2-AMINOOXAZOLES AND THEIR DERIVATIVES (REVIEW)

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The literature data on methods for the synthesis of 2-aminooxazoles and their benzo derivatives and their physicochemical properties and transformations are correlated.

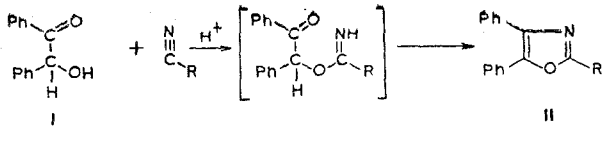
The advances in the chemistry of oxazole up to 1972 have been correlated in a review paper [1]. However, in this review and in a number of other reviews devoted to the chemistry of oxazoles the properties of 2-aminooxazoles and their condensed derivatives are dealt with very superficially or are not discussed at all. The interest in 2-aminooxazoles is associated with the high biological activity and broad spectrum of the action of some of their derivatives. Thus antivirus [2], diuretic [3], antiphlogistic [4], antihelminthic [5], and fungicidal [5, 6] activity of compounds that contain a 2-aminooxazole ring has been observed in recent years. Oxazolyl carbamates display antiallergic [7] and antiasthmatic activity [8]. A number of 2-iminooxazolines have fungicidal and bactericidal activity [9], while 4-substituted 2-guanidinooxazolines display an antihistamine effect [10]. 2-Aminobenzoxazoles and a number of its derivatives are used as muscle relaxants [11, 12]; they also have curarelike activity [13, 14] and are finding application in the treatment of cardiovascular diseases [15]. Some alkylaminobenzoxazoles display tuberculostatic activity [16]. Isothiocyanate derivatives of 2-aminobenzoxazole are used as antihelminthic agents [17]. Like benzoxazolyl carbamates and thiocarbamates [19, 20] and 2-iminooxaolines [21], they display pesticidal activity. 2-Aminobenzoxazole derivatives are also finding application in the aniline-dye industry [22-24]; their fluorescence properties are also of practical value [25].

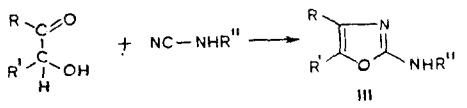
In the present review we attempted to correlate the factual material on the synthesis and properties of 2-aminooxazoles and 2-iminooxazolines and their derivatives, including those that are condensed with benzene and pyridine rings.

METHODS OF PREPARATION

A. Formation of an Oxazole Ring

1. Syntheses by Means of Cyanogen Halides, Cyanamides, and Cyanoguanidines. Substituted oxazoles II were obtained in 1893 by the reaction of benzoin (I) with nitriles or hydrogen cyanide in the presence of concentrated sulfuric acid [26]. An oxazole ring is formed not only when aromatic and aliphatic acyloins are used but also when reagents that give acyloins in the course of the synthesis are employed [27-31]. Cyanamide, sodium and calcium cyanamides, p-aminophenylsulfonylcyanamide, N-cyanoamidine, and other compounds have been used as the nitrile component. A number of substituted 2-aminooxazoles (III) have been obtained by this method.





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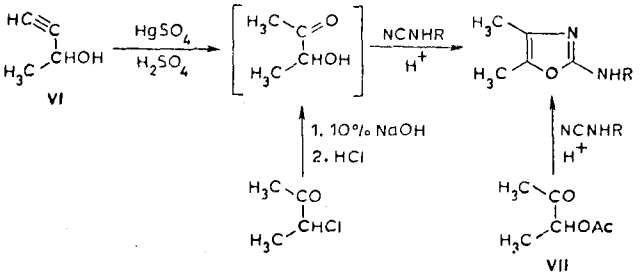
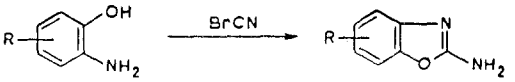
The reaction of mandelonitrile with cyanamide in benzene led to oxazoline IV, which under the influence of dilute potassium hydroxide solution gave 4,5-diphenyl-2-aminooxazole (V) [32]. 2-Aminooxazoles III were also obtained in up to 90% yields in the reaction of α-hydroxy ketones with substituted cyanamides in the presence of sodium hydroxide [33, 34]. 4-Methyl-5-phenyl-2-aminooxazole was synthesized from α-aminopropiophenone hydrochloride and cyanogen bromide in a mixture of ether with aqueous potassium hydroxide solution [35]. Substituted 2-aminooxazoles are obtained when acetylenic alcohols of the propargyl type (VI) are heated with cyanamides in the presence of mercury salts [36] and also by heating α-acetoxy ketones VII with nitriles in sulfuric acid [37].

IV V



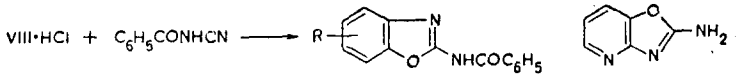
VI VII

One of the most important methods for the preparation of 2-aminobenzoxazoles (IX) is the reaction of o-aminophenols VIII with cyanogen bromide in methanol, ethanol, or aqueous ethanol [11, 38-44].



VIII IX

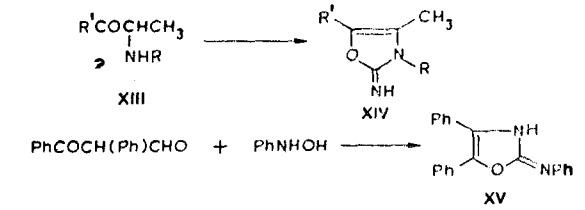
2-Benzamido- and 5-chloro-2-benzamidooxazoles (XI) were obtained by the reaction of the hydrochlorides of the corresponding o-aminophenols with N-cyanobenzamide (X) in an alcohol solution of hydrogen chloride [45]. 2-Sulfonamidobenzoxazole was similarly synthesized [46]. 2-Arylaminobenzoxazoles are obtained in the cyclization of N-(o-hydroxyphenyl)-N',N''-diarylguanidines under various conditions [47].



X XI XII

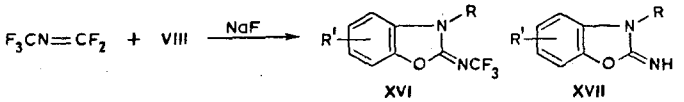
The only method for the preparation of 2-aminooxazolo[4,5-b]pyridine (XII) that has thus far been described consists in the cyclization of 2-amino-3-hydroxypyridine with cyanogen bromide in water at 50-60°C [48].

2-Iminooxazolines XIV (R = alkyl, benzyl; R' = phenyl, 2-thienyl) are formed in the cyclization of α-amino ketones XIII with cyanogen halides in 55-70% yields [49-51]. The condensation of benzoylphenylacetaldehyde with N-phenylhydroxylamine leads to iminooxazoline XV [52].



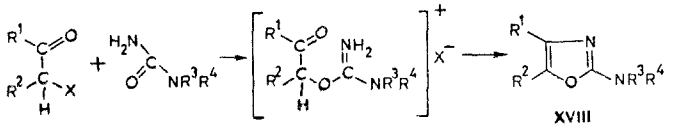
XIII XIV XV

2-Trifluoromethyliminobenzoxazolines XVI (R = methyl, sulfonylmethyl, etc.; R' = H, 5-methyl, 5-fluoro) were obtained in the reaction of o-aminophenols with $F_3CN{=}CF_2$ in the presence of sodium fluoride [21]. The preparation of 3-substituted 2-iminobenzoxazolines XVII from the corresponding o-aminophenols and cyanogen bromide has been described [53].



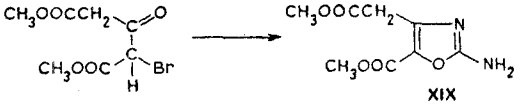
XVI XVII

2. Syntheses by Means of Ureas and Thioureas. Gomper and Christmann have described the condensation of α-halo ketones with urea and N-monosubstituted and N,N-disubstituted ureas in dimethylformamide (DMF), which leads to the corresponding 2-aminooxazoles XVIII [54, 55]. The yields of 2-aminooxazoles are usually good, but imidazoles and imidazolones are obtained as side products in some cases. A number of 2-aminooxazoles that are substituted in the 4 and 5 positions and at the amino group have been synthesized by this method [56-60]. Substituted 2-aminooxazoles or imidazoles are obtained, depending on the reaction conditions [6]. Najer and co-workers [62] obtained 4,5-tetramethylene- and 4,5-pentamethylene-2-aminooxazoles from the corresponding α bromo-cycloalkanone and urea. Bromo-substituted acetaldehyde [63] and propionaldehyde and butyraldehyde [64] react with urea and alkyl- and arylureas to give 2-amino-, 2-alkylamino-, or 2-arylaminooxazoles XVIII.

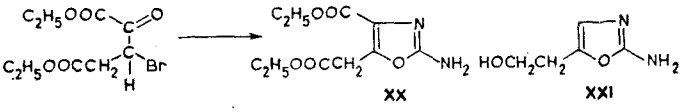


XVIII

Japanese scientists [65, 66] synthesized aminooxazoles XIX and XX by heating the esters of the corresponding bromoketoglutaric acids with urea in ethanol. 2-Amino-5-(2-hydroxyethyl)oxazole (XXI) was obtained in low yield by refluxing 2,3-dichlorotetrahydrofuran with urea in water [67, 68].

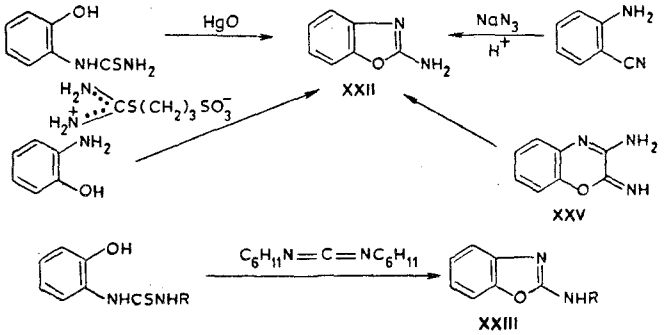


XIX



XX XXI

2-Aminobenzoxazole (XXII) was obtained by cyclization of o-hydroxyphenylthiourea under the influence of mercuric oxide [69] and was later obtained by the action of lead(IV) oxide [38, 70]. Amino-substituted 2-aminobenzoxazoles XXIII are formed in the cyclization of N'-substituted N-(o-hydroxyphenyl)thioureas in an ammoniacal solution of silver oxide hydrate [71] or in the presence of dicyclohexylcarbodiimide [72]. 2-Aminobenzoxazole was obtained by heating o-aminophenol with 3-sulfopropylisothiuronium in aqueous methanol [73]. p-Tolylaminobenzoxazole and the 4-nitro and 4-chloro derivatives were synthesized by heating isothiocarbamate esters of o-aminophenol [74].



XXII XXV XXIII

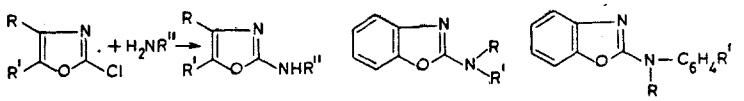
3. Other Methods. Substituted o-aminobenzonitriles react with nitrous acid to give 2-aminobenzoxazoles [75]. The reaction takes place in chloroform when sodium azide is added in portions in the presence of concentrated sulfuric acid. However, under similar conditions salicylaldehyde and its chloro defivatives react with sodium azide to give the corresponding 2-aminobenzoxazoles [76]. The oxidative cyclization of Schiff bases obtained on the basis of o-aminophenol in the presence of "$Pb(H_2PO_4)_4$" leads to 2-aminobenzoxazole derivatives [77]. Dialkylaminobenzoxazoles are obtained in the reaction of o-aminophenol with trichloromethyldialkylamines [78] or N,N-dimethyl-N-dichloromethyleneammonium chlorosulfate [79, 80].

XXIV

Aminobenzoxazole XXII is obtained when 3-amino-2-imino-2H-1,4-benzoxazine is refluxed with a dilute solution of potassium hydroxide [81].

B. Syntheses Based on Nucleophilic Substitution Reactions

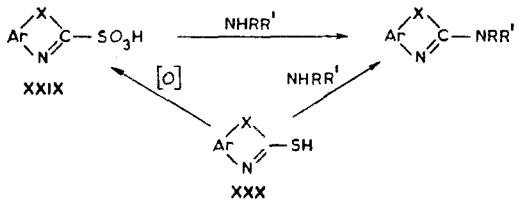
1. From 2-Halooxazoles. The preparation of 2-aminooxazoles XXVI from 2-chlorooxazoles and amines has been described [82, 83]. 4,5-Diphenyl-2-aminooxazoles are formed in the reaction of 4,5-diphenyl-2-chlorooxazole with ammonia and amines [84-86]. Derivatives of 2-iminooxazolines were also similarly synthesized after quaternization of 2-chlorooxazoles and treatment with primary amines [83]. Amino-substituted 2-aminobenzoxazoles XXVII were obtained by the reaction of 2-chlorobenzoxazoles with various amines [87]. The reaction of 2,5-dichlorobenzoxazole with excess ammonia at room temperature leads to 5-chloro-2-aminobenzoxazole [88]. 2-Dimethylamino-, 2-diphenylamino-, and 2-piperidinobenzoxazoles were obtained from 2-chlorobenzoxazoles and an excess amount of the hydrochloride of the corresponding amine in DMF by refluxing with triethylamine as the catalyst [89]. 2-Dimethylaminobenzoxazole was also obtained by heating 2-chlorobenzoxazole with N,N-dimethyl-N-dimethoxymethylamine [90]. 2-Anilinobenzoxazoles were synthesized by heating 2-chlorobenzoxazole with substituted anilines in benzene [91]. Substituted 2-aminobenzoxazoles and their derivatives were obtained by heating 2-chlorobenzoxazole with N-benzyl-N',N'-dimethyl-1,3-propanediamine and N-benzyl-N',N'-dimethylethylenediamine [93].



XXVI XXVII XXVIII

N-(2-Benzoxazolyl)amino acid derivatives XXVII (R = H, R' = $CH_2COOC_2H_5$, CH_2COOH, etc.) were synthesized from 2-chlorobenzoxazole and amino acids in dry benzene in the presence of triethylamine [94].

2. From Oxazole-2-thiones and Oxazole-2-sulfonic Acids. 2-Aminoazole derivatives were obtained in the reaction of azole-2-sulfonic acids XXIX (Ar is a benzene or naphthalene ring, X = S, O, or NH) with the corresponding amines or ammonia [95]. 2-Aminobenzoxazole derivatives were synthesized in the reaction of the potassium salt of benzoxazolesulfonic acid — the product of oxidation of benzoxazole-2-thione — with ammonia or amines, including heterocyclic amines [16, 96]. 2-Aminobenzoxazole derivatives are obtained when benzoxazole-2-thione (XXX) and its phenyl ring-substituted derivatives are heated with ammonia or amines [38, 69, 71, 87, 97, 98].



XXIX XXX

3. Other Methods. One of the earliest methods for the preparation of 2-aminobenzoxazole is the reaction of benzoxazole with hydroxylamine hydrochloride in sodium hydroxide solution [99]. Similar conditions were used to obtain 2-hydroxylaminobenzoxazolines, which were converted by alkaline hydrolysis to the corresponding 2-aminobenzoxazoles [100]. Heating benzoxazole with sodium amide also leads to 2-aminobenzoxazole [101].

PHYSICOCHEMICAL PROPERTIES

The basicities of oxazoles are lower by a factor of 10^4 than the basicities of the corresponding pyridines [102]. A comparison of the dissociation constants of derivatives of 2-aminooxazoles and 2-aminothiazoles [103] shows that the latter are stronger bases; this is explained by the effect of the heteroatom.

The UV spectra of some benzoxazolines [104] and benzoxazoles, including 2-anilinobenzoxazole [105] and 5-chloro-2-aminobenzoxazole [106], have been investigated. Passerini

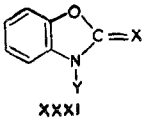
[105] notes that the principal chromophore is the benzene ring, while the effect of the oxazole ring is manifested only in a bathochromic shift of the absorption bands.

The spectra of oxazoles in the IR region have been studied by a number of authors [107-110]. A shift of the band of the vibrations of the C=N bond to the lower-frequency region is noted in the oxazoline, oxazole, and benzoxazole series [111]. A band of stretching vibrations of the N—H bond is observed at 3200-3300 cm^{-1} in the case of amino-monosubstituted aminooxazoles and is of medium intensity; two bands of primary amines at 3200 and 3400 cm^{-1} are characteristic for unsubstituted 2-aminooxazoles [62, 63]. The band at 1630-1690 cm^{-1} corresponds to the stretching vibrations of the azomethine bond of the oxazole ring for 2-aminooxazole derivatives [112, 113].

The PMR spectra of some phosphorylated 2-iminooxazolines have been described [114]. The effect of the unshared pair of electrons of the endocyclic nitrogen atom [115] and the effect of substituents on the chemical shifts in the PMR spectra of substituted 2-aminooxazoles [29] have been discussed.

The presence of peaks of fragment ions corresponding to the elimination of HCN and CO from the molecular ion is characteristic for the mass spectra of substituted 2-aminobenzoxazoles [116].

The structures of compounds of the XXXI type (where X = S, O, and $NCH_2C_6H_5$; Y = H and CH_3) were determined in 1973 by x-ray diffraction analysis. It was shown that methylation and replacement of the sulfur atom by a nitrogen (oxygen) atom do not change the geometry of the compounds. 2-Benzyliminobenzoxazoline molecules form dimers with an N—H···N—H bond length of 2.933 Å, and this leads to a small difference in the geometric parameters between this and the other investigated compounds [117].



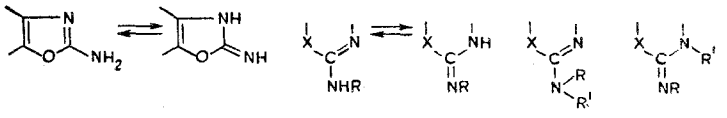
XXXI

TAUTOMERISM

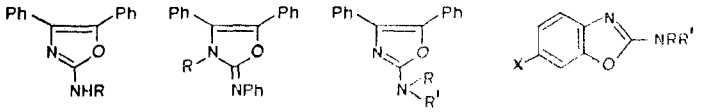
Some derivatives of 2-aminooxazole and 2-aminobenzoxazole display the ability to undergo tautomerism of the imino-enamine type. The tautomeric equilibrium can be studied by physical methods by means of a comparison of the properties of potentially tautomeric and model compounds that have a fixed structure [118, 119]. A comparison of the basicities indicates predominance of the amino form in compounds of the XXXII type, particularly in 4,5-tetramethylene- and 4,5-pentamethylene-2-aminooxazoles [62, 120]. This conclusion was drawn on the basis of the significantly greater closeness of the pK values of compounds of the XXXII type to the pK value of model compound XXXIII with a fixed amino group than to the pK value of XXXIV, which models the imino form.

A comparison of the UV spectra of 4,5-diphenyl-2-aminooxazole (XXXV) and model structures XXXVI and XXXVII also indicates predominance of the amino form. A similar comparison of the UV spectra of 5-chloro-2-aminobenzoxazole and its methyl derivatives led to the conclusion that this compound exists in the amino form in solution, although the IR spectra of the solid indicate predominance of the imino form [122].

The shift of the band of the N—H stretching vibrations in the IR spectra of 5-phenyl-2-aminooxazole and 4,5-tetramethylene-2-aminooxazole relative to the same bands in the spectra of model compounds made it possible to ascertain a shift of the tautomeric equilibrium to favor the amino form [123]. A comparison of the frequencies of the C=N stretching vibrations of 2-aminobenzoxazole derivatives XXXVIII indicates a shift of the equilibrium to favor the amino form in dilute solutions and to favor the imino form as the concentration and acidity of the solution are increases [124].



XXXII XXXIII XXXIV

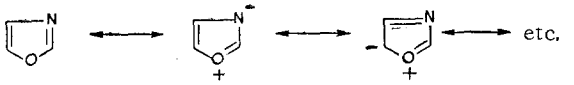


XXXV XXXVI XXXVII XXXVIII

The prototropic tautomerism of 2-anilinooxazoles has been studied by means of quantum-chemical calculations [self-consistent-field molecular orbital (SCFMO) calculations] of the heats of atomization, the σ and π energies, the ionization potentials, the bond lengths, and the charges; predominance of the amino form was noted in these calculations [125].

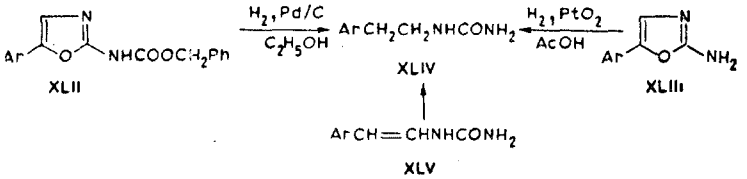
CHEMICAL PROPERTIES

The oxazole structure can be represented by resonance structures XXXIX-XLI, including dipolar structures, the contribution of which is greater in the case of oxazole than in the case of benzene. This explains why despite its aromatic character, oxazole is characterized by greater reactivity and lower stability with respect to nucleophilic and electrophilic reagents [1]. In general, the chemical properties of 2-aminooxazole and its derivatives are determined by the character of the oxazole ring, the benzene ring condensed with it, and the amino group. The presence of an amino group leads to the development of new properties that are associated with the manifestiation of basicity and, in addition to this, changes the properties of the oxazole ring. The carbon atom in the 2 position has a relatively high partial positive charge [126], and this leads to a decrease in the basicity of the amino group bonded to this atom, as a result of which it does not undergo diazotization [44, 65]. We will discuss the reactions involving the oxazole ring and the amino group separately.



XXXIX XL XLI

1. Reactions of the Oxazole Ring. The hydrogenation of substituted 2-aminooxazoles takes place with cleavage of the heteroring [127-130]. Thus the hydrogenation of 5-aryl-2-oxazolylcarbamic acid esters (LXII) or 5-aryl-2-aminooxazoles (LXIII) leads to (2-aryl-ethyl)ureas (XLIV). The hydrogenation mechanism proposed by Tanaka [131] includes the intermediate formation of an unsaturated urea of the XLV type.



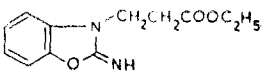
XLII XLIV XLIII XLV

The alkaline hydrolysis of 2-aminobenzoxazole is also accompanied by cleavage of the oxazole ring to give o-aminophenol and by rearrangement to a benzimidazolone [132]. The instability of the benzoxazole ring with respect to alkaline agents is also confirmed by the fact that 2-aminobenzoxazole undergoes decomposition with the evolution of ammonia when it is treated with hot sodium chloroacetate in order to obtain complexes similar to those formed from 2-aminobenzothiazole and 2-aminobenzimidazole [133]. The acidic hydrolysis of 5-substituted 2-aminobenzoxazoles and 3-methyl-2-iminobenzoxazolines leads to the corresponding benzoxazolones [11, 122].

Electrophilic-substitution reactions involve the oxazole ring, the phenyl groups in phenyloxazoles, or the benzene ring in benzoxazoles. The halogenation of oxazoles takes place in the 5 position or in the 4 position if the 5 position is occupied [134, 135]. The chlorination of 5-substituted 2-aminooxazoles leads to the 4-chloro derivatives [136]. Halogenation of 2-aminobenzoxazole in chlorofrom in the cold takes place in the 6 position [11]. 6-Bromo-5-chloro-2-aminobenzoxazole was obtained from 5-chloro-2-aminobenzoxazole by bromination in the cold in methanol [137]. The nitration of 4-phenyl-2-dimethylamino-oxazole with a mixture of concentrated sulfuric and nitric acids leads to 5-nitro-2-dimethylamino-4-(p-nitrophenyl)oxazole. This is the only case of the direct nitration of oxazoles in the heteroring that has been described thus far [55]. In general, however, nitration and sulfonation involve only the phenyl rings and almost always take place in the para position relative to the oxazole ring [1, 138]. The nitration of 2-amino- [97] and

2-anilinobenzoxazole [139] leads to the 6-nitro derivatives. The acylation of 4-phenyl-2-aminooxazole with acetylsulfanilic acid chloride gives the acetyl derivatives of 4-phenyl-2-sulfanilamidooxazole [140].

2-Aminobenzoxazole and its 5-chloro derivative are methylated at the nitrogen atom of the heteroring when they are heated with methyl iodide [69, 122] or with dimethyl sulfate [141]. 2-Aminobenzoxazole also undergoes alkylation by ethyl 2-bromopropionate at the endocyclic nitrogen atom to give 3-(2-ethoxycarbonyl)-2-iminobenzoxazoline (XLVI) [11].

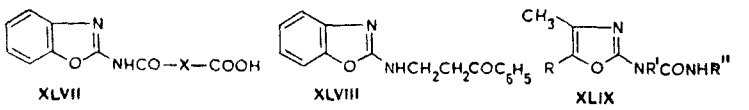


XLVI

2. Reactions with the Participation of the Amino Group. Spectroscopic and other physicochemical studies show that the acylation of substituted 2-aminooxazoles involves only the exocyclic nitrogen atom [142], in connection with which the assumption [143] that 3-acetyl-2-iminooxazolines are formed in the acylation of 2-aminooxazoles with acetic anhydride in acetic acid is erroneous. Treatment of 4,5-diphenyl-2-aminooxazole with acetic anhydride also gives the acetyl derivative involving the exocyclic nitrogen atom [49]. Acetylated 2-aminobenzoxazoles [53] and 5-chloro-2-aminobenzoxazoles [144] have been obtained. The reaction of 5-chloro-2-aminobenzoxazole with benzoyl chloride leads to 5-chloro-2-benzamidobenzoxazole [45]. Phosphorylated and thiophosphorylated derivatives have been obtained from 2-aminobenzoxazole, as well as from 3-methyl-2-iminobenzoxazoline, and ClP(Z)RR' (where Z = O, S; R = CH_3, OC_2H_5; R' = OC_2H_5, OC_6H_5) [145]. Monoamides XLVII are obtained by refluxing 2-aminobenzoxazole and its phenyl ring-substituted derivatives with dicarboxylic acid anhydrides in tetrahydrofuran (THF). The acylation of 2-aminooxazolo-[4,5-b]pyridine also takes place at the amino group [48].

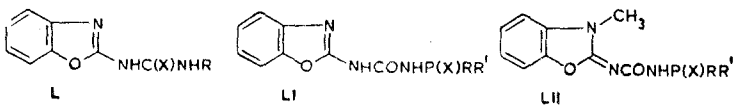
Alkylation of the exocyclic nitrogen atom was observed in the reaction of 2-aminobenzoxazole with β-diethylaminopropiophenone and led to β-(2-benzoxazolylamino)propiophenone (XLVIII) [147]. The nucleophilic addition of derivatives of α,β-unsaturated acids of the methyl methacrylate and acrylonitrile type also takes place at the exocyclic nitrogen atom [148]. The reaction of 4,5-diphenyl-2-aminoisoxazole with formamide led to 4,5-diphenyl-2-formamidooxazole [55, 149].

2-Aninooxazoles react with isocyanates to give oxazolylureas and carbamates. Ureas of the XLIX type were obtained from 4-methyl-2-butylaminooxazole and ethyl isocyanate [7]. 2-Aminobenzoxazoles react with isocyanates and isothiocyanates to give derivatives of the L type [17, 18, 92, 150, 151]. Phosphorylated ureas LI are obtained when 2-aminobenzoxazole is refluxed with phosphoryl and thiophosphoryl isocyanates in organic solvents [152, 153]. Phosphorylated benzoxazolylureas LII are formed in 80-99% yields from 3-methyl-2-aminobenzoxazoline and the corresponding isocyanates in benzene at room temperature [154].



XLVII

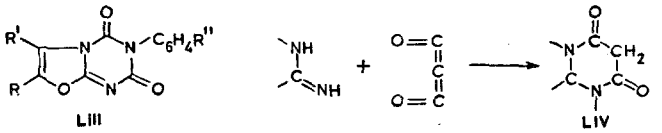
XLVIII XLIX



L LI LII

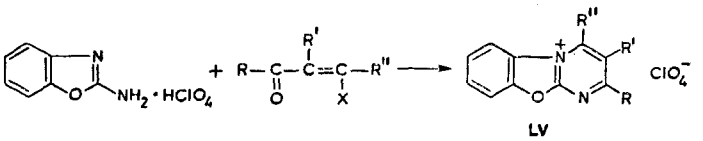
XLVII X = CH=CH, CH_3C=CCH_3, CH_2CH_2 etc.; L–LII X = S, O

3. Cyclization Reactions. Oxazolo[3,2-a]-s-triazine-5,7-diones LIII are obtained by refluxing 2-aminooxazoles with phenyl isocyanate in pyridine [4] and by refluxing 2-acetamidooxazoles with aryl isocyanates [3]. Condensed dioxotetrahydropyrimidines are obtained in the reaction of carbon suboxide with compounds that are capable of amino-imino tautomerism [155, 156]. 2-Aminooxazole and 2-aminobenzoxazole undergo this reaction to give 2,4-dioxotetrahydropyrimidooxazolines LIV and benzoxazolines [157].



LIII LIV

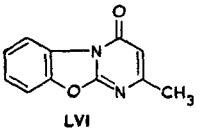
Chuiguk and co-workers have studied the condensation of salts of 2-aminoazoles with β-diketones [158-160], β-chlorovinyl ketones [161], β-chlorovinyl aldehydes [162], and 1,1,3,3-tetraethoxypropane. 2-Aminobenzoxazole perchlorate reacts to give pyrimido[2,1-b]-benzoxazolium salts LV in 54-97% yields [163].



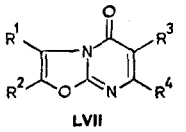
LV

The condensation of 2-aminobenzoxazole with ethyl β-aminocrotonate leads to 2-methyl-4-oxopyrimido[2,1-b]benzoxazole (LVI) [164]. 2-Aminobenzoxazole reacts with diphenylcyclopropene to give the corresponding 4-pyrimidone through the intermediate ketene [165]. 2-Aminooxazoles undergo reaction with ethoxymethylenemalonic ester to give oxazolo[3,2-a]-pyrimidin-5-ones LVII, which react with hydrazine to give substituted pyrimido[2,1-c]-triazin-6-ones LVIII [6, 166].

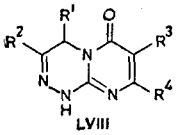
Cyclocondensation processes that lead to three-ring azoles, including imidazo[2,1-b]-benzoxazoles [172], have been described. The reaction of 2-aminobenzoxazole with esters of propiolic and acetylenedicarboxylic acids gives 2-oxopyrimido[2,1-b]benzoxazoles LIX [173]. The reaction of 2-aminobenzoxazole with ethoxymethylenemalonic ester leads to addition products (with ring opening), which undergo cyclization to 3-ethoxycarbonyl-4-oxopyrimido-[2,1-b]benzoxazoles LX when they are heated with Dowtherm [173]. 2-Oxopyrimido[2,1-b]-benzoxazole was obtained in 70% yield in the reaction of 2-aminobenzoxazole with dimethyl acetylenedicarboxylate [174].



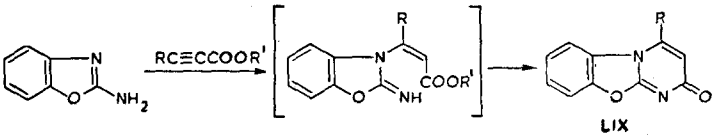
LVI



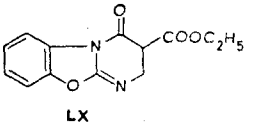
LVII



LVIII



LIX

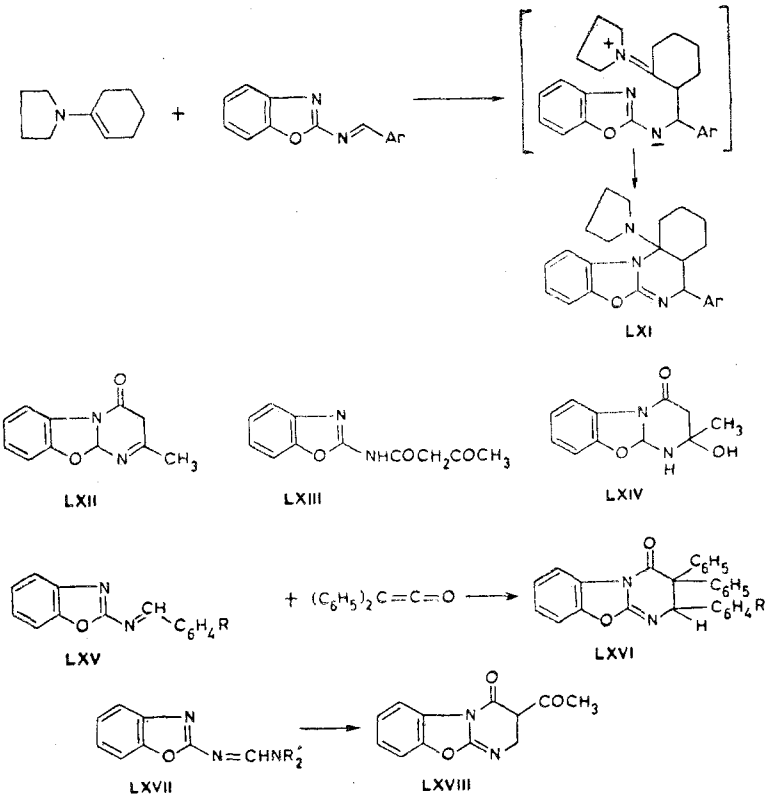


LX

Little study has been devoted to the cycloaddition of enamines to carbon—nitrogen conjugated double bonds. The reaction of 1-pyrrolidinocyclohexene with 2-(p-nitrobenzylideneamino)benzoxazole led to an adduct (LXI) of the Diels—Alder type [175].

2-Aminobenzoxazole reacts with diketene in refluxing benzene to give pyrimidobenzoxazole LXII and acetoacetamidobenzoxazole LXIII [176]. If the reaction is carried out at room temperature, hydroxypyrimidobenzoxazole LXIV is obtained.

A number of new diazadienes, including benzoxazole derivatives LXV, which are obtained from the corresponding amines and aldehydes, undergo cyclocondensation with diphenylketene to give 1,4-cycloaddition products LXVI [177]. In the opinion of Sakamoto and co-workers [178] the mechanism of their formation consists in initial nucleophilic attack by the endocyclic nitrogen atom at the C=C bond in the ketene with subsequent nucleophilic attack at the azomethine carbon atom. Formamidine derivatives of 2-aminobenzoxazole (LXVII) react with diketene in benzene to give pyrimidobenzoxazole LXVIII; it is assumed that the reaction proceeds via 1,4-dipolar cycloaddition with the elimination of a dialkylamine [179].



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SYNTHESIS OF β,γ-UNSATURATED AMINES OF THE TETRAHYDROPYRAN SERIES

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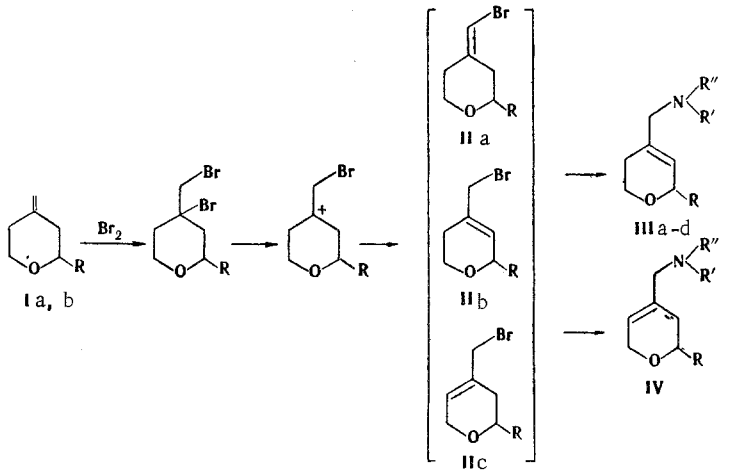
Dibromides of 4-methylenetetrahydropyran and 4-methyldihydro-2H-pyran were synthesized and subjected to reaction with excess amounts of amines to give β,γ-unsaturated amines of the tetrahydropyran series, the structure of which was proved on the basis of data from gas–liquid chromatography and PMR and IR spectroscopy.

In a continuation of our earlier research [1, 2] we have shown that 4-methylenetetrahydropyran and 4-methyldihydro-2H-pyran and their 2-isopropyl derivatives, which were isolated from mixtures of the isomers by preparative gas–liquid chromatography (GLC), form dibromides readily in high yields. The dibromides react with excess amounts of amines to give unsaturated amino derivatives in high yields.

It is assumed that the carbonium ion formed by heterolysis of the tertiary bromine atom is stabilized primarily by ejection of β protons from the heteroring rather than by ejection of the acidic protons of the bromomethyl group. The resulting intermediate unsaturated halide IIb (IIc) then reacts via the well-known scheme [3].



I a R=H; b R=*i*-C_3H_7; III R=H; a R′=R″=C_2H_5; b R′=R″=C_4H_9; c R′+R″=$(CH_2)_5$; d R′+R″=$(CH_2CH_2)_2O$; IV R=*i*-C_3H_7, R′=R″=C_2H_5

The structure of amines III was proved on the basis of data from GLC and IR and PMR spectroscopy. Absorption at 1678 cm^{-1}, which is characteristic for a trisubstituted double bond [4], is observed in the IR spectra of IIIa-d. The signal of a hydrogen atom attached to a double bond shows up distinctly at 5.5 ppm in the PMR spectra of these compounds. A signal from the protons of an NCH_2 group at 2.8 ppm, a triplet signal from the protons of a 6-CH_2 group at 3.7 ppm, and a multiplet signal of a 2-CH_2 group at 4.0 ppm are also observed. A similar result is obtained when an alkyl substituent is introduced in the α position of pyran system: We observed the formation of only the IV isomer (by GLC), the IR spectrum of

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