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ADVANCES IN THE CHEMISTRY OF IMIDAZOLE

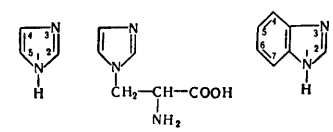
A. F. Pozharskii, A. D. Garnovskii, and A. M. Simonov

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I. INTRODUCTION

In recent times progress in the chemistry of certain classes of organic compounds has been closely related to advances in molecular biology. A striking example of this is the chemistry of imidazole (I) and its derivatives. Numerous natural compounds (enzymes, nucleic acids, alkaloids, etc.), which include in their composition the imidazole group, have been known for a long time. A new antibiotic, azomycin (2-nitroimidazole)[1-3] and a new amino-acid, isohistidine (II)[4], are further additions to this series of compounds.



(I) (II) (III)

At the beginning of the 1950's it was shown that purines are not the only condensed imidazole system which plays a role in vital processes. It was found that the structure of vitamin B_{12} incorporates a 5,6-dimethylbenzimidazole fragment[5]. This finding greatly stimulated the development of the chemistry of imidazoles condensed with aromatic rings, and in the first place of benzimidazole (III).

The advances in the elucidation of the role of the imidazole group of enzymes and nucleic acids in the chemistry of the most important living processes has been particularly remarkable[6,7]. All these discoveries naturally enough also required a considerable effort in research on the chemistry of imidazole. In terms of the volume and importance of the studies on imidazole and its derivatives the last decade may be compared to the entire preceding period. In this connection it is necessary to sum up all this work, particularly as the latest reviews on the chemistry of imidazole[8] and benzimidazole[9] cover the literature only up to 1951. In a number of monographs on the chemistry of heterocyclic compounds[10-15] the chemistry of imidazole is dealt with in a very brief and incomplete manner.

The present review covers the literature on the chemistry of imidazole and the most important imidazole derivatives condensed with aromatic rings from 1952 to 1963

(partly also 1964) inclusive. In view of their unusual properties, it is desirable to consider separately condensed imidazole systems consisting of two and more heterocyclic rings (imidazopyridines, purines, etc.)[16]. The extensive biochemical and pharmacological data on imidazoles, which themselves can be and already have been[6] the subject of a review, will be used only partially in dealing with the main problem — the exposition of the present state of the chemistry of imidazole.

II. SYNTHESIS OF IMIDAZOLES

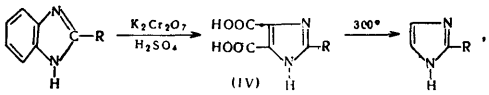
A. NON-CONDENSED IMIDAZOLES

The classical synthesis of imidazoles by the method of Debus and Radziszewski (reaction of α-diketones with ammonia and aldehyde) has a number of disadvantages[8]. In the 1930's two important modifications of this method were proposed: Weidenhagen's method, consisting in the reaction of α-hydroxy-ketones with ammonia and an aldehyde in the presence of copper acetate (sometimes copper citrate or sulphate is used) and Davidson's method, consisting in the reaction of α-diketones with an aldehyde and ammonium acetate in glacial acetic acid. Both these modifications have not lost their value even now. They are widely used for the preparation of a wide variety of mono-, di-, and tri-*C*-substituted (substituent — alkyl, cycloalkyl, aralkyl, aryl, or a heterocyclic residue) derivatives of imidazole[17-25] and 2-imidazolyl ketones[26].

One of the most important achievements in the chemistry of imidazole in recent years is the formamide synthesis of imidazoles proposed by Bredereck and Theilig[27]. It consists in the reaction between α-diketones or α-substituted ketones (substituents — halogeno-, hydroxy-, amino-, or isonitroso-groups) and formamide. As a rule high yields and simplicity are the main advantages of this method. However, it has limited applicability for the preparation of 2-substituted imidazoles, since it is then necessary to replace formamide by the amides of more complex acid and this reaction has so far been relatively little investigated[28,29]. Although a review of formamide syntheses was published in 1959[30], we shall consider this question briefly, since a number of new papers have been published since then.

1. Imidazole and Its Simplest 2-Alkyl(Aryl) Derivatives

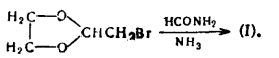
A widely used synthesis of imidazole is from imidazole-4,5-dicarboxylic acid (IV) obtained by the oxidation of benzimidazole with chromic acid mixture[31]. 2-Methyl- and 2-ethyl-imidazoles are synthesised similarly[32-34]:



where R = H, CH_3, C_2H_5.

It is interesting that *N*-substituted benzimidazole derivatives cannot be converted in this way to the corresponding di-acid (IV).[31] Imidazole-4,5-dicarboxylic acid is also readily formed on hydrolysis[35] of its diethyl ester. In their synthesis of 2-cycloalkylimidazoles, Schubert and Ladish[37] also started from the corresponding di-acids obtained by Maquenne's method[8].

A new and probably the most economical synthesis of imidazole itself is the reaction between the glycol acetal of α-bromoacetaldehyde and formamide[38]:

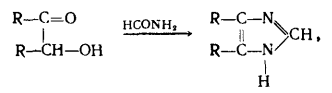


The preparation of imidazole and its 2-alkyl(aryl) derivatives by the reaction of ethylenediamine with the corresponding alcohol, aldehyde, or acid at a high temperature in the presence of Pt/Al_2O_3 has been patented[39,40]. The yields of products are very high, but the method is experimentally very complex. 2-Benzyl- and 2-α-naphthylmethyl-imidazoles are comparatively readily obtained from ethylenediamine and phenyl- or α-naphthyl-acetic acids[41].

Reductive aminolysis of glyoxal, methylglyoxal, and acetoin with ammonia or hydroxylamine leads to the formation of imidazole only in the case of glyoxal[42].

2. *C*-Alkyl-, *C*-Aralkyl-, and *C*-Aryl-imidazoles

a. From α-hydroxy-ketones. 4,5-Disubstituted imidazoles can be obtained in excellent yield by boiling α-hydroxy-ketones with formamide for 2–4 h[24,27]:

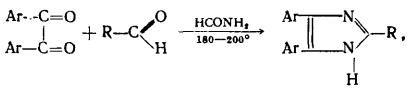


where R = alkyl, aryl, α-furyl, 4,5-octamethylene, etc. Highly branched α-hydroxy-ketones (hexamethylacetoin, tetrabenzylacetoin) do not form imidazole on heating with formamide.

A small amount of 4,5-disubstituted oxazole forms as a side-product. If conditions in which the imidazole ring is formed preferentially (large excess of formamide, t = 180–200°) are not maintained, the formation of oxazole may begin to predominate. This situation is also favoured by the use of sulphuric acid as a condensing medium[43].

b. From carbohydrates. This pathway has been used in recent years mainly for the preparation of 4-hydroxymethylimidazole used in the synthesis of histamine[44,45]. An improved method of synthesis of 4-methylimidazole from glucose has been described[46].

c. From α-diketones. On reaction with aldehydes and formamide, α-diketones give 2,4,5-trisubstituted imidazoles in yields of 27–67%:[28]

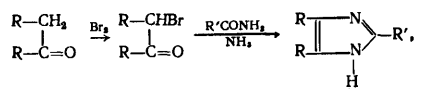


where Ar = C_6H_5, *p*-BrC_6H_4, *p*-$CH_3OC_6H_4$, *o*-ClC_6H_4; R = H, C_6H_5, 3,4-$Cl_2C_6H_3$.

On boiling with formamide (190°, 4 h) di-(2-furyl)-ethane-1,2-dione gives 2,4,5-trifurylimidazole; on the other hand, if a mixture of formamide and formic acid is used, 4,5-difurylimidazole is formed[47].

d. From α-halogeno-ketones. When α-halogeno-derivatives of aliphatic and aliphatic-aromatic ketones are boiled in formamide, 4,5-disubstituted imidazoles are formed[22,27]. 4-Phenylimidazole can be

obtained by this reaction from phenylacyl bromide in 90% yield. It is very convenient to brominate the ketone with an equimolar amount of bromine in formamide[48] or acetamide[29] and then, without isolating the α-bromo--derivatives, pass ammonia into the mixture heated to 180°:

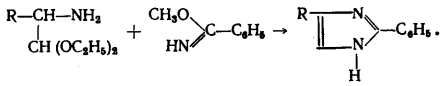


where R′ = H, CH_3.

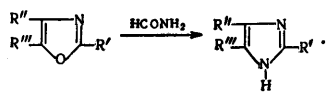
The preparation of 4,5-disubstituted imidazoles from 1-chloro-1,2-epoxides and formamide described by Durgaryan[49] may be regarded as a special case of this reaction. As before, imidazoles are also synthesised from α-halogeno-ketones by Kunckell's amidine method[20,50].

e. From α-amino-ketones and α-iso-nitroso-ketones. α-Amino-ketones and their α-acyl derivatives form the corresponding imidazoles in good yields on reaction with formamide[27,51] or ammonium acetate in acetic acid[51,52]. When benzil mono-oxime reacts with formamide in the presence of sodium hydrosulphite, 4,5-diphenylimidazole is formed in 71% yield[27]. The reaction of benzil mono-oxime with benzaldehyde is more unusual[53], resulting in an almost quantitative yield of 2,4,5-triphenylimidazole instead of the expected oxazole.

2-Phenylimidazole and its 4(5)-alkyl derivatives may be obtained[54] by the condensation of the acetals of α-amino--aldehydes with benzimidates in aqueous alcohol at pH 7:

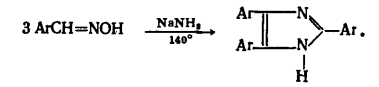


f. From oxazoles. It follows from what has been said above that formamide syntheses of imidazoles are frequently complicated by the formation of oxazoles. In order to find the optimum conditions for the formation of imidazoles from α-substituted ketones, Theilig studied the reaction of oxazoles with formamide[55]. After boiling for 3–6 h with formamide, most oxazoles were converted into the corresponding imidazoles in satisfactory yields:

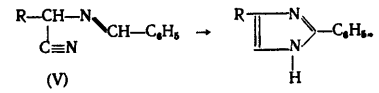


Oxazoles containing aliphatic radicals (C_3H_7, C_4H_9) in positions 2 and 5 were an exception. Some of these "difficult" oxazoles are converted into the imidazoles on reaction with formamide and ammonia in an autoclave at 200–210°.[56] Aromatic substituents, in particular in position 4 of the oxazole ring, facilitate the imidazole synthesis, probably by lowering the electron density at the oxygen atom[57,58]. Hence it follows that halogenoalkylated oxazoles should form imidazole even more readily; this is in fact found to be the case[57]. Benzimidazole cannot be obtained from benzoxazole in this way, although it would appear that a condensed benzene ring should also facilitate this reaction[57]. The mechanism of the formation of the imidazole ring from oxazoles and formamide has been discussed by Theilig[55]. A case is also known of the opposite conversion — of the imidazole ring into the oxazole ring[59].

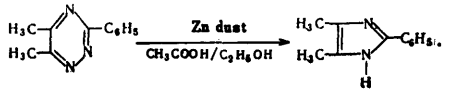
g. Other methods. 2,4,5-Triarylimidazoles are formed in yields of 72–77% when aldoximes are heated with sodium amide in absolute xylene[60]:



On prolonged storage or on distillation, benzylideneamino--derivatives (V) are converted into 2-phenyl- or 2,4(5)-diphenyl-imidazoles[61]:

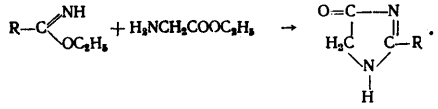


Metze and Scherowsky[62] observed an interesting case of contraction of the 1,2,4-triazine ring to the imidazole ring. They suggested the following mechanism for this reaction[62]:



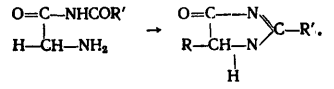
3. Hydroxyimidazoles

Relatively little work has been done on 4(5)-imidazolones. The principal method for their preparation is still the reaction of imidates with the ethyl ester of glycine:



Finger's classical work in this field[8] was checked[63,64] and a number of improvements have been made in the method of preparation of imidazolones. The synthesis of imidazolones from imidates is described in greater detail in the review of Roger and Neilson[65].

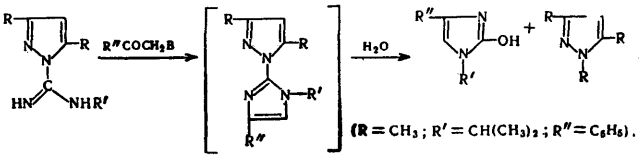
A new method for the synthesis of 4(5)-imidazolones consists in the spontaneous cyclisation of *N*-acylated amides of α-amino-acids[66,67]:



The substituent R in this reaction is usually an electrophilic group, such as CN, COOR, COR, etc.

2-Hydroxyimidazole and its 4(5)-substituted derivatives can be conveniently obtained by the action of potassium cyanate on solutions of amino-aldehydes made by the reduction of α-amino-acids with sodium amalgam[68].

Recently 2-hydroxy-1-isopropyl-4-phenylimidazole was synthesised in 51% yield by a fundamentally different procedure[69]:



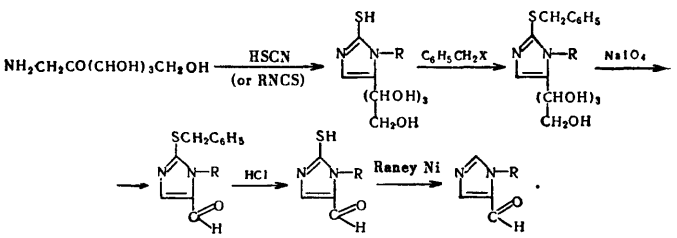
Some problems concerning the synthesis of imidazolones are also discussed by Roger et al. [70] and Wieland and Biener [71].

4. Mercaptoimidazoles

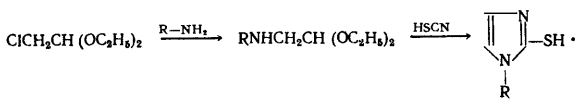
2-Mercaptoimidazoles are biochemically important as antithyroid agents, and Marckwald's synthesis of imidazoles [8] [reaction of α-amino-carbonyl compounds with thiocyanic acid or alkyl(aryl) isothiocyanates] is second in importance only to the method of Debus and Radziszewski, since sulphur can be readily removed from the resulting 2-mercaptoimidazoles with nitric acid, ferric chloride, hydrogen peroxide, or Raney nickel.

The principal problem in the preparation of 2-mercaptoimidazoles remains the synthesis of the initial α-amino-aldehydes and α-amino-ketones. The reduction of α-amino-acids with sodium amalgam [72-74] is in this case preferable to phthalimide methods [75,76] or the Dakin–West reaction [77-79], since it does not require the preliminary isolation of the α-amino-aldehyde from the reaction mixture and because the initial α-amino-acids are available.

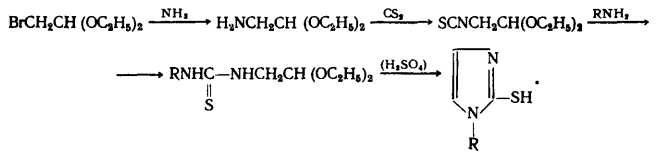
D-Glucosamine [80-83] or 1-alkylamino-1-deoxy-*D*-fructose [84] can serve as a source of 2-mercapto-4-(arabotetrahydroxybutyl)imidazoles which can be converted into 4-formylimidazoles:



N-Alkyl(aralkyl)-2-mercaptoimidazoles can be conveniently synthesised starting with *N*-substituted amino-acetals [85,86]:



A number of 2-mercaptoimidazoles containing alkyl, aralkyl, aryl, and 2-thiazolyl groups in position 1 have been obtained by a somewhat more complicated procedure [87]:

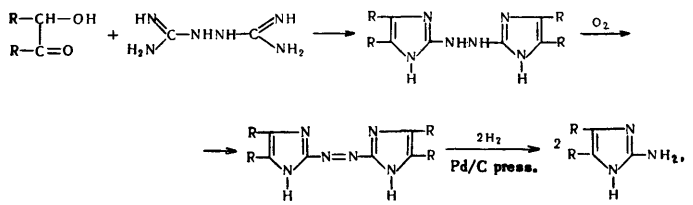


The condensation of the hydrochlorides of α-amino-ketones with potassium thiocyanate is best carried out in non-aqueous solvents (absolute alcohol, glacial acetate acid, etc.), since in aqueous media a certain amount of a pyrazine derivative is also formed as a result of the hydrolysis of the α-amino-ketones [88].

The methods of preparation of 4,5-dialkyl(diaryl)- and 1,4,5-triaryl(trialkyl)-imidazoles from α-hydroxy-ketones and thiourea or its *N*-substituted derivatives has been improved [89].

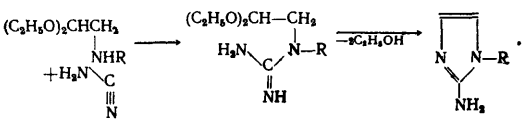
5. Aminoimidazoles

2-Aminoimidazoles have been little investigated so far because of the lack of convenient methods for their synthesis. The classical procedure for the synthesis of 2-aminoimidazoles consists in the reduction of azo-imidazoles obtained by coupling diazonium salts with imidazoles containing a free NH group [8]. However, not only are the yields low but the method is not always applicable [90]. A new promising modification of this method is via the synthesis and reduction of 2,2′-azo-imidazoles [91]:



where R = C_6H_5, $CH_3OC_6H_4$, β-$C_{10}H_7$, α-pyridyl. The yields of 2-amino imidazoles reach 89.5% in this case.

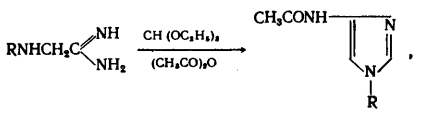
2-Amino-4,5-diarylimidazoles can also be obtained by the benzidine-like rearrangement of 2-phenylhydrazino-imidazoles [92] or by the reduction of the relatively readily available derivatives of 2-benzylidenehydrazinoimidazoles [93]. The most convenient method for the preparation of 2-aminoimidazole and its 1-alkyl derivatives is by the reaction of cyanamide with α-amino-acetals [94]:



The reaction of D-glucosamine with cyanamide gives 2-amino-4-(arabotetrahydroxybutyl)imidazole [95,96]. The preparation of 2-guanidino-4(5)-phenylimidazoles from phenylacylamines and cyanoguanidines is based on a similar reaction [97].

6. 4(5)-Aminoimidazoles and 4(5)-Aminoimidazole-5(4)-carboxamides

Two new methods for the preparation of 4(5)-amino-imidazoles have been proposed recently. In one of them the starting materials are the hydrochlorides of benzyl-oxycarbonyl or tosyl derivatives of aminoacetamidine and orthoformic ester [98]:

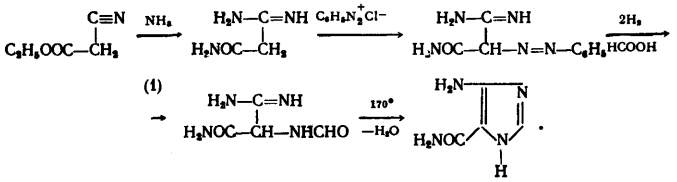


where R = *p*-$CH_3C_6H_4SO_2$ (a) and R = $C_6H_5CH_2OCO$ (b).

In the other method dinitriles RN(CN)CH(CN)R′ are cyclised into 4(5)-amino-2-bromoimidazoles by treatment with anhydrous hydrogen bromide [99].

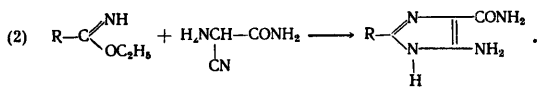
4(5)-Aminoimidazole-5(4)-carboxamides are of exceptional interest as the biosynthetic precursors of

purines [100]. At present several methods are known for the preparation of these compounds:

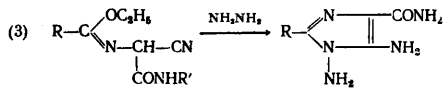


This method, proposed for the first time by Shaw and Woolley [101], is most convenient, after certain modifications [102-104], for the synthesis of large amounts of 4(5)-aminoimidazole-5(4)-carboxamides under laboratory conditions.

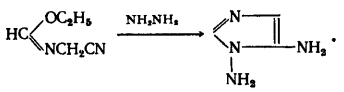
The reaction of amidines [105] or imino-esters [106] with aminocyanoacetamide proceeds as follows:



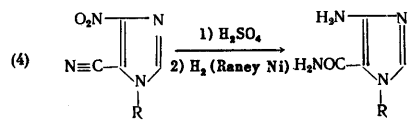
The reaction between *N*-(carbamoylcyanomethyl)imidates and hydrazine, phenylhydrazine, or 1,1-dimethylhydrazine yields the corresponding 1,5-diamino-4-carbamoylimidazoles [107,108]:



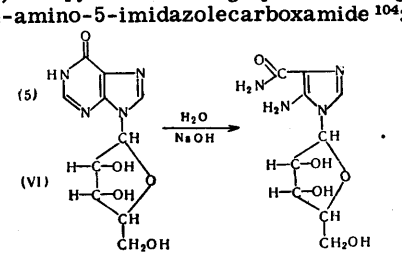
The parent compound of the series, 1,5-diaminoimidazole, is formed from ethyl *N*-cyanomethylformimidate and hydrazine [107]†:



Hydrazines not containing a free NH group, for example 1,2-dimethylhydrazine, do not give imidazoles in this reaction but 1,2,4-triazines. If a primary amine is used instead of hydrazine, it is possible to obtain 1-alkyl-(glucosyl)-5-amino-4-carboxamidoimidazoles [110-113]:



In the alkaline hydrolysis of certain purines, for example (VI), the pyrimidine ring opens forming the corresponding 4-amino-5-imidazolecarboxamide [104]:



In an acid medium the carbohydrate residue also hydrolyses.

† 1-Amino-2-mercaptoimidazoles have been described recently [109].

B. BENZIMIDAZOLES

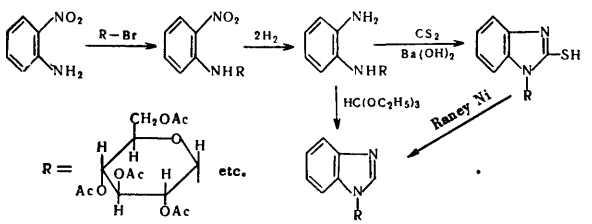
The principal method for the preparation of benzimidazoles is still condensation of *o*-arylenediamines with carboxylic acids and their derivatives. Attempts to find new ways of synthesising benzimidazoles, such as thermal decomposition of 1,5-diaryltetrazoles and 1,2,4-oxadiazol-5-ones [114-119] or the rearrangement of *N*-aryl-*N*-hydroxyamidines [120] are not of any preparative importance.

At the same time the classical synthesis of benzimidazoles from *o*-arylenediamines has been significantly modified. The method involving the ring closure of the imidazole ring of benzimidazole using directly the corresponding *o*-nitroanilines has been further developed, the reduction and cyclisation stages being combined into one [121-123]. Phillips' method for the synthesis of 2-arylbenzimidazoles has been improved [124-130], and many new modifications have been introduced into the reaction of *o*-arylenediamines with aldehydes [131-134].

1. Benzimidazoles without a Substituent in Position 2

The formation of benzimidazole from *o*-phenylenediamine and formic acid proceeds with exceptional ease: close to physiological conditions (18°, pH 0.5) the yield of benzimidazole after five days is 83%. [135] At 100–110° the time required for this yield is reduced to 2 h. Various benzimidazoles substituted in the benzene ring (substituents — alkyl, halogeno-, hydroxy-, alkoxy-, amino-, and nitro-groups, etc.) can be obtained just as readily by means of this reaction.

In connection with the interest attaching to vitamin B_{12}, much work has been done on the preparation of 5,6-dimethylbenzimidazole [121,136-141] and *N*-glycosidobenzimidazole [142-148]; particular attention has been devoted to 5,6-dichloro- and 5,6-dimethyl-1-glycosidobenzimidazoles [149], in view of their high physiological activity. 1-Glycosidobenzimidazoles are synthesised starting with the corresponding *o*-nitroaniline and acetylated glycosyl bromide:



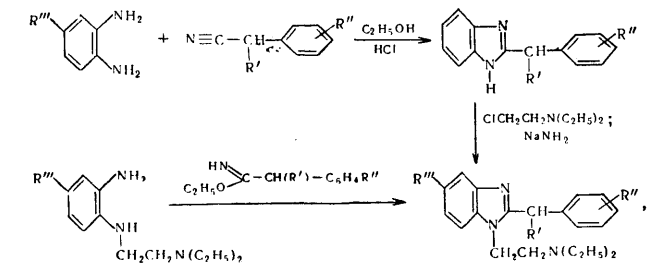
The condensation of *N*-substituted *o*-phenylenediamine is achieved with the aid of orthoformic ester, ethyl formate, or ethyl formimidate. Cyclisation under mild conditions can also be carried out by reaction with carbon disulphide in the presence of barium hydroxide [144,146]. The mercapto-group is subsequently eliminated with Raney nickel. A large number of *N*-arylbenzimidazoles have been obtained from *o*-aminodiphenylamine derivatives and formic acid.

2. 2-Alkyl(Aralkyl)benzimidazoles

The reaction of *o*-phenylenediamine and its 4-methyl-, chloro-, amino-, and alkoxy-derivatives with a number of aliphatic, aliphatic–aromatic, and aromatic acids in the presence of hydrochloric acid has been investigated [124-127].

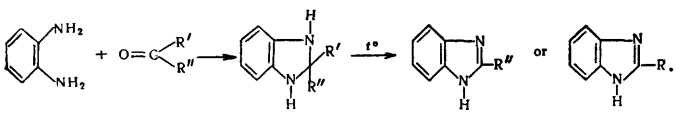
The yield of the 2-substituted benzimidazole depends on the nature of the diamine and carboxylic acid and on the concentration of hydrochloric acid. For example, it proved possible to obtain 2-benzyl- and 2-β-phenylethylbenzimidazoles in yields up to 88–99%.

Many 2-benzylbenzimidazoles have been synthesised according to the following scheme [151–154]:



where R′ = H, $CH_2CH_2N(C_2H_5)_2$, $CONH_2$; R″ = H, Cl, CH_3, AlkO; R‴ = H, NO_2. Many of these substances are muscle relaxants and are effective analgesics.

The reaction of *o*-phenylenediamine (VII) with aliphatic or aliphatic–aromatic ketones yields imidazolines which on thermal decomposition lose a hydrocarbon molecule (R′H or R″H) and are converted into 2-substituted benzimidazoles [155–157]:



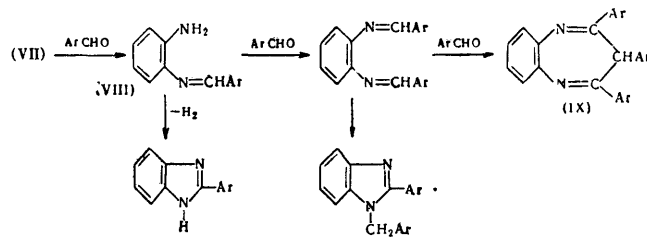
(VII)

The primary product of the reaction of *o*-phenylenediamine with benzophenone and its derivatives is not imidazoline but a Schiff's base [156] which on prolonged heating at 250–280° is converted into 2-arylbenzimidazole.

3. Benzimidazoles with Aryl or Heterocyclic Substituents in Position 2

Many new successful methods have been proposed for the synthesis of 2-acrylbenzimidazoles [124–133,158–162]. For example, 2-phenylbenzimidazole can be obtained in 76–95% yields from *o*-phenylenediamine and benzoic acid [124–127,129] or its derivatives: esters [129], nitrile [129,160], amide [129,161], and imidates [65,158,159]. The reaction is usually carried out by fusing together the components at 180–250° or by heating in a high-boiling solvent in the presence of condensing agents (hydrochloric acid, polyphosphoric acid, and others). We believe that the simplest and most convenient procedure is that of Porai-Koshits and coworkers in which equimolar amounts of *p*-phenylenediamine and benzoic acid are heated in a sealed tube at 180° in the presence of 25% hydrochloric acid. After heating for 40 min the yield of 2-phenylbenzimidazole is 95%. In the absence of hydrochloric acid the yield falls to 65% and when halogenobenzoic acids are used it is only 49% or less [162–163].

In the reaction of *o*-phenylenediamine with an equimolar amount of an aromatic or heterocyclic aldehyde a monoanil (VIII) is formed in the first stage and in the presence of oxidising agents can then yield a 2-substituted benzimidazole. The most successful oxidising agent, which at the same time serves as a solvent, proved to be nitrobenzene [131–133]. Sometimes (with 9-formylanthracene [164] and furfural [165]) the anil (VIII) is spontaneously oxidised by atmospheric oxygen to 2-substituted benzimidazole:



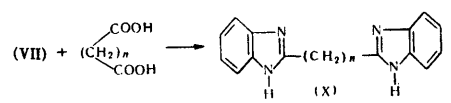
Depending on the conditions and on the nature of the reactants, in the reaction of *o*-arylenediamines with two and more moles of an aldehyde there is preferential formation of the corresponding 1-benzyl-2-arylbenzimidazole, 2-arylbenzimidazole, or, most often, their mixture with a small amount of 2,3,4-triaryldiazepine (IX). There is a review on the preparation of benzimidazoles from *o*-phenylenediamines and aromatic aldehydes [134].

None of these methods is universal but together they make it possible to synthesise any benzimidazole derivative. Thus in the synthesis of benzimidazoles with heterocyclic substituents in position 2 (pyridyl, quinolyl, furyl, thienyl, pyrrolyl, thiazolyl, etc.) best results are obtained by using aldehydes in the presence of oxidising agents, imidates [165], or acid amides [166].

Weidenhagen's classical method has been widely used in the synthesis of a large number of new 2-arylbenzimidazoles and their *N*-alkyl(aryl) derivatives [150,167]. The synthesis of 2-arylbenzimidazoles by the reaction of *o*-phenylenediamine with anil cyanides, ω-cyanoacetophenone, nitrones [168], and αβ-unsaturated compounds of the type ArCH=CHCOR [169] while not of preparative importance is of theoretical interest. 2-Phenylbenzimidazole forms in 40% yield in the pyrolysis of *N*-benzyl-*o*-nitroaniline in the presence of iron oxalate [123].

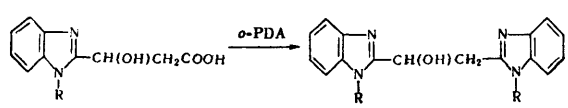
4. Bis(2-benzimidazolyl)alkanes and Related Compounds

In the reaction of *o*-phenylenediamine with dicarboxylic acids using Phillips' procedure [130,170–172] or at 190° [173] the corresponding bis(2-benzimidazolyl)alkanes (X) are formed:

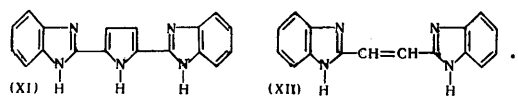


The synthesis of compound (X) with $n = 0$ and 1 can be achieved by using the diamide of oxalic or malonic acid [161,174]. For large values of n (8–10), the synthesis of compound (X) becomes difficult. Best results are then obtained when polyphosphoric or concentrated sulphuric acids are used as the catalysts [130].

Equimolar amounts of *o*-phenylenediamine (PDA) and malic acid give a β-hydroxy acid which on boiling with *o*-phenylenediamine gives a bis-derivative [171]:



The reaction between saccharic acid and *o*-phenylenediamine yields 1,4-bis(2-benzimidazolyl)-2,2,3,4-tetrahydroxybutane which can be converted to αα-bis(2-benzimidazolyl)pyrrole (XI) [175]:

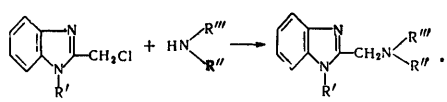


The furan analogue of compound (XI) has also been described [176].

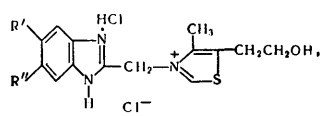
Various derivatives of 1,2-bis(2-benzimidazolyl)ethylene (XII) have been synthesised [177-179]. In the oxidation of bis(2-benzimidazolyl)methane or tetra(2-benzimidazolyl)-ethane Arnold obtained tetra(2-benzimidazolyl)ethylene, which is a powerful yellow chromophore [180].

5. 2-Aminoalkylbenzimidazoles and Amino-Acids of the Benzimidazole Series

2-Aminoalkylbenzimidazoles of various structures are readily obtained in the reaction between 2-chloromethylbenzimidazoles and a wide variety of primary and secondary amines [181-185]:



With tertiary amines quaternary ammonium salts are obtained. In particular, benzimidazolylmethyl analogues of thiamine have been prepared [186]:



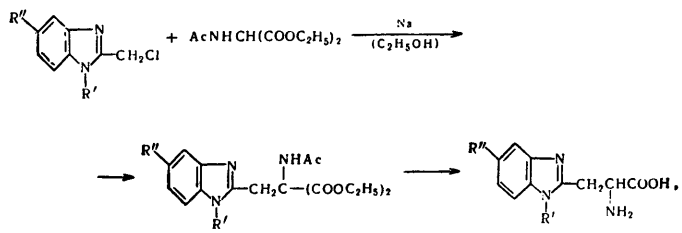
where R′ = H, CH_3; R″ = H, CH_3, Cl, CH_3O, $COOC_2H_5$.

Primary 2-aminoalkylbenzimidazoles can also be obtained by the reduction of nitriles [187], Hofmann degradation of amides, or by the Gabriel synthesis [188]. Until recently it was believed that the reaction between α-amino-acids and *o*-phenylenediamine does not give benzimidazole derivatives. However, it has been shown in a recent study [189] that, when the duration of heating is greatly prolonged, 2-aminoalkylbenzimidazoles can be obtained in satisfactory yield by this procedure. The reactivity of α-amino-acids in this reaction falls in the series glycine, alanine, α-aminoisobutyric acid. β-Amino-acids enter into this reaction much more readily.

Methods have been developed for the synthesis of 2-aminoalkylbenzimidazoles from *o*-phenylenediamines and peptides [190], benzyloxycarbonyl and *p*-tosyl derivatives of amino-acids, and their imino-ethers [191,192]. The reaction of *o*-phenylenediamine with peptides has been suggested for the identification of *C*-terminal amino-acid residues in peptides.

Attempts are being made to synthesise biologically active amino-acids containing a 2-benzimidazole residue.

Usually the synthesis is begun with 2-chloromethylbenzimidazoles and ethyl acetamidomalonate [187,193-196]:



where R′ = H, Alk, Ar; R″ = H, NO_2, CH_3, $N(CH_2CH_2Cl)_2$. In those cases where the method is inapplicable, a different procedure is followed, for example via the corresponding hydantoin [189]. The methods for the preparation of *N*-(2-benzimidazolylmethyl)amino-acids have been discussed [197].

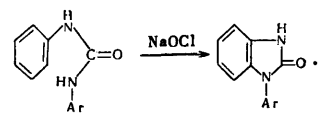
6. 2-Polyhydroxyalkylbenzimidazoles

The syntheses of 2-polyhydroxyalkylbenzimidazoles have been described in the monograph of Zhdanov and Dorofeenko [198].

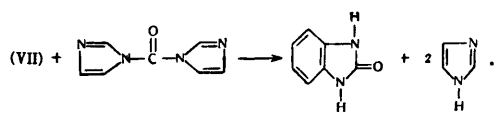
7. 2-Hydroxy- and 2-Mercapto-Benzimidazoles

2-Hydroxybenzimidazoles are readily formed from *o*-phenylenediamines and urea or phosgene [199-202]. In the first case the reaction components are fused together at 140–180° and in the second phosgene is bubbled through an acid aqueous solution of the diamine. Similarly 2-mercaptobenzimidazoles are formed from thiourea and phosgene [203-208].

A new method for the preparation of *N*-arylbenzimidazol-2-ones consists of the oxidation of *NN′*-diarylurea with sodium hypochlorite [209,210]:



Benzimidazolones are also formed in high yields in the reaction of *o*-phenylenediamines with *NN′*-carbonyldiimidazole [211]:



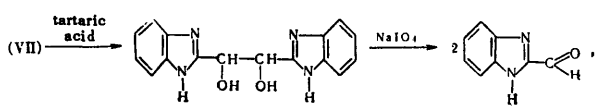
These compounds have been shown by means of electronic and vibrational absorption spectra to have the benzimidazolone and not the hydroxybenzimidazole structure [212,213].

8. 2-Formylbenzimidazoles

Aldehydes of the benzimidazole series have been investigated only in recent years. 2-Formylbenzimidazole [214-217] and its 6-chloro- [217], *N*-methyl-, and *N*-methyl-5-nitro-derivatives [218] are known. The oximes, arylhydrazones, products of condensation with compounds containing a reactive CH_3 group, and certain other derivatives have been obtained [214-219]. A study has been made

of the reaction of 2-formylbenzimidazoles with organomagnesium compounds [220] and their infrared spectra have been examined [221].

2-Formylbenzimidazole is formed in almost quantitative yield on oxidation of bis(2-benzimidazolyl)dihydroxyethylene with sodium periodate [214]:



or on hydrolysis of 2-dichloromethylbenzimidazole (yield 65%). [216] Oxidation of 2-hydroxymethylbenzimidazole [219,222] and 2-methylbenzimidazole with potassium persulphate or selenium dioxide gives less satisfactory results. Complications frequently arise in attempts to obtain *N*-substituted 2-formylbenzimidazoles by the above methods [219].

2-Formylnaphth[1,2-*b*]imidazole forms in 54% yield on oxidation of 2-methylnaphth[1,2-*b*]imidazole with selenium dioxide in acetic anhydride [223].

9. 2-Aminobenzimidazoles

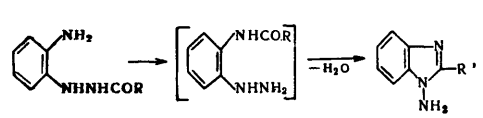
The best methods for the synthesis of 2-aminobenzimidazoles with an unsubstituted NH group is still the reaction of *o*-phenylenediamines with cyanogen bromide [224-227]. Cyanamide has also been suggested for this purpose [228]. 2-Amino-derivatives of 1-alkyl(aryl)benzimidazoles can be obtained by direct amination of *N*-substituted benzimidazoles using sodamide (see below). 2-Amino-1-*p*-nitrophenylbenzimidazole has been synthesised by fusing together guanidinium carbonate and 2-aminophenyl--4′-nitrophenylamine [229]. However, the attempts to use this method for the preparation of 2-aminobenzimidazole and 2-amino-1-phenylbenzimidazole were unsuccessful [202].

2-Guanidinobenzimidazoles form in the reaction between *o*-phenylenediamine and dicyanodiamide or its *N*-alkyl derivatives [230].

10. 1-Aminobenzimidazoles

Ried and Urlass [231] were the first to attempt the preparation of 1-aminobenzimidazoles, by the reduction of *N*-nitrosobenzimidazoles with zinc in acetic acid. However, this resulted only in the removal of the nitroso--group. Lithium aluminium hydride is also unsuitable in this case [232].

1-Aminobenzimidazoles can be obtained by heating acyl derivatives of *o*-aminophenylhydrazines with an aqueous solution of *m*-nitrobenzenesulphonic acid [233], which catalyses this reaction, or with a carboxylic acid [232]:

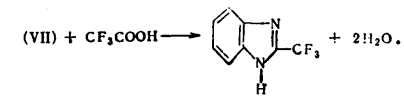


where R = H, CH_3, C_6H_5. When the Phillips procedure (4 *N* HCl) is used, this reaction yields benzo-1,2,4-triazine.

The amino-group in 1-aminobenzimidazoles is readily acylated and reacts with *p*-nitrobenzaldehyde with formation of an azomethine.

11. Fluorobenzimidazoles and Perfluoroalkylbenzimidazoles

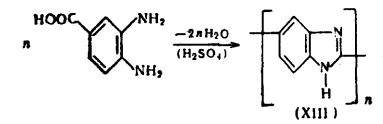
Trifluoroacetic acid and its homologues readily yield 2-perfluoroalkylbenzimidazoles on boiling with *o*-phenylenediamines [234-237]:



Benzimidazoles with a trifluoromethyl substituent in the benzene ring are usually obtained by an indirect procedure [236-241]. 2-Fluorobenzimidazole has not so far been obtained. The fluorine atom in the benzene ring of the benzimidazole molecule can be introduced by the Schiemann reaction [242] or indirectly, starting with fluorophenylenediamines [205,235-240].

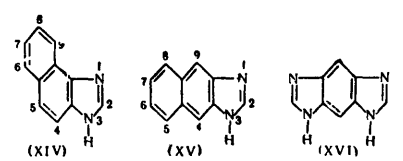
12. Polybenzimidazoles

The first polybenzimidazoles were obtained by Brinker and Robinson [243]. However, attempts, albeit unsuccessful, to obtain polybenzimidazoles of the type of compound (XIII) were made as early as 1953. [244] The synthesis of polybenzimidazole (XIII) in high yield was achieved in 1961 by Marvel and coworkers, who heated 3,4-diaminobenzoic acid in boiling concentrated sulphuric acid [245,246]. Methods for the synthesis of other polybenzimidazoles have also been developed in Marvel's laboratory [247]. All these compounds possess high thermal stability. The mechanism of the reactions resulting in the formation of polybenzimidazoles has been recently investigated by Korshak and coworkers [248]:



C. NAPHTHIMIDAZOLES

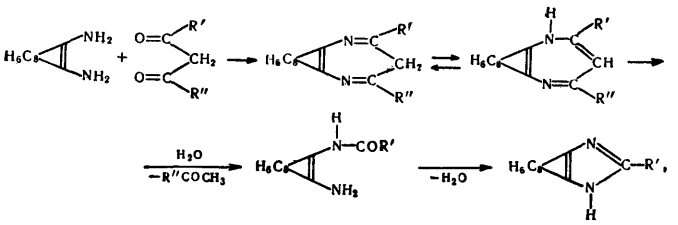
The yield of naphth[1,2-*b*]imidazole (XIV) in the condensation of formic acid with 1,2-naphthylenediamine is low [90]. However, when the sulphate of 1,2-naphthylenediamine is used, the yields of compound (XIV) reach 85% and more [90,249].



Relatively little work has been done on the chemistry of naphth[2,3-*b*]imidazole (XV) because the corresponding diamines are less readily available. The stage involving the cyclisation of the diamines with formic acid into compound (XV) and its 5,6,7,8-tetrahydro-derivative does not present any difficulties [250].

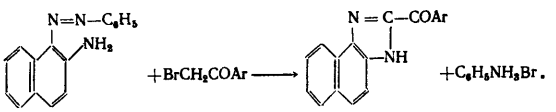
1,2- and 2,3-naphthylenediamines react with 1,3-diketones (acetylacetone, benzoylacetone, dibenzoylmethane) in acetic acid with formation of seven-membered products whose hydrochlorides are almost quantitatively converted

into the corresponding naphthimidazoles after heating with water for a short time [251,252]:



where R′ = CH_3, C_6H_5.

The reactions of acetoacetic and benzoylacetic acids with naphthylenediamines give satisfactory yields of 2-acetonyl(benzoyl)naphthimidazoles. Arylnaphthimidazolyl ketones can be obtained from phenylazo-β-naphthylamine and ω-bromo-ketones [253]:



Like *o*-phenylenediamine, *o*-naphthylenediamines readily react with phosgene, urea, and their sulphur analogues and also with cyanogen bromide, yielding 2-hydroxy(mercapto, amino)naphthimidazoles [226,254,255].

For the synthesis and properties of 1,2,4,5-diimidazobenzene (XVI), see Refs. 256 and 257.

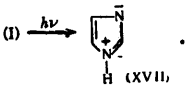
III. PHYSICAL PROPERTIES AND STRUCTURE

A. PHYSICAL PROPERTIES

Both experiment [258-264] and calculation [265-267] show that the dipole moment of imidazole and its derivatives (without polar substituents) is of the order of 3.8–4.0 D. The anomalously high dipole moments of imidazole (6.2 D) and 4-methylimidazole (6.3 D) found by Hückel and Jahneutz [268] are probably due to the fact that the measurements were made in too concentrated solutions where it was impossible to avoid the effect of association.

Substituents of low polarity have little effect on the dipole moments of imidazole derivatives [263]. The nitro-group increases the dipole moment by 2–2.5 D. [263] The replacement of the hydrogen in the NH group by an alkyl has almost no effect on the dipole moment [261,262]. However, *N*-arylation lowers appreciably the dipole moment, due to π-conjugation of the imidazole and aryl rings [264].

Imidazole almost does not absorb in the near ultraviolet, which indicates its high aromatic stability. The absorption in the region 207–208 mμm is due, according to Italian workers [167], to the conversion of symmetric species with a covalent structure into asymmetric and polar species [for example, (XVII)].



(XVII)

The introduction of alkyl groups into any position in the imidazole ring causes a small bathochromic shift of this absorption band [167,269-274] while in *N*- and *C*-arylimidazoles new very intense bands appear in the region 250–300 mμm, characterising the conjugation of the two aromatic rings (Table 1). Bands of this type are also present in the spectra of 2-arylbenzimidazoles [133,167,273-276].

The absorption spectrum of benzimidazole is much more complex. The short-wavelength absorption band (244–248 mμm) is attributed to electron transitions localised in the imidazole ring while the long-wavelength absorption is regarded as a displaced *B*-band of benzene (λ_{max} = 255 mμm). [167,270,277] In the spectrum of benzimidazole, as in those of other benzazoles, there is no absorption band corresponding to the interaction between the condensed benzene and heterocyclic rings. The reason for this phenomenon is still obscure.

The ultraviolet spectra of benzimidazoles have proved useful in the solution of problems associated with the elucidation of the structure of vitamin B_{12}. [278,279] The ultraviolet spectra of 2-imidazolones [212], benzimidazolones [213], 2-aminobenzimidazoles [202,280], and many other derivatives [208,281-284] have also been investigated.

The absorption spectra of naphthimidazoles are still more complex and have not been investigated in detail. There is a marked bathochromic shift in the series imidazole–benzimidazole–angular naphthimidazole–linear naphthimidazole.

The infrared spectra of imidazole [285,286] and its derivatives [283,284,287,288] are characterised by a series of intense absorption bands in the regions 760–880 cm^{-1} (imidazole ring), 1500–1620 cm^{-1} (aromatic C–C and C–N bonds), and 2200–3600 cm^{-1} (NH bond involved in association). The greatest interest attaches to the intense absorption in the region 2200–3600 cm^{-1}, which is attributed to the formation of intermolecular hydrogen bonds of the type $\gg N\ldots H-N$ [283,284,288-291] or the formation of the immonium structure $\gg N^+-H$. [285] A similar absorption is observed in the infrared spectra of benzimidazole and its 2-substituted derivatives [292], 4,5-diphenylimidazole [293], solutions of the *N*-anilides of imidazolecarboxylic acids [294,295], imidazolones [212], and imidazolethiones [212,296]. When the hydrogen atom of the NH group is replaced by a metal [285], deuterium [286], an acyl group [297], or an aryl group [293] the above absorption disappears, as would be expected.

TABLE 1. Ultraviolet absorption spectra of certain imidazoles.

Compound	λ_{max} and (log ε)	Refs.
Imidazole	207—208 (3.70)	167,269
1-Methylimidazole	212 (3.63)	167
1-Phenylimidazole	225*; 243; 266*; (3.79; 3.84: 3.27)	270
2-Phenylimidazole	271 (4.20)	167
4(5)-Phenylimidazole	257 (4.2)	269
4,5-Diphenylimidazole	225*; 252; 280 (4.23; 4.00; 4.10)	212
Benzimidazole	244; 248; 266*; 272; 279 (3.74; 3.73; 3.69; 3.71; 3.73)	167
Naphth[1,2-*b*]imidazole	222; 240; 273; 279; 313; 319; 326 (4.54; 4.57; 3.63; 3.65; 3.46; 3.38; 3.54)	255
Naphth[2,3-*b*]imidazole	235; 317; 327; 342 (4.79; 3.83; 3.88 3.74)	255

* Inflection.

The Raman [260,285,286,298] and fluorescence [212,299] spectra of imidazole and benzimidazole derivatives have also been investigated.

The nuclear magnetic resonance spectrum of imidazole contains two lines associated with the proton in position 2 and the two protons in positions 4 and 5. [300-305] The proton of the NH group gives rise to a distinct signal only in concentrated benzene and acetone solutions of imidazole and 4(5)-methylimidazole [304].

Imidazoles are amphoteric compounds and therefore the knowledge of the basicity and acidity (for derivatives with an unsubstituted NH group) constitutes some of the most reliable evidence in the elucidation of various structural problems [263,284,290,306-314]. In the series imidazole (pK_a = 7.03)–benzimidazole (pK_a = 5.53)–angular and linear naphthimidazoles (pK_a = 5.28 and 5.24 respectively) there is a decrease in the basicity of the pyridine-type nitrogen hetero-atom. On the other hand, the acidity of the NH group increases in this series (pK_a = = 14.5, 13.2, 12.54, and 12.52 respectively) [255].

The thermodynamic properties of imidazole have been investigated only recently [315]. The enthalpy of formation of imidazole (in the crystalline state) is 14.6 ± 0.8 kcal × × mole^{-1}, its heat of sublimation is 16.0 ± 1 kcal mole^{-1}, and the heat of formation of gaseous imidazole is 30.6 ± ± 1.8 kcal mole^{-1}. These data made it possible to calculate the resonance energy of imidazole as 14.2 kcal × × mole^{-1}. [315,316]

Crystallographic [317], X-ray diffraction [318,319], and semiconductor [320] properties of imidazoles, and their ionophoresis [321] and paper chromatography [322] have been investigated; determinations have been made of the association energy [260,289], the dielectric relaxation time [323], and the ionisation potential [324]; calculations have been made of the dissociation constant in an aqueous medium [289] and of the formal charge on the C and N atoms, using Wheland's equation [308].

B. QUANTUM-MECHANICAL CALCULATIONS ON THE IMIDAZOLE MOLECULE

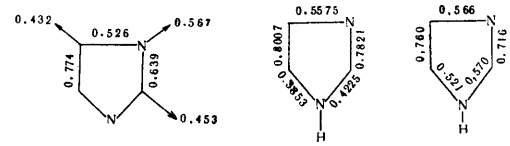
The values given for the π-electron density at various positions in the imidazole molecule (Table 2) are extremely contradictory, which reflects the gradual development of the computational technique by the MO LCAO method. Brown's early calculations [325,326], within the framework of the molecular orbital method, failed to take into account the difference between the two nitrogen atoms in imidazoles and show that in the neutral molecule the electron density in positions 4 and 5 is higher than in position 2, while in the imidazole anion the opposite situation obtains. Brown's latest data, based on the self-consistent field (VESCF) method, which do take into account the difference between the N_1 and N_3 atoms, show qualitatively the same picture [267]. It should be noted that the localisation energies in the imidazole molecule predict a different course of C-electrophilic substitution reactions, which is sometimes found to occur (see below).

TABLE 2. π-Electron density in imidazole.

Neutral molecule					Anion			Cation			Refs.
N_1	C_2	N_3	C_4	C_5	$N_{1(3)}$	C_2	$C_{4(5)}$	$N_{1(3)}$	C_2	$C_{4(5)}$	
1.502	0.884	1.502	1.056	1.056	0.903	1.429	1.323	—	—	—	325
1.479	0.907	1.479	1.067	1.067	0.835	1.458	1.436	—	—	—	326
1.650	1.100	1.401	1.037	1.112	1.197	1.207	1.200	1.512	0.997	0.990	267
0.2308	0.0216	—0.1709	0.037	—0.0853	—	—	—	—	—	—	266
1.347	0.991	1.286	1.104	1.072	—	—	—	—	—	—	327

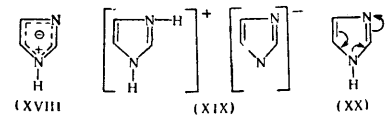
The molecular orbital method has also been used to calculate the reactivity of the benzimidazole molecule [327,328].

Bond orders and free valences in imidazole [266,326,327]:



C. STRUCTURE AND ASSOCIATION

The case of tautomeric transformations, bond equivalence, aromaticity, and the high dipole moment of imidazole are inconsistent with the classical structure (I). For this reason the structural formulae (XVIII)–(XX) have also been proposed for imidazole:



(XVIII) (XIX) (XX)

On the basis of their measurements of the dipole moments (4.8–6.2 D), Hückel and coworkers [268,329] attributed to the imidazole ring the structure of a dipolar ion (XVIII) in which the positive charge is centred on the immonium nitrogen and the negative charge in the centre of the five-membred ring. The calculated dipole moment for this structure (5.5 D) agrees satisfactorily with Hückel's data but is inconsistent with numerous subsequent determinations [258,260-267].

On the basis of data obtained from the potentiometric titration of benzimidazole derivatives, Efros and Porai-Koshits [313] suggested the possibility of the formation of ionic saltlike compounds (XIX) in aqueous solutions. Otting [285] arrived at a similar treatment of the imidazole structure in solid and non-polar media. However, Zimmerman obtained evidence from X-ray diffraction analysis [318], ultraviolet and infrared spectra [271,289,291], acid–base equilibria [289], measurements of the energy of association and mesomerism [289,316], and dipole moments [260] that the saltlike structure (XIX) cannot form.

Analysis of the dipole moments [261-263] shows that the imidazole ring is polarised in the direction of the C–N bond but this polarisation falls far short of that required for the formation of the dipolar structure let alone the ionic structure. The properties of the imidazole ring are most satisfactorily represented by the mesomeric structure (XX). [261,262]

The problem of the causes of the association of compounds containing the imidazole ring with an unsubstituted NH group, is immediately related to the considerations set out above. The investigators who have adopted structures (I), (XVIII), and (XX) for the imidazole ring explain association by the formation of intermolecular hydrogen bonds [259,263,288,290-293,304,305,318,320,325,330]. Nevertheless, Otting [285] attributes the association of imidazole to the formation of an ionic bond in the saltlike structures (XIX).

In Otting's opinion this view is confirmed by the unusual displacement of the NH band to the region 2500–3200 cm^{-1} in the infrared spectrum of imidazole. However, infrared spectroscopic data cannot be regarded as a convincing demonstration that the association of imidazole is of an ionic type, because similar bands (2500–3200 cm^{-1}) are also present in the infrared spectra of compounds which form hydrogen bonds of the type E... HE. [288,331] Furthermore, dilute benzene and acetone solutions of imidazole and 4(5)-methylimidazole do not give rise to a band in the region of 2500–3200 cm^{-1} despite the fact that in such solutions the compounds are present as dimers [292]. At high imidazole concentrations in non-aqueous media the coefficient of association reaches 5–20, [8,290,332] and not 2 as would be expected from Otting's postulate [285],

Finally, other evidence in favour of intermolecular hydrogen bonds as the principal cause of the association of imidazole is the association energy (5 kcal $mole^{-1}$), [289] the distance between the nitrogen atoms in neighbouring molecules (3 Å), [318] and the dependence of the dielectric constant on the concentration of the solutions [262] (the coefficient α varies in the same sense as the concentration [333]).

D. TAUTOMERISM

The isomers of imidazoles with an unsubstituted NH group (the difference between which consists in substituents being present in positions 4 or 5 [8,57,334,335]) cannot be isolated, although they enter into chemical reactions predominantly in one of the tautomeric forms [336–339]. This is due to continuous migration of the proton of the NH group between the two nitrogen atoms of the imidazole ring and also the equivalence of the cations and anions of both isomers. However, there does exist one claim that the above isomers have been separated in the case of sparingly soluble imidazole derivatives [335].

IV. CHEMICAL PROPERTIES

In this section there is no subsection headed "Radical substitution", since homolytic reactions in the imidazole series have been virtually uninvestigated (it is possible that free radicals participate in the formation of 2-mercaptoimidazoles when imidazoles are heated with sulphur [340]). Nor is the extensive class of imidazole metal complexes discussed, a separate review being desirable for these compounds.

In conformity with the guiding principle of this review, in examining the chemistry of arylimidazoles the authors have dealt only with the chemical properties of the imidazole part of the molecule.

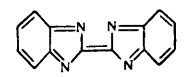
A. AROMATICITY OF THE IMIDAZOLE RING: REDUCTION, OXIDATION, DIENE SYNTHESIS

The imidazole ring is distinguished by high stability with respect to reduction. In the catalytic reduction [22,24,341] of a wide variety of arylimidazoles and furylimidazoles only the aryl or furyl rings reduced and not the imidazole rings, as was believed earlier [342]. The reduction of benzimidazole and its *N*-alkyl derivatives over platinum oxide leads to 4,5,6,7-tetrahydrobenzimidazoles [343]. Naphth[1,2-*b*]imidazole is hydrogenated on the same catalyst to 6,7,8,9-tetrahydronaphth[1,2-*b*]imidazole, while phenanthr[9,10-*b*]imidazole is reduced to an octahydro-derivative [343].

However, 2-methyl-4,5-diphenylimidazole may be reduced over a palladium catalyst to 2-methyl-4,5-diphenylimidazolidine [18]. In the reduction of benzimidazole with lithium aluminium hydride, Bohlmann obtained a substance to which he attributed on inadequate grounds the structure of 2,3-dihydrobenzimidazole [344]. Bayer showed that imidazole and benzimidazole are hydrogenated in acetic acid over platinum oxide *NN'*-diacetylimidazolidine and *NN'*-diacetylbenzimidazoline [345]. The corresponding derivatives of 2,3-dihydroimidazole are formed on addition of the dimethyl ester of acetylenedicarboxylic acid to 1,2-dialkylimidazoles in a reaction of the Diels–Alder type [346,347] (*cf.* Refs. 348 and 349).

The imidazole ring is more stable than benzene and naphthalene rings in oxidation reactions, as shown by the oxidation of benzimidazole with potassium permanganate, potassium dichromate [31–34], or hydrogen peroxide [350] to imidazole-4,5-dicarboxylic acid. In the oxidation of naphth[1,2-*b*]imidazole the product is 4-(*o*-carboxyphenyl)-5-carboxyimidazole and not imidazole-4,5-dicarboxylic acid [10]; napth[2,3-*b*]imidazole is oxidised to imidazo-4,9-naphthoquinone [249].

The oxidation of benzimidazole with lead peroxide [351] is quite unusual, leading to the formation of $\Delta^{2,2'}$-diisobenzimidazolidene (XXI). The same substance was also obtained in the oxidation of 2,2'-dibenzimidazolyl with PbO_2:[351]



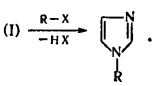
(XXI)

Selenium dioxide in dioxan oxidises 2-methylbenzimidazole to *o*-hydroxyacetanilide [352].

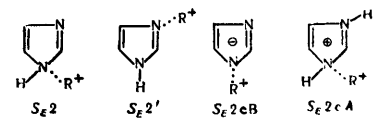
B. ELECTROPHILIC SUBSTITUTION

1. *N*-Substitution

In this section we shall consider the methods of direct introduction of substituents into position 1 of the imidazole ring (indirect methods have been examined above). Disregarding the mechanism of the process, the reaction may be represented in a general form as a simple substitution of the hydrogen atom of the NH group by a radical R:

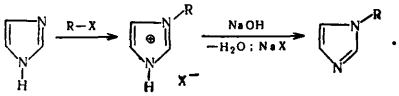


a. Alkylation of imidazoles. Reaction mechanisms. *N*-Substitution in the imidazole ring is by no means as simple as is suggested in a number of reviews [8–10]. It must be borne in mind that, depending on the conditions, imidazole can enter into alkylation reactions in several forms (sometimes several forms at the same time) — as a base (S_E2 and S_E2' mechamisms), anion (S_E2 cB mechanism), or as the conjugate acid (S_E2 cA mechanism):

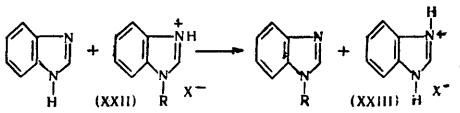


S_E2 S_E2' S_E2cB S_E2cA

The classical method for the preparation of *N*-alkylimidazoles consists in the reaction between the heterocyclic compound and an alkyl iodide (bromide, or, less frequently, chloride) in a sealed tube at 100–150° (Wallach, Wyss, Fischer, Pyman)[8-10]. Under these conditions the reaction involves preferentially the pyridine-type nitrogen atom (S_E2' mechanism)[337,353]:



If the process stopped at the stage in which the hydrochloride of the *N*-substituted derivative is formed, this method could yield the theoretical amount of 1-alkylimidazole (after treating the salt with alkali). However, in fact the yield of the *N*-substituted derivative when imidazole is alkylated in a neutral medium reaches 50% at most. Using benzimidazole as an example, it has been shown that the initial base which fails to enter into the main reaction then reacts with the hydrochloride of benzimidazole[353] and the resulting 1-alkylbenzimidazole is further alkylated with the alkyl halide to a 1,3-dialkylbenzimidazolium salt. Thus these side-reactions lead to an irreversible conversion [the conjugate acids (XXII) and (XXIII) cannot undergo further alkylation[337,353]] of about 50% of the starting compound into benzimidazolium (XXIII) and 1,3-dialkylbenzimidazolium salts. The use of two moles of imidazole (to bind the HX) per mole of the alkylating agent cannot be regarded as a successful solution of this problem:

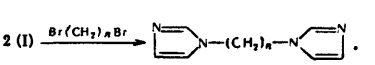


The most satisfactory results are obtained when imidazoles are alkylated in the presence of alkaline agents. Apart from alkali metal hydroxides, sodium alkoxides[354,357], sodium acetate[358], sodium carbonate[359], sodamide[360-363], sodium hydride[348], etc. have been used. The reaction is carried out in alcohol, less often in hydrocarbons[354,362], water[359], dioxan[360,363,364], acetone[366], and liquid ammonia[361,365].

The enhanced nucleophilic character of the nitrogen atoms in the imidazole anion makes it possible to achieve the alkylation at a lower temperature and thereby avoid the formation of a large amount of quaternary salts. In the case of benzimidazole it is permissible to vary the initial amounts of alkyl halide and alkali in order to improve the yield[366]. The maximum yield of 1-alkylbenzimidazole (76–83% for primary and 50–60% for secondary alkyl and aralkyl bromides) can be achieved by using two moles of alkyl bromide and 1.5 moles of alkali per mole of benzimidazole.

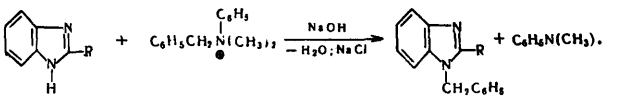
The ease of formation of quaternary salts constitutes a serious obstacle in the alkylation of imidazole itself, since the latter is much more basic than benzimidazole. Here it is almost impossible to use an appreciable excess of the alkylating agent and temperatures higher than 20–40°.[355,361,367] Best results are obtained when imidazole is alkylated in liquid ammonia in the presence of sodamide[361].

Bis(1-imidazolyl)alkanes are formed in the reaction of benzimidazole[368] and imidazole[369] with dibromoalkanes:



In the presence of alkaline agents the imidazole ring is readily alkylated with ethylene chlorohydrin[370,371], chloroacetic acid or its ethyl ester[132,372,373], and dialkylaminoalkyl chlorides[363,374-376].

It is extremely convenient to introduce primary aralkyl radicals (benzyl, α-naphthylmethyl, etc.) into the NH group of benzimidazole by allowing the latter to react with dimethylphenylaralkylammonium chlorides[219,353,377,378]. The reaction proceeds rapidly and almost with a quantitative yield in an aqueous solution of sodium hydroxide:



In the imidazole series this reaction has not been investigated.

The use of the silver salts of imidazoles or *N*-chloromercuri-imidazoles is the only method available for the introduction into position 1 of the imidazole ring of substituents such as triphenylmethyl[379,380] or glycosyl[381-389]. The alkylation of 2-arylbenzimidazoles in an alkaline medium proceeds with considerable difficulty because of steric hindrance[133,353]. In this case it is also desirable to use the corresponding silver salts.

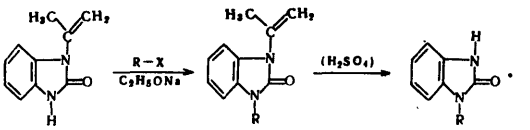
As a result of the formation of two isomers, the alkylation of asymmetric imidazole and benzimidazole derivatives proceeds in a very complex manner. This problem has been recently thoroughly reexamined on the basis of information derived from kinetics and spectroscopy[337,338]. The data obtained are however inconsistent not only with the old results but also with the results of many new studies[358,390-392] and therefore final conclusions would probably be premature. Also contradictory are the results obtained on the alkylation of the asymmetric napth[1,2-*b*]-imidazole[8,10,90,393]. There is a review of work done on the alkylation of asymmetric imidazoles[353].

Benzimidazoles[394,395], benzimidazolones[396], and benzimidazolethiones[397] react with formaldehyde and secondary amines (Mannich reaction), forming *N*-aminomethyl derivatives.

The reaction of benzimidazole derivatives with ethylene oxide, yielding *N*-β-hydroxyethylbenzimidazoles, has been investigated in detail[398-400].

Imidazole, benzimidazole, and their substituted derivatives are alkylated at the NH group by a wide variety of unsaturated compounds: acetylene[401,402], acrylonitrile[313,392,403] and other derivatives of acrylic acid[404,405], and vinyl acetate[406]. The methylation of imidazole with diazomethane proceeds smoothly[393,407,408].

The reaction of *o*-phenylenediamine with acetoacetic ester in a neutral medium gives 1-isopropenylbenzimidazol-2-one, from which *N*-monoalkyl derivatives of benzimidazolone can be obtained[356,357]:

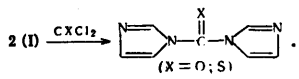


2-Mercapto-derivatives of imidazole [36,409-413] and benzimidazole [204,414,415] are alkylated with alkyl halides [36,409,410,204,414,415], α-halogeno-ketones [411,412], α-halogeno--aldehydes [412], and α-halogeno-acids [35,413]: the reaction involves initially the SH group, this being followed by *N*-alkylation.

In alkaline [225] and neutral [416,417] media 2-aminobenzimidazoles are alkylated at the ring nitrogen.

b. *N*-Arylation of imidazoles. Until recently the only example of direct *N*-arylation of the imidazole ring was the ready synthesis of *N*-dinitrophenyl- and picryl--imidazole derivatives, starting with 2,4-dinitrohalogenobenzenes and picryl chloride [293,418-420]. Not long ago a method was developed for the direct arylation of imidazole and benzimidazole with aryl halides, without substituents activating the halogen atom in the arylating agent [421,422]. The reaction is carried out in nitrobenzene in the presence of potassium carbonate and cuprous bromide (catalyst). The yield of *N*-aryl derivatives reaches 73%. The replacement of nitrobenzene by other solvents (tetralin, diethylaniline, excess of aryl bromide) gives worse results.

c. Acylation of imidazoles. Studies made in the 1950's established that *N*-acylimidazoles and their reactions are of fundamental importance in enzymic transacylation [6,7]. Staab synthesised unusually reactive acylimidazoles which served as models for the most important biochemical reactions (see Staab's review [423]):



Imidazolides of this type have found application in the synthesis of aldehydes, amidines, esters, acid anhydrides, and in peptide synthesis [424,427], the last application being particularly important.

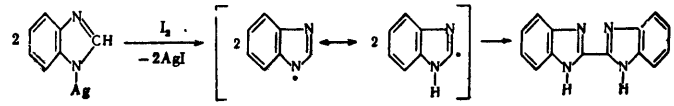
N-Formylimidazoles [428] and *N*-benzyloxycarbonylimidazoles [429] can be used as formylating and benzyloxycarbonylating agents.

The reaction of imidazole with potassium thiocyanate in a neutral medium yields *N*-carbamoylimidazole [430], while aryl cyanates react with imidazoles in a more complex manner, involving not only the N but also the C_2 atom [431].

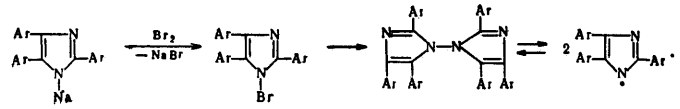
The chlorides of aromatic sulphonic acids readily acylate imidazole and benzimidazole at the NH group in the presence of weakly basic agents (potassium carbonate, sodium acetate) [432-434].

2-Mercapto- and 2-hydroxy-derivatives of imidazole and benzimidazole are acylated with acid anhydrides and chlorides at the N atoms [435-437]. 2-Aminobenzimidazoles are acylated at the exocyclic amino-group [416]. In the reaction of acetic anhydride with the *N*-oxide of benzimidazole the product is 1,3-diacetylbenzimidazolone [437] and not 1-acetyl-2-acetoxybenzimidazole [438].

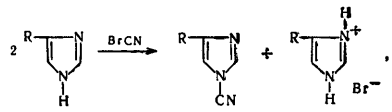
d. Halogenation and cyanation. It has been established that the product obtained [8,9] by the action of iodine on an alkaline solution of benzimidazole is *N*-iodobenzimidazole and not the 2-iodo-derivative [439,440]. It might have been supposed that on reaction with iodine the silver salt of benzimidazole would also yield *N*-iodobenzimidazole and then the hitherto unknown *NN'*-dibenzimidazolyl. Actually the reaction is more complicated, apparently involving the 2-benzimidazolyl radical, and leading to the formation of 2,2'-dibenzimidazolyl [351]:



Imidazole reacts with halogens, yielding *C*-substituted derivatives, but it has been demonstrated convincingly [441] that here too the intermediates are *N*-halogenoimidazoles (*trans*-halogenation). For example, the reaction between the sodium salts of 2,4,5-triarylimidazoles and bromine in absolute ether gives *NN'*-diimidazolyls, since the intermediate *N*-bromoimidazoles formed in this reaction cannot undergo a rearrangement to the *C*-bromo-derivatives [441]. The N–N bond in diimidazolyls readily undergoes homolytic splitting with formation of two *N*-imidazolyl radicals [441,442]:

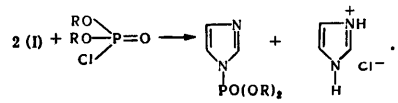


Cyanogen bromide is known [8] to react with *N*-substituted imidazoles with formation of 2-bromoimidazoles. Imidazoles with a free NH group undergo *N*-cyanation [443]:

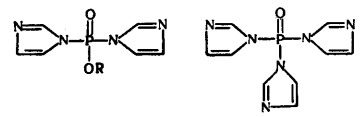


where R = H, CH_3. Cyanogen bromide introduces the CN group into 2-mercaptoimidazole at the SH group [444].

e. Phosphorylation. *N*-phosphorylimidazoles play an important role in enzymic transphosphorylation [6]. They form in the reaction of two moles of imidazole or benzimidazole with one mole of a dialkyl(diaryl)phosphoric acid chloride [445,446].



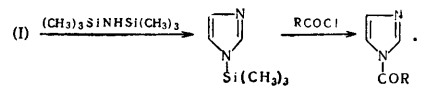
Di- and tri-imidazolides of phosphoric acid can be obtained similarly from phosphoric acid dichloride or from phosphorus oxychloride [447,448]:



The reaction between *NN'*-carbonyldiimidazole and phosphoric acid esters also yields *N*-phosphoroimidazoles [449]. *N*-phosphoroimidazole is extremely unstable and rapidly undergoes autocatalytic hydrolysis. Its derivatives, in which the phosphoryl residue is combined with an organic radical, are more stable. These compounds readily phosphorylate amines, alcohols, and the carboxy--group at room temperature [450].

f. Silylation. Imidazole, benzimidazole, and other heterocyclic compounds with a nitrogen atom of the pyrrole

type react with hexamethyldisilazane with formation of *N*-trimethylsilyl derivatives[451], which exhibit remarkably high reactivity. They are acylated with the chlorides of organic and mineral acids with almost quantitative yields even at 0°:



g. Nitrosation. When an acetic acid solution of benzimidazole and its 2-substituted derivatives is treated with aqueous sodium nitrite, *N*-nitrosobenzimidazoles, giving a positive response to the Lieberman test, are formed[173,231].

2. *C*-Substitution

Electrophilic substitution (azo-coupling, nitration, halogenation, etc.) of the carbon atoms in the imidazole ring is characteristic only of imidazole itself and those condensed systems in which the imidazole ring is linked to a non-aromatic ring: tetrahydrobenzimidazole, phenanthr[9,10-*b*]imidazole, etc.[90] For compounds such as benzimidazole or naphthimidazoles, nucleophilic substitution reactions at the 2-carbon atom of the imidazole ring (see below) are typical, as a result of the electrophilic effect of the aromatic ring condensed with the imidazole ring.

One of the classical problems of imidazole chemistry is associated with electrophilic substitution. Only in recent years has it become more or less clear why in some cases (nitration, sulphonation, etc.) electrophilic substitution takes place at positions 4 and 5 of the imidazole ring while in others (coupling with diazonium salts) position 2 is involved. As late as 1950 Schofield suggested that the imidazolium cation is involved in nitration and sulphonation while the neutral molecule is involved in the coupling reaction[452] (the latter hypothesis subsequently proved to be erroneous). Kinetic studies of iodination[453] and diazo-coupling[454] of imidazole and molecular-orbital calculations[325,326] made a decisive contribution towards the solution of this problem. It was found that the mechanisms of the halogenation and coupling reactions involve the formation of the conjugate base of imidazole (iodination proceeds via the imidazole anion B^- even at pH 7). This is confirmed by the fact that 1-methylimidazole does not undergo the coupling reaction. Furthermore, deuteration of imidazole in a neutral medium with D_2O leads to 4(5)-substitution, while in NaOD solution the C_2 atom is deuterated preferentially[300].

The data on the halogenation of imidazole are contradictory. Earlier it was found that bromination proceeds preferentially in position 4(5), while iodination leads to a 2-substituted derivative. However Ridd[454] reported that, even in the presence of a 20-fold excess of imidazole, the main iodination product is the di-iodo-derivative (see also Refs. 455 and 456). Study of the iodination of deuteroimidazoles (the kinetic isotope effect method) showed that the iodination proceeds, like bromination, in position 4(5).[457] This finding lent support to Brunings'[458] hypothesis of primary *N*-iodination of imidazole with subsequent rearrangement of the *N*-iodoimidazole to the *C*-iodo-derivative. The kinetic equation for the iodination of imidazole includes, in addition to the term corresponding to the reaction of the imidazole anion with the I^+ or H_2OI^+ cations, a second term which depends on the concentration of imidazole and indicates that the reaction may be catalysed by imidazole itself:

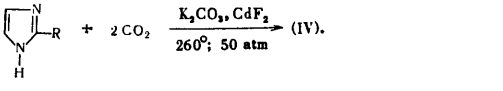
$$V = k[B^-][H_2OI^+] + k'[B^-][BHI^+].$$

This finding can be understood as a special case of a *trans*-reaction with participation of the imidazole ring. Recently yet another report of the conversion of *N*-bromoimidazoles into *C*-bromo-derivatives has appeared[441]. We may also recall that in an alkaline medium benzimidazole is iodinated at the N atom[439,440].

How then can we explain why two reactions, iodination and coupling, apparently equivalent as regards mechanism and involving the same intermediate (imidazole anion), result in attack at different positions? As stated above, molecular-orbital calculations on the conjugate base of imidazole lead to two different conclusions: the charge densities suggest that electrophilic substitution should occur in position 2, while according to the values of the localisation energies, electrophilic agents should attack the imidazole rings in positions 4 and 5. It is believed that in the above two reactions iodination follows the values of localisation energies, i.e. depends on the transition state of the reaction, in which the removal of the proton determines the rate of the process as a whole. The overall kinetics of imidazole iodination are very complex and the reason for the instantaneous iodination of the monoiodo-compound to give the di-iodo-derivative still remains obscure. Certain phenylimidazoles substituted in position 2 can couple with diazonium salts also in position 4(5).[464]

In the presence of sodium ethoxide, pentyl nitrite nitrosates phenylimidazoles with an unsubstituted NH group in position 4(5). If positions 4 and 5 are occupied, nitrosation in position 2 does not occur. The properties of the resulting 4(5)-nitrosoimidazoles have been investigated in detail[459-465].

The synthesis of imidazole-4,5-dicarboxylic acids by the reaction of carbon dioxide with imidazole and its 2-alkyl derivatives constitutes a new electrophilic substitution reaction in the imidazole series[466]:



Sulphur tetrafluoride converts both carboxy-groups of the acid into trifluoromethyl groups[467].

It has been known for a long time that formaldehyde or paraformaldehyde hydroxymethylate *N*-substituted imidazoles in position 2. Unexpectedly this reaction was achieved also with *N*-vinylbenzimidazole[468]. It would be desirable to verify this unique electrophilic *C*-substitution reaction in the imidazole ring of benzimidazole.

N-substituted imidazoles undergo thermal condensation with aliphatic (except for acetaldehyde) and aromatic aldehydes with formation of imidazol-2-yl carbinols[361], which can also be obtained by the action of the aldehydes on 2-lithioimidazoles[361,469].

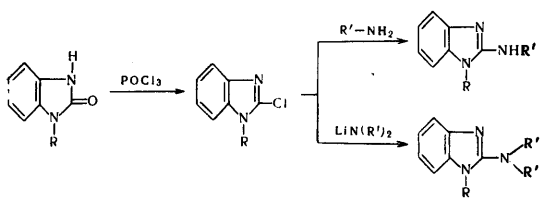
C. NUCLEOPHILIC SUBSTITUTION

In monographs and reviews on the chemistry of imidazole[8-15] little attention has been given to nucleophilic

substitution, because reactions of this type in the imidazole series began to be investigated systematically only in recent years.

1. Substitution of Groups in Position 2 of the Imidazole Ring

The first example of nucleophilic reactions in the imidazole series is the synthesis of 2-chlorobenzimidazole from benzimidazolone and phosphorus oxychloride [470]. Later this reaction was studied in detail [440] and extended to 4,5-diphenylimidazolone [471], benzimidazolone derivatives [201,202,393,471-478], naphthimidazolone [479], and tetrahydronaphthimidazolone [480]. The chlorine atom in position 2 of the imidazole ring can be relatively readily exchanged for amino-, alkylamino-, arylamino-, and hydrazino-groups [255,393,440,472,475,477,480,484]:

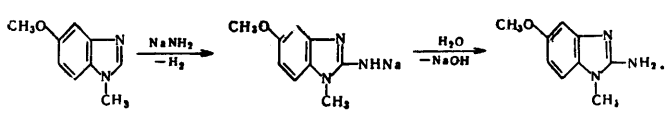


where R′ = alkyl, aryl, NH_2. Chlorine is exchanged even more readily in quaternary benzimidazolium salts [485].

It should be noted that all these reactions have been mainly investigated for condensed systems containing the imidazole ring, but not for imidazole itself. Other groups in position 2 of the imidazole ring also exhibit considerable mobility. Thus the methylthio-group can be exchanged for amino-, benzylamino- [255], and hydrazine-groups [481]. The sulpho-group is readily replaced by chloro- [485], hydroxy-, alkylamino-, and cyano-groups [9]. The ready hydrolysis of sulphones of the benzimidazole series probably belongs to the same class of reactions [486,487].

2. The Action of Sodamide on Imidazole Derivatives (Chichibabin Reaction)

By allowing sodamide to react with 5-methoxy-1-methylbenzimidazole in xylene, Simonov and Uglov obtained the corresponding 2-amino-derivative in good yield [488]:



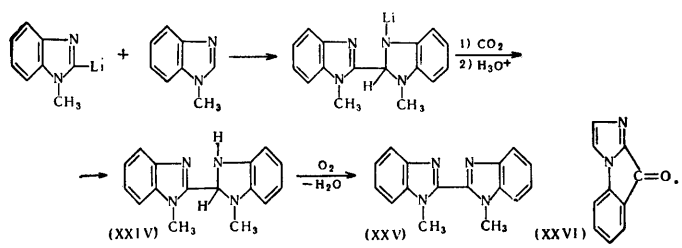
Later this reaction was extended to other *N*-alkyl, aralkyl, and aryl derivatives of benzimidazole [90,202,368,375,377,378,433], naphth[1,2-*b*]imidazole, and tetrahydronaphth[1,2-*b*]imidazole [489]. Heterocyclic compounds with an unsubstituted NH group are not aminated by sodamide, since the anion formed initially, clearly cannot be subject to nucleophilic attack [433,488].

Apart from the formation of the 2-amino-derivative, in the amination of *N*-arylbenzimidazoles the imidazole ring opens as a result of the p,π-conjugation of the *N*-aryl and imidazole rings with consequent loss of aromaticity by the latter [202,264].

Amination of *N*-alkylbenzimidazoles substituted in the benzene ring showed that this reaction is significantly influenced by the nature of the substituent in position 5 of the benzene ring. Whereas 5-alkyl- and 5-alkoxy-1-alkylbenzimidazoles form 2-amino-derivatives, 5-hydroxy-, 5-halogeno-, 5-nitro-, and 5-carboxy-derivatives do not enter into this reaction [490,491]. Attempts to extend the Chichibabin reaction to *N*-alkyl derivatives of 4,5-diphenylimidazole, 4,5,6,7-tetrahydrobenzimidazole, and phenanthr[9,10-*b*]imidazole were unsuccessful [492]. Thus amination of the imidazole ring at the 2-carbon atom occurs only when the former is condensed with an aromatic ring (in 4,5-diphenylimidazole the phenyl rings are not coplanar with the imidazole ring while in phenanthrimidazole the aromaticity of the middle benzene ring of phenanthrene cannot be compared with the aromaticity of the benzene ring in benzimidazole — a well known fact). From this point of view, the derivatives of imidazole itself should not enter into the Chichibabin reaction either.

3. Metalation Reactions

N-alkylimidazoles [361,469] and *N*-alkylbenzimidazoles [365] undergo metalation under the action of butyl-lithium at low temperatures with formation of 2-lithio-derivatives. In the metalation of 1-methylimidazole a small amount of the 5-substituted derivative also forms [469]. The reaction of butyl-lithium with 1-methylbenzimidazole at room temperature yields the corresponding 2,2′-dibenzimidazolyl (XXIV) and its dihydro-derivative (XXV), which can be explained by the following mechanism [365]:

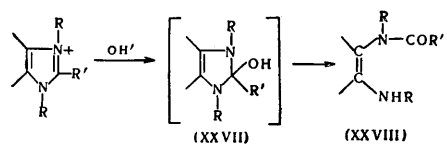


1-Alkylbenzimidazoles are also readily metalated in position 2 by phenyl-lithium [122] and phenylsodium [493].

The reaction of 1-phenylimidazole with an excess of butyl-lithium followed by reaction with carbon dioxide leads to the formation of 4-oxoimidazo[1,2-*a*]indoline (XXVI), which also constitutes evidence that the imidazole ring is metalated at the 2-carbon atom [469]. *N*-arylbenzimidazoles are not metalated by butyl-lithium at low temperature but at room temperature butyl-lithium adds to the C–N bond [122], a reaction which was observed earlier also for *N*-methyl-2-t-butylbenzimidazole [494].

4. Imidazolium Salts and Their Reactions

1,3-Dialkylimidazolium salts are known to be converted under the action of bases into the so-called "pseudo-bases". This reaction is a consequence of the nucleophilic attack by the hydroxide ion on the C_2 atom of the imidazole ring [418,419,495]:



Pseudo-bases have been regarded for a long time as cyclic carbinols (XXVII) and it was not until a study had been made of their infrared spectra and their acylation reaction that their non-cyclic structure (XXVIII) was established[293,418,419,496]. The existence of a ring–chain tautomerism between the cyclic and non-cyclic forms has been suggested[495].

The benz- and naphth-[1,2-*b*]imidazolium salts, containing the 2,4-dinitrophenyl substituent at the N atom are converted irreversibly into derivatives of 2-amino-2',4'-dinitrodiarylamine even under the action of bases as weak as aniline and pyridine[418,419] (*cf.* Ref. 497). The conversion of 4,5-diphenylimidazolium and 4,5,6,7-tetrahydrobenzimidazolium salts occurs similarly although under somewhat more severe conditions (ammonia, sodium carbonate)[498,499].

ADDED IN PROOF

After this review had been sent for editing, the following papers were published:

On Physical Properties

Spectra: infrared[500,501], nuclear magnetic resonance[502], ultraviolet[503].
Phototropic transformations and chemiluminescence[504–507].

On 1-Substituted Imidazoles

Methylation of 2-perfluoroalkylimidazoles with diazomethane[508].
Preparation of 1-vinylimidazoles[509].
New synthesis of glucopyranosides of benzimidazole[510].
Acylation of benzimidazoles[511].
Acylation of the OH group of serine with *N*-acetyl derivatives of histidine[512].
New stereospecific synthesis of olefins from 1,2-diols and *NN'*-dithiocarbonylimidazole[513].
Imidazolide method for the preparation of diacetyl peroxides and per-acid esters[514].
N-Carbamoylimidazoles[515].
N-hydroxyimidazoles[516] and benzimidazoles[517–520].

On 2-Substituted Imidazoles

Syntheses of 2-nitroimidazole (azomycin)[521], 2-aminoimidazole[522], 2-arylaminoimidazole[523], 2-arylaminobenzimidazole[524], 2-piperidino-2-dimethylaminobenzimidazole[525].
Reaction of 2-aminobenzimidazoles with halogeno-esters[526].
Synthesis and reactions of 1-phenyl-2-hydrazinobenzimidazole[527].
Benzimidazol-2-ones[528] and dihydrobenzimidazoles[529,530].
Benzenesulphonyl- and methanesulphonyl-benzimidazolones[531].
Nucleophilic substitution of chlorine in 2-chlorobenzimidazoles: preparation of 2-hydroxy- and 2-mercapto-benzimidazoles[532,533].
2-Acetyl- and 2-benzoyl-benzimidazoles[534].
Structure and chemical properties of 2-formylbenzimidazoles[535].
Preparation of 2-mercaptobenzimidazole by direct thiolation of benzimidazole[536].
2-Imidazolone and its derivatives[537].
2-Aroyl-4(5)-arylimidazoles[538,539].
Formation of 2-acylbenzimidazole from *N*-acylaminophenylpiperidine and its homologues[540].
2-Cyanomethyl-[541] and 2-(3-thienyl)benzimidazoles[542].
Synthesis of benzimidazoles from *N*-arylamidines (thiabendazole)[543].
2-Arylbenzimidazoles from *o*-phenylenediamines and carboxylic acid hydrazides[544].
2-Substituted benzimidazoles from *o*-phenylenediamine and carboxylic acids[545].
Perfluoroalkyl-[546] and polyfluoro-benzimidazoles[547].
Synthesis of 1,2,4,5-tetra(benzimidazol-2-yl)benzene[548].
[Thermal decomposition of benzylidene-2-azidoanilines[549] (Ed. of Translation)].
2-Styrylbenzimidazoles from *o*-phenylenediamines and cinnamic acid[550].
Bis-(2-benzimidazolyl)alkanes[551].

On 4(5)-Substituted Imidazoles

4(5)-Halogeno- and 4,5-dihalogeno-imidazoles[552–554].
Nitration of 2-methylimidazole[555].
4(5)-Nitroimidazoles[556].
4,5-Diaminoimidazoles[557].
4(5),4'(5')-Polymethylenediimidazoles[558].
Cyclo-octyl- and cyclononyl-imidazoles[559].

On the Reactivity of the Imidazole Ring[560–562].

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REACTION OF NUCLEIC ACIDS WITH METALS

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1. INTRODUCTION

Nucleic acids play an important part in the processes of the biosynthesis of protein, growth, reproduction, and heredity of living organisms. However, even now very little is known about the actual mechanism of their participation in these processes; this explains the considerable interest of investigators in the various types of reaction of nucleic acids.

In recent years it has been found that nucleic acids react with ions of many metals, the result being a change in several properties of the acids. It is extremely probable that the reaction with metals is of great importance in the biological functions of nucleic acids but there have been very few investigations in this direction and there is still no direct proof that metals play an essential part in the biological functions of the nucleic acids.

The study of the reactions of complex formation between metals and nucleic acids is also of independent interest in connection with the search for so-called electronic stains for electron microscopy of nucleic acids (metal ions in compounds with the nucleic acids can act as electron dyestuffs) and for obtaining especially pure preparations of nucleic acids.

In order to understand the reactions which take place between metals ions and nucleic acids, we will briefly consider the structure and properties of the latter.

2. STRUCTURE AND PROPERTIES OF NUCLEIC ACIDS

The nucleic acids are linear polymers [1] the chains of which are composed of residues of phosphoric acid, pentoses [deoxyriboses in deoxyribonucleic acid (DNA) and riboses in ribonucleic acid (RNA)] and heterocyclic nitrogen bases (purines and pyrimidines).