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SYNTHESIS AND PROPERTIES OF 2-OXOOXAZOLOPYRIDINES (REVIEW)

D. Shantare, E. Gudriniece, and M. Yure

Published data on the synthesis and properties of 2(3H)-oxooxazolo[4,5-b]-, 2(1H)-oxooxazolo[5,4-b]-, and 2(3H)-oxooxazolo[4,5-c]pyridines up to 1997 are reviewed.

Compared with other condensed systems of the pyridine series the derivatives of 2-oxooxazolopyridines have been studied not enough. Interest in these compounds has increased more and more in recent years, since substances exhibiting a wide spectrum of biological activity have been found among them.

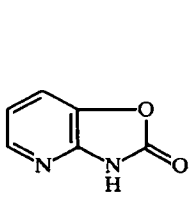
Among the derivatives of 1(3H)-oxooxazolo[4,5-*b*]pyridines there were substances that exhibited analgesic [1-10] and antiinflammatory [8, 9] activity. Some derivatives were depressants of the central system [8]. The thiophosphates of 2(3H)-oxooxazolo[4,5-*b*]pyridines were characterized by high insecticidal, acaricidal, and antihelminthic [10-24] activity.

The derivatives of 2(1H)-oxooxazolo[5,4-*b*]pyridines included compounds that exhibited antiinflammatory [25] and analgesic [25-27] activity.

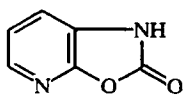
Data on the synthesis and properties of 2-oxooxazolopyridines have not been reviewed in the literature. We set ourselves the task of classifying the published data on this extremely interesting group of heterocyclic substances.

1. SYNTHESES OF 2-OXOOXAZOLOPYRIDINES

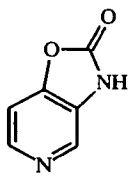
The isomeric forms (I-IV) are possible for 2-oxooxazolopyridines:



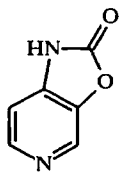
I



II



III



IV

The methods of synthesis and characteristics have been studied most widely for the derivatives of 2(3H)-oxooxazolo[4,5-*b*]pyridine (I). The derivatives of 2(1H)-oxooxazolo[5,4-*b*]pyridine (II) and 2(3H)-oxooxazolo-[5,4-*c*]pyridine (III) have been studied less, and there are no published data on 2(1H)-oxooxazolo[5,4-*c*]pyridine (IV).

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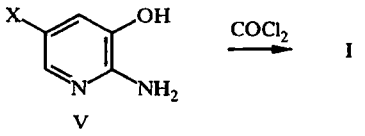
1.1. Methods for the Synthesis of 2(3H)-Oxooxazolo[4,5-*b*]pyridines

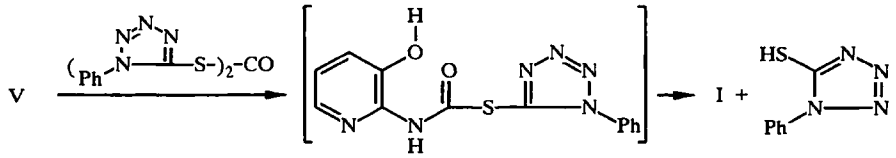
1.1.1. Carbonylation of 2-Amino-3-hydroxypyridines. Several reagents have been proposed for carbonylation: phosgene [8, 11-14, 16, 23, 28-32], carbonyldiimidazole [2, 3, 7, 28, 29, 33], disuccinimidocarbonate [34], S,S′-bis[1-phenyl-(1H)-tetrazol-5-yl] dithiocarbonate [35, 36], carbon monoxide under pressure in the presence of selenium [37, 38], and urea [39].

If 2-amino-3-hydroxypyridine (V) (X = H) is heated with phosgene in pyridine, oxazolopyridine (I) is formed with a yield of 95% [11, 28]. The corresponding 6-methylpyridine reacts similarly [13]. With the less toxic carbonyldiimidazole in THF a smaller yield (75-77%) of compound (I) was obtained [2].



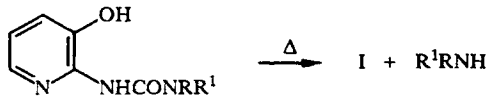
V

The action of S,S′-bis[1-phenyl-(1H)-tetrazol-5-yl] dithiocarbonate on the pyridine (V) even at room temperature leads to the required condensed system (I) through the intermediate formation of compound (VI) [35].



VI

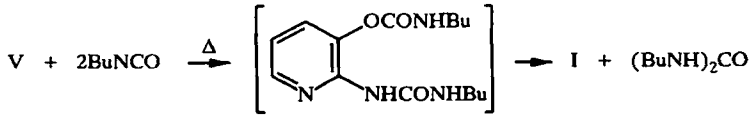
1.1.2. Intramolecular Cyclization of 3-Hydroxy-2-pyridylureas and Urethanes. When N-(3-hydroxy-2-pyridyl)ureas (VII) are heated in inert solvents, intramolecular cyclization with the elimination of the amine occurs, and oxooxazolopyridine (I) is formed [30].



VII

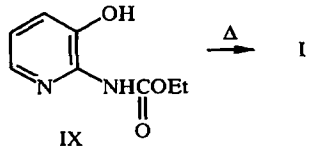
R, R^1 = alkyl

2(3H)-Oxooxazolo[4,5-*b*]pyridine (I) is obtained with 62% yield [30] under refluxing of compound (V) with a twofold excess of butyl isocyanate in toluene without isolation of the urea (VIII) that forms.



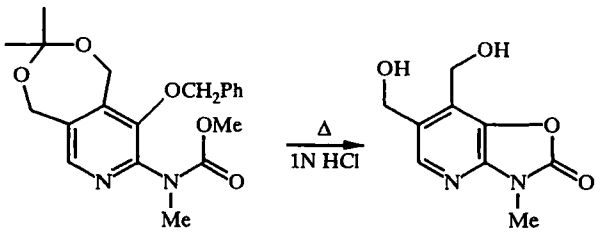
VIII

When heated at 200°C in diphenyl ether 3-hydroxy-2-ethoxycarbonylaminopyridine (IX) undergoes cyclization to oxooxazolopyridine (I) [40].



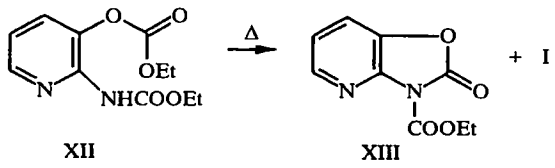
IX

Compound (XI) was obtained with a yield of 51% by heating the methyl carbamate (X) in 1 N hydrochloric acid [41].



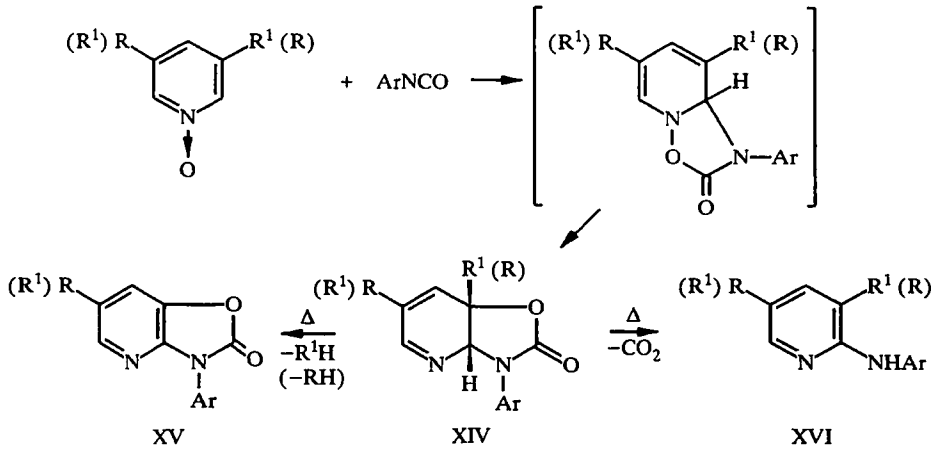
X XI

During vacuum distillation the carbamate (XII) gives a mixture of compounds (XIII) and (I) [40].



XII XIII

1.1.3. Reactions of Pyridine N-Oxides with Isocyanates. The 1,3-dipolar cycloaddition of aryl isocyanates to pyridine N-oxides leads to the formation of 3-aryl-3a,7a-dihydro-2-oxooxazolo[4,5-*b*]pyridines (XIV), 3-aryl-2-(3H)-oxooxazolo[4,5-*b*]pyridines (XV), and 2-arylaminopyridines (XVI) [42-51]. It was suggested [42, 44, 46, 48, 49] that an initial cyclic adduct is formed first and then undergoes 1,5-sigmatropic rearrangement to compound (XIV). The reactivity of the N-oxides in this reaction depends on the substituents at the β-position of the pyridine ring. The reaction does not occur in the presence of strong electron-accepting groups (R, R^1 = cyano, nitro), and this is explained by the increased aromaticity of the corresponding pyridine oxides [49]. Electron-donating groups (R, R^1 = methyl, ethyl, phenyl) on the other hand increase the dipolar character of the pyridine oxides, promoting cycloaddition. The obtained 3-aryl-3a,7a-dihydro-2-oxooxazolo[4,5-*b*]pyridines (XIV) can be isolated, but when heated at 110°C in DMF or boiled with potassium hydroxide in alcohol solution they are converted into 2-anilinopyridines (XVI). The unsubstituted pyridine oxide (R = R^1 = H) reacts in the same way [42, 49].

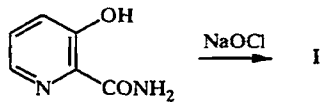


XV XIV XVI

At increased temperature (and also in the presence of triethylamine) the pyridine oxides bearing a methoxy group or halogen at position 3 (R = H, Cl, Br, R^1 = OMe, Cl, Br) eliminate a molecule of methanol or hydrogen halide to give 2(3H)-oxooxazolo[4,5-*b*]pyridines (XV). Sometimes a small amount of 2-anilinopyridines (XVI) is obtained [46].

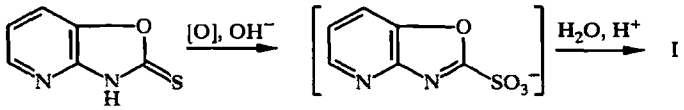
Japanese investigators have studied the effect of electron-donating and electron-accepting groups in the pyridine oxide [46, 47, 50] and in the aryl isocyanate [43, 50], the influence of temperature, reaction time [42, 43], and solvents [43, 44, 48] on the course of the reaction. These reactions have been explained in terms of the theory of frontier molecular orbitals [45], secondary orbital interaction [48], the steric and dipole—dipole effect, aromaticity [48, 49], and charge-transfer complexes [44, 49].

1.1.4. 2-Aminocarbonyl-3-hydroxypyridines in the Hoffmann Reaction. Only one paper is known in which 2(3H)-oxooxazolo[4,5-*b*]pyridine (I) was produced with a 74% yield by treating 3-hydroxypicolinamide (XVII) with an aqueous solution of sodium hypochlorite [11].



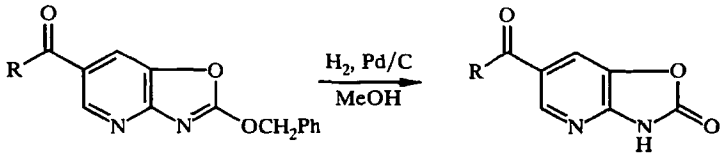
XVII

1.1.5. Transformations of 2-Substituted Oxazolo[4,5-*b*]pyridines. The oxidation of 2(3H)-thioxooxazolo[4,5-*b*]pyridine (XVIII) by potassium permanganate has only been discussed in one paper [52]. Subsequent acid hydrolysis of the obtained sulfonate (XIX) gave the oxooxazolopyridine (I).



XVIII XIX

Reductive debenzylation of 2-benzyloxyoxazolo[4,5-*b*]pyridines (XX) led to the corresponding 2-oxo derivatives (XXI) [5].



XX XXI

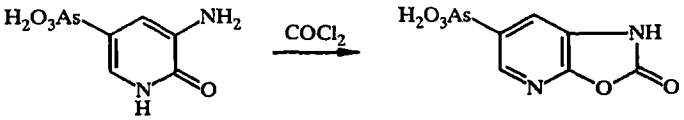
R = Me, Ph

1.2 Methods for the Synthesis of 2(1H)-Oxooxazolo[5,4-*b*]pyridines

2(1H)-Oxooxazolo[5,4-*b*]pyridine (II) and its derivatives have been slightly studied. Researches into methods for the synthesis of such structures have developed rapidly, particularly in recent years, in connection with the clearly defined biological activity of compounds in this series.

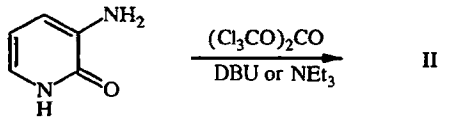
Methods for the synthesis of oxooxazolopyridine derivatives (II) are mostly based on the same principles as those used for the production of 2(3H)-oxooxazolo[4,5-*b*]pyridine (I).

1.2.1. Carbonylation of 3-Amino-2(1H)-pyridones. The carbonylation of a derivative of 3-amino-2-pyridone was first described in the case of the corresponding 6-arsenic acid (XXII). Thus, the action of a 20% solution of phosgene in toluene in the presence of sodium carbonate on compound (XXII) gave an 80% yield of the corresponding oxooxazolo[5,4-*b*]pyridine (XXIII) [53].



XXII XXIII

Later the phosgene was replaced by the less hazardous and more convenient bis(trichloromethyl) carbonate ("triphosgene") [25, 26]. The oxooxazolopyridine (II) was obtained from 3-amino-2(1H)-pyridone (XXIV) with triphosgene in the presence of diazabicycloundecene (DBU) with a 50% yield in a 1:1 mixture of dichloromethane and THF at -78°C [26] and with a 78% yield in the presence of triethylamine [25, 26].

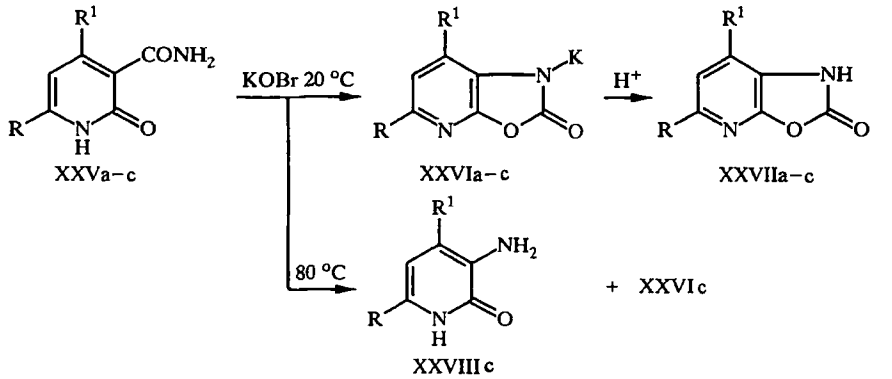


XXIV

For the carbonylation of 3-amino-2(1H)-pyridones it is also possible to use ethyl chlorocarbonate [54] or carbonyldiimidazole in the presence of diazabicycloundecene [26].

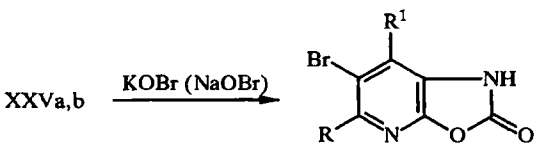
3-Substituted aminopyridones and phosgene were used for the synthesis of 1-substituted oxooxazolopyridines (II) [55].

1.2.2. 3-Aminocarbonyl-2(1H)-pyridones in Hoffmann Reactions. Before our researches the use of the Hoffmann reaction for the synthesis of 2(1H)-oxooxazolo[5,4-*b*]pyridines was unknown. As stated above, the only example of the use of this reaction was described for the synthesis of 2(3H)-oxooxazolo[4,5-*b*]pyridines [11], although the oxooxazolopyridine (II) had been obtained in the Curtius reaction [54]. We were able to synthesize 2(1H)-oxooxazolo[5,4-*b*]pyridines for the first time with high yields using the Hoffmann rearrangement [56-58]. The reaction of the amides (XXVa-c) with potassium hypobromite in aqueous solution at room temperature led to the salts (XXVIa-c), the acidification of which gave 2-oxooxazolopyridines (XXVIIa-c). In the case of compound (XXVc) at higher temperatures (80-85°C), however, a 3:1 mixture of the aminopyridone (XXVIIIc) and the oxooxazolopyridine (XXVIc) was formed [57, 58].



a R = R¹ = Me, b R = Ph, R¹ = Me, c R = Ph, R¹ = CF_3

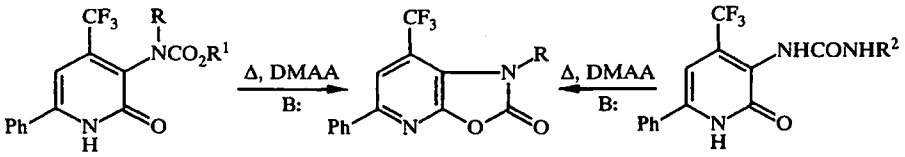
The reaction of a threefold excess of sodium or potassium hypobromite with compounds (XXVa, b) at room temperature led to the formation of the bromine derivatives (XXIXa, b) [56, 58].



XXIXa,b

The method that we developed for the synthesis of 2(1H)-oxooxazolo[5,4-*b*]pyridines [57, 58] makes it possible by varying the conditions of the Hoffmann reaction to obtain the potassium salts of 2(1H)-oxooxazolo[5,4-*b*]pyridines (XXVIb, c), the 2(1H)-oxooxazolo[5,4-*b*]pyridines (XXVIIa-c), the 6-bromo-2(1H)-oxooxazolo[5,4-*b*]pyridines (XXIXa, b), and 3-aminopyridone (XXVIIIc).

1.2.3. Intramolecular Cyclization of 2-Oxo-3-pyridylurethanes and Ureas. 7-Trifluoromethyl-5-phenyl-2(1H)-oxooxazolo[5,4-*b*]pyridine (XXVIIc) and its 1-methyl derivative (XXX) were obtained by boiling the corresponding 2-oxo-3-pyridylcarbamates (XXXIa, b) with diethylamine, diphenylamine, or morpholine in N,N-dimethylacetamide (DMAA). The oxooxazolopyridine (XXVIIc) was also obtained by boiling the ureas (XXXII) with triethylamine in dimethylacetamide [59].



XXXIa R = H, R^1 = Et, b R = R^1 = Me

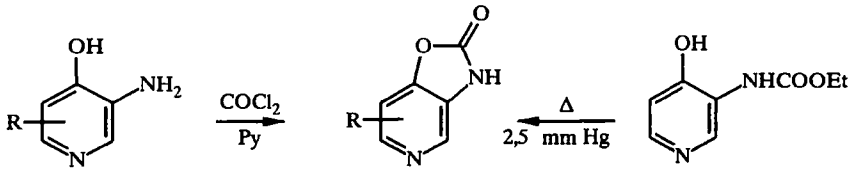
XXVIIc R = H; XXX R = Me

XXXII R^2 = alkyl

Vacuum distillation of ethyl N-(2-oxo-3-pyridyl)carbamate led to its partial conversion into the oxazolopyridine (II) [55].

1.3. Methods for the Synthesis of 2(3H)-Oxooxazolo[4,5-*c*]pyridines

According to patent data [28, 29, 60-62], a series of 2(3H)-oxooxazolo[4,5-*c*]pyridine derivatives (III) were synthesized from the corresponding 3-amino-4-hydroxypyridines (XXXIII) and phosgene. 3-Amino-4-hydroxyquinolines and their derivatives were also used in the reactions. The obtained compounds were then used for the synthesis of various ureas, including compounds in the penicillin and cephalosporin series (see section 3.2.1).



XXXIII III XXXIV

Attempts to synthesize 2(3H)-oxooxazolo[4,5-*c*]pyridines from 3-amino-4-hydroxypyridines (XXXIII) by heating them with urea or by treating them with ethyl chlorformate in the presence of a base were unsuccessful [40, 55]. Negative results were also obtained by heating ethyl N-(4-hydroxy-3-pyridyl)carbamate (XXXIV) [40]. However, the vacuum distillation of compound (XXXIV) (2.5 mm Hg, 180-210°C) led to 2(3H)-oxooxazolo-[4,5-*c*]pyridine (III) (R = H) with a 30% yield [63].

2. THE PHYSICAL CHARACTERISTICS OF 2-OXOOXAZOLOPYRIDINES

The IR spectra of the 2(3H)-oxooxazolo[4,5-*b*]pyridines and 2(1H)-oxooxazolo[5,4-*b*]pyridines contain bands for the stretching vibrations of CO in the region of 1820-1755 and C—H in the region of 3000-2700 [1, 2, 10, 11, 25-27, 37, 39, 46, 48, 50, 52, 56], for ν_{N-H} in the region of 3220-3500 [25, 48, 56], for $\delta_{C=N}$ and δ_{N-H} in the region of 1680-1620 [10, 11, 52], and for δ_{C-H} of the pyridine ring in the region of 1620-1500 cm^{-1} [1, 2, 27, 29]. The PMR spectrum of compound (I) (DMSO-d_6) contains the signals of protons at 7.13 (1H, dd, J = 8.2 and 5.1 Hz, 6-H); 7.63 (1H, dd, J = 8.2 and 1.0 Hz, 7-H); 8.05 (1H, dd, J = 5.1 and 1.0 Hz, 5-H); 11.90 ppm (1H, bs, NH) [2, 11, 37, 39]. The signals of the protons in oxooxazolopyridine (II) appear at 7.17 (1H, dd, J = 8.0 and 5.0 Hz, 6-H); 7.46 (1H, dd, J = 8.0 and 1.5 Hz, 7-H); 7.92 (1H, dd, J = 5.0 and 1.5 Hz, 5-H); 11.80 ppm (1H, bs, NH) [25, 26].

The dissociative ionization of type (I) and (II) compounds takes place with cleavage of the oxazolone ring — the characteristic peak in the mass spectrum in addition to the lines of the molecular ion and polyisotopic ions [1, 2, 48] is [M^+ - CO_2] [39, 46, 47, 50] and in the case of 6-bromo-3-phenyl-2(3H)-oxooxazolo[4,5-*b*]pyridine also [M^+ - CO_2 - Br] [47]. The fragmentation of the N-substituted oxazolopyridines takes place with elimination of the substituent [50].

Data on the spectral characteristics of compounds (III) and (IV) were not found in the literature.

3. THE CHEMICAL CHARACTERISTICS OF 2-OXOOXAZOLOPYRIDINES

2-Oxooxazolopyridines are reactive substances. Their transformations involve both opening and retention of the oxazolone ring. The most widely investigated are the chemical characteristics of 2(1H)-oxooxazolo[4,5-*b*]-pyridines.

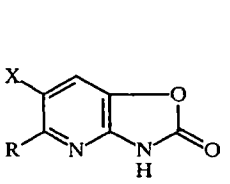
3.1. Reactions with Retention of the Oxazolone Ring

Reactions with retention of the oxazolone ring can take place at the reaction centers of both the pyridine and the oxazolone rings.

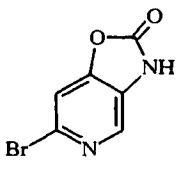
3.1.1. Reactions in the Pyridine Ring. Electrophilic substitution in the pyridine ring (halogenation, nitration) and alkylation of the condensed heterocycles have been investigated in greatest detail.

The treatment of solutions of 2(3H)-oxooxazolo[4,5-*b*]pyridines (I) in DMF with chlorine, bromine [2, 4, 11-13, 28, 64], N-bromosuccinimide [28, 29], or an excess of alkali-metal hypobromites [9] gave the 6-halogeno derivatives (XXXV).

The halogenation of 2(3H)-oxooxazolo[4,5-*c*]pyridine (III) with N-bromosuccinimide or bromine gave the 6-bromo derivative (XXXVI) [28].



XXXV

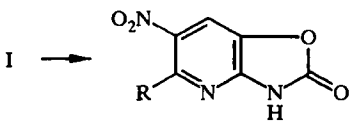


XXXVI

X = Cl, Br; R = H, Me

The 6-chloro and 6-bromo derivatives (XXIX) (R = Ph, R^1 = CF_3, X = Cl, Br) were isolated after the chlorination or bromination of oxooxazolo[5,4-*b*]pyridine (XXVIIc) in DMF [57, 58].

The nitration of compound (I) with a nitrating mixture [11-13] or fuming nitric acid [9] led to the 6-nitro derivatives (XXXVII).

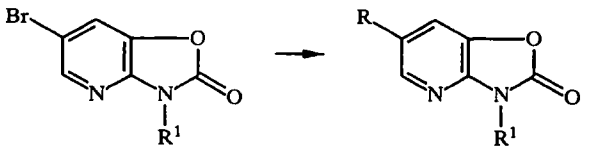


XXXVII

R = H, Me

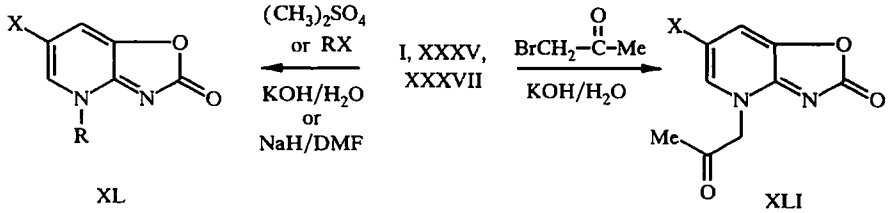
The 6-alkyl, 6-alkenyl, 6-acyl, and 6-aryl derivatives (XXXIX) were obtained from 3-alkyl-6-bromo-2(3H)-oxooxazolo[4,5-*b*]pyridines (XXXVIII) by the Heck, Stille, and Suzuki methods [5, 6, 28, 29, 64]. The reactions of 6-bromooxooxazolo[4,5-*b*]pyridines and 6-bromooxooxazolo[4,5-*c*]pyridines with isopropenyl acetate catalyzed by Pd(0) gave the respective 6-(2-oxopropyl) derivatives [28, 29]. The reaction of 6-bromo-2(3H)-

oxooxazolo[4,5-*b*]pyridine (XXXVIII) (R^1 = Me) with the organozinc compound obtained from benzyl bromide in the presence of $(Ph_3P)_4Pd$ gave a 91% yield of the benzyl derivative (XXXIX) (R = CH_2Ph, R^1 = Me) [5].



XXXVIII XXXIX

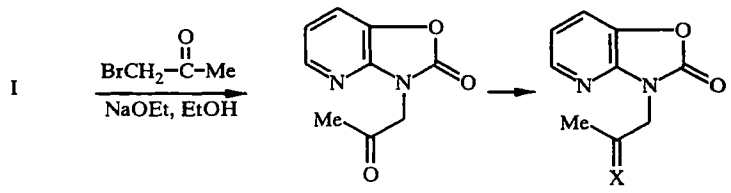
The alkylation of compounds (I, XXXV, XXXVII) with dimethyl sulfate and α-halogeno ketones in the presence of potassium hydroxide in aqueous solution or with alkyl halides in DMF led to the 4-substituted derivatives (XL) and (XLI) [9, 10]. The derivatives (XL) were formed during the acylation of 2-oxooxazolo[4,5-*b*]pyridine (I) by acyl halides in DMF in the presence of sodium hydride. It was noted that the 3-alkyl derivatives were not formed under the given alkylation conditions, although the yields of the 4-alkyl derivatives (XL) were not always indicated [9].



XL XLI

R = alkyl, acyl ; X = H, Br, NO_2

3.1.2. Reactions in the Oxazolone Ring. The alkylation of the oxazolopyridine (I) with bromoacetone in absolute ethanol in the presence of sodium ethoxide at 0-5°C led to the 3-substituted oxazolopyridine (XLIIa) [10]. The latter, like the oxazolopyridines (XLI), gave the usual derivatives of carbonyl compounds (XLIIb-e) (hydrazones, oximes, etc.) [10, 52, 65].

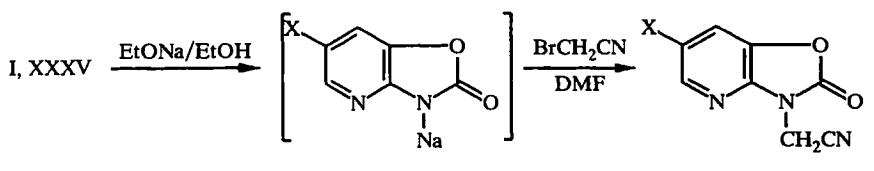


XLIIa XLIIb–e

b X = NNH_2, c X = NNHPh, d X = $NNHCONH_2$, e X = NOH

It was established by PMR spectroscopy [66] that the oxime (XLIIe) and the phenylhydrazone (XLIIc) exist only in the *E*-isomeric form irrespective of the polarity of the employed solvent, while the configuration of the hydrazone (XLIIb) changes, depending on the solvent. In less polar solvents the *Z*-conformation of compound (XLIIc), stabilized by an intramolecular hydrogen bond, predominates. With increase in the polarity of the solvent a 50:50 *E*:*Z* conformational equilibrium is observed. The use of a highly polar solvent promotes the formation of intermolecular hydrogen bonds and a stable *E*-conformation.

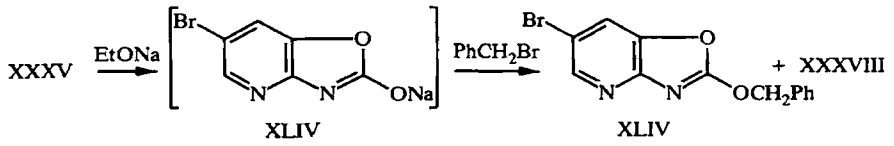
The 3-cyanomethyl derivatives (XLIII) were obtained during the treatment of the sodium salt of compounds (I) or (XXXV) with bromoacetonitrile in DMF [67].



XLIII

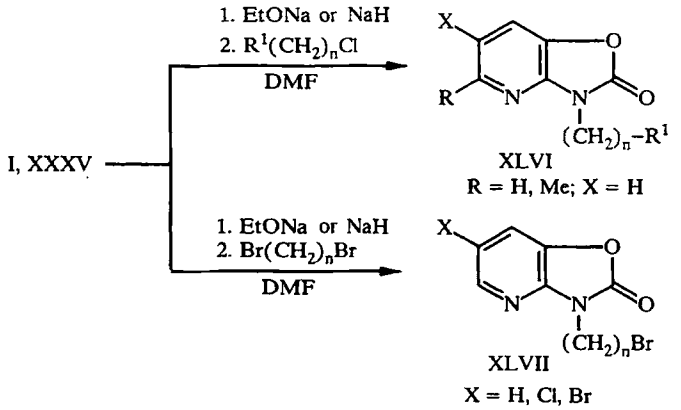
X = H, Cl, Br

During the benzylation of the sodium salt (XLIV) in DMF a mixture of the O-benzyl derivative (XLV) (38%) and 3-benzyloxooxazolopyridine (XXXVIII) ($R^1 = CH_2Ph$) (53%) was obtained [5].



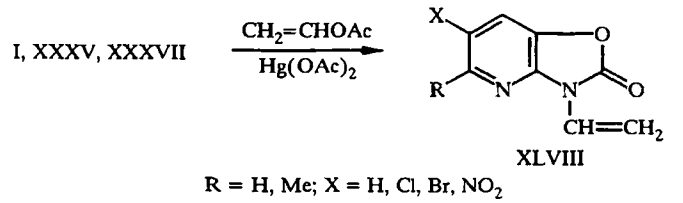
Alkylation of the lithium salt obtained by the treatment of 6-bromo-2(3H)-oxooxazolo[4,5-*b*]pyridine (XXXV) with $LiN(TMS)_2$ in THF by dimethyl sulfate or benzyl chloride led to the corresponding 3-alkyl derivative (XXXVIII) (R^1 = Me, CH_2Ph) [28, 29].

Oxazolo[4,5-*b*]pyridine (I) and its 5-alkyl and 6-bromo derivatives enter into reaction with mono- and dihalogenoalkanes in the presence of bases, forming the derivatives (XLVI) and XLVII) respectively [1, 2, 4, 7, 68, 69].



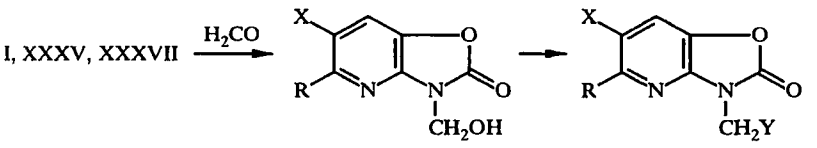
The 3-substituted derivatives (XXXIX) (R = Br) were obtained when 6-bromo-2(3H)-oxooxazolo[4,5-*b*]-pyridine (XXXV) was boiled with alkyl-, acyl-, and arylsulfonyl halides in acetone in the presence of triethylamine [48].

Compound (I) (R = H, Me) and its 6-halogeno and 6-nitro derivatives (XXXV, XXXVI) react with vinyl acetate in the presence of mercury(II) salts with the formation of 3-vinyl derivatives (XLVIII) [11, 12, 14].



The alkylation of compound (XXXV) (R = H, X = Br) by alkenes was realized by heating the reagents for 2 h without a solvent or in DMF in the presence of triethylamine; 3-substituted 6-bromo-2(3H)-oxooxazolo[4,5-*b*]-pyridines (XLVI) (n = 2, X = Br, R = H, $R^1 = CO_2Me$, CN, 2-pyridyl, 4-pyridyl) were obtained with yields of 52-87% [6].

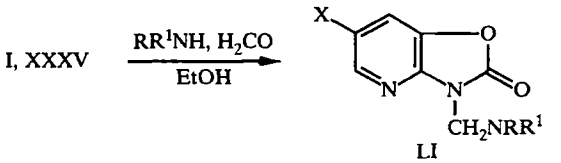
The hydroxy- and aminomethylation reactions are well known in the series of 2(3H)-oxooxazolo[4,5-*b*]-pyridine derivatives (I). When compound (I) or its derivatives (XXXV) and (XXXVII) were treated with a 37% aqueous solution of formaldehyde, 3-hydroxymethyl derivatives (XLIX) were obtained. On heating to 60°C with thionyl halides or phosphorus oxyhalides they gave 3-halogenomethyl-2-oxooxazolopyridines (L) [11-16].



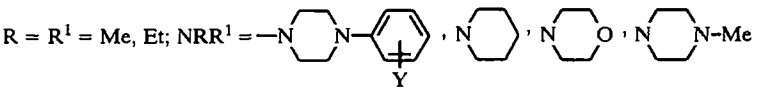
XLIX L

X = H, Cl, Br, NO_2; R = H, Me; Y = Cl, Br

N,N-Disubstituted 3-aminomethyl-2(3H)-oxooxazolo[4,5-*b*]pyridines (LI) were synthesized from compounds (I) and (XXXV) (X = Cl, R = H) by the Mannich reaction [2, 3, 7, 11].



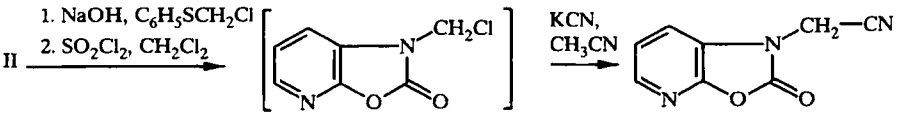
LI



X = H, Cl; Y = Cl, F, CF_3, OMe, OPh

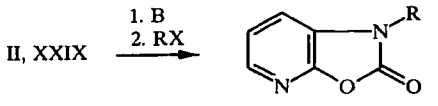
Compounds (XLVIII-LI) were used as the starting material for the production of compounds with high biological activity — the thiophosphoric and thiophosphonic acid esters of 2(3H)-oxooxazolo[4,5-*b*]pyridine [11-16, 18-23, 32].

Alkylation of 2(1H)-oxooxazolo[5,4-*b*]pyridines (II) only takes place at the nitrogen atom of the oxazolone ring. 1-Cyanomethyl-2(1H)-oxooxazolo[5,4-*b*]pyridine (LII) was obtained from compound (II) by a three-stage process through the intermediate chloromethyloxooxazolopyridine (LIII) by treating the latter with potassium cyanide [1, 26].



LIII LII

1-Substituted 2(1H)-oxooxazolo[5,4-*b*]pyridines (LIV) are formed in the reactions of the oxazolopyridine (II) and (XXIX) salts, produced by the action of sodium hydride or ethoxide and also $LiN(TMS)_2$ or diazabicycloundecene (R = R^1 = H, X = Cl) with benzyl halides, monohalogeno- and dihalogenoalkanes [1, 25-29].



LIV

B = NaH, EtONa, $LiN(TMS)_2$, DBU

As substrate it is also possible to use the potassium salt of 2(1H)-oxooxazolo[5,4-*b*]pyridine (XXVIc) for alkylation by alkyl halides, benzyl chloride, or methyl chloroacetate, leading to the 1-substituted derivatives (XXX) (R = alkyl, CH_2Ph, CH_2CO_2Me) [57, 58].

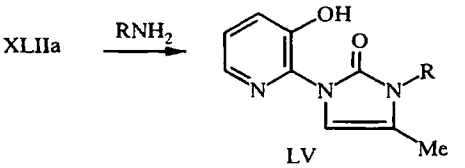
3.2. Reactions with Opening of the Oxazolone Ring

The 2-oxooxazolopyridines (I-IV) can be regarded as cyclic carbamates with a reactive functional group — NH—CO—O— particularly toward nucleophilic reagents.

There are data in the literature on the reaction of compounds (I-III) with N- and O-nucleophiles.

3.2.1. Reactions with N-Nucleophiles. The best known of the reactions of 2-oxooxazolopyridines with N-nucleophiles are the reactions with primary amines. 2(3H)-Oxooxazolo[4,5-*b*]pyridine (I) in reaction with primary alkyl-, arylalkyl-, cycloalkylamines and also with morpholine and piperidine gives N-(3-hydroxy-2-pyridyl)-N′-substituted ureas (VII). The effects of the solvents and the basicity of the amine on the rate and yield of the reactions are described in [30]. On the basis of the IR spectra the authors suppose that the intermediates in these reactions are the corresponding alkylammonium salts of 2(3H)-oxooxazolo[4,5-*b*]pyridine.

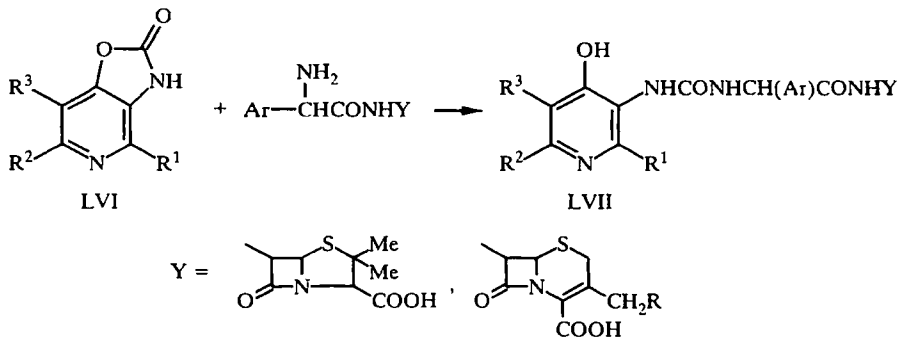
It was noted [52] that the 3-substituted oxazolo[4,5-*b*]pyridine (XLIIa) in reaction with primary amines gives compounds (LV).



LV

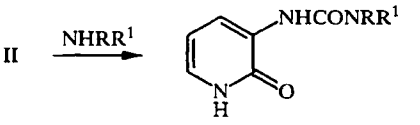
R = alkyl, benzyl, cyclohexyl

With amino derivatives of the penicillin or cephalosporin series in the presence of DMF and triethylamine at 20°C the oxazolone ring in compounds (LVI) is cleaved over 1-2 h with the formation of 3-pyridylureas (LVII) [60-62].



LVI LVII

2(1H)-Oxooxazolo[5,4-*b*]pyridine (II) reacts with amines, forming N-(2-oxo-3-pyridyl)ureas (LVIII) [26].

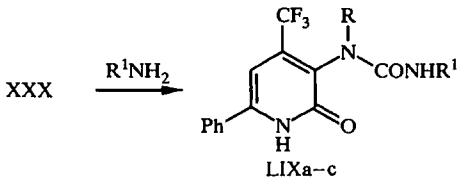


LVIII

R, R^1 = $-(CH_2)_5-$, $-CH_2CH_2OCH_2CH_2-$;

R = H, R^1 = Pr (n)

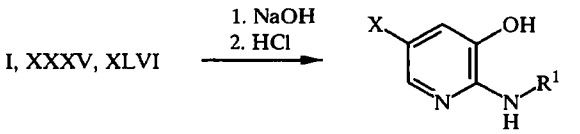
In the reactions of 7-trifluoromethyl-5-phenyl-2(1H)-oxooxazolo[5,4-*b*]pyridine (XXVIIc) with primary alkyl- and arylamines, amino alcohols, and compounds containing a secondary amino group it was established that in all cases the oxazolone ring is opened with the formation of the respective 2-oxo-3-pyridylureas (XXXII) [56, 58, 59, 70]. With amines having higher basicity the reaction takes place even at room temperature, while with ammonia it takes place at 150°C and only under pressure. 1-Substituted oxooxazolopyridines (XXX) also react with amines with the formation of N,N′-dialkyl-N-(2-oxo-3-pyridyl)ureas (LIXa-c) [59].



LIXa–c

a R = Me, $R^1 = CH_2Ph$; b R = Me, $R^1 = (CH_2)_4Me$; c $R = R^1 = CH_2Ph$

3.2.2. Reactions with O-Nucleophiles. The reactions of 2-oxooxazolopyridines with O-nucleophiles have been studied not enough. In the series of 2(3H)-oxooxazolo[4,5-*b*]pyridines (I), (XXXV) and 3-substituted oxazolo[4,5-*b*]pyridines (XLVI) the reaction with a 10% aqueous solution of sodium hydroxide is known. It leads to the formation of 2-amino-3-hydroxypyridines (V) or (LX) respectively [1, 64].

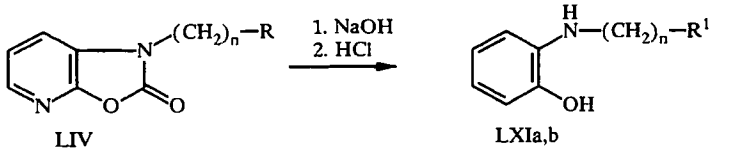


V R^1 = H, X = Br

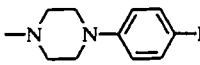
LX R^1 = alkyl, heteryl, X = H

The *in vitro* metabolic biotransformation of 2-oxooxazolo[4,5-*b*]pyridine hydrochloride (XLVI) (R = X = H; n = 2; R^1 = 4-phenyl-1-piperazinyl) also gives a compound of type (LX) [71].

Cleavage of the oxazolone ring of 1-substituted 2(1H)-oxooxazolo[5,4-*b*]pyridines (LIV) by a 10% aqueous solution of sodium hydroxide leads to good yields of the pyridines (LXIa, b). According to the statement by the authors in [1], compounds (LXIa, b) actually exist in the hydroxy form, as demonstrated by IR and PMR spectroscopy.

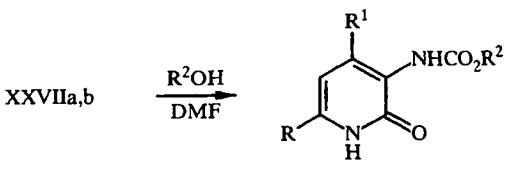


LIV LXIa,b

a R = R^1 =  (n = 2...4), b R = –CN; R^1 = –COOH (n = 2)

After prolonged boiling with water 2(1H)-oxooxazolo[5,4-*b*]pyridine (II) [26] and its derivative (XXVIIc) [70] gave the corresponding 3-amino-2-(1H)-pyridones (XXIV) and (XXVIIIc). The relative instability of 2-oxooxazolo[4,5-*b*]pyridines [2, 27] and 2-oxooxazolo[5,4-*b*]pyridines in an acidic medium [70], leading to opening of the oxazolone ring, was also mentioned.

When the oxooxazolo[5,4-*b*]pyridines (XXVIIa-c) were boiled in a mixture of DMF and alcohol, the oxazole ring was cleaved with the formation of the corresponding carbamates (LXII) [57, 58, 70].



LXII

R^2 = alkyl, propargyl, hydroxyethyl, metoxyethyl

The carbamates (XXXI) were obtained similarly from the 1-substituted 2-oxooxazolo[5,4-*b*]pyridines (XXX) in the presence of potassium hydroxide [59].

It follows from a review that 2-oxooxazolopyridines have been studied insufficiently, but they open up broad possibilities for the synthesis of the most varied nitrogen structures, i.e., 3-amino-2(1H)-pyridines, the corresponding trisubstituted carbamates, and N,N,N′-trisubstituted ureas, which have until now been slightly investigated. The prospects for this series of compounds are also determined by the high biological activity of the 2-oxooxazolopyridine derivatives.

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