SYNTHESIS AND TRANSFORMATION OF 2-AMINOBENZIMIDAZOLES (REVIEW)

A. M. Simonov and V. A. Anisimova

UDC 547.785.5.07

A review of papers published after 1965 that deals with methods for the synthesis of 2-aminobenzimidazoles and their properties is given.

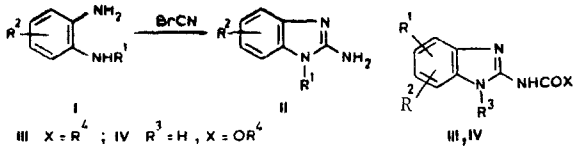
2-Aminobenzimidazole was first obtained by Pierron by the action of cyanogen bromide on o-phenylenediamine [1] but did not attract the attention of researchers for a long time. Research on the chemistry of 2-aminobenzimidazoles has become more intense in recent years, when the high biological activity of some representatives of this series was established [2-4].

Taking into account the fact that data on 2-aminobenzimidazoles have been presented in reviews of the chemistry of imidazole and benzimidazole [5-7], in the present review we included primarily papers that were published after 1965.

METHODS FOR THE PREPARATION OF 2-AMINOBENZIMIDAZOLES

1. Synthesis by Means of Cyanogen Halides, Cyanamide, and Cyanoguanidines

The Pierron method remains one of the most valuable methods for the preparation of various 2-aminobenzimidazoles (II) [1, 3, 8-13]:



I III X = R^4 ; IV R^3 = H, X = OR^4 II III, IV

2-Amino- and 2-dimethylaminobenzimidazoles can also be obtained in low yields by fusion of salts of o-phenylenediamine with cyanamide and dimethylcyanamide, respectively [14]. The best results are obtained when the reaction is carried out in an aqueous medium at 100°C [15]; however, the results are not always reproducible because of polymerization of cyanamide. To avoid this it has been proposed [16] that the reaction be carried out in an organic solvent that forms an azeotropic mixture with water with a boiling point below 90°C.

The use of acyl- or ethoxycarbonyl-substituted cyanamides, which are obtained by reaction of acyl chlorides and chlorocarbonic acid esters with cyanamide in the presence of sodium hydroxide [17], triethylamine [18], or pyridine [19-21], or with calcium cyanamide [22, 23] makes it possible to synthesize 2-acylamino- (III) and 2-alkoxycarbonylaminobenzimidazoles (IV). The latter find application as fungicides and anthelminthic agents.

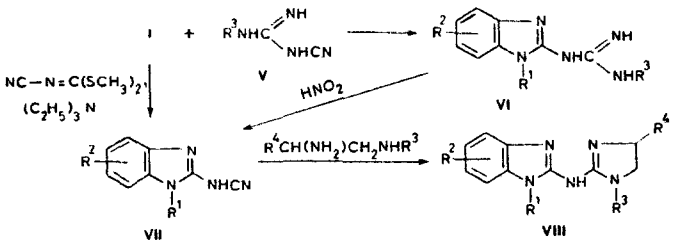
2-Aminobenzimidazole has also been synthesized from o-nitrochlorobenzene and sodium cyanamide [24].

The reaction of o-phenylenediamines I with cyanoguanidines V gives 2-guanidinobenzimidazoles VI [25-27], which are readily converted to 2-(cyanoamino)benzimidazoles VII [26-28]. The latter were also obtained in 41-65% yields from o-phenylenediamines and N-cyanodi(methylthio)imidocarbonate in the presence of triethylamine [29]. Electron-donor substituents (CH_3) in the benzene ring promote the reaction, whereas electron-acceptor substituents (Cl, NO_2) hinder it. When triethylamine is absent, this reaction leads to 2-(methylthio)-benzimidazole [30], i.e., in this case replacement of the elements of cyanamide takes place more rapidly than

Rostov State University. Scientific-Research Institute of Physical and Organic Chemistry, Rostov-on-Don 344006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 867-887, July, 1979. Original article submitted May 22, 1978.

0009-3122/79/1507-0705$07.50

replacement of a second methylthio group. Cyanobenzimidazoles VII serve as starting compounds for the synthesis of 2-(2-imidazolinylamino)benzimidazoles VIII [26, 27]:



Some other 2-(hetarylamino)benzimidazoles can be obtained directly from o-phenylenediamines and hetarylcyanamides. Thus 2-(2-benzimidazolylamino)-4-hydroxypyrimidines have been synthesized by cyclization of 2-cyanamino-4-hydroxy-6-methylpyrimidine with substituted o-phenylenediamines [31].

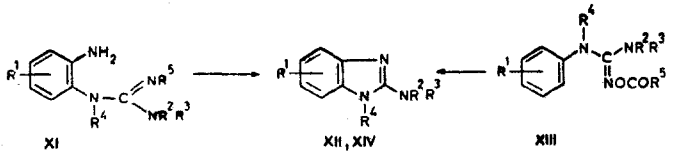
2. Syntheses on the Basis of Urea Derivatives with Aryl-Substituted Guanidines

When o-(N-Phenacylamino)phenylurea is heated with phosphorus oxychloride for 10 min, it undergoes cyclization to 1-phenacyl-2-aminobenzimidazole (X) [32, 33]. When 1-(o-aminophenyl)-3-benzylurea is refluxed in toluene in the presence of p-toluenesulfonic acid, it is converted to 2-benzylaminobenzimidazole (XI, in 17% yield) [34]. An aminobenzimidazole is not formed when the reaction is carried out without p-toluenesulfonic acid or when the urea derivative indicated above is pyrolyzed.

IX, X

IX $R^1 = CH_2COC_6H_5$, $R^2 = H$; X $R^1 = H$, $R^2 = CH_2C_6H_5$

N-(o-Aminophenyl)-N-methyl-N',N''-disubstituted guanidines XI undergo cyclization to aminobenzimidazoles XII when they are allowed to stand for a long time, when they are heated, or when they are treated with CS_2, $CSCl_2$, and $HC(OC_2H_5)_3$ [35]. 2-Acyloxyguanidines XIII undergo decomposition to 2-dialkylaminobenzimidazoles XIV at room temperature or when they are heated briefly to their melting points [36]. It is assumed [36] that the reaction, as in the case of the rearrangement of N-aryl-N-hydroxyamidines [37, 38] to benzimidazoles, proceeds through an iminonitrene intermediate. Despite the ease of cyclization of guanidine derivatives,

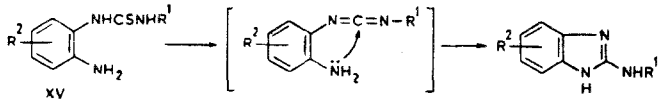


XI, XII $R^2 = H$, $R^4 = CH_3$; XIII, XIV $R^2 = R^3 = CH_3, C_3H_7$; $R^2\text{-}R^3 = (CH_2CH_2)_2O$; $R^4 = H$; $R^5 = C_6H_5, NHC_6H_5, NHCH_3$

the yields of amines do not exeed 27%, and these methods of synthesis therefore are hardly of preparative value.

3. Syntheses Based on Thiourea and Similarly Constructed Compounds

2-Alkyl-, 2-aryl-, and 2-acylaminobenzimidazoles can be synthesized by cyclization of 1-(2-aminophenyl)thiourea XV. It is assumed [39] that the reaction proceeds through intermediate carbodiimides.



XV

R^1 = alkyl, aryl, benzoyl,etc; R^2 = H, Cl, CF_3, CH_3, CH_3CO, CH_3O etc.

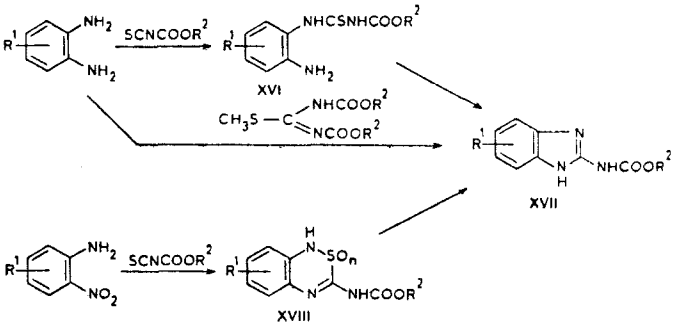
The cyclization was initially carried out by means of lead oxide and, preferably, yellow mercuric oxide in anhydrous chloroform [39] or absolute alcohol [19]. Mercury(II) chloride [40, 41], methyl iodide in ethanol [35, 42], and dimethyl sulfate [43, 44] were subsequently proposed as reagents. It is assumed [35] that in the case of alkylating agents the formation of the aminobenzimidazoles proceeds through thiuronium salt intermediates. The presence of electron-donor groups in the phenylenediamine ring promotes the cyclization [45]. The rate of the conversion also depends on the nature of the second substituent in the thiourea residue [39].

Attempts to synthesize unsubstituted 2-aminobenzimidazole by cyclization of (o-aminophenyl)thiourea have been unsuccessful; benzimidiazolethione was obtained instead of the desired product [39]. However, according to patent data [46], 2-aminobenzimidazole was obtained in 85% yield by this method.

4-(o-Aminophenyl)-3-thioallophanic acid esters (XVI, R^1 = H) readily undergo cyclization when they are heated in strong proton-donor solvents [44, 47]. The cyclization is accelerated by heavy metal ions and (or) hydrogen peroxide [47].

The condensation of o-phenylenediamines with alkyl esters of carbalkoxythiocarbamic [48] and N-[alkoxy(methylthio)methylene]carbamic [49] acids also leads to 2-alkoxycarbonylaminobenzimidazoles (XVII). The same compounds were obtained by heating benzothiadiazines XVIII (n = 1, 2), synthesized from substituted o-nitroanilines [50], in 2 N HCl and methanol.

A convenient method that consists in the reaction of o-phenylenediamine with 1,3-bis(alkoxycarbonyl)-S-methylisothiourea [52] was proposed for the synthesis of carbamates XVII in 1934 [51]. However, diverse benzimidazole-2carbamic acid esters that have various substituents in the benzene ring were obtained by an



XVI

XVII

XVIII

analogous scheme [53-61] only after reports [53, 54] of the existence of systemic fungicidal activity in benzimidazole derivatives of this type [53-61]. Most of the compounds obtained have been patented as anthelminthics and as agents for the protection of plants.

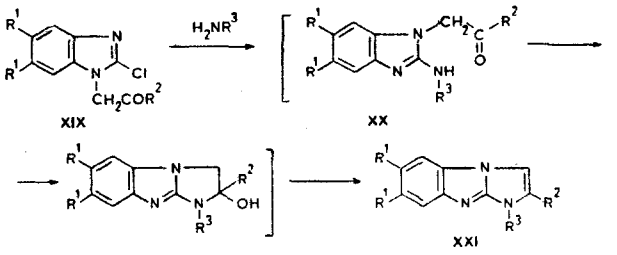
2-Arylamino- [62], 2-acylamino- [63], and 2-methylmercaptocarbonylaminobenzimidazoles [64, 65] were also synthesized by this method when the corresponding 1,3-disubstituted S-methylisothioureas were used.

4. Syntheses by Means of Replacement of a Halogen Atom by an Amino Group and an N-Hetaryl Group

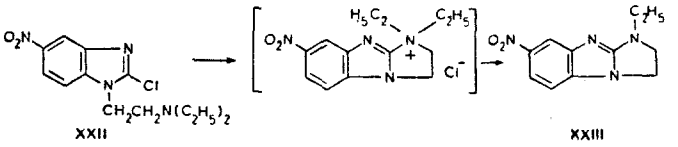
Replacement of a chlorine atom by an amino group, which was first described in 1912 [66], continues to remain one of the most widely used methods for the synthesis of 2-amino-substituted benzimidazoles. This method has been used to obtain 2-aminobenzimidazole derivatives that have the most diverse substituents in the 1 position of the benzimidazole ring, in the amino group, and in the benzene ring [12, 67-75]. In most cases the reactions with aliphatic amines are carried out in ampuls or autoclaves at 150-160°C for 8-16 h. Low-boiling amines such as dimethylamine undergo the reaction in the form of methanol [67] or aqueous [70] solutions. However, the reaction proceeds at 100°C in 3 h to give the product in excellent yield when liquified dimethylamine and a catalytic amount of methanol are used [68].

The reactivities of 2-chlorobenzimidazoles with respect to piperidine are similar to the reactivity of p-nitrochlorobenzene but lower than the reactivities observed for 2-chlorobenzothiazole and 2-chlorobenzoxazole [76]. In the case of 4 (or 7)-substituted benzimidazoles the reactivities depend on the electronic and steric effects of the substituents [77].

In addition to nucleophilic substitution of the chlorine atom, the intermediate 2-amino-1-acylmethylbenzimidazoles (XX) undergo dehydration to give 1H-imidazo[1,2-a]benzimidazole derivatives XXI when 1-acylmethyl-2-chlorobenzimidazoles (XIX) are heated with ammonia or primary amines in lower alcohols or dimethylformamide at 140-180°C [78-80].

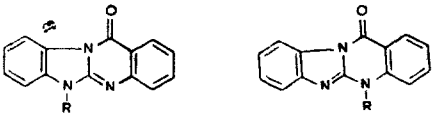


An attempt to exchange the chlorine in 1-(β-diethylaminoethyl)-2-chlorobenzimidazole XXII with a diethylamino or arylamino group led to 2,3-dihydroimidazo[1,2-a]benzimidazole XXIII, since the temperature at which bimolecular exchange is possible is higher than the temperature at which intramolecular cyclization takes place [67].

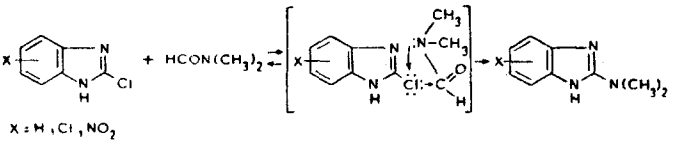


Exchange of halogen proceeds with greater difficulty with aromatic amines [67, 71], and the best results are obtained when their lithium derivatives [67] are used in place of the free aromatic amines.

Benzimidazo[2,1-b]quinazolin-12-one derivatives (XXIV and XXV, R = CH_3) were obtained in the reaction of 2-chlorobenzimidazole and its 1-methyl-substituted derivative with esters of anthranilic and N-methylanthranilic acids [81].



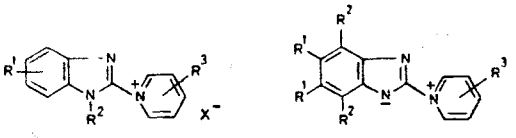
2-Dimethylamino-substituted derivatives were obtained in good yields (45-90%) instead of the expected 2-diphenylaminobenzimidazoles in an attempt to exchange the chlorine with a diphenylamino group in DMF [82].



Benzimidazole-2-carbamic acid ester also could not be obtained from 2-chlorobenzimidazole and urethane; instead of the desired product, a cyclic benzimidazole trimer was isolated [83].

Fusion of 2-chlorobenzimidazoles with five-membered heterocycles that contain an NH group in the ring such as, e.g., imidazole, benzimidazole, indazole, indole [84], and 1,2,3-triazole [85] and substituted 1,2,3-triazoles [86] leads to 2-(N-hetaryl)benzimidazoles.

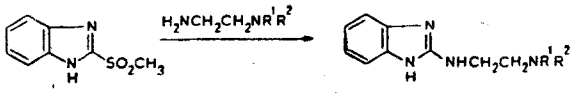
Benzimidazolylpyridinium salts XXVI have been prepared by condensation of pyridine and its derivatives with 2-chlorobenzimidazoles [87]. Compounds XXVII with a zwitterion structure were obtained as a result of heating 2-chlorobenzimidazoles that do not contain substituents in the 1 position with excess pyridine and its derivatives [88, 89].



XXVI XXVII

5. Replacement of Sulfur-Containing Groups by an Amino Group

It is known that sulfur-containing groups such as, for example, CH_3S [90] and CH_3SO [91] in the 2 position of benzimidazole, like halogens, can be replaced by various amino groups, sometimes with even greater ease than in the case of halogens. Thus, for example, 2-dialkylaminoethylaminobenzimidazoles (XXVIII) cannot be synthesized from 2-chlorobenzimidazole. At the same time, these compounds have been obtained in 13-50% yields by heating 2-methylsulfonylbenzimidazole and dialkylaminoethylamines (for 4 h at 140-150°C) [92].



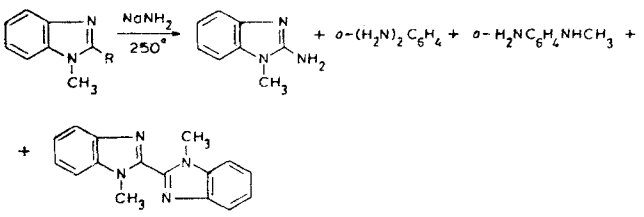
XXVIII

It has been recently shown [93] that the sulfo group in benzimidazole-2-sulfonic acids is also readily replaced by various amino groups. The reaction takes place with highly basic aliphatic amines by heating the starting compounds in aqueous solutions; in the case of high-boiling amines the process can be carried out without a solvent at 160-180°C. This method, owing to the ease of obtaining the starting compounds and the simplicity in the execution of the syntheses, has definite advantages over some other methods described above.

6. Chichibabin Amination

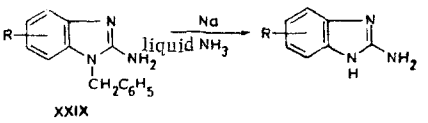
Chichibabin amination is widely used for the synthesis of 1-substituted 2-aminobenzimidazoles. Since this reaction has been examined in a number of monographs and reviews [6, 94-96], we will restrict ourselves to citing these sources.

Nucleophilic substitution by an amino group of not only the hydrogen atom in the 2-position of benzimidazole but also the alkyl, aralkyl, and aryl groups occurs under the influence of sodium amide [97, 98]. However, this method cannot be used for preparative purposes, since it is accompanied by side processes, and the yields of the amines do not exceed 40-56%.



2-Aminobenzimidazole with an unsubstituted NH group in the 1 position cannot be obtained by amination because the N-anion that is formed by the action of sodium amide on benzimidazole is not capable of nucleophilic substitution reactions in the 2 position (see [99]). This difficulty can be overcome by using debenzylation of 1-benzyl-2-aminobenzimidazoles (XXIX), which are readily formed in the amination of 1-benzylbenzimidazoles (see, e.g., [100-102]) with sodium or potassium in liquid ammonia. The process must be carried

out in the absence of air, and a source of protons (for example, NH_4Cl) must be added to the reaction mixture after the addition of the metal [103].

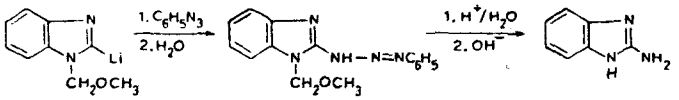


XXIX

In the nitrogen heterocycle series it is more convenient in some cases to use naphthyllithium for the removal of the N-benzyl protective group [104]. However, in contrast to 1-benzyl-2-benzylaminobenzimidazole, which is converted in good yield to 2-benzylaminobenzimidazole, 1-benzyl-2-aminobenzimidazole cannot be debenzylated by means of this reagent.

7. Cleavage of Triazepines

N-Protective groups such as benzyloxymethyl and alkoxyalkyl can easily be removed under acid hydrolysis conditions [104]. Since the synthesis of 1-methoxymethyl-2-aminobenzimidazole by direct amination is impossible [105], a new method has been developed for the preparation of 2-aminobenzimidazole; this method consists in cleavage of phenyl-(1-methoxymethyl-2-benzimidazolyl)triazene (XXX) with a mineral acid. In this case the methoxymethyl group is split out simultaneously with cleavage of the triazene grouping (see [106]).

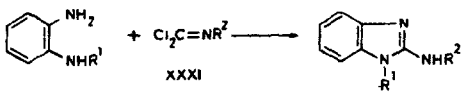


XXX

8. Different Methods

An attempt to synthesize [107] the corresponding amine derivative from 2-sodio-1-methylbenzimidazole and O-methylhydroxylamine by the method in [108] was unsuccessful. However, the action of BrN $(C_2H_5)_2$ on the 2-sodio derivative led to 2-diethylamino-1-methylbenzimidazole in a yield of only 11% [109].

N-Substituted carbonimidoyl dichlorides (XXXI) have found application in the synthesis of 2-aminobenzimidazole derivatives [110]. Thus 2-arylaminobenzimidazoles and 1-phenyl-2-anilinobenzimidazole were obtained in high yields in the reaction of N-arylcarbonimidoyl dichlorides with o-phenylenediamine [111] and N-phenyl-o-phenylenediamine [112]. 2-Alkoxycarbonylaminobenzimidazoles were synthesized by means of N-alkoxycarbonylcarbonimidoyl dichlorides [113]. The reaction proceeds very readily at room temperature in the presence of triethylamine and chloroform and dioxane.

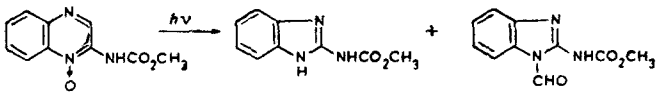


XXXI

$R^1 = H, C_6H_5$; $R^2 = C_6H_5$, COOAlk

The condensation of o-phenylenediamine with 1,1,1-trichloromethyldimethylamine in dioxane is a convenient method for the synthesis of 2-dimethylaminobenzimidazole (in 95% yield) [114].

Some quinoxaline derivatives undergo photochemically initiated rearrangement to benzimidazole derivatives, the yields of which depend on the pH of the medium and the solvent [115]. Thus, when 2-methoxycarbonylaminoquinoxaline N-oxide (XXXII) is irradiated with UV light in dry acetonitrile, it undergoes rapid rearrangement to 2-methoxycarbonylaminobenzimidazole (XXXIII) and its N-formyl derivative (XXXIV). The latter cannot be obtained in methanol because of rapid solvolysis of the formyl group.



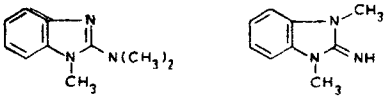
XXXII XXXIII XXXIV

1. Tautomerism

The existence of two tautomeric forms, viz., the amine (XXXV) and imine (XXXVI) forms, is possible in the case of 2-aminobenzimidazole and 1-substituted 2-aminobenzimidazoles.

XXXV XXXVI

A comparison of the IR and UV spectra of 2-amino-1-methylbenzimidazole (XXXV, R = CH_3) and fixed model forms XXXVII and XXXVIII has shown that, as in the case of many other α-hetarylamines [116], amine XXXV exists in the crystalline state almost entirely in the amino form [117, 118]. According to the data in [118], the tautomeric equilibrium constant $K_T = K_{XXXVIII}/K_{XXXVII}$, where K_{XXXVII} and $K_{XXXVIII}$ are the ionization constants of the model forms, is only 0.0019.



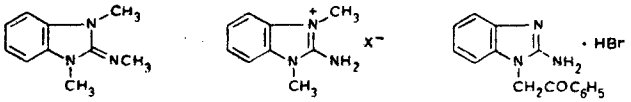
XXXVII XXXVIII

However, the tendency for conversion of the amino to the imino form is expressed more markedly in the case of 2-aminobenzimidazoles than in a number of other α-aminoheterocycles. It is manifested distinctly in the case of 2-acylamino derivatives, where the mono- and dichloroacetyl compounds exist in the imino form [117].

α-Amino derivatives of more complex imidazole systems, viz., linear and angular naphthimidazoles [118] and benzo[1,2-d:3,4-d']diimidazole [119], also exist in the amino form in the crystalline state. The sodium salt of 2-amino-1-ethylbenzimidazole has the same structure [120].

2. N-Alkylation

Alkylation of 2-Aminobenzimidazoles with an Unsubstituted NH Group. In the methylation of 2-aminobenzimidazole with dimethyl sulfate (3.5 moles) all three nitrogen atoms undergo reaction, and 2-methylimino-1,3-dimethylbenzimidazoline (XXXIX) is formed in 45% yield [112].



XXXIX XL XLI

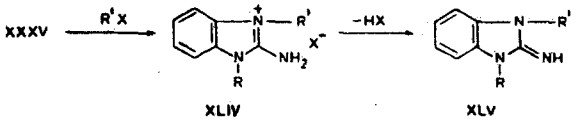
Methylation with dimethyl sulfate at 20°C can be carried out in the presence of sodium bicarbonate without involving the amino group; in this case benzimidazolium salt XL is obtained [121]. The reaction of 2-aminobenzimidazole with phenacyl bromide at room temperature leads to the formation of 1-substituted salt XLI in a mixture with a quaternization product of the XL type [33, 122, 123]. The use of propargyl bromide gives similar results [124].

1-Substituted 2-aminobenzimidazoles (XLII) are formed when 2-aminobenzimidazole is heated with ω-dialkylaminoalkyl chlorides in the presence of sodium ethoxide; bromoacetaldehyde acetal reacts similarly [33]. Substitution at the NH group also occurs in the reaction of methoxymethyl chloride with the Na derivative of 2-aminobenzimidazole in refluxing dioxane [125]. The alkylation of this salt with 2-chloroethyl isothiocyanate is accompanied by cyclization in the substituting group with the formation of XLIII [126].

XLII XLIII

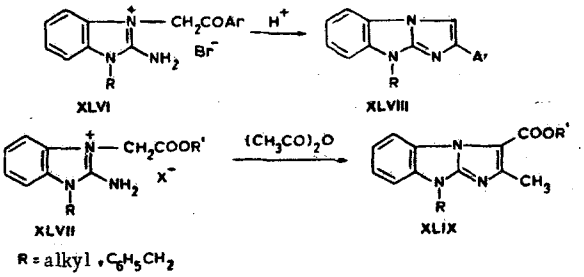
XLII $n = 2, 3$; R = CH_3, C_2H_5

Alkylation of 1-Substituted 2-Aminobenzimidazole. The nitrogen atom in the 3 position always undergoes attack in the alkylation of 2-amino-1-alkylbenzimidazoles. Thus, under the influence of methyl iodide, 2-amino-1-methylbenzimidazole (XXXV, R = CH_3) undergoes almost quantitative conversion to iodide XLIV (R = R' = CH_3) [127]. Other alkyl halides [128] and chloromethyl alkyl ethers [129] react similarly. 2-Imino-1,3-dialkylbenzimidazolines (XLV) are isolated from the quaternization products by the action of a solution of alkali [127].

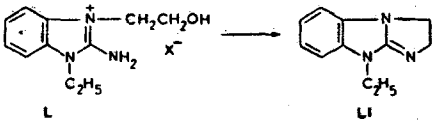


Azomethines obtained from 2-amino-1-alkylbenzimidazoles can also be converted to quaternary benzimidazolium salts, but the quaternization proceeds with greater difficulty and only under the influence of methyl iodide [130].

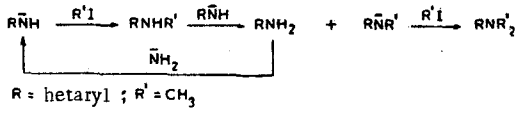
2-Amino-1-alkylbenzimidazoles readily form quaternary salts on reaction with esters [131] and arylamides of chloroacetic acid [132], bromoacetone [133], and phenacyl bromides [134-136]; the products, such as, e.g., XLVI and XLVII, undergo cyclization under the influence of condensing agents to give imidazo[1,2-a]benzimidazole derivatives (XLVIII and XLIX) [33, 135-137].



Ethylene halohydrins also react with amine XXXV at the heteroatom to give alkylation products L [131, 138], which can be subsequently converted to dihydroimidazo[1,2-a]benzimidazole derivatives LI [138].



The methylation of the amino group in the 2 position with methyl iodide can be accomplished by carrying out the reaction in liquid ammonia in the presence of sodium amide [139]. The conversion is a stepwise process and, since the rate of methylation of the $R\bar{N}CH_3$ anion is considerably higher than the rate of methylation of the $R\bar{N}H$ anion, the dimethylamino derivative accumulates almost exclusively in the reaction mixture, regardless of the N-anion:alkyl halide ratio. This transformation is a convenient method for the synthesis of 2-dimethylamine derivatives of nitrogen heterocycles [140].

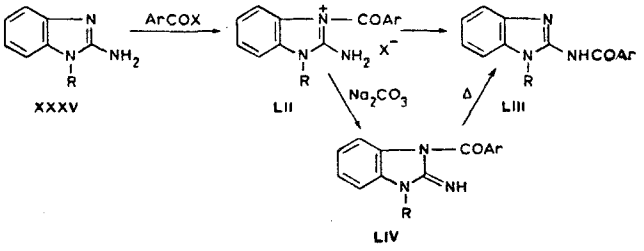


The reaction of the N anion of 2-amino-1-ethylbenzimidazole in liquid ammonia with C_2-C_4 alkyl halides leads to the formation of a mixture of mono- and dialkylation products, usually with predominance of the latter [141, 142]. The monobenzyl derivative is obtained in large amounts by the action of benzyl chloride.

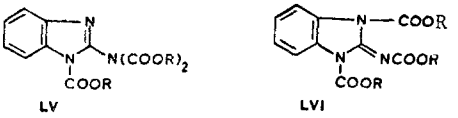
A good method for the benzylation of 2-amino-1-alkylbenzimidazoles to 2-monobenzylamino derivatives by the action of benzyl alcohol in the presence of alkali has been worked out [143].

3. N-Acylation

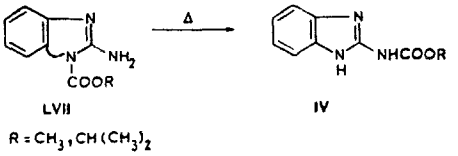
Under the influence of monocarboxylic acid chlorides and anhydrides, 2-aminobenzimidazoles are converted to monoacylamino derivatives [12, 19, 144, 145]. In the case of the reaction of 2-amino-1-methylbenzimidazole (XXXV, R = CH_3) with aroyl chlorides it has been shown that in the first step the acyl group attacks the nitrogen heteroatom, and unstable 2-amino-3-acyl-1-methylbenzimidazolium salts (LII) are formed; these salts can be isolated by carrying out the reaction in a stream of nitrogen at 20°C in dry acetone. They readily (and more rapidly when they are heated) undergo rearrangement to 2-acylamino derivatives LIII [146, 147]. When salts LII are treated with sodium carbonate in the cold, they can be converted to 1-acyl-2-iminobenzimidazolines (LIV), which are also unstable and are readily rearranged to 2-acylamino derivatives LIII. The nature of the substituent in the aryl grouping of the acyl group has an extremely pronounced effect on the rate of rearrangement: A methoxy group in the para position slows down the rate of conversion, while a nitro group accelerates the process.



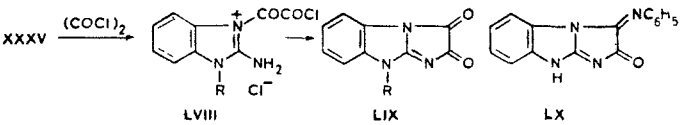
Two acetyl groups can be incorporated in the amino group when amine XXXV is heated with acetic anhydride [12, 145]. Acylation with an alkyl chloroformate in pyridine at 20°C leads to 1-alkoxycarbonyl-2-(dialkoxycarbonylamino)benzimidazoles (LV) and the isomeric 2-alkoxycarbonylimino-1,3-dialkoxycarbonylbenzimidazolines (LVI) [148].



The rearrangement of alkyl 2-aminobenzimidazole-1-carboxylates (LVII) to 2-alkoxycarbonylamine derivatives IV by heating to the melting point or by refluxing a solution in cumene has been described [149].

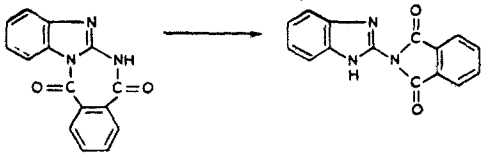


Hetarylcarboxylic acid chlorides acylate 2-aminobenzimidazole to give quaternary salts LII (R = H; Ar = 2-furyl, 4-thiazolyl, 3-pyridyl, etc.). Like monocarboxylic acid chlorides, oxalyl chloride attacks the ring nitrogen atom; when the resulting salts LVIII are heated in the presence of triethylamine, they are converted to 2,3-dihydroimidazo[1,2-a]benzimidazole derivatives (LIX) [150].



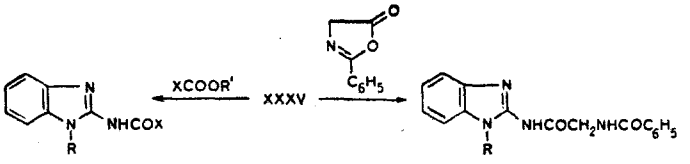
Analogs of LIX (viz., LX) are formed by the action of phenyliminooxalic acid [151] and arylazochloroacetic acid chlorides [152] on 2-aminobenzimidazole. Diamides $RNHCOC_6H_4CONHR$ (R = 2-benzimidazolyl) were obtained by means of terephthalic and isophthalic acid chlorides [153].

The reaction of 2-aminobenzimidazole with phthalic anhydride leads to condensation product LX, which undergoes rearrangement to 2-phthalimido derivative LXII at 200°C [154].



LXI LXII

The acylation of aminobenzimidazoles can be accomplished by means of esters such as, for example, cyanoacetic [155] and oxalic acid [150] esters. A similar transformation takes place under the influence of 2-phenyl-5-oxazolone [156].

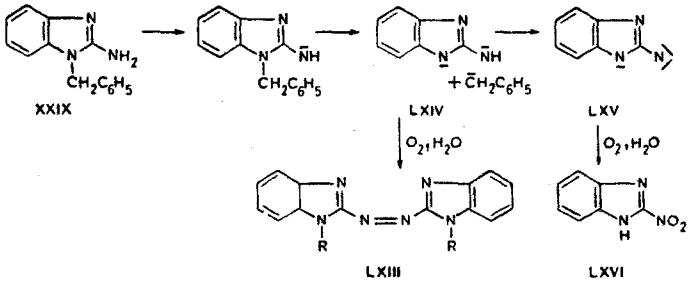


X = CH_2CN, $COOCH_3$

4. Oxidative Transformations

Under the influence of a 30% aqueous solution of sodium hypochlorite, 2-aminobenzimidazoles are oxidized to brightly-colored 2,2'-azo derivatives LXIII (R = H, Alk, C_6H_5) [157]; this process can be used as a qualitative reaction for these amino compounds. The oxidation of the 1-phenyl-substituted compound gives the best results (the product is obtained in 72% yield). In the case of 1-alkyl-substituted compounds the reaction is accompanied by the formation of deeply colored resinous compounds, and the yields of the azo compounds are reduced.

2-Amino-1-benzylbenzimidazole (XXIX, R = H) can be made to undergo a peculiar oxidative transformation [158, 159]. If 3-4 moles of sodium (or potassium) is added to a solution of this compound in liquid ammonia and the ammonia is evaporated, the di- (LXIV) and trianion (LXV) of aminobenzimidazole that are formed under the influence of bases (sodium amide and the benzyl anion) are oxidized by air oxygen to, respectively, 2,2'-azobenzimidazole (LXIII, R = H; in up to 55% yield) and 2-nitrobenzimidazole (in up to 43% yield) [160]. Under the indicated conditions, 2-amino-1-methyl(ethyl)benzimidazoles form only small amounts of the azo compounds [161]. 5-Methyl-, 5-methoxy-, and 5,6-dimethyl-2-amino-1-benzylbenzimidazoles behave like XXIX in this reaction.



XXIX LXIV LXV

LXIII LXVI

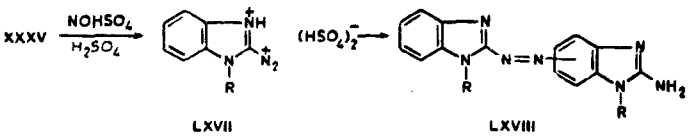
The participation of the benzyl anion as a base in the formation of dianion LXIV and trianion LXV is extremely significant: An azo compound and a nitro compound are formed in low yields (18 and 10%, respectively) from NH-unsubstituted 2-aminobenzimidazole. However, if the amine is subjected to the reaction in the presence of 1-benzylbenzimidazole, which generates a benzyl anion, the yields of the azo and nitro derivatives are 52 and 44%.

The oxidation of the anions formed from 2-aminobenzimidazole in liquid ammonia by means of potassium permanganate, potassium persulfate, air, or iodine gives only the azo compounds. The reactions proceed through a step involving the formation of a hydrazo derivative [161].

5. Reaction with Nitrous and Nitrosylsulfuric Acids

2-Aminobenzimidazoles behave peculiarly with respect to nitrous acid. Virtually no diazotization of these compounds is observed in 2 N hydrochloric acid. Diazotization proceeds very slowly in 25-40% sulfuric

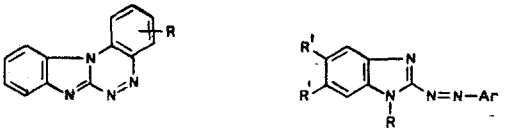
and 30% fluoboric acids, and the reaction gives the products in very low yields and is accompanied by side transformations [162]. The difficulty involved in the diazotization of 2-aminobenzimidazoles is due to the high electrophilicity of the benzimidazolyl grouping [163]. However, the fact that N-nitrosamines of the benzimidazole series, which, according to the generally accepted concepts regarding the mechanism of diazotization, should be formed in the first step of the reaction, are resistant to the action of dilute mineral acids [164] and are converted to diazonium salts only under special conditions is more important. These amines were first successfully converted to diazonium compounds by the action of nitrosylsulfuric acid in solution in concentrated sulfuric and concentrated phosphoric acids [162]; diazonium salt LXVII is distinguished by its instability and extremely high reactivity: If the 5 and 6 positions in the benzimidazole ring are unsubstituted, as in the case of 2-amino-β-naphthothiazole [165], diazo coupling with a second nondiazotized molecule of the starting amine ("self-coupling") occurs, and a mixture of 5- and 6-azo derivatives LXVIII is formed. The presence of a CH_3 group in the 5 (6) position of the ring accelerates the process, whereas the presence of a bromine atom slows it down [166]. Diazotization does not occur if there is a nitro or azo group in the 5 (6) position of the ring [167]. Apparently, as a consequence of this, self-coupling of salts LXVII stops at the step involving the formation of monoazo compounds LXVIII.



LXVII LXVIII

In addition to intermolecular diazo coupling, an intramolecular transformation – the diazo group attacks the ortho position of the N-aryl group [168] to give LXIX – is observed in the reaction of nitrosylsulfuric acid with 2-amino-1-arylbenzimidazoles.

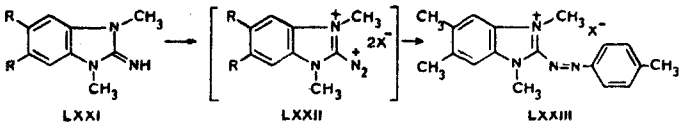
The activity of benzimidazole-2-diazonium salts obtained in concentrated sulfuric acid is so high that diazo coupling even with the simplest arenes, viz., benzene and toluene, becomes possible [169]. The latter should be added to the sulfuric acid solution beforehand so that the unstable diazonium salt that forms can rapidly undergo the coupling reaction. In order to avoid the occurrence of a competitive "self-coupling" reaction, one should in this case use 5,6-disubstituted 2-aminobenzimidazoles [166, 169].



LXIX LXX

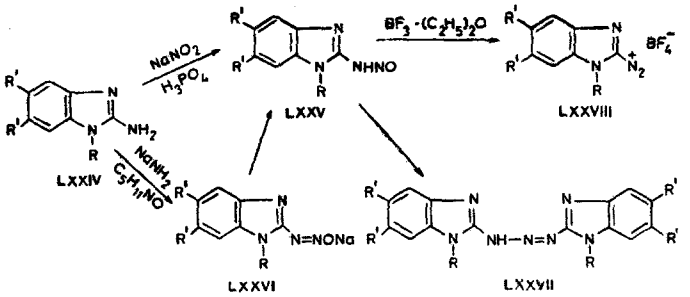
LXX R' = CH_3; Ar = C_6H_5; p-$CH_3C_6H_4$, 2,4-$(CH_3)_2C_6H_3$, mesityl

The clearly expressed ability of benzimidazole-2-diazonium salts to undergo diazo coupling is determined by the high electrophilicity of the grouping bonded to the diazo group, which is due to protonation of the imidazole ring (see LXVII). The transformations that take place in the reaction of nitrosylsulfuric acid with 2-imino-1,3-dialkylbenzimidazolines (LXXI) confirm this point of view. The initially formed diazonium salt LXXII undergoes self-coupling when R = H, whereas if the 5 and 6 positions are substituted (R = CH_3), it reacts with toluene to give azo compounds LXXIII [170].



LXXI LXXII LXXIII

The reaction of sodium nitrite with 2-amino-1-alkyl(aralkyl)benzimidazoles (LXXIV) in 60% phosphoric acid at −5°C gives N-nitroso compounds LXXV, which are stable when they are stored in the dark [164]; 5-alkyl- and 5-alkoxy-substituted compounds undergo "self-coupling" under these conditions. Nitrosamines LXXV were also obtained from diazotates LXXVI [171], which are formed by the action of isoamyl nitrite on the Na derivatives of amines LXXIV [172]. In aqueous solutions or in organic solvents the nitrosamines in the presence of acids are spontaneously converted to triazenes LXXVII [173].

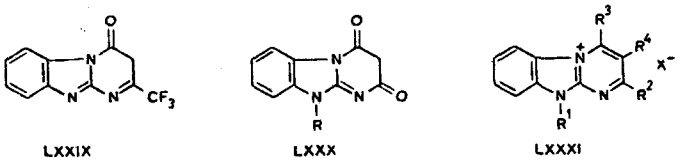


In concentrated sulfuric acid nitrosamines LXXV undergo partial denitrosation and subsequently, if the 5 and 6 positions are not occupied, form self-coupling products of the LXVIII type through a number of transformations. In acids with low protonating capacities the nitrosamines are converted to diazonium salts LXXVIII, which are not protonated in the imidazole ring and are therefore less active than diazonium salts LXVII [171]. These salts can also be obtained by the action of boron trifluoride etherate on nitrosamines LXXV in an aprotic medium [173]. They do not react with the simplest arenes, but they do react with ethers of phenols to give azo compounds in good yields [174].

6. Reactions with Bifunctional Compounds – Formation of a Six-Membered Heterocyclic Ring That Is Annelated with an Imidazole Ring

Although many reactions of 2-aminobenzimidazoles with bifunctional compounds have been known for a long time [6, 175], transformations of this type continue to attract the attention of researchers, since the condensation products can be used as biologically active compounds [31, 176] and starting reagents for the preparation of cyanine dyes [177].

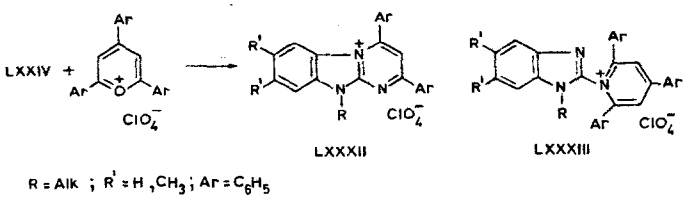
The reaction of 2-aminobenzimidazole with esters of β-keto acids gave 4-oxo-3,4-dihydropyrimido[1,2-a]benzimidazoles such as, e.g., LXXIX [31]. Carbon suboxide undergoes condensation with 2-aminobenzimidazole and its 1-alkyl-substituted derivatives to give 2,4-dioxotetrahydropyrimido[1,2-a]benzimidazoles (LXXX) [178]. Quaternary pyrimido[1,2-a]benzimidazolium salts LXXXI are obtained from the reaction of the



LXXX R = H, Alk ; LXXXI $R^1 = CH_3, C_6H_5$; $R^2 = H, CH_3$; $R^3 = CH_3, C_2H_5$; $R^4 = H, CH_3$

hydrochloride or picrate of 2-aminobenzimidazole with β-diketones or β-chlorovinyl ketones [179].

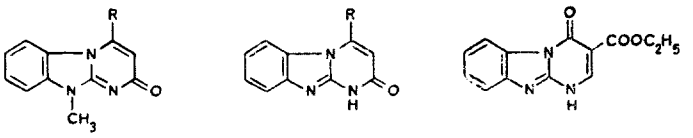
Similarly constructed quaternary salts LXXXII are also formed in the peculiar condensation of 2-amino-1-alkylbenzimidazole (LXXIV) with pyrylium salts, which takes place with opening of the pyran ring and subsequent formation of a pyrimidine ring [180]. N-(2-Benzimidazolyl)pyridinium salts LXXXIII are obtained as side products (when R = CH_3 and C_2H_5) [180, 181].



R = Alk ; $R^1 = H, CH_3$; Ar = C_6H_5

The synthesis of pyrimido[1,2-a]benzimidazole derivatives LXXXIV from 2-aminobenzimidazoles and unsaturated acids such as, e.g., esters of propiolic and phenylpropiolic acids, has been described [182-184]; it

has been established [184] that the oxo group is located in the 2 position. When R = H, the reaction product exists in the LXXXV form.



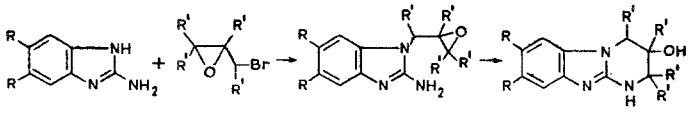
LXXXIV LXXXV LXXXVI

LXXXIV R = H, C_6H_5 ; LXXXV R = H, C_6H_5, $COOCH_3$

2-Aminobenzimidazole reacts with acrylic, crotonic, and methacrylic acid chlorides to give 2-oxo-1,2-dihydropyrimido[1,2-a]benzimidazoles [185, 186] and with ethoxymethylenemalonic ester to give 4-oxo derivative LXXXVI [183, 186].

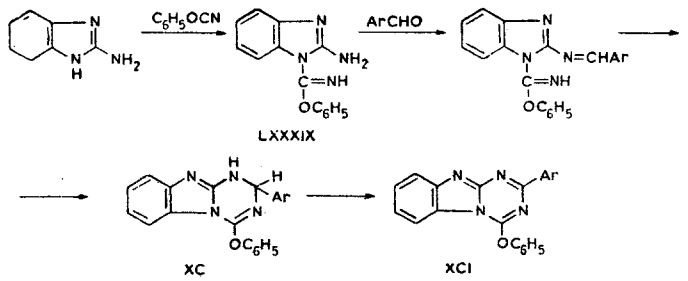
The condensation of 2-aminobenzimidazole with methyl anthranilate gives benzimidazo[2,1-b]quinazoline derivative XXV (R = H) in low yield [81].

2-Aminobenzimidazoles react with epoxy bromides LXXXVII to give 3-hydroxy-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazoles LXXXVIII [187].



R, R' = H, CH_3 LXXXVII LXXXVIII

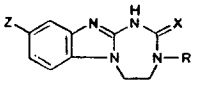
The reaction of 2-aminobenzimidazole with benzoyl isothiocyanate led to the formation of a sym-triazine ring that is annelated with a benzimidazole ring [188]. This heterocyclic system (XCI) was also obtained from 2-amino-1-benzimidazolylimidophenyl ester (LXXXIX) and aromatic aldehydes with subsequent oxidation of 1,2-dihydro derivative XC [189]:



LXXXIX XC XCI

A number of other sym-triazino[1,2-a]benzimidazole derivatives have been obtained from 2-amino-1-cyanobenzimidazole [189].

Compounds with an annelated seven-membered ring, viz., 4,5-dihydro-1,3,5-triazepino[1,2-a]benzimidazole derivatives, have been synthesized from 2-amino-1-β-hydroxyethylbenzimidazole [9]:

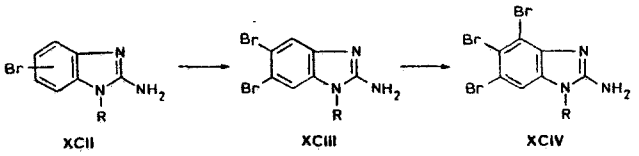


Z = H, Cl ; X = O, S, $NSO_2C_6H_5CH_3$-p ; R = C_4H_9

7. Electrophilic Substitution Reactions in the Benzene Ring

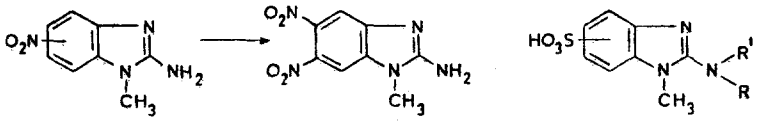
Because of the effect of the amino group, electrophilic substitution reactions in the benzene ring of 2-aminobenzimidazole proceed under milder conditions than in the case of unsubstituted benzimidazole. Chlorination to the 5(6)-monochloro-substituted compound was accomplished almost quantitatively by the addition of

hydrogen peroxide (1 mole) to a hydrochloric acid solution of the amine [190]. The bromination of 2-amino-1-methyl(ethyl)benzimidazole by the action of potassium bromate (0.33 mole) in hydrobromic acid at 20°C leads to a mixture of monobromo-substituted XCII through the intermediate formation of perbromides. The bromine atom, like the chlorine atom, is incorporated in the 5 and 6 positions, which are the most reactive positions in electrophilic substitution. 5,6-Dibromo derivative XCIII was obtained by using 0.66 mole of potassium bromate. 4,5,6-Tribromo derivative XCIV was obtained under more severe conditions [191].



XCII XCIII XCIV

The nitration of 2-amino-1-methylbenzimidazole proceeds smoothly at −5°C with potassium nitrate (1 mole) in concentrated sulfuric acid [192] to give a mixture of 5- and 6-substituted derivatives XCV in a ratio of 5:4. 5,6-Dinitro-2-amino-1-methylbenzimidazole (XCVI) was obtained under the same conditions using 2 moles of potassium nitrate.

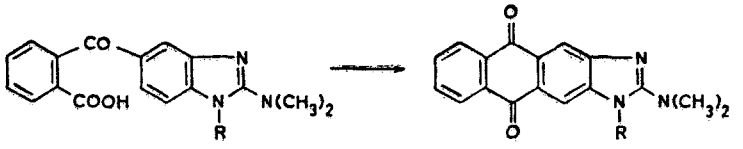


XCV XCVI XCVII

XCVII R, R' = H, CH_3

A mixture of isomeric 5- and 6-sulfonic acids XCVII was obtained by the action of chlorosulfonic acid on 1-alkyl-2-aminobenzimidazoles [193].

Acylation in the benzene ring (with phthalic anhydride in the presence of aluminum chloride) has been described only for the 2-dimethylamino derivative [194]. The possibility of this transformation is due to the effect of the dimethylamino group, since benzimidazole itself and its 2-methyl-substituted derivative are not acylated. The resulting keto carboxylic acid (XCVIII) readily undergoes cyclization to anthraquinone derivative XCIX.



XCVIII XCIX

LITERATURE CITED

1. P. Pierron, Ann. Chim. Phys., 15, No. 8, 189 (1908).
2. F. Domino, K. R. Unna, and J. Kerwin, J. Pharmacol. Exp. Ther., 105, 486 (1952).
3. L. Joseph, J. Med. Chem., 6, 601 (1963).
4. R. W. Marsh (ed.), Systemic Fungicides, Halsted Press (1973).
5. R. Elderfield (ed.), Heterocyclic Compounds, Vol. 5, Wiley (1957).
6. Z. N. Nazarova (ed.), Outline of the Chemistry of Azoles [in Russian], Rostov-on-Don (1965).
7. A. F. Pozharskii, A. D. Garnovskii, and A. M. Simonov, Usp. Khim., 35, 261 (1966).
8. R. J. North and A. R. Day, J. Heterocycl. Chem., 6, 655 (1969).
9. B. Agai, G. Doleschall, Gy. Hornyak, K. Lembert, and G. Simig, Tetrahedron, 32, 839 (1976).
10. R. G. Haugwitz and V. L. Narayanan, German Patent No. 2310076 (1973); Chem. Abstr., 79, 126496 (1973).
11. L. R. Mandel, C. C. Porter, F. A. Kuehl, N. P. Jensen, S. M. Schmitt, T. B. Windholz, T. R. Beattie, J. A. Carty, B. G. Christensen, and T.-Y. Shen, J. Med. Chem., 13, 1043 (1970).
12. E. Bellasio, A. Campi, A. Trani, E. Baldoli, A. M. Caravaggi, and G. Nathanson, Farmaco Ed. Sci., 28, 164 (1973).

13. L. Skaletzky, US Patent No. 3928526 (1973); Chem. Abstr., 84, 74270 (1976).
14. B. Adcock, A. Lawson, and D. H. Miles, J. Chem. Soc., No. 12, 5120 (1961).
15. S. Weiss, H. Michaud, H. Prietzel, and H. Krommer, Angew. Chem., 85, 866 (1973).
16. K. Sawatari, T. Mukai, K. Suenobu, S. Kamenozono, and T. Ika, Japanese Patent No. 76.16669 (1976); Chem. Abstr., 85, 63069 (1976).
17. C. De Witt Adams and R. Schlatter, Republic of South Africa Patent No. 6706.589 (1968); Chem. Abstr., 70, 57837 (1969).
18. C. DeWitt Adams and R. Schlatter, Republic of South Africa Patent No. 6906.326 (1970); Chem. Abstr., 73, 120629 (1970).
19. P. N. Craig and J. R. E. Hoover, British Patent No. 1111957 (1966); Chem. Abstr., 69, 96721 (1968).
20. Smith, Kline, and French Laboratories, British Patent No. 1122957 (1968); Chem. Abstr., 70, 87805 (1969).
21. D. R. Hoff, M. M. Fischer, and R. J. Bochis, French Patent No. 1580830 (1970); Chem. Abstr., 73, 3915 (1970).
22. K. Harsanyi, G. Toth, A. Simay, C. Gonczi, K. Takacs, and I. K. Aizert, Hungarian Patent No. 5800 (1973); Chem. Abstr., 79, 78801 (1973).
23. M. Akbarova, S. A. Khasanov, Ch. Sh. Kadyrov, and S. Yu. Yunusov, Dokl. Akad. Nauk Uzb. SSR, No. 7, 33 (1974).
24. J. C. Watts, West German Patent No. 2204479 (1973); Chem. Abstr., 79, 115592 (1973).
25. T. Waratani, K. Soda, and T. Aka, Japanese Patent No. 16517 ('66) (1963); Chem. Abstr., 66, 10936 (1967).
26. E. A. Watts, West German Patent No. 2267312 (1973); Chem. Abstr., 79, 53321 (1973).
27. R. Ruegg and G. Ryser, West German Patent No. 2252805 (1973); Chem. Abstr., 79, 53325 (1973).
28. E. A. Watts, British Patent No. 1408408 (1975); Chem. Abstr., 84, 17355 (1976).
29. L. S. Wittenbrook, J. Heterocycl. Chem., 12, 37 (1975).
30. J. J. D'Amico, K. Boustany, A. B. Sullivan, and R. H. Campbell, Int. J. Sulfur Chem., 2, 37 (1972).
31. L. M. Werbel, A. Curry, E. F. Elslager, and C. Hess, J. Heterocycl. Chem., 10, 363 (1973).
32. H. Ogura and T. Itoh, Kitasato Arch. Exp. Med., 42, Nos. 3-4, 65 (1969).
33. H. Ogura, H. Takayanagi, Y. Yamazaki, S. Yonezawa, H. Takagi, S. Kobayashi, T. Kamioka, and K. Kamoshita, J. Med. Chem., 15, 923 (1972).
34. G. Depost, R. Salle, and B. Sillion, Compt. Rend., C, 275, 697 (1972).
35. P. Lugosi, B. Agai, and Gy. Hornyak, Period. Polytech. Chem. Eng., 19, 307 (1975); Ref. Zh. Khim., 1Zh260 (1977).
36. P. Held, M. Gross, and H. Schubert, Z. Chem., 13, 292 (1973).
37. M. W. Partridge and H. A. Turner, J. Chem. Soc., No. 6, 2086 (1958).
38. W. Kirmse, Angew. Chem., 71, 537 (1959).
39. D. Kiffer and R. Levy, Compt. Rend., C, 267, 1730 (1968).
40. A.-M. M. E. Omar, Pharmazie, 27, 798 (1972); Chem. Abstr., 78, 72005 (1973).
41. A.-M. M. E. Omar, M. S. Ragab, A. M. Farghaly, and A. M. Barghash, Pharmazie, 31, 348 (1976); Ref. Zh. Khim., 7Zh255 (1977).
42. A.-M. M. E. Omar, Synthesis, No. 1, 41 (1974).
43. A.-M. M. E. Omar, Sh. A. Shams El-Dine, and A. A. B. Hazzaa, Pharmazie, 30, 85 (1975); Ref. Zh. Khim., 20Zh295 (1975).
44. C. W. Adams and J. B. Wommack, West German Patent No. 2133658 (1972); Chem. Abstr., 76, 99665 (1972).
45. D. Kiffer, Bull. Soc. Chim. France, No. 6, 2377 (1970).
46. R. J. Stedman, US Patent No. 3455948 (1969); Chem. Abstr., 71, 81369 (1969).
47. T. Matsui, M. Nagano, J. Tobitsuka, and K. Oyamada, Yakugaku Zasshi, 93, 977 (1973); Chem. Abstr., 79, 105139 (1973).
48. K. Oyamada, T. Matsui, J. Tobitsuka, and M. Nagano, J. Agr. Chem. Soc. Jpn., 50, No. 1, 29 (1976); Ref. Zh. Khim., 21Zh284 (1976).
49. P. R. Atkins, S. E. J. Glue, and I. T. Kay, J. Chem. Soc., Perkin Trans. I, No. 22, 2644 (1973).
50. A. C. Barker and R. G. Foster, West German Patent No. 2246605 (1973); Chem. Abstr., 79, 5341 (1973).
51. I. A. Murray and F. B. Dains, J. Am. Chem. Soc., 56, 144 (1934).
52. I. F. Olin and F. B. Dains, J. Am. Chem. Soc., 52, 3326 (1930).
53. H. L. Klopping, US Patent No. 2933502 (1960); Chem. Abstr., 55, 3617 (1961).
54. H. L. Klopping, US Patent No. 2933504 (1960); Chem. Abstr., 55, 9131 (1961).

55. C. A. Littler, B. L. Richards, and H. L. Klopping, French Patent No. 1532380 (1968); Chem. Abstr., 71, 70598 (1969).
56. C. C. Beard, J. A. Edwards, and J. H. Fried, US Patent No. 3929821 (1975); Ref. Zh. Khim., 20O370P (1976).
57. Smith, Kline, and French Laboratories, British Patent No. 1123317 (1968); Chem. Abstr., 69, 96722 (1968).
58. J. Ishida, Japanese Patent No. 7035.764 (1973); Chem. Abstr., 78, 97658 (1973).
59. C. C. Beard, J. A. Edwards, and J. H. Fried, US Patent No. 3929823 (1975); Ref. Zh. Khim., 20O119P (1976).
60. E. A. Averkin, C. C. Beard, C. A. Drovak, J. A. Edwards, J. H. Fried, J. G. Kilian, R. A. Schiltz, T. P. Kistner, J. H. Drudge, E. T. Lyons, M. L. Sharp, and R. M. Corwin, J. Med. Chem., 18, 1164 (1975).
61. Z. Budesinsky, J. Sluka, J. Novak, and J. Danec, Collect. Czech. Chem. Commun., 40, 1089 (1975).
62. S. Lecolier and G. Trouiller, Chim. Ther., 2, No. 1, 16 (1967); Chem. Abstr., 67, 73555 (1967).
63. L. L. Skaletzky, West German Patent No. 2127960 (1971); Chem. Abstr., 76, 59628 (1972).
64. E. H. Pommer, H. Osieka, K. H. Koenig, and G. Bolz, West German Patent No. 2012589 (1971); Chem. Abstr., 76, 25294 (1972).
65. H. Osieka, K. H. Koenig, G. Bolz, and A. Amann, West German Patent No. 2012219 (1971); Chem. Abstr., 76, 3858 (1972).
66. O. Kym and L. Ratner, Ber., 45, 3238 (1912).
67. A. Hunger, J. Kebrle, A. Rossi, and K. Hoffman, Helv. Chim. Acta, 44, 1275 (1961).
68. Yu. M. Yutilov, Master's Dissertation, Rostov-on-Don (1966).
69. É. R. Zakhs, V. I. Minkin, and L. S. Efros, Zh. Org. Khim., 1, 1466 (1965).
70. W. G. Woods, H. Goldsmith, and R. F. Crawford, US Patent No. 3401174 (1968); Chem. Abstr., 69, 106707 (1968).
71. D. R. D. Osborne, British Patent No. 1171904 (1969); Chem. Abstr., 72, 31792 (1970).
72. E. Bellasio, French Patent No. 2209558 (1975); Ref. Zh. Khim., 14O214P (1975).
73. V. J. Baner and S. R. Safir, J. Heterocycl. Chem., 1, 288 (1964).
74. S. Chimetron, French Patent No. 4.761 (1967); Chem. Abstr., 69, 67383 (1968).
75. T. Kodama, A. Takai, M. Nakabayashi, I. Watanabe, H. Sadaki, N. Abe, and A. Kurokawa, Japanese Patent No. 75126682 (1975); Chem. Abstr., 84, 44060 (1976).
76. A. Ricci and P. Vivarelli, Gazz. Chim. Ital., 97, 741 (1967); Chem. Abstr., 67, 64300 (1967).
77. A. Ricci, G. Seconi, and P. Vivarelli, Gazz. Chim. Ital., 99, 542 (1969); Chem. Abstr., 71, 124326 (1969).
78. P. M. Kochergin and V. S. Ponomar', USSR Inventor's Certificate No. 230827 (1968); Byul. Izobr., No. 35, 22 (1968).
79. P. M. Kochergin, B. A. Priimenko, V. S. Ponomar', M. V. Povstyanoi, A. A. Tkachenko, I. A. Mazur, A. N. Krasovskii, E. G. Knysh, and M. I. Yurchenko, Khim. Geterotsikl. Soedin., No. 2, 177 (1969).
80. V. S. Ponomar' and P. M. Kochergin, Khim. Geterotsikl. Soedin., No. 2, 253 (1972).
81. W. H. W. Lunn and R. W. Harper, J. Heterocycl. Chem., 8, 141 (1971).
82. L. Joseph and A. H. Albert, J. Heterocycl. Chem., 3, 107 (1966).
83. G. I. Gofen, Ch. Sh. Kadyrov, and M. N. Kosyakovskaya, Khim. Geterotsikl. Soedin., No. 2, 282 (1971).
84. A. M. Simonov and S. N. Kolodyazhnaya, Khim. Geterotsikl. Soedin., No. 1, 141 (1967).
85. A. J. Hubert and H. Reimlinger, Chem. Ber., 103, 3811 (1970).
86. J. Shiokawa and S. Ohki, Chem. Pharm. Bull. (Tokyo), 21, 981 (1973); Curr. Abst. Chem., 50, Issue No. 507, 206969 (1973).
87. S. Chimetron, French Patent No. 1476568 (1967); Chem. Abstr., 68, 114604 (1968).
88. H. Roechling, E. Frasca, and K. H. Buechel, Z. Naturf., B, 25, 954 (1970).
89. I. Ya. Postovskii, V. P. Mamaev, G. A. Mokrushina, O. A. Zagulyaeva, and M. A. Kosareva, Khim. Geterotsikl. Soedin., No. 7, 978 (1975).
90. D. J. Brown, J. Chem. Soc., No. 5, 1957 (1958).
91. E. Hoggarth, J. Chem. Soc., No. 12, 3311 (1949).
92. S. M. Deshpande and K. Nain, Bull. Chem. Soc. Jpn., 40, 998 (1967); Chem. Abstr., 67, 43740 (1967).
93. A. M. Simonov and V. N. Komissarov, Khim. Geterotsikl. Soedin., No. 6, 826 (1975).
94. A. F. Pozharskii and A. M. Simonov, Chichibabin Amination of Heterocycles [in Russian], Rostovsk. Univ., Rostov-on-Don (1971).
95. P. N. Preston, Chem. Rev., 74, 279 (1974).

96. A. F. Pozharskii, A. M. Simonov, and V. P. Doron'kin, Usp. Khim., 47, 1934 (1978).
97. I. I. Popov, P. V. Tkachenko, A. M. Simonov, A. F. Pozharskii, and Yu. G. Bogachev, Zh. Org. Khim., 10, 1789 (1974).
98. I. I. Popov, Yu. G. Bogachev, P. V. Tkachenko, A. M. Simonov, and B. A. Tertov, Khim. Geterotsikl. Soedin., No. 4, 521 (1976).
99. N. D. Vitkevich and A. M. Simonov, Zh. Obshch. Khim., 29, 2614 (1959).
100. A. M. Simonov, N. D. Vitkevich, and B. M. Martsokha, Zh. Obshch. Khim., 30, 3062 (1960).
101. A. M. Simonov and A. N. Lomakin, Zh. Obshch. Khim., 32, 2228 (1962).
102. A. M. Simonov, A. F. Pozharskii, and V. M. Mar'yanovskii (Marianovskii), Indian J. Chem., 5, 81 (1967).
103. É. A. Zvezdina, Master's Dissertation, Rostov-on-Don (1967).
104. V. V. Bessonov, Master's Dissertation, Rostov-on-Don (1974).
105. A. F. Pozharskii, A. M. Simonov, É. A. Zvezdina, and N. K. Chub, Khim. Geterotsikl. Soedin., No. 5, 889 (1967).
106. B. A. Tertov, V. V. Burykin, and A. V. Koblik, Khim. Geterotsikl. Soedin., No. 11, 1552 (1972).
107. B. A. Tertov, A. V. Koblik, and N. I. Avdyunina, Khim. Geterotsikl. Soedin., No. 9, 1238 (1971).
108. N. I. Sheverdina and K. A. Kocheshkov, Zh. Obshch. Khim., 8, 1825 (1938).
109. A. V. Koblik, Master's Dissertation, Rostov-on-Don (1968).
110. D. B. Murphy, J. Org. Chem., 16, 139 (1951).
111. D. B. Murphy, J. Org. Chem., 29, 1613 (1964).
112. J. Musco and D. B. Murphy, J. Org. Chem., 36, 3469 (1971).
113. A. Widdig and E. Kuehle, West German Patent No. 1932297 (1971); Chem. Abstr., 74, 76426 (1971).
114. V. P. Kukhar', V. I. Pasternak, and G. V. Pesotskaya, Zh. Org. Khim., 9, 39 (1973).
115. R. A. Burrell, J. M. Cox, and E. G. Savins, J. Chem. Soc., Perkin Trans. I, No. 22, 2707 (1973).
116. A. R. Katritzky, Usp. Khim., 41, 700 (1972).
117. Yu. N. Sheinker, A. M. Simonov, Yu. M. Yutilov, V. N. Sheinker, and E. I. Perel'shtein, Zh. Org. Khim., 2, 917 (1966).
118. A. F. Pozharskii, I. S. Kashparov, Yu. P. Andreichikov, A. I. Buryak, A. A. Konstantinchenko, and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 6, 807 (1971).
119. Yu. V. Koshchienko and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 6, 807 (1973).
120. A. F. Pozharskii and A. A. Konstantinchenko, Khim. Geterotsikl. Soedin., No. 3, 363 (1973).
121. H. Quast and E. Schmitt, Chem. Ber., 101, 4012 (1968).
122. V. A. Anisimova, A. M. Simonov, and A. F. Pozharskii, Khim. Geterotsikl. Soedin., No. 6, 797 (1973).
123. H. Ogura, West German Patent No. 2003825 (1970); Chem. Abstr., 74, 53787 (1971).
124. I. I. Popov, P. V. Tkachenko, and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 4, 523 (1975).
125. T. P. Filipskikh, A. F. Pozharskii, V. N. Koroleva, A. M. Simonov, and É. A. Zvezdina, Khim. Geterotsikl. Soedin., No. 6, 809 (1972).
126. R. D. Haugwitz, B. V. Maurer, A. J. Martinez, G. A. Jacobs, and V. L. Narayanon, Synthesis, No. 5, 336 (1976).
127. N. D. Vitkevich and A. M. Simonov, Zh. Obshch. Khim., 30, 2868 (1960).
128. A. M. Simonov and Yu. M. Yutilov, Zh. Obshch. Khim., 32, 2670 (1962).
129. Yu. V. Koshchienko, A. M. Simonov, T. N. Vashchenko, G. M. Suvorova, and V. A. Makarov, Khim.-Farm. Zh., No. 4, 14 (1977).
130. A. M. Simonov and A. F. Pozharskii, Khim. Geterotsikl. Soedin., No. 2, 203 (1965).
131. Yu. M. Yutilov, V. A. Anisimova, and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 3, 416 (1965).
132. A. M. Simonov, T. A. Kuz'menko, and L. G. Nachinennaya, Khim. Geterotsikl. Soedin., No. 10, 1394 (1975).
133. A. M. Simonov, V. A. Anisimova, and L. E. Grushina, Khim. Geterotsikl. Soedin., No. 6, 838 (1970).
134. A. M. Simonov and P. M. Kochergin, Khim. Geterotsikl. Soedin., No. 2, 316 (1965).
135. P. M. Kochergin and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 1, 133 (1967).
136. A. M. Simonov, A. A. Belous, V. A. Anisimova, and S. V. Ivanovskaya, Khim.-Farm. Zh., No. 1, 7 (1969).
137. A. M. Simonov, V. A. Anisimova, and T. A. Borisova, Khim. Geterotsikl. Soedin., No. 1, 111 (1973).
138. P. M. Kochergin, Khim. Geterotsikl. Soedin., No. 1, 137 (1967).
139. A. F. Pozharskii, É. A. Zvezdina, I. S. Kashparov, Yu. P. Andreichikov, V. M. Mar'yanovskii, and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 9, 1230 (1971).

140. I. S. Kashparov, A. F. Pozharskii, V. M. Mar'yanovskii, É. A. Zvezdina, Yu. P. Andreichikov, and A. M. Simonov, USSR Inventor's Certificate No. 330167 (1971); Byul. Izobr., No. 8 (1972).
141. V. I. Sokolov, A. F. Pozharskii, and B. I. Ardashev, Khim. Geterotsikl. Soedin., No. 7, 967 (1973).
142. A. F. Pozharskii, É. A. Zvezdina (Zwesdina), V. I. Sokolov, and I. S. Kashparov, Chem. Ind., No. 6, 256 (1972).
143. É. A. Zvezdina, A. F. Pozharskii, and V. I. Sokolov, Khim. Geterotsikl. Soedin., No. 3, 419 (1970).
144. A. M. Simonov and N. D. Vitkevich, Zh. Obshch. Khim., 30, 590 (1960).
145. P. N. Craig and J. R. E. Hoover, US Patent No. 3336191 (1967); Chem. Abstr., 68, 59585 (1968).
146. B. I. Khristich, A. M. Simonov, and G. M. Suvorova, Khim. Geterotsikl. Soedin., No. 9, 1292 (1973).
147. B. I. Khristich, G. M. Suvorova, and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 10, 1398 (1974).
148. K. H. Mayer, D. Laurer, and H. Hetzer, Synthesis, No. 10, 673 (1975).
149. B. I. Dittmar, US Patent No. 3647817 (1972); Chem. Abstr., 76, 140813 (1972).
150. A. M. Simonov, Yu. V. Koshchienko, G. M. Suvorova, B. A. Tertov, and E. N. Malysheva, Khim. Geterotsikl. Soedin., No. 10, 1391 (1976).
151. M. O. Lozinskii, A. F. Shivanyuk, and P. S. Pel'kis, Khim. Geterotsikl. Soedin., No. 4, 471 (1971).
152. M. O. Lozinskii, A. F. Shivanyuk, and P. S. Pel'kis, Khim. Geterotsikl. Soedin., No. 7, 930 (1971).
153. N. Grier, West German Patent No. 1945452 (1970); Chem. Abstr., 72, 132730 (1970).
154. A. R. Katritzky and F. Jates, J. Chem. Soc., Perkin Trans. I, No. 3, 309 (1976).
155. M. Ridi and S. Checchi, Ann. Chim. (Roma), 44, 28 (1954); Chem. Abstr., 49, 4658 (1955).
156. R. A. Glennon and M. Strandtmann, J. Heterocycl. Chem., 12, 135 (1975).
157. A. F. Pozharskii, É. A. Zvezdina, and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 2, 185 (1967).
158. A. F. Pozharskii, É. A. Zvezdina, and A. M. Simonov, Zh. Org. Khim., 2, 1900 (1966).
159. A. F. Pozharskii, É. A. Zvezdina, and A. M. Simonov, Tetrahedron Lett., No. 23, 2219 (1967).
160. A. F. Pozharskii, É. A. Zvezdina, Yu. P. Andreichikov, A. M. Simonov, V. A. Anisimova, and S. F. Popova, Khim. Geterotsikl. Soedin., No. 9, 1267 (1970).
161. T. P. Filipskikh, A. F. Pozharskii, and É. A. Zvezdina, Khim. Geterotsikl. Soedin., No. 2, 238 (1972).
162. S. N. Kolodyazhnaya and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 1, 186 (1967).
163. S. N. Kolodyazhnaya, A. M. Simonov, Yu. V. Kolodyazhnyi, O. A. Osipov, V. A. Bren', and I. D. Sadekov, Khim. Geterotsikl. Soedin., No. 2, 238 (1970).
164. S. N. Kolodyazhnaya, A. M. Simonov, and L. N. Podladchikova, Khim. Geterotsikl. Soedin., No. 11, 1573 (1974).
165. R. Passerini and L. Pentimalli, Gazz. Chim. Ital., 85, 744 (1955).
166. S. N. Kolodyazhnaya, A. M. Simonov, and I. G. Uryukina, Khim. Geterotsikl. Soedin., No. 12, 1690 (1972).
167. A. M. Simonov and S. N. Kolodyazhnaya, Khim. Geterotsikl. Soedin., No. 3, 543 (1969).
168. S. N. Kolodyazhnaya, A. M. Simonov, N. N. Zheltikova, and A. F. Pozharskii, Khim. Geterotsikl. Soedin., No. 5, 715 (1970).
169. A. M. Simonov and S. N. Kolodyazhnaya, Zh. Org. Khim., 3, 1145 (1967).
170. A. M. Simonov and S. N. Kolodyazhnaya, Khim. Geterotsikl. Soedin., No. 11, 1562 (1970).
171. A. M. Simonov, S. N. Kolodyazhnaya, and L. N. Podladchikova, Khim. Geterotsikl. Soedin., No. 5, 869 (1974).
172. A. E. Chichibabin and M. D. Ryazantsev, Zh. Russ. Fiz.-Khim. O., 47, 1571 (1915).
173. S. N. Kolodyazhnaya, A. M. Simonov, and L. N. Podladchikova, Khim. Geterotsikl. Soedin., No. 6, 829 (1975).
174. A. M. Simonov, S. N. Kolodyazhnaya, and L. N. Divaeva, Summaries of Papers Presented at the Eleventh Mendeleev Conference on General and Applied Chemistry: Organic Chemistry and the Technology of Organic Substances [in Russian], Nauka, Moscow (1974).
175. W. L. Mosby, Heterocyclic Systems with Bridgehead Nitrogen Atoms, Vol. 2, Interscience, New York–London (1961), p. 808.
176. W. H. Lunn, R. W. Harper, and R. L. Stone, J. Med. Chem., 14, 1069 (1971).
177. L. Basaglia and B. Mariani, Ann. Chim. (Roma), 59, 755 (1963).
178. L. B. Dashkevich and É. S. Korbelainen, Khim. Geterotsikl. Soedin., No. 4, 602 (1966).
179. G. M. Golubushkina and V. O. Chuiguk, Ukr. Khim. Zh., 37, 1132 (1971).
180. É. A. Zvezdina, M. P. Zhdanova, A. M. Simonov, and G. N. Dorofeenko, Khim. Geterotsikl. Soedin., No. 9, 1180 (1975).

181. É. A. Zvezdina, M. P. Zhdanova, V. A. Bren', and G. N. Dorofeenko, Khim. Geterotsikl. Soedin., No. 11, 1461 (1974).
182. H. Reimlinger, M. A. Peiren, and R. Merény, Chem. Ber., 105, 794 (1972).
183. H. Ogura, M. Kavana, and T. Itoh, Chem. Pharm. Bull. (Tokyo), 21, 2019 (1973); Curr. Abst. Chem., 51, Issue No. 521, 210589 (1974).
184. D. W. Dunwell and D. Evans, J. Chem. Soc., Perkin Trans. I, No. 15, 1588 (1973).
185. A. W. Show, US Patent No. 3468888 (1969); Chem. Abstr., 72, 3489 (1970).
186. A. W. Show, D. R. Jakas, B. P. Trotter, N. M. Hall, and J. R. E. Hoover, J. Heterocycl. Chem., 10, 71 (1973).
187. H. Alper and L. Pepper, Can. J. Chem., 53, 894 (1975).
188. L. Capuano and H. J. Schrepfer, Chem. Ber., 104, 3039 (1971).
189. M. Augustin and K. R. Kuppe, Tetrahedron, 30, 3533 (1974).
190. N. J. Leonard, D. Y. Curtin, and K. M. Beck, J. Am. Chem. Soc., 69, 2459 (1947).
191. S. N. Kolodyazhnaya and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 4, 714 (1969).
192. A. M. Simonov, Yu. M. Yutilov, and V. A. Anisimova, Khim. Geterotsikl. Soedin., No. 6, 913 (1965).
193. V. G. Sayapin, Master's Dissertation, Rostov-on-Don (1969).
194. L. S. Éfros, B. A. Porai-Koshits, and S. G. Farbenshtein, Zh. Obshch. Khim., 23, 1691 (1953).

SYNTHESIS AND STEREOCHEMISTRY OF 2,2-DIMETHYL-5-ARYL-4-BENZOYL-1,3-DIOXOLANES

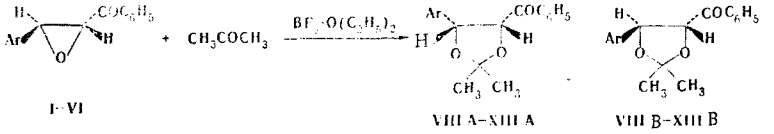
O. N. Bubel', I. G. Tishchenko,
G. Z. Stasevich, I. L. Romanko,
A. F. Abramov, and E. D. Skakovskii

UDC 547.729.7.07:541.634

The reaction of 3-aryl-2-benzoyloxiranes with acetone in the presence of catalytic amounts of boron trifluoride etherate leads to the formation of mixtures of cis and trans isomers (~30:70) of 2,2-dimethyl-5-aryl-4-benzoyl-1,3-dioxolanes, the structures and stereochemistry of which were established on the basis of data from their PMR spectra, measurement of the Overhauser nuclear effect, and some chemical transformations.

Acetyloxiranes of the aliphatic series react with ketones in the presence of boron trifluoride etherate with inversion of the configuration of the oxirane carbon atom that undergoes attack, and this leads to the formation of cis-1,3-dioxolanes [1, 2]. At the same time, the reaction of trans-2-acetyl-3-phenyloxirane with acetone in the presence of boron trifluoride etherate gives a mixture (35:65) of cis- and trans-2,2-dimethyl-5-phenyl-4-acetyl-1,3-dioxolanes [2], whereas trans- and cis-2-methyl-3-phenyloxiranes react with acetone in the presence of anhydrous copper sulfate to give a mixture (35:65) of the corresponding cis- and trans-dioxolanes; the latter do not undergo interconversion under the given conditions [3].

In the present research we studied the reaction of a number of trans-3-aryl-2-benzoyloxiranes (I-VI) with acetone in the presence of catalytic amounts of boron trifluoride etherate. In all cases we obtained mixtures of cis- and trans-5-aryl-4-benzoyl-1,3-dioxolanes (VIII-XIII) (Table 1), the ratios of which were



I-VI VIII A-XIII A VIII B-XIII B

VIII Ar = C_6H_5; IX Ar = 4-$CH_3C_6H_4$; X Ar = 3-$CH_3C_6H_4$; XI Ar = 4-ClC_6H_4; XII Ar = 3-ClC_6H_4; XIII Ar = 4-$CH_3OC_6H_4$

V. I. Lenin Belorussian State University, Minsk 220080. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 888-891, July, 1979. Original article submitted October 30, 1978.

0009-3122/79/1507-0723$07.50