IMIDAZOLE AND BENZIMIDAZOLE N-OXIDES (REVIEW)

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Information on the synthesis, properties, and chemical transformations of imidazole N-oxides that are aromatic in nature is correlated.

N-Oxides of five-membered aromatic nitrogen heterocycles — pyrazole, imidazole, 1,2,3- and 1,2,4-triazole, and tetrazole — have been investigated to a considerably lesser extent than N-oxides of azines. Furazan N-oxides (furoxans), exhaustive information regarding which has been presented in a two-volume monograph [1], constitute an exception. Individual problems in the chemistry of azole N-oxides have been dealt with in monographs by Ochiai [2] and Katritzky [3].

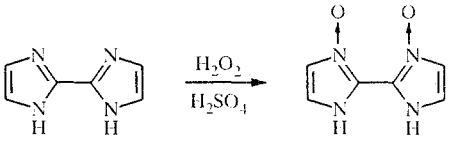
Reviews devoted to N-oxides of pyrazole [4] and 1,2,3-triazole [5] have been published only recently. A brief review on the chemistry of imidazole and benzimidazole N-oxides was published in 1970 [6], while a monograph by Volodarskii and coworkers, in which research on imidazoline N-oxides and imidazoline nitroxyl radicals was correlated, was published in 1988 [7]; problems in the chemistry of aromatic imidazole N-oxides are dealt with in passing.

In the present review we present information on the chemistry of imidazole and benzimidazole N-oxides that are aromatic in nature.

1. METHODS FOR OBTAINING IMIDAZOLE N-OXIDES

1.1. Oxidation of Imidazoles

In contrast to azine N-oxides, for which oxidation by peracids is the standard method of preparation [2, 3], the use of this method for azoles is very limited. The literature contains only individual examples of obtaining imidazole N-oxides (or the tautomeric N-hydroxyimidazoles) by oxidation. The preparation of 2,2′-diimidazolyl N,N′-dioxide (I) by oxidation of 2,2′-diimidazolyl with dilute hydrogen peroxide in an acidic medium was described in [8].



I

However, the compound obtained does not give the reactions that are characteristic for N-oxides, which makes one doubt the correctness of structure I. In a later report [9] it is pointed out that the method in [8] is not reproducible. A patent report regarding the production of 1-hydroxyimidazole (II) in 2.5% yield in the oxidation of imidazole with perphthalic acid was recently published [10].

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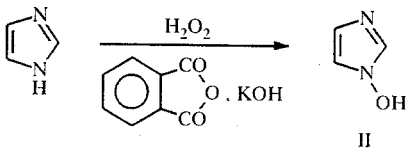
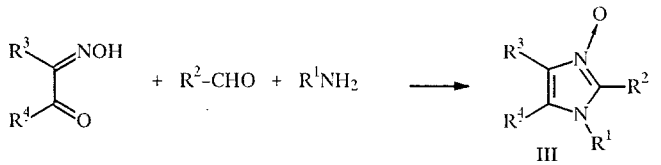


II

The available data on the production of imidazole N-oxides by direct oxidation are restricted to the indicated examples.

1.2. Cyclization of Derivatives of α-Dicarbonyl Compounds

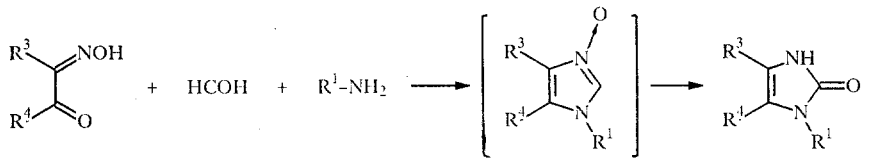
A general method for the synthesis of imidazoles III, which contain an N-oxide (N-hydroxy) group, is the cyclization of α-hydroxyimino ketones with aldehydes and amines [6, 11-22]:



III

R^1,R^2 = H, alkyl, aryl, α-furyl, functional alkyl;
R^3,R^4 = H, alkyl, aryl, acetyl, hydroximinomethyl, carbalkoxy
R^3R^4 = cycloalkyl, cycloalkenyl

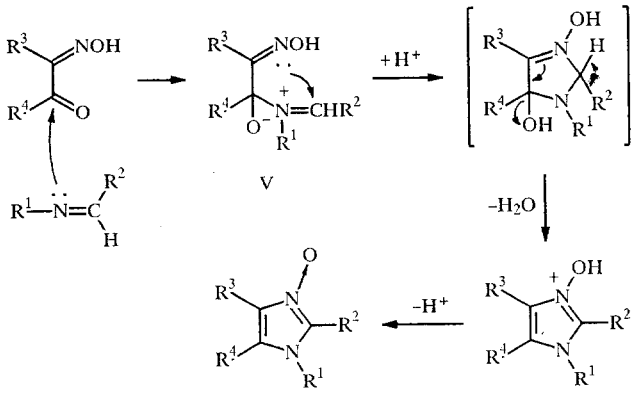
When formaldehyde is used as the aldehyde component, the resulting 2-unsubstituted imidazole N-oxides III (R^2 = H) are unstable and undergo rapid rearrangement to 2-imidazolones IV, frequently during the cyclization process [21]:



IV

This rearrangement can be avoided by subjecting previously prepared azomethine derivatives (or hexahydrotriazines) to the reaction with α-hydroxyimino ketones [18, 20]. A similar effect is achieved if a carboxy group is present in the alkyl(aryl)amino component [22].

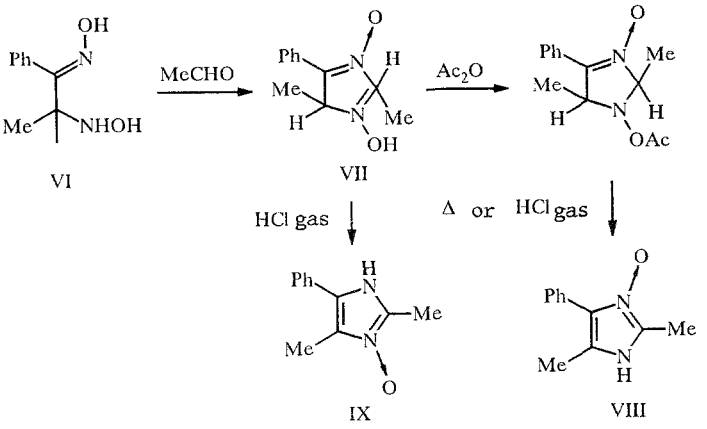
The mechanism of the cyclization has not been investigated in detail. It is assumed [6, 15, 17] that the determining step in the synthesis is the α-aminoalkylation of the hydroxyimino ketones with subsequent cyclization of C-(α-acylalkyl)-N-(α-aminoalkyl)nitrones V to imidazoline N-oxides and dehydration of the latter to give imidazole N-oxides:



V

1.3. Cyclization of α-Hydroxyamino Oximes and Their Derivatives

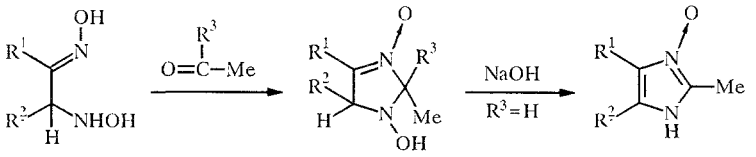
α-Hydroxyamino oximes VI in the anti configuration react with aldehydes to give 1-hydroxy-3-imidazoline 3-oxides VII, which are converted to imidazole N-oxides VIII by acylation and subsequent vacuum pyrolysis or the action of gaseous HCl [23, 24]:



VI VII IX VIII

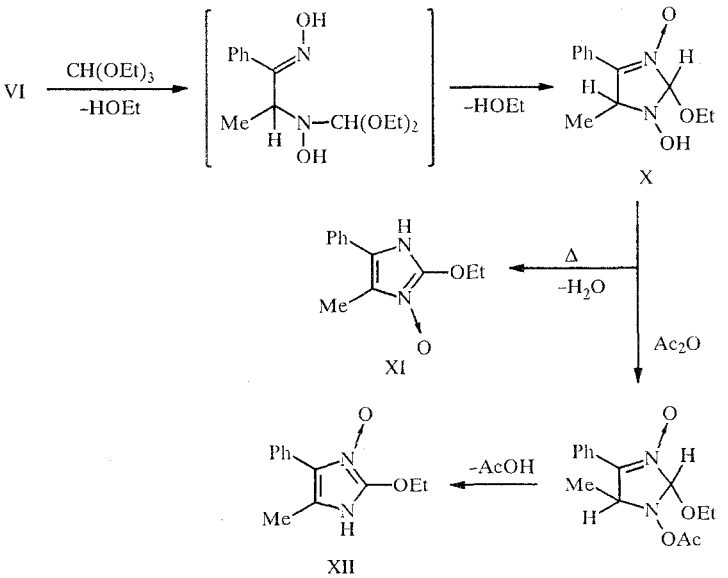
The isomeric (with respect to VIII) N-oxide IX is formed by the action of gaseous hydrogen chloride on imidazoline VII [23, 24].

The conversion of 1-hydroxyimidazoline 3-oxides to imidazole N-oxides is also possible by the action of an alkali [25]:



R^1,R^2 = Me; $R^1+R^2=(CH_2)_4$, $R^1+R^2=(CH_2)_5$

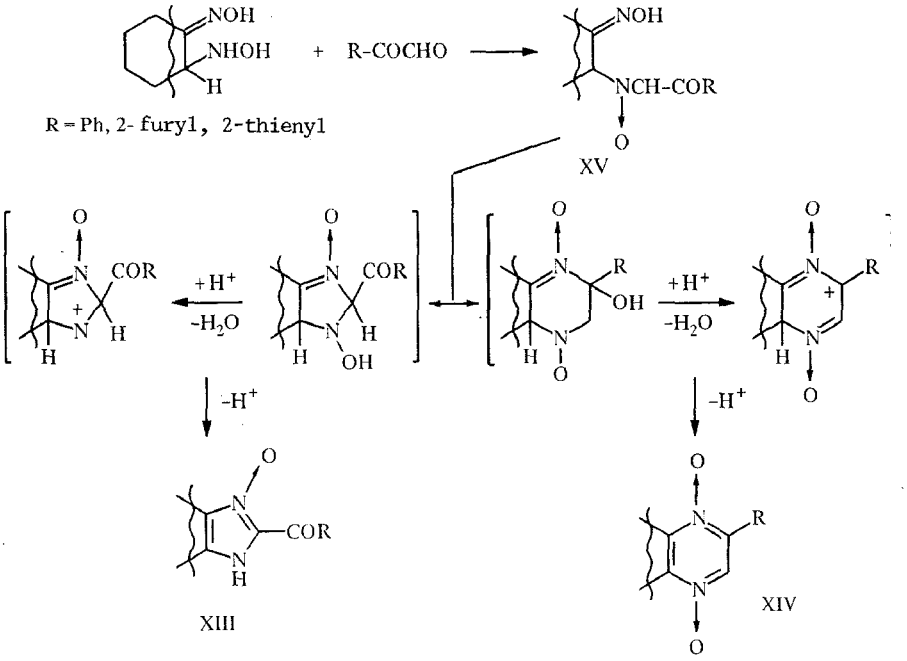
The reaction of α-hydroxyamino oximes VI with ethyl orthoformate leads to 1-hydroxy-3-imidazoline 3-oxides X, the heating of which leads to dehydration to give imidazole N-oxides XI, which contain an ethoxy group in the 2 position. The acylation of X with subsequent deacylation gives isomeric N-oxide XII [26]:



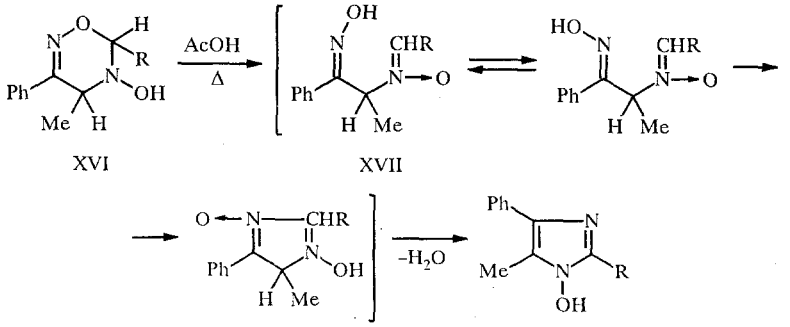
X XI XII

Aryl(hetaryl)carbonyl compounds react with α-hydroxyamino oximes via two pathways: to give imidazole N-oxides and pyrazine 1,4-dioxides [27].

Phenylglyoxal reacts with 2-hydroxyaminocyclohexanone oxime to give a mixture of 40% imidazole derivative XIII and 30% pyrazine XIV, while 2-furylglyoxal and 2-thienylglyoxal react to give primarily imidazole derivatives XIII. Grigor'eva and coworkers [27] assume that the intermediate nitrone XV can undergo cyclization via two pathways: at the carbon atom of the nitrone group to give imidazole ring XIII and at the carbon atom of the carbonyl group to give pyrazine ring XIV:

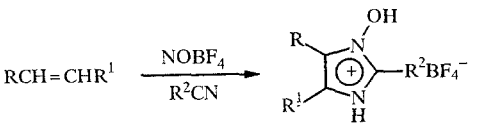


The 5-hydroxy-5,6-dihydro-4H-1,2,5-oxadiazines XVI that are formed in the reaction of syn-α-hydroxyamino oximes with aliphatic aldehydes are converted in acetic acid to imidazole N-oxides [28]. Ring contraction evidently occurs through the noncyclic tautomeric form of the oxadiazine — the corresponding nitrone XVII. Since the formation of an imidazole ring occurs in the cyclization of the anti isomers of hydroxyamino oximes and their derivatives [23-29], it may be assumed that conversion of the syn form of oxime XVII to the anti form should occur during the recyclization of oxadiazines XVI to imidazole N-oxides:



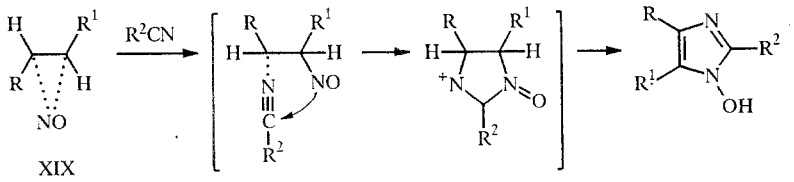
1.4. Formation of Imidazole N-Oxides in the Nitrosation of Olefins in Solutions of Nitriles

The nitrosation of olefins by nitrosonium salts in acetonitrile or benzonitrile leads to the corresponding imidazole N-oxide salts [30, 31]:



R = Me, Ph, RR^1 = $(CH_2)_4$; R^1 = H, Me; R^2 = Me, Ph

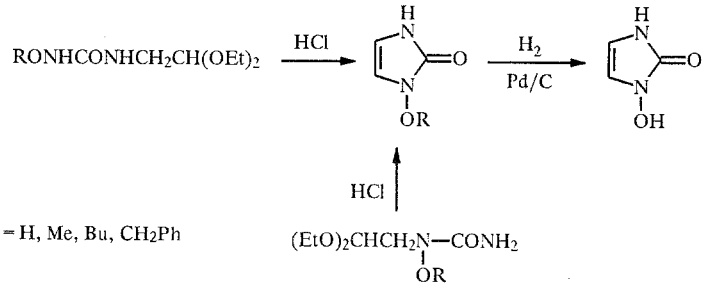
The hypothetical mechanism of this reaction consists in the reaction of the initially formed adduct XIX of the olefin with the nitrosonium cation with a molecule of the nitrile and subsequent cyclization:



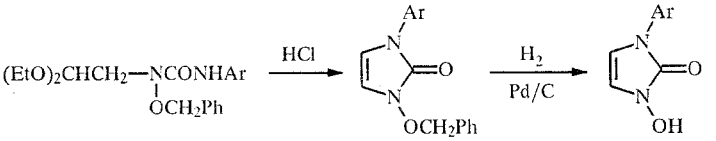
XIX

1.5. Cyclization of N-Alkoxyurea Derivatives

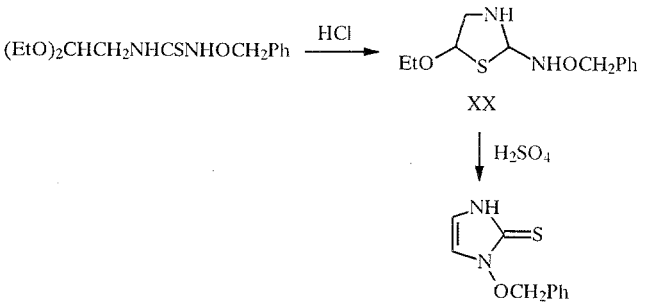
The action of hydrochloric acid on 1-alkoxy-3-(2,2-diethoxy)ethylureas and 1-alkoxy-1-(2,2-diethoxy)ethylureas gives N-alkoxy-2-imidazolones [32, 33]:



1-Arylalkoxy-1-(2,2-diethoxy)ethyl-3-arylureas give 1-benzyloxy-3-aryl-2-imidazolones under similar conditions [32]:

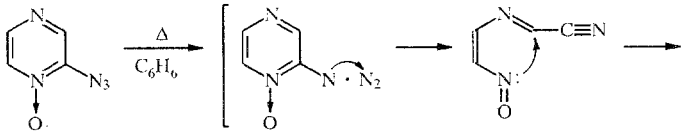


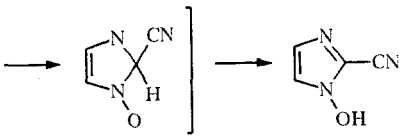
In the cyclization of the corresponding thiourea derivative the initial product is thiazolidine XX, which undergoes recyclization to 1-benzyloxyimidazole-2-thione under the influence of sulfuric acid [33]:



1.6. Recyclization of 2-Azidopyrazine 1-Oxide

2-Azidopyrazine 1-oxide undergoes rearrangement to 2-cyanoimidazole N-oxide when it is refluxed in benzene [34]. It is assumed that the reaction proceeds through synchronous (with opening of the six-membered ring) splitting out of a molecule of nitrogen from the azido group with the subsequent formation of a five-membered ring:

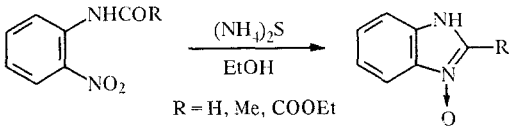




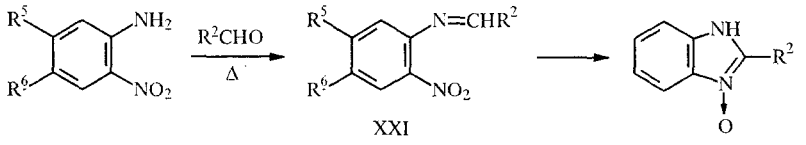
2. METHODS FOR OBTAINING BENZIMIDAZOLE N-OXIDES

2.1. Cyclization of o-Nitroaniline Derivatives

The most general method for obtaining benzimidazole N-oxides is the cyclization of N-substituted o-nitroanilines. This synthesis was carried out for the first time in 1910; 2-substituted benzimidazole N-oxides were obtained in the reaction of o-nitroacylanilines with ammonium sulfide [35]:*



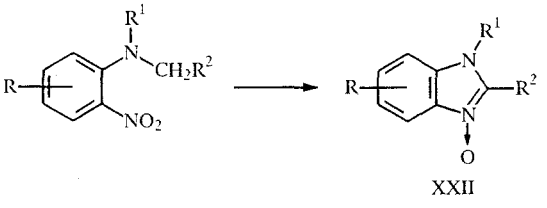
2-Substituted benzimidazole N-oxides are formed by prolonged heating of o-nitroanilines with aldehydes [36, 37]:



R^2 = Ph, 4-thiazoly; R^5,R^6 = H,F

The reaction evidently proceeds through benzylidene derivatives XXI.

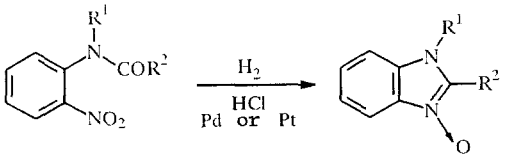
The production of various 2-substituted benzimidazole N-oxides XXII is also possible in the alkaline [38-46], acidic [45, 47], reductive [38, 45, 48-51], or photochemical [52, 53] cyclization of the corresponding o-nitroaniline derivatives:



R^2= H_2C–C6H4–F [45]

R = H [37, 38, 41, 44, 48—50]; 4-AcNH, 5AcNH, 6AcNH [42]; 5-F [37]; 6-NO_2 [46, 52, 53]; R^1= = H [36, 39, 42—44, 48, 50, 52, 53]; Ph [49]; Me [51]; R^2 = H [47]; CH_2COOEt [42]; CN [43], $CH{=}CH_2$ [44]; 4-thiazolyl [37, 39]; $CH_2C_6H_4F$-r [45]

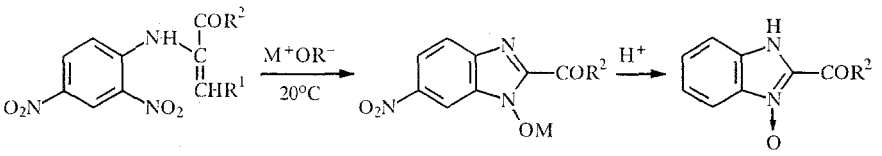
o-Nitroacylanilines undergo cyclization to 2-substituted benzimidazole N-oxides by the action of reducing agents in an acidic medium [45, 49-51]:



R^1 = H, Me, Ph; R^2 = H,Me,Ph, $CH_2C_6H_4F$-*p*

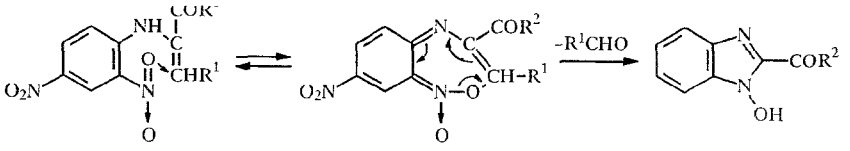
*In [35] an annelated oxaziridine structure was assigned to the compounds obtained.

Benzimidazole N-oxides are formed readily by the action of alkali metal alkoxides on derivatives of α-(2,4-dinitrophenylamino)-α,β-unsaturated acids [46]:



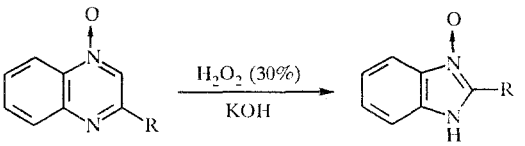
R^1 = H, Me, Ph; R^2 = OMe, NHPr

The hypothetical mechanism consists in intramolecular oxidation of the multiple bond by the oxygen atom of the nitro group with splitting out of the terminal carbon atom in the form of an aldehyde and subsequent ring formation:



2.2. Recyclization of Quinoxaline N-Oxides to Benzimidazole N-Oxides

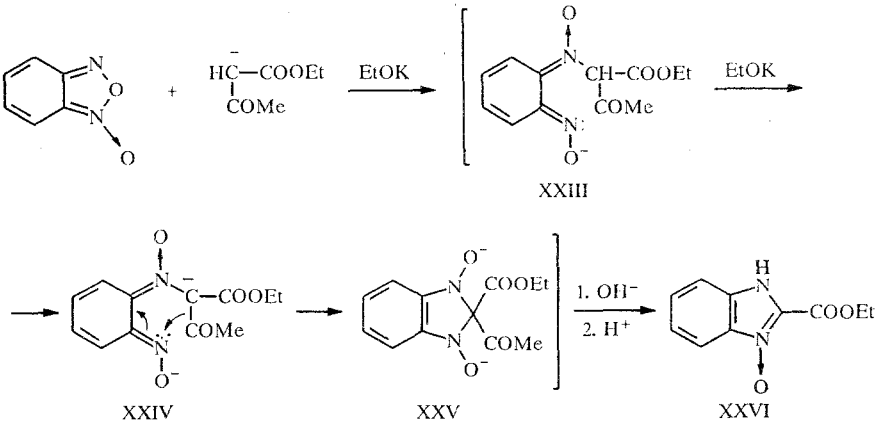
The action of hydrogen peroxide in an alkaline medium on 2-substituted quinoxaline 4-oxides gives 2-substituted benzimidazole N-oxides [54, 55]:



R = Me, Et, *i*-Pr, MeOH, *t*-Bu, Ph, OMe, OEt

2.3. Recyclization of Benzofuroxans to Benzimidazole N-Oxides

The reaction of benzofuroxans with nucleophilic reagents, which leads to transformation of the furoxan ring (the Beirut reaction), may proceed to favor the formation of benzimidazole N-oxides under certain conditions. The reaction takes place by the action of enolate anions on benzofuroxan in the presence of strong bases or via heating [56, 57]:



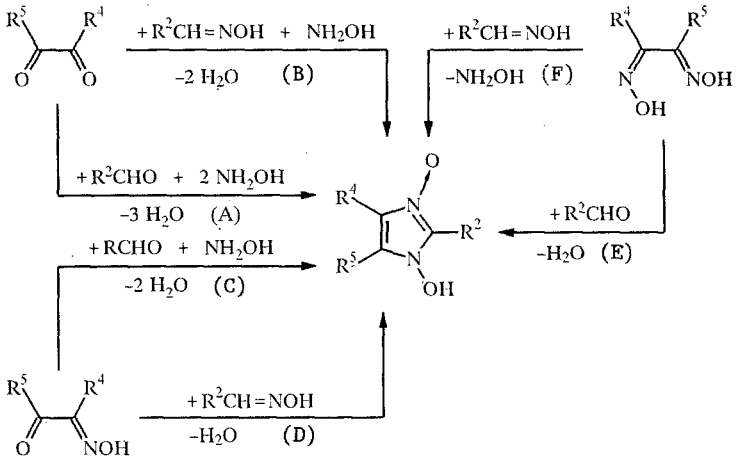
XXIII XXIV XXV XXVI

The conditions for the formation of a benzimidazole N-oxide ring via this reaction are as follows: 1) the possibility of splitting out of a proton from the nucleophilic center in intermediate XXIII; 2) the possibility of subsequent attack by the newly formed nucleophilic center at the second nitrogen atom of the furoxan ring (intermediate XXIV) with the subsequent splitting out of an acyl group from intermediate XXV and the formation of final compound XXVI.

3. METHODS FOR OBTAINING 1-HYDROXYIMIDAZOLE 3-OXIDES AND 1-HYDROXYBENZIMIDAZOLE 3-OXIDES

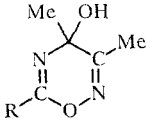
3.1. Synthesis of 1-Hydroxyimidazole 3-Oxides from α-Dicarbonyl Compounds, Hydroxylamine, and Aldehydes

The reaction of α-dicarbonyl compounds with hydroxylamine and aldehydes is the most general method for obtaining 1-hydroxyimidazole 3-oxides. The reaction can be carried out via several variations (A-F): by simultaneous mixing of the reagents, by reaction of glyoximes with aldehydes or their oximes, and by reaction of monoximes of α-dicarbonyl compounds with aldoximes [12, 15, 26, 31, 56-70]:

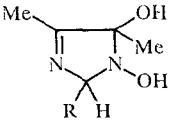


R^2 = H [31, 65, 66]; Me [31, 61, 64]; Et [31, 61]; Pr, Bu [68], Ar [15, 31, 60, 62, 63, 68]; CH=NOH [64—66]; COMe, COPh [66]; R^4, R^5 = H [31, 63, 65, 69]; Me [31, 61, 64, 66]; Ar [15, 31, 62, 64]; CONHAr, CONHAlk, COOEt [15]

Diels, who was the first to obtain products of the reaction of diacetyl monoxime with aldoximes [58, 59], assigned oxadiazine structure XXVII or 1,5-dihydroxyimidazoline structure XXVIII to them:



XXVII

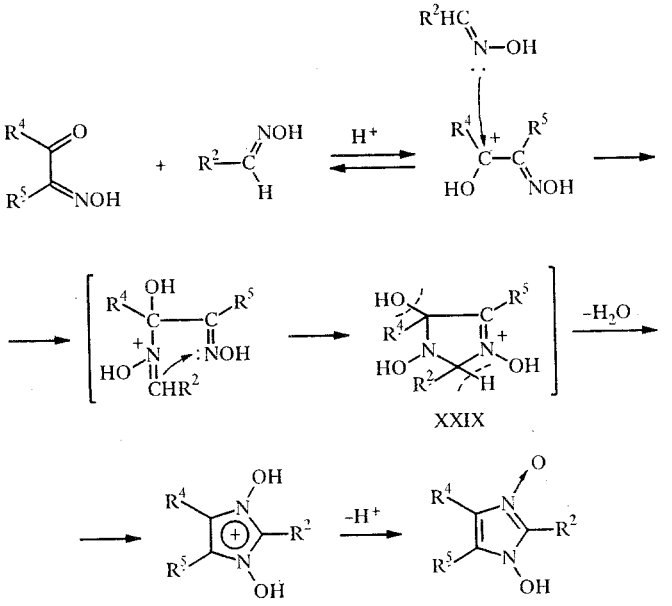


XXVIII

The structures of these compounds as 1-hydroxyimidazole 3-oxide derivatives was later established [61].

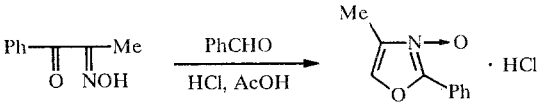
The reaction of glyoximes with aldehydes can be carried out by fusion of the components [61] or in alcohol solutions in the presence of acidic catalysts (most often hydrochloric acid or gaseous hydrogen chloride) with subsequent isolation of the desired compounds by neutralization of the reaction mixtures [60, 62-69].

The mechanism of the cyclization has not been investigated. The determining step of the reaction is evidently nucleophilic addition of the nitrogen atom of the aldoxime group to the carbon atom of the carbonyl group of the α-ketoxime with subsequent cyclization and dehydration of the resulting intermediate XXIX [61, 62, 66]:



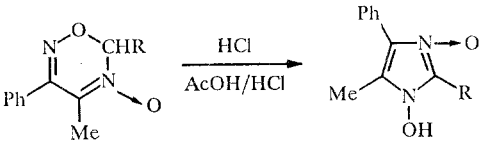
XXIX

As side products of the reaction one sometimes observes isoxazole N-oxide derivatives XXX, which may be obtained by the reaction of the α-hydroxyimino ketones with the aldehyde formed by saponification of the aldoxime [62]:



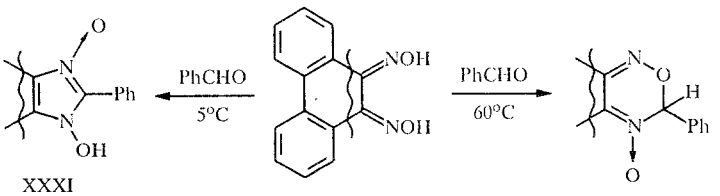
XXX

The formation of 1-hydroxyimidazole 3-oxide occurs in the recyclization of 6H-1,2,5-oxadiazine 5-oxide in acetic acid in the presence of HCl or in hydrochloric acid [28]:



R = H, Me

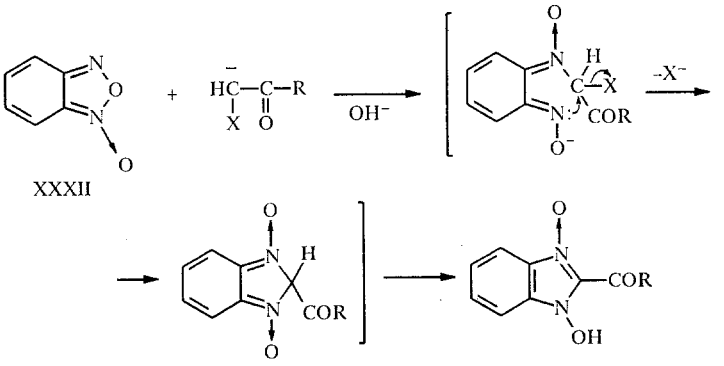
The possibility of the formation of dihydro-1,2,5-oxadiazine N-oxide XXXI in the reaction of benzaldehyde with phenanthrene-o-quinone dioxime at elevated temperatures was also noted in [12]:



XXXI

3.2. Formation of 1-Hydroxybenzimidazole 3-Oxides in the Recyclization of Benzofuroxans

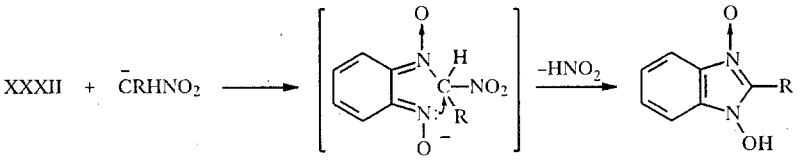
The conversion of the benzofuroxan ring to a benzimidazole ring with two N-oxide groups can be accomplished via the Beirut reaction by the reaction of benzofuroxans with α-cyano, α-sulfonyl, and α-nitro ketones, diphenyldiazomethane, β-dicarbonyl compounds, and aliphatic nitro compounds. The reaction proceeds in an alkaline medium through the addition of a carbanion that contains a good leaving group X (CN, SO_2Ph, NO_2) attached to the nucleophilic center to a nitrogen atom of the furoxan ring with subsequent intramolecular nucleophilic substitution at this center by the second nitrogen atom of the furoxan fragment, splitting out of X^- anions, and ring formation [71-74]:



XXXII

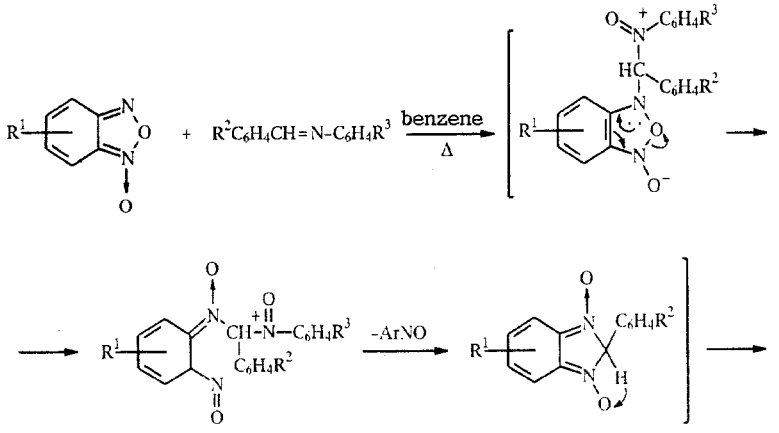
R = NHR^1, NH_2, NR^1_2, OEt, Ar, Alk; X = CN, SO_2Ph, NO_2

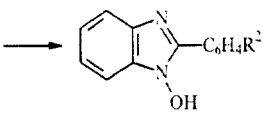
The anions of primary and secondary aliphatic nitro compounds react similarly with benzofuroxan [75-79]:



R = H, Me, Et, Pr, Ph, $CH_2CH_2CONH_2$, CH_2CH_2COOH, COOEt

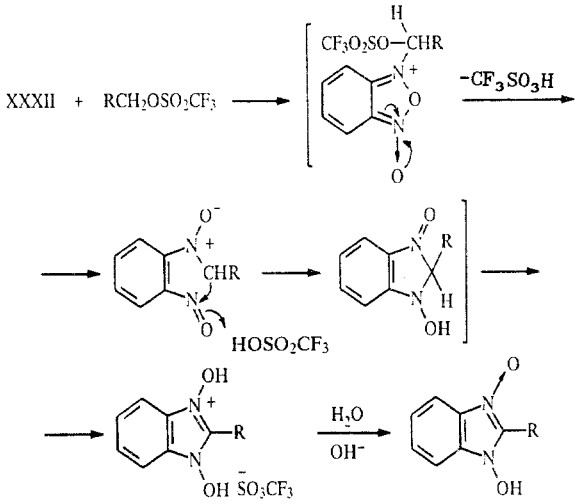
An original transformation of benzofuroxans to 1-hydroxybenzimidazole 3-oxides occurs in their reaction with nitrones [80]. The reaction proceeds through the addition of the carbon atom of the nitrone group to a nitrogen atom of the furoxan ring with its subsequent opening, ejection of a molecule of nitrosobenzene, and the formation of an imidazole ring:





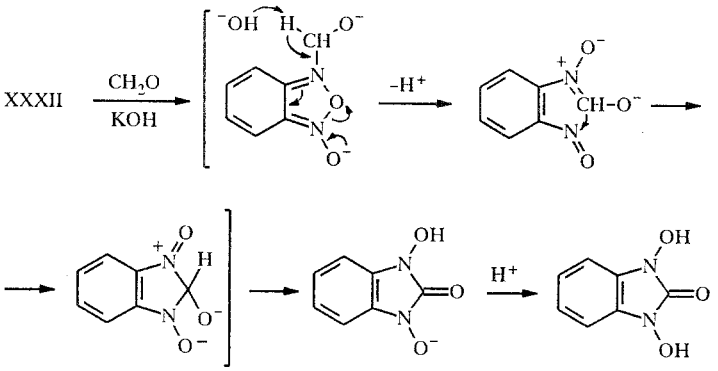
R^1 = H, 4(5)-Me, 4(5)-Cl; R^2 = H, 4-OMe; R^3 = H, 4-Me

Opening of the furoxan ring in benzofuroxans with recyclization to a hydroxyimidazole N-oxide is also possible in the action of very strong alkylating agents (alkyl trifluoromethanesulfonates) on benzofuroxan [81, 82]:

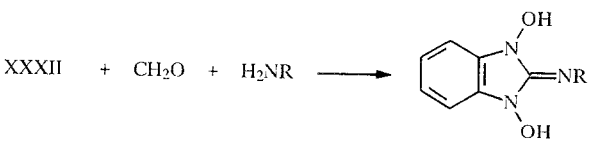


R = H, Ph

The reaction of benzofuroxans with formaldehyde in an alkaline medium leads to 1,3-dihydroxybenzimidazolone, evidently via a similar mechanism [83, 84]:



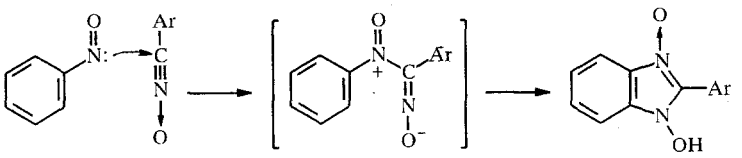
The corresponding 2-alkylimino derivatives of 1,3-dihydroxybenzimidazolone are formed in the reaction of benzofuroxan in aqueous methanol with a mixture of formaldehyde and a primary amine (or hexahydrotriazine) [85]:



R = Alk, $CH_2CH{=}CH_2$, CH_2CH_2OH, CMe_2CH_2OH, $(CH_2)_3NMe_2$, CH_2Ph

3.3. Production of 1-Hydroxybenzimidazole 3-Oxides from Benzonitrile Oxides

The reaction of benzonitrile oxide with aromatic nitroso compounds leads to 1-hydroxybenzimidazole 3-oxides [86]. Their formation occurs through intermediate XXXIII, which is obtained in the addition of the nitrile oxide to the nitrogen atom of the nitroso group with subsequent ring formation:

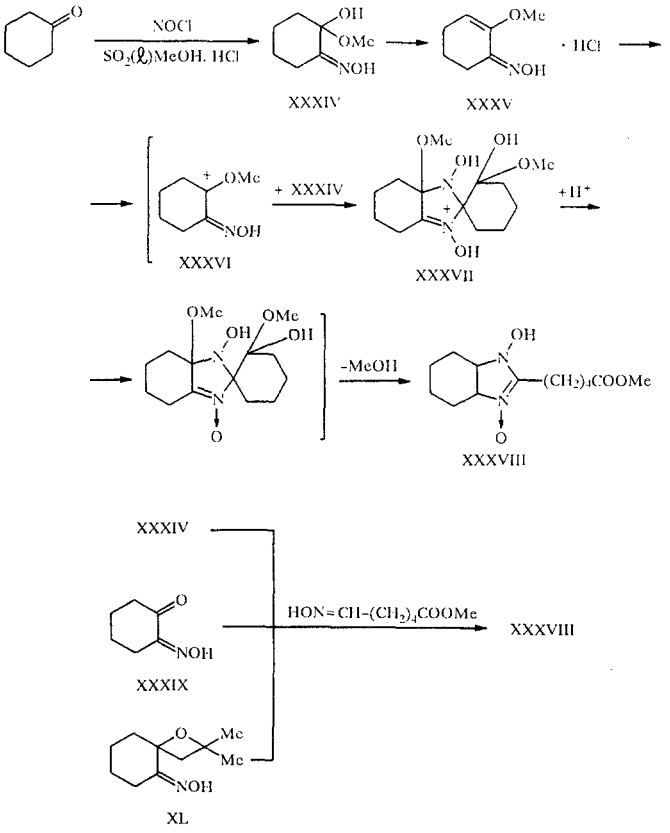


XXXIII

Intermediate XXXIII can be detected in the reaction mixture at low temperatures.

3.4. Formation of a 1-Hydroxyimidazole 3-Oxide Ring in the Nitrosation of Cyclohexane and Its Derivatives

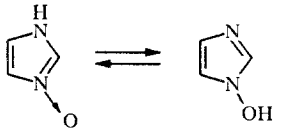
An unusual transformation of cyclohexanone and some of its derivatives to a 1-hydroxy-2-substituted tetrahydrobenzimidazole 3-oxide was described in [87]. The action on cyclohexanone of nitrosyl chloride in liquid sulfur dioxide in the presence of methanol and hydrogen chloride gives 1-hydroxy-1-methoxy-2-hydroxyiminocyclohexane (XXXIV), which could be isolated at −70°C. With a rise in the temperature XXXIV undergoes dehydration to cyclohexene XXXV, from which carbonium ion XXXVI is generated. The latter reacts with XXXIV to give intermediate spiro compound XXXVII, which in subsequent transformations gives 1-hydroxy-2-(methoxycarbonylbutyl)-4,5,6,7-tetrahydrobenzimidazole 3-oxide (XXXVIII). The same XXXVIII is also obtained in the reaction of XXXIV and 2-hydroxyiminocyclohexanone (XXXIX) or 2-hydroxyiminocyclohexanone dimethylketal (XL) with methyl ω-hydroxyiminocaproate [87]:



4. PHYSICOCHEMICAL PROPERTIES OF IMIDAZOLE N-OXIDES

Aromatic imidazole N-oxides are, as a rule, high-melting solid substances that are only slightly soluble in nonpolar solvents and somewhat more soluble in polar solvents.

N-Unsubstituted imidazole and benzimidazole N-oxides can exist in the N—H or O—H tautomeric form:

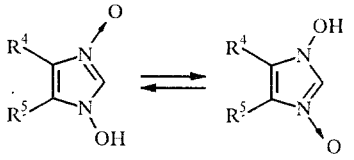


It is evident that the predominance of one or the other tautomer is associated with the nature of the substituents in the ring and the character of the solvent, and the problem of the structures of compounds should be solved for each specific case.

According to the data in [40, 48, 53, 88], benzimidazole N-oxide exists in an aqueous medium primarily in the N-oxide form (with tautomeric-equilibrium constant K_T = 12) [88]; in organic solvents (ethanol, chloroform, acetonitrile, cyclohexane) the equilibrium is shifted to favor the N-hydroxy tautomer. In both water and organic solvents 2,4,5-triphenylimidazole N-oxide exists in the form of a mixture of tautomers [88].

Volkamer and Zimmermann [12] asserted that they were able to separate these tautomers; however, later an investigation of the mass spectra of the hypothetical tautomers made it possible to interpret the differences in their properties as not being a consequence of tautomerism but rather as being a result of polymorphism [89].

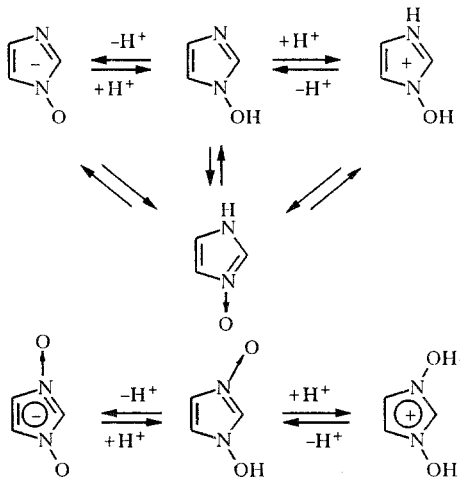
In principle, tautomeric forms are possible for 1-hydroxyimidazole 3-oxides if unlike substituents are present in the 4 and 5 positions:



However, they cannot be detected.

A characteristic feature of imidazole N-oxides is their association in solutions as a consequence of the formation of strong hydrogen bonds [17, 24]. This is manifested particularly markedly for 1-hydroxyimidazole 3-oxides. A study of solutions of 1-hydroxy-2,4,5-trimethylimidazole 3-oxide in chloroform shows that at low concentrations the compound is associated to form a cyclic trimer, while at higher concentrations it is associated to form an open-chain polymer [90, 91]. This gives rise to a strong shift of the absorption bands of the stretching vibrations of the O—H group (to 1400-1500 cm^{-1}), which hinders the use of IR spectra in the study of the compounds. In the PMR spectra the signal of the protons of the hydroxy group is shifted to weak field to 17 ppm [90]. A shift of the signal of the protons of the methyl group in the 2 position as a function of the concentration of the substance in solution is also noted (from 1.97 ppm to 2.3 ppm as the concentration changes from 10^{-2} to 1 mole/liter) [90]. Proton transfer between the polymeric chains and the formation of polymeric cations and anions are responsible for the electrical conductivity of solutions of 1-hydroxy-2,4,5-trimethylimidazole 3-oxide in chloroform [90].

O- and N-Unsubstituted imidazole N-oxides and 1-hydroxyimidazole 3-oxides are amphoteric and can form both cations and anions:



N(O)-Substituted compounds have only basic properties. The available data on the acid-base properties of imidazole N-oxides are meager (Table 1). 1-Hydroxyimidazole 3-oxides are stronger acids and weaker bases as compared with compounds with one N-oxide (hydroxy) group.

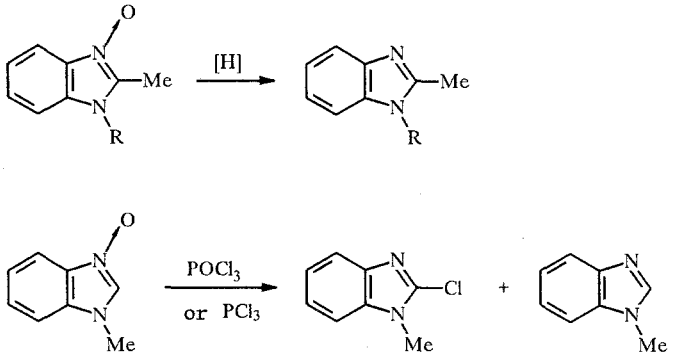
Some of the values presented in the literature are doubtful [61] and require additional verification.

5. REACTIONS OF IMIDAZOLE AND BENZIMIDAZOLE N-OXIDES

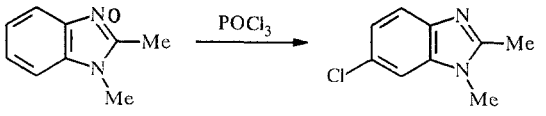
A large part of the research on the chemical transformations of imidazole N-oxides pertains to benzimidazole N-oxide and its derivatives. The reactions of noncondensed imidazole N-oxides have been studied to a lesser extent.

5.1. Deoxygenation

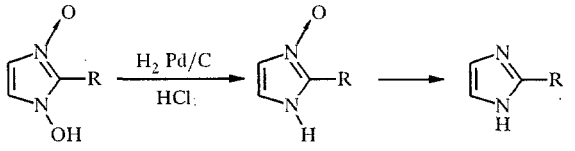
Imidazole and benzimidazole N-oxides, like other aromatic N-oxides, are deoxygenated by the action of reducing agents [23, 61, 93, 94], phosphorus trichloride or pentachloride [18, 51, 95, 96], or phosphorus oxychloride [51, 95]. In the latter cases if the 2 position in the imidazole ring is not substituted, deoxygenation may be accompanied by simultaneous chlorination in this position [18, 94]:



Under the influence of phosphorus oxychloride 1,2-dimethylbenzimidazole 3-oxide is simultaneously chlorinated in the 6 position and deoxygenated [51]:



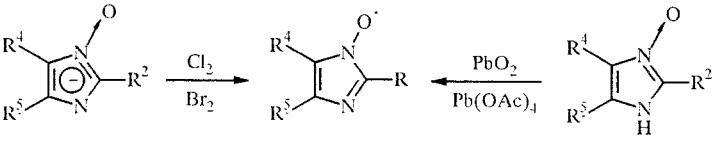
1-Hydroxyimidazole 3-oxides can be reduced stepwise with the removal of only one or both oxygen atoms [64-66, 69]:

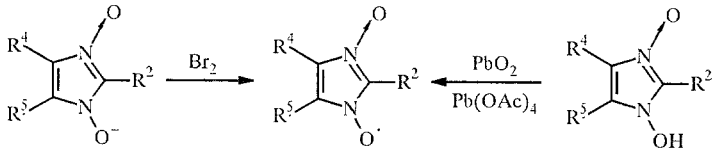


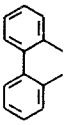
The deoxygenation of imidazole N-oxides in a number of cases may serve as a convenient method for the synthesis of imidazoles that are inaccessible when other methods are used.

5.2. Oxidation

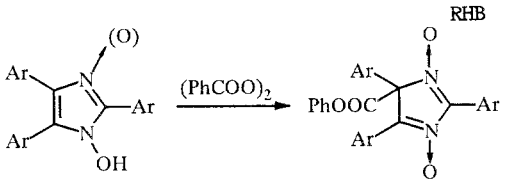
When alkali salts of 1-unsubstituted imidazole N-oxides and 1-hydroxyimidazole 3-oxides are oxidized by halogens or lead tetraacetate or lead dioxide, they give quite stable free radicals, which are detected by means of EPR spectra [97-99]:





R^2=Ph, R^2=Me; R^4=R^5=Ph; R^4=R^5=  , R^4=R^5= 

The reaction of 1-hydroxy-2,4,5-triarylimidazoles and 1-hydroxy-2,4,5-triphenylimidazole 3-oxide with benzoyl peroxide proceeds peculiarly. Products of addition (XLI) of the benzoyl radical to the $C_{(4)}$—$C_{(5)}$ multiple bond of the imidazole ring are formed during the reaction [100]:

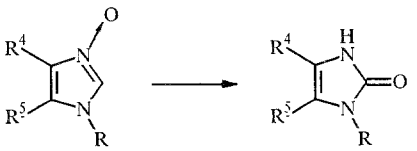


XLI

Ar = Ph, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$

5.3. Rearrangement to Imidazolones

Imidazole and benzimidazole N-oxides that do not have a substituent in the 2 position readily undergo rearrangement to the corresponding 2-imidazolones and 2-benzimidazolones [21, 48]:



R = H, Alk, Ar [21]; R^4 = Ar, Me; R^5 = Me, Et, COMe, COOEt [21]; R^4 + R^5= benzene ring [48]

This rearrangement proceeds especially readily for 1-alkyl(aryl) derivatives, and this causes difficulties in the synthesis of 1-substituted imidazole 3-oxides.

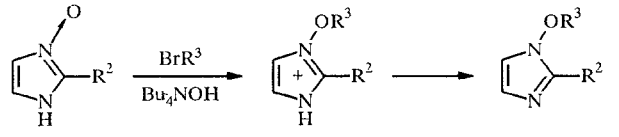
In contrast to imidazole N-monoxides, 1-hydroxyimidazole 3-oxides do not undergo this sort of rearrangement.

5.4. Reaction with Electrophilic Reagents

Rather little study has been devoted to the reactions of imidazole N-oxides with electrophilic reagents. The available literature data pertain primarily to alkylation. There are only individual reports of other electrophilic substitution reactions.

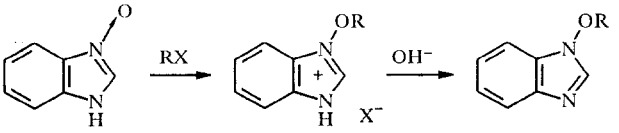
5.4.1. Alkylation. The alkylation of imidazole N-oxides is possible at both the N-oxide (hydroxy) oxygen atom and at the heteroring nitrogen atom. As a rule, only alkylation at the oxygen atom is realized.

The formation of N-alkoxyimidazolium and N-alkoxybenzimidazolium salts occurs in the action of alkylating agents (dimethyl sulfate, alkyl halides) on alkali salts of imidazole N-oxides [44, 48, 69, 93, 101]:



XLIII

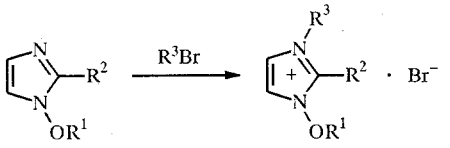
R^2 = H, Me, Et; R_3 = Me, Et, *i*-Pr, Ph_3C [101]



XLII

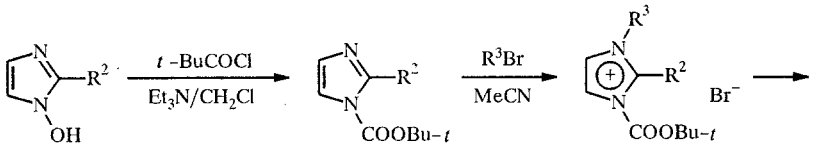
R = Me, Et, CH_2=CH-CH_2 [44, 48, 93]; X = I, Br

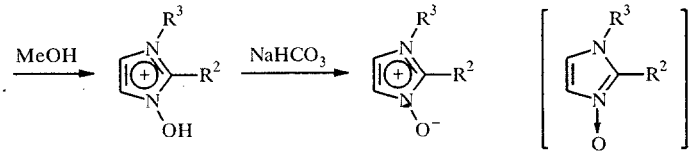
The further alkylation of N-alkoxy derivatives XLII and XLIII leads to N-alkoxy-N′-alkylimidazolium and N-alkoxy-N′-alkylbenzimidazolium salts [101, 102]:



R^1 = Me, Et, CH_2=CH-CH_2, $PhCH_2CH_2$-, Ph, $PhCH_2$, 2,4-$Cl_2C_6H_4CH_2$ [101]; R^2 = H, Me, Et [101]; R^3 = Me, CH_2COAr [101].

Prior acyl protection of the hydroxy group with subsequent removal of the protective group by methanolysis is used to obtain 3-substituted imidazole 1-oxides in the alkylation of imidazole N-oxides [101]:



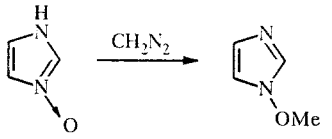


XLIV

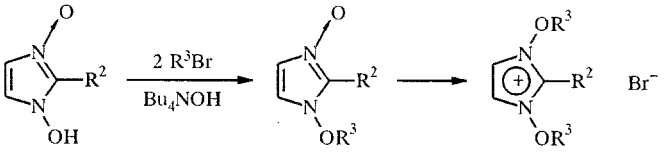
R^2 = H, Me, Et; R^3 = CH_2COAr [101]

It has been noted [101] that 2-unsubstituted XLIV (R^2 = H) are considerably less stable.

The alkylation of imidazole N-oxides can also be accomplished by means of diazomethane; O-methyl derivatives were isolated from the reaction products:



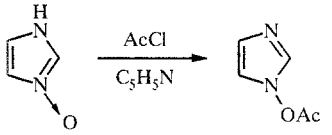
The alkylation of 1-hydroxyimidazole 3-oxides proceeds in two steps to give mono- and dihydroxyalkyl derivatives XLV and XLVI; in the case of 2-unsubstituted compounds a monoalkyl derivative cannot be isolated [101]. Interphase catalysis by tetrabutylammonium hydroxide was used in the alkylation of 1-hydroxyimidazole 3-oxides [101]:



XLV XLVI

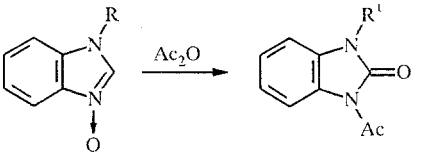
R^2 = H, Me, Et; R^3 = CH_2Ar

5.4.2. Acylation. N-Unsubstituted imidazole N-oxides are acylated by acid chlorides in the presence of pyridine to give N-acyloxyimidazoles [101]:



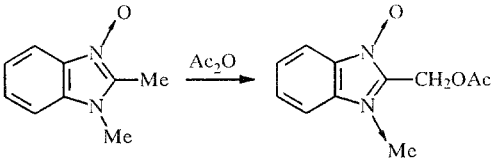
The acetyl and benzoyl derivatives are unstable; tert-butylacyloxyimidazoles are more stable [101].

Under the influence of acetic anhydride benzimidazole N-oxides form 1,3-diacetylbenzimidazolones [96, 103] or 1-acyl-3-methylbenzimidazolone [95]:



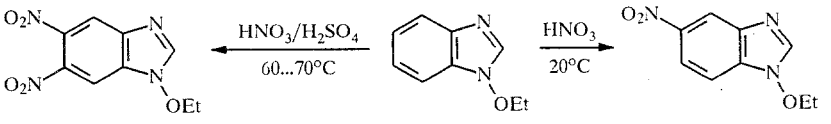
R = H, R^1 = Ac [96, 103]; R = R^1 = Me [95]

Under similar conditions, 1,2-dimethylbenzimidazolone 3-oxide reacts with acetic anhydride at the 2-methyl group with retention of the N-oxide oxygen atom [51]:



5.4.3. Nitration. The information on the nitration of imidazole and benzimidazole N-oxides is quite meager.

A 5-nitro derivative is formed in the nitration of N-ethoxybenzimidazole with nitric acid at 20°C, while the action of a sulfuric acid—nitric acid mixture with heating leads to 1-ethoxy-5,6-dinitrobenzimidazole [93]:



The kinetics of the nitration of 1,4,5-trimethylimidazole 3-oxide with sulfuric acid—nitric acid mixtures were investigated in [104]. A nitro group enters the 2 position of the ring. In contrast to imidazole, which is nitrated in the protonated

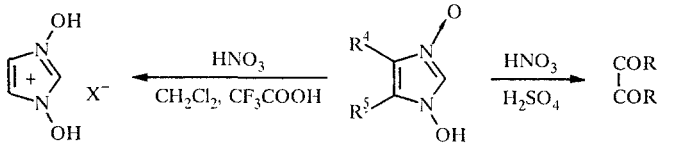
TABLE 1. Acid–Base Properties of Imidazole N-Oxides

Compound	pK_{BH^+}	pK_A	Lit. data
Benzimidazole-3-oxide	2,90	7,86	[88]
1-Methylbenzimidazole-3-oxide	2,89	—	[88]
1-Methoxybenzimidazole	3,95	—	[88]
2,4,5-Triphenylimidazole-3-oxide	3,28	8,39	[88]
1-Methyl-2,4,5-triphenylimidazole-3-oxide	3,32	—	[88]
1-Methoxy-2,4,5-triphenylimidazole	3,78	—	[88]
2-Phenyl-4,5-dimethylimidazole-3-oxide	4,14	9,41	[11]
1-Hydroxy-2,4,5-dimethylimidazole-3-oxide	4,05	6,30	[61]
1-Hydroxyimidazole-3-oxide	—	4,01	[92]
1-Hydroxy-4-methylimidazole-3-oxide	—	4,34	[92]
1-Hydroxy-4,5-dimethylimidazole-3-oxide	-0,40	4,38	[92]
1-Hydroxy-2-acetyl-4-methylimidazole-3-oxide	—	6,22	[66]
1-Hydroxy-4-phenylimidazole-3-oxide	—	6,68	[66]

form under these conditions, the N-oxide enters into the nitration reaction as a neutral molecule at a rate that exceeds the rate of nitration of imidazole.

A study of the nitration of 1-hydroxyimidazole 3-oxides showed that the presence of a substituent in the 2 position of the imidazole ring and its nature, as well as the nitration conditions, have the greatest effect on the progress of the reaction and the character of the products formed [105].

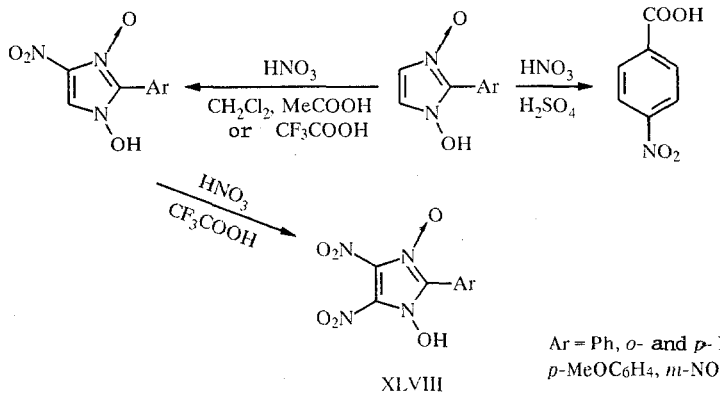
Ring destruction occurs in the nitration of 2-unsubstituted hydroxyimidazole oxides with sulfuric acid—nitric acid mixtures, nitric acid, or nitrogen pentoxide. Salts XLVII (nitrates, trifluoroacetates) of the starting compounds are formed by the action of nitric acid in organic solvents (methylene chloride, dichloroethane) or trifluoroacetic acid:



XLVII

R = OH for $R^4 = R^5 = H$; R = Me for $R^4 = R^5 = Me$;
X = NO_3, CF_3COO

The nitration of 1-hydroxy-2-arylimidazole 3-oxides in sulfuric acid—nitric acid mixtures takes place in the benzene ring with subsequent rapid decomposition of the imidazole ring. In methylene chloride and acetic or trifluoroacetic acid nitration with nitric acid takes place in the 4(5) position of the imidazole ring [105]:



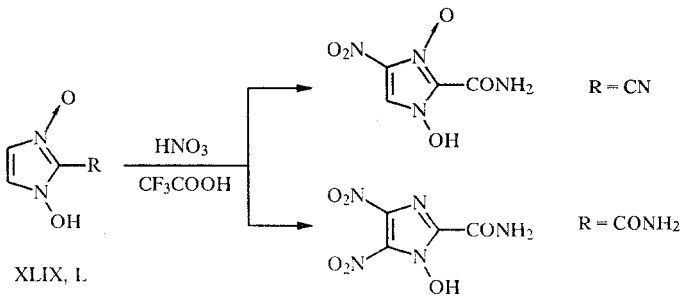
XLVIII

Ar = Ph, *o*- and *p*- FC_6H_4, *p*-$MeOC_6H_4$, *m*-$NO_2C_6H_4$

When the reaction is carried out for a longer time, nitration in trifluoroacetic acid gives 4,5-dinitro derivative XLVIII (Ar = Ph).

1-Hydroxy-2-cyano- and 1-hydroxy-2-carboxamidoimidazole 3-oxides XLIX and L are also nitrated in nitric acid—trifluoroacetic acid with retention of the ring; the cyano group in XLIX is saponified to an amido group, while in carbox-

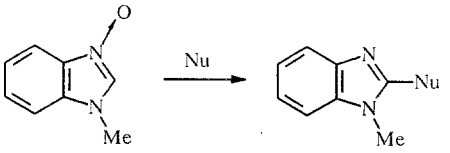
amido derivative L two nitro groups are introduced into the ring with simultaneous deoxygenation to give 1-hydroxy-2-carboxamido-4,5-dinitroimidazole [105]:



5.5. Nucleophilic Substitution Reactions with Simultaneous Deoxygenation

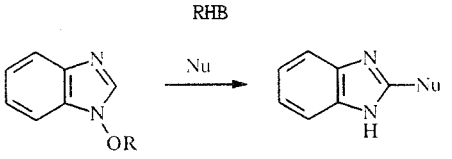
Reactions with nucleophilic reagents with simultaneous deoxygenation have been studied chiefly for benzimidazole N-oxides and their derivatives.

Thus nucleophilic substitution in the 2 position with simultaneous deoxygenation takes place in the reaction of 1-methylbenzimidazole 3-oxide with nucleophilic reagents (the bisulfite anion, hydrazine hydrate, and the cyanide anion) [95]:



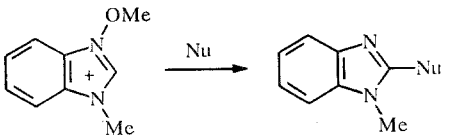
Nu = SO_3H^-, N_2H_4, CN^-

The reactions of 1-alkoxybenzimidazoles with nucleophilic reagents proceed similarly with splitting out of the OR group [93]:

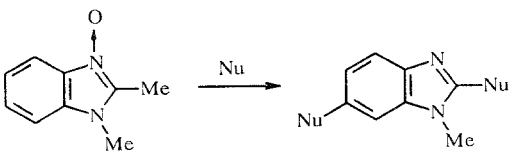


R = Me, Et; Nu = OR^-, N_2H_4, CN^-, HSO_3^-

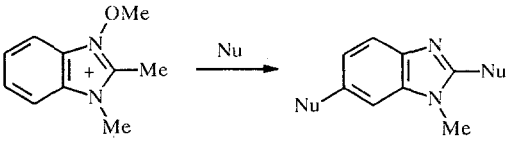
1-Methyl-3-methoxybenzimidazolium iodide also reacts with nucleophilic reagents in the 2 position [102]. When there is a substituent in the 2 position, attack by the nucleophilic reagent is directed to the 6 position of the benzene ring [51, 102, 106]:



Nu = CN^-, OH^-, HSO_3^-, MeO^-, $i\text{-}PrO^-$, N_2H_4, $MeNH_2$, Me_2NH, $PhNH_2$, $MeOOC(CN)CH^-$, $(CN)_2CH^-$ [102, 106]

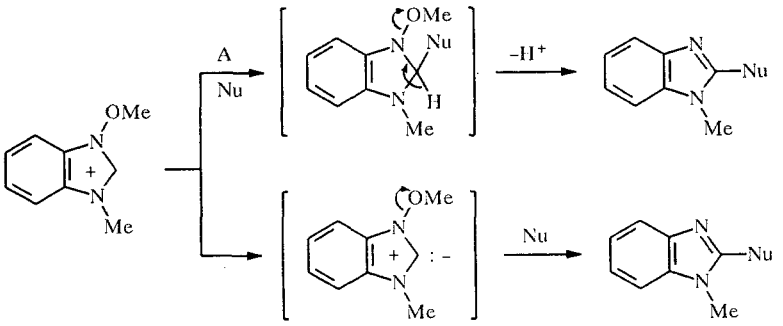


Nu = CN^-, $MeOOC(CN)CH^-$ [51]



Nu = CN^-, $MeOOC(CN)CH^-$ [102]

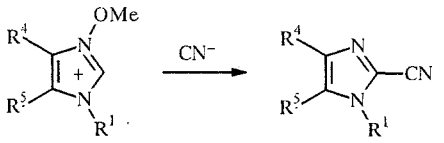
These reactions may proceed either via a cine-substitution mechanism (A) or with splitting out of a proton from the 2 or 6 position (B) to give carbonium zwitter-ion intermediate LI:



LI

Pathway B is more likely in connection with the observed ease of splitting out of a proton from the 2 position [106].

The reaction of nonannelated imidazole N-oxides with nucleophilic reagents was described in the case of 1-R-substituted 3-methoxyimidazolium ions [18]:



$R^1 = CH_2Ph$; $R^4 = R^5 = H$, Me

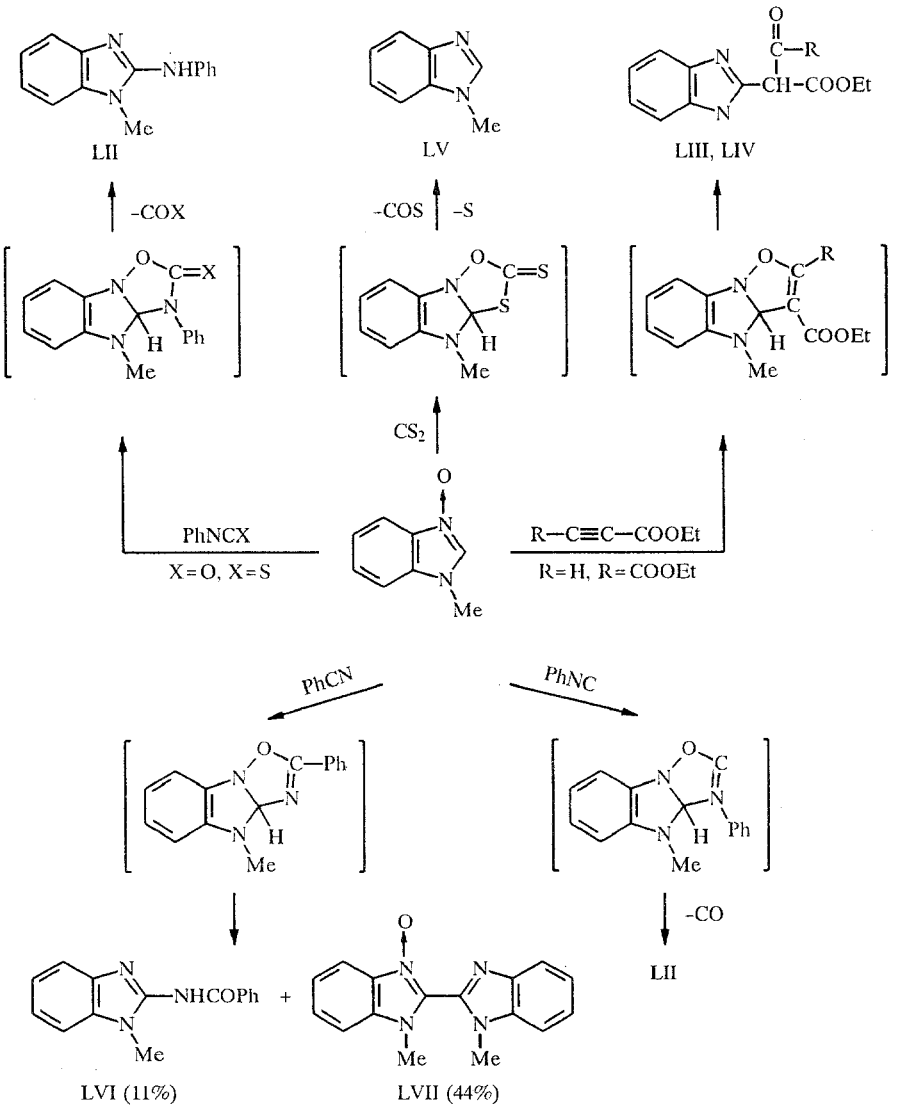
5.6. 1,3-Dipolar Cycloaddition Reactions

The N-oxide group in imidazole N-oxides in combination with the adjacent ring carbon atom has the properties of a 1,3-dipole, which makes it possible to subject imidazole N-oxides to 1,3-dipolar cycloaddition reactions [18, 107-109]. The resulting cyclic adducts are unstable and undergo further transformations with ring opening, transfer of the N-oxide oxygen atom, and the formation of 2-substituted imidazole (benzimidazole) derivatives LII-LV. Phenyl isocyanate, phenyl isothiocyanate, acetylenecarboxylic and acetylenedicarboxylic acid esters, sulfur dioxide, benzonitrile, benzonitrile, and phenyl isonitrile were used as dipolarophiles [107, 108]. (See Scheme 1 at the top of the next page 1.)

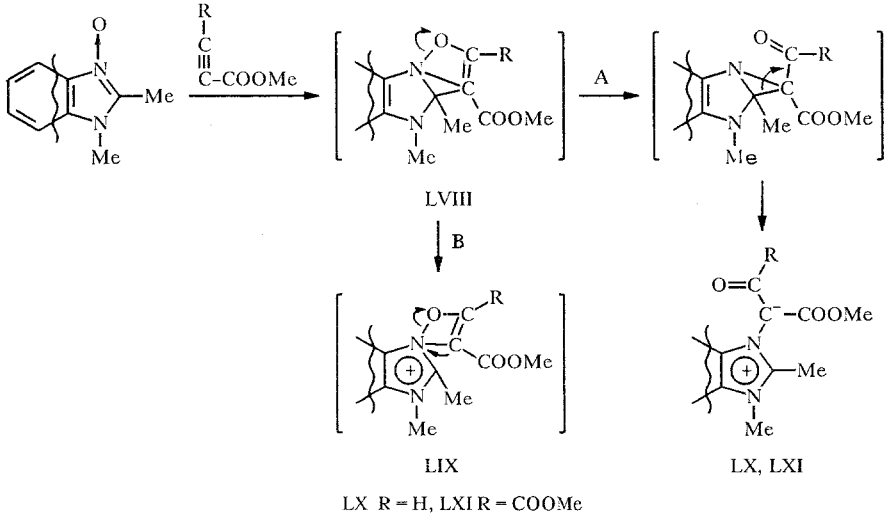
It should be noted that dimer LVII, which retains one of the N-oxide oxygen atoms, is also formed in addition to cycloaddition product LVI in the reaction of 1-methylbenzimidazole 3-oxide with benzonitrile [107, 108].

When there is a substituent in the 2 position, the cycloaddition of acetylene derivatives takes place through initial adduct LVIII with subsequent cleavage of the N—O bond and migration of the group bearing the carbonyl function from the carbon atom to the nitrogen atom through a 1,2 shift (A) or via an alternative mechanism (B) through betaine structure LIX to give, ultimately, 1,2-dimethyl-3-(β-hydroxyvinyl)benzimidazolium betaines LX and LXI [109]. (See Scheme 2 in the middle of the next page.)

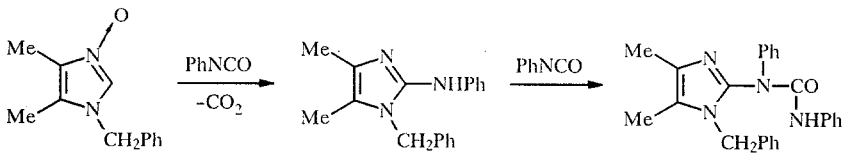
Scheme 1



Scheme 2



The reaction of 1-benzyl-4,5-dimethylimidazole 3-oxide with phenyl isocyanate proceeds via the same pathway to give 2-anilino derivative LXII, which reacts with a second molecule of phenyl isocyanate to give N-(1-benzyl-4,5-dimethyl-2-imidazolyl)-N,N′-diphenylurea (LXIII) [18]:



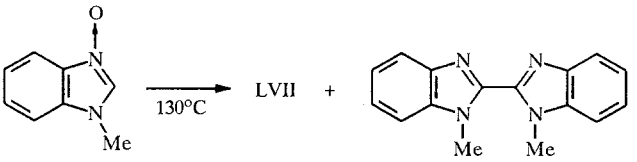
LXII LXIII

1-Benzyl-4-methyl- and 1-benzyl-4,5-dimethylimidazole 3-oxides react with dimethyl acetylenedicarboxylate to also give cycloaddition products with subsequent rearrangement (LXIV, LXV) [18]:

LXIV R = H, LXV R = Me LXIV, LXV

5.7. Dimerization

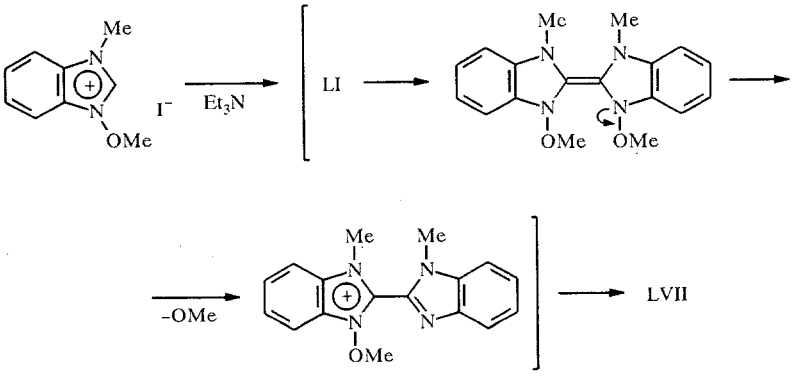
Heating 1-methylbenzimidazole 3-oxide at 130°C leads to dimerization in the 2 position to give 2,2′-bis(benzimidazole 3-oxide) LVII and 2,2′-bis(benzimidazole) LX [95]:



LXV

The formation of dimer LVII in the reaction of 1-methylbenzimidazole 3-oxide with benzonitrile has already been mentioned (section 5.6).

Compound LVII is also formed by the action of triethylamine on 1-methoxy-3-methylbenzimidazolium iodide [102]. The hypothetical mechanism of this reaction includes the formation of carbonium intermediate LI and its dimerization:



6. APPLICATION

Data on the practical application of imidazole and benzimidazole N-oxides are set forth primarily in patents and are rather limited, although the potential possibilities of this class of compounds may prove to be extremely significant.

A large part of the published materials deals with the possible use of imidazole and benzimidazole N-oxides as preparations for medical and veterinary use and intermediates for their synthesis.

Thus 2-(4-thiazolyl)-5,6-disubstituted benzimidazole N-oxides have been patented as anthelminthic preparations [37, 39, 110]; a number of benzimidazole N-oxides with aromatic and heterocyclic substituents in the 2 position have been proposed as veterinary nematocides [45].

1-(Dialkylaminoethoxy)-2-phenylbenzimidazole and its 3-oxide, as well as other similar derivatives that contain substituents in the 4 and 6 positions of the benzimidazole ring, have a depressive effect on the central nervous system and are muscle relaxants [38, 111].

A number of 1-hydroxybenzimidazole 3-oxides have been proposed as antimicrobial preparations [74, 112]. (4,5-Dialkyl-1-imidazolyl-3-oxido)acetic acids are regarded as phytovirucides and intermediates [22].

Information on the technical application of imidazole N-oxides is limited to one report in which the use of 1-hydroxybenzimidazole 3-oxides as modifiers of rubber mixtures that decrease the hysteresis losses and increase the electrical resistance is proposed [113].

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