaction, including those formed in very small amounts. That is why this method is laborious.

(A) Factors Responsible for Orientation Effects

The orienting effect of a directing group consists in changing the free energy of activation, $G^{\star}$, of the transition state as related to unsubstituted benzene (see also on page 37). Directing groups of the first kind (*ortho-para* directors) diminish the free energy for the transition state of the entry of a new electrophilic substituent, especially in the *ortho*- and *para*-positions (Fig. 7.6). As a result, according to the expression for the reaction rate constant (see Vol-

ume I, page 121)

$$k = \frac{\varkappa T}{h} e^{-\frac{\Delta G^{\star}}{RT}}$$

the rate constant for a substituted benzene sharply increases (in the exponent!) as compared with that for unsubstituted benzene. A decrease of $G^{\star}$ occurs due to the release of electrons by an *o,p*-

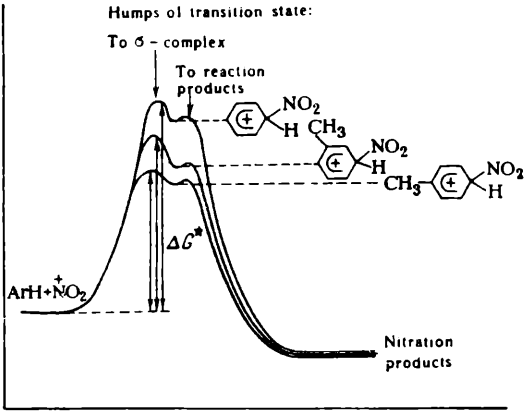
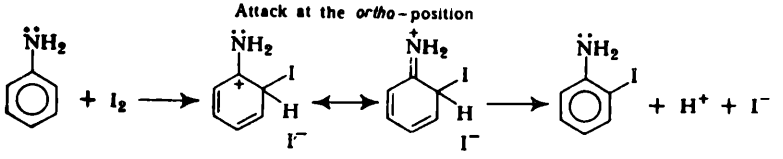
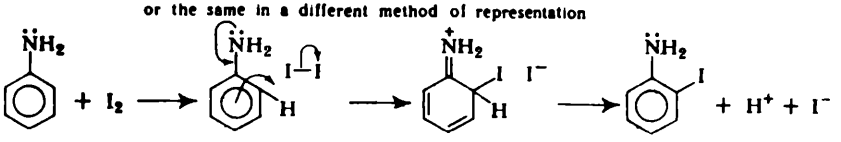


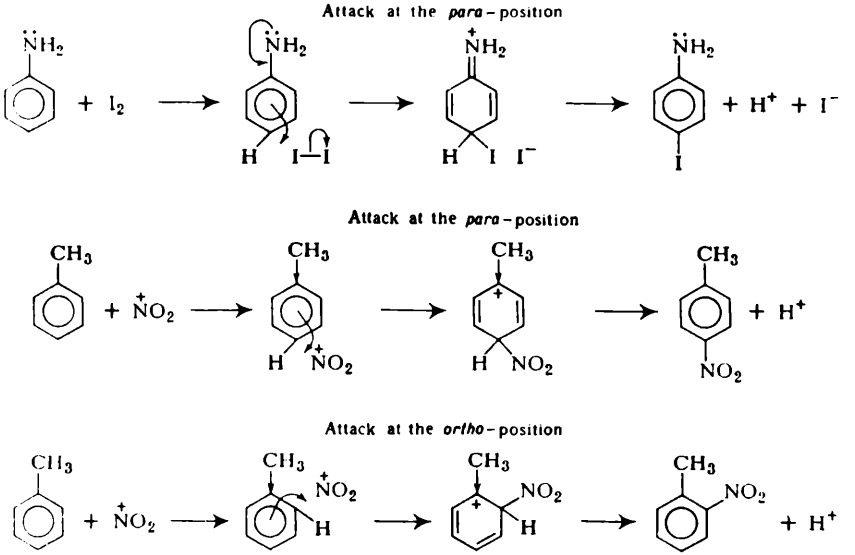
Fig. 7.6.
Energy diagram for the replacement by an electrophilic reagent ($\overset{+}{N}O_2$) in benzene and in the *meta*- and *para*-positions of toluene.

directing group to the carbon atom to which this group is attached and on which a positive charge predominantly appears in the transition state.

Let us consider the following examples:







From the schemes given it is seen that the electrophilic reagent, while attacking the benzene ring, withdraws a pair of electrons from the aromatic sextet* and becomes attached with the aid of this electron pair to the carbon atom being attacked, which remains to be bonded to the hydrogen as well in the transition state and in the σ-complex.

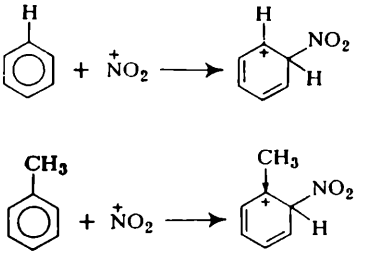
The carbon atom attacked becomes a tetrahedral carbon in the σ-complex, and the remaining four π-electrons are arranged in the form of two conjugated double bonds in the ring. Owing to the withdrawal of the electron pair that formed a bond with the attacking group, a positive charge appears on the carbon atom adjacent to the carbon being attacked. This positive charge may be partly neutralized (compensated) if it is on a carbon atom bearing an *ortho-para* directing group, i.e., an electron donor, provided that the attack is directed to the carbon atom in the *ortho-* or *para*-position with respect to the carbon atom that carries the directing group.

The mechanism of compensation of a positive charge varies, depending on the nature of the *ortho-para* directing group. If the *o,p*-directing group bears, on the key atom, a free (unshared) pair of electrons ($-\ddot{N}H_2$, $-\ddot{O}H$, $-\ddot{O}CH_3$, $-\ddot{C}l$: and others) then it shares this electron pair for bond formation with the ring carbon atom attached to it, forming a double bond with this carbon atom, assuming,

* The preliminary stage of formation of the π-complex is not taken into consideration here and is therefore omitted.

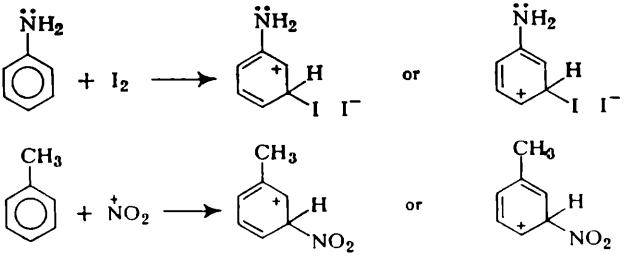
as a result, a positively charged (ammonium, oxonium, etc.) state. This is the familiar $+T$ effect (cf. Volume I, page 419).

Such a system is much poorer in energy than the system of a positive carbonium-ion carbon. Therefore the free activation energy of the transition state is lower than in the absence of a directing group. If an *ortho-para* directing group, say, an alkyl, has no free pair of electrons, it partly compensates for the positive charge on the carbonium-ion carbon attached to it by way of shifting the pair of bonding electrons from the alkyl to the benzene carbonium-ion carbon according to the $+I$ effect inherent in alkyl groups (it must be remembered that the concept of the $+I$ effect arises only when comparing the effect exerted by an alkyl group with that of the standard—the hydrogen atom). Let us compare, for example, benzene with toluene:



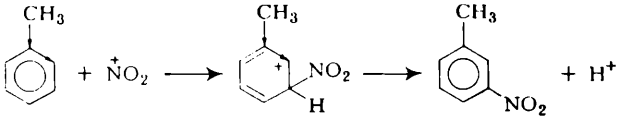
In the case of attack by the nitro group (the nitronium ion NO_2^+) the positive charge arising in the *ortho*-position to the site of attack is neutralized by the neighbouring CH_3 group (toluene) better than by hydrogen (benzene) since the electron pair of the $H_3C : C$ linkage serves the benzene carbon to a greater extent than the electron pair of the $H : C$ bond.

In the case of electrophilic attack in the *meta*-position no charge compensation due to the directing group takes place:



Therefore, for example, the nitration of toluene in the *meta*-position should have taken place at the same velocity as that of unsubstituted benzene. In fact, *o,p*-directing groups that speed up sharp-

ly the process of electrophilic substitution in the *ortho-* and *para*-positions accelerate substitution in the *meta*-position as well. For instance, toluene is nitrated in the *ortho-* and *para*-positions about 40 times as faster as benzene, and only 2-3 times faster in the *meta*-position. This transmission of the effect to the *meta*-position is usually accounted for by the inductive effect (the $+I$ effect) designated by a straight arrow which symbolizes the shifting of the electron pair of a single (σ-) bond as compared with the standard:



Since the $+I$ effects are rapidly suppressed along the chain of atoms, they are relatively very weak as compared with the T effects and the rate of substitution in the *meta*-position increases little.

(B) Hyperconjugation and *Ortho-Para* Orientation

All the alkyl groups increase the rate of electrophilic substitution in the benzene ring by many times. Baker and Nathan noted, however, the unexpected sequence in which the alkyl groups as *ortho-para* directors can be arranged according to their orienting effect, in particular, to the rate of chlorination and bromination. The relative rates of halogenation at 24°C in 15-percent aqueous acetic acid vary in the following way:

Alkylbenzenes		CH_3	CH_2CH_3	$CH(CH_3)_2$	$C(CH_3)_3$
Rate of:					
chlorination	0.29	100	94	51	32
bromination	—	110	76	44	23

This sequence is directly proportional to the series of the same alkyl groups arranged in order of diminishing $+I$ effect:

$$-C(CH_3)_3 > -CH(CH_3)_2 > -CH_2CH_3 > -CH_3$$

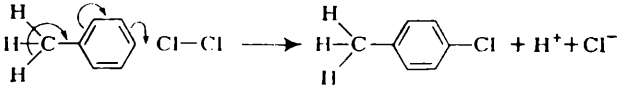
If we compare, in the same sequence, the dipole moments of alkylbenzenes, it will turn out that toluene has the lowest dipole moment in this series (neglecting benzene), and *tert*-butylbenzene the highest, i.e., that the methyl group (in a non-reacting molecule) imparts a smaller negative charge to the nucleus than the *tert*-butyl group. This is consistent with the concept of the inductive $+I$ effect (see

Volume I, page 244) as the effect of transfer of a covalent pair of bonding electrons by atom X to atom Y in the combination X → Y as compared with H → Y.

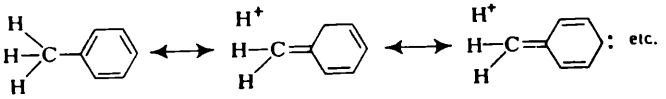
It is clear that the more alkyl groups attached to the key carbon atom (linked to benzene), the stronger the $+I$ effect of this carbon atom:

Alkylbenzenes	$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-C_6H_5$	$H-\overset{CH_3}{\underset{CH_3}{C}}-C_6H_5$	$CH_3-CH_2-C_6H_5$	$CH_3-C_6H_5$
Dipole moment, D . .	0.7	0.65	0.58	0.37

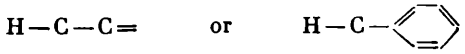
The paradox described, which has come to be known as the **Baker-Nathan effect,** has been explained by the increased polarizability of the H—C bond as compared with the C—C bond and by the possibility of electron release from an alkyl group due to the $+T$ effect being the greater the larger the number of hydrogen atoms linked to its key atom (**hyperconjugation**):



In terms of the resonance theory symbolizm the hyperconjugation in the toluene molecule is represented as follows:



The concept of hyperconjugation is not restricted to the case considered above or to the phenomena of interaction of the alkyl groups with the aromatic ring but is also of general importance. This is a partial but the most important case of the σ,π-conjugation (cf. Volume II, page 88), which refers not only to the interaction of the systems

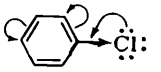


but also to systems with other (non-hydrogen) atoms.

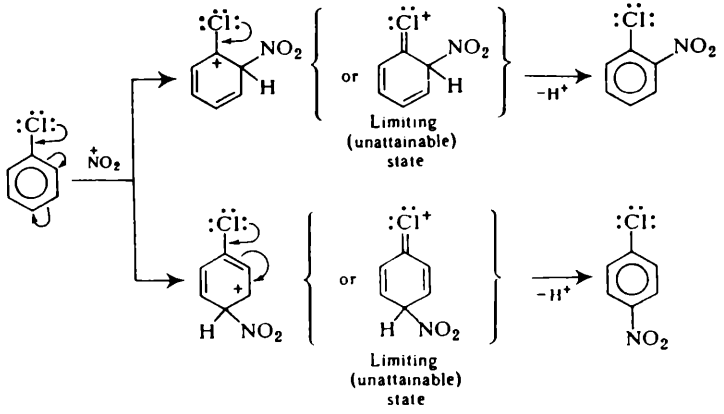
(C) The Orienting Effect of Halogen Substituent

A specific case is the orienting effect of the halogens. The halogens are the weakest of the usual *ortho-para* directing groups. But, in contrast to all other *o,p*-directing groups, the halogen atoms slow

down electrophilic substitution reactions rather than accelerate them. This is explained by the opposite signs of their $-I$ and $+T$ effects. The halogens exert a strong $-I$ effect (withdrawal of electrons from the nucleus as compared with the standard H—C bond) and a weak $+T$ effect (ability to supply a pair of electrons at the moment of attack on the *ortho-* and *para*-positions and thereby to neutralize the positive charge arising on the first carbon atom of the ring). This is expressed by the following scheme:



This is to be understood in the following way: the straight arrow indicates that the benzene ring of chlorobenzene is impoverished in electrons as compared with benzene itself. In the case of electrophilic attack on the *ortho-* or *para*-positions there, however, arises a transition state of the type usual for *ortho-para* orientation. True, the level of the free energy of this transition state is higher than in the case of unsubstituted benzene since the compensation of the positive charge on the first carbon atom due to the unshared electrons of the halogen is less complete than for any other ordinary *o,p*-director. Even the electron release that has taken place because of the strong inductive effect of chlorine is not compensated for completely (as compared with benzene).



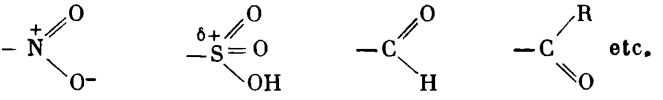
The operation of the $+T$ effect described would have been sufficient to explain the *ortho-para* orientation of electrophilic substitution by a halogen. In fact, as is often the case, the $+T$ effect is accompanied by a $+M$ effect, i.e., the mesomeric effect, which is a permanent

component (and not only at the moment of the reaction) of the tautomeric effect. The curved arrows pointing from the chlorine to the benzene ring—in the *ortho-* and *para*-positions—represent the interaction of the halogen with the benzene ring outside the reaction sphere, but this interaction is weak. This can best be understood if one considers (see Volume I, page 440) the difference between the dipole moment of chlorobenzene (1.56 D) and that of a chloroalkane, say, chloroethane (2.00 D). The chlorine in chlorobenzene supplies electrons to the benzene nucleus if it is compared with the chlorine of chloroethane, and pulls electrons from benzene strongly if benzene itself is taken as a reference standard (i.e., if chlorine is compared with hydrogen). One should not forget this possibility of comparing the electronic effects.

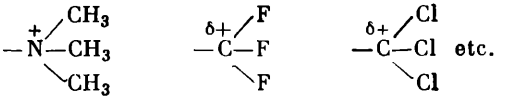
Another example of the deactivating effect of an *ortho-para* director is given in the consideration of triphenyloxonium (page 155). The same deactivating effect is exerted by the *o,p*-directing groups $-CH_2Cl$ and $-CH=CH-NO_2$

(D) Meta-Orientation

The *meta*-directing groups are subdivided into two types—groups operating by the $-M$ effect and those operating by the $-I$ effect. The former have their π-bonds at the key atom



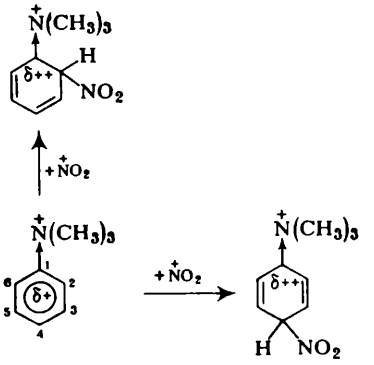
and the latter operate only owing to the presence of a positive charge on the key atom:



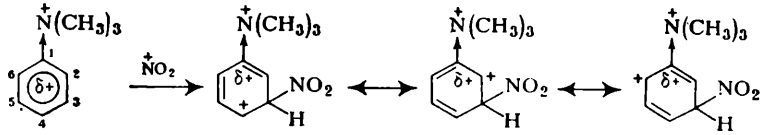
In both cases, this action due to the withdrawal of electrons gives rise to a positive charge on that carbon atom of the benzene ring which bears a *meta*-directing group. We have seen that the attack of an electrophilic reagent on the *ortho-* and *para*-positions relative to any substituent also gives rise to a positive charge on the same carbon atom. Therefore, the corresponding transition state and the σ-complex are less favourable (higher in energy) than those of unsubstituted benzene.

No such unfavourable combination is formed during the attack on the *meta*-positions, which turns out to be the most favourable.

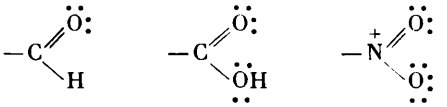
Since there also occurs a general withdrawal of electrons from the benzene ring, in particular, from the *meta*-positions, (—*I* effect), the attack in the *meta*-positions is also more difficult than in unsubstitut-



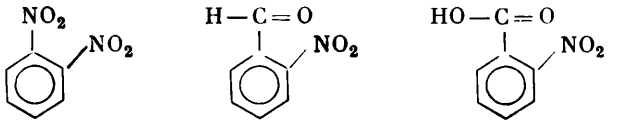
ed benzene, and the benzene ring substituted by a *meta*-directing group proves to be as a whole less sensitive to electrophilic substitution:



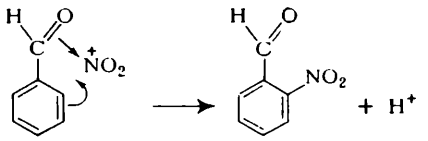
When an electrophilic reagent attacks a benzene derivative which contains *meta*-directing groups bearing free electron pairs, for example,



then, apart from the predominant entry of the electrophilic substituent into the *meta*-position, the substitution also occurs in a rather considerable degree in the *ortho*-position. Therefore, in the examples given, the nitration gives *ortho*- as well as *meta*-isomers:

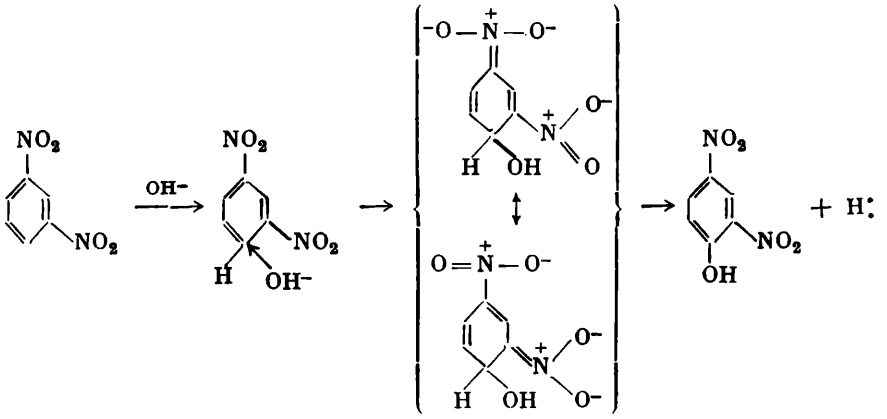


This is probably explained by the primary binding of the attacking electrophile by the *p*-pairs or π-electrons of the directing group with subsequent migration of the electrophile to the nearest *ortho*-position:



XXVIII. Orientation in Nucleophilic Substitution

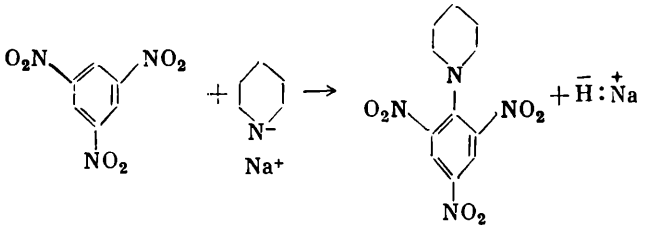
We have so far considered only electrophilic attack on the benzene ring. It is natural to suppose that the presence of powerful *meta*-directing groups capable of withdrawing electrons and rendering the positive charges on carbon bare, must favour nucleophilic attack. The foregoing reasoning shows that the *ortho*- and *para*-positions in a benzene, which bears a *meta*-directing substituent, are most sensitive to nucleophilic attack. Indeed, *m*-dinitrobenzene reacts with alkali and with sodamide, one of the *ortho*- or *para*-hydrogen atoms being replaced by OH or. accordingly, by NH_2. This hydrogen must leave the molecule taking with it a pair of electrons, i.e., in the form of hydride ion:



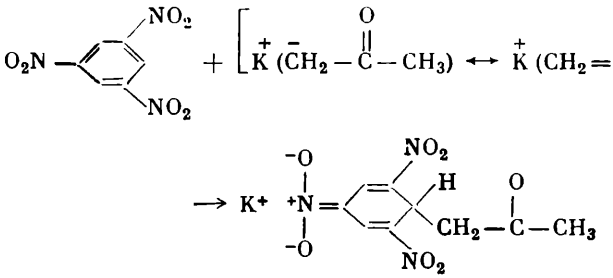
In this particular case, the otherwise energetically unfavourable reaction is favoured by the oxidation of the hydride ion with an excess of dinitrobenzene to a hydrogen ion.

Note that the orienting influence of the nitro group in the case of nucleophilic attack takes the form of the $-T$ effect, in contrast to electrophilic attack, in which case the action of the nitro group, like that of the directing group $\overset{+}{N}(CH_3)_3$, is restricted by the $-I$ effect. In other words, when the *o*- or *p*-carbon atoms of nitrobenzene (or dinitrobenzene, etc.) undergo nucleophilic attack, the negative charge arising on these carbon atoms (owing to the nucleophile being bonded by its pair of electrons) migrates to the oxygen of the nitro group through the system of conjugated bonds.

Sodium or potassium derivatives of the amines, say, of piperidine, exert a similar effect on *m*-dinitrobenzene and 1,3,5-trinitrobenzene (page 383). Below is shown only the result of the reaction:

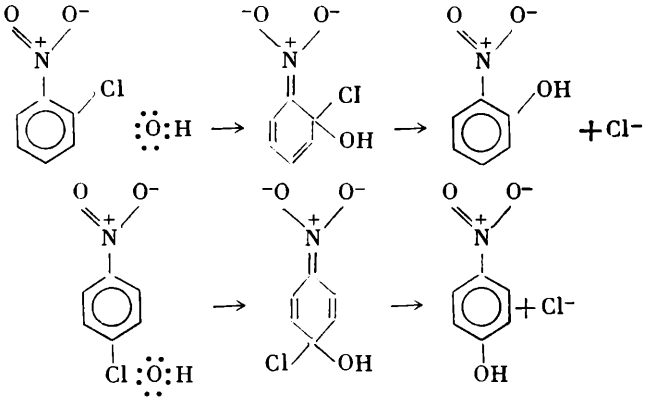


Hantzsch found that many potassium salts of "C —H acids", i.e., carbanions (see Volume IV, "Carbanions"), exert a nucleophilic attack on trinitrobenzene, in which case the attack destroys the aromaticity and is stopped as if halfway—the hydride ion does not leave the molecule. Thus, for example, trinitrobenzene in the presence of potassium methoxide reacts with acetone in the way shown below, giving a black-violet addition product—a σ-complex:



If not the hydride ion but, for example, the chloride ion has to leave the molecule of the product, the situation is much easier. In this case, there is no need for the concerted effect of two powerful *meta*-directing groups on the site of attack; one *meta*-director is sufficient. For example, the molecules of *o*- and *p*-nitrochlorobenzenes

and other analogous compounds are said to have a "mobile" chlorine (the discovery made by P. A. Lachinov and A. N. Engelhardt), a feature distinguishing these molecules from chlorobenzene, in which the chlorine only under severe conditions and slowly enters into exchange reactions. This mobile chlorine atom is easily exchanged for nucleophilic groups (OH, NH_2, SH, etc.). The factor responsible for this mobility of chlorine is the nucleophilicity of the carbon atom to which it is attached, which becomes sensitive towards nucleophilic attack owing to the ability of a *meta*-director to compensate for the negative charge imparted by the attacking nucleophile:

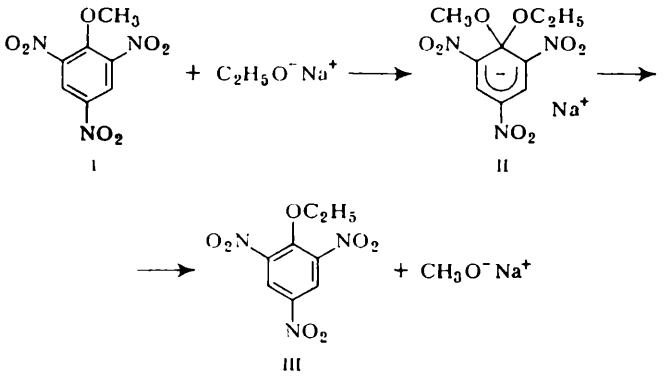


When the *meta*-position is attacked, no such charge compensation occurs, and therefore the chlorine atom in *m*-nitrochlorobenzene is "immobile".

An effect similar to that of the nitro group is also exerted by other *meta*-directing groups. This phenomenon is only a different manifestation of the laws of substitution orientation in the benzene ring. The cause is thus not the mobility of the halogen atom but the enhanced nucleophilicity of the carbon atom attached to it. Of course, electron-attracting substituents in the *ortho*- and *para*-positions facilitate the replacement not only of the halogens (and of the hydride ion) by nucleophiles, but also of other groups capable of leaving the molecule in the form of an anion (NH_2, OH, etc.).

As electron-attracting substituents are accumulated the nucleophilic attack may cease at the σ-complex stage, this complex being quite stable in this case. We have already seen this while considering the interaction of trinitrobenzene with the anion of acetone (Hantzsch; see above). Meisenheimer, while acting by the ethoxide of an alkali metal on 2,4,6-trinitroanisole (anisole is methoxybenzene, $C_6H_5OCH_3$), obtained an addition product II which splits off an alkoxyl group under more vigorous conditions, giving the product

of replacement of a methoxyl by an ethoxyl group (III):



It is easy to see that the σ-complex II is analogous, but opposite in sign, to the σ-complexes resulting from an electrophilic attack, among which identifiable compounds are also encountered (pages 39 and 43).

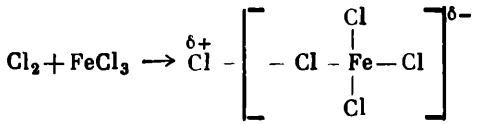
7.2. Halogen Derivatives of the Benzene Series

From what has been said in the preceding section it follows that benzene, its homologues and their derivatives readily undergo substitution by chlorine or bromine but only in the presence of catalysts, so-called halogen carriers ($FeCl_3$, $AlCl_3$, ICl_3 and other halides). The general property of these halides is the ability to form, with the halogen anion, more or less stable anions such as $[FeCl_4]^-$, $[AlCl_4]^-$, $[ICl_4]^-$, $[FeBr_4]^-$, etc.

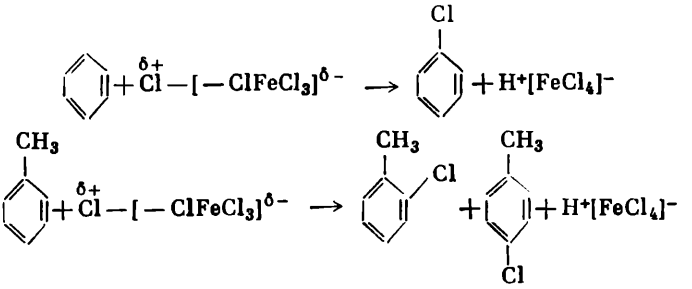
According to their power the bromine carriers are arranged in the following series (B. V. Tronov):

$$FeBr_3 > AlBr_3 > ZnBr_2 > IBr_3 > SbBr_3 > CuBr_2 > S_2Br_2 > PBr_3$$

In the case of a neutral halogen molecule (only chlorine or bromine) this halogen molecule is polarized due to the capture (complete or for sharing) of one of the two atoms of the molecule by a halogen carrier, in which case the second atom receives a δ^+ charge and functions as an electrophilic reagent:



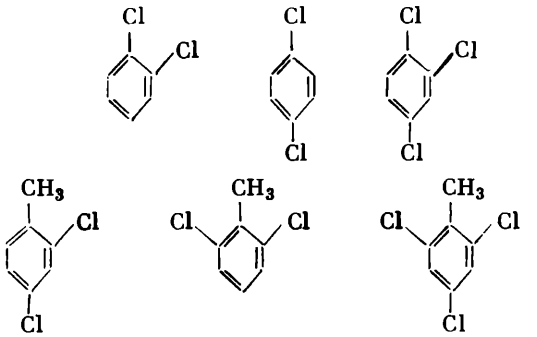
Thus, the nuclear chlorination in benzene and toluene is expressed by the following summary equations:



Nuclear bromination takes place in the same way.

Chlorobenzene was first obtained in 1865 by N. V. Sokolov.

The action of a large amount of halogen results in the formation of more halogenated aromatic hydrocarbons (A. A. Kurbatov):



Benzene can be chlorinated by an excess of chlorine to give hexachlorobenzene. As a by-product hexachlorobenzene is produced by the chlorination of numerous aliphatic and alicyclic hydrocarbons and petroleum fractions under vigorous conditions (Yu. G. Mamedaliev).

The methyl group of toluene when subjected to electrophilic chlorination with a carrier remains intact. But if toluene and other homologues of benzene are chlorinated (or brominated) in the light, better at the boiling temperature (in the vapour), provided that the absence of iron or other carriers is carefully secured, then the halogenation proceeds according to the laws of chain reactions only into the alkyl group. In this process, toluene is converted into benzyl chloride (or bromide), benzylidene chloride and benzotrichloride, and ethylbenzene changes to α-chloroethylbenzene and α, α-dichloroethylbenzene. It is the α-position of the side chain that is easily halogenated, while the positions more remote from the benzene nucleus

are halogenated more difficultly, namely, in the same way as in saturated hydrocarbons. This is because free radicals of the benzyl type $C_6H_5\dot{C}H_2$, or of the α-phenylethyl type, $C_6H_5\dot{C}HCH_3$, which are intermediates in the chain reaction, are more stable and, hence, are formed with a lower activation energy (and, hence, at a higher speed) than the isomeric radicals, say, $C_6H_5CH_2\dot{C}H_2$:

$$Cl_2 \xrightarrow{\text{light}} 2Cl\cdot \text{ (chain initiation)}$$

$$C_6H_5CH_3 + Cl\cdot \longrightarrow C_6H_5\dot{C}H_2 + HCl \text{ (chain step)}$$

$$C_6H_5\dot{C}H_2 + Cl_2 \longrightarrow C_6H_5CH_2Cl + Cl\cdot \text{ etc.}$$

Benzylidene chloride and benzotrichloride are formed in the same way (only the summary equations are given):

$$C_6H_5CH_3 + 2Cl_2 \longrightarrow C_6H_5CHCl_2 + 2HCl$$

$$C_6H_5CH_3 + 3Cl_2 \longrightarrow C_6H_5CCl_3 + 3HCl$$

With the aid of an electrophilic substitution reaction it is possible to introduce the CH_2Cl group into the aromatic hydrocarbons. This reaction is known as the **chloromethylation** reaction. For this reaction to be effected an aromatic hydrocarbon is made to react with formaldehyde (in the form of formalin or paraform) in the presence of zinc chloride with simultaneous addition of hydrogen chloride (Blanc):

$$CH_2O + H^+ \longrightarrow \overset{+}{C}H_2OH \longleftrightarrow CH_2{=}\overset{+}{O}{-}H$$

$$ArH + \overset{+}{C}H_2OH \xrightarrow[-H^+]{} ArCH_2OH \xrightarrow{HCl(ZnCl_2)} ArCH_2Cl$$

An interesting exchange reaction between toluene and carbon tetrachloride (225-235°C) has been described by Yu. A. Oldekop:

$$C_6H_5CH_3 + CCl_4 \longrightarrow C_6H_5CH_2Cl + CHCl_3$$

No iodination into the side chain takes place. Chain-iodinated or fluorinated products are obtained by the exchange reaction between the corresponding chlorides and AgF, SbF_3, NaI.

Iodination requires no halogen carriers but proceeds only in the presence of a sufficiently active *o*,*p*-directing group. Neither benzene nor alkylbenzenes are iodinated directly, but aromatic amines, acyl amines and phenols undergo iodination very readily. Benzene and its homologues can however be directly iodinated if the hydrogen iodide evolved is simultaneously acted on by an oxidizing agent. The iodination reaction is reversible: hydrogen iodide reduces the iodobenzene obtained (in the case of benzene) to benzene, and the oxidation of hydrogen iodide is the reverse reaction. The oxidation is often effected by iodic acid. The iodination by the Tronov method is very convenient: an aromatic compound is acted

TABLE 7.4. **Halogen Derivatives of Benzene and Toluene**

Formula	Name	m.p., °C	b.p., °C	Density d_4^{20}	Refractive index n_D^{20}	Dipole moment in benzene at 20°C, D
C_6H_5F	Fluorobenzene	−41.9	85.0	1.0240	1.4646	1.39
C_6H_5Cl	Chlorobenzene	−45.0	132.0	1.066	1.5246	1.56 (at 21°C)
C_6H_5Br	Bromobenzene	−30.6	156.0	1.4951	1.5597	1.49
$C_6H_4F_2$	Difluorobenzene					
	o- or 1,2-	−34.0	92.0 (at 751 mm Hg)	1.1599 (at 18°C)	1.4451 (at 18°C)	2.38 (at 22°C)
	m- or 1,3-	−59.0	83.0	1.1552 (at 18°C)	1.4404 (at 18°C)	1.58 (gas)
	p- or 1,4-	−13.0	89.0	1.1684 (at 18°C)	1.4422 (at 18°C)	—
$C_6H_4Cl_2$	Dichlorobenzene					
	o- or 1,2-	−17.5	183.0	1.3048	1.5518 (at 22°C)	2.33
	m- or 1,3-	−24.8	172.0	1.2881	1.5457 (at 20.9°C)	1.48
	p- or 1,4-	+53.0	173.4	1.4581	1.5210 (at 80.3°C)	0 (at 25°C)
$C_6H_4Br_2$	Dibromobenzene					
	o- or 1,2-	5.6	221.0	1.9557	1.6117 (at 17.5°C)	1.87
	m- or 1,3-	−6.9	218.0	1.9523	1.6083 (at 17.5°C)	1.46
	p- or 1,4-	+86.9	220.0	2.261 (d_4^{17})	1.5743	0
C_6F_6	Hexafluorobenzene	5.29	80.5	—	—	—
C_6Cl_6	Hexachlorobenzene	227	326	2.044 (at 23°C)	—	0.1
C_6Br_6	Hexabromobenzene	306; 316	Subl.	—	—	—
$CH_3C_6H_4F$	Fluorotoluene					
	o- or 1,2-	−80	114	1.0041 (at 13.0°C)	1.4704	1.30 (at 30°C)

	m- or 1,3-	—[illegible]	[illegible]	[illegible] at 13°C	[illegible]	[illegible] (at 30°C)
	p- or 1,4-	—	117.0	1.001 (at 15°C)	1.470	1.88 (at 30°C)
$CH_3C_6H_4Cl$	Chlorotoluene					
	o- or 1,2-	—34.0	159.0	1.0817	1.5238	1.43
	m- or 1,3-	—47.8	162.0	1.0722	1.5214 (at 19°C)	1.77
	p- or 1,4-	+7.5	162.0	1.070	1.5199 (at 19°C)	1.94
$CH_3C_6H_4Br$	Bromotoluene					
	o- or 1,2-	—27.0	181.8	1.4220	—	1.44
	m- or 1,3-	—39.8	183.7	1.4099	1.551	1.75
	p- or 1,4-	+28.0	185.0	1.3898	1.549	1.93
$CH_3C_6F_5$	Pentafluorotoluene	—	—	—	—	—
$CH_3C_6Cl_5$	Pentachlorotoluene	218	301.0	—	—	1.55 (at 25°C)
$CH_3C_6Br_5$	Pentabromotoluene	288	—	2.970 (at 17°C)	—	—
$C_6H_5CH_2F$	Benzyl fluoride	—35.0	139.9	1.0228 (at 25°C)	—	1.77 (at 25°C)
$C_6H_5CH_2Cl$	Benzyl chloride	—43.0	179.0	1.1026 (at 18°C)	1.5415 (at 15°C)	1.87 (at 25°C)
$C_6H_5CH_2Br$	Benzyl bromide	—4.0	198	1.4380 (at 22°C)	—	1.85 (at 25°C)
$C_6H_5CHF_2$	Benzylidene fluoride	—	—	—	—	—
$C_6H_5CHCl_2$	Benzylidene chloride	—16.0	207.0	1.2557 (at 14°C)	1.5502	2.03 (at 25°C)
$C_6H_5CHBr_2$	Benzylidene bromide	—	140 (at 20 mm Hg)	1.510 (at 15°C)	1.541	—
$C_6H_5CF_3$	Benzotrifluoride	—29.0	102.4	1.196 (at 14°C)	1.4171 (at 14°C)	2.54 (at 25°C)
$C_6H_5CCl_3$	Benzotrichloride	—22.0	214.0	1.3803	1.5573	2.07 (at 25°C)

on by iodine in the nitrating mixture (i.e., a mixture of concentrated nitric and sulphuric acids).

Aromatic hydrocarbons cannot be fluorinated by undilute elemental fluorine since the reaction goes too far, giving rise to carbon tetrafluoride and hydrogen fluoride. Therefore, aromatic fluorine derivatives are obtained via diazo compounds by the Schiemann reaction (page 125). Introduction of several fluorine atoms by direct fluorination of benzene, say, with CoF_3 or MnF_3, leads to polyfluorocyclohexanes, which must be aromatized by dehydrofluorination in order to obtain a mixture of polyfluorobenzenes.

It turns out that the pyrolysis at 630-640°C of CBr_3F and also of freons (e.g., CF_2Cl_2) gives hexafluorobenzene (Desiran).

According to N. N. Vorozhtsov, jr., G. G. Yakobson, and V. E. Platonov, hexafluorobenzene can be made by heating hexachlorobenzene with anhydrous potassium fluoride up to 450-530°C. This reaction also gives pentafluorochlorobenzene, tetrafluorodichlorobenzenes and other polyhalobenzenes.

Hexafluorobenzene is a liquid boiling at 80.26°C. The fluorine in hexafluorobenzene is relatively easily exchanged by a nucleophilic reaction. For example, by reacting hexafluorobenzene with a 30-percent aqueous solution of ammonia at 150°C for 4 hours, N. N. Vorozhtsov, jr., and his coworkers obtained pentafluoroaniline (85 per cent) and a certain amount of tetrafluoro-*m*-phenylenediamine. Under similar conditions, **pentafluorophenol** was produced by the action of an aqueous solution of sodium hydroxide on hexafluorobenzene. **Pentafluorochlorobenzene** (and also **pentafluorobromobenzene**) form a Grignard reagent. On the basis of these and other starting compounds N. N. Vorozhtsov, jr. and his coworkers developed the chemistry of perfluoroaromatic compounds.

Table 7.4 lists the physical properties of halogen derivatives of benzene and toluene.

Mention should be made of the fact that the replacement of hydrogen by fluorine which is heavier (by 19 times) does not practically change the boiling point of the compound. This depends on the exclusively low polarizability of fluorine (cf. the low refractive indices of fluorine derivatives with the corresponding data for other halogen derivatives) and, hence, on the smallness of dispersion forces (van der Waals forces). For the same reason, articles made of fluoroplast (polytetrafluoroethylene) are not wetted by any liquids at all.

A. Chemical Properties of Aromatic Halogen Derivatives

The halogen atoms linked directly to the carbon atoms of the benzene ring are "immobile" and enter into nucleophilic substitution reactions with difficulty. Iodine is the most and fluorine the least capable of entering into reactions of this type.

1. Aromatic halogen derivatives (except fluorine derivatives) enter into reaction with lithium, sodium, and magnesium. Iodobenzene and bromobenzene react in an ethereal solution with magnesium only a little more slowly than alkyl halides and form a phenylmagnesium halide. The homologues of these halobenzenes react in the same manner. A similar reaction with chlorobenzene occurs at a higher temperature (ca. 150°C) and it can therefore be converted into phenylmagnesium chloride in an autoclave in the absence of ether (P. P. Shorygin) or in tetrahydrofuran under ordinary conditions. In the laboratory, of course, use is preferably made of bromides and iodides for Grignard synthesis. Phenyllithium solutions employed for the same reactions as solutions of a phenylmagnesium halide are prepared in the same way in ether or in a hydrocarbon solution from metallic lithium. Both reactions proceed through the stage of formation of a free radical:

$$C_6H_5Br + Mg \longrightarrow C_6H_5\bullet + \bullet MgBr \longrightarrow C_6H_5MgBr$$

$$C_6H_5Br \xrightarrow[-LiBr]{Li} C_6H_5\cdot \xrightarrow{Li} C_6H_5Li$$

This is clear from the fact that a rather large amount of diphenyl is formed as a by-product:

$$2C_6H_5\cdot \longrightarrow C_6H_5-C_6H_5$$

(bromobenzene and iodobenzene are indifferent with respect to a Grignard reagent).

The reaction of halobenzene with sodium can be stopped at the stage of formation of an organosodium compound:

$$C_6H_5Br \xrightarrow[-NaBr]{Na} C_6H_5\bullet \xrightarrow{Na} C_6H_5Na$$

but phenylsodium reacts with bromobenzene

$$C_6H_5Br + C_6H_5Na \longrightarrow NaBr + C_6H_5-C_6H_5$$

so that the reaction can immediately be carried out as the Wurtz reaction:

$$2C_6H_5Br + 2Na \longrightarrow C_6H_5-C_6H_5 + 2NaBr$$

Two different aryl halides or an aryl halide and an alkyl halide may also be used as the starting materials:

$$C_6H_5Br + C_2H_5Br + 2Na \longrightarrow C_6H_5-C_2H_5 + 2NaBr$$

2. When reacted with copper aryl halides also form a diaryl (Ullmann reaction):

$$2C_6H_5I + 2Cu \longrightarrow C_6H_5-C_6H_5 + 2CuI$$

3. The nucleophilic replacement of a halogen (except fluorine) in aryl halides is catalysed by metallic copper (Ullmann), sometimes by cuprous oxide and cupric salts, so that the following types of reactions can be effected under vigorous conditions:

$$C_6H_5Cl + 2NaOH \xrightarrow{Cu} C_6H_5ONa + NaCl + H_2O$$

$$C_6H_5I + NaO-\overset{\overset{O}{\|}}{C}-CH_3 \xrightarrow{Cu} C_6H_5O-\overset{\overset{O}{\|}}{C}-CH_3 + NaI$$

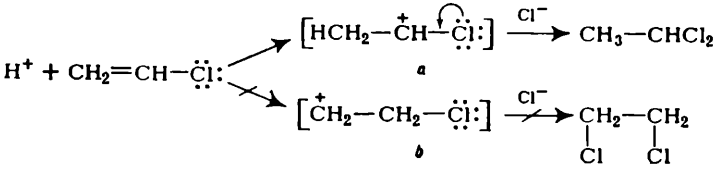
$$C_6H_5Br + NaCN \xrightarrow{Cu} C_6H_5CN + NaBr$$

In the absence of copper, chlorobenzene can also be hydrolysed by alkali, but this requires very drastic conditions, say, the prolonged action of 10-20-percent alkali at 300°C and under a pressure of 150 kg/cm^2. It has been found relatively recently that the relative reactivity of different halogen atoms depends on the reagent and reaction conditions; the vapour of chlorobenzene reacts with water vapour at atmospheric pressure and about 500°C on a silica gel promoted by a cupric salt (the Raschig method). This process formed the basis of one of the industrial methods for producing phenol, but it is not highly promising.

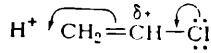
The cause of the inertness is the same as that of the inertness of the halogen in vinyl halide (Volume I, page 384) and is associated with the low dipole moment of the C—Hal bond in aromatic and vinyl halides as compared with the corresponding saturated compounds. The halogen atoms which possess free electron pairs interact with the π-bonds of the vinyl group and with the π-system of bonds of the benzene ring. This is the mesomeric effect (the $+M$ effect, see Volume I, pp. 236 *et seq.*, 318 *et seq.*), which is not strong since the activity of the *p*-electrons of chlorine is low. On the contrary, the inductive effect of chlorine (the $-I$ effect, i.e., migration of a pair of bonding electrons to chlorine as a very electronegative element) is always strong, and it imparts a positive charge to the carbon atom attached to this chlorine and further to the *ortho*- and *para*-carbon atoms of benzene or to the β-carbon atom of vinyl chloride (it corresponds to the *ortho*-carbon of benzene). These $\delta+$ charges in the *ortho*-, *para*-, and accordingly, β-positions are, however, smaller than they would have been if it were not for the mesomeric effect of chlorine, which has a reverse direction (the $+M$ effect, which supplies electrons) and decreases the $\delta+$ charges indicated. The validity of this statement can be confirmed if we compare the dipole moments of a number of halides (see page 68). Because of the $\delta+$ charges being decreased (on the *ortho*-, *para*- or β-carbon atoms of chlorobenzene

and, accordingly, of vinyl chloride and their bromide analogues), the dipole moments of these halides are considerably lower than those of saturated alkyl halides which exert only the $-I$ effect but not the $+M$ effect of the halogen. We have already explained above that the presence of the $-I$ effect retards the electrophilic attack on the carbon atoms of chlorobenzene—they become impoverished in electrons which are withdrawn by the chlorine. In a similar way, vinyl chloride too, in spite of the weak $+M$ effect, owing to the strong $-I$ effect on the whole (of course, its carbon atoms) is impoverished in electrons. Therefore, addition of acids or hydrogen halides (electrophilic attack) to vinyl chloride proceeds more slowly than to ethylene and the more so to propylene. Electrophilic attacks, however, also occur in the aromatic halides (in the *ortho*- and *para*-positions) and in an ethylene halide (in the β-position).

This has been explained earlier with regard to halobenzenes (page 52). The orientation of proton addition (electrophilic attack) in the β-position of vinyl chloride is accounted for in an analogous way:



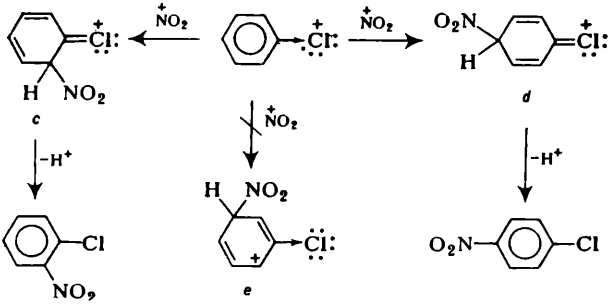
The intermediate cation *a* is poorer in energy than the cation *b* because the chlorine compensates for the positive charge which arises on the adjacent carbon atom as a result of the addition of proton to the terminal carbon atom. This may be expressed in the following way:



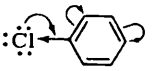
which symbolizes not the small mesomeric $+M$ shift of electrons characteristic of a molecule at rest, which reflects in the decreased dipole moment, but rather the full tautomeric $+T$ (or, what is the same thing, electromeric) shift with migration of an electron pair from the orbital of one atom to that of another.

The situation is quite analogous with chlorobenzene, the only difference being that the chlorine here is able, owing to its $+T$ effect, to compensate at least partly for the positive charge introduced by the attacking electrophile, say, by $\overset{+}{N}O_2$, when the *ortho*- and *para*-positions (the σ-complexes *c* and *d*) are attacked rather than the

meta-position (the σ-complex *e*):



The supply of electrons by means of the $+T$ effect of chlorine into the ring, which is impoverished in electrons by its $-I$ effect, reaches only the *ortho*- and *para*-positions where exactly the replacement of hydrogen by an electrophile takes place (though slowly):



As pointed out on page 52, all the four halogens are *ortho-para* directing groups which however retard electrophilic substitution in the benzene ring. The $+M$ effect of fluorine is stronger than that of the other halogens. The rates of nitration of fluoro-, chloro-, and bromobenzenes are in the ratio of 5 : 1.1 : 1 (Ingold). But with orientation in the *ortho*-position chlorine has an advantage. Thus, according to the data obtained by N. N. Vorozhtsov, jr., in the case of the competing orientation by chlorine and fluorine the place of entry of NO_2 is determined by chlorine. For example, 1,3-difluoro-4,6-dichlorobenzene is nitrated in the *ortho*-position to both chlorine atoms and in the *meta*-position to fluorine atoms.

It is natural that the diminished polarity of the C—X bond in halobenzenes and vinyl halides (the $+M$ effect superimposable on the $-I$ effect) reduces the exchanging ability of the halogen. For instance, the nucleophilic attacks of OH^-, NH_2^- and CN^- on a carbon atom bearing a halogen are here much less effective and require more vigorous conditions than in alkyl halides.

As seen from the data given below, the dipole moments of vinyl halides and halobenzenes are, as a matter of fact, considerably lower than those of the corresponding saturated halides:

	D		D
C_2H_5Cl	2.0	C_2H_5Br	2.09
$CH_2=CHCl$	1.44	$CH_2=CHBr$	1.41
C_6H_5Cl	1.56	C_6H_5Br	1.54

The halogen-bearing carbon atom in aromatic and vinyl halides is less positive and therefore less sensitive to nucleophilic attack. Once its positive character is enhanced by introducing into the *ortho-* or *para*-position an electron-attracting group such as, for example,

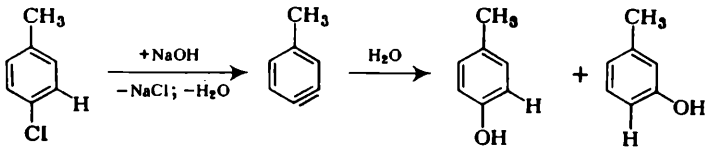
$$-NO_2, -SO_3H, \quad -C\begin{matrix}O\\H\end{matrix}, \quad >C=O, \quad \text{or} \quad -C\begin{matrix}O\\OH\end{matrix}$$

which withdraws electrons from it, the carbon atom becomes sensitive to nucleophilic attack (see page 56), and it means that the halogen becomes mobile and capable of exchanging readily with such groups as

$$OH^-, \quad NH_2^-, \quad CN^-, \quad R-C\begin{matrix}O\\O^-\end{matrix}, \text{ etc.}$$

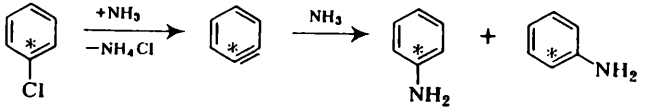
It is interesting that the fluorine in *p*-nitrofluorobenzene is even more readily replaced by nucleophiles than the chlorine in *p*-nitrochlorobenzene. Therefore, nitrofluorobenzenes, especially 2,4-dinitrofluorobenzene, are widely used to introduce the 2,4-dinitrophenyl residue, for example, into the terminal amino groups of proteins (see Volume II, "Amino Acids", and Volume IV, "Proteins"). It will be recalled that in saturated compounds, on the contrary, chlorine is more mobile than fluorine. This is easily accounted for by the fact that though fluorine supplies its free electrons to the carbon atom attached to it, its ability to compensate for the positive charge imparted to this carbon by the nitro group is much weaker than that of chlorine.

As regards halobenzenes containing no electron-attracting groups, the substitution of a halogen by nucleophiles proceeds not in a straightforward way but through the preliminary splitting-off of hydrogen halide with the formation of an unstable, highly reactive benzyne or dehydrobenzene (see page 75) which contains one triple bond in the ring and is capable of adding on water, ammonia and other nucleophilic molecules. This conclusion (Roberts) has been made on the basis of the fact that the action of alkali on *p*-chlorotoluene gives two isomers, *p*- and *m*-cresols:



This mechanism was conclusively proved by the preparation of aniline through the action of ammonia on chlorobenzene, in which

the chlorine was linked to the radioactive isotope of carbon ^{14}C:



The amino group was found to be linked with radioactive carbon in 50 per cent of aniline and to the adjacent carbon atom in another 50 per cent. This indirect substitution is referred to as **cine substitution.**

The situation is quite different with the α-halogens of the side chain. Whereas the more remote halogens of the side chain possess the normal mobility of the halogen in saturated compounds, the α-halogen is more mobile. Benzyl chloride is a lachrymatory compound. It has a powerful irritant action on the eyes and nose because of its high reactivity. An even more powerful irritant action is displayed by benzyl iodide—a police lachrymator.

Benzyl halides are hydrolysed and, in general, enter into exchange reaction with nucleophiles in alcoholic solution, the reaction being first order, which means that they first dissociate electrolytically (the slow reaction step determining the first order of the entire process), and then the benzyl cation very rapidly attaches itself to the nucleophile. Since the concentration of the nucleophile does not affect at all the rate of the electrolytic dissociation of the benzyl halide, the reaction rate is proportional only to the concentration of the latter (first-order reaction):

$$C_6H_5CH_2Cl \longrightarrow C_6H_5\overset{+}{C}H_2 + Cl^-$$

$$C_6H_5\overset{+}{C}H_2 + H_2O \longrightarrow C_6H_5CH_2OH + H^+$$

Such is the course of the reaction in well-solvating media with a high dielectric constant.

The ease of the electrolytic dissociation of a benzyl halide (as compared with alkyl halides) is accounted for by the high stability (the lower energy level) of the benzyl cation as compared with alkyl cations. But when benzyl chloride is hydrolysed by the S_N2 mechanism, it also reacts more rapidly than alkyl halides. This can partly be explained by the strong $-I$ effect of the phenyl group.

Benzyl chloride finds wide application in **benzylation** reactions, for introducing the benzyl group.

As always, the accumulation of two and more chlorine atoms at one carbon atom renders the compound more stable and less sensitive to nucleophilic attacks. When heated benzylidene chloride is hydro-

lysed to benzaldehyde:

$$C_6H_5CHCl_2 + H_2O \longrightarrow C_6H_5CHO + 2HCl$$

and benzotrichloride is hydrolysed by water (one mole) at a high temperature in the presence of sulphuric acid to benzoyl chloride—the acid chloride of benzoic acid:

$$C_6H_5CCl_3 + H_2O \longrightarrow C_6H_5C\begin{matrix}O\\ \diagup\!\!\diagdown\\ Cl\end{matrix} + 2HCl$$

This process is used on the industrial scale.

With excess water benzotrichloride is hydrolysed to benzoic acid:

$$C_6H_5CCl_3 + 2H_2O \longrightarrow C_6H_5C\begin{matrix}O\\ \diagup\!\!\diagdown\\ OH\end{matrix} + 3HCl$$

The action of antimony trifluoride readily converts benzotrichloride into benzotrifluoride:

$$C_6H_5CCl_3 + SbF_3 \longrightarrow C_6H_5CF_3 + SbCl_3$$

This compound is exclusively stable, is not hydrolysed at all and is not liable to enter into exchange reactions. The CCl_3 and, particularly, CF_3 groups are powerful *meta*-directors, which deactivate the benzene ring towards electrophilic attacks.

B. Compounds with Polyvalent Halogens

Organic compounds of polyvalent iodine, discovered by Victor Meyer, were the earliest known (the nineties of the 19th century). The synthesis of organic compounds of tri- and pentavalent iodine devised by V. Meyer is as follows:

$$C_6H_5I + Cl_2 \longrightarrow C_6H_5I\begin{matrix}Cl\\ \diagdown\!\!\diagup\\ Cl\end{matrix} \xrightarrow{2Ag_2O+H_2O} C_6H_5I{=}O$$

Phenyliodochloride — Iodosobenzene

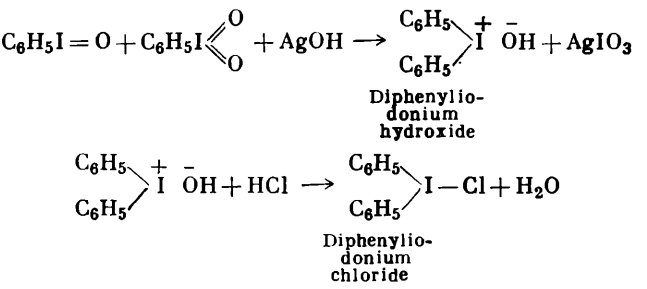
When iodosobenzene is heated up to 100°C, it disproportionates to iodobenzene and iodoxybenzene:

$$C_6H_5I{=}O \xrightarrow{\text{steam distillation}} C_6H_5I + C_6H_5{-}I\begin{matrix}O\\ \diagdown\!\!\diagup\\ O\end{matrix}$$

Iodobenzene — Iodoxybenzene

Iodoxybenzene is a specific phenylating agent capable of exchanging the $C_6H_5^-$ group for O^{2-}, which accounts for the course of this

unusual reaction:



Diphenyliodonium hydroxide

Diphenyliodonium chloride

The route of the synthesis of these compounds by the Meyer method is however relatively complicated.

Perhaps, the most clear-cut is the route of synthesis of certain types of organic polyvalent iodine compounds that has been accomplished by one of the authors of this book in collaboration with R. Kh. Freidlina. When iodine trichloride is reacted with diphenylmercury, the chlorine is replaced by phenyl and, depending on the ratio of the reagents used, two reactions may be carried out:

$$ICl_3 + (C_6H_5)_2Hg \longrightarrow \underset{\text{Phenyliodochloride}}{C_6H_5ICl_2} + C_6H_5HgCl$$

$$ICl_3 + 2(C_6H_5)_2Hg \longrightarrow \underset{\text{Diphenyliodonium chloride}}{(C_6H_5)_2ICl} + 2C_6H_5HgCl$$

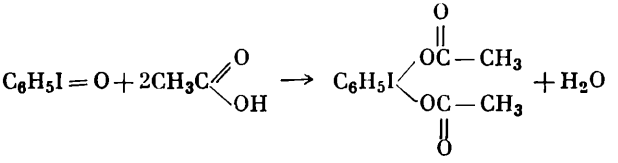
The second reaction probably involves two stages: the phenyliodochloride formed at the first stage undergoes then the Willgerodt reaction:

$$C_6H_5ICl_2 + Hg(C_6H_5)_2 \longrightarrow (C_6H_5)_2ICl + C_6H_5HgCl$$

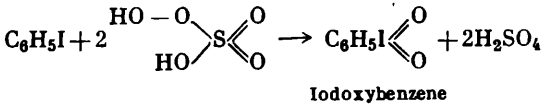
Phenyliodochloride (iodobenzene dichloride), $C_6H_5ICl_2$, which can also be obtained by the direct action of chlorine on iodobenzene dissolved, say, in chloroform, is a yellow crystalline compound. It decomposes slowly to hydrogen chloride and *p*-iodochlorobenzene. The action of alkali on $C_6H_5ICl_2$ gives iodosobenzene:

$$C_6H_5ICl_2 + 2NaOH \longrightarrow C_6H_5I{=}O + 2NaCl + H_2O$$

Iodosobenzene is a weak base and forms salt-like derivatives with certain acids:



Both iodosobenzene and iodobenzene are oxidized by Caro's acid to iodoxybenzene:



Iodoxybenzene

Iodine compounds and, in particular, iodoxybenzene, are crystalline colourless explosive compounds. Both iodoxybenzene and iodosobenzene are reduced (for example, by H_2SO_3 or HI) to iodobenzene.

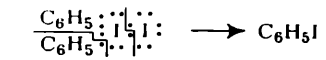
Diphenyliodonium chloride, $(C_6H_5)_2ICl$, forms water-soluble crystals; in solution it dissociates electrolytically into the diphenyliodonium cation, $(C_6H_5)_2I^+$, and the Cl^- anion. The latter can be easily exchanged for any other anion. The action of AgOH gives a solution of diphenyliodonium hydroxide, $(C_6H_5)_2\overset{+}{I}\ OH^-$, which is a base rendering litmus paper blue. By its analytical characteristics the diphenyliodonium cation resembles the cation of univalent thallium (forms insoluble iodide, chromate, sulphide and a soluble hydroxide). The halide salts of diphenyliodonium decompose on heating up to the melting point:

$$(C_6H_5)_2IX \longrightarrow C_6H_5I + C_6H_5X$$

Diphenyliodonium iodide, $(C_6H_5)_2II$ is the dimer of iodobenzene, which is converted to the parent compound on melting. The decomposition of diphenyliodonium salts in aqueous solution proceeds heterolytically, and in non-ionizing media they decompose by a homolytic mechanism, which is illustrated by the following typical reactions:

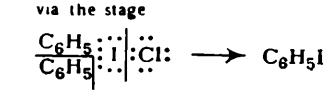
$$(C_6H_5)_2II + Hg \longrightarrow C_6H_5HgI + C_6H_5I$$

via the stage



$$(C_6H_5)_2ICl + HO^- \longrightarrow C_6H_5OH + C_6H_5I + Cl^-$$

via the stage



The simplest way of preparing iodonium salts is by the direct action of a solution of iodic acid in sulphuric acid on an aromatic

compound (Masson):

$$2C_6H_6 + HO-I\langle^{O}_{O} + H_2SO_4 \longrightarrow \begin{matrix} C_6H_5 \\ C_6H_5 \end{matrix}\rangle \overset{+}{I}\ \overset{-}{SO_4}H + 2H_2O + O$$

Masson discovered and Beringer studied more thoroughly a new type of diaryliodosyl salts prepared by the condensation of iodine compounds with benzene or with its derivatives in alkaline medium with subsequent oxidation:

$$C_6H_5IO_2 + C_6H_6 \longrightarrow C_6H_5-\overset{+}{I}(O^{-})-C_6H_5 \xrightarrow{HCl} C_6H_5-\overset{+}{I}(O)-C_6H_5\ Cl^{-}$$

In the period 1950-1960 one of the authors of this book together with T. P. Tolstaya prepared and investigated the chlorine and bromine analogues of diphenyliodonium salts, $(C_6H_5)_2Cl^+\ X^-$ and $(C_6H_5)_2Br^+\ X^-$. The method of their preparation via diazo compounds will be described on page 127. The essence of this method is as follows. The phenyl cation $C_6H_5^+$ generated from a phenyldiazonium salt attacks the free electron pair of chloro- or bromobenzene, as a result of which the halogenonium ion—diphenylchloronium or diphenylbromonium ion—is formed:

$$C_6H_5-\ddot{\underset{\cdot\cdot}{Cl}}: + C_6H_5^+ \longrightarrow \begin{matrix} C_6H_5 \\ C_6H_5 \end{matrix}\rangle \overset{+}{\underset{\cdot\cdot}{Cl}}:$$

If X^- is a stable complex ion, such as BF_4^- or HgI_3^-, the salts of both diphenylhalogenonium ions (diphenylchloronium and diphenylbromonium ions) are quite stable and decompose only at the temperatures indicated: $(C_6H_5)_2Br \cdot BF_4$ at 120°C and $(C_6H_5)_2Cl \cdot BF_4$ at 110°C. The halides are much less stable; for example, $(C_6H_5)_2BrI$ decomposes at 81°C and $(C_6H_5)_2ClI$ at 56°C.

Diphenylbromonium and diphenylchloronium salts are similar in chemical properties to diphenyliodonium salts, but they even more readily enter into reaction with nucleophilic reagents: they react even in the cold with an aqueous solution of alkali according to the scheme:

$$(C_6H_5)_2\overset{+}{Cl}\ X^- + OH^- \longrightarrow C_6H_5OH + C_6H_5Cl + X^-$$

They are capable of homolytic decomposition and react with metals in the same manner as diphenyliodonium salts:

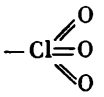
$$(C_6H_5)_2Cl-I + Hg \longrightarrow C_6H_5HgI + C_6H_5Cl$$

In reactions of synthesis of diphenylbromonium and diphenylchloronium salts, the free electron pairs of the halogen of the parent halobenzene are responsible for the manifestation of nucleophilic

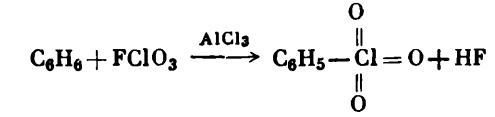
properties by the halogen. These are rare reactions, in which the covalently bonded halogen reacts like trivalent nitrogen and bivalent oxygen; in the latter, however, the free (unshared) pairs of electrons are much more active.

Diphenylbromonium and diphenylchloronium salts are sensitive to and are decomposed by nucleophilic reagents, but they are stable towards the action of electrophilic reagents. For example, diphenylbromonium borofluoride can be nitrated under drastic conditions by the nitrating mixture with the formation of di-(*m*-nitrophenyl)-bromonium borofluoride. Thus, the positively charged halogen atom of the bromonium is a sharply pronounced *meta*-director.

In 1958, Osterling and his coworkers described the **perchloryl derivatives** of benzene and its derivatives, which contain the group



Perchlorylbenzene (a liquid with m.p. —3°C, b.p. 232°C, d_4^{30} = 1.185) is made by passing the gaseous acid fluoride of perchloric acid, $FClO_3$, into warm benzene in the presence of aluminium chloride:

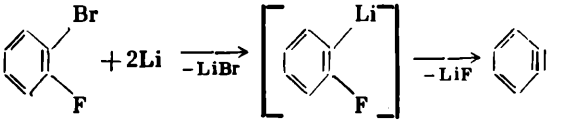


It can be nitrated by a nitrating mixture (in the *meta*-position) and sulphonated at a temperature of up to 280°C, but on boiling with alkali it is slowly hydrolysed to a phenol. Perchloryl derivatives have also been obtained for benzene homologues.

Perchloryl compounds are explosive.

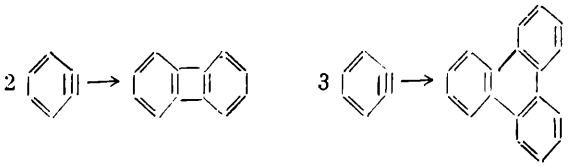
7.3. Dehydrobenzene (Benzyne)

Wittig discovered a remarkable reaction leading to the formation of dehydrobenzene (benzyne) by the action of lithium amalgam on *o*-fluorobromobenzene:

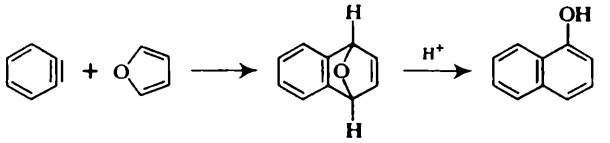


The presence in the reaction products of dehydrobenzene is adduced by its reactions since the compound is unstable and has not been

isolated in the free state. If no suitable reagent is available, dehydrobenzene dimerizes to diphenylene and trimerizes to triphenylene:



In the presence of a diene that withstands the reaction conditions (for example, is not polymerized), diene synthesis takes place, dehydrobenzene playing the role of a dienophile (page 330). The suitable diene is furan:



7.4. Sulphonic Acids and Other Aromatic Sulphur Compounds

A. Sulphonation Reactions in the Benzene Series

Benzene is sulphonated slowly when it is poured on stirring (even at room temperature) into 100-percent sulphuric acid (a so-called monohydrate) and rapidly when acted on by oleum (sulphuric acid containing dissolved sulphur trioxide):

$$C_6H_6 + H_2SO_4 \longrightarrow C_6H_5-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-OH + H_2O$$

Benzenesulphonic acid

The liberated water dilutes sulphuric acid and the rate of sulphonation rapidly falls, for which reason an excess of sulphuric acid must be taken. If the order of addition of reagents is reversed, then the hydrocarbon will be in excess, which leads to the formation of diphenyl sulphone as a by-product:

$$2C_6H_6 + H_2SO_4 \longrightarrow C_6H_5-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-C_6H_5 + 2H_2O$$

Diphenyl sulphone

Benzenesulphonic acid is separated from the sulphuric acid by either of the following two methods described below.

1. The reaction solution is poured into a concentrated solution of sodium chloride. Sodium benzenesulphonate is precipitated, which is but slightly soluble in solutions of sodium chloride, like most of the sodium salts of sulphonic acids.

2. Sulphuric acid is precipitated by baryta water. Then barium benzenesulphonate remains in solution and the free sulphonic acid can be obtained by adding an exactly equivalent amount of sulphuric acid (until no more $BaSO_4$ is precipitated) and by evaporating the filtrate to dryness. With calcium salts the separation is less complete because of the solubility of gypsum. The salts of sulphonic acids with alkali-earth metals are all soluble in water.

Sulphonic acids are strong acids, comparable in strength to sulphuric acid.

Toluene is sulphonated more readily than benzene, forming a mixture of *o*- and *p*-toluenesulphonic acids. The sulphonation reaction is basically a typical electrophilic substitution reaction and obeys the regularities considered on page 44. Since the sulphonic acid group is itself a *meta*-director, a second sulphonic acid group enters benzene in the *meta*-position to the first, and the *m*-benzenedisulphonic acid thus obtained (by the action of oleum) is so deactivated by the presence of two strong *meta*-directing groups that no other (third) sulphonic acid group can be introduced into benzene by sulphonation.

An evidence for the direct linkage between sulphur and carbon (and not through oxygen as is the case in sulphuric acid esters) in sulphonic acids is their genetic relationship to mercaptans. When sulphonic acids are reduced by the strongest reducing agents, they are converted into mercaptans, and the oxidation of mercaptans by nitric acid yields sulphonic acids:

$$C_6H_5-SO_3H \xrightarrow{LiAlH_4} C_6H_5-SH$$

$$C_6H_5SO_3H \xrightarrow{PCl_5} C_6H_5SO_2Cl \xrightarrow{H_2SO_4+Zn} C_6H_5-SH$$

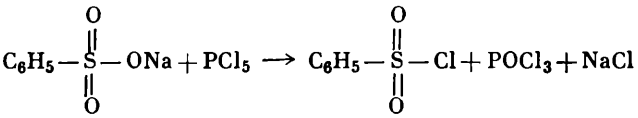
$$C_6H_5-SH \xrightarrow{HNO_3} C_6H_5-SO_3H$$

B. Functional Derivatives of Sulphonic Acids

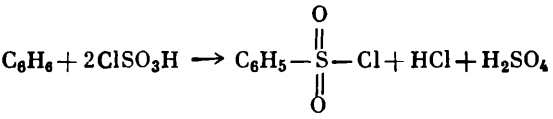
Aromatic sulphonic acids, like sulphonic acids in general, form the following functional derivatives obtained by the reactions described below.

The **acid chlorides of sulphonic acids (sulphonyl chlorides)** can be synthesized by the action of phosphorus pentachloride on a sulphonic

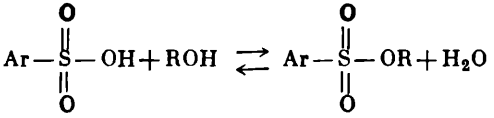
acid or its salt:



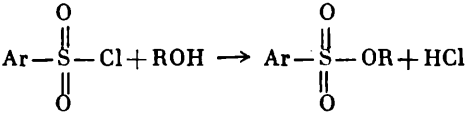
Sulphonyl chlorides can also be prepared by the sulphonation of a hydrocarbon with chlorosulphonic acid taken in excess:



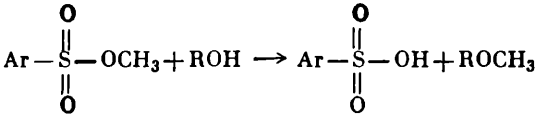
Esters of aromatic sulphonic acids are obtained by the esterification reaction:



or by the action of a sulphonyl chloride on alcohols:

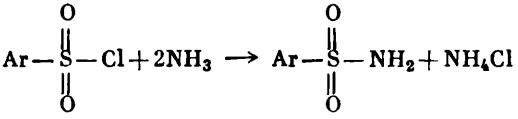


Sulphonic acid esters, like esters of sulphuric acid, are alkylating agents which find practical application:



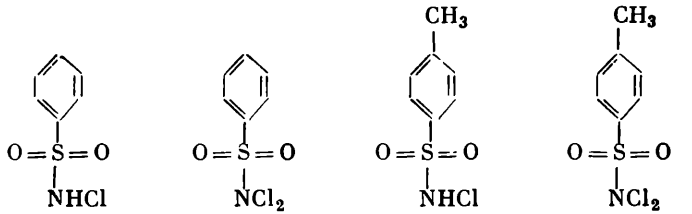
Here ROH may be an alcohol, phenol, or a carboxylic acid; the amines may also be alkylated.

The **amides of sulphonic acids**, or **sulphonamides**, are prepared by the action of ammonia, and the substituted amides are obtained by reacting sulphonyl chlorides with amines:



Sulphonamides with NaOH give salts of the type $ArSO_2NHNa$.

When sulphonamides are subjected to chlorination, one or both hydrogens of the amido group are replaced by chlorine and the so-called **chloramines** are obtained, which on hydrolysis yield HOCl and the starting sulphonamide. Chloramines are good disinfectants.



Chloramine B — Dichloramine B — Chloramine T — Dichloramine T

C. Reactions of Sulphonic Acids with Replacement of the Sulpho Group

The most important of these reactions is the fusion with alkali (Kekulé), which is still used at present to prepare a synthetic phenol:

$$C_6H_5-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-ONa + 2NaOH \longrightarrow C_6H_5ONa + Na_2SO_3 + H_2O$$

A point of interest here is the reduction of sulphur to the tetravalent state due to the oxidation of the carbon atom that becomes attached to oxygen as the result of the reaction.

An analogous course is taken by the reaction with a salt of hydrocyanic acid, which is of no substantial preparative value (M. G. Kuchierov):

$$C_6H_5-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-ONa + NaCN \longrightarrow C_6H_5-C\equiv N + Na_2SO_3$$

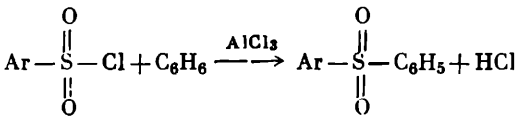
D. Other Aromatic Sulphur Functions

The reduction of sulphonyl chlorides with zinc and acid leads to the formation of **sulphinic acids** which are weak acids and are not particularly stable:

$$Ar-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-Cl \xrightarrow{Zn+HCl} Ar-S\begin{matrix}=O\\ \diagdown OH\end{matrix}$$

These acids can easily be oxidized to sulphonic acids or reduced to mercaptans.

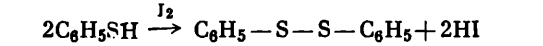
The acid chlorides of sulphonic acids react with aromatic hydrocarbons in the presence of aluminium chloride to yield **sulphones**:



Sulphones are very stable compounds. The sulphone group is a powerful *meta*-director which deactivates the benzene ring towards electrophilic substitution. Sulphones are very difficultly reduced to **sulphides**.

Diphenyl sulphide is oxidized in two stages: first to **diphenyl sulphoxide**, $(C_6H_5)_2S \rightarrow O$, by a calculated amount of an oxidizing agent (e.g., H_2O_2), and then to **diphenyl sulphone**, $(C_6H_5)_2SO_2$, by an excess of a strong oxidizing agent.

Mercaptans when reacted with weak oxidizing agents are converted into **disulphides**:

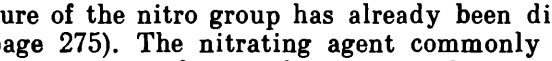


When strong oxidizing agents are used for the reaction, they yield sulphonic acids.

Like aliphatic mercaptans, ArSH form characteristic stable colourless insoluble mercaptides with Hg^{2+}, Pb^{2+} and cations of other heavy metals.

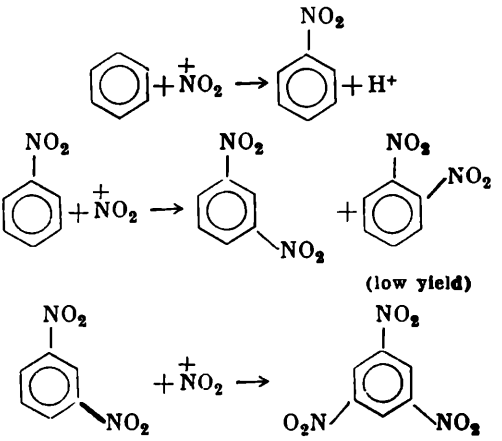
7.5. Aromatic Nitro Compounds

The structure of the nitro group has already been discussed (see Volume I, page 275). The nitrating agent commonly used is the *nitrating mixture*, i.e., a solution of concentrated nitric acid (60-100 per cent) in concentrated sulphuric acid. In such a solution nitric acid behaves as a base:



It is the nitronium ion which is an electrophilic nitrating agent. Nitric acid itself nitrates more slowly, and since it is a strong oxidizing agent, oxidation reactions predominate.

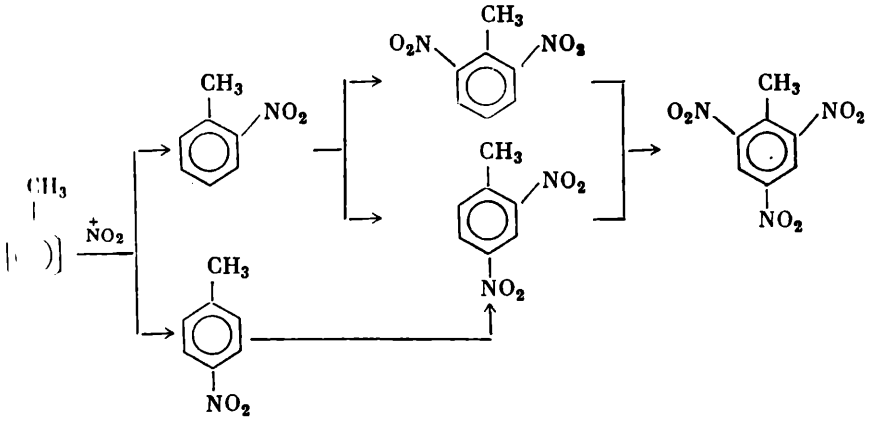
The reactions of successive nitration of benzene may be represented as follows:



The second stage of the nitration gives also small amounts of *o*-dinitrobenzene.

Trinitrobenzene (an ideal high explosive) is formed only under drastic conditions and in poor yield. Despite the efforts made by the chemists of many countries, this reaction could not be effected with a satisfactory yield during the World War II.

Like all alkylbenzenes, toluene is more readily nitrated at all the stages than benzene. The stages of its nitration are as follows:



In this way, 2,4,6-trinitrotoluene (*trotyl*) is obtained, which is a high explosive and is used for loading shells. In contrast to 1,3,5-trinitrobenzene, trotyl is obtained in good yield.

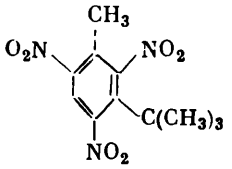
TABLE 7.5 Aromatic

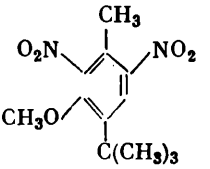
Formula	Name	Melting point, °C
$C_6H_5NO_2$	Nitrobenzene	5.7
$C_6H_4(NO_2)_2$	Dinitrobenzene	
	o- or 1,2-	118
	m- or 1,3-	89.57
	p- or 1,4-	173.5
$C_6H_3(NO_2)_3$	Trinitrobenzene	
	1,3,5-	123
	1,2,3-	127.5
	1,2,4-	61.0
$CH_3C_6H_4NO_2$	Nitrotoluene	
	o- or 1,2-	−4.1 (β-form)
		−10.6 (α-form)
	m- or 1,3-	+15.5
	p- or 1,4-	51.3
$CH_3C_6H_3(NO_2)_2$	2,4-Dinitrotoluene	70.5
$CH_3C_6H_2(NO_2)_3$	2,4,6-Trinitrotoluene	80.7
$ClC_6H_4NO_2$	Nitrochlorobenzene	
	o- or 1,2-	32.5
	m- or 1,3-	44.4
	p- or 1,4-	83.5
$BrC_6H_4NO_2$	Nitrobromobenzene	
	o- or 1,2-	42.0
	m- or 1,3-	56.0
	p- or 1,4-	127.0
$IC_6H_4NO_2$	Nitroiodobenzene	
	o- or 1,2-	49.4
	m- or 1,3-	36.0
	p- or 1,4-	171.5

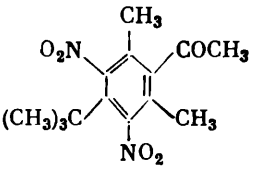
Nitro Compounds

Boiling point, °C	Density, d_4^{20}	Refractive index, n_D^{20}	Dipole moment μ in benzene at 20°C, D
210.9	1.2030	1.5529	3.97
319 (at 773 mm Hg)	1.565 (at 17°C)	—	5.98
302.8 (at 770 mm Hg)	1.571 (d_4^0)	—	3.78
299 (at 777 mm Hg)	1.625	—	0.00
Sublimes	1.688	—	0.8
—	—	—	—
—	1.73 (d_4^{16})	—	—
222.3	1.1630	1.5474	3.69; 4.22
231.0	1.1571	1.5475	4.17
238.0	1.1286	1.5346 (at 62.5°C)	4.44
300 (dec.)	1.521 (at 15°C)	1.662	4.33 (at 25°C)
240 (expl.)	1.654	—	1.15 (at 25°C)
245.7	1.368 (d_4^{22})	—	4.33
235.5	1.534	—	3.40
242	1.520 (d_4^{18})	—	2.57
261	1.6245 (d_4^{80})	—	4.20
256.5	1.7036	1.5979	3.41
256.0	1.934 (d_4^{22})	—	2.65
290.0	1.810 (d_4^{16})	—	3.92 (at 22°C)
280.0	1.804 (d_4^{16})	—	3.43 (at 22°C)
288.1	1.809 ($d_4^{15.5}$)	—	3.04 (at 22°C)

The nitration of *m-tert*-butyltoluene to a trinitro product leads to the formation of "artificial musk" which has a smell similar to the smell of vegetable musk (see Volume II, page 269). The formulas of a number of artificial musk are given:


Toluene musk


Musk ambrette


Ketone musk

They find application in perfumery as flavouring matter and odour fixatives.

When dilute nitric acid is allowed to react with toluene at a high temperature (100-150°C), nuclear electrophilic nitration is suppressed by dilution of nitric acid and toluene is homolytically nitrated by a chain mechanism into the methyl group (M. I. Konovalov, A. I. Titov):

$$C_6H_5CH_3 + \cdot NO_2 \longrightarrow C_6H_5CH_2\cdot + HNO_2 \text{ initiation (one of the variants possible)}$$

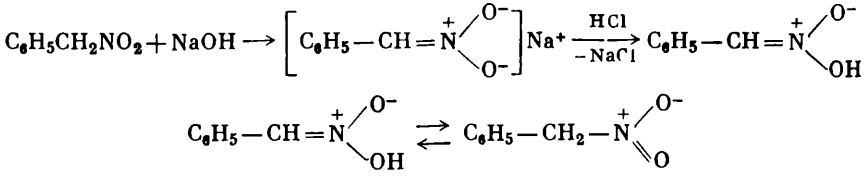
$$\left.\begin{aligned} C_6H_5CH_2\cdot + HONO_2 &\longrightarrow C_6H_5CH_2NO_2 + HO\cdot \\ C_6H_5CH_3 + \cdot OH &\longrightarrow C_6H_5CH_2\cdot + H_2O \end{aligned}\right\} \text{ chain step}$$

Benzene homologues with a longer side chain are also nitrated under these conditions in the alpha-position.

The same α-nitrotoluene can be obtained by the action of benzyl chloride on sodium nitrite (see also Volume I, page 274):

$$C_6H_5CH_2Cl + NaNO_2 \longrightarrow C_6H_5CH_2NO_2 + NaCl$$

Nitrotoluene is one of a few nitro compounds for which an unstable strongly acidic *aci*-form can be isolated (see Volume I, page 277), which is tautomeric with α-nitrotoluene:

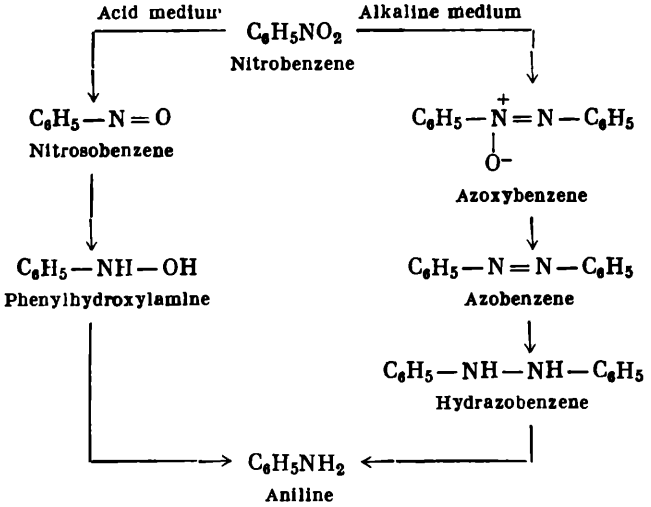

aci-form

Mononitro compounds produced by the chemical industry on a large industrial scale are mainly used for further reduction into the amines (see Sec. 7.7., "Aromatic Amines"). This reaction (N.N. Zinin) serves as a proof that the nitrogen of the nitro group is linked to carbon directly and not through oxygen.

The physical properties of a number of aromatic nitro compounds are given in Table 7.5.

7.6. Functions Formed by Incomplete Reduction of Nitro Compounds

Depending on the medium (acidic or alkaline) and current density, the electrochemical reduction of aromatic nitro compounds leads to the formation of a number of products containing functional groups with nitrogen which are new to us:



Each of these products can also be prepared by the reduction of a nitro compound through the agency of a suitable reagent. The end product of a series of reduction reactions both in acid and alkaline solutions is a primary amine—aniline.

The physical properties of the products of incomplete reduction of nitrobenzene are given in Table 7.6.

TABLE 7.6. **Products of Incomplete Reduction of Nitrobenzene**

Formula	Name	m.p., °C	b.p., °C	Density, d_4^{20}
$C_6H_5-N=O$	Nitrosobenzene	68	59 (at 18 mm Hg)	—
$C_6H_5-N=N-C_6H_5$	Azobenzene	68	293	1.203
$C_6H_5-\overset{\downarrow}{N}=N-C_6H_5$ (O)	Azoxybenzene	36	Dec.	1.246
$C_6H_5-NH-NH-C_6H_5$	Hydrazobenzene or diphenylhydrazine	126; 131	Dec.	1.158 (d^{6})
C_6H_5-NHOH	Phenylhydroxylamine	82	—	—

A. Nitrosobenzene

The reduction of nitrobenzene in an acid medium is difficult to stop at the stage of formation of nitrosobenzene. This compound is more easily made by the oxidation of the next reduction product of nitrobenzene—phenylhydroxylamine (Bamberger). This is the ordinary pathway for synthesis of nitrosobenzene:

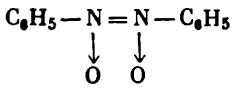
$$3C_6H_5-NHOH+H_2Cr_2O_7+6H^+ \longrightarrow 3C_6H_5-N=O+7H_2O+2Cr^{3+}$$

A direct method of reduction of nitro to nitroso compounds by iron pentacarbonyl, $Fe(CO)_5$, has recently been reported in the literature

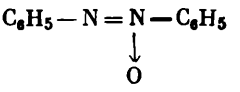
Aromatic nitroso compounds are colourless crystalline compounds which are dimeric in the solid state. In solution, in the molten state, and in the form of vapour they dissociate into two molecules of a mononitroso compound which has an emerald-green-blue colour, an equilibrium being established:

$$2C_6H_5NO \rightleftarrows [C_6H_5NO]_2$$

The dimer of the nitroso compound has a structure analogous to the structure of azoxy compounds discussed below*:



Nitrosobenzene dimer



Azoxybenzene

Perhaps, this accounts for the facile reduction of nitroso compounds to azoxy and then to azo compounds.

An argument in favour of such a structure is the recently discovered existence of the geometric isomerism of the dimers of nitroso compounds in the aliphatic series. As regards aromatic nitroso compounds, there are also *cis*- and *trans*-isomers (or, what is the same thing, *syn*- and *anti*-isomers) for them. But the dimeric nitrosobenzene itself is known to exist only in the *cis*-form, as evidenced by the analogy of its infrared and Raman spectra with the known

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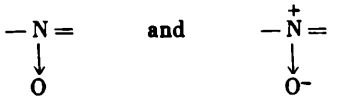
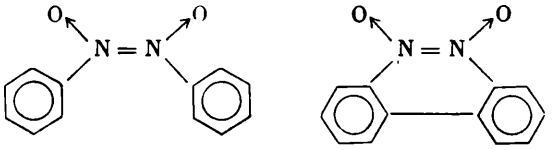
* It will be recalled that the symbols



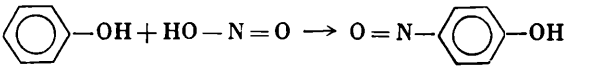
are equivalent and signify a semipolar bond—a covalent pair of electrons, which link the atoms bearing full ionic positive and negative charges.

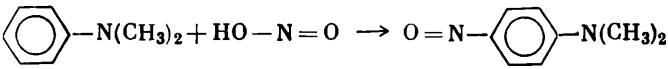
as form of *o,o'*-nitrosobiphenyl (it is colourless but monomeric):



Both compounds are characterized by two absorption bands between 1389 and 1397 cm^{-1} and a band at 1409 cm^{-1}; for aromatic *trans*-dimers there is observed only one absorption band between 1253 and 1299 cm^{-1}.

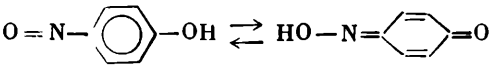
Other pathways for the formation of aromatic nitroso compounds are as follows: the action of N_2O_3 or ClNO on organometallic compounds, say, on diphenylmercury; a benzene ring containing strong *ortho-para* directing groups [—OH, $—N(CH_3)_2$], which are inert to nitrous acid, can be directly nitrosated in aqueous solution by the action of nitrous acid:





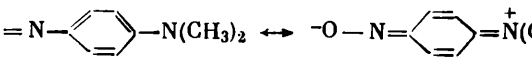
The nitrosation proceeds in the cold in acidic aqueous solution and almost entirely in the *para*-position.

Nitrosophenol is a special type of a nitroso compound. In its solutions there is observed a tautomerism of the nitrosophenol and quinone-oxime forms (cf. page 140, the tautomerism of nitrophenols):



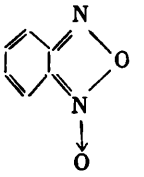
The position of the tautomeric equilibrium depends on the solvent used.

Nitrosodimethylaniline also differs from ordinary nitroso compounds. Owing to the concerted interaction of the electron-releasing dimethylamino group and the electron-withdrawing nitroso group the structure of nitrosodimethylaniline is found to be noticeably shifted to the side of the quinonoid form (see page 183), and it may be described as a resonance hybrid:

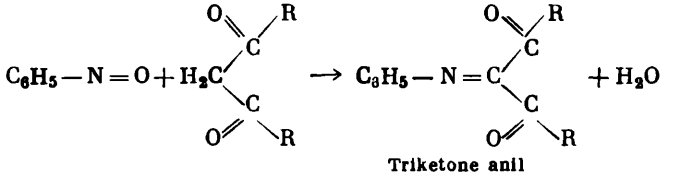


This is detected by the enhanced dipole moment, the bathochromic shift of light absorption and the inability to form a dimer. A different interaction between two nitroso groups is observed in *o*-dinitroso-

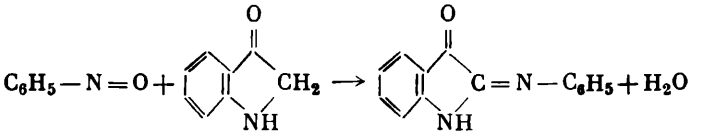
benzene which is essentially a heterocyclic compound—benzfurasan:



Nitroso compounds are capable of entering into numerous condensation reactions. They react with elimination of water with compounds containing the grouping $H_2N—X$ (they will be discussed at a later time) and with compounds having a mobile methylene group. For example,

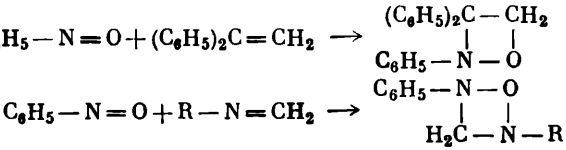


Triketone anil

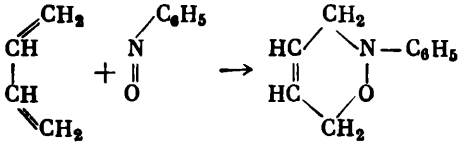


Isatin anil*

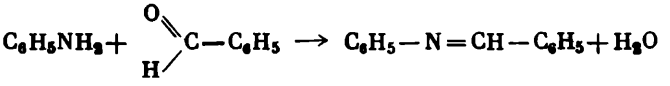
The second group of reactions includes additions to the nitroso group with formation of a four-membered ring:



Finally, with dienes there takes place a diene synthesis in which the nitroso group plays the role of a dienophile (Yu. A. Arbuzov):



* Anils (page 168) are the products resulting from the interaction of aromatic amines with carbonyl compounds. For example,



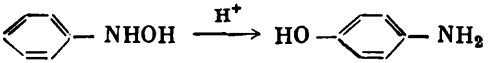
B. Phenylhydroxylamine

Phenylhydroxylamine is obtained by reducing nitrobenzene (in the form of a suspension in aqueous solution of ammonium chloride) with zinc dust. Phenylhydroxylamine is salted out of the aqueous solution with sodium chloride. It is a white crystalline substance. The powdered substance induces violent sneezing. Phenylhydroxylamine is very readily oxidized by atmospheric oxygen and becomes dark, and on more energetic oxidation is converted into nitrobenzene. With nitrosobenzene in alkaline solution it forms azoxybenzene:

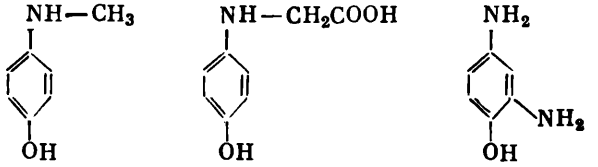
$$C_6H_5-NHOH+O=N-C_6H_5 \longrightarrow C_6H_5-\underset{\downarrow}{\overset{}{N}}=N-C_6H_5+H_2O$$
$$O$$

This accounts for the formation of an azoxy compound upon reduction of nitrobenzene in alkaline medium.

Phenylhydroxylamine is a very weak base. A remarkable property (which is utilized in practice) of phenylhydroxylamine is its rearrangement (isomerization) on heating with acid to a stronger base—*p*-aminophenol:



p-Aminophenol is a patented photographic developer. Its derivatives are also utilized for this purpose:



Metol Glycin Amidol

The industrial process for preparing *p*-aminophenol is sometimes accomplished electrochemically in a single cell by reducing nitrobenzene and rearranging phenylhydroxylamine.

C. Azoxybenzene

Azoxybenzene which was first prepared by N. N. Zinin can be synthesized by reducing nitrobenzene with sodium methoxide:

$$4C_6H_5-NO_2+3CH_3ONa \longrightarrow 2C_6H_5-\underset{\downarrow}{\overset{}{N}}=N-C_6H_5+3HCOONa+3H_2O$$
$$O$$

Azoxybenzene in its turn is reduced (by Zn, Fe) to azobenzene. The unsymmetrical position of the oxygen in azoxybenzene follows from the existence of an isomerism of the type (Angeli):

$$Ar-\overset{\downarrow}{\underset{O}{N}}=N-Ar' \quad \text{and} \quad Ar-N=\overset{\downarrow}{\underset{O}{N}}-Ar'$$

The oxidation of Ar—N=N—Ar′ gives rise to both isomers. The two isomers are also formed in the reaction:

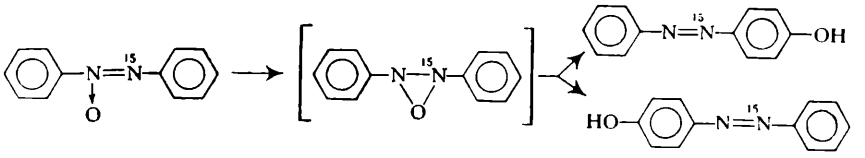
$$Ar-NHOH+O=N-Ar' \longrightarrow [Ar-\overset{+}{N}H(HO)-N(O^-)-Ar'] \rightleftarrows$$

$$\rightleftarrows [Ar-N(HO)-N(OH)-Ar'] \xrightarrow{-H_2O} Ar-\overset{\downarrow}{\underset{O}{N}}=N-Ar' + Ar-N=\overset{\downarrow}{\underset{O}{N}}-Ar'$$

When heated in acid medium azoxy compounds rearrange into *p*-hydroxyazo compounds (Wallach rearrangement):

$$C_6H_5-\overset{\downarrow}{\underset{O}{N}}=N-C_6H_5 \xrightarrow{H^+} HO-C_6H_4-N=N-C_6H_5$$

According to M. M. Shemyakin, azoxybenzene gives oxygen to the *para*-positions of both phenyls, which is proved by experiments with azoxybenzene containing one labelled nitrogen atom (the isotope ^{15}N). That a symmetrically built molecule is transiently formed is evidenced by reduction to a mixture of products resulting from the interaction between aniline and *p*-aminophenol, the isotope ^{15}N being equally distributed between them:



D. Azobenzene

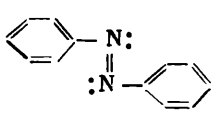
Azobenzene, $C_6H_5-N=N-C_6H_5$, is prepared by the reduction of nitrobenzene with sodium stannite or other reducing agents in alkaline solution:

$$2C_6H_5-NO_2+4Sn(ONa)_2 \longrightarrow C_6H_5-N=N-C_6H_5+4Na_2SnO_3$$

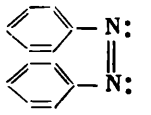
It can also be prepared by the reaction of nitrosobenzene with aniline:

$$C_6H_5-N=O+H_2N-C_6H_5 \longrightarrow C_6H_5-N=N-C_6H_5+H_2O$$

All these reactions lead to azobenzene with m.p. 68°C. When irradiated with ultraviolet light this azobenzene is converted into its unstable geometric isomer, which is energetically richer (by about 11 kcal/mole) and has a melting point of 71°C. This is the *cis-trans* isomerism which is commonly termed the *syn-anti* isomerism for the cases of geometric isomerism involving nitrogen:



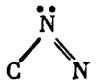
Ordinary *trans-* or *anti*-azobenzene (m.p. 68°C)



cis- or *syn*-azobenzene (m.p. 71°C)

syn-Azobenzene (or *cis*-azobenzene) is a nonplanar compound since if it were flat the benzene residues would have superimposed upon each other. The configurations of both compounds have been established by X-ray studies.

The geometric isomerism due to the arrangement of substituents about nitrogen atoms at double bonds has been considered earlier in the discussion of nitroso compounds. Further in the text we shall return to this phenomenon, which has been investigated especially well for aldoximes and ketoximes. The point is that the double N=N bond (and also the C=N bond in oximes) does not allow, just like the C=C bond, free rotation, and the angle



is different from 180° (it is closer to 120°). The latter circumstance is associated with the fact that the unshared (free) *p*-electron pair of nitrogen requires space.

Azobenzene is an even weaker base than phenylhydroxylamine. It is soluble in concentrated sulphuric acid but is precipitated from it by water due to hydrolysis of the salt formed. Such a salt when in a solution of concentrated sulphuric acid easily extracts a hydrogen atom with two electrons (hydride ion) from numerous types of organic compounds and, being converted into hydrazobenzene (page 92), rearranges then into benzidine (A. N. Nesmeyanov, R. V. Golovnya).

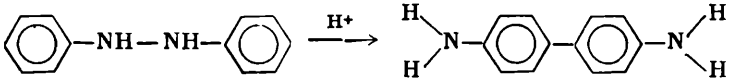
The azo group is one of the most important functions of the aromatic series, and numerous azo compounds in the form of azo dyes are produced synthetically in enormous quantities. The method of formation of the azo group in the synthesis of azo dyes is however different (through diazo compounds) and will be described after the discussion of diazo compounds.

Azobenzene forms bright-orange low-melting crystals soluble in organic solvents. But its colour differs markedly from that of azo dyes in intensity and it is incapable of being kept in the fibre.

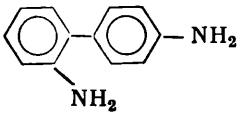
Azo compounds when boiled with a solution of stannous chloride or when acted on by titanium trichloride are reduced quantitatively to primary amines. By reducing azobenzene with zinc dust in alkali it is possible to prepare colourless crystalline hydrazobenzene

$$C_6H_5-N=N-C_6H_5 \xrightarrow{2H} C_6H_5-NH-NH-C_6H_5$$

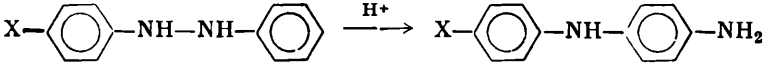
which is slowly oxidized even by atmospheric oxygen to azobenzene. The most remarkable property of hydrazobenzene is the rearrangement to **benzidine** (4,4′-diaminobiphenyl) which is a quantitative reaction proceeding on boiling in aqueous solutions of strong acids:



The **benzidine rearrangement** discovered by N. N. Zinin has been studied by many investigators. It has been found that, apart from *p*,*p*′-rearrangement, there also takes place *o*,*p*-rearrangement, a small amount of diphenyline (2,4′-diaminobiphenyl) being formed along with the benzidine:

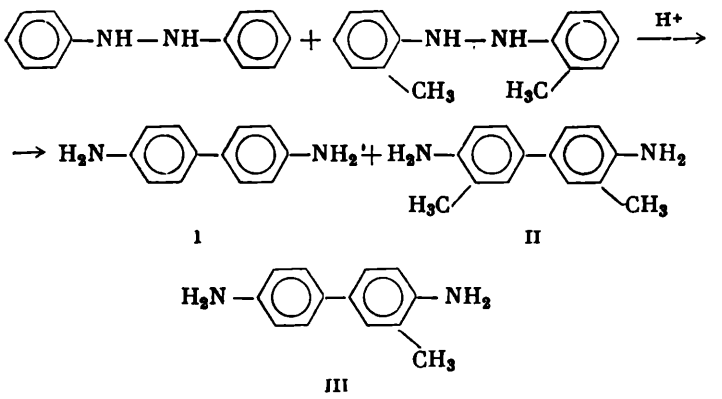


If one of the two *para*-hydrogen atoms of hydrazobenzene is already replaced by a substituent, a semi-benzidine or **semidine rearrangement** occurs, which leads to a primary-secondary diamine of the benzene series (and not diphenyl)—a **semidine** which is a *para*-substituted derivative of *p*-aminodiphenylamine:

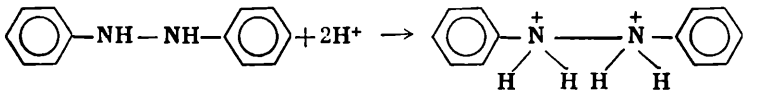


The benzidine rearrangement is an *intra*molecular change, i.e., it takes place within one molecule, and not an *inter*molecular transformation involving the interaction of two (or more) molecules. This is proved by the fact that from a mixture of two different hydrazo compounds there are obtained two and only two different benzidines,

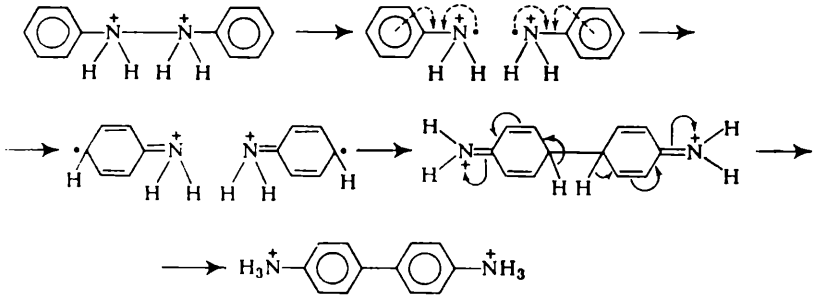
I and II, and no trace of product III can be detected:



Perhaps, the most probable hypothesis regarding the mechanism of the reaction is the version of Robinson's hypothesis put forward by the Czech scientist Veczerz. The first stage is the fixation of protons by the two nitrogen atoms:

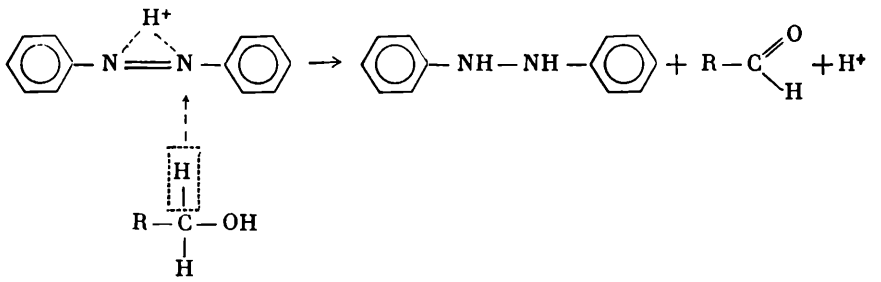


Such a state with two full positive charges on neighbouring nitrogen atoms is unstable. Since each nitrogen atom assumes a tetrahedral configuration, the opposite (*para*-) ends of benzene rings approach each other. For a homolytic cleavage of the N—N bond there is required one extra electron for each nitrogen atom. These electrons are supplied by the *para*-carbon atoms which in their turn acquire a free-radical character. The benzene rings are fused with the aid of their *para*-carbon free-radical atoms into a diphenyl system*:



* The dashed arrows signify the shift of one electron.

When azobenzene is allowed to react with sulphuric acid and a hydride hydrogen donor, say, with a primary or secondary alcohol, a benzidine rearrangement also takes place. Hydrazobenzene is first formed:



which then undergoes rearrangement as shown on page 92.

7.7. Aromatic Amines

The simplest aromatic amine is aniline, $C_6H_5NH_2$. Aniline was first prepared by dry distillation of natural indigo (Fritzsche, 1826), hence its name (*anil* means indigo in Spanish). Traces of aniline are also found in coal tar. Aniline became industrially important after it had been prepared by N. N. Zinin by reducing nitrobenzene with hydrogen sulphide:

$$C_6H_5NO_2 + 3H_2S \longrightarrow C_6H_5NH_2 + 2H_2O + 3S$$

Until recently the main industrial method of preparing aniline and a number of other aromatic amines has been a modification of the Zinin reaction—the reduction of nitro compounds with iron filings in the presence of a small amount of hydrochloric acid (Béchamps):

$$4C_6H_5NO_2 + 9Fe + 4H_2O \longrightarrow 4C_6H_5NH_2 + 3Fe_3O_4$$

With increasing production of aniline the catalytic reduction of nitro compounds assumes great industrial importance:

$$C_6H_5NO_2 + 3H_2 \xrightarrow{Ni} C_6H_5NH_2 + 2H_2O$$

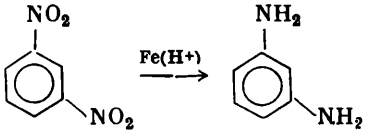
In the laboratory, use is most often made of metallic tin with strong hydrochloric acid as a reducing agent:

$$2C_6H_5NO_2 + 3Sn + 14HCl \longrightarrow 2C_6H_5NH_2 \cdot HCl + 3SnCl_4$$

The reduction of the corresponding nitro compounds yields homologues of aniline: *o*-, *m*-, and *p*-toluidines, $CH_3C_6H_4NH_2$, and also substituted anilines: *o*-, *m*-, and *p*-chloranilines, $ClC_6H_4NH_2$,

o- and *p*-anisidines, $CH_3OC_6H_4NH_2$, *o*- and *p*-phenetidines, $C_2H_5OC_6H_4NH_2$, etc.

The reduction of *m*-dinitrobenzene (with iron filings or catalytically) gives *m*-phenylenediamine:



But when polynitro compounds are reduced with sulphur-containing metals, only one nitro group is reduced and *m*-nitroaniline is formed from *m*-dinitrobenzene.

When *o*- and *p*-nitroanilines are subjected to reduction, *o*- and *p*-phenylenediamines are obtained; for example,

$$H_2N-C_6H_4-NO_2\text{-}o \xrightarrow{Fe(H^+)} H_2N-C_6H_4-NH_2\text{-}o$$

Another important method of preparing aromatic amines is the exchange of a chlorine atom for an amino group by the action of an aqueous solution of ammonia at elevated temperature under pressure. Of the greatest importance is the preparation of *o*- and *p*-nitroanilines by this method from the corresponding isomers of chloronitrobenzene. Compounds containing no electron-attracting groups (for example, chlorobenzene) enter into reaction only in the presence of copper salts.

Other methods of preparing aromatic amines are less important and are employed as subsidiary procedures. Some of these are cited below.

1. Reduction (for example, with the aid of tin and hydrochloric acid) of any of the intermediate products of the reduction of nitro compounds, in particular azo compounds (page 92).

2. The action of hydrazoic acid on aromatic hydrocarbons (Schmidt):

$$C_6H_6+H-N=\overset{+}{N}=\overset{-}{N} \longrightarrow C_6H_5NH_2+N_2$$

3. The action of sodamide under drastic conditions on halogen derivatives of benzene. The reaction with a halobenzene, in which the labelled carbon (e.g., radioactive ^{14}C) is linked to halogen, has shown (Roberts) that the amino group becomes attached to this carbon only by 50 per cent, the other 50 per cent being linked to the *ortho*-carbon atom. This is accounted for by the preliminary elimination of a hydrogen halide by strongly basic $NaNH_2$ and by the formation of dehydrobenzene, which then adds on NH_3 to the triple bond

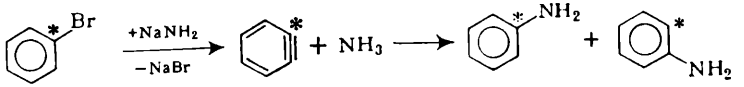
TABLE 7.7

Formula	Name	Melting point, °C	Boiling point, °C
$C_6H_5NH_2$	Aniline	−6.2	184.4
$CH_3C_6H_4NH_2$	Toluidine		
	o- or 1,2-	−24.4 (α-form)	
		−16.3 (β-form)	199.8
	m- or 1,3-	−31.5	203.3
	p- or 1,4-	+45	200.3
$NO_2C_6H_4NH_2$	Nitroaniline		
	o- or 1,2-	71.5	284.1
	m- or 1,3-	111.8	306.3
	p- or 1,4-	147.5	331.7
$ClC_6H_4NH_2$	Chloroaniline		
	o- or 1,2-	−14 (α-form)	
		−3.5 (β-form)	208.8
	m- or 1,3-	−10.4	229.8
	p- or 1,4-	+70	231
$HSO_3C_6H_4NH_2$	Aminobenzenesulphonic acid		
	o- or 1,2- (orthanilic)	Dec.	—
	m- or 1,3- (metanilic)	Dec.	—
	p- or 1,4- (sulphanilic)	280 (dec.)	—
$C_6H_5NHCH_3$	Methylaniline	−57	195.7
$C_6H_5N(CH_3)_2$	Dimethylaniline	+2.5	193.5
$(C_6H_5)_2NH$	Diphenylamine	53	302
$(C_6H_5)_3N$	Triphenylamine	126.5	365

Aromatic Amines

Density, d_4^{20}	Refractive index, n_D^{20}	K_a at 25°C	K_b at 25°C	Dipole moment μ in benzene at 20°C, D
1.022	1.5863	—	3.82×10^{-10}	1.53
1.004	1.5728	—	2.47×10^{-10}	1.60
0.989	1.5711 (at 22°C)	—	4.92×10^{-10}	1.45
1.046	1.5532 (at 59°C)	—	1.18×10^{-9}	1.31
1.442	—	—	6×10^{-4} (at 0°C)	4.96
1.430	—	—	2.7×10^{-5} (at 0°C)	4.85
1.424	—	—	—	6.32 (at 25°C)
1.213	1.5895	—	—	1.77
1.216	1.5942	—	—	2.68
1.427	—	—	8.51×10^{-5}	2.97
—	—	3.3×10^{-3}	—	—
—	—	1.85×10^{-4}	—	—
—	—	5.9×10^{-4}	—	—
0.986	1.5702 (at 21°C)	—	5×10^{-10}	1.64
0.955	1.5582	—	1.15×10^{-9}	1.56
1.159	—	—	7.6×10^{-14} (at 15°C)	0.95
0.774 (at 0°C)	1.353 (at 16°C)	—	—	0.52

(cine substitution; see also page 70):



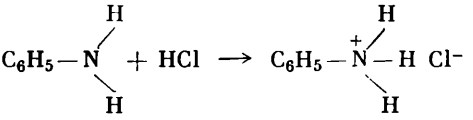
4. The action of hydroxylamine-O-sulphonic acid on aromatic compounds in the presence of $AlCl_3$ on heating (Kovacic, Bennett). the *ortho-para* substitution predominating:

$$CH_3C_6H_5 + NH_2-O-SO_3H \xrightarrow{AlCl_3} CH_3C_6H_4NH_2 + H_2SO_4$$

Some of the physical properties of aromatic amines are given in Table 7.7. The homologues of aniline are known as *o*-, *m*-, and *p*-toluidines (one CH_3 group) and xylidines (two CH_3 groups).

A. Basic Properties of Aromatic Amines

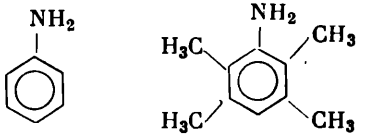
Aniline is a much weaker base than ammonia and aliphatic amines. Thus, K_b is 5×10^{-4} for methylamine and 3.8×10^{-10} for aniline (K_a for the conjugate acid is $10^{-4.6}$). Indeed, aniline. being only sparingly soluble in water, gives solutions which impart no colour either to litmus paper or to phenolphthalein. It forms no salts with weak acids such as carbonic, hydrocyanic or hydrosulphuric acids; with strong acids aniline forms solid salts, for example,



which are strongly hydrolysed in aqueous solution.

The weakening of the basic properties of the trivalent nitrogen in aniline is caused by the mesomeric effect of the amino group or, in other words, by the conjugation of the free electron pair of nitrogen with the π-electrons of the aromatic ring (*p*,π-conjugation). This means that the *p*-electron orbital of nitrogen (a free pair) is overlapped by the π-orbitals of the benzene ring. This interaction is evidently possible only in those cases where the axes of the *p*-electron orbitals of nitrogen are approximately parallel to those of the *p*-electron orbitals of the ring carbon atoms. Indeed, withdrawal of the amino group (conditionally) out of the plane of the ring immediately increases its basic properties and diminishes the dipole moment of the molecule. Such a disturbance of the coplanarity is possible only in the presence of two sufficiently bulky *ortho*-substituents, and its influence is seen, for example, from a comparison of the dipole moments of aniline and 2,3,5,6-tetramethyl-1-aminobenzene

(aminodurene):

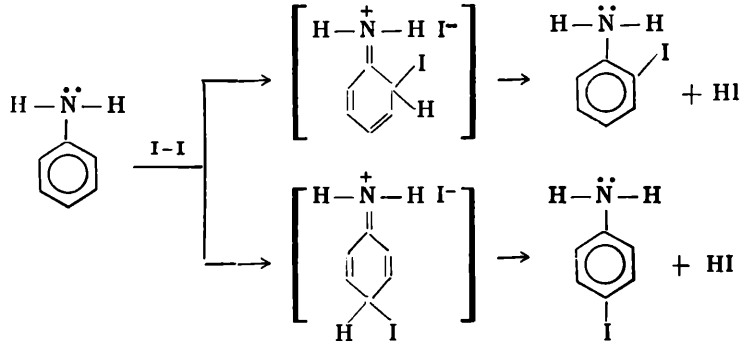


μ=1.53D μ=1.39D

Methyl groups, which in general impart only a small dipole moment to the aromatic nucleus, are arranged symmetrically in this particular case, so that their net effect on the dipole moment is zero. Unfortunately, we cannot compare the basic properties of the amino groups in both compounds since in the case of the *ortho*-arrangement of methyl groups the fields of their hydrogens repel the attacking hydrogen ion, which weakens the basic properties and masks the effect concerned. The difference in the dipole moments of the two aromatic amines is due only to the presence of the mesomeric effect in the case of aniline and to its absence in aminodurene.

B. Electrophilic Substitution in the Benzene Ring of Amines

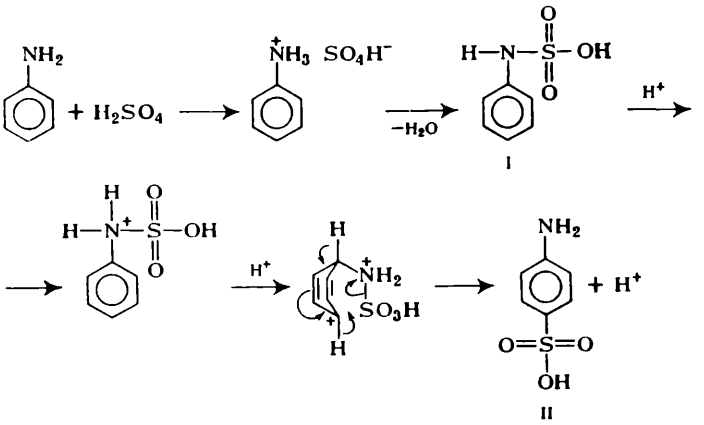
The interaction of the amino group with the benzene ring is especially pronounced at the moment of electrophilic attack on the *ortho*- and *para*-positions, say, in halogenation reactions. σ-Complexes (see page 38) have the following structures in such cases:



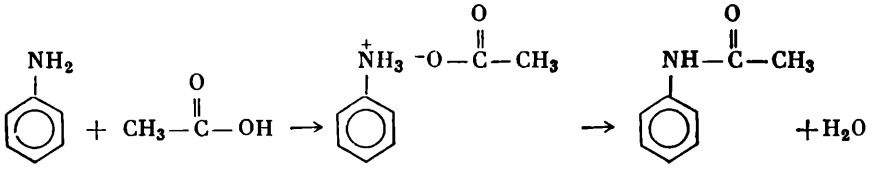
The ability of nitrogen to readily become the positively charged ammonium nitrogen and to assume (in the intermediate σ-complex) the positive charge arising on the ring carbon linked to it at the moment of attack of an electrophile on the *o*- and *p*-carbon atoms is exactly the cause of the decrease in the level energy of the transition state and of the high velocity (page 38) of electrophilic substitution reactions. Thus, the weak basic properties of the aromatic amino group and its strong *ortho-para* directing effect are of the same origin.

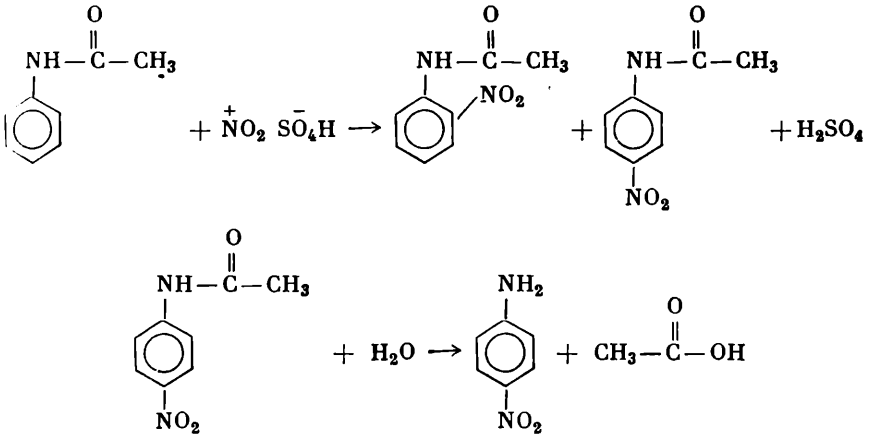
The orienting effect of the amino group in aniline and its homologues is so strong that the direct action of iodine at room temperature iodates aniline to 2,4,6-triiodoaniline. Aniline reacts even more vigorously with bromine and chlorine, forming 2,4,6-trihaloanilines.

The sulphonation of aniline requires elevated temperature since the salt is first formed, in which the nitrogen atom no longer acts as an *ortho-para* director because it has become an ammonium nitrogen. Besides, in this case the sulphonation occurs first at the amino group, and only then is the initially formed phenylsulphamic acid (I) converted into *p*-aminobenzenesulphonic acid (II) (sulphanilic acid) as the result of the intramolecular rearrangement into the *para*-position: the velocity of the rearrangement is proportional to the concentration of phenylsulphanilic acid and to the acidity function (Vrba, Allan, 1968). These authors suggest the following plausible mechanism of the rearrangement:



Aniline must not be nitrated directly because the reaction is too vigorous, and the oxides of nitrogen liberated as a result of the oxidation of aniline diazotize the unoxidized aniline. Therefore aniline is preliminarily acetylated (or formylated), and the acyl derivative (anilide) formed is nitrated to give a mixture of *o*- and *p*-nitroacetanilides (or of *o*- and *p*-nitroformanilides). The hydrolysis of the protecting acyl group yields a mixture of *o*- and *p*-nitroanilines which are then separated.





Here the amino group is protected from the diazotizing action of oxides of nitrogen, and the benzene ring becomes less accessible for oxidation and excess nitration due to the weakening of the directing power of the NH_2 group (the $-NH-\overset{\overset{O}{\|}}{C}-CH_3$ group is a weaker *ortho-para* directing group).

C. Substitution in the Amino Group

Anilides. We have already discussed the reaction of acylation of aniline. Aromatic amines can be acylated by acid chlorides and anhydrides or by strong heating of the amines with acids until the water is eliminated:

$$C_6H_5NH_2 + R-\overset{\overset{O}{\|}}{C}-Cl \longrightarrow C_6H_5-NH-\overset{\overset{O}{\|}}{C}-R + HCl$$

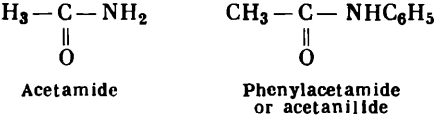
$$C_6H_5NH_2 + R-\overset{\overset{O}{\|}}{C}-O-\overset{\overset{O}{\|}}{C}-R \longrightarrow C_6H_5NH-\overset{\overset{O}{\|}}{C}-R + R-\overset{\overset{O}{\|}}{C}-OH$$

$$C_6H_5NH_2 + R-\overset{\overset{O}{\|}}{C}-OH \longrightarrow C_6H_5\overset{+}{N}H_3\ {}^{-}OOC-R \longrightarrow C_6H_5NH-\overset{\overset{O}{\|}}{C}-R + H_2O$$

Only the last method is suitable for formylation.

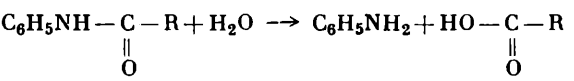
Acylated aromatic amines are collectively termed the **anilides.** The anilides of toluidines are known as **toluidides**, and the anilines of anizidines are called the **anizidides**, etc.

Anilides may also be regarded as the phenylated amides of acids:



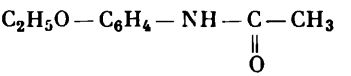
Acetamide — Phenylacetamide or acetanilide

Like all amides, they are hydrolysed on heating both in acid and alkaline medium:



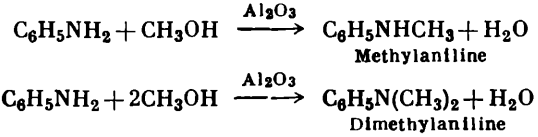
Anilides have no basic properties.

Some of the anilides are employed in medicine as analgesics and antipyretics. Examples are acetanilide (used as a febrifuge under the name of antifebrin); *p*-acetylphenetidine

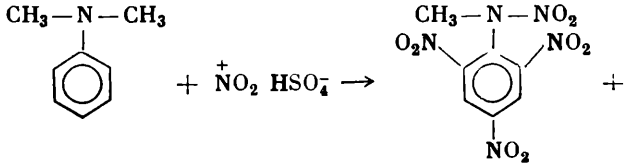


which is known as phenacetin.

Alkylanilines. When aniline sulphate is heated with methanol under pressure, one or two hydrogen atoms of the amino group are replaced by a methyl group and methyl- and dimethylaniline are formed (the predominance of either of them depends on the reaction conditions). The same purpose can be achieved by passing the vapours of aniline and methanol over a dehydrating catalyst (Al_2O_3) on heating:

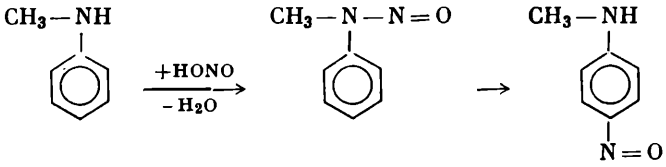


Methyl- and dimethylaniline are produced in large quantities since monoalkylanilines are used in some countries as antiknock additives to motor fuels. They are also utilized (especially, dialkylanilines) in the dyestuff industry for producing synthetic dyes (azo dyes and triphenylmethane dyes). Besides, when dimethylaniline is nitrated, apart from 2,4,6-substitution into the nucleus, there also takes place the replacement of one methyl group by a nitro group, as a result of which **tetryl** is obtained, which is a powerful high explosive:

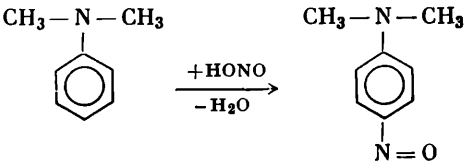


+ Oxidation products of CH_3-

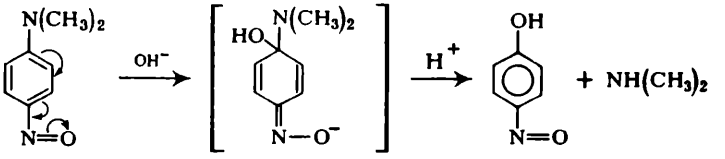
Monomethylaniline, like secondary amines in general, forms nitrosamine when reacted with nitrous acid; when heated nitrosamine rearranges to *p*-nitrosomethylaniline:



This distinguishes monomethylaniline from aniline itself, which when allowed to react with nitrous acid is diazotized (page 111). As regard dimethylaniline, under the action of nitrous acid it is nitrosated directly in the *para*-position to give *p*-nitrosodimethylaniline:



A dilute aqueous solution of nitrous acid has to be used for nitrosation. It is for this reason that the given reaction of electrophilic substitution in the aromatic nucleus can be effected only with aromatic rings that are the most sensitive towards electrophilic attack, for example, those containing such substituents as $-N(CH_3)_2$ or $-OH$. The nitroso group as a substituent (in solutions where a nitroso compound is monomeric; see page 86) is a strong electron-attracting group owing to its $-T$ effect and withdraws electrons from *ortho*- and *para*-carbon atoms. As a result, the *para*-carbon atom that bears a dimethylamino group becomes sensitive to nucleophilic attack. Therefore, nitrosodimethylaniline on boiling with alkali splits off dimethylamine and is converted into nitrosophenol:

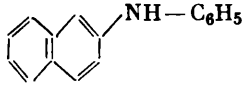


D. Secondary and Tertiary Aromatic Amines

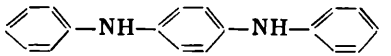
When aniline hydrochloride (known technically as *aniline salt*) is heated, a purely aromatic secondary amine—**diphenylamine**—is formed:

$$2C_6H_5NH_3^+Cl^- \longrightarrow C_6H_5NHC_6H_5 + NH_4Cl + HCl$$

Diphenylamine is an antioxidant. Many analogously built secondary aromatic amines, for example,



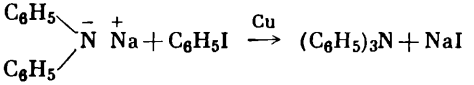
Phenyl-β-naphthylamine



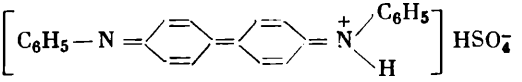
p-(N,N'-Diphenyl)-phenylenediamine

serve as a means of protecting plastic materials against oxidative degradation. Diphenylamine itself is used as a stabilizer for pyroxylin powders (binding of nitrogen oxides).

When the sodium derivative of diphenylamine is phenylated by the Ullmann reaction through the action of iodobenzene in the presence of powdered copper, a tertiary amine—**triphenylamine**—can also be obtained:



Even diphenylamine is practically devoid of basic properties, but nevertheless it is soluble in concentrated sulphuric acid (in such a solution the K_a of its conjugate acid is equal to 10^{-1}); water (being a stronger base) precipitates diphenylamine from this solution. With oxidizing agents, say, nitric acid, diphenylamine gives an intense blue coloration in sulphuric acid solution, which is a sensitive test for the NO_3^- ion. The reaction consists in the conversion of diphenylamine into a coloured *immonium salt* of the following structure:

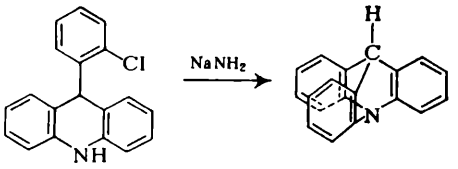


In contrast to other tertiary amines, triphenylamine is not methylated by methyl iodide and does not form quaternary ammonium salts. It is inert even to concentrated sulphuric acid. With the most powerful acid—perchloric acid—it nevertheless forms a salt (perchlorate).

In triphenylamine, the overlap of the *p*-orbitals of the free electron pair of nitrogen by the π-orbitals of all the three benzene rings and the dispersion of this pair is so complete that it does not practically manifest itself (except for the reaction with perchloric acid). Triphenylamine is in particular incapable of complex formation and, as has already been noted, does not react with methyl iodide.

The triphenylamine molecule is flat, otherwise *p*,π-conjugation would have been impossible. When the planar structure is disturbed, the basicity of nitrogen increases. Wittig succeeded in closing a spatial heterocycle—**azatryptycene**—by elimination of HCl from 9-(*o*-chlorophenyl)-9,10-dihydroacridine with the aid of $NaNH_2$ in liquid ammonia. The compound obtained is, as it were, a triphenylamine

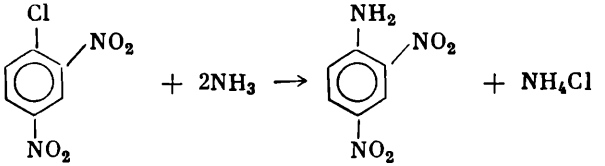
in which the HC< group binds the three *o*-carbon atoms of three phenyl groups and takes the latter out of the plane:



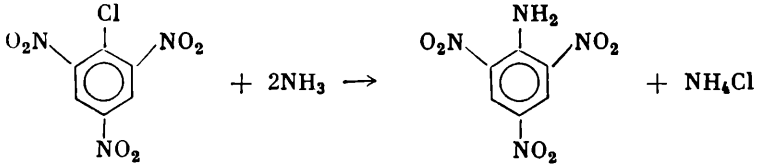
Azatryptycene is a strong base, which forms iodomethoxide with methyl iodide. In this compound, the *p*-electron orbitals of nitrogen are incapable of conjugation with the orbitals of the π-electrons of three phenyl groups because of their axes being mutually perpendicular. Thus, no delocalization of the electrons of nitrogen over the phenyl rings takes place, and one may say with certainty that the *ortho*- and *para*-directing effect of the amine nitrogen in azatryptycene is completely absent.

E. Nitroanilines

The methods of preparing all the three isomeric mononitroanilines have already been described (see page 100 *et seq.*). 2,4-Dinitroaniline can be produced both by the nitration of acetanilide and, what is simpler, by the ammonolysis of dinitrochlorobenzene:



An analogous reaction gives 2,4,6-trinitroaniline from 2,4,6-trinitrochlorobenzene:



This compound is called **picramide** because of its amide-like properties. It is the amide of picric acid, i.e., 2,4,6-trinitrophenol (page 136).

Picramide is practically devoid of basic properties.

Of the three mononitroanilines the *meta*-isomer is the strongest base, which forms a salt with aqueous hydrochloric acid; *o*- and *p*-nitro-

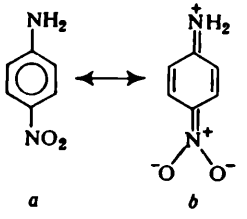
anilines are dissolved in an excess of sufficiently concentrated aqueous hydrochloric acid, but when the acid is evaporated, free bases are left. When hydrogen chloride is passed into an ethereal solution of *o*- and *p*-nitroanilines, their hydrochlorides can be precipitated, which are instantly hydrolysed by the action of water. Thus, they are very weak bases.

The conjugate acids of nitroanilines have the following values of pK_a:

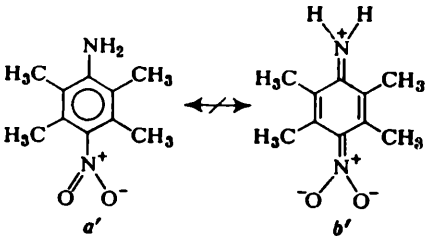
o-Nitroaniline	−0.29
m-Nitroaniline	+2.5
p-Nitroaniline	+1.02
2,4-Dinitroaniline	−4.53
2,4,6-Trinitroaniline	−9.41

In 3,5-dimethyl-4-nitroaniline, however, the neighbouring methyl groups take the nitro group out of the plane of the benzene ring, as a result of which the conjugation (resonance) of the latter with the nucleus and with the amino group is disturbed and the $-T$ effect of the nitro group is completely suppressed. As always, the $-I$ effect of the nitro group is not transferred far along the chain of atoms. Therefore, 3,5-dimethyl-4-nitroaniline as a base is considerably superior to *p*-nitroaniline and does not differ significantly from aniline.

We have already discussed the suppression of conjugation due to the withdrawal of the amino group out of the plane of the benzene ring (page 98). This suppression of conjugation can also be traced out from the difference in the dipole moments if withdrawing substituents are chosen so that the contributions to the dipole moments introduced by them give zero in total. As an example, we shall consider the derivatives of durene (2,3,5,6-tetramethylbenzene). A comparison of the dipole moments of *p*-nitroaniline and nitroaminodurene (in a benzene solution) shows that the dipole moment of the latter is 1.2 D lower than that of *p*-nitroaniline. This is also a consequence of the suppression of the conjugation of the NO_2 and NH_2 groups with the nucleus and, hence, with each other:

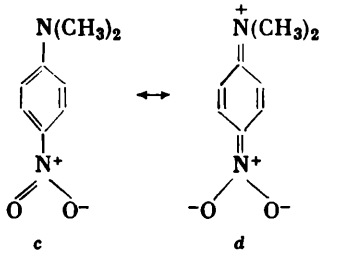


$\mu = 6.18$ D
(instead of the calculated 5.17 D for structure *a*)



$\mu = 4.98$ D

The interaction between the NO_2 and $N(CH_3)_2$ groups which are in the *para*-position to each other is even more sharply pronounced than in *p*-nitroaniline:



c *d*

The dimethylamino group is a stronger electron-releasing group than the NH_2 group. An increase in the dipole moment as compared with the additive dipole moment reaches 1.2-1.3 D.

The contribution of the structure *d* is here greater than the contribution of the analogous structure *b* in *p*-nitroaniline.

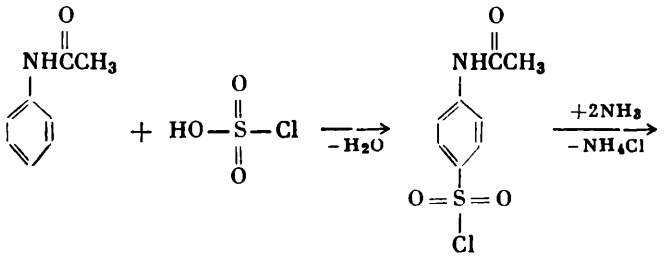
All the three mononitroanilines are widely used in the synthesis of dyes (especially, azo dyes) and for the preparation of the corresponding phenylenediamines.

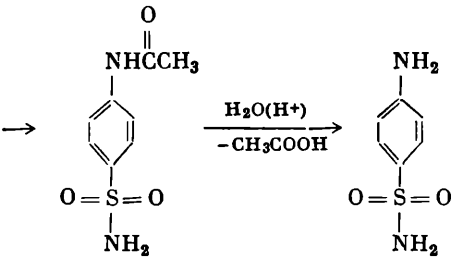
F. Anilinesulphonic Acids

The most common acids are *p*-anilinesulphonic or **sulphanilic acid** and *m*-anilinesulphonic or **metanilic acid.** Both acids find application in the synthesis of azo dyes. The preparation of sulphanilic acid by sulphonation of aniline has already been described (page 100). Metanilic acid is obtained by sulphonating nitrobenzene under drastic conditions and reducing the *m*-nitrobenzenesulphonic acid formed.

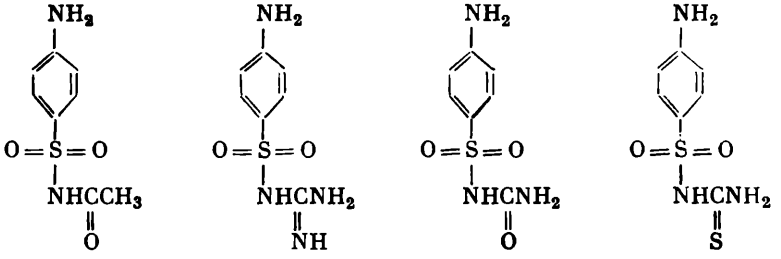
Of great importance are the amide of sulphanilic acid and some of its numerous derivatives substituted in the amino group.

Sulphanilamide itself is prepared by the following series of reactions:

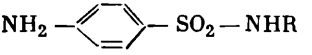




Sulphanilamide, $H_2NC_6H_4SO_2NH_2$, is a valuable bacteriostatic substance used for the treatment of streptococcal infections, in particular erysipelas. The following substituted sulphanilamides are also employed in medicine:



Use is also made of compounds of the type



where R is a heterocycle: pyridine (in sulphapyridine), pyrimidine (in sulphadimidine), thiazole (in sulphathiazole).

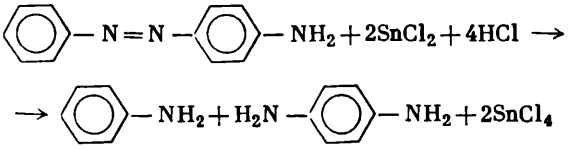
The discovery of **sulphanilamides** or **sulpha drugs** during the period 1930-1940 was an advance of the greatest significance in the chemotherapy of a number of infectious bacterial diseases. These drugs made possible the successful treatment of some dangerous and lethal diseases for which no satisfactory treatment had hitherto been evolved—croupous pneumonia, blood poisoning, streptococcal angina, etc. The importance of sulpha drugs was somewhat faded after the discovery of a number of antibiotics headed by penicillin, which are active against a wider range of bacterial diseases.

The antibacterial activity of sulpha drugs is based on a quite new principle—the use of "antimetabolite". The point is that nearly all organisms, including bacterial microorganisms, are in need of **folic acid**, which is essential to their activity. The molecule of folic acid contains *p*-aminobenzoic acid (vitamin H_1), which is the "growth

factor" of bacteria. The amide of sulphanilic acid is closely related to *p*-aminobenzoic acid in the physical and geometrical parameters of the molecule and is therefore consumed by bacteria instead of this acid and does not give rise to substances possessing fermentative activity. Bacteria cease to reproduce and are rapidly suppressed by the host organism. Thus, in the case of sulpha drugs we are dealing with something fundamentally different from the toxic action which kills the bacteria. Sulpha drugs are not directly toxic to bacteria. Their action is based on the replacement of the natural metabolite (the product of metabolism). The action of sulpha drugs reveals their activity when present in sufficient concentrations which far exceed the concentration of natural *p*-aminobenzoic acid and can be removed by the addition of the latter.

G. Aromatic Diamines

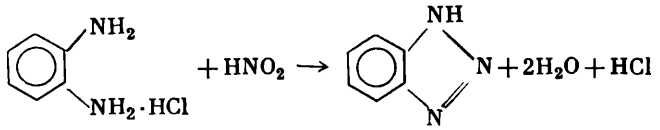
The methods of synthesis of three diamines, *o*-, *m*-, and *p*-phenylenediamines, from *m*-dinitrobenzene and *o*- and *p*-nitroanilines have already been considered (page 95). *p*-Phenylenediamine can also be easily obtained from aminoazobenzene (page 118) by its reduction with $SnCl_2$ or $TiCl_3$ in aqueous solution:



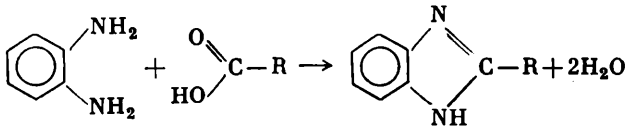
p-Phenylenediamine

Phenylenediamines are solid compounds which are rapidly oxidized and become dark in air and are well soluble in water.

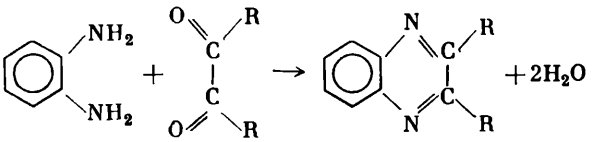
o-Phenylenediamine is noted for its ability to form heterocycles easily. For example, upon diazotization it gives an inner diazoamino compound—**azimidobenzene** (benzotriazole):



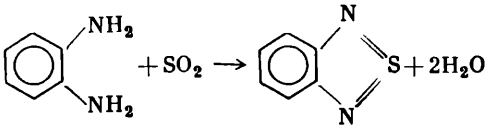
When heated with carboxylic acids *o*-phenylenediamine yields heterocyclic amidines called **benzimidazoles**:



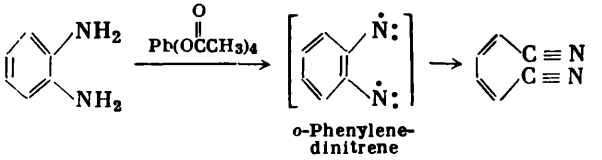
The reaction with α-dicarbonyl compounds gives **quinoxalines**:



and the interaction with SO_2 results in the formation of **piazothiole**:

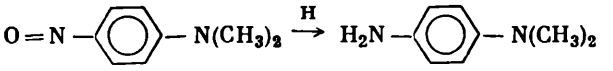


An interesting degradation of *o*-phenylenediamine, which proceeds via *o*-phenylenedinitrene, has been discovered by Nakagawa and Onoue. By oxidizing *o*-phenylenediamine with lead tetraacetate they obtained the dinitrile of muconic acid (with a yield of 50 per cent):

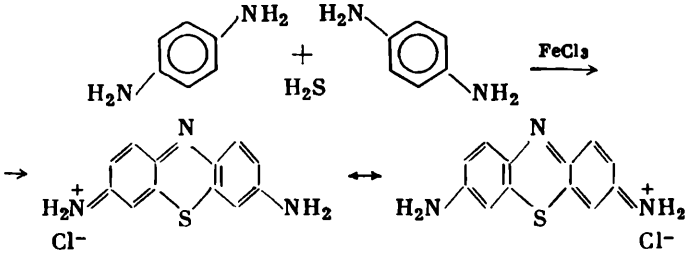


m-Phenylenediamine serves as the first and the second component in the synthesis of azo dyes (page 121). Along with *p*-aminodimethylaniline, it is used in the synthesis of thiazine dyes.

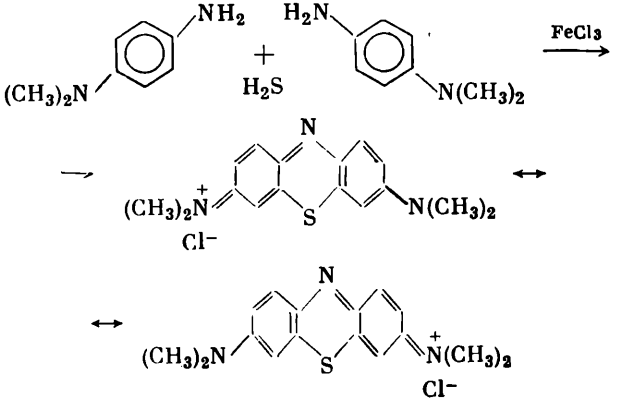
p-Aminodimethylaniline is prepared by reducing nitrosodimethylaniline:



The oxidation of *p*-phenylenediamine with ferric chloride in the presence of hydrogen sulphide gives a dye, Lauth's violet (thionine):



The synthesis of methylene blue proceeds in an analogous way (Caro):



7.8. Diazo Compounds

The salts of aromatic amines (in the presence of an excess of a strong acid) in aqueous solution are *diazotized* by nitrous acid and are converted into aryl diazonium salts:

$$C_6H_5-\overset{+}{N}\begin{matrix}H\\-H\\H\end{matrix}\ Cl^- + HO-N=O \longrightarrow C_6H_5\overset{+}{N}\equiv N\ Cl^- + 2H_2O$$

This reaction was discovered in 1858 by Griess.

The kinetic studies carried out by Ingold show that the reaction in fact proceeds in a different way (not according to the above equation):

$$H-O-N=O + H^+ \longrightarrow H_2\overset{+}{O}-N=O$$

$$C_6H_5-NH_2 + H_2\overset{+}{O}-N=O \longrightarrow C_6H_5-NH-N=O + H_3\overset{+}{O}$$

$$C_6H_5-N=N-OH$$

$$\downarrow\ HCl$$

$$C_6H_5-\overset{+}{N}\equiv N\ Cl^- + H_2O$$

This interpretation of the process follows from the fact that diazotization is a third-order reaction, the rate constant of which is proportional to the product of the concentrations of a free amine, nitrous

acid and hydrogen ion (and not of nitrous acid and a salt of an amine). This also accounts for the fact that amines having weaker basic properties are diazotized at a faster rate (a higher concentration of the amine due to hydrolysis). Aromatic amines containing *meta*-directing substituents in the nucleus (especially in the *ortho*- and *para*-positions) are diazotized more rapidly than unsubstituted ones and give more stable diazonium salts. The converse is also true. In the case of very weakly basic amines, like 2,4,6-trinitroaniline, diazotization has to be carried out in concentrated sulphuric acid.

Aryl diazonium salts with simple anions are unstable and they are not isolated from aqueous solution and are immediately subjected to further transformations. It is possible, however, to precipitate complex (double) salts from aqueous solution (by addition of the corresponding salt or acid). Examples of such salts are the following:

$$C_6H_5-\overset{+}{N}\equiv N\ HgCl_3^- \qquad (C_6H_5-\overset{+}{N}\equiv N)_2\ SnCl_6^{2-}$$

$$C_6H_5-\overset{+}{N}\equiv N\ BF_4^- \qquad (C_6H_5-\overset{+}{N}\equiv N)_2\ SiF_6^{2-}$$

$$C_6H_5-\overset{+}{N}\equiv N\ SbCl_4^- \qquad C_6H_5-\overset{+}{N}\equiv N\ SbCl_6^-$$

$$C_6H_5-\overset{+}{N}\equiv N\ ZnCl_3^- \qquad C_6H_5-\overset{+}{N}\equiv N\ FeCl_4^-$$

For aryl diazonium chloride to be prepared in the solid state, the hydrochloride of the amine is dissolved in alcohol and diazotized by an ester of nitrous acid; the aryl diazonium chloride formed is precipitated by the ether.

Apart from the principal route of synthesis of diazonium salts—the diazotization of amines, diazonium salts can also be prepared by the Bamberger method in two ways: nitroso compounds are reacted either with hydroxylamine (the formation of diazo hydroxide or "diazohydrate"; for more detail, see page 114) or with NO:

$$C_6H_5-N=O+H_2NOH \longrightarrow C_6H_5-N=NOH+H_2O$$

$$C_6H_5-N=O+2NO \longrightarrow C_6H_5-\overset{+}{N}\equiv N\ NO_3^-$$

and since the oxides of nitrogen (N_2O_4 and N_2O_3) nitrosate many of the organometallic compounds, diazonium salts can be produced by the action of this mixture of nitrogen oxides on the following organometallic compounds (A. N. Nesmeyanov and L. G. Makarova):

$$(C_6H_5)_2Hg \qquad (C_6H_5)_2Cd \qquad (C_6H_5)_4Sn \qquad (C_6H_5)_3Bi$$

A new route for synthesis of aromatic diazonium salts has recently been described in the literature by Bott. It is accomplished by the reaction of arylsulphinylimides (a class of compounds that has not yet been considered in this book) with nitrosyl perchlorate (enclo-

ved in square brackets is the hypothetical intermediate of the reaction):

$$Ar-N=S=O+NO^+\ ClO_4^- \longrightarrow \left[\begin{array}{c} N=O \\ | \\ Ar-\overset{+}{N}=S=O \end{array}\ ClO_4^-\right] \longrightarrow$$

$$\longrightarrow Ar\overset{+}{N} \equiv N\ ClO_4^- + SO_2$$

Aryl diazonium salts are ionic compounds and their aqueous solutions are electrolytes. They dissolve well in water, worse in alcohol and are insoluble in ether and hydrocarbons. Phenyldiazonium chlorides, sulphates and nitrates explode on heating and are highly unstable (at room temperature they may be stored usually for not more than 24 hours). The salts with complex anions are less soluble and more stable. The most stable salts are those of the $Ar\overset{+}{N}_2\ BF_4^-$ type, which can be stored for months.

The structure of diazonium salts that are similar in many respects to ammonium salts was established in 1869 by Bloomstrand. Diazonium salts may be regarded as the onium compounds of the *nitrogen molecule* if they are compared with ammonium, oxonium, sulphonium and other compounds which are the onium derivatives of the *atoms* N, O, S (cf. Volume I, page 30). The reactions of diazonium salts with anions of weak acids, however, proceed differently than those of other onium salts. Ordinary onium salts can arylate (or alkylate, accordingly) the anion only by an electrophilic mechanism, the onium cation being transferred to it without a pair of bonding electrons:

$$Ar_3\overset{+}{O} + OH^- \longrightarrow ArOH + Ar-O-Ar$$

In this reaction, with anions of weak acids (CN^-, SO_3H^-, OH^-) the diazonium cations form covalently built diazo compounds:

$$Ar-\overset{+}{N} \equiv N: + OH^- \longrightarrow Ar-\ddot{N}=\ddot{N}-OH$$

$$Ar-\overset{+}{N} \equiv N: + CN^- \longrightarrow Ar-\ddot{N}=\ddot{N}-C \equiv N$$

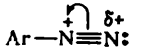
$$Ar-\overset{+}{N} \equiv N: + {}^-SO_3H \longrightarrow Ar-\ddot{N}=\ddot{N}-SO_3H$$

or in terms of electronic interpretation:

$$Ar-\overset{+}{N}\equiv N: + :\ddot{\underset{\cdot\cdot}{O}}: H \longrightarrow Ar-\ddot{N}=\ddot{N}:\ddot{\underset{\cdot\cdot}{O}}:H$$

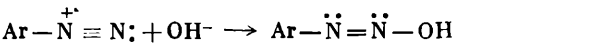
The difference is due to the participation of a second nitrogen atom which assumes a $\delta+$ charge as a result of the partial withdrawal

of a pair of bonding electrons from it and thus becomes susceptible



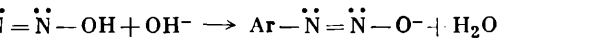
to nucleophilic attack.

The interaction of aryl diazonium cations with the hydroxyl anion has been studied most thoroughly. The first rather slow reaction is the formation of diazohydroxide described earlier



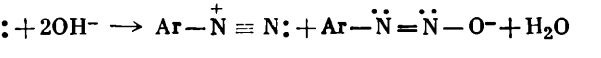
(1)

which reacts rapidly with alkali as an acid, forming the diazotate anion:



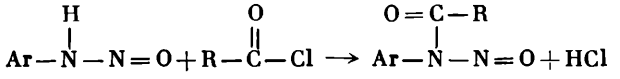
(2)

When equivalent amounts of a diazonium salt and alkali are mixed, only half of the diazonium salt is converted into diazohydroxide and then (rapidly) into the diazotate anion and half of it is left in the form of the diazonium cation due to the rapid occurrence of reaction (2):

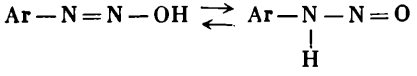


According to the old observations of Hantzsch, the diazotate (of sodium or potassium) formed by the action of excess alkali, is at first active in the azo coupling reaction with phenols and tertiary amines (page 119) and is then spontaneously converted into the isomeric inactive form. The first is called **normal diazotate** (with normal diazohydroxide corresponding to it), and the second is known as the **isodiazotate** (to which there corresponds isodiazohydroxide).

Bamberger, who was one of the scientists of the last century who studied diazo compounds most thoroughly, assigned the structure of primary nitrosamine to isodiazohydroxide on the basis of its acylation reaction:



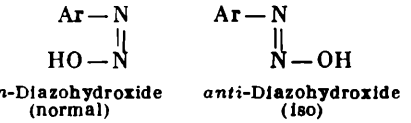
Another investigator, Hantzsch, believed that isodiazohydroxide and primary nitrosamine are tautomers, this viewpoint being generally accepted at present:



As pointed out above, the formation of isodiazohydroxide by the reaction

$$Ar-\overset{+}{N}\equiv N: + OH^- \longrightarrow Ar-\ddot{N}=\ddot{N}-OH$$

proceeds slowly. Adding alkali to a diazonium salt in the cold, Hantzsch succeeded in precipitating a substance which, unlike isodiazohydroxide, reacted with phenols, forming azo dyes (page 121) and giving a different absorption spectrum. This seemingly more reactive compound was named **normal diazohydroxide** by Hantzsch. He thought that the normal diazohydroxide isolated by him and isodiazohydroxide were related to each other as geometrical *syn*- and *anti*-isomers:



syn-Diazohydroxide (normal) — *anti*-Diazohydroxide (iso)

this kind of isomerism being similar to the stereoisomerism of oximes studied by him (Volume I, page 179):

syn-Oxime — *anti*-Oxime

Bamberger considered the stereoisomerism of diazohydroxides unproved and assigned structural isomerism to them:

Normal diazohydroxide (according to Bamberger) — Isodiazohydroxide (according to Bamberger)

Müller, who was the first to obtain unstable primary nitrosamines by the action of nitrosyl chloride on primary aromatic amines at 70°C, converted these nitrosamines into solid potassium diazotates by adding potassium ethoxide:

$$ArNH_2 + ClN=O \longrightarrow Ar-NH-N=O + HCl$$
$$Ar-NH-N=O + C_2H_5OK \longrightarrow ArN=NOK$$

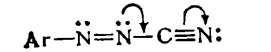
He established that such diazotates reacted differently in azo coupling reactions for different Ar, namely, that $NO_2C_6H_4-N=NOH$ (I) reacted less readily than $C_6H_5N=NOH$ (II). He therefore considered that diazotate (I) was the "normal" Hantzsch diazotate, and diazotate (II) was isodiazotate. But no direct evidence has been obtained for the existence of two stereoisomeric forms of the same diazohydroxide or diazotate of a metal.

Thus, a conclusion has to be made that the stereoisomerism of aryl diazo compounds for diazohydroxides and their salts has not been established with certainty and that at present there is no ground for assigning a configuration to the only known form of diazohydroxides or diazotates.

Hantzsch assigned stereoisomerism to diazo compounds linked not only to OH^- but also to other anions of weak acids, say, to CN^-. These aryl diazo cyanides have been studied by many investigators. Probably, no stereoisomerism exists in this case; two series of diazo cyanides are structurally isomeric to one another. This has been established by O. A. Reutov and L. A. Kazitsyna by means of IR spectroscopic studies of the two series of isomeric aryl diazo cyanides. When solutions of an aryl diazonium salt and potassium cyanide were mixed in the cold (—15°C), "labile" aryl diazo cyanides separated out, which showed IR-spectrum frequencies close to the frequencies of isonitriles (ca. 2150 cm^{-1}). On storage these "labile" diazo cyanides changed to higher-melting "stable" products with frequencies close to the frequencies of the C≡N bond (40 cm^{-1} higher than those of the "labile" products). On this basis, O. A. Reutov and L. A. Kazitsyna arrived at the conclusion that the "labile cyanides" are isocyanides and that the following isomeric structures may be assigned to the two series of compounds:

Stable cyanides — Labile cyanides (isocyanides)

The frequency of the IR spectra of the C≡N bond in nitriles is usually higher than in isonitriles. True, the difference in the frequencies is greater than that found experimentally (40 cm^{-1}) and is equal to about 100 cm^{-1}, and the frequency of stable aryl diazo cyanides is somewhat lower than the ordinary frequency in nitriles, but this can be accounted for by conjugation which decreases the "multiplicity" of the C≡N bond.



The uncertainties about the structure of diazo compounds, that have been existing for over a century, were due to the low stability of these compounds, which forced chemists to work with solutions of the compounds at an unestablished equilibrium, and to the impossibility of normal isolation of the solid products because of their rapid decomposition. Only diazonium salts, whose structures have been firmly established, and the cyanides just mentioned are more stable in the solid state.

Aromatic diazo compounds are widely used in laboratory and industrial syntheses in which advantage is taken of their high reactivity.

Two types of chemical transformations of aryl diazonium salts and aryl diazo compounds are distinguished: reactions with loss of nitrogen and those with retention of nitrogen.

A. Reactions of Diazo Compounds Without Loss of Nitrogen

1. When diazo compounds are reduced by salts of sulphurous acids (sulphites), the initially formed aryl diazo sulphonate is reduced to aryl hydrazine sulphonate, which undergoes hydrolysis in acid solution to give the salt of phenylhydrazine:

$$C_6H_5-\overset{+}{N}\equiv N + {}^{-}SO_3Na \longrightarrow C_6H_5-N=N-\overset{O}{\overset{\|}{\underset{O}{\underset{\|}{S}}}}-ONa \xrightarrow[-H_2SO_4]{H_2SO_3;\ H_2O}$$

$$\longrightarrow C_6H_5-NH-NH-\overset{O}{\overset{\|}{\underset{O}{\underset{\|}{S}}}}-ONa \xrightarrow{H_2SO_4;\ H_2O}$$

$$\longrightarrow C_6H_5-NH-\overset{+}{N}H_3\ {}^{-}SO_4H + NaHSO_4$$

Phenylhydrazine is produced on the industrial scale by this process.

2. The action of bromine on a solution of an aryl diazonium salt precipitates the perbromide which gives **phenylazide** with ammonia:

$$C_6H_5-\overset{+}{N}\equiv N\ Br^- + Br_2 \longrightarrow C_6H_5-\overset{+}{N}\equiv N\ Br_3^- \xrightarrow{+4NH_3}$$

$$\longrightarrow C_6H_5-N=\overset{+}{N}=\overset{-}{N} + 3NH_4Br$$

3. The interaction between aryl diazonium salts and primary aromatic amines gives **diazoamino compounds** which are called **triazenes**:

$$Ar-\overset{+}{N}\equiv N + H_2N-Ar' \longrightarrow Ar-N=N-NH-Ar' + H^+$$

Triazenes show **three-nitrogen tautomerism**:

$$Ar-N=N-NH-Ar' \rightleftarrows Ar-NH-N=N-Ar'$$

The equilibrium is shifted to the side of the compound in which the proton is linked to the more basic nitrogen.

Diazoamino compounds are also formed by the action of an aryl magnesium halide on aryl azides:

$$Ar-N=\overset{+}{N}=\overset{-}{N}+Ar'MgBr \longrightarrow Ar-N=N-\underset{\underset{MgBr}{|}}{N}-Ar' \xrightarrow[-MgBrOH]{H_2O} \longrightarrow Ar-N=N-NH-Ar'$$

This reaction can also be used to prepare aliphatic triazenes.

When acted on by strong acids, diazoamino compounds split into a diazonium salt and a primary amine:

$$Ar-N=N-NH-Ar'+HCl \longrightarrow Ar-\overset{+}{N}\equiv N\ Cl^- + Ar'-NH_2$$

Because of tautomerism the acidolysis actually proceeds in both possible directions, $ArNH_2$ and $Ar'\overset{+}{N}\equiv N\ Cl^-$ being also formed in the reaction.

This reaction enables the preparation of diazonium salts in those cases when diazotization is impossible or an amine is not available. For example, one of the authors of this book, V. A. Sazonova and V. N. Drozd have obtained the diazo compounds of ferrocene (this compound will be discussed in Volume IV) which is susceptible to nitrous acid. The reaction proceeds according to the following scheme (Fc = ferrocene):

$$FcBr+NaN_3 \xrightarrow{Cu^{2+}} Fc-N=\overset{+}{N}=\overset{-}{N} \xrightarrow{C_6H_5MgBr} \longrightarrow Fc-N=N-\underset{\underset{MgBr}{|}}{N}-C_6H_5 \xrightarrow{H_2O} \longrightarrow Fc-N=N-NH-C_6H_5 \xrightarrow{2HCl} Fc-\overset{+}{N}\equiv N\ Cl^- + C_6H_5\overset{+}{N}H_3\ Cl^-$$

Diazoamino compounds when heated with the salt of an amine undergo a rearrangement to aminoazo compounds (known as the **diazoamino rearrangement**). For instance, diazoaminobenzene on heating with a solution of aniline hydrochloride is converted into *p*-aminoazobenzene:

$$C_6H_5-N=N-NH-C_6H_5 \xrightarrow{C_6H_5\overset{+}{N}H_3\ Cl^-} C_6H_5-N=N-C_6H_4-NH_2$$

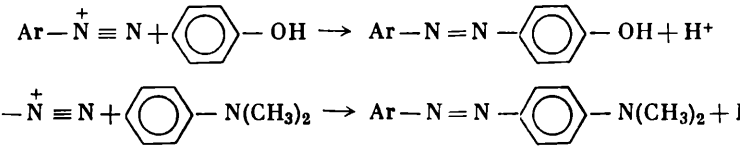
In contrast to benzidine and other intramolecular rearrangements, the transformation of diazoaminobenzene into aminoazobenzene is an **intermolecular rearrangement**. It involves the acidolysis of a diazoamino compound to its diazonium salt and an amine, which enter into an azo coupling reaction (see below):

$$C_6H_5-N=N-NHC_6H_5+C_6H_5\overset{+}{N}H_3\ Cl^- \longrightarrow C_6H_5-\overset{+}{N}\equiv N\ Cl^- + 2C_6H_5NH_2$$

$$C_6H_5NH_2+C_6H_5-\overset{+}{N}\equiv N\ Cl^- \longrightarrow C_6H_5-N=N-C_6H_4NH_2\text{-}p$$

p-Aminoazobenzene which contains an azo group as one of its functional groups is the simplest representative of azo dyes. It is a weak base: the pK_a value of its conjugate acid is 2.82, and the pK_a of aniline is 4.6. Thus, the introduction of an azo group into the *para*-position of aniline decreases the base strength by two orders of magnitude.

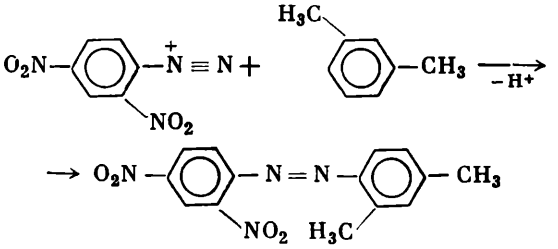
4. When aryl diazonium salts are reacted with aromatic compounds containing very powerful *ortho-para* directing groups (NH_2, NHR, NR_2, OH) an **azo coupling reaction** takes place and a hydroxyazo or aminoazo compound is formed:



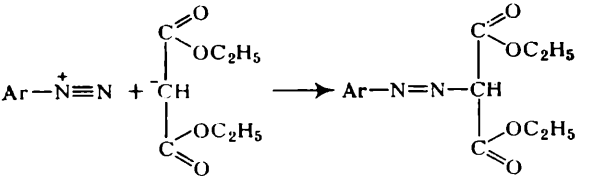
Azo coupling is a new example of electrophilic substitution in the benzene ring (of a phenol or amine). Substitution occurs predominantly in the *para*-position, or in the *ortho*-position if the *para*-position is occupied. This preference of the *para*-position is usually accounted for by the fact that the reaction product (and the transition state too) has a longer conjugation chain of π-bonds than in the case of substitution in the *ortho*-position. In this reaction, the free energy level in the transition state is lower and, as a consequence, the rate of the reaction is higher.

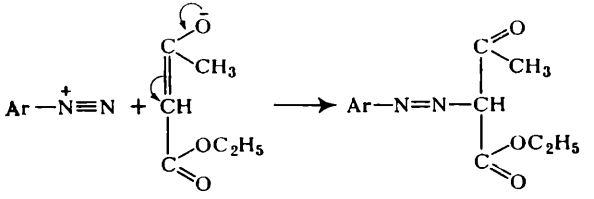
The azo coupling reaction is widely employed in the dyestuff industry for preparing hundreds of grades of azo dyes, which provide a considerably wider range of shades and colours than all types of synthetic dyes.

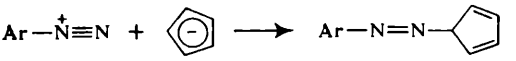
Diazo compounds that enter into azo coupling reactions are called the first or **diazo component**, and the aromatic phenol or amine is termed the second or **azo component**. The stronger are the *m*-directing groups that are in the *ortho*- or *para*-positions in the diazo component, the more rapid and vigorous is the azo coupling. The diazotized 2,4-dinitroaniline and 2,4,6-trinitrophenyldiazonium salt (from picramide) enter into azo coupling reactions with polymethylbenzenes, say, with *m*-xylene:



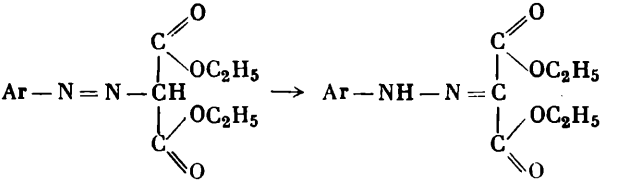
The azo coupling reaction is also accomplished with aliphatic azo components if they contain a mobile methylene hydrogen, like malonic ester, acetoacetic ester and cyclopentadiene (the reaction basically takes place between the aryl diazonium cation and the anion of an aliphatic compound, i.e., an alkaline medium is required for expulsion of a proton from the methylene group):

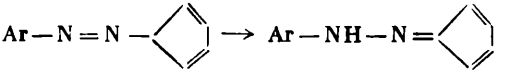






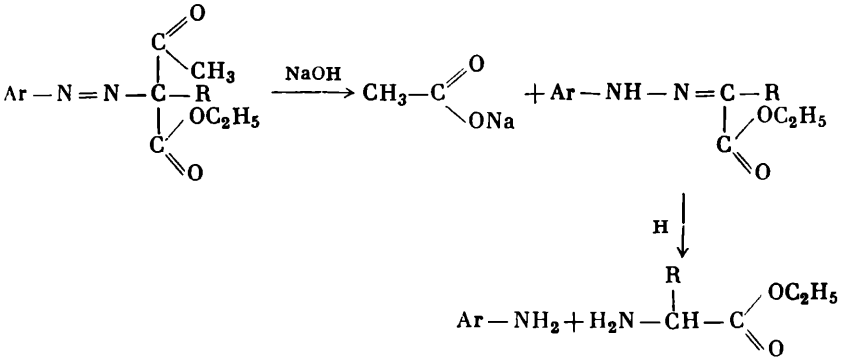
Azo coupling with compounds containing an active methylene group is complicated by the subsequent migration of the second hydrogen of this group to the nitrogen adjacent to the aromatic radical and also by the transformation of the azo compound into an arylhydrazone. In the case of malonic ester the arylhydrazone of the ester of mesoxalic acid is formed, and with cyclopentadiene, the arylhydrazone of cyclopentadienone results:





In the case of acetoacetic ester, an acid cleavage takes place in alkaline medium (see Volume II, page 78). The azo derivative of acetoacetic ester (replaced by R in this case) undergoes acid cleavage in alkaline solution and is converted into the arylhydrazone of the

ester of an α-keto acid, which can be reduced to the ester of an α-amino acid (the method has been worked out by V. V. Feofilaktov):



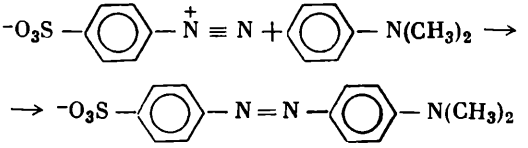
As regards the azo coupling reaction with aromatic azo components, only phenols and amines are used for this purpose. Phenols undergo coupling in an alkaline solution, while amines are coupled in a weakly acid solution. The activity of *ortho-para* directors in these azo components decrease, as is always the case, in the following sequence:

$$\bar{O}-Ar > H_2N-Ar > HO-Ar > \overset{+}{H_3N}-Ar$$

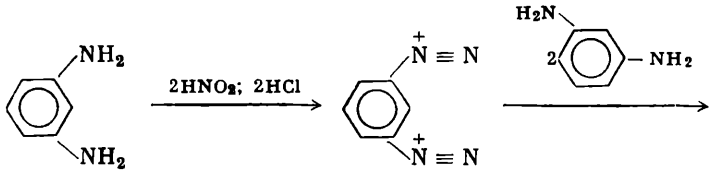
In the last case, the NH_2 group too acts as a directing group, though in a low concentration since it is formed as a result of the hydrolysis of a salt:

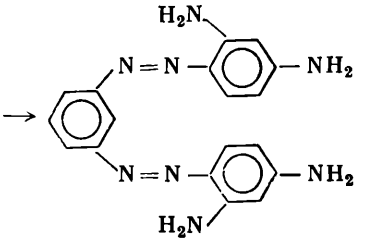
$$\overset{+}{H_3N}-Ar + H_2O \longrightarrow H_2N-Ar + \overset{+}{H_3O}$$

The azo dyes used in practice usually contain two or more azo groups. There are various methods for introducing several azo groups and preparing bis-, tris- and tetrakis-azo dyes. We shall consider only a few examples of synthesis of known azo dyes, which will give an idea of the introduction of several azo groups:

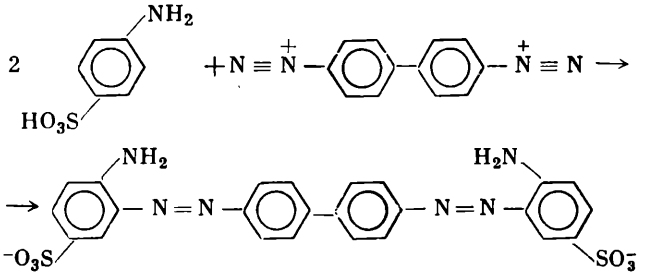


Methyl orange



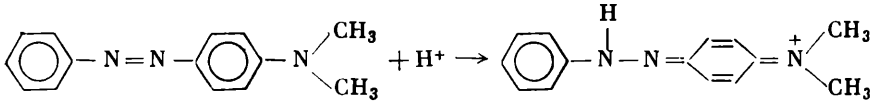


One of azo compounds of vesuvin



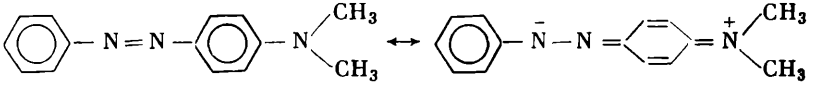
The simplest dye of the Congo type

In acid solution, azo dyes add on a proton at the azo group, which is accompanied by the rebuilding of the bonds in the benzene ring bearing the amino (or hydroxy) group, and by a change of colour (indicator properties):



The resulting salt of the azo dye has a **quinonoid** (page 183) rather than a benzenoid structure. The proton has added on not to the dimethylamino group but to the nitrogen of the azo group, as the result of the reaction with transfer of the reaction centre, but the nitrogen of the dimethylamino group has nevertheless become the ammonium nitrogen.

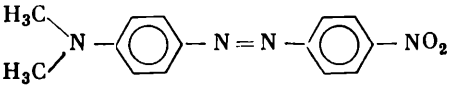
The coloration of azo dyes is due to the mesomerism of their structure, which is expressed by the following two extreme resonating structures for the above example:



The contribution of the first structure is greater, as seen from the direction of proton attack, the contribution of the second structure being also significant.

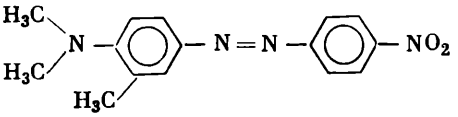
Associated with the presence of conjugation is the approach of the ground energy level of an azo dye to its excited level. Therefore it absorbs in the longer wavelength region of the spectrum than does not only benzene but also azobenzene. This **bathochromic shift**, i.e., the shift of the absorption band to the longer wavelength region of the spectrum as compared with azobenzene, is due to the presence in the *para-* (or, what is also possible, in the *ortho-*) position of an *ortho-para* director capable of bearing a positive or negative charge (positive in this particular case). Such a substituent is called an **auxochrome**. The auxochromes may act in two ways. On the one hand, they may, by their presence, impart basic properties (a negative charge in this case) to the remote nitrogen atom; and on the other, their introduction may result in a bathochromic shift of absorption only in the presence of a conjugated system, which is feasible if the arrangement of the molecule is planar. Only on this condition (and also depending on the extent of planarity) are conjugation (mesomerism) and its effects revealed.

Thus, according to A. I. Kiprianov and coworkers, in going from dye *A*



A

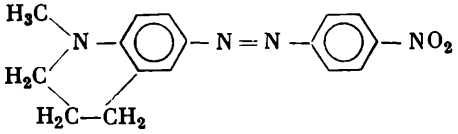
to dye *B*



B

there is observed a **hypsochromic shift** (the shifting of the absorption band to shorter wavelengths) due to the fact that the *o*-methyl substituent makes the dimethylamino group twist out and thereby (partly) be removed from the conjugation chain (see page 98).

If, however, the dialkylamino group is closed into a ring, which will hold it firmly in an almost planar position



C

then, on the contrary, the shift of the absorption band will be bathochromic as compared with *A*.

What has been said above refers to all dyes.

B. Reactions of Diazo Compounds with Loss of Nitrogen

Diazonium salts and diazo compounds* are unstable and can decompose either *heterolytically*

$$C_6H_5-\overset{+}{N}\equiv N \longrightarrow \overset{+}{C_6H_5}+N_2$$

or *homolytically*

$$C_6H_5-\overset{+}{N}\equiv N\ Cl^- \longrightarrow C_6H_5-N=N-Cl \longrightarrow C_6H_5\cdot + N_2 + Cl\cdot$$

The direction of the decomposition depends on the anion of the diazonium salt and the solvent used. The homolytic decomposition (*homolysis*) is largely assisted by anions of weak acids, but in non-aqueous solutions even the chlorides decompose in this way. Solvents of high dielectric constant favour heterolytic decomposition. The aryl diazonium borofluorides decompose only by a heterolytic mechanism. The mechanism of decomposition has not been elucidated for all types of substitution reactions of the diazonium group. From the examples given below it follows that, probably, the mechanism is heterolytic in reactions 1, 2, 6, 11a, and 12, and homolytic in reactions 3, 5, 7, 8, 9, 10, 11, and 13.

Diazo compounds are extensively used (especially in the laboratory) for syntheses involving the replacement of the diazonium group by various atoms and groups. In such displacement reactions, the diazo group is removed as N_2 as the result of this or that type of decomposition. The following types of reactions may serve as typical examples.

1. The replacement of the diazonium group by a hydroxyl group on heating an aqueous solution of a diazonium salt:

$$Ar-\overset{+}{N}\equiv N+H_2O \longrightarrow ArOH+N_2+H^+$$

2. The replacement of the diazonium group by an alkoxyl group by heating a diazo compound with alcohols:

$$Ar-\overset{+}{N}\equiv N+ROH \longrightarrow ArOR+N_2+H^+$$

The reaction is of limited use since it is accompanied by the replacement of the diazonium group by hydrogen according to reaction 3, especially for diazonium salts with *meta*-directing groups in the nucleus. The reaction proceeds smoothly for non-oxidized alcohols.

3. The replacement of the diazonium group by hydrogen is effected by many reducing agents and, in particular, by primary alcohols

* The name *diazo compounds* will be used here as a generic term for diazonium salts and diazo compounds proper.

(in which case the competing reaction is reaction 2):

$$\overset{+}{\mathrm{ArN}} \equiv \mathrm{N} + \mathrm{CH_3{-}CH_2OH} \longrightarrow \mathrm{ArH} + \mathrm{N_2} + \mathrm{CH_3{-}C}\begin{matrix}\overset{\overset{\mathrm{O}}{\|}}{}\\ \underset{\mathrm{H}}{}\end{matrix} + \mathrm{H^+}$$

The best way therefore is to eliminate (i.e., to replace by hydrogen) the diazonium group through the agency of H_3PO_2, formic acid, or sodium stannite:

$$\overset{+}{\mathrm{ArN}} \equiv \mathrm{N} + \mathrm{Sn(ONa)_2} + \mathrm{H_2O} \longrightarrow \mathrm{ArH} + \mathrm{N_2} + 2\mathrm{Na^+} + \mathrm{HSnO_3^-}$$

Besides, the homolytic decomposition of diazo compounds in a medium of compounds containing a saturated aliphatic hydrogen (even in alkanes, ketones, acids) leads to the capture of a hydrogen atom by the radical Ar and to formation of ArH.

4. The replacement of the diazonium group by iodine through the direct action of potassium iodide on an aqueous solution of a diazonium salt. There is evidence that the first act of the reaction is the transfer of one electron of the iodide ion to the diazonium cation, as a result of which the diazo radical formed undergoes homolytic decomposition:

$$\overset{+}{\mathrm{ArN}} \equiv \mathrm{N} + \mathrm{I^-} \longrightarrow \mathrm{Ar{-}N{=}N\cdot} + \mathrm{I\cdot} \longrightarrow \mathrm{ArI} + \mathrm{N_2}$$

5. The replacement of the diazonium group by chloride, bromide, and cyano and thiocyano groups, which is accomplished by the Sandmeyer reaction. Cuprous salts and salts of these anions decompose diazonium salts, the place of the diazonium group being taken by the anion (X=Cl, Br, CN or SCN):

$$2\overset{+}{\mathrm{ArN}} \equiv \mathrm{N\ SO_4H^-} + 2\mathrm{CuX} \longrightarrow 2\mathrm{ArX} + 2\mathrm{N_2} + \mathrm{Cu_2SO_4} + \mathrm{H_2SO_4}$$

One has to use a diazonium sulphate as a starting material or to take measures so that the halide anion in the diazonium salt coincides with the anion of the cuprous salt.

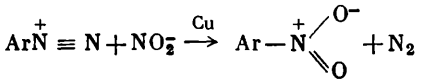
6. The replacement of the diazonium group by fluorine by decomposition on heating the dry complex diazonium borofluoride (Balz-Schiemann diazotization):

$$\overset{+}{\mathrm{ArN}} \equiv \mathrm{N\ BF_4^-} \longrightarrow \mathrm{ArF} + \mathrm{N_2} + \mathrm{BF_3}$$

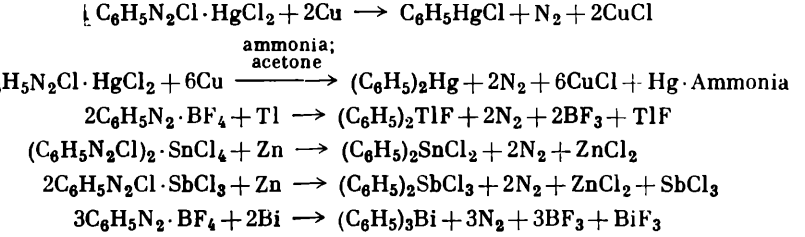
7. The replacement of the diazonium group by the sulphinic acid residue with the aid of SO_2 in the presence of a catalyst (copper powder). This is the Gattermann reaction:

$$\overset{+}{\mathrm{ArN}} \equiv \mathrm{N} + \mathrm{SO_2} \xrightarrow{\mathrm{Cu}} \mathrm{Ar{-}S}\begin{matrix}\overset{\overset{\mathrm{O}}{\|}}{}\\ \underset{\mathrm{O^-}}{}\end{matrix} + \mathrm{N_2}$$

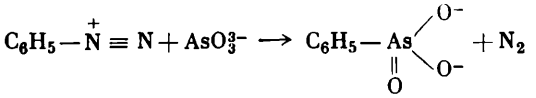
8. The replacement of the diazonium group by a nitro group through the action of sodium nitrite in the presence of powdered copper (Gattermann reaction):



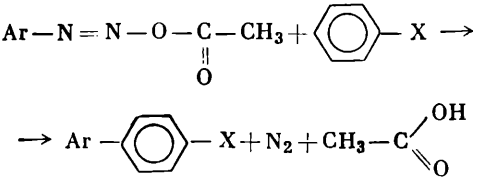
9. The replacement of the diazonium group by metals (A. N. Nesmeyanov, E. I. Kan, K. A. Kocheshkov, O. A. Reutov, L. G. Makarova) by reducing double diazonium salts with a metal halide or a diazonium salt with the anion of BF_4 by a metal:



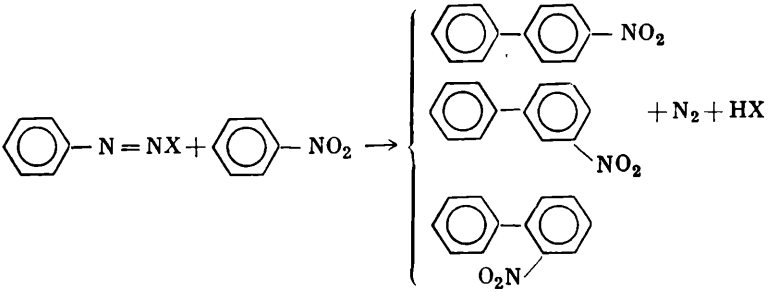
10. The replacement of the diazonium group by the arsenic acid residue (Bart reaction):



11. The Gomberg reaction. When diazonium salts react (in the presence of sodium acetate) with aromatic compounds incapable of azo coupling, the aromatic radical of the diazo compound becomes attached through a carbon-carbon bond to the aromatic nucleus of the second reagent, replacing the hydrogen in it. In this way the derivatives of diphenyl are formed (see page 234):



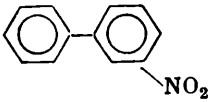
and *meta*-substituted diphenyls are also formed:



11a. If the decomposition of phenyldiazonium borofluoride takes place in nitrobenzene, the intermediate product of the reaction is not the free aryl radical but the aryl cation, and the attack of nitrobenzene is electrophilic:

$$C_6H_5-\overset{+}{N}\equiv N\ BF_4^- \longrightarrow C_6H_5^+ + N_2 + BF_4^-$$

The predominating product of substitution in the nitrobenzene ring is *m*-nitrodiphenyl (A. N. Nesmeyanov and L. G. Makarova):



12. When phenyldiazonium borofluoride decomposes in chloro-, bromo-, or iodobenzene and in diphenyl ether, apart from the Gomberg reaction, there occurs the addition of the phenyl cation formed across the free electron pair of the halogen or oxygen and the salts (borofluorides) of onium cations—diphenylchloronium, diphenylbromonium, diphenyliodonium and triphenyloxonium—are formed (A. N. Nesmeyanov, T. P. Tolstaya):

$$C_6H_5-\overset{+}{N}\equiv N\ BF_4^- + C_6H_5Cl \longrightarrow C_6H_5-\overset{+}{Cl}-C_6H_5\ BF_4^- + N_2$$

$$C_6H_5-\overset{+}{N}\equiv N\ BF_4^- + C_6H_5Br \longrightarrow C_6H_5-\overset{+}{Br}-C_6H_5\ BF_4^- + N_2$$

$$C_6H_5-\overset{+}{N}\equiv N\ BF_4^- + C_6H_5-O-C_6H_5 \longrightarrow C_6H_5-\overset{+}{\underset{\displaystyle C_6H_5}{O}}-C_6H_5\ BF_4^- + N_2$$

The resulting salts of onium cations are soluble in water and can thus be extracted from the reaction mass and isolated, though they are produced in low yield (ca. 6 per cent).

13. The decomposition of diazo compounds in α,β-unsaturated acids, ketones, etc., leads to the addition of the aryl and anion of the diazo compound across the double bond (Meerwein-Koelsch

reaction), involving the violation of the rule of orientation of electrophilic addition (see Volume II, page 52) since the reaction proceeds homolytically:

$$Ar-\overset{+}{N}\equiv N\ Cl^- \longrightarrow Ar-N=N-Cl \longrightarrow Ar\cdot + N_2 + Cl\cdot$$

$$Ar\cdot + CH_3-CH=CH-C(=O)-OC_2H_5 + Cl\cdot \longrightarrow CH_3-\underset{Ar}{CH}-\underset{Cl}{CH}-C(=O)-OC_2H_5$$

But the decomposition of aryl diazonium borofluoride leads to the reverse order of addition (A. N. Nesmeyanov, L. G. Makarova):

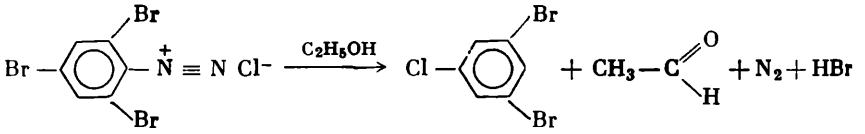
$$Ar-\overset{+}{N}\equiv N\ BF_4^- + CH_3-CH=CH-C(=O)-OC_2H_5 \longrightarrow$$

$$\longrightarrow CH_3-\underset{F}{CH}-\underset{Ar}{CH}-C(=O)-OC_2H_5 + N_2 + BF_3$$

In this case, the reaction is complicated by the subsequent elimination of HF:

$$CH_3-\underset{F}{CH}-\underset{C_6H_5}{CH}-C(=O)-OC_2H_5 \longrightarrow CH_3-CH=\underset{C_6H_5}{C}-C(=O)-OC_2H_5 + HF$$

14. It is natural that the diazonium grouping itself is a strong electron-attracting group which pulls the electrons from the nucleus and activates the *o*- and *p*-carbons towards nucleophilic attacks. Reactions of the following type have been described:



The replacement of Br by Cl is the result of the presence of the group $-\overset{+}{N}\equiv N$ and precedes the substitution of hydrogen for this group.

7.9. Phenols

The term "phenols" arose from the old name of benzene, phene, introduced by Laurent (1837). The phenols are aromatic hydroxy compounds in which the hydroxyl group is attached directly to a carbon atom of the aromatic ring.

The physical properties of phenols and some of their derivatives are given in Table 7.8.

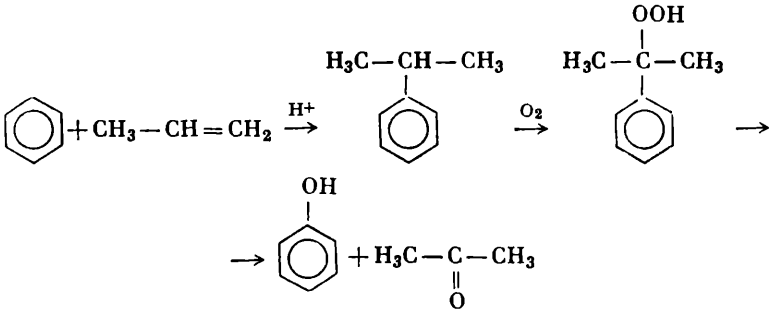
As previously mentioned, coal tar contains the simplest of the phenols—hydroxybenzene (phenol proper) and its homologues: *o*-, *m*-, and *p*-cresols, the amount being the greater the lower the temperature of coal coking. Some additional quantities of phenol, the world consumption of which amounts to millions of tons, are produced from benzene. For this purpose, use is made (on a decreasing scale) of the old method of alkali fusion of a salt of benzenesulphonic acid:

$$C_6H_5SO_3Na + NaOH \longrightarrow C_6H_5OH + Na_2SO_3$$

A certain amount of phenol is produced when chlorobenzene is hydrolysed by superheated steam (450-500°C) over a catalyst—silica gel promoted by Cu^{2+} ions (Raschig process):

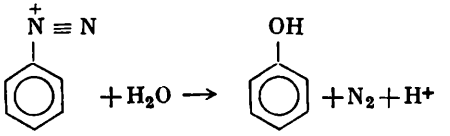
$$C_6H_5Cl + H_2O \xrightarrow{\text{silica gel; } Cu^{2+}} C_6H_5OH + HCl$$

The most promising way is the decomposition of cumene (isopropylbenzene) hydroperoxide by dilute acids. The process consists in the following:



The mechanism of the decomposition of cumene hydroperoxide will be described in Volume IV ("Rearrangements").

The manner in which a hydroxyl group is substituted for the diazo group



which is not economical for production of phenol, is used for the synthesis of pure *o*-, *m*-, and *p*-cresols, guaiacol (see below) and other phenols. Technical-grade cresol (a mixture of the three isomers) is prepared from coal tar.

TABLE 7.8.

Formula	Name	m. p., °C	b. p., °C	Density d_4^{20}
C_6H_5OH	Phenol	41	182	1.072
$CH_3C_6H_4OH$	Cresol			
	o- or 1,2-	30	191.5	1.0465
	m- or 1,3-	11	202.8	1.034
	p- or 1,4-	36	202.5	1.035
ClC_6H_4OH	Chlorophenol			
	o- or 1,2-	7 (α-form) 0 (β-form)	175.6	1.241 (at 18°C)
	m- or 1,3-	32.8	214	1.268 (at 25°C)
	p- or 1,4-	43	217	1.306
$NO_2C_6H_4OH$	Nitrophenol			
	o- or 1,2-	45	214.5	1.657
	m- or 1,3-	96	194 (at 76 mm Hg)	1.485
	p- or 1,4-	114	279 (dec.)	1.479
$NH_2C_6H_4OH$	Aminophenol			
	o- or 1,2-	174	Sublimes	—
	m- or 1,3-	123	—	—
	p- or 1,4-	184 (dec.)	Sublimes	—

Phenol, *carbolic acid*, C_6H_5OH, is a weak acid which has a dissociation constant of 1.3×10^{-10} at room temperature in aqueous solution (the dissociation constants of other phenols are listed in Table 7.8).

Thus, phenol is more acidic (by several orders of magnitude) than water, not to mention aliphatic alcohols, but much weaker than acetic acid (1.8×10^{-5}). Phenol is sparingly soluble in water (8 per cent at 15°C). Water dissolves in phenol with the formation of a liquid (at room temperature) solution. Phenol itself is a colourless low-melting (+41°C) crystalline substance, which becomes pink

Phenols

Refractive index n_D^{20}	K_a at 25°C	pK_a at 25°C	Dipole moment in benzene at 25°C, D
1.5425 (at 40°C)	1.3×10^{-10} (at 20°C)	9.89	1.53
1.5453	6.3×10^{-11}	10.20	1.41
1.5398	9.8×10^{-11}	10.08	1.54
1.5395	6.7×10^{-11}	10.17; 10.26	1.57
1.5473 (at 40°C)	7.73×10^{-9}	9.11	1.30
1.5565 (at 40°C)	6.64×10^{-9}	9.08	2.10
1.5579 (at 40°C)	6.28×10^{-9}	9.42	2.22
—	5.9×10^{-8}	7.21	3.10
—	4.5×10^{-9}	8.39	3.90
—	7.08×10^{-8}	7.16	5.01
—	2.18×10^{-10}	9.7	—
—	—	—	—
—	6.6×10^{-9} (at 15°C)	8.16	—

in air due to oxidation. The cresols are less soluble in water than phenol and are, like phenol, well soluble in ether, alcohols, chloroform, benzene.

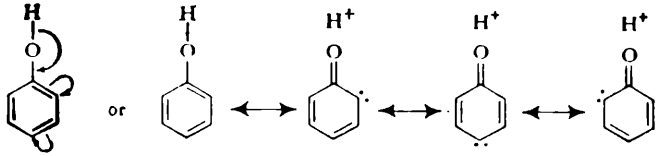
The phenols dissolve well in aqueous solutions of alkalis as the result of formation of alkali metal phenoxides:

$$ArOH + NaOH \rightleftarrows ArO^- Na^+ + H_2O$$

The hydrolysis of the phenoxide (the reverse reaction) proceeds too far because of the acidic properties of phenol, and an excess

of alkali is required to displace the equilibrium to the right. Phenol is precipitated from the phenoxide solution even with carbon dioxide.

The acidic properties of the hydroxyl group of phenol are due to the mesomeric interaction with the aromatic nucleus, which is expressed in the following manner:



The valence electrons of the oxygen atom (including those linking hydrogen to oxygen) are found to be partly delocalized over the *ortho-* and *para*-positions of the benzene ring, the hydrogen atom of the hydroxyl group being removed as a proton. Thus, the increased acidity of phenol (as compared with alcohols) is the other side of the powerful *ortho-para* directing effect of the hydroxyl group in electrophilic substitution reactions. The relations here are rather reminiscent of the relations in enols which are more acidic than alcohols, and in enolates with their $\delta-$ charge on the second carbon atom (which corresponds to the $\delta-$ charge on the *o*-carbon atoms of the phenoxide).

A. Reactions of the Phenolic Hydroxyl Group

1. The formation of phenoxides (see above).
2. The formation of the ethers of phenols by the alkylation of phenoxides:

$$ArONa + RI \longrightarrow ArOR + NaI$$

$$ArONa + (CH_3O)_2SO_2 \longrightarrow ArOCH_3 + CH_3O-SO_2ONa$$

3. The esters of phenols (in contrast to the esters of alcohols) cannot be prepared by the interaction of phenols with acids; they can be produced only by the acylation of phenols (better in alkaline medium) by acid halides or anhydrides:

$$ArONa + Cl-\overset{\overset{O}{\|}}{C}-R \longrightarrow ArO-\overset{\overset{O}{\|}}{C}-R + NaCl$$

$$ArONa + \begin{matrix} O \\ \| \\ C-R \\ / \\ O \\ \backslash \\ C-R \\ \| \\ O \end{matrix} \longrightarrow ArO-\overset{\overset{O}{\|}}{C}-R + R-\overset{\overset{O}{\|}}{C}-ONa$$

4. The replacement of the hydroxyl group by chlorine through the action of PCl_5 proceeds much more difficultly than in the case of alcohols, and with poor yield. In this case, the chlorination in the ring is the principal reaction, phosphorus pentachloride being converted into phosphorus trichloride, PCl_3. With PCl_3 the formation of triphenyl phosphite (the ester of phosphorous acid) predominates over the replacement of the hydroxyl group by chlorine. With phosphorus oxychloride, $POCl_3$, the reaction gives the phenyl ester of phosphoric acid.

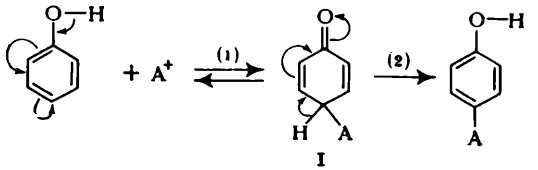
5. The distillation with zinc dust converts phenols into hydrocarbons:

$$ArOH + Zn \longrightarrow ArH + ZnO$$

B. Reactions of the Aromatic Ring of Phenols

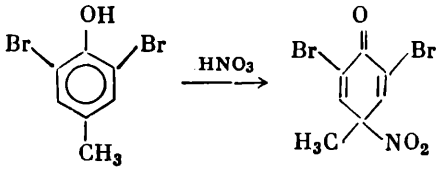
The hydroxyl group is one of the most powerful, and in alkaline solution, the strongest *ortho-para* directing group. On account of this, the reactions of electrophilic substitution proceed easily for phenols.

The mechanism of electrophilic substitution in phenols usually differs from the substitution in benzene, its homologues and even in the esters of phenols. This difference is associated with the ease of heterolysis of the O—H bond since, instead of an unstable and charged σ-complex, there is obtained a relatively stable compound with a quinonoid structure of the type I:



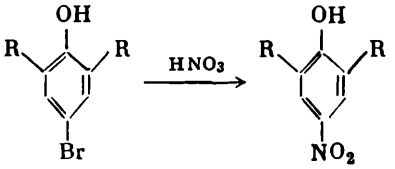
I

It has been established that the first stage of most reactions of the phenols is fast and usually reversible, and the second is slow. In a number of cases, compounds of the type I were isolated in the pure state, but only for those phenols in which all the *ortho-* and *para-*positions are occupied (with ordinary phenols the aromatization occurs too rapidly). For example,



If the *ortho-* and *para*-positions in a phenol are occupied, the substituents present may be replaced by other groups (especially on nitra-

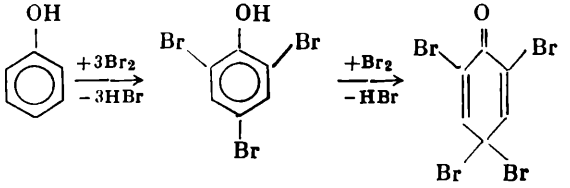
tion). The ease of the substitution increases in the following order: $Br < SO_3H < COOH < H$. For example,



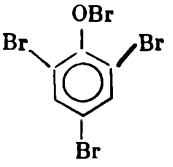
The replacement of the hydroxyl group takes place even in an azo coupling reaction.

Halogenation of Phenols. In a non-aqueous medium, the halogenation of phenols at an appropriate ratio of the reagents leads to a mixture of *o*- and *p*-halogenophenols, then to 2,4-dihalogenophenols and, finally, to 2,4,6-trihalogenophenols (these are better prepared in an aqueous-alkaline medium). In the case of *ortho*- and *para*-substituted phenols, say, cresols, the sites occupied by the substituents (for example, by a methyl group) remain untouched by halogenation.

The bromination of phenols by an excess of bromine water proceeds according to the following scheme:

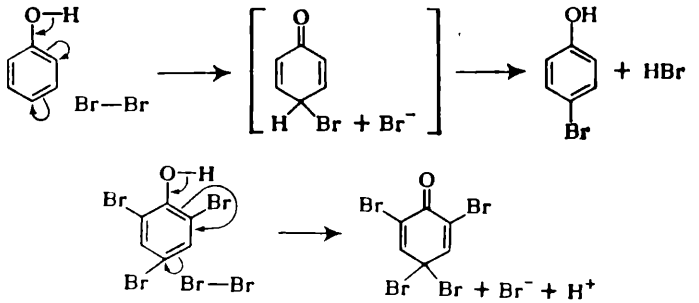


The formation of "tribromophenolbromine" or 2,4,4,6-tetrabromocyclohexadienone—is instructive. It has long been considered to be the ester of hypobromous acid:



The directing power of the hydroxyl group, i.e., the ability of the hydroxyl group to impart nucleophilic activity to a *p*-carbon atom is such that this carbon atom is susceptible to electrophilic attack by the electropositive bromine atom even after the hydrogen atom linked to it has been replaced. The addition of a second bromine

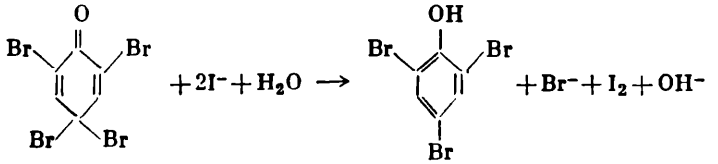
atom fixes the cyclohexadiene structure:



The ordinary tautomeric change to the phenolic form is impossible because tribromophenolbromine has no hydrogen atom in the *para*-position.

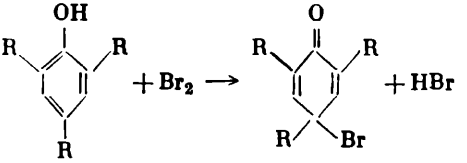
It is interesting to compare the bromination reaction with the Friedel-Crafts methylation of benzene (see page 42) when, apart from the six methyl groups that have replaced the hydrogens of benzene, one more methyl group can be introduced into the compound to form a stable analogue of the intermediate σ-complex of electrophilic substitutions.

The reaction of formation of tribromophenolbromine is quantitative and is used for the determination of phenols. First, the bromination is accomplished with an excess of bromine, then potassium iodide is added and the precipitated iodine is titrated. Tribromophenolbromine gives up its fourth bromine atom in this process:



The bromine consumption is six atoms per molecule of phenol (or *m*-cresol) and four atoms per molecule of *o*- and *p*-cresols and, in general, of *ortho*- and *para*-substituted phenols.

Other 2,4,6-trisubstituted phenols, say, trialkylphenols, also give 4-bromo-2,4,6-trialkylcyclohexadienones on bromination:

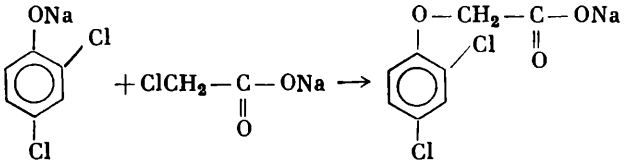


It is evident that on iodometric titration the bromine consumption in this case will be found to be equal to zero.

The introduction of a halogen into the *ortho*- and *para*-positions enhances the acidic properties of the phenols.

o- and *p*-Chlorophenols (see Table 7.8) are low-melting compounds possessing a very obtrusive, peculiar pungent carbolic smell. They are even more powerful disinfectants than phenols. The bismuth salt of 2,4,6-tribromophenol is used in the form of ointment or powder as an external antibacterial drug.

The ether of 2,4-dichlorophenol and glycolic acid, which is obtained by the action of monochloroacetic acid on sodium 2,4-dichlorophenoxide



is used as a weed-killer (2,4-dichlorophenoxyacetic acid or 2,4-D).

Sulphonation of Phenols. The sulphonation of a phenol at room temperature gives largely *o*-phenolsulphonic acid; the *para*-isomer is obtained at 100°C, and under more drastic conditions 2,4-phenoldisulphonic acid is formed.

Nitration of Phenols. To prepare mononitrophenols one has to nitrate phenols in the cold with dilute nitric acid (ca. 30-percent), which is best obtained by mixing an aqueous solution of potassium nitrate with sulphuric acid (in order to avoid the presence of oxides of nitrogen). A mixture of *o*- and *p*-nitrophenols is produced, from which *o*-nitrophenol is removed by distillation with steam, and the *p*-isomer is isolated by crystallization. The *m*-isomer has to be prepared in an indirect way, say, from *m*-nitroaniline via *m*-nitrophenyldiazonium. 2,4-Dinitrophenol is most simply produced by the hydrolysis of 2,4-dinitrochlorobenzene.

On the industrial scale, *o*- and *p*-nitrophenols are usually produced from the corresponding chloronitrobenzenes which are allowed to react with an aqueous solution of sodium hydroxide at about 150°C under pressure.

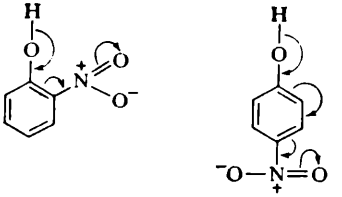
Trinitrophenol, which is called **picric acid**, is produced on an industrial scale by the nitration, with a strong nitrating mixture, of 2,4-phenoldisulphonic acid obtained by the sulphonation of phenol, without isolating the acid from the sulphonating mass. In this process, not only the free sixth position is nitrated, but also the sulphonic acid groups are replaced by nitro groups, a phenomenon also observed in a number of other cases. The presence of sulphonic groups in phenol protects it from oxidation and from the action of oxides of nitrogen. Picric acid can also be prepared directly from benzene if the latter is nitrated in the presence of a mercury salt,

which catalyses the oxidation of the transiently formed *m*-dinitrobenzene to 2,4-dinitrophenol which is then converted to picric acid.

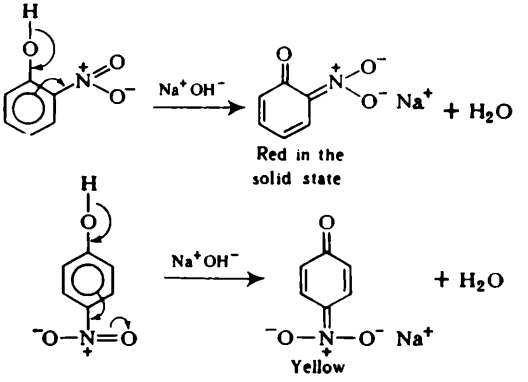
Properties of Nitrophenols. The introduction of a nitro group into the *ortho*- and *para*-positions increases the dissociation constant of phenol considerably; the lower acidifying effect is exerted by the *meta*-nitro group. 2,4-Dinitrophenol is six times more acidic than acetic acid, and trinitrophenol is a very powerful acid:

	K_a
Phenol	1.3×10^{-10}
o-Nitrophenol	5.9×10^{-8}
p-Nitrophenol	7.08×10^{-8}
m-Nitrophenol	4.5×10^{-9}
2,4-Dinitrophenol	1×10^{-4}
Trinitrophenol	1.6×10^{-1}

The concerted action of both directing groups (OH and NO_2), which are in the *ortho*- or *para*-positions to each other, on the benzene ring is expressed by the following scheme:

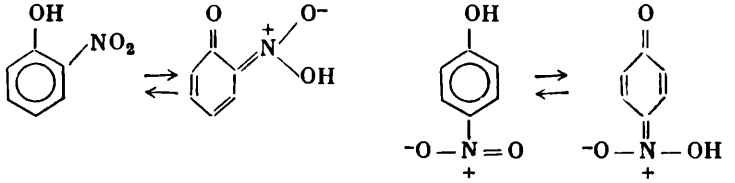


Alkali binds the proton of the hydroxyl group and allows the shift of electrons shown by curved arrows. Therefore, sodium nitrophenoxides are essentially devoid of the structure of phenoxides: the charge of the anion is largely concentrated on the nitro group, and not on the oxygen of the former hydroxyl group, and the nucleus has an almost quinonoid arrangement of the double bonds.

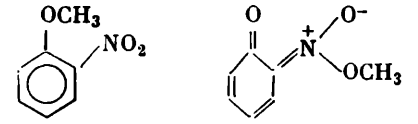


Such a migration of bonds results in a sharp change of the light absorption region and is responsible for the properties of nitrophenols (and also of dinitrophenols) as indicators of the hydrogen ion concentration.

The migration of the proton from the hydroxyl to the nitro group, which is accompanied by the quinonoid shifting of the bonds, occurs, though to a small extent, in nitrophenols themselves, especially in solvents capable, like water, of binding a proton, i.e., tautomerism is implied here:

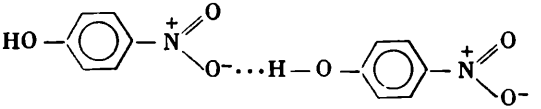


Isomeric esters have been obtained for *o*-nitrophenol:

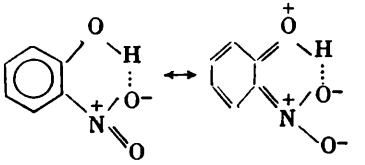


Colourless Coloured

o-Nitrophenol is sharply different from its *para*-counterpart and from phenol itself in that it is not associated in hydrocarbon solutions. Phenol, like all hydroxyl compounds, is associated owing to the hydrogen bonding of the hydroxyl groups with one another, and the association of *p*-nitrophenol is due, in addition, to the hydrogen bond between the hydroxyl group of one molecule and the nitro group of another:



In *o*-nitrophenol, hydrogen bonding is formed within the molecule, and therefore the hydroxyl group is no longer capable of forming a hydrogen bond outside the molecule:



Such a peculiar structure of *o*-nitrophenol is also responsible for its higher solubility, lower melting point, steam-volatility (the

molecules are not bound chemically to one another) and also its coloration.

2,4,6-Trinitrophenol (picric acid) is a strong acid. With a large number of even weak bases (say, alkaloids) it forms well-developed crystalline salts, widely used for the isolation, characterization and analysis of bases. Besides, with condensed aromatic systems such as naphthalene and anthracene, picric acid also forms crystalline molecular compounds (Fritzsche) in a simple 1:1 molecular ratio. This property is not associated with the acidity of picric acid since all trinitro derivatives form such compounds, say, trinitrobenzene with naphthalene. In such molecular compounds one molecule is an electron-donor, and the other an electron-acceptor (charge-transfer compounds will be discussed below).

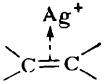
Picric acid was formerly used as a yellow dye. Like all aromatic trinitro compounds, picric acid was also used (say, in the Russian-Japanese War, 1904) as a high explosive under the names of **melenite**, **lyddite**, and **chimose**. Later picric acid was replaced by trotye because its acidic properties cause the corrosion of metals and tht formation of salts which are extremely sensitive to shock. A sal. of picric acid, ammonium picrate, also finds some use as an explosive.

XXIX. Molecular Charge-Transfer Complexes

There are compounds formed by 2,4,6-trinitrobenzene with naphthalene and other condensed aromatic hydrocarbons and also with mesitylene (1,3,5-trimethylbenzene) and, in general, with highly alkylated benzenes, such as the above-mentioned picrates of aromatic hydrocarbons. They all have a molecular composition of 1 : 1 and a deeper and more intense coloration than the original compounds. As a rule, in such molecular compounds the planes of the two aromatic members of the complexing pair are one above the other. It has been established that the linkage between the two molecules is such that there is some charge transfer, a transfer of one of the π-electrons from one of these molecules (a condensed aromatic compound or an alkylbenzene) to the orbital of the other (a nitro compound). Such molecular compounds are referred to as **charge-transfer complexes** or **π-complexes**. In certain cases, they are formed only in solution when the components are mixed, and the process can be traced out quantitatively by spectrophotometric means until the equilibrium is established. In other cases, they form beautiful crystals. The ability to form such charge-transfer complexes is exhibited not only by aromatic molecules but also by other substances containing π-bonds if the complexing pair consists of a strong donor molecule and a strong acceptor molecule. An example of a strong acceptor molecule in the aliphatic series is tetracyanoethylene which when mixed with

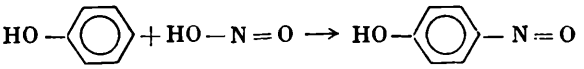
benzene forms a bright-orange complex. Ostromyslensky proposed tetranitromethane as a reagent for detection of a double bond since when it is mixed with unsaturated compounds, a yellow-coloured solution is obtained, due evidently to a phenomenon of the same kind.

Finally, the π-complexes of metals (see Volume IV), beginning with the π-complexes formed between the silver (I) cation and olefins

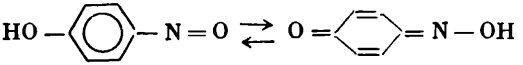


may also, with some reservations, be regarded as the analogues of charge-transfer complexes. In these compounds, the π-bond is a donor and the metal cation is an acceptor. Among such analogues are also unstable intermediate π-complexes of olefins or aromatic compounds with attacking electrophilic particles, which were described in the discussion of the reactions of olefins (see Volume I, page 335) and of the reactions of aromatic compounds (see page 37). The distinguishing feature of the compounds described here is that the two organic molecules are the charge-donors and -acceptors.

Nitrosation of Phenols. When acted on by an aqueous solution of nitrous acid phenol is nitrosated in the *para*-position:

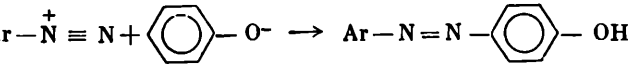


Nitrosophenol is tautomeric to the monoxime of *p*-benzoquinone (for quinones, see page 183):



The presence of the nitrosophenol-quinoneoxime tautomerism and the tautomeric equilibrium constant in various solvents can be established from the absorption spectra of solutions of nitrosophenol. The nitrosophenol form is characterized by an absorption maximum in the region of 730 nm. The value of the extinction coefficient of this maximum provides information on the content of the nitrosophenolic form.

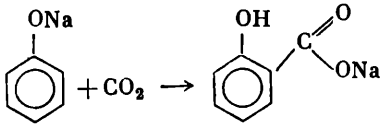
The azo coupling of phenols as an electrophilic substitution reaction has already been considered. It proceeds in a weakly alkaline solution according to the scheme:



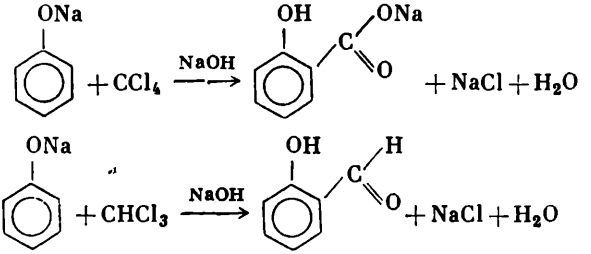
If there is a substituent in the *para*-position, the azo group enters the *ortho*-position.

Electrophilic Substitution in Phenols with the Formation of a Carbon-Carbon Bond. We know many such reactions. They are employed for the preparation of bifunctional compounds, say, phenolic acids, phenolic aldehydes and phenolic alcohols. We shall briefly consider only some of these reactions.

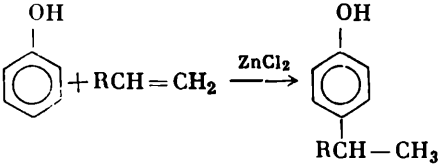
When sodium phenoxide is heated in a current of CO_2, sodium salicylate is obtained (Kolbe reaction):



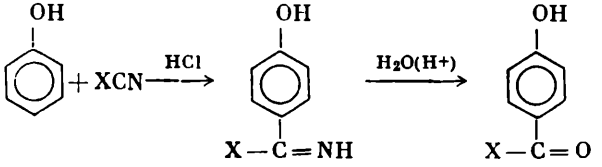
When sodium phenoxide (in excess alkali) is allowed to react with carbon tetrachloride, sodium salicylate is also formed, and the action of chloroform gives salicylaldehyde (Reimer-Tiemann reaction; for more detail, see page 160):



By the action of olefins on phenols in the presence of Lewis acids it is possible to obtain *p*-alkylphenols (a special case of the Friedel-Crafts reaction):



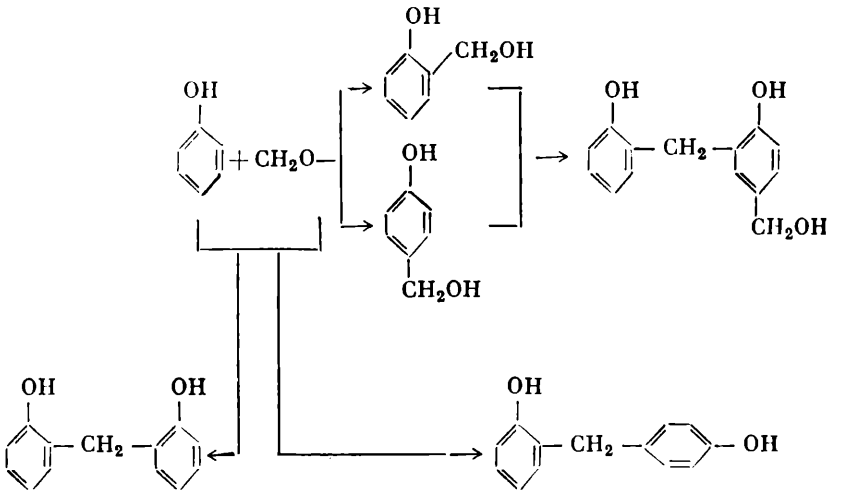
With hydrogen cyanide (or nitriles) in the presence of hydrogen chloride phenols give iminoaldehydephenols or iminoketonephenols (aldimine or ketimine hydrochlorides) (Hoesch reaction) and the hydrolysis of the imino group yields aromatic hydroxyaldehydes or hydroxyketones:

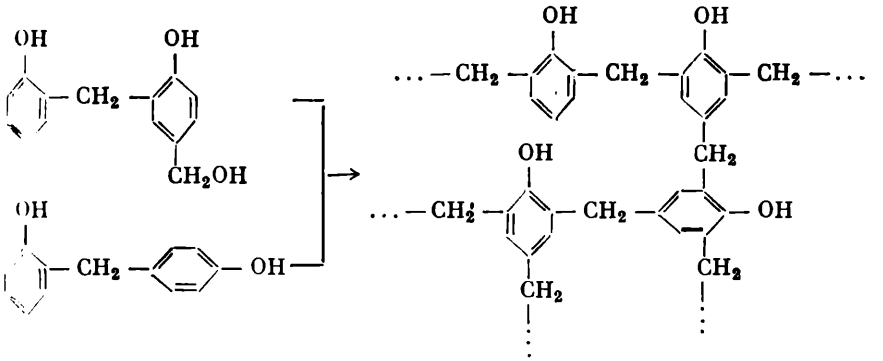


(X=H, aryl or alkyl)

The most important reaction of this kind is the reaction of phenols with formaldehyde, which proceeds in the presence of either acids or alkalis. When phenol (in excess) is heated with formalin and sulphuric acid, a vigorous reaction takes place, leading to the formation of a linear polymer, novolak, which is soluble in alcohols, acetone and esters. The alkaline condensation of phenol with an excess of formalin first gives a relatively low-molecular-weight, low-melting polymer, **resol** (*A-stage resin*), which, like novolak, is soluble in organic solvents. This is a so-called thermosetting polymer: on heating there takes place a further condensation of the free hydroxymethylene groups with the formation of methylene bridges, and the polymer becomes cross-linked. The resulting **resitol**, or *B-stage resin*, is insoluble in organic solvents but retains a certain degree of plasticity. On heating up to 150°C the condensation proceeds further and a chemically very stable, non-melting and insoluble polymer, **resite** or *C-stage resin*, is produced, which may be heated up to about 300°C. Such are the three stages of the condensation process, which are collectively referred to as "bakelization" (after the inventor of Bakelite, L. H. Baekeland). Usually, prior to the next stage of condensation resol is mixed with a filler (a mineral filler, such as asbestos, or an organic filler, such as wood, lignin, or cellulose) or else wood or fibrous materials are impregnated with resol and then subjected to further bakelization. This type of phenol-formaldehyde resins discovered in 1909 is still of value at present.

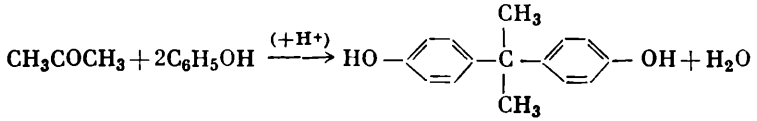
The major proportion of phenol and cresols produced is used for preparing phenol-aldehyde polymers. The chemical meaning of the processes taking place is expressed by the following approximate scheme:





Thus, an increasing amount of phenol molecules are gradually cross-linked by methylene bridges into randomly built macromolecules of resol, resitol and, finally, of resite. The chemical stability of resite is explained not so much by the fact that a considerable number of active *ortho*- and *para*-positions of phenol are replaced by methylene groups as by the fact that because of the complete insolubility of Bakelite the reagents can affect it only from the surface.

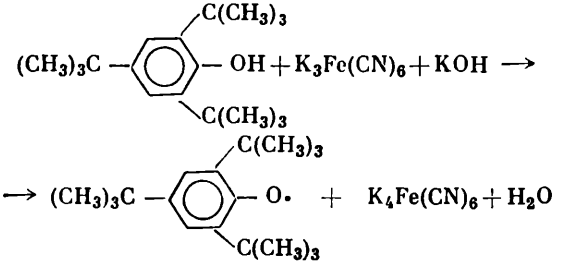
Aliphatic ketones in acid medium react with phenol, forming di-*p*-hydroxyphenylalkanes:



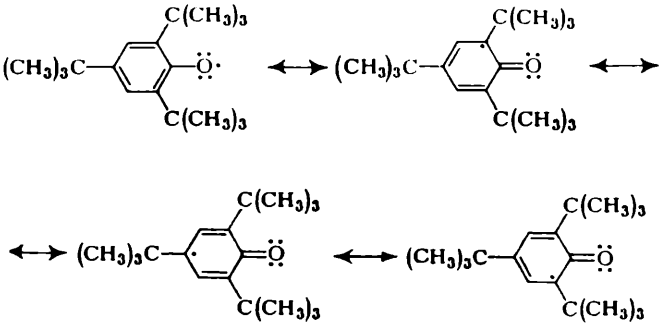
This 2,2-bis-(4,4′-hydroxyphenyl)-propane (the so-called diphenylolpropane) is used in the synthesis of highly heat-resistant plastic materials produced by the esterification of phenolic hydroxyl groups by aromatic dicarboxylic acids, such as terephthalic acid.

C. Aroxyls

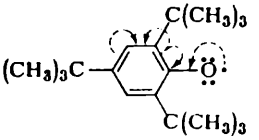
Phenols alkylated into both *ortho*-positions and the *para*-position, especially by tertiary alkyls, can be oxidized by silver oxide or potassium ferricyanide to **aroxyls**—substances possessing the properties of free radicals (E. Müller):



These are stable free radicals. In the absence of air and reagents they are capable of existing for an indefinitely long period of time. We shall consider at a later time (page 260) stable free radicals of this kind, in which there is an atom with an unpaired electron in the α-position to the aromatic nucleus or, better, to two or three aromatic rings (if there is a carbon atom in the α-position). They all are stabilized due to the spreading of the unpaired electron over the entire aromatic system, which is expressed in resonance terms as follows:

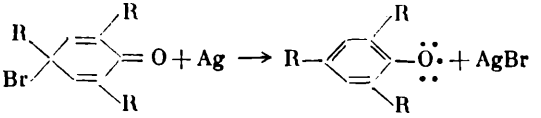


This phenomenon is more difficult to express in terms of the symbolism of the English school because the curved arrow designates the migration of a pair of electrons, and in this case only one electron is delocalized. Sometimes this is represented by dashed curved arrows:



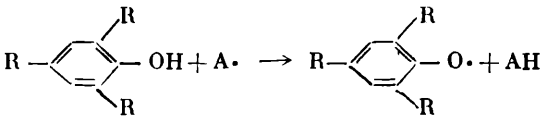
Aroxyls are dark-blue crystalline substances soluble in ether and benzene. Their paramagnetic properties prove the presence of an unpaired electron in the molecule.

Another method of producing aroxyls is the elimination of bromine by metallic silver from the bromination product of 2,4,6-trialkylphenol (page 135):

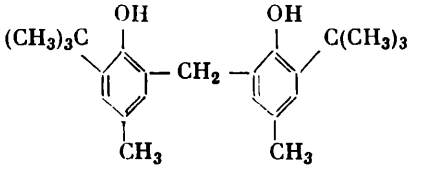


2,4,6-Trialkylphenols serve as good antioxidants and are, in general, chain-reaction inhibitors since they deactivate active free

radicals which propagate the chain in chain reactions:



In this process they themselves are converted into inactive stable radicals, and the reaction chain is terminated. Phenols capable of giving aroxyls are therefore used as chain-oxidation inhibitors and inhibitors of the associated degradation (ageing) of plastics, say, polypropylene. An example of the phenols employed in practice for this purpose is

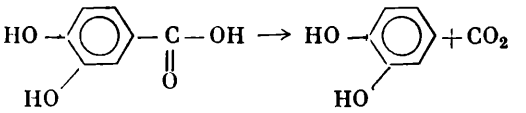


D. Polyhydric Phenols

(a) Dihydroxybenzenes

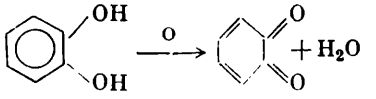
The isomeric dihydroxybenzenes have the following names: *o*-dihydroxybenzene, catechol or pyrocatechin; resorcinol (*m*-isomer), and hydroquinone (*p*-isomer). These are solid, odourless compounds well soluble in water. The properties of these compounds are presented in Table 7.9.

Catechol is known as the product of decarboxylation of protocatechuic acid found in plants:



It can also be prepared by the hydrolysis of *o*-dichlorobenzene (silica gel-copper salt) by superheated steam.

Catechol is a strong reducing agent and when oxidized heterolytically (say, with the Ag^+ ion) is converted into *o*-benzoquinone:

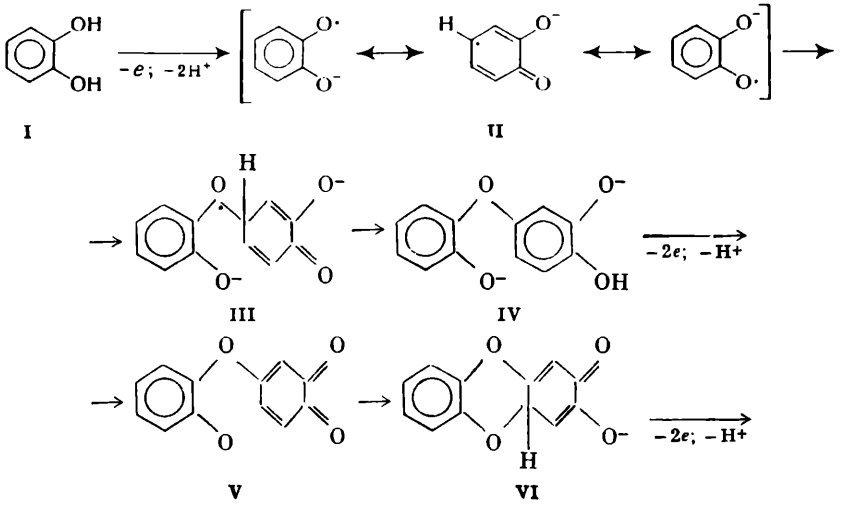


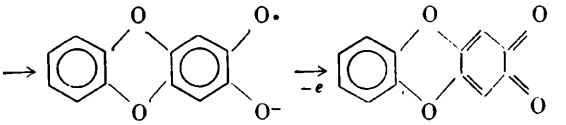
The homolytic oxidation with atmospheric oxygen proceeds in a more complicated manner. As shown by electron paramagnetic resonance (EPR) studies, the oxidation first gives semiquinone II

TABLE 7.9. **Polyhydric Phenols**

Formula	Name	m.p., °C	b.p., °C	Density, d_4^{15}	Refractive index, n_D
$C_6H_4(OH)_2$	Catechol, 1,2- or *o*-dihydroxybenzene	105	240; 245	1.371	1.615 (at 20°C)
$C_6H_4(OH)_2$	Resorcinol, 1,3- or *m*-dihydroxybenzene	110	276.5; 281	1.285	—
$C_6H_4(OH)_2$	Hydroquinone, 1,4- or *p*-dihydroxybenzene	170.5-173.1	286.2	1.358 (d_4^{20})	—
$C_6H_3(OH)_3$	Pyrogallol, or 1,2,3-trihydroxybenzene	133.5	171 (at 12 mm Hg)	1.453 (d_4^4)	—
$C_6H_3(OH)_3$	Hydroxyhydroquinone, or 1,2,4-trihydroxybenzene	140.5	—	—	—
$C_6H_3(OH)_3$	Phloroglucinol, or 1,3,5-trihydroxybenzene	219 (anhydrous)	Sublimes, decomposes	—	—

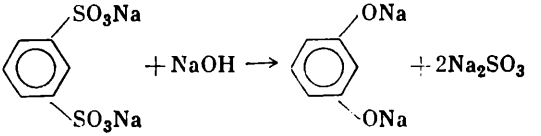
(see page 189), which is easily identified by the EPR spectrum. This spectrum is then replaced by the spectrum of the free radical VII which oxidizes to quinone VIII. The entire picture may be visualized as follows:



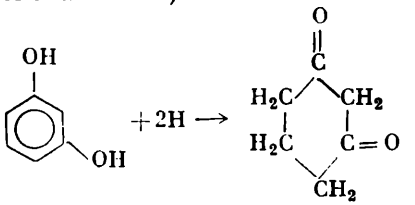


VII VIII

Resorcinol (*m-hydroxybenzene*) is produced industrially by alkali fusion with sodium *m*-benzenedisulphonate:

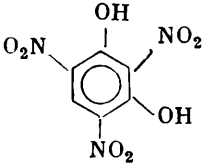


Resorcinol is more stable to oxidation than its isomers. Its acidic properties are more pronounced than those of phenol. It is reduced even by nascent hydrogen (sodium amalgam and water) to dihydroresorcinol (1,3-cyclohexanedione):

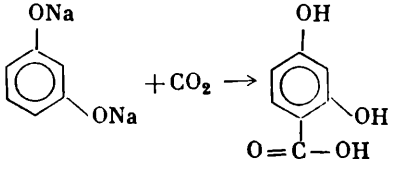


Resorcinol is even more susceptible to the various electrophilic attacks than phenol since both its hydroxyl groups exert a concerted orienting effect. Resorcinol therefore is easily halogenated, sulphonated, nitrated, nitrosated, and enters into azo coupling reactions. One of its principal applications is the synthesis of azo dyes, in which it serves as the azo component.

The exhaustive nitration of resorcinol gives trinitroresorcinol or **styphnic acid**

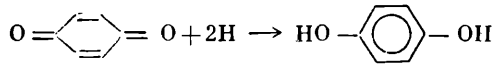


which is reminiscent in many respects of picric acid. For resorcinol to be decarboxylated it will suffice to heat it in a solution of sodium bicarbonate:

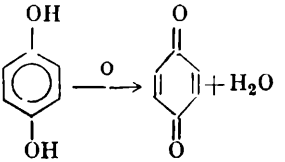


The resulting compound is known as **resorcylic acid**. The corresponding resorcylaldehyde can be obtained by the Reimer-Tiemann reaction and also by the action of hydrogen cyanide and hydrogen chloride (page 160).

Hydroquinone, *quinol* or *p*-dihydroxybenzene, is prepared by the reduction of *p*-benzoquinone (page 183):



Like catechol, hydroquinone is a strong reducing agent, which on oxidation forms *p*-benzoquinone:



Catechol and hydroquinone are used as photographic developers, which reduce silver bromide to the metal. Hydroquinone is extensively employed as an antioxidant (page 188).

XXX. Clathrate Compounds of Hydroquinone

Just as in the case of phenol, hydroquinone molecules are associated due to the hydrogen bonding of hydroxyl groups. Solid hydroqui-

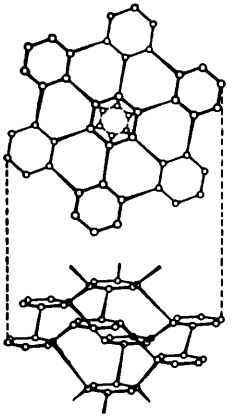


Fig. 7.7.
Formation of the framework of hydroquinone with the aid of hydrogen bonds.
Top: each regular hexagon stands for six hydrogen bonds between oxygen atoms; lines of different thickness represent hexagons lying at different levels; the skew lines which represent the O—O axes of the hydroquinone molecules show the mode of bonding resulting in the formation of an infinite three-dimensional cage-like (clathrate) compound, each such line pointing away from the observer.
Bottom: a perspective projection of the top drawing: the hexagons represent hydrogen bonds; the longer skew lines connecting the different hexagons are the O—O axes of the hydroquinone molecules.

none (its β-modification) has a three-dimensional lattice thanks to these bonds (Fig. 7.7), which is pierced with vacancies about 5 Å long, which easily capture foreign molecules (SO_2, H_2S, CH_3OH, and even noble gases, say, argon). The resulting **clathrate compounds**

(clathrates) of hydroquinone (Fig. 7.8) were first obtained and thoroughly studied by Powell. The formation of clathrates is character-

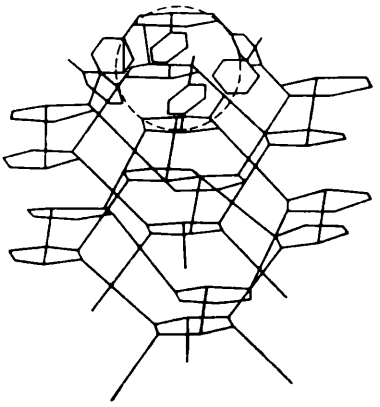


Fig. 7.8.

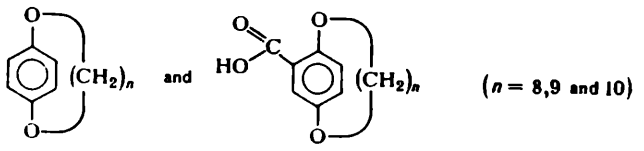
The structure of the hydroquinone clathrate. The dashed circle at the top picks out a single cage.

istic of many phenols, including phenol itself, for which B. A. Nikitin discovered "molecular compounds" with noble gases and with hydrogen sulphide.

In the absence of "guest" molecules, hydroquinone crystallizes preferentially without vacancies, in a denser α-modification (density 1.35 g/cm^3); the density of the β-modification is 1.26 g/cm^3.

XXXI. "Ansa" Compounds of Hydroquinone. Atropisomerism I

By alkylating hydroquinone and hydroquinonecarboxylic acid with a series of dibromides, of the general composition $Br(CH_2)_nBr$, Lüttringhaus obtained two series of ethers of the types I and II with bridges at the benzene ring (so-called *ansa*-compounds):



I II (n = 8,9 and 10)

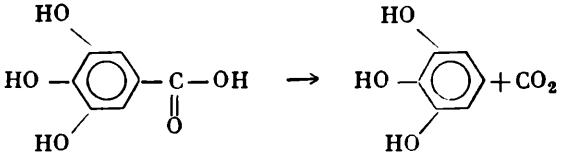
Compounds of the type II have no plane of symmetry, and therefore their mirror image is non-superimposable with the original

molecule. It is for this reason that such compounds can be resolved into their antipodes by conventional methods, say, by crystallization of their salts with an optically active alkaloid (see Volume II, page 45). This case of optical isomerism (namely, enantiomerism) is remarkable by the fact that no asymmetric carbon atom is present in the compound; asymmetry is characteristic of the molecule as a whole due to the impossibility (because of steric hindrances) of rotation of the benzene ring. Indeed, compounds of the type II at $n = 8$ show complete stability of the levorotatory and dextrorotatory forms even in chemical transformations. At $n = 9$ there takes place (as a result of the rotation of the benzene ring) a slow racemization, i.e., the interconversion of the levorotatory and dextrorotatory forms, and at $n = 10$ the racemization proceeds very rapidly.

This type of optical isomerism is called **atropisomerism** (meaning no rotation). We shall encounter atropisomerism in the discussion of diphenyls (page 237).

(b) Polyhydroxybenzenes

The vicinal trihydroxybenzene is called **pyrogallol** since it is prepared by pyrolysis (decarboxylation) of gallic acid which is isolat-

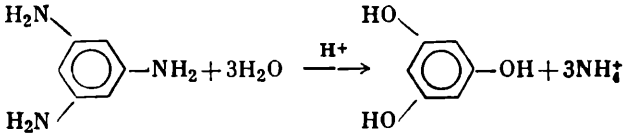


ed from the hydrolysis products of tanning compounds of the tannin type (page 216).

Pyrogallol in alkaline solutions is readily oxidized even by atmospheric oxygen, therefore such solutions are used for absorption of oxygen. Pyrogallol is employed as a developer in photography.

The symmetrical trihydroxybenzene, **phloroglucinol**, occurs widely in the form of its derivatives in the vegetable kingdom. Many of these derivatives are produced synthetically via phloroglucinolaldehyde, which in its turn is synthesized from phloroglucinol by the Reimer-Tiemann reaction, or by the action of hydrogen cyanide and hydrogen chloride (page 160).

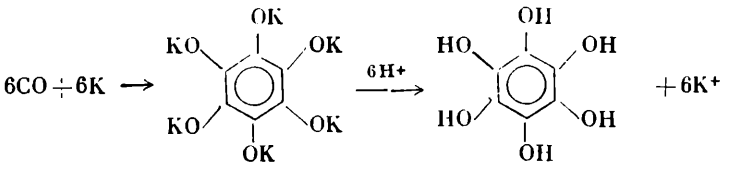
The usual way of preparing phloroglucinol is the hydrolysis of symmetrical triaminobenzene (obtained by reduction of trinitrobenzene):



Phloroglucinol is similar to resorcinol in its properties.

1,2,4-**Trihydroxybenzene** can be synthesized by adding acetic anhydride to *p*-benzoquinone and hydrolysing the acetate formed (page 187).

Hexahydroxybenzene is prepared by the acidification of the product resulting from the union of metallic potassium and carbon monoxide:

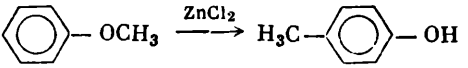


E. Ethers and Esters of Phenols

The synthesis of ethers and esters of phenols has already been discussed (see page 132). Phenolic esters are hydrolysed by the method usual for this type of compounds, in acid or alkaline medium. The ethers are hydrolysed, as is always the case, with difficulty, though more readily than the saturated aliphatic ethers. They are hydrolysed in the presence of aluminium chloride and hydrogen chloride. They are also cleaved by the use of reagents such as concentrated hydriodic or hydrobromic acid with evolution of the alkyl halide.

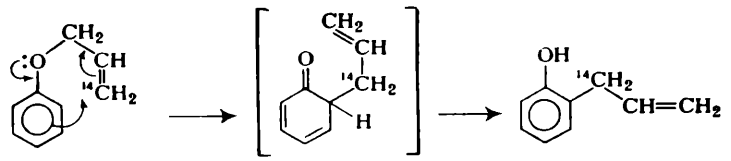
The simplest and most important phenolic ethers are the methyl ether, **anisole** (*methoxybenzene*), $C_6H_5 \cdot OCH_3$, and the ethyl ether, **phenetole** (*ethoxybenzene*). They find application as solvents and are mainly used in the synthesis of dyes and medicinal drugs after they are nitrated and then reduced to *o*- and *p*-methoxyanilines (**anisidines**) and *o*- and *p*-ethoxyanilines (**phenetidines**). The hydrazo compounds obtained from them rearrange, respectively, into 2,2-dimethoxybenzidine (**dianisidine**) and 2,2-diethoxybenzidine.

When heated with Lewis acids alkoxybenzenes rearrange to *o*- and *p*-alkylphenols (N. I. Kursanov):

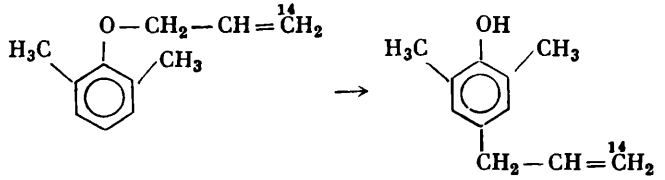


Phenyl allyl ether readily undergoes an interesting intramolecular change, known as the Claisen rearrangement, without the aid of catalysts (without Lewis acids). The allyl group migrates only to the *ortho*-position if it is not occupied and to the *para*-position if both *ortho*-positions are occupied. It has been proved, by labelling the third (terminal) carbon atom of the allyl group through the introduction of radioactive ^{14}C into this position, that in the first case the

allyl group migrates to the *ortho*-position and attaches itself to the benzene ring by its third (tagged) carbon atom, probably via the cyclic transition state:

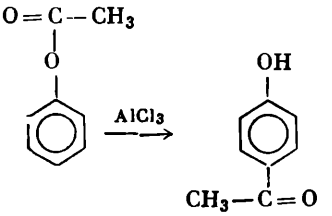


In the case of the Claisen *para*-rearrangement the allyl group is found to be attached to the first carbon atom:



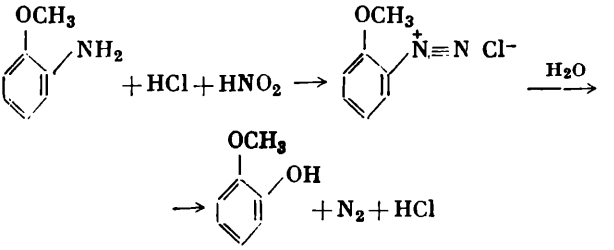
This makes the Claisen *para*-rearrangement similar to other migrations of the allyl group from the side chain of the benzene ring to the *para*-position: the rearrangement of phenylhydroxylamine to *p*-aminophenol, of azoxybenzene to *p*-hydroxyazobenzene, etc. Of course, in order to locate the site of ^{14}C in the reaction product, it is necessary to subject this product to degradation in such a way as to separate the terminal allylic carbon atom (for example, by ozonization or any other type of oxidation) and to find out which of the two degradation products is radioactive.

Phenolic esters also undergo, under the action of Lewis acids, a rearrangement with migration of the acyl group into the benzene ring, chiefly, to the *para*-position, and with formation of phenolic ketones (*Fries rearrangement*):

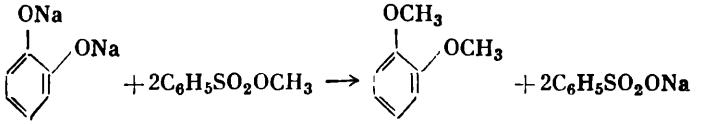


Of the ethers of dihydroxybenzenes we shall mention the methyl ether of catechol, **guaiacol**, $HO \cdot C_6H_4 \cdot OCH_3$, which occurs in the crude creosote of beech tar and is used in the pharmaceutical industry.

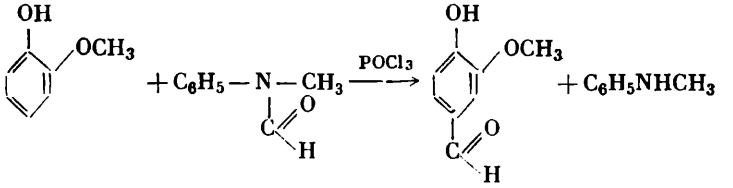
It is prepared from *o*-anisidine:



Veratrole (the dimethyl ether of catechol) is synthesized by the following reaction:

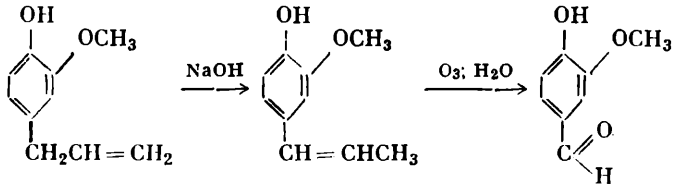


Guaiacol is in kinship with important fragrant substances. By introducing into guaiacol, by the use of any suitable method, the aldehyde group (into the *para*-position to the hydroxyl) it is possible to obtain vanillin. Such a formylation reaction can be effected by the action of methylformanilide in the presence of phosphorus oxychloride (*Vilsmeier reaction*):

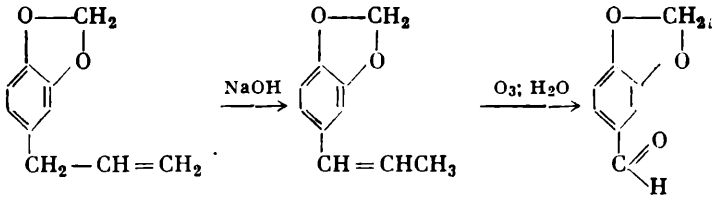


Vanillin, *m-methoxy-p-hydroxybenzaldehyde*, is the active constituent of the vanilla pod. At present it is prepared more simply, by the oxidation of lignin (page 157).

The flavouring principle of clove oil—**eugenol**—is 4-allyl-2-methoxyphenol. Its close relationship to vanillin is established in the following way: when heated with alkali eugenol undergoes an allylic rearrangement to give isoeugenol (4-propenyl-2-methoxyphenol), the oxidation of which (say, with ozone) leads to vanillin:



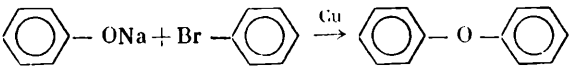
Analogous relations are exhibited by safrole (the chief constituent of oil of sassafras) and piperonal, which possesses a very pleasant smell resembling that of heliotrope and is placed on the market as a perfume under the name of heliotropin:



Safrole Isosafrole Piperonal

F. Purely Aromatic Ethers

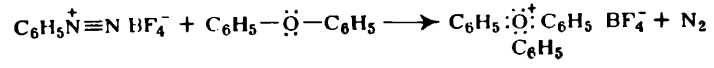
The simplest representative of this class of compounds is diphenyl ether, $C_6H_5 \cdot O \cdot C_6H_5$, also called diphenyl oxide, a substance with a melting point of 28°C and a boiling point of 259°C and with a smell resembling that of geranium leaves. It is used in perfumery and also as a heat transfer medium in heating systems. Diphenyl ether can be prepared by the Ullmann method, by heating bromobenzene and sodium phenoxide with copper up to about 200°C:



Diphenyl ether is formed also as a by-product in the alkali hydrolysis of chlorobenzene (in the presence of copper).

G. Triphenyloxonium Salts

When phenyldiazonium borofluoride is decomposed in an acetone solution of diphenyl ether, triphenyloxonium borofluoride is obtained in low yield as the result of addition of the phenyl cation formed (the heterolytic decomposition of phenyldiazonium) to the free electron pair of oxygen (A. N. Nesmeyanov, T. P. Tolstaya):



In distinction to the other components of the reaction, this oxonium salt is soluble in water and can be extracted into the aqueous layer after the acetone is distilled, then precipitated in the form, say, of the slightly soluble iodide.

Triphenyloxonium salts are very stable thermally and to electrophilic reagents, which differentiates them from trialkyloxonium

salts. The oxonium oxygen bearing a positive charge behaves as a strong deactivating (towards electrophilic substitution) substituent, but directs the entering substituent to the *para*-position. For example, when a triphenyloxonium salt is nitrated (100°C, 60 hours, 100-percent HNO_3 + 100-percent H_2SO_4), tri-(*p*-nitrophenyl)-oxonium salt is formed.

Triphenyloxonium is the only one of the aromatic onium cations, which is nitrated in the *para*-position; all the others are nitrated in the *meta*-position. The cause is evidently the same as in chlorobenzene: the presence in this case of a free pair of electrons on oxygen and, as a result, the $+T$ effect coupled with the very strong $-I$ effect of the positively charged oxygen.

The triphenyloxonium cation is much more stable towards nucleophiles than aliphatic oxonium compounds, but not very stable. For example, on heating the following reactions take place:

$$(C_6H_5)_3\overset{+}{O}\ BF_4^- + NaOH \longrightarrow C_6H_5OH + (C_6H_5)_2O + NaBF_4$$

$$(C_6H_5)_2\overset{+}{O}\ BF_4^- + NaNO_2 \longrightarrow C_6H_5NO_2 + (C_6H_5)_2O + NaBF_4$$

7.10. Aromatic Alcohols

The simplest aromatic primary alcohol is **benzyl alcohol**, *phenylcarbinol*, $C_6H_5CH_2OH$. It can be prepared from benzaldehyde (page 158) by the hydrolysis of benzyl chloride

$$C_6H_5CH_2Cl + H_2O \longrightarrow C_6H_5CH_2OH + HCl$$

or by the Grignard reaction

$$C_6H_5MgBr + CH_2O \longrightarrow C_6H_5{-}CH_2OMgBr \xrightarrow{H_2O} C_6H_5CH_2OH$$

Secondary and tertiary aromatic alcohols are produced by the Grignard reaction—the interaction of phenylmagnesium bromide with aldehydes and ketones, and secondary ones, also by reduction of ketones.

Benzyl alcohol is quite similar in its functional behaviour to aliphatic primary alcohols. Its rather distinguishing feature is the facile donation of an α-hydrogen atom with a pair of electrons (hydride ion); benzyl alcohol itself is oxidized to benzaldehyde:

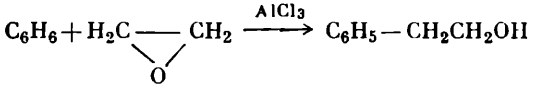
$$C_6H_5{-}\overset{H}{\underset{H}{C}}{-}O{-}\overset{\cdot\cdot}{H} + A^+ \longrightarrow C_6H_5{-}\overset{H}{C}{=}O + AH + H^+$$

where A^+ is the hydride-ion acceptor, for example, $(C_6H_5)_3\overset{+}{C}$.

Besides, just as the chloride ion splits off from benzyl chloride, so the hydroxyl group is easily removed by acids from benzyl alcohol, leaving the relatively stable benzyl cation which then undergoes further transformations.

Benzyl acetate has a pleasant flowery odour. It is contained in the essential oil of jasmin and is used in perfumery.

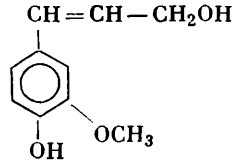
β-Phenylethanol whose hydroxyl group is more remote from the phenyl nucleus is quite similar to aliphatic alcohols. This compound is prepared from benzene and ethylene oxide by a modification of the Friedel-Crafts reaction:



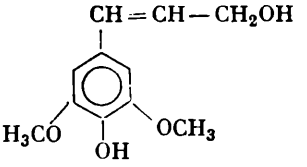
β-Phenylethanol is used in perfumery (its odour resembles the odour of roses).

7.11. Phenolic Alcohols and Their Ethers

Compounds of this class are important since, for one thing, some of them are structurally closely related to lignin, for example,



Coniferyl alcohol (coniferol)

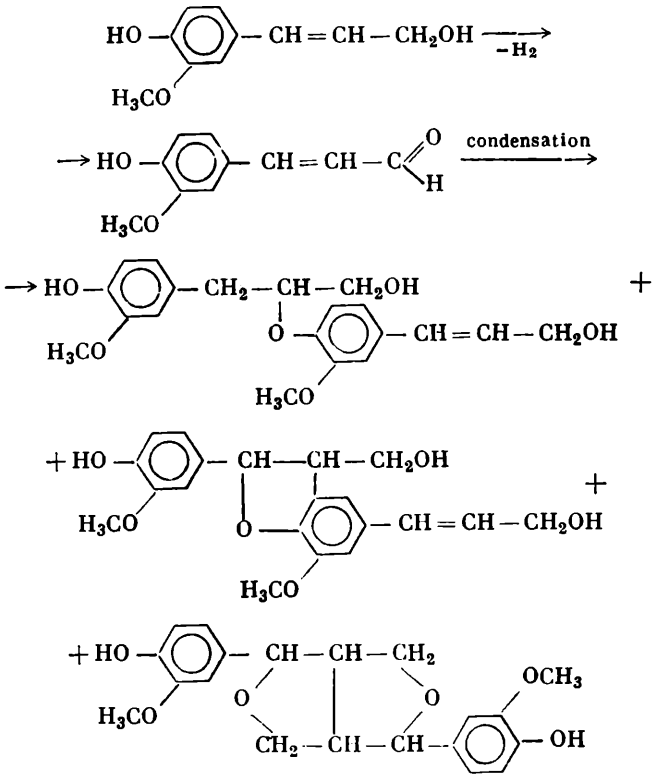


Sinapic alcohol (sinapinol)

Lignin is a polymeric structural material of woody plants (30 per cent of the dry weight of wood) and is associated with cellulose and hemicelluloses. In the plant it serves as a matrix in which the fibrous cellulosic cells and specialized structures are imbedded. When wood is processed by the sulphite method to give cellulose, the sulpho groups from the sulphite enter the macromolecules of lignin and there occurs a rupture at the oxygen linkages. Lignin passes into the solution, leaving cellulose. In the sulphate method the dissolution of lignin is achieved by the action of alkalis due to the free phenolic hydroxyl groups of lignin.

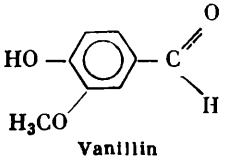
In the acid hydrolysis of wood aimed at preparing glucose, lignin remains undissolved. Large quantities of hydrolysis lignin and ligninsulphonic acids are obtained as industrial wastes. Lignin is a valuable material and work should be carried out on the more efficient utilization of lignin.

The structure of lignin has been thoroughly studied by Freudenberg who reproduced the biosynthesis of lignin by treating coniferyl alcohol with a dehydrating enzyme—dehydrase isolated from the juice of meadow mushrooms. The nature of the condensation processes taking place during the dehydration can be deduced from the by-products (or intermediates) obtained:



The ^{14}C-labelled coniferyl alcohol converted into the glycoside coniferin, when being introduced into the cambium juice of pines, is in fact (as proved by radioactive labelling) found to be a component of the pine lignin.

The oxidation of lignin with nitrobenzene gives vanillin and is therefore an industrial method of preparing this compound.

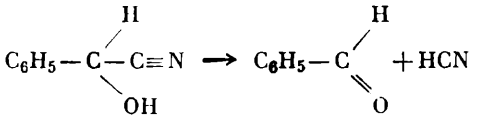


Vanillin

7.12. Aromatic Aldehydes

We shall mainly consider those aldehydes whose carbonyl group is directly attached to the benzene ring since it is these compounds that possess certain specific properties and are synthesized by special methods. A typical representative of this class of aromatic compounds is benzaldehyde. Aldehydes such as phenylacetaldehyde, $C_6H_5CH_2CHO$, or those in which the aldehyde group is more remote from the benzene ring, such as phenylhydrocinnamaldehyde, $C_6H_5CH_2CH_2CHO$, are similar to aliphatic aldehydes in methods of synthesis and reactions, for which reason they will not be discussed here. Unsaturated aldehydes too, such as cinnamaldehyde, $C_6H_5CH{=}CHCHO$ (the active principle of cinnamon) do not differ essentially from the aliphatic aldehydes with a conjugated system of π-bonds, such as crotonaldehyde, and can also be made by the condensation (this time, by the condensation of two different aldehydes—benzaldehyde and acetaldehyde).

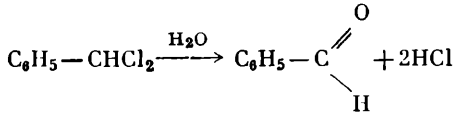
As has already been said, **benzaldehyde**, $C_6H_5 \cdot CHO$, has long been known as the oil of bitter almonds. It is prepared by the hydrolysis of the glycoside amygdalin occurring in bitter almonds (and also in the kernels of cherries, apricots, etc.). On hydrolysis the glycoside decomposes into the disaccharide gentiobiose and the benzaldehyde hydroxynitrile, which readily regenerates the aldehyde itself and hydrogen cyanide:



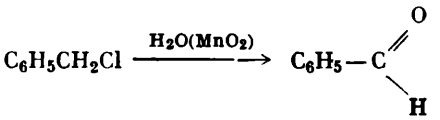
Thus, benzaldehyde had become known to chemists before benzene was discovered.

A. Synthesis of Aromatic Aldehydes

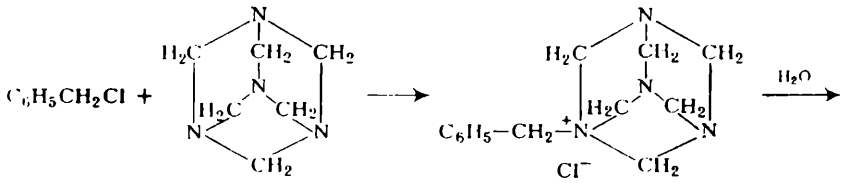
1. Methods based on the oxidation of the methyl group. The industrial preparation of benzaldehyde reduced formerly either to the hydrolysis of benzal chloride (sometimes called benzylidene chloride):



or to the oxidative hydrolysis of benzyl chloride:

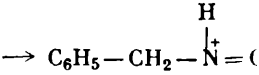


An important general method of conversion of the $-CH_2Cl$ group into the aldehyde group is Sommelet's method in which benzyl chloride is boiled with an aqueous solution of urotropine (see Volume I, page 177):

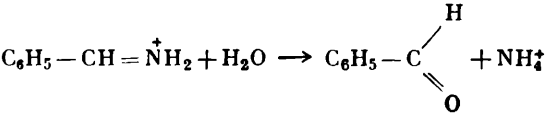


$$\longrightarrow C_6H_5-CH_2-NH_2+3CH_2O+3NH_3$$

$$C_6H_5-CH_2-NH_2+CH_2O \longrightarrow C_6H_5-CH_2-N=CH_2 \xrightarrow{H^+}$$



$$C_6H_5-CH_2-\overset{+}{N}H=CH_2+C_6H_5-CH_2-NH_2 \longrightarrow$$



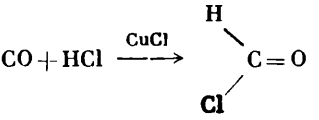
Direct oxidation of toluene to benzaldehyde is also possible (and, in general, the oxidation of the methyl groups linked to the aromatic ring to the aldehyde groups). In laboratory conditions, this can be accomplished with the aid of *Etard's reaction* (the action of chromyl chloride):

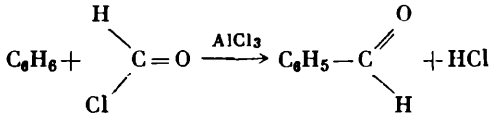
$$3C_6H_5-CH_3+4CrO_2Cl_2 \longrightarrow 3C_6H_5-CHO+H_2O+4Cr(OH)Cl_2$$

On an industrial scale, the oxidation of methyl groups is carried out by the use of chromic acid or manganese peroxide with sulphuric acid, in which case certain precautions must be taken.

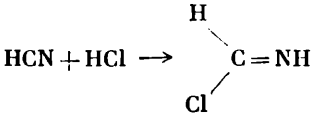
2. No less important are the methods involving the substitution of the formyl group, CHO, for a hydrogen atom of the aromatic ring. Thus, the Gattermann-Koch reaction makes use of the action of carbon monoxide and hydrogen chloride on benzene (and, in general,

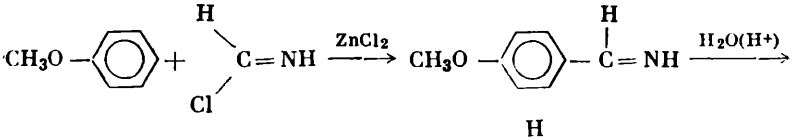
on aromatic hydrocarbons) in the presence of a mixture of aluminium chloride and cuprous chloride. Formyl chloride is probably formed as an intermediate by carbon monoxide and hydrogen chloride; then formyl chloride reacts by the Friedel-Crafts reaction mechanism:

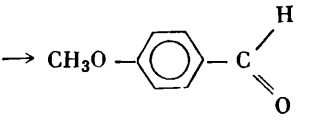




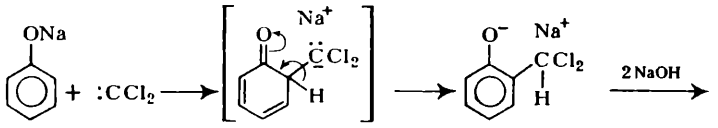
The introduction of the aldehyde group into phenols and their ethers is achieved by the Gattermann reaction in which hydrogen cyanide is used instead of carbon monoxide and zinc chloride instead of aluminium chloride:



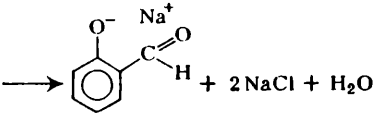




The aldehyde group can be introduced into the *ortho*-position by means of the Reimer-Tiemann method. In this method, a concentrated alkaline solution of phenol is allowed to react with chloroform. Probably, the reaction consists of the elimination of hydrogen chloride from chloroform and formation of **dichlorocarbene**, CCl_2, which then reacts with sodium phenoxide:

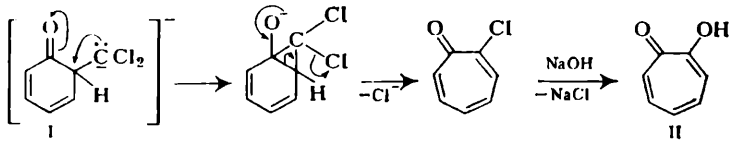


I



In this way, *o*-hydroxybenzaldehyde (salicylaldehyde) is obtained from phenol.

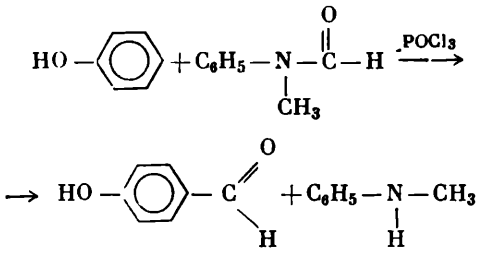
Apart from salicylaldehyde, there is formed a small amount of tropolone II, which is accounted for by the rearrangement of the intermediate carbanion I:



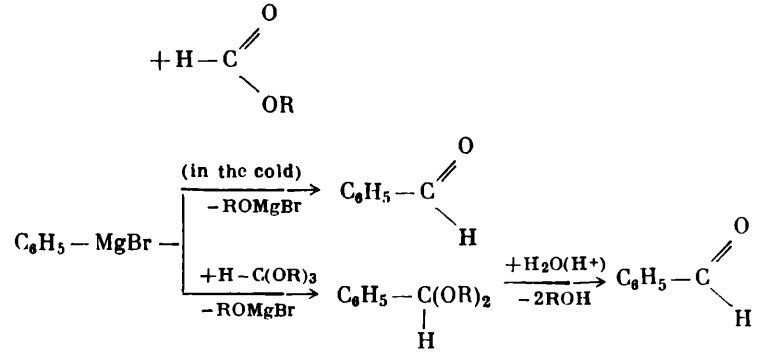
I II

Such an insertion is a typical reaction of carbenes (see Volume IV).

In the Vilsmeier method, the aldehyde group is introduced by allowing aromatic compounds (possessing sufficient nucleophilic activity) to react with formyl derivatives of secondary amines, say, with N-methylformanilide, in the presence of phosphorus oxychloride:

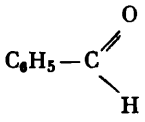
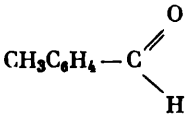
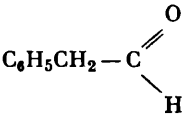
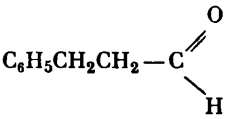
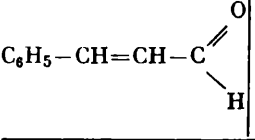
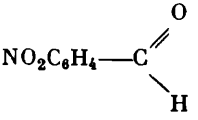


Of course, the aldehyde group can be introduced into the benzene ring by means of a Grignard reaction as well:



(A. E. Chichibabin)

TABLE 7.10. Aromatic

Formula	Name	m.p., °C	b.p., °C
Aldehydes			
	Benzaldehyde	—26	179.5
	Tolualdehyde *o*- *m*- *p*-	 — — —	 195.5 199 205
	Phenylacetaldehyde	< —10	194
	Hydrocinnamaldehyde or β-phenylpropionaldehyde	+47	280
	Cinnamaldehyde	—7.5	251 (dec.)
	Nitrobenzaldehyde *o*- *m*- *p*-	40 (α-); 37.9 (β-) 58 106.5	156 (at 15 mm Hg) 164 (at 23 mm Hg) Sublimes

Carbonyl Compounds

Dipole moment μ in benzene at 25°C, D	Melting point of functional derivatives of aldehydes, °C		
	oxime	phenylhydrazone	semicarbazone
2.75	35 (α-*syn*-isomer) 130 (β-*anti*-isomer)	156	222
— — 3.30	49 — 108-110	106 90 121	212 223-224 234
2.48 (at 20°C)	98.5	62-63	—
2.31 (at 20°C)	93-94.5	—	127
3.71 (at 18°C)	138.5 (α-); 64-65 (β-)	168	208
4.30	154 (α-); 103 (β-)	—	256
3.28	85 (α-); 121 (β-)	—	246
2.4	182-184 (α-); 133 (β-)	153-154	211

Formula	Name	m.p., °C	b.p., °C
Ketones			
$C_6H_5-\overset{\overset{O}{\|}}{C}-CH_3$	Acetophenone	20	202.3
$C_6H_5-\overset{\overset{O}{\|}}{C}-C_2H_5$	Phenyl ethyl ketone or propiophenone	21	218
$C_6H_5-\overset{\overset{O}{\|}}{C}-C_6H_5$	Benzophenone	49 (α-); 26 (β-); 45 (γ-)	306

3. The aldehydes can also be made by reducing the functional derivatives of carboxylic acids, say, by reduction of benzoyl chloride by the Zaitsev-Rosenmund reaction:

$$C_6H_5-\overset{\overset{O}{\|}}{C}-Cl \xrightarrow{H_2/Pd} C_6H_5-\overset{\overset{O}{\|}}{C}-H + HCl$$

B. Properties of Aromatic Aldehydes

The physical properties of aromatic aldehydes, their formulas and names are listed in Table 7.10.

Benzaldehyde and other aldehydes in which the —CHO group is directly attached to the aromatic ring are in many respects similar to aliphatic aldehydes. For example, they are reduced to secondary alcohols, and oxidized to carboxylic acids. Reactions of these types deserve attention.

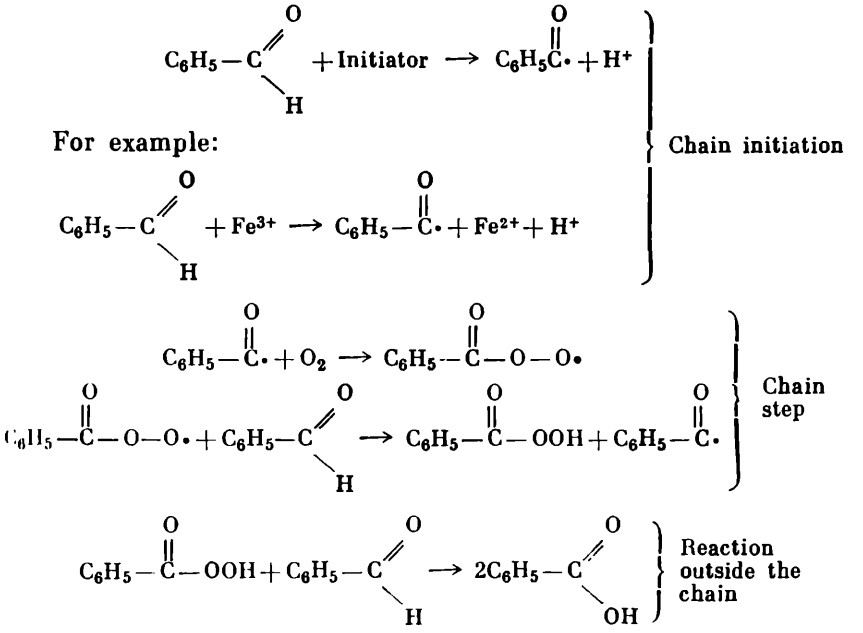
Oxidation. For aromatic aldehydes, just as for aliphatic aldehydes, there are two types of oxidation reactions, which in the long run lead to the formation of the corresponding acids: homolytic chain oxidation and heterolytic oxidation.

(a) *Homolytic oxidation.* In air, benzaldehyde poured in a thin layer changes in a few hours into benzoic acid. Salts of transition metals, say, of iron and manganese, speed up the process. The course

Table 7.10 (continued)

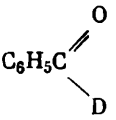
Dipole moment μ in benzene at 25°C, D	Melting point of functional derivatives of aldehydes, °C		
	oxime	phenylhydrazone	semicarbazone
2.97 (at 18°C)	58	106	203
—	53-54	—	182
2.95 (at 13°C)	144	137	167

of the reaction is as follows:

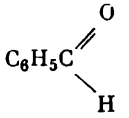


(b) *Heterolytic oxidation.* An example is the heterolytic oxidation by permanganate. This is a reaction catalysed by hydrogen ions,

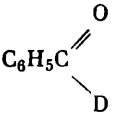
the mechanism of which has been studied with the use of oxygen-labelled permanganate, $KMn^{18}O_4$, and deuterium-labelled benzaldehyde



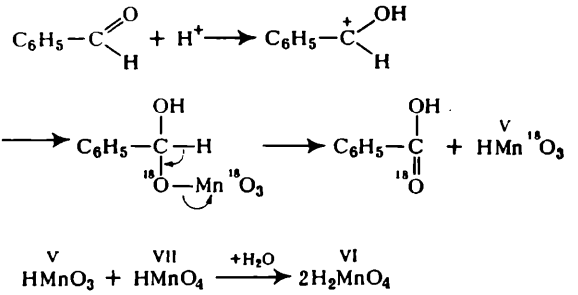
It has been found that the rate of the reaction for



and

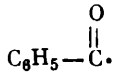


is quite different: deuterated benzaldehyde oxidizes 7 times slower than does the undeuterated compound! This means that the rate-determining step of the reaction involves the C—D and C—H bonds. Since the resulting benzoic acid contains 50 per cent of labelled ^{18}O from permanganate, oxygen required for the oxidation of benzaldehyde is supplied not from water but from $KMn^{18}O_4$. On the basis of all these data we can draw a conclusion concerning the mechanism of the heterolytic oxidation:

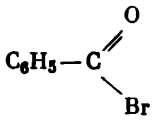


The mechanism of the oxidation reaction is given here not for comparison of aliphatic and aromatic aldehydes, which behave in a similar manner in these and following reactions, but for the purpose of emphasizing that the mechanisms of reactions identical by their final results, say, the oxidation by air and permanganate, may be quite different and must be studied.

Photolysis. The photolysis of benzaldehyde gives rise to the free benzoyl radical

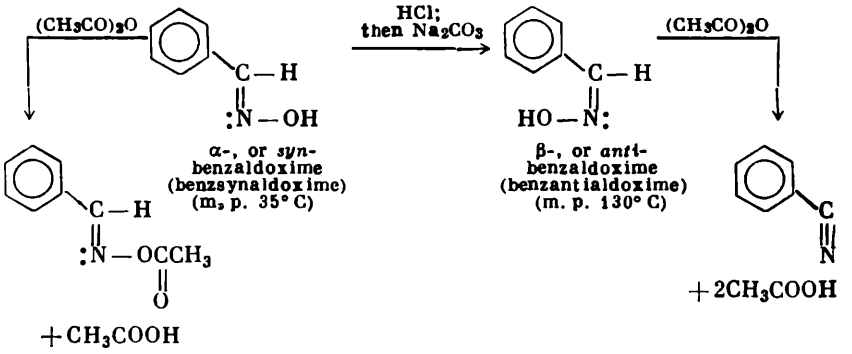


which is stable at —200°C, and at —140°C adds bromine slowly (within minutes), being converted into benzoyl bromide



The benzoyl radical is an orange-red substance, gives an EPR signal (see Volume IV, "Free Radicals"), and adds on to the olefinic linkages (Schmidt).

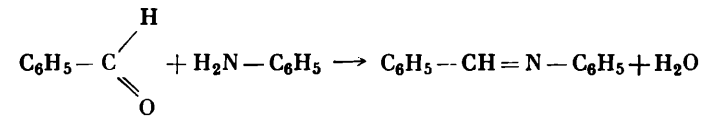
Aromatic aldehydes, just as aliphatic aldehydes, add on sodium bisulphite, hydrogen cyanide, and a Grignard reagent (see Volume I, page 175). A number of reactions of displacement of the aldehydic oxygen also proceed in a manner quite analogous to the corresponding reactions of aliphatic aldehydes. They include reactions with hydrazine, semicarbazide, arylhydrazines (see Volume I, page 180). The reaction with hydroxylamine leads to two stereoisomeric oximes of benzaldehyde, which differ not only by their physical constants but also by their reactions. Under the action of acetic anhydride (and other dehydrating agents) the *anti*-isomer loses water and forms benzonitrile, and the *syn*-isomer is acetylated at the hydroxyl group:



The *syn-anti* isomerism which has already been discussed with respect to azobenzene (page 91) is quite similar to *cis-trans* isomerism of compounds with a carbon-carbon π-bond. The role of the second substituent at nitrogen is played by a free pair of electrons. *Trans*-elimination (the elimination of H and OH from the *trans*-position in this particular case) is a general rule (cf. "Elimination Reactions" in Volume IV).

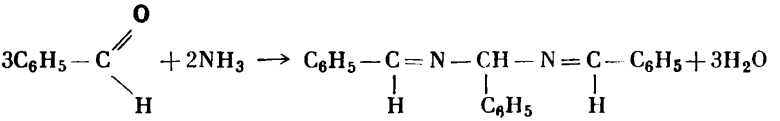
Condensation Reactions. A new reaction of aromatic aldehydes, as compared with aliphatic aldehydes, is the reaction with aromatic

amines, which yields an important class of **anils** or **Schiff's bases**:



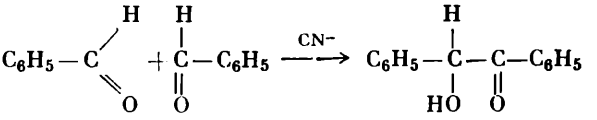
(For reactions of aliphatic aldehydes with anilines, see "Quinoline and Its Derivatives".)

With ammonia the aromatic aldehydes also react differently from aliphatic aldehydes and give not aldehyde-ammonias but **hydrobenzamides:**



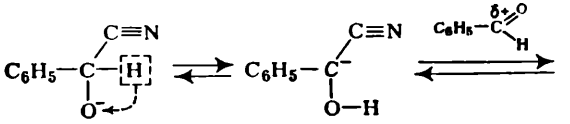
One of the fundamental differences between aromatic and aliphatic aldehydes is that the former show no reactions leading to the formation of polymers in general and, in particular, no reactions of formation of trimers, such as paraldehyde, which is so characteristic of aliphatic aldehydes.

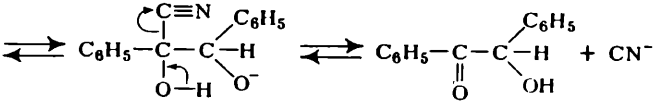
Of course, neither aldol nor croton condensation is possible for aromatic aldehydes since for such condensation reactions to be effected the presence of a methylene linkage adjacent to the aldehyde group is required. But benzaldehyde and, in general, aromatic α-aldehydes, are capable of participating in a different, **benzoin condensation**, which occurs in the presence of potassium cyanide:



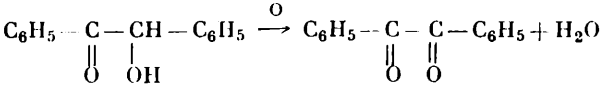
Benzoin

One may think that the role of the cyanide ion is to add on initially to an aldehyde (just as in the case of addition of hydrogen cyanide) and to withdraw the bonding electrons from the aldehydic hydrogen left, until the hydrogen is ionized and becomes capable of migrating as a proton to the carbonyl oxygen of the second molecule, following which a carbon-carbon bond is formed and the CN^- ion is ejected:

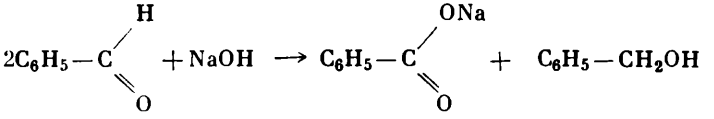




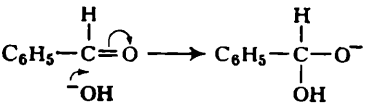
The structure of benzoin follows from its oxidation to 1,2-diketone—**benzil**:

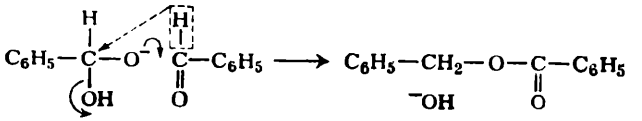


As mentioned previously, benzaldehyde does not undergo self-condensation under the action of alkali, but there is possible for it a different manifestation of the action of alkali: two molecules of benzaldehyde disproportionate into benzyl alcohol and benzoic acid (*Cannizzaro reaction*):

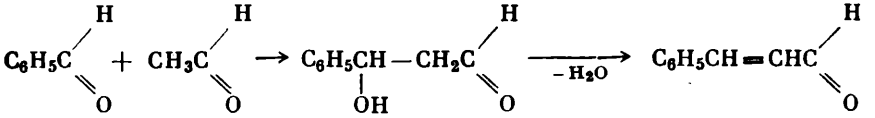


The mechanism of the Cannizzaro reaction is elucidated by the Tishchenko reaction which is characteristic of both aliphatic and aromatic aldehydes and which is effected by the action of aluminium alkoxides and also of tetraalkylhydroxytitaniums (A. N. Nesmeyanov, O. V. Nogina). In the Tishchenko reaction (see Volume I, page 182), two molecules of an aldehyde are converted into a molecule of an ester of the corresponding alcohol and acid, and, in the case of benzaldehyde, into the benzyl ester of benzoic acid (benzyl benzoate). The Cannizzaro reaction may be considered to be a special case of the Tishchenko reaction, being characterized by the fact that the ester formed is hydrolysed by alkali to the alcohol and salt of the acid. The reaction consists in the *hydride transfer*, i.e., the migration of one of the hydrogen atoms together with its pair of electrons to the carbonyl carbon of another molecule of the aldehyde:

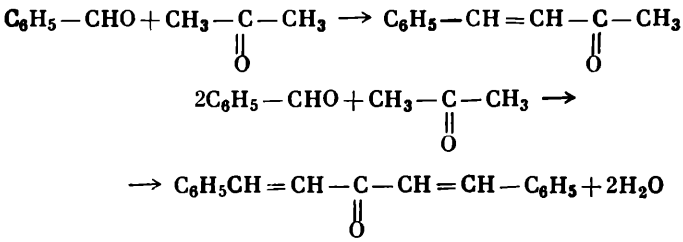




As regards aldol and croton condensations of benzaldehyde with aliphatic saturated aldehydes, these processes take place in a normal way, and with acetaldehyde, for example, lead to the formation first of β-hydroxy-β-phenylpropionaldehyde, and then of cinnamaldehyde (occurs in cinnamon and is responsible for its odour):

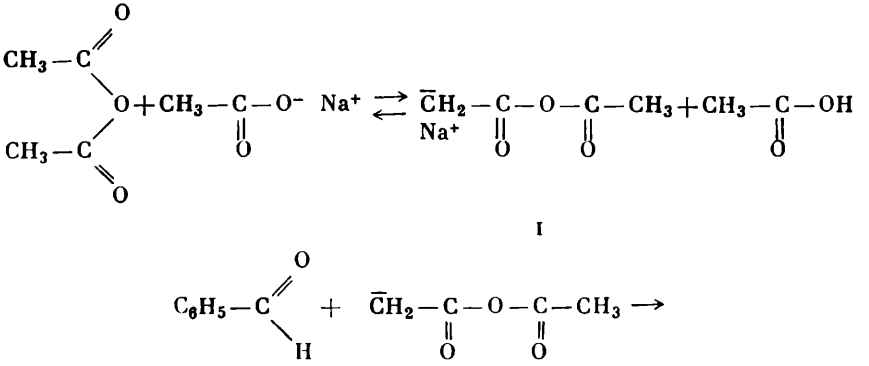


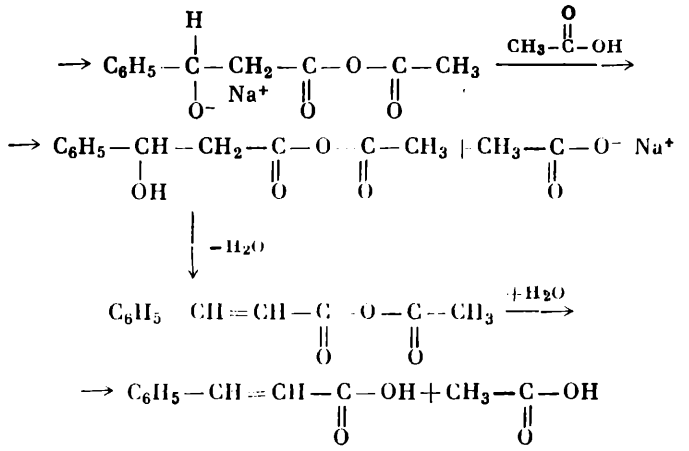
The croton condensation of benzaldehyde witn acetone (and also with aromatic ketones) in the presence of dilute alkalis proceeds very readily. Depending on the ratio of the reagents, benzalacetone or dibenzalacetone may be obtained:



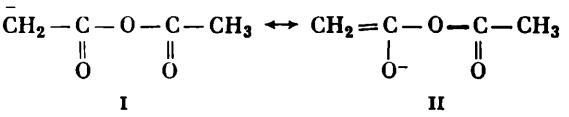
Both unsaturated ketones are yellow crystalline substances.

Especially important is the **Perkin condensation**, i.e., the condensation of aromatic aldehydes with the anhydrides of aliphatic acids in the presence of bases, which leads to unsaturated acids, such as cinnamic acid. The role of the base can be played by a salt, say, potassium carbonate or sodium acetate. The reaction proceeds at 150-180°C and begins with nucleophilic attack of the carbanion I of the anhydride on the carbonyl carbon:





Of course, the anion I is mesomeric:



I II

the greater contribution must belong to structure II. So, the reaction of this anion with an aldehyde is basically a reaction involving the reaction-centre transfer.

In recent years, the **Wittig reaction** has gained wide recognition. This reaction enables introducing the $R_2C=$ group in place of oxygen into aldehydes and ketones (for more detail, see Volume IV).

Substitution Reactions of Benzaldehyde into the Ring. The aldehyde group is a *meta*-directing group of medium orienting power, deactivates the aromatic nucleus and directs the entering substituent chiefly into the *meta*-position. The nitration of benzaldehyde yields, in addition to *m*-nitrobenzaldehyde, a considerable amount of the *o*-isomer.

7.13. Aromatic Ketones

In the case of ketones, a distinction is also made between ketones in which the carbonyl is directly attached to the aromatic ring, and ketones with a carbonyl group in the side chain. Only the former have certain specific properties and routes of synthesis.

Common names of the ketones are built as the names of acylated hydrocarbons with addition of the ending *-one*: acetophenone, propiophenone, butyrophenone, benzophenone (phene is the old Laurent name of benzene).

A. Synthesis of Aromatic Ketones

1. Ketones with the carbonyl group attached to the aromatic ring are most conveniently synthesized by the Friedel-Crafts reaction:

$$C_6H_6 + R-\overset{\overset{O}{\|}}{C}-Cl \xrightarrow{AlCl_3} C_6H_5-\overset{\overset{O}{\|}}{C}-R + HCl$$

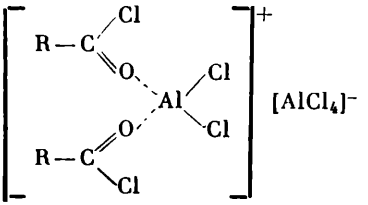
$$C_6H_6 + R-\overset{\overset{O}{\|}}{C}-O-\overset{\overset{O}{\|}}{C}-R \xrightarrow{AlCl_3} C_6H_5-\overset{\overset{O}{\|}}{C}-R + R-\overset{\overset{O}{\|}}{C}-OH$$

where R is the aromatic or aliphatic radical.

Aluminium chloride has to be taken for this reaction in an amount equivalent to that of the acid chloride since it is completely bound into a complex and is found to be linked with the ketone even after its formation. This complex might be expected to have a structure analogous to the structure of what is known as the Zeele complex:

$$R-\overset{\overset{O}{\|}}{C}-F + BF_3 \longrightarrow R-\overset{\overset{:O:}{\|}}{C}^{+}\,[BF_4]^{-}$$

which is capable, though to a small extent, of acylating the aromatic ring. But this conjecture has not been proved; and in the complexes of acid chlorides with aluminium chloride the linkage is formed via oxygen, just as in the case of ketones. Studies of the ultraviolet spectrum which has, as with ketonic complexes, shifts to longer wavelengths, thermochemical investigations and data on the molecular weight have enabled N. N. Lebedev to propose the following structure for the complex in question:

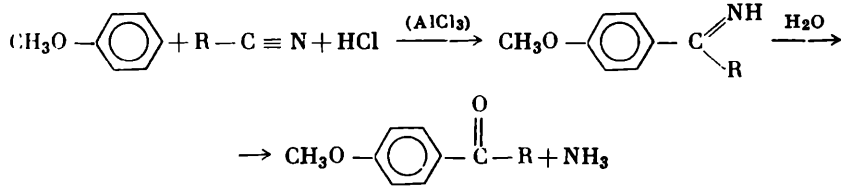


It is natural that the linkage with aluminium increases the positive charge on the carbonyl carbon and makes it more liable to electrophilic attack.

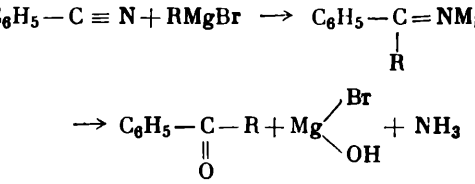
The aromatic ring deactivated by the presence of a *meta*-directing group does not enter into this reaction. Therefore, a second acyl group cannot be introduced into the benzene ring by the use of the

Friedel-Crafts reaction. Nitrobenzene, benzenesulphonic acid, etc., cannot be acylated in this way either.

2. If the aromatic ring is more nucleophilic than the benzene ring (polyhydric phenols, their ethers), ketones are synthesized by the Hoesch reaction—the action of a nitrile and hydrogen chloride (a modification of the Gattermann reaction):

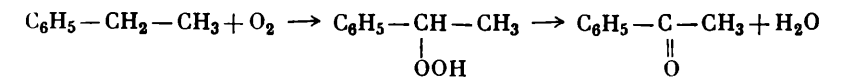


3. The reaction of a Grignard reagent with aromatic nitriles is also quite suitable for the purpose:



where R is the aromatic or aliphatic radical.

4. The oxidation of ethylbenzene (and its homologues) by atmospheric oxygen, initiated in the liquid phase by manganese or cobalt salts, leads to the formation of a hydroperoxide, which decomposes to a ketone (a chain reaction):

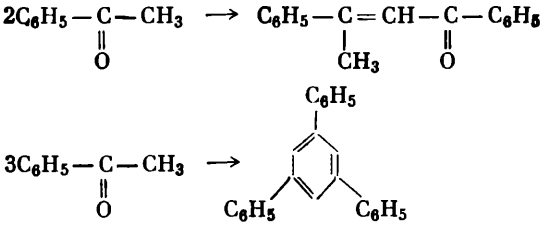


B. Properties of Aromatic Ketones

The physical properties of ketones, their formulas and names are given in Table 7.10.

Ketones containing one aliphatic and one aromatic radical attached directly to the carbonyl group are termed **mixed** or **fatty-aromatic ketones**. A representative of fatty-aromatic ketones is **acetophenone**, *phenyl methyl ketone* (m. p. 20°C, b.p. 202.3°C). This is a liquid with the odour of bird-cherry flowers, which finds application in perfumery. All that has been said about the properties of acetone (see Volume I, page 175) refers to acetophenone as well. It is capable, almost to the same extent, of addition reactions at the carbonyl double bond and of replacement of the carbonyl oxygen. Like all ketones, it is not polymerized, but undergoes condensation reactions. The

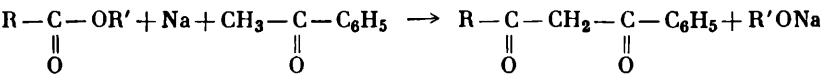
products of the croton condensation of acetophenone is dypnone (an analogue of mesityl oxide) and triphenylbenzene:



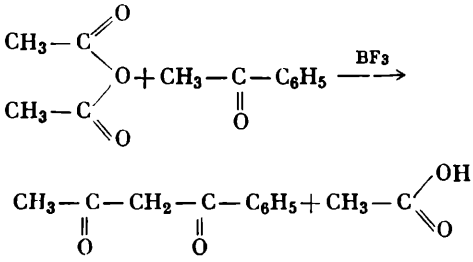
Even these reactions demonstrate the usual mobility of α-hydrogen atoms of the methyl group. Other similar reactions could also be cited.

The condensation with the functional derivatives of acids to give 1,3-diketones is as follows:

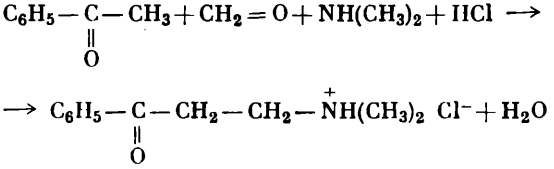
(a) ester condensation:



(b) the Meerwein condensation with acid anhydrides:



The Mannich reaction. When acetophenone is allowed to react with a mixture of formaldehyde, an amine and hydrochloric acid, the α-hydrogen atom is replaced by a monoalkylaminomethyl or dialkylaminomethyl group:



The intermediate product in this reaction is the methylol derivative of the amine, which is formed by the interaction of formalde-

hyde with the amine:

$$CH_2O + HN(CH_3)_2 \longrightarrow HO-CH_2-N\begin{matrix}CH_3\\CH_3\end{matrix}$$

This intermediate product is converted in acid medium into the carbonium ion stabilized by the shift of the free electron pair of the nitrogen:

$$HO-CH_2-\ddot{N}\begin{matrix}CH_3\\CH_3\end{matrix} + H^+ \longrightarrow H_2O + \overset{+}{C}H_2-\ddot{N}\begin{matrix}CH_3\\CH_3\end{matrix}$$

The halogenation of acetophenone at the methyl group proceeds according to the equation:

$$C_6H_5-\underset{\underset{O}{\|}}{C}-CH_3 + Cl_2 \longrightarrow C_6H_5-\underset{\underset{O}{\|}}{C}-CH_2Cl + HCl$$

Chloroacetophenone with its very mobile halogen causes a very strong irritation of mucous membranes. It was formerly used as a tear gas during the war time. Chloroacetophenone can also be produced by the Friedel-Crafts reaction from benzene and $ClCH_2\underset{\underset{O}{\|}}{C}-Cl$, which proves its structure.

Acetophenone and ketones with the remote position of the carbonyl group when reacted with sulphur and ammonia undergo a remarkable Willgerodt reaction—the conversion into an acid with the same number of carbon atoms:

$$C_6H_5-\underset{\underset{O}{\|}}{C}-(CH_2)_n-CH_3 + S + NH_3 \xrightarrow[-H_2O]{}$$

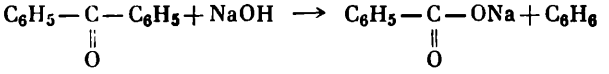
$$\longrightarrow C_6H_5-(CH_2)_{n+1}-\underset{\underset{S}{\|}}{C}-NH_2 \xrightarrow{+2H_2O}$$

$$\longrightarrow C_6H_5-(CH_2)_{n+1}-C\begin{matrix}OH\\\diagup\\=O\end{matrix} + NH_3 + H_2S$$

Aliphatic ketones are also capable of undergoing this reaction (N. Kh. Freidlina).

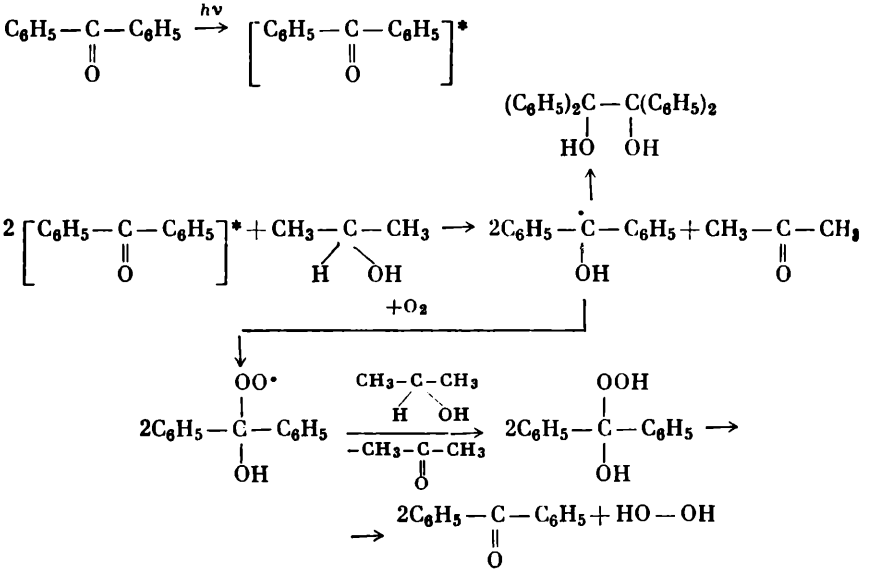
The purely aromatic ketone **benzophenone** is noticeably less active than acetophenone in additions at the carbonyl group (for example, does not add $NaHSO_3$) and in substitution reactions which proceed much more slowly.

Purely aromatic ketones are characterized by the cleavage in the presence of concentrated alkali at a high temperature:



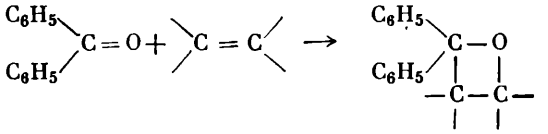
The reactions of electrophilic substitution in these ketones occur largely in the *meta*-position to the carbonyl group.

Benzophenone is excited by near ultraviolet radiation and is therefore used in photochemical processes as an **inductor**. The action of the excited benzophenone molecule as an inductor on secondary propyl alcohol in the presence and absence of oxygen is illustrated by the following examples (the asterisk indicates a photochemically excited molecule):

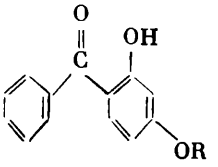


Some of the derivatives of benzophenone are also excited by the action of light, giving off the absorbed energy in the form of radiation—they fluoresce. 2,2′-Dihydroxy-4,4′-dimethoxybenzophenone is used under the name of **uvinul** for protection of fabrics and plastic materials against the destructive action of light since it "takes up the blow" and then gives off the absorbed energy, in the form of harmless, longer-wavelength fluorescent radiation.

Benzophenone, like acetophenone, adds on to olefins on irradiation, forming four-membered heterocyclic ethers:



Hydroxyketones of the type



where R = C_8H_{17} or $C_{12}H_{25}$, are used under the trade name of cyanosorb for protection of plastic materials against the destructive action of ultraviolet, short-wavelength and visible regions of the spectrum.

A specific reaction of addition of sodium is effected by the action of a metal on the aromatic ketones (Schlenk). This reaction yields deeply coloured paramagnetic (an odd electron!) **metal ketyls** with a trivalent carbon

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

which are readily oxidized to ketones.

In the aliphatic series, the existence of metal ketyls for sterically hindered ketones has been proved by A. E. Favorsky and I. N. Nazarov.

C. Ketoximes and Beckmann Rearrangement

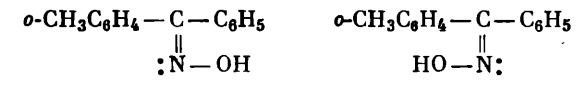
Asymmetrically built ketones of the general formula

$$R-\underset{\underset{O}{\|}}{C}-R'$$

both aromatic as well as aliphatic, when made to react with hydroxylamine form each two isomeric oximes, which differ in physical constants (in particular, in melting point) and in their behaviour in the Beckmann rearrangement (see Volume II, page 166). For instance, *o*-methylbenzophenone when reacted with NH_2OH forms two isomeric oximes with melting points of 105 and 69°C.

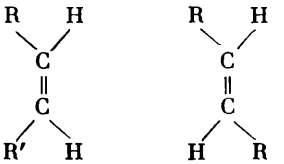
Studies of this isomerism have led to the conclusion that this is *syn-anti* isomerism similar to the isomerism discussed with respect

to azo compounds (page 91):



syn-Phenyl-*o*-tolylketoxime *anti*-Phenyl-*o*-tolylketoxime

and analogous to the *cis-trans* isomerism of olefins and their derivatives:

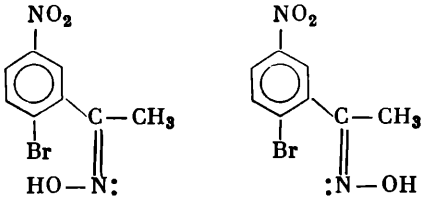


cis-Isomer *trans*-Isomer

As has been said earlier, for the geometrical isomerism of nitrogen compounds the prefix *cis-* is replaced by *syn-*, and *anti-* is used instead of *trans-*.

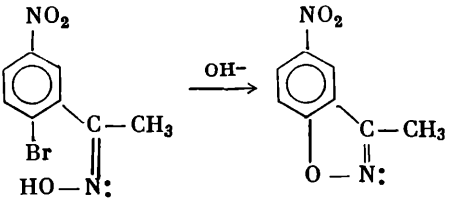
At present, the *syn-* and *anti*-configurations of an oxime can be established from its dipole moment if at least one hydrocarbon radical of the ketone has a dipole moment directed in the manner known. For this to be done, it is necessary that a substituent, such as, for example, a halogen, be present in the *para*-position in one of the radicals.

The configurations have been established by purely chemical means (Meisenheimer) for the following oximes:



syn- *anti*-

syn-2-Bromo-5-nitroacetophenoxime which contains a mobile bromine atom due to the presence of a *p*-nitro group undergoes cyclization into a benzisoxazole heterocycle under the action of alkali

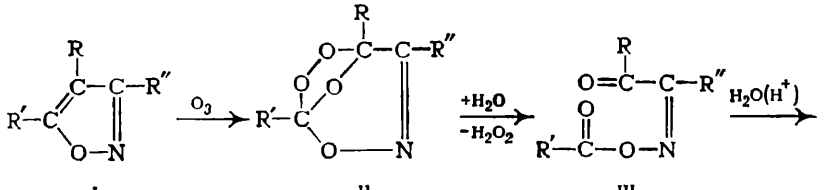


whereas its *anti*-isomer is not capable of such ring-closure.

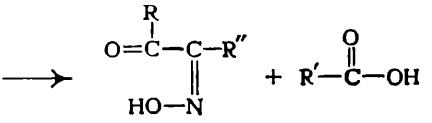
Since the cyclization does not affect the bonds between the atoms responsible for the configuration ($\diagdown$C=N—), the ring closure occurred without change of configuration and, hence, the isomer capable of ring closure is a *syn*-compound with closely spaced bromine and hydroxyl.

Another purely chemical way is the reverse one: it is based on the disclosure of the heterocyclic compound.

The hetero ring of the structure shown below undergoes ozonization which affects only the multiple C=C bond and not the C=N bond:

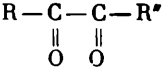


I II III

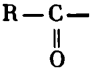


IV

The ester of oxime III resulting from the ozonolysis is converted by hydrolysis into the monoxime IV of the diketone

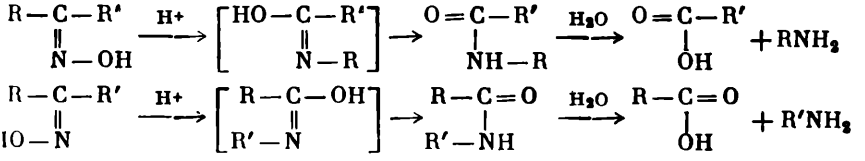


The *syn*-configuration of the oxime group with respect to the radical



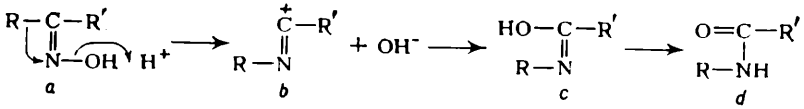
follows from the method of its formation (which does not disturb the bonds of the $\diagdown$C=N— grouping either).

The oximes when made to react with acids, Lewis acids, or with PCl_5, are converted into the substituted acid amides according to the scheme:

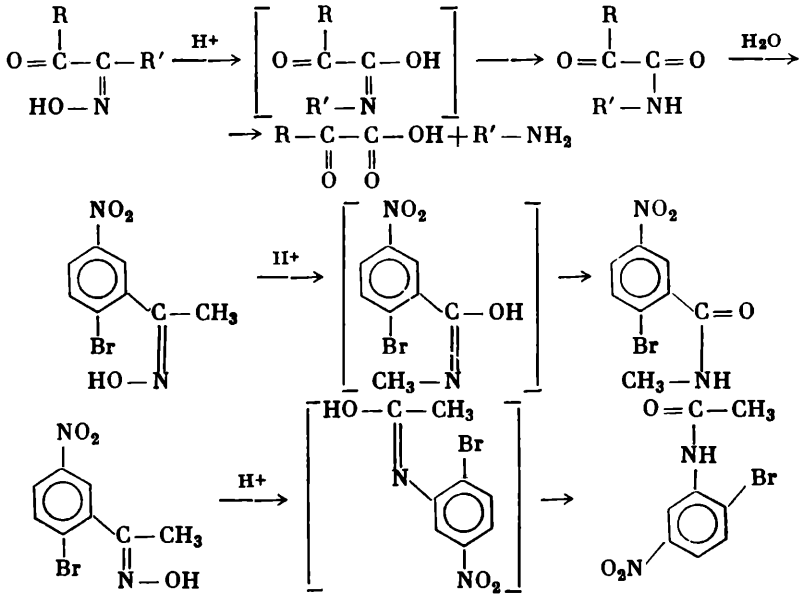


Stereoisomeric oximes in this transformation, which is called after its discoverer (Beckmann, 1886) the **Beckmann rearrangement**, form structurally isomeric substituted amides, whose structure is easily established by hydrolysis to a primary amine and an acid, which are different for two stereoisomeric starting oximes.

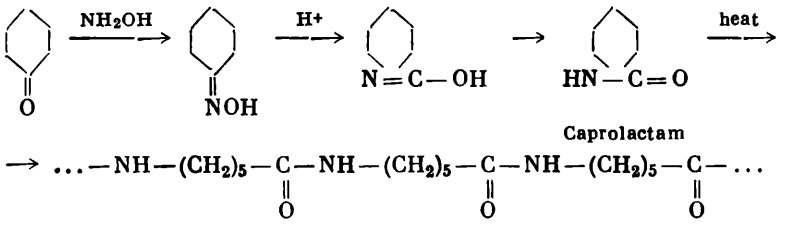
Just a few words about the mechanism of the rearrangement which has been left unexplained by the above scheme. In the Beckmann rearrangement, first the hydroxyl of the oxime group is split off as an anion carried away by the hydrogen ion, and then to the positively charged nitrogen left there migrates, simultaneously with the elimination of OH^-, the radical (with a pair of electrons) from the *anti*-position to the hydroxyl, leaving the carbonium ion, which captures the hydroxyl from the medium:



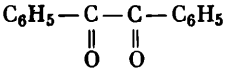
According to the Eltekov-Erlenmeyer rule, the intermediate compound *c* with the hydroxyl group attached to a carbon atom with a double bond rearranges to the amide *d*. The fact that the Beckmann rearrangement takes place due to the migration of the *anti*-radical and not of the more closely arranged *syn*-radical has been proved by Meisenheimer for the above oximes with the configuration established chemically by him:



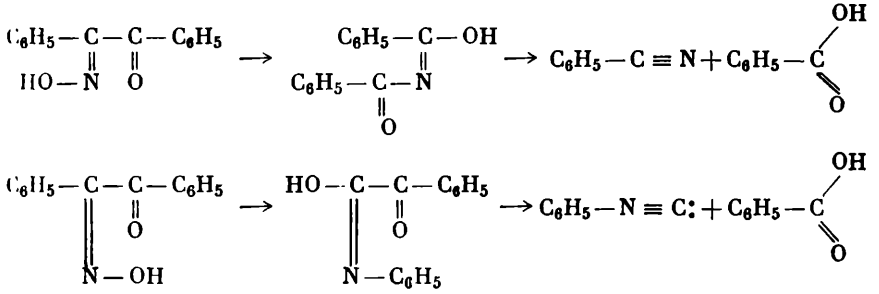
The Beckmann rearrangement is known also for the aliphatic and alicyclic oximes. It is of commercial value since it is used in the production of caprolactam which is the starting material for the manufacture of a high-molecular-weight polycapramide—Nylon 6:



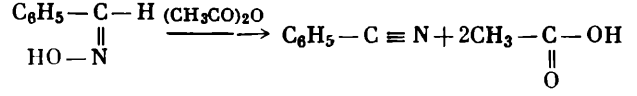
In certain processes, apart from the normal Beckmann rearrangement just described, there occurs another type of Beckmann rearrangement. For example, when the stereoisomeric monoximes of the α-diketone



is treated with toluenesulphochloride, $CH_3C_6H_4SO_2Cl$, in pyridine, the following changes take place: the *anti*-isomer yields benzoic acid and benzonitrile, and the *syn*-isomer gives benzoic acid and phenylcarbylamine (isonitrile):

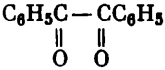


From the schemes given above it is seen that the second type of the Beckmann rearrangement of the *anti*-ketoxime is closely related to the cleavage of *anti*-aldoximes leading to the formation of nitriles (see page 167):

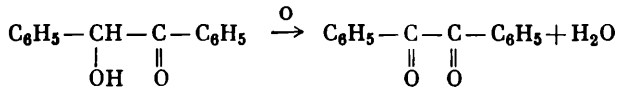


D. Diketones

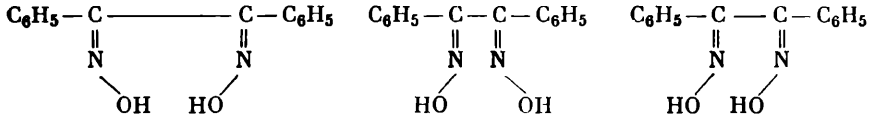
The simplest representative of the aromatic **α-diketones**



is known under the historical name **benzil** (not to be confused with the radical $C_6H_5CH_2$—, which is called benzyl). This 1,2-diketone can be prepared by the oxidation of benzoin (page 169):

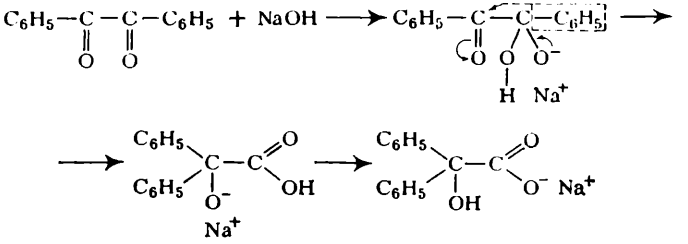


Benzil forms three distinct stereoisomeric dioximes:



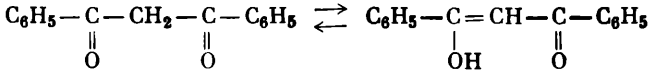
β- or *syn*-Benzildioxime (m.p. 206°C) | α- or *anti*-Benzildioxime (m.p. 237°C) | γ-, *amphi*-, or *syn-anti*-Benzildioxime (m.p. 166°C)

The most remarkable property of benzil is its rearrangement to benzilic acid, which proceeds readily and quantitatively by the action of alkali on alcoholic solutions of the diketone. The mechanism of the **benzilic acid rearrangement** is formulated as follows:



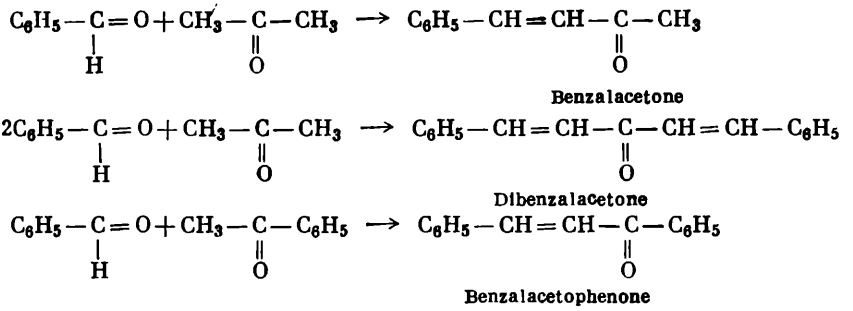
Rearrangements of the benzilic acid type are widespread not only in the aromatic series. They are also exhibited by alicyclic 1,2-diketones, in which case the rearrangement proceeds with contraction of the ring by one unit.

β-Diketones of the aromatic series are prepared by the condensation methods described earlier (page 174). Like their aliphatic analogues, they are capable of keto-enol tautomerism:



and can form chelates with cations of many metals (see Volume II, page 76). Also, β-diketones give sodium derivatives which are alkylated at carbon:

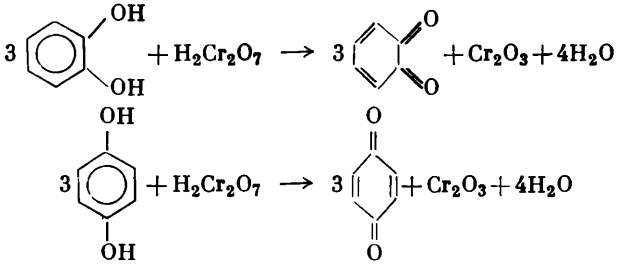
Unsaturated ketones with a system of conjugated bonds, C=C—C=O, are formed by the croton condensation of aromatic aldehydes with ketones; for example,



The properties of these ketones are typical of ketones with conjugated C=C—C=O bonds (see Volume I, page 401).

7.14. Quinones

The oxidation of catechol (pyrocatechin) and hydroquinone yields *o*- and, accordingly, *p*-benzoquinones:

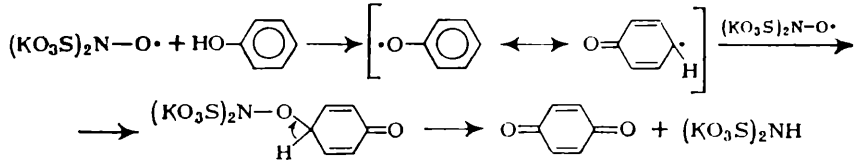


p-Benzoquinone was discovered in 1837 by A. A. Voskresensky.

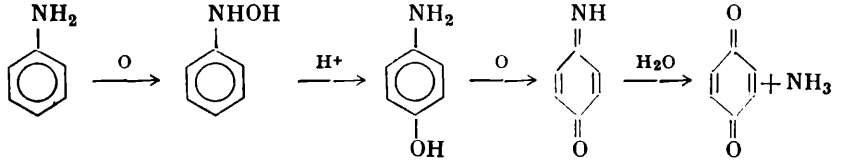
Quinones are coloured (*p*-quinone is yellow, *o*-quinone is red) crystalline compounds with a pungent smell, which sublime on heating. They are extremely reactive and behave as unsaturated ketones with a conjugated system of C=C—C=O bonds. The structure of quinones follows from the methods of their synthesis and from their properties.

We shall now consider methods of synthesizing *p*-quinones.

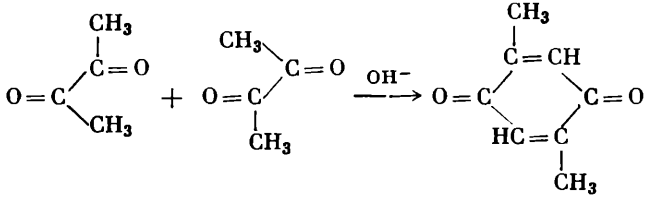
1. *p*-Benzoquinone (benzoquinone) is formed in a number of reactions of oxidation of phenol. Information on the mechanism of these reactions is provided by the thoroughly studied oxidation of phenol by Fremy's salt (potassium nitrodisulphonate), $\cdot O-N(SO_3K)_2$, which is a free radical—a single-electron oxidizing agent:



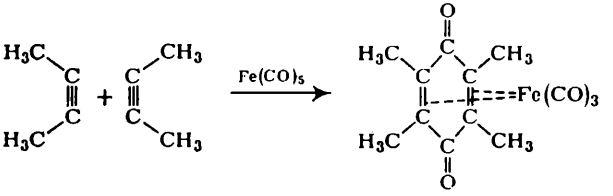
2. The preparation of *p*-benzoquinone by the oxidation of aniline with chromic acid passes through the stage of phenylhydroxylamine which rearranges into *p*-aminophenol, the latter compound being then oxidized to a monoquinonimine. The quinonimine is hydrolysed to the quinone:



3. The condensation of aliphatic 1,2-diketones in alkaline solution yields 2,5-dialkylbenzoquinones:



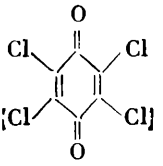
4. By allowing iron pentacarbonyl, $Fe(CO)_5$, to react with dimethylacetylene Reppe obtained a complex of duroquinone with $Fe(CO)_3$:



which can be decomposed by acid to give duroquinone itself.

In this way, acetylene and iron carbonyl form hydroquinone.

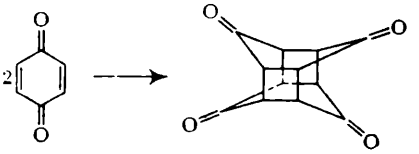
5. By the action of aqua regia (HNO_3 + HCl) on the derivatives of benzene, in particular on aniline, it is possible to obtain tetrachloro-*p*-benzoquinone (chloranil):



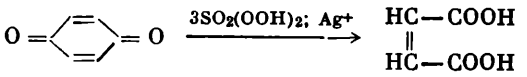
A. Reactions of Benzoquinones

As has already been said (page 148), quinones when reduced are converted into the starting dihydroxybenzenes.

p-Benzoquinone when subjected to radiation is dimerized (Cookson):



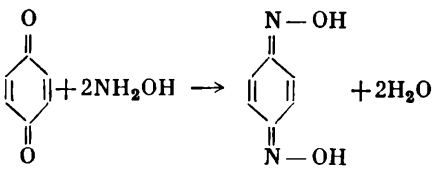
The oxidation of *p*-benzoquinone with persulphuric acid (in the presence of Ag^+) leads to the formation of maleic acid:



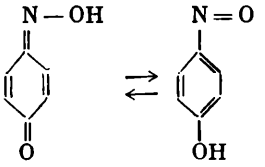
This reaction is important since it proves the structure of benzoquinone.

Of the reactions of *p*-benzoquinone as an unsaturated ketone we shall consider the following:

With hydroxylamine *p*-benzoquinone forms a dioxime:



The monoxime of *p*-benzoquinone is tautomeric with nitrosophenol:



The monoxime is partially converted into nitrosophenol only in solutions. Figure 7.9 gives the absorption curves for *p*-nitrosophenol in different solvents. The intensity of absorption in the region of 720-735 mμ (nm) is a measure of the content of the nitroso form in the solution which is characterized by an absorption maximum within that wavelength range.

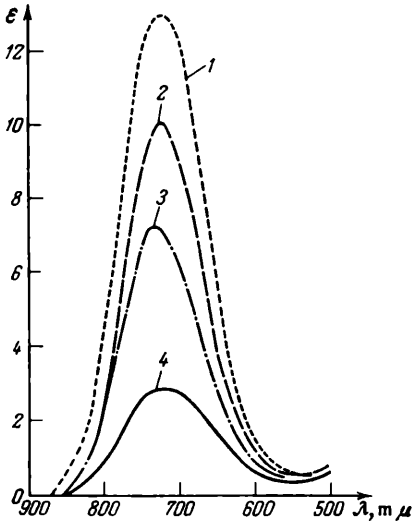
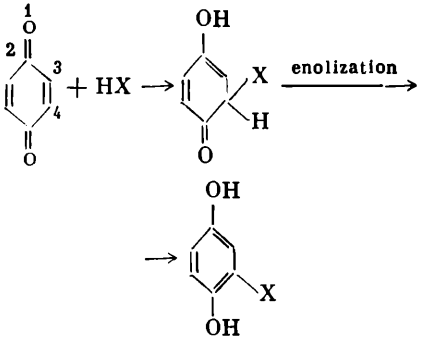


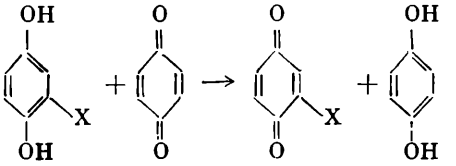
Fig. 7.9.
Absorption curves for *p*-nitrosophenol in various solvents:
1—ethyl acetate; *2*—pyridine; *3*—dioxan; *4*—chloroform.

Inorganic acids (weak and those of medium strength), organic acids, alcohols, primary and secondary amines react with *p*-benzoquinone, adding on to it, just as to an unsaturated ketone, in the 1,4-positions (see Volume I, page 402). As a result of this, the quinonoid system is converted into the benzenoid system and a substituted hydroquinone is formed:

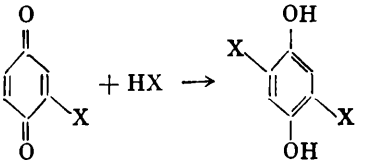


where HX=acid, alcohol, or amine; X=Cl, $-N=\overset{+}{N}=\overset{-}{N}$, $^{-}OCCH_3$, $-S_2O_3^-$, $-OCH_3$, $-NHC_6H_5$, etc.

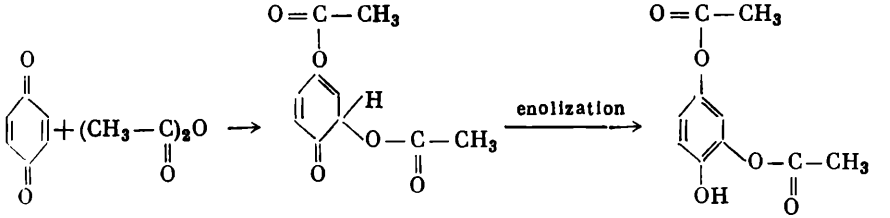
This substituted hydroquinone can be oxidized by an excess of quinone to a substituted quinone:



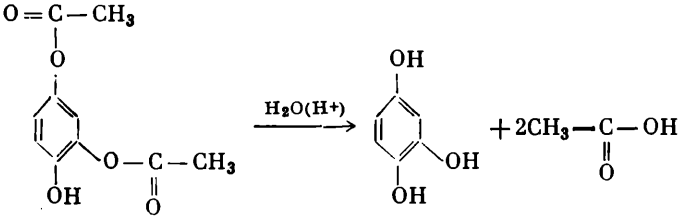
which is capable of adding again a molecule of HX:



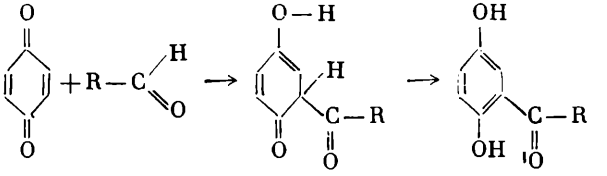
In a similar way, acetic anhydride too can be added to quinone:



In this particular case, the addition is completed at this stage. In this way 1,2,4-trihydroxybenzene is produced (after hydrolysis):



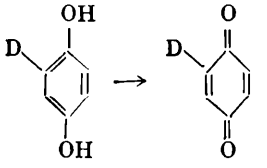
When a solution of quinone is subjected to the action of light in an aldehyde, the latter adds on (probably, homolytically) to quinone (Ciamician):



As seen, the range of compounds that add on to quinone is considerably wider than in the case of ordinary α,β-unsaturated ketones.

An additional driving force for this addition is here the liberation of the energy of transformation of the quinonoid into the benzenoid form.

Based on the oxidation of hydroquinone to quinone on developing the illuminated silver bromide is one of the methods of colour photography. The paper is covered with three layers of silver-bromide emulsion, each of which is sensibilized to one of the three regions of the spectrum—red, yellow, and blue-green. Into each layer is introduced a dye-developer which has a structure of the type I (where D is the dye residue of the corresponding colour). The dye-developer is oxidized on the illuminated portions with "seeds" of metallic silver to give the quinone II:

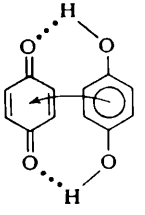


I II

The amount of the quinone corresponds to the quantity of the "developed" silver bromide and to the amount of layer blackening on this portion. After this, the excess un-used dye-developer is leached out with alkali, in which, unlike the quinone, it is soluble. It remains to remove the metallic silver covering the picture, and this is done by treatment with an oxidizing agent in the presence of a halide ion and removal of the silver halide formed by means of thiosulphate.

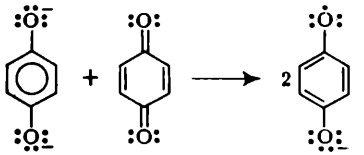
XXXII. Quinhydrone and Semiquinones

When solutions of equimolar amounts of *p*-benzoquinone and hydroquinone are mixed, slightly soluble, nearly black crystals of quinhydrone begin to separate out. **Quinhydrone** is a molecular compound consisting of these two substances, in which the molecules are united through hydrogen bonds and, besides, by charge transfer from hydroquinone to the quinone:

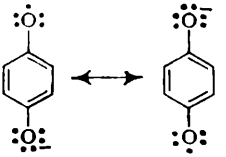


Quinhydrone

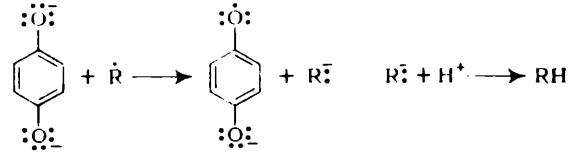
If we label, say, benzoquinone, by introducing deuterium into it, just as has been done by Miklukhin and Graigerov in the laboratory headed by A. I. Brodsky, it will turn out that the two halves of the quinhydrone molecule do not interconvert, as might be expected. But if quinhydrone is dissolved in alkali, i.e., if the bonding hydrogen atoms (protons) are removed, the hydroquinone anion will donate one electron to the quinone, and both compounds will be converted into two identical molecules of **semiquinone**



Semiquinone is a radical-ion which has a benzenoid structure in which the delocalization of electrons over both oxygen atoms is equilibrated mesomerically, so that each oxygen atom bears half of an electron charge and half of an unpaired electron, which is symbolized by the following formulas:



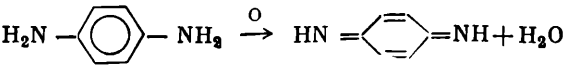
The presence of an unpaired electron in semiquinones is proved by their paramagnetic properties. Thus, semiquinones are free radicals with free-radical properties, which are distributed between the two oxygen atoms. By virtue of this delocalization, semiquinones are sufficiently stable and do not show the ordinary tendency of free radicals to pull an atom with an unpaired electron from the molecule encountered and thereby to initiate a chain reaction. Owing to the ability to be converted into a semiquinone (under the action of oxidizing agents or by reactions with free radicals) hydroquinone is a chain-reaction inhibitor—it captures chain-propagating free radicals from the reaction medium:



Since semiquinone (its anion) may accept one electron, being converted into the hydroquinone anion, and lose one electron to be converted into quinone, semiquinones (and quinhydrone) are often employed as redox systems which serve as electron-transfer agents.

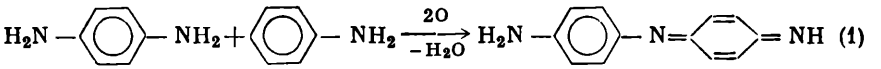
B. Quinonimines

Just as the oxidation of hydroquinone gives *p*-benzoquinone, so the oxidation of *p*-phenylenediamine leads to the formation of *p*-benzoquinonimine:

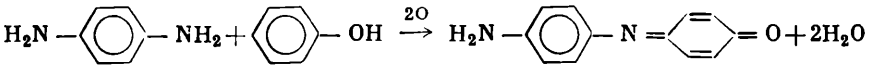


When hydrolysed quinonimine gives quinone.

The oxidation of *p*-phenylenediamine and aniline yields the simplest indamine, and an analogous reaction with phenol gives indophenol:



Indamine

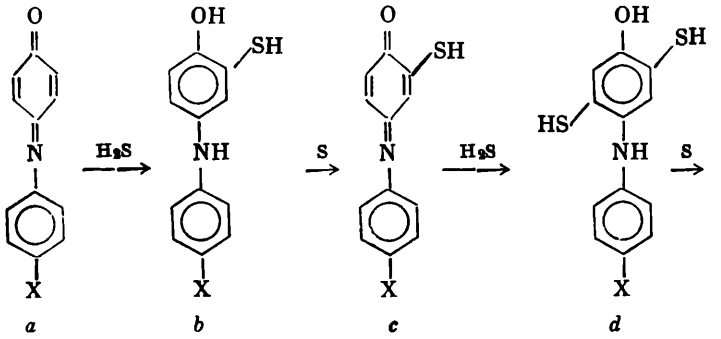


(2)

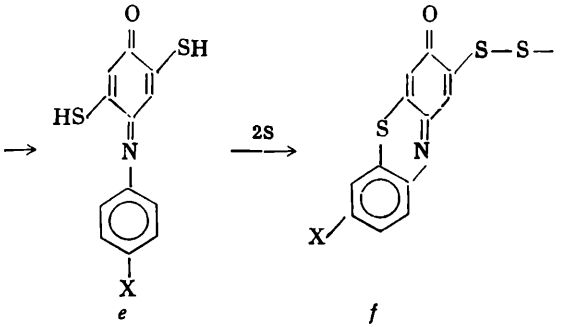
Indophenol

Simple and substituted indophenols and indamines are blue dyes. They are chiefly used for synthesis of more complex dyes. In particular, indophenols of various structures are employed for the production of so-called sulphur dyes.

For this purpose, indophenols are treated with sodium polysulphides. The processes that take place may be represented by the following scheme:



a *b* *c* *d*

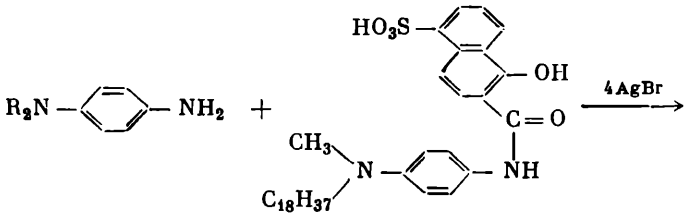


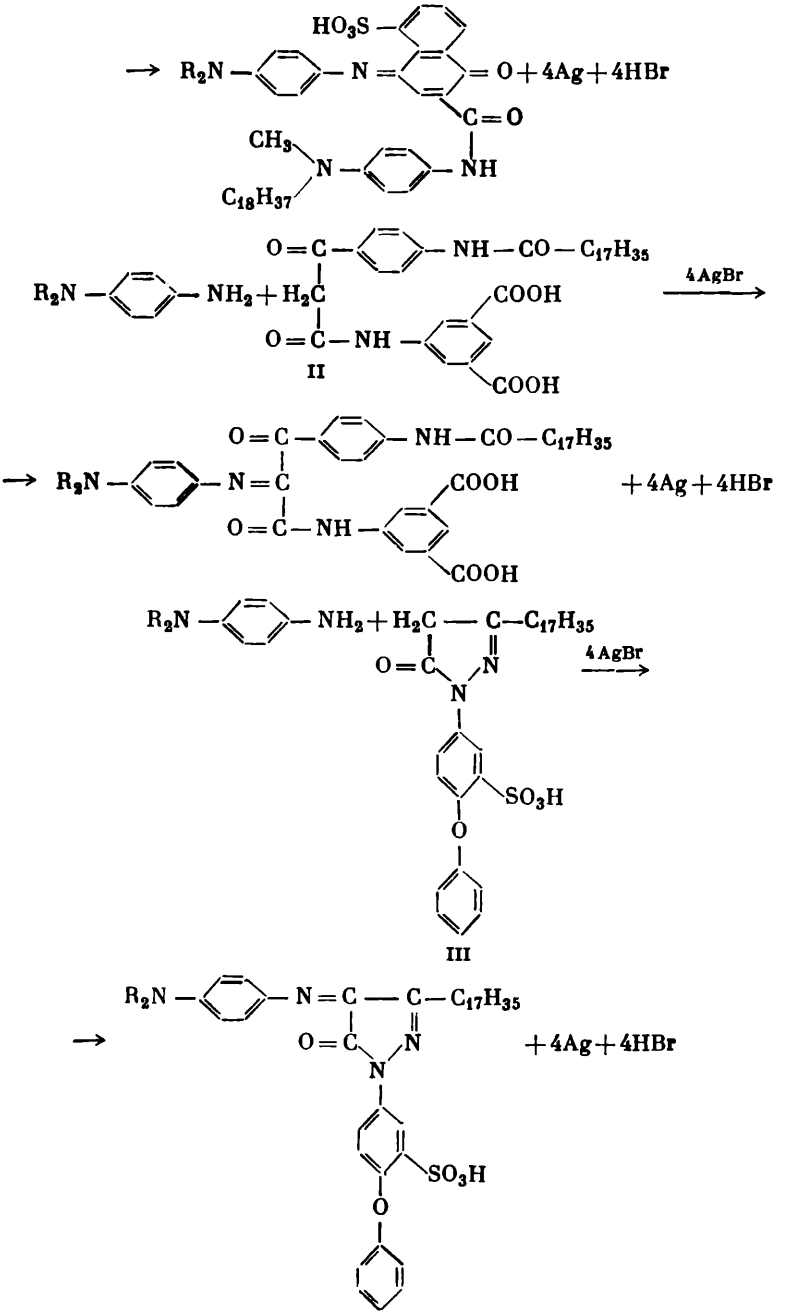
e *f*

The reactions $a \rightarrow b$ and $c \rightarrow d$ are ordinary additions to quinones (page 187), and the reactions $b \rightarrow c$ and $d \rightarrow e$ are reactions of oxidation to quinonoid forms. The last stage involves cyclization into the heterocycle thiazine and cross-linking of the fragments with disulphide bridges. Various aromatic nuclei may take the place of the phenyl in formula *a* and the other formulas.

Sulphur dyes are also discussed under "Heterocyclic Compounds".

The oxidation of a mixture of *p*-phenylenediamine and phenol (see above, reaction *2*) can be effected, in particular, with the aid of silver bromide. This process is used in another technique of colour photography and colour cinematography. Along with silver bromide, a second component of the reaction is introduced into the emulsion, namely, a dye of the phenolic type or one with an active methylene group. Only some of the dyes of this kind are indophenols. But, in method of their formation all these dyes are closely related and are therefore discussed together here. The compounds shown below, I, II, and III, serve as such components for reproducing three principal colour shades: blue-green (I), yellow (II), and purple-red (III). These compounds must be insoluble in water and must not be able to diffuse in the layer. This is achieved through the presence of side chains ($C_{17}H_{35}$ or $C_{18}H_{37}$). The exposed three-layer plate containing in each layer compounds I, II, and III and silver bromide, sensibilized in a given spectral region, is then developed with N′,N′-substituted *p*-phenylenediamine, which reduces silver bromide on portions illuminated on exposure and when oxidized is coupled into an indophenol (or a similar) dye by the following reactions. The precipitated silver and silver salts are removed as has been described above.




HO3S
R2N
N
O
+4Ag+4HBr
C=O
CH3
N
C18H37
NH
O=C
NH—CO—C17H35
R2N
NH2+H2C
4AgBr
COOH
O=C—NH
II
COOH
O=C
NH—CO—C17H35
R2N
N=C
COOH
+4Ag+4HBr
O=C—NH
COOH
R2N
NH2+H2C
C—C17H35
O=C
N
4AgBr
N
SO3H
O
III
R2N
N=C
C—C17H35
O=C
N
+4Ag+4HBr
N
SO3H
O

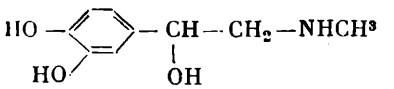
7.15. Heterofunctional Amines with the Amino Group in the Side Chain

We have not described the methods of preparation and properties of the simplest amines with the amino group in the side chain (and the corresponding quaternary bases), such as benzylamine, dibenzylamine, tribenzylamine, or tetrabenzylammonium salts because in their methods of preparation and properties they are similar to their aliphatic analogues. We shall consider some of the amines with the β-position of the amino group in the side chain of the aromatic ring since they are of physiological and therapeutic importance.

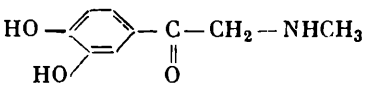
Benzedrine or **Dexedrine** which are trade names for amphetamine and has the formula

$$C_6H_5CH_2-\underset{\displaystyle NH_2}{\underset{|}{CH}}-CH_3$$

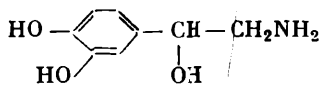
is a stimulating drug used to ward off sleep and to remove fatigue. It can be obtained from benzyl methyl ketone by the action of formamide (Leuckart reaction). **Adrenaline** (also called *epinephrine*) is the hormone secreted by the adrenal medulla. It brings about constriction of blood capillaries, increased heart action, a rise in blood pressure, and has a mobilizing effect: at the moment of danger epinephrine is released directly into the bloodstream by the adrenal glands. Epinephrine (along with **norepinephrine** or *noradrenaline*) is involved in the functioning of the sympathetic nervous system, its role being the same as that played by acetylcholine (see Volume II, page 13) in the parasympathetic nervous system (the vagus nerve system). The structure of epinephrine follows from its conversion by fusion with alkali into protocatechuic acid and also from the data of functional analysis, according to which it is a secondary amine and a secondary alcohol, which is oxidized to a ketone—adrenalone:



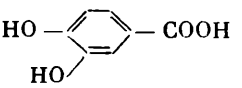
Epinephrine (adrenaline)



Epinephrone (adrenalone)

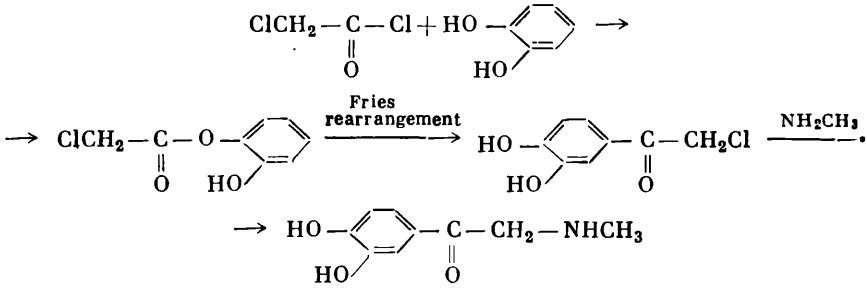


Norepinephrine (noradrenaline)



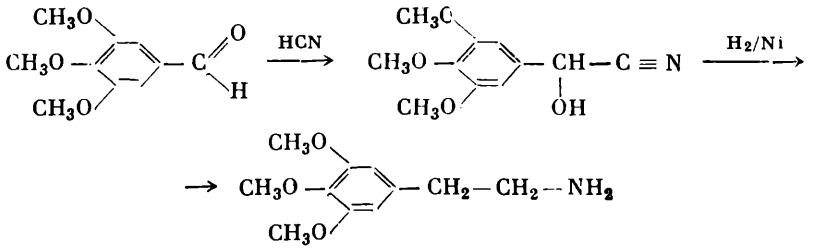
Protocatechuic acid

Epinephrone (adrenalone) can be synthesized from catechol in the following way:



By reducing epinephrone it is possible to prepare the racemic epinephrine which can be resolved with tartaric acid into its antipodes. Natural epinephrine is levorotatory; it is this compound that has a strong physiological effect.

Mescaline (3,4,5-*trimethoxyphenylethylamine*), $C_{11}H_{17}NO_3$, is the alkaloid of the cactus of the *Anhalonium* family. It is a central nervous system depressant—causes poisoning similar to alcoholic intoxication—euphoria, and visual hallucinations which are often in colour. Mescaline can be prepared by the addition of hydrogen cyanide to the aldehyde of trimethylgallic acid with subsequent catalytic reduction of the hydroxynitrile formed:



Mescaline (3,4,5,-trimethoxypherylethylamine)

Various species of *Ephedra* contain an aromatic aminoalcohol the alkaloid **ephedrine**, $C_6H_5CH(OH)CH(NHCH_3)CH_3$, which is an antispasmodic agent for relief of bronchial asthma. Its two asymmetric carbon atoms have an *erythro*-configuration.

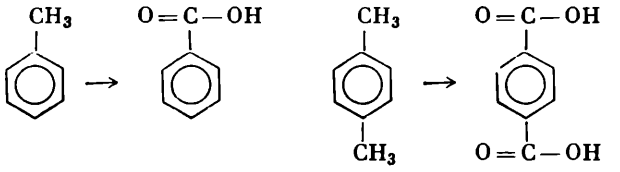
7.16. Aromatic Carboxylic Acids

Aromatic carboxylic acids are usually known under their trivial names: benzoic acid, C_6H_5COOH; toluic acids (*o*-, *m*-, and *p*-), $CH_3C_6H_4COOH$; phthalic acid, o-$C_6H_4(COOH)_2$. The names of fatty

aromatic (aryl-fatty) acids, i.e., compounds with a carboxyl group in the side chain, are derived from the names of the corresponding aliphatic acids, for example, phenylacetic acid, $C_6H_5CH_2COOH$, or else trivial names are used (Table 7.11).

A. Methods of Introducing Carboxyl into the Aromatic Ring

Of the greatest importance are the methods of oxidation of aromatic hydrocarbons. On vigorous oxidation the side chains of the homologues of benzene are "burned off" and the corresponding aromatic acids are formed. The oxidizing agents used are chromic acid and an alkaline solution of permanganate. For instance, benzoic acid is produced from toluene, and phthalic, isophthalic or terephthalic acids are obtained from xylenes:

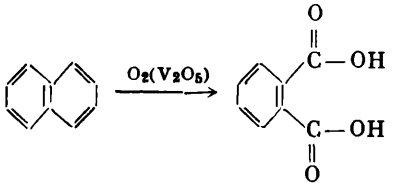


Benzoic acid Terephthalic acid

The higher homologues of benzene (with one alkyl substituent) can also be oxidized to benzoic acid:

$$C_6H_5C_2H_5 \xrightarrow{O} C_6H_5COOH + CO_2 + 2H_2O$$

Phthalic acid is made by the oxidation of naphthalene with atmospheric oxygen over vanadium pentoxide at 450°C; in this reaction, one of the aromatic rings is "burned away":



Thus, the hydrocarbon side chain in an aromatic compound is oxidized at the α-carbon (with respect to the aromatic nucleus) linkage.

Specific for the aromatic series is the synthesis of carboxylic acids by the Friedel-Crafts reaction; if phosgene or chlorocarbonic ester is used as an acylating agent, then a carboxyl group enters the aro-

TABLE 7.11. **Benzoic Acid and**

Formula	Name of acid	m.p., °C	b.p., °C
C_6H_5COOH	Benzoic acid	122.0	249.0
$CH_3C_6H_4COOH$	Toluic acid		
	o- or 1,2-	104; 108	259.2
	m- or 1,3-	109; 112	263
	p- or 1,4-	179.6	275 (subl.)
ClC_6H_4COOH	Chlorobenzoic acid		
	o- or 1,2-	142	Sublimes
	m- or 1,3-	158	Sublimes
	p- or 1,4-	243	Sublimes
$NO_2C_6H_4COOH$	Nitrobenzoic acid		
	o- or 1,2-	147.5	—
	m- or 1,3-	141.4	—
	p- or 1,4-	242.4	Sublimes
$NH_2C_6H_4COOH$	Aminobenzoic acid		
	o- or 1,2- (anthranilic)	145	Sublimes
	m- or 1,3-	174; 179.5	Sublimes
	p- or 1,4-	187	—
HOC_6H_4COOH	Hydroxybenzoic acid		
	o- or 1,2- (salicylic)	159	76 (subl.)
	m- or 1,3-	201.3	—
	p- or 1,4-	213.0	76 (subl.)

Its Substituted Derivatives

Density, d_4^{20}	K_a (at 25°C)	pK_a	Refractive index, n_D^{20}	Dipole moment in dioxan at 25°C, D
1.2659 (d_4^{15})	6.46×10^{-5}	4.19	1.5397 (at 15°C)	1.78 (at 30°C)
1.062 (d_4^{115})	1.350×10^{-5}	3.91	1.512 (at 115°C)	1.70 (at 30°C in benzene)
1.054 (at 112°C)	5.32×10^{-5}	4.27	1.509 (at 111.6°C)	2.05 (at 30°C in benzene)
—	4.33×10^{-5}	4.36	—	—
1.544	1.20×10^{-3}	2.92	—	2.43 (at 30°C)
1.496 (d_4^{25})	1.51×10^{-4}	3.82	—	2.20 (at 30°C)
1.541 (d_4^{24})	1.04×10^{-4}	3.98	—	2.00 (at 30°C)
1.575 (d_4^4)	6.95×10^{-3} (at 18°C)	2.16	—	—
1.494 (d_4^4)	3.4×10^{-4}	3.47	—	4.03
1.610	3.93×10^{-4}	3.41	—	4.02
—	1.07×10^{-7}	4.97	—	1.51
1.511	1.67×10^{-5}	4.78	—	2.70
—	1.2×10^{-5}	4.92	—	3.51
1.443	1.07×10^{-3}	2.97	1.565	2.63
1.473 (d_4^4)	8.7×10^{-5}	4.06	—	2.37
1.443	3.3×10^{-5}	4.48	—	2.73

matic nucleus:

$$Ar-H+ClCOCl \xrightarrow{AlCl_3} Ar-COCl \xrightarrow{H_2O} Ar-\underset{\underset{O}{\|}}{C}-OH$$

$$Ar-H+ClC(=O)-OC_2H_5 \xrightarrow{AlCl_3} Ar-C(=O)-OC_2H_5$$

The cyano group (and, hence, the potential carboxyl group) can be introduced in place of the sulphonic group by fusion of the salts of sulphonic acids with sodium cyanide or in place of the amino group—via a diazo compound:

$$C_6H_5SO_3Na+NaCN \longrightarrow C_6H_5CN+Na_2SO_3$$

$$2C_6H_5\overset{+}{N}_2\ \overset{-}{S}O_4H+Cu_2(CN)_2 \longrightarrow 2C_6H_5CN+2N_2+Cu_2SO_4+H_2SO_4$$

These methods too have no analogues in the aliphatic series.

Organomagnesium compounds retain their value also for synthesis of aromatic acids:

$$ArMgBr+CO_2 \longrightarrow Ar-C(=O)-OMgBr \xrightarrow{HCl} Ar-C(=O)-OH+MgBrCl$$

Acids with a carboxyl group in the aromatic ring are also formed as a result of the carboxylation of aryl-sodium and -lithium compounds, which are prepared by the interaction of an aryl halide with metals or by metalation of an aromatic compound; for example,

$$C_6H_5Br+2Li \longrightarrow C_6H_5Li+LiBr; \quad C_6H_5Li+CO_2 \longrightarrow C_6H_5C(=O)-OLi$$

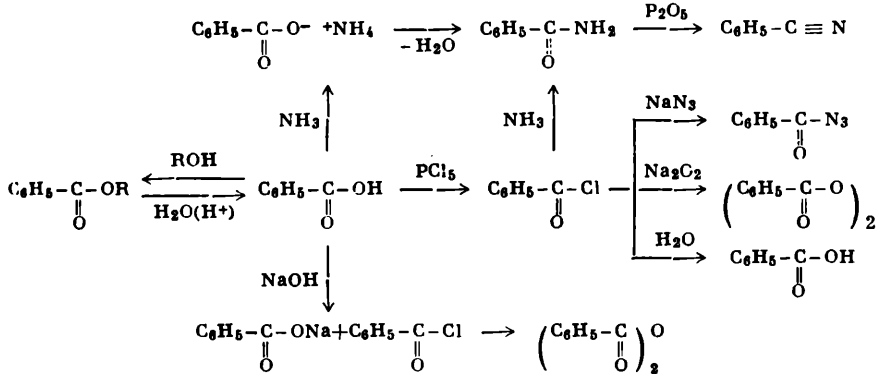
$$C_6H_6+C_2H_5Na \longrightarrow C_6H_5Na+C_2H_6; \quad C_6H_5Na+CO_2 \longrightarrow C_6H_5C(=O)-ONa$$

As regards acids with a carboxyl group in the side chain, they can be synthesized by the usual methods used for aliphatic acids, and in special cases, by certain specific methods (see below).

B. Benzoic Acid and Its Functional Derivatives

Aromatic acids are crystalline compounds which are usually sparingly soluble in water and well soluble in polar organic solvents. Their dissociation constants are slightly higher than the dissociation constants of the homologues of acetic acid (but lower than the dissociation constant of formic acid). This is attributed to the stronger positive inductive effect of the alkyls as compared with the phenyl group. Aromatic acids exhibit all the properties common to carbo-

xylic acids and, as regards the behaviour of the carboxyl group, differ little from the carboxylic acids of the aliphatic series. Differences, if any, are more of quantitative than of qualitative nature. All the known functional derivatives have been prepared for benzoic acid too:



Benzoic acid is contained in some natural resins, but is prepared almost exclusively by the oxidation of toluene. It is used in the manufacture of dyes and certain medicinal drugs. The esters of benzoic acid are employed as high-boiling solvents.

Of great commercial importance is **benzoyl chloride**, $C_6H_5 \cdot COCl$, the acid chloride of benzoic acid (the acyl of benzoic acid is called the **benzoyl group**, and the anion is called the **benzoate ion**). Benzoyl chloride is made by the partial hydrolysis of benzotrichloride, which in its turn is prepared by the chlorination of toluene in the light:

$$C_6H_5-CH_3 \xrightarrow[-3HCl]{+3Cl_2\,(light)} C_6H_5-CCl_3 \xrightarrow[-2HCl]{+H_2O} C_6H_5-\underset{\underset{O}{\|}}{C}-Cl$$

Benzoyl chloride can also be obtained by the chlorination of benzaldehyde (a reaction unusual for the aliphatic series):

$$C_6H_5-\underset{\underset{O}{\|}}{C}-H+Cl_2 \longrightarrow C_6H_5-\underset{\underset{O}{\|}}{C}-Cl+HCl$$

Benzoyl chloride is used for preparing benzoyl peroxide and perbenzoic acid (benzoyl hydroperoxide); it is frequently used as an acylating agent. Benzoyl chloride is also employed to benzoylate alcohols, phenols, amines, and as a means of introducing the benzoyl group, $C_6H_5 \cdot CO-$, by the Friedel-Crafts reaction, etc. Benzoyl chloride is somewhat less reactive than the acid chlorides of aliphatic acids, in particular, is much more slowly attacked by water. The slowness with which it is attacked by water is used to advantage in the Schotten-Baumann reaction, which consists in allowing a

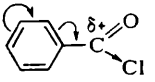
substance to react with benzoyl chloride in an aqueous-alkaline medium. For example, benzoyl chloride is gradually added to a solution, say, of phenol in dilute alkali (the rate of benzoylation of sodium phenoxide is considerably higher than the rate of hydrolysis of an acid chloride):

$$Ar-\underset{\underset{O}{\|}}{C}-Cl + ArONa \longrightarrow Ar-\underset{\underset{O}{\|}}{C}-O-Ar$$

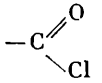
Benzoylation of phenols and amines is also effected in non-aqueous solutions in the presence of pyridine or tertiary amines.

The high reactivity of acid chlorides towards nucleophilic reagents (water, amines, etc.) is ascribed to the sharp decrease of electron density on the carbonyl group carbon due to the simultaneous withdrawal of the electrons both by the oxygen and the chlorine atom.

With benzoyl chloride, such a decrease of electron density on carbon is compensated for, to a certain extent, by the supply of electrons from the benzene ring:



The benzene ring may act either as an electron acceptor or as an electron donor. It will suffice to recall that aromatic amines are weaker bases than aliphatic amines, due to the withdrawal of the electron pair of nitrogen by the benzene ring; aromatic acid chlorides are also less reactive than aliphatic acid chlorides, this time due to the shift of electron density from the benzene ring. Hence, in the aromatic series there is observed a partial levelling of the properties of the substituents; the benzene ring here plays the role, so to say, of an electron condenser on a molecular level. The more pronounced the electron-attracting properties of the substituent, the higher its "requirements", the more electrons are supplied by the benzene ring. In the case of acid chlorides of acids such a requirement on the part of the group



is high, and it is satisfied by the positive inductive effect to a considerably less extent than by the conjugated system of benzene.

The situation is different with carboxylic acids themselves. The carboxyl group is a relatively weak electron acceptor, and its requirements can be satisfied by the supply of electrons from the alkyl groups which have a stronger positive inductive effect than the phenyl group. Therefore, the homologues of acetic acid, except formic acid, are weaker than benzoic acid.

The reaction of benzoyl chloride with sodium peroxide leads to **benzoyl peroxide:**

$$2C_6H_5-\overset{\overset{O}{\|}}{C}-Cl + Na_2O_2 \longrightarrow C_6H_5-\overset{\overset{O}{\|}}{C}-O-O-\overset{\overset{O}{\|}}{C}-C_6H_5 + 2NaCl$$

Benzoyl peroxide is in widespread use as an initiator of many free-radical and chain reactions, especially polymerization reactions which are of great industrial importance.

Perbenzoic acid (benzoyl hydroperoxide) is produced by benzoylation of hydrogen peroxide by benzoyl chloride in alkaline medium:

$$C_6H_5-\overset{\overset{O}{\|}}{C}-Cl + H_2O_2 + 2NaOH \longrightarrow C_6H_5-\overset{\overset{O}{\|}}{C}-O-ONa + NaCl + 2H_2O$$

or by the action of sodium methoxide on benzoyl peroxide:

$$C_6H_5-\overset{\overset{O}{\|}}{C}-O-O-\overset{\overset{O}{\|}}{C}-C_6H_5 + NaOCH_3 \longrightarrow$$

$$\longrightarrow C_6H_5-\overset{\overset{O}{\|}}{C}-O-ONa + C_6H_5-\overset{\overset{O}{\|}}{C}-OCH_3$$

Perbenzoic acid is more stable than the acyl hydroperoxides of the aliphatic series and can be prepared in the crystalline form (m.p. 41°C). It is more often used, however, at the moment of its formation and is not isolated in the pure form. Its main application is for the synthesis of α-oxides from unsaturated compounds (Prilezhaev reaction):

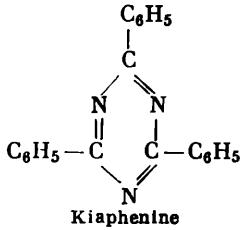
$$RCH=CHR' + C_6H_5-\overset{\overset{O}{\|}}{C}-O-OH \longrightarrow RCH-CHR' + C_6H_5-\overset{\overset{O}{\|}}{C}-OH$$

For this purpose it is more convenient than aliphatic peracids.

Benzonitrile which can be prepared from benzoic acid by heating its amide with phosphoric anhydride or by introducing the cyano group into the aromatic ring by one of the above-mentioned methods, has the properties common to all nitriles. The condensation effected by the action of metallic sodium is characteristic:

$$3C_6H_5-C\equiv N \xrightarrow{Na}$$

Benzonitrile



Kiaphenine

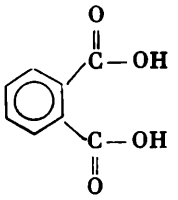
Table 7.12 gives the constants of some derivatives of benzoic acid.

TABLE 7.12. Selected Derivatives of Benzoic Acid

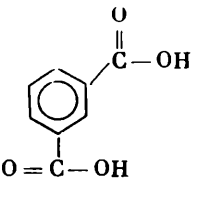
Formula	Name	m.p., °C	b.p., °C	Density
C_6H_5COOH	Benzoic acid	122	249	1.2659 (d_4^{15})
$C_6H_5COOCH_3$	Methyl benzoate	−12.5	199.6	1.0886 (d_4^{20})
$(C_6H_5CO)_2O$	Benzoic anhydride	42	360	1.199 (d_4^{15})
C_6H_5COCl	Benzoyl chloride	−1	197	1.2187 (d_{15}^{15})
$C_6H_5CONH_2$	Benzamide	130	290	1.341 (d_4^{4})
C_3H_5CN	Benzonitrile	−13	190.7	1.0102 (d_{15}^{15})

C. Polybasic Aromatic Acids

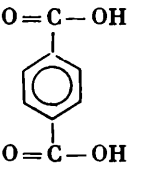
The dicarboxylic acids of benzene are represented by three possible isomers (Table 7.13):



Phthalic acid

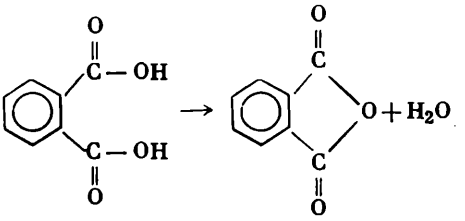


Isophthalic acid

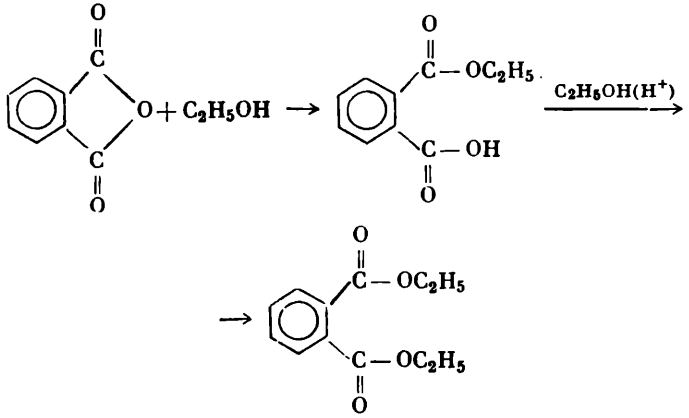


Terephthalic acid

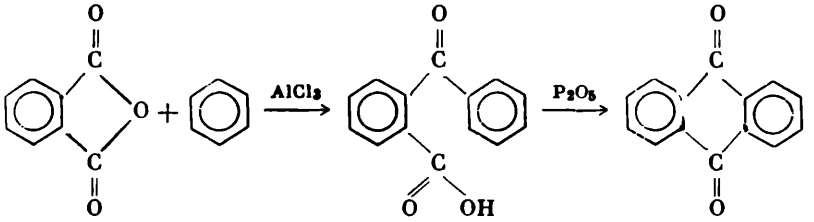
Phthalic acid is the most important of these isomers and is prepared industrially, as has been said earlier, by the oxidation of naphthalene or *o*-xylene. Owing to the *ortho*-position of the functional groups, phthalic acid gives a number of cyclic derivatives (in this respect it resembles maleic or succinic acid). Phthalic anhydride is formed even on heating of phthalic acid:



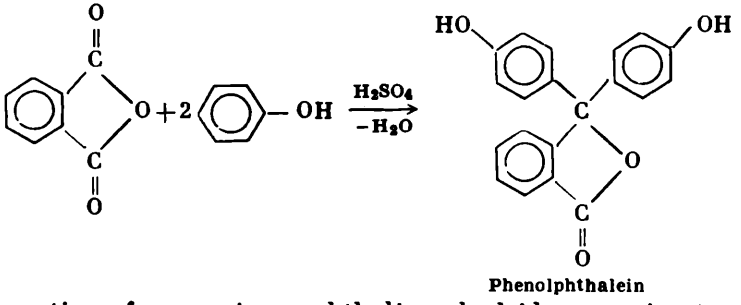
Phthalic anhydride is a colourless crystalline substance with m.p. 130-131°C. When heated with alcohols phthalic anhydride adds on a molecule of alcohol to give acid esters of phthalic acid, which can be converted into neutral esters by the ordinary esterification reaction (in the presence of mineral acids):



Phthalic anhydride readily enters into the Friedel-Crafts reaction, say, with benzene, giving *o*-benzoylbenzoic acid, which under more drastic conditions (addition of P_2O_5), can be turned into anthraquinone:



In the presence of H_2SO_4 or $ZnCl_2$, phthalic anhydride condenses on heating with phenols:



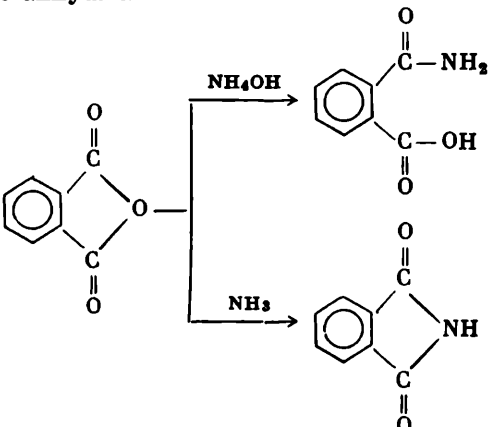
Phenolphthalein

The action of ammonia on phthalic anhydride may give two products: phthalamic acid and phthalimide (the imide of phthalic acid).

TABLE 7.13. Benzene

Formula	Acid	m.p., °C	b.p., °C	Density, d_4^{20}
o-$C_6H_4(COOH)_2$	o-Phthalic	206-208 (dec.)	191 (dec.)	1.593
m-$C_6H_4(COOH)_2$	m-Phthalic or isophthalic	330	Sublimes	—
p-$C_6H_4(COOH)_2$	p-Phthalic or terephthalic	Sublimes	ca. 300 (subl.)	1.510
$C_6H_3(COOH)_3$	Hemimellitic or 1,2,3-benzenetricarboxylic	190	Decomposes	1.546
$C_6H_3(COOH)_3$	Trimesic or 1,3,5-benzenetricarboxylic	350	<300 (subl.)	—
$C_6H_3(COOH)_3$	Trimellitic or 1,2,4-benzenetricarboxylic	224-225 (dec.)	—	—
$C_6H_2(COOH)_4$	Pyromellitic or 1,2,4,5-benzenetetracarboxylic	264; 272	—	—
$C_6H(COOH)_5$	Benzenepentacarboxylic	238 (anhydr.)	—	—
$C_6(COOH)_6$	Mellitic or benzenehexacarboxylic	286	Decomposes	—

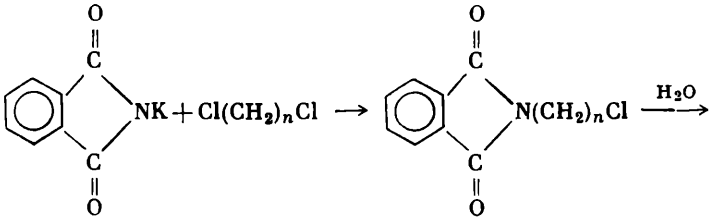
The action of aqueous ammonia in the cold leads to phthalamic acid, and phthalimide is formed when gaseous ammonia is passed over heated phthalic anhydride:

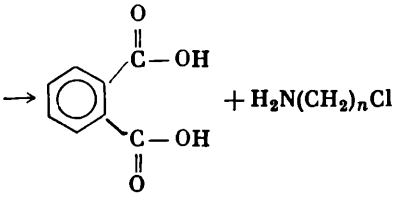


polycarboxylic Acids

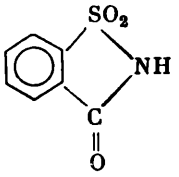
Dissociation constants (in water at 20°C)						Dipole moment μ at 25°C, D
K_1	K_2	K_3	K_4	K_5	K_6	
1.123×10^{-3}	3.90×10^{-6} (at 30°C)	—	—	—	—	2.30 (in dioxan)
2.4×10^{-4}	2.5×10^{-5}	—	—	—	—	2.37 (in dioxan)
2.9×10^{-4}	3.5×10^{-5}	—	—	—	—	—
1.60×10^{-3}	6.3×10^{-5}	1.35×10^{-6}	—	—	—	—
7.5×10^{-3}	1.28×10^{-4}	2.0×10^{-5}	—	—	—	—
3.0×10^{-3}	1.45×10^{-4}	6.3×10^{-6}	—	—	—	—
1.20×10^{-2}	1.34×10^{-3}	3.2×10^{-5}	2.35×10^{-6}	—	—	—
1.60×10^{-2}	1.85×10^{-3}	1.08×10^{-4}	5.6×10^{-6}	3.5×10^{-7}	—	—
4.0×10^{-2}	6.4×10^{-3}	4.9×10^{-4}	1.65×10^{-5}	1.28×10^{-6}	1.10×10^{-7}	—

Phthalamic acid is also obtained by the partial hydrolysis of phthalimide which in its turn is formed when phthalamic acid is heated. Phthalamic acid is used as a starting material for preparing a technically valuable product—anthranilic acid (see below). Phthalimide finds application in Gabriel's syntheses for introducing the amino group in place of a halogen. The starting point here is potassium phthalimide which reacts with alkyl halides with the formation of a substituted phthalimide; the latter when subjected to hydrolysis gives the corresponding amine and phthalic acid. This method is particularly important for the production of aliphatic amines containing other substituents in the chain; for example,





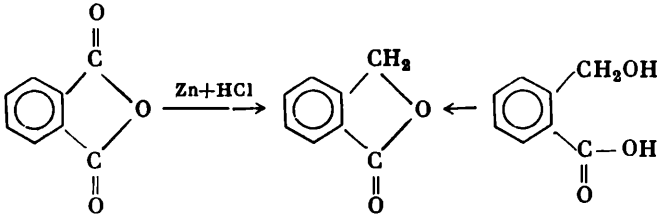
Potassium phthalimide is made by the reaction of phthalimide with strong bases, say, with potassium alkoxides or alcoholic solutions of alkali. Thus, phthalimide has weak acidic properties, which is accounted for by the presence of two electron-attracting groups directly at the nitrogen atom. Stronger acidic properties are exhibited, for instance, by saccharin (or the imide of *o*-sulphobenzoic acid) in which the nitrogen atom carries a strong electron-attracting group—the SO_2 group.



Saccharin

(For synthesis of saccharin, see page 209.)

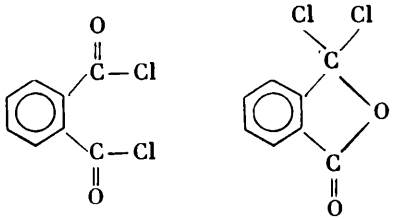
Phthalic anhydride is readily reduced to **phthalide** which is the lactone of 2-hydroxymethylbenzoic acid. Phthalide can also be obtained by heating this acid:



By esterifying phthalic anhydride with polyhydric alcohols it is possible to prepare polyester resins; the esterifying component often used is glycerol. **Glyphthalic resins** formed in this process serve as the base of varnishes and films.

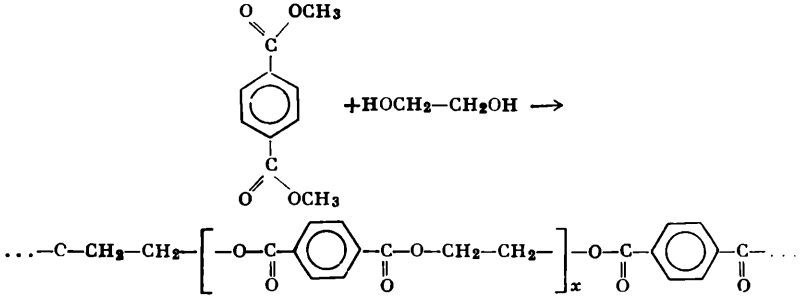
The acid chloride of phthalic acid, **phthalyl chloride**, is capable of reacting both in a normal way (in accordance with the structure of an acid chloride) and, in certain cases, in accordance with the

Isomeric (tautomeric?) structure:



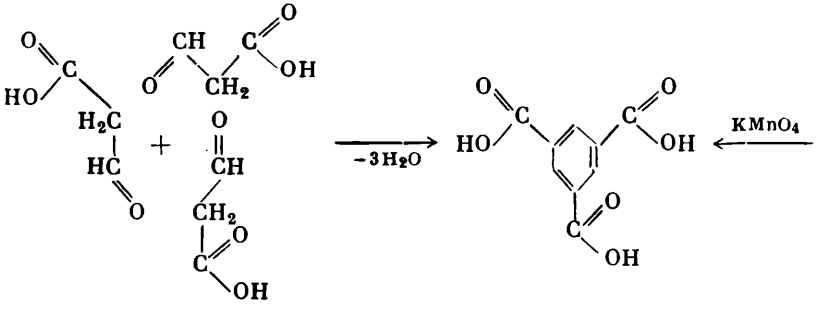
The esters of phthalic acid and butyl and octyl alcohols are used as high-boiling solvents and plastisizers. Dimethyl, diethyl, and dibutyl phthalates are used as mosquito and gnat **repellents**.

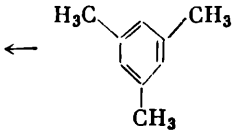
The potassium salt of phthalic acid isomerizes to a salt of terephthalic acid at 400°C in the presence of zinc or cadmium phthalate. Terephthalic acid is produced in large quantities by oxidizing *p*-xylene. It is used in the production of polyethylene terephthalate, from which the synthetic fibre Terylene (Lavsan) is made. Polyethylene terephthalate is produced on an industrial scale by way of trans-esterification of dimethyl terephthalate by ethylene glycol:



The other polybasic acids presented in Table 7.13 are less important.

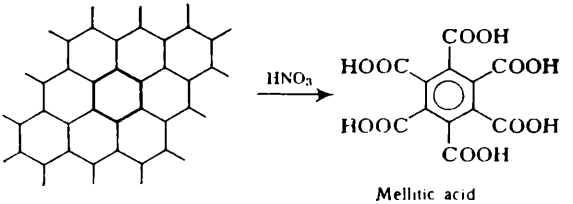
The condensation of malonaldehyde in situ or the oxidation of mesitylene gives 1,3,5-benzenetricarboxylic acid—**trimesic acid**:





Benzenehexacarboxylic acid, or **mellitic acid**, has been prepared from the mineral mellite (honeystone) which is the aluminium salt of the acid. Mellitic acid is also formed as a result of the oxidation of graphite by nitric acid.

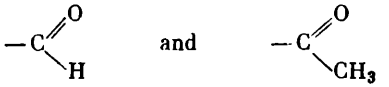
This reaction shows that graphite is built up of polymer-condensed aromatic rings:



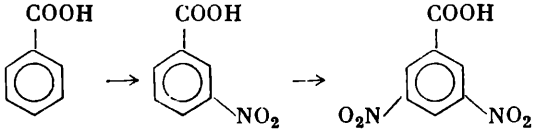
Mellitic acid

D. Substituted Carboxylic Acids

The carboxyl group is a *meta*-directing group, though weaker than the groups



and therefore the nitration, sulphonation and halogenation of benzoic acid give chiefly meta-substituted products. On nitration there is also formed a rather large amount of the *o*-isomer. The nitration with a mixture of fuming nitric acid and sulphuric acid can yield 3,5-dinitrobenzoic acid:

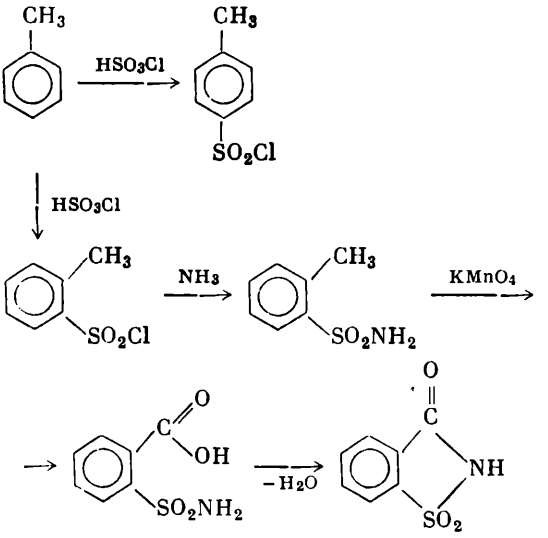


The acid chloride of this acid is used for identification of alcohols owing to good yields of the esters formed, their relatively high melting points and, finally, the relatively high molecular weight of dinitrobenzoic acid.

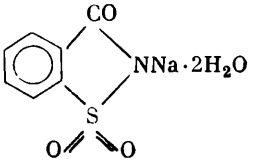
p- and *o*-Nitrobenzoic acids are prepared by the nitration of toluene followed by the oxidation of the methyl group to a carboxyl group. In this way, it is also possible to synthesize other nonfunctional

derivatives of benzoic acid with substituents such as bromine, chlorine, or the sulphonic group.

Saccharin, i.e., the imide of *o*-sulphobenzoic acid (the sulphinide of benzoic acid) is synthesized as follows. Toluene is sulphonated with chlorosulphonic acid; this gives a mixture of *o*- and *p*-toluenesulphochlorides. The crystalline *p*-isomer is usually freezed out of the solution in the liquid *o*-isomer. After this, the *o*-isomer still contains a large amount of *p*-isomer; it is removed at the next stage. The enriched *o*-toluenesulphochloride is treated with ammonia and the resulting *o*-toluenesulphamide is oxidized to the *o*-sulphamide of benzoic acid, which readily undergoes cyclization:



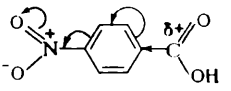
The imide hydrogen of saccharin has acidic properties and is replaced by a metal atom in the presence of bases. Use is ordinarily made of the crystal hydrate of the sodium salt of the imide of *o*-sulphobenzoic acid, which is called **crystallose.**



Crystallose

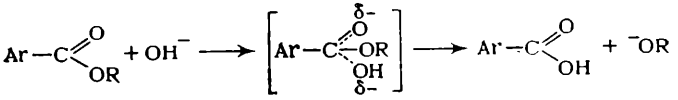
This compound is 400 times sweeter than sugar, i.e., a solution of saccharin with a concentration of 1/400 has the same sweet taste as a solution of sucrose at a concentration equal to unity.

The properties of benzoic acids and their derivatives depend on the substituents present in the benzene ring (page 196). For instance, electron-attracting groups, especially those in the para-position enhance the dissociation constants of the acids and the reactivity of acid chlorides and also the rate of esterification of these acids. The opposite effect is exerted by electron-releasing groups. This is attributed to the increase or decrease of the electron density of the reaction centre:



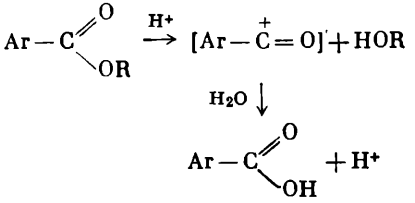
But the presence of two substituents in the ortho-position, independently of the nature of these substituents, deactivates the carboxyl group. For example, mesitylenecarboxylic and *o*-dinitrobenzoic acids are poorly esterified by alcohols under ordinary conditions, and the esters of these acids are hydrolysed with great difficulty. This is associated with the blocking of the reaction centre by bulky substituents which hinder the approach of the reagent. These concepts of steric hindrances were developed by V. Meyer in the eighties of the last century. They acquired a new meaning during the last decade. The problem of whether the accumulation of steric factors will impede the reaction can be solved by analysing the steric hindrances in the starting and the transition state. If the steric hindrances in the transition state are greater than those in the initial state (upon introduction of some bulky groups in the vicinity of the reaction centre), the reaction is hindered since the energy barrier between the starting and transition states is increased. Therefore, estimation of steric hindrances requires a knowledge of the mechanism of the reaction. Let us analyse, as an example, the hydrolysis of the esters of *o*,*o*′-dinitrobenzoic and mesitylenecarboxylic acids.

In an alkaline medium, the hydrolysis of the esters proceeds by a bimolecular mechanism. In the transition state, four groups add on to the reaction centre, while the original state contains only three groups:



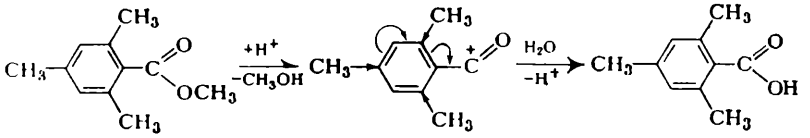
Any additional increment in the volume of one of the substituents will increase the potential energy of the more sterically hindered transition state more sharply than that of the original state. Thus, the alkaline hydrolysis of the esters of these acids is strongly impeded.

The acid .hydrolysis of esters may occur by a monomolecular mechanism:



Monomolecular hydrolysis is practically impossible for the esters of *o*,*o'*-dinitrobenzoic acid because the nitro groups interfere with the formation of a positively charged centre.

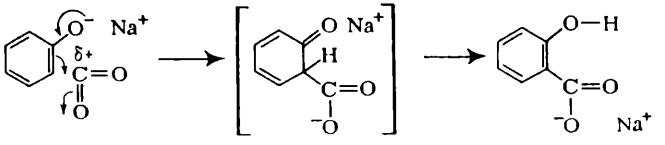
In the corresponding cation of mesitylenecarboxylic acid, the methyl groups facilitate the delocalization of the charge. Such a cation is found to be more stable and steric hindrances can increase its energy only a little; in any case, they will affect the energy of the starting ester more strongly since only two residues are found to be linked to carbon: oxygen and the aromatic radical. Therefore, in a strongly alkaline medium the hydrolysis of an ester of mesitylenecarboxylic acid proceeds smoothly and by a monomolecular mechanism S_N1:



7.17. Hydroxybenzoic Acids (Phenolic Acids)

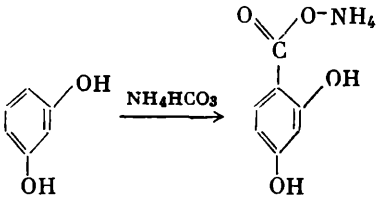
Phenolic acids can be prepared by introducing the carboxyl group into phenols or the hydroxyl group into benzoic acids.

The most important of phenolic acids is *o*-hydroxybenzoic acid or **salicylic acid** which is produced industrially by the Kolbe reaction, by heating (130°C) dry sodium phenoxide with carbon dioxide under pressure (5 kg/cm²):



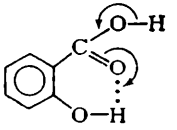
If the starting point is potassium phenoxide, *p*-hydroxybenzoic acid results instead of the ortho-isomer.

With polyhydric phenols, say, with resorcinol, this reaction proceeds more readily. For example, resorcylic acid is formed even when resorcinol is heated with a solution of ammonium bicarbonate:

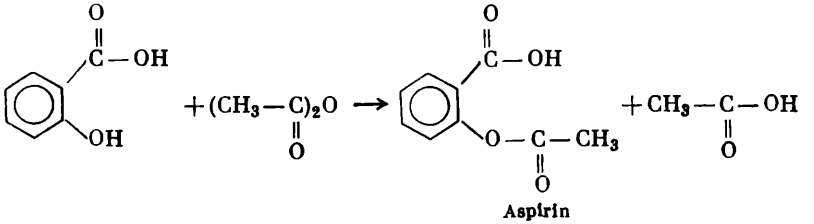


Salicylic acid can also be prepared by oxidizing salicylaldehyde or by the action of carbon tetrachloride and alkali on sodium phenoxide (page 141).

Salicylic acid is considerably stronger than its isomers and benzoic acid. Such an ortho-effect of the hydroxy group is explained by the formation of a hydrogen bond between the functional groups, which increases the $\delta+$ charge on the carboxyl carbon:

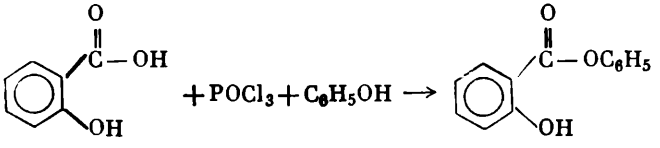


Salicylic acid forms two series of derivatives (according to both functional groups). Acyl chlorides and acid chlorides acylate it at the hydroxy group (i.e., it behaves as a phenol):



Aspirin

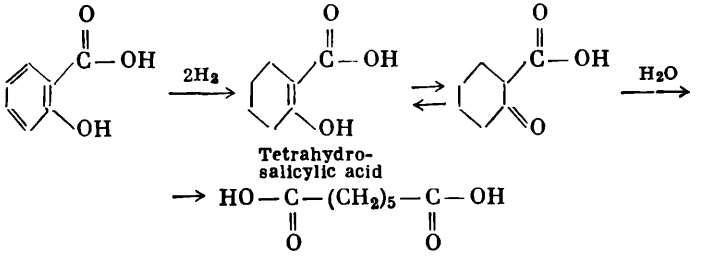
The acid chloride of salicylic acid forms, with phenols and alcohols, esters of a different type (across the carboxyl group); for example,



Salol

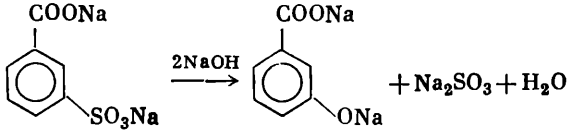
Aspirin (acetylsalicylic acid) is used as a mild analgetic agent and a febrifuge; **salol** (phenyl salicylate) is an antiseptic recommended for the treatment of gastro-intestinal disturbances. Salicylic acid itself is a strong antiseptic; its sodium salt (sodium salicylate) is used as a drug for treatment of rheumatoid arthritis. Salicylic acid is utilized on a large scale in the manufacture of azo dyes.

The hydrogenation of salicylic acid leads to pimelic acid; the transiently formed compound, tetrahydrosalicylic acid, is hydrolysed by the mechanism of the "acid cleavage" of acetoacetic ester:



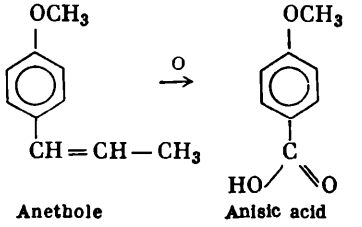
The methyl ester of salicylic acid occurs as a glycoside in various plants and is used in medicine.

m-Hydroxybenzoic acid is prepared by the alkaline fusion of *m*-sulphobenzoic acid



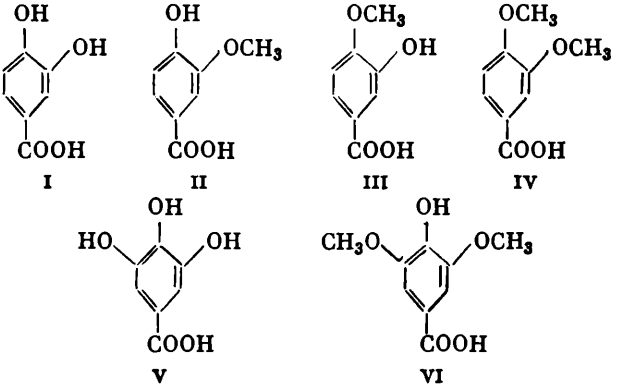
and is also used in the manufacture of dyestuffs.

p-Hydroxybenzoic acid is synthesized by Kolbe's method, using potassium hydroxide. Its methyl ester (across the hydroxy group), called **anisic acid** (*p*-methoxybenzoic acid), may be prepared by the oxidation of anethole (the methyl ester of *p*-propenylphenol):

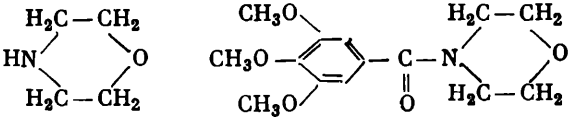


Polyhydroxybenzoic acids occur rather widely in nature. They are contained in the form of glycosides or other derivatives in many plants. Such are, for example, **protocatechuic acid** I and its derivatives: vanillic II, isovanillic III and veratric IV acids.

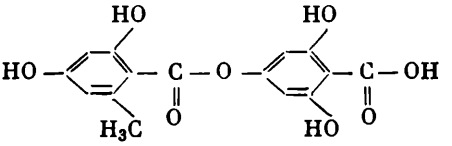
The most important of the trihydroxybenzoic acids is 3,4,5-trihydroxybenzoic acid or **gallic acid**. It occurs free in nut-galls, tea leaves, the oak bark, the root of pomegranate (Punica granatum), and in many other plants. It is usually obtained from nut-galls. Gallic acid has long been used in the manufacture of black ink and dyestuffs. The basic bismuth salt of gallic acid is used as a strong antiseptic under the name of Dermatole. The dimethyl ester of gallic acid, **syringic acid** VI, is obtained by the cleavage of many natural compounds, say, lignin.



The amide formed by 3,4,5-trimethoxybenzoic acid and a heterocyclic amine, morpholine, is known as meprobamate and is used medicinally as a tranquilizing agent.



The esters formed by the combination of two aromatic polyhydroxy acids, one playing the role of an acid and the other that of a phenol, are called **depsides***. Examples are lecanoric acid



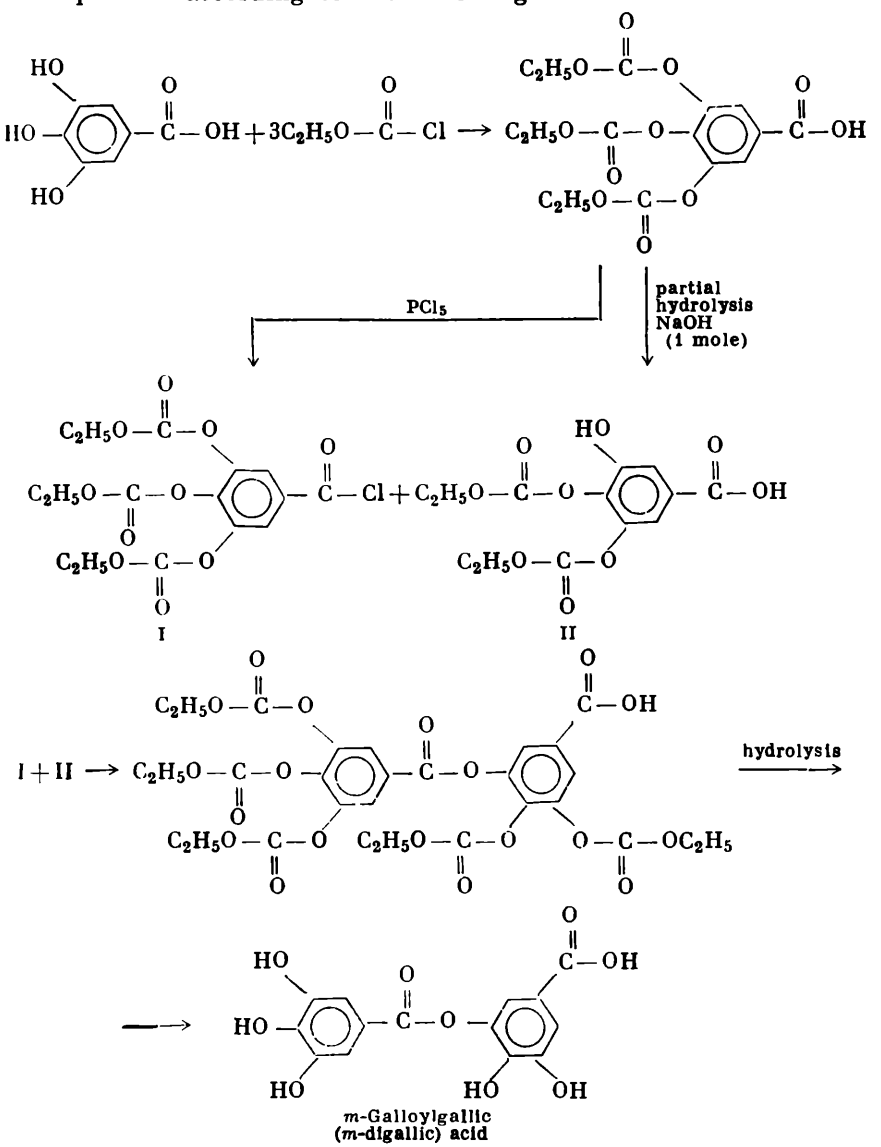
and galloylgallic acid given below.

Tannins extracted from some plant tissues, say, from the oak bark, are derivatives of depsides. Tannins are divided into two

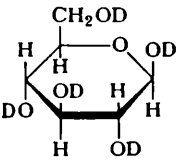
* From the Greek word meaning *to tan.—Tr.*

classes: **hydrolysable tannins** (it is these tannins which are the esters of depsides) and **non-hydrolysable tannins** (phlobatannins). Hydrolysable tannins are often derivatives of gallic and *m*-galloylgallic (*m*-digallic) acids.

The synthesis of *m*-galloylgallic acid from gallic acid has been accomplished according to the following scheme:



Tannins extracted from nut-galls are a glucose acylated by *m*-galloylgallic acid residues



General formula of tannins
(D=residue of gallic or
m-galloylgallic acid, or H)

The hydrolysis of tannins gives a glucose, *m*-digallic acid and a small amount of gallic acid.

Tannins that are produced from the various kinds of nut-galls differ somewhat by the number of acyl groups and the ratio of gallic and digallic acid residues. Even tannins isolated from a single plant are a mixture of individual compounds.

Tannins are used to mordant cotton fabrics during the dyeing process (to fix the dye), in medicine and in other fields.

The features common to all tannins, including synthetic tannins, are high molecular weight, aromatic nature and acidic properties. All these enable tannins to display their principal useful property—to combine with proteins, and modify them, for example, they precipitate proteins from their solutions, as in the case of tannin with albumins, or to combine with animal hide, converting it into leather. An aqueous solution of tannin when applied to the burnt skin binds the toxic protein products of decomposition of tissues and contributes to curing the tissues.

Tannin-combined albumin (*tannalbin*), having found its way into the digestive tract, liberates the tannin as the albumin is being digested, the tannin binding the protein toxins of pathiogenic bacteria.

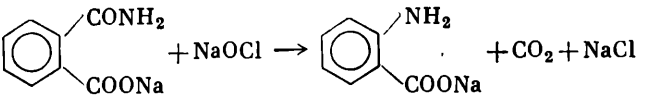
7.18. Aromatic Amino Acids

Aminobenzoic acids can be prepared by reducing the corresponding nitrobenzoic acids:

$$O_2NC_6H_4COOH \longrightarrow H_2NC_6H_4COOH$$

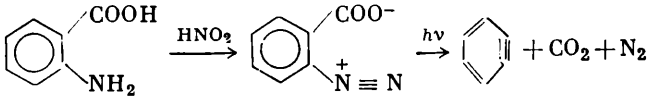
This method is employed industrially to synthesize *p*- and *m*-aminobenzoic acids. The *ortho*-isomer (anthranilic acid) is obtained from phthalamic acid by the Hofmann rearrangement (see Volume I,

page 283):

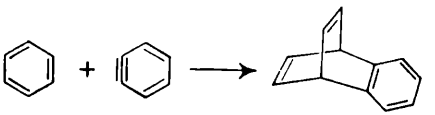


Thus, the starting material for the production of anthranilic acid is phthalic anhydride and, in the long run, naphthalene.

The diazotization of anthranilic acid leads to *o*-diazobenzenecarboxylic acid, which is basically an inner salt. When being illuminated it decomposes to give dehydrobenzene:

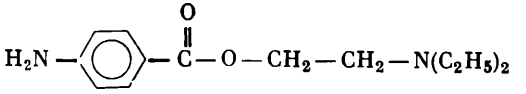


Dehydrobenzene then undergoes di- and trimerization (page 75 *et seq.*). It may also enter into other addition reactions described earlier. For example, with benzene an addition reaction takes place, in which dehydrobenzene acts as a dienophile and benzene as a diene:

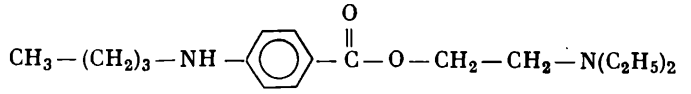


Anthranilic acid is an important intermediate product in the technical preparation of indigo (page 359) and also of a number of azo dyes (as the diazo component). The methyl ester of anthranilic acid (*methyl anthranilate*) is contained in the oil of jasmine blossom (together with benzyl acetate and a small amount of indole); it has the odour of strawberry and is used in perfumery.

p-Aminobenzoic acid is employed for the synthesis of a number of anesthetics: anesthesine (ethyl *p*-aminobenzoate), novocaine (the diethylamino-ethyl ester of *p*-aminobenzoic acid), and pantocaine.



Novocaine



Pantocaine

p-Aminobenzoic acid is a growth factor in many microorganisms. The action of sulpha drugs, based on the principle of replacement of the bacterial metabolite, consists in that these preparations act

as a substitute for *p*-aminobenzoic acid (vitamin H) required to sustain the bacterial activity. A sufficient concentration of these substances in the blood stream causes the death of bacteria. The drug ***p*-aminosalicylic acid** (PAS) prepared from *m*-aminophenol by the Kolbe reaction has come into extensive clinical use in the treatment of tuberculosis; its functioning is based on the same principle.

7.19. Carboxylic Acids with Carboxyl in the Side Chain

The simplest representativs of this class of compounds is **phenylacetic acid** which is prepared from benzyl chloride via its nitrile

$$C_6H_5CH_2Cl + KCN \xrightarrow[-KCl]{} C_6H_5CH_2CN \xrightarrow{H_2O(H^+)} C_6H_5-CH_2-COOH$$

or from the same starting material by the Grignard reaction. The next homologue, **hydrocinnamic acid**, is made by the hydrogenation of cinnamic acid:

$$C_6H_5-CH=CH-\underset{\underset{O}{\|}}{C}-OH \xrightarrow{H_2/Ni} C_6H_5-CH_2-CH_2-\underset{\underset{O}{\|}}{C}-OH$$

Cinnamic acid is synthesized by one of the following methods.

1. The oxidation of benzalacetone (the product of condensation of benzaldehyde with acetone) with hypochlorous acid (the haloform cleavage), which is the industrial method of preparing cinnamic acid:

$$C_6H_5-CHO + CH_3-\underset{\underset{O}{\|}}{C}-CH_3 \xrightarrow{NaOH} C_6H_5-CH=CH-\underset{\underset{O}{\|}}{C}-CH_3 \xrightarrow{NaOCl}$$

$$\longrightarrow C_6H_5-CH=CH-\underset{\underset{O}{\|}}{C}-CCl_3 \xrightarrow{NaOH} C_6H_5-CH=CH-COONa + CHCl_3$$

2. The condensation of benzaldehyde with acetic anhydride by the Perkin reaction (page 170):

$$C_6H_5-CHO + (\underset{\underset{O}{\|}}{CH_3-C})_2O \xrightarrow{\overset{CH_3CONa}{\overset{\|}{O}}} C_6H_5-CH=CH-\underset{\underset{O}{\|}}{C}-ONa + 2CH_3COOH$$

3. The condensation of benzaldehyde with malonic acid in the presence of bases (Knoevenagel):

$$C_6H_5-CHO+CH_2(COOR)_2 \xrightarrow{\text{piperidine}} C_6H_5-CH=C(COOH)_2 \longrightarrow$$
$$\longrightarrow C_6H_5-CH=CH-COOH+CO_2$$

Cinnamic acid obtained by these methods has a *trans*-configuration. When irradiated by ultraviolet light the *trans*-isomer is converted

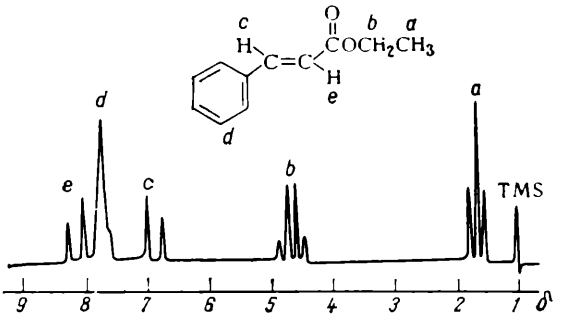
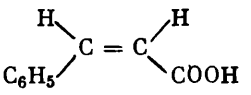


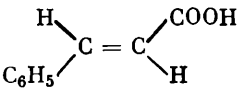
Fig. 7.10.

NMR spectrum of ethyl ester of *trans*-cinnamic acid (J = 15.8 Hz).

into the *cis*-isomer. *cis*-Cinnamic acid can exist in the form of crystalline modifications having different melting points.



cis-Cinnamic acid
(m.p. 57°C)



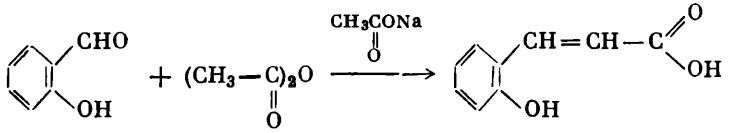
trans-Cinnamic acid
(m.p. 133°C)

Such *cis-trans* isomers as cinnamic acids, with hydrogen atoms at the double bond, differ significantly from each other spectroscopically and can be easily identified. Figure 7.10 shows the NMR (PMR) spectrum of the ethyl ester of cinnamic acid—ethyl cinnamate (the assignment of lines is given in the spectrum). The protons of the ethyl group give a quadruplet *b* and a triplet *a* (Volume II, page 292 *et seq.*). The protons of the phenyl group (benzene with one substituent), which usually differ little in chemical shift, give a broadened peak or a narrow multiplet *d*. The signals of *trans*-protons at the double bond (*c* and *e*) have a high spin-spin splitting constant J, which is usually almost twice as high (in Hz) as the constant J for *cis*-protons.

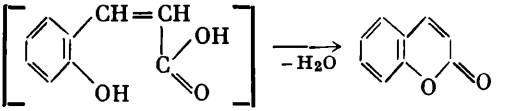
Such *cis*- and *trans*-isomers can also be easily distinguished with the aid of infrared or Raman spectra. For example, the infrared

spectra of *trans*-compounds of the type indicated are characterized by a band of the out-of-plane deformation vibration at 990-965 cm^{-1}, which is absent from the spectra of pure *cis*-compounds. *trans*-Crotonic, cinnamic and coumaric acids and their esters also absorb in the region of 980-974 cm^{-1}. The band intensity varies for different compounds from a medium to a high value.

Using substituted aldehydes instead of benzaldehyde, one can prepare cinnamic acids with different substituents in the ring; for example,

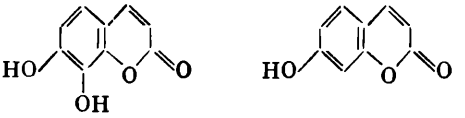


o-Hydroxycinnamic acid is represented by two stereoisomers: *cis*- (coumaric acid) and *trans*- (*o*-coumaric acid). The former is known to exist only in the form of derivatives since the free *cis*-acid immediately changes to its lactone—coumarin:



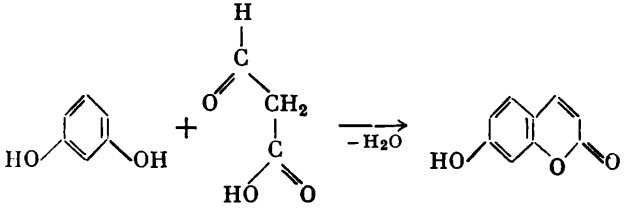
Coumarin

Coumarin has the smell of hay; it is the odorous ingredient of melilot (sweet clover). Just like its hydroxy derivatives (*esculetin* and *umbelliferone*), coumarin occurs widely in the vegetable kingdom.



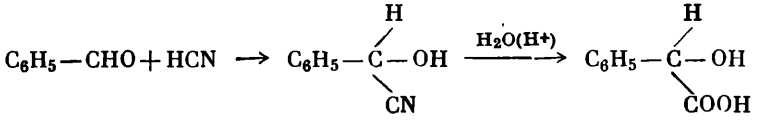
Esculetin Umbelliferone

Esculetin and umbelliferone can be synthesized by the Pechmann method: the corresponding phenol is heated with malic acid in the presence of sulphuric acid. In this reaction, malic acid is cleaved to yield formylacetic acid which condenses with the phenol:

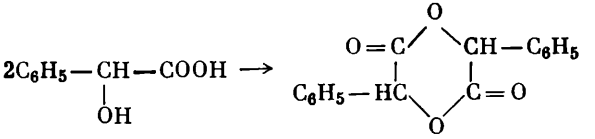


Resorcinol Umbelliferone

Benzaldehyde also serves as a starting material for preparing another important hydroxy acid—**mandelic acid:**

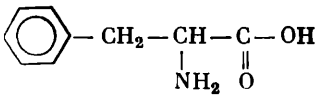


Like any α-hydroxy acid, mandelic acid forms two series of derivatives. It readily loses water to form a lactide:

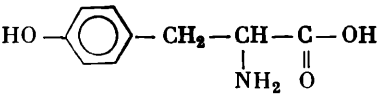


Mandelic acid has one asymmetric carbon atom and exists in the form of two optically active stereoisomers: D(—)- and L(+)-mandelic acids. The former is prepared by the hydrolysis of the glycoside of bitter almonds—amygdalin, and the latter can be isolated from the glycoside contained in the elder. The racemic acid, known as **paramandelic acid**, which is always formed in the synthesis, can be resolved into its optical antipodes with the aid of cinchonine salts. Mandelic acid has long been a favourite object for stereochemical investigations (along with tartaric and malic acids). For example, it was used, along with other compounds, to demonstrate the Walden inversion (see Volume II, page 50).

Among amino acids with functional groups in the side chain the most important is **phenylalanine** and **tyrosine:**



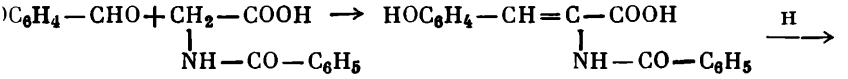
Phenylalanine



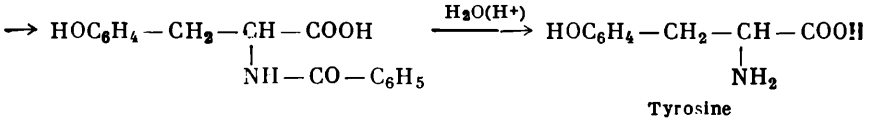
Tyrosine

Both these amino acids are among the 20 amino acids that participate in the building of proteins. Phenylalanine is one of the nine essential amino acids, i.e., it cannot be synthesized by the organism and must therefore be invariably present in the protein composition of food.

Tyrosine was synthesized by the condensation of hippuric acid and *p*-hydroxybenzaldehyde with subsequent hydrogenation of the double bond and saponification of the product formed:

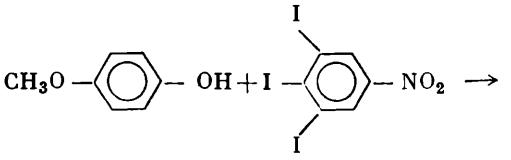


Hippuric acid

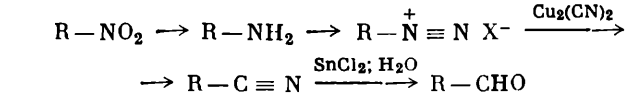


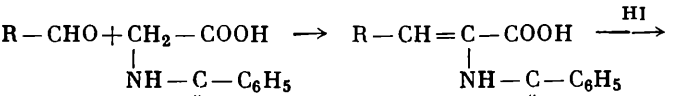
Tyrosine

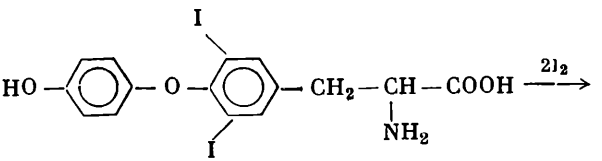
Natural L(—)-tyrosine and L(—)-phenylalanine are formed by the hydrolysis of nearly all proteins. An especially large amount of tyrosine is contained in casein and silk fibroin. Some derivatives of tyrosine, in particular **diiodotyrosine** and **thyroxine**, are also physiologically important. Thyroxine is the hormone that regulates metabolism; it is produced by the thyroid gland. The structure of thyroxine is confirmed by synthesis (Harington, 1926) by the following scheme:

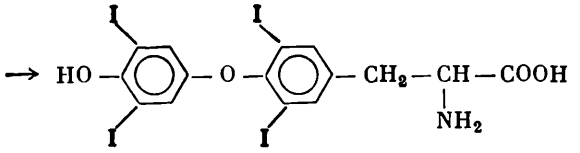


(designated hereafter as R—NO$_2$)





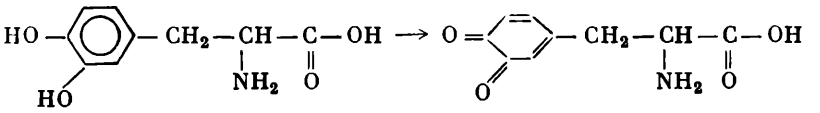




Thyroxine

The thyroid gland produces a definite amount of thyroxine. A deficiency of thyroxine in the organism (hypothyrosis) may lead to general weakness, apathy, and, to cretinism. Hyperthyrosis (the high activity of the thyroid gland) leads to disturbances of heart action, increased nervousness, increased blood pressure, exophthalmos (Basedow's disease). When sick with hypothyrosis the patients have to take drugs containing the appropriate hormones; hyperthyrosis is reduced with the aid of certain drugs which play the role of antihormones (for example, methyl thiouracyl), and sometimes an operation is required (part of the thyroid gland is removed).

The dark pigments contained in skin, hairy integument and in the cornea of the eyes of animals and humans, are formed by the oxidation of another amino acid in the organism—**dihydroxyphenylalanine** (abbreviated to DOPA), which in its turn results from the oxidation of thyrosine. Dihydroxyphenylalanine is oxidized further to a quinone (DOPA-quinone):



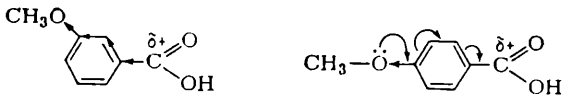
which is condensed to form a dye of the phenoxazine structure (page 439).

XXXIII. Transmission of the Effect of Substituents Via the Benzene Ring. Correlational Equations

The dissociation constants of carboxylic acids depend largely on the partial positive $\delta+$ charge on the carboxyl carbon atom. The electron-releasing groups attached to the benzene ring reduce this charge (and hence the dissociation constant); electron-attracting groups exert an opposite effect. Table 7.11 (see page 196) presents dissociation constants for a number of benzoic acids. As can be seen, the strength of benzoic acids also depends on the electron-attracting

ability of the substituent and on its position relative to the carboxyl group.

The nitro group has strong $-M$ and $-I$ effects and greatly contributes to the dissociation constant, especially when it is in the *para*-position. The methoxy group has a weak negative inductive effect ($-I$); on the other hand, it is capable of supplying unpaired electrons down the conjugated system of bonds. The inductive effect manifests itself mainly when the methoxy group is in the *meta*-position where there is no conjugation between the substituents and the carboxyl group; therefore, the introduction of a methoxy group into the *meta*-position increases the dissociation constant of a benzoic acid. In the case of *p*-methoxybenzoic acid there is observed a decrease in the dissociation constant since the conjugation (mesomeric or resonance) effect prevails over the inductive effect:



A similar competition between the inductive and the mesomeric effect is well known for halogen substituents, but during the dissociation of benzoic acids the inductive effect predominates since the mesomeric ($+M$) effect is very weak for the halogens. The dissociation constant varies in the series of acids as follows:

m-chlorobenzoic > *p*-chlorobenzoic > benzoic

An analogous polar influence is exerted by substituents on other reaction centres at the aromatic ring. Having studied numerous series of reactions, Hammett (1937) came to the conclusion that the rate constants of many reactions can be quantitatively related directly to the polar effects of the substituent. He derived the following equation:

$$\log \frac{K}{K_0} = \sigma\rho \qquad \text{or} \qquad \log K - \log K_0 = \sigma\rho$$

where K and K_0 are, respectively, the rate or equilibrium constants of any reaction for compounds containing a substituent in the benzene ring and also for an unsubstituted compound. For example, if K is the rate constant for the hydrolysis of *p*-nitrobenzoyl chloride by water in acetone at 20°C, then K_0 is the same constant for benzoyl chloride itself. The reaction constant ρ depends on the type of reaction, the nature of the reaction centre and on the reaction conditions (temperature, solvent); the constant σ depends only on the polar effect of the substituent and on its position in the benzene ring.*

* Values of σ are given separately for *meta*- and *para*-substituents (σ_m and σ_p). The effect of *ortho*-substituents does not obey the Hammett equation since in this case the substituent exerts not only polar but also steric effects.

The standard reaction chosen by Hammett is the dissociation of substituted benzoic acids in water at 25°C since these dissociation constants can be determined with the utmost accuracy. For this equilibrium the constant ρ is assumed to be equal to unity and the Hammett equation acquires the following form:

$$\log \frac{K}{K_0} = \sigma$$

This equation has been used to determine the constants σ for the various substituents. A graphical representation of the Hammett equation is given in Figs. 7.11 and 7.12. The values of σ are plotted

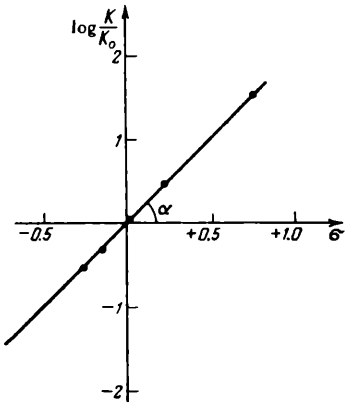


Fig. 7.11.

Graphic representation of the Hammett equation for the dissociation of substituted benzoic acids in water at 25°C (ρ = 1.00; log K_0 = −4.203).

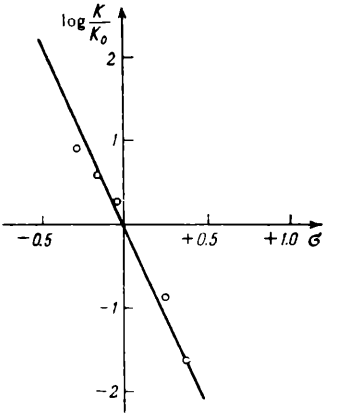


Fig. 7.12.

Graphic representation of the Hammett equation for the hydrolysis of benzyl chlorides by water at 30°C in 47-percent ethanol (ρ = −2.20; log K_0 = = −5.61).

along the abscissa and the values of log K/K_0 along the ordinate. If the reaction obeys the Hammett equation, then the points lie on a straight line passing at a certain angle α to the abscissa, ρ = tan α; for the dissociation of benzoic acids the angle α is equal to 45°. If several points are used to construct a graph, which requires an experimental determination of log K for several substituents, then we can determine the values of log K for dozens of other substituents, using the values of σ reported in the literature. This is one of the applications of the Hammett equation.

As has already been noted, the constant σ is a measure of the polar effect of the substituent: a positive value of σ corresponds to an electron-attracting substituent, and a negative value to an electron-

releasing substituent. The reaction constant ρ characterizes the sensitivity of the reaction to polar effects. The positive value of ρ means that the reaction rate increases with increasing electron-attracting ability of the substituent; with negative values of ρ the opposite effect is observed. The steeper is the straight line passing the coordinate origin (the higher the absolute value of ρ), the more sensitive is the reaction towards the polar effect of the substituent. From the value (and particularly the sign) of the reaction constant ρ we can, in certain cases, draw inferences about the reaction mechanism. This is also one of the important applications of the Hammett equation.

Table 7.14 gives values of σ for the most typical *meta-* and *para-*substituents.

TABLE 7.14. **Constants σ for Some Substituents**

Substituent	σ_p	σ_m	Substituent	σ_p	σ_m
NH_2	−0.66	−0.16	H	0.00	0.00
$N(CH_3)_2$	−0.60	−0.21	F	+0.062	+0.337
OH	−0.357	−0.002	Br	+0.232	+0.39
OCH_3	−0.268	+0.115	$COCH_3$	+0.516	+0.306
CH_3	−0.170	−0.069	$COOCH_3$	+0.522	+0.398
tert-C_4H_9	−0.198	−0.120	NO_2	+0.778	+0.710

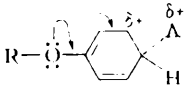
Thousands of various series of reactions obeying the Hammett equation have been studied. We present here only some examples of such reactions and the values of ρ for them:

Ionization of phenols in water at 25°C . . . . . +2.113
Alkaline hydrolysis of methyl benzoate in 60-percent acetone at 0°C . . . . . +2.46
Acid hydrolysis of ethyl benzoates in 60-percent ethanol at 0°C . . . . . +0.144
Hydrolysis of benzyl chlorides in 50-percent aqueous acetone at 60°C . . . . . −1.69
Bromination of acetophenone into the side chain in water at 25°C . . . . . +0.417
Reduction of nitrobenzene by $SnCl_2$ in water at 90°C +1.15

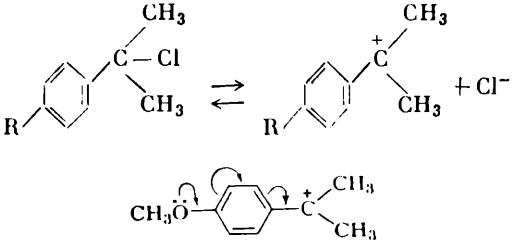
The Hammett equation is not obeyed by some important reactions in the transition state of which the reaction centre acquires a positive (or negative) charge conjugated via the benzene ring with substituents exhibiting a $+M$ or $-M$ effect. Such substituents exert a stronger effect and values of σ that have to be assigned to them are higher

than the commonly used constants σ. Such reactions include, for example, many reactions of electrophilic substitution in the aromatic ring.

In electrophilic substitutions the positively charged electrophilic reagent attacks the benzene ring, pulling an electron pair and developing a positive charge in the ring. If the attack occurs in the *para*-position to groups such as OH, OR, NR_2, they will take an effective part in the delocalization of charge due to their $+T$ effect, and their p electron pairs will be conjugated with the developing positive charge (A is an electrophile):



For processes that do not obey the Hammett equation, Okamoto and Brown proposed another standard reaction highly sensitive towards the $+T$ effect of substituents—the alcoholysis of aryldimethylchloromethanes. This reaction proceeds by the monomolecular S_N1 mechanism, i.e., the slow step is the ionization of the chloride; the $+T$ effect of the substituent is completely transmitted to the positively charged reaction centre (just as in electrophilic substitution reactions):



The value of ρ for this reaction is assumed equal to unity and values of σ^+ have been obtained for many substituents. The Brown-Okamoto equation has the same form as the Hammett equation:

$$\log \frac{K}{K_0} = \rho\sigma^+$$

but σ^+ differs in magnitude from σ. Below are given the values of σ^+ for some substituents:

	σ_p^+	σ_m^+		σ_p^+	σ_m^+
CH_3O	−0.78	+0.045	Cl	+0.114	+0.40
CH_3	−0.31	−0.066	CN	+0.56	+0.66
F	−0.073	+0.011	NO_2	+0.79	+0.67

Thus, both the Hammett equation and the Brown-Okamoto equation are used with equal right but for different series of reactions. Unfortunately, they are applicable only to the benzene series and to some aromatic and heterocyclic compounds. In those cases where steric interactions between the substituent and the reaction centre are considerable, such a correlation is absent. Interactions of this kind exist in aliphatic compounds, even if the substituent is remote from the reaction centre since the aliphatic chain is flexible. By **steric interactions** are meant here any interactions between the substituent and the reaction centre, which are transmitted not via the bond system. They include, for example, the steric hindrance arising in the transition state, the polar mutual attraction or repulsion between the reaction centre and the substituent R, and other factors.

For the aliphatic series, Taft suggested, as standard reactions, the proton-catalysed alkaline and acid hydrolyses of esters having the general formula RCH_2COOCH_3. With the approach considered below Taft succeeded in separating the inductive and steric effects for these reactions. The quantitative measure of the inductive effect (σ^*) derived by him is general for the aliphatic series. The inductive and steric effects are independent quantities and therefore the following equation must hold for any series of reactions*:

$$\log \frac{K}{K_0} = \sigma^* \rho^* + E_S$$

where σ^* is the measure of the inductive effect of the substituent; E_S is its steric contribution, which varies from one series of reactions to another.

Hence, the alkaline hydrolysis (subscript B) and acid hydrolysis (subscript A) are described by the following equations:

$$\log \left(\frac{K}{K_0}\right)_B = \sigma^* \rho_B^* + (E_S)_B$$

$$\log \left(\frac{K}{K_0}\right)_A = \sigma^* \rho_A^* + (E_S)_A$$

Further, Taft introduced two postulates.

Postulate 1: the steric effects of substituents on acid and alkaline hydrolysis reactions are identical, or

$$(E_S)_B = (E_S)_A \equiv E_S$$

This assumption suggested earlier by Ingold is theoretically substantiated by the fact that the transition states for both reactions (or equilibria) differ little from each other.

* A series of reactions in which only the substituent R is varied, the conditions and type of reaction remaining constant.

Postulate 2: it is assumed that $\rho_A^* \equiv 0$. On the basis of numerous experimental data it has been established that the equilibrium constant of the acid hydrolysis of esters is practically independent of the electronegativity (or electron-releasing ability) of the substituent. For instance, the constants for *m*-nitro- and *p*-methoxy benzoates are almost the same. Thus, if $\rho_A^* = 0$, then

$$\log \left(\frac{K}{K_0}\right)_A \equiv E_S$$

Subtracting this equation from the equation for the alkaline hydrolysis and taking into account the equality of the steric effects, we obtain:

$$\log \left(\frac{K}{K_0}\right)_B - \log \left(\frac{K}{K_0}\right)_A = \sigma^* \rho^*$$

For the convenience of comparing the constant σ^* with the Hammett constant σ the value of ρ^* for the alkaline hydrolysis is taken to be equal to 2.48. Thus,

$$\sigma^* = \frac{1}{2.48}\left[\log \left(\frac{K}{K_0}\right)_B - \log \left(\frac{K}{K_0}\right)_A\right]$$

For other reactions, the quantity ρ^* will naturally have other values.

Thus, σ^* is a quantitative expression of the inductive effect since the steric effect is separated from it. For the aliphatic series the quantity K_0 is the hydrolysis constant for an ester of acetic (and not of formic) acid; in this case $\sigma^* \equiv 0$.

The Taft equation has been used to establish a number of relationships, say, the additivity of the inductive effect of the substituent. For example, if the value of σ^* for the substituent C—Cl equals +0.37, then for the substituent

it will have a doubled value (+0.74).

The Taft equation has an outward resemblance to the Hammett equation:

$$\log \frac{K}{K_0} = \sigma^* \rho^*$$

The area of application of the Taft equation is limited and is determined only by experiment. This equation can be used only in those cases where the steric effects are not strong. The σ^* values of a number of substituents are given in Table 7.15.

TABLE 7.15. **The Constants σ* for the Aliphatic Series**
(a measure of the polarity of substituents according to Taft)

R	σ*	R	σ*	R	σ*
CH_3	0	FCH_2	+1.10	$C_6H_5CH_2$	+0.215
Cl_3C	+2.65	$ClCH_2$	+1.05	C_2H_5	−0.10
F_2CH	+2.05	$BrCH_2$	+1.00	*n*-C_3H_7	−0.115
$COOCH_3$	+2.00	ICH_2	+0.85	*iso*-C_3H_7	−0.125
$(CH_3)_3\overset{+}{N}CH_2$	+1.90	$C_6H_5C \equiv C$	+1.35	*cyclo*-C_5H_9	−0.20
$N \equiv CCH_2$	+1.30	C_6H_5	+0.60	$(CH_3)_3C$	−0.30
		H	+0.49		

7.20. Aromatic Hydrocarbons with Unsaturated Side Chains

The simplest hydrocarbon of this type—**styrene** (vinylbenzene)—has become industrially very important in the production of plastics and synthetic rubbers. Styrene is manufactured at present from ethylbenzene (which is prepared by the condensation of benzene with ethylene in the presence of $AlCl_3$) by dehydrogenation over a catalyst containing chromium oxide (A. A. Balandin, G. M. Marukyan):

$$C_6H_5-C_2H_5 \xrightarrow{Cr_2O_3/Al_2O_3} C_6H_5-CH=CH_2+H_2$$

The structure of styrene can be elucidated either by the reverse of the catalytic hydrogenation (over Pt) to ethylbenzene or by the oxidation to benzoic acid and ozonization followed by the hydrolysis to benzaldehyde. Its structure also follows from its preparation by decarboxylation of cinnamic acid or dehydration of methylphenylcarbinol:

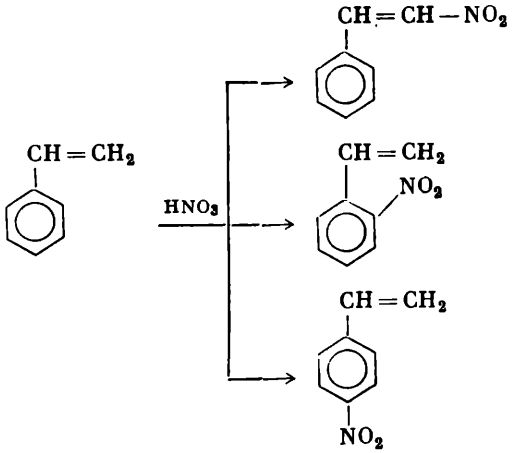
$$C_6H_5-CH=CH-COOH \longrightarrow C_6H_5-CH=CH_2+CO_2$$

$$C_6H_5-\underset{\displaystyle OH}{\underset{|}{CH}}-CH_3 \longrightarrow C_6H_5-CH=CH_2+H_2O$$

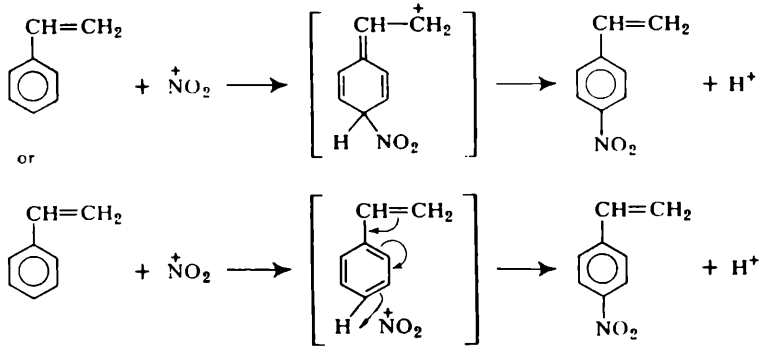
Styrene is a liquid with b.p. 145°C and m.p. −30.6°C.

It is natural that the presence in styrene of an active olefinic bond in the side chain determines the principal direction of electrophilic attack on that chain. But when styrene is subjected to nitration, apart from the main product of this reaction, ω-nitrostyrene, there

are formed both products of nitration into the ring: *o*- and *p*-nitrostyrenes:



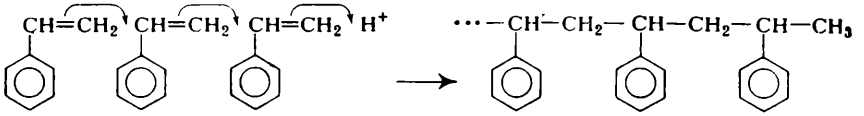
From here it follows that the double bond conjugated with the benzene ring exhibits (in the transition state during the electrophilic attack on the nucleus) an electron-releasing tendency:



ω-Nitrostyrene is nitrated into the *ortho*- and *para*-positions, though more slowly than benzene. Thus, the group $-CH=CHNO_2$ furnishes one more example of the rare combination of deactivation with *ortho-para* orientation.

The principal application of styrene is its polymerization to polystyrene, a light, transparent thermoplastic material with excellent insulating properties. The polymerization is effected by the action of boron trifluoride (traces of water form the strong acid $H^+HOBF_3^-$) at a low temperature. This reaction proceeds as an ionic process

initiated by H^+:



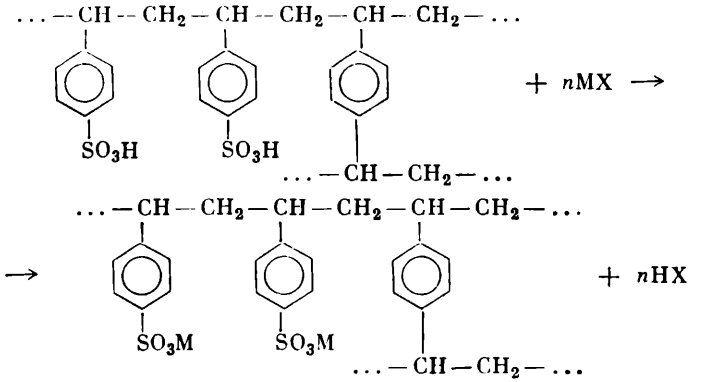
Isotactic polystyrene has already been described (see Volume II, page 54).

When subjected to cracking polystyrene is sufficiently smoothly depolymerized, i.e., the cracking occurs across the newly formed bonds in polystyrene.

Large quantities of styrene are used for copolymerization with butadiene for the manufacture of the styrene-butadiene rubber (containing up to 30 per cent of styrene) which is noted for its high wear-resistance and is therefore particularly valuable for the production of automobile tyres. Styrene in air gradually thickens and becomes hard, undergoing spontaneous polymerization, so that it has to be stored with an inhibitor added.

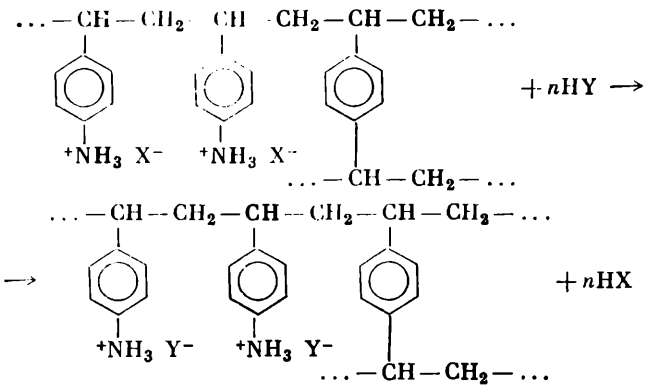
The dehydrogenation of diethylbenzene over Cr_2O_3/Al_2O_3 yields **divinylbenzene**. When mixed with styrene divinylbenzene polymerizes to a cross-linked space-network (not linear) polymer in which additional cross links in the macromolecule are formed at the expense of the second vinyl group of divinylbenzene.

Such space-network polymers may contain sulphonic groups in the benzene ring. In this case they serve as ion-exchangers, namely, as **cation-exchange resins**:



If the copolymers of styrene and divinylbenzene are nitrated and the nitro groups are then converted to amino groups, **anion-exchange**

resins will obtain:



The entire mass of the resin is basically one macromolecule of a polybasic acid (or base) which is absolutely insoluble because of its enormous size. When a solution of an electrolyte is passed through an ion-exchange resin there takes place an exchange of the cation (or anion), which goes to completion owing to the insolubility of the resin-acid or -salt. This process is extensively employed in modern engineering and in preparative analytical chemistry for isolating acids, bases, and salts in a pure form, say, for desalting of water. Styrene copolymers are particularly suited for this purpose.

Phenylacetylene is the simplest aromatic hydrocarbon with a triple bond in the side chain. It is prepared by the method common to all acetylenes—by adding a bromine molecule to an olefin and eliminating HBr by the action of alcoholic alkali:

$$C_6H_5-CH=CH_2+Br_2 \longrightarrow C_6H_5-CHBr-CH_2Br \xrightarrow[-2HBr]{} C_6H_5-C\equiv CH$$

Phenylacetylene (b.p. 141.6°C) has the properties of monosubstituted acetylenes. This hydrocarbon has not found industrial application.

Chapter 8

Polycyclic aromatic compounds

8.1. Compounds with Isolated Benzene Rings

A. Biphenyl

Biphenyl (or *diphenyl*), $C_6H_5 \cdot C_6H_5$, is most simply prepared by the Berthelot method—by passing benzene vapour through a red-heated tube:

$$2C_6H_6 \longrightarrow C_6H_5-C_6H_5+H_2$$

The structure of biphenyl follows from its synthesis by the Wurtz-Fittig reaction:

$$2C_6H_5Br+2Na \longrightarrow C_6H_5-C_6H_5+2NaBr$$

It is also obtained as a by-product in the synthesis of a Grignard reagent from a halogenobenzene and magnesium by a similar reaction

$$2C_6H_5Br+Mg \longrightarrow C_6H_5-C_6H_5+MgBr_2$$

Biphenyl and its various derivatives can be prepared by the Gomberg reaction (page 126) through the action of a phenyldiazonium salt in the presence of sodium acetate on benzene and substituted benzenes:

$$X-C_6H_4-N=N-O-\overset{\displaystyle O}{\overset{\|}{C}}-CH_3 + C_6H_5Y \longrightarrow$$

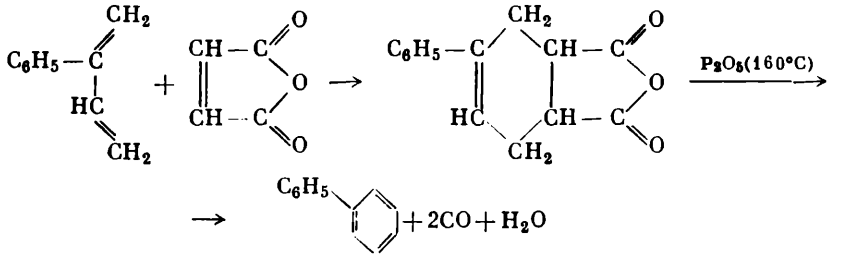
$$\longrightarrow X-C_6H_4-C_6H_4-Y + N_2 + CH_3-\overset{\displaystyle O}{\overset{\|}{C}}-OH$$

Since the reaction proceeds in a homolytic manner, the place of entry of the diazo compound into the benzene ring depends little on the nature of the directing group. This reaction yields a mixture of *o*-, *m*-, and *p*-substituted biphenyls with the *p*-isomer predominating.

Biphenyl with an impurity of **terphenyl**, $C_6H_5-C_6H_4-C_6H_5$, and **quarterphenyl**, $C_6H_5-(C_6H_4)_2-C_6H_5$, is a usual by-product

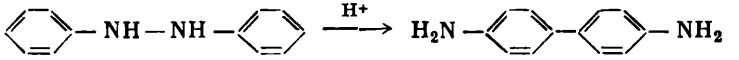
in the homolytic decomposition of diazonium salts (for example, in the presence of copper by the Gattermann reaction). It is prepared due to the coupling of the transiently formed free phenyl radicals. Terphenyl and quarterphenyl are formed as a result of the Gomberg reaction between biphenyl and diazonium salts.

R. Ya. Levina and V. R. Skvarchenko have developed a version of their method of synthesis of aromatic hydrocarbons, which leads to biphenyl and its derivatives. The method is based on the diene condensation of 2-arylbutadiene with maleic anhydride:

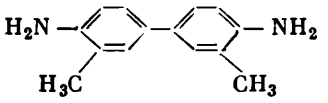


In this way, substituted biphenyls are obtained from arylbutadienes.

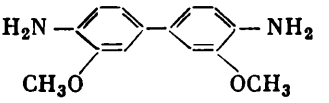
The most important derivative of biphenyl is **benzidine** (4,4′-diaminobiphenyl or *p,p′*-diaminobiphenyl) produced industrially by the benzidine rearrangement of hydrazobenzene (page 92):



An analogous reaction is used to prepare *o*-tolidine and *o*-dianisidine:



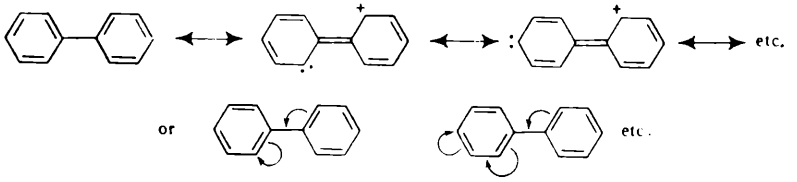
o-Tolidine



o-Dianisidine

The structure of these compounds as derivatives of biphenyl can be proved by diazotization of both amino groups followed by the elimination of the diazo groups through their replacement by hydrogen (page 124). These reactions as applied to benzidine lead to biphenyl, and in the case of *o*-tolidine and *o*-dianisidine, to the corresponding substituted diphenyls. In benzidine, the *para*-position of the amino groups is established from the fact that when an electrophilic substituent is introduced, say, on halogenation, benzidine (or its acyl derivative) affords the only monosubstituted product. Benzidine and its derivatives are widely used in the synthesis of azo dyes.

Biphenyl is a typical aromatic hydrocarbon in which both nuclei are independent of each other to a more considerable extent than might be expected on the basis of its planar structure and the decreased (as compared with normal) distance between the singly bonded carbon atoms of the two benzene rings (1.48 instead of 1.54 Å). This distance is a clear-cut expression of double-bond character, i.e., the overlap of the π-orbitals of the two nuclei in the sense of the formulas



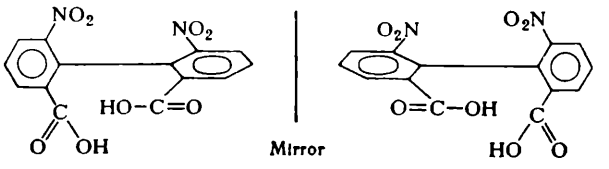
When biphenyl is nitrated, one nitro group enters mainly the *para*-position to a carbon atom linking the nuclei, and second, unexpectedly, also enters the *para*-position in the second nucleus (cf. the nitration of ω-nitrostyrene). The resulting *p,p'*-dinitrobiphenyl on reduction gives benzidine.

Biphenyl in which the C—C bond between the phenyls is formed between labelled ^{14}C atoms, when acted on by $AlCl_3$ with an impurity of $HAlCl_4$ (in benzene solution) redistributes the ^{14}C label over all the *o*-, *m*-, and *p*-carbon atoms (Weinberg and Wolff, 1963), i.e., the carbon-carbon bond of both phenyls is broken and is then reformed, this time between the new carbon atoms. In this process, however, the phenyl radicals do not go into the bulk and the changes take place within the same biphenyl molecule.

XXXIV. Atropisomerism II

Kenner and Christie (1922) found that the *o,o'*-substituted diphenic acids can be resolved into optical antipodes by converting them into salts with an optically active alkaloid, separating the resulting diastereomeric salts and isolating the free enantiomers of the substituted diphenic acids by the action of acid. It is easy to see that neither biphenyl nor diphenic acids contain (and they cannot contain) asymmetric carbon atoms since both the ring carbon atoms and the carboxyl carbon atoms are linked only to three (and not to four) different atoms or groups. The isomerism of substituted diphenic acids is an optical isomerism without asymmetric carbon atoms and with no other asymmetric atoms at all. This isomerism is due

to the non-planar structure of these substituted biphenyls, the impossibility of rotation about the C—C bond joining the two benzene nuclei together. Rotation is interfered with by groups being in contact with one another in the *ortho*-position. As a result, the molecule has no plane of symmetry and its mirror image is not identical with the original, as can be shown with the aid of the following model:



This type of stereoisomerism associated with the impossibility of rotation and therefore called **atropisomerism** has already been discussed (page 150). The atropisomerism of biphenyl derivatives has especially extensively been studied by R. Adams who found out which *ortho*-substituents interfere with the rotation and cause the appearance of stereoisomerism. Neither diphenic acids themselves nor their *para*-substituted derivatives have stereoisomers.

The accumulation of substituents in the *ortho*-positions in biphenyl, which impede or make impossible the conjugation of its two rings because of the disturbance of their coplanarity, immediately affects the ultraviolet spectrum (see Volume II, page 308) of substituted biphenyls. Figure 8.1 shows the spectra of biphenyl and dimethylbiphenyl with different disposition of the methyl groups in the rings. Especially clearly seen is the change of the second peak which is possibly a combination of the bands *K* and *B*. The height of this peak for *meta*- and *para*-substituted compounds differ insignificantly and the band intensity of the *ortho*-substituted biphenyl is very low and resembles the *B*-band of benzene.

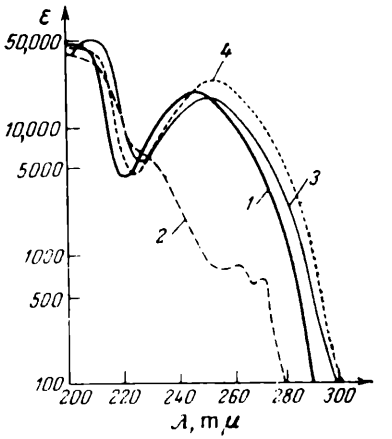


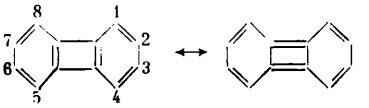
Fig. 8.1.

UV spectra of biphenyl and its substituted compounds:

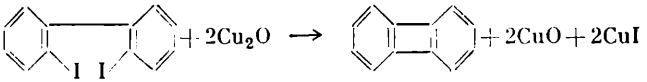
1—biphenyl; *2*—2,2′-dimethylbiphenyl; *3*—3,3′-dimethylbiphenyl; *4*—4,4′-dimethylbiphenyl.

B. Diphenylene (Biphenylene)

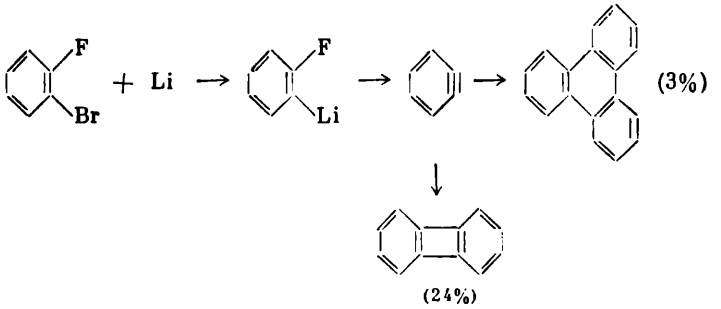
Diphenylene, or dibenzocyclobutadiene, which has the structure



was first obtained by Lothrop by the action of cuprous oxide on *o,o'*-diiodobiphenyl:



Later Wittig found that the polymerization of dehydrobenzene, along with the trimer of the latter, tri-*o*-phenylene, gives the dimer, diphenylene, as well:



Diphenylene is a solid (m.p. 111°C) with the smell of naphthalene. When oxidized by chromic acid it forms phthalic anhydride, and when acted on by hydrogen-saturated Raney nickel it gives biphenyl (one carbon-carbon bond is broken). Diphenylene is acetylated by the Friedel-Crafts reaction in the position *2*; sulphonated, forming even at room temperature 2,6-disulphonic acid; nitrated to form 2-nitrodiphenylene; it is also mercurated and halogenated in the position *2*.

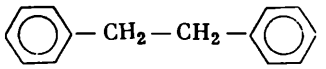
The conjugation of the π-systems of the two benzene rings has a stronger effect on a number of reactions of diphenylene than in the case of biphenyl. Thus, when a second acetyl group is introduced by the Friedel-Crafts reaction, only 2,6-diacetyldiphenylene is formed. If the influence of the first acetyl group were not transmitted through the conjugation system, 2,7-diacetylbiphenyl would also be formed.

Of considerable interest is the presence in diphenylene of a cyclobutadiene ring which is unstable itself.

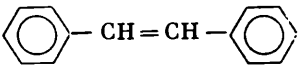
C. 1,2-Diphenylethane, 1,2-Diphenylethylene, and 1,2-Diphenylacetylene

1,2-Diphenylethane (m.p. 52°C; b.p. 285°C), which is usually known as **dibenzyl**, is easily prepared from benzyl chloride by the action of sodium (Wurtz reaction) or by the interaction between benzyl chloride and benzyl-lithium or benzylmagnesium halide. Of course, dibenzyl can also be obtained from benzoin, and most simply by the Friedel-Crafts reaction from 1,2-dichloroethane and benzene.

Stilbene (1,2-diphenylethylene) exists as *cis*- and *trans*-forms. The stable *trans*-form has m.p. 124°C and b.p. 306°C, and the *cis*-isomer has a melting point of +5°C. The ordinary routes of synthesis lead to the *trans*-isomer; it can be made from phenyl benzyl ketone by reduction to the alcohol followed by dehydration.

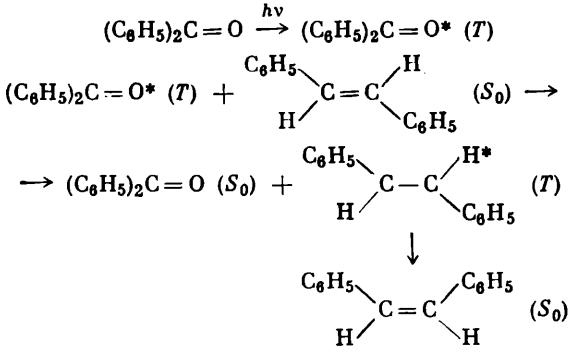


Dibenzyl



Stilbene

The *cis*-stilbene can be obtained from the *trans*-isomer by *induced irradiation*. We shall give this reaction as a typical example of conversion with the aid of induced radiation. To *trans*-stilbene there is added benzophenone which becomes excited by ultraviolet light to a triplet state ($p \rightarrow \pi^*$ transition; see Volume II, page 322). The triplet state is then exchanged with *trans*-stilbene (T—triplet state, S_0—ground state):

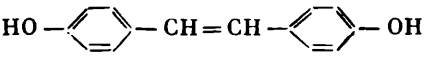


In the triplet state of *trans*-stilbene the π-electrons of the double bond acquire parallel spins, and this bond becomes a single bond. When free to rotate stilbene is no longer planar. From the T-state the excited stilbene molecule regains either the S_0-state of *cis*-stilbene (with a somewhat higher energy level, as is usual with *cis*-compounds)

or the S_0-state of *trans*-stilbene, giving off excess of energy as heat. An equilibrium mixture of *cis*- and *trans*-stilbenes is also formed under the same conditions by *cis*-stilbene whose triplet state differs energetically from its *trans*-analogue (see above) and which is converted into the *trans*-compound.

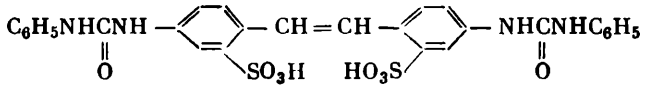
cis-Stilbene can be obtained also by the partial hydrogenation of tolane (see below).

Among the derivatives of stilbene we shall mention 4,4′-dihydroxystilbene



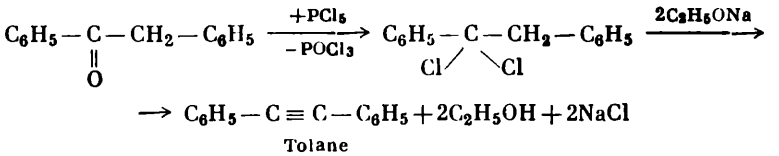
which is called **stilboestrol** for its estrogenic effect (see Volume IV).

4,4′-Bis-(phenylureido)-2,2′-stilbenedisulphonic acid (Blankophor B)



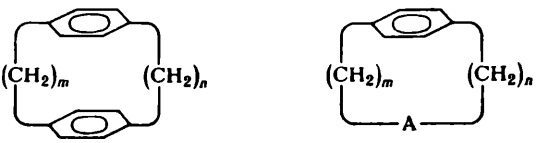
is used as a whitening agent for cotton and rayon fabrics. It gives a blue fluorescence and plays the role of an active bluing agent.

Diphenylacetylene, or **tolane**, is prepared by the usual routes of synthesis of acetylenic compounds; for example,



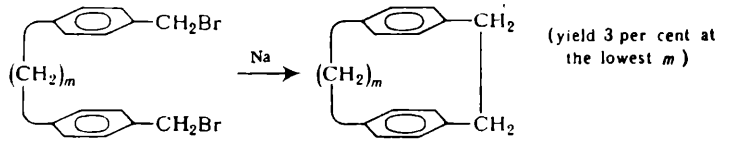
D. Cyclophanes

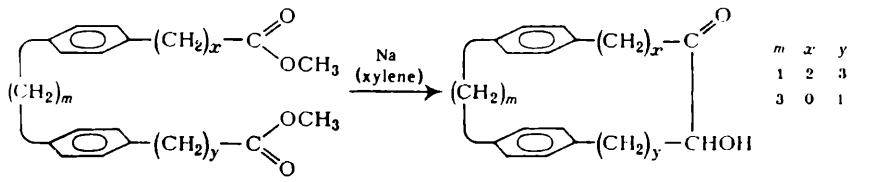
Cram succeeded in accomplishing the synthesis of the various paracyclophanes. Compounds of the following types were named paracyclophanes by Cram:



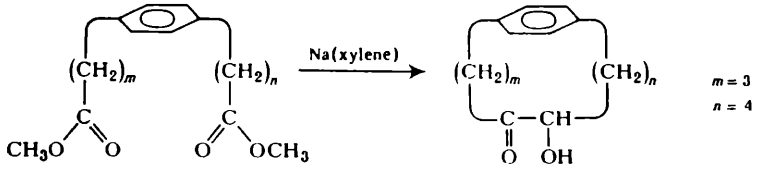
where *m* and *n* are equal to a minimum of 2; A is one or two aliphatic carbon units carrying the functional groups —OH, =O, etc. The

methods of synthesis of cyclophanes will become clear from the following schemes:

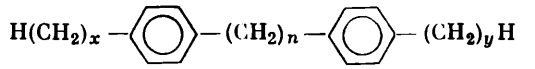




The acyloin condensation of an ester (see Volume II, page 261) is as follows:



The most interesting specific feature of the cyclophanes is the interaction of the π-electron systems of the benzene rings arranged in a sandwich manner (one above the other). This interaction can be traced from the ultraviolet spectra which differ most strongly (the shift of the absorption maximum to longer wavelengths) from the spectra of open non-sandwich systems of the type



where $n = 2$, $m = 2$, i.e., at the maximum approach of the benzene rings (Fig. 8.2). In such cyclophanes with distorted ultraviolet spectra, the distance between the benzene rings may be reduced to a value smaller than that between the planes of the benzene rings in a crystal (lower than 3.4 Å). The distortion of the spectrum is associated, according to Cram, with the distortion of the planar structure of benzene rings and the disturbance of the ideal delocalization of the π-electron system (i.e., with the shift towards the unsaturated system).

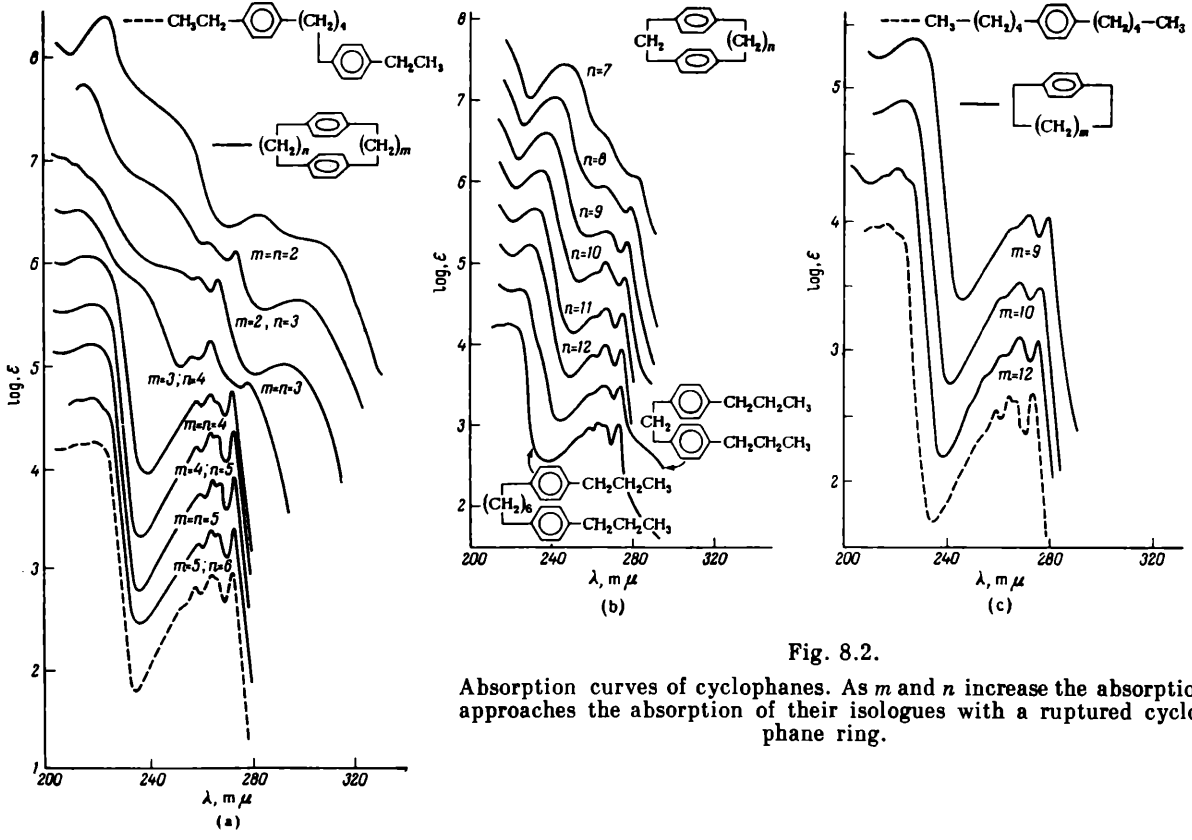
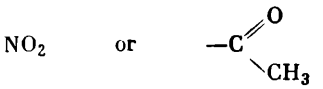


Fig. 8.2.

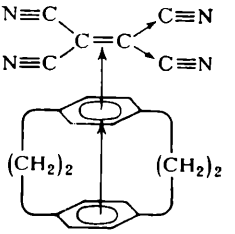
Absorption curves of cyclophanes. As m and n increase the absorption approaches the absorption of their isologues with a ruptured cyclophane ring.

Very interesting are the results of acetylation of cyclophanes by the Friedel-Crafts reaction and their nitration reactions. 3,4- and 2,2-Paracyclophanes give only monosubstituted products—a ketone and, respectively, a nitro compound. Thus, in paracyclophanes with a distorted (or strongly distorted) spectrum the transannular interaction of benzene rings is such that the replacement of hydrogen by an electron-attracting group, such as



renders the second nucleus insensitive towards an electron attack as a result of the withdrawal of the π-electrons from it by a substituted benzene nucleus. Such relations are observed in the formation of complexes of paracyclophanes with tetracyanoethylene. The relationships of aromatic rings to this unsaturated compound furnish an example of the relations between a π-base and a π-acid. A π-acid pulls an electron from a π-base to form, in the limiting case, an anion and to convert an aromatic nucleus into a cation. Such an electron migration may be incomplete, but it binds the two components into a molecular charge-transfer compound (see page 139). In this process, the absorption of light shifts from the ultraviolet to the visible region.

The absorption maximum is at 5210 Å for complexes of 2,2-paracyclophanes with tetracyanoethylene and at 5110 Å for 2,3-paracyclophanes, while the complex of a model compound with two benzene nuclei linked by an open saturated chain of carbon atoms has an absorption maximum at 4460 Å. This difference is accounted for by the transannular "contribution" of the second benzene nucleus which increases the electron supply by the cyclophane:



An interesting course is revealed by the hydrogenation of paracyclophanes. 6,6-Paracyclophanes are catalytically hydrogenated to the corresponding cyclohexane derivatives, each benzene nucleus being hydrogenated independently of each other. 2,2-Paracyclophane is reduced by lithium in ethylamine (nascent hydrogen) and cataly-

tically with the same result: 4 moles of hydrogen are added and a diene compound with an unestablished position of double bonds is formed. This compound is hydrogenated only with difficulty over a catalyst to an entirely cyclohexane derivative.

E. Polyphenylmethanes

The following hydrocarbons (beginning with diphenylmethane) belong to compounds of this type:

	m.p., °C	b.p., °C
Toluene, $C_6H_5CH_3$ . . .	−95	262
Diphenylmethane, $(C_6H_5)_2CH_2$	+27	359
Triphenylmethane, $(C_6H_5)_3CH$	92	—
Tetraphenylmethane, $(C_6H_5)_4C$	285	—

Of these compounds only toluene has been discussed in this book. To synthesize diphenylmethane, use may be made of two versions of the Friedel-Crafts reaction:

$$2C_6H_6 + CH_2Cl_2 \xrightarrow{AlCl_3} C_6H_5-CH_2-C_6H_5 + 2HCl$$

$$C_6H_6 + C_6H_5CH_2Cl \xrightarrow{AlCl_3} C_6H_5-CH_2-C_6H_5 + HCl$$

Triphenylmethane can most simply be synthesized from chloroform and benzene by the same reaction:

$$3C_6H_6 + CHCl_3 \xrightarrow{AlCl_3} (C_6H_5)_3CH + 3HCl$$

Tetraphenylmethane cannot be obtained by an analogous reaction since the interaction with carbon tetrachloride stops at the stage of formation of triphenylchloromethane:

$$3C_6H_6 + CCl_4 \xrightarrow{AlCl_3} (C_6H_5)_3CCl + 3HCl$$

A fourth phenyl can be introduced by the action of a Grignard reagent on triphenylchloromethane (the yield is low):

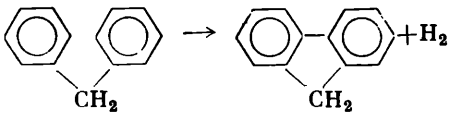
$$(C_6H_5)_3CCl + C_6H_5MgBr \longrightarrow (C_6H_5)_4C + MgClBr$$

Some of the compounds already described in the book, such as benzophenone, $C_6H_5COC_6H_5$, the product of its reduction—the secondary alcohol benzhydrol, $C_6H_5-CH(OH)-C_6H_5$, and the so-called Michler ketone, the last-named compound being prepared by the action of phosgene on dimethylaniline

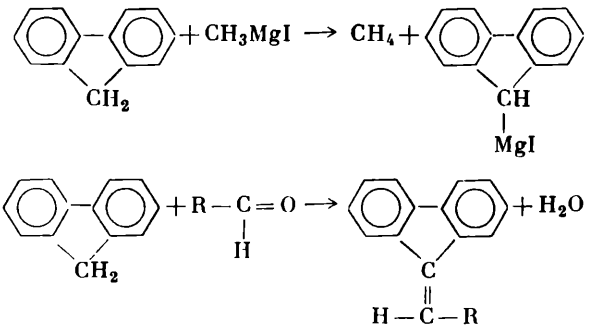
$$COCl_2 + 2C_6H_5N(CH_3)_2 \longrightarrow (CH_3)_2N-C_6H_4-\underset{\underset{O}{\|}}{C}-C_6H_4-N(CH_3)_2$$

are derivatives of diphenylmethane.

When diphenylmethane vapour is passed through a red-heated tube, *o,o'*-diphenylmethane or **fluorene** (m.p. 115°C, b.p. 294°C) results:

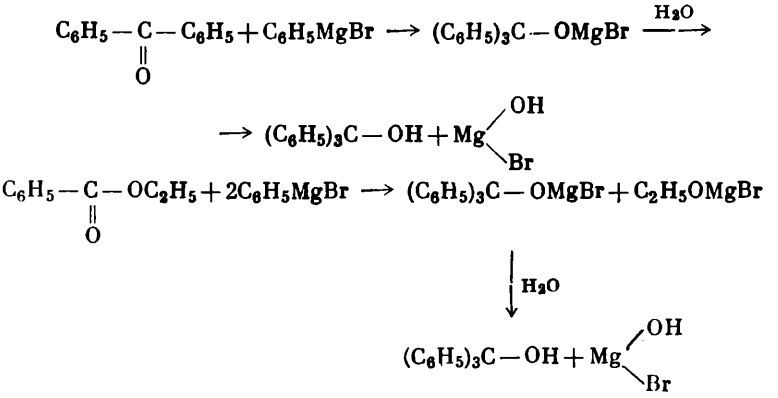


The five-membered ring of fluorene is found to be similar to five-membered cyclopentadiene and indene. This similarity reveals itself chiefly in the facile ionization of the hydrogen atoms of the methylene group in reactions with strongly basic reagents, say, with CH_3MgI, and in reactions of condensation with aldehydes:



Among the derivatives of polyphenylmethanes the most important from the practical and theoretical point of view are triphenylmethane compounds which deserve more detailed attention.

Apart from the Friedel-Crafts synthesis, compounds of the triphenylmethane series can be obtained, first, with the aid of a Grignard reagent:



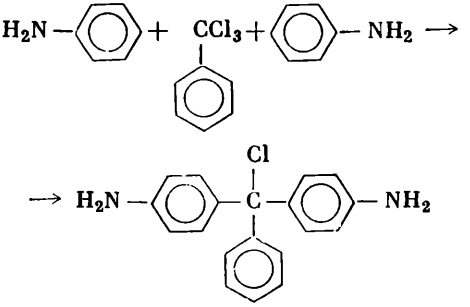
The second method for preparing many of the compounds of this series is the condensation of aromatic carbonyl compounds with hydrocarbons under severe conditions (concentrated sulphuric acid) or with aromatic compounds containing *ortho-para* directors under less drastic conditions:

$$C_6H_5-C(=O)-H + 2C_6H_6 \xrightarrow{H_2SO_4} (C_6H_5)_3CH + H_2O$$

$$C_6H_5-C(=O)-H + 2C_6H_5N(CH_3)_2 \xrightarrow{ZnCl_2} C_6H_5-CH(C_6H_4N(CH_3)_2)_2 + H_2O$$

$$(CH_3)_2N-C_6H_4-C(=O)-C_6H_4-N(CH_3)_2 + C_6H_5-N(CH_3)_2 \xrightarrow{ZnCl_2} \longrightarrow [(CH_3)_2N-C_6H_4]_3C-OH$$

Finally, the condensation of aromatic amines with benzotrichloride is finding application for this purpose:



The Properties of Compounds of the Triphenylmethane Series. The most remarkable are the properties of the central "methane" carbon atom of triphenylmethane derivatives. In triphenylmethane itself, the hydrogen atom linked to this carbon is relatively easily (for a hydrocarbon) eliminated as a proton and is replaced by a metal by the action of strong oxidizing agents, such as KNH_2 or $NaCH_3$:

$$(C_6H_5)_3CH + NaCH_3 \longrightarrow (C_6H_5)_3\overset{-}{C}\,\overset{+}{Na} + CH_4$$

$$(C_6H_5)_3CH + KNH_2 \longrightarrow (C_6H_5)_3\overset{-}{C}\,\overset{+}{K} + NH_3$$

Triphenylmethylsodium can also be prepared by the action of sodium amalgam on an ethereal solution of triphenylchloromethane. Triphenylmethylsodium is an ionically built compound; its intense cherry-red ethereal solution conducts electricity.

By studying optically equilibria of the type

$$RH + A^- \rightleftarrows R^- + AH$$

(where RH = hydrocarbon, and A^- = anion of a strong base) it is possible to estimate the acidity of such "acidic" hydrocarbons. When compared even with water and alcohols, not to mention oxy-acids, this acidity is extremely low:

	K_a		K_a
Triphenylmethane	10^{-33}	Water	10^{-16}
Diphenylmethane	10^{-35}	CH_3OH	10^{-17}
Phenylacetylene	10^{-21}		

However small are these values, they nevertheless have a marked effect on the behaviour of di- and triphenylmethanes, primarily in the metalation reactions given above.

Triphenylmethylsodium is an exceedingly reactive compound, which is decomposed immediately by water or alcohols:

$$(C_6H_5)_3CNa + H_2O \longrightarrow (C_6H_5)_3CH + NaOH$$

With carbon dioxide and carbonyl compounds triphenylmethylsodium reacts like a Grignard reagent:

$$(C_6H_5)_3CNa + CO_2 \longrightarrow (C_6H_5)_3C-\overset{\overset{O}{\|}}{C}-ONa$$

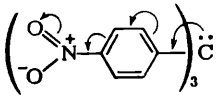
Triphenylmethylsodium is oxidized by atmospheric oxygen to triphenylmethyl peroxide:

$$2(C_6H_5)_3CNa + 2O_2 \longrightarrow [(C_6H_5)_3CO]_2 + Na_2O_2$$

Even more readily ionizable is the hydrogen of tri-*p*-nitrotriphenylmethane. For this compound to be neutralized, the action of an alcoholic-alkaline solution is sufficient:

$$(O_2N-C_6H_4)_3CH + NaOH \longrightarrow (O_2N-C_6H_4)_3\overset{-}{C}\,\overset{+}{Na} + H_2O$$

Tri-*p*-nitrotriphenylmethylsodium is also an ionically built compound, but much more stable and less reactive than triphenylmethylsodium. An alcoholic solution of this intensely deep-blue compound is stable in air; water hydrolyses it slowly, rendering it colourless. It is easy to understand that in this nitro compound the charge of the anion does not remain on the methane carbon atom but is spread over the three nitro groups (i.e., over their oxygen atoms):



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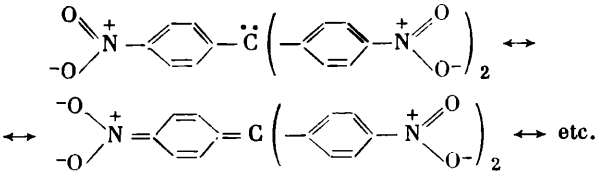
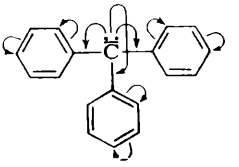


Hence the higher stability of this anion.

As regards the existence of the triphenylmethyl anion, which is very reactive, it is possible owing to the delocalization of the negative charge of the methane carbon atom (i.e., an electron pair) over all the *o*- and *p*-carbon atoms of the benzene rings:



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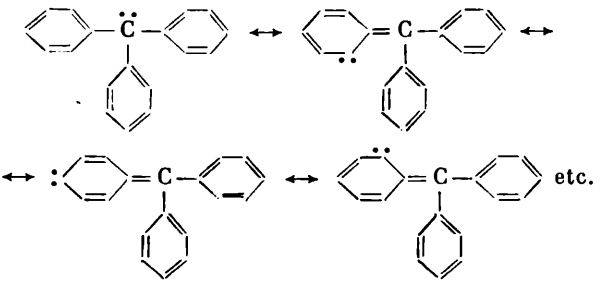


Thus, the negative charge of the anion is not concentrated on the central methane atom but is distributed between it and the nine carbon atoms (all the *o*- and *p*-atoms) of the benzene rings. Of course, the delocalization of the charge over carbon atoms play a certain (but only subordinate) role in the trinitrotriphenylmethyl anion as well, in which the charge is largely concentrated on the oxygen atoms of the nitro groups.

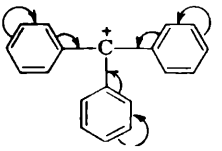
A similarly opposite situation is observed in triphenylchloromethane. In this compound, the chlorine atom is sufficiently mobile and is readily hydrolysed by water:

$$(C_6H_5)_3CCl + H_2O \longrightarrow (C_6H_5)_3COH + HCl$$

Triphenylchloromethane is used (in pyridine solution) as a tritylating agent (for introducing a **trityl**, or triphenylmethyl, group).

For instance, primary alcoholic groups in sugars undergo tritylation (secondary alcohols are not tritylated).

In solution in liquid SO_2, triphenylchloromethane is electrolytically dissociated (in water and alcohols the dissociation cannot be detected because of the hydrolysis or alcoholysis) and forms a triphenylmethyl cation. The stability of this carbonium ion is provided by the delocalization of the positive charge (the supply of electrons by benzene rings) over the ten carbon atoms:



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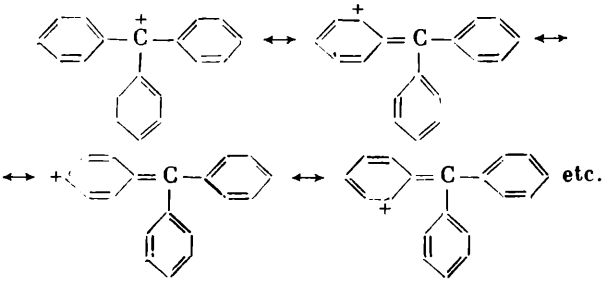
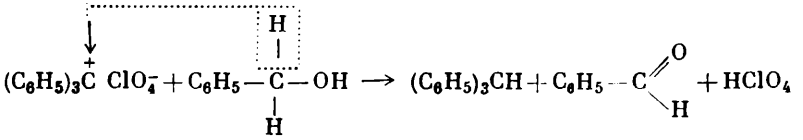
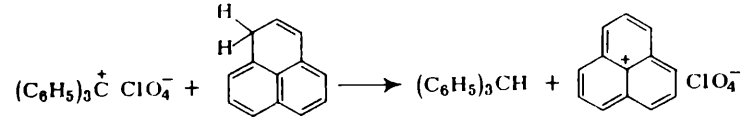


The triphenylmethyl cation (for example, a solution of triphenylmethyl perchlorate in acetic acid) is capable of withdrawing the hydride ion with an electron pair from a hydrogen donor, say, from benzyl alcohol:



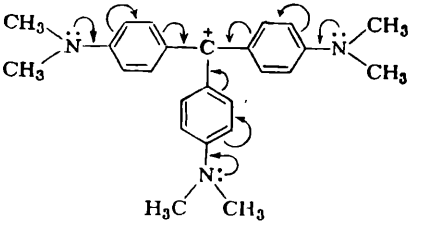
An elegant reaction of such a hydride transfer was effected by Bonton (1959) who obtained the coloured **perinaphthylium** cation:



Perinaphthylium

Could the triphenylmethyl cation be stabilized by introducing substituents, just as in the case of the anion being stabilized by the

introduction of nitro groups? Probably, in this case, electron-releasing groups, such as $-NH_2$, $-N(CH_3)_2$, must be introduced. Indeed, tri-(*p*-dimethylaminophenyl)-chloromethane gives even in aqueous solution a completely stable cation, in which the positive charge is delocalized over the three benzene nuclei, and mainly over the nitrogen atoms of the dimethylamino groups:



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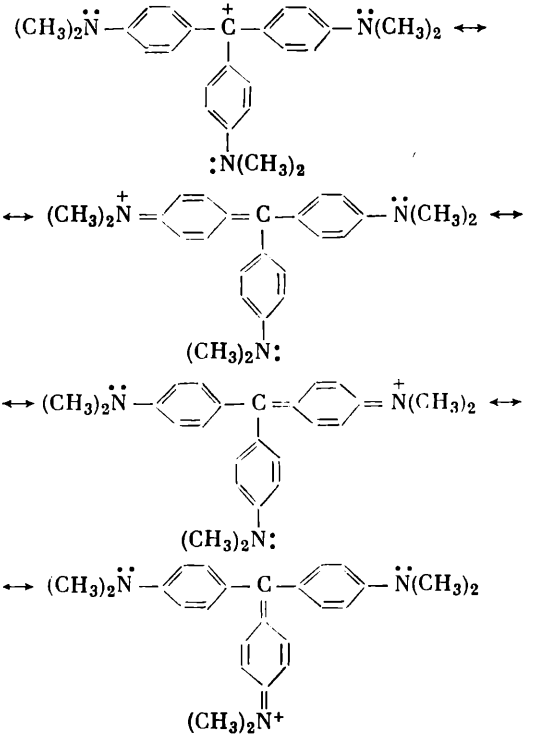
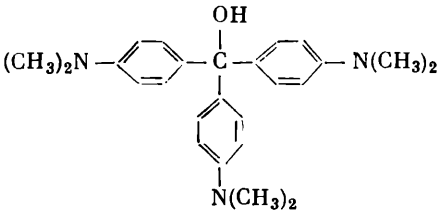


The deep-violet cation shown (the cation of the dye crystal violet) is exceedingly stable and is not hydrolysed by water. Only concentrated alkali decolorizes this cation slowly, converting it into colourless

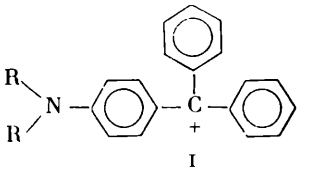
tri-(*p*-dimethylaminophenyl)-carbinol:



In the cation of crystal violet, the positive charge is delocalized largely over three nitrogen atoms, and also, to a small extent, over the nine *o*- and *p*-carbon atoms of the benzene rings.

The delocalization of the charge of a cation or anion over two or more atoms linked by a π,π-conjugation system always entails a decrease in the energy level of the first excited state of the molecule. Therefore, such coloured molecules are excited by quanta of lower energy, i.e., by radiation of longer wavelength as compared with ultraviolet radiation which excites, for example, colourless triphenylchloromethane. If triphenylchloromethane dissociated into ions (say, in solution in SO_2), its cation would be excited by violet quanta, absorb them and assume a yellow colour complementary to violet. When changed to the cation of crystal violet which has a sharply reduced energy level in the excited state, the wavelength of exciting (and hence absorbed) quanta shifts sharply to the side of the yellow spectral region and a violet colour develops. A similar situation is observed with all triphenylmethyl cations and anions, and they all are intensely coloured. But in practice, only compounds with more stable cations are employed as dyes.

The principal group of triphenylmethane dyes includes amino derivatives of triphenylchloromethane. They may have any one of the following structures:



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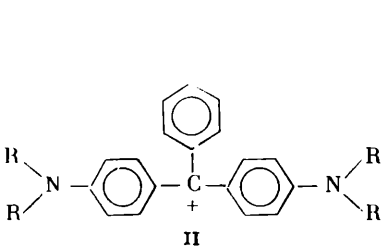

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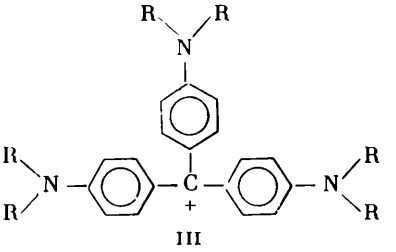
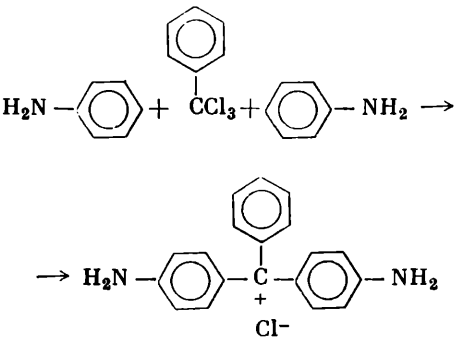


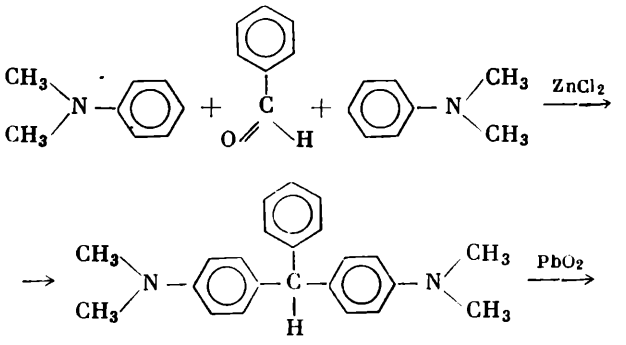
III

where R may be hydrogen, alkyl, benzyl or phenyl. Only one of the resonance structures is given for each of the types; the remaining ones can be built by the reader. Dyes of type I are of no practical importance. Those of type II are important dyes: malachite green ($R = CH_3$), brilliant green ($R = C_2H_5$), and also Döbner's violet ($R = H$) which is one of the simplest dyes in structure but is not used in practice. The ordinary methods of synthesizing dyes of this type are illustrated by the example of Döbner's violet and malachite green.

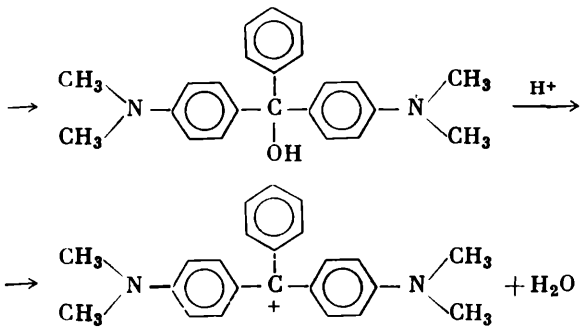
Heating of amines with benzotrichloride leads directly to the formation of the cation of a dye. When amines are condensed with benzaldehyde, an amino derivative of triphenylmethane is formed, which is a colourless compound called a **leuco base** (from the Greek *leukos* meaning white), which is easily oxidized even by air or (as is usually done) by lead dioxide to a carbinol—the base of the dye; the carbinol when acted on even by dilute hydrochloric (or other) acid gives its hydroxyl group and forms the dye cation:



Döbner's violet



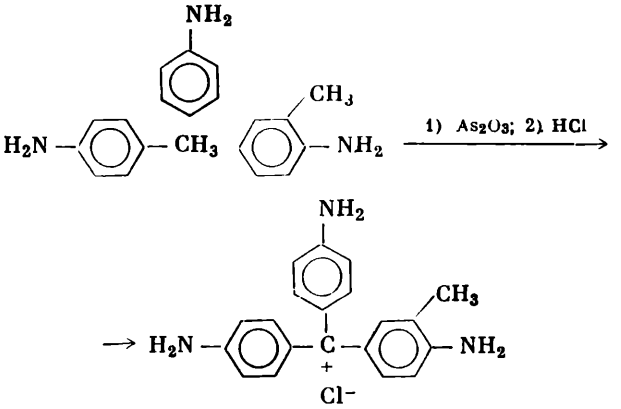
Leuco base of malachite green



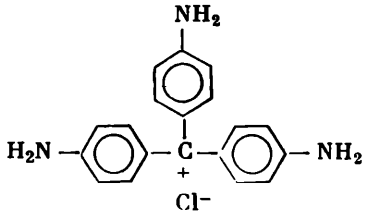
Malachite green (cation)

Dyes of type III are: parafuchsin (R = H), fuchsin (ditto, but there is a CH_3 group being in the *ortho*-position to one of the amino groups), and crystal violet (R = CH_3).

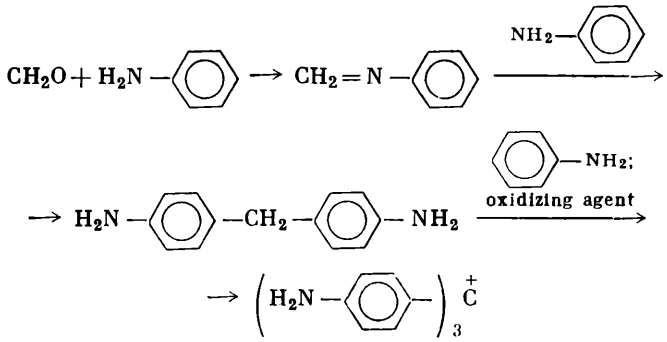
The first representative of triphenylmethane dyes was **fuchsin** (or *rosaniline*), which was produced by the oxidation of aniline containing an impurity of the homologues (*o*- and *p*-toluidines) by arsenic anhydride, As_2O_5:



When the same oxidizing agent or nitrobenzene is used to oxidize (Coupier) a mixture of aniline and *p*-toluidine, a lower homologue of fuchsin, **parafuchsin**, is obtained:

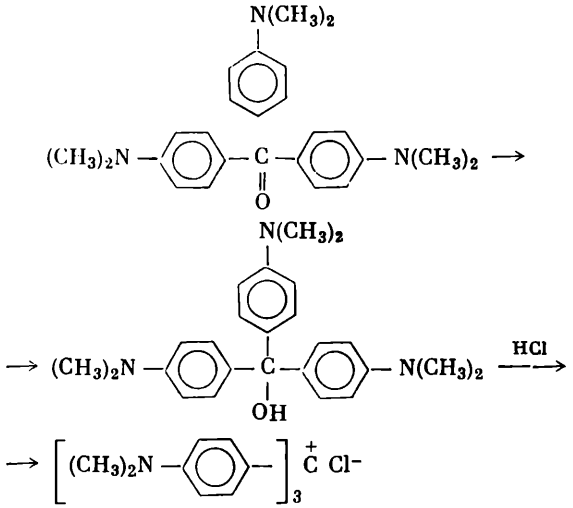


The "new fuchsin process" (Gomolka) consists in heating aniline with formalin and an oxidizing agent. The reactions that take place are supposed to proceed in the following sequence:



By methylating parafuchsin with methyl iodide it is possible to obtain the dye **methyl violet**—a mixture of nitrogen-methylated tri-*p*-aminotriphenylchloromethanes, in which the pentamethyl derivative predominates and which also contains a hexamethyl derivative (crystal violet). Methyl violet (it closely resembles crystal violet in colour) is well known since violet ink is made from it.

Crystal violet is prepared in pure form by the condensation of di-(*p*-dimethylamino)-benzophenone (Michler's ketone) with dimethylaniline followed by acidification:



A number of other triphenylmethane dyes which find practical application are made by the same principles but they contain one or two chlorine atoms, and one or two sulphonic groups in one of

the phenyl residues. The fusion of parafuchsin with aniline and benzoic acid (used as a condensing agent) gives **aniline blue**:

$$(C_6H_5-NH-C_6H_5)_3\overset{+}{C}\ Cl^-$$

From the foregoing it is clear that the amino groups of the triphenylmethane dye cation play a decisive role also in the stability of the cation and in its light absorption; such groups, as we know (page 123), are called **auxochromic groups** or **auxochromes**. Both these effects result from the delocalization of the charge from the methane carbon atom over the nitrogen atoms, but these effects do not operate concurrently. As in the triphenylmethyl cation the number of auxochromes in the nucleus increases from one to two and then to three the stability of the cation increases and the rate of discoloration by the hydroxyl ion falls. This occurs because more and more of the charge is removed from the methane carbon atom, which leads to an ever increasing activation energy of interaction of the compound with the hydroxyl ion. As regards light absorption, as the number of auxochromes increases from one to two, the yellow or yellow-orange colour (the complementary colour absorbed is violet) turns to green (the purple-red colour is absorbed), and when three auxochromes are introduced, it changes to violet (the yellow or yellow-orange colour is absorbed), i.e., the bathochromic effect is maximal in the case of two and not three auxochromes. This is because the energy level of the first excited state is most close to the unexcited state if the charge is delocalized linearly and not in a branch-like manner, as in the case of three auxochromic groups.

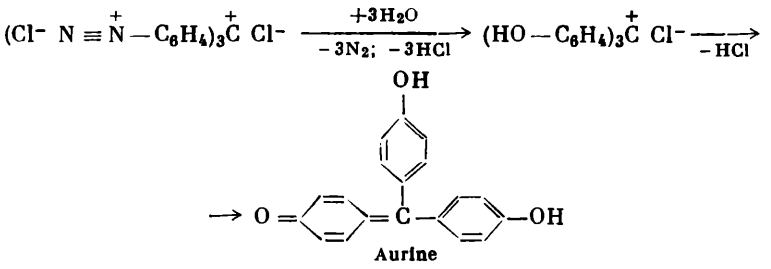
Auxochromic groups function owing to the presence of free electron pairs on nitrogen atoms. If these electron pairs are bound by addition of hydrogen ions to them through the action of acid (or by conversion into a quaternary ammonium salt by the action of CH_3I), then the chemical and optical effect of auxochromes will cease operating. Therefore, when concentrated hydrochloric acid is poured into a solution of crystal violet, there is observed a gradual change to a green colour, which exactly resembles malachite green (one auxochrome is removed) and then to orange-yellow (two auxochromes are removed), and, finally, a feebly coloured yellow solution is obtained.

The structure of parafuchsin was established by E. and O. Fischer through the diazotization of the primary amino groups of its leuco base and elimination (replacement by hydrogen) of the diazo groups (page 125), as a result of which triphenylmethane was obtained:

$$(H_2N-C_6H_4)_3CH+3HCl \longrightarrow (Cl^-\ H_3\overset{+}{N}-C_6H_4)_3CH \xrightarrow{3HNO_2}$$

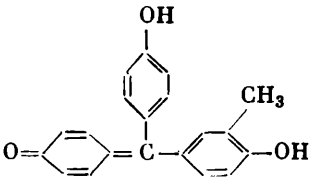
$$\longrightarrow (Cl^-\ N\equiv\overset{+}{N}-C_6H_4)_3CH \xrightarrow[3C_2H_5OH]{\text{reduction;}} (C_6H_5)_3CH+3N_2+3CH_3CHO+3HC$$

Diazotization of the parafuchsin cation and replacement of the diazo groups by hydroxyl groups on boiling with water leads to the formation of **aurine**:

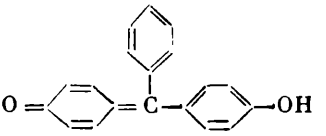


Aurine

In this way, **rosolic acid** is formed from fuchsin, and **benzaurine** from Döbner's violet:

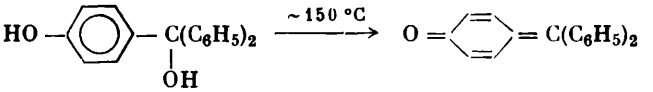


Rosolic acid

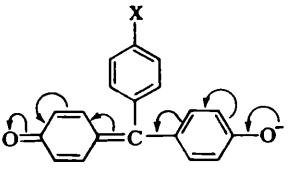


Benzaurine

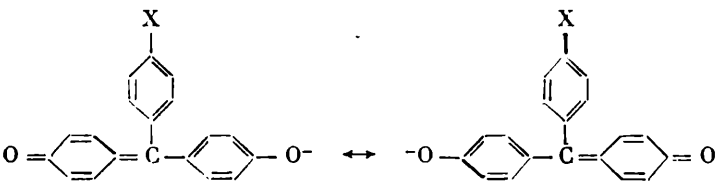
All the three are dyes of the triphenylmethane series with hydroxyl groups as auxochromes. As seen from the formulas, hydroxytriphenylmethane dyes are the derivatives of **fuchsone**, which can be obtained by eliminating water on heating from hydroxytriphenylcarbinol:



In alkaline solution the colour of these dyes is sharply deepened, especially that of benzaurine (the bathochromic shift of the absorption region); yellow aurine becomes red with alkali, and benzaurine turns even violet. All the three compounds are used as indicators:



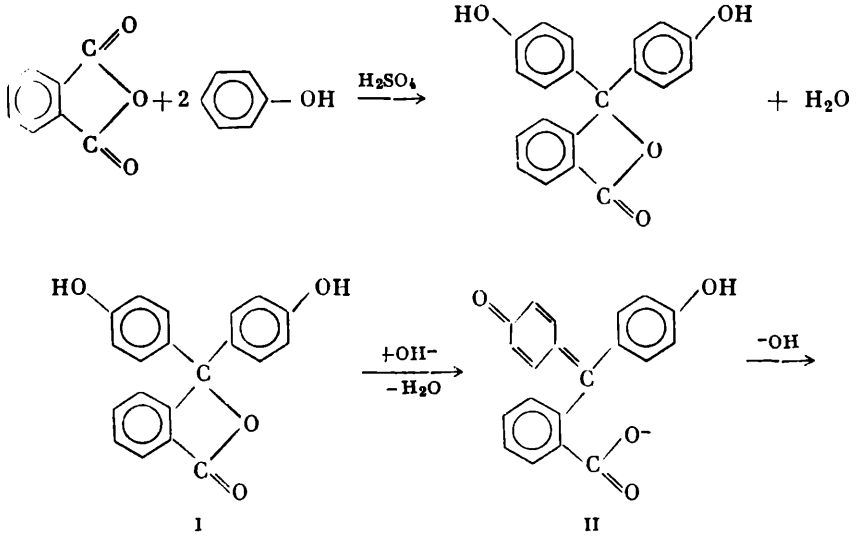
or



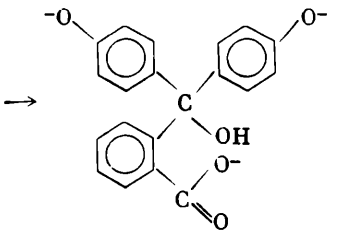
The formulas show the delocalization of charge in the benzaurine anion (X = H) and in aurine (X = OH); in aurine containing three auxochromes, the charge delocalization is branched, and the deepening of the colour is less.

F. Phthaleins, Fluorescein, Rosamines and Rhodamines

Phenol and phthalic anhydride when heated with sulphuric acid form **phenolphthalein**. In analytical chemistry, this compound is used as an acid-base indicator, and in medicine as a purgative. When acted on by alkali colourless phenolphthalein I forms red-violet anion II having the same mesomeric delocalization of the anionic charge between the two benzene rings as in benzaurine. An excess of alkali, as is always the case, decolorizes the triphenylmethane dye, converting it into carbinol III:



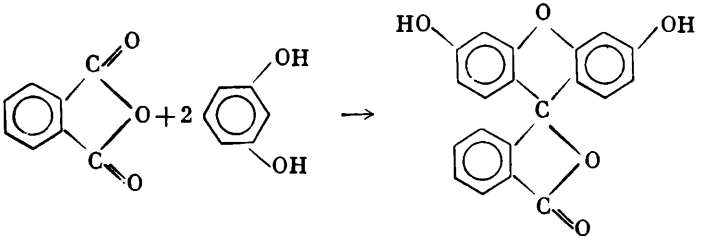
I II



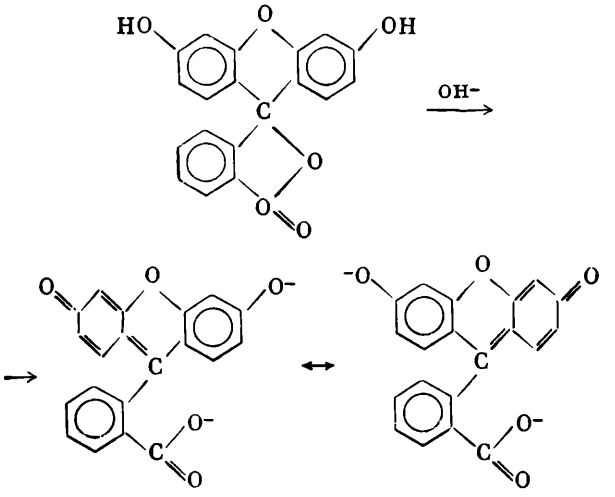
III

A number of phthaleins used as indicators are also known.

When phthalic anhydride is fused with resorcinol and zinc chloride, a similar condensation takes place, which is complicated by the additional elimination of a water molecule at the expense of the two phenol hydroxyls and by the formation of a heterocyclic ring:



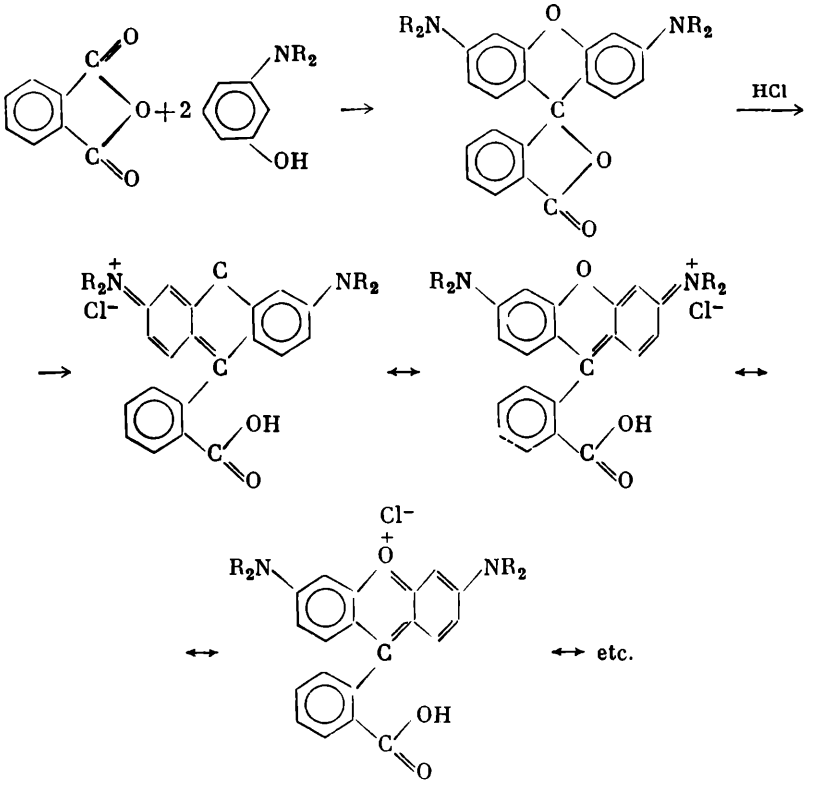
In alkaline medium the lactone ring of this compound is opened to form an anion with a magnificent green fluorescence, which is called **fluorescein.**



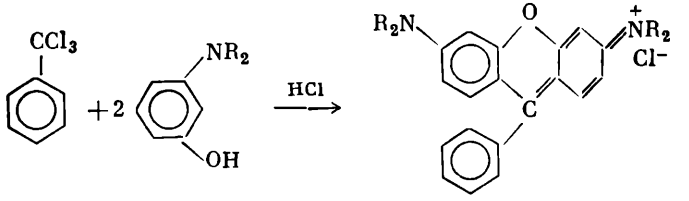
Fluorescein

Bromination of fluorescein leads to the formation of **tetrabromofluorescein**, also known as **eosin** (all the four *ortho*-positions to the hydroxyl groups are occupied by bromine atoms).

The condensation of phthalic anhydride with *m*-dialkylaminophenols gives dyes called **rhodamines** which are of practical importance:



Rhodamines that have no carboxyl group are called **rosamines** They are obtained by the condensation of benzotrichloride with *m*-dialkylaminophenols:



G. Free Radicals of the Triphenylmethyl Series

In 1900 Gomberg, while attempting to prepare hexaphenylethane by the Wurtz reaction, accomplished this synthesis by the action of zinc, copper, mercury, or silver on triphenylchloromethane:

$$2(C_6H_5)_3CCl + Zn \longrightarrow (C_6H_5)_3C-C(C_6H_5)_3 + ZnCl_2$$

The hydrocarbon obtained has unusual properties. In air it oxidizes to the familiar triphenylmethyl peroxide (page 247):

$$(C_6H_5)_3C-C(C_6H_5)_3 + O_2 \longrightarrow (C_6H_5)_3C-O-O-C(C_6H_5)_3$$

With sodium it gives triphenylmethylsodium:

$$(C_6H_5)_3C-C(C_6H_5)_3 + 2Na \longrightarrow 2(C_6H_5)_3CNa$$

and with halogens gives a quantitative yield of a triphenylhalomethane:

$$(C_6H_5)_3C-C(C_6H_5)_3 + I_2 \longrightarrow 2(C_6H_5)_3I$$

The subsequent studies carried out by Gomberg, Chichibabin, Schlenk, Schmidlin provided a conclusive proof that hexaphenylethane and, in general, hexaarylethanes similar to it, dissociate homolytically in solutions (for example, in ether) into two free triarylmethyl radicals:

$$(C_6H_5)_3C-C(C_6H_5)_3 \rightleftarrows 2(C_6H_5)_3C\cdot$$

This dissociation can be traced out by a decrease in the molecular weight of hexaphenylethane, which occurs on dilution, this being associated with the increase of the degree of dissociation on dilution (Ostwald's dilution law). The dissociation can also be traced by the change of the colour of the solution since hexaphenylethane is colourless and triphenylmethyl is yellow. Triarylmethyls having a rather intense colour are also known.

For the hexaarylethane series there have been found the following values of the degree of homolytic dissociation in 0.1*M* solution in benzene at room temperature (in per cent):

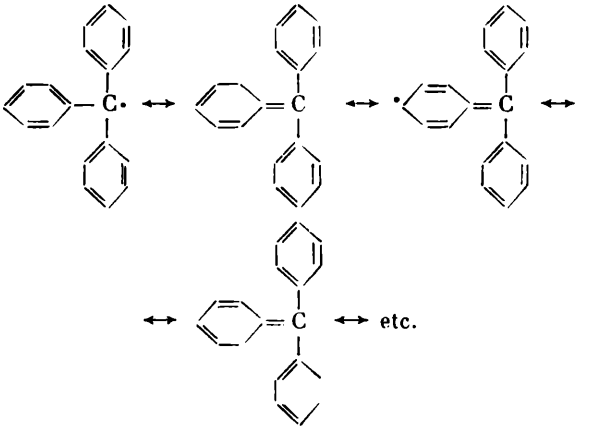
$(C_6H_5)_3C-C(C_6H_5)_3$	2-3
$(p\text{-}C_6H_5C_6H_4)(C_6H_5)_2C-C(C_6H_5)_2(C_6H_4C_6H_5\text{-}p)$	15
$(p\text{-}C_6H_5C_6H_4)(C_6H_5)_2C-C(C_6H_5)(C_6H_4C_6H_5\text{-}p)_2$	18
$(p\text{-}C_6H_5C_6H_4)_3C-C(C_6H_4C_6H_5)_3$	26
$(p\text{-}FC_6H_4)(C_6H_5)_2C-C(C_6H_5)_2(C_6H_4F\text{-}p)$	20
$(p\text{-}NO_2C_6H_4)_3C-C(C_6H_4NO_2\text{-}p)_3$	100
$(o\text{-}CH_3C_6H_4)_3C-C(C_6H_4CH_3\text{-}o)_3$	82
Ditto, *m*-isomer	7
Ditto, *p*-isomer	5.5

The presence in solutions [and also in the solid state for $(p\text{-}NO_2C_6H_4)_3C\cdot$] of free triarylmethyl radicals is established by

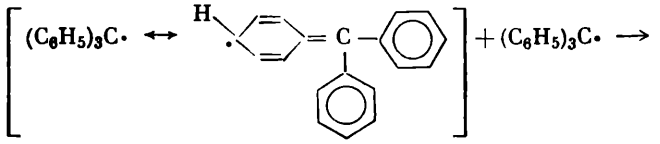
means of the paramagnetic properties of these particles which have one unpaired electron on the methane carbon atom. It is the uncompensated spin of this electron that creates a magnetic field around each free radical. As a matter of fact, it is precisely triaryl free radicals (and not hexaarylethane) that react with oxygen, sodium, and the halogens:

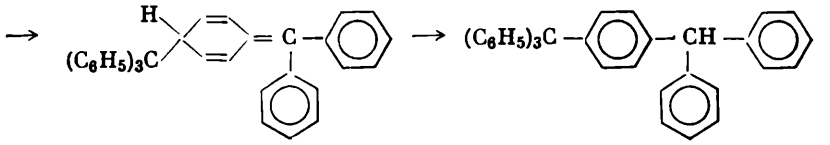
$$2Ar_3C \begin{cases} \xrightarrow{O_2} Ar_3C-O-O-CAr_3 \\ \xrightarrow{2Na} 2Ar_3CNa \\ \xrightarrow{I_2} 2Ar_3CI \end{cases}$$

Whereas 85 kcal/mole is required for ethane to be dissociated into two free methyl radicals, as little as 12 kcal/mole is needed for dissociation of hexaphenylethane. That is why this process occurs so easily. The cause of this sharp decrease of the energy level of the triphenylmethyl radical, as compared with that of the methyl radical, is that the unpaired electron in triphenylmethyl is not concentrated on the methyl carbon atom but is delocalized over all the benzene nuclei, more exactly, over all their nine *o*- and *p*-carbon atoms, which thus assume, to a certain extent, a free-radical character:



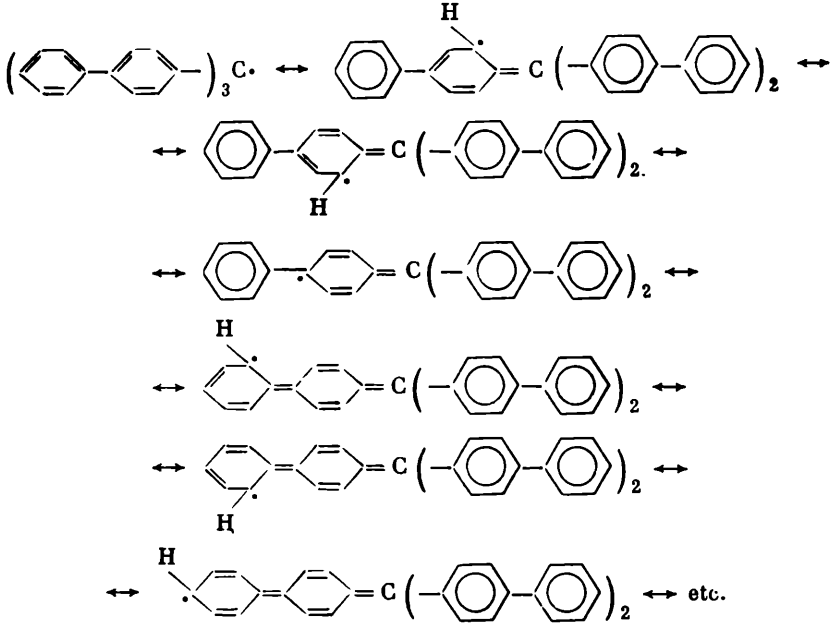
That the *p*-carbon atoms of triphenylmethyl exhibit some of the free-radical properties can be judged by the fact that hexaphenylethane when heated is converted into a high-melting (m.p. 231°C) hydrocarbon, which has been found (A.E. Chichibabin) to have the structure of *p*-benzhydryltetraphenylmethane:



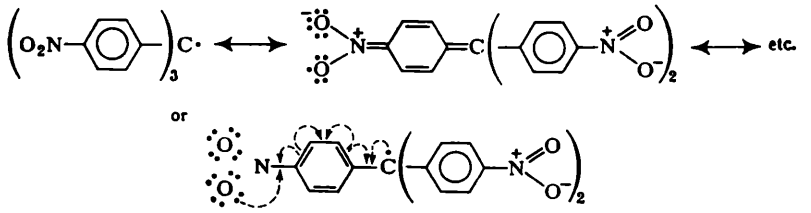


Benzhydryl is the name of the $(C_6H_5)_2CH-$ residue.

Naturally, the greater are the possibilities of delocalization provided for the unpaired electron by the aryl groups adjacent to the methyl carbon atom, the higher is the homolytic dissociation constant of hexaarylethane. Therefore, **hexadiphenylethane** (or *hexabiphenylethane*) dissociates more strongly than hexaphenylethane:



The even greater delocalization of the electron from the methyl carbon atom is evidently achieved through withdrawal of the electron by a nitro group.



Though the main cause of the homolytic dissociation of polyarylethanes is the mesomeric delocalization of a free electron in aromatic rings, there is still another factor capable of enhancing the dissociation, namely steric hindrances to the recombination of the radical into a dimeric molecule. This may be expressed in another form as well: three bulky aryl groups at each methyl carbon atom undergo strong mutual repulsion (*I*-strain according to Brown) and repulsion from the three aryl groups at the second methyl carbon atom (*F*-strain according to Brown). On dissociation the *F*-strain disappears completely, and the *I*-strain decreases as a result of the triarylmethyl radical assuming a propeller-like form. From a comparison of the degrees of dissociation of hexatolylethanes (page 260) it can be seen that *ortho*-substituents sharply increase the degree of dissociation as compared with *meta*- and *para*-substituents. This effect is observed not only in hexaarylethanes but in symmetric tetraarylethanes as well. An even stronger effect in the same direction is exerted by the replacement of the two hydrogens left in tetraarylethanes by *tert*-butyl radicals.

It is interesting to note that the silicon, germanium, and tin analogues of hexaphenylethane do not dissociate with the formation of free radicals, which can only partly be accounted for by the larger size of Si, Ge, and Sn atoms and, hence, by the smaller steric hindrances to association.

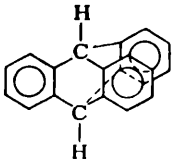
Thus, the phenyl and, in general, aryl groups adjacent to the methane carbon atom can accomplish three functions: they delocalize the negative charge, thus rendering the Ar_3C^- anion more or less stable; they delocalize the positive charge and stabilize the cation Ar_3C^+; and, finally, they convert the completely unstable free methyl radical into a "long-lived" stable triarylmethyl radical due to the delocalization of the unpaired electron.

The "mobility" (facile elimination in the form of a proton) of the methane hydrogen of triarylmethanes is attributed to the stability of the triarylmethyl anion, and the stability of the triarylmethyl cation is responsible for the mobility of the chlorine atom in triarylchloromethanes.

It should be noted that the possibility of charge delocalization by means of three aryl nuclei would have been greater if the triaryl grouping could have been quite flat. In fact, even the triphenylmethyl grouping has a propeller-like form. Otherwise there would be no place enough for the *ortho*-hydrogen atoms and they would interfere with one another. This can be confirmed by building the structure of triphenylmethyl through the use of the lengths of interatomic distances (see Volume I, page 450), and by describing semicircles with a radius equal to the van der Waals radius of hydrogen for *ortho*-hydrogen atoms.

Thus, the overlap of the π-orbitals of electrons in triphenylmethane derivatives is incomplete.

That the steric requirements of the overlap of the π-bond electrons are not fulfilled is especially clearly reflected in the properties of the hydrocarbon tryptycene, whose synthesis is given on page 206.



Tryptycene

This hydrocarbon, which seems to be similar to triphenylmethyl, is absolutely incapable of losing its hydrogens as protons and, in general, of substitution reactions involving its methine hydrogens. The chlorine atom at the methine carbon in chlorotryptycene is also "immobile". The long-lived tryptycyl free radical is also incapable of existence. The cause is that because of the rigid structure of tryptycene there can be no overlap of the π-electrons of any of the three benzene rings either with the perpendicularly arranged *p*-orbital of the odd electron on the methine carbon in the tryptycyl radical or with the *p*-orbital of the electron pair in the tryptycyl anion, or with the vacant *p*-orbital of the tryptycene cation. Hence the impossibility of charge delocalization over the benzene nuclei.

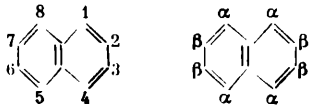
There is another cause for the "immobility" of the halogen atom in a halotryptycene. Whereas the factor just described excludes the possibility of halogen exchange by the S_N1 mechanism, the second factor accounts for the impossibility of exchange by the S_N2 mechanism either (Volume I, page 104). This is the impossibility of a Walden inversion in the exchange of the chlorine atom in chlorotryptycene by the S_N2 mechanism.

8.2. Condensed Aromatic Systems

A. Naphthalene and Its Derivatives

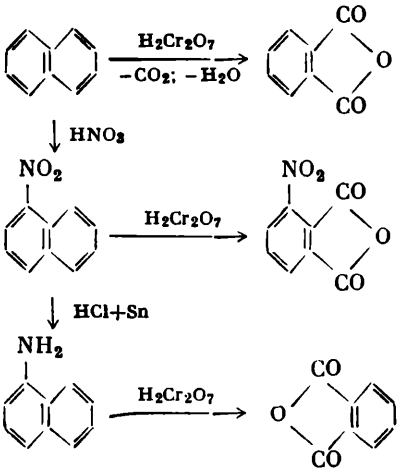
Naphthalene is contained in coal tar in an amount of about 10 per cent and is isolated (by crystallization) from the distillation fraction known as "middle or carbolic oil" boiling at temperatures up to 240°C. It is also obtained from the pyrolysis products of petroleum. Naphthalene is a crystalline substance with m.p. 80°C; it sublimes very readily, is volatile even at room temperature, and is distilled together with steam. Its smell is well known since it is used as a preventative against moths. Naphthalene was first discovered by Gardner in

1820, i.e., before the discovery of benzene (1825). Its composition has been established by Voskresensky and its structure as a benzenoid compound consisting of two benzene rings fused together has been elucidated by Erlenmeyer and Graebe, who used Kekulé's benzene formula.



The evidence in favour of this formula is as follows. Naphthalene is explicitly an aromatic compound since to the molecular formula $C_{10}H_8$ there must correspond six double bonds ($C_{10}H_{22}—C_{10}H_8 = 14H$; $14/2 = 7$; $7 - 1 = 6$) if one ring is present, and five double bonds in the presence of two rings, etc., but usual reactions for double bonds are absent.

Besides, in the catalytic addition of hydrogen (over Ni), which proceeds in two stages, tetralin is first formed, which is the product of addition of 4H, followed by the formation of decalin—the product of addition (in total) of 10H. This points to the presence of five aromatic ("concealed") double bonds and, hence, of two rings. The oxidation of naphthalene by atmospheric oxygen over V_2O_5 and by sulphuric acid with $HgSO_4$ as a catalyst or else by other oxidizing agents leads to phthalic anhydride, which proves the presence of one benzene ring and the *ortho*-position of the carbon atoms of the second ring. Nitration of naphthalene gives α-nitronaphthalene, which on oxidation forms *o*-nitrophthalic anhydride and on reduction yields α-naphthylamine, which is also converted on oxidation into phthalic anhydride, in which case the nucleus containing an amino group and being activated by it is burned off:



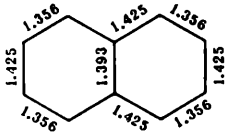
From this it is clear that the naphthalene molecule is composed of two benzene rings having two *ortho*-carbon atoms in common.

Whereas in benzene the aromatic sextet of π-electrons is delocalized completely uniformly with respect to the six carbon atoms, in naphthalene such an equilibration is impossible and this is why it is less aromatic and less saturated than benzene. Accordingly, the energy of naphthalene is lower than the calculated energy of an unsaturated hydrocarbon corresponding in structure to the Erlenmeyer formula with fixed double bonds (resonance energy). This decrease of energy amounts to 61 kcal/mole for naphthalene, i.e., is markedly lower than the doubled value ($36 \times 2 = 72$) for benzene.

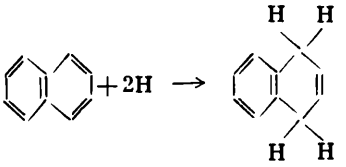
Indeed, in terms of resonance theory, the structure of naphthalene must be one intermediate between the Erlenmeyer-Graebe structure and the structures in which one of the benzene rings contains three and the other one only two π-bonds:

a *b* *c*

The lower symmetry of each of the benzene rings of naphthalene is also reflected in the alternation of the carbon-carbon distance (X-ray crystal analysis data are given for bond lengths in Å):

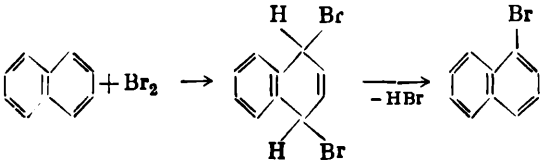


The specific features of structures *b* and *c*, each of which contains one benzenoid ring and one quinonoid ring, are reflected in the particular activity of the α-carbon atoms towards electrophilic attacks and also towards addition reactions characteristic of diene hydrocarbons. Thus, in contrast to benzene, naphthalene is reduced by nascent hydrogen, being converted into 1,4-dihydronaphthalene:

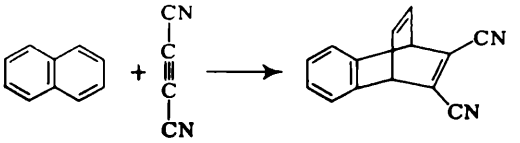


This reaction is exothermic (4.5 kcal/mole).

Bromine adds on to naphthalene in the 1,4-positions, the addition product readily losing HBr to form α-bromonaphthalene:

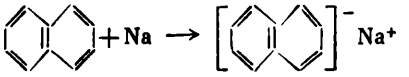


Just like benzene, naphthalene is known (Cookson, Dance, 1962) to be capable of adding on strong dienophiles under vigorous conditions (at about 150°C):



The reactions of electrophilic substitution in naphthalene (nitration, sulphonation) take place mainly at the α-positions.

Like benzene, but more readily, naphthalene is capable of capturing an electron to form the anion. This reaction occurs even with sodium:



Isomerism of Naphthalene Derivatives. Even the monoderivatives of naphthalene are known to exist in two series of isomers: α-substituted and β-substituted compounds. According to the Erlenmeyer-Graebe formula, there are 10 isomers in the case of two identical substituents:

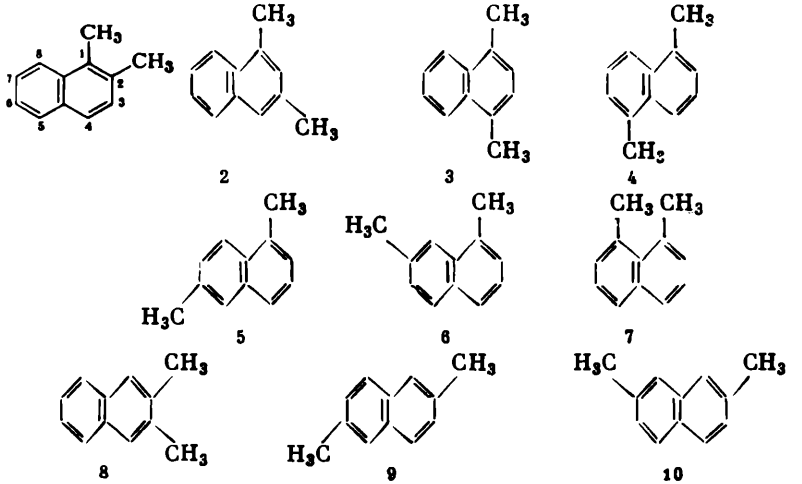


TABLE 8.1. **Condensed Aromatic Compounds**

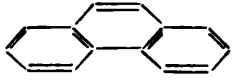
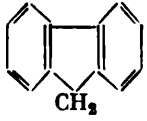
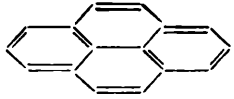
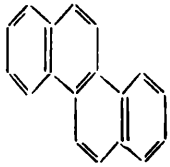
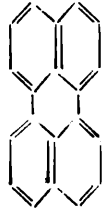
Name	Formula	Colour	Stabilization energy, kcal/mole	m.p., °C	b.p., °C	Density, d_{4}^{t}
Naphthalene		Colourless	71	80.2	218	1.145
Anthracene		Colourless	104	217.0	354.5; 218.4 (at 40 mm Hg)	1.25 (d_4^{27})
Phenanthrene		Colourless	111	100	340.1	1.063 (at 100°C)
Fluorene		Colourless	—	116	295	—
Pyrene		Colourless	—	150	> 360	1.277

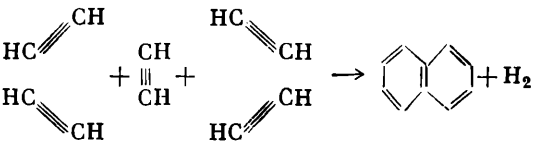
Table 8.1 (continued)

Name	Formula	Colour	Stabilization energy, kcal/mole	m.p., °C	b.p., °C	Density, d_4^{20}
Chrysene		Colourless	—	256	448	—
Naphthacene or tetracene		Orange-yellow	130	335	—	—
Perylene		Golden-yellow	—	273-274	—	—

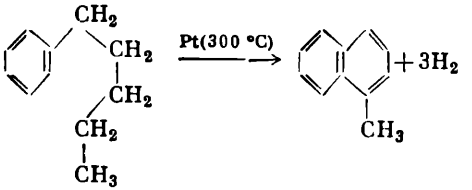
In order to indicate the position of substituent atoms or radicals, use is made of the numbering of carbon atoms (only those bearing replaceable hydrogen atoms) given in formula 1. The dimethylnaphthalene shown above is therefore called 1,2-dimethylnaphthalene. The 1,2- or 2,3-positions are called the *ortho*-positions, just as for benzene, but in the case of naphthalene this notation is not unambiguous; the 1,3-, 1,4-, 1,8-, and 2,6-positions are known as the *meta*-, *para*-, *peri*-, and *amphi*-positions, respectively. The prefixes invented for the remaining positions have not become established. If the two substituents are different, the number of isomers increases up to 14. All the predictions based on the formula of naphthalene are justified in practice.

The physical properties of naphthalene and other condensed aromatic compounds are presented in Table 8.1.

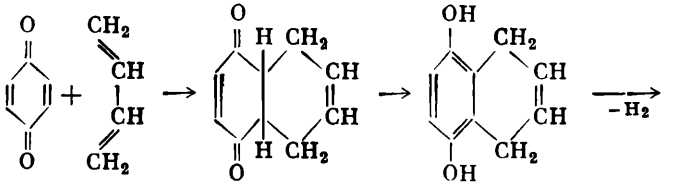
Synthesis of Naphthalene and Its Derivatives. When acetylene is passed over charcoal at 400°C, naphthalene is formed along with benzene (N. D. Zelinsky, B. A. Kazansky):

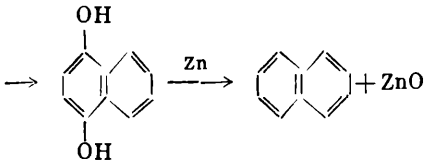


The dehydrocyclization of benzene homologues with a side chain containing four or more carbon atoms over platinum at 300°C results in the formation of naphthalene and its homologues (N. D. Zelinsky, B. A. Kazansky, A. F. Plate, S. I. Khromov):

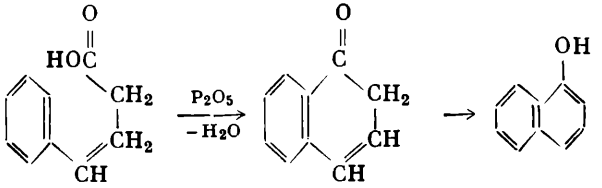


Various modifications of diene synthesis lead to naphthalene and its derivatives:





The oldest method which proved the Erlenmeyer-Graebe formula is the ring-closure of phenylvinylacetic acid into α-naphthol:



The homologues of naphthalene can be obtained from naphthalene by the Friedel-Crafts alkylation or acylation followed by the reduction of the ketones to alkylnaphthalenes by the Clemmensen method. The acetylation with $AlCl_3$ by the Friedel-Crafts method in carbon disulphide as a solvent proceeds largely in the α-position, and in nitrobenzene—in the β-position.

Electrophilic Substitution Reactions in Naphthalene. 1. We have already said that in the absence of a catalyst the addition of halogens (Cl_2 and Br_2) takes place at the 1,4-positions of naphthalene. If salts of iron or other halogenation catalysts are present, the substitution takes place predominantly at the α-position (in chlorination reactions, 95 per cent occurs at the α-position and only 5 per cent at the β-position).

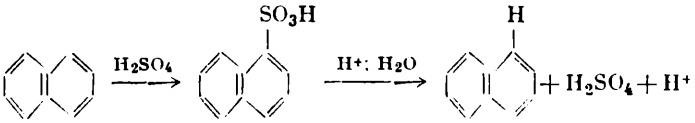
The halogen derivatives of naphthalene have an ordinary slightly mobile aromatic halogen and are not suitable for reactions of secondary replacement of halogen by other groups.

2. The nitration of naphthalene takes place easily, and the nitro group enters the α-position. In order to introduce one more nitro group more drastic conditions are required, in which case the second nitro group enters the other naphthalene ring also at the α-position and 1,8-dinitronaphthalene is obtained together with the 1,5-isomer. This is evidence that both rings are, to a certain extent, independent of each other: the nitro group deactivates that ring towards nucleophilic attacks which it enters.

By reducing α-nitronaphthalene N. N. Zinin obtained α-naphthylamine.

β-Nitronaphthalene can be prepared only by indirect methods, for example, by oxidizing β-naphthylamine with Caro's acid or via β-naphthyldiazonium by the Gattermann method ($NaNO_2$ + Cu).

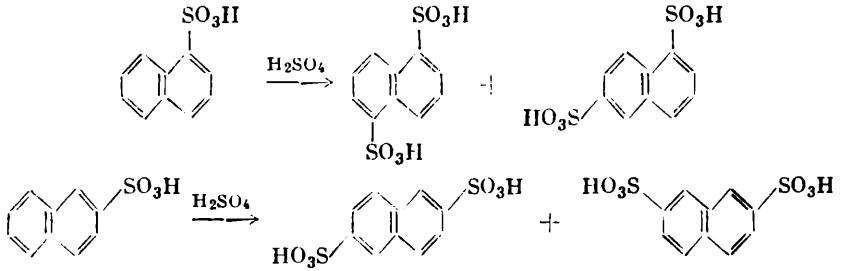
3. Naphthalene is sulphonated easily by concentrated sulphuric acid; at temperatures lower than 100°C the reaction yields naphthalene-α-sulphonic acid, and at temperatures higher than 150°C naphthalene-β-sulphonic acid is obtained. This is accounted for by the fact that, owing to the high nucleophilic activity of the α-carbon atoms of naphthalene, the α-sulphonic group is readily eliminated at an increased temperature in acid medium in the form of sulphuric acid (the electrophilic attack of H^+) and is replaced by hydrogen:



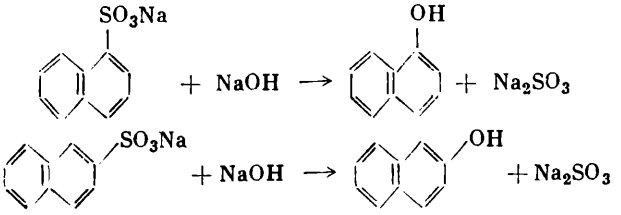
In such an acidolytic reaction only the sulphonic group that has occupied the β-position is capable of remaining intact.

Thus, two isomers, α- and β-naphthalenesulphonic acids, are available and are used as starting materials for syntheses in the naphthalene series.

With an excess of more concentrated sulphuric acid, α-naphthalenesulphonic acid undergoes further sulphonation to give two isomeric disulphonic acids: 1,5- and 1,6-acids; β-naphthalenesulphonic acid too gives two isomers: 2,6- and 2,7-naphthalenedisulphonic acids:

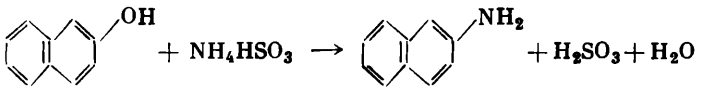


Secondary Substitution in Naphthalene Derivatives. The reaction of alkali fusion is used to manufacture large quantities of the phenols of naphthalene, α- and β-naphthols, from α- and β-naphthalenesulphonic acids, respectively:



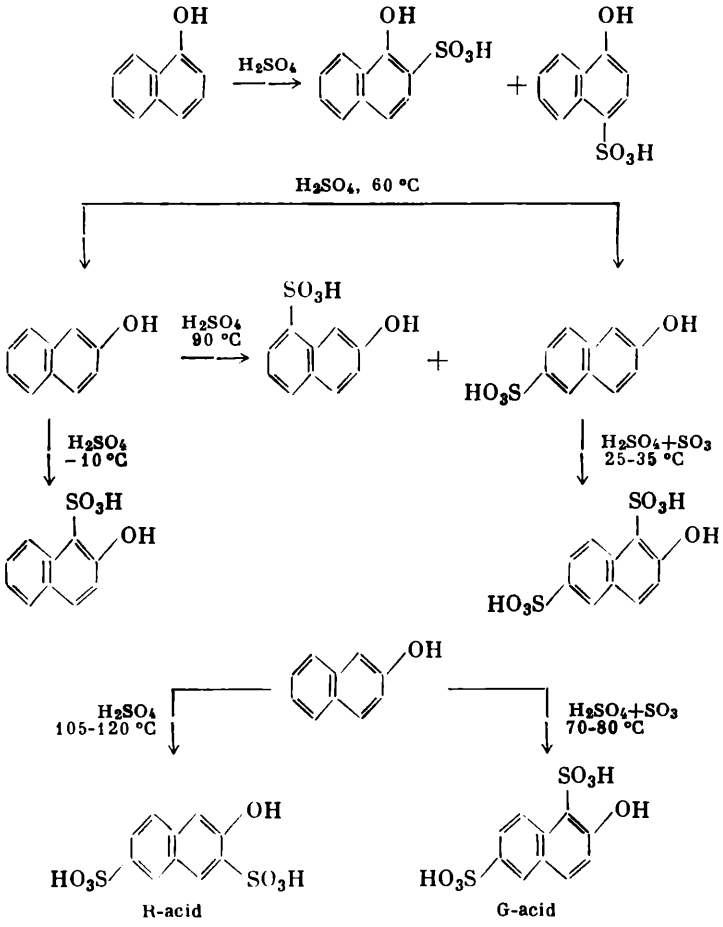
They are used as the second components in azo-coupling reactions.

β-Naphthol is the only starting material for synthesis of β-naphthylamine which is produced by the action of NH_4HSO_3 (or, formerly, by the complex $NH_3 + ZnCl_2$) on β-naphthol:

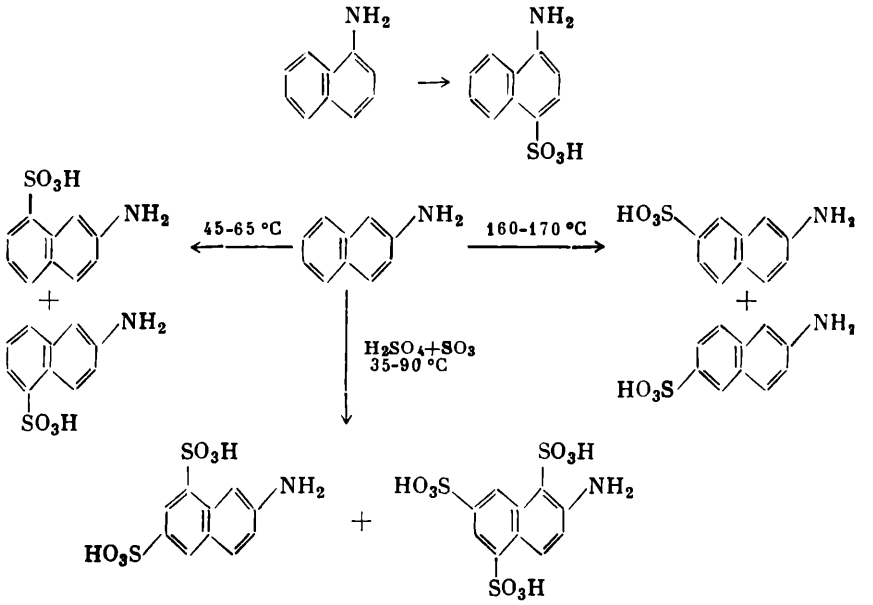


The charts given below provide information about mono- and disulphonic acids and also about the naphthylaminosulphonic acids obtained by the sulphonation of both naphthols and naphthylamines.

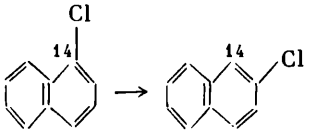
1. *Synthesis of naphtholsulphonic acids*:



2. *Synthesis of naphthylaminosulphonic acids:*



In the naphthalene ring, just as in the benzene ring, numerous rearrangements may take place. We have already considered the rearrangement of α-naphthalenesulphonic acid to β-naphthalenesulphonic acid effected by the action of sulphuric acid. This is an intermolecular rearrangement. According to N. N. Vorozhtsov, jr., when α- or β-chloronaphthalene is passed over alumina at a high temperature, both compounds are converted into an equilibrium mixture of the two isomers; as shown by experiments with the α-isomer labelled with ^{14}C, the rearrangement proceeds according to the following scheme:

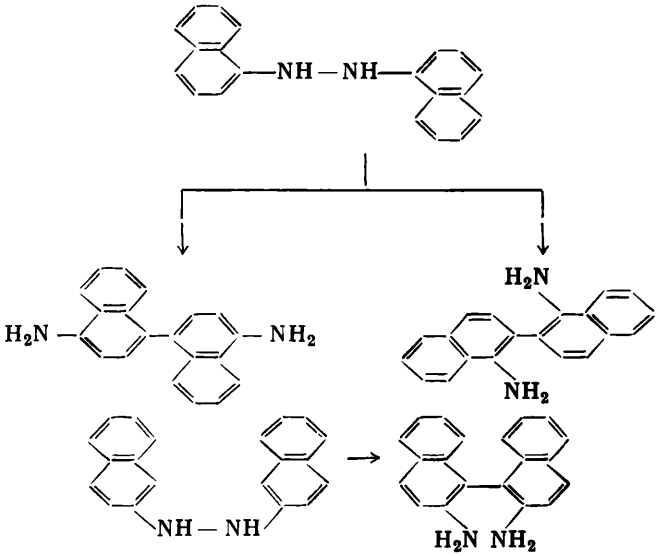


that is, intramolecularly.

According to N. N. Vorozhtsov, sr., and V. V. Kozlov, heating of the sodium salt of 1-aminonaphthalene-4-sulphonic acid leads to its isomerization to the salt of 1-aminonaphthalene-2-sulphonic acid; 1-aminonaphthalene-2-sulphonic acid (its sodium salt) rearranges to 2-aminonaphthalene-6-sulphonic acid. Similar rearrangements occur with the salts of naphtholsulphonic acids (E. A. Shilov and V. V. Kozlov): sodium 1-hydroxynaphthalene-4-sulphonate isomerizes at

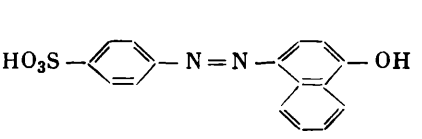
170°C to sodium 1-hydroxynaphthalene-2-sulphonate, and sodium 2-hydroxynaphthalene-1-sulphonate is converted at a higher temperature (about 200°C) into sodium 2-hydroxynaphthalene-6-sulphonate.

The benzidine rearrangement of hydrazonaphthalenes, which has been thoroughly studied by V. O. Lukashevich, proceeds in the same way as in the benzene series, even in the absence of a mineral acid:

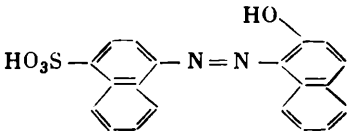


Naphthols and their derivatives, chiefly mono- and disulphonic acids, naphthylamines and their sulphonic acids are largely used for synthesis of the various azo dyes, the structures of some of which are given below as examples. The sequence of diazotization and azo coupling becomes clear from the formulas of the azo dyes:

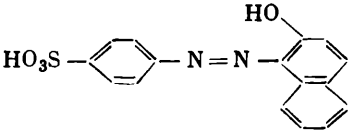
1. *Monoazo dyes*:



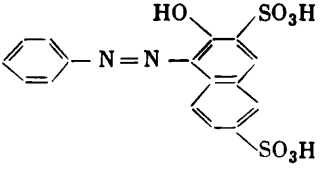
Orange I



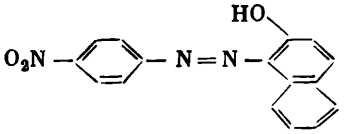
Fast Red



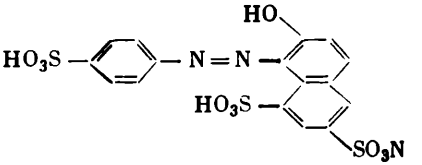
Acid Orange



Orange P

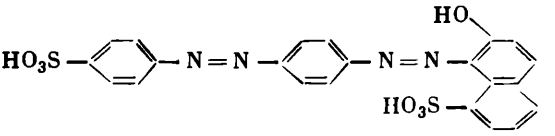


Para Red
(Paranitraniline Red)

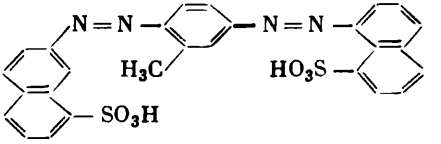


Bright Crimson

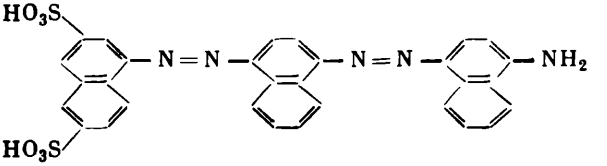
2. *Bisazo dyes*:



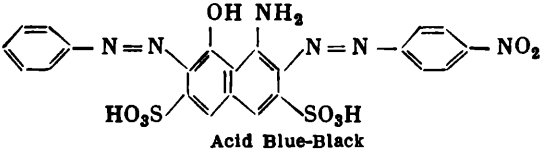
Crocein Scarlet 3B



Crocein Bright 9B

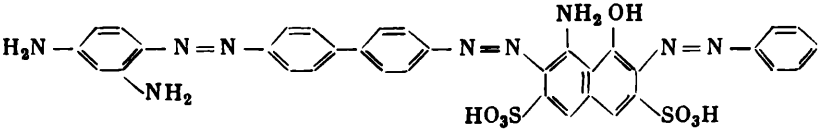


Naphthylamine Black

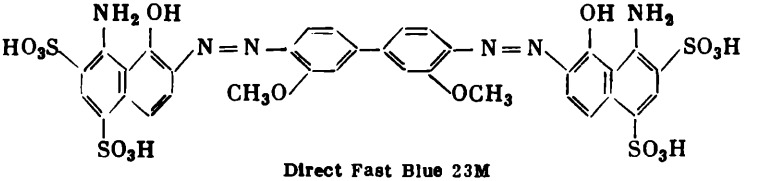


Acid Blue-Black

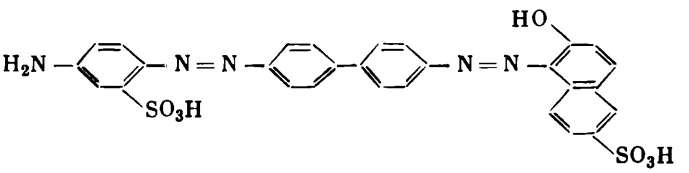
3. *Direct dyes*:



Direct Black 3



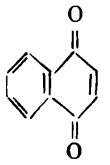
Direct Fast Blue 23M



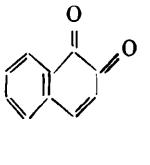
Diaminogen Blue

(a) Naphthoquinones

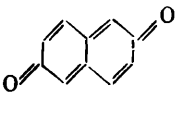
When 1,4-, 1,2- and 2,6-dihydroxynaphthalenes or aminonaphthols are oxidized by chromic acid, three naphthoquinones are obtained:



p-Naphthoquinone



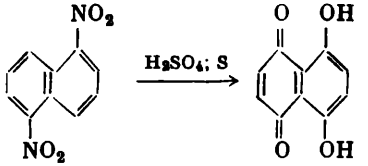
o-Naphthoquinone



amphi-Naphthoquinone

In their properties they are true quinones and are similar to benzoquinones.

The derivatives of *p*-naphthoquinone are a number of natural and synthetic dyes. Of these we shall mention only **naphthazarine** which is analogous to quinizarin (page 292) and which is obtained by the action of sulphuric acid and sulphur on 1,5-dinitronaphthalene:



It is believed that this reaction proceeds through the following stages: the reduction of the nitro groups to NHOH; the rearrangement of arylhydroxylamine to *p*-hydroxyarylamine; the partial (in one ring) oxidation of hydroxyarylamine to quinoneimine and the hydrolysis of the imino group to a carbonyl group and of the amino group to a hydroxyl group.

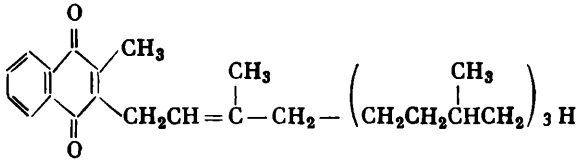
The derivatives of *p*-naphthoquinone also include vitamins of the K group: **vitamin K_1** (phytonadione) and **vitamin K_2**.

Vitamin K_1 is present in the green tissue of leafy vegetables and vitamin K_2 occurs in bacteria and fish.

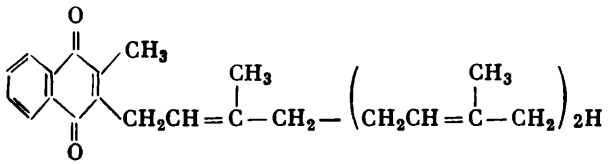
Both these vitamins are similar in structure to 2-methyl-1,4-naphthoquinone, which is evidenced by the similarity of their absorp-

tion spectra (in all the three compounds the structure of 1,4-naphthoquinone is chromophoric).

The structure of vitamins K_1 and K_2, which has been established by Fieser and Doisy, is as follows:

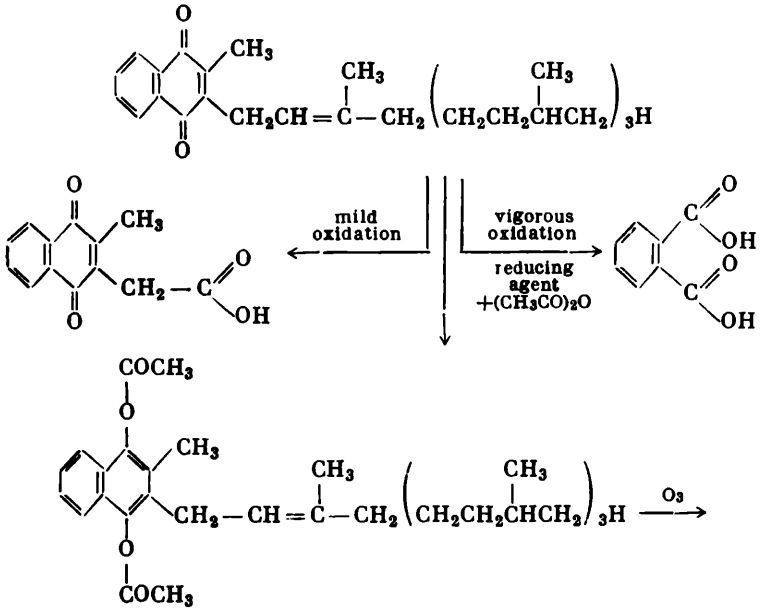


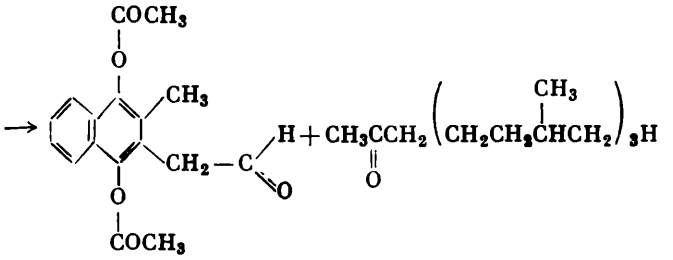
Vitamin K_1 (phytonadione or 2-methyl-3-phytyl-1,4-naphthoquinone)



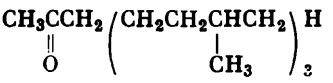
Vitamin K_2 (1-methyl-3-difarnesyl-1,4-naphthoquinone)

The paths for elucidation of the structure of K vitamins are illustrated by the example of phytonadione:



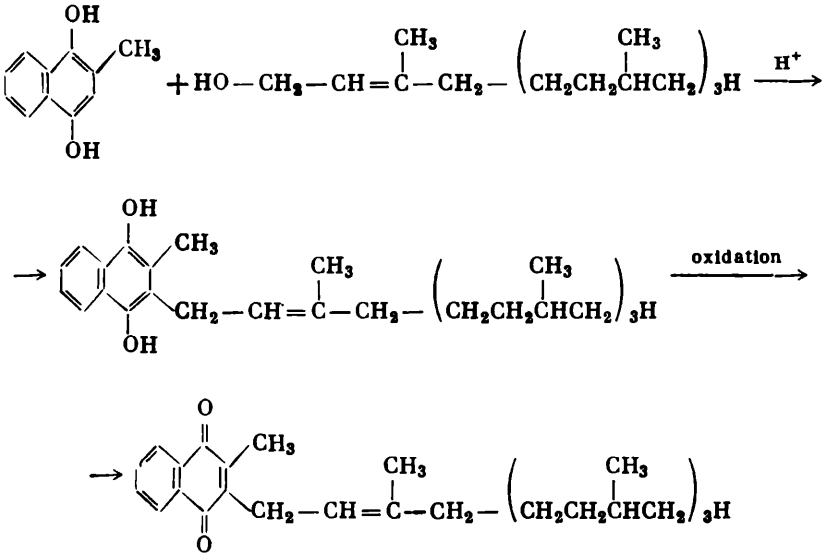


The resulting ketone



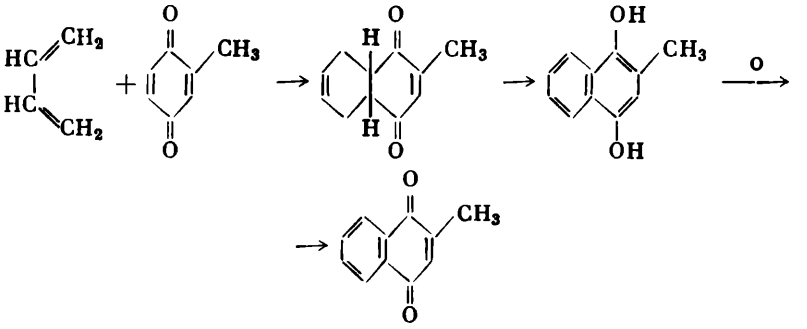
is the same as that obtained in the ozonolysis of the alcohol phytol.

The synthesis of phytonadione from 2-methyl-1,4-dihydroxynaphthalene and phytol was also accomplished by Fieser and Doisy:



The vitamins K_1 and K_2 play an important role in the blood-clotting function since they shorten the clotting time of blood. The same effect is exhibited by synthetic 2-methyl-1,4-naphthoquinone, which is produced by a modification of the Fieser method, which has

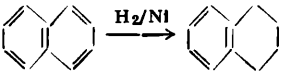
been developed by A. I. Korolev:



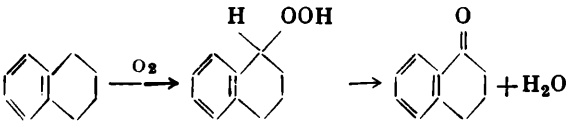
(b) Hydronaphthalenes

We have already said above that the hydrogenation of naphthalene by amalgamated sodium in aqueous alcohol gives mainly 1,4-dihydronaphthalene (but some of 1,2-dihydronaphthalene is also formed).

The catalytic hydrogenation of naphthalene may lead to **tetrahydronaphthalene** or **tetralin**:



Tetralin exhibits the aromatic character of benzene homologues. It is a liquid with b.p. 205-207°C. Like xylenes, though more readily, tetralin is oxidized by atmospheric oxygen even at room temperature to the hydroperoxide (a chain reaction) which when heated is converted into a ketone, **tetralone**:

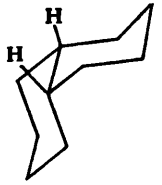


This compound can also be obtained by direct oxidation of tetralin with the chromic acid mixture.

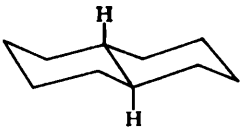
Tetralin can be nitrated (and the nitro compounds reduced to the amines), sulphonated, and halogenated. All methods of dehydrogenation—catalytic (Pt or Cr_2O_3) or with the aid of Se and S—can be employed to convert tetralin into naphthalene. Tetralin is used as an additive to motor fuel (in petroleum-poor countries) and as a solvent.

The exhaustive hydrogenation of very pure naphthalene by hydrogen over nickel (Sabatier, Sanderan) gives **decahydronaphthalene**

or **decalin**, which is known to exist in the form of two stereoisomers:



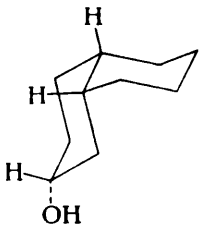
cis-Decalin
(b.p. 195°C; heat of combustion 1499.9 kcal/mole)



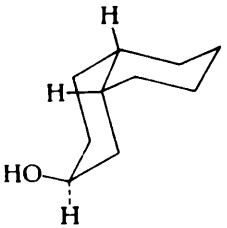
trans-Decalin
(b.p. 185°C; heat of combustion 1497.1 kcal/mole)

Isomeric decalins have been discussed in Sec. 6.4 devoted to condensed alicyclic compounds (see Volume II, page 255).

The hydrogenation of β-naphthol gives four stereoisomeric decalols, one pair of which has the skeleton of *cis*-decalin, and the other, that of *trans*-decalin:

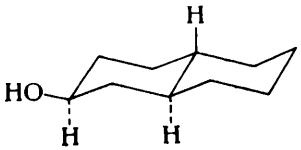


(m.p. 105°C)

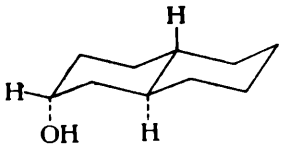


(m.p. 17°C)

cis-Decalols



(m.p. 75°C)



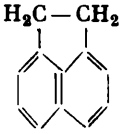
(m.p. 53°C)

trans-Decalols

The oxidation of decalols to ketones—**decalones**—reduces the stereoisomerism to that of the skeleton, and from the first two decalols there is obtained one β-*cis*-decalone, and from the second two, its *trans*-isomer. The reduction of decalones leads to *cis*- and *trans*-decalins, respectively. When *cis*-decalone is oxidized, two acids are formed—*cis*-2-carboxycyclohexyl-β-propionic and *cis*-cyclohexylene-1,2-diacetic acids; when oxidized *trans*-decalone yields the *trans*-isomers of the same acids.

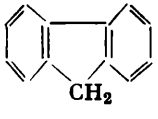
B. Acenaphthene, Indene, Fluorene

These hydrocarbons are contained in coal tar.



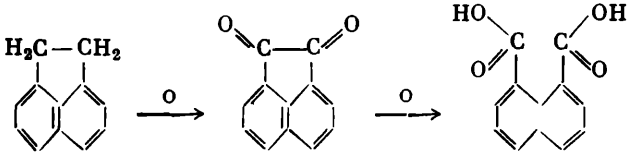
Acenaphthene
(m.p. 95 °C;
b.p. 278 °C)

Indene
(b.p. 182 °C)

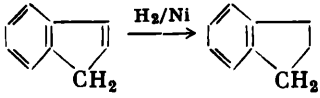


Fluorene
(m.p. 116 °C;
b.p. 295 °C)

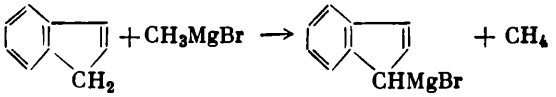
Acenaphthene is oxidized to acenaphthenequinone (m.p. 261°C) and further to *peri*-naphthalenedicarboxylic (naphthalene-1,8-dicarboxylic) or **naphthalic** acid, which establishes the chemical constitution of the acid:



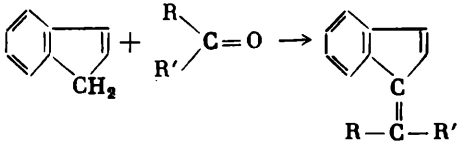
Indene is hydrogenated to indane:



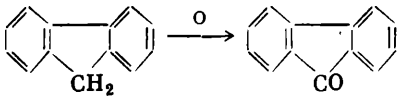
Like cyclopentadiene, indene when acted on by a Grignard reagent forms an organomagnesium derivative, which can be used in its turn as a Grignard reagent:



Indene which has an extremely reactive methylene group (CH_2) can enter into the same condensation reactions with aldehydes and ketones as cyclopentadiene. This leads to the formation of the analogues of fulvenes:



Fluorene is oxidized to fluorenone:



Though to a lesser degree than in indene and especially in cyclopentadiene, the methylene group in fluorene has a tendency to lose a hydrogen as a proton and to react with a Grignard reagent and with aldehydes.

By studying a state of equilibrium of the type

$$RH + CH_3O^- \rightleftarrows R^- + CH_3OH$$

with the aid of optical methods it has become possible to estimate the acidities of indene and fluorene and to compare them with those of diphenylmethane and triphenylmethane:

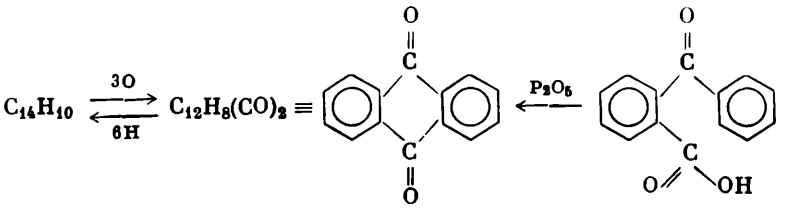
	K_a		K_a
Indene	10^{-21}	Diphenylmethane	10^{-35}
Fluorene	10^{-25}	Triphenylmethane . . .	10^{-33}

C. Anthracene and Its Derivatives

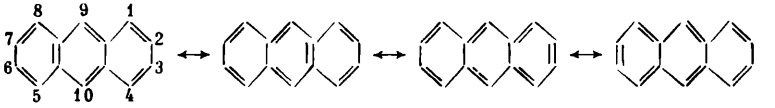
Anthracene is a high-melting (m.p. 217°C) hydrocarbon with b.p. 354°C. It is present to the extent of about 1 per cent in coal tar and crystallizes out together with its lower-melting and more soluble isomer, phenanthrene, from the highest-boiling fraction of coal tar—anthracene, or green, oil.

The structure of anthracene has been established by Armstrong and Ginsberg. Information on its constitution can be gained from the following facts. Anthracene is hydrogenated by nascent hydrogen, adding on two hydrogen atoms and forming dihydroanthracene; when subjected to exhaustive catalytic reduction (Ni) it adds on 14 hydrogen atoms. The molecular formula of anthracene, $C_{14}H_{10}$, differs from that of the corresponding saturated hydrocarbon $C_{14}H_{30}$ by 20 hydrogen atoms, i.e., the structure of anthracene must contain ten π-bonds, or one ring and nine π-bonds, two rings and eight π-bonds, three rings and seven π-bonds, etc. The addition of 14 hydrogen atoms on hydrogenation confirms the last of the possibilities indicated. Anthracene has an aromatic character. Its oxidation leads to anthraquinone, a diketone retaining the number of carbon atoms of anthracene and its cyclic structure since anthraquinone can be converted back to anthracene by reduction. The structure of anthraquinone follows from its synthesis from *o*-benzoylbenzoic acid which

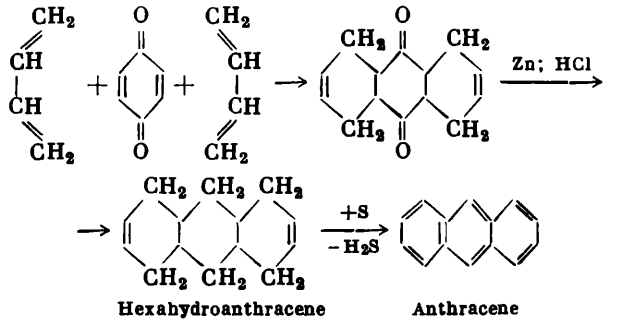
undergoes ring closure when reacted with phosphorus pentoxide

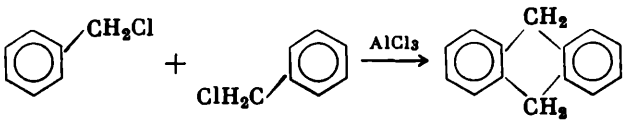


Thus, for anthracene itself we arrive at the structure of the fused ring aromatic tricyclic hydrocarbon 2,3-benznaphthalene.* This structure represented by the following resonance forms



is confirmed by synthesis of anthracene and also by syntheses of dihydroanthracene and anthraquinone. The numbering in the first formula is the system of numbering of carbon atoms adopted for anthracene. As is always the case, only those carbon atoms which bear a hydrogen atom are numbered. Below are given the diene synthesis of anthracene from benzoquinone and butadiene and the synthesis of dihydroanthracene by the Friedel-Crafts method:

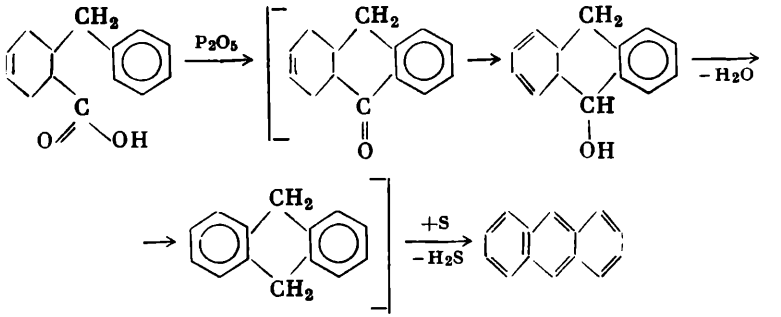




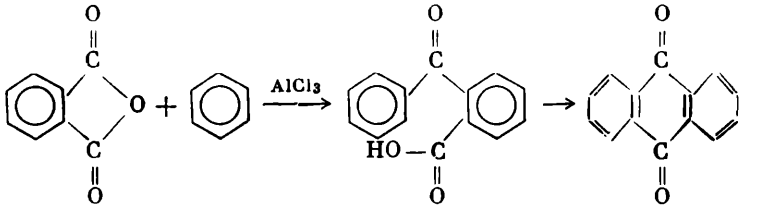
* According to this system of nomenclature the prefix *benz* signifies the presence of one more fused-on benzene ring, and the numerals indicate the points of fusion of carbon atoms closing the new benz ring. Naphthalene should have been called benzbenzene in accord with this nomenclature.

Dihydroanthracene is readily dehydrogenated (or oxidized) to anthracene.

According to R. Ya. Levina, it is possible to prepare anthracene and its derivatives by heating *o*-benzyltetrahydrobenzoic acids with phosphoric-anhydride and sulphur:

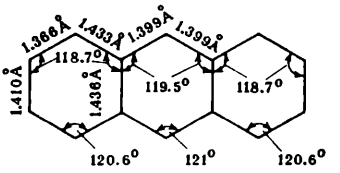


Anthraquinone can also be synthesized by the Friedel-Crafts acylation of benzene, using phthalic anhydride, to *o*-benzoylbenzoic acid which is then subjected to ring closure through the action of P_2O_5 to give anthraquinone:



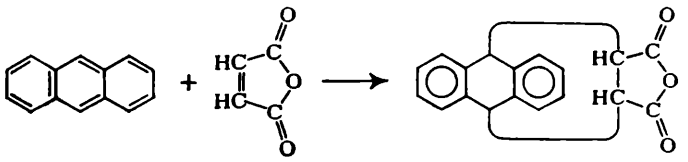
Anthraquinone

Properties of Anthracene. The X-ray analysis of anthracene crystals provides the following picture of its molecule:



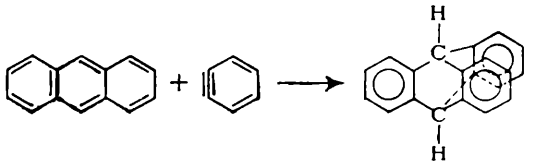
From what has been said above it follows that the most reactive carbon atoms in anthracene (addition of two hydrogen atoms; oxidation) are carbon atoms 9 and 10, which are also called the *meso*-carbon atoms. These *meso*-carbon atoms differ in behaviour from the aromatic benzene atoms to a greater extent than the α-atoms of naphthalene, and are closely reminiscent of the terminal carbon atoms of

dienic conjugated systems, say, of butadiene. For example, anthracene readily adds on maleic anhydride and other dienophiles (see Volume I, page 369), a reaction used for quantitative determination of anthracene in mixtures:

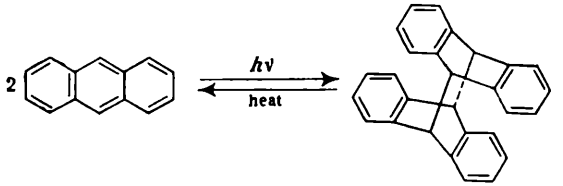


The adduct of the indicated structure is easily (even on gentle heating) cracked across the newly formed σ-bonds to regenerate the starting compounds. Advantage may be taken of this reaction to purify anthracene.

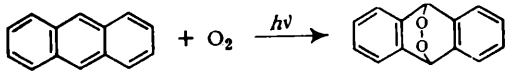
Another remarkable case of diene synthesis involving anthracene is the formation of tryptycene from anthracene and dehydrobenzene by the Wittig reaction:



When illuminated anthracene dimerizes to **dianthracene** which spontaneously depolymerizes in the dark to the monomer:

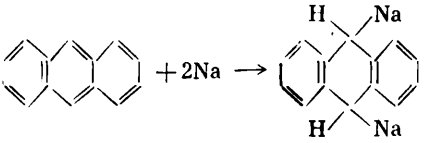


On illumination molecular oxygen also adds on to anthracene in the 9,10-positions (photo-oxidation):



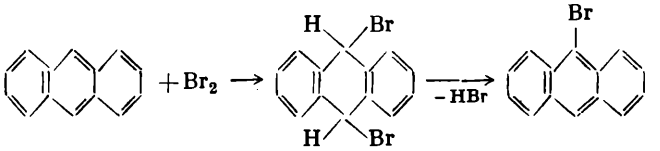
The peroxide obtained in the same way from 9,10-diphenylanthracene loses molecular oxygen on heating *in vacuo* up to 180°C, reverting to the starting hydrocarbon (Dufraisse).

Like diene hydrocarbons, anthracene directly adds alkali metals in the positions 9 and 10:

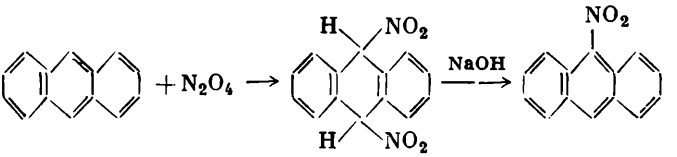


The bonds between sodium and carbon are ionic, as usual.

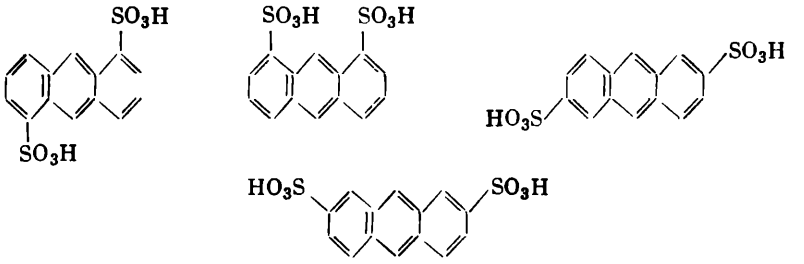
With chlorine and bromine, there also takes place addition to the 9,10-positions, this being followed by the elimination of a molecule of hydrogen halide:



Concentrated nitric acid oxidizes anthracene to anthraquinone, but nitric acid dissolved in acetic acid nitrates it in the 9-position. Nitrogen dioxide adds on to anthracene in the 9,10-positions. The elements of nitrous acid are eliminated by alkali from the addition product, as a result of which the same 9-nitroanthracene is formed:



Concentrated sulphuric acid sulphonates anthracene in the α-position (probably, in the *meso*-position the sulphonic group readily undergoes acidolysis), and more dilute sulphuric acid sulphonates anthracene on heating in the β-position, so that four disulphonic acids of anthracene are available:



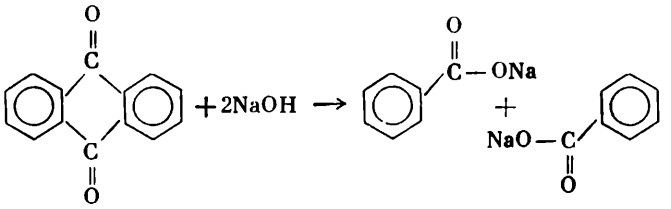
Despite all these possibilities, anthracene is employed in the chemistry of dyestuffs almost exclusively for its oxidation to anthraquinone

which is subjected to the various substitution reactions. No less important is the synthesis of derivatives of anthraquinone from phthalic anhydride and phenols.

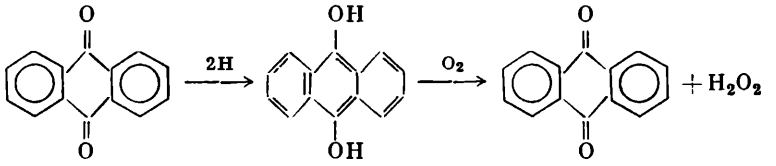
(a) Anthraquinone and Its Derivatives

The preparation of anthraquinone by the oxidation of anthracene and synthesis from phthalic anhydride and benzene has already been considered.

Anthraquinone is a relatively high-melting (m.p. 86°C), non-volatile (b.p. 382°C), stable compound, which, despite its name, is little reminiscent of quinones and is completely devoid of the chemical activity of an unsaturated ketone. Its π-electrons, which could have formed carbon-carbon π-bonds conjugated with carbonyl π-bonds, are contained in aromatic sextets. In just the same way, the addition to π-bonds (in this particular case, across the π-bonds of either of the two end benzene rings) would give no gain of energy but lead, instead, to its consumption because of the loss of the benzenoid character of the end rings. Hence, anthraquinone stands much closer to benzophenone and other aromatic ketones. It forms oximes and other nitrogen derivatives; on fusion with alkali it decomposes in the same manner as benzophenone, which in this case leads to benzoic acid:



Anthraquinone is reduced to anthrahydroquinone, this being one of its few "quinone" reactions. Anthrahydroquinone is oxidized even more readily than hydroquinone, the oxidation being effected directly by atmospheric oxygen:

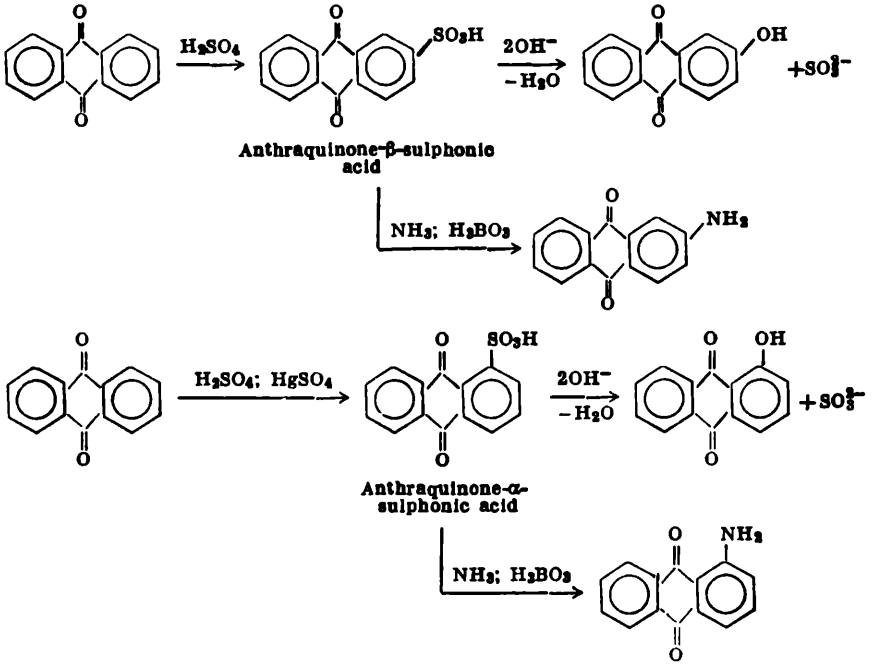


This gives hydrogen peroxide, and it is this reaction which is used to prepare concentrated hydrogen peroxide.

One of the important industrial processes is the sulphonation of anthraquinone. In this process, the first sulphonic group enters the β-position of one of the rings, and the next one enters the α-position

of the second nucleus. When a mercuric salt is added to the reaction mixture, the first sulphonic group is directed to the α-position, and the next one, to the α-position of the other ring (M. A. Il'insky). All these sulphonic products are employed in the synthesis of dyestuffs.

When anthraquinone-α-sulphonic acid (or anthraquinone-β-sulphonic acid) is heated with alkali, say, with $Ca(OH)_2$, the sulphonic groups are replaced by hydroxyls and α-hydroxy- or β-hydroxyanthraquinones are respectively obtained. When sulphonic acids are heated with ammonia up to about 200°C in the presence of a catalyst (boric acid), aminoanthraquinones are formed, which are employed in the synthesis of so-called indanthrene dyes. An analogous reaction with aniline yields phenylaminoanthraquinones.

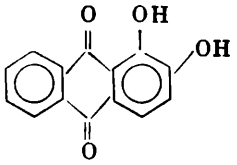


The oldest anthraquinone dye is **alizarin** which has retained its value up to the present time. Prior to 1869 alizarin (1,2-dihydroxyanthraquinone) was exclusively prepared from the root of madder (*Rubia tinctorum*), a shrub which was cultivated in Europe. It contains a glycoside (ruberythric acid), which on hydrolysis yields alizarin.

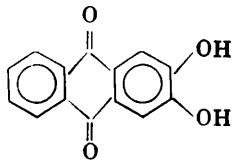
Alizarin forms orange-red crystals with m.p. 289°C, which sublime and are soluble in alkali (the solution assumes a violet colour).

The constitution of alizarin was elucidated in 1868 by Graebe and Liebermann, and shortly after this Graebe, Liebermann and Caro prepared alizarin artificially. In subsequent years synthetic alizarin completely displaced the natural product from the market.

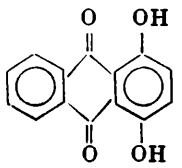
The facts that establish the constitution of alizarin are as follows. The molecule contains two carbonyl and two hydroxyl groups. When distilled with zinc dust alizarin is converted into anthracene. On oxidation it forms phthalic acid, which means that both hydroxyl groups are contained in the same benzene ring. For dihydroxyanthraquinone having hydroxyl groups in the same nucleus the following isomers are possible:



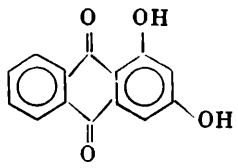
I



II

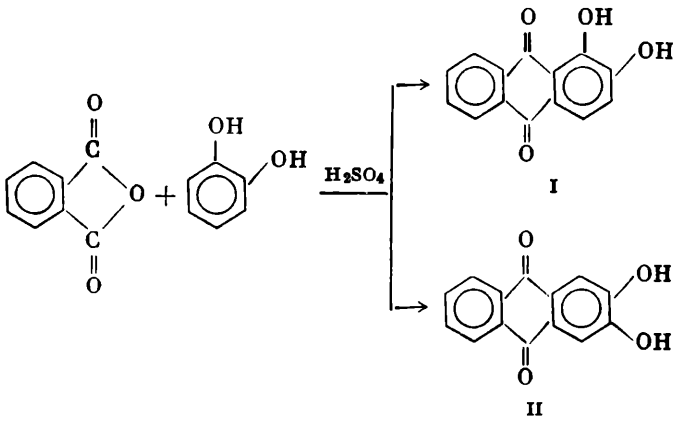


III



IV

Formulas III and IV are rejected on the basis that alizarin can be prepared synthetically from phthalic anhydride and catechol:



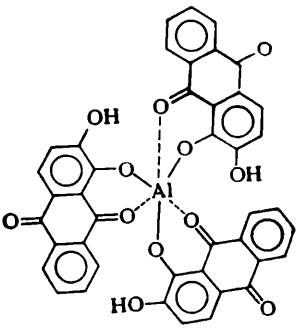
I

II

Of the two isomeric products obtained in this way, one is identical with natural alizarin and the other has no properties of a mordant dye and does not form coloured "lakes" with Al^{3+} or Cr^{3+}. Based

even on this fact it may be stated that the structure of alizarin is best represented by formula I. This is confirmed by the fact that in electrophilic substitution reactions (halogenation, nitration) alizarin gives rise to two isomeric derivatives, and the isomer II formed simultaneously from catechol can give only one substitution product. Thus, alizarin has the structure I.

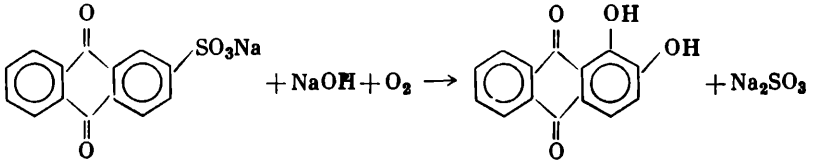
With trivalent metals, say, with aluminium, alizarin gives inner-complex coloured insoluble compounds, which are called lakes, of the following structure:



The formation of coloured lakes is the basis of the method of dyeing by alizarin.

The dyeing by alizarin is always done with the use of a binder or "mordant". The fabric to be dyed is first steeped in a solution of a salt of sulphonated castor oil and then in a solution of aluminium alum to produce a red (blood-red) colour, and chromium alum to develop a violet-black colour. The sulphonic acid that becomes attached to the fabric is converted into an insoluble salt of a trivalent metal. When such a "mordanted" fabric is heated with alizarin, the latter forms a coloured insoluble lake with the trivalent metal.

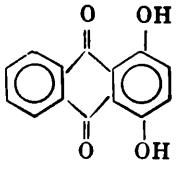
The commonest route for synthesis of alizarin consists of the combined action of alkali and an oxidizing agent on anthraquinone-β-sulphonic acid (the air is blown or sodium chlorate is added to the melt):

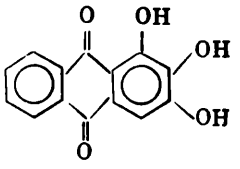


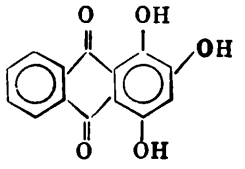
In all probability, the reaction begins with the nucleophilic attack of $\bar{O}H^-$ on the most electron-deplenished α-position of the sulphonated nucleus of anthraquinonesulphonic acid (the electrons

are withdrawn by the *o*-sulphonic group and the *o*-carbonyl group and also, to a lesser extent, by the *m*-carbonyl group). The attack is facilitated by the presence of an oxidizing agent which carries away the hydride ion being subjected to nucleophilic replacement. After the hydroxyl is introduced into the α-position, there takes place an ordinary, also nucleophilic, replacement of SO_3Na by OH.

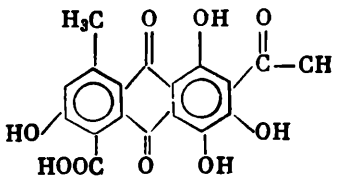
Numerous other, purely synthetic anthraquinone dyes are synthesized from phthalic anhydride (or substituted phthalic anhydrides) and phenols. Such are **quinizarin** (from hydroquinone), **anthragallol** (from pyrogallol), **purpurin:**

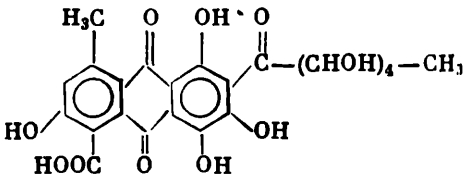

Quinizarin


Anthragallol


Purpurin

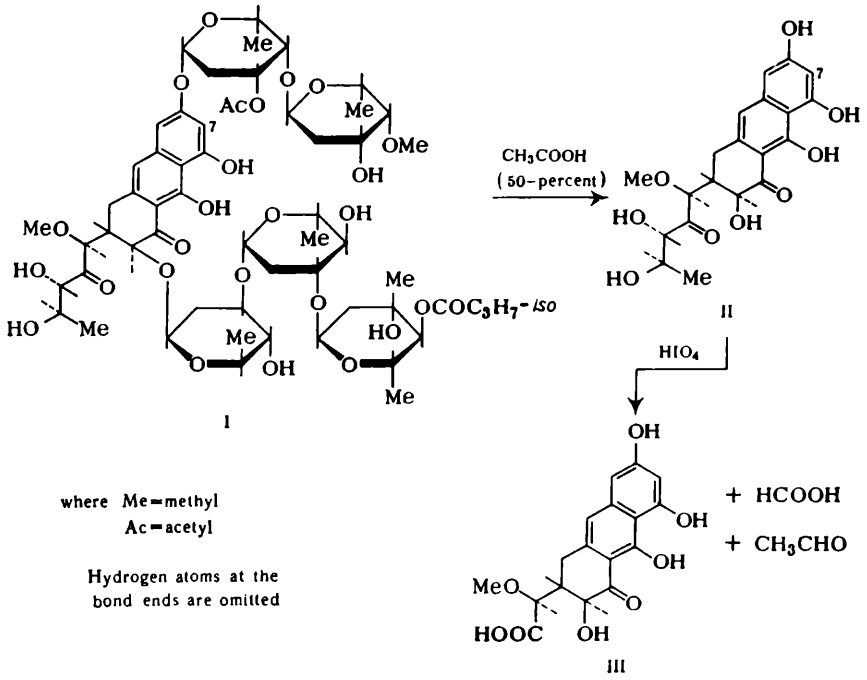
It is interesting to note that the anthraquinone dyes are also found in the animal kingdom. An example is **kermesic acid,** which had been produced before the discovery of America from scale insects (kermes) and later displaced by **carminic acid,** whose aluminium lake is known as **carmin.** Carminic acid is obtained from an insect which lives in the cactuses growing in Mexico.


Kermesic acid


Carminic acid

The derivatives of tetrahydroanthracene include the antibiotic **olivomycin** which has the remarkable property of depressing the biosynthesis of the information nucleic acids (see Volume IV, "Nucleotides") and thus hinder the growth of certain malignant tumors. The elucidation of the full spatial formula of olivomycin (M. M. Shemyakin, M. N. Kolossov) is a typical example of how the structure of complex molecules can be promptly established through the joint application of modern chemical and physical methods of investigation. For example, the sequence of the monosaccharides in the carbohydrate chains of olivomycin I has been determined by way of stepwise hydrolysis which has led, in the long run, to the aglycon—

olivine II:



Elucidation of the structure of olivine by physical methods alone presents formidable difficulties and that is why it was subjected to partial oxidation by periodic acid. As a result, **olivinic acid** III was obtained along with formic acid and acetaldehyde, which threw light on the structure of the oxidized portion of the side chain. On the other hand, spectral studies of the derivatives of olivinic acid, especially of their mass-spectra and NMR spectra, enabled direct elucidation of the structure of all the remaining part of the aglycon molecule, and hence that of olivomycin itself.

For instance, the NMR spectrum of the tetraacetate of the methyl ester of olivinic acid (Fig. 8.3) shows six three-proton singlets, which, judging by their chemical shifts, correspond to two methoxyl and four acetyl groups. In the region of 6-8 ppm, which is characteristic of aromatic systems, there are three single-proton peaks, one of them being a singlet (the only proton in the middle ring) and the other two being doublets with a small spin-spin splitting constant, which points to the *meta*-positions of the corresponding hydrogen atoms. The signals of the protons H_2 and $H_{1'}$ are split into doublets as the result of their interaction with the same hydrogen atom (this can be

demonstrated with the aid of double nuclear magnetic resonance, i.e., by measuring the NMR spectrum upon imposition of an extra radio-

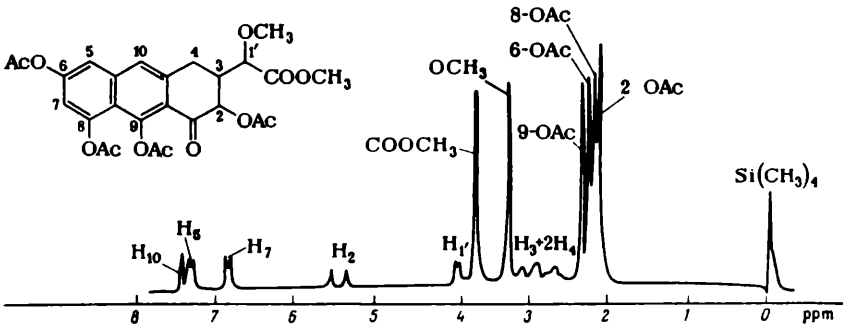


Fig. 8.3.

NMR spectrum of the tetraacetate of methyl ester of olivinic acid at a generator frequency of 60 MHz in $CDCl_3$ with tetramethylsilane as an internal standard.

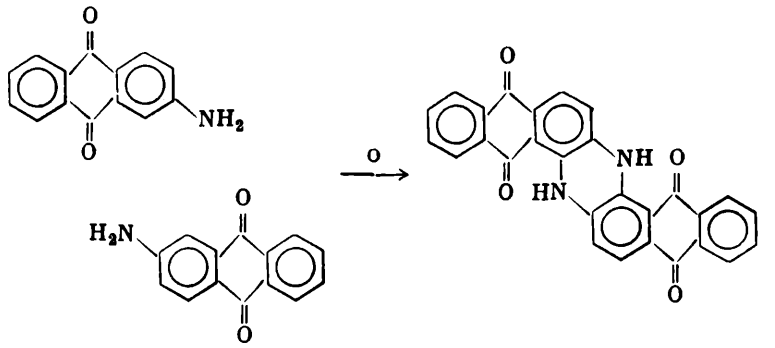
frequency). Hence, the molecule contains the branched grouping CH_2—CH(—CH)—CH and the side chain is in the position 3 of the saturated ring.

An analogous structure is shown by the related antitumor antibiotics olivomycins B and C and also chromomycins.

They all contain olivine or 7-methylolivine as the aglycon and differ only by the acyl groups in the carbohydrate residues.

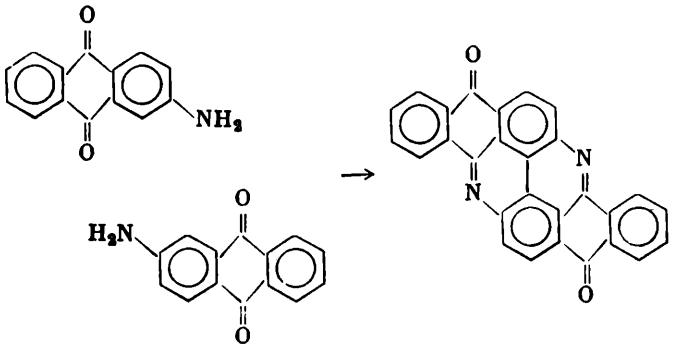
(b) Indanthrene and Polycycloketonic Dyes

The alkali fusion of β-aminoanthraquinone followed by oxidation gives an excellent vat dye known as **indanthrene blue** I:



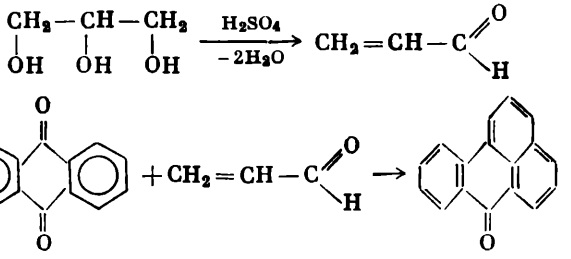
I

In the presence of $SbCl_5$ the condensation proceeds with the formation of the yellow dye **flavanthrene** II:



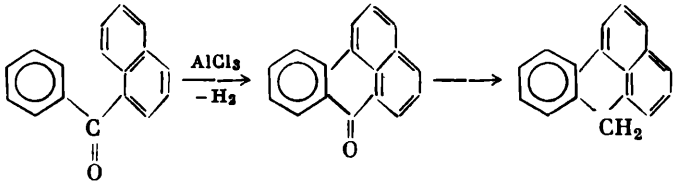
II

The most valuable vat dyes are produced from **benzanthrone** III which is synthesized from anthraquinone and glycerol by heating them with sulphuric acid up to 120°C. In this reaction, glycerol forms acrolein which supplies the three carbon atoms required for building up the benz ring of benzanthrone:



III

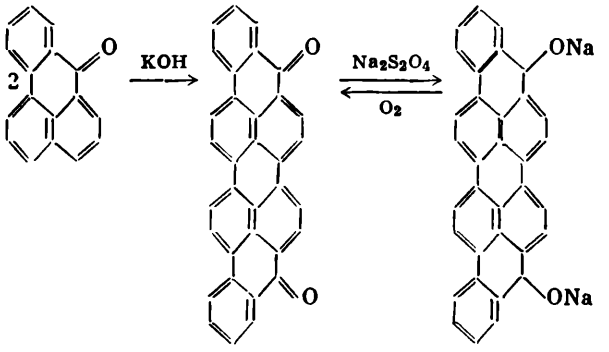
The structure of benzanthrone follows from its synthesis effected by the action of aluminium chloride on α-benzoylnaphthalene followed by the reduction of the resulting benzanthrone to benzanthrene:



α-Benzoyl-naphthalene Benzanthrone Benzanthrene

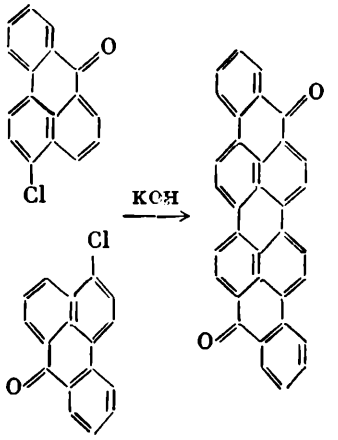
When benzanthrone is fused at 225°C with potassium hydroxide, it undergoes oxidative condensation to give **dibenzanthrone** IV, a

deep blue polycycloketonic vat dye, which is called **violanthrone** or **indanthrene dark blue:**



IV V

The chlorination or bromination of benzanthrone followed by its fusion with alkali yields an isomer of violanthrone—the dark blue-violet vat dye **isoviolanthrone** VI:



VI

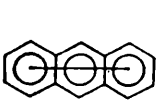
In these dyes all the rings, except those containing a keto group, are aromatic. Polycycloketones can be reduced under severe conditions to hydrocarbons: the fusion of violanthrone with zinc dust gives the hydrocarbon **violanthrene**—red subliming plates (b.p. 478°C) By reducing with sodium hyposulphite, $Na_2S_2O_4$, polycycloketonic dyes are converted into alkali-soluble phenoxides—leuco compounds of the type V, in which the fabric is heated; as a result, the leuco compounds are readily absorbed by the fibre. In air the leuco compound is oxidized back to the original dyestuff (polycycloketone IV),

which remains firmly embedded in the cloth. In this way very fast colours are obtained. This dyeing process in which the dye reduced to a soluble leuco-form is then recovered through oxidation by atmospheric oxygen in the cloth is called **vat dyeing**, the name arising from the vats used in the reduction step.

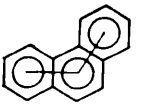
Indanthrene and polycycloketonic vat dyes are often collectively called **indanthrene dyes**. They are considered to be among the most valuable dyes, exceeding in quality the azo and other dyes.

D. Phenanthrene

Phenanthrene is an *angular* isomer of linear anthracene and the simplest angular condensed aromatic hydrocarbon.



Anthracene

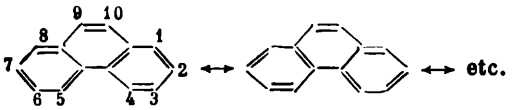


Phenanthrene

As has been noted, phenanthrene is found together with its structural isomer anthracene in anthracene oil—the highest-boiling fraction of coal tar.

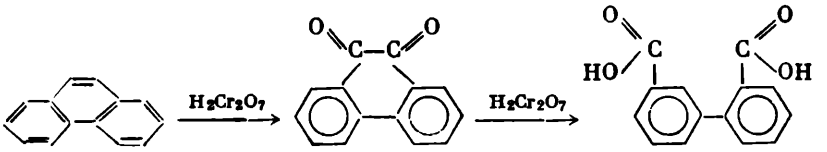
Phenanthrene has a lower melting point (m.p. 100°C; b.p. 340°C) and is more soluble than anthracene, and can therefore be easily separated from anthracene. Also, it has a higher resonance energy (99 against 86 kcal/mole for anthracene); in other words, the energy of its formation from C and H is 99 kcal/mole lower than that calculated, with account taken of the heats of formation of the C—H, C—C and C=C bonds characteristic of aliphatic and alicyclic compounds.

The following system of numbering of carbon atoms is adopted for phenanthrene:

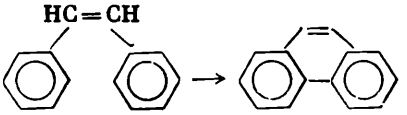


The structure of phenanthrene is clear from the following facts. Phenanthrene is hydrogenated catalytically, adding on 14 hydrogen atoms and forming perhydrophenanthrene. Thus, it has 14 π-electrons and three rings. Phenanthrene is an aromatic compound. When oxidized it first forms phenanthraquinone and then diphenic acid, which points to the presence of two benzene rings joined by a linkage of the biphenyl type. The *ortho*-position of the carboxyl groups in diphenic acid relative to the linked carbon atoms of the two rings

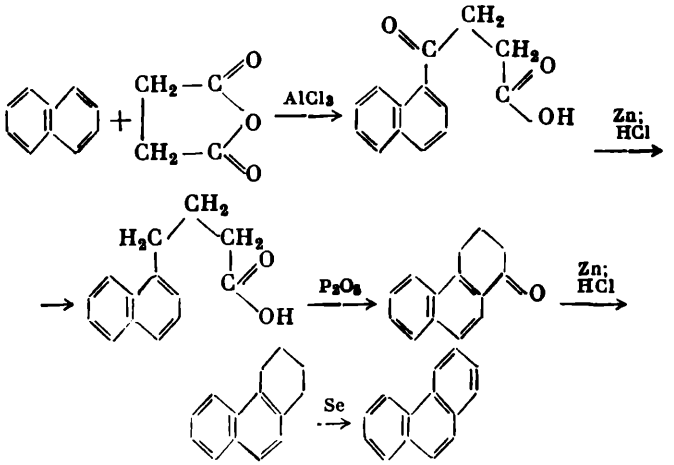
indicates the position of the third benzene ring:



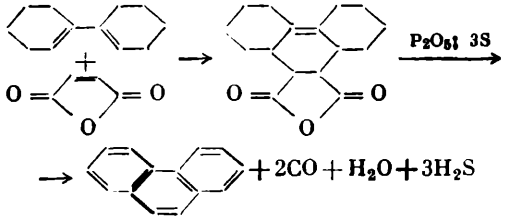
Stilbene when passed through red-heat tubes forms phenanthrene (a synthesis analogous to the synthesis of biphenyl from benzene):



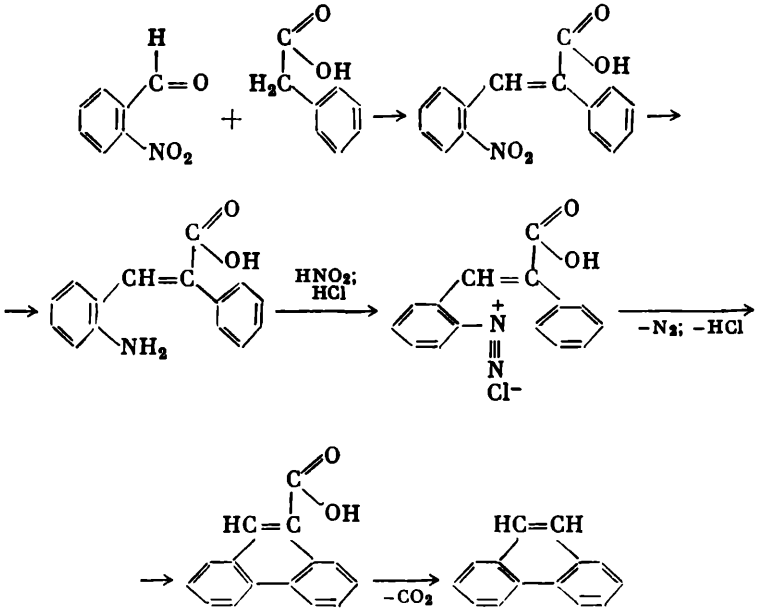
This reaction can also be effected photochemically by irradiating stilbene with ultraviolet light in the presence of 5 molar per cent of iodine (in a cyclohexane solution). The synthesis of phenanthrene confirms the structure deduced for it on the basis of these facts. The presence in phenanthrene of the naphthalene system is proved by the Haworth synthesis:



The same follows from the elegant synthesis developed by R. Ya. Levina and V. R. Skvarchenko:

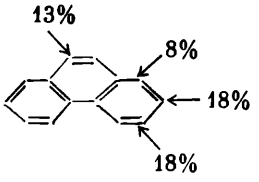


The best known method of preparing phenanthrene is Pschorr's synthesis which begins with the Perkin condensation (page 170) and ends with the Gomberg reaction (page 126):



All the three syntheses can also be used to prepare a large number of phenanthrene derivatives.

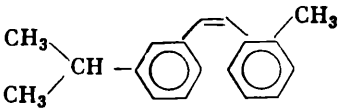
Like anthracene, but to a lesser degree, phenanthrene has active 9,10-positions. Hydrogenation, oxidation, and electrophilic attacks are directed, in the first place, to these positions. Thus, the main product in the nitration reaction (with nitric acid in glacial acetic acid) is 9-nitrophenanthrene, 2- and 4-nitrophenanthrenes being formed in smaller quantities. In the sulphonation reaction at 60°C the yields of the isomeric sulphonic acids are as follows:



At an increased temperature the sulphonic acids 9 and 10 are not formed. The Friedel-Crafts acylation is mainly directed to the

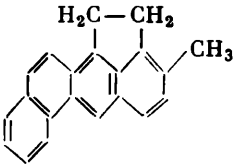
position 3. Bromination takes place first as a 9,10-addition followed by the elimination of HBr.

Unlike anthracene, phenanthrene has not found wide application in industry. But the derivatives containing the partially or fully hydrogenated phenanthrene skeleton occur extensively in the animal and vegetable kingdoms. Examples are **resin acids**—abietic and levopimaric acids which are the constituents of rosin (see Volume IV). The first acid on dehydrogenation with selenium, which is invariably accompanied by decarboxylation, forms 1-methyl-7-isopropylphenanthrene known as **retene:**



Retene is present in certain fossil coniferous resins.

The phenanthrene skeleton is contained in all steroids (see Volume IV), in particular in steroid alcohols, bile acids, sex hormones, and also in alkaloids of the morphine group (see Volume IV). When subjected to dehydrogenation accompanied by the loss of some of the side-chain alkyl groups many steroids form carcinogenic **methylcholanthrene:**



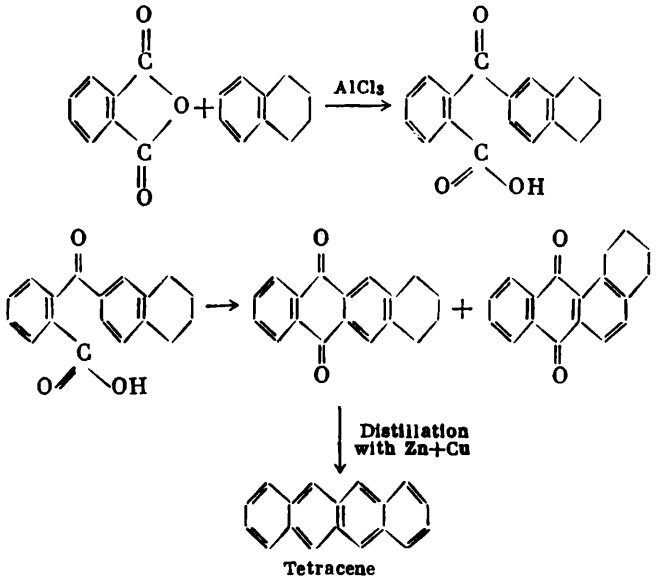
E. Higher Condensed Aromatic Hydrocarbons

Anthracene and phenanthrene may serve as the prototypes of higher condensed hydrocarbons. Similar in structure to anthracene are linearly built condensed hydrocarbons with four, five, six, and seven benzene rings, which are called **acenes**. The higher acenes are probably unstable and are unknown, though some of their derivatives, including undecacene, have been described in the literature.

Structurally similar to phenanthrene are angular condensed hydrocarbons which are more stable than the acenes; they include closed polycyclic compounds (such as **coronene**), which are exceedingly stable thermally and chemically. All these hydrocarbons readily form intensely coloured charge-transfer complexes with trinitrobenzene, picric acid, tetracyanoethylene, tetranitromethane, etc.

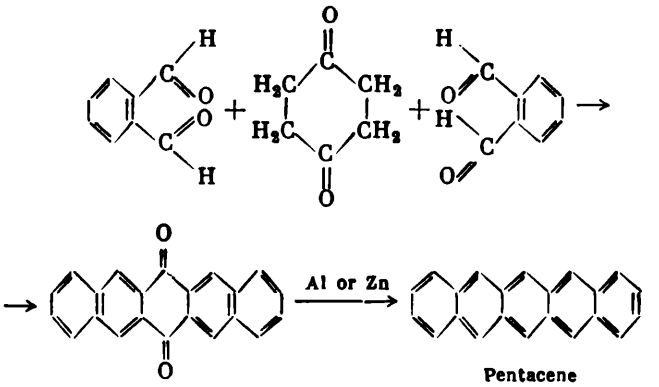
(a) Acenes

The synthesis of the "acenes" is exemplified by the following reactions. Starting from phthalic anhydride and tetralin it is possible to obtain **tetracene:**



Tetracene

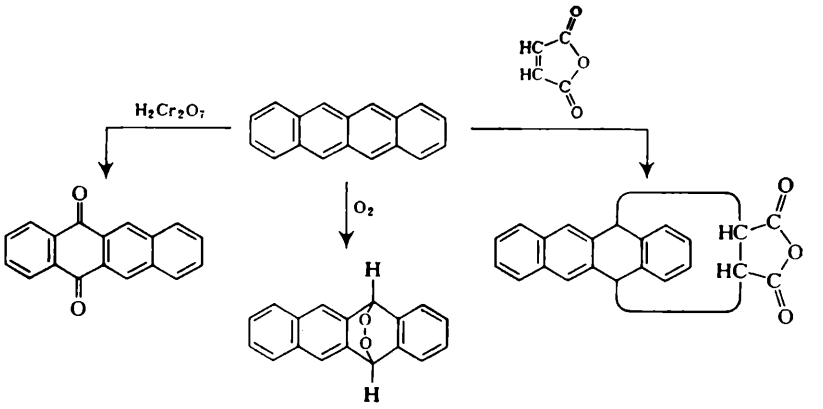
An analogous reaction of phthalic anhydride with tetralin leads to **pentacene**, which can also be synthesized by another modification of the method:



Pentacene

The acenes are chemically reactive: they are oxidized by atmospheric oxygen, add on dienophiles, are hydrogenated (in the first

place, at the central carbon atoms), and form quinones on oxidation. Some of these reactions are given below for tetracene:



The acenes readily capture the electrons of alkali metals. As the number of rings increases in the acene series the intensity of light absorption increases and a sharp bathochromic shift of the absorption maximum is observed, so that tetracene is orange in colour, pentacene has a deep violet-blue colour, and hexacene is black-green.

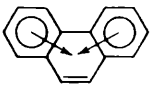
The lower members of the acene series have typical benzenoid absorption bands with the following characteristics (benzene is given for comparison purposes):

	λ_{max}, Å	ε_{max}
Benzene	2550	230
Naphthalene	3140	316
Anthracene	3800	7900
Tetracene	4800	11,000
Pentacene	5800	12,600

The larger the number of six-membered rings fused together in a linear manner, the stronger the bathochromic shift of light absorption and the more intensive the absorption. At the same time, the stability of the compound decreases sharply, its aromaticity is diminished, and it becomes increasingly unsaturated and closes to a polyenic hydrocarbon with conjugated bonds. This is easily understandable since only one ring of an acene has a sextet of electrons. Since, however, the system of any acene, as we have seen for anthracene, is symmetrical, it may be stated that two electrons in the sextet are mobile and migrate from one end of the system to the other, which, according to Clar, is expressed by the following scheme (the

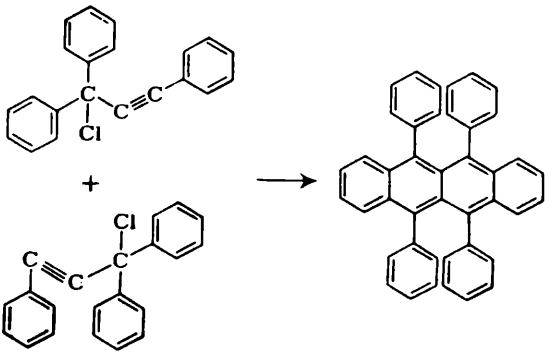
arrow indicates the migration of a pair of electrons of the sextet):

The angular condensed hydrocarbons, beginning with phenanthrene, contain a larger number of completely aromatic rings and the path covered by the pair of electrons from the sextet is shorter:

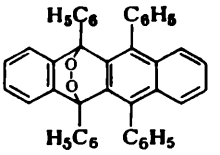


These hydrocarbons absorb light in a longer-wavelength region of the spectrum, are more stable and aromatic.

A very interesting compound is 9,10,11,12-tetraphenyltetracene, or **rubrene**, discovered by Dufraisse when he carried out the condensation of 3-chloro-1,3,3-triphenylpropyne at 100-120°C in vacuo:

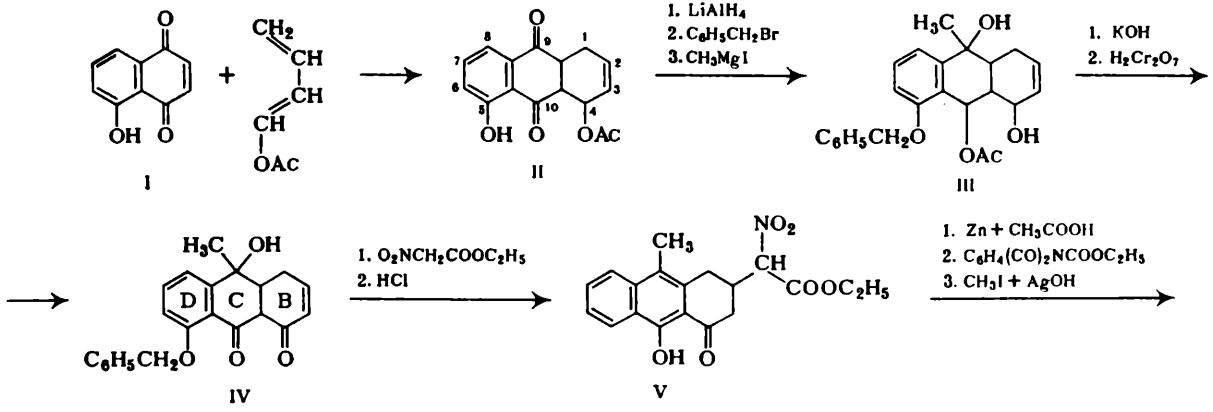


Solutions of this red-coloured hydrocarbon are decolorized in sunlight by atmospheric oxygen, this resulting in the formation of the peroxide

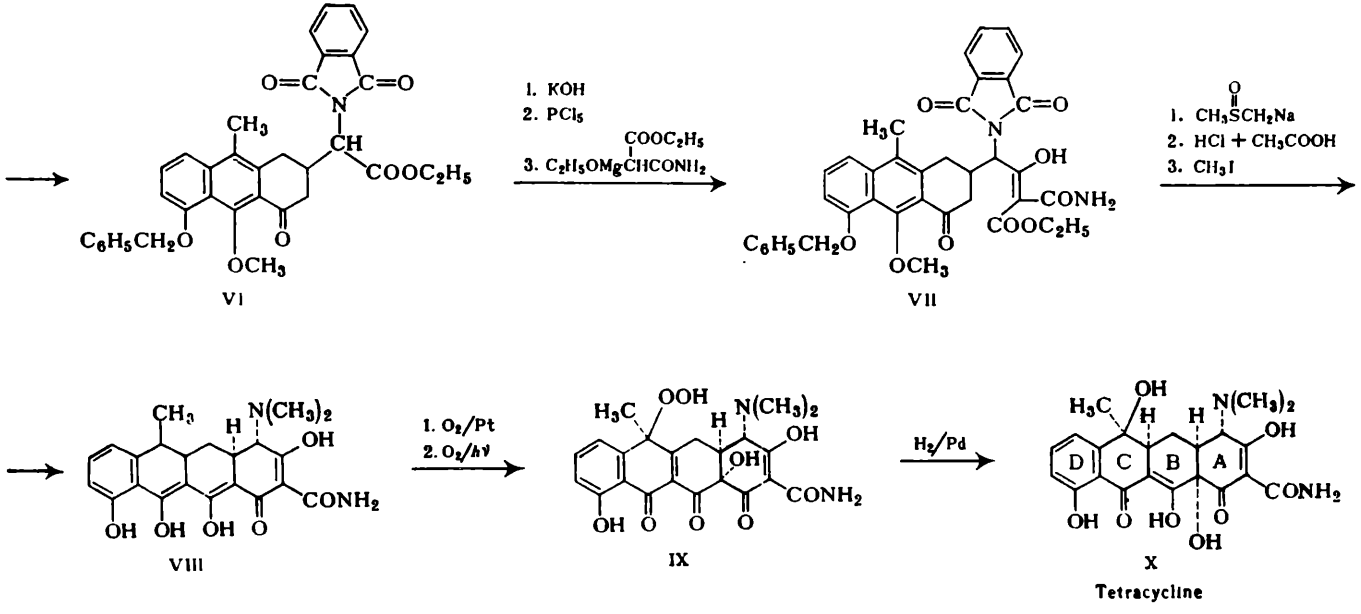


This rubrene peroxide decomposes in vacuum at 140-150°C into molecular oxygen and rubrene. The oxygen is evolved in the active (singlet) state, and as such it is capable of adding on to the conjugated carbon-carbon π-bonds in a manner similar to that of the diene syn-

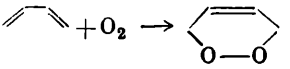
Synthesis of tetracycline



3,0 - 0198


1. KOH
2. PCl5
3. C2H5OMgCHCONH2
COOC2H5
1. CH3SCH2Na
2. HCl + CH3COOH
3. CH3I
1. O2/Pt
2. O2/hν
H2/Pd
VI
VII
VIII
IX
X
Tetracycline

thesis:



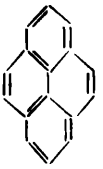
Partially hydrogenated and substituted tetracenes have been found in the egesta of unicellular fungi and are used as antibiotics known collectively as **tetracyclines**. Tetracycline and its derivatives, 7-chlortetracycline (Aureomycin) and 5-oxytetracycline (Terramycin), are valuable antibiotics. They possess high antibiotic activity and are used for the treatment of many infectional diseases. The antibiotic properties of these compounds are attributed to the suppression of protein biosynthesis on ribosomes in bacterial cells.

The work on the elucidation of the structure and on the synthesis of antibiotics of this group was begun in 1950 by a number of notorious chemists (Woodward, Muxfeldt, and others) but only in 1967 was the full synthesis of natural tetracycline accomplished (M. M. Shemyakin, M. N. Kolossov). This twenty-stage synthesis (see above) was planned in such a way that the building of the most complex part of the molecule (ring A) and the stereodirected creation of asymmetric centres of desired configuration were effected at the last stages, which excluded the work with complex and highly unstable compounds at most of the stages involved. Moreover, it proved necessary, during the course of the synthesis, to protect or modify the groupings present in the molecule with a view to recover them at later stages. Thus, of the two keto groups in compound II the most reactive is the keto group in the 10-position; therefore, before the Grignard reaction was carried out this keto group was selectively reduced to a secondary alcoholic group, which was then oxidized (together with the hydroxyl group in the 4-position) to a carbonyl group.

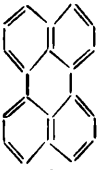
In an analogous way, it proved expedient to aromatize the ready ring C in the middle of the synthesis and then to reconvert it into the cyclohexanol ring at the final stages.

(b) Angular Higher Aromatic Condensed Hydrocarbons

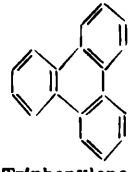
Coal tar also contains the following highly condensed aromatic hydrocarbons:



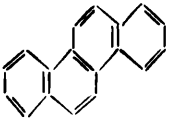
Pyrene (m.p. 156 °C; b.p. 399 °C; colourless)



Perylene (m.p. 265 °C; golden-yellow)

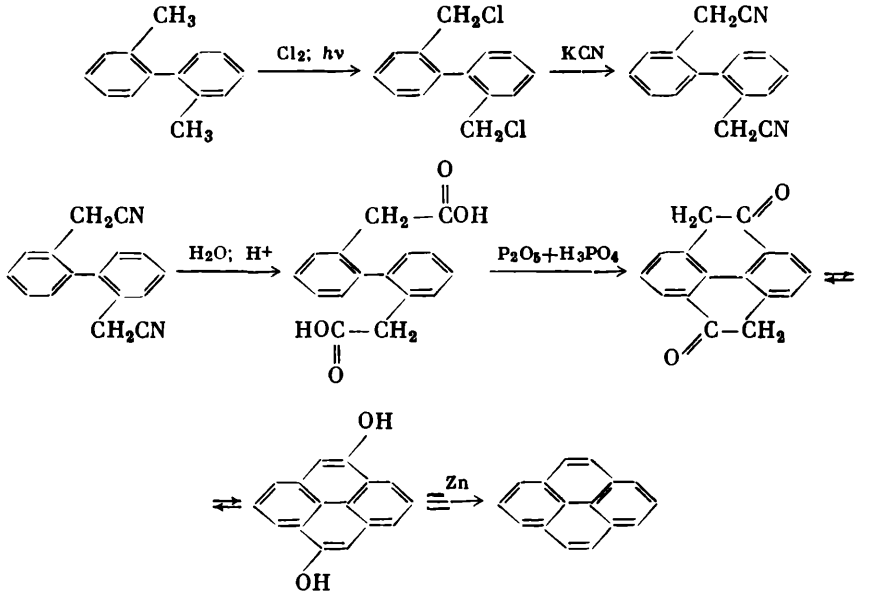


Triphenylene (m.p: 199 °C; colourless)

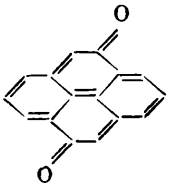


Chrysene (m.p. 255 °C; colourless)

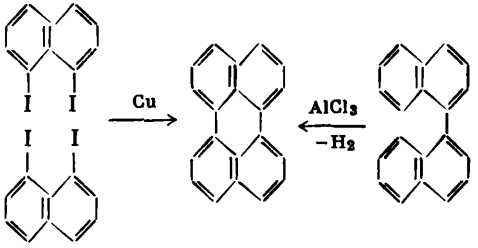
Pyrene was first synthesized by Weitzenbeck as follows:



The oxidation of pyrene yields pyrenequinone

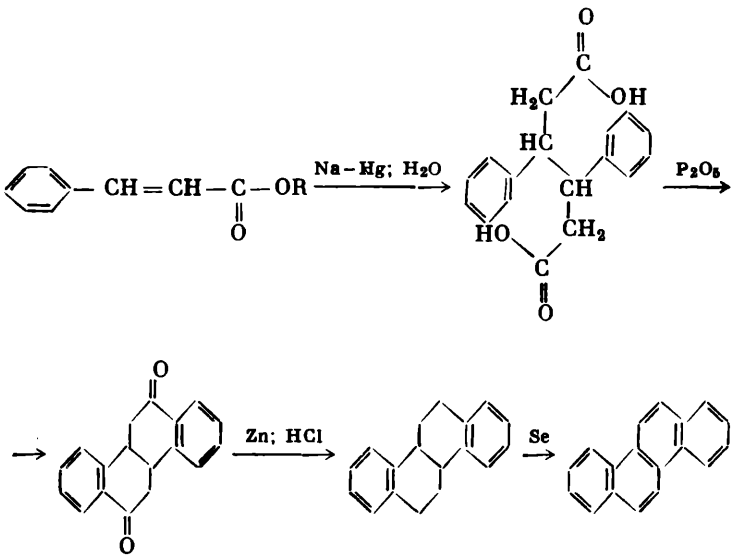


Scholl and Weitzenbeck obtained **perylene** from 1,8-diiodonaphthalene, using the Ullmann method. This reaction proves the structure of perylene. The same result (in poor yield) is furnished by the direct action of aluminium chloride on naphthalene or α,α-dinaphthyl:

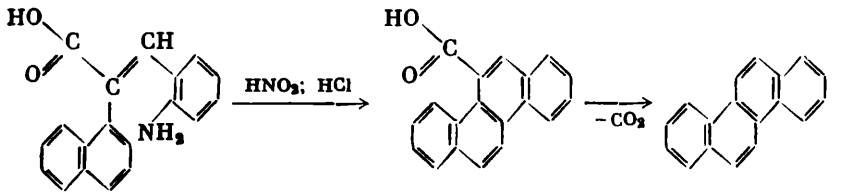


The synthesis of **triphenylene** has already been considered: it is the product of the trimerization of Wittig's dehydrobenzene (page 75).

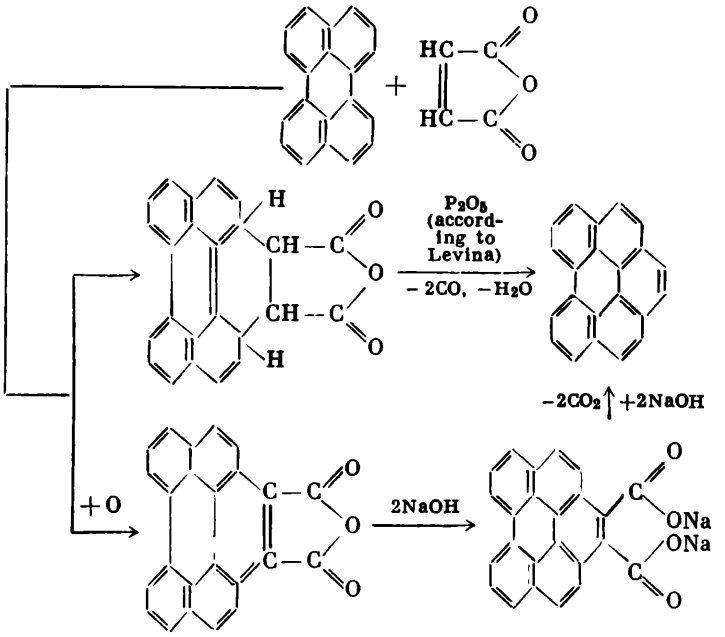
Chrysene can be prepared by the Robinson-Vogel reaction:



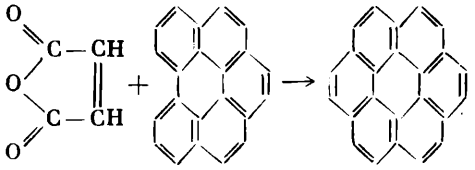
Chrysene can also be prepared by Pschorr's synthesis (page 299):



Of the hydrocarbons just described golden-yellow perylene is the most reactive; for example, it readily adds on maleic anhydride, forming an unstable adduct. If the addition is carried out in the presence of an oxidizing agent, such as CuO, or better tetrachloroquinone (chloroanil), the adduct is aromatized and benzperylene results:



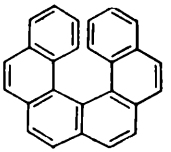
The same route of synthesis via maleic anhydride converts benzperylene into **coronene:**



Coronene is a light-yellow compound (m.p. 438-440°C) emitting a blue fluorescence when exposed to hard radiation. It is employed for the detection and measurement of the radiation intensity. It is interesting that Todd has found the derivatives of coronenequinone in the pigments of certain insects.

Coronene undergoes hydrogenation; the first product of its hydrogenation—**hexahydrocoronene**—is a derivative of triphenylene. Coronene can be sulphonated, nitrated to mono-, di-, tri- and hexanitrocoronenes; it can also be halogenated; an aminocoronene has also been obtained.

It remains to consider the last compound among those in the group of the highly condensed aromatic hydrocarbons. It is **hexahelicene** (m.p. 231-233°C; solutions with a bluish-red fluorescene) which is noted for its optical activity.

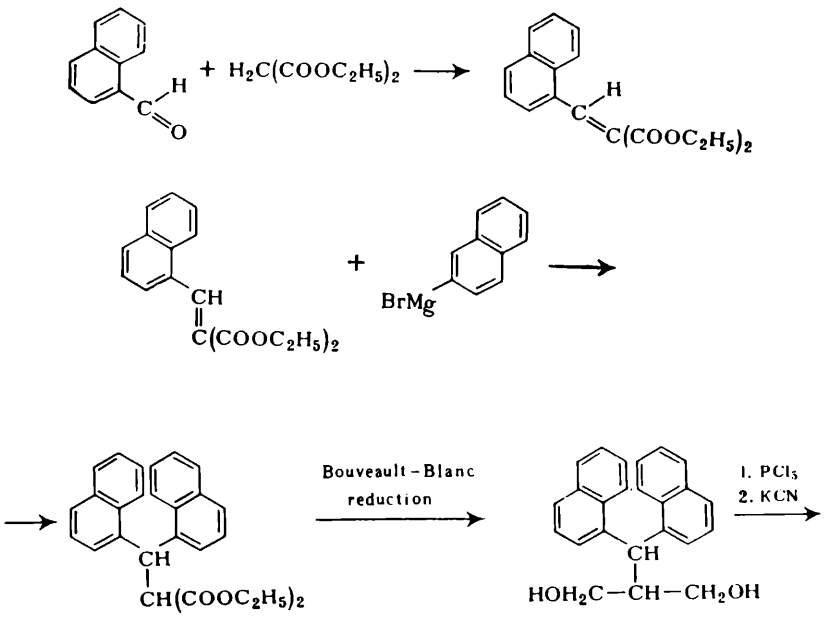


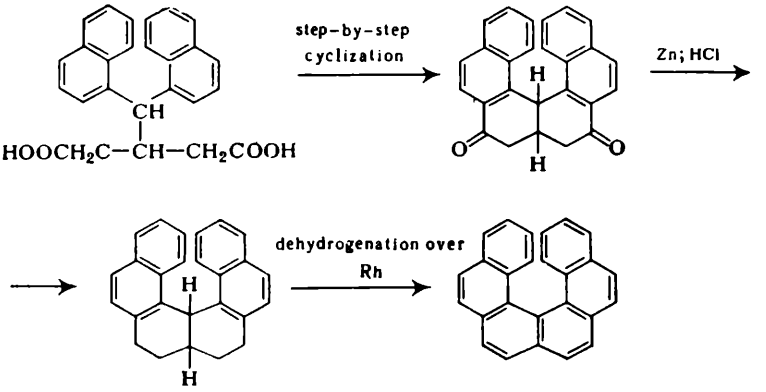
Hexahelicene

The charge-transfer complex formed from hexahelicene and an optically active polynitro aromatic acid is resolved in a usual way into diastereomers and two antipodes are isolated in the free state—the left-handed and right-handed hexahelicenes with an unusually high molecular rotation $[\alpha]_D^{24} = 3640$. The molecule of hexahelicene (in the absence of asymmetric carbon atoms) is non-superimposable with its mirror image since the terminal rings prevent the molecule to be arranged in a single plane and it assumes a spiral form.

Hexahelicene has been synthesized by M. S. Newman. The following is the abbreviated and simplified scheme of its synthesis (the 1,4-addition of a Grignard reagent proceeds in a manner similar to the interaction with α-unsaturated ketones):

Synthesis of hexahelicene




step-by-step
cyclization
Zn; HCl
dehydrogenation over
Rh
HOOCH2C–CH–CH2COOH
CH
H
O
O
H
H

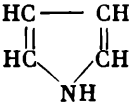
HETEROCYCLIC COMPOUNDS

Chapter 9

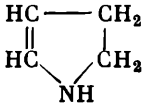
Introduction

Cyclic compounds in which a ring containing at least one atom of an element other than carbon (a hetero-atom) is present are classed under the name of **heterocyclic compounds.** Thus, some of the compounds that have already been described in this course (e.g. ethylene oxide, succinic and phthalic anhydrides, butyrolactone, glycolide, paraldehyde, dioxan, phthalimide, succinimide) belong, strictly speaking, to the class of heterocycles and should be sought for in handbooks among the heterocyclic compounds. But at the same time these compounds are functionally so closely related to the parent aliphatic (or aromatic) compounds that it was more convenient to consider them in the aliphatic (or aromatic) section. There are, however, heterocyclic compounds whose electronic structure includes an aromatic sextet of electrons (and, in general, $4n + 2$ electrons, though other systems, except six-electron ones, have been studied to a lesser extent). It is such compounds that will be discussed here. We shall also consider the corresponding hydrogenated systems which refer to an aromatic heterocycle in the same way as the cyclohexane and cyclohexene refer to benzene.

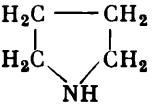
Such relationships for five- and six-membered heterocyclic compounds may be illustrated by the following examples:



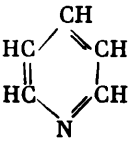
Pyrrole



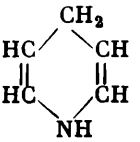
Dihydropyrrole or pyrroline



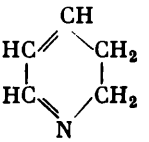
Tetrahydropyrrole or pyrrolidine



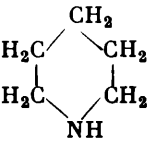
Pyridine



1,4-Dihydropyridine



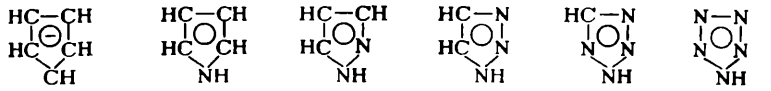
2,3-Dihydropyridine



Hexahydropyridine or piperidine

Heterocyclic compounds may, in principle, contain any hetero-atom if the valency of the latter is not less than two. Particularly important, however, are only those heterocycles which have O, S, and N as hetero-atoms; our discussion will be restricted to these heterocyclic compounds.

Heterocyclic compounds may be classified according either to the kind of the hetero-atoms or to the number of hetero-atoms present in the ring; for example:



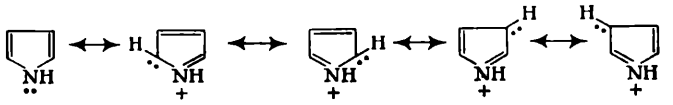
Cyclopentadienylium ion | Pyrrole | Pyrazole | Triazole | Tetrazole | Pentazole

This series begins and ends with isocyclic structures, only the four middle formulas belong to heterocycles.

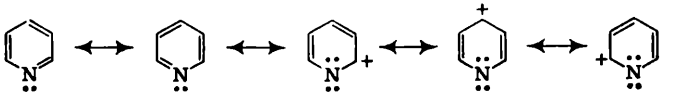
But perhaps the most important criterion for classifying heterocyclic compounds is the number of hetero-atoms present in the ring. As a matter of fact, we shall limit our consideration to five- and six-membered rings. In certain cases, condensed heterocyclic compounds are of importance. Such condensed systems, like condensed systems consisting of two benzene rings in naphthalene, may be built up of a heterocycle and a benzene ring or else of two heterocyclic rings. Some (few) systems of this kind are exceedingly important and are therefore the only subject matter in our discussion.

The physical properties of aromatic heterocyclic systems, their names and the numbering of atoms adopted are presented in Table 9.1.

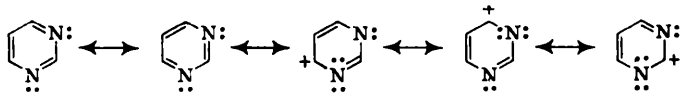
The aromaticity of five-membered heterocyclic compounds with two π-bonds is attributed to the fact that one free electron pair of O, S, or N participates in the aromatic delocalization and formation of the aromatic sextet. In terms of resonance theory, this delocalization of π-electrons (and *p*-electrons) for five- and six-membered rings will be expressed, for example, by the following schemes:



Pyrrole



Pyridine



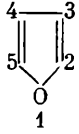
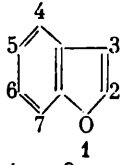
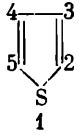
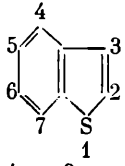
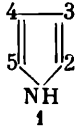
Pyrimidine

Although the above method of representation of heterocyclic compounds is complicated, it nevertheless illustrates well the delocalization of the π-bonds and p-pair of electrons of the hetero-atom in five-membered rings and provides an explanation for the increased activity towards electrophilic substitution reactions (the increased nucleophilicity of carbon atoms), the decreased nucleophilicity of the hetero-atom, the enhanced acidity of hydrogen at the hetero-atom (the involvement of ammonium forms in the resonance structure). The analogy between six-membered heterocyclic compounds and benzene is illustrated in the same way. This symbolism takes into account the increased electrophilicity of carbon atoms in six-membered rings, such as pyridine (or pyrimidine), especially in the α- and γ-positions, and the decreased nucleophilicity as compared with benzene because of the nitrogen atom being more electronegative than the carbon atom.

The formation of an aromatic sextet which includes the free (unshared) pair of electrons of the hetero-atom is responsible, on the one hand, for all the aromatic properties of the heterocycle and, on the other, for the loss of nucleophilic properties by the hetero-atom. Thus, the nitrogen of pyrrole is devoid of basic properties; the nitrogen, oxygen, and sulphur atoms of pyrrole, furan, and thiophen are, accordingly, only slightly capable or not capable at all of complex formation, alkylation to onium cations and of oxidation across the hetero-atom (for example, no change from $>$S to $>$S=O and $>S\begin{matrix}=O\\=O\end{matrix}$ is possible for them). It does not mean, however, that systems similar to thiophenesulphone cannot exist; they have to be prepared by indirect methods.

This of course refers only to those hetero-atoms whose electron pairs are part of the aromatic sextet (or, more generally, of the $4n + 2$ group), and this refers neither to the second hetero-atom of five-membered rings nor even to the first hetero-atom of six-membered rings. The "double bonds" of heterocyclic compounds differ in their aromatic character, resembling the bonds of dienic hydrocarbons in some cases and those of benzene in others. Completely or partially hydrogenated rings, such as di- or tetrahydropyridine, di- and tetrahydrofuran and thiophen, hexahydropyridine (piperidine) are reminiscent, in their functional manifestations, of their aliphatic counterparts. The remaining double bonds exhibit ordina-

TABLE 9.1. **Heterocyclic Compounds**

Formula	Name	Stabilization energy, kcal/mole	m.p., °C	b.p., °C	Density, d_4^{20}	K_b^{25}
	Furan	16	—	32	0.9366	—
	Coumarone	—	—18	174	1.0776 (at 15°C)	—
	Thiophen	11	—38.30	84.12	1.0644	—
	Benzothiophen or thionaphthene	—	32	221	1.165	—
	Pyrrole	16	—	131	0.969	5.4×10^{-15}

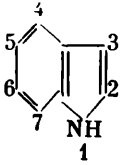
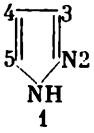
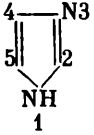
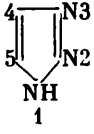
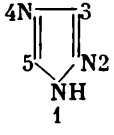
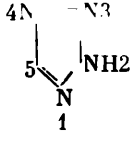
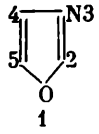
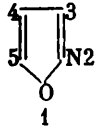
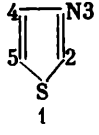
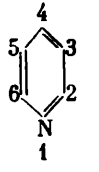
	Indole	48	52.5	254	—	—
	Pyrazole	—	70	188	—	3.0×10^{-12}
	Imidazole	—	90	256	—	1.1×10^{-7}
	1,2,3-Triazole	—	23	204 (at 740 mm Hg)	—	—
	1,2,4-Triazole	—	121	260	—	2×10^{-12}
	1,2,3,4-Tetrazole	—	155	Sublimes	—	—

Table 9.1 (continued)

Formula	Name	Stabilization energy, kcal/mole	m.p., °C	b.p., °C	Density, d_4^{20}	K_b^{25}
	Oxazole	—	—	70	—	—
	Isoxazole	—	—	—	—	—
	Thiazole	—	—	116.8	1.199	3.3×10^{-12}
	Pyridine	21	−42	115.3	0.982	1.7×10^{-9} (at 27°C) 6.46×10^{-6}

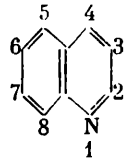
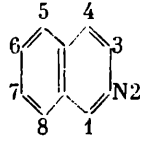
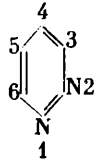
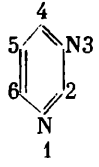
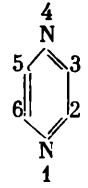
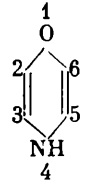
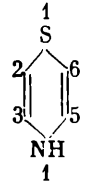
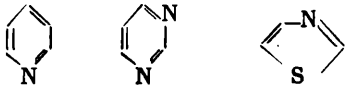
	Quinoline	55	−19.5	237.7	1.095	6.3×10^{-10}
	Isoquinoline	—	+23	243	1.0986	3.6×10^{-10}
	Pyridazine	—	−8	208	1.107	—
	Pyrimidine	—	+22	124	—	2.0×10^{-13} (at 20°C)

Table 9.1 (continued)

Formula	Name	Stabilization energy, kcal/mole	m.p., °C	b.p., °C	Density, d_4^{20}	K_b^{25}
	Pyrazine	—	53	118	1.031 (at 61°C)	4×10^{-14} (at 20°C)
	Oxazine	—	—	—	—	—
	Thiazine	—	—	77	—	—

ry activity, and the hetero-atom displays the presence of a free pair of electrons and is active in a nucleophilic way, just as in the aliphatic compounds of the corresponding functions.

The names of heterocycles are trivial and have not been unified according either to the structural principle or to the endings. The names of substituted heterocyclic compounds are built in the same way as those of substituted aromatic hydrocarbons. The position of the substituent is designated by a numeral in accordance with the numbering system adopted for each heterocycle. Besides, in the simplest cases the position of substituents is labelled as α, α', β, β' or γ (the last one is used for six-membered rings), the carbon atoms nearest to the hetero-atom being designated by the letters α and α', and those coming next by β and β'. There is still another method of building the names of heterocyclic compounds, according to which they are regarded as systems in which the CH group of an aromatic hydrocarbon (or a simpler heterocycle) is replaced by a hetero-atom. According to this system, the name of a heterocyclic compound is built as the name of a hydrocarbon (or the corresponding simpler heterocyclic ring) with prefixes *oxa*, *aza*, *thia*, which denote the replacement of the CH group by an oxygen, nitrogen, or sulphur atom; for instance,

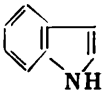


Pyridine or azabenzene

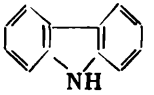
Pyrimidine or 1,3-diazabenzene or 3-azapyridine

Thiazole or 3-azathiophene

Such names are practically used in more complicated cases—for those rings which have not yet been given trivial names. For heterocyclic rings fused with a benzene ring one may (in more complicated cases as well) use the prefix *benz* (or *benzo*) in the same way as for condensed aromatic compounds, namely,



Indole or 2,3-benzopyrrole



Carbazole or 2,3,4,5-dibenzopyrrole

The commission of the International Union on Pure and Applied Chemistry has adopted a new nomenclature for heterocyclic compounds. The names are composed of the prefixes indicating the hetero-atom (*aza* for N, *oxa* for O, *thia* for S)*, which are preceded by

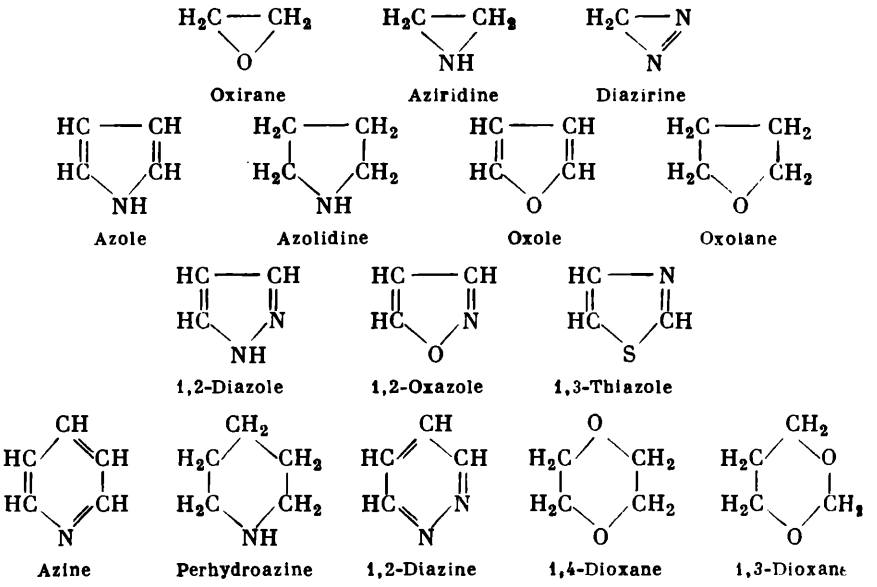
* When two vowels come together, then "a" of the prefix is omitted.

the prefixes *di-*, *tri-*, and so on, according to the number of heteroatoms present in the ring; then follows the stem denoting the number of members in the ring (*-irine* or *-irane* for three-membered, *-en* for four-membered, *-ole* for five-membered, *-in* for six-membered); then follow the suffixes for saturated and unsaturated compounds, as is the usual case in ordinary nomenclature (only for saturated nitrogen-containing rings there have been adopted the suffixes *-ine* and *-irine*).

Below are given some examples of the stem + suffix systems (the number of members is designated by a numeral, the designations for nitrogenous rings being enclosed in parentheses):

	Saturated	Unsaturated
3	-irane (N-iridine)	-irene (N-irine)
4	-etane (N-etidine)	-ete
5	-olane (N-olidine)	-ole
6	-ane (N-perhydro ...ine)	-in

This is illustrated by the following examples:



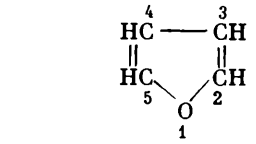
As seen, the new nomenclature coincides with the usual one in some cases and differs from it in others. For long-known heterocyclic compounds, use is made of trivial names (for example, pyrrole, pyridine, etc.). The new nomenclature has become widespread for three-membered rings.

Chapter 10

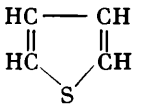
Five-Membered Heterocycles

10.1. Rings with One Hetero-Atom

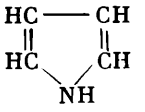
This group includes furan, thiophen and pyrrole and also their hydrogenated derivatives (the numbering of atoms common to five-membered rings is exemplified by furan):



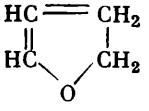
Furan



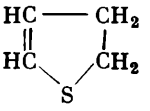
Thiophen



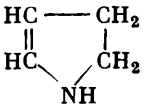
Pyrrole

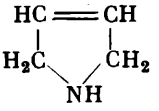


Dihydrofuran

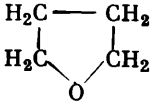


Dihydrothiophen

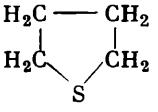




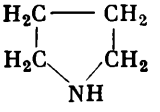
2,3-and 2,5-Dihydropyrrole or pyrroline



Tetrahydrofuran or furanidine



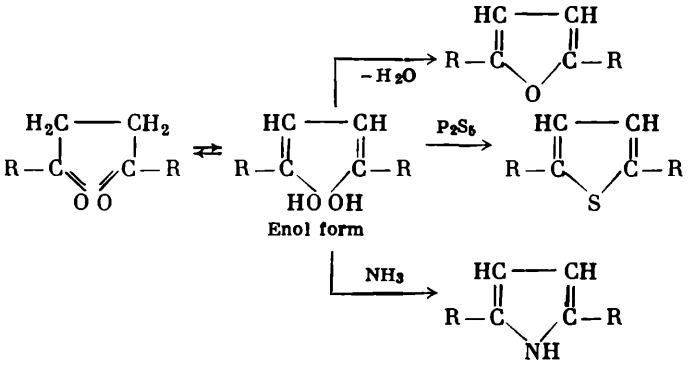
Tetrahydrothiophen or thiophane



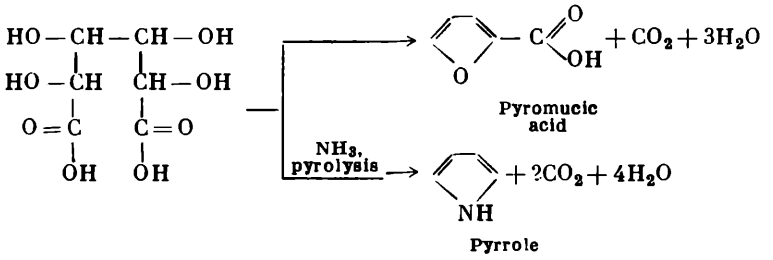
Tetrahydropyrrole or pyrrolidine

Let us consider the general methods of synthesizing aromatic five-membered heterocyclic compounds; special methods to each one of the group will be discussed in their description. Then we shall discuss the general properties of these compounds (by way of comparison), following which the specific properties of each compound will be described.

1. The starting materials in one of the most general methods of synthesizing aromatic heterocycles with one hetero-atom are 1,4-dicarbonyl compounds which are reacted with dehydrating agents (P_2O_5, CH_3COCl) to prepare furan and its homologues, with phosphorus pentasulphide to give thiophen and its homologues, and with ammonia to synthesize pyrrole and its derivatives:



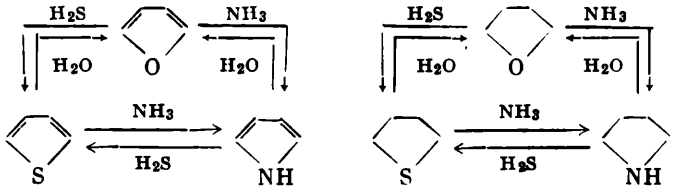
2. Five-membered heterocyclic compounds can be obtained from mucic acid and other dicarboxylic acids—the oxidation products of sugars. Dry distillation of mucic acid leads to pyromucic acid (α-furancarboxylic acid), and the pyrolysis of the ammonium salt of mucic acid is the usual route for synthesis of pyrrole. In the first case, one carboxyl group is lost in the form of CO_2, and in the second, complete decarboxylation takes place:



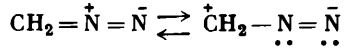
This type of reaction is not used for synthesis of thiophen and its derivatives but thiophen can be obtained by the action of P_2S_5 on succinic acid (see page 334).

3. Yu. K. Yuriev discovered the reaction of interconversion of five-membered heterocycles, both aromatic and hydrogenated ones, over a dehydrating catalyst (Al_2O_3) at 400°C in a current of H_2S, NH_3 or H_2O, respectively. Good yields are however obtained only

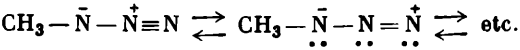
in the conversions of furan and furanidine (tetrahydrofuran):



4. Huisgen generalized a number of long-known reactions (discovered by Hantzsch, Dimroth and Kilico, and by others) and found a series of new reactions of "1,3-addition" to olefins, acetylenes, and also to nitriles, which result in closure into five-membered heterocycles. As an example of the systems to be added may serve aliphatic diazo compounds, hydrazoic acid and azides, nitrile oxides and nitrons. Huisgen provides an evidence that these reactions proceed as a monomolecular addition via the five-membered transition state; the molecules to be added must be capable of partial localization (in the resonance structure) of the positive and negative charges on the terminal atoms of triads; for example,



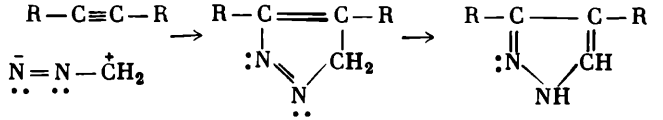
Diazomethane



Methylazide

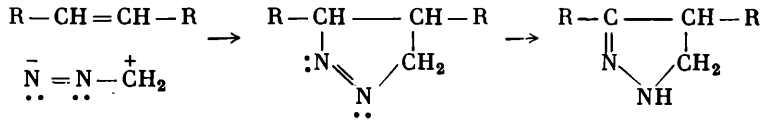
This type of addition has therefore been called **dipolar addition.** Addition across the multiple bond of a **dipolarophile** (by analogy with dienophiles, dipolarophiles are compounds, such as acetylene, olefin, etc., which add a dipolar triad) proceeds according to the following scheme:

The number of potentially dipolar compounds capable of 1,3-addition, as well as of the types of dipolarophiles, is great, and the number of possible combinations is still greater. Below are given some examples:

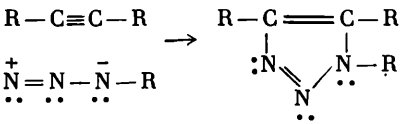


Diazomethane

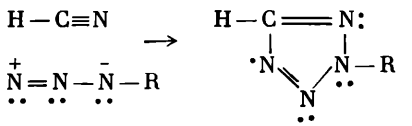
R,R-Pyrazole



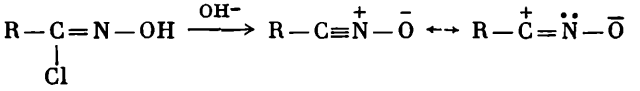
R,R-Pyrazoline



Substituted 1,2,3-triazole

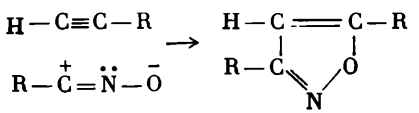


Substituted tetrazole

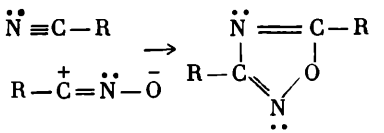


Acid chloride of hydroxamic acid

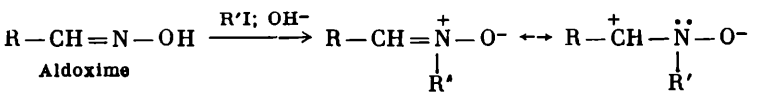
A nitrile oxide



A substituted isoxazole

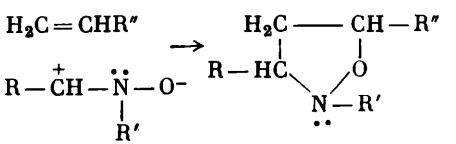


A substituted 1,2,4-oxadiazole



Aldoxime

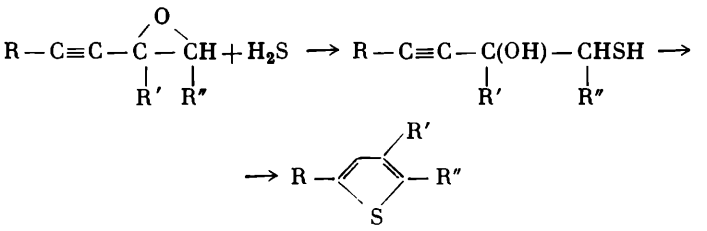
Nitron



Nitron

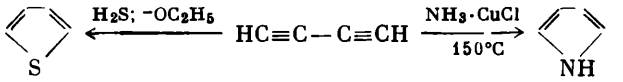
Substituted isoxazolidine

5. F. Ya. Perveev and coworkers developed (1948) a general method for synthesis of five-membered heterocyclic compounds with one hetero-atom, which is illustrated here by the example of synthesis of thiophens:



Instead of hydrogen sulphide, use may be made of hydrogen selenide or ammonia (in which case pyrroles are obtained).

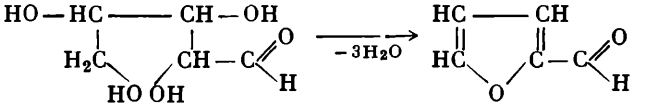
6. Schulte worked out the synthesis of five-membered heterocycles with one hetero-atom starting with diacetylene:



A. Furan

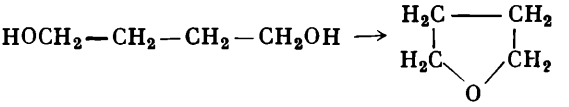
Synthesis of Furan and Its Derivatives. The general method of synthesizing furan or its derivatives consists in dehydrating aliphatic 1,4-diols or 1,4-diketo compounds.

1. The dehydration of pentoses gives furfural:

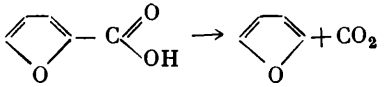


2. When γ-diketo compounds are heated with dehydrating agents, they are converted into the homologues of furan (see page 326).

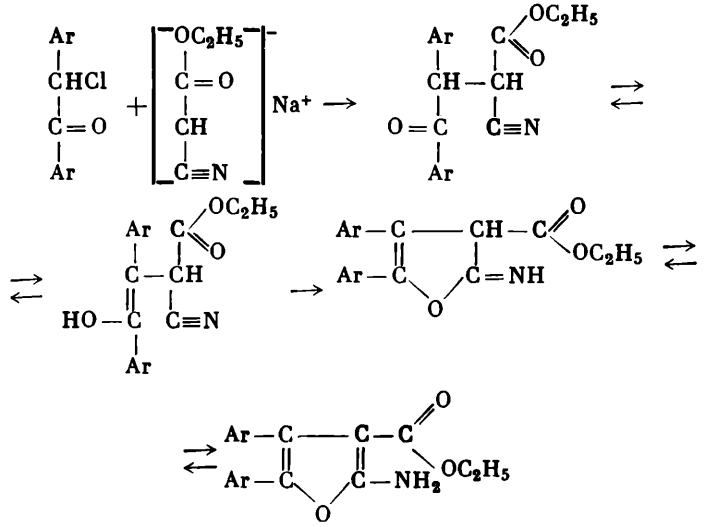
3. Tetrahydrofuran is prepared by dehydrating 1,4-butanediol:



4. Furan is synthesized by decarboxylation of pyromucic acid:

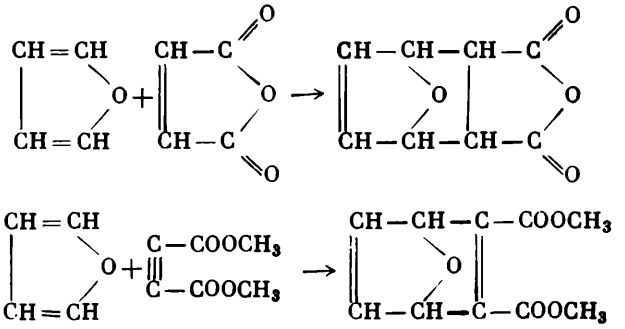


5 Substituted α-aminofuran can be synthesized by the method proposed by T. I. Temnikova:

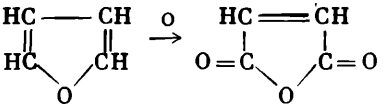


Cyclization with addition of a hydroxyl (or amino) group to the nitrile group is a widely used method of synthesizing furan derivatives. It will be discussed later for the synthesis of purine derivatives according to Traube.

Properties of the Furan Ring. Furan possesses a dual set of properties: it behaves on the one hand as aromatic substances and on the other as ordinary dienes. Furan undergoes addition reactions more readily than other heterocycles. The ability to participate in addition reactions is more characteristic of furan than of other heterocycles. The most striking example is the participation of furan in diene synthesis with dienophiles such as maleic anhydride or an ester of acetylenedicarboxylic acid:

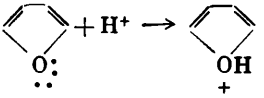


Furan is considerably more readily oxidized and resinified by the action of acids than thiophen. It can be oxidized to maleic anhydride:



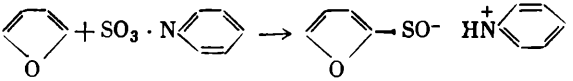
The air oxidation of furan is accompanied by polymerization.

The resinifying action of mineral acids consists in that furan is first protonated at the oxygen:

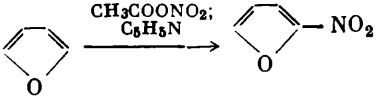


In this process a pair of electrons is removed from the conjugation with double bonds, the aromatic character is disturbed and the diene is polymerized and resinified.

In spite of its low stability, furan is capable of undergoing electrophilic substitution reactions (sulphonation, nitration, Friedel-Crafts acylation, halogenation), though the conditions of these reactions sharply differ from those in the case of benzene. For example, furan has been sulphonated with pyridinesulphotrioxide (A. P. Terentiev):

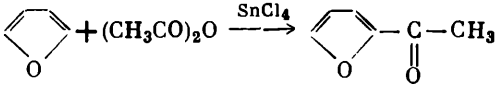


Furan can be nitrated with acetyl nitrate in the presence of pyridine:



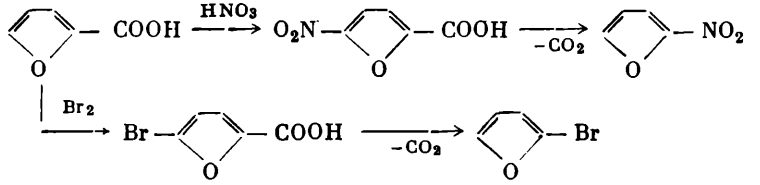
Direct interaction with bromine may lead to the oxidation and resinification of furan. Therefore, complexes of pyridine or dioxan with bromine are used for bromination. In all cases, α-hydrogen atoms are replaced first.

Acetyl substituents are introduced into furan or its derivatives by the Friedel-Crafts reaction, milder catalysts being however used instead of aluminium chloride (G. L. Stadnikov, Ya. L. Goldfarb):

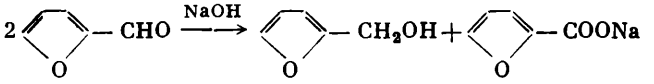


Furan derivatives containing electron-attracting substituents, such as CHO, COOH, NO_2, are more stable and are not so readily resini-

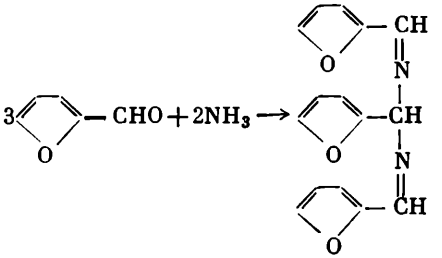
fied. It is therefore more convenient to nitrate or chlorinate a furan derivative, say, pyromucic acid, and then to remove the carboxyl group:



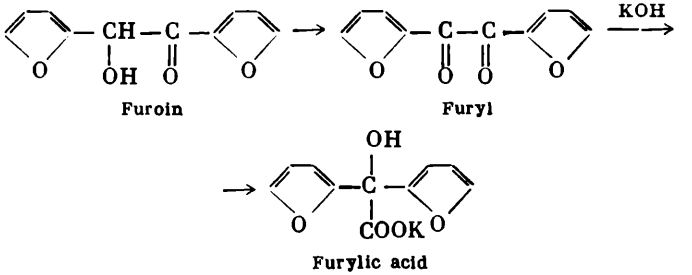
Of greatest importance among furan derivatives is **furfural,** an aldehyde whose properties resemble those of aromatic aldehydes. It enters into reactions typical of aromatic aldehydes, say, into condensation reactions of the benzoin type, the Cannizzaro reaction:



With ammonia furfural forms **hydrofuramide** (an analogue of hydrobenzamide):



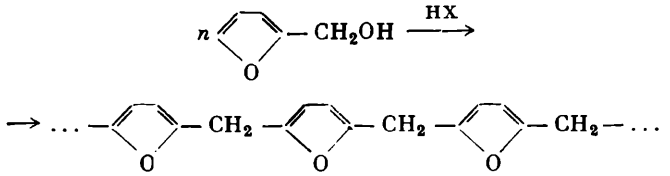
The ketonic alcohol **furoin,** which is formed by the condensation of furfural under the action of KCN, is readily oxidized, like benzoin, to a diketone, **furyl,** which in the presence of alkali rearranges to **furylic acid** (benzilic acid rearrangement, page 182):



Furylic acid

Furfural readily enters into reactions of condensation, say, with phenols. This results in the formation of resins similar in properties

to phenol-formaldehyde resins (page 142). Furfural is also used for the manufacture of **furyl alcohol** (hydrogenation), **tetrahydrofuryl alcohol**, etc. Furyl alcohol is polymerized by the action of mineral acids:



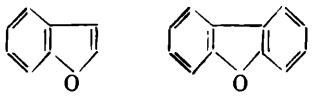
These resins can be used as coatings and glues.

Furan undergoes hydrogenation over nickel or platinum catalysts to give **tetrahydrofuran** which can also be obtained from 1,4-butanediol. Tetrahydrofuran (furanidine, THF) is used in some methods of production of adipic acid and nylon. It is a valuable solvent. For example, it turned out that with tetrahydrofuran used as a solvent it is possible to synthesize organomagnesium compounds with magnesium at a double bond (Normant); as known, the Grignard reagent cannot be synthesized from vinyl halide in diethyl ether.

Tetrahydrofuran forms the basis of five-membered cyclic forms of sugars, which are therefore called **furanoses** (see Volume II). Its dipole moment ($\mu = 1.7$D) is considerably higher than that of furan ($\mu = 0.7$D), a fact which demonstrates the delocalization of the *p*-electrons of the oxygen atom in furan.

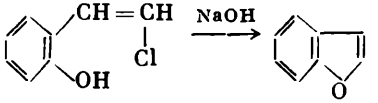
B. Condensed Systems with the Furan Ring

Such compounds are contained in coal tar, for example,

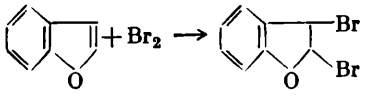


Coumarone Dibenzofuran

The structure of coumarone follows from the following method of its preparation:

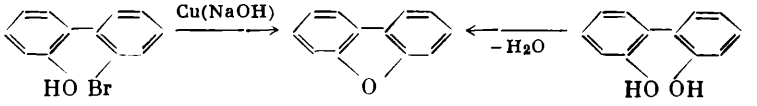


Like furan, it is readily oxidized and resinified by the action of acids. Halogens add on to coumarone across the double bond:



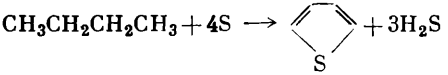
Unlike furan, coumarone does not enter into diene synthesis.

Dibenzofuran should have been classed by its properties as belonging to the derivatives of biphenyl from which it can readily be obtained:

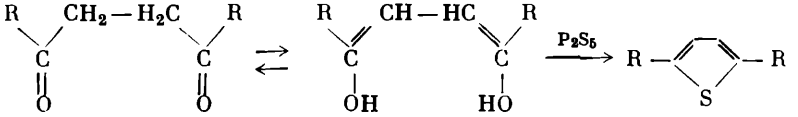


C. Thiophen

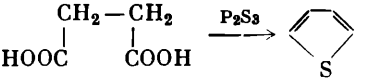
Thiophen is a companion of benzene in the commercial production of the latter from coal tar. It was detected as an impurity in benzene by Victor Meyer who also established its structure. Thiophen is present to about 0.5 per cent in technical-grade coal-tar benzene. The boiling point of thiophen (84.1°C) is close to that of benzene (80.4°C) and therefore it cannot be extracted by ordinary distillation. Thiophen is prepared on the commercial scale from butane or butylene and sulphur at temperatures of the order of 700°C:



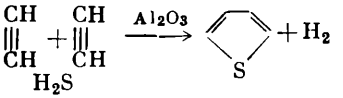
Thiophen and its homologues have been obtained from γ-diketones and P_2S_5



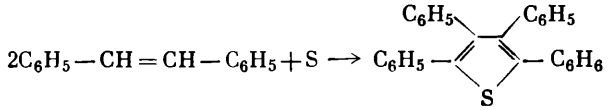
and also by heating salts of succinic acid with P_2S_3, which in this case plays the role of a reducing agent:



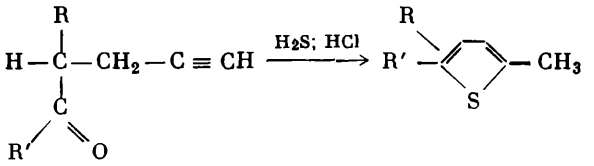
Acetylene reacts with hydrogen sulphide at 400-450°C over alumina to give thiophen (A. E. Chichibabin):



Thiophen derivatives can also be prepared by heating certain olefins with sulphur. For instance, tetraphenylthiophen is obtained from stilbene:

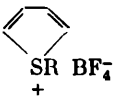


When acted on by hydrogen sulphide and hydrogen chloride in alcoholic solution 1-alkyn-5-ones undergo ring closure into thiophen derivatives (the yield amounting to 70 per cent):

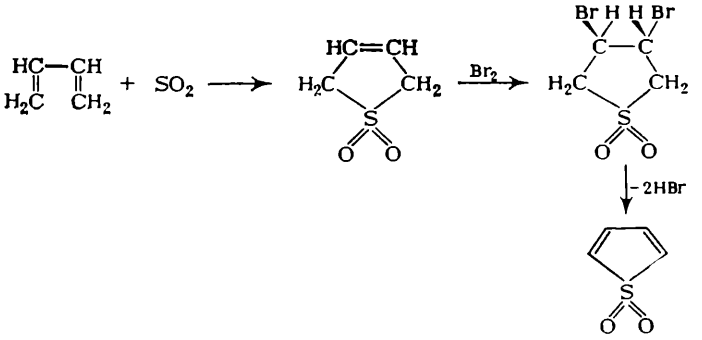


Many derivatives and homologues of thiophen are conveniently obtained from thiophen itself since it is a sufficiently stable and reactive compound.

Chemical Properties of Thiophen. Thiophen resembles benzene more closely than furan and pyrrole. The π-electrons of thiophen are incapable of addition reactions and, unlike furan, thiophen does not react with dienophiles. The sulphur atom in thiophen is inert and does not add methyl iodide. Thiophen is not oxidized by peroxides and by any oxidizing agents either to the sulphoxide or sulphone. Tertiary oxonium compounds, such as $R_3\overset{+}{O}\ BF_4^-$, however, alkylate thiophen at the sulphur atom with the formation of

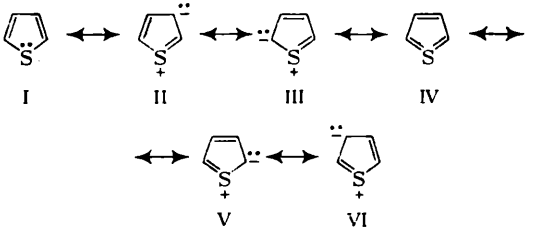


Thiophen sulphone nevertheless exists and can be prepared by the 1,4-addition of SO_2 to butadiene with the subsequent addition of bromine and elimination of hydrogen bromide by alkali:



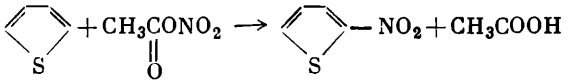
It is possible that the high stability of the aromatic ring of thiophen is mainly associated with the more complete equilibration of the π-electron density in the thiophen molecule as compared with

the molecules of pyrrole and furan since in the given case the delocalization is likely to involve the *d*-orbitals of the sulphur atom. In terms of resonance theory it may be stated thus: the resonance involves the favourable contributing (canonical) structure IV which cannot be taken into account in the case of pyrrole or furan since nitrogen and oxygen are not capable of expanding their outer electron shell beyond the octet (they are in the minor period):

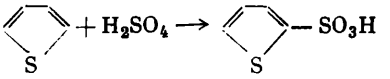


Thiophen enters into many electrophilic substitution reactions, being much more reactive than benzene.

Though thiophen is considerably more stable towards acids and oxidizing agents than furan, it can however be oxidized by nitric acid, its molecule being degraded. Thiophen is therefore nitrated by acetyl nitrate:

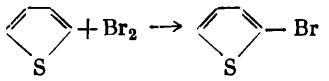


In contrast to benzene, thiophen is sulphonated by sulphuric acid in the cold:



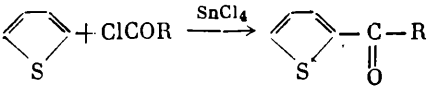
This reaction is employed for the purification of coal-tar benzene from an impurity of thiophen.

Thiophen is halogenated by bromine and chlorine at a low temperature in the absence of catalyst. This results in the formation of mono- and polyhalothiophens:

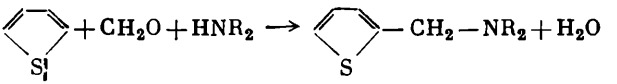


Acylation by the Friedel-Crafts method proceeds smoothly at the α-position if the catalyst used is stannic chloride (G. L. Stad-

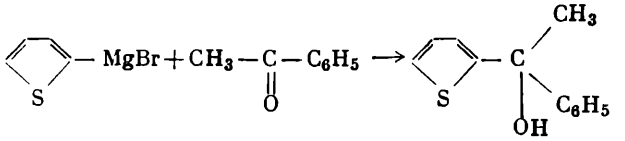
nikov, Ya. L. Goldfarb) or boron trifluoride:



Thiophen readily condenses with aldehydes and, in particular, enters into the Mannich reaction:

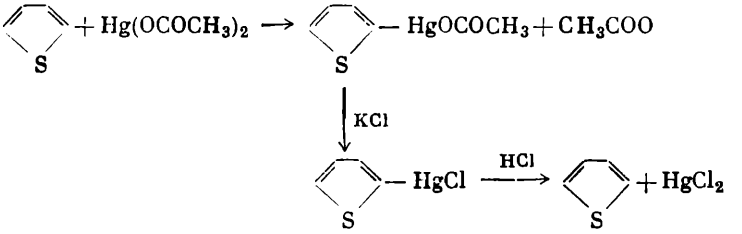


Bromothiophen forms organomagnesium compounds in a normal way, which can be used in the synthesis of thiophen derivatives. For example,



The reduction of nitrothiophen gives aminothiophen which, like aminofuran, is very readily oxidized and cannot be diazotized. But those aminothiophens which have electron-attracting substituents in the ring are diazotized in a normal way.

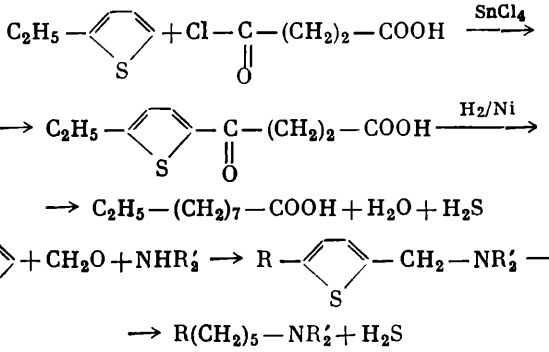
A reaction characteristic of thiophen and furan is the mercuration with mercuric acetate even in the cold; depending on the conditions of the reaction, mono- or polymercurated compounds can be obtained. On treatment with hydrochloric acid thiophen is recovered by the mercury derivative:



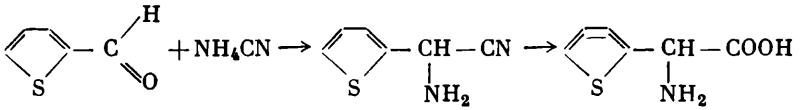
This reaction is also used to separate thiophen from benzene which is mercurated only when heated, and to determine the content of thiophen in benzene.

When thiophen (and its derivatives) is acted on by Raney nickel, sulphur is eliminated and the carbon skeleton is hydrogenated. Based on the ease with which electrophilic substituents are introduced into thiophen, Goldfarb suggested using the hydrogenation reaction for synthesis of the various organic compounds, say, ali-

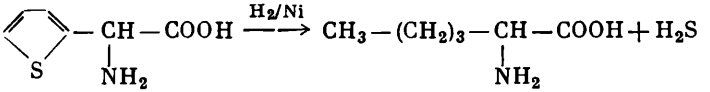
phatic acids or amines with a long saturated chain:



A method of synthesizing amino acids has been developed (Ya. L. Goldfarb, B. P. Fabrichny, I. F. Shalavina), which is analogous in principle to the previous one:



The Zelinsky-Strecker method gives α-thienylalanine which on hydrogenation gives the corresponding amino acid:



The synthesis may be varied, depending on the homologues or substituted derivatives of thiophen aldehyde used as the starting material.

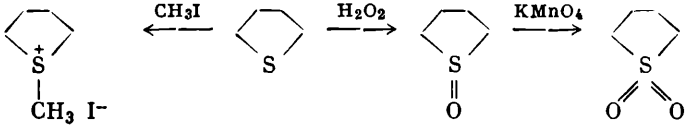
As we have seen, thiophen is more aromatic than furan. This is reflected in the higher stability of the thiophen ring, in the masked characteristic properties of the double bonds, and in the greater resonance energy. But the diene character of furan is more pronounced than that of thiophen. This difference could possibly be partly accounted for by the increased electronegativity of oxygen as compared with sulphur and, as a result, by the lower ability to donate a pair of electrons for the formation of an aromatic sextet and by the different degrees of the *p*- and *s*-character of free pairs of electrons in oxygen and sulphur.

D. Tetrahydrothiophen (Thiophane)

Apart from Δ^2- and Δ^3-dihydrothiophens, the reduction of thiophen (with sodium in ammonia and alcohol) gives tetrahydrothiophen. Nickel and platinum catalysts cannot be used for hydrogena-

tion because they are poisoned by thiophen and tetrahydrothiophen. The tetrahydrothiophen ring can be formed as the result of cyclization as well.

Thiophane and its homologues are contained, along with aliphatic thioesters and mercaptans, in sulphur-containing crude petroleum. In contrast to thiophen, the electrons of sulphur in the thiophane ring are "free"—they do not participate in the formation of an aromatic sextet of electrons. It is for this reason that thiophane, like ordinary thioesters, is readily oxidized and can be oxidized to the sulphoxide and sulphone; alkyl iodides alkylate thiophane with the formation of sulphonium salts:



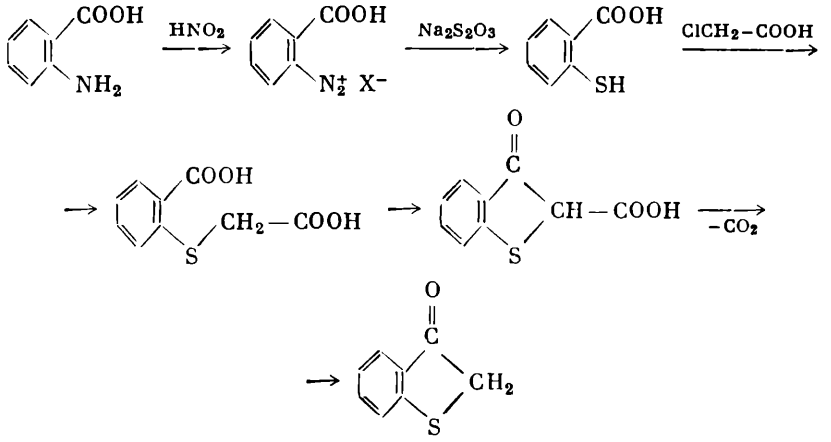
The most important natural compounds whose molecules contain the thiophane ring are biotins (page 368).

E. Benzothiophen and Its Derivatives

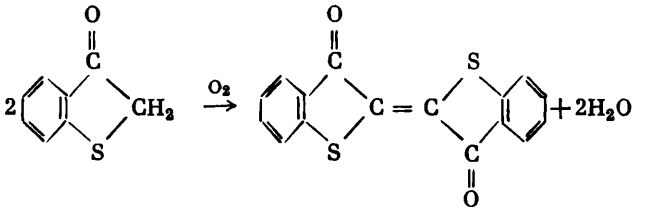
Benzothiophen resembles naphthalene in its properties. Its most important derivative is thioindoxyl:

Benzothiophen Thioindoxyl

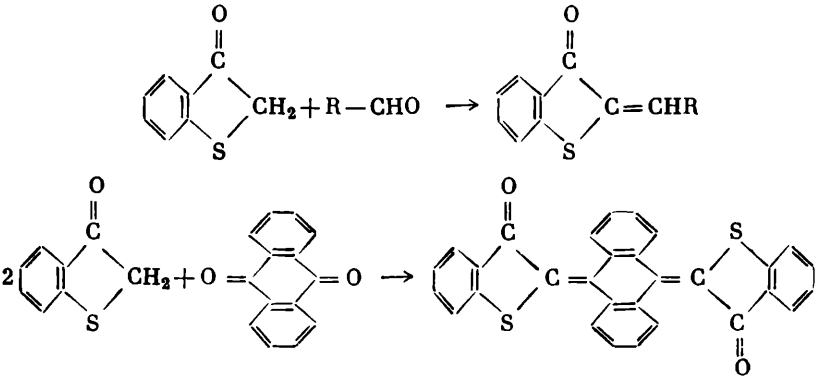
Thioindoxyl is synthesized in the same way as indoxyl (page 358):



When oxidized with oxygen thioindoxyl gives a red dye—**thioindigo:**



Thioindoxyl condenses with aldehydes and ketones to form **thioindigoids:**



Some thioindigoids also find application as dyes.

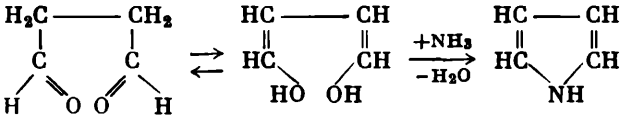
F. Pyrrole

Pyrrole was detected in bone oil (the product of dry distillation of bones) and in a small amount in coal tar (Runge, 1834). The structure of pyrrole was established in 1870 by A. Baeyer.

The pyrrole and hydrogenated pyrrole rings enter as a structural unit into the composition of important biogenic compounds—amino acids (proline, hydroxyproline, tryptophan), alkaloids, hemoglobin, a number of oxidation coenzymes, chlorophyll, etc.

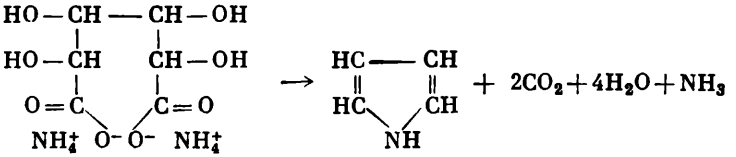
Pyrrole (or its homologues and derivatives in a number of cases) can be synthesized by the following reactions which provide information on its structure.

1. The action of ammonia on 1,4-dicarbonyl compounds (Paal-Knorr synthesis):



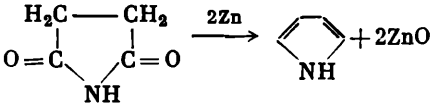
This method is analogous to the synthesis of furan and thiophen and establishes the structural resemblance between pyrrole compounds and those of furan and thiophen.

2. An ordinary method of synthesis of pyrrole, which is closely related to the synthesis of α-furancarboxylic (pyromucic) acid, is the pyrolysis of ammonium mucate:

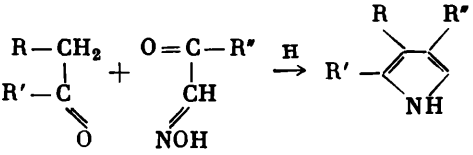


If a primary amine is used instead of ammonia, N-substituted pyrroles are obtained (see the synthesis of nicotine, Volume IV).

3. The distillation of succinimide with zinc dust yields pyrrole:

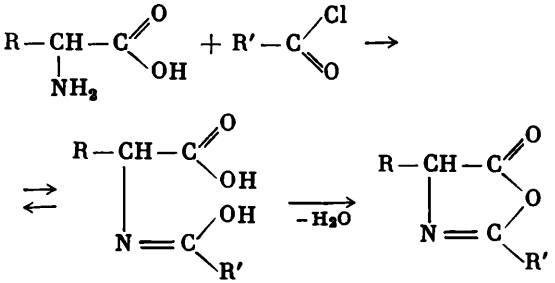


4. The reduction of a mixture of a ketone and an isonitrosoketone (see Volume I) gives homologues or substituted pyrroles (Knorr):

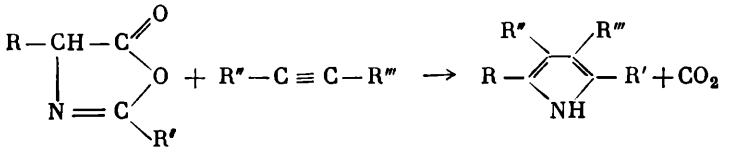


The reaction also gives an aminoketone as an intermediate.

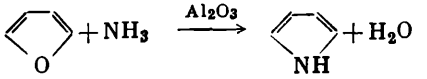
5. In 1964 Huisgen proposed a new method for synthesizing pyrrole derivatives from azlactones and, hence, from nitrogen-acylated α-amino acids (in 60-90 per cent yield):



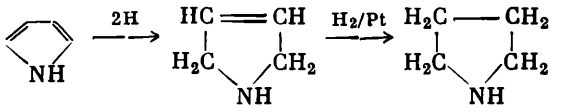
Azlactone or R,R′-oxazolone



6. When furan vapour together with ammonia is passed over aluminium oxide at 400°C, pyrrole is formed (Yu. K. Yuriev):

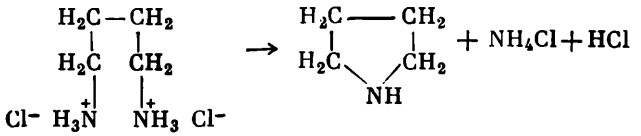


Properties of Pyrrole. When pyrrole is reduced with nascent hydrogen (but not in an acid medium), Δ^3-**pyrroline** is formed; when the latter or pyrrole itself is catalytically hydrogenated, **pyrrolidine** (tetrahydropyrrole) results:

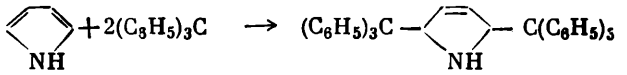


Pyrrole Δ^3-Pyrroline Pyrrolidine

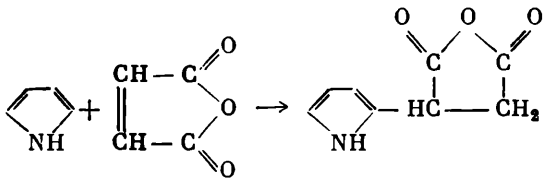
Pyrrolidine can also be obtained by dry distillation of putrescine hydrochlorate:



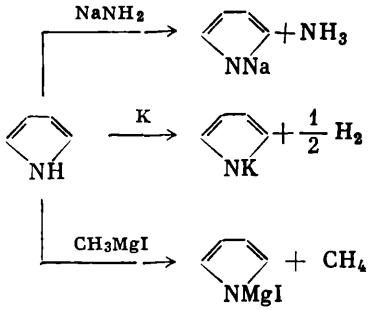
Thus, pyrrole behaves towards nascent hydrogen in the same way as a diene. It also reacts analogously with the free triphenylmethyl radical:



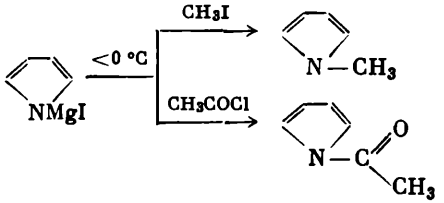
In contrast to furan, pyrrole does not show other diene reactions and with maleic anhydride it does not give the typical condensation but instead forms 2-pyrrolesuccinic anhydride:



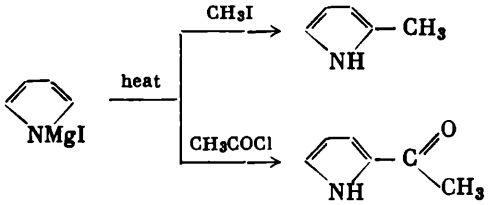
As previously mentioned, the nitrogen atom of pyrrole is completely devoid of basic properties, and its imino group, like phenol, exhibits very weak acidic properties. N-substituted metallic derivatives of pyrrole, which are widely used in syntheses, can be prepared by a number of reactions:



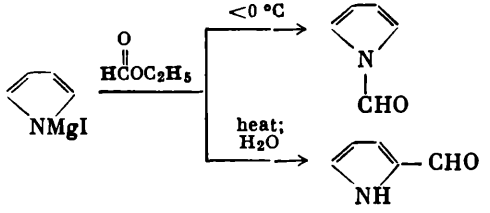
The alkylation and acylation of these metallic derivatives (at present, preference is given to pyrrylmagnesium halides) at a temperature below 0°C yield, respectively, N-alkyl- and N-acylpyrroles:



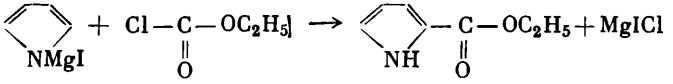
and α-alkyl- and α-acylpyrroles, respectively, on heating:



The place of acid chlorides may be taken by esters. An ester of formic acid gives N-formylpyrrole at a low temperature and pyrrole-α-aldehyde at a high temperature:

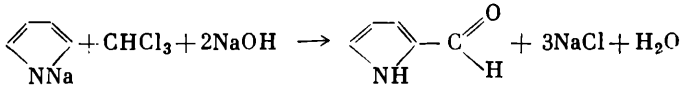


When pyrrylmagnesium halide is allowed to react with chlorocarbonic ester, an ester of α-pyrrolecarboxylic acid is obtained:

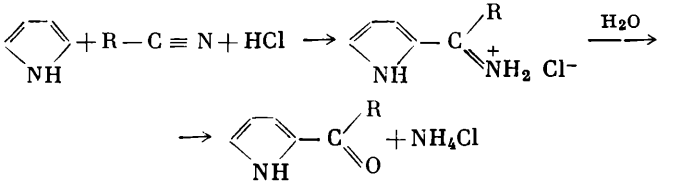


Homologues of pyrrole can also be prepared by reducing the carbonyl compounds of pyrrole (for example, by the Wolff-Kishner method).

In a number of reactions, the N-substituted metallic derivatives of pyrrole resemble the phenoxides of alkali metals. For example, aldehydes can be synthesized by the Reimer-Tiemann reaction as well (page 160).



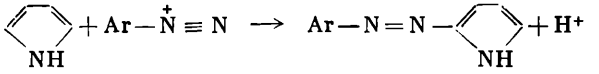
Although pyrrole is very sensitive to acids (it is polymerized), pyrrole aldehydes and ketones can nevertheless be obtained by using the Hoesch reaction applicable to phenols:



where R = H or hydrocarbon radical.

These reactions demonstrate the special sensitivity of the α-positions of pyrrole (just as of the *ortho*-positions of phenols) towards electrophilic attacks. If both α-positions are occupied, most of these and the following reactions take place at the β-position.

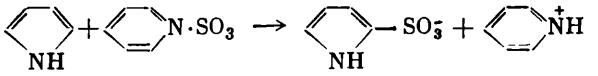
Pyrrole may serve as the azo component in azo-coupling reactions:



This is another feature common to pyrrole and phenols.

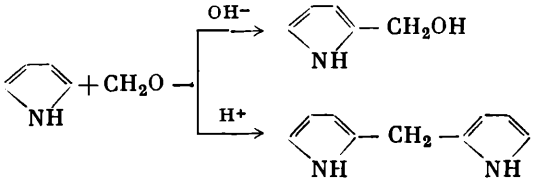
Of the main reactions of electrophilic aromatic substitution mention should be made of bromination and iodination which give tetrabromopyrrole and tetraiodopyrrole (an antiseptic called Iodole), and chlorination with sulphuryl chloride which is the simplest route to α-chloropyrrole, and also sulphonation by the Terentiev method using pyridinesulphotrioxide (the method of sulphonation of "aci-

dophobic" compounds):



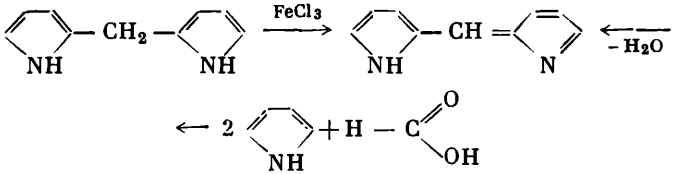
Since pyrrole is "acidophobic", nitration with acid is impossible, and α-nitropyrrole is obtained by the action of ethyl nitrate on pyrrole.

Exceedingly important are reactions of condensation of pyrrole with formaldehyde and formic acid. In alkaline medium, formaldehyde hydroxymethylates pyrrole, and in acid medium the reaction goes further—2 moles of pyrrole are crosslinked by a methylene bridge into the α-position with the formation of dipyrrylmethane (pyrromethane):

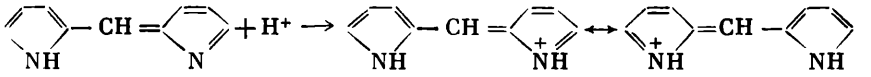


This reaction has been thoroughly studied for the homologues of pyrrole as well.

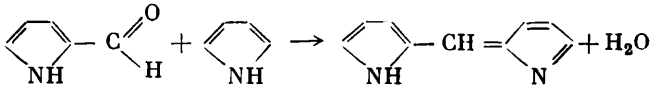
Dipyrrylmethane is oxidized with ferric chloride, losing two hydrogen atoms and being converted into coloured pyrromethene; the same product is obtained by the direct condensation of pyrrole with formic acid in acid medium.



Pyrromethenes form stable salts with acids; after the pyrrolenine ring is protonated both rings assume identical structures and become indistinguishable:



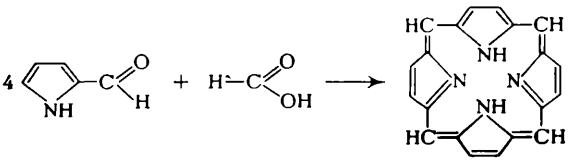
Pyrromethenes can also be obtained by a condensation reaction of the following type:



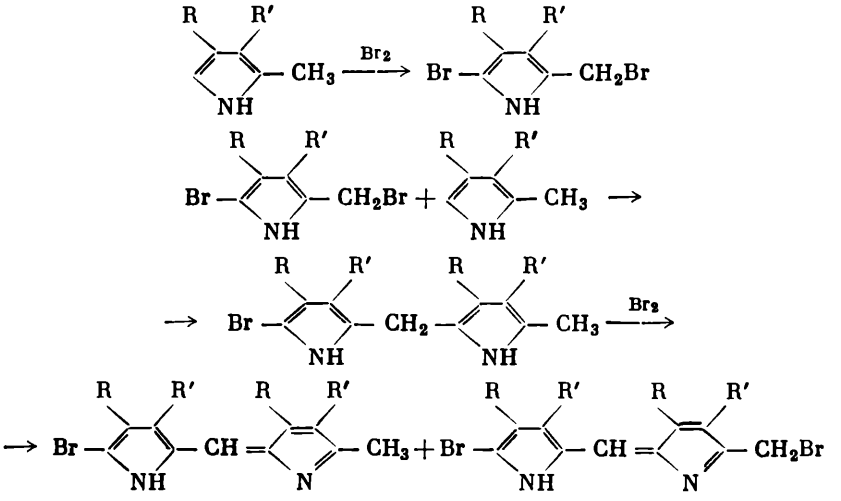
All these reactions proceed more readily with the homologues of pyrrole (provided the α-position is free) than with pyrrole itself.

G. Porphin. Porphyrins

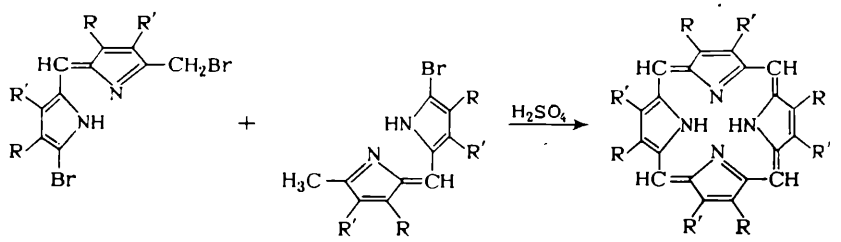
When pyrrole-α-aldehyde is heated with formic acid, a new, exceedingly important aromatic heterocyclic system is formed in about 1 per cent yield, which is the main constituent part of chlorophyll and blood haem and is known as **porphin** (Hans Fischer):



These high-melting (decomposing above 360°C) dark-red crystals are stable to the action of acids. The two hydrogen atoms linked to nitrogen atoms can be replaced by a metal with the aid of MgO, $FeCl_3$, $Cu(OCOCH_3)_2$. Fischer developed some other methods for synthesis of porphins with unsymmetrically arranged substituents, thereby discovering the route for synthesis of haemin and chlorophyll*. The following is an important method:



* A complete synthesis of haemin was achieved by H. Fischer in 1929, and his contributions were rewarded with a Nobel Prize (1930).—*Tr.*

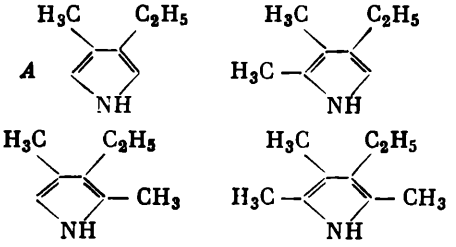


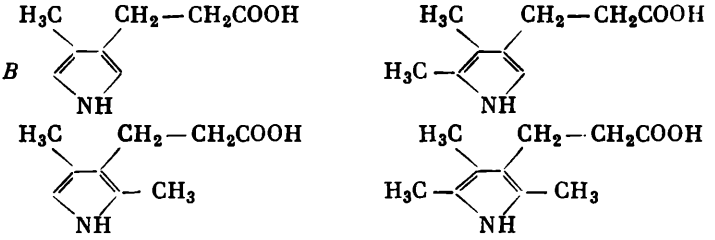
Porphins are true stable aromatic compounds capable of undergoing sulphonation, nitration, Friedel-Crafts acylation (if some R = H). Their π-electrons are delocalized and, in fact, the molecule has a symmetrical structure (the double bonds are written arbitrarily in the formula given). The counting of delocalized electrons (11 double bonds + 4 free electron pairs of nitrogen; 22 + 8 = 30 electrons) shows that the porphin system satisfies the requirements of Hückel's rule for aromatic systems: $4n + 2$ ($7 \times 4 + 2 = 30$).

Porphins with hydrocarbon substituents in the pyrrole and pyrrolenine rings are called **porphyrins.**

Haem. The red colouring matter of blood, which transports oxygen in the blood stream from the lungs to the cells of the body is the protein **globin** linked to a derivative of porphyrin containing ferrous iron in the centre of the molecule (this heterocyclic compound is called **haem**). The linkage between globin and haem is probably a coordinate bond—the nitrogen of histidine (one of the amino acids of the protein globin) is linked to the iron atom of the haem molecule. Haem linked to globin through a coordinate bond forms **haemoglobin** which readily combines with an oxygen molecule to yield oxy**haemoglobin**, in which form oxygen is carried in the blood stream to various parts of the organism.

Haem is separated from globin by the action of hydrochloric acid. The iron of haem, which is in the ferrous state, is oxidized (in air) to the ferric iron and haemin is formed, which differs in composition from haem by the presence of a chloride ion. Haemin forms bright-red crystals. When broken down by hydrogen iodide it gives a mixture of homologues of pyrrole (group *A*) and β-pyrrylpropionic acids (group *B*) (Nencki):



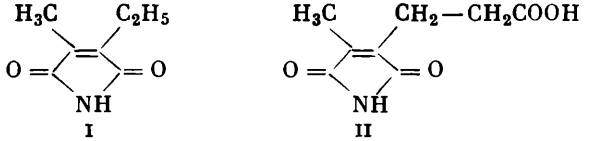


All these compounds were identified and synthesized by Hans Fischer using the Knorr method.

Thus, haemin, $C_{34}H_{32}N_4O_4FeCl$, consists of pyrrole rings with side chains. Analysis has shown that there are four pyrrole rings in haemin.

Under the action of acids in the presence of metallic iron haemin loses its iron atom and is converted into **protoporphyrin**. Functional analysis has detected the presence of two carboxyl groups in haemin, evidently those which are present in group *B* of the products resulting from the decomposition of haemin by hydrogen iodide. Moreover, by way of catalytic hydrogenation it has been established that there are two active double bonds, each of which can be hydrogenated to a secondary alcoholic group. Such a glycol is known as **haematoporphyrin**.

The hydrogenation of the two active double bonds of protoporphyrin leads to **mesoporphyrin**. When the latter is oxidized, products I and II are obtained, which are important in establishing the structure of the entire group of compounds:

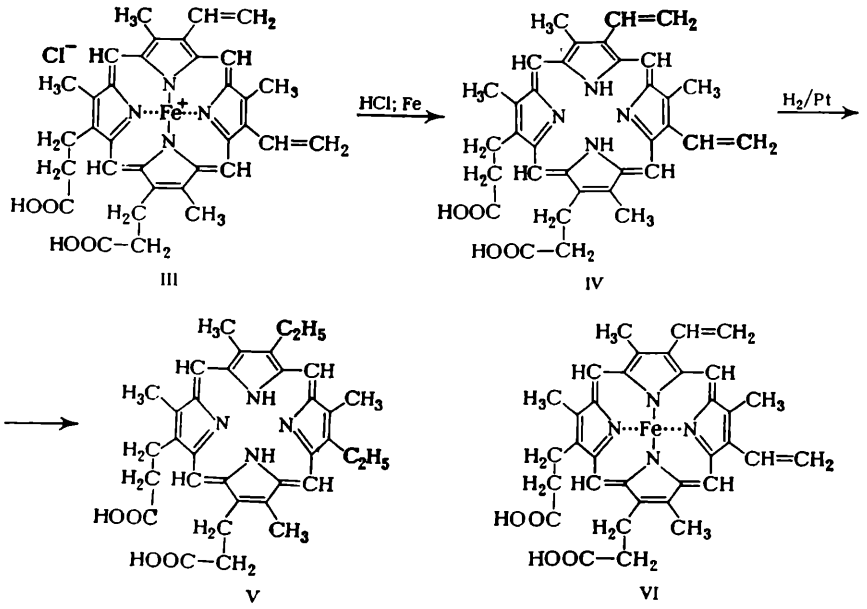


The oxidation of haemin gives product II only.

It is clear that the pyrrole rings in haemin were linked at the α-positions. But what bonds joined them? Since the products of degradation with hydrogen iodide (group *B* as well as group *A*) retain a methyl group or a hydrogen atom, it is clear that this linkage was formed via one carbon atom. Since the entire system of haemin and protoporphyrin is analogous in properties to the aromatic porphin structure described earlier, it is natural to assume that the carbon atom which links the pyrroles is, just as in porphin, in the form of a CH group joined by one double and one single bond. Both unsaturated bonds could belong to vinyl groups which on reduction (catalytic or with hydrogen iodide) are converted into ethyl groups.

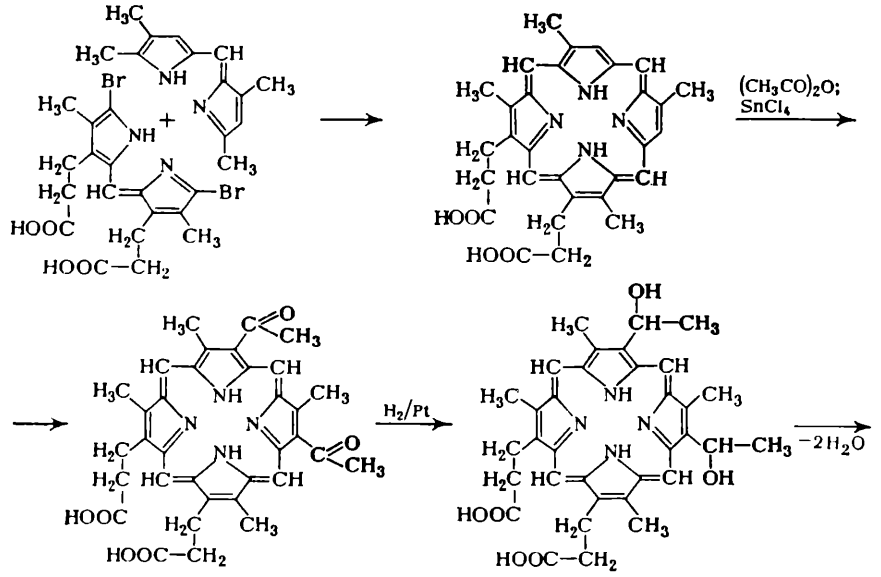
All this reasoning leads to formula III for haemin, formula IV for protoporphyrin and formula V for mesoporphyrin. Structure VI

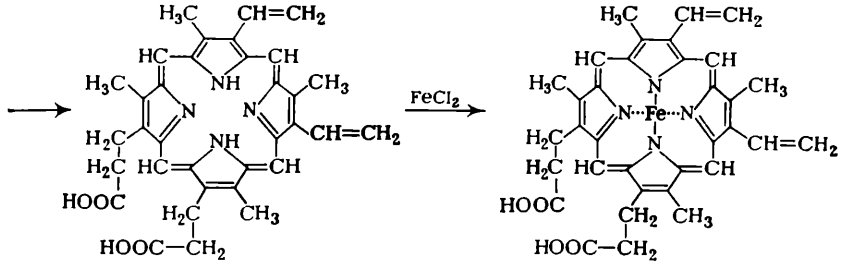
is assigned to haem:



III IV V VI

These structures were confirmed by synthesis (Hans Fischer):

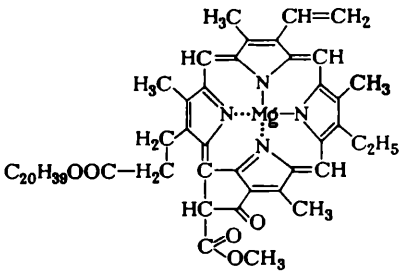




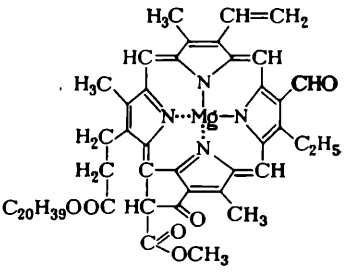
Chlorophyll. All green vegetable matter contains the alcohol-soluble pigment **chlorophyll**, with the help of which plants assimilate carbon dioxide from the atmosphere, converting it and water into oxygen and carbohydrates. As was shown by M.S. Tsvett (who discovered chromatography, a very important method at present, when he isolated chlorophyll from plants), by adsorbing a solution of chlorophyll on a solid adsorbent, it is possible to separate it into two individual substances—chlorophyll *a* and chlorophyll *b* differing somewhat in colour. Functional analysis has established the presence of a methyl group in chlorophyll *a* and of an aldehyde group in chlorophyll *b*. This is the only difference between them. Both chlorophylls are esters. Their *trans*-esterification, say, with ethanol, gives the alcohol **phytol** (see Volume I, page 394), while the chlorophylls themselves are converted into ethyl chlorophyllides.

When chlorophylls are treated with mineral acids, the magnesium ion is removed in the form of a complex ion and simultaneously the ester linkage is hydrolysed (this again yields the alcohol phytol). As a result, **pheophorbides** *a* and *b* are obtained, the investigation of which has provided principal data on the structure of chlorophylls. The action of hydriodic acid on chlorophylls (and, of course, on pheophorbides) leads, by a route which seems surprising at first glance, to the same mixture of the pyrrole derivatives of groups *A* and *B* (page 347) obtained by the analogous treatment of haemin.

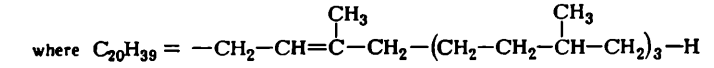
As the result of the experiments described and an extensive series of investigations, which cannot be outlined here (and which were carried out by Marchlewski, Nencki, Willstätter and H. Fischer), the following structures have been established for chlorophylls:



Chlorophyll a

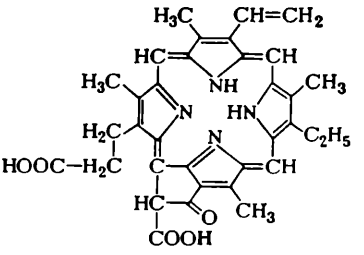


Chlorophyll b



Phytol residue

Pheophorbide *a* has the following structure:



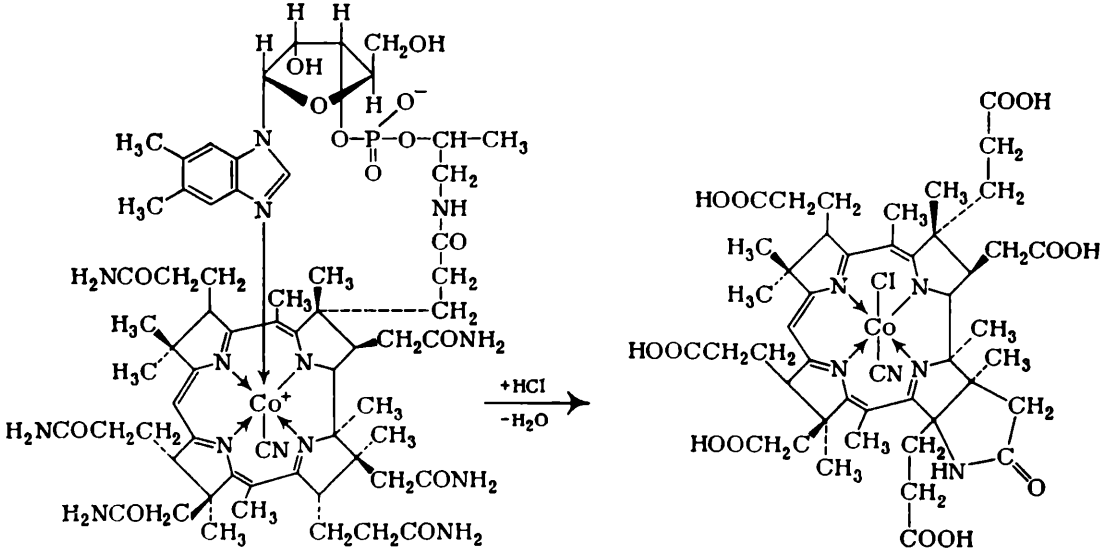
Pheophorbide a

A complete synthesis of chlorophyll was accomplished in 1960 by R. B. Woodward.

Vitamin B_{12}. In 1948 the American and English scientists (K. Folkers and L. Smith) succeeded in isolating from the liver extract of warm-blooded animals rubin crystals of vitamin B_{12} or cyanocobalamin, a porphyrin-cobalt complex.

This vitamin is given in microgram doses (up to 3 μg per day) to cure the lethal disease pernicious anaemia (but not leukemia) and, being complexed with a specific protein, participates, evidently as a coenzyme, in the functioning of hematogenic organs (bone marrow), namely in the production of red blood globules (erythrocytes).

The man's daily requirement of this vitamin is very low—from 1 to 5 μg, but its assimilation through the digestive tract is slow and incomplete, and therefore doses 100 times larger are required. The point is that cyanocobalamin can penetrate the intestine walls only when associated with the so-called internal factor—**mucoprotein**, which is secreted by the mucous membranes of the digestive tract; avitaminosis may develop because of a deficiency of this factor.

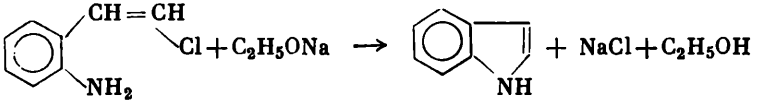

+HCl
-H2O

At present vitamin B_{12} is prepared microbiologically on the industrial scale, by the growth of Actinomycetes which produce this vitamin.

The structure of cyanocobalamin has been elucidated through the investigations carried out by Todd in Cambridge (see facing page) and by the X-ray studies performed by D. Crowfoot.

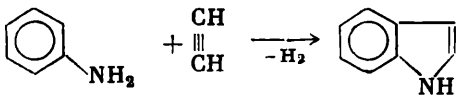
H. Indole (Benzopyrrole)

The structure of indole follows from its synthesis by the ring closure of *o*-amino-ω-chlorostyrene under the action of sodium ethoxide:



Indole

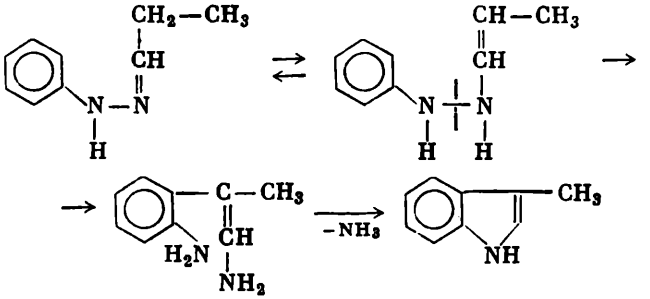
Indole can also be obtained by the Chichibabin reaction—a mixture of aniline vapour and acetylene is passed through red-hot tubes:



This reaction is analogous to the synthesis of pyrrole from acetylene and ammonia.

Indole homologues are most often synthesized by the reaction developed by Emil Fischer and commonly called the **Fischer indole synthesis**, in which the hydrazones of aldehydes or ketones are heated with zinc chloride, or by the Arbuzov reaction, in which the hydrazones are heated with a catalytic amount of cuprous chloride. These reactions are of little value for the preparation of indole itself.

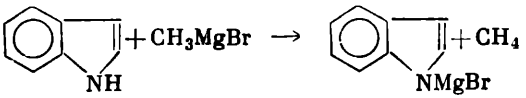
The remarkable Fischer reaction consists, according to R. Robinson, of the rearrangement of the tautomeric form of a phenylhydrazone, which is analogous to the benzidine rearrangement:



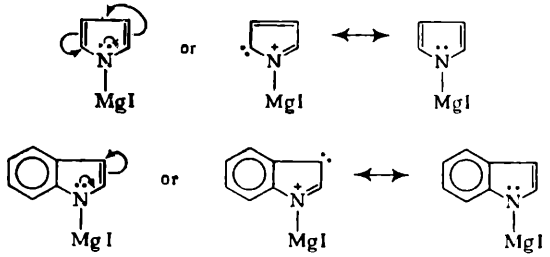
Indole occurs in small amounts in coal tar. It has a pleasant odour when present in a low concentration and an unpleasant faecal odour when contained in a high concentration. Indole is also present in jasmine-flower oil and in black yellow-locust oil. It is used in perfumery.

The following derivatives of indole are important: tryptophan (β-indolylalanine), which is an essential (in food) amino acid and a constituent of proteins (see Volume IV); β-indolylacetic acid (heteroauxin) and β-indolylbutyric acid, which are growth and root-forming stimulants in plants; indigo which was formerly produced from natural sources and is now a synthetic dye (it is the attempt to synthesize indigo that stimulated the investigation of the indole series by Baeyer).

Properties of Indole. It is natural that indole possesses many of the properties of pyrrole. The hydrogen atom of indole can be replaced by metals, use being made of the reaction with a Grignard reagent:

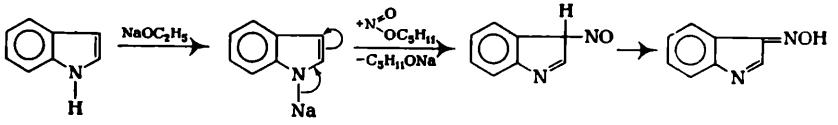


With indolylmagnesium halides one can carry out the same reactions as with pyrrylmagnesium halides, but the difference between these reactions is that the substituents enter at a high temperature not the α- but the β-position in the indole nucleus. This is accounted for by the fact that in indole one of the electron π-pairs of the pyrrole ring belongs also to benzene and is bound in the benzene ring more firmly than in the pyrrole ring. Thus, in pyrrole and indole the labile pair of electrons binding nitrogen to magnesium causes different effects of electron localization:

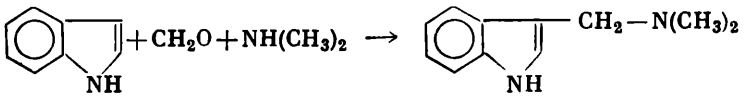


Electrophilic substitutions in indole itself are limited to the same extent as in pyrrole (indole is sensitive to acids) but those substitution reactions which are possible occur in the β-position; in certain cases the mechanism described finds pictorial confirmation.

Thus, the nitrosation of indole with amyl nitrite in alkaline medium proceeds according to the following scheme:

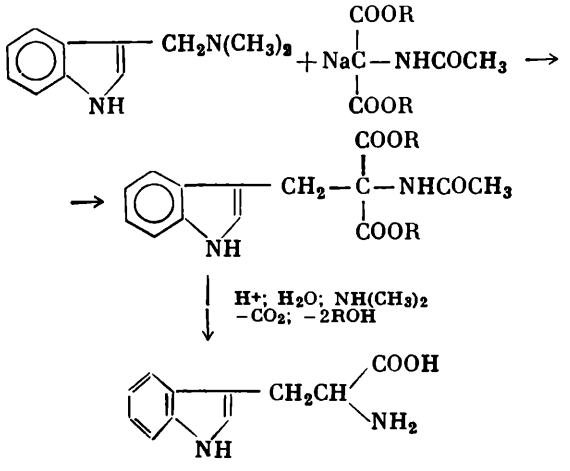


Another example of electrophilic substitution reactions in the β-position is the Mannich reaction:



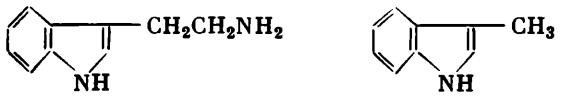
Gramine

The alkaloid **gramine** (3-dimethylaminomethylindole) formed by the Mannich reaction serves as a starting material in the synthesis of the essential protein amino acid tryptophan:



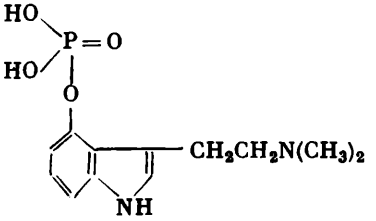
Tryptophan

When proteins undergo putrefaction, **tryptamine** and **skatole** (β-*methylindole*) are formed from tryptophan. Skatole is a substance possessing an extremely repulsive odour and is present in human faeces.



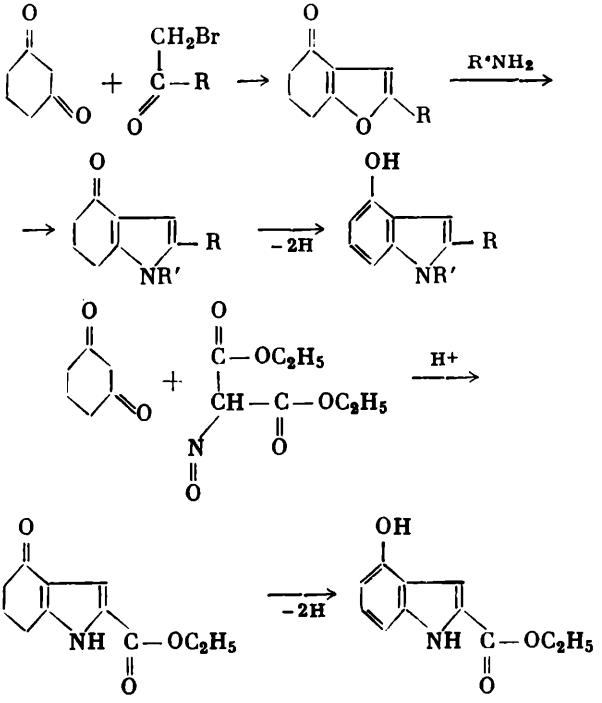
Tryptamine Skatole

Mexican mushrooms of the *Psilocybe* species contain a derivative of 4-hydroxyindole (indoxyl) called **psilocin** (4-hydroxy-N,N-dimethyltryptamine)



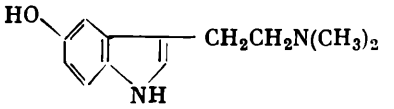
This compound belongs to the class of so-called **psychomimetic substances** which produce powerful psychic effects and are classified in the group of drugs known as hallucinogens. When administered inside in an amount of about 10 mg man becomes sleepy and colour hallucinations are produced, an effect that had long been used by the ancient population of Mexico in religious and ceremonial rites.

The synthesis of 4-hydroxyindoles is conveniently carried out by the method developed by A. N. Kost, in which the starting material is 1,3-cyclohexanedione (dihydroresorcinol). Below are given two variants of the method:

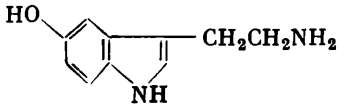


An isomer of psilocin (with respect to phenol) is 5-hydroxy-N,N-dimethyltryptamine known as **bufotenin** which was isolated by Wieland from the poisonous skin secretion of toads.

Another isomer of 5-hydroxyindole is **serotonin** (5-hydroxytryptamine), a hormone which regulates the blood pressure and the transport of blood via the kidneys and has an important function in establishing a stable pattern of mental activity. When its normal concentration in the brain is disturbed, the schizophrenic state ensues.

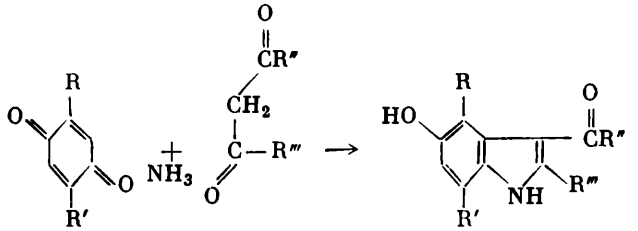


5-Hydroxy-N,N-dimethyltryptamine (bufotenin)



5-Hydroxytryptamine (serotonin)

The derivatives of indole with a hydroxyl group in the 5-position are conveniently synthesized by the Nenitzescu method which has been thoroughly worked out by A. P. Terentiev and A. N. Grinev and which is based on the interaction of *p*-benzoquinone with 1,3-diketone and ammonia or an amine:

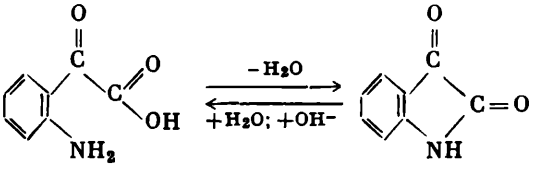


There are many compounds related to indoles, which are part of a class of natural products known as alkaloids and which will be discussed in Volume IV.

I. Indigo

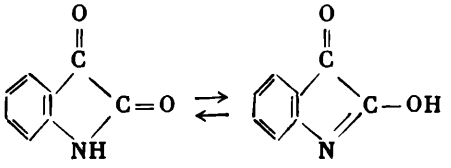
The juice of tropical plants of the *Indigofera* species and of the plant woad grown in Europe contains **indican** which is the glycoside of indoxyl. When these plants are wetted in water, indican passes into the aqueous solution and is hydrolysed to yield indoxyl. Indoxyl is oxidized by atmospheric oxygen to indigo which precipitates in the form of blue flakes. Indigo has been used as a dyestuff since ancient times. In dyeing textiles indigo is reduced to leuco indigo (indigo white) soluble in a weak alkali, the fabric is steamed and is allowed to be oxidized with air to the insoluble **indigo blue** or **indigotin**. This method of dyeing is called **vat dyeing**, and indigo belongs to a large class of vat dyes (page 294 *et seq.*).

Dry distillation of indigo gives aniline, and when oxidized with nitric acid indigo is converted into isatin which is hydrolysed by alkali to *o*-aminophenylglyoxylic (isatic) acid. Isatin is the lactam of this acid, as follows from the facile cyclization of isatic acid into isatin with loss of water:

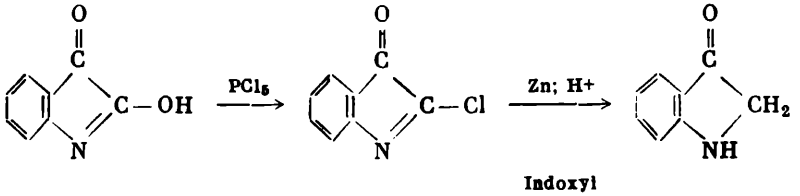


Isatin

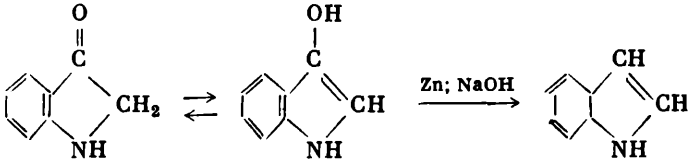
The relationship of isatin to indole and its other carbonyl derivatives is established by the following reactions:



Isatin
(tautomeric forms)

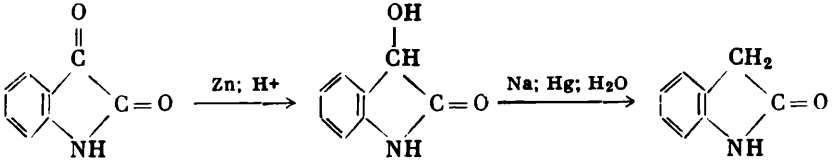


Indoxyl



Indoxyl
(tautomeric forms)

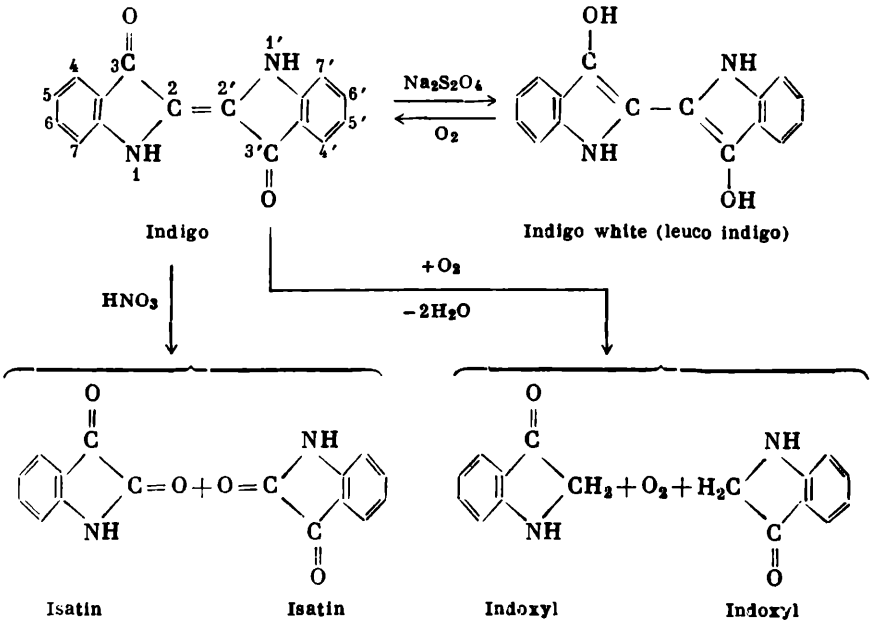
Indole



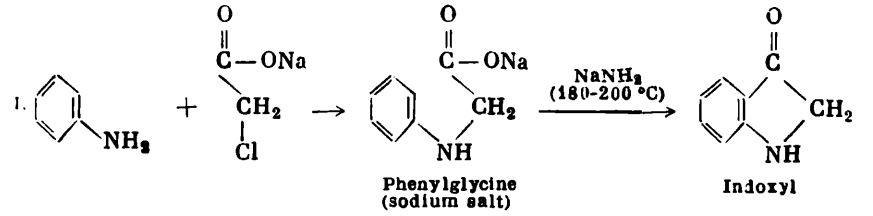
Isatin Dioxindole Oxindole

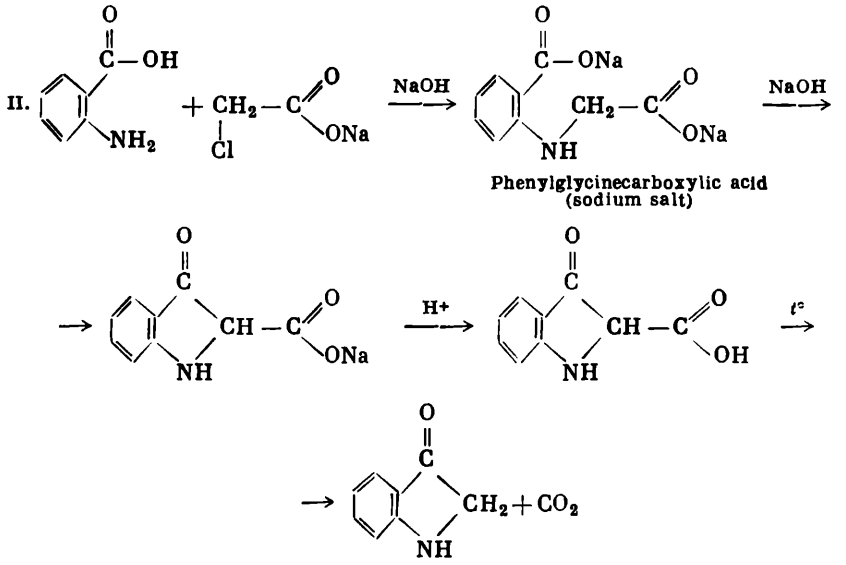
The carbonyl derivatives of indole (more exactly, indoline) are characterized by the tautomerism shown in the above schemes.

Isatin exhibits lactam-lactim tautomerism, and indoxyl shows keto-enol tautomerism. Indican is the glycoside of the enol form of indoxyl. Indoxyl is oxidized in alkaline solution by atmospheric oxygen to indigo which has the composition $C_{16}H_{10}N_2O_2$; two molecules of indoxyl, C_8H_7NO, form quantitatively one molecule of indigo, losing four hydrogen atoms in the form of water. One molecule of indigo is oxidized by HNO_3 to two molecules of isatin, $C_8H_5NO_2$, losing a double bond and adding two oxygen atoms. From this and also from a number of other considerations follows the formula of indigotin established by Baeyer. The formula presented below in the *trans*-form is based on new data:



After several syntheses of indigo had been accomplished by Baeyer two methods were devised (K. Heumann) which became industrially important. These methods made it possible to produce indigo so cheaply that the growing of indigogenic plants was discontinued.



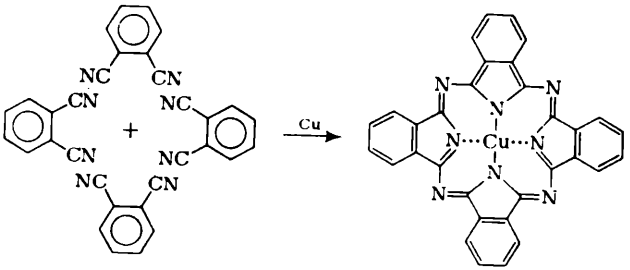


Both methods lead to indoxyl which is then oxidized to indigo. Pure synthetic indigo is a dark-blue powder insoluble in ordinary solvents and slightly soluble in nitrobenzene; it melts at 390°C, and forms red-coloured vapour. Many other indigoid dyes (page 340) are produced synthetically at present. An example is the purple of the ancients, Tyrian purple (royal purple), a violet dye highly valuable in ancient times which was isolated from mollusks. It has been proved by Friedländer to be 6,6′-dibromoindigo.

J. Phthalocyanines

The chemists of the English concern ICI noticed by chance in 1928 during the preparation of phthalimide from ammonia and phthalic anhydride in a copper vessel that there was obtained a product contaminated with a blue substance. Investigating this substance, Linstead found that the same substance could be prepared by heating *o*-phthalonitrile with copper salts and established the structure of the new dye copper phthalocyanine known under the name of Monastral Fast Blue, which has found wide application (employed chiefly for printing inks and paints, automotive finishes, for dyeing synthetic fibres and also in research work). Copper phthalocyanine is a bright-blue substance which sublimes at temperatures above 550°C, i.e., has an extremely high thermal stability. Even this stability and the ease of formation point to the aromaticity of the system. Indeed, copper phthalocyanine has the symmetric structure of tetra-

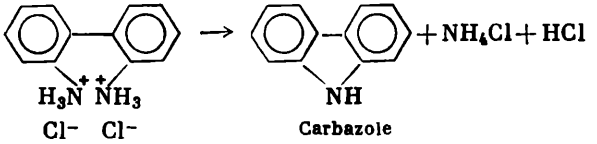
benzotetraazaporphin:



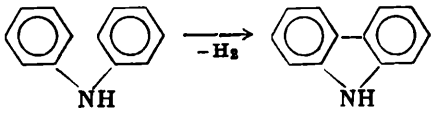
There exist phthalocyanine complexes of other metals and also phthalocyanines with substituents present in aromatic nuclei, which have been prepared by synthesis from substituted phthalonitriles or by the subsequent electrophilic substitution, say, by sulphonation. Neither acids nor alkalis can remove the copper from the phthalocyanine complex.

K. Carbazole

Anthracene oil, a fraction of coal tar, contains, apart from anthracene and phenanthrene, a nitrogenous heterocyclic compound known as dibenzopyrrole or **carbazole** which can be separated from neutral hydrocarbons owing to its weakly acidic properties, for example, the ability to form metallic derivatives. The structure of carbazole is proved by its formation on heating the salt of *o,o'*-diaminodiphenyl:



Carbazole can also be obtained by passing diphenylamine through red-heated tubes (cf. page 234, the preparation of biphenyl from benzene):



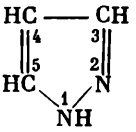
This compound shows a closer resemblance to diphenylamine than to pyrrole derivatives, which is understandable since the gain of energy in the aromatic delocalization of π-electrons over the benzene nuclei is much greater than over the pyrrole ring.

Carbazole finds limited application in the production of sulphurous dyes and plastics based on N-vinylcarbazole. The latter is obtained from acetylene and carbazole by the action of alkali.

10.2. Five-Membered Heterocycles with Several Identical Hetero-Atoms

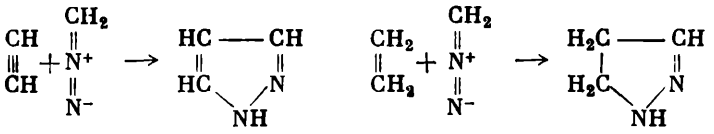
A. Pyrazole

Pyrazole and its derivatives have not been found in nature. Pyrazole itself



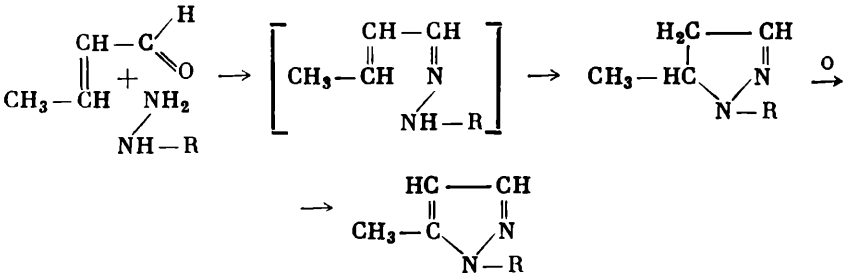
and also its homologues and derivatives can be prepared by the following reactions.

1. The addition of aliphatic diazo compounds to acetylenes gives pyrazoles. The same reactions as applied to olefins leads to dihydropyrazoles which are termed *pyrazolines* (Pechmann):

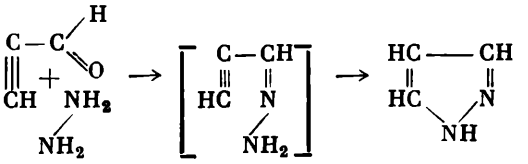


Pyrazole Pyrazoline

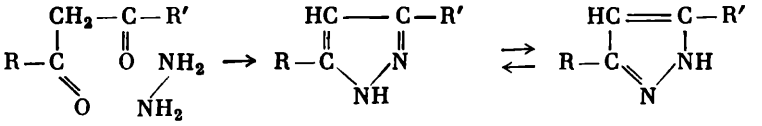
2. The action of hydrazine or its derivatives on α,β-unsaturated aldehydes or ketones yields pyrazolines (the initially formed hydrazones undergo intramolecular addition to the double bond). Pyrazolines can then be oxidized to pyrazoles:



The action of hydrazines on α,β-acetylenic carbonyl compounds leads directly to the formation of pyrazoles (Claisen):



3. The oldest synthetic method which was used by Knorr for preparing the first homologues of pyrazole consists in the action of hydrazine (or a monosubstituted hydrazine) on 1,3-dicarbonyl compounds:



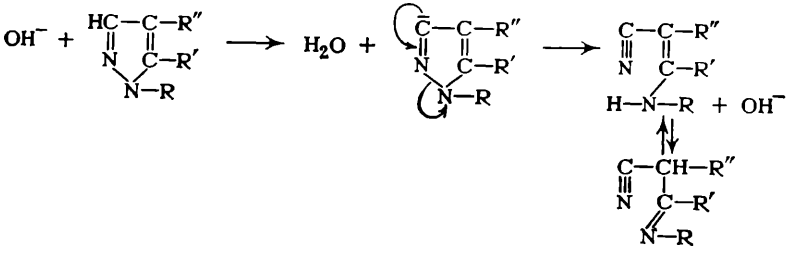
The compound (the formula on the right) which is isomeric with the R,R′-substituted pyrazole formed and which should have been formed in this synthesis is in fact identical with the substituted pyrazole obtained as the reaction product. In pyrazole, not only the double bonds are delocalized, as must be in an aromatic compound, but also the proton migrates freely from one nitrogen atom to another.

Like pyrrole, pyrazole is a very weak acid, capable of giving metallic derivatives, say, with silver oxide. But at the same time, the presence of a second nitrogen atom (with a free pair of electrons not involved in the aromatic sextet) imparts the properties of a weak base to the compound: with strong acids it forms salts.

Pyrazole is sulphonated by oleum, chlorinated and brominated, nitrated, and mercurated. Electrophilic substitutions proceed in the 4-position. It is very stable not only towards acids but also towards oxidation. Just as in the homologues of benzene, the side chains of pyrazole can be oxidized to carboxyl groups by the action of potassium permanganate with the heterocycle remaining intact. When N-phenylpyrazole is oxidized, the phenyl group is destroyed and pyrazole is formed.

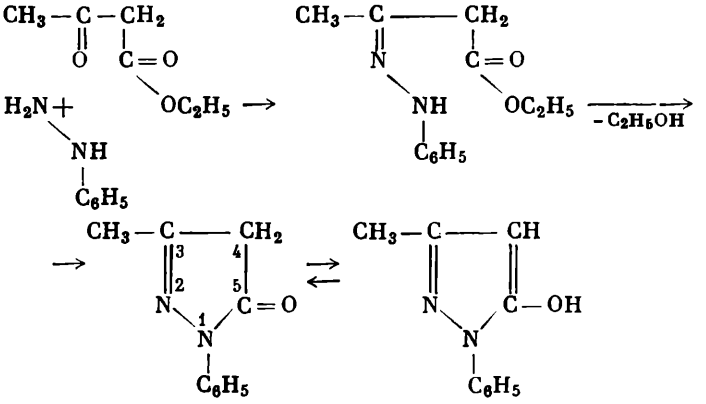
Under the action of strong nucleophilic reagents, however, pyrazoles undergo **nitrile cleavage** across the N—N bond (A. P. Kost,

N. I. Grandberg):



Chloropyrazole has a slightly mobile chlorine atom; 4-aminopyrazole prepared by the reduction of 4-nitropyrazole is diazotized.

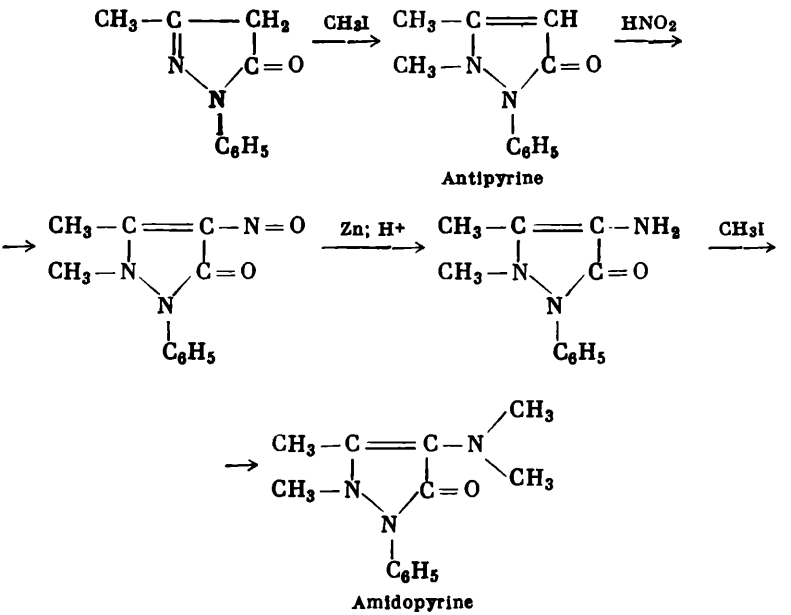
Pyrazolones. In describing the properties of acetoacetic ester we pointed out that the formation of a hydrazone (say, phenylhydrazone) is accompanied by the elimination of the ester ethoxyl group and cyclization of methylpyrazolone (or, of N-phenylmethylpyrazolone in the case of phenylhydrazine). The reaction of esters of β-carbonyl acids with hydrazines serves as a simple method of synthesizing pyrazolones, which is also employed on an industrial scale:



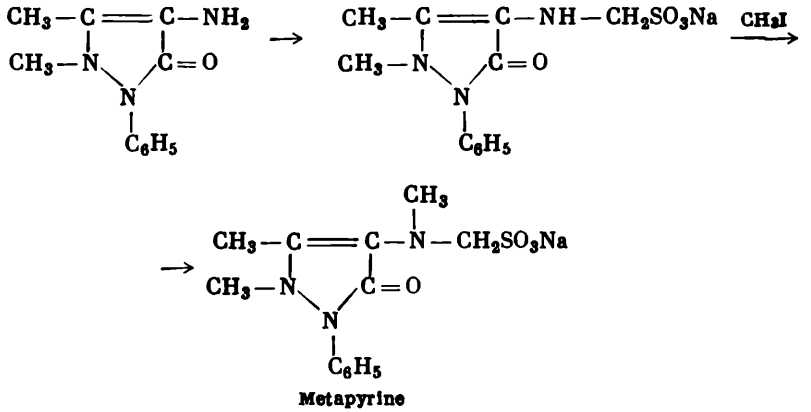
The enol form of pyrazolones has the pyrazole structure and is therefore aromatic.

Electrophilic substitution reactions in 5-pyrazolones take place in the position 4. Methyl iodide attacks the second nitrogen, forming 1-phenyl-2,3-dimethyl-5-pyrazolone known in medicine as **antipyrine** or **phenazone**. Electrophilic substitution in this compound also takes place in the 4-position; like phenylmethylpyrazolone, it is nitrosated to a nitroso compound which is reduced to a primary amine. When aminoantipyrine is methylated, a tertiary amine, dimethylaminoantipyrine, is formed (Knorr), which is a widely

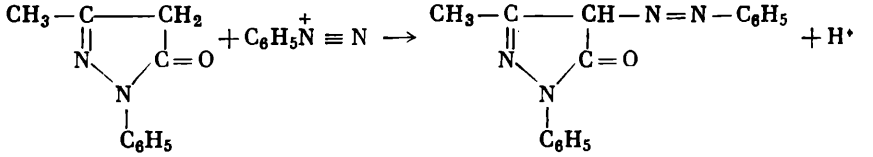
used analgesic known as **pyramidon** or **amidopyrine**:



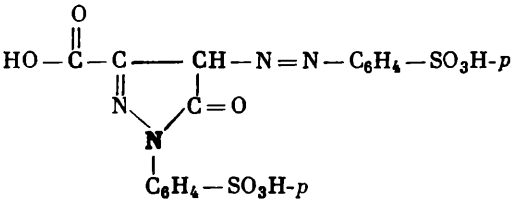
An even stronger analgesic agent, **analginum** or **metapyrine**, is obtained if aminoantipyrine is allowed to react with a bisulphite compound of formaldehyde (if $-CH_2-SO_3Na$ is introduced into the primary amino group) and the amine is then methylated to a tertiary amine:



1-Phenyl-3-methyl-5-pyrazolone itself enters into azo coupling reactions with aryldiazonium compounds:



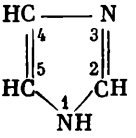
This reaction is employed on an industrial scale since the azo dyes produced have a high light fastness.



Tetrazine (a yellow acid azo dye)

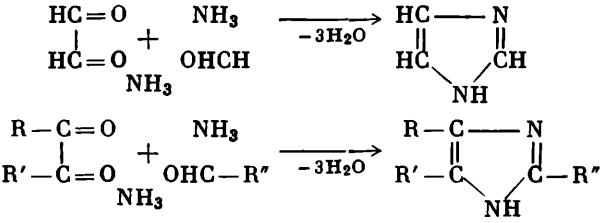
B. Imidazole (Glyoxaline)

In contrast to the isomeric pyrazole, imidazole

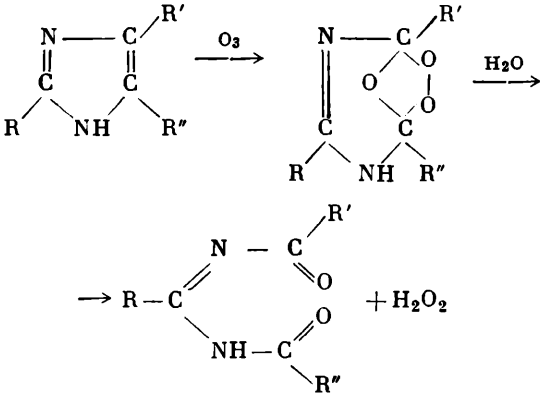


occurs widely in the form of its derivatives (the amino acid histidine, histamine, alkaloids, purine compounds) in the animal and plant kingdoms and is of biological importance.

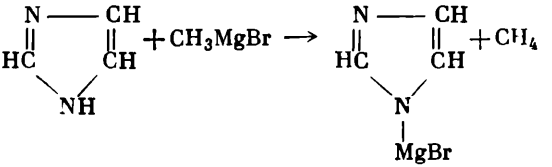
Imidazole itself was first prepared by Debus by the action of ammonia on glyoxal. The best result is obtained if to glyoxal there is added first formaldehyde and then ammonia. The homologues and derivatives of imidazole are prepared from other 1,2-dicarbonyl compounds, aldehydes and ammonia:



Imidazole is resistant to the action of chromic acid but on oxidation with potassium permanganate is converted into the amide of oxalic acid. Ozone ruptures the olefinic linkage and gives the diacyl derivative of amidine:



These reactions prove the structure of the imidazole ring. Reducing agents have no effect on imidazole. Imidazole is a sufficiently strong base (stronger than pyridine), which forms solid salts with strong acids. At the same time, it has pronounced acidic properties owing to its N—H bond, forming metallic derivatives, for example, with Grignard reagents:



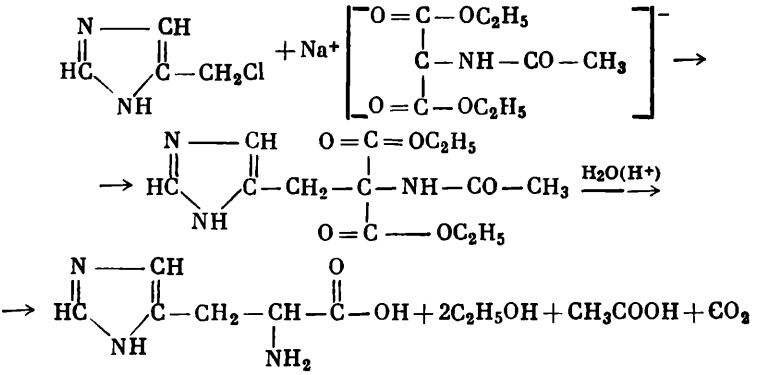
These derivatives may be used for preparing N-alkyl (the action of RHal) or 2-C-alkyl (the same, on heating) derivatives. Owing to the acidic properties of the N—H group N-methylimidazole can be produced by the direct action of diazomethane on imidazole. Both nitrogen atoms of imidazole and, hence, positions 4 and 5, are equivalent. The hydrogen of imidazole migrates freely from N^1 to N^3. Thus, this is a case of prototropy with a high velocity of proton transfer.

Imidazoles can enter into all the principal types of aromatic electrophilic substitution reactions—halogenation, sulphonation, nitration (in position 4 or, what is the same thing, in position 5).

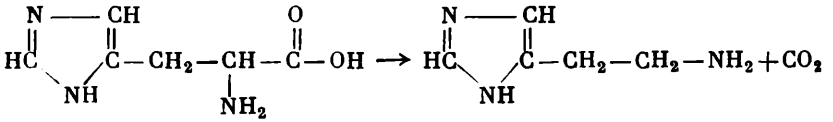
A striking property of imidazole is its unusually high boiling point (250°C); the isomeric pyrazole boils at 187°C, and pyrrole boils at 130°C. This has been explained (Hückel) as being due to association through hydrogen bonds and confirmed by measurements

of the N ··· N distance in two molecules of imidazole (equal to 3 Å). Hydrogen bonds of this kind play a very important part in nucleic acids (see Volume IV, "Nucleotides and Polynucleotides").

One of the important natural derivatives of imidazole is the amino acid **histidine**, a common decomposition product of proteins, which has been proved to be β-(4-imidazolyl)-alanine or β-(5-imidazolyl)-alanine. The structure of histidine follows from its synthesis:



Like other α-amino acids, histidine on bacterial putrefaction decarboxylates and is converted into **histamine**:



Histamine has a strong physiological effect. Even when present in low concentrations histamine sharply lowers blood pressure, causes dilation of the capillaries, activates smooth muscles and, hence, enhances peristalsis. Histamine is believed to be responsible for certain allergic symptoms such as asthma, rhinitis, and hives. A number of compounds, anti-histamines, which neutralize or alleviate the effects of histamine, have been prepared. One is diphenylhydramine hydrochloride, $(C_6H_5)_2CH—O—CH_2—CH_2—N(CH_3)_2$.

C. Biotins

Of the condensed biheterocyclic compounds mention should be made of α- and β-**biotins** which belong to the class of vitamins (vitamin H). β-Biotin is contained in small amounts in plants, in the liver of animals, in milk and in the egg yolk. Its absence from the food disturbs the metabolism of proteins and fats in the organism, prevents growth and causes the dermatitis of skin.

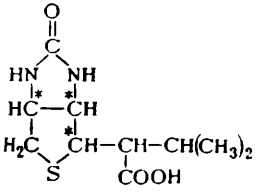
Biotins are substances required for maintaining the life activity

not only of animals but also of the lower unicellular organisms. The daily requirement of biotins by man is 6 to 10 μg.

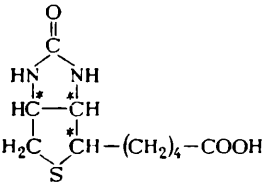
β-Biotin is contained in enzyme systems, say, in α-decarboxylases which are responsible for the decarboxylation of oxaloacetic to pyruvic acid and of oxalosuccinic to α-ketoglutaric acid, and also for the reverse reaction—the introduction of a carboxyl group into ketonic acids (see Volume II, Krebs cycle, and Volume IV, "Enzymes").

α-Biotin was isolated by Kögl in 1936 from egg yolk (1.1 mg of biotin from 250 kg of dry egg yolk); β-biotin was isolated by du Vigneaud in 1940 from liver (and from milk).

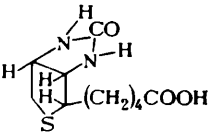
The molecules of biotins have each in their bicyclic rings three asymmetric carbon atoms. The *cis-cis-cis* configuration has been established for the two biotins:



α - Biotin

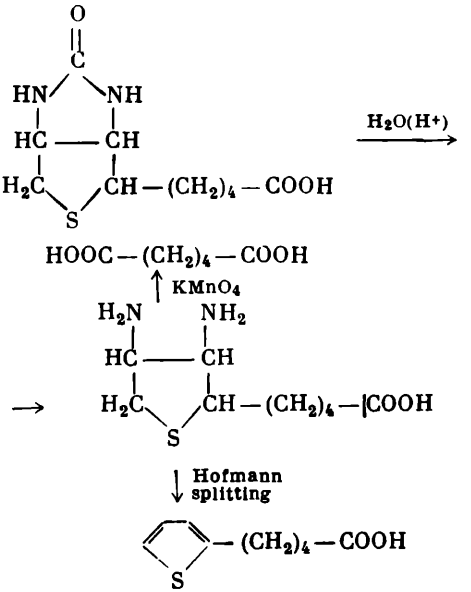


β - Biotin



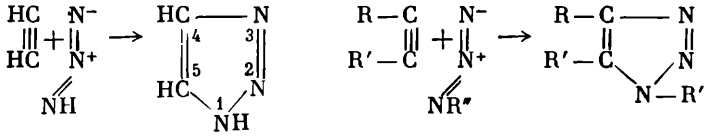
cis-cis-cis Configuration of β - biotin

The structure of β-biotin is confirmed by the following reactions:



D. Triazoles

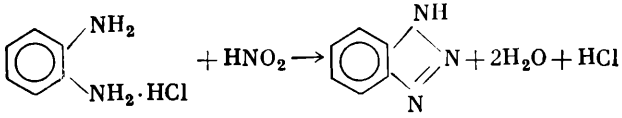
Vicinal triazole (1,2,3-triazole) and symmetric triazole (1,3,4-triazole) are known to exist. The first is synthesized by the reaction between hydrazoic acid and acetylene, and its derivatives are obtained by the interaction of organic azides with acetylenes:



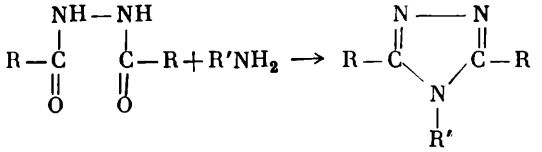
Reactions of this type were termed 1,3-dipolar additions by Huisgen (see page 327).

In 1,2,3-triazoles the proton migrates freely over all the three nitrogen atoms, the π-electrons are delocalized, the pair of *p*-electrons of one of the nitrogen atoms is involved in the aromatic sextet, and both positions of CH are equivalent. 1,2,3-Triazole is aromatic and quite stable. It has weakly acidic and weakly basic properties: it forms salts both with Ag^+ and with strong acids.

Vicinal benzotriazole is formed by the diazotization of *o*-phenylenediamine and is an inner diazoamino compound; the reaction is however irreversible in the sense that no ordinary decyclization of the diazoamino compound by acid into an amine and a diazonium salt takes place:



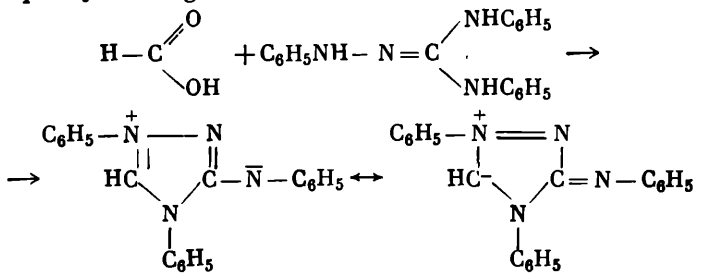
1,3,4-Triazoles can be obtained from symmetric diacylhydrazines by the action of ammonia or amines:



Triazole rings of both types are stable towards oxidizing agents, and the side chains are burned off, being converted into carboxyl groups.

The best-known derivative of 1,3,4-triazole is **nitron**, whose acetate salt is used in analytical chemistry for precipitating the nitrate ion (the nitron nitrate is insoluble in water). Nitron is prepared

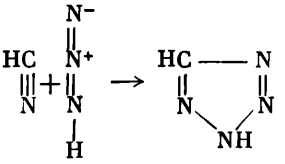
from triphenylaminoguanidine and formic acid:



Its structure is dipolar (it has a zwitterion structure), and its charges as well as π-electrons are delocalized.

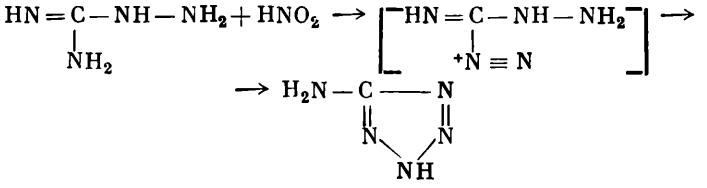
E. Tetrazole

Tetrazole has been synthesized by the addition of hydrazoic acid to hydrogen cyanide, and its derivatives are prepared by an analogous reaction from nitriles (Hantzsch):

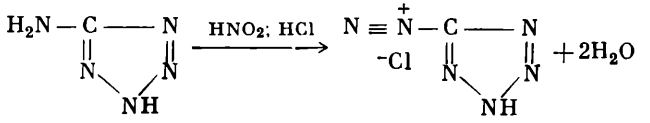


The proton in tetrazole migrates over the nitrogen atoms. Tetrazole is a weak acid, is quite stable towards oxidizing agents, and aromatic; electrophilic substitution reactions take place across the CH group.

When aminoguanidine is allowed to react with nitrous acid, **aminotetrazole** is formed:



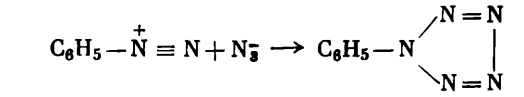
This compound undergoes diazotization to form tetrazolediazonium salts which are extremely explosive even in aqueous solution:



The diazonium salts are capable of entering into azo coupling reactions.

F. Pentazole

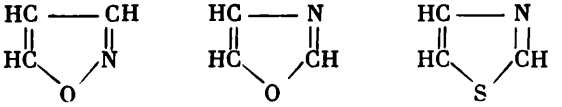
Pentazole, of course, cannot be classed as a heterocyclic compound. Organic derivatives of pentazole have been prepared in recent years Thus, **phenylpentazole** is formed by the union of the azide ion with the phenyldiazonium cation:



This compound is stable at temperatures below —70°C (Huisgen).

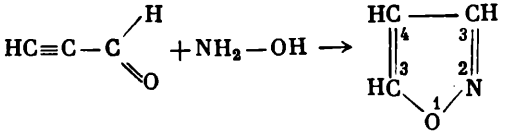
10.3. Five-Membered Heterocycles with Two Different Hetero-Atoms

We shall briefly consider only the most important heterocyclic compounds of this kind:

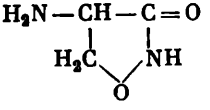


A. Isoxazole

Isoxazole can be prepared by the reaction of hydroxylamine with propargyl aldehyde:

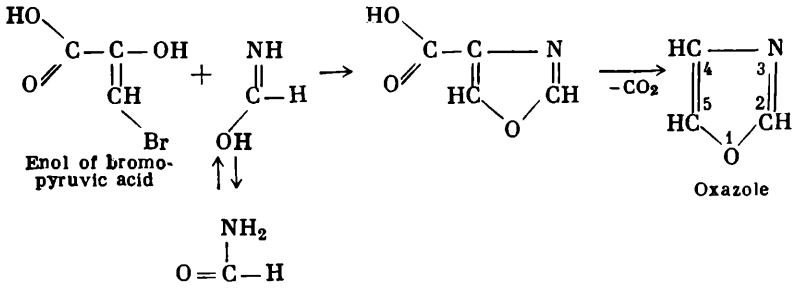


This is a weak base and smells like pyridine. Isoxazole has pronounced aromatic properties; it is considerably less susceptible to electrophilic attacks than furan. The markedly pronounced aromatic properties of isoxazole have been studied by N. K. Kochetkov, who synthesized **cycloserine**, an antibiotic of the isoxazolidine series (the completely hydrogenated isoxazole). Cycloserine is 4-amino-3-isoxazolidone



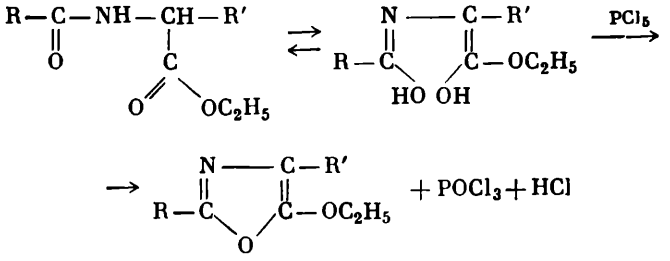
B. Oxazoles

A general method for the synthesis of oxazoles is by the condensation of α-bromoketones with acid amides. The condensation of bromopyruvic acid with formamide can yield oxazole-4-carboxylic acid which is then decarboxylated to give oxazole:



Oxazole is a liquid with a smell like that of pyridine. It boils at 69-70°C and possesses the properties of a weak base.

Another route for synthesizing oxazoles is by the action of phosphorus pentachloride on acylamino acids:

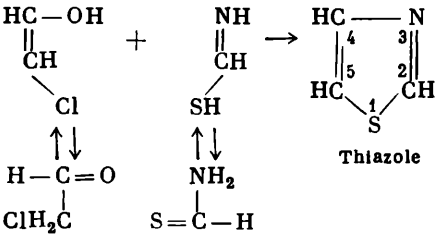


Oxazoles are less stable towards oxidizing agents and oxidation than other nitrogen-containing rings. They possess aromatic properties, though they have been little studied in this respect.

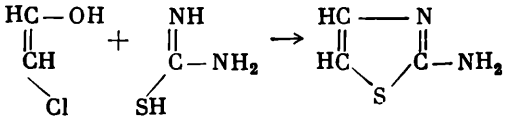
C. Thiazole

The thiazole ring is closed by a reaction analogous to the first of the reactions for preparing oxazoles. α-Halogen-substituted carbonyl compounds are made to react with acid thioamides. In this way, thiazole itself is prepared from chloroacetaldehyde and thiofor-

mamide:



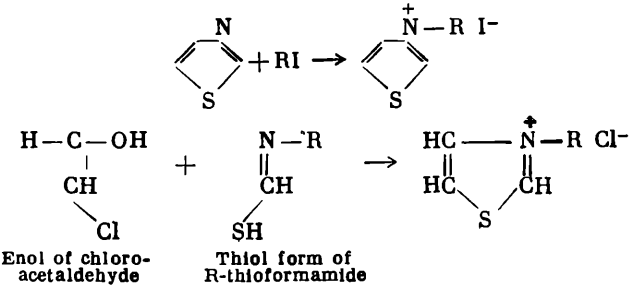
and 2-aminothiazole is obtained from chloroacetaldehyde and thiourea:



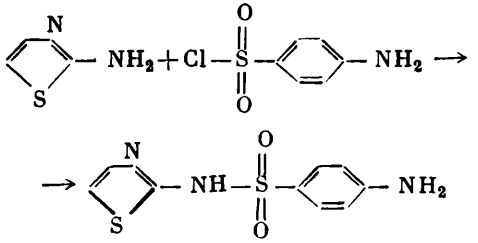
Thiazole is a liquid with the smell and boiling point of pyridine and, in general, stands in the same relationship to pyridine as thiophen does to benzene. Thiazole is highly stable to oxidation and is resistant to the action of potassium permanganate and hot concentrated nitric acid. It is nitrated under drastic conditions in position 5, and, hence, is characterized by the combined orientation—that of thiophen (in the α-position with respect to sulphur) and that of pyridine (in the β-position with respect to nitrogen), but the ring is strongly deactivated. Sulphonation too takes place in the 5 position (200°C, oleum). Electrophilic substitutions proceed under drastic conditions and with difficulty even for methylthiazoles (a case that has been studied most thoroughly); the substitution takes place in position 5 if it is vacant and in position 4 if the methyl group is in position 5.

Thiazole resembles pyridine to such an extent that at 150°C it is aminated by sodamide in the 4-position. Like pyridine, thiazole is a moderately strong base.

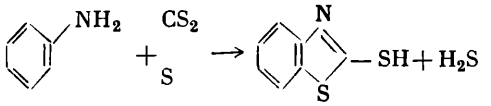
When thiazole is allowed to react with alkyl halides, thiazolinium salts are formed, which can also be prepared by the cyclization of N-alkyl-(or aryl-) thioamides with α-chlorocarbonyl compounds:



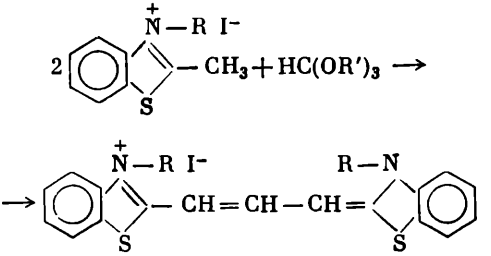
The above-mentioned 2-aminothiazole is used as the starting material for preparing an important sulphamide drug, **sulphathiazole:**



Of great importance are the derivatives of benzothiazole. **Mercaptobenzothiazole** (called Captax in industry) is used as a rubber vulcanization accelerator. It is prepared by heating aniline with sulphur and carbon disulphide:



Like α-substituted quinolines, 2-methylbenzothiazoleiodoalkylates are used for the synthesis of cyanine dyes (thiocyanine dyes in this case) which can act as photosensitizers for silver bromide emulsions which are made sensitive towards red and infrared rays. The simplest example of syntheses of a dye of this kind demonstrates the easy ionization of the hydrogens of the methyl group of 2-methylbenzothiazole, which is similar to the mobility of the hydrogen atoms of α- and γ-methyl groups of pyridine and quinoline:



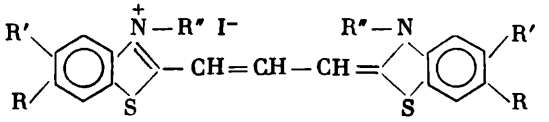
Of course, the left and right halves of the molecule are here fully symmetrical, the positive charge is spread between the two nitrogen atoms, and the π-bonds of the polymethine chain are delocalized.

The investigations on cyanine dyes carried out in the USSR are largely due to the school of A. I. Kiprianov and I. I. Levkoev. As seen from the formula given above dyes of this type are continuous

systems of conjugation of π-electrons. Therefore, a disturbance of the conjugation, say, through withdrawal of a part of the molecule out of the plane due to steric hindrances, must inevitably cause a hypsochromic shift of absorption (page 123). On the contrary, the introduction of an auxochromic group, say, $N(CH_3)_2$, into a conjugated system will cause a bathochromic shift.

Table 10.1 presents the data obtained by A. I. Kiprianov on the shift of the absorption region, depending on the substituent in thiocyanine dyes. In dye IV two dimethylamino groups (R′) play the role of auxochromes providing a bathochromic shift as compared with dye I. But if methyl groups (R) are introduced *ortho* to these dimethylamino groups which are thereby somewhat taken out of the

TABLE 10.1. **The Effect of Substituents on the Shift of the Absorption Maximum in the Cyanine Dye**



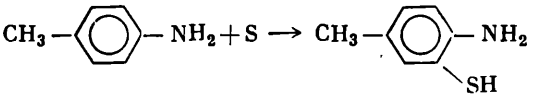
Dye	R	R′	R″	λ_{max}, Å	ε×10⁻⁴
I	H	H	C_2H_5	5560	16.5
II	CH_3	H	C_2H_5	5630	14.5
III	$C(CH_3)_3$	H	CH_3	5630	14.9
IV	H	$N(CH_3)_2$	C_2H_5	6080	8.2
V	CH_3	$N(CH_3)_2$	CH_3	5750	10.1
VI	$C(CH_3)_3$	$N(CH_3)_2$	CH_3	5700	14.1
VII	H	$NH(CH_3)$	C_2H_5	5580	15.4

conjugation plane (dyestuff V), the bathochromic shift will decrease. In dyestuff VI, *o-tert*-butyl groups take the dimethylamino groups out of the plane completely, and the bathochromic effect of the dimethylamino auxochromes disappears completely (the absorption maxima nearly coincide for dyestuffs III and VI).

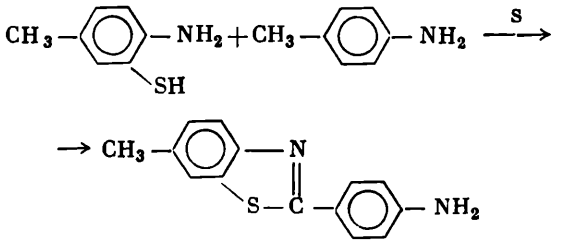
The auxochrome can be deactivated, as always, not only by steric factors but also by binding a free pair of electrons by a hydrogen ion (by salt formation, as in the case of dyestuff VII).

The derivatives of benzothiazole also include a group of important sulphur dyes, such as primuline, which are light- and wash-fast dyes whose colour ranges from yellow to brown to black. The first stage in their preparation is the direct "sulphidation" of an aromatic

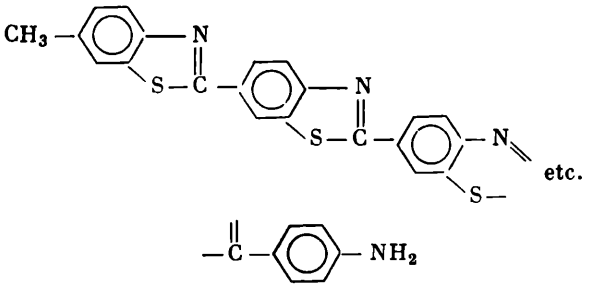
amine by sulphur:



The aminomercaptan obtained is oxidized by sulphur mixed with *p*-toluidine at an elevated temperature to a derivative of benzothiazole:

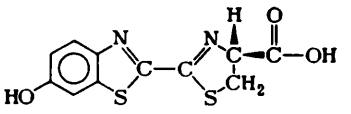


At an even higher temperature (>100°C) the process is repeated with the heterocyclic amine formed, new benzothiazole rings are built up and structures of the following type are produced:



The primulines are used as such or by way of their diazotization and azo coupling on fabrics. (For sulphur dyes, see also page 191.)

A curious derivative of benzothiazole is **luciferin**, the enzymatic oxidation of which produces the characteristic luminescence of the firefly.



D-Luciferin

Thiazolinium salts also include vitamin B_1 or **aneurin** (*thiamin*) which will be discussed at a later time under pyrimidine (page 411) since its molecule has a pyrimidine ring as well.

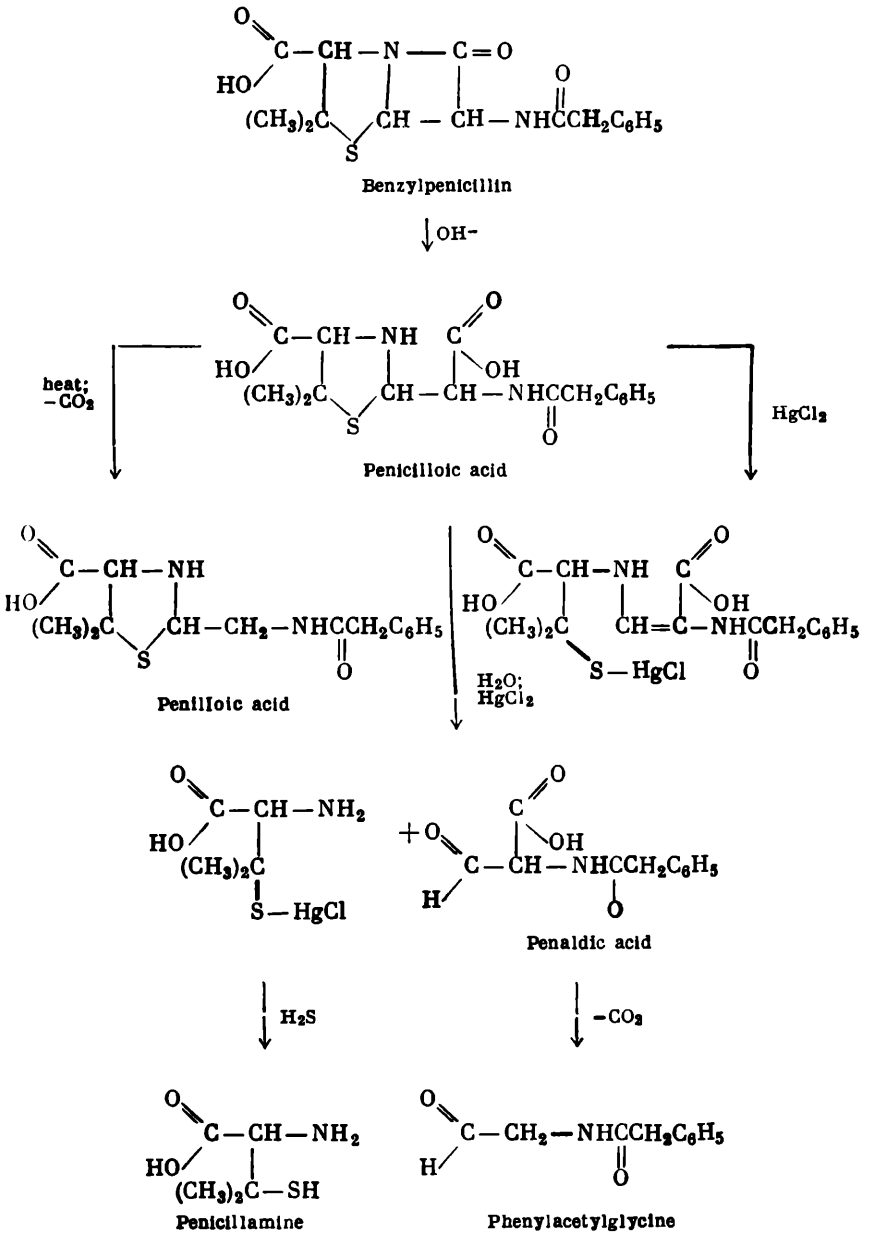
The derivatives of **thiazolidine** (i.e., tetrahydrothiazole) include a group of the antibiotics **penicillins**, the discovery of which during the Second World War ushered the era of antibiotics in medicine and the victory of man over bacterial diseases. Five penicillins are known, which are similar to one another in their antibiotic action and differ according to the nature of the acyl group that acylates the amino group: $C_6H_5CH_2CO$ in benzylpenicillin, p-$HOC_6H_4CH_2CO$ in hydroxybenzylpenicillin, p-$C_5H_{11}CO$ in amylpenicillin, $CH_3CH_2CH=$ $=CHCH_2CO$ in pentenylpenicillin, and $C_7H_{15}CO$ in heptylpenicillin. This group of antibiotics has been discovered by Fleming and Florey, and the structure has been elucidated by the chemists at the Oxford University under the guidance of R. Robinson and finalized through X-ray studies by D. Crowfoot. The most difficult task was the establishment of the presence of the exceedingly labile and easily isomerizable β-lactam ring in penicillin. The reactions that prove the structure of benzylpenicillin, which is the commonest of these antibiotics, are given below.

As the result of alkaline hydrolysis, one of the hetero rings (namely, the nitrogenous ring) of the bicyclic system of benzylpenicillin is opened, and mercurolysis with the aid of mercuric chloride (attack at the S—C bond) ruptures the second sulphide ring and leads to the formation of two fragments: **penaldic acid** and **penicillamine**, the latter containing a primary amino group, a thiol and a carboxyl group in the isobutane skeleton. Penaldic acid is α-phenylacetylaminomalonic semialdehyde. The malonic arrangement of the carboxyl and aldehyde groups follows from the facile decarboxylation of penaldic acid as early as in solution with the formation of phenylacetylglycine. That penicillamine and penaldic acid are actually two fragments of penicilloic acid which is formed with the structure remaining basically undisturbed is proved by a repeated synthesis of penicilloic acid from these two fragments (penaldic acid is taken in the form of an ester).

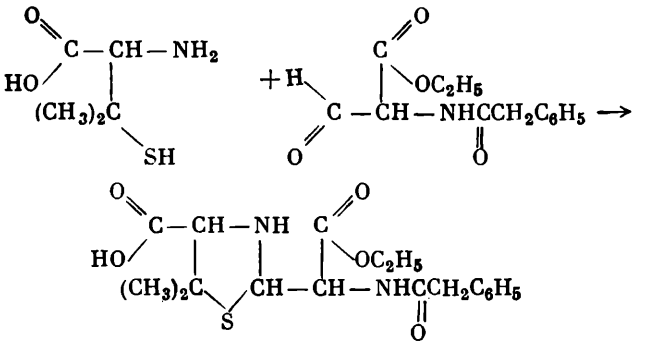
Penicillin that is hydrolysed to penicilloic acid differs in composition from this acid by having one water molecule less and only one free carboxyl group (instead of two in the acid.) How does the carboxyl group undergo ring-closure upon loss of water and which of the two groups?

Let us first answer the second question: which of the two carboxyl groups undergoes ring-closure? When penicillin is reacted with an amine, aminolysis takes place, which involves the incorporation of the amine into the molecule (in place of water) and the formation of the amide of the acid at the expense of one of the carboxyl groups. This is the carboxyl group that is lost in the form of carbon dioxide when penicilloic acid is heated, penilloic acid being formed as a result.

1. *Proof of the Structure of Benzylpenicillin*

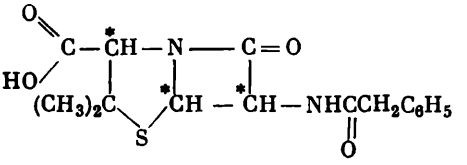


2. *Resynthesis of Penicilloic Acid*

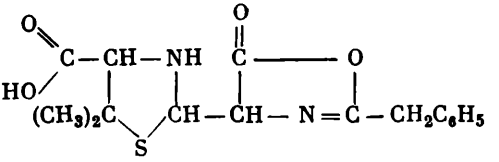


Penilloic acid retains the carboxyl group linked to the thiazolidine ring, which can be proved by its mercurolysis with mercuric chloride (penicillamine is formed in this reaction, just as in the mercurolysis of penicilloic acid). This means that it is the carboxyl group of the side chain of penicilloic acid which is incorporated into the second ring in the penicillin molecule since otherwise a water molecule would not have been introduced on hydrolysis and the penicillin molecule would have been cleaved into two portions.

Of the two most probable structures of benzylpenicillin



I

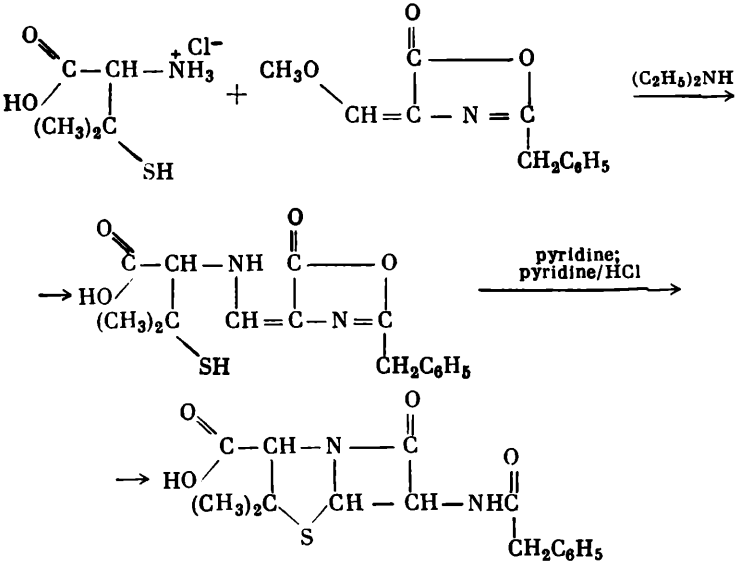


II

preference is given to the first formula because penicillin has no basic properties. The free NH group in formula II must react as a principal group. The formula I has also been confirmed by the X-ray analysis of penicillin. We shall not dwell on the complicated stereochemistry of penicillin which has three asymmetric carbon atoms. It has also been elucidated by chemical and X-ray studies.

As pointed out above, the synthesis of penicilloic acid is simple. The synthesis of penicillamine and penaldic acid, which are the

starting materials for the preparation of penicilloic acid, presents no difficulties either. Numerous attempts to close the unstable β-lactam ring and to convert penicilloic acid into penicillin have, however, failed. One can hardly cite another case in the history of organic chemistry when such great efforts were expended by a number of notorious investigators with no success. In 1948 du Vigneaud succeeded in synthesizing penicillin only in low yield by the following scheme



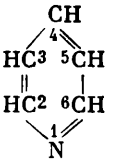
Chapter 11

Six-Membered Heterocycles

II.I. Heterocycles with One Nitrogen Atom

A. Pyridine

It is convenient to begin the discussion of six-membered heterocyclic compounds with pyridine since it has markedly pronounced aromatic properties. The formula of pyridine is



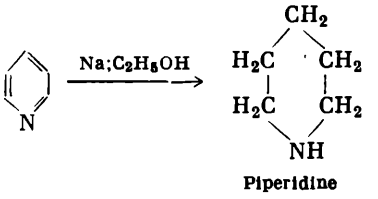
Pyridine

Pyridine and its homologues occur in small amounts in coal tar. Upon distillation they pass into the fraction of the tar boiling between 80° and 170°C ("light oil") from which they are easily extracted into an aqueous solution of acid, then isolated in the pure state by alkali and separated by distillation.

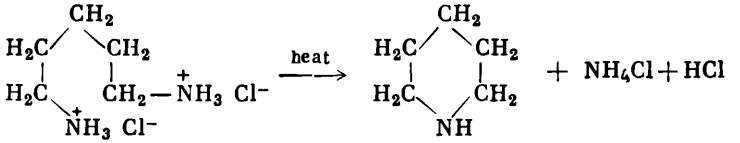
Pyridine has an unpleasant, penetrating smell. It boils at 115°C, melts at —38°C. It is miscible in all proportions with water; its dipole moment is 2.20D and its resonance energy is 37 kcal/mole. Its aqueous solution is alkaline and turns litmus dark blue; the basicity constant of pyridine is $K_b = 1.8 \times 10^{-9}$. Pyridine forms salts with more or less strong acids. It is very resistant to oxidation. The homologues of pyridine when oxidized by chromic acid form (like the homologues of benzene) the corresponding pyridinecarboxylic acids.

The structure of pyridine follows from the following facts. When reduced by nascent hydrogen (through the action of sodium on an alcoholic solution of pyridine, A. N. Vyshnegradsky) or over a cata-

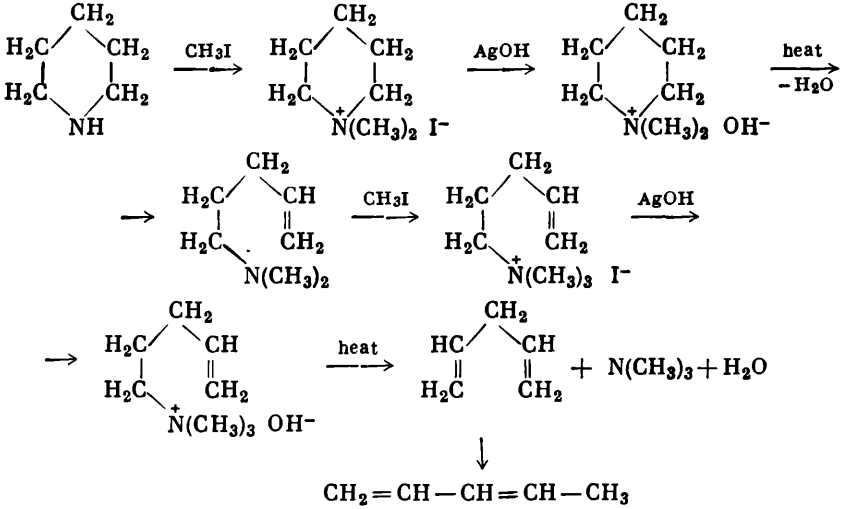
lyst pyridine is converted into **piperidine:**



The structure of piperidine is proved by its synthesis effected by heating pentamethylenediamine hydrochloride



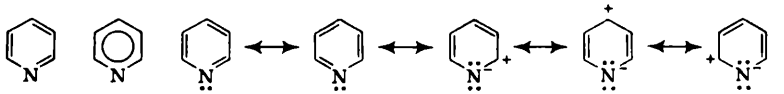
and also by the Hofmann degradation (exhaustive methylation)



The Hofmann degradation of nitrogen-containing heterocycles consists of a series of successive methylation reactions effected with methyl iodide, which proceed until the stage of formation of a quaternary ammonium salt is reached, the replacement of the iodide ion by a hydroxyl group and the pyrolysis of the ammonium base. This eliminates water and leads to the formation of an unsaturated amine, and the last stage gives trimethylamine and a diene or polyene hydrocarbon having the same sequence of carbon-carbon bonds as in the parent heterocyclic compound (the final stage—the conversion of

1,4-pentadiene into 1,3-pentadiene—is caused by the greater stability of a system of conjugated π-bonds). The method is employed for establishing the sequence of carbon-carbon bonds in a heterocycle. In this particular case, it is the unbranched chain of five carbon atoms which is elucidated. The structure of pyridine homologues can also be established in this way.

When being converted into piperidine (hexahydropyridine), pyridine adds six hydrogen atoms and, hence, it has three double bonds. The aromatic properties of pyridine are evidence of the benzenoid character of these bonds. All these facts lead to the Körner formula I or its modified present-day form II for pyridine. In terms of resonance theory, the structure of pyridine as a resonating compound is represented by a series of contributing forms (III):

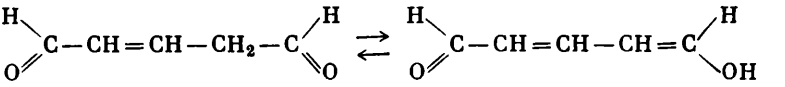


I II III

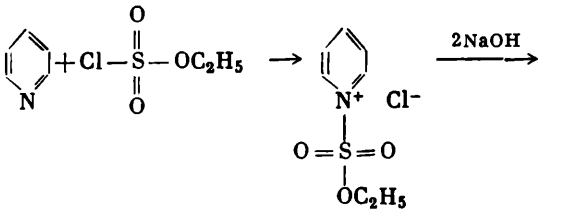
The three formulas on the right (III) show the π-electrons attracted to the nitrogen atom (as compared with the CH group in benzene) and the electron impoverishment (also in comparison with benzene) of the other units of the heterocycle, which is distinctly reflected in the properties of pyridine described below.

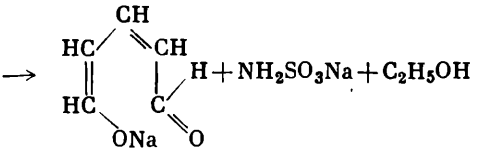
This structure is also clearly confirmed by the action of bases on the products resulting from the N-addition to pyridine of alkyl or aryl halides (Zincke) or of substances of acid chloride type, such as chlorocyanogen or chlorosulphonic ester. The nitrogen atom of pyridine has a free pair of electrons and, by virtue of this, has basic properties. Therefore, like all amines, it readily adds methyl iodide and also the halogen derivatives mentioned above.

In all similar cases, the derivatives of glutaconic dialdehyde or its tautomeric enol form are produced:

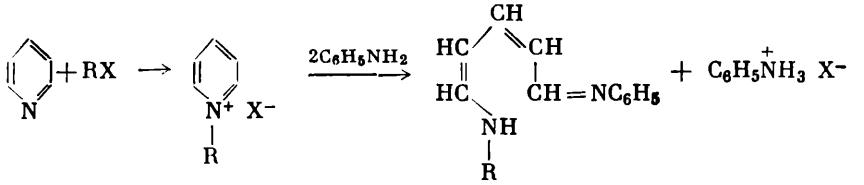


When pyridine is reacted first with chlorosulphonate and then with alkali, the sodium enolate of glutaconic dialdehyde is formed:





The interaction with an alkyl halide and then with aniline yields the enamine form of the dianil of glutaconic dialdehyde:

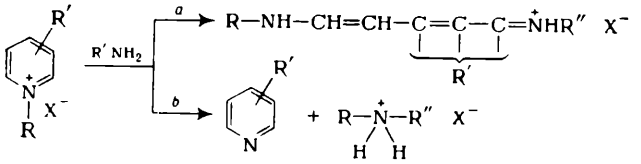


This type of fission of the pyridine ring is used in the synthesis of open-chain systems with conjugated double bonds. The resulting compounds of the general formula

$$RNHCH=CH-CH=CH-CH=NC_6H_5$$

where R = C_6H_5 or a substituted phenyl, usually 2,4-$(NO_2)_2C_6H_3$, are intensely coloured polymethine dyes (see also the synthesis of azulene according to Ziegler, Volume IV).

Whether the reaction proceeds in the direction of ring-opening with the formation of a derivative of glutaconic dialdehyde (pathway *a*) or to the side of separation of the ring from RX (pathway *b*) depends on the ratio of the bond strengths between the radicals and the nitrogen in the resulting ammonium (pyridinium) salt*:



As to the radicals R, the ease of their detachment from the nitrogen atom and, hence, the predominance of pathway *b* diminishes in the following series (M. I. Kabachnik):

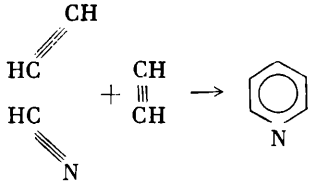
$$-CN > -SO_2O^- > -SO_2OR > C_6H_3(NO_2)_2 > C_6H_2(NO_2)_3 > > C_{10}H_5(NO_2)_2- > -COC_6H_5 > Br$$

The enhanced electron-releasing properties of the substituent R′ in the pyridine ring and the transfer of this substituent from the

* The manner in which the substituent R′ is written in the formula implies the possibility of finding it at any (2, 3 or 4) carbon atom.

β- to the γ-position decrease the electrophilic properties of alpha-carbon atoms and, consequently, increase the resistance to the nucleophilic attack of the ring-opening amine. As a result, the elimination of RX by the amine (pathway *b*) becomes predominating The more powerful the attacking amine as a base, the more probable is pathway *a* (A. F. Vompe).

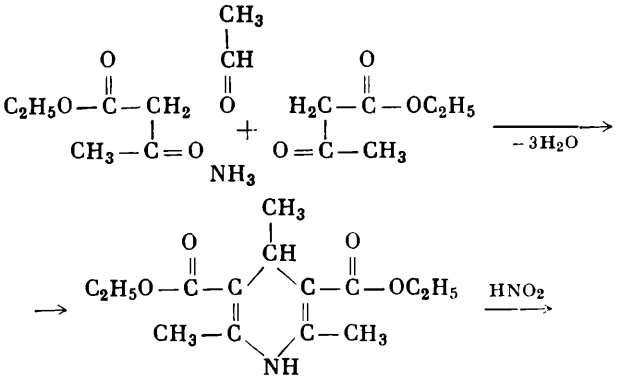
Synthesis of the Pyridine Ring. In 1877 Ramsay prepared pyridine using the modified Berthelot synthesis (page 22), by passing a mixture of acetylene and hydrocyanic acid through a red-heat tube:

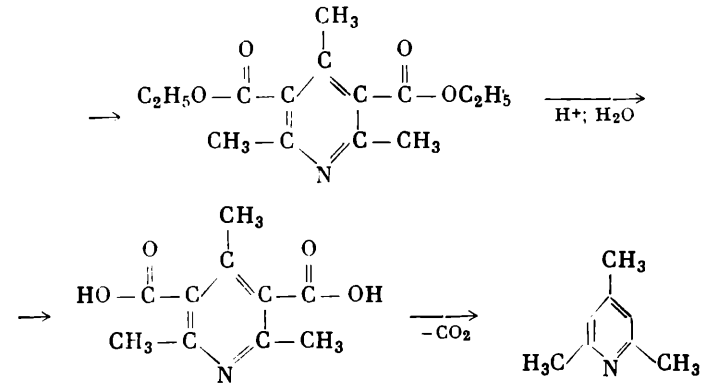


Passing a nitrogen atom excited by a high-frequency electromagnetic field through benzene, B. M. Mikhailov observed the formation of pyridine. The nitrogen atom in this case displaced the CH group.

Though these syntheses are rather graphic, they are of no preparative value and give a negligible yield of the product.

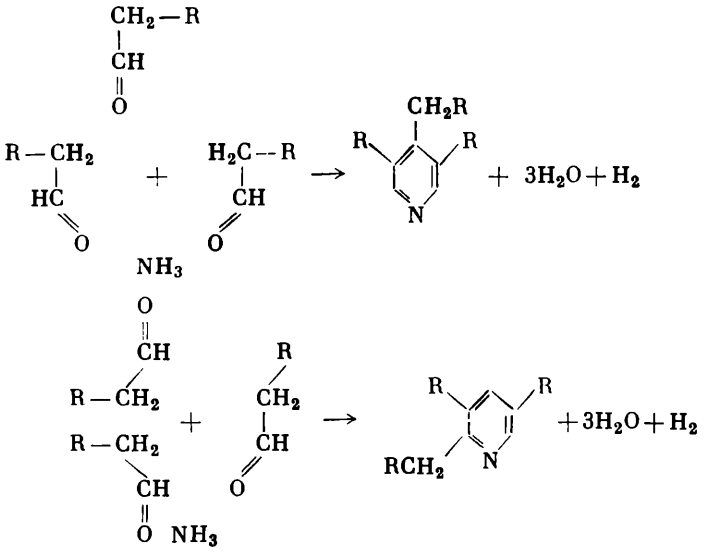
An important confirmation of the structure of the pyridine ring is afforded by the Hantzsch synthesis, the first stage of which is the interaction of acetoacetic ester with an aldehyde and ammonia (aldehydeammonia is taken for the reaction) leading to the ethyl ester of 2,4,6-trimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid. Under the influence of nitrous acid this ester loses two hydrogen atoms and is transformed into the aromatic system of pyridine. Then the ester groupings are subjected to hydrolysis and decarboxylation (aromatic carboxylic acids are known to readily lose their carboxyl groups when heated in the presence of alkali). In this way, 2,4,6-trimethylpyridine or **collidine** is synthesized:





By oxidizing its methyl groups to carboxyl groups and decarboxylating once more it is possible to obtain pyridine.

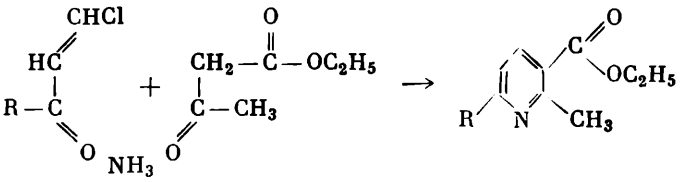
The passage of a mixture of the aldehyde RCH_2CHO with ammonia over alumina at 400°C yields a mixture of pyridine homologues which are formed by a scheme similar to that of the Hantzsch synthesis (A. E. Chichibabin, M. P. Oparina, P. A. Moshkin):



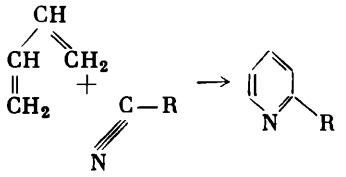
Thus, this synthesis gives a mixture of isomers subject to separation.

A scheme similar to the preceding schemes is used to synthesize dialkylpyridinemonocarboxylic acids from β-chlorovinyl ketones, acetoacetic ester and ammonia (A. N. Nesmeyanov, N. K. Kochet-

kov):

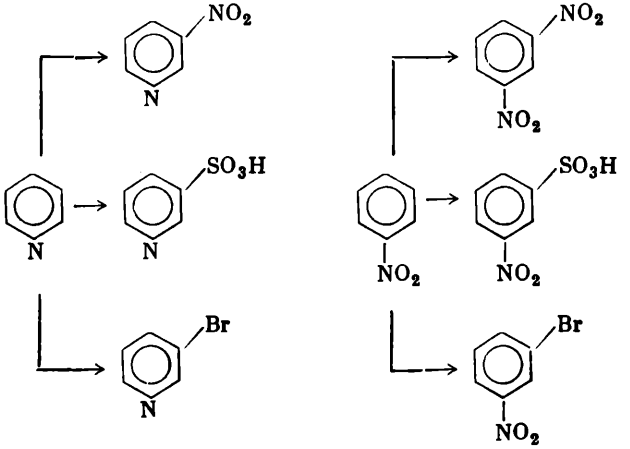


When a mixture of a nitrile and a diene hydrocarbon is heated up to 400°C, substituted pyridines are smoothly formed (Janz and MacKellogg):



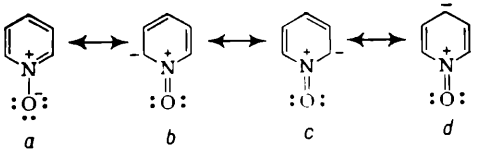
Piperidine (obtained by synthesis from pentamethylened iamine) when subjected to dehydrogenation over a catalyst (metals of Group VIII) is converted into pyridine.

Pyridine as an Aromatic Heterocycle. Electrophilic Substitution Reactions Pyridine is much more resistant to electrophilic attacks than benzene and even nitrobenzene. Only under severe conditions and with low yields can pyridine be nitrated, sulphonated and brominated in the β-position The scheme below shows the similarity to the substitution in nitrobenzene:



A second substituent cannot be introduced at all by these reactions. Thus, the nitrogen atom of pyridine, because of its stronger electronegative character than that of the CH group, has an attraction for

electrons, which results in a general lowering of the electron density on all the carbon atoms in the hydrocarbon chain of the ring. This is enhanced by the fact that in acid media (nitration, sulphonation) pyridine is converted to the salt, and the nitrogen atom becomes an ammonium nitrogen, i.e., positively charged, and therefore even more electron-attracting and capable of deactivating the ring towards electrophilic attacks. H. J. den Hertog worked out a method for overcoming this orientational effect of the nitrogen atom through the oxidation of pyridine by hydrogen peroxide to the N-oxide of pyridine:

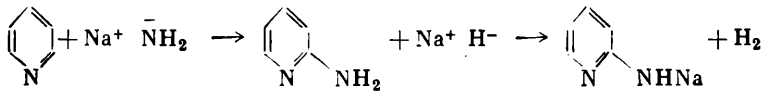


a *b* *c* *d*

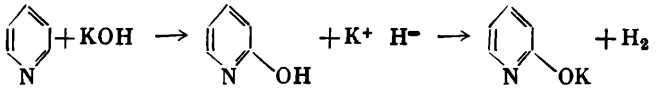
The oxides of tertiary amines, say, $(CH_3)_3\overset{+}{N}—\bar{O}$, have a semipolar bond, $\overset{+}{N}—\bar{O}$. In the pyridine oxide, at the moment of attack on the α- or γ-position by an electrophilic reagent, there may occur a rearrangement of the electronic system according to the schemes given in the three formulas on the right: oxygen becomes attached to the nitrogen atom through a double bond due to the migration of one π-pair of electrons to the α- or γ-carbon atom, as a result of which α- or γ-electrophilic substitution is possible. Thus, the nitration with an almost quantitative yield occurs at the γ-position. The oxygen atom can then be removed by reducing agents. By reducing γ-nitropyridine one can easily prepare γ-aminopyridine.

A remarkable property of the N-oxide of pyridine is its susceptibility to nucleophilic attacks similar to those described below for pyridine itself. This is accounted for by the fact that in the absence of electrophilic attacks the pyridine N-oxide has a structure close to structure *a* and its nitrogen atom, owing to its positive charge, is even more capable of attracting electrons than the nitrogen atom in pyridine. This is what reveals itself during nucleophilic attacks on the α- and γ-positions.

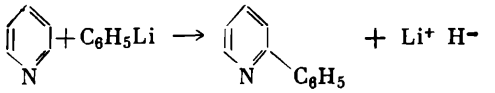
Nucleophilic Substitution Reactions in Pyridine. A. E. Chichibabin and O. A. Zeide have found that when pyridine is heated to about 130°C in xylene solution with sodamide, α-aminopyridine is obtained in good yield. The reaction with potassamide gives α-aminopyridine and its γ-isomer. The reaction with sodamide is a typical nucleophilic attack on the aromatic nucleus:



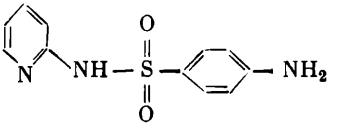
At a considerably higher temperature (about 400°C) such a reaction occurs also between pyridine and solid potassium hydroxide:



Even more powerful nucleophiles, such as organometallic compounds of alkali metals, exert an analogous effect on pyridine but only under milder conditions:



Especially important is the Chichibabin amination reaction. Numerous α-substituted derivatives of pyridine have been obtained by this reaction. Among them mention should be made of the sulpha drug **sulphapyridine** which was formerly extensively used in medicine:

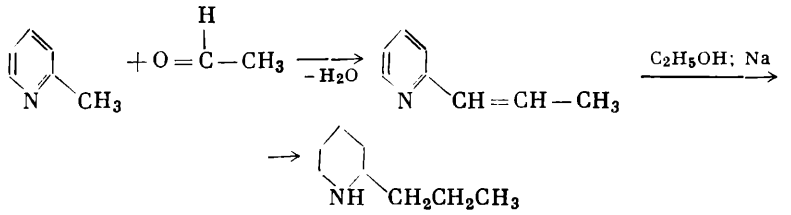


Reactions of the Side Chains of Pyridine Homologues (and Derivatives). It has already been pointed out that on oxidation, say, with the chromic acid mixture or potassium permanganate the side chains of pyridine (like those of benzene) are lost, the carboxyl groups being left. Particularly important is the preparation by this method of β-pyridinecarboxylic or **nicotinic acid**, which is produced by oxidizing the alkaloids nicotine and anabasine (neonicotine) (see Volume IV). In this way, from γ-methylpyridine there can be obtained γ-pyridinecarboxylic or **isonicotinic** acid. For the uses of these acids, see below.

The air oxidation of methylpyridines over vanadium pentoxide leads to the corresponding aldehydes.

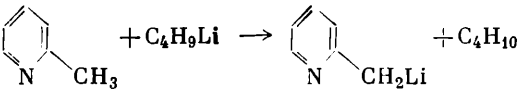
The hydrogen atoms of α- and γ-methyl groups in methylpyridines are highly replaceable and are similar in this respect to the hydrogens of the methyl groups in *o*- and *p*-nitrotoluenes. Thus, methylpyridines enter into croton-type condensation reactions with aldehydes, a fact used by Ladenburg for the synthesis of one of the simplest alkaloids, **coniine** (a poison present in the plant hemlock), which

is *n*-propylpiperidine:

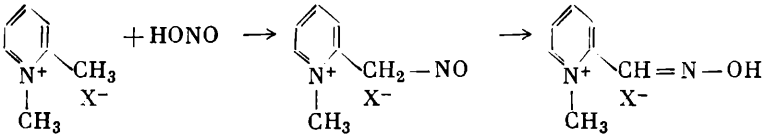


When α-methylpyridine is made to condense with formaldehyde and the resulting β-(α-pyridyl)-ethanol is dehydrated, α-vinylpyridine is obtained, which is used for copolymerization with butadiene in the industrial production of special types of rubber.

The hydrogen atom of α-methylpyridine is readily replaced under the influence of alkyl-lithium by lithium to give α-lithiummethylpyridine, which can be used for ordinary syntheses of organometallic compounds (recall that in toluene the hydrogen atom of the methyl group is replaced only on metalation by means of alkylsodium but not alkyl-lithium):



The reactivity of methyl groups is even higher in halogen methoxides of pyridine homologues, which are nitrosated to yield the oximes of the corresponding aldehydes (see Volume I, page 185):

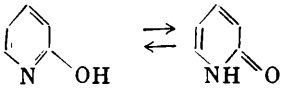


B. Hydroxypyridines and Aminopyridines

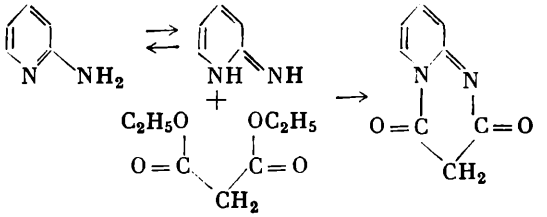
Hydroxypyridines (or pyridones) and aminopyridines (α- and γ-) are synthesized by means of the direct nucleophilic substitution reaction in pyridine described above or by electrophilic substitution in pyridine N-oxide. The β-derivatives are produced via the β-sulpho- and β-nitro derivatives of pyridine, which are synthesized by direct electrophilic substitution or Hofmann degradation (NaOCl) of the amide of nicotinic acid (nicotinamide) with the formation of β-aminopyridine.

The β-hydroxy- and β-aminopyridines sharply differ from the α- and γ-derivatives. Thus, the β-aminopyridines more closely resemble the corresponding derivatives of benzene. For instance, in contrast

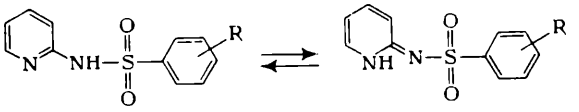
to α- and γ-aminopyridines, β-aminopyridine is readily diazotized; α- and γ-hydroxypyridines are tautomeric with the corresponding pyridones:



An analogous (aminopyridine-pyridoneimine) tautomerism is also characteristic of aminopyridines (Chichibabin). In particular, this type of tautomerism accounts for the formation of numerous cyclic derivatives from α-aminopyridine and bifunctional compounds, such as malonic ester:

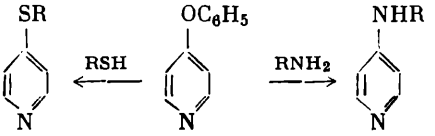


The position of tautomeric equilibrium in the case of substitution in aminopyridines is essentially dependent on the substituent in NHX. For example, as shown by M. I. Kabachnik, T. A. Mastryukova, Yu. N. Sheinker and I. K. Kuznetsova, in the arylsulphoaminopyridine series, depending on the nature of the radical R, the acidic properties of the forms are basically altered and the position of the equilibrium is changed. Thus, a 80-percent aqueous solution of dioxan contains 90 per cent of imido-form II with R = *p*-NO_2, and about 90 per cent of amido-form I with R = *p*-$N(CH_3)_2$. A complete quantitative determination of the acidity and of the position of tautomeric equilibrium for this system has been made by means of spectroscopy and the Hammett method of σ,ρ-analysis:



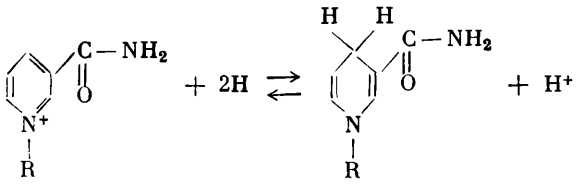
I II

The α-alkoxy- and readily available γ-phenoxypyridines smoothly exchange their alkoxy (or phenoxy) group with amines, mercaptans, etc., being converted into the corresponding γ-substituted pyridines (A. F. Vompe):

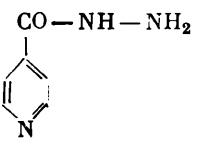


C. Physiologically Active Substances with the Pyridine Ring

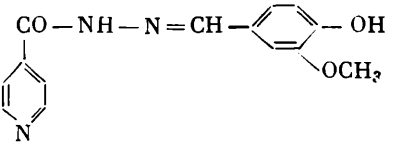
We have already mentioned β-pyridinecarboxylic, or nicotinic, acid (niacin). Its amide, **nicotinamide** or niacinamide, is nothing more than vitamin PP. The absence or deficiency of this vitamin in the human diet (the daily requirement is from 0.03 to 0.05 mg) causes the disease pellagra which is more widespread in localities where natives live almost exclusively on "polished" rice. The point is that nicotinamide is part of certain vital enzymes, say, codehydrogenases I and II which function as a dehydrogenation-hydrogenation catalyst in accordance with the following scheme (for the meaning of R, see Volume IV under "Enzymes"):



The diethylamide of nicotinic acid is used as a cardiac stimulant under the trade name of **Coramine** (*nikethamide*). The derivatives of isonicotinic acid, **isonicotinic acid hydrazide** (*isoniazide*) and **phthivazid** (*vanicide*), are employed medicinally in the treatment of tuberculosis.



Isonicotinic acid hydrazide (isoniazide)



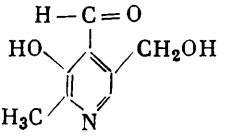
Phthivazid (vanicide)

The important derivatives of pyridine are the alkaloids **nicotine**, its isomer **anabasine**, and **nicotyrine** (see Volume IV, "Alkaloids").

4-Amino-3,5,6-trichloropyridine-2-carboxylic acid is one of the most potent herbicides: 2 grams of this acid can destroy vegetables over an area of 1 hectare.

The term vitamin B_6, which was formerly applied to a single substance, **pyridoxin** (*adermin*), was found to include not only pyridoxin II but also the related substances **pyridoxal** I and **pyridoxamine** III, in which the CH_2OH group in position 4 is replaced by CHO and CH_2NH_2, respectively (pyridoxin was isolated from rice-

bran in 1939 by Odake):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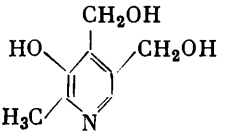
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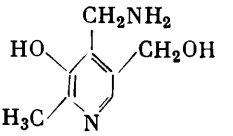

III

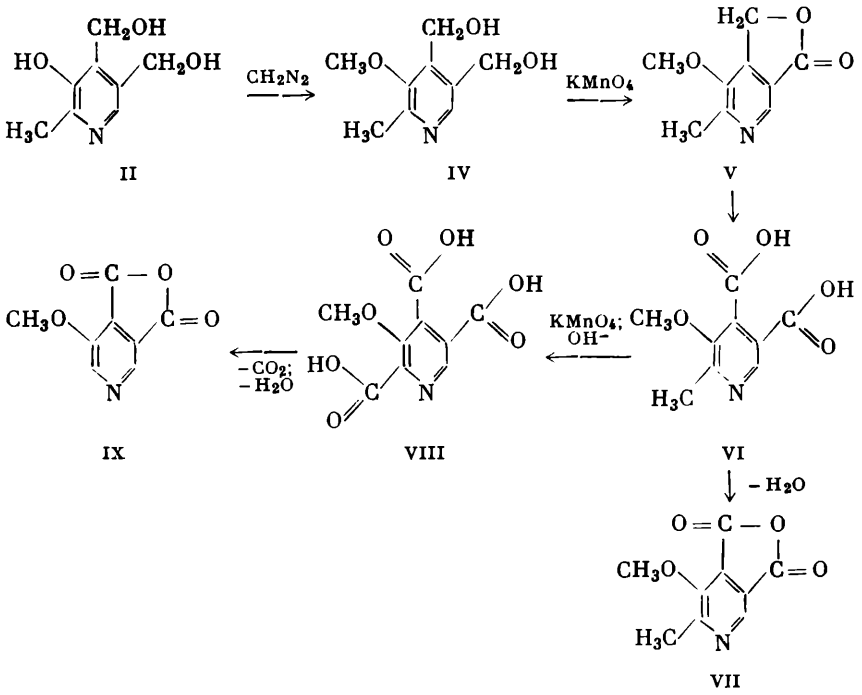
These vitamins are part of the structure of enzymes that regulate the protein metabolism and catalyse, say, the reactions of *trans*-amination of amino acids and their decarboxylation.

As an example, let us consider the elucidation of the structure of pyridoxin, $C_8H_{11}O_3N$, accomplished by R. Kuhn and others. Pyridoxin gives characteristic reactions of the pyridine ring and has three active hydrogen atoms (according to Tserevitinov).

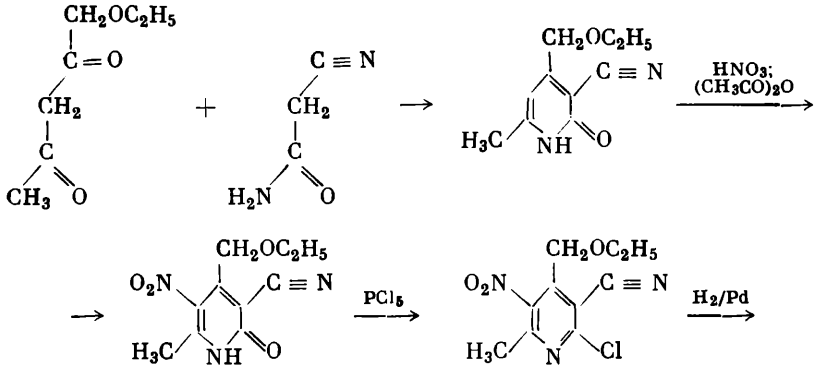
The Schotten-Baumann benzoylation of pyridoxin gives the tribenzoate, and when pyridoxin is treated with diazomethane only a monomethyl derivative (a phenol ether) is formed, i.e., two of the three mobile hydrogen atoms belong not to the phenolic but to the alcoholic hydroxyl groups of the side chains which are not methylated by diazomethane. These chains can have each only one carbon atom, i.e., both groupings must be methylol ones (CH_2OH) since five of the eight carbon atoms are present in the pyridine ring and one in the methyl group (its presence has been proved by oxidation). This reasoning is supported by the fact that the acids resulting from the oxidation of pyridoxin retain the same number of carbon atoms as in the parent compound. The monomethyl (with respect to the phenolic hydroxyl group) ether mentioned above can be oxidized in the following sequence: lactone V, dicarboxylic acid VI and tricarboxylic acid VIII, the methoxyl group remaining intact.

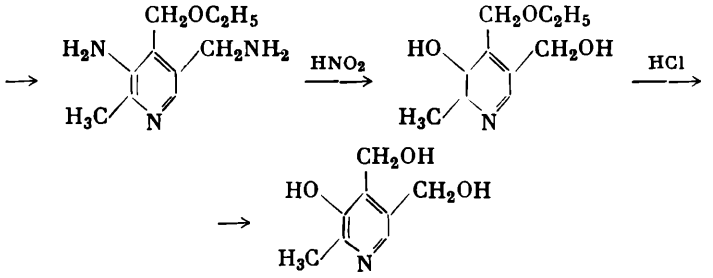
The formation of lactone V proves that the alcoholic groups carry chains occupying the neighbouring positions. This is also confirmed by the ring-closure of dibasic acid VI formed after the oxidation of the lactone, to give cyclic anhydride VII. Finally, on energetic oxidation in alkaline medium the methyl group is lost and tricarboxylic acid VIII is formed, which on heating decarboxylates to a dibasic acid capable of giving anhydride IX. The acid VIII with ferric chloride gives a colour characteristic of α-pyridinecarboxylic acids; the dibasic acid corresponding to anhydride IX does not give this colour. Thus, the following conclusions can be made: (a) the methyl group oxidized to a carboxyl group and then removed had occupied the α-position; and (b) the other two carboxyl groups which are next to each other occupy not the α-position but are in the β- and γ-positions. The phenolic hydroxyl group of pyridoxin occupies another β-position, which has been established on the basis of an analogy between the UV spectra of pyridoxin and β-hydroxypyridine. The

disposition of the groups has been conclusively proved by the synthesis of acid VIII.

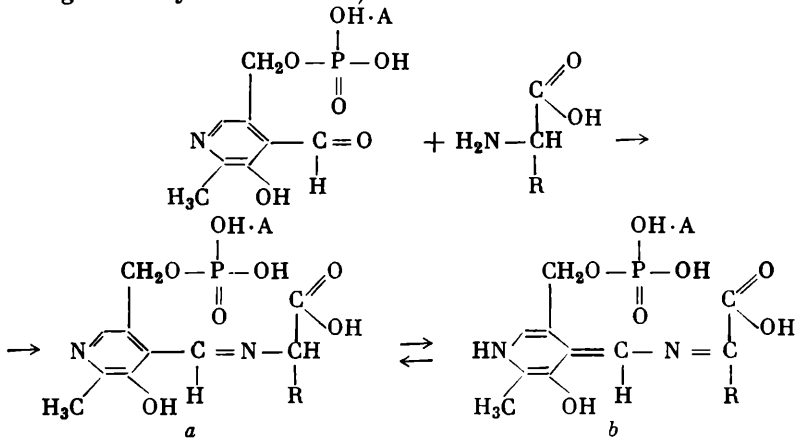


Numerous methods have been devised for synthesis of vitamins B_6, in particular, pyridoxin. They are all rather complicated. Below is given one of the methods:

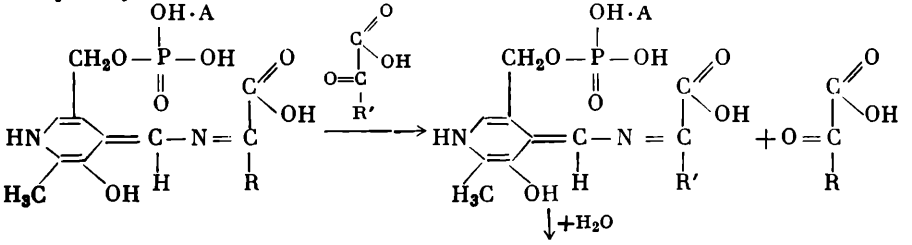


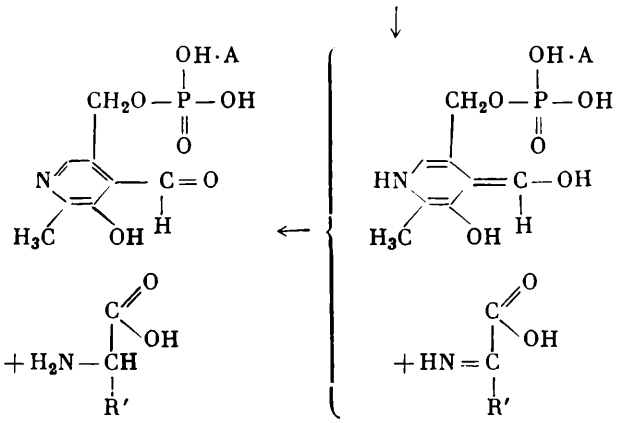


M. M. Shemyakin and A. E. Braunshtein have developed the theory of catalysis of amino-acid conversions by means of pyridoxal-containing enzymes. Pyridoxal esterified at the alcoholic hydroxyl group by phosphoric acid is bound by the same acid to a specific protein molecule (apoenzyme). With an amino acid the aldehyde function forms a Schiff's base—azomethine (the protein apoenzyme is designated by the letter A):

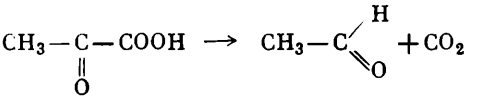


In the tautomeric form *b* the amino-acid part of the molecule becomes similar to an α-ketonic acid residue, say, of the pyruvic acid type. It has a very reactive group, —N=C(R)—COOH, which is capable of exchanging with other ketonic acids and which is readily hydrolysed with elimination of the amino acid:





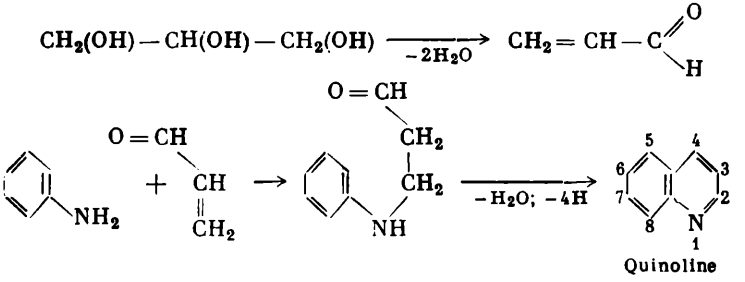
Thus, the ketonic acid is converted into an amino acid, and also one amino acid is transformed into another one (*trans*-amination). Moreover, the decarboxylation of α-ketonic acids (and also of α-aminoacids) also proceeds via the tautomeric form *b*. An example is the decarboxylation of pyruvic acid to acetaldehyde:



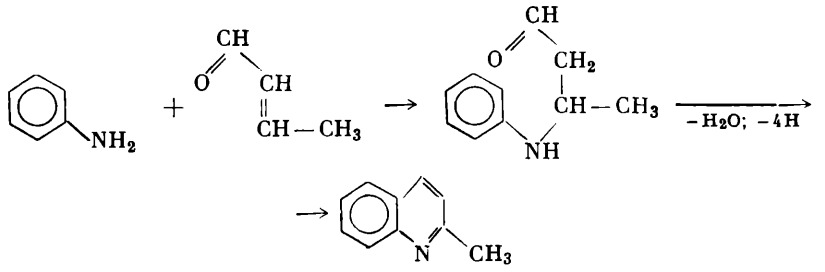
A number of other conversions could also be cited, in which the functional groups in the radical R of an amino acid (if there are any) remain intact.

D. Quinoline and Its Derivatives

Quinoline, C_9H_7N (2,3-benzopyridine) is prepared by the well-known Skraup synthesis, in which aniline is heated with glycerol and sulphuric acid in the presence of nitrobenzene as an oxidizing agent. Glycerol and sulphuric acid form acrolein which adds on aniline; the resulting β-phenylaminopropaldehyde (with the participation of an oxidizing agent which removes the extra hydrogen atoms) undergoes ring-closure to give quinoline:



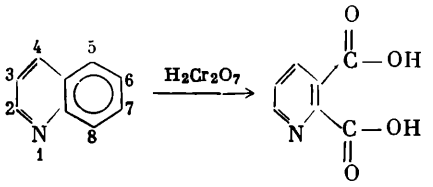
The use of ring-substituted anilines leads to quinolines substituted in the benzene ring. If acetaldehyde (or its trimer paraldehyde) is used instead of glycerol, then the intermediate stage of addition of aniline to the crotonaldehyde resulting from the condensation leads to α-methylquinoline which is known as **quinaldine** (Döbner-von Miller synthesis):



In this case, nitrobenzene is not needed since the aldehyde itself serves as an oxidizing agent (hydrogen-acceptor).

Both methods using different amines and aldehydes make it possible to synthesize a great variety of quinoline derivatives and are therefore employed in the chemical-pharmaceutical and aniline-dye industries.

The structure of quinoline as 2,3-benzopyridine or, what is the same thing, 1-azanaphthalene, is proved by its oxidation to **quinolinic acid**—the aza analogue of phthalic acid:

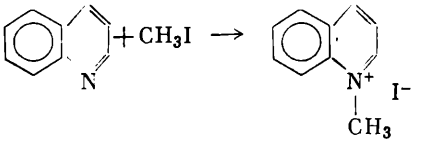


The synthesis from aniline also affords a clear proof of the α,β-benzopyridine structure of quinoline.

Quinolinic acid can be decarboxylated to pyridine. The *ortho*-position of its carboxyl groups is deduced from the formation of an anhydride analogous to phthalic anhydride. It is interesting that the pyridine ring is found to be more stable on oxidation than the benzene ring.

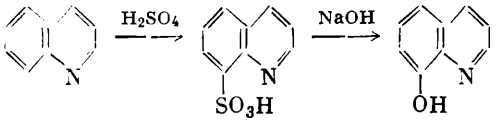
Quinoline is an oily liquid with a characteristic unpleasant smell, which boils at 338°C. It is almost insoluble in water. Quinoline is an even weaker base than pyridine, but it forms salts with strong

acids and quinoline iodomethoxide with methyl iodide:



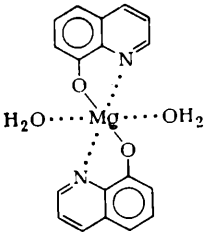
Electrophilic substitutions (nitration, sulphonation) in quinoline proceed more difficultly than in benzene, and chiefly in the benzene ring, in positions 5 and 8; bromination under drastic conditions (180°C) occurs in position 3.

Sulphonation of quinoline gives 8-quinolinesulphonic acid, from which **8-hydroxyquinoline** (*oxine*) is obtained by alkali fusion:



8-Hydroxyquinoline is widely used in analytical chemistry owing to its outstanding ability to form **oxinates**—insoluble inner-complex salts (**chelates**)—due to the participation of the free electron pair of nitrogen.

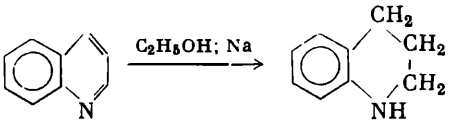
An example is the chelate oxinate of magnesium with two molecules of water bound into a complex:



8-Hydroxyquinoline and its sulphonic acid are used as antiseptics (**quinosol** or *chinosol*); 5-chloro-7-iodo-8-hydroxyquinoline (**enteroseptol**) is employed for the treatment of intestinal diseases. The last-named compound forms such a stable complex with ionic cobalt (but not the cobalt of cyanocobalamin—vitamin B_{12}) that the life of bacteria becomes impossible.

Nucleophilic attacks occur in the pyridine ring (at the α- and γ-position). In this way it is possible to prepare α-aminoquinoline and α-hydroxyquinoline (**carbostyril**), which are similar to their pyridine analogues in properties and, in particular, in tautomerism.

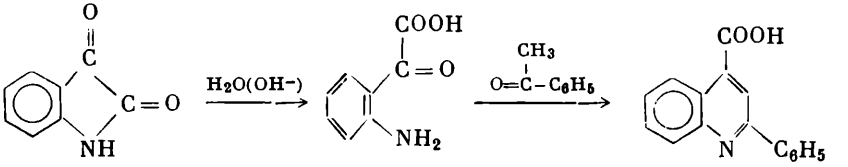
When reduced by the method developed by A. N. Vyshnegradsky quinoline forms **tetrahydroquinoline**



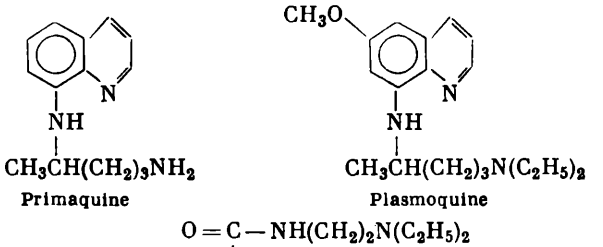
which has the properties of a secondary aromatic amine.

Among the natural derivatives of quinoline mention should be made of the alkaloids **quinine** and **cinchonine** (see Volume IV under "Alkaloids"). Many of the quinoline derivatives prepared synthetically are used as drugs and dyes.

Among the compounds used in medicine, the following should be mentioned: **atophan** (*cinchophen*) synthesized from isatin and acetophenone by the Friedländer method:

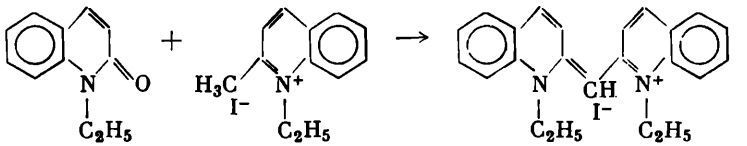


which is used as a remedy in arthritic diseases; **primaquine** and **plasmoquine** (*pamaquine*) which are antimalarial drugs affecting the gametes of the malarial plasmodium; and the anesthetic **percaine** (*sovcaine*).



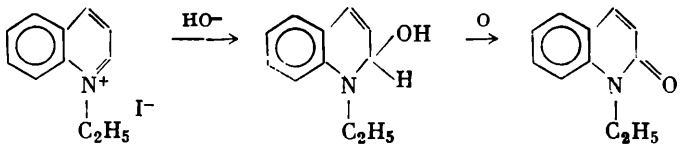
Particularly important are **cyanine dyes** used for sensitizing photographic emulsions as far as the red and infrared which do not affect silver bromide without a photosensitizing dye being included in the emulsion. The simplest dye of this type is **Ethyl Red** prepared by the condensation of N-ethyl carbostyril with quinaldine ethiodide (α-me-

thylquinoline):

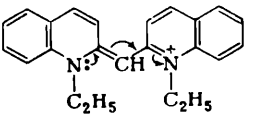


N-ethyl carbostyril Ethyl Red

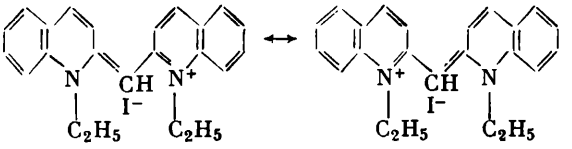
N-Ethyl carbostyril in its turn is prepared *in situ* through the air oxidation of N-ethyl-α-hydroxy-1,2-dihydroquinoline which results from action of alkali on quinoline ethiodide:



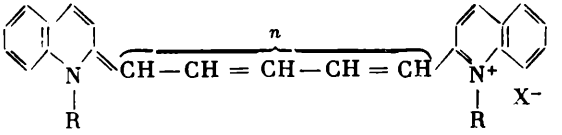
It should be noted that both halves in the formula of ethyl red (on the left and right of the central CH group) are identical in the arrangement of atoms and differ only in the disposition of electrons in the system of conjugated π-bonds. The ammonium positive charge is shown only on one nitrogen atom, the one on the right; in fact, as is always the case in such situations, mesomeric equilibration occurs, which may be expressed as follows:



or



Photosensitizing dyes that absorb light of a longer-wavelength region of the spectrum have a similar structure, the only difference being that the central CH group is replaced by a system of *n* CH groups joined together by a conjugated system of π-bonds:



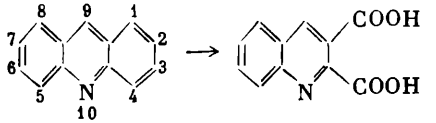
In this type of system, too, the positive charge is equilibrated mesomerically between the two nitrogen atoms along the system of conjugated bonds and, as a consequence, the energy difference between the first excited state and the ground state of the molecule becomes smaller.

The absorption region for such dyes can be accurately calculated with the aid of a simplest "box" model (see Volume IV, "Non-Benzenoid Systems").

E. Acridine

Acridine occurs in a small amount in the crude anthracene (green oil) of coal tar in which it was discovered by Graebe and Caro (1870).

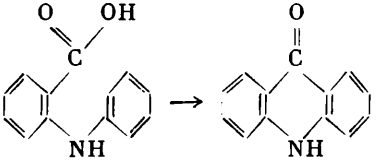
When subjected to oxidation acridine forms acridic or 2,3-benzopyridine-5,6-dicarboxylic acid*:



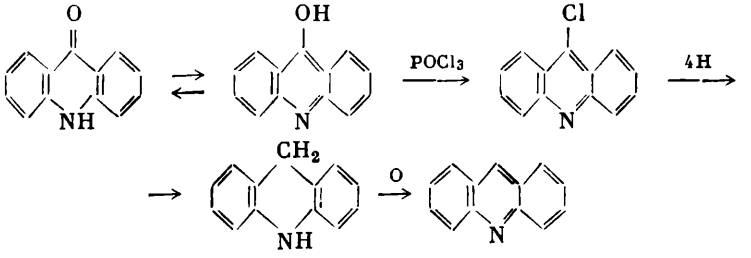
Acridine

Acridine melts at 111°C; it has very weak basic properties.

When N-phenylanthranilic acid is allowed to react with sulphuric or phosphoric acid, it undergoes ring-closure and forms **acridone**:

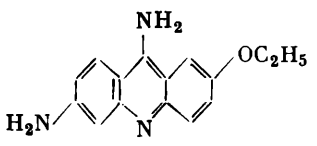


By reacting acridone (its tautomeric form, 9-hydroxyacridine) with PCl_5 or $POCl_3$, 9-chloroacridine is obtained. The reduction of 9-chloroacridine yields 9,10-dihydroacridine which is then oxidized to acridine:

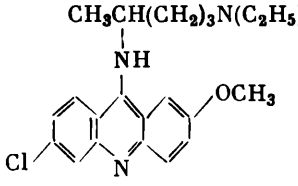


* The numbering system shown is also usually found in German and American publications. A different numbering of the nucleus is adopted in British publications.—*Tr.*

Hydroxy and amino derivatives of acridine are dyestuffs. Some of them are used as bactericides. Examples are yellow **rivanol** (*ethodin*) the aqueous solutions of which are used for disinfection of mouth, etc., and **atebrin** or **mepacrine** which is employed in medicine to combat the schizonts (the agamous stage) of the malarial plasmodium.

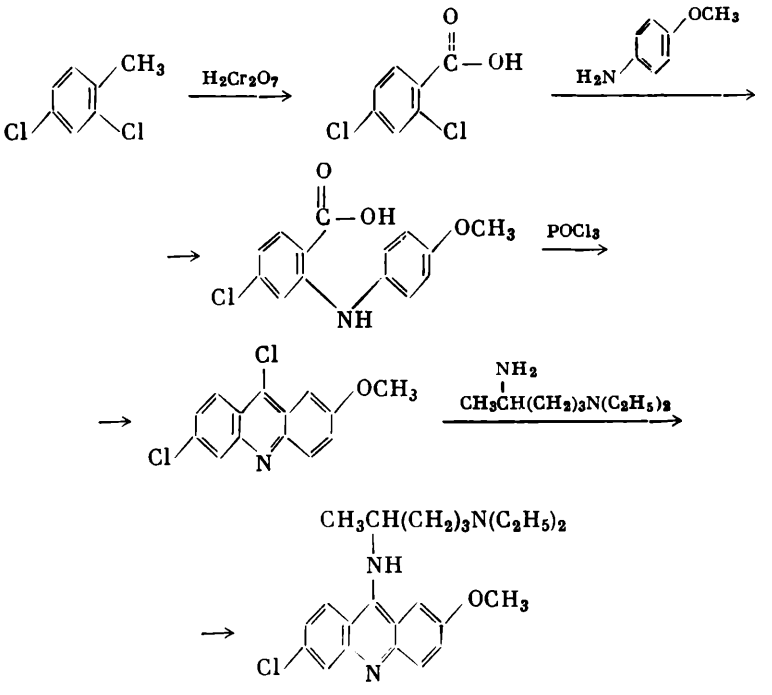


Rivanol (ethodin)



Atebrin (mepacrine)

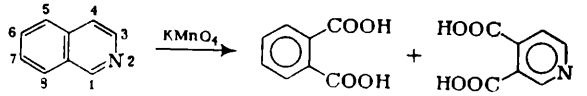
The synthesis of atebrin is as follows:



F. Isoquinoline

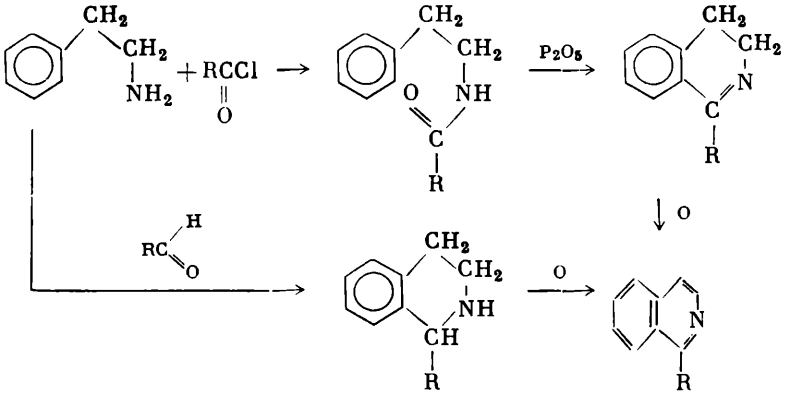
Isoquinoline (3,4-benzopyridine) is an isomer of quinoline. When isoquinoline is oxidized by potassium permanganate, it forms a mixture of phthalic acid and 3,4-pyridinedicarboxylic or **cinchomeronic**

acid, the last-named compound being isomeric with quinolinic acid:



Isoquinoline

This proves the presence and the relative positions of the benz and pyridine rings. Isoquinoline (m.p. 24°C, b.p. 240°C) is a somewhat stronger base than quinoline. The di- and tetrahydroisoquinolines hydrogenated in the pyridine ring are synthesized from β-aminoethylbenzene by the following two routes:



where R = H, alkyl, or aryl.

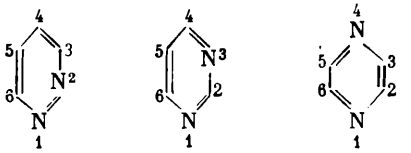
When these hydroisoquinolines are carefully oxidized or dehydrogenated, isoquinoline itself is obtained.

The skeleton of isoquinoline, usually hydrogenated, is present in the structure of a number of important alkaloids of complex structure: morphine, papaverine, the alkaloids of curare, etc. (see also Volume IV under "Alkaloids").

II.2. Six-Membered Heterocycles with Two Nitrogen Atoms (Diazines)

Three structures of diazines are known: 1,2-diazine, or **pyridazine**, 1,3-diazine, or **pyrimidine**, and 1,4-diazine, or **pyrazine** (they are all the simplest azines containing a ring composed of four carbon

atoms and two nitrogen atoms):

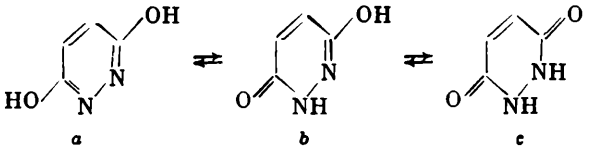


Pyridazine Pyrimidine Pyrazine

The first one is nothing more than the azine of maleic dialdehyde and can therefore be prepared from this dialdehyde and hydrazine hydrate.

A. Pyridazine

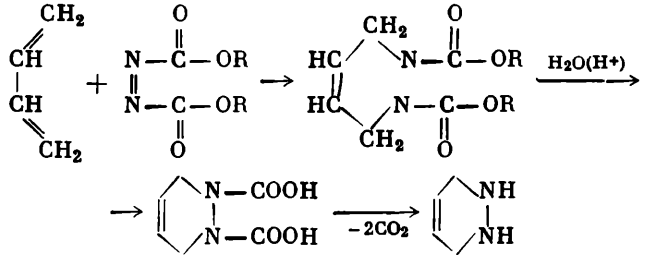
Pyridazine (m.p. 6.4°C, b.p. 207°C) is a very weak base, much weaker than pyridine but still stronger than pyrimidine and pyrazine. The resonance energy of pyridazine has been calculated to be equal to 22 kcal/mole. Pyridazine does not undergo electrophilic substitution reactions. The chlorine atoms in chloropyridazines, especially those in positions 3 and 6, are mobile to the same extent as they are in *p*-nitrochlorobenzene. Dihydroxypyridazine (the hydrazide of maleic acid), however, is more reactive in the form *b*.



a *b* *c*

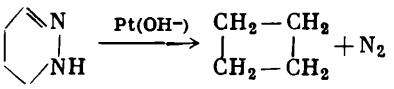
Thus, the methylation with diazomethane affords the O-methyl derivative of the form *b*.

The pyridazine ring is very resistant to oxidation. Tetrahydropyridazines can be obtained by diene synthesis:



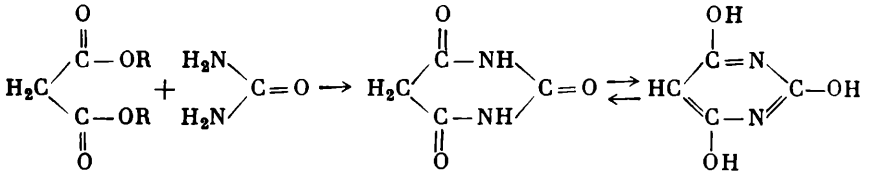
In the presence of alkali and platinum tetrahydropyridazines decompose with evolution of nitrogen and formation of cyclobutane

(R. Ya. Levina, Yu. S. Shabarov):



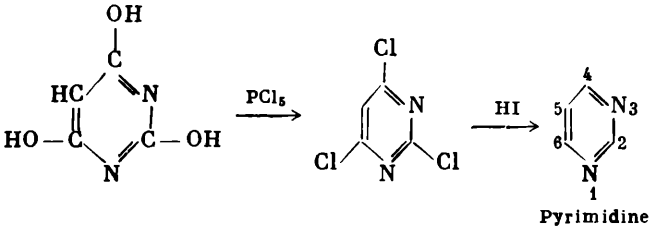
B. Pyrimidine

A very important heterocycle is **pyrimidine**. The pyrimidine nucleus is contained, along with purine derivatives (page 419), in physiologically highly important nucleic acids essential for the biosynthesis of proteins. Pyrimidine itself (m.p. 22°C, b.p. 124°C; readily soluble in water) does not show alkaline reactions but forms salts with strong acids (with one equivalent of acid). It can be synthesized via barbituric acid (the ureide of malonic acid or malonylurea) which itself is a very important derivative of pyrimidine:



Urea Barbituric acid

The reaction of barbituric acid with phosphorus pentachloride gives 2,4,6-trichloropyrimidine, the reduction of which with hydrogen iodide yields pyrimidine itself:

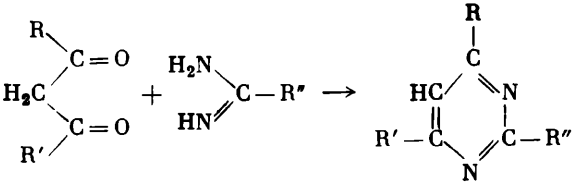


Pyrimidine

The tendency of pyrimidine for substitution reactions has been studied little. It may, however, be said that in this respect it differs from pyridine in just the same way as pyridine differs from benzene. Thus, pyrimidine is even less capable of electrophilic substitutions than pyridine, and if substitution does take place, the substituent enters position 5 (the β-position with respect to both nitrogen atoms). The action of sodamide on 6-methylpyrimidine leads, as the result of nucleophilic substitution, to 2-amino-6-methylpyrimidine, though the methyl group must have weakened the electrophilicity of the pyrimidine ring. In methylpyrimidines, the methyl groups 2, 4 and 6 enter into croton-type condensation reactions with aldehydes, just like the methyl groups of α- and γ-methylpyridines. 2-, 4-, and 6-Chloropyrimidines possess (like 2-, 4- and 6-chloronitrobenzenes)

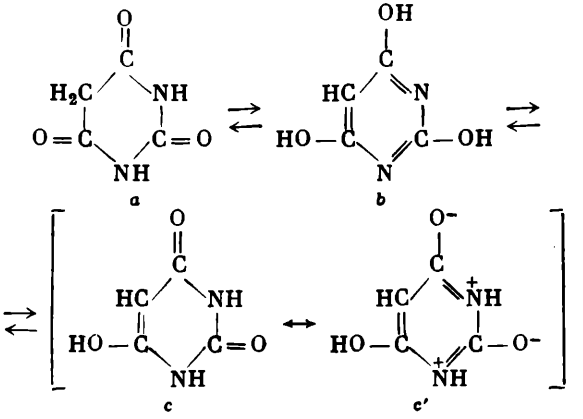
a reactive halogen which not only is replaced as the result of nucleophilic attacks but also enters into the Friedel-Crafts reaction with aromatic hydrocarbons. The hydroxy derivatives of pyrimidine have stronger acidic properties than phenols. The side-chain alkyl groups of pyrimidine homologues can be oxidized to carboxyl groups without disturbing the pyrimidine ring which is very resistant to oxidation. Substituted pyrimidines containing OH, NH_2 or other activating groups as substituents are nitrated, nitrosated and undergo azo coupling in position 5; the substituents are naturally in positions 2, 4 or 6 and direct into the *ortho*- and *para*-positions with respect to themselves. The amino group in position 5 is capable of undergoing diazotization, and the amino groups in positions 2, 4 and 6 are not affected by nitrous acid in the cold and when gently heated are displaced by a hydroxyl group.

The most general route for synthesis of pyrimidine derivatives is the condensation of 1,3-dicarbonyl compounds with substances having two amino groups (or an amino group and an imino group) at one carbon atom, such as urea, guanidine, or amidines:

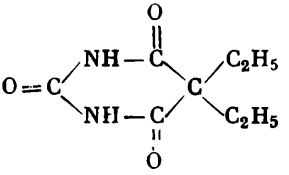


We have already seen in the case of barbituric acid that the hydroxy derivatives of pyrimidine exhibit tautomerism. Barbituric acid itself shows keto-enol and lactam-lactim tautomerism.

The main structure characteristic of barbituric acid in the solid state is structure *c*, i.e., the enol-lactam structure, which is anticipated to undergo a mesomeric shift to the side of the aromatic betaine structure *c'* (the resonance of structures *c* and *c'*).



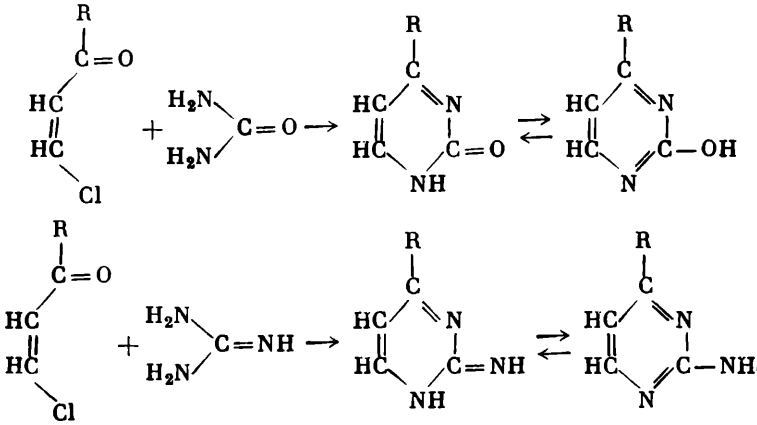
The condensation of urea with the ester of diethylmalonic acid yields diethylbarbituric acid (which is known as **Veronal**, *barbital* or *barbitone*, a well-known hypnotic).



For this acid, no conversion either into the tautomeric structure of the type *b* or into a structure of the type *c-c'* is possible, which accounts for a sharp decrease of the acidity ($K_a = ca.\ 10^{-4}$ for barbituric acid, and $K_a = 3.7 \times 10^{-8}$ for diethylbarbituric acid).

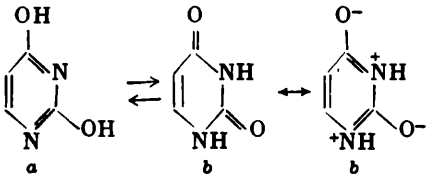
Apart from Veronal ($R=R'=C_2H_5$), many other dialkylbarbituric acids are known, which are used as hypnotics, for example: **Nembutal** [$R=C_2H_5$; $R' = CH_3CH_2CH_2CH(CH_3)$], **Amytal** [$R=C_2H_5$; $R'=(CH_3)_2CHCH_2CH_2$]; **Luminal** or *phenobarbital* ($R=C_2H_5$; $R'=C_6H_5$); **evipan** or *hexobarbitone* ($R=CH_3$; $R'=$ ); **Medinal** (the sodium salt of Veronal), etc., the number exceeding one hundred.

A good method for synthesizing 2-hydroxy- and 2-aminopyrimidines is the cyclization of β-chlorovinyl ketones with urea and guanidine:

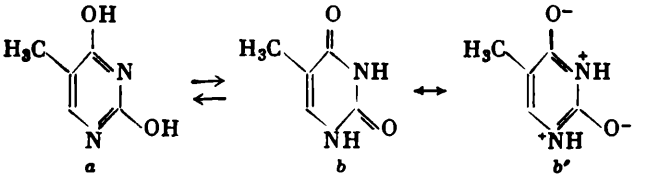


The hydrolysis of nucleic acids present in the cell nuclei results in the formation of three important derivatives of pyrimidine:

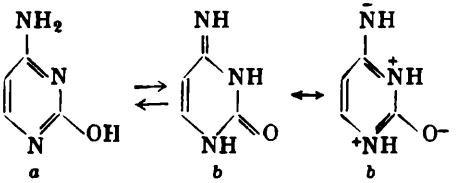
(a) uracil



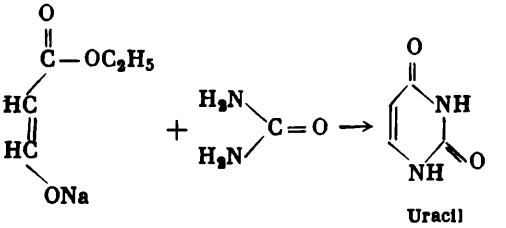
(b) thymine



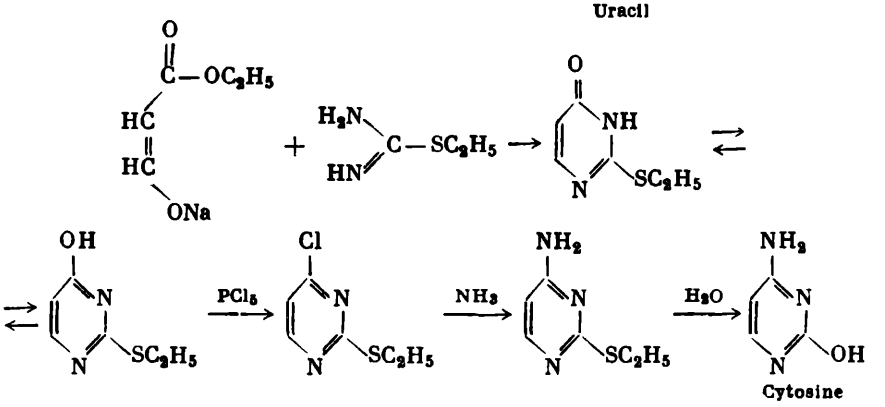
(c) cytosine



They can also be made synthetically, for example, starting from the sodium enolate of formylacetic ester and urea, thiourea or their derivatives. This is illustrated by the syntheses of uracil and cytosine:

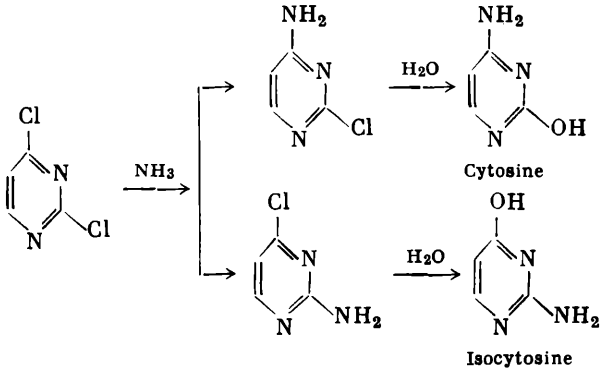


Uracil



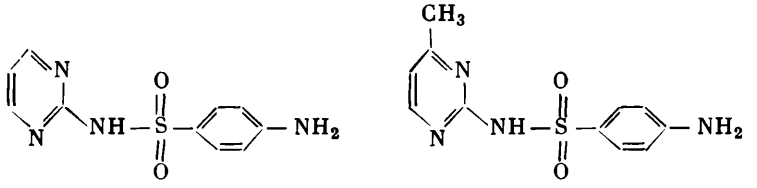
Cytosine

In the synthesis of cytosine, one can also start from 2,6-dichloropyrimidine (which in its turn is obtained from uracil and $POCl_3$) which is reacted first with ammonia and then with water:



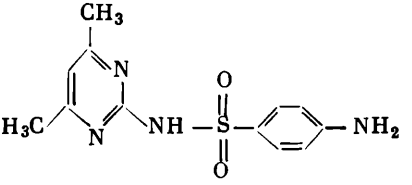
According to the data obtained predominantly by physical investigations, the structures *b* (page 409) should be regarded as the main tautomeric forms of thymine, uracil and cytosine. The electronic system of these structures is mesomerically shifted to the side of structures *b'* which have an aromatic character. Thus, these substances retain some aromaticity, despite the fact that the tautomers *a* are present only in solutions and in a rather small amount.

The group of pyrimidine derivatives include the most efficient of the sulpha drugs: **sulphadiazine** (*sulphapyrimidine*), **sulphamerazine,** and **sulphadimidine:**



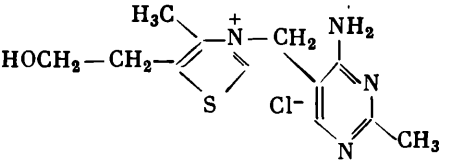
Sulphadiazine

Sulphamerazine



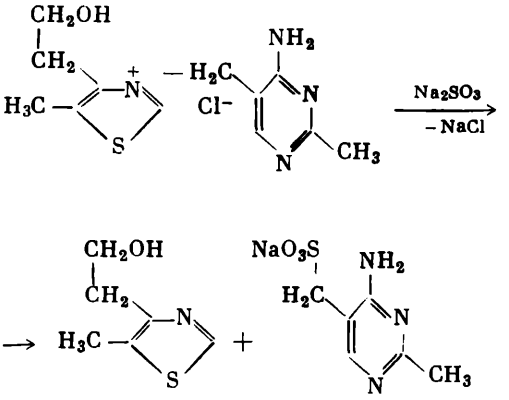
Sulphadimidine

Vitamin B_1, thiamin (*aneurin*), also contains the pyrimidine ring



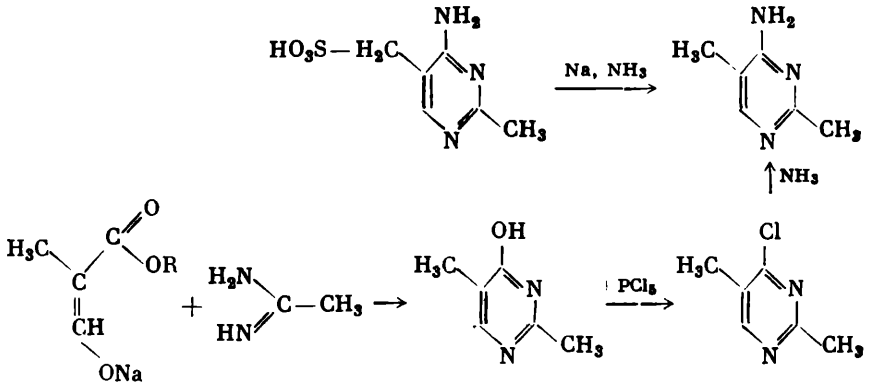
A deficiency of vitamin B_1 in food, say, in polished rice (the powdery "rice-polishings" constituting the outer surface of the grain is a source of the vitamin) may lead to beri-beri, a nervous disease known among natives in the East. The man's daily requirement of vitamin B_1 amounts to 4 mg. The need for this vitamin is accounted for by the fact that thiamin (in the form of its pyrophosphate ester) is present in the structure of the enzyme carboxylase which catalyses certain stages of metabolism in the organism (elimination of carbon dioxide from pyruvic acid) (see Volume II, page 163).

The determination of the structure of vitamin B_1 was mainly due to R. R. Williams and R. Grewe. The critical point in the elucidation of its structure is the disruption of thiamin by the action of sodium sulphite into the thiazole and pyrimidine rings:

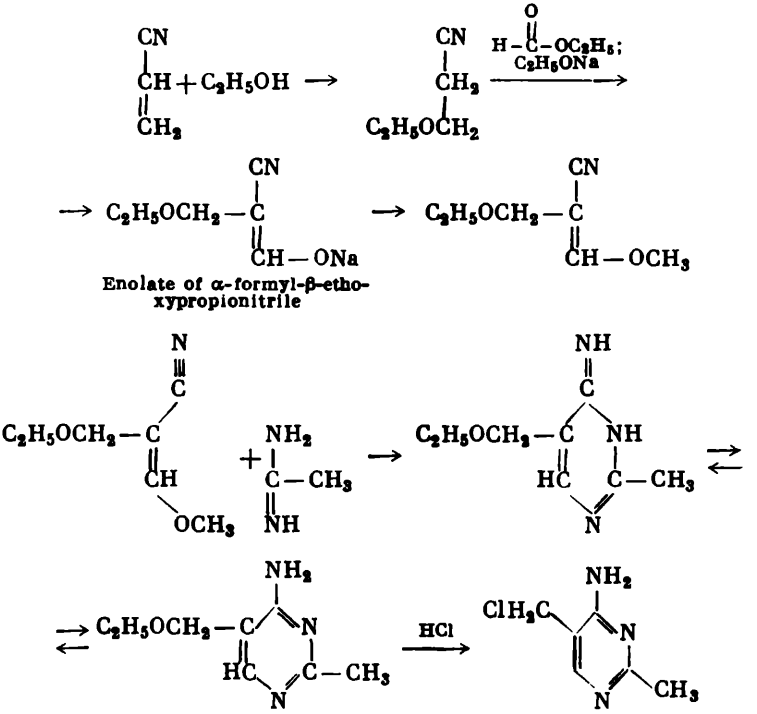


The reduction of the pyrimidine fragment by sodium in liquid ammonia led to dimethylaminopyrimidine, whose structure was

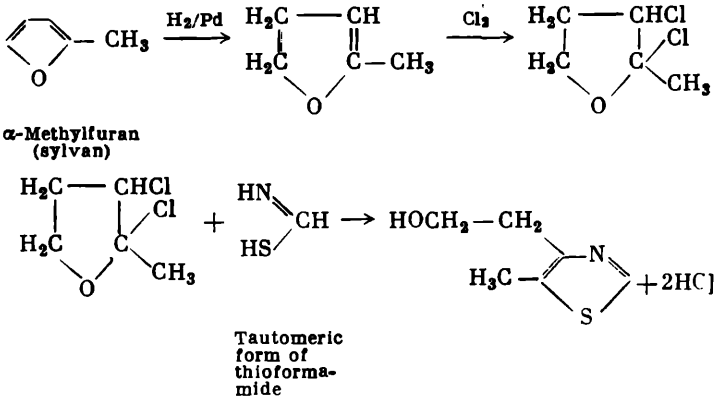
proved by the reverse synthesis:



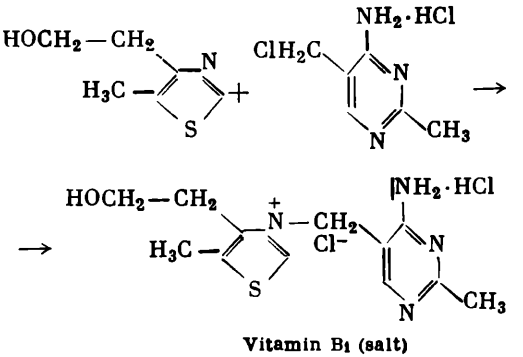
At present, in this country, thiamin is synthesized by a modification of the Williams-Andersag method, which has been developed by G. V. Chelintsev and Z. V. Benevolenskaya. The synthesis of the pyrimidine part of the vitamin B_1 molecule is as follows:



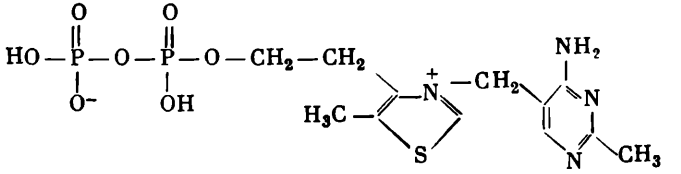
The thiazole part of the molecule is synthesized in the following way:



The union of the two moieties takes place as follows:



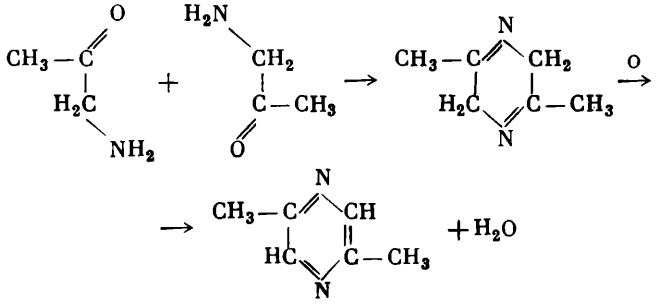
The conversion of thiamin into the pyrophosphate ester leads to a substance identical to the coenzyme of carboxylase—cocarboxylase



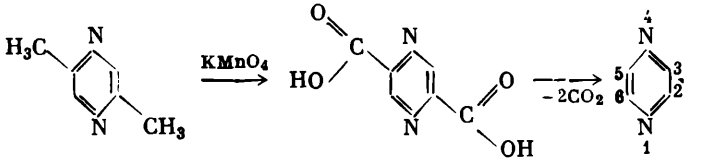
The enzyme carboxylase is formed by the union of the coenzyme with the corresponding protein.

C. Pyrazine

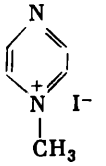
The spontaneous condensation of α-aminoketones yields dialkyldihydropyrazines which on oxidation by atmospheric oxygen or mercury oxide are converted into dialkylpyrazines:



The side-chain groups of pyrazine homologues can be transformed by gentle oxidation into carboxyls and the latter removed by decarboxylation. This results in the formation of pyrazine:

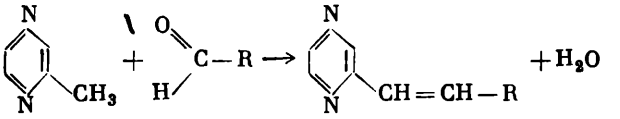


Pyrazine is a considerably weaker base than pyridine. It forms salts with one equivalent of acid in aqueous solution and with two equivalents of acid in nonaqueous media; with one equivalent of CH_3I it gives a quaternary ammonium salt:

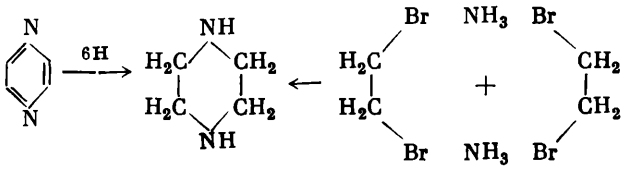


Pyrazine is even less capable of electrophilic substitution reactions than pyridine, and only the halogenation reaction is known at present for pyrazine. As an example of the susceptibility of pyrazine to nucleophilic attack may serve the amination effected by the action of sodamide. Methylpyrazine condenses with aldehydes in the same

way as α- and β-methylpyridines:

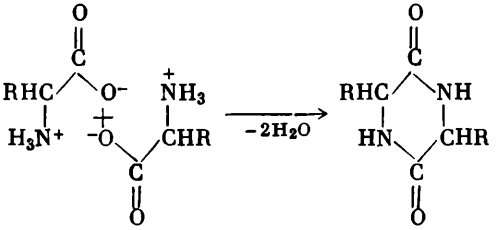


Pyrazine hydrogenates to give **piperazine** (hexahydropyrazine) which is more simply prepared (along with ethylenediamine) from dibromoethane and ammonia:



With primary amines (used instead of ammonia) there are obtained N-substituted piperazines.

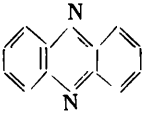
In contrast to pyrazine, piperazine is a strong base. **Diketopiperazines** which have already been described (see Volume II, pp. 170, 179) are made by heating α-amino acids:



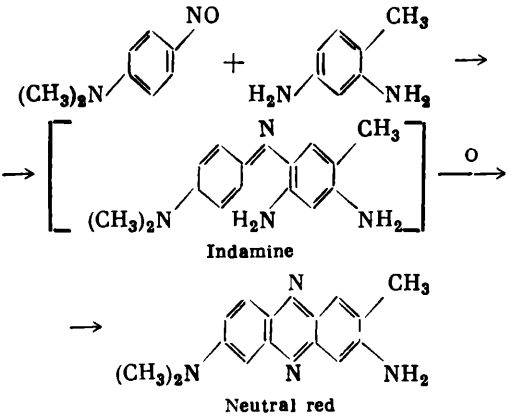
They can be reduced to piperazines.

Dyes of the indanthrene blue type which have been described in the section devoted to anthracene may also be referred to as pyrazines or more exactly, as dibenzopyrazines called **phenazines**.

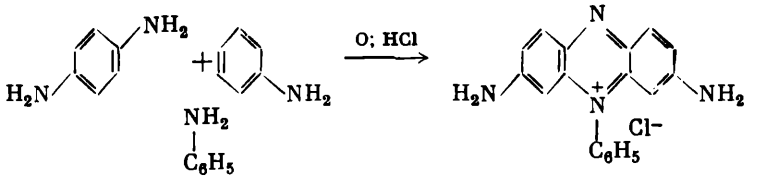
Indanthrene blue has a more complex skeleton than phenazine dyes which are prepared, for example, by the oxidation of a mixture of nitrosodimethylaniline and *m*-phenylenediamine (or its homologues). The reaction proceeds via the stage of condensation yielding indamine:



Phenazine

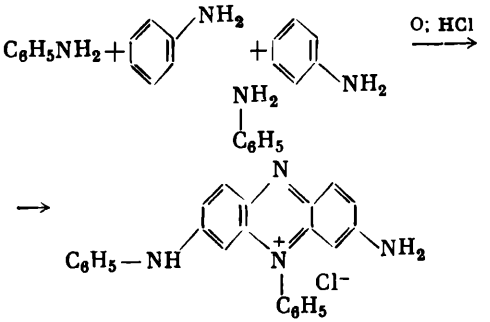


N-Phenylated phenazine dyes are called **safranines**, the simplest representative of which, **phenosafranine**, is obtained by the oxidation of a mixture of 1 mole of *p*-phenylenediamine and 2 moles of aniline:



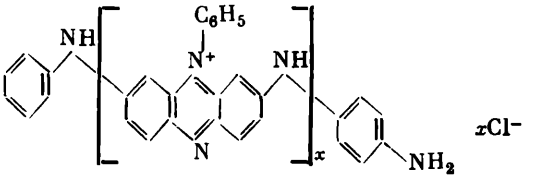
The positive ammonium charge is of course delocalized over all the four nitrogen atoms.

To this class also belongs the first (historically) aniline dye **Perkin's mauveine** (1856) which was prepared by oxidizing crude aniline



and therefore contained, along with the substance of the indicated structure, its homologues as impurities. The dye aniline black resulting from the oxidation of aniline with dichromate is assumed to have

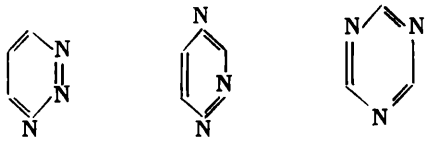
the phenazine structure too:



At present only those safranines which have a more complex structure find practical application.

11.3. Six-Membered Heterocycles with Three Nitrogen Atoms

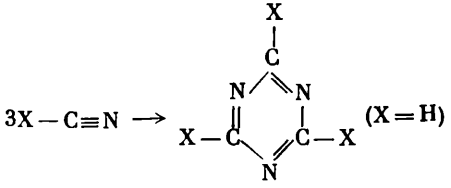
Of the three triazines given



1,2,3-Triazine, *vic.*-triazine | 1,2,4-Triazine, *as.*-triazine | 1,3,5-Triazine, *sym.*-triazine

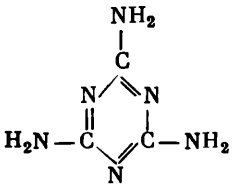
we shall briefly consider only the third one.

Symmetrical 1,3,5-triazine itself can be prepared by trimerization of hydrocyanic acid in the presence of acids (Grundemann and Kreuzberger):

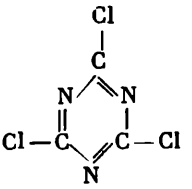


Numerous derivatives of this triazine are prepared by the polymerization (often spontaneous) of derivatives of hydrocyanic acid such as chlorocyanogen (X = Cl), the esters of cyanic acid (X = alkoxyl), cyanamide NH_2—C≡N (X = NH_2). Thus, melamine formed by the trimerization of cyanamide is used for the manufacture of valuable plastics which are made from this triamine and formalin by cross-linking melamine molecules through methylene bridges at the nitrogen atom of amino groups, just in the same way as is known

for urea-formaldehyde resins (Volume II, p. 22). The trimer of chloro cyanogen, **cyanuric chloride**, is also produced on an industrial scale and is used in the manufacture of dyestuffs and herbicides.

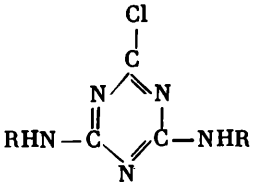


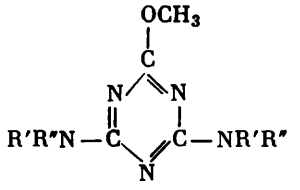
Melamine

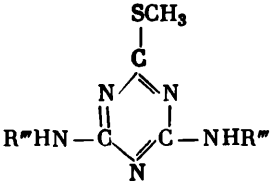


Cyanuric chloride

Herbicides of the triazine series, which are used as weed-killers, belong to three types of compounds:



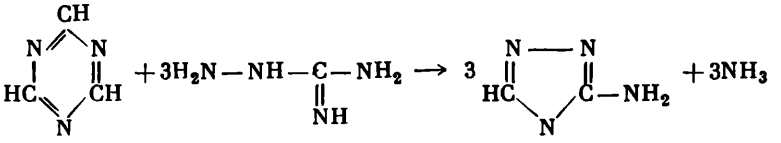




Their trade names are as follows:

Simazine	$R = C_2H_5$	Simetone	$R' = R'' = C_2H_5$
Atrazine	$R = C_6H_5$	Simetrine	$R''' = C_2H_5$
Prometone	$R' = CH(CH_3)_2$ $R'' = H$	Prometrine	$R''' = CH(CH_3)_2$

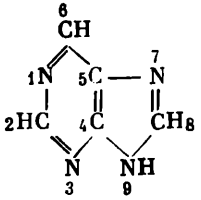
Grundemann and Kreuzberger have described an interesting conversion of 1,3,5-triazine into 2-amino-1,3,4-triazole in the presence of aminoguanidine:



II.4. Nitrogen Biheterocycles

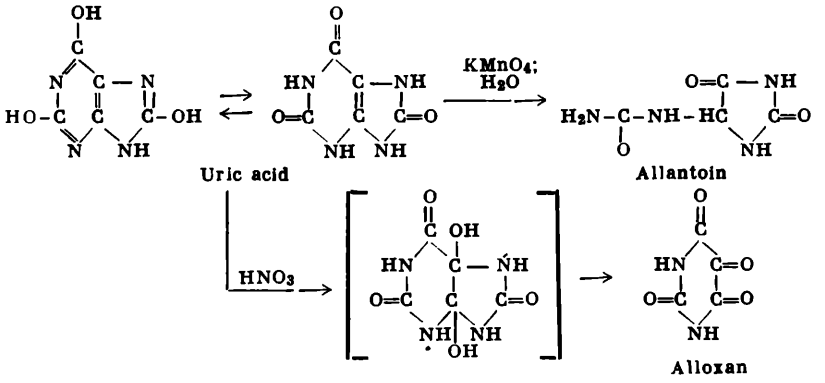
A. Purine and Its Derivatives

A biheterocyclic compound which is a condensed system consisting of a pyrimidine ring fused to an imidazole ring is called **purine**

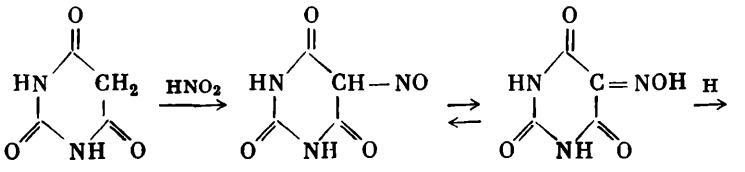


Purine derivatives are of great biological importance primarily because some of its hydroxy and amino derivatives are contained, along with pyrimidine bases, in the structure of nucleic acids and are thus involved in the programming of protein synthesis in the organism and in the phenomena of heredity. These also include a number of other vitally important substances, such as adenosine triphosphate (ATP) which is the primary source of energy (a phosphate carrier and a phosphate supplier) in biological reactions and is also a phosphorylating agent. The alkaloids caffeine and theobromine are also derivatives of purine.

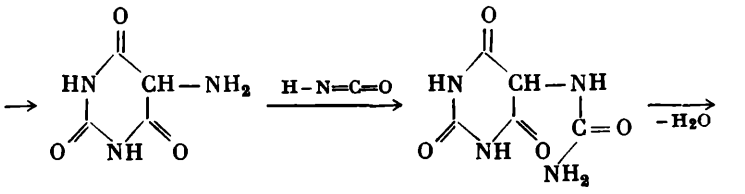
One of the key compounds in the synthesis of purine derivatives is **uric acid** which removes an excess of nitrogen in birds and reptiles (just like urea in mammals). The salts of uric acid (**urates**) accumulate in joints and as renal calculi in the improper functioning of the organism. The structure of uric acid is deduced from its oxidation. Permanganate oxidizes uric acid to **allantoin**, the pyrimidine ring being ruptured. When uric acid is oxidized by nitric acid the pyrimidine moiety of uric acid remains intact but the imidazole ring is broken with the formation of **alloxan**:



Several syntheses of uric acid have been accomplished since 1888. We shall consider two of them: the synthesis carried out by Fischer in 1895, one of the main investigators of compounds of the purine group, and the synthesis due to Traube. In the Fischer synthesis, the starting point is barbituric acid (page 406) which is subjected to nitrosation at the mobile methylene group followed by reduction to an amine (uramil); and further, by building up the urea grouping on the amino group by the action of isocyanic acid there is obtained **pseudo-uric acid** which when heated with hydrochloric acid undergoes ring-closure with the formation of **uric acid**:

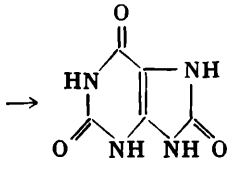


Barbituric acid



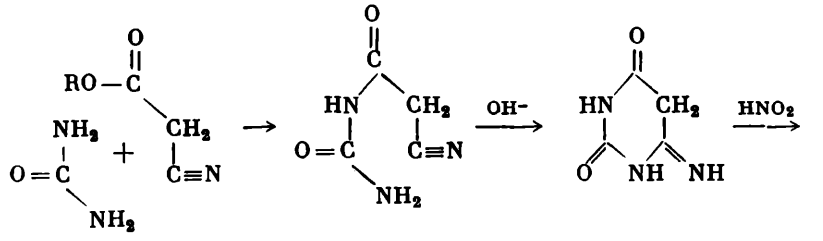
Uramil

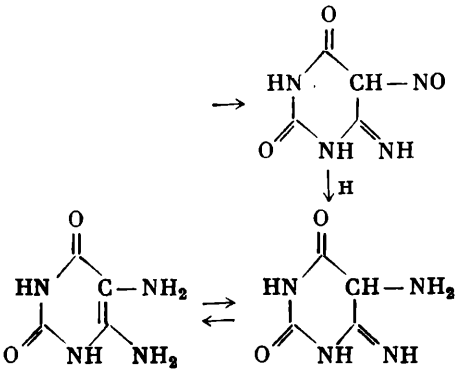
Pseudo-uric acid



Uric acid

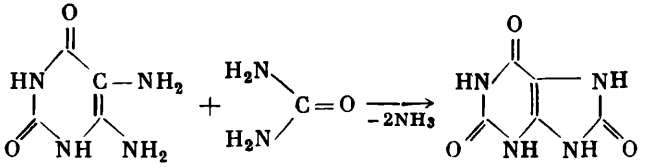
Traube's synthesis is as follows:





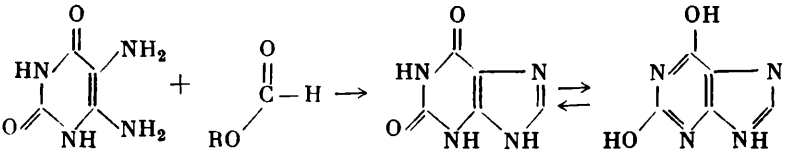
In this synthesis, the first stage is the acylation of urea through the agency of cyanacetic ester; the second stage is the ring-closure of the heterocycle by an intramolecular addition of the NH_2 group to the $C \equiv N$ group.

The reaction of *trans*-amination of urea on heating with amines is an ordinary one: ammonia is evolved and N-substituted ureas (uric acid in this case) are formed.



Uric acid

The Traube method opens up wide possibilities for the synthesis of purine bases. Thus, on acylation (or in other words, on conversion into a substituted amidine) of 4,5-diaminouracil by the action of the esters of various acids it is possible to prepare **xanthine** (the action of formate ester) and its various derivatives substituted in position 8:

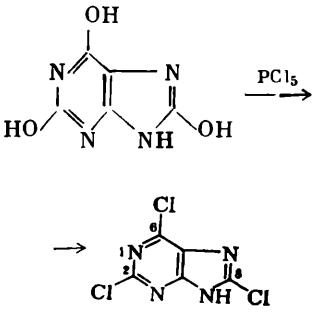


Xanthine

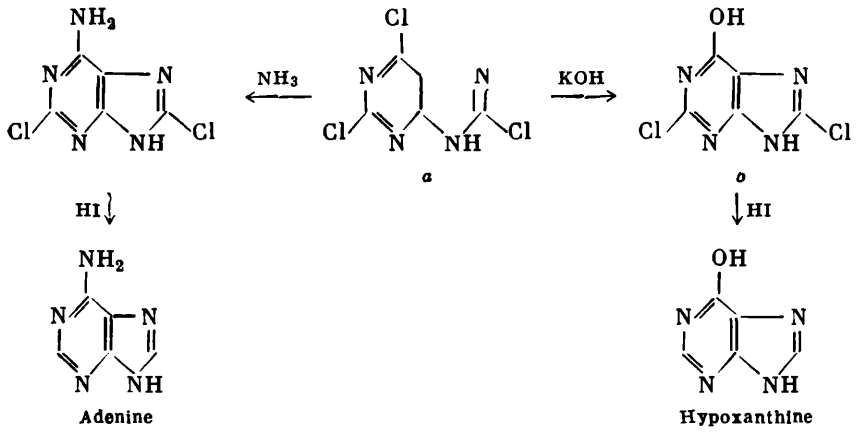
Let us recall that the hydrogen atom in the imidazole ring is free to migrate between the two nitrogen atoms.

When uric acid is made to react with phosphorus pentachloride. it reacts in the tautomeric (trihydroxypurine) form, being converted

into 2,6,8-trichloropurine:

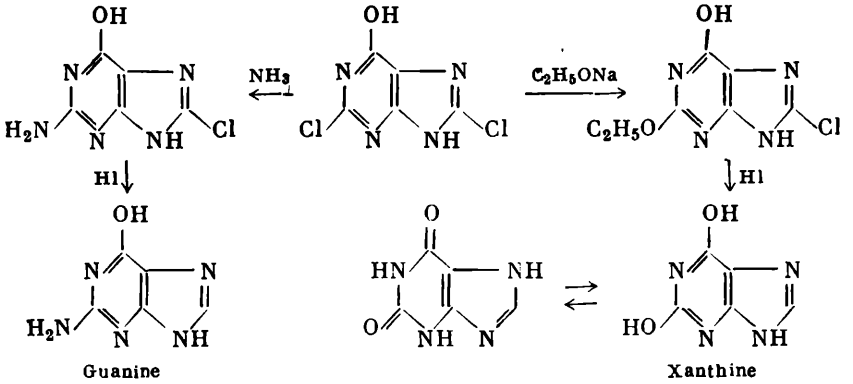


The three chlorine atoms in the trichloropurine exhibit different activity towards the nucleophile attacking the molecule. These chlorine atoms are replaceable by nucleophiles with diminishing ease in the order: 6 > 2 > 8. It is for this reason that only the chlorine atom in position 6 is displaced by an OH or NH_2 group under the action of alkali (100°C) or ammonia. After this it is possible to replace the other two chlorine atoms by a hydrogen atom through the action of hydrogen iodide and to prepare two very important purine derivatives: 6-hydroxypurine or **hypoxanthine** (*sarkine*) and 6-aminopurine or **adenine:**



If a more powerful nucleophile is used at the stage *b*, say, sodium alkoxide or ammonia under vigorous conditions, then it is possible to replace also the chlorine in position 2, and when hydrogen iodide (HI) is introduced into the reaction, two, also very important,

purine derivatives are formed: **xanthine** and **guanine:**

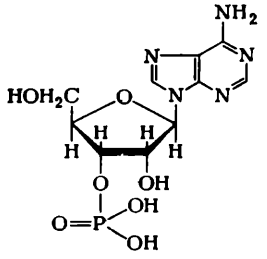


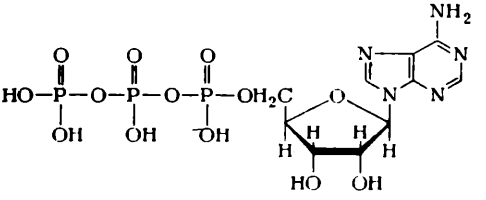
Guanine and adenine, together with pyrimidine bases (page 409), take part in the building of nucleic acids which are responsible for the synthesis of proteins specific for a given organism and which determine the hereditary properties of the organism.

Guanine (2-amino-6-hydroxypurine) occurs in certain fish scales and is responsible for their lustre. The guanine extracted from the scales by a solvent is used for the production of artificial pearl (it crystallizes out on the internal side of hollow beads).

B. Nucleotides

Adenine, hypoxanthine and guanine play a very important part in the metabolism in the animal organism. When combined with a monosaccharide (ribose) and phosphoric acid they form so-called **nucleotides** (*nucleoside phosphates*) and their derivatives, examples of which are **adenylic acid** and **adenosine triphosphate** (ATP), the latter being a phosphoric-acid and energy transporter in the organism.



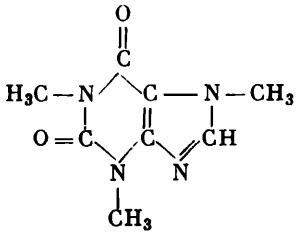


Nucleotides, such as adenylic acid, are the structural units of high-molecular-weight nucleic acids, where each of them is joined

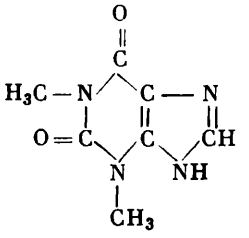
through the ester linkage of the phosphoric-acid residue to the hydroxyl group of the ribose of the next nucleotide (see Volume IV under "Nucleotides").

C. Purine Alkaloids

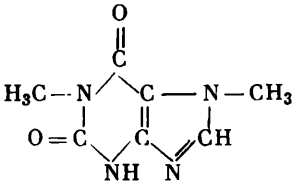
Purine derivatives include the following alkaloids: **theobromine** (present in the cocoa bean), **caffeine** (in the coffee bean and tea leaves) and **theophylline** or **euphylline** (in tea leaves). These compounds are nitrogen-methylated xanthines.



Caffeine



Theophylline

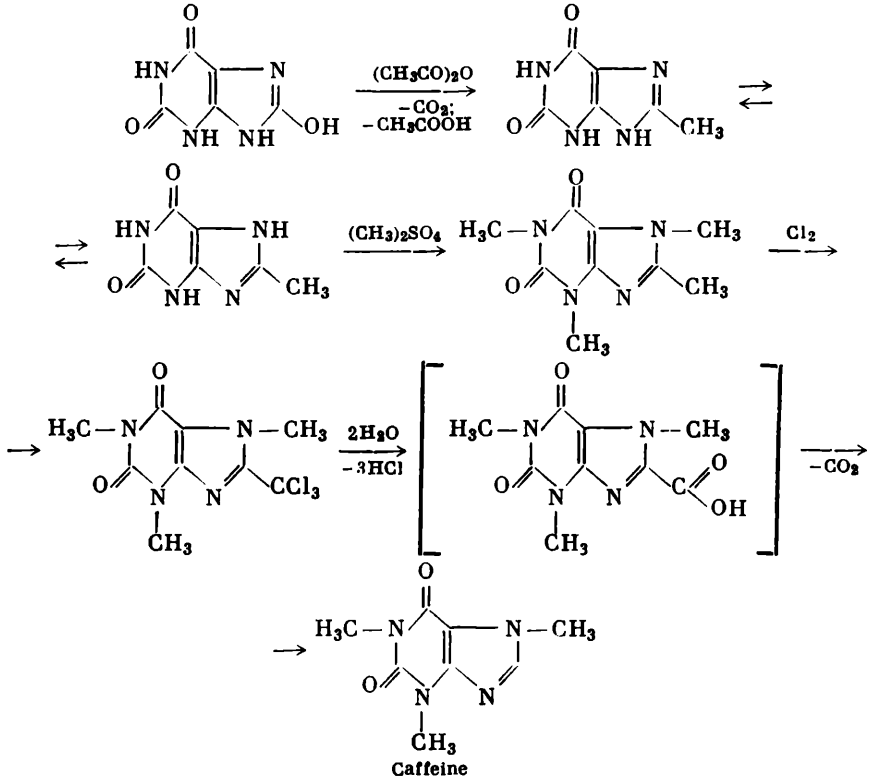


Theobromine

Caffeine and theophylline occur in tea leaves (up to 5 per cent of caffeine on dry basis) and are produced from powdered tea leaves. Theobromine is produced from cocoa beans. Caffeine is used in medicine for it has a stimulating action on the nerves and heart and increases the pulse beat. Theobromine and theophylline are used as diuretics and also as vasodilators employed in the treatment of hypertension. The structures of these alkaloids can be deduced from their oxidation. When oxidized caffeine is converted into dimethylalloxan and methylurea, theophylline into dimethylalloxan and urea, and theobromine gives methylalloxan and methylurea. Caffeine can be prepared by methylating xanthine, and theophylline by means of the Traube synthesis, starting from symmetrical dimethylurea.

Apart from being extracted from powdered tea leaves, caffeine is also synthesized on the industrial scale, starting with uric acid produced from the excrement of birds. The hydroxyl group in the imidazole ring is replaced by a methyl group (i.e.,the carbonic-acid residue is replaced by an acetic-acid residue) by the action of

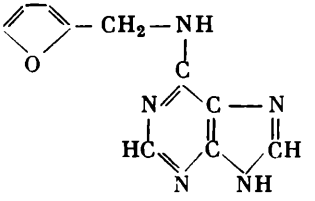
acetic anhydride on uric acid with the result that 8-methylxanthine is obtained, which is subjected to methylation at the three nitrogen atoms by dimethyl sulphate. The remaining methyl group is eliminated by chlorinating it to a trichloromethyl group, this being followed by hydrolysis and decarboxylation:



Caffeine

D. Kinetin

In 1955 Snoog isolated from plants **kinetin** (zeatin), a substance which sharply accelerates the growth of plants since it promotes cell division. Kinetin has also proved to be a derivative of purine:

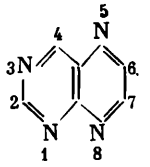


Kinetin

E. Pteridines

In contrast to the long-known purines (caffeine was discovered in 1820, uric acid and its derivative even earlier), their analogues, pteridines, became known only in the thirties of this century.

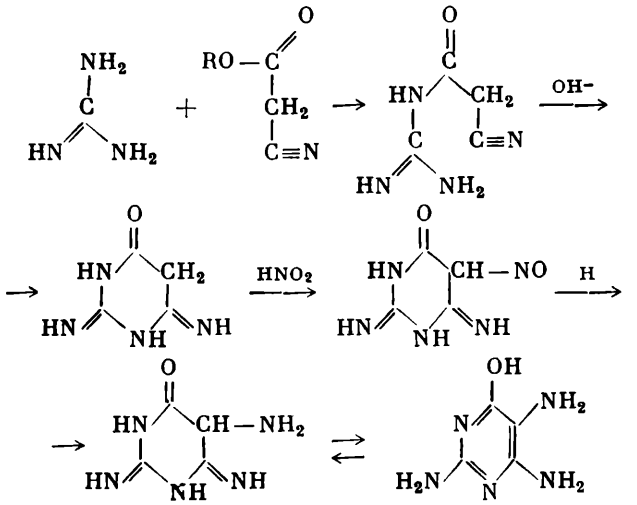
The parent compound of this class of heterocycles consisting of two fused ring systems is **pteridine** (1,3,5,8-tetraazanaphthalene), which is a condensed system containing a pyrimidine ring fused to a pyrazine ring:



Pteridine

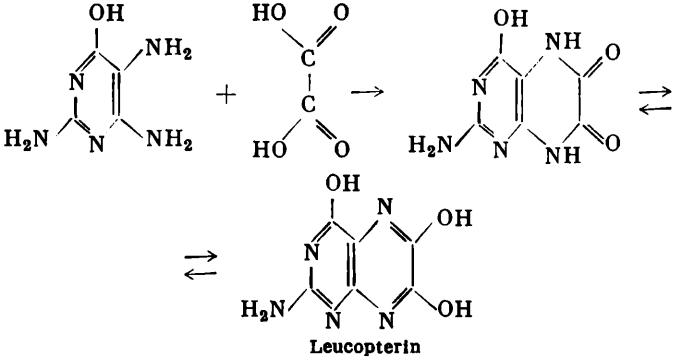
The pteridine derivatives (called **pterins**) are naturally occurring compounds; they are butterfly wing pigments. Particularly important is the presence of the pteridine cyclic system in the structure of the important vitamins **folic acid** and **riboflavin** (vitamin B_2).

Examples of substances that colour butterfly wings are **leucopterin**, the white pigment in the wings of the cabbage butterfly, and **xanthopterin**, the yellow pigment in the brimstone butterfly. The synthesis of pterins can be ascertained from the synthesis of leucopterin. The synthesis is started in the same way as the Traube synthesis of uric acid, with the only difference that guanidine is used instead of urea:



2,5,6-Triamino-4-hydroxypyrimidine

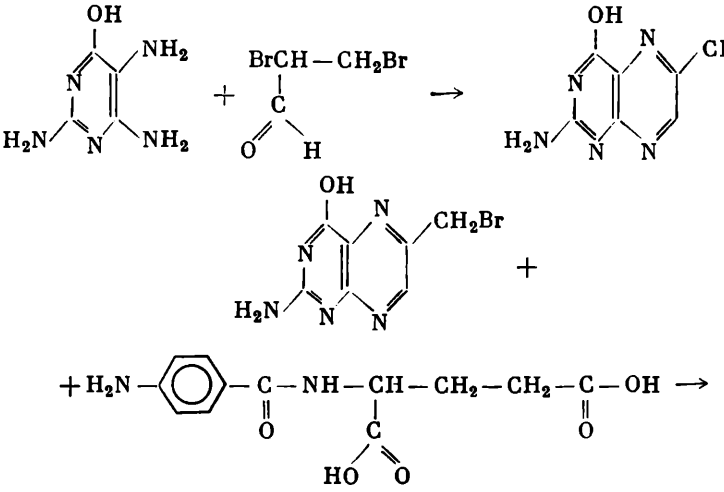
The resulting 2,5,6-triamino-4-hydroxypyrimidine is then acylated by fusion with oxalic acid to give leucopterin:

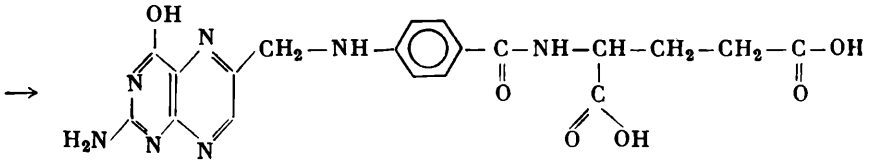


Leucopterin

F. Folic Acid

One of the most important vitamins for many organisms is **folic acid** (pteroylglutamic acid) discovered in 1938 by Stockstadt in the liver extract. Folic acid proved to be widely distributed in the vegetable kingdom, especially in the green leaves. It enters into the composition of enzymes that provide the transfer of one carbon atom in the form, say, of the formyl group. The structure of folic acid is confirmed by synthesis (Tschesche, Weygand); at present it can be produced commercially. The starting point in its synthesis is 2,4,5-triamino-6-hydroxypyrimidine which is treated with the product of addition of bromine to acrolein, and then with *p*-aminobenzoylglutamic acid. In this way folic acid is produced (though in low yield):



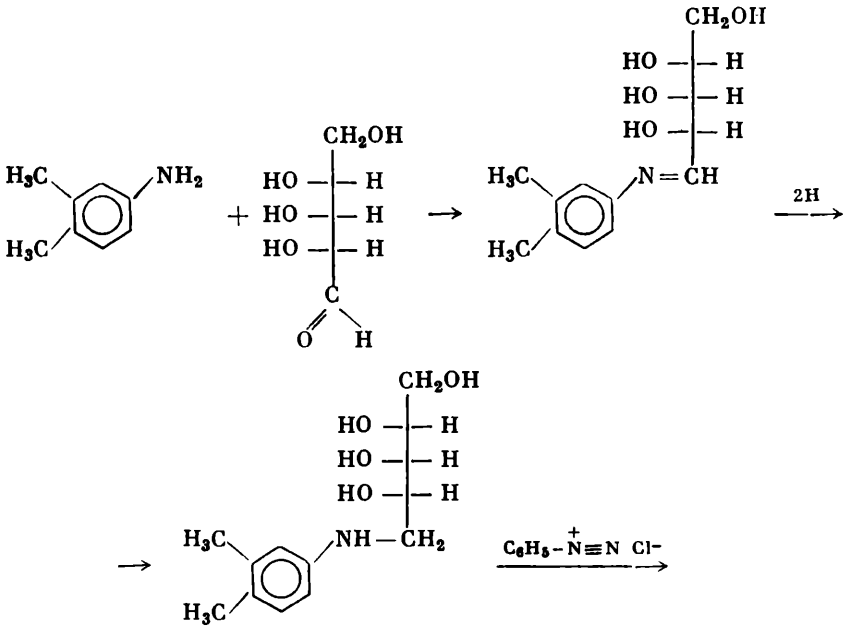


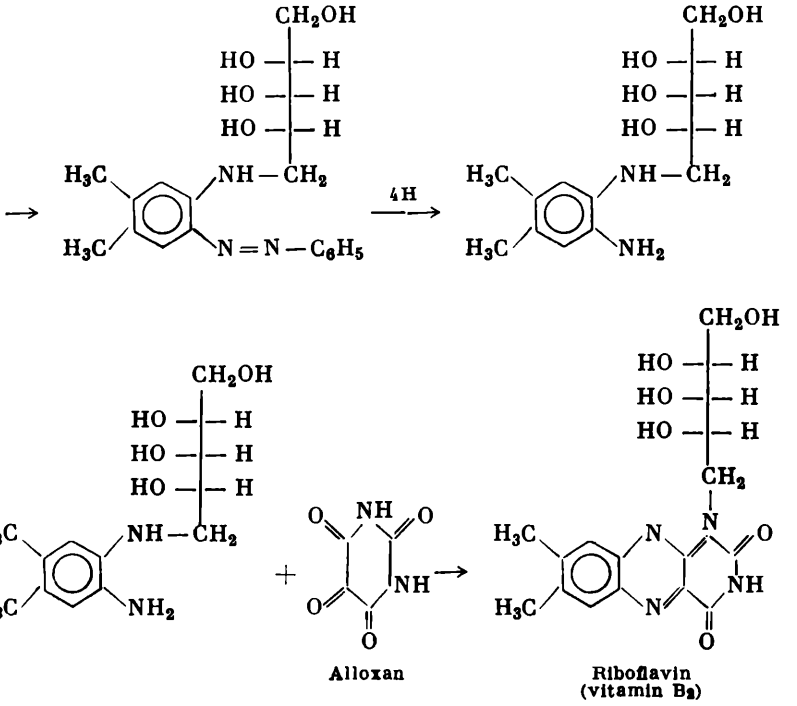
Folic acid

G. Riboflavin

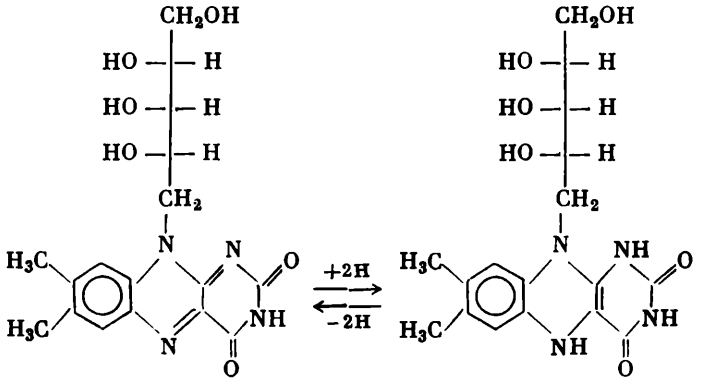
Lastly, this class of compounds include vitamin B_2 (riboflavin, lactoflavin) which is present in the structure of oxidative enzymes in the human and animal organisms. Riboflavin was first isolated by R. Kuhn from whey; it is also contained in eggs. Its synthesis was effected by R. Kuhn and P. Karrer.

Riboflavin is produced on the industrial scale. First, D-ribonic acid is prepared from D-glucose via D-arabinose and D-arabonic acid; then D-ribonic acid is reduced via a lactone to D-ribose. D-Ribose is condensed with *o*-xylidine to give a Schiff's base which is reduced to a secondary amine. The azo coupling of the secondary amine with a phenyldiazonium salt gives an azo compound which is reduced at the azo group to an amine, following which the amine is condensed with alloxan to yield riboflavin:





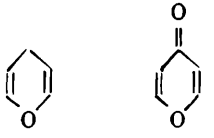
Riboflavin in the form of its phosphate (at the primary CH_2OH group) enters into the composition of Warburg's "yellow enzymes" (**flavoproteins**) and play the role of a hydrogen transporter, two hydrogen atoms readily adding on to two nitrogen atoms (one nitrogen atom of the pyrazine ring and the other of the pyrimidine ring).



11.5. Six-Membered Heterocycles with an Oxygen Atom

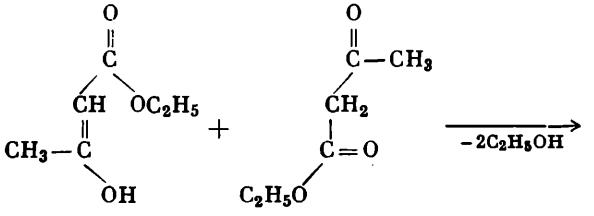
A. Derivatives of γ-Pyran

Of the oxygen-containing six-membered heterocycles we shall consider only the derivatives of γ-pyran. A well-known derivative of this structure is **γ-pyrone**, and the most interesting derivatives are **pyrylium salts** which are structurally analogous to pyridinium salts.



γ-Pyran γ-Pyrone

The most available and thoroughly studied compound of this group is γ-dimethylpyrone III. It is prepared from dehydroacetic acid II, which in its turn is synthesized by the ester condensation of two tautomeric forms of acetoacetic ester I. The condensation takes place when the vapours of acetoacetic ester are heated:



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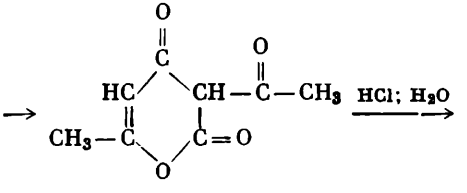
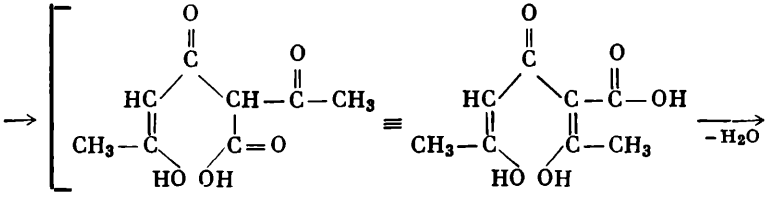
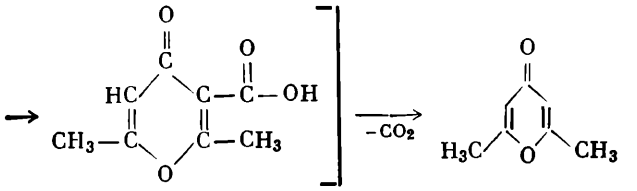


II

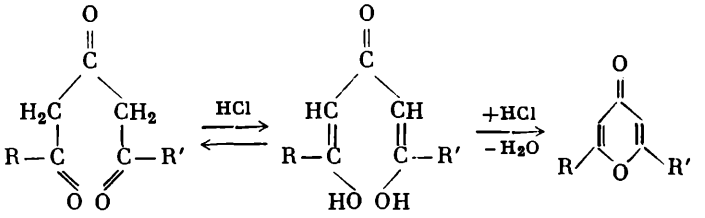




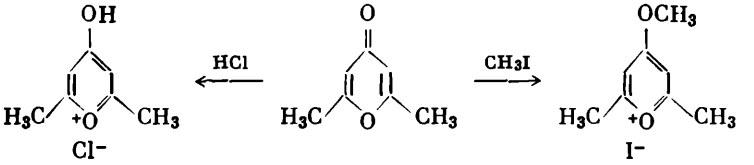
III

Dehydroacetic acid (α-methyl-β′-acetylpyrone) is a derivative of α- and γ-pyrones. When acted on by concentrated hydrochloric acid it is converted into α,α′-dimethyl-γ-pyrone.

The general method of preparation of derivatives of γ-pyrone consists of the action of HCl on 1,3,5-tricarbonyl compounds:



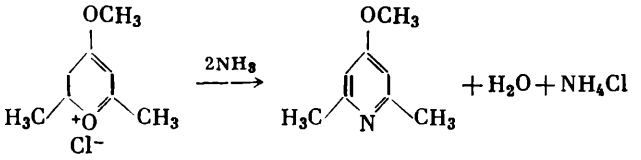
A remarkable feature of γ-pyrone and its homologues is their basic properties which are more sharply pronounced than those of all ordinary oxygen functions. This is accounted for by the fact that when γ-pyrone is being converted into pyrylium salts, which occurs through the action of acids and also of methyl iodide, it is aromatized, one of the free electron pairs of the ester oxygen atoms being involved in the aromatic sextet:



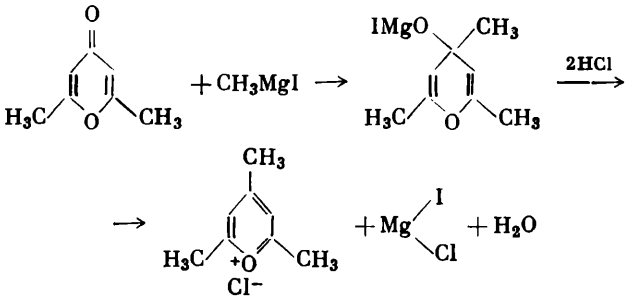
Thus, though H^+ or $\overset{+}{C}H_3$ attacked the ketonic oxygen atom, converting it into a hydroxyl or an alkoxyl group, the role of the principal oxygen atom was played by the ester oxygen, which became an oxonium positively charged oxygen. Oxonium salts of this kind, which were prepared and studied by Collie and Tickle, had long been known (since 1899). In contrast to the products of addition of HCl to alcohols, esters and carbonyl compounds, in this case solid characteristic salts are formed also with halogen anions and the anions of strong oxy acids.

The structure of such salts, say, of the product of iodomethylation of dimethylpyrone, is proved by its conversion under the action of

ammonia into 2,6-dimethyl-4-methoxypyridine:

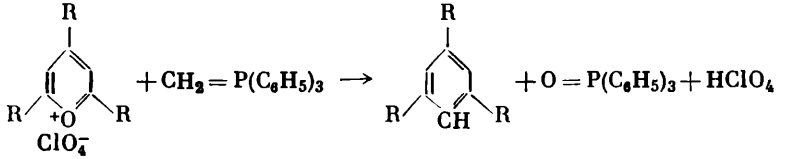


With Grignard reagents γ-pyrones react in a normal way across the carbonyl group. The resulting alkoxide when acted on by hydrochloric acid gives a pyrylium salt which has lost its hydroxyl (or alkoxyl) group in the γ-position:

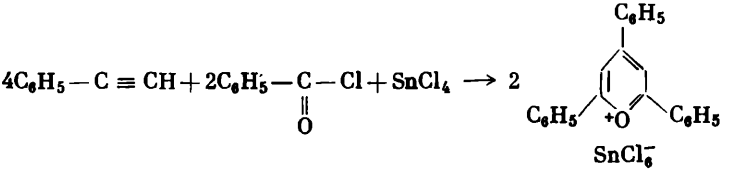


Such a salt when allowed to react with ammonia is also converted into 2,4,6-trimethylpyridine.

The oxygen of pyrylium salts can be replaced by a CH group by converting the salts into the corresponding derivatives of benzene by the action of an equimolecular amount of the Wittig reagent (Dimroth, Wolff, Wache):

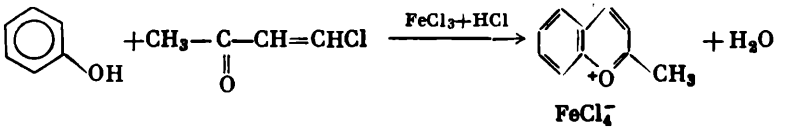


A simple method of synthesis of 2,4,6-triarylpyrylium salts was described by R. Schmidt in 1964. The reaction for triphenylpyrylium salt, taken as an example, is formulated as follows:

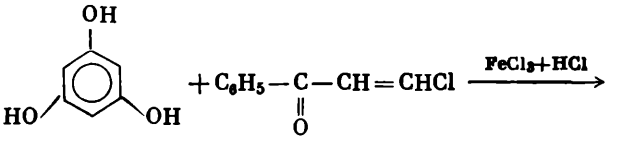


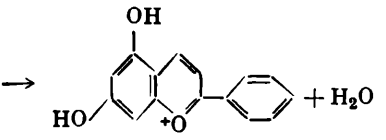
Benzopyrylium and α-phenylbenzopyrylium salts, which are known as **flavylium salts**, can be synthesized by the method developed by

A. N. Nesmeyanov, N. K. Kochetkov and M. I. Rybinskaya, in which the starting point is phenols and alkyl- or aryl-β-chlorovinyl ketones:



2-Methyl-5,6-benzopyrylium ferrichloride

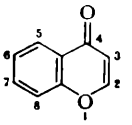




5,7-Dihydroxyflavylium ferrichloride

B. Chromone, Flavone and Related Compounds

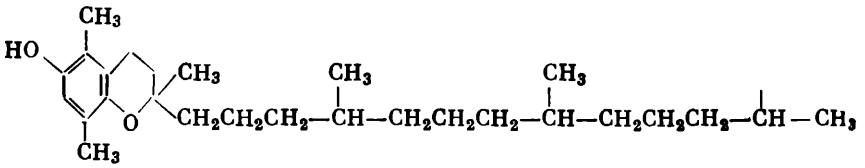
2,3-Benz-γ-pyrone is called **chromone** which has the following formula



This skeleton forms the basis of many important naturally occurring compounds. Here belongs the group of vitamins E,* known as **tocopherols**, which are anti-sterility factors necessary alike for fertility of the male and the birth processes of the female.* The vitamins of this group were first isolated from the oil of wheat-germ. At present seven compounds are known, which exhibit the effect of vitamins E, which are structurally related and are partially isomeric with one

* The term *tocopherol* is derived from the Greek—*tocos* (childbirth) and *phero* (to bear).—*Tr.*

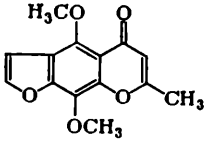
another. We shall give the formula of one of them, that of β-tocopherol:



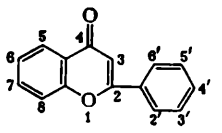
α-Tocopherol is the homologue of β-tocopherol and differs from the other tocopherols by the presence of one more methyl group in the benzene nucleus (in position 7) and γ-tocopherol is an isomer of the β-compound and has two methyl groups in the benzene nucleus (in positions 7 and 8). A long aliphatic skeleton consisting of 20 carbon atoms (including those contained in the dihydropyran ring fused to the benzene ring) is the same as that in the isoprenoid alcohol phytol (see Volume I, p. 394). The racemic α-tocopherol was synthesized by Karrer by the action of phytyl bromide on 2,3,6-trimethylhydroquinone in the presence of $ZnCl_2$. In this reaction the primary carbon atom of phytyl (the one bearing a bromine atom) became attached to the aromatic nucleus and the ortho-hydroxyl group added on to the allyl double bond of the phytyl residue, closing the pyran heterocycle.

A derivative of chromone is *khellin* which occurs in the seeds of the plant *Ammi Visnaga*. It is used as a vasodilator in the treatment of *angina pectoris* and also as a drug with a positive effect on the cardiac muscle. The structure of khellin has been elucidated by E. Späth.

Particularly widely distributed in the plant kingdom are the derivatives of 2-phenylchromone which was termed **flavone** by Kostanecki (who has carried out the major investigations of this group of compounds):



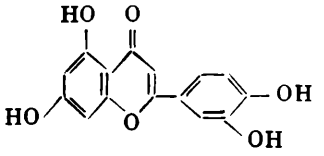
Khellin



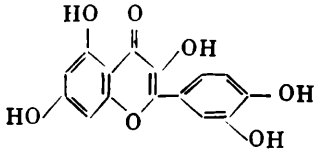
Flavone

The naturally occurring derivatives of flavone are hydroxy derivatives which always contain hydroxyl groups in positions 5 and 7, sometimes in position 3 and usually in positions 3′ and 4′. They are yellow in colour and are the ordinary colouring matter of yellow flowers. Examples are **luteolin**, the colouring matter of dyer's weld, *Reseda luteola*, and **quercetin**, a compound widely distributed in

yellow flowers.



Luteolin

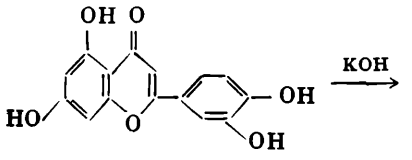


Quercetin

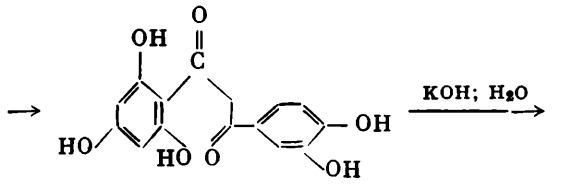
They occur in plants in the form of glycosides. The glycoside of quercetin combined with the disaccharide 6[β-L-rhamnosido-D-glucose] is called **rutin**. This is one of the compounds belonging to the vitamin P group, the deficiency of which in food makes the capillaries of blood vessels permeable, which leads to "purple disease"—multiple punctate haemorrhages. The other vitamins of this group are structurally related to rutin.

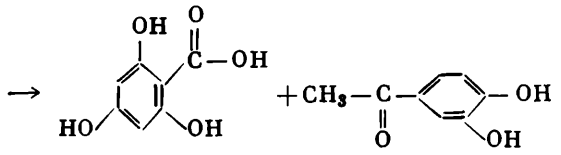
The activity of vitamins P is also displayed (A. L. Kursanov) by the tannins **catechins** which are found in the vegetable kingdom, for example, hydrogenated cyanidin (see below). The hydrogenation of anthocyanidins (see below) establishes their relationship to the catechins.

The structure of flavones was determined by Kostanecki by splitting them with the aid of alkali, as shown below for luteolin:



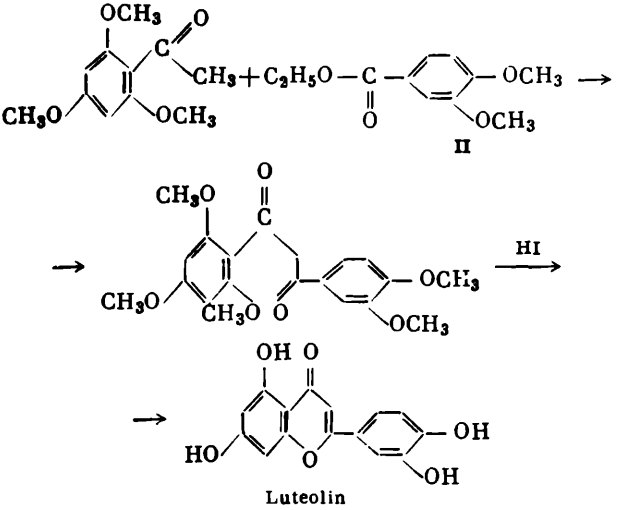
Luteolin





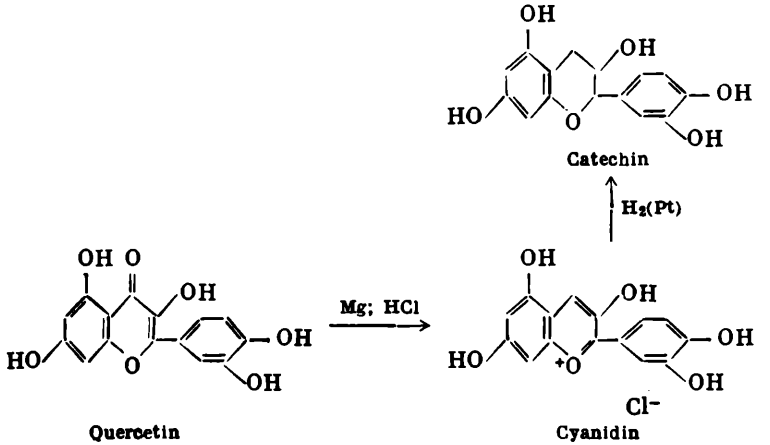
The synthesis of luteolin (and other flavones) was carried out by Kostanecki by means of the condensation of the ester of dimethoxybenzoic acid II with the methyl ester of acetylfluoroglycine I with the subsequent ring-closure of the pyrone ring and demethylation

with HI:



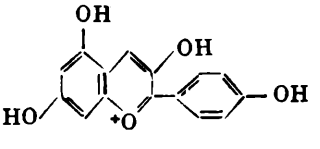
C. Anthocyanidins

When hydroxyflavones are reduced (for example, with magnesium and oxygen), anthocyanidins can be prepared. Thus, quercetin gives **cyanidin** in this reaction, which is a typical representative of anthocyanidins. The hydrogenation of cyanidin leads to catechin:

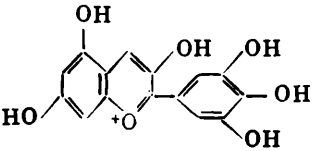


Anthocyanidins, as seen from this example, are the hydroxyderivatives of α-phenylbenzopyrylium salt with an oxonium oxygen in the aromatic ring. These are relatively stable intensely coloured solid salts. In the form of the glycosides, **anthocyanins**, they are the colouring matters of flowers, berries and vegetables (*anthocyanin* is

a Greek word meaning the colour of flowers).* All anthocyanins are acid-base indicators. Their colour varies with the pH of the solution: it becomes red in acid medium, blue (or blue-green) in alkaline medium, and violet in neutral medium. Thus, cyanidin is responsible for the colour of cornflower (the alkaline medium of the juice) and the red rose. Other representatives of anthocyanidins are **pelargonidin** (responsible for the colour of the pelargonium bloom), **delphinidin** (the colouring matter of blue delphinium flowers and also of the red grape and wine). These compounds differ in the number of hydroxyl groups in the phenyl ring: pelargonidin has one hydroxyl group less and delphinidin one hydroxyl group more than cyanidin:



Pelargonidin

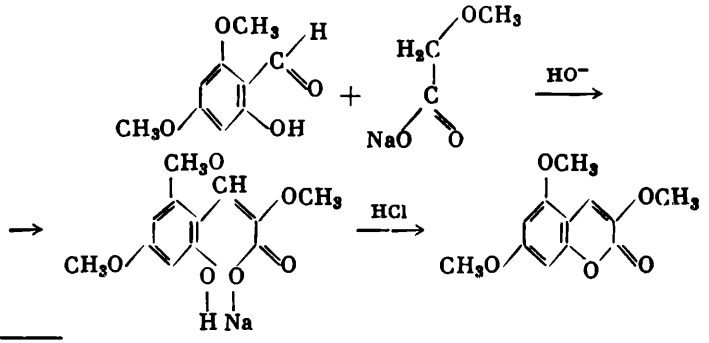


Delphinidin

All these three anthocyanidins are responsible for a great variety of colour tints of the blue-red gamut. Some of the anthocyanins, which are the derivatives of the three anthocyanidins given above, differ in that one or two hydroxyl groups in the phenyl ring are methylated, and the glycosides are formed by the various sugars. The structure of the anthocyanidins has been revealed by the alkaline decomposition (Willstätter). For instance, pelargonidin decomposes to give phloroglucine and *p*-hydroxybenzoic acid.

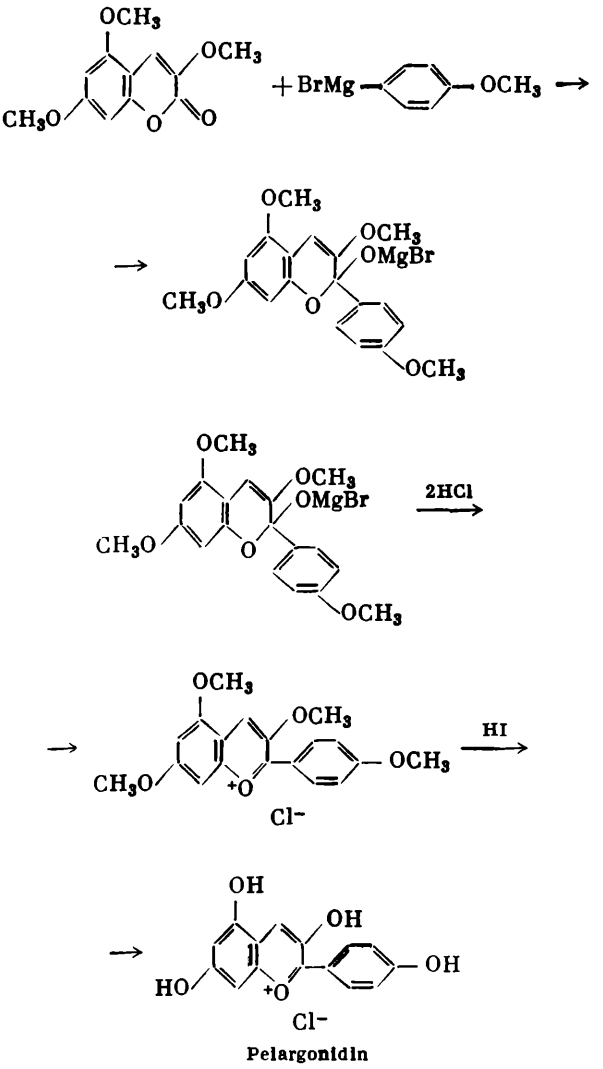
Two classical syntheses of anthocyanidins are known, those of Willstätter and R. Robinson, who have carried out major investigations on this group of compounds.

In the Willstätter synthesis, 2,4-dimethoxy-6-hydroxybenzaldehyde is prepared from phloroglucinaldehyde and is condensed by the Perkin method (page 170) with methoxyacetic acid:



* The other colouring matters in vegetables are *carotenoids*, e.g., carotenes in carrots and lycopene in the tomato (see Volume IV).

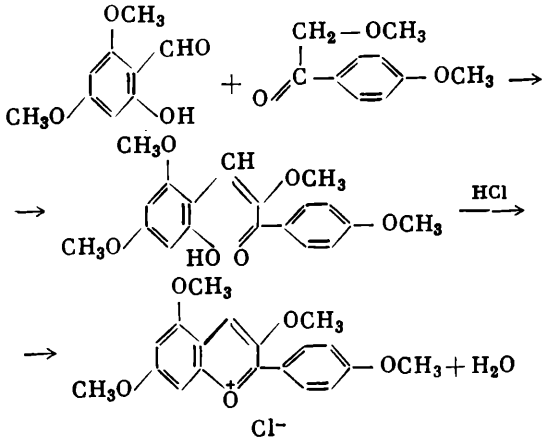
The resulting derivative of coumarin (page 220) is acted on by a Grignard reagent. The final stage is the demethylation of the tetramethyl ester by hydrogen iodide:



Pelargonidin

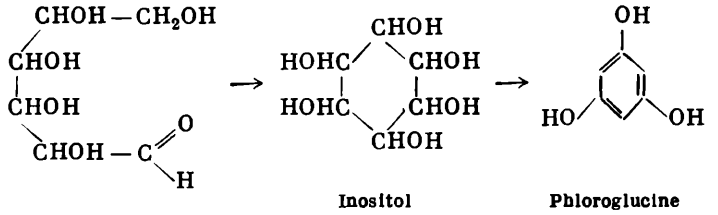
The Robinson synthesis is very typical for the ring-closure of the pyrylium ring in general and is exceptionally elegant in its conci-

seness:



This is followed by the demethylation with the aid of hydrogen iodide.

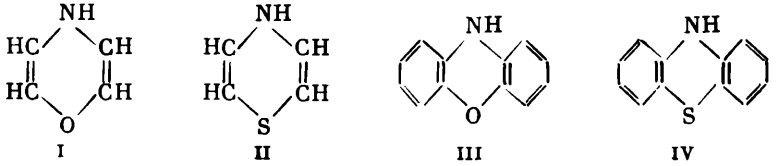
As regards the biosynthesis of all the derivatives of phloroglucine in plants, the following route has been suggested (Fodor): first the aldol ring-closure of the aldehyde form of glucose takes place, which gives the stereoisomeric inositols, this being followed by the dehydration to phloroglucine and by the synthesis of the anthocyanin and flavone pigments:



Inositol Phloroglucine

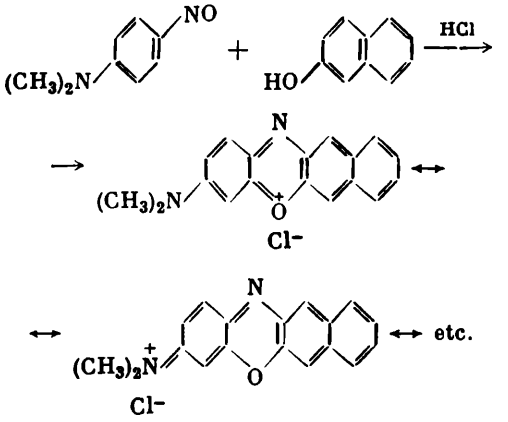
11.6. Six-Membered Heterocycles with Two Different Hetero-Atoms

The ring I is known as **oxazine**, and the ring II is **thiazine**. Mention should also be made of their dibenzo derivatives called **phenoxazine** III and **phenthiazine** IV:

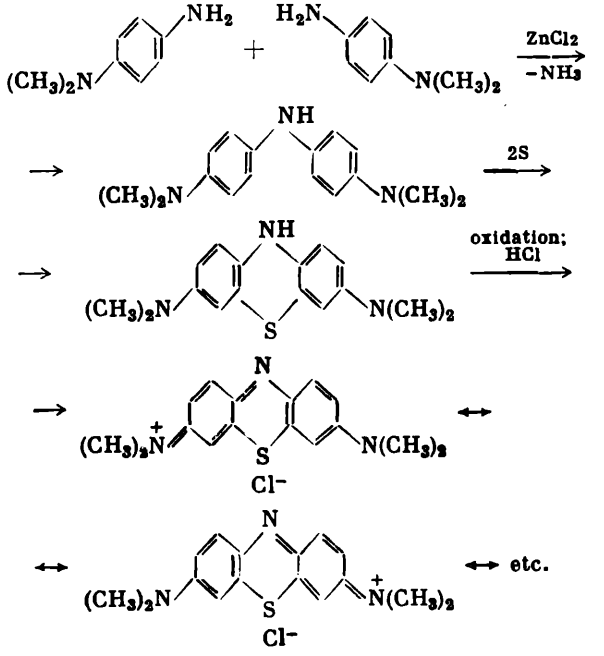


I II III IV

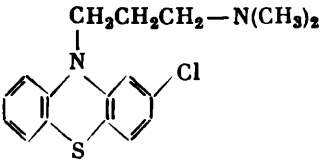
Some of the derivatives of phenoxazine are used as dyestuffs prepared, say, by heating nitrosodimethylalanine with phenols; for example:



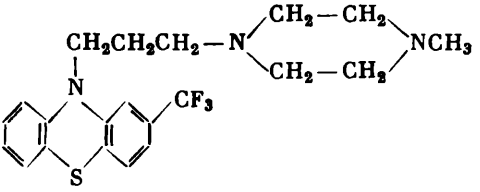
An example of phenthiazine dyes is **methylene blue** which is produced from *p*-aminodimethylaniline by the action of sodium thiosulphate and sodium dichromate in the presence of zinc chloride. The thiosulphate gives off sulphur which is then incorporated into the ring:



In the fifties of this century the phenthiazine preparations have found an entirely new application as neurolytic drugs used for the treatment of schizophrenia and maniacal diseases. Examples of drugs of this kind are chlorpromazine (aminazine) and stelasine:



Aminazine



Stelasine

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Brief Contents of Volume IV

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Academician ALEKSANDR NIKOLAEVICH NESMEYANOV was one of the most distinguished organic chemists of our time. He conducted fundamental research in the field of organoelement chemistry and authored important and original works on organic and theoretical chemistry. The concept of organoelement (elemento-organic) chemistry was introduced by A.N. Nesmeyanov. He devised diazo method of synthesis of organometallic compounds, discovered new classes of compounds, demonstrated relationship between structure and reactivity of metallic derivatives of tautomeric systems. His principal areas of interest were the chemistry of organometallic compounds and general problems of organic chemistry. Nesmeyanov initiated and directed a number of new trends of investigation, one of which was the preparation of synthetic and artificial food. Among the practical achievements in the investigations carried out by Nesmeyanov and his school may be mentioned the development of valuable medicinal preparations, the synthesis of a new antiknock compound and the preparation of a number of materials for special technical applications.

Nesmeyanov was awarded the State Prize for his investigations in the field of organoelement compounds and the Lenin Prize for his remarkable contributions to the development of the science and practical implementation of the scientific achievements in the national economy.

A. Nesmeyanov was an honorary member of the Royal Society (Great Britain), and of academies of science of many countries, including the New York Academy of Sciences (USA).

A.N. Nesmeyanov died in 1980.

Professor NIKOLAI ALEKSANDROVICH NESMEYANOV is Doctor of Chemical Sciences and serves presently as Lecturer in Organic Chemistry at the Moscow State University. His main research interests are in the general theoretical problems of organic chemistry, the properties of organic compounds of Group V elements. He has authored over 50 scientific papers devoted primarily to the chemistry of the ylides of phosphorus, arsenic and antimony and also to the penta-coordination compounds of Group V elements. Based on his kinetic studies, he has proved the advantages of the ylides of arsenic as Witting reagents and proposed a new mechanism of the Witting reaction.