RESEARCH ON THE CHEMISTRY OF HETEROCYCLES AT ROSTOV STATE UNIVERSITY (REVIEW)

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A summary of the research on the chemistry of heterocyclic compounds conducted at Rostov State University is given. The results of research on the chemistry of azoles conducted in Rostov from 1957 to 1982 are presented. The data obtained relative to the chemistry of benzimidazole and other condensed azole systems (imidazo-[1,2-a]benzimidazole and indazole) and the chemistry of 2-diazo- and 2-azobenzimidazoles, unsaturated compounds in the azole series, and organometallic derivatives of azoles are examined.

Brief Summary of Research on the Chemistry of Heterocycles in Rostov-on-Don*

Research on the chemistry of heterocycles in Rostov-on-Don was begun at the end of the nineteen fifties. Two principal directions were created: One was created by Professor G. N. Dorofeenko in the department of chemistry of natural compounds (pyrylium salts and other heterocyclic compounds), and the other was created by Professor A. M. Simonov in the department of organic chemistry (nitrogen heterocycles, primarily azoles). After the organization in 1971 of the Scientific-Research Institute of Physical and Organic Chemistry at Rostov State University, these studies were also carried out in its divisions. At the present time the indicated scientific directions are under the supervision of their students: Professor A. F. Pozharskii and B. A. Tertov (the chemistry of nitrogen heterocycles) and V. V. Mezheritskii (heterocyclic cations). Research on the chemistry of furan has also been under way for a number of years (Associate Professor Z. N. Nazarova).

Nitrogen Heterocycles. The principal research on nitrogen heterocycles has been accomplished in the area of the chemistry of condensed imidazole systems, as well as indazole and pyrazole. The most important results in the chemistry of azoles are more fully illuminated in the present review.

A new actively developing area in the chemistry of heterocycles is the chemistry of peri-condensed heteroaromatic systems. Research on the chemistry of perimidine and condensed systems based on it has been in progress in the department of organic chemistry of Rostov State University since 1968. Perimidines have unique chemical amphoteric character inasmuch as they react both with nucleophiles and with electrophiles at the level of the most active π-deficient and π-surplus heterocycles. A series of fundamentally new (for the chemistry of heteroaromatic systems) reactions of perimidines with nucleophiles was discovered. General methods for the synthesis of previously difficult-to-obtain N-substituted 1,8-naphthalenediamines were proposed on the basis of developments in the chemistry of perimidine. 1H-1,2-Diazaphenalenes, which are isomers of perimidines, were synthesized by the reaction of 1-hydroxy-8-acylnaphthalenes with hydrazines. These compounds have even stronger π-donor properties than perimidines, as well as very high activities with respect to electrophiles.

Pyrylium Salts and Other Oxygen-Containing Cations. Fundamental research on the synthesis, study of the structures, and properties of pyrylium cations and other heterocyclic cations has also been conducted in Rostov.

The subjects of the detailed and in-depth research were acid-catalyzed (primarily by perchloric acid) reactions involving the acylation of carbonyl compounds and their derivatives. Among the results obtained we should single out the synthesis of pyrylium salts by acylation of olefins, ketones, and tertiary alcohols; a new method for the construction of annelated heteroaromatic 2-benzopyrylium cations by acylation of aliphatic-aromatic ketones activated by electron-donor substituents; maximally simple methods for the formation of stable nonaromatic 1,3-dioxolanium cations by acylation of 1,2-glycols, as well as 4(5H)-oxazolonium and

*The summary was prepared by A. F. Pozharskii, V. V. Mezheritskii, and É. A. Zvezdina.

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4-oxo-1,3-oxazinium cations and their benzo analogs by acylation of amides and nitriles of α-hydroxy, β-keto, and aromatic o-hydroxy acids.

A general approach to the construction of the pyrylium ring based on the three-component condensation of methyl(ene) ketones with compounds that furnish one carbon atom in the composition of the heteroring was developed.

Also developed were synthetic methods based on the recyclization of pyrylium salts, as a result of which difficult-to-obtain pyridines and isoquinolines — analogs of natural alkaloids, tetrahydroquinolines, β-carbolines, steroidopyridines, ferrocenyl-, carboranyl-, and heterylpyridines, pyridines condensed with heterorings, as well as a large number of pyridinium salts — were obtained.

A group of new reactions involving the recyclization of pyrylium salts under the influence of hydrazine, amidines, guanidines, S-substituted isothioureas, 2-aminobenzimidazoles, 2-aminobenzothiazoles, semi- and thiosemicarbazides, arylhydroxylamines, and aldonitrones was discovered. These reactions proceed both with retention of the size of the ring and with contraction and expansion of the ring and open up a route to the synthesis of biologically active pyrazoles, pyrimidines, pyrimido[1,2-a]benzimidazolium salts and their sulfur analogs, pyrazolo[1,5-c]pyrimidines, and new seven-membered cations with eight π electrons, viz., 3,5,7-triaryl-1,2-oxazepinium salts. Pyrylium salts with a free 2 or 4 position undergo pyrylation of electron-surplus compounds, and 2- or 4-substituted pyrylium salts are obtained as a result of the pyrylation of di-N-substituted anilines, azulenes, azomethines, pyrroles, indoles, pyrazoles, lithium-substituted heterocycles, lithium phenylacetylide, and triphenylphosphine.

Pyranyl radicals were obtained for the first time by one-electron reduction of pyrylium salts with powdered metals, and some of their transformations were studied.

The number of styryl derivatives of pyrylium and isobenzofurylium ions has been increased substantially. They were used to produce difficult-to-obtain styrylpyridines and styryliso-quinolines, as well as photochromic spiropyrans that contain dihydropyran, oxepine, and oxacine rings annelated with aromatic fragments.

The possibility of the extensive use of 1,3-dioxolanium salts as universal starting substances for the syntheses of aldehydes, ketones, and carboxylic acids was demonstrated. 4(5H)-Oxazolonium and 4-oxo-1,3-oxazinium salts and their benzo analogs undergo recrystallization reactions, which opens up a route to o-hydroxyphenyl- and hydroxyalkyl-substituted triazines, triazoles, and oxadiazoles, as well as dihydropyrimidones and their salts, which have high pharmacological activity.

The data presented above demonstrate the promising character of heterocyclic cations as synthetic reagents in organic chemistry.

Sulfur- and Tellurium-Containing Heterocyclic Compounds. A large number of tautomeric systems of the benzo[b]thiophene, benzo[b]furan, and oxindole series, which were synthesized by means of original methods, were investigated. The principles discovered made it possible to formulate a rule for evaluating the position of benzenoid-quinoid equilibria in prototropic systems and their organometallic derivatives.

New heterocyclic compounds, viz., telluraxanthene and phenotellurazine derivatives, were synthesized, and their structures and reactivities were investigated. The first representatives of heteroaromatic cations that contain tellurium in a six-membered ring, viz., 10-telluroniaanthracene perchlorates, were obtained by the reaction of telluraxanthen-9-ols with perchloric acid or telluraxanthenes with trityl perchlorate.

C-Hetaryl Derivatives of Carbohydrates. The discovery of C-glycosyl derivatives of heterocycles in numerous natural substances and their significant biological activity have stimulated the synthesis of C-hetaryl-substituted sugars, which has become one of the research directions of the Rostov school of chemists headed by Professor Yu. A. Zhdanov. Methods for the glycosylation of heterocyclic compounds, among which the most fruitful have been found to be organometallic synthesis, the Wittig reaction, variants of the condensation of the al form of sugars with methylene-active heterocycles, and glycosylation by means of carbohydrate keto carbenes, have been developed. Carbohydrate residues have been introduced into furan, thiophene, pyrrole, indole, pyridine, quinoline, indolopyrylium, β-carboline, and other molecules by means of these methods.

Other research. The research of the schools cited above have also affected the subject matter of other scientific collectives in Rostov-on-Don. Thus research on complexes of azoles

with salts of transition and nontransition metals, as well as with H donors, has been under way for many years under the supervision of Professors O. A. Osipov and A. D. Garnovskii, and the conformations of azoles with carbonyl-containing substituents have been under investigation. Research on the application of quantum-chemical and physical methods to the problems of the chemistry of heterocycles is being conducted under the supervision of Professor V. I. Minkin, who, together with Associate Professor M. I. Knyazhanskii, is also investigating the photochemistry of spiropyrans, pyridinium salts, and other heterocyclic systems. Professor O. Yu. Okhlobystin has studied the mechanisms of dehydrogenation of dihydro derivatives of heterocyclic compounds and has shown that they may proceed via a one-electron stepwise mechanism.

Research on the Chemistry of Azoles

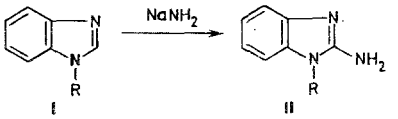
Azoles constitute an important class of heterocyclic compounds that are of interest in a theoretical respect and are of practical value in many cases.

Research on the chemistry of these peculiar heterocycles has been in progress since 1957 in the department of organic chemistry of Rostov State University and in the group of organic synthesis of the Scientific-Research Institute of Physical and Organic Chemistry. The results of this research have often been examined in reviews [1-5], and the results of further observations in this area are primarily described in the present paper.

Comprehensive studies of the chemistry of perimidine — a system that is close to the imidazole system — have been reflected in a review paper [6].

Research on the Chemistry of Benzimidazole

Compounds that contain benzimidazole rings have recently been the subject of extensive study as possible medicinals, pesticides, monomers, and dyes. The Chichibabin amination of N-substituted benzimidazoles is a relatively new transformation [3]:



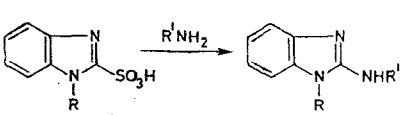
I II

R = alkyl, aralkyl, aryl, etc.

The benzimidazole ring undergoes this reaction more readily than the pyridine ring [7]; however, amination is possible only under the condition that the hydrogen atom in the NH group is replaced, and the imidazole ring is condensed in the 4,5 position with an aromatic system: N-Alkylimidazole and N-alkyl-4,5,6,7-tetrahydrobenzimidazole do not undergo the reaction. The mechanism of this transformation has been examined in detail [5]. An attempt to study the kinetics of the reaction by determining the rate of hydrogen and ammonia evolution has been made [8].

Of substantial interest is the observation that 2-alkyl(aryl)benzimidazoles also undergo nucleophilic substitution to give 2-amino derivatives under the influence of sodium amide [9].

The effect of the nature of the substituents in the benzene ring [2, 5] and the structure of the alkyl groups in the 1 position [10] on the reaction has also been studied. The presence of electrophilic substituents in the ring hinders the transformation. As a consequence of these limitations, and taking into account the explosiveness of sodium amide, one may carry out the synthesis of 2-aminobenzimidazoles by replacing a sulfo group in the 2 position by an amino group by the action of ammonia, as well as amines [11]:

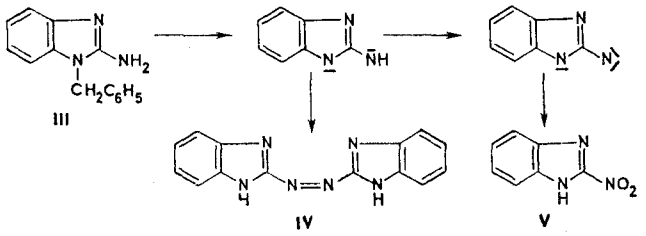


R = H, CH_3; R' = H, $CH_2C_6H_5$, C_6H_5, C_2H_4OH

2-Aminobenzimidazoles are valuable starting compounds for a number of syntheses (see below).

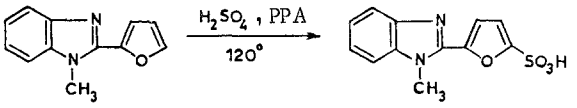
A new oxidative transformation of 2-amino-1-benzylbenzimidazole (III) and its analogs has been studied in detail. The addition of 3-4 moles of sodium to a solution of III in

liquid ammonia gives the di- and trianion of 2-aminobenzimidazole, which, after evaporation of the ammonia, are oxidized by air oxygen to 2,2'-azo- (IV) and 2-nitro-benzimidazole ["benzazomycin" (V)]. These compounds are obtained only in low yields from 2-aminobenzimidazole, i.e., in the absence of the benzyl anion [12].



III IV V

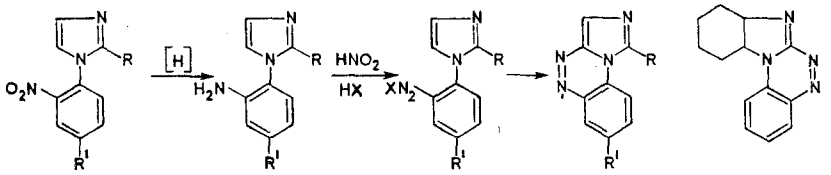
The 2-benzimidazole radical has clearly expressed electrophilic character, which is intensified upon protonation, and stabilizes the hetaryne ring connected to it in the 2 position. This makes it possible to carry out electrophilic substitution (nitration, sulfonation, chloromethylation, and acylation) in this ring under extremely severe conditions (such as those in [13, 14]):



The ease of conversion of the cation formed in the decomposition of 2-diazomethylbenzimidazole to 2-halomethyl- and 2-nitromethyl benzimidazole, which is subsequently converted to a nitrolic acid [15], is evidently associated with this property of the benzimidazole ring.

Synthesis of Condensed Three-Ring Imidazole Systems

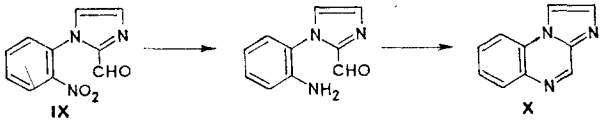
Methods have been developed for the synthesis of three-ring systems from N-arylimidazoles by crosslinking the imidazole and benzene rings by means of a link from two atoms. For this purpose, N-(2-nitroaryl)imidazoles VI, which were synthesized by direct arylation of imidazole, are converted to 2-amino derivatives and subsequently to diazonium salts; the latter undergo intramolecular diazo coupling upon neutralization of the acidic solution. Although imidazole usually does not couple in the form of a neutral molecule, in this case the process turns out to be energically favorable owing to the development of a new aromatic system. Substitution takes place in the 5 position of the imidazole ring, in which the electron density, according to the results of calculations, is higher than in the 2 position. This method was used to obtain imidazo[5,1-c]-1,2,4-benzotriazine and its derivatives (VII); the ring is formed at the 2 position (VIII) only when the 5 position is occupied [16].



VI VII VIII

VI–VII a R=R'=H; b R=CH$_3$, R'=H; c R=H, R'=CH$_3$O; d R=H, R'=NO$_2$

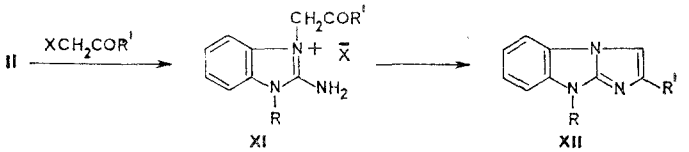
Another condensed system — imidazo[1,2-a]quinoxaline — was obtained by a similar method, viz., by annelation of the pyrazine ring to the imidazole ring. The reduction of 1-(o-nitrophenyl)-2-formylimidazole (IX), obtained by oxidation of the 2-hydroxymethyl derivative [17], by means of sodium dithionite in the presence of ammonia leads to the o-aminophenyl derivative, which during its formation undergoes cyclization to give X [18]; the bisulfite compound of the amino aldehyde and, from its aldimine, the 4-amino derivatives are also obtained [19]:



IX X

7-Methyl-, 7-methoxy-, and 7-bromo-substituted imidazo[1,2-a]quinoxalines were synthesized by the same method [20].

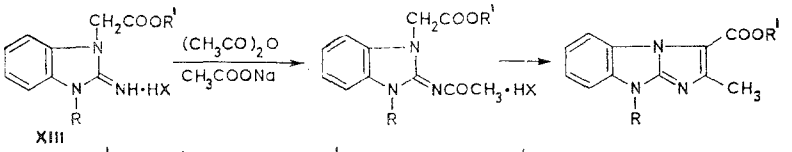
2-Amino-1-alkyl(aralkyl)benzimidazoles (II) have been used as the starting compounds for the synthesis of the extremely important three-ring imidazo[1,2-a]benzimidazole system. Their reaction with α-halo ketones leads to benzimidazolium salts XI, which upon heating with mineral acids undergo cyclization to give 2,9-substituted imidazo[1,2-a]benzimidazoles (XII) [21].



XI XII

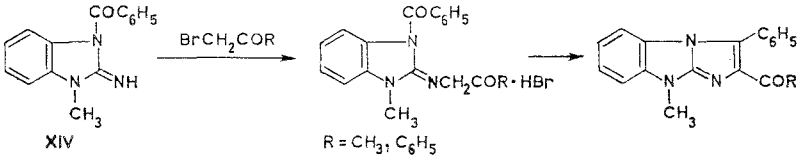
R = CH_3, C_6H_5, $CH_2CH_2N(C_2H_5)_2$, etc.; R' = CH_3, C_6H_5, etc.

Chloroacetic acid anilides react in the same way as α-halo ketones to give 2-amino-substituted XII [R' = NH(Alk)Ar] [22]. 2-Iminobenzimidazoline derivatives such as XIII [23] and XIV [24] were subsequently used for the synthesis of this imidazole system.



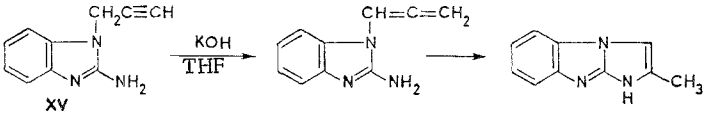
XIII

XIII a R = R' = CH_3; b R = $C_6H_5CH_2$, R' = CH_3; c R = CH_3, R' = C_7H_{15}

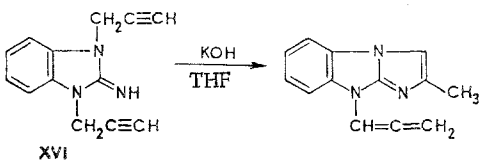


XIV R = CH_3, C_6H_5

It was found that it was also possible to synthesize 2- and 2,9-substituted imidazo[1,2-a]benzimidazoles by cyclization of unsaturated compounds of the imidazole series, viz., 2-amino-1-(2-propynyl)benzimidazole (XV) and 1,3-di(2-propynyl)-2-iminobenzimidazoline (XVI). The reaction proceeds through prior isomerization of the propynyl grouping to a propadienyl grouping [25]:

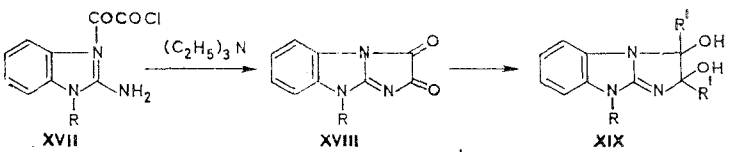


XV



XVI

Methods for the preparation of some 2,3-dihydroimidazo[1,2-a]benzimidazoles have been developed. As in the case of other acyl chlorides [26], the reaction of oxalyl chloride with 2-amino-1-alkyl(aralkyl)benzimidazoles leads to 1-chlorooxalyl-2-aminobenzimidazolium salts (XVII), which upon heating with triethylamine are converted to 2,3-dioxo- and 2,3-dihydroimidazo[1,2-a]benzimidazoles XVIII. 2,3-Dihydroxy derivatives XIX are obtained by their reduction with lithium aluminum hydride or by reaction with ethylmagnesium bromide [27].

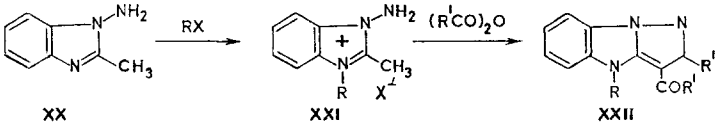


XVII XVIII XIX

XVII R = CH_3, C_2H_5, $C_6H_5CH_2$; XIX R = $C_6H_5CH_2$, R' = H, C_2H_5

1-Aminobenzimidazoles XX and XXIII, which are readily obtained by amination of benzimidazole and C-substituted benzimidazoles with hydroxylamine O-sulfonic acid, have been proposed

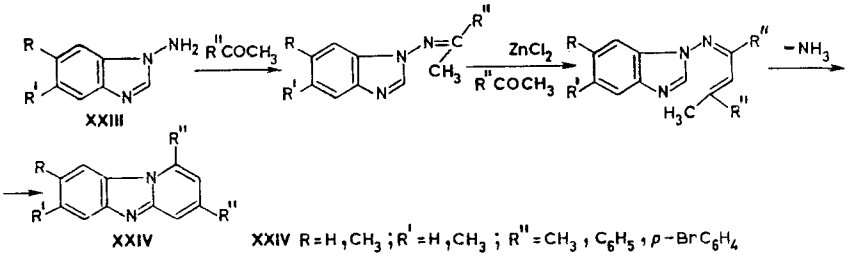
as extremely promising starting substances for the synthesis of imidazole condensed systems. Thus 2-substituted 4-alkyl-3-acylpyrazolo[1,5-a]benzimidazoles (XXII) have been synthesized by the action of carboxylic acid anhydrides on 1-amino-2-methylbenzimidazolium salts (XXI) [28].



XX XXI XXII

XXII R = CH_3, C_2H_5, C_3H_7 ; R' = CH_3, C_2H_5, C_6H_5

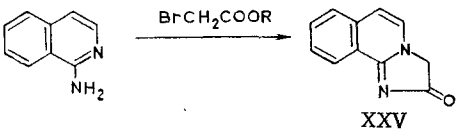
1,3-Disubstituted pyrido[1,2-a]benzimidazoles (XXIV) are formed unexpectedly in the reaction of 1-aminobenzimidazoles with cations under the conditions of the Fischer reaction via a complex transformation [29].



XXIII XXIV

XXIV R = H, CH_3; R' = H, CH_3 ; R'' = CH_3, C_6H_5, p-BrC_6H_4

2-Oxo-2,3-dihydroimidazo[2,1-a]isoquinoline (XXV) was synthesized on the basis of 1-aminoisoquinoline and α-haloacetic acid esters [30].



XXV

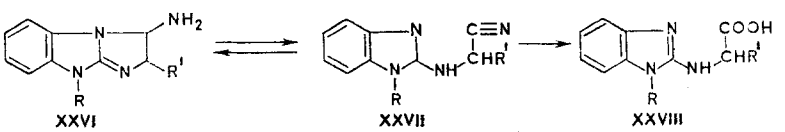
Properties and Transformations of Imidazo[1,2-a]benzimidazole Derivatives

Many derivatives of this heterocyclic system are distinguished by high biological activity of practical value [31-33], and their chemical properties are sometimes peculiar. A great deal of attention has therefore been directed to the study of compounds of this class.

Whereas in the case of 9-alkyl-substituted compounds electrophilic substitution reactions (bromination [34], nitrosation and diazo coupling [35], Vilsmeier formylation [36], C acylation [37], and nitration [38]) proceed extremely readily and primarily in the 3 position, in agreement with the results of calculations of the electron densities in the molecules [39], the 1-alkyl-substituted compounds, in which the electron density in the 3 position is decreased, do not undergo electrophilic substitution reactions under similar conditions (with the exception of bromination, as well as hydroxymethylation).

The resulting imidazo[1,2-a]benzimidazole derivatives have been subjected to further transformations.

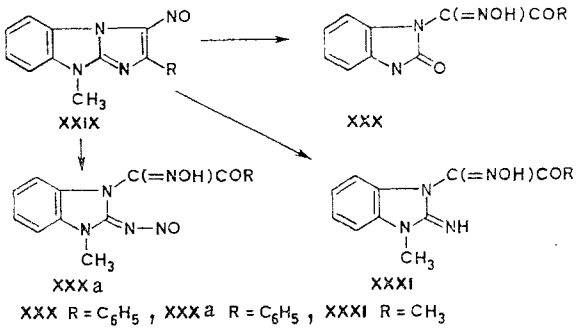
Amines XXVI, which are formed in the reduction of the nitro or nitroso compounds, may, during their production, open up the outer imidazole ring [40]. They are tautomeric compounds that react with ring opening in the nitrile form (XXVII) (hydrolysis to carboxylic acid XXVIII) or in the amino form (with benzaldehyde and acetic anhydride) [41].



XXVI XXVII XXVIII

Opening of the outer imidazole ring of imidazo[1,2-a]benzimidazole occurs readily if other electrophilic groups are bonded to it. The imidazole ring of 1-methyl-3-nitroso-2-phenylimidazo[1,2-a]benzimidazole (XXIX, R = C_6H_5) opens under the influence of alkali or acid [35]. Nitroso derivatives XXIX (R = CH_3) could not be isolated at all, since the ring-

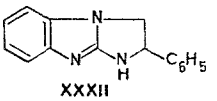
opening product, viz., 2-imino-3-oximinoacetonylbenzimidazoline (XXXI), is formed immediately during nitrosation. N-Nitrosoimine XXXa is obtained in glacial acetic acid in the presence of excess nitrous acid [42].



XXIX XXX XXXa XXXI

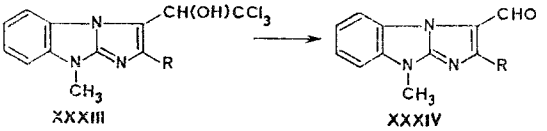
XXX R = C_6H_5, XXXa R = C_6H_5, XXXI R = CH_3

The lower aromatic character of the outer imidazole ring as compared with the other rings of the system is also manifested in the ease of its hydrogenation: The debenzylation of the 9-benzyl-2-phenyl-substituted compound with sodium in liquid ammonia gives, in addition to 2-phenylimidazo[1,2-a]benzimidazole, significant amounts of its 2,3-dihydro derivatives XXXII [43]; when excess sodium is present, its yield reaches 90%.



XXXII

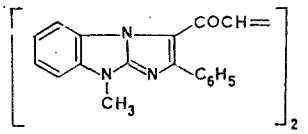
The reaction of 2-methyl(phenyl)-9-methylimidazo[1,2-a]benzimidazole with aldehydes and the transformations of the compounds obtained have been studied [44]. The reaction with chloral is particularly promising [45]. The resulting trichloroethanols XXXIII are converted by the action of bases to aldehydes XXXIV. Thus chloral acts here as a convenient formylating agent. It can also be used for this purpose in a number of other bridged systems.



XXXIII XXXIV

R = CH_3, C_6H_5, naphthyl

The haloform reaction proceeds peculiarly in the imidazo[1,2-a]benzimidazole series: An unsaturated diketone with the following structure is formed instead of the 3-carboxylic acid from the 3-acetyl-9-methyl-2-phenyl derivative:



Trichloro ketones were therefore obtained by acylation of the heteroring with trichloroacetyl chloride and were subsequently converted to esters by the action of sodium methoxide [46].

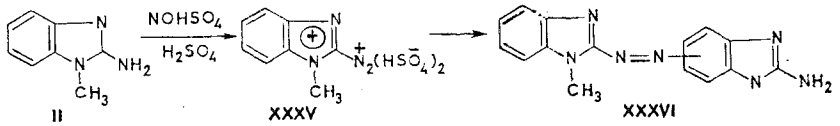
Synthesis and Transformations of 2-Diazo- and 2-Azobenzimidazoles

Compounds of this class have been subjected to detailed study in connection with their peculiar properties and the possibility of practical application.

Virtually no diazotization of 2-aminobenzimidazoles occurs in dilute aqueous solutions of mineral acids, and diazo compounds are formed only in concentrated acids. The properties of the diazobenzimidazoles of this series differ from those of diazo compounds of other azoles. Thus the existence of two types of benzimidazole-2-diazonium salts that differ markedly in activity has been established [47].

Highly active and very unstable diazonium salts XXXV are formed in a mixture of concentrated sulfuric and phosphoric acids (1:1) by the action of nitrosylsulfuric acid on 2-amino-

1-alkylbenzimidazoles. If the 5 and 6 positions in the amine are not substituted, the diazonium salt immediately undergoes self-coupling to give a mixture of 2,5'- and 2,6'-azobenzimidazoles (XXXVI) [48].

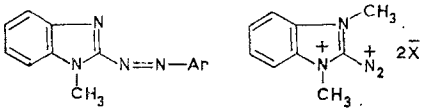


II XXXV XXXVI

Diazonium salts obtained from 2-amino-1-arylbenzimidazoles (XXXVII) in concentrated phosphoric acid undergo primarily intramolecular diazo coupling to give XXXVIII [4].

XXXVII XXXVIII

If the 5 and 6 positions in the benzene ring are substituted by, for example, methyl groups and an azo component such as an arene is previously introduced into the solution, diazo coupling to give arylazobenzimidazoles XXIX takes place after reaction with nitrosylsulfuric acid [49]. Thus benzene (30% yield), toluene (42% yield), and isomeric xylenes were subjected to diazo coupling for the first time [50]*:



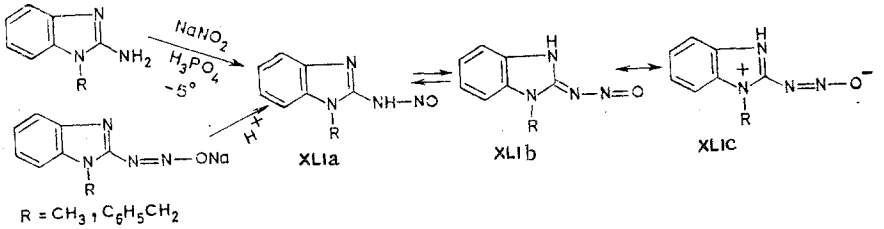
XXXIX XL

Ar = C_6H_5, $CH_3C_6H_4$, $(CH_3)_2C_6H_3$

The reason for the high activity of diazonium salts of this type is protonation of the imidazole ring (the formation of a diazonium dication), which sharply increases the electrophilicity of the grouping bonded to the diazo group.† The observation that a salt with a similar structure (XL), obtained from 1,3-dimethyl-2-iminobenzimidazoline, couples with toluene to give an azo compound, although in low yield (23%), serves as a confirmation of this point of view [51].

Less active unprotonated benzimidazole-2-diazonium salts are obtained by diazotization of the amine in concentrated phosphoric acid by the introduction of sodium nitrite. Diazonium salts of this type can also be synthesized by the action of boron tribromide etherate on primary 2-(N-nitrosamino)benzimidazoles (XLI). They do not react with the simplest arenes but couple readily with ethers of phenols and tertiary aromatic amines to give azo compounds in high yields [52].

If sodium nitrite is added to a solution of 2-amino-1-alkylbenzimidazole in 60% phosphoric acid at −5°C, N-nitrosamines (XLI) rather than diazonium salts are formed [53]; they can also be obtained from benzimidazole-2-diazotates [54].



XLIa XLIb XLIc

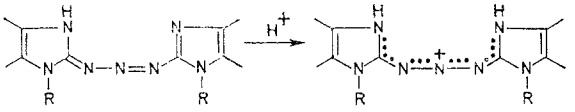
R = CH_3, $C_6H_5CH_2$

*It was recently established that to obtain arylazobenzimidazoles from toluene and xylenes one can also use the benzene ring-unsubstituted and more accessible 2-amino-1-alkylbenzimidazole if the amount of sulfuric acid in the mixture with phosphoric acid is decreased to a ratio of 1:5.

†In agreement with this, the diazonium salt formed in sulfuric acid solution by the action of nitrosylsulfuric acid on 2-amino-4,5-diphenylimidazole is also quite active — it couples with toluene in 18% yield [86].

A distinctive property of primary nitrosoamines in this series is their high stability in acidic solutions and in the dry state. It is evidently due to their existence in the nitrosimine form; the latter is polarized to a certain extent (XXXIc). The ease of conversion of 2-(N-nitrosamine)benzimidazoles to symmetrical diazo amino compounds is also characteristic. The reaction proceeds, for example, in alcohol solution in the presence of catalytic amounts of sulfuric acid. An N-nitrosotriazene is formed intermediately from a nitrosamine and a diazonium cation [55].

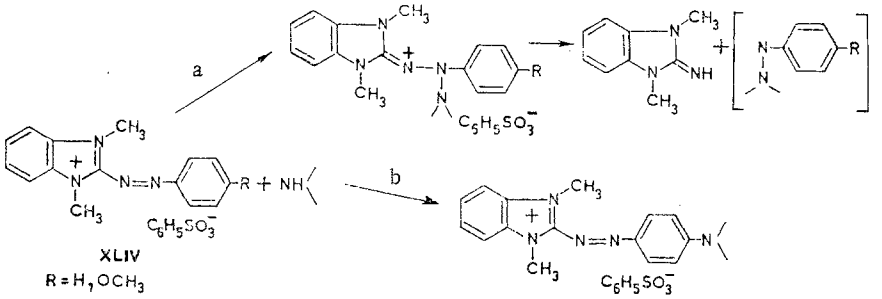
Triazenes of the benzimidazole series, which, according to spectral data, exist in the XLII form, are, in contrast to the triazenes of other azoles, resistant to the action of acids. This property is probably associated with the possibility of complete delocalization of the charge in protonated form XLIII.



XLII XLIII

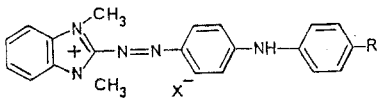
Under the influence of methyl benzenesulfonate 2-arylazo-1-methylbenzimidazoles are converted to quaternary salts XLIV, which have peculiar properties: They can react with amines via two pathways. In contrast to the azo derivatives of other heterocycles (pyridine and benzothiazole), reductive cleavage at the azo group occurs under the influence of excess alkyl- and dialkylamines and secondary cyclic amines (for example, piperidine) on the quaternization products (XLIV) [56]; the reaction takes place under mild conditions, viz., at room temperature, but with a greater than threefold excess of the amine. More severe conditions are necessary when donor groups are present in the molecule.

Under the influence of amines, including aromatic amines, quaternary salts of arylazobenzimidazoles under very mild conditions undergo nucleophilic substitution of the hydrogen atom in the para position relative to the azo group by an amino group [57, 58]. The effect of various factors, viz., the basicity and nature of the amine, the temperature, the reaction time, and the structure of the arene part of the salt molecule, on the process has been studied [58]. It was established that the three-dimensional structures of the reacting substances affect the course of substitution under the influence of alkyl- and dialkylamines; steric factors play a secondary role when aromatic amines are used, and the fractional positive charge in the para position relative to the azo group proves to be more important.



XLIV
R = H, OCH_3

If there is a methoxy group in this position, it is replaced smoothly by an amino group by the action of amines [59]. Azo compounds (XLV) that contain a diphenylamine fragment are formed in the reaction with arylamines.* They color nitron fiber in deep violet and blue tones, and the color is fast to light and to wet treatment. These substances are of great interest as cationic dyes.



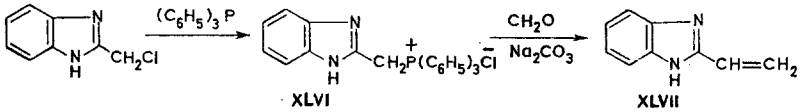
XLV

Some of the azo compounds of the benzimidazole series have been proposed as analytical reagents for cobalt, copper, and mercury ions [60].

*The diazo coupling of benzimidazole-2-diazonium salts with diphenylamine and its derivatives with an unsubstituted NH group does not give satisfactory results.

Synthesis and Properties of Unsaturated Compounds in the Azole Series

The Wittig reaction has been successfully used to obtain unsaturated compounds in this series. Thus, 2-chloromethylbenzimidazole is converted by the action of triphenylphosphine to phosphonium salt XLVI, and 2-vinylbenzimidazole (XLVII) is obtained from it by the action of formaldehyde and sodium carbonate [61].

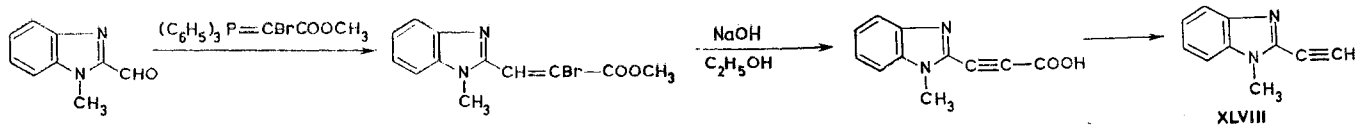


XLVI XLVII

5-Substituted 2-vinyl-1-methylbenzimidazoles were similarly synthesized [62].

Acetylenic derivatives of azoles are of considerable interest.

(1-Methyl-2-benzimidazolyl)propiolic acid was obtained from 1-methyl-2-formylbenzimidazole by means of the Wittig reaction, and 1-methyl-2-ethynylbenzimidazole (XLVIII) was obtained by decarboxylation of this acid [63].

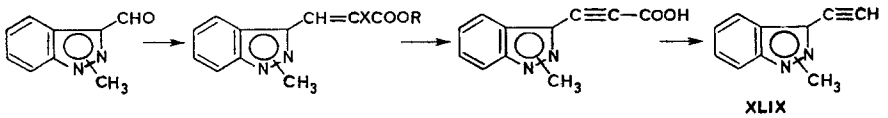


XLVIII

Several other 2-ethynylbenzimidazoles have been synthesized by the same method [64].

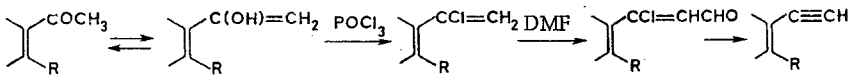
The use of the more accessible 2-(chloromethyl)benzimidazole in place of 2-formyl-1-methylbenzimidazole as the starting compound in the Wittig reaction makes it possible to simplfy the synthesis [65].

Similar transformations in the indazole series led to the production of 1- and 2-methyl-3-ethynylindazole (XLIX) [66]:

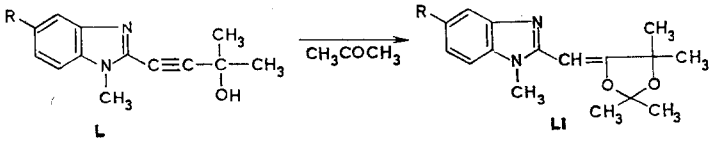


XLIX

Another method has been used to obtain 2,9-substituted 3-ethynylimidazo[1,2-a]benzimidazoles [67]:



Azolylacetylenes are extremely reactive compounds. Thus 1-methyl-2-ethynylbenzimidazoles react with acetone and methyl ethyl ketone at −5°C in the presence of potassium hydroxide via the Favorskii reaction to give tertiary alcohol L; at a somewhat higher temperature (20°C) the reaction product reacts with a second molecule of the ketone and is converted to 1,3-dioxolane LI [68].

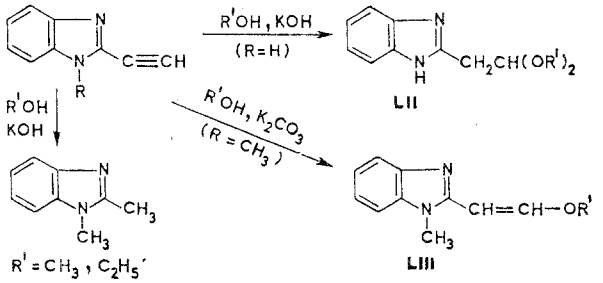


L LI

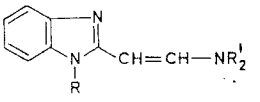
The reaction of 2-ethynylbenzimidazoles with alcohols proceeds in different ways, depending on whether or not the hydrogen atom in the NH group of the imidazole ring is substituted. When the NH group is unsubstituted, 2-(2,2-dialkoxyethyl)benzimidazoles LII are formed by the action of an alcohol solution of potassium hydroxide at the boiling point as a result of the addition of two molecules of alcohol.

N-Methyl-substituted compounds under these conditions are converted to 1,2-dimethylbenzimidazole, evidently as a consequence of cleavage of the initially formed vinyl ether LIII.

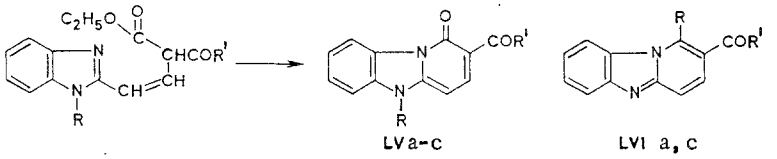
The latter can be obtained if the process is carried out for a long time in the presence of potassium carbonate or in liquid ammonia [69, 70].



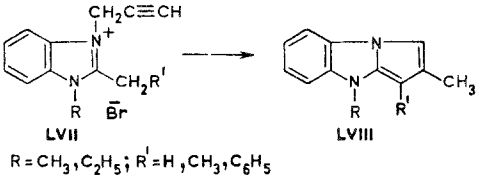
Ethynylbenzimidazoles react identically with secondary amines (dialkylamines and piperidine), regardless of the substitution in the NH group, to give vinylamines LIV [70].



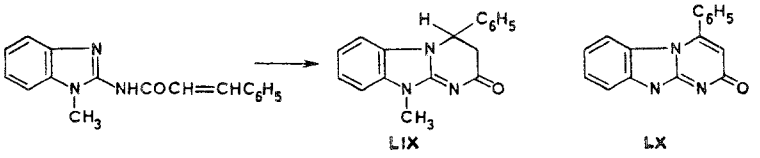
In the reaction with 2-ethynylbenzimidazole with certain CH acids the latter undergo nucleophilic cycloaddition. 2-Ethynylbenzimidazole and its 1-methyl-substituted derivative react with diethyl malonate to give 2-oxopyrido[1,2-a]benzimidazole derivatives (LVa, b). Only the N-methyl-substituted compound reacts with acetoacetic ester via the same method to give LVc, while 2-ethynylbenzimidazole reacts with acetoacetic ester in the second stage of the process, in the same way as acetylacetone, at the acyl group to give pyridobenzimidazoles LVIa, b.



Benzimidazoles that contain multiple bonds in the substituting group (XV, XVI) can be used for the synthesis of condensed imidazole systems such as imidazo[1,2-a]benzimidazole derivatives. When 3-(2-propynyl)-1,2-dialkylbenzimidazolium salts (LVII) are refluxed in an aqueous solution of sodium bicarbonate and bisulfite, they undergo cyclization to give pyrrolo[1,2-a]benzimidazole derivatives (LVIII) [71].



When cinnamic and phenylpropiolic acid (1-methyl-2-benzimidazolyl)amides are heated in an alcohol solution in the presence of alkaline agents, they are converted to pyrimido[1,2-a]-benzimidazol-2-one derivatives (LIX, LX) [72].



Organometallic Compounds of Azoles

The synthesis of many organolithium and organomagnesium and almost all organosodium compounds of imidazole, benzimidazole, pyrazole, indazole, and benzothiazole has been realized for the frist time [73-77]. They were obtained primarily by means of metallation with the utilization of accessible metallating agents:

$$RH + R'M \longrightarrow RM + R'H$$

RH = hetarene; R' = Alk, Ar; M = Li, Na, Mg

1-Alkylbenzimidazoles are capable of undergoing metallation by alkali metals [78].

It should be noted that organosodium compounds of nitrogen heterocycles are quite stable and can be obtained in hydrocarbon media, which excludes the necessity for work with ether and tetrahydrofuran, which are used in syntheses of hetaryllithium and hetarylmagnesium compounds.

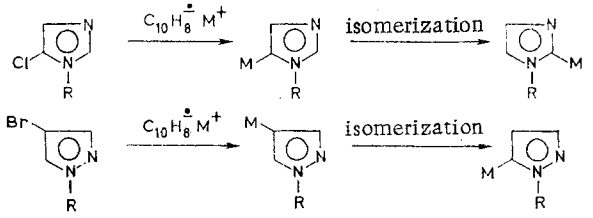
It has been established that hetaryl-C-metal compounds are also formed by the action of naphthyllithium and naphthylsodium on haloarenes. The reaction evidently proceeds via a redox mechanism [79].

$$RX + C_{10}H_8^{\bullet-}M^+ \longrightarrow R^{\bullet} + C_{10}H_8 + MX$$
$$R^{\bullet} + C_{10}H_8^{\bullet-}M^+ \longrightarrow RM + C_{10}H_8$$

R = hetaryl; X = Cl, Br; M = Li, Na

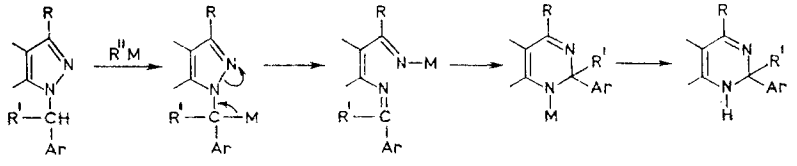
This method for replacement of halogen atoms in organic halides by active metals substantially supplements one of the principal methods for the synthesis of organometallic compounds, which is based on the exchange reaction $RX + R'M \rightleftarrows RM + R'X$ (R = alkyl, aryl, hetaryl; R' = alkyl, aryl; X = halogen; M = Li, Na, Mg).

Organometallic compounds of azoles that are formed from haloazoles sometimes contain the metal in a position other than that which the halogen occupied. The following reaction schemes have been proposed [79]:



R = Alk, Ar; M = Li, Na

A new rearrangement of organometallic compounds of N-substituted pyrazoles and indazoles that proceeds with expansion of the pyrazole ring to give a dihydropyrimidine ring was observed in a study of the metallation of heterocycles [80, 81].*

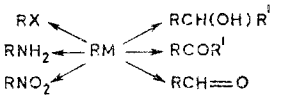


R = Alk; R' = H, Ar; R'' = Alk, Ar, NH_2; M = Li, Na, Mg

The effect of N→MX coordination (MX is the metallating agent, viz., a metal halide), CH acidity, and aromatic stabilization of the heteroring on the formation of hetarene-C-metal compounds has been ascertained [76, 82].

*Opening the pyrazole ring and its expansion to a pyrimidine ring were also observed in the action of sodium amide on 1-aralkylindazoles with a free 3 position. In this case the reaction proceeds through a step involving the formation of 3-sodio-1-aralkylindazoles [85].

Organometallic compounds of heterocycles have been converted to many previously difficult-to-obtain compounds [73-81, 83, 84]:



R='hetaryl; R'=Alk,Ar; X=halogen; M=Li,Na,Mg

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CHEMISTRY OF sym-TETRACYANOETHANE.

2.* CONDENSATION WITH CARBONYL COMPOUNDS

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The reaction of tetracyanoethane with carbonyl compounds proceeds via the scheme of aldol addition with subsequent cyclization of the resulting adducts to give 5-amino-2,3-dihydrofuran derivatives, the structures of which were confirmed by the ^{13}C NMR and mass spectra.

We have recently developed convenient methods for the preparation of sym-tetracyanoethane (TCE) (I) [2, 3] and have subsequently reported [4, 5] that it reacts readily with some carbonyl compounds to give derivatives of the 2,3-dihydrofuran series. In order to ascertain the limits of applicability of this reaction, and to definitively establish the structures of the resulting compounds, we investigated the reaction of TCE with a series of aliphatic, aromatic, and heterocyclic carbonyl compounds IIa-o and thoroughly analyzed their PMR, ^{13}C NMR, and mass-spectrometric behavior.

*See [1] for Communication 1.

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