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SYNTHESIS AND PROPERTIES OF 3-CYANOPYRIDINE-2(1H)-CHALCOGENONES. REVIEW

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Data published over the last 10 years on the synthesis, reactivity, and biological activity of 3-cyanopyridine-2(1H)-chalcogenones are reviewed.

1. INTRODUCTION

The chemistry of chalcogen-containing pyridines has developed quite vigorously over the last decade, and the greatest attention has been paid to 3-cyanopyridine-2(1H)-chalcogenones. This is due to their unique properties, which make it possible to use them not only in the production of dyes, pigments, and fuel and oil additives but also for the creation of medicinal products became of the broad spectrum of biological activity of their derivatives.

The chemistry of 3-cyanopyridin-2(1H)-ones, 3-cyanopyridine-2(1H)-thiones, and 3-cyanopyridine-2(1H)-selenones and their derivatives has been reviewed up to 1990 [1, 2]. The ever-increasing interest in the production and biological activity of derivatives of these heterocyclic systems, as witnessed in particular by the considerable number of patents, has brought about the need to analyze and classify the data published on these matters over the recent years. Two approaches to classification of the data are possible, i.e., according to the biological activity of the pyridinechalcogenones or the methods of their synthesis. We chose the second method and classified them according to the type of initial substrate.

2. METHODS FOR THE SYNTHESIS OF 3-CYANOPYRIDINE-2(1H)-CHALCOGENONES

2.1. Syntheses Based on Carbonyl and Enaminocarbonyl Compounds

As previously, some of the main methods used in the synthesis of biologically active 3-cyanopyridine-2-(1H)-chalcogenones over the last decade employed carbonyl compounds and their β-enamino (alkoxy) derivatives as the starting materials. Here, on account of their high reactivity [3] the latter have often made it possible to achieve a specific synthesis and to obtain higher yields of the final products. As before, cyanoacetamides and the corresponding thio- and selenoamides I were most widely used as the second component. Thus, the reaction of β-dimethylaminoacroleins II with cyanoacetamide Ia when heated in alcohol in the presence of alkali-metal alkoxides took place in a well defined manner with the formation of 5-monosubstituted 3-cyanopyridin-2(1H)-ones III and their salts IV [4-14]. In this case both nucleophilic substitution of the dialkylamino group and condensation of the cyanoacetamide Ia with the aldehyde group of the aminoacrolein II are possible with subsequent cyclocondensation of the intermediates V and VI to pyridone III.

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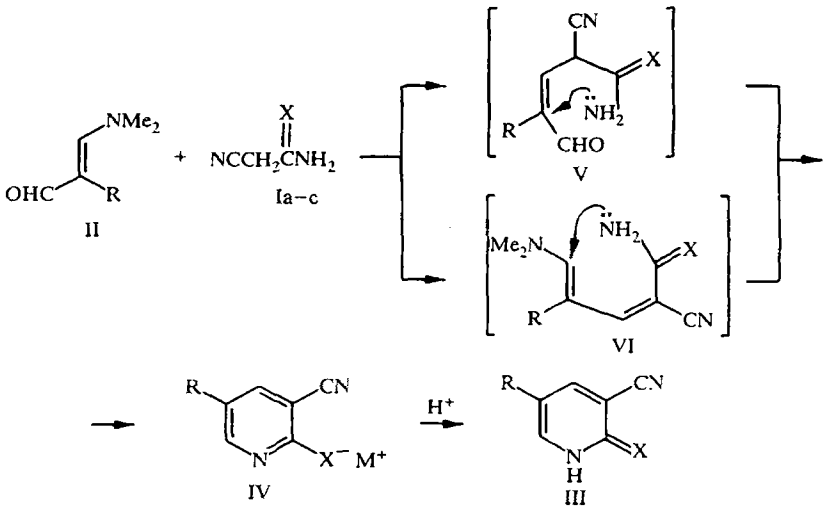
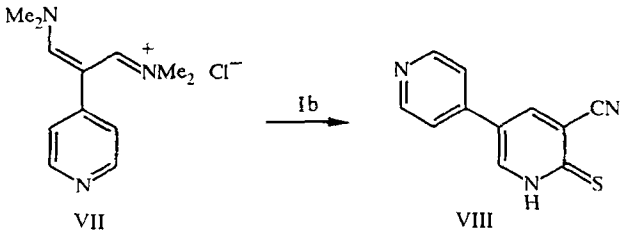
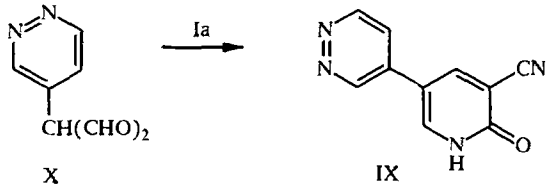


R =Ar, Het; X = O (a), S (b), Se (c)

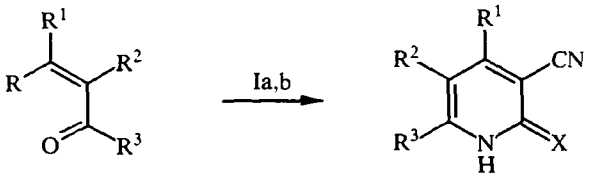
The analogous reaction of the enamine VII with cyanothioacetamide Ib leads to 3-cyano-5-(4-pyridyl)-pyridine-2(1H)-thione VIII [15].



In a similar way the reaction of the dialdehyde X with cyanoacetamide Ia in ethanol in the presence of sodium ethoxide was used successfully for the synthesis of the pyridone IX [16].

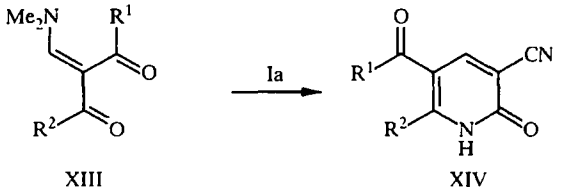


It must be emphasized that a fairly wide range of compounds based on the pyridinechalcogenones XI can be obtained if α-substituted β-enamino(alkoxy) ketones are used. They were successfully synthesized by the condensation both of β-enamino ketones having functionally substituted heterocyclic fragments at the α-position and of substituted ethylenes XII with the amides Ia,b in alcohol or DMF in the presence of sodium methoxide or hydroxide [9-27].



R = OEt, NMe_2, N⟨⟩O ; R^1 = H, Alk; R^2 = Ar, Het; R^3 = Alk, X = O, S

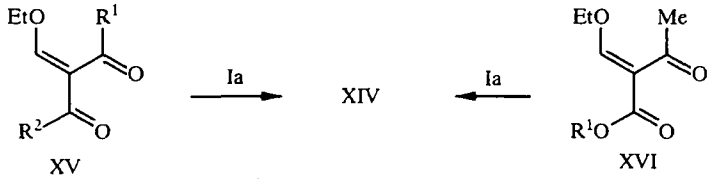
It is necessary to mention the prospects of using the β-enamino ketones derived from symmetrical and unsymmetrical 1,3-diketones in the synthesis of functionally substituted pyridones [28-41]. Thus, for example, the reaction of substituted 2-dimethylaminomethylene-1,3-diones XIII with cyanoacetamide Ia takes place when they are heated under argon in the presence of sodium hydride in anhydrous THF [28-31, 36] or DMF [37] or treated with alkali-metal alkoxides in alcohol [30, 38-41] and leads to the formation of the pyridones XIV.



XIII XIV

R^1, R^2 = Alk, Ar, Het, cycloalkyl

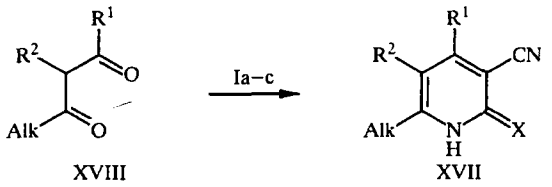
The pyridones XIV can also be obtained by the reaction of ethoxymethylene-1,3-diketones XV [42] or ethoxymethyleneacetoacetic esters XVI [43, 44] with cyanoacetamide Ia.



XV XVI

R^1, R^2 = H, Alk, cycloalkyl

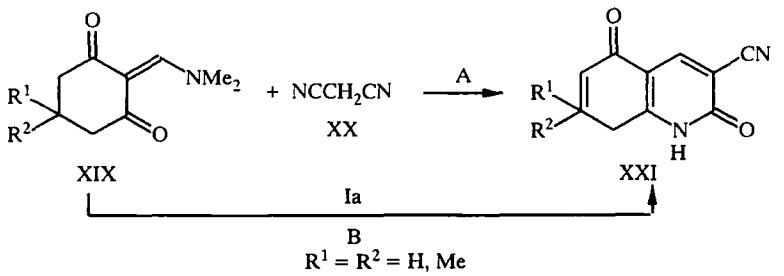
1,3-Dicarbonyl compounds have been used quite widely in the synthesis of various 3-cyanopyridine-2-chalcogenones XVII. The major strategy here lies in the choice of the appropriate 1,3-diketones XVIII and their subsequent condensation with the amides Ia-c in the presence of basic catalysts [45-76].



XVIII XVII

R^1, R^2 = H, Alk, Ar, Het; X = O, S, Se

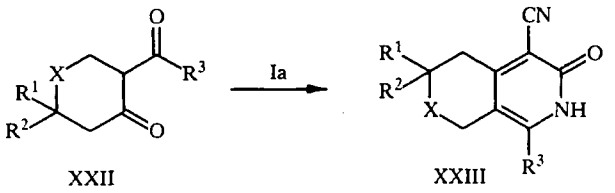
Enamines of the 1,3-cyclohexanedione series have been used successfully in the synthesis of hydrogenated quinolines. Thus, the reaction of 2-dimethylaminomethylenecyclohexane-1,3-diones XIX with an equimolar amount of malononitrile XX (method A) [77] or cyanoacetamide Ia (method B) [41, 78] in boiling alcohol in the presence of sodium ethoxide gives fairly high yields of 3-cyano-6,8-dihydroquinoline-2,5-diones XXI.



XIX XXI

$R^1 = R^2$ = H, Me

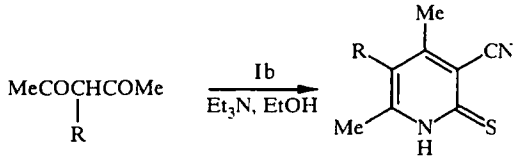
It was also shown that the 3-oxopyrano[3,4-*c*]dihydropyridines and naphthiridines XXIII are formed during the reaction of the diketones XXII with cyanoacetamide Ia [45, 49]



XXII XXIII

X = O, NR^4; R^1 = R^2 = H, Me;
R^3, R^4 = Alk, Ar, Het

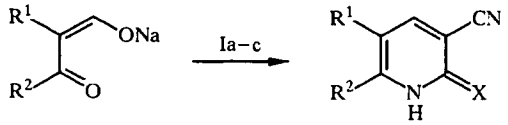
In turn, the 3-substituted 2,4-pentanediones XXIV, obtained by alkylation of the Na(K) salts of acetylacetone with the respective halides, react with the cyanothioacetamide Ib in absolute ethanol in the presence of triethylamine with the formation of 5-substituted 3-cyano-4,6-dimethylpyridine-2(1H)-thiones XXV [79].



XXIV XXV

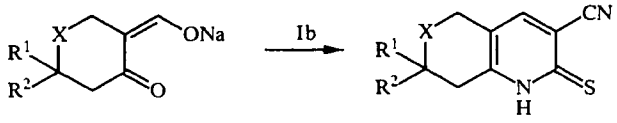
R = CH_2COPh, $CH_2COC_6H_4$-Br-4, $CH_2CH{=}CH_2$, $CH_2CH{=}CHMe$

The regioselective reactions of the sodium salts of β-ketoaldehydes XXVI [60, 80-88] and of their cyclic analogs XXVII [89-91] with the amides Ia-c are interesting. They lead to substituted 3-cyanopyridin-2(1H)-ones, 3-cyanopyridine-2(1H)-thiones, and 3-cyanopyridine-2(1H)-selenones XXVIII and their condensed analogs XXIX, which are used in the synthesis of biologically active products, including products for the treatment of AIDS.



XXVI XXVIII

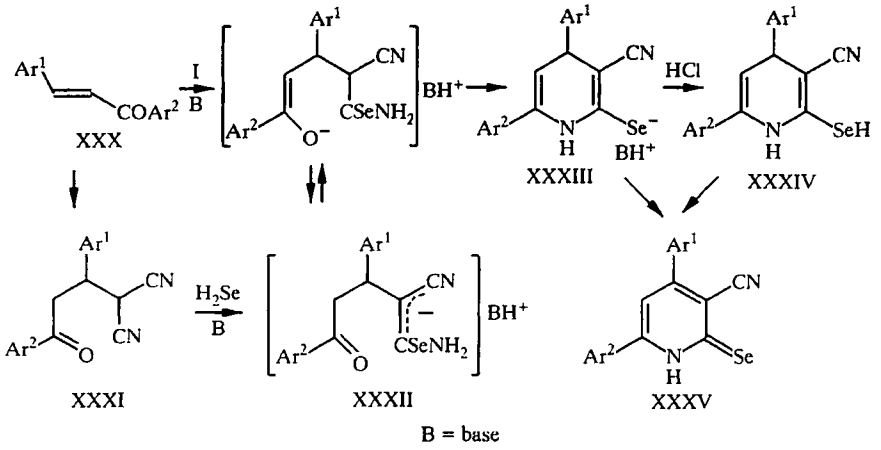
R^1 = Et, Pr; R^2 = Me; X = O; R^1 = R^2 = Me; X = S; R^1 = H;
R^2 = 1-adamantyl, X = Se



XXVII XXIX

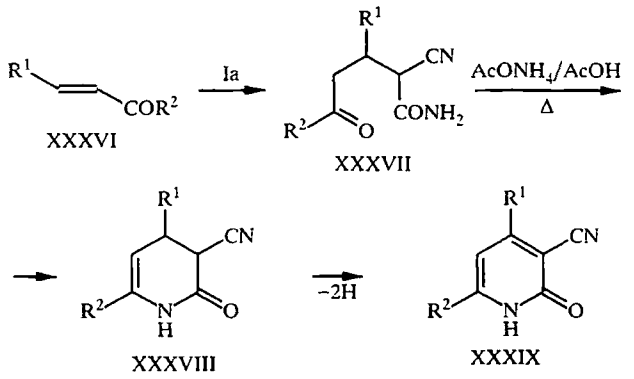
R^1 = R^2 = H, Me; X = O, S, $(CH_2)_n$, where n = 0–3, 5

Among the other carbonyl compounds the chalcones XXX and the butanone derivatives XXXI have also been used in the synthesis of pyridinechalcogenones. Thus, the reactions of chalcones XXX with the amide Ic and of the butanone XXXI with hydrogen selenide in the presence of an excess of an organic base give the pyridine derivatives XXXIII-XXXV through a stage involving the formation of the Michael adducts XXXII [92-94].



B = base

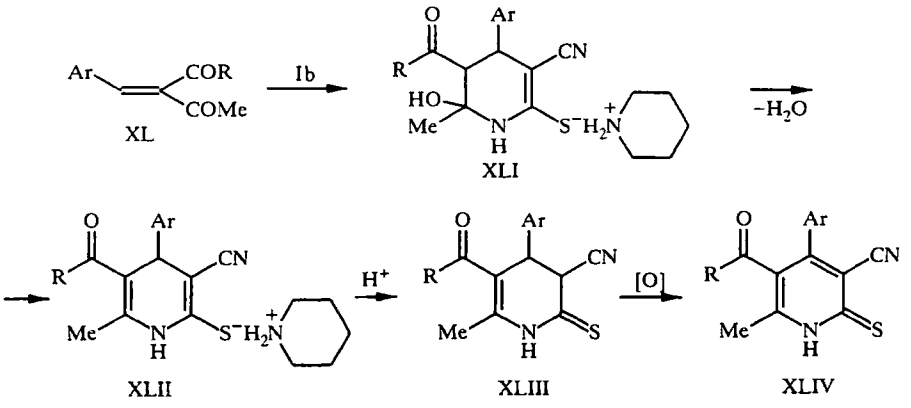
In the analogous reaction of the ketones XXXVI with the cyanoacetamide Ia it is possible to isolate the amide XXXVII, which undergoes cyclization when heated in acetic acid in the presence of ammonium acetate to give the partially hydrogenated pyridone XXXVIII; during oxidation the latter is dehydrogenated to the pyridone XXXIX [95, 96].



R^1, R^2 = Ar, Het

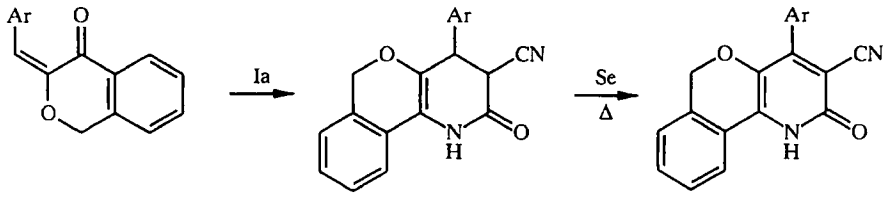
The ketones XXXVI react similarly with ethyl cyanoacetate to form the pyridones XXXVIII and XXXIX [96-98].

Compounds XL react with cyanothioacetamide Ib in alcohol in the presence of piperidine with the formation of the tetrahydropyridines XLI, which are dehydrated to the 1,4-dihydropyridine-2-thiolates XLII. The acidification of the latter gives the thiones XLIII and XLIV [99, 100].



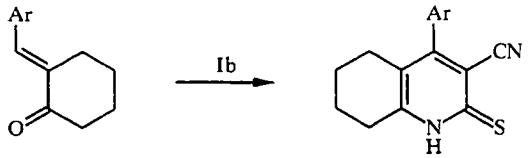
R = Me, OEt

The reaction of α,β-unsaturated cyclic ketones with the amides Ia,b or cyanoacetic ester takes place in a similar way with the formation of the corresponding annellated 3-cyanopyridin-2(1H)-ones and 3-cyanopyridine-2(1H)-thiones. Thus, 3-cyano-3,4-dihydroisochromano[3,4-*b*]pyridin-2(1H)-ones XLVI and their dehydrogenated analogs XLVII were obtained from isochroman-4-one XLV and cyanoacetamide by boiling in alcohol in the presence of piperidine [101].



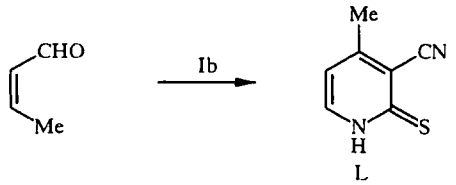
XLV XLVI XLVII

The analogous condensation of the cyclic ketone XLVIII with cyanothioacetamide Ib in methanol in the presence of sodium methoxide leads to the formation of the quinolines XLIX. In this case it was not possible to isolate the intermediate 3,4-dihydropyridines of type XLVI [102-105].



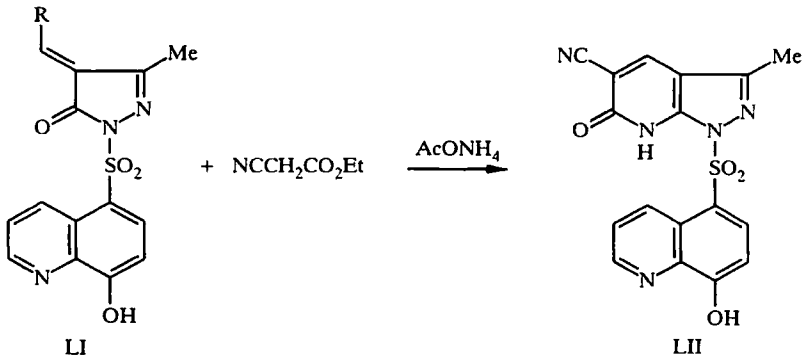
XLVIII XLIX

The reaction of crotonaldehyde with the amide Ib in boiling ethanol in the presence of sodium ethoxide, giving a 48% yield of 3-cyano-4-methylpyridine-2(1H)-thione (L) has been described [106].



L

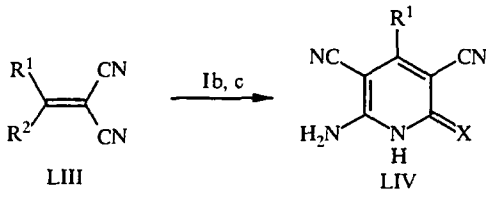
To conclude this section it is necessary to mention the important example of the reaction of hetaryl-5-sulfonyl-8-hydroxyquinolines LI with cyanoacetic ester in the presence of ammonium acetate, leading to a new heterocyclic system LII [107].



LI LII

2.2. Syntheses Based on α,β-Unsaturated Nitriles

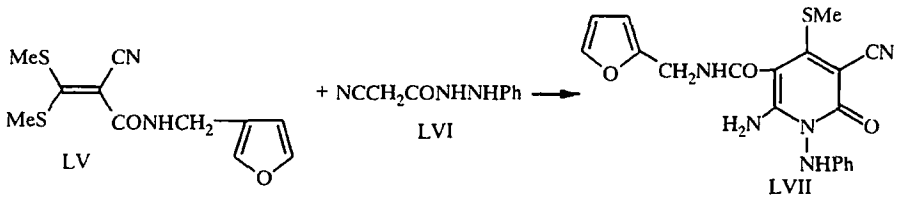
Another type of compounds used extensively in the synthesis of 3-cyanopyridine-2-chalcogenones and their derivatives is α,β-unsaturated nitriles and particularly those containing a leaving group at β-position [60, 92, 108-115]. Thus, 3,5-dicyanopyridine-2(1H)-thiones and 3,4-dicyanopyridine-2(1H)selenones LIV were obtained by the reaction of substituted acrylonitriles LIII with the amides Ib,c in DMF in the presence of triethylamine [109] or in ethanol in the presence of sodium ethoxide [60, 92, 108, 110, 111].



LIII LIV

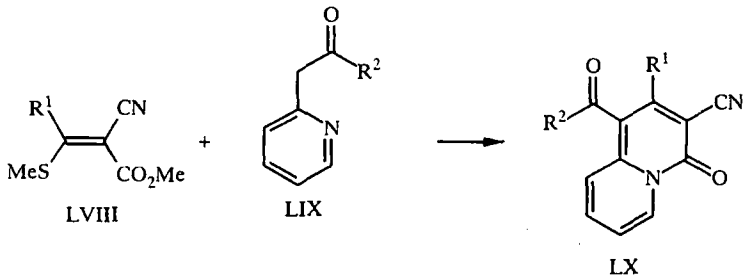
R^1 = H, Ar, SMe; R^2 = OMe, OEt, SMe; X = S, Se

Substituted 3-cyanopyridone LVII was obtained in the reaction of N-furfurylacrylamide LV with cyanoacetohydrazide LVI [113].



LV LVI LVII

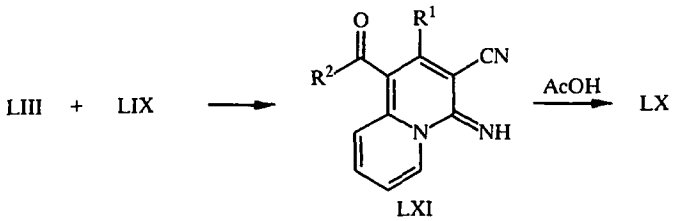
The use of 2-cyanoacrylic ester LVIII and the ketone LIX in the analogous reaction leads to derivatives of 4H-quinolizinones LX [114, 116-119].



LVIII LIX LX

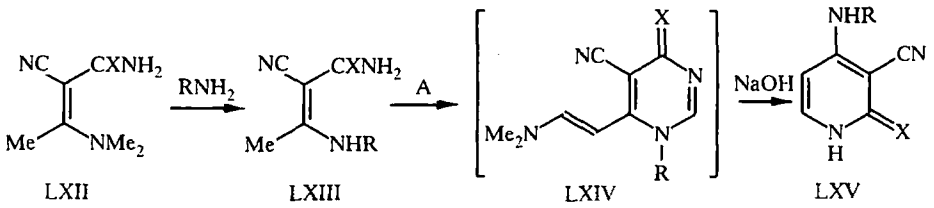
R^1 = SMe, Ar, Het; R^2 = Alk, OAlk

Compounds LX were also obtained by the reaction of dicyanoethylene LIII with the ketone LIX in DMF with subsequent boiling of the obtained iminoquinolizine LXI in acetic acid [114].



LXI

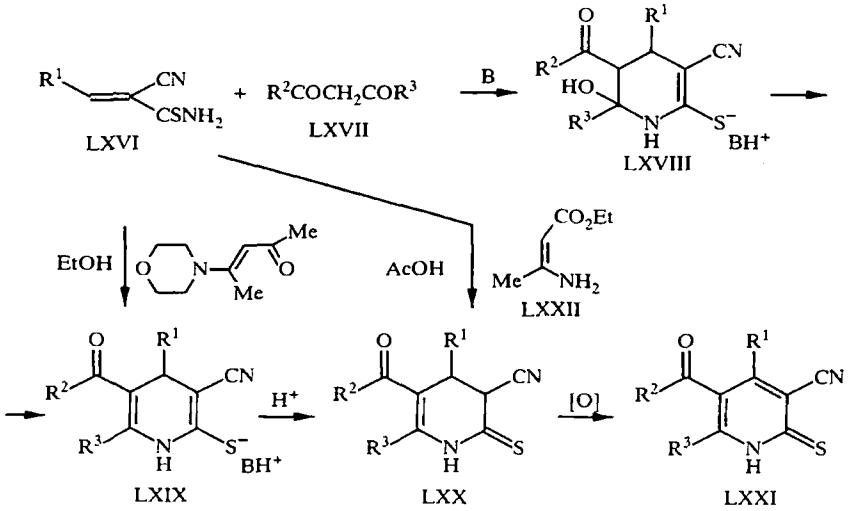
The transamination of α-cyanocrotonamides LXII in acetic acid gave the enamines LXIII, the reaction of which with an excess of DMF acetal gave the pyrimidine LXIV. When the latter was treated with aqueous alkali, the pyrimidine ring was opened, and spontaneous cyclization to the pyridinechalcogenones LXV occured [120, 121].



LXII LXIII LXIV LXV

A = $Me_2NCH(OEt)_2$; R = Ph, $Me_2N(CH_2)_2$, $Ph_2NCH(CH_2CH_2)_2N(CH_2)_3$, 3-piperidinopropyl, 3-morpholinopropyl, 3-pyridylmethyl; X = O, S

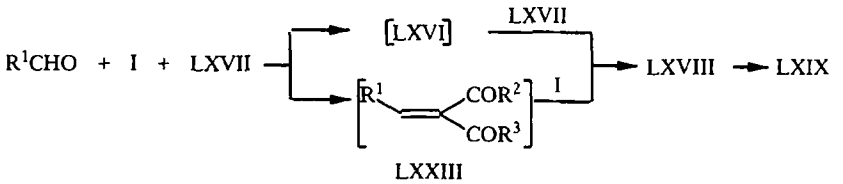
The reaction of substituted acrylonitriles LXVI with 1,3-diketones LXVII in alcohol in the presence of organic bases, in analogy with the reaction of compounds XL with Ib, leads to the formation of tetrahydropyridines LXVIII. Subsequent transformations of the latter leads to 1,4-dihydropyridine-2-thiolates LXIX and thiones LXX and LXXI [99, 100, 122-127].



LXVI LXVII LXVIII LXIX LXX LXXI LXXII

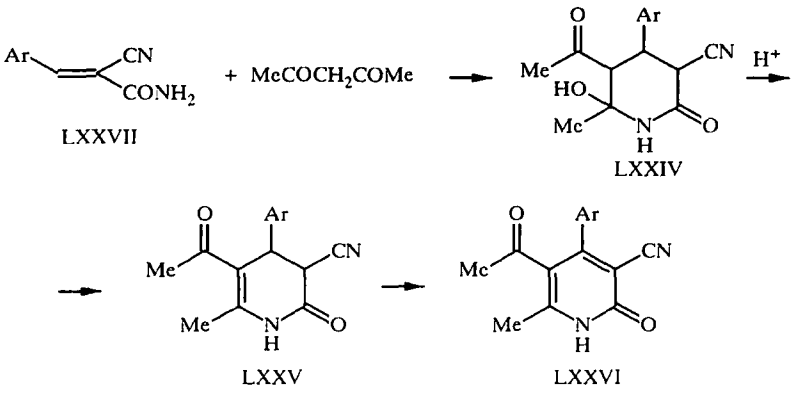
R^1 = Ar, Het; R^2 = Me, NH_2, OMe, OEt; R^3 = Me, Ph;
B = morpholine, piperidine

The pyridinethiones LXX and LXXI were also obtained by the condensation of ethyl β-aminocrotonate LXXII with acrylonitrile LXVI followed by intramolecular cyclization of the respective δ-keto- and δ-imino-thioamides in the presence of bases and acids [100]. In addition a one-step procedure for the production of the pyridinethione LXXI from compounds LXVI and LXVII without isolation of the hydrogenated pyridines LXVIII-LXX has been reported [128, 129]. It should be noted that in the three-component condensation of the aldehydes LXXII, cyanothioacetamide Ib, and 1,3-diketone LXVII in the presence of piperidine [123, 124, 130] substituted alkenes LXVI and LXXIII are formed and their subsequent reaction with the CH acids LXVII and Ib, respectively, leads to the salts LXVIII and LXIX.

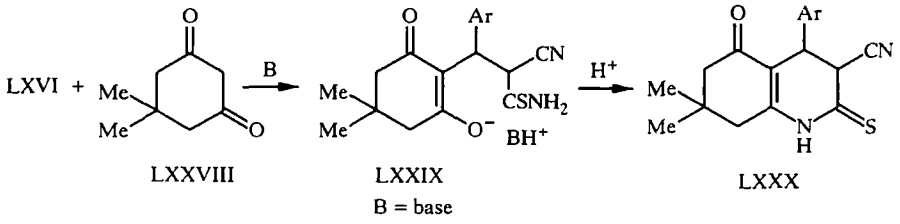


LXXIII

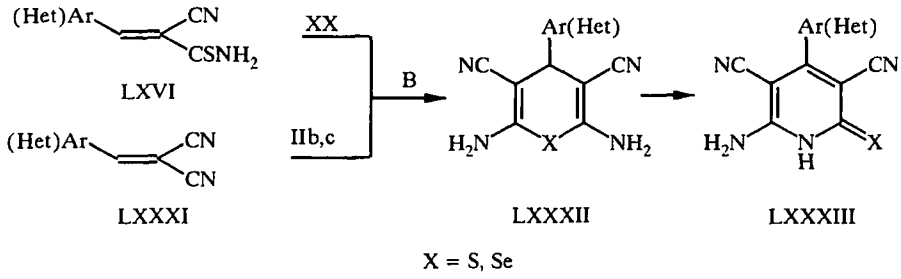
The acrylamide LXXVII and acetylacetone were used in the synthesis of the derivatives of 3-cyanopyridin-2(1H)-ones LXXIV-LXXVI, but the formation of salts of the LXVIII and LXIX type was not observed [131].



The reaction of the substituted acrylonitriles LXVI with the cyclic 1,3-dicarbonyl compound dimedone LXXVIII in the presence of an organic base leads to the formation of the Michael adducts LXXIX as intermediates. On heating and subsequent acidification they are transformed into the 3-cyanohexahydro-quinolinethiones LXXX [132-136].

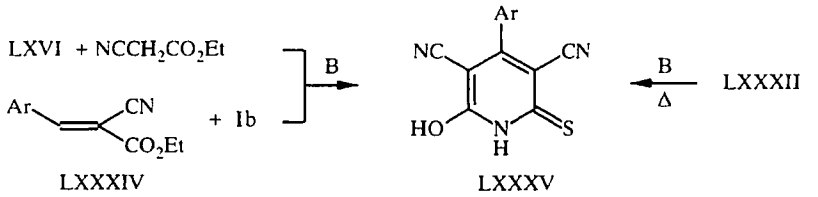


The reactions of the acrylonitriles LXVI with malononitrile XX or of the aryl(hetaryl)-methylenemalononitriles LXXXI with the amides IIb,c in boiling ethanol in the presence of an organic base take place by a Michael reaction with the formation of thio(seleno)pyrans LXXXII, which recyclize under thermodynamically controlled conditions to the 3,5-dicyanopyridine-2(1H)-chalcogenones LXXXIII with fairly high yields [137-152].



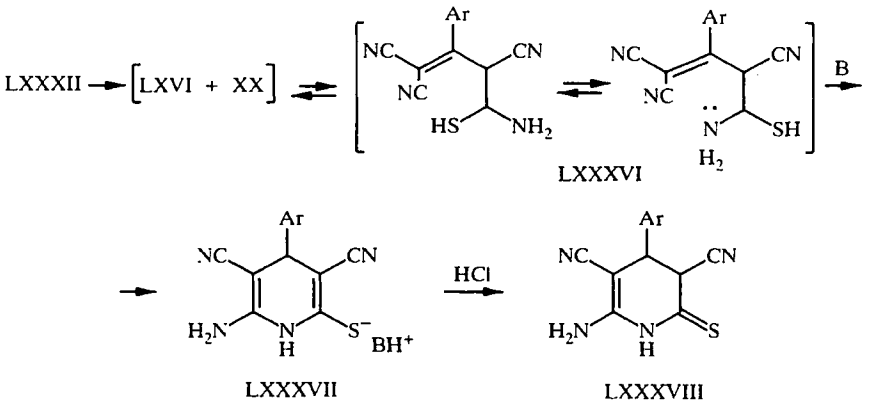
The synthesis of compounds LXXXIII was simplified considerably by use of the three-component condensation of aromatic aldehydes, malononitrile, and cyanothioacetamide Ib [148, 149], in the course of which any of the paths mentioned above can be realized, and by the reaction of substituted acrylonitriles LXVI with the amide Ib in boiling alcohol in the presence of a base [140, 153].

In the reaction of the acrylonitriles LXVI with ethyl cyanoacetate [153, 154] or of arylmethylenecyanoacetic ester LXXXIV with the amide Ib [138, 145, 153-155] in alcohol in the presence of an organic base the pyridinethiones LXXXV are formed. The latter were also obtained by the recyclization of the thiopyrans LXXXII in boiling aqueous alcohol in the presence of triethylamine, which takes place with the simultaneous hydrolysis of one amino group [138].



LXXXIV LXXXV

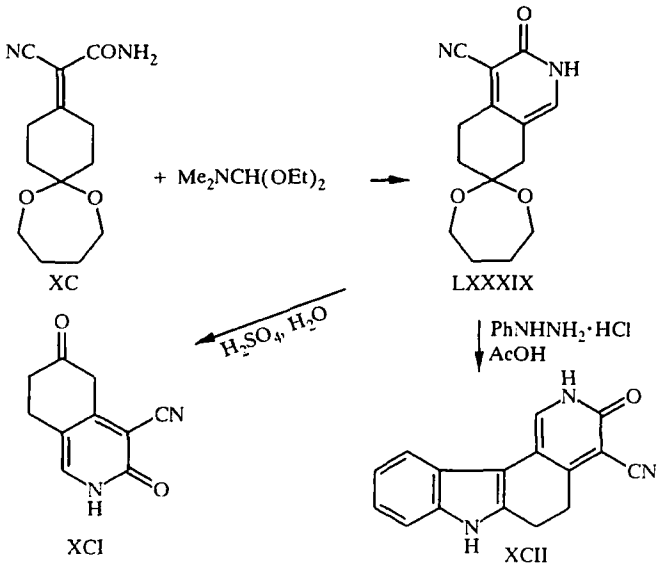
Recyclization of thiopyrans was also used successfully in the synthesis of partially hydrogenated pyridinethiones. Thus, when heated in alcohol in the presence of N-methylmorpholine thiopyrans LXXXII undergo cycloelimination with the formation of arylmethylenecyanothioacetamides LXVI and malononitrile XX, the subsequent reaction of which leads to the Michael adducts LXXXVI. Further intramolecular cyclization of the adducts LXXXVI by the action of a base gives high yields of the substituted 1,4-dihydropyridine-2-thiolates LXXXVII, which as a result of hydrolysis form stable 6-amino-4-aryl-3,5-dicyano-3,4-dihydropyridine-2(1H)-thiones LXXXVIII [156, 157].



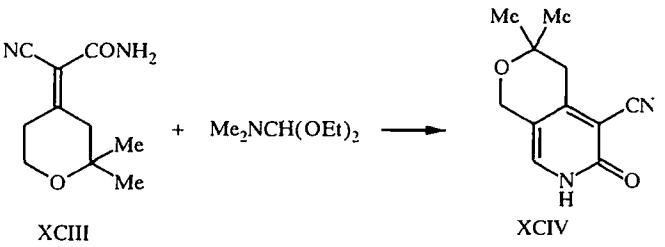
LXXXVII LXXXVIII

The ever-increasing interest over the last decade in the development of methods for the synthesis of functionally substituted di- and tetrahydropyridinechalcogenones is due to their significant synthetic potential in the production of practically important substances, including those having various types of biological activity. We note above all the systematic investigation of the reaction of α,β-unsaturated carbonyl compounds and nitriles with CH acids. This made it possible to discover the principal rules governing these processes and to develop rational approaches to the regio- and stereoselective synthesis of a large number of new biologically important alkyl-, aryl-, heteroaryl-, and spirocycloalkane-substituted di- and tetrahydropyridinechalcogenones [2, 136, 158-199]. A detailed analysis of these papers was published in the review [200]. Here we mention only that the partially hydrogenated pyridine ring was constructed almost in a single operation from simple and readily available substrates and reagents. This was one of the main advantages of all the developed methods for the synthesis of the indicated types of compounds.

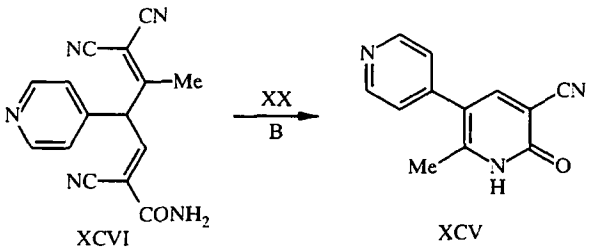
Among the other papers on the synthesis of hydrogenated N-heterocyclic chalcogenides it is necessary to mention a new approach to the synthesis of tetrahydroisoquinolinone LXXXIX, involving the reaction of the unsaturated nitrile amide XC with DMF acetal. This allowed to obtain a partially hydrogenated isoquinolinedione XCI and pyrido[3,4-*c*]carbazole XCII [201].



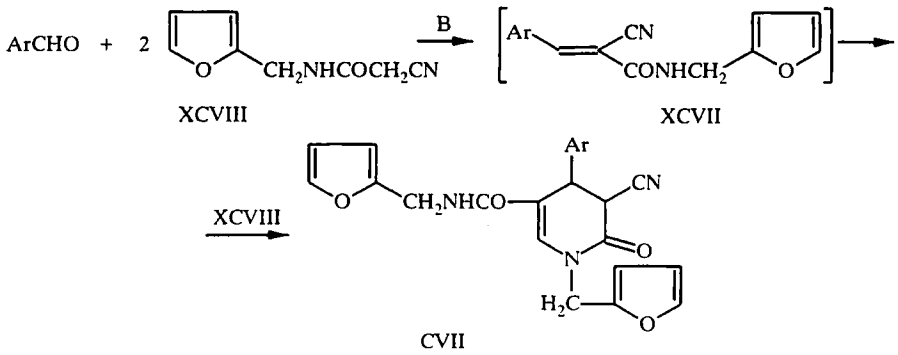
The analogous reaction of the nitrile amide XCIII with DMF acetal was also used for the production of substituted 3-oxopyrano[3,4-*c*]pyridine XCIV [45].



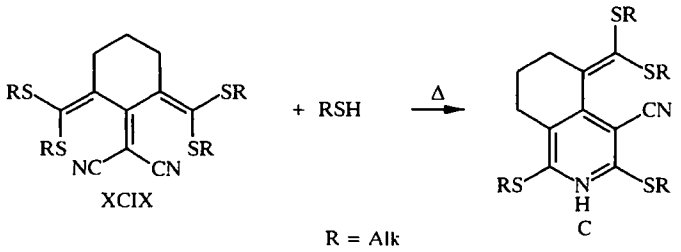
There are patent data on the production of milrinone XCV by the cyclization of the tricyano-1,4-dienecarboxamide XCVI, accompanied by the elimination of malononitrile XX, in the presence of sodium hydroxide, sodium carbonate, or sodium alkoxide in alcohol [202].



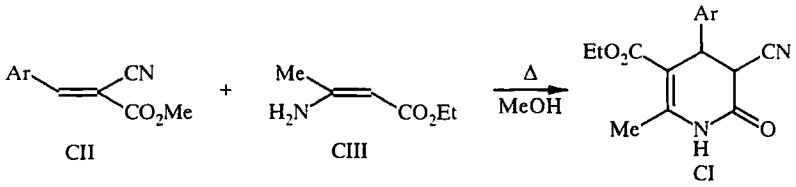
An interesting method for the synthesis of substituted tetrahydronicotinonitriles XCVII is the reaction of N-(furylmethyl)cyanoacetamides XCVIII with aromatic aldehydes in protic solvents in the presence of bases at 10-30°C [203].



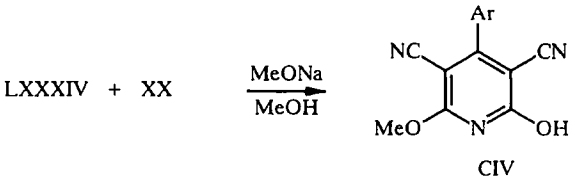
The hydrogenated isoquinolines C were obtained by boiling cyclohexylidenemalononitrile XCIX with alkanethiols in the presence of potassium carbonate in dry DMF [204].



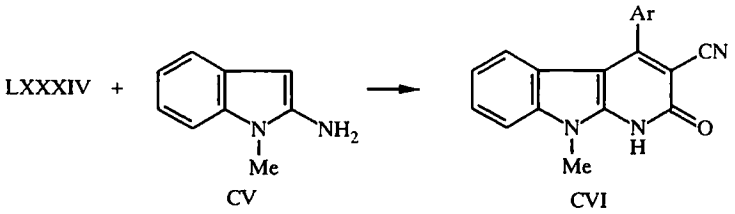
To obtain the substituted hydrogenated pyridones CI the acrylonitrile CII was boiled for 15 h with β-aminocrotonic ester CIII in methanol [205].



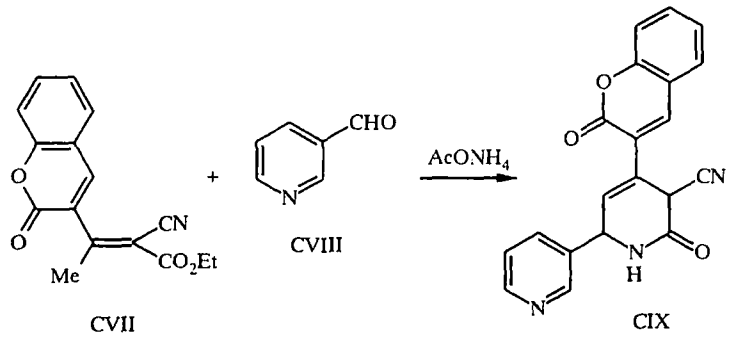
4-Aryl-3,5-dicyano-6-methoxypyridines CIV were obtained by the reaction of the esters LXXXIV with malononitrile XX in methanol in the presence of sodium methoxide [206].



On the other hand, the reaction of the esters LXXXIV with 2-amino-1-methylindole CV leads to derivatives of pyrido[2,3-*b*]indole CVI [207, 208].

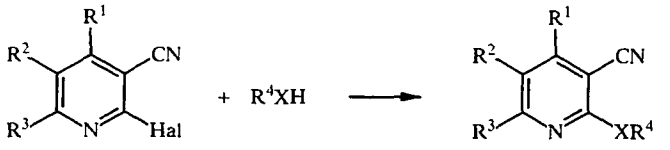


The reaction of the ester CVII with the aldehyde CVIII in the presence of an excess of ammonium acetate leads to the formation of a substituted partially hydrogenated 3-cyanopyridone CIX [98].



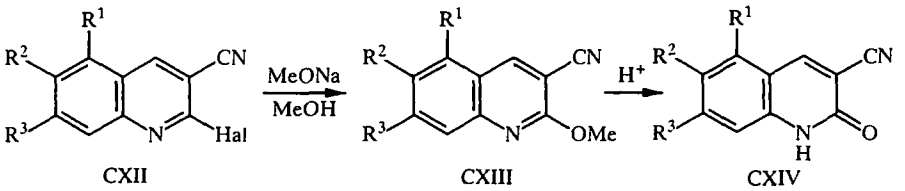
2.3. Syntheses Based on Halogeno(amino)pyridines

Nucleophilic substitution in the series of 2-halogenopyridines CXI has also been used successfully for the synthesis of derivatives of 3-cyanopyridin-2(1H)-ones and 3-cyanopyridine-2(1H)-thiones CX. The nucleophilic reagents were alcohols [209-213], phenols [214-218], naphthols [219-222], hydroxyquinolines [223, 224], and hydroxyindoles [225, 226] in the presence of alkali-metal hydrides, hydroxides, or salts.



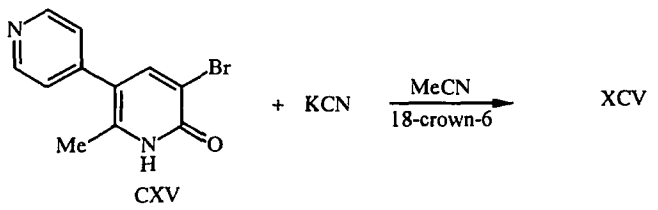
R^1, R^2, R^3 = H, Alk, Ar, RNH, CN, Hal, $CHal_3$, CF_3SO_2, CF_3O, NO_2,
R^4 = Alk, Ph, quinolyl, indolyl; Hal = Cl, Br, I; X = O, S

The methoxylation of 2-halogeno-3-cyanoquinolines CXII gives the 2-methoxy derivatives CXIII, the acid hydrolysis of which leads to the quinolinones CXIV [227-231].

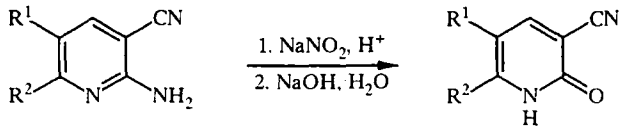


R^1 = H, Alk, CN, NO_2, Hal; R^2 = H, Alk, Het, Hal, HSO_3; R^3 = Het

A simple method was also proposed for the preparation of milrinone XCV by the reaction of 3-bromopyridin-2(1H)-one CXV with potassium cyanide in acetonitrile in the presence of 18-crown-6 [232].



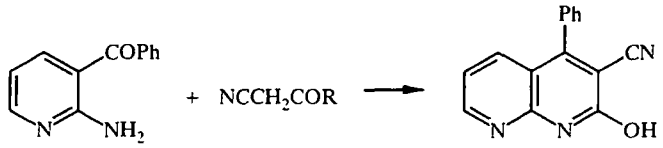
The diazotization of 2-amino-3-cyanopyridines CXVII followed by hydrolysis of the diazotization products was used for the synthesis of 3-cyanopyridin-2(1H)-ones CXVI [233, 234].



CXVII CXVI

R^1 = Ar, Het; R^2 = H, Alk, OAlk, SAlk, OPh, OH

The condensation of 2-amino-3-benzoylpyridine (CXVIII) with CH acids in the presence of piperidine, followed by hydrolysis of the reaction product, gave 1,8-naphthiridine CXIX [235].

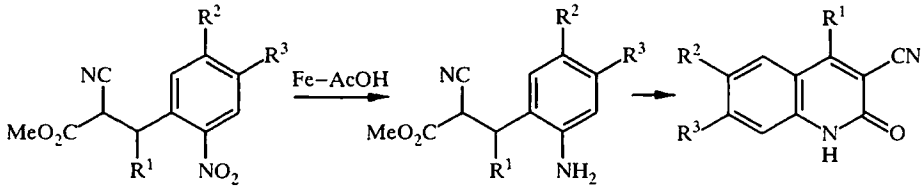


CXVIII CXIX

R = NH_2, OMe, OEt

2.4. Other Methods of Synthesis

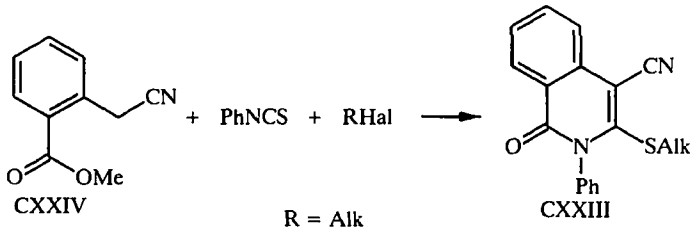
The reduction of the NO_2 group of the nitrophenyl-substituted cyanopropionic ester CXX to the amine CXXI, followed by an intramolecular cyclization leads to the quinolinones CXXII [229, 230].



CXX CXXI CXXII

R^1 = H, Alk, CN, Hal; R^2, R^3 = H, Alk, Hal

The isoquinolinones CXXIII were obtained by the reaction of the ester CXXIV, phenyl isocyanate, and alkyl halides in anhydrous THF in the presence of 60% sodium hydride [236].



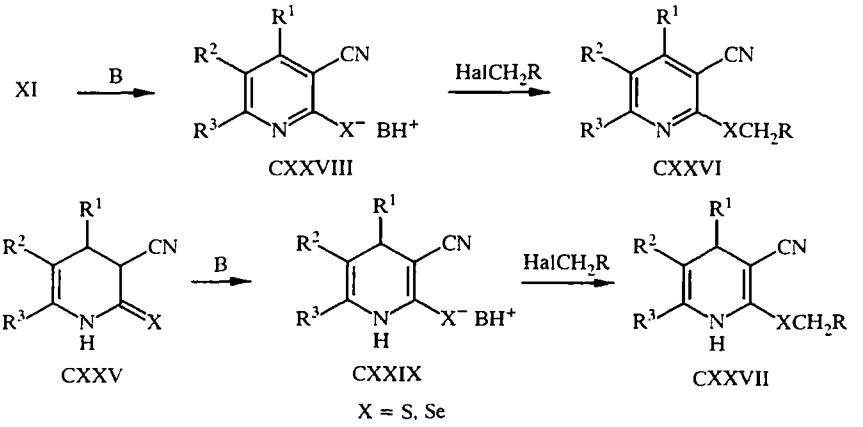
CXXIV CXXIII

R = Alk

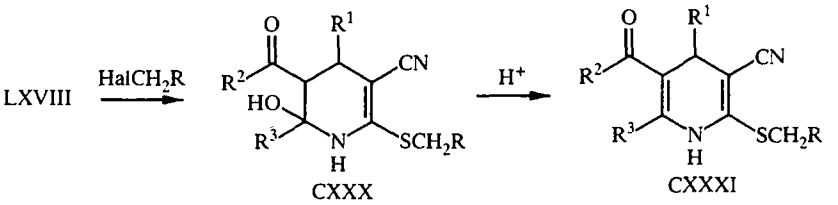
3. REACTIVITY OF 3-CYANOPYRIDINE-2(1H)-CHALCOGENONES

3.1. Alkylation

The largest number of papers on the reactivity of 3-cyanopyridine-2-(1H)-chalcogenones in the last decade are concerned with various aspects of alkylation by alkyl halides in the presence of bases [50, 60, 69, 92-94, 102, 103, 108-110, 112, 115, 120, 122, 123, 125, 127, 129, 132, 154, 158, 180, 213, 242-250]. In particular, it was established that the alkylation of 3-cyanopyridine-2(1H)-thiones(selenones) XI and their hydrogenated analogs CXXV takes place regioselectively at the chalcogen atom with the formation of the substituted 3-cyanopyridines CXXVI and CXXVII *via* the corresponding salts CXXVIII and CXXIX.

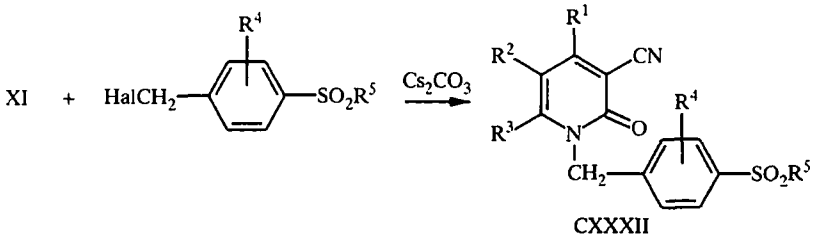


When the alkylation of the tetrahydropyridinethiolate salts LXVIII was used, the tetrahydropyridines CXXX were obtained, and after the elimination of a water molecule they were converted to 1,4-dihydropyridines CXXXI [99, 122].



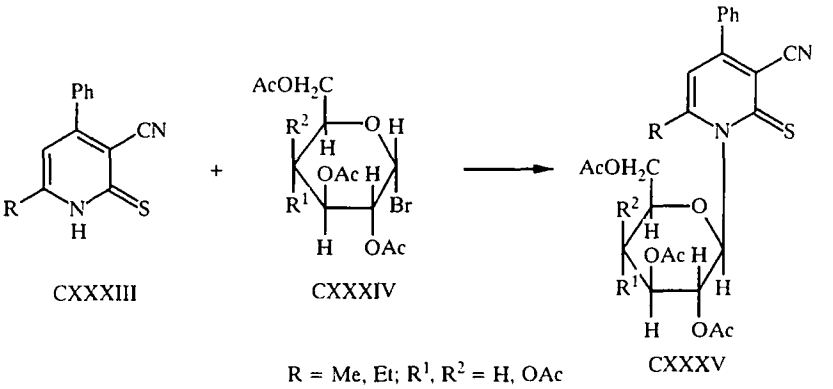
The ready dehydrogenation of compounds CXXIX-CXXXI during oxidation has been noted [122, 130].

The benzoylation of the pyridones XI in 1,2-dimethoxyethane in the presence of Cs_2CO_3 leads to the formation of the N-sulfonylbenzyl derivatives of pyridines CXXXII [251].



R^1, R^2 = H, Alk, Ph, Ac, CN, COOH, perfluoroalkyl, alkoxycarbonyl;
R^3 = Alk, cycloalkyl; R^4 = H, Alk, perfluoroalkyl; R^5 = Het

In 1994 a series of papers appeared on alkylation at the cyclic nitrogen atom in the series of 3-cyanopyridine-2(1H)-thiones [7, 252, 253]. Thus, for example, the authors [253] assume that 4,6-disubstituted 3-cyanopyridine-2(1H)-thiones CXXXIII react with 2,3,4,6-tetra-O-acetyl-α-*D*-gluco- and 2,3,4,6-tetra-O-acetyl-α-*D*-galactopyranosyl bromides CXXXIV in an aqueous solution of potassium hydroxide with the formation of the corresponding N-glucosides CXXXV.



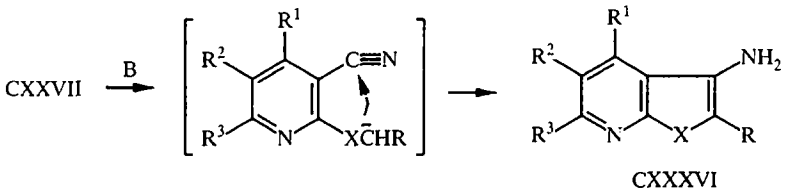
CXXXIII CXXXIV

R = Me, Et; R^1, R^2 = H, OAc

CXXXV

3.2. Cyclization of Derivatives of Pyridinechalcogenones to Annellated Heterocycles

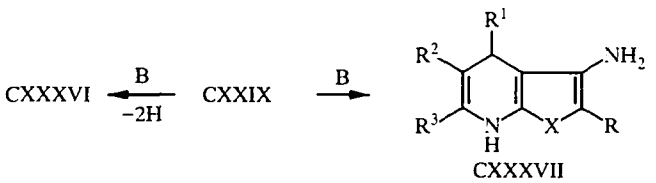
Researchers have also paid considerable attention to substituted 3-aminothieno- and 3-aminoselenopheno-[2,3-*b*]pyridines CXXXVI, obtained by the cyclization of 3-cyano-2-alkylthio(seleno)pyridines CXXVII by the Thorpe – Ziegler reaction in DMF or alcohol in the presence of bases [2, 60, 62, 68, 70, 81, 92, 102, 105, 110, 115, 120, 127, 129, 134, 158, 208, 231-234, 242-244, 246-248, 250].



CXXXVI

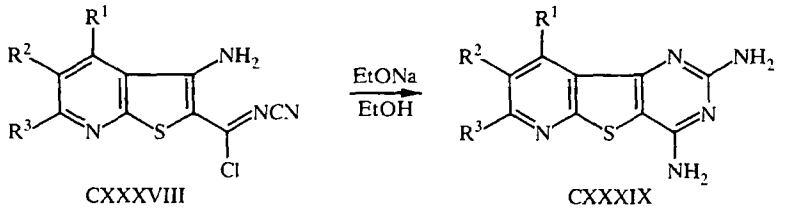
X = S, Se

During the cyclization of hydrogenated pyridines CXXIX to thieno(selenopheno)[2,3-*b*]pyridines CXXXVII under analogous conditions dehydration processes often take place simultaneously, forming thieno(selenopheno)pyridines CXXXVI [92, 99, 122, 127, 158].



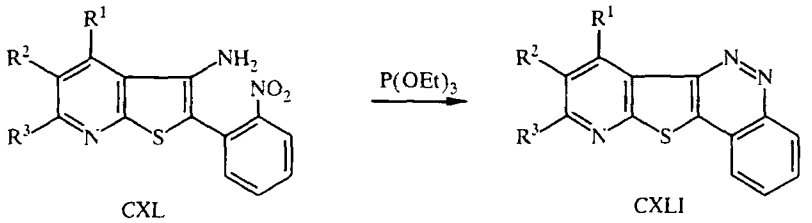
CXXXVII

Functionally substituted thieno(selenopheno)pyridines, obtained by cyclization of derivatives of 3-cyanopyridinechalcogenones, have successfully been used in the synthesis of other types of compounds, including polyannellated heterocyclic systems [2, 60, 64, 68, 69, 102, 104, 105, 129, 154, 232, 236, 246-250, 254-272]. Thus, for example, substituted 3-aminothieno[2,3-*b*]pyridines CXXXVIII are converted into 2,4-diaminopyrido[3', 2':4,5]thieno[3,2-*b*]pyrimidines CXXXIX with yields of up to 70% when boiled in alcohol in the presence of sodium ethoxide [242, 273-275].



CXXXVIII CXXXIX

3-Amino-2-(2-nitrophenyl)thieno[2,3-*b*]pyridines CXL close the pyridazine ring when boiled in triethyl phosphite with the formation of pyrido[3',2':4,5]thieno[3,2-*c*]cinnolines CXLI with yields of 30-40% [247].

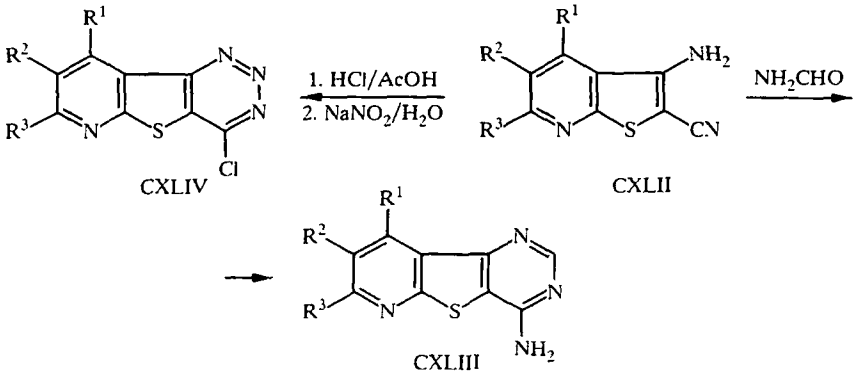


CXL CXLI

$R^1 = R^2 = Me$, $R^3 = H$; $R^1 = R^2 = H$, $R^3 = Het$;

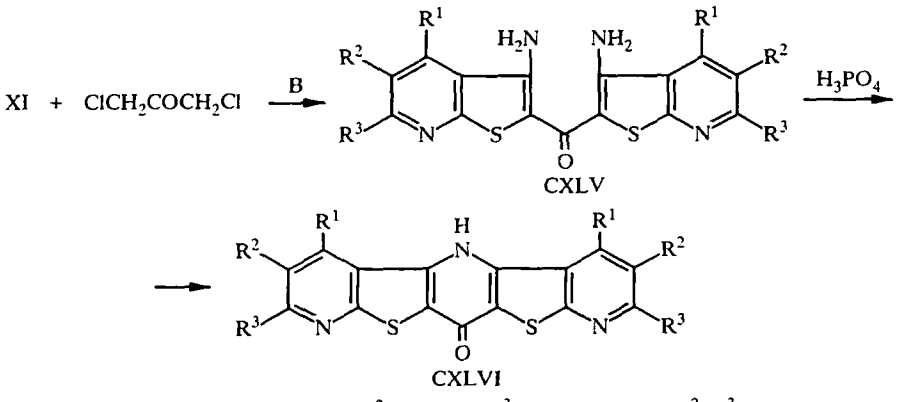
$R^1 = CF_3$, $R^2 = H$, $R^3 = Het$

In reaction with formamide 2-amino-2-cyanothieno(selenopheno)[2,3-*b*]pyridines CXLII give good yields of the pyrimidines CXLIII [60, 232]. When treated with sodium nitrite in the HCl–AcOH–H_2O system they are transformed into triazines CXLIV [236].



CXLIV CXLII CXLIII

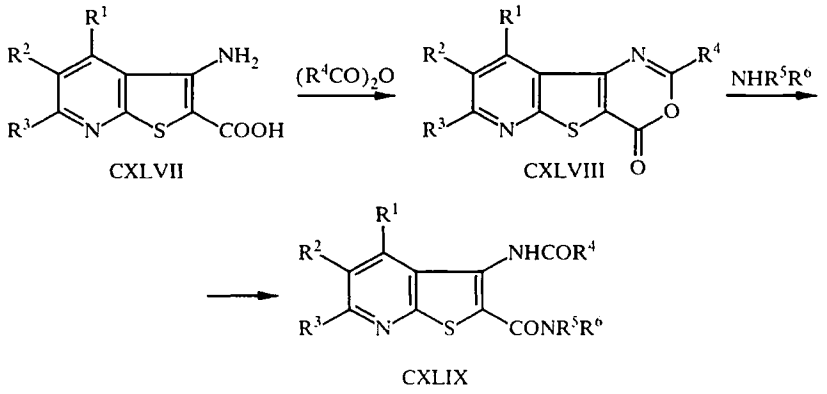
The reaction of 3-cyanopyridine-2(1H)-thiones XI with 1,3-dichloroacetone followed by cyclization of the obtained S-alkylation products leads to the formation of the ketones CXLV, which are transformed into pyridothienopyridines CXLVI by treatment with phosphoric acid [272].



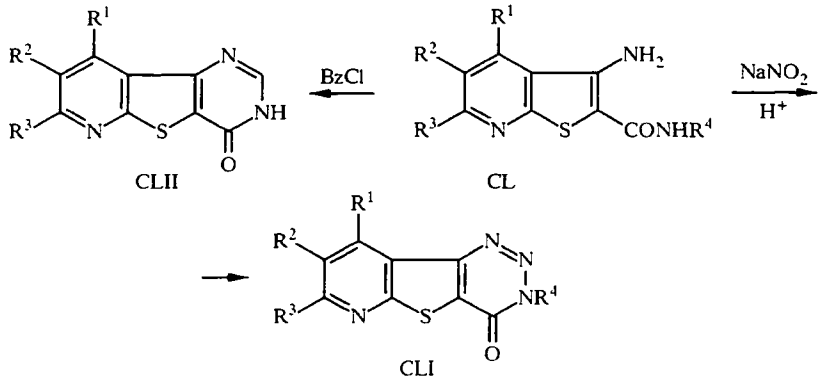
CXLV CXLVI

R^1 = Me, SMe, 4-BrC_6H_4; R^2 = H, CN; R^3 = Me, Ph, NH_2; R^2, R^3 = $(CH_2)_4$

3-Amino-2-carboxythieno[2,3-*b*]pyridines CXLVII have been used successfully in the synthesis of oxazin-4-ones CXLVIII, which are readily converted into compounds CXLIX in reaction with amines [64, 104, 154]

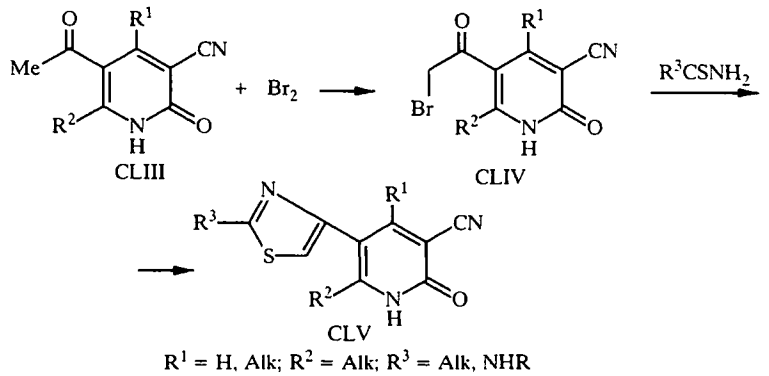


The amides CL, obtained from the acids CXLVII, form the triazines CLI when treated with sodium nitrite [68, 102, 105]. By fusion with benzoyl chloride amides CL are converted into pyridothienopyrimidines CLII [102].



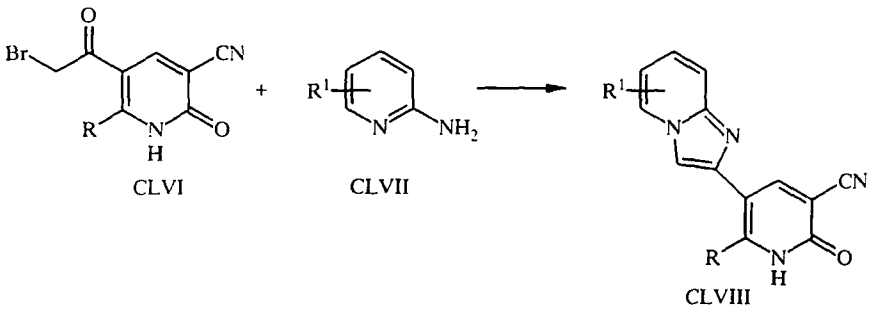
3.3. Halogenation of pyridinechalcogenones

Bromination of 5-acetyl-3-cyanopyridines CLIII in chloroform, acetic acid, or DMF give the bromine derivatives CLIV, the reaction of which with thioamides leads to the formation of 5-(4-thiazolyl)pyridin-2-ones CLV [38-42, 276].



R^1 = H, Alk; R^2 = Alk; R^3 = Alk, NHR

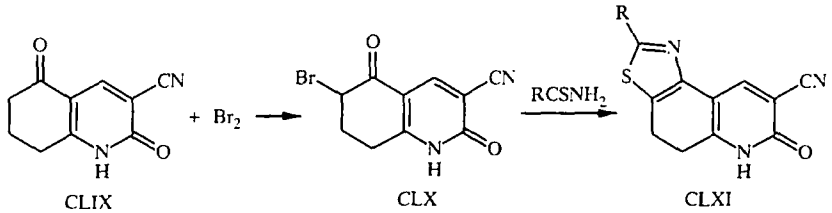
The similarly obtained bromine derivative CLVI forms imidazo[1,2-*a*]pyridines CLVIII when boiled with 2-aminopyridines CLVII in acetonitrile [277].



CLVI CLVII CLVIII

R = Me, Et; R^1 = Me, OMe, CN, F, CF_3

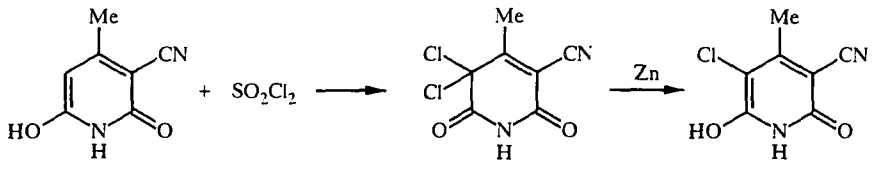
The thiazolo[4,5-*f*]quinolines have been obtained similarly from the quinoline CLIX through the formation of the brominated derivative CLX [41].



CLIX CLX CLXI

In a number of cases 3-cyanopyridin-2(1H)-ones XI were halogenated with phosphorus pentahalides to give 2-halogeno-3-cyanopyridines CXI – intermediates in the synthesis of substances with a broad spectrum of biological activity [201, 204-213, 278-281].

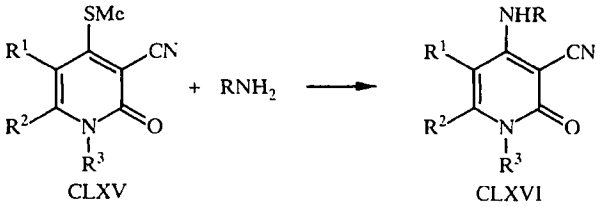
Warming the pyridone CLXII with sulfuryl chloride in carbon tetrachloride gives a high yield of 5,5-dichloropyridine-2,6-dione CLXIII. The latter is converted to the pyridone CLXIV by treatment with zinc dust in alcohol in the presence of a 10% solution of potassium hydroxide [282].



CLXII CLXIII CLXIV

3.4. Other Reactions

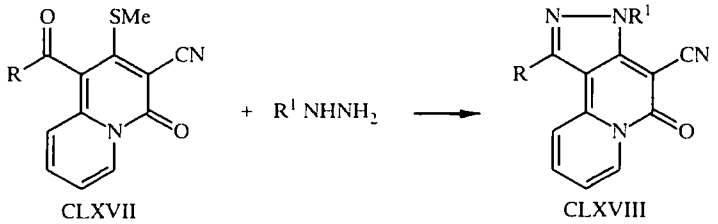
The reaction of substituted pyridones with amines has been studied. Thus, treatment of the pyridones CLXV with amines leads to nucleophilic substitution of the methylthio group by an amino group with the formation of compounds CLXVI [109, 116, 118, 119].



CLXV CLXVI

R = Alk, Ar; R^1 = CN, $COOR^4$; R^2 = NH_2; R^3 = H;
$R^2 + R^3$ = CH=CH–CH=CH; R^4 = Alk, Ar

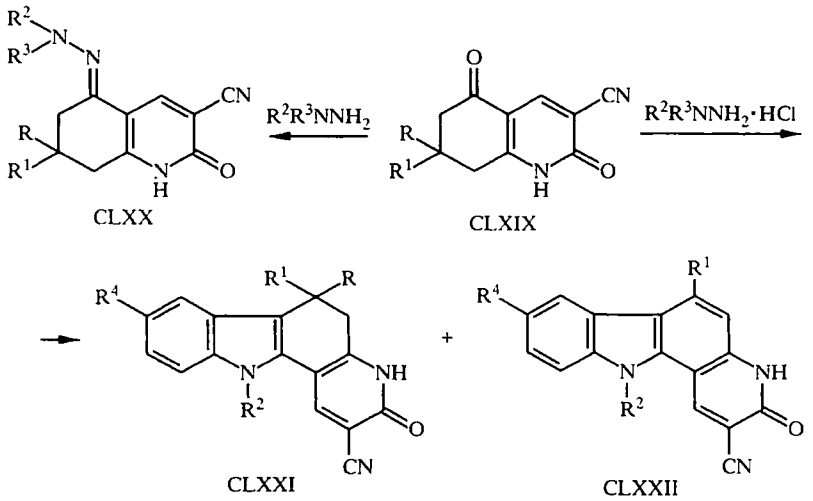
A special case of this reaction is the reaction of compounds CLXVII with hydrazines, leading to the formation of pyrazolo[3,4-*a*]quinolizinones CLXVIII [117, 283].



CLXVII CLXVIII

R = Alk, Ph, $AlkC_6H_4$; R^1 = H, Alk, Ph

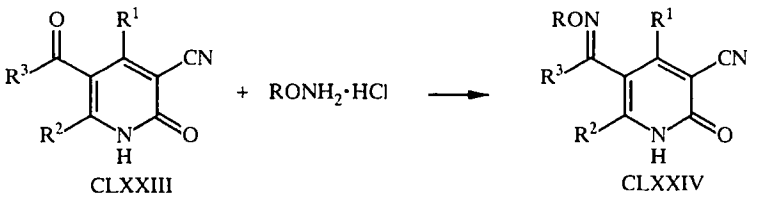
The reactions of the quinolinediones CLXIX with hydrazines gave derivatives of 5,6,7,8-tetrahydroquinoline-2,5-dione LXX as well as pyrido[2,3-*c*]carbazol-3-ones CLXXI and CLXXII [77].



CLXX CLXIX CLXXI CLXXII

R, R^1, R^2 = H, Me, Ph; R^3 = Ph, C_6F_5, 4-$NO_2C_6H_4$, 2-Py; R^4 = H, Me

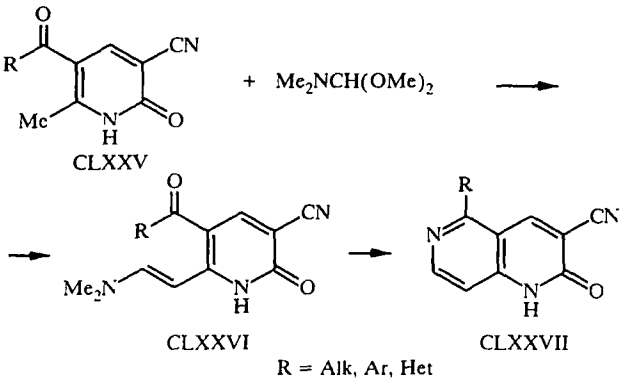
The transformation of the pyridones CLXXIII into the corresponding oximes and O-alkyloximes CLXXIX has been reported [37].



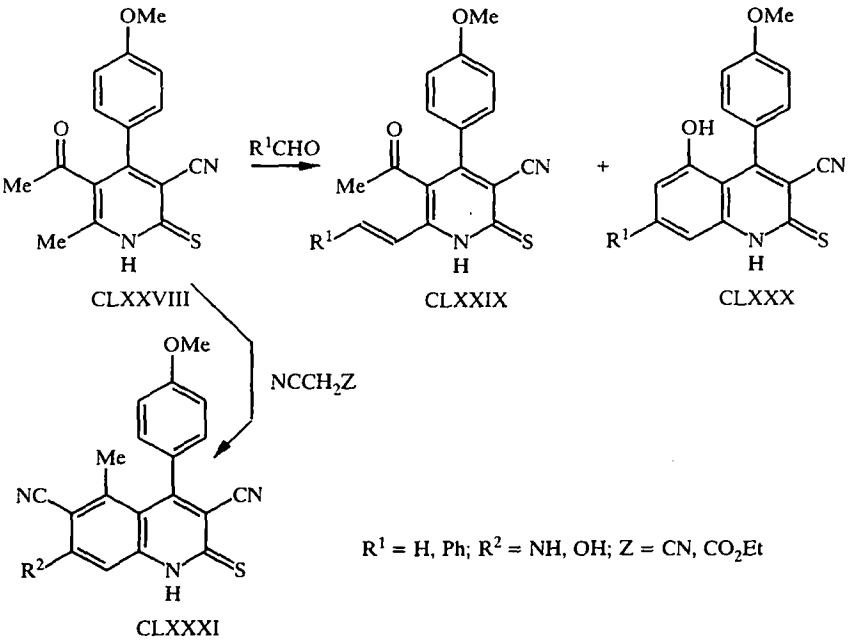
CLXXIII CLXXIV

R = H, C_1–C_{10}–Alk; R^1 = H, Alk; R^2 = H, C_1–C_{10}–Alk. Ar, OH, OAlk;
R^3 = Ar, Het, OH, OAlk

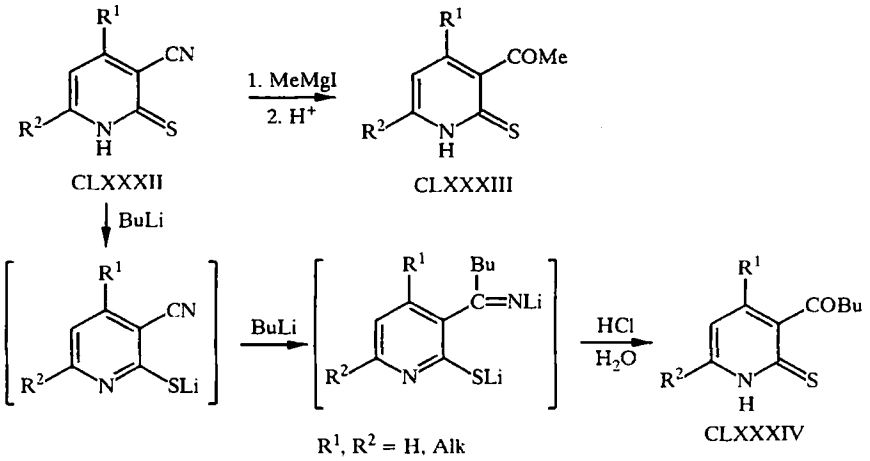
In reaction with dimethyl acetal in DMF the pyridones CLXXV form the enamines CLXXVI, which give 1,6-naphthiridin-2(1H)-ones CLXXVII when treated with formamidine [284-287].



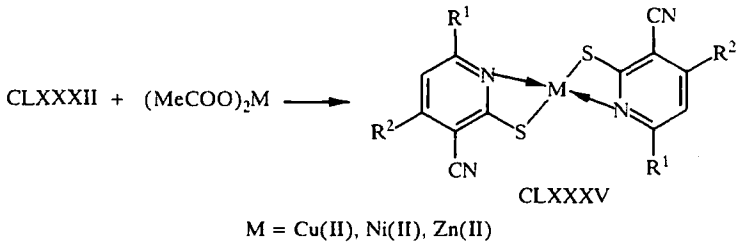
The reaction of pyridinethione CLXXVIII with benzaldehyde in alcohol in the presence of triethylamine was studied, and it was found that a mixture of pyridinethione CLXXIX and quinolinethione CLXXX was formed [129]. It was also noted that the quinolinethione CLXXX was the only product in the reaction of the pyridinethione CLXXVIII with formaldehyde, while the condensation of the thione CLXXVIII with CH acids led to the formation of quinolinethiones CLXXXI.



The reaction of 3-cyanopyridine-2(1H)-thiones CLXXXII with organometallic compounds was used to convert the nitrile group into an acyl group. The ketones CLXXXIII and CLXXXIV were obtained [243, 288, 289].



The presence of NH, CN, and C=S groups, capable of complexation with the ions of transition metals, in the molecule of 3-cyanopyridine-2(1H)-thiones allows to form complexes based on these compounds. However, the first reports on the synthesis of Cu(II), Ni(II), and Zn(II) complexes CLXXXV, obtained as a result of boiling the pyridinethiones CLXXXII with alcohol solutions of salts of the metals, appeared only in 1993 [290, 291].



CONCLUSION

The derivatives of 3-cyanopyridine-2(1H)-thiones have been used in the manufacturing of dyes, pigments, additives for fuels and lubricants [1, 292-301], stabilizers for polymers and varnishes [302], acid–base indicators in titrimetric analysis [303], and other practically important materials. However, as before, in the last decade researchers have paid the greatest attention to derivatives of pyridinechalcogenones on account of their broad spectrum of biological activity. It is necessary to mention the cardiotonic activity of a large number of compounds of this series [9-23, 28-62, 77, 83, 88, 99, 100, 121, 205, 208-213, 231, 234, 276, 277, 284-287, 304-314]. Substances with cardiovascular [15], coronary [45], and clearly defined vasodilatory activity have been found (providing the basis for the creation of milrinone and amrinone [9-23, 205]). Substances that improve the blood circulation have also been found [236]. Among the other types of biological activity in compounds of this class it is necessary to mention the analgesic and antihypertensive [120, 121, 315], antianaphylactic [62, 68, 105, 236], inotropic [277], neurotropic [126], antidiabetic [316], diuretic and sodiodiuretic [235], antioxidant [120, 125, 317, 318], antiviral [60, 63, 102, 214, 215, 225, 226, 232, 236], antiinflammatory [60, 101, 102], and antimicrobial [98, 102-105, 107, 154] activity. Efficient tranquillizers [319-324], antiallergens for the treatment of bronchial asthma, renitis, dermatitis, and dermanaphylaxis [70, 114, 116-119, 283, 319], and compounds showing promise for the treatment of hepatitis [123], hypertonia and atherosclerosis [78, 251] and diseases associated with the formation of the *E* antibodies of immunoglobulin [48, 109, 116, 119] have also been found. In connection with the last fact it is necessary to draw particular attention to the discovery of inhibitors of reverse transcriptase HIV-1 among the pyridone derivatives [80-87, 320-325]. In addition, they can serve as models of oxidation–reduction coenzymes NAD and NADF [236] and synthons for the production of analogs of folic acid [327], vitamin B_6 [328], and other biologically active compounds [329-334].

Biologically degradable agrochemical products [129], plant growth regulators, pesticides, and herbicides [92-96, 108, 132, 158, 206, 216-224, 227-231, 233-235] have been created from derivatives of pyridinechalcogenones.

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