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ADVANCES IN THE CHEMISTRY OF 3-CYANOPYRIDIN-2(1*H*)-ONES, -THIONES, AND -SELENONES

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ADVANCES IN THE CHEMISTRY OF 3-CYANOPYRIDIN-2(1*H*)-ONES, -THIONES, AND -SELENONES

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This review is concerned with the synthesis, structure, physico-chemical properties and reactivity of 3-cyanopyridin-2(1*H*)-ones, -thiones, and -selenones and their derivatives. The 3-cyanopyridin-2(1*H*)-ones, -thiones, and -selenones being bifunctional compounds containing nitrile and amide, thioamide, or selenoamide groups with an endocyclic nitrogen atom are widely used in the synthesis of different classes of annelated heterocycles possessing practically important properties.

Key words: 3-Cyanopyridin-2(1*H*)-one, -thione, -selenone; annelated pyridine-containing heterocycles; derivatives of cyanoacetic acid; Thorpe reaction.

CONTENTS

1. INTRODUCTION

3-Cyanopyridin-2(1*H*)-ones, -thiones, -selenones, and their derivatives constitute an important class of heterocyclic compounds of considerable interest due to a diversity of chemical conversions and possibilities of practical application. These bifunctional compounds containing nitrile and amide, thioamide, or selenoamide groups with an endocyclic nitrogen atom in a vicinal position have turned out to be excellent starting materials for the synthesis of previously inaccessible annelated heterocyclic systems. Among 3-cyanopyridin-2(1*H*)-ones, -thiones, -selenones, and their derivatives pesti-

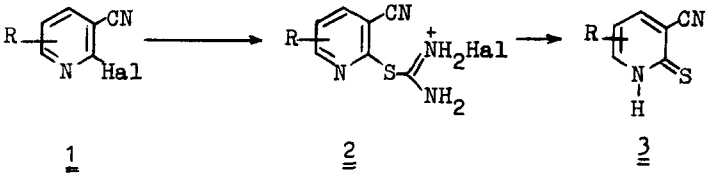
cides, medicinal preparations, vitamins, antioxidants, pigments, and other practically important compounds can be found.

This review generalizes and classifies data on the methods of synthesis, physico-chemical properties and chemical conversions of 3-cyanopyridin-2(1*H*)-ones, -thiones, and -selenones. Reviews available in the literature on sulfur- and selenium-containing pyridines[1-14] contain only incomplete data on the synthesis and properties of 3-cyanopyridine-2(1*H*)-thiones and -selenones. The synthesis of 3-cyanopyridine-2(1*H*)-thiones starting from 1,3-dicarbonyl compounds and 2-halopyridines has been described in detail in reviews.[15-17] However, until the present time the literature lacks reviews on the synthesis of 3-cyanopyridin-2(1*H*)-ones with enamino carbonyl compounds as starting materials.

2. SYNTHESIS OF 3-CYANOPYRIDIN-2(1*H*)-ONES, -THIONES, AND -SELENONES

2.1. 2-Halo(hydroxy)-3-cyanopyridines in the Synthesis of 3-Cyanopyridin-2(1H)-thiones

The introduction by nucleophilic substitution of a mercapto group in 2-halopyridines is widely used in the synthesis of pyridine-2(1*H*)-thiones.[3,18-20] As a rule, hydrosulfides of alkali metals as well as thiourea and its derivatives are used as nucleophilic reagents. It is probable that the interaction of 2-halopyridines **1** with thiourea proceeds via formation of a thiouronium salt **2**, the alkaline decomposition of which gives rise to the pyridines **3**.



1 **2** **3**

Scheme 1

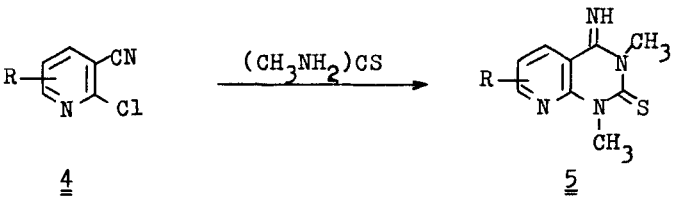
If in **1** electron-acceptor substituents are present in position 3 or 5 of a pyridine nucleus, the substitution of the halogen atom occurs with particular ease. Thus, upon mixing of 2-chloro-5-nitropyridine with methanolic potassium hydrosulfide 5-nitropyridine-2(1*H*)-thione is obtained in 90% yield after gentle heating.[19] It may be pointed out that the presence of a cyano group in position 3 of the halopyridine **1** also favors nucleophilic substitution. Interaction of thiourea with 2-halo-3-cyanopyridines[21,22] or 2-halo-3-cyanoquinones[23] gives high yields of the corresponding pyridinethiones and quinolinethiones. The synthesis of substituted 3-cyanopyridine-2(1*H*)-selenones has been carried out in a similar way.[24,25] The nucleophilic exchange of a halogen atom by a hydroselenide group proceeds more easily in comparison with the substitution by a

hydrosulfide group. The analogous reaction with sodium hydrotelluride proceeds still more easily.[26]

Thus, regarding the ease of halogen atom substitution in **1**, the nucleophiles may be arranged in the following order:

$$HO < HS < HSe < HTe$$

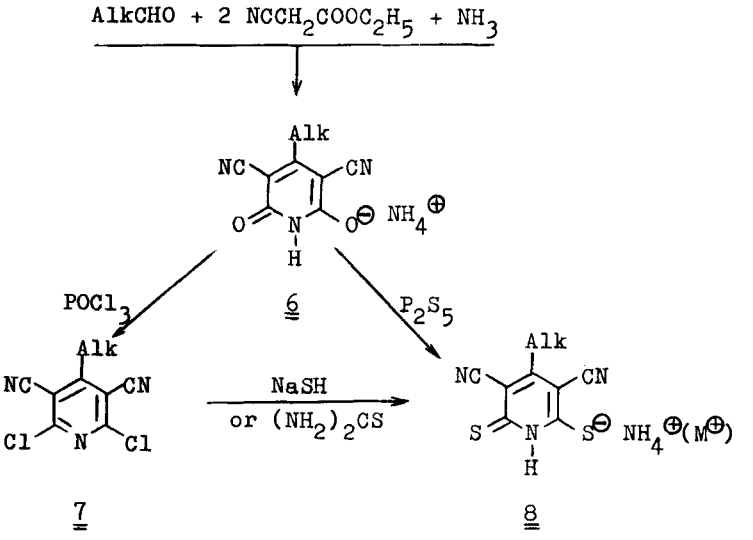
It has been noted that the interaction of 2-chloro-3-cyanopyridines **4** with N^1,N^2-dimethylurea results in the formation of 3,4-dihydro-4-imino-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2(1*H*)-thiones **5**.[27]



4 **5**

Scheme 2

A particularly interesting synthesis of 4-alkyl-3,5-dicyano-6-mercaptopyridine-2(1*H*)-thiones has been advanced in paper.[28] The salts **6** can be obtained by condensation of aliphatic aldehydes, cyanoacetic esters, and ammonia in methanol.



7 **8**

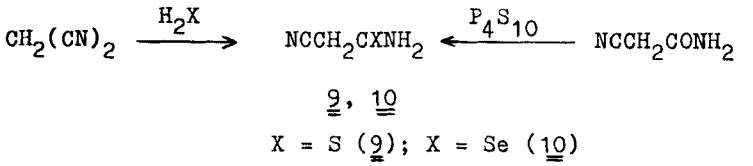
Scheme 3

The subsequent treatment of **6** with $POCl_3$ gives 2,6-dichloropyridines **7**, transformed subsequently to salts of pyridinethione **8** by standard methods. Compounds **8** could be obtained in one step by reaction of the pyridines **6** with P_2S_5 in xylene.

In a number of cases, the preparation of pyridinethiones is preferably carried out with Lawesson's reagent rather than with P_2S_5.[11]

2.2. Synthesis of 3-Cyanopyridin-2(1H)-ones, -thiones, and -selenones from 1,3-Dicarbonyl Compounds and their Enamines

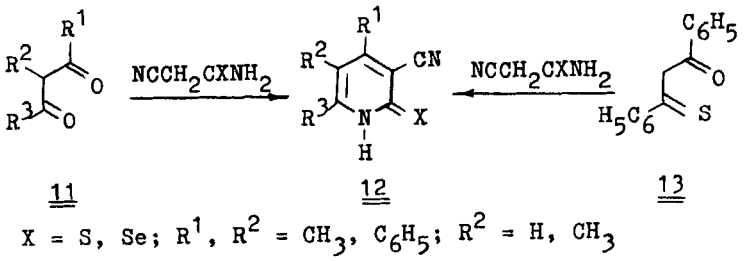
In the synthesis of 3-cyanopyridin-2(1*H*)-ones, -thiones, and -selenones, amides of cyanoacetic acid,[9-11] cyanoacetic ester, malononitrile, 1,3-dicarbonyl compounds, and their enamines have found wide application as the starting materials. Cyanothio-(seleno)acetamide **9** and **10** have been obtained by treatment of malononitrile with hydrogen sulfide and hydrogen selenide, respectively, in the presence of an organic base.[24,29-31]



Scheme 4

Cyanothioacetamide **9** has also been obtained by reaction of P_4S_{10} with cyanoacetamide in ethyl acetate.[32] However, the yield of **9** does not exceed 36% in this case.

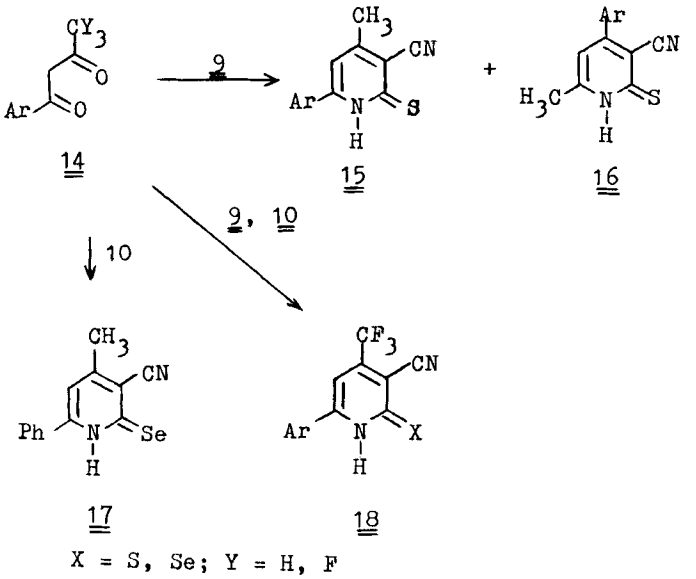
2.2.1. Synthesis from 1,3-dicarbonyl compounds The reaction of cyanothio(seleno)acetamide **9** and **10** with symmetric 1,3-diketones **11** proceeds in the presence of basic catalysts to give high yields of substituted 3-cyanopyridine-2(1*H*)-thiones and -selenones **12**.[24,31,33-37]



Scheme 5

The condensation of monothiodibenzoylmethane **13** with cyanoselenoacetamide **10** takes place under milder conditions, thus giving a high yield of 4,6-diphenyl-3-cyanopyridine-2(1*H*)-thiones **12**.[34]

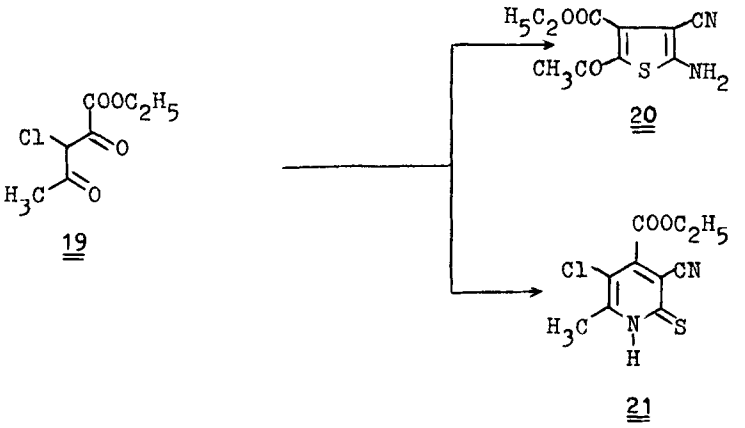
The interaction of asymmetric 1,3-diketones **14** with the amides **9** and **10** proceeds ambiguously.[38–40]



Scheme 6

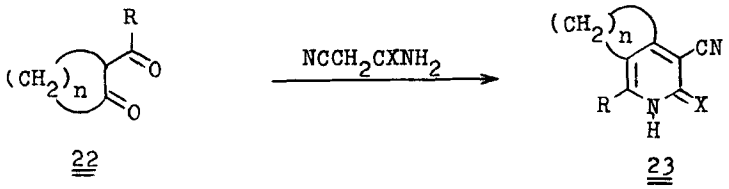
It had been shown earlier that the reaction of benzoylacetone **14** with **9** results in the formation of 4-methyl-6-phenyl-3-cyanopyridine-2(1*H*)-thione **15**.[31] However, actually a mixture of the isomeric pyridinethiones **15** and **16** in the ratio 3 : 1 is formed during this reaction.[38] It was shown earlier that the reactions of cyanothioacetamide **9** with the heterocyclic 1,3-diketones **14** (Ar = pyridyl, thienyl) proceed in an analogous manner with formation of a mixture of **15** and **16**.[39,40] By contrast, the condensation of **14** with **10** leads to the formation of 4-methyl-6-phenyl-3-cyanopyridine-2(1*H*)-selenone **17** only. The condensation of the aryltrifluoroacetones **14** (Ar = phenyl, 2-thienyl; Y = F) with the amides **9** and **10** to the 6-aryl-4-trifluoromethyl-3-cyanopyridine-2(1*H*)-chalcogenones **18** proceeds with high regioselectivity.[41]

Compound **9** reacts with esters of arylpyruvic acids with formation of 6-aryl-3-cyanopyridine-2(1*H*)-thiones.[42] At the same time, the use of ethyl β-chloroacetoacetate **19** for the synthesis of 3-cyanopyridine-2(1*H*)-thiones produces an ambiguous result.[43,44] The reaction of **19** with **9** proceeds with the formation of the 2-aminothiophene **20** or the pyridinethione **21**.



Scheme 7

The reaction of the cyclic 1,3-diketones **22** with **9** in the presence of bases takes place with high regioselectivity, followed by formation of the 4,5-polymethylene-3-cyanopyridine-2(1*H*)-thiones **23**.[25,45,46]

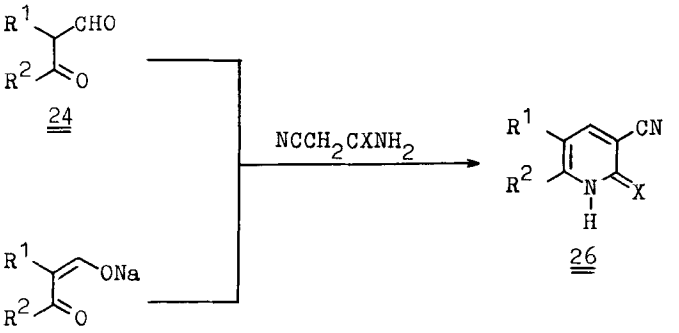


n = 3, 4; R = CH_3, C_2H_5, C_3H_7, Ph, $PhCH_2$;

X = S, Se

Scheme 8

In the synthesis of substituted 3-cyanopyridine-2(1*H*)-thiones and -selenones, β-keto aldehydes **24** and their sodium salts **25** are widely used.[25,26,31,47–53] These reactions proceed with high regioselectivity and with formation of 6-alkyl-, 6-aryl-, 6-hetaryl-, 6-(1-adamantyl)-, and 6-cyclopropylpyridine-2(1*H*)-thiones and -selenones as well as of 5,6-polymethylene-3-cyanopyridine-2(1*H*)-chalcogenones **26**.

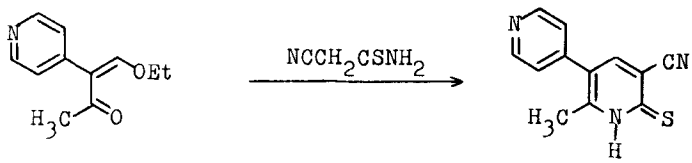


X = S, Se; R^1 = H; R^1,R^2 = $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_5$;

R^2 = CH_3, Ph, 3-Py, 1-Ad, C_3H_5

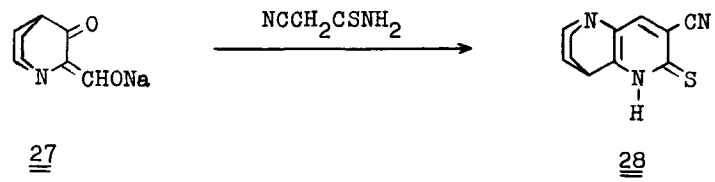
Scheme 9

The sulfur analog of milrinone (**26**, X = S, R^1 = 4-Py, R^2 = CH_3) has been obtained by reaction of 1-(4-pyridyl)-1-acetyl-2-ethoxyethylene with **9**.[20]



Scheme 10

β-Keto aldehydes of a heterocyclic series have also been applied in the reaction with **9**.[54,55] The condensation of the sodium salt of 2-formylquinuclidone **27** with **9** proceeds with high stereoselectivity, followed by formation of the 1,5-naphthyridine **28**.[54]

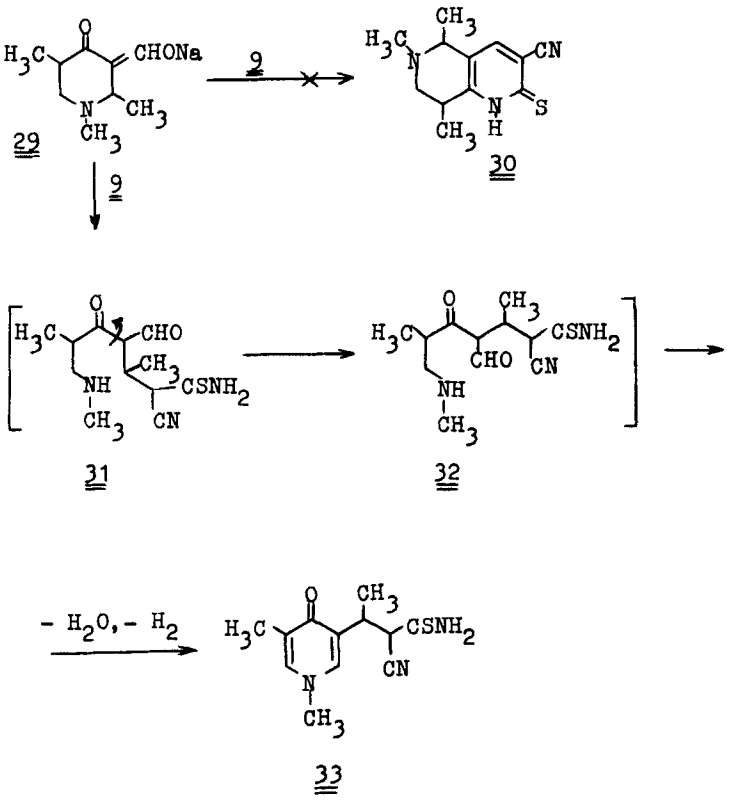


27 28

Scheme 11

In contrast to this, the reaction of the sodium salt of formylpiperidone **29** involves a recyclization.[55] The interaction of salt **29** with **9** in the presence of acetic acid led to the thioamide of 3-[1,5-dimethyl-4(1*H*)-pyridonyl-3]-2-cyanobutyric acid instead of the

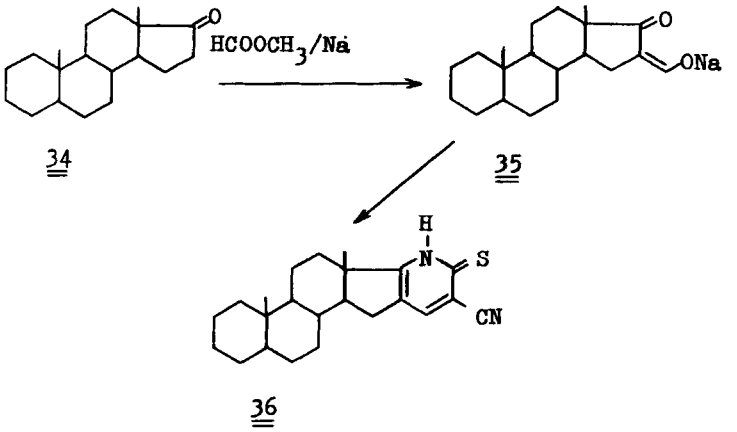
expected naphthyridinethione **30**. It might be supposed that in the first stage of the process a nucleophilic attack on the heterocyclic salt by the cyanoacetamide **9** anion occurs resulting in breaking of the N^1–C^2 bond and formation of an intermediate **31**. Subsequent conversion **31** → **32**, intramolecular condensation, and dehydration lead to the 4(1*H*)-pyridone **33**. The structure of **33** has been confirmed by physical and chemical analysis including X-ray diffraction data.[55]



Scheme 12

This transformation is believed to proceed according to an S_NANRORC mechanism, in a manner like the degenerated transformation of azines detected previously.[56]

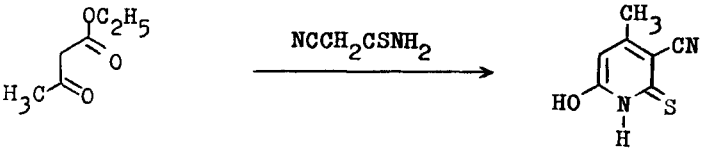
These reactions have been applied to the synthesis of steroids annelated with pyridine.[57] Thus, 3-cyano-5-androsteno[17,16-*b*]pyridine-2(1*H*)-thione **36** has been prepared according to the scheme:



34 35 36

Scheme 13

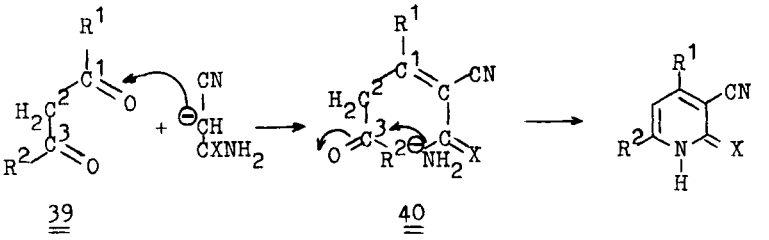
In the synthesis of substituted pyridinethiones, the acetoacetic ester **37** was used.[31] The interaction of **37** with **9** proceeds in a mixture of 1-hexanol and pyridine in the presence of β-diethylaminoethanol at 160 °C giving a 42% yield of 6-hydroxy-4-methyl-3-cyanopyridine-2(1*H*)-thione **38**.



37 38

Scheme 14

In the majority of cases the reactions of 1,3-dicarbonyl compounds with cyanothio(seleno)acetamide **9** and **10** proceed with high regioselectivity except in the case of aroylacetones. Evidently, the high regioselectivity of these reactions can be explained by the nonuniform distribution of electron density in the $O{=}C^3{-}C^2{-}C^1{=}O$ fragment of the dicarbonyl compound. The carbon atoms C^1 and C^2 in **19**, **22**, **24**, **25**, **27**, **34** and in aroyltrifluoroacetones differ greatly in the degree of their electrophilicity. For this reason, the nucleophilic attack of a more electrophilic atom C^1 of a 1,3-dicarbonyl compound **39** on the anion of cyanothio(seleno)acetamide is more probable.



39 40

X = S, Se

Scheme 15

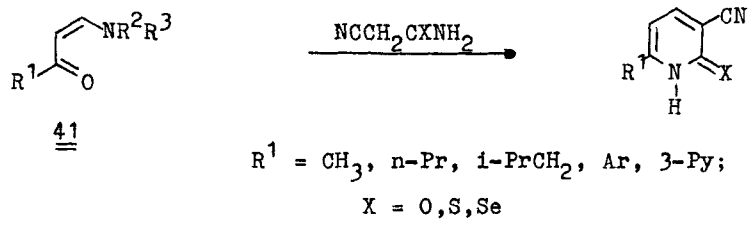
The different electrophilicities of the carbonyl carbon atoms of 1,3-dicarbonyl compounds contributes to the regioselective generation of the δ-oxoalkenylthio(seleno)-amide **40**, a key intermediate in the synthesis of 3-cyanopyridine-2(1*H*)-thiones and -selenones.

2.2.2. β-Enamino carbonyl compounds in the synthesis of 3-cyanopyridin-2(1H)-ones, -thiones, and -selenones β-Aminovinyl ketones and aldehydes have proved to be convenient starting materials for the regioselective synthesis of substituted 3-cyanopyridin-2(1*H*)-ones, -thiones, and -selenones. Monosubstituted pyridines have been obtained by reaction of derivatives of cyanoacetic acid with β-aminovinyl ketones **41** or with monosubstituted β-aminovinyl aldehydes **42**.

Scheme 16

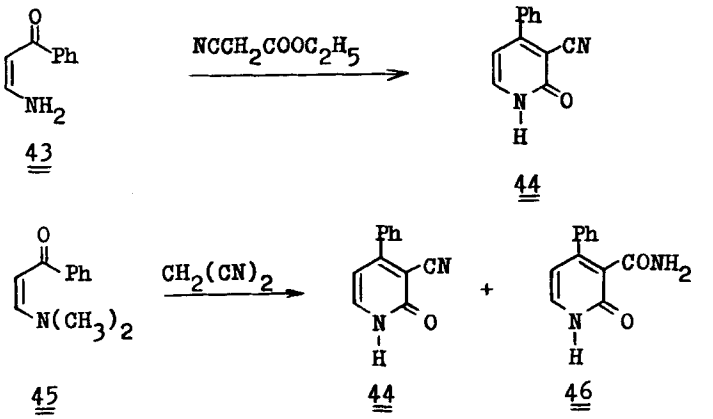
In connection with the presence of two electrophilic centers (C^2 and C^4) in the five-atom chain of **41** and **42**, formation of 4- or 6-substituted pyridines is possible depending on the initial direction of the nucleophilic attack of the derivatives of cyanoacetic acid.

The reactions of aliphatic and aromatic β-aminovinyl ketones **41** with amides of cyanoacetic acid proceed regioselectively with the formation of 6-substituted 3-cyanopyridin-2(1*H*)-ones, -thiones, and -selenones.[49,53,58,59]



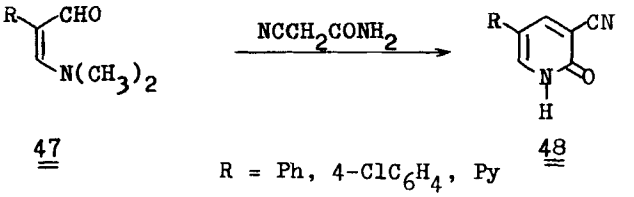
Scheme 17

3-Cyanopyridin-2(1*H*)-ones substituted in position 4 **44** have been obtained by interaction of 1-amino-2-benzoylethylene **43** with ethyl cyanoacetate.[60] The reaction of the enamino ketone **45** with malononitrile takes place in the presence of HCl and results in the formation of a mixture of **44** and **46**.[61]



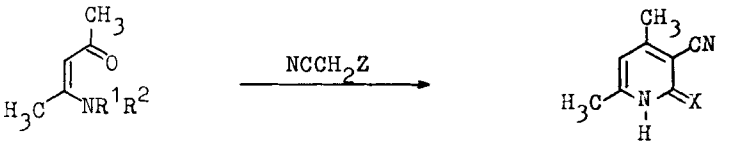
Scheme 18

For the synthesis of 3-cyanopyridin-2(1*H*)-ones **48**, substituted in position 5, β-enamino aldehydes **47** and cyanoacetamide have found wide application.[62-70]



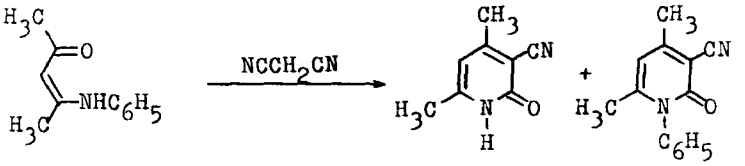
Scheme 19

Disubstituted 3-cyanopyridin-2(1*H*)-ones, -thiones, and -selenones are obtained by the regiospecific synthesis from the corresponding β-enamino ketones and derivatives of cyanoacetic acid.[15,25,71-74] In the case of β-enamino ketones and derivatives of symmetrical 1,3-diketones a single reaction product is formed. Thus, 4,6-diethylpyridine **50** was obtained by condensation of 2-amino-2-penten-4-one **49** with malononitrile, cyanoacetic ester, or amides of cyanoacetic acid.



Scheme 20

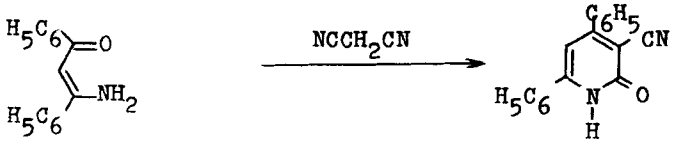
It should be noted that the reaction conditions and the nature of the enamine used exert a significant effect on the reaction course. In the reaction of the enamino ketone **49** (R^1 = Ph) with excess malononitrile in acetic acid the pyridone **50** (X = O), in a yield of 31%, was isolated after reflux of the reaction mixture.[71] Condensation of the same reagents in THF in the presence of triethylamine and at 20 °C, the pyridone **51** and with pyridine **50** (X = O) were formed in 20 and 80% yield, respectively.



49 50 51

Scheme 21

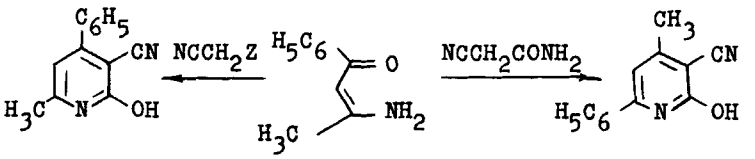
Interaction of enamine **52** with malononitrile results in the formation of 4,6-diphenyl-3-cyanopyridin-2(1*H*)-one **53** in 91% yield.[72]



52 53

Scheme 22

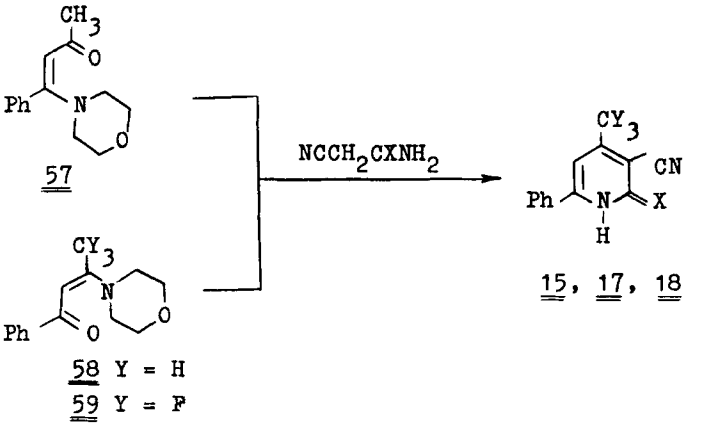
The condensation of β-enamino ketones, derivatives of asymmetric 1,3-diketones, with derivatives of cyanoacetic acid also results in the formation of disubstituted 3-cyanopyridin-2(1*H*)-ones. However, these reactions may proceed with the formation of either of the two possible isomers. The investigation of this reaction is of interest with regard to the relative activities of the keto and the amino groups depending upon the substitution pattern and the reaction conditions. It was shown that 1-amino-1-methyl-2-benzoylethylene **54** in ethanol reacts with ethyl cyanoacetate or cyanoacetamide in the presence of sodium ethoxide at reflux for 6 h to form 6-methyl-4-phenyl-3-cyanopyridin-2(1*H*)-one **55**.[15,16,75,76] The interaction of **54** with cyanoacetamide at 150 °C for 1 h results in the formation of 4-methyl-6-phenyl-3-cyanopyridin-2(1*H*)-one **56**, not of **55**.[15,77]



55 54 56

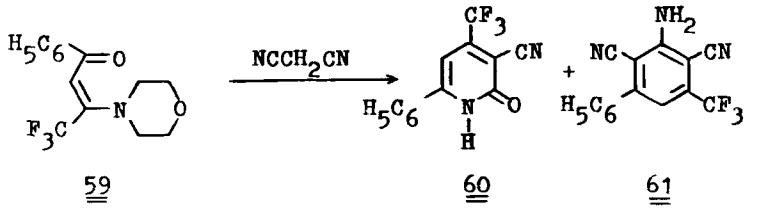
Scheme 23

Of interest is the interaction of the β-enamino ketones **57** and **58** with cyanothio-(seleno)acetamide **9** and **10**. Whatever the structure of the basic enamino ketone, only one regioselective process occurs with the formation of a single isomer, 4-methyl-6-phenyl-3-cyanopyridine-2(1*H*)-thione **15** or -selenone **17**, respectively.[38] The condensation of β-enamino ketone **59** with amides of cyanoacetic acid proceeds with high stereoselectivity[41] and high yields of the 6-aryl-4-trifluoromethyl-3-cyanopyridine-2(1*H*)-chalcogenones **18** have been obtained.



Scheme 24

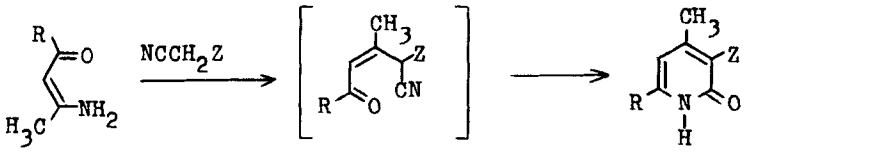
The condensation of the enamine of benzoyltrifluoroacetone **59** with malononitrile leads to the formation of a mixture of the corresponding pyridone **60** and of 5-phenyl-3-trifluoromethyl-2,6-dicyanoaniline **61** in the ratio 5:2. The reaction is carried out in alcohol without a catalyst and, after reflux during a short period, kept at 20 °C for 8 h.[41]



Scheme 25

With a corresponding diketone in this reaction, the corresponding aniline derivative was formed.[78]

From the data given in paper[72] and confirmed by IR, ^{1}H and ^{13}C NMR, and mass-spectrographic studies it was found that the condensation of the β-enamino ketones **62** with malononitrile or ethyl cyanoacetate in THF in the presence of triethylamine at 20 °C results in the regiospecific formation of the 3-cyanopyridin-2(1*H*)-ones **64** and the 3-carbethoxypyridin-2(1*H*)-ones **65**, respectively.



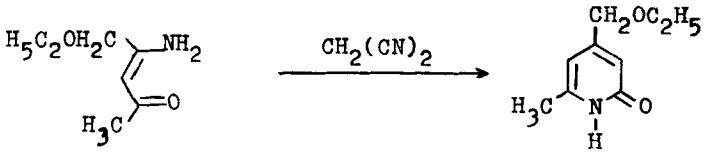
62 **63** **64** Z = CN; **65** Z = $COOC_2H_5$

R = C_2H_5, i-Pr, n-Pr, C_6H_5, $(CH_2)_2C_6H_5$;
Z = CN, $COOC_2H_5$

Scheme 26

In this case the yields of the pyridones **64** are rather high, 80–89%. It is supposed that under these conditions a condensation to an amino group occurs at first with subsequent cyclization of the intermediate **63** in which a cyano group of the CH acid is taking part.

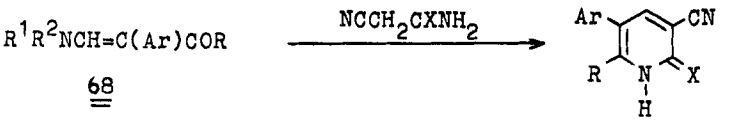
6-Methyl-4-ethoxy-3-cyanopyridin-2(1*H*)-one **67**, an intermediate in the synthesis of vitamin B, has been prepared by interaction of 2-amino-1-ethoxy-2-penten-4-one **66** with malononitrile.[79,80] The reaction is carried out without a catalyst or by heating in the presence of ammonia in alcohol or water.



66 **67**

Scheme 27

β-Enamino ketones may be used in the synthesis of 5,6-disubstituted 3-cyanopyridin-2(1*H*)-ones. 5-Aryl-6-alkyl-3-cyanopyridin-2(1*H*)-ones **69** possessing cardiotonic activity are obtained, as a rule, by condensation of 1-aryl-1-acyl-2-dimethylaminoethylene **68** with cyanoacetamide in DMF in the presence of sodium methoxide.[81–87]



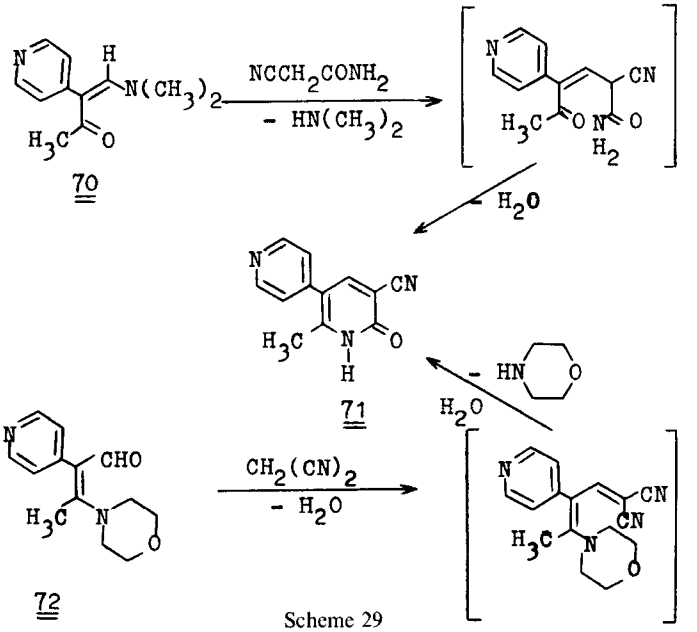
68 **69**

X = O, S; Ar = C_6H_5, 4-Py, $4\text{-}CH_3SC_6H_4$, $4\text{-}O_2SC_6H_4$, $3,4\{CH_3O)_2C_6H_3$; R = CH_3, cycloalkyl, $CH(OCH_3)_2$

Scheme 28

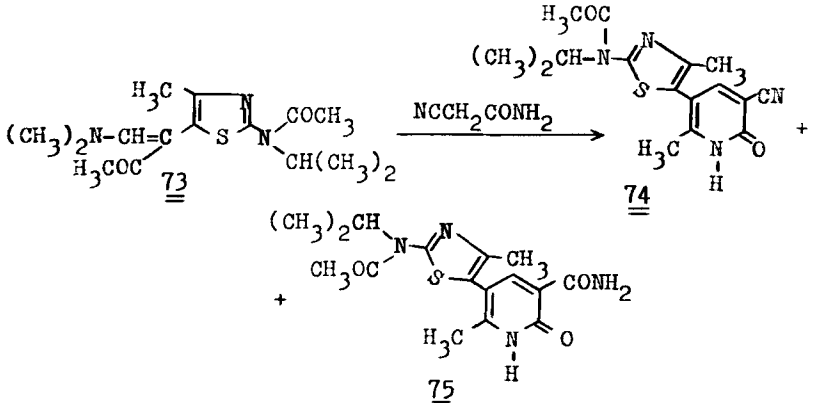
Starting with **68** [R^1, R^2 = $(CH_2)_2O(CH_2)_2$], the authors of paper[20] have carried out a synthesis of the 5-aryl-6-methyl-3-cyanopyridine-2(1*H*)-thiones **69** (X = S).

In a similar manner a well-known cardiotonic drug, milrinone **71**, has been obtained from the enamine **70**. It was found[88] that **71** can also be prepared by condensation of 1-(4-pyridyl)-2-methyl-2-(1-morpholino)-1-formylethylene **72** with malononitrile. Thus, the attack of cyanothioacetamide **9**, as well as that of malononitrile proceeds at the carbon atom of enamine **70** or **72** remote from the methyl group or aryl substituent.



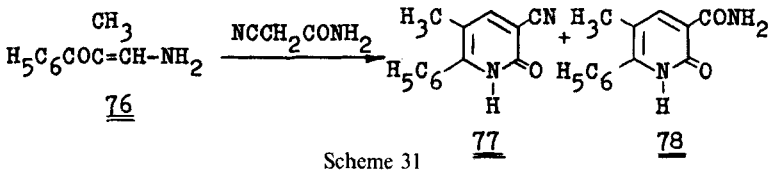
Scheme 29

A change in the reaction conditions of the condensation of type **68** enamines with cyanoacetamide has a profound impact on its outcome. Thus, the interaction of enamine **73** with cyanoacetamide in propanol in the presence of sodium alkoxides results in the formation of a mixture of pyridones **74** and **75**.[89]



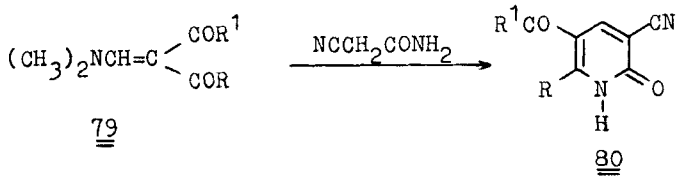
Scheme 30

The character of this transformation is confirmed by the data presented in paper.[90] The interaction of 1-amino-2-benzoyl-1-propene **76** with cyanoacetamide results in the formation of 5-methyl-6-phenyl-3-cyanopyridin-2(1*H*)-one **77** in 75–80% yield, admixed with a minor amount of the pyridone **78**.



Scheme 31

5,6-Disubstituted 3-cyanopyridin-2(1*H*)-ones **80** have also been produced in the reaction of 2-aminomethylene-1,3-diones **79** with cyanoacetamide and sodium hydride in THF[91] or sodium methoxide in DMF.[92] Derivatives of symmetric[91,92] and asymmetric[93–95] β-diketones have been used in the reaction.

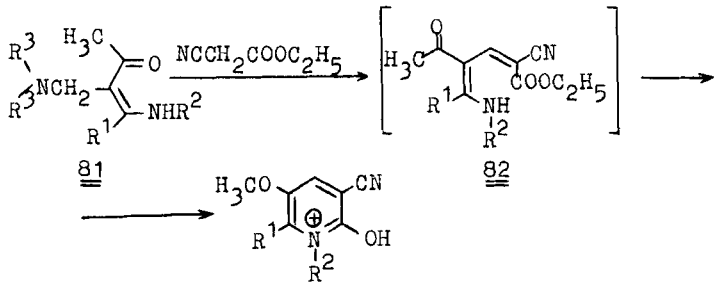


$R, R^1 = CH_3, (CH_3)_2CH, (CH_3)_3C, C_4H_9, OC_2H_5, C_6H_5$

Scheme 32

In the case of the asymmetric diones **79** (R = Me, R^1 = Bu, OEt), the reaction proceeds regioselectively with the formation of one isomer only.

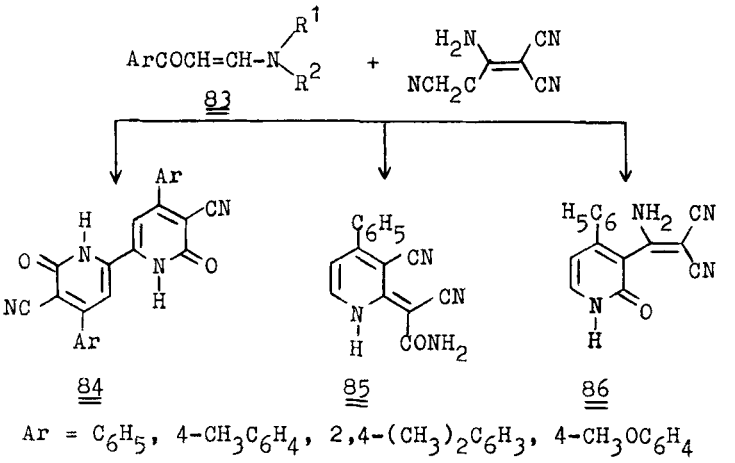
Unlike the enamines of type **49**, the Mannich bases **81** containing a β-enamino carbonyl fragment react with ethyl cyanoacetate in xylene in the presence of potassium *t*-butoxide first at the aminomethylene group. The subsequent cyclization of intermediate **82** proceeds with the incorporation of the enamine nitrogen into the ring. Thus, the preponderance of this process over condensation to an enamine fragment or a carbonyl group has been demonstrated.[96]



$R^1 = H, CH_3$; $R^2 = CH_3, C_6H_5, C_6H_5CH_2$; $R^3{}_2N = (CH_3)_2N$

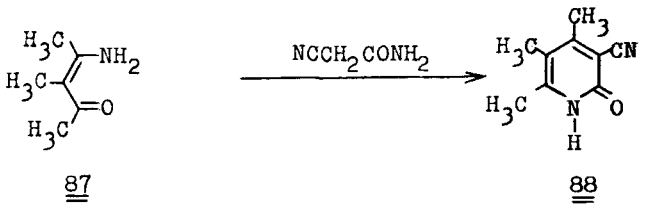
Scheme 33

In the synthesis of disubstituted 3-cyanopyridin-2(1*H*)-ones, 1-amino-2-aroylethylenes **83** have been used. Thus, interaction of **83** with malononitrile dimer leads to the formation of the dipyridyls **84**. However, if a phenyl substituent is present the reaction proceeds nonselectively, the dipyridyls **84** are accompanied by the azines **85** and **86**.[97-99]



Scheme 34

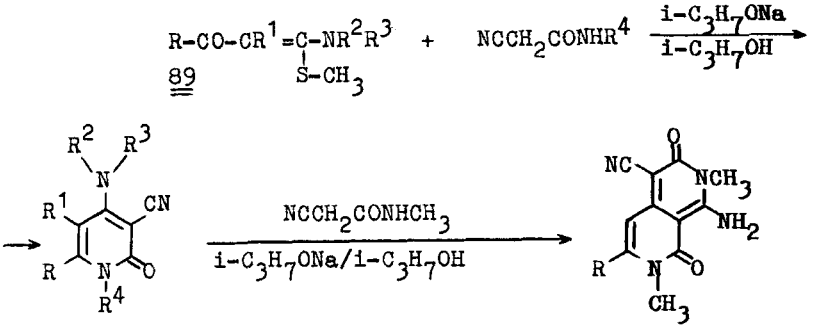
4,5,6-Trimethyl-3-cyanopyridin-2(1*H*)-one **88** has been obtained by heating of cyanoacetamide and 1-amino-2-acetyl-1,2-dimethylethylene **87** to 150 °C for 0.5 h.[77]



Scheme 35

The pyridone **88** has been obtained in 96% yield in the reaction of enamine **87** with malononitrile in THF in the presence of triethylamine at 20 °C.[72]

In the case of the *β*-enaminocarbonyl compounds **89** the condensation with cyanoacetamide proceeds initially by elimination of methanethiol and not an amine, followed by formation of the 4-dialkylaminopyridine **90**.[100]

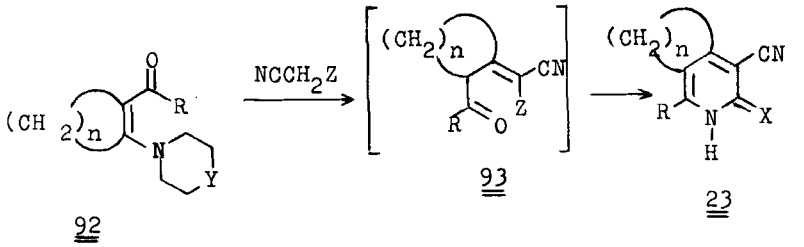


$R = C_6H_5$, 4-ClC_6H_4, 4-$CH_3OC_6H_4$, CH_3; $R^1 = H$; RR^1 = 2,5-$CH_2S(CH_3)C_6H_5$, o-$C_6H_3CH_2CH_2$; $R^2 = C_6H_5$, C_2H_5, $CH_2CH(OC_2H_5)_2$, $CH_2C_6H_5$; $R^3 = H$; R^2R^3 = $CH_2CH_2OCH_2CH_2$; $R^4 = H$, CH_3

Scheme 36

The 4-amino-3-cyanopyridin-2(1*H*)-one **90** contains a β-enamino amide fragment with an endocyclic nitrogen atom of an amide group. When **90** and *N*-methylcyanoacetamide interact a substitution of the amino group occurs with subsequent cyclization of the naphthyridinedione **91**.[100]

In the synthesis of condensed 3-cyanopyridin-2(1*H*)-ones, -thiones, and -selenones, cyclic β-enamino ketones are widely used as starting materials. The condensation of the β-enamino ketones **92**, intermediates in the synthesis of the corresponding acylcycloalkanes, with derivatives of cyanoacetic acid proceeds selectively with the formation of one of two possible isomers, namely the isoquinoline **23**.[45,46,101,102] Evidently, nucleophilic substitution of amine occurs at first. The subsequent closure of a pyridine ring in the β-keto nitrile **93** formed results in the formation of the isoquinoline **23**.



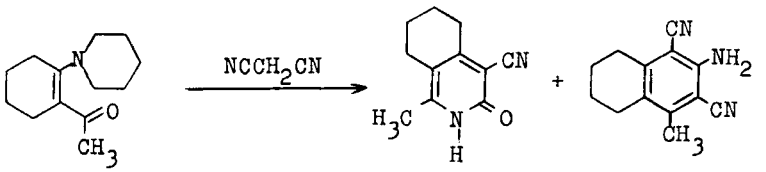
n = 3, 4; R = CH_3, C_2H_5, C_6H_5, $CH_2C_6H_5$; X = O, S, Se; Y = O, CH_2; Z = CN, $CONH_2$, $CSNH_2$, $CSeNH_2$

Scheme 37

The introduction of enamines of 1,3-diketones **92** into the reaction without the addition of basic catalysts leads to high yields of **23** in comparison with the application of their dicarbonyl analogs.

The substitution of an alkyl group for an aryl one requires more stringent conditions in the reaction procedure. To obtain 6-phenyl-4,5-tetramethylene-3-cyanopyridin-2(1*H*)-one **23** (n = 4, X = O, R = Ph), a mixture of 2-benzoyl-1-(1-piperidyl)-1-cyclohexane and an equimolar amount of cyanoacetamide is boiled in isopropanol for 1.5 h and then acidified with 50% AcOH. The yield of the pyridone **23** (n = 4, X = O, R = Ph) is 73%.

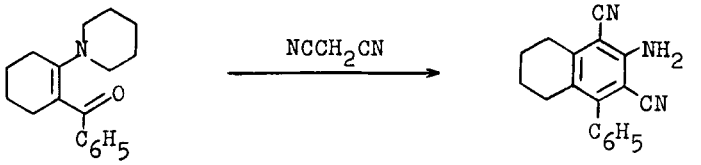
However, the application of certain β-enamino ketones in reactions with malononitrile does not always lead to homogeneous results. Thus, interaction of the enamine **94** with two equivalents of malononitrile proceeds at 50 °C with the formation of a mixture of the pyridone **95** (66%) and 2-amino-1,3-dicyano-4-methyl-5,6,7,8-tetrahydronaphthalene **96** (11%).[45]



94 95 96

Scheme 38

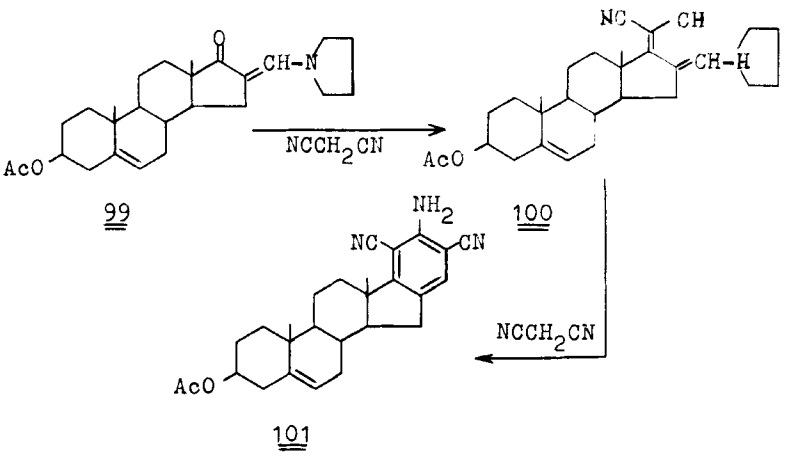
A study of the reaction of 2-benzoyl-1-(1-piperidyl)-1-cyclohexane **97** with malononitrile showed that it here takes another direction.[103] Thus, interaction of **97** with malononitrile in a wide range of ratios leads solely to 2-amino-1,3-dicyano-4-phenyl-5,6,7,8-tetrahydronaphthalene **98**; hence the maximum yield (90%) is reached with twofold excess malononitrile.



97 98

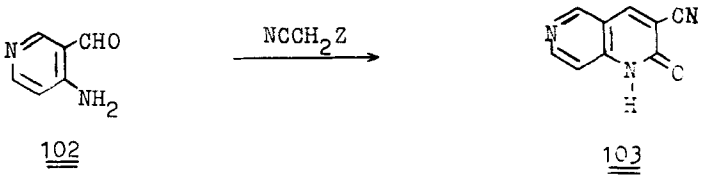
Scheme 39

Similar results have been obtained in the interaction of 3-β-acetoxy-16-(1-pyrrolidinyl)methylene-5-androsten-17-one **99** with malononitrile in the presence of bases.[104] The 3-β-acetoxy-17-dicyanomethylene-16-(1-pyrrolidinyl)methylene-5-androstane **100** being formed cyclizes to the androstenoaniline **101** in 42% overall yield.



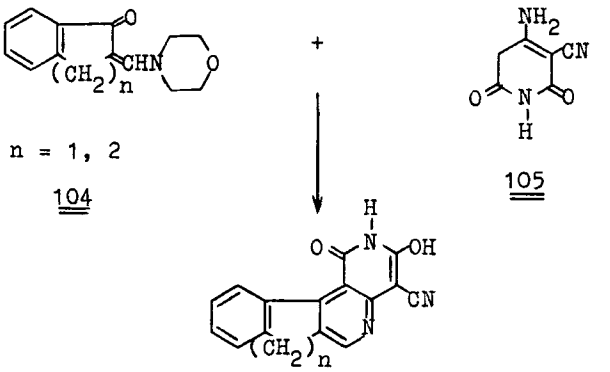
Scheme 40

In the case of the heterocyclic β-amino aldehyde **102** condensation with methylene active nitriles in the presence of piperidine gives the 1,6-naphthyridinone **103**.[105]



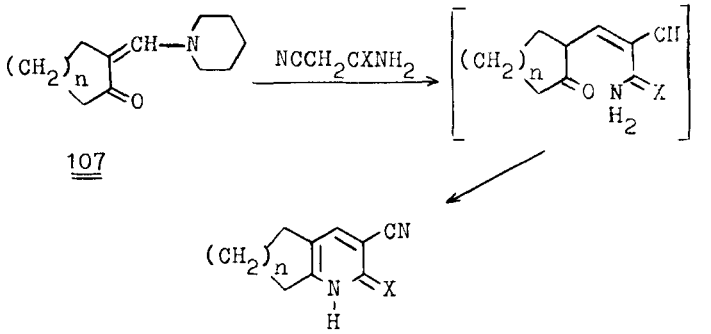
Scheme 41

An interesting method for the construction of condensed heterocyclic systems consists in the interaction of the cyclic β-enamino ketones **104** with 4-amino-3-cyanopyridine-2,6-dione **105**.[106,107] The formation of the heterocyclic system **106** occurs with the involvement of a cyano and a carbonyl gruop of the initial pyridone in vicinal positions.



Scheme 42

5,6-Polymethylene-3-cyanopyridine-2(1*H*)-thiones and -selenones **108** have been obtained in high yield by condensation of 2-(1-piperidinomethylene)cyclohexanone or -heptanone **107** with cyanothio(seleno)acetamide **9** and **10** in ethanol in the presence of acetic acid.[25] Probably, the primary attack of the nucleophilic reagent takes place at the carbon atom of the aminomethylene group of the enamine **107**, not at the keto group.



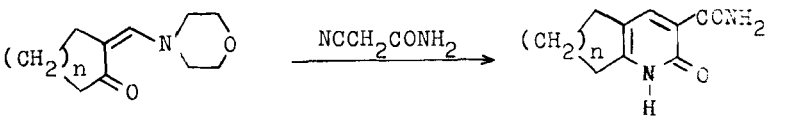
107

108

n = 2, 3; X = S, Se

Scheme 43

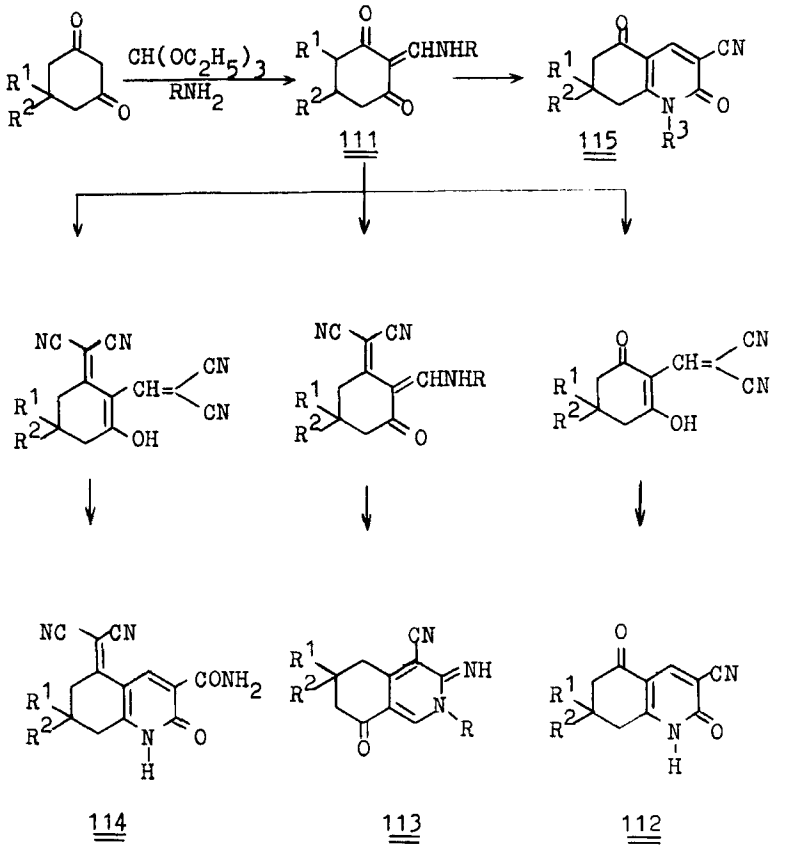
The enamines **109** in their reactions with cyanoacetamide in the presence of piperidine form 3-carbamoylpyridin-2(1*H*)-ones **110** rather than 3-cyanopyridines.[101]



109 n = 4, 5, 6, 10 **110**

Scheme 44

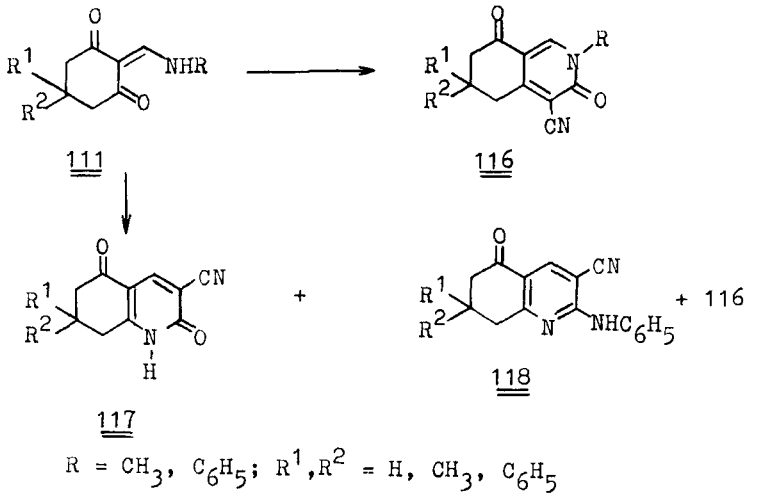
In the synthesis of hydroquinolines and -isoquinolines, reactions of enamines of 1,3-cyclohexanedione **111** with derivatives of cyanoacetic acid are widely used.[101,108-111] Boiling for 1 h 5,5-dimethyl-2-phenylaminomethylenecyclohexane-1,3-dione **111** ($R^1 = R^2 = Me$, R = Ph) in ethanol in the presence of KOH with an equimolar amount of malononitrile results in the formation of 6,8-dihydro-7,7-dimethyl-3-cyano-quinoline-2,5-dione **112**,[101,108] with the double amount of malononitrile of 5,7-dihydro-6,6-dimethyl-3-imino-4-cyano-2-phenylisoquinolin-8-one **113** ($R^1 = R^2 = Me$, R = Ph).[108,109] The yields of **112** and **113** amount to 20 and 27%, respectively.[108]



Scheme 45

The course of the reaction is significantly affected by the nature of the catalysts and solvents. Upon boiling with the twofold amount of malononitrile in ethanol in the presence of piperidine and subsequent decomposition of the reaction mass, 5-dicyanomethylene-3-carbamidoquinolin-2-one **114** is obtained in 42% yield.[108]

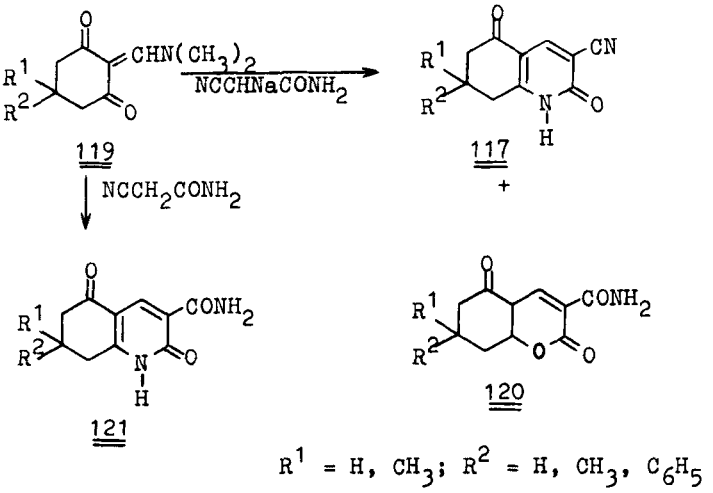
Unlike the data of refs.[101,108,109] interaction of 2-aminomethylenecyclohexane-1,3-dione **111** with malononitrile in DMF in the presence of KOH proceeds with the formation of *N*-aryl substituted 3-cyanoquinolin-2-ones **115**.[110] It has been found in ref.[111] that the ratio of reactants and the reaction conditions have a profound impact on the course of the reaction. When the enamines **111** (R = Me, Ph; R^1, R^2 = H, Me, Ph) are allowed to reflux with a small excess of malononitrile in ethanol in the presence of a catalytic amount of morpholine for 1 h, the isoquinolines **116** are exclusively formed.



Scheme 46

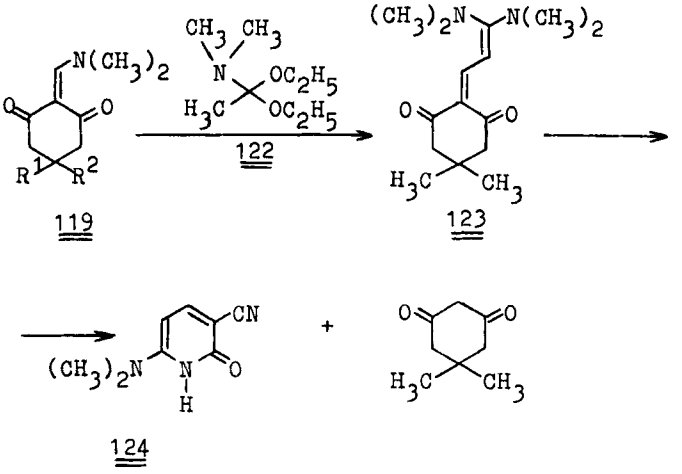
Equimolar amounts of these reagents react in the presence of excess morpholine to form **117** ($R^1 = R^2 = Me$), **118**, and **116** ($R^1 = R^2 = Me$, R = Ph) in yields of 46, 25, and 17%, respectively. Without catalyst, based on the data of ref.,[111] the reaction results in the formation of the quinoline **117** ($R^1 = R^2 = Me$).

The reaction of the 2-dimethylaminomethylenecyclohexanediones **119** with cyanoacetamide in THF in the presence of sodium hydroxide forms a mixture of the cyanopyridones **117** and the pyranones **120**. Upon boiling of the reaction mixture in absolute ethanol the 3-carbamidopyridone **121** was isolated in high yield as the only product.[91]



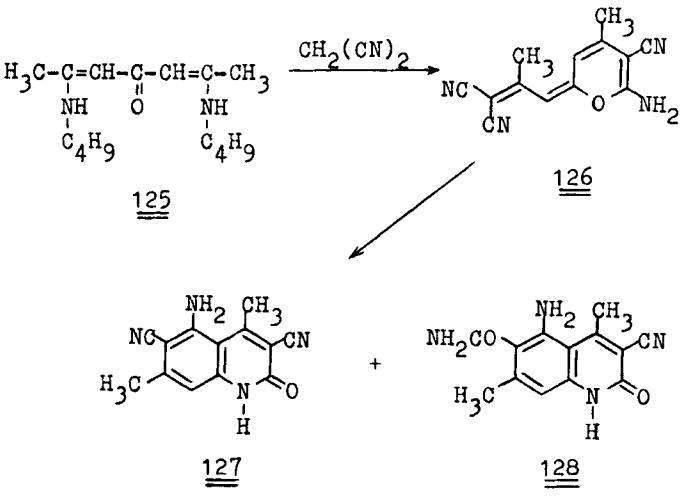
Scheme 47

An interesting version of the use of dimethylaminomethylenedimedone **119** ($R^1 = R^2 = Me$) for the synthesis of 6-dimethylamino-3-cyanopyridin-2(1*H*)-one **124** has been proposed in ref.[112] Interaction of enamine **119** ($R^1 = R^2 = Me$) with the diethyl acetal of *N*,*N*-dimethylacetamide **122** leads to a high yield of dienodiamino ketone **123** which in turn forms the pyridone **124** in its reaction with cyanoacetamide.



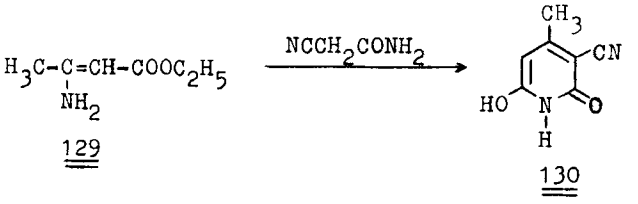
Scheme 48

Interaction of the β-enamino ketone **125** with malononitrile results in 6-amino-5-cyano-2-(3,3-dicyano-2-methylallylidene)-4-methyl-2*H*-pyran **126** which recyclizes under the action of NaOH with formation of a mixture of the quinolines **127** and **128**.[113]



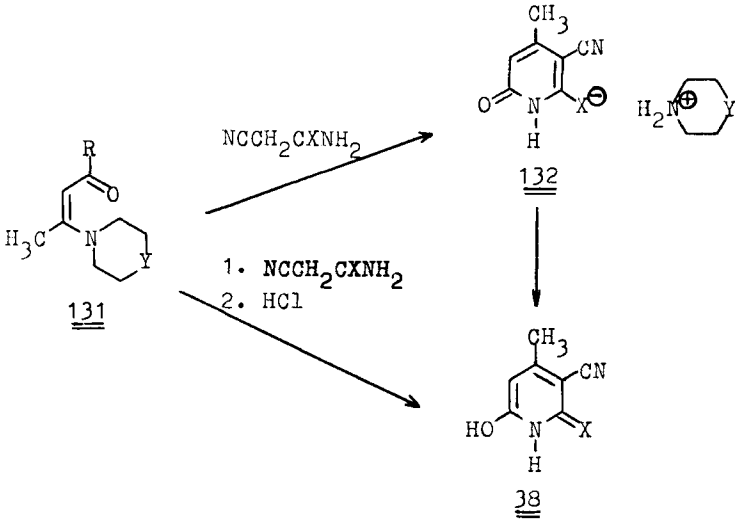
Scheme 49

For the synthesis of substituted 3-cyanopyridin-2(1*H*)-ones, β-enamino esters and amides have been used. 6-Hydroxy-4-methyl-3-cyanopyridin-2(1*H*)-one **130**, widely used for the synthesis of pigments, has been obtained by condensation of ethyl β-aminocrotonate **129** with cyanoacetamide.[77]



Scheme 50

However, the reaction of ethyl β-piperidinocrotonate **131** (Y = CH_2, R = OEt) with cyanoacetamide takes place under milder conditions;[114] carried out in alcohol at 20 °C it results in the formation of the piperidinium salt of 6-hydroxy-4-methyl-3-cyanopyridin-2(1*H*)-one **132** (X = O, Y = CH_2). In aqueous ethanol the salt **132** smoothly transforms to the corresponding pyridone **38** (X = O) upon treatment with HCl.



X = O, S, Se; Y = O, CH_2; R = OC_2H_5, NHC_6H_5

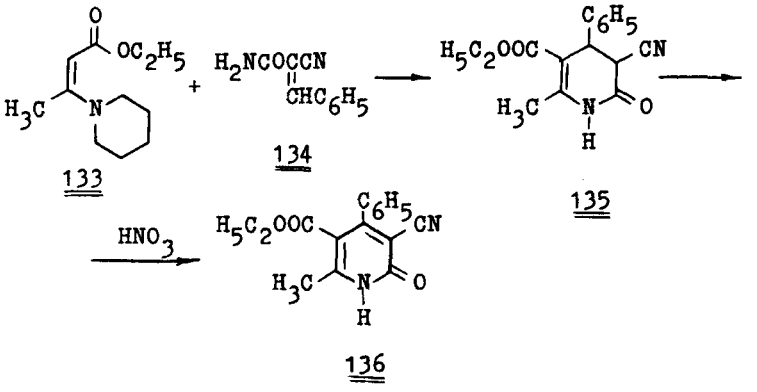
Scheme 51

A high yield of pyridone **38** has also been obtained by condensation of ester **131** (Y = CH_2, R = OEt) with cyanoacetamide in an aqueous medium and by subsequent acidification of the reaction mixture.

It has been found that enamines of acetoacetic ester **131** or anilides of acetoacetic acid are more active in this reaction compared with acetoacetic ester.[114] Thus, the process was

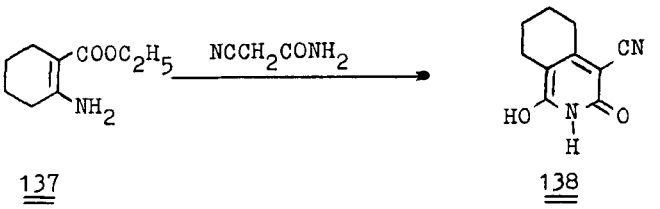
essentially improved. It has been shown that the reaction of enamines **131** with cyanothioacetamide **9** takes place readily in ethanol or water giving a quantitative yield of salts of 6-hydroxy-4-methyl-3-cyanopyridine-2(1*H*)-thione **132** (X = S, Y = O). The salts **132** (X = S, Y = O) transform smoothly to the pyridinethione **38** (X = S) upon treatment with HCl. Salts of the pyridineselenone **132** (X = Se, Y = O) and of 6-hydroxy-4-methyl-3-cyanopyridine-2(1*H*)-selenone **38** (X = Se) have been obtained in a similar way.[115]

Ethyl β-aminocrotonate **133** also reacts with benzylideneacetamide **134**. The 3,4-dihydropyridone **135** separates out and transforms later to the corresponding 5-carbethoxy-6-methyl-4-phenyl-3-cyanopyridin-2(1*H*)-one **136** after acidification with dilute nitric acid.[116]



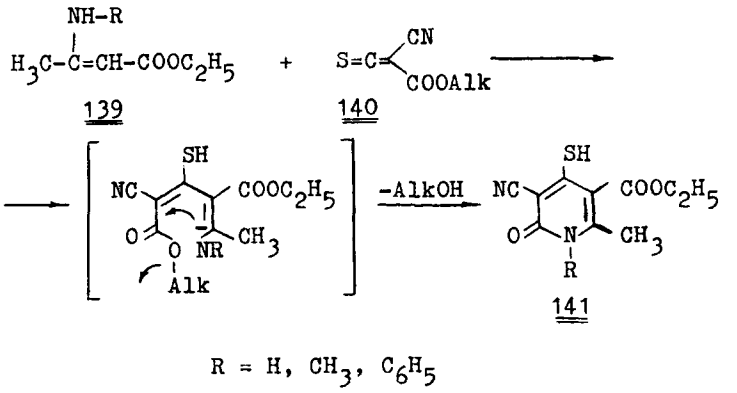
Scheme 52

The condensation of the β-enamino esters **137** with cyanoacetamide, followed by formation of the tetrahydroisoquinoline **138**, proceeds in a similar way.[77]



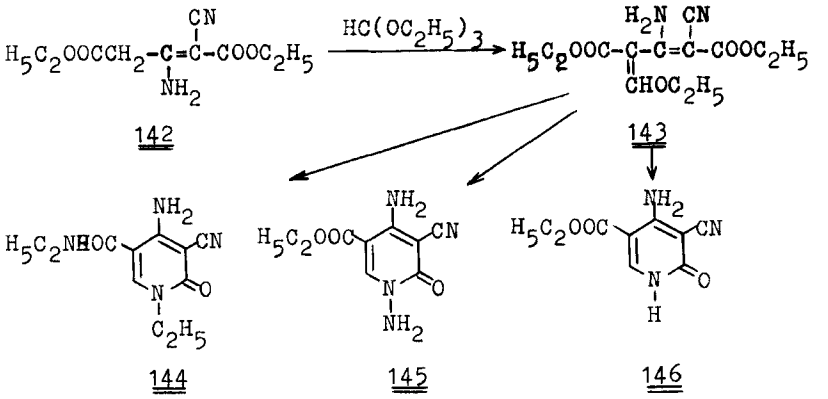
Scheme 53

The functionally substituted 3-cyanopyridin-2(1*H*)-ones **141** are obtained from ethyl β-aminocrotonate **139** and the thioketenes **140**.[117] Enamine **139** initially adds to **140**.



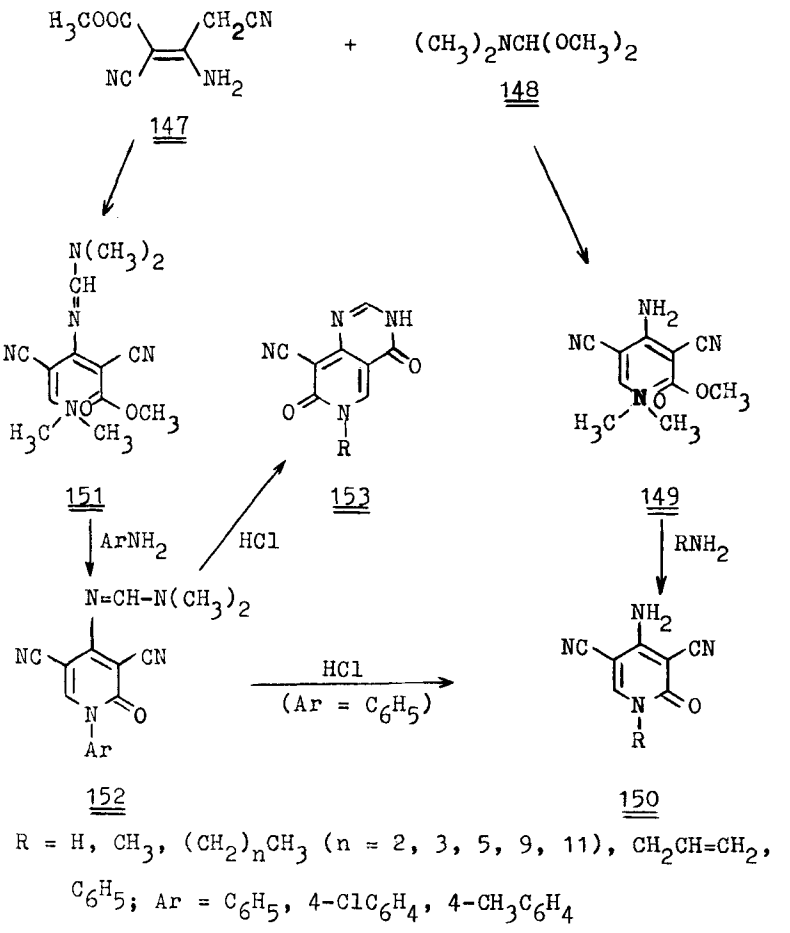
Scheme 54

β-Enamino esters of the type **142** and ortho esters form the corresponding ethoxymethylene derivatives **143**, convenient synthons for the synthesis of the 3-cyanopyridines **144**–**146**.[118]



Scheme 55

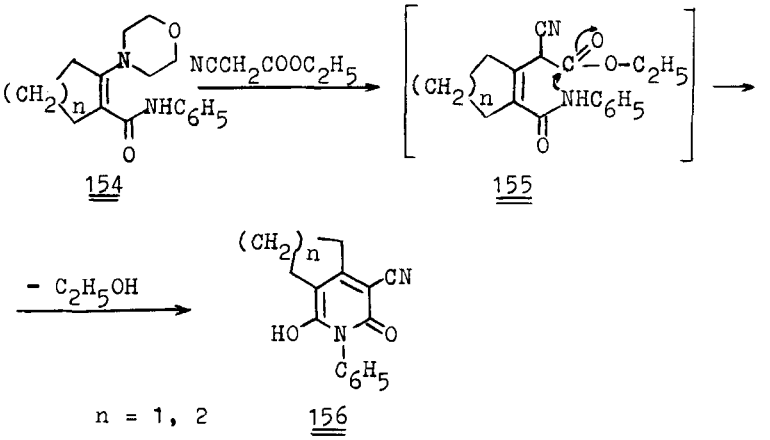
The aminomethylene derivatives of enamino esters **149**, obtained by condensation of enamine **147** with the diethyl acetal of DMF **148**, have also been found to be convenient synthons for the 3-cyanopyridines **150**.[119]



Scheme 56

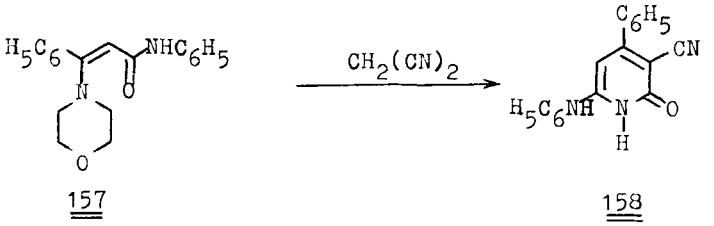
Condensation of **147** and **148** produced the enamine **151** which cyclizes to the pyridones **152** upon brief heating with anilines to 100 °C. Upon boiling of **152** with concentrated HCl, the pyrido[4,3-*d*]pyrimidines **153** have been obtained. Prolonged boiling of **152** (Ar = Ph) with dilute HCl results in the formation of the pyridone **150** (R = Ph).

In the synthesis of substituted 3-cyanopyridin-2(1*H*)-ones, β-enamino amides have been used.[102,120,121] The condensation of cyclic β-enamino amides **154** with cyanoacetic ester is a classical example of such a reaction.[102] Probably the initial nucleophilic substitution of morpholine by cyanoacetic ester is accompanied by subsequent intramolecular cyclization of the intermediate **155** to 4,5-polymethylene-6-hydroxy-3-cyanopyridin-2(1*H*)-one **156**.



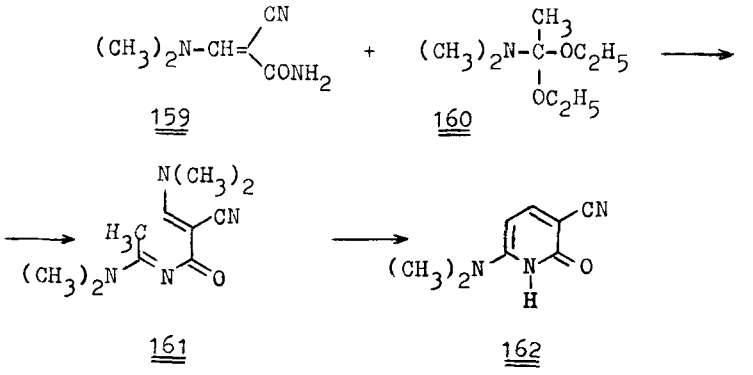
Scheme 57

The condensation of the β-enamino amide **157** with malononitrile leads to the formation of 6-aminophenyl-4-phenyl-3-cyanopyridin-2(1*H*)-one **158**.[120]



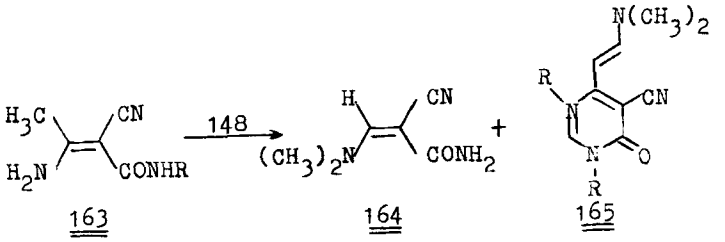
Scheme 58

The amide of α-cyano-β-dimethylaminoacrylic acid **159**, when interacting with the diethyl acetal of *N*,*N*-dimethylacetamide **160**, forms the intermediate **161** which cyclizes to 6-dimethylamino-3-cyanopyridin-2(1*H*)-one **162**.[122]



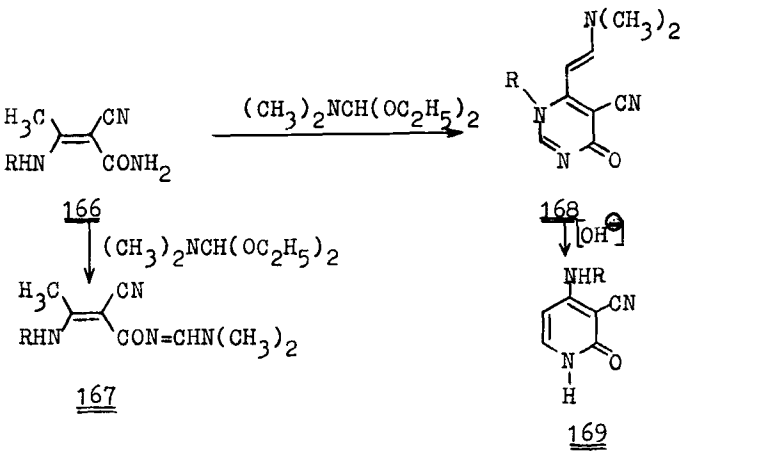
Scheme 59

An illustrative example of the influence of the structure of the β-enamino amide is the interaction with the diethyl acetal of DMF **148**. In the case of the amide of β-amino-crotonic acid **163** and **148** the amide of β-dimethylaminoacrylic acid **164** and the pyrimidone **165** are formed.



Scheme 60

In the case of the *N*-substituted enamines **166**, steric effects exert an essential influence on the course of the reaction[123] where the enaminoacylamidine **167** is the main product. The pyrimidines **168** are formed under more severe conditions such as heating.

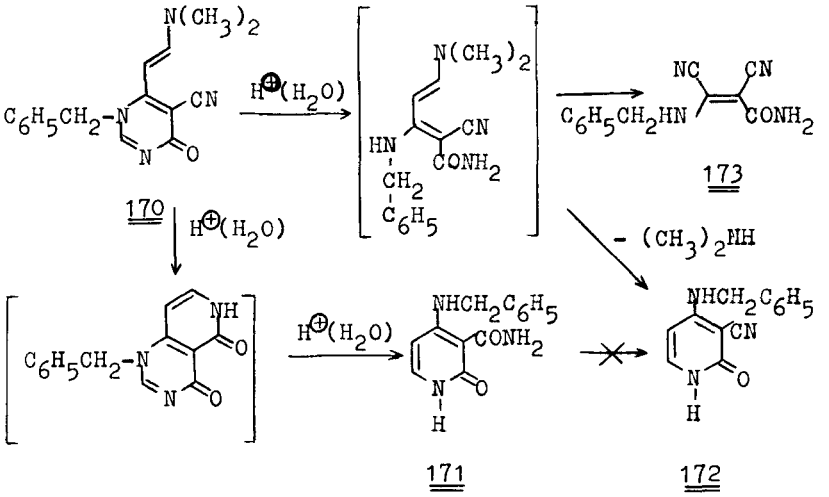


R = $C_6H_5CH_2CH(CH_3)$, $C_6H_5CH_2CH_2$, $(CH_3O)_2C_6H_3CH_2CH_2$

Scheme 61

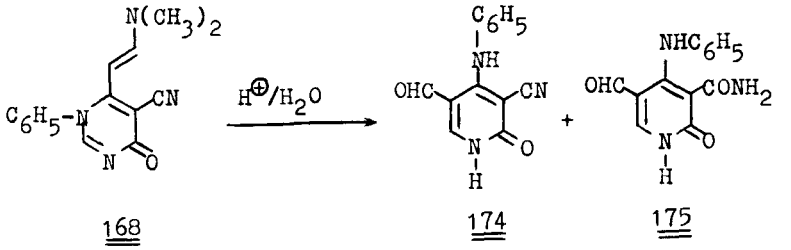
The pyrimidines obtained recyclize to the 3-cyanopyridin-2(1*H*)-ones **169** on heating in the presence of alkali and subsequent neutralization of the mixture. By contrast, the reaction proceeds further in the presence of acidic agents with the participation of an enamino nitrile fragment.[124] After treatment of 1-benzyl-5-cyano-6-(β-dimethylamino-vinyl)pyrimidin-4-one **170** with HCl at 60–65 °C the 3-cyanopyridine **172** and the enamino amide **173** were detected together with the main product of the reaction **171**.

The authors of ref.[124] found that the formation of the 3-carbamidopyridin-2(1*H*)-one **171** is not due to the hydrolysis of a cyano group of the pyridone **172**. This permitted to suggest the following scheme:



Scheme 62

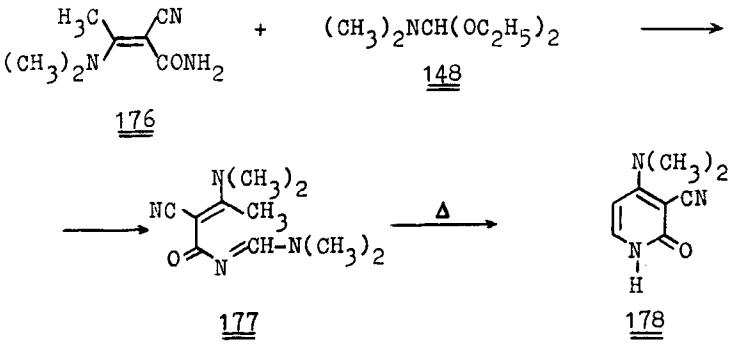
The substitution of a benzyl group by phenyl in position 1 of the pyrimidine alters the course of the hydrolysis in acid medium.[124] Under these conditions 5-cyano-1-phenyl-6-(β-dimethylaminovinyl)pyrimidin-4-one **168** (R = Ph) recyclizes with formation of a mixture of 4-anilino-3-cyano-5-formylpyridin-2-one **174** (67%) and 4-anilino-3-carbamido-5-formylpyridin-2-one **175** (10%).



Scheme 63

The different ways of the opening of a pyrimidine ring and the subsequent cyclization depend on the nature of the substituents, probably determined by the stability of the intermediates with aryl or alkyl groups, respectively.

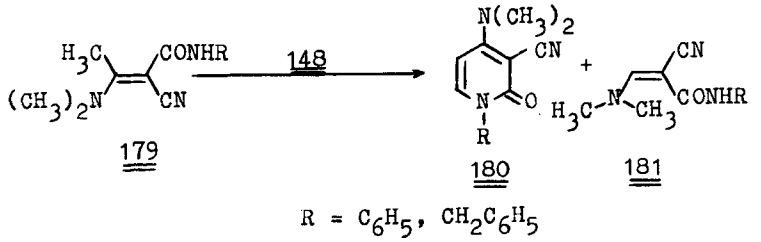
In the case of the β-enamino amide **176** and the diethyl acetal **148**, 4-dimethylamino-3-cyanopyridin-2(1*H*)-one **178** is formed.[125,126]



Scheme 64

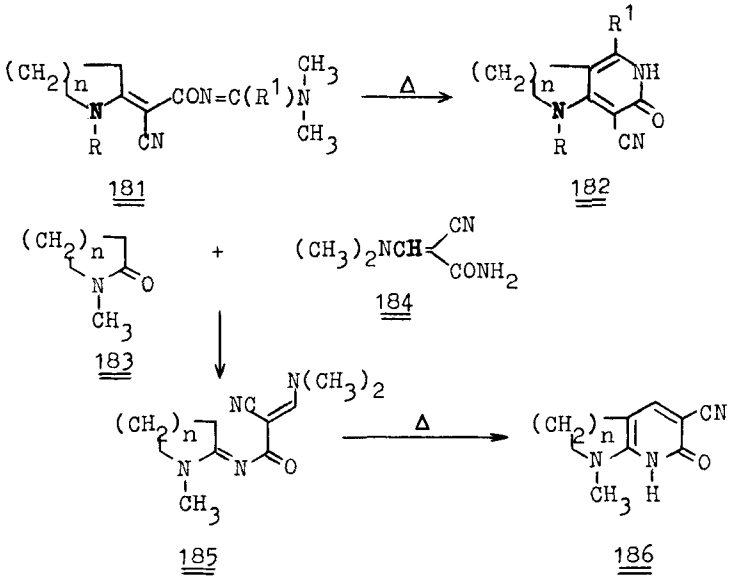
Thus, in the formation of 6-dimethylamino-3-cyanopyridin-2(1*H*)-one **162** the cyclization procedure is accompanied by elimination of the dimethylamino group entering into the β-enamino carbonyl fragment of compound **161**. The cyclization of amidine **177** is accompanied by elimination of a dimethylamino group without incorporation into the β-enaminocarbonyl fragment which results in the formation of an isomeric compound, i.e. **178**. In turn, the character of the elimination is determined by the position of a condensable methyl group in the initial compounds.

4-Dimethylamino-1-phenyl(benzyl)-3-cyanopyridin-2(1*H*)-one **180** has been obtained as a mixture with the aniline **181** by condensation of α-cyano-β-dimethylamino-*N*-phenyl(benzyl)crotonamide **179** with the diethyl acetal **148**.[121,127] Upon exchange of a polar solvent for an unpolar one (toluene) the pyridone **180** as the main product was obtained in high yield.[127] Thus, changing the condensation procedure allows the required reaction pathway to be attained.



Scheme 65

The enamino acylamides **181** and **185** containing a β-enaminocarbonyl fragment have been found to be promising starting materials for the synthesis of the condensed pyridones **182** and **186**,[122,125,126,128-140] respectively.

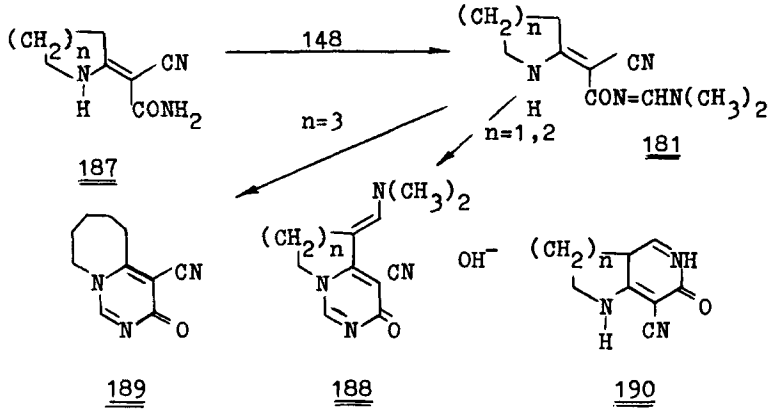


Scheme 66

A study of the kinetics of these reactions showed that the rate of cyclization is much higher for **181** than for the amidine **185**,[126,128,129] i.e. faster cyclization of the positively charged amidine system compared to that of the enamine system. The rate of the cyclization of **185** depends in turn on the ring size. Thus, the reaction rate decreases in the series $n_2 > n_3 > n_1$ which can be explained by the rehybridization of a ring carbon atom from the sp^2-hybridized state to the *sp*-hybridized state at the stage of formation of a transient complex. It is supposed that tautomers with an endocyclic double bond $C^2{=}C^3$ enter into the cyclization procedure.

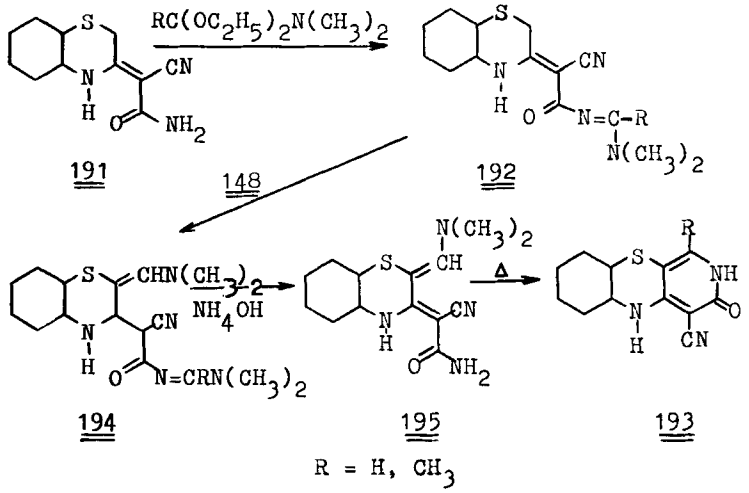
The enamino acylamidines **185** have been obtained as intermediates in the synthesis of the condensed compounds **186** during the interaction of the *N*-methyllactams **182** with the enamino amide **184**.

The enamino acylamidines **181** obtained by interaction of the enamino amides **187** with the diethyl acetal **148** are intermediates in a synthesis of the condensed pyrimidines **188** and **189**.[128–130,136–140] It is interesting that depending on the ring size different compounds are formed.[128–131,136] With n = 1, 2 the corresponding 8- or 9-dimethylaminomethylene derivatives of the condensed pyrimidones **188** are formed which hydrolyze easily in alkaline medium with subsequent recyclization to derivatives of 3-cyanopyridin-2(1*H*)-one **190**.[128,129,131,136–138]



Scheme 67

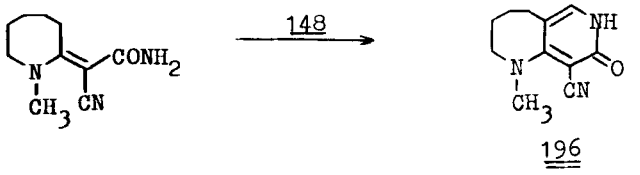
With n = 3, the pyrimido[3,4-*a*]azepine **189** was isolated which does not undergo dimethylaminomethylation due to steric hindrance and, therefore, does not recyclize to a pyridone.[129,131] In the corresponding reaction of the enamino amide **191**, obtained from benzothiazin-2-one, the intermediate acylamidine **192** cyclizes upon heating to the pyridobenzothiazine **193** and not to the corresponding pyrimidine.[116,128]



Scheme 68

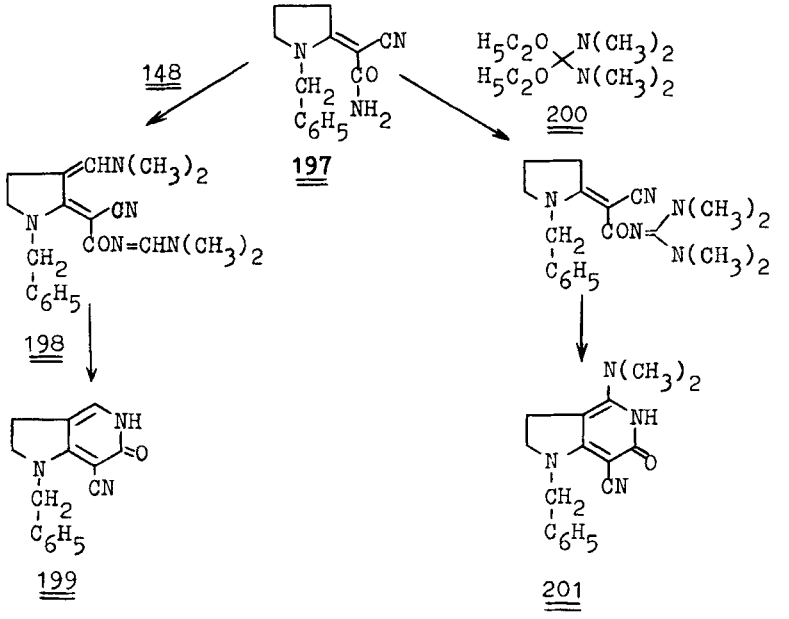
The pyridone **193** has also been obtained from the enamine **192** via the derivatives **194** and **195**.

9-Cyano-1-methyl-2,3,4,5,7,8-hexahydropyrido[4,3-*a*]-azepin-3-one **196** has been obtained in a similar way.[133]



Scheme 69

Reaction of 1-benzyl-2-cyanocarbamoylmethylenepyrrolidine **197** with excess **148** at 130–140 °C results in the formation of **198**, boiling of which in water leads to the saponification of a formamidine group and cyclization to the 5-azaindolinone **199** in 97% yield.[132]



Scheme 70

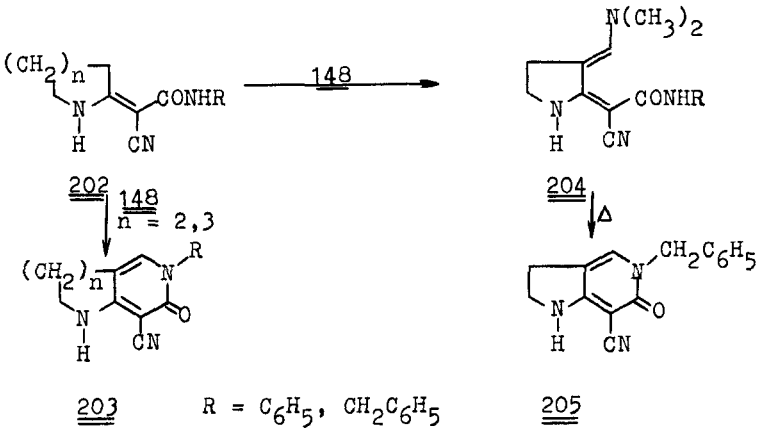
With diethoxydiaminomethane **200** as the formylating agent the 5-azaindolinone **201** was obtained.[134]

Thus, secondary and tertiary enamino amides can be transformed to condensed 3-cyanopyridin-2(1*H*)-ones unsubstituted on the pyridine nitrogen.[123,125] The synthesis of *N*-substituted pyridones presents difficulties due to the inaccessibility of the required starting materials.

The authors of ref.[135] have suggested a method of synthesis of *N*-substituted pyridones from the enamino amides **202** substituted on the amide nitrogen.

The rate of the cyclization of the enamino amides **202** depends on the ring size. In the

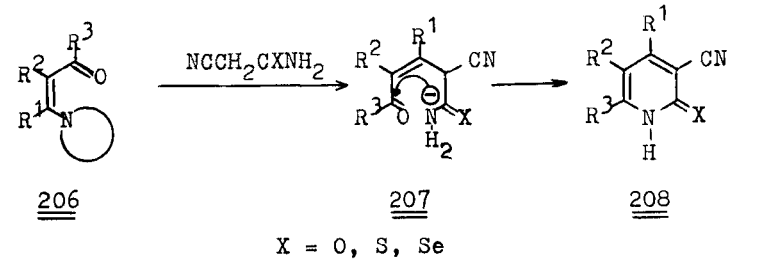
interaction of the six- and seven-membered derivatives **202** (n = 2, 3) with the diethyl acetal **148** in boiling xylene the condensed pyridones **203** are formed. In the case of a five-membered ring the enamino amide **204** was obtained which in turn cyclized to the pyridone **205** upon heating.[135]



Scheme 71

On the strength of the above-mentioned data it can be concluded that β-enamino ketones are convenient reagents for the regiospecific synthesis of 3-cyanopyridin-2(1*H*)-ones.

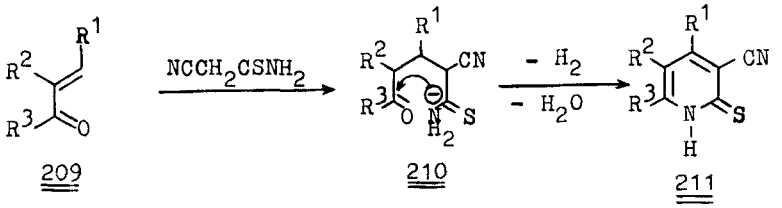
By correlating 1,3-dicarbonyl compounds with their β-enaminocarbonyl analogs one can conclude that the high regioselectivity of their condensation can be explained by the nonuniform distribution of electron density in the $O=C^3-C^2H=C^1-N$ fragment of the enamines. In this case, the atoms C^1 and C^3 differ considerably from those of the corresponding 1,3-dicarbonyl compound with regard to their electrophilicity. For this reason, a nucleophilic attack of the more electrophilic carbon atom in the C^1-N part of the β-enaminocarbonyl compound **206** on the anion of a methylene active nitrile is more probable.[25,49]



Scheme 72

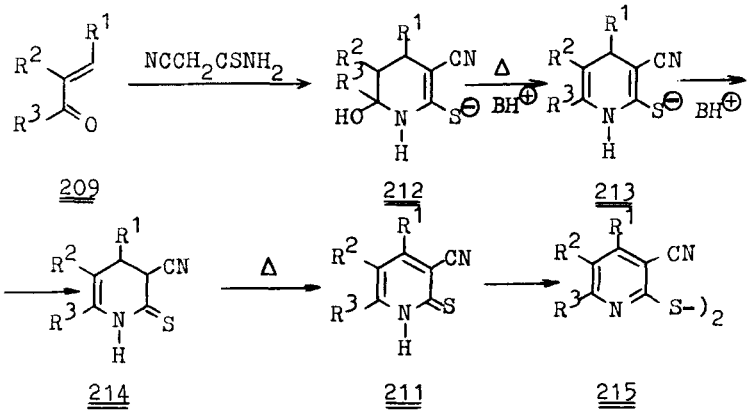
As this takes place, a δ-oxoenethio-(seleno)amide **207**, a key intermediate in the synthesis of 3-cyanopyridin-2(1*H*)-ones, -thiones, and selenones **208**, is generated.

2.2.3. Synthesis from α,β-unsaturated carbonyl compounds In the synthesis of 3-cyanopyridin-2(1*H*)-thiones α,β-unsaturated carbonyl compounds have found wide application. In this case the basic synthetic strategy amounts to the construction with cyanothioacetamide **9** of δ-oxo thioamide **210** from the unsaturated carbonyl compound **209**. Subsequent condensation and dehydration lead to 3-cyanopyridine-2(1*H*)-thiones **211**.



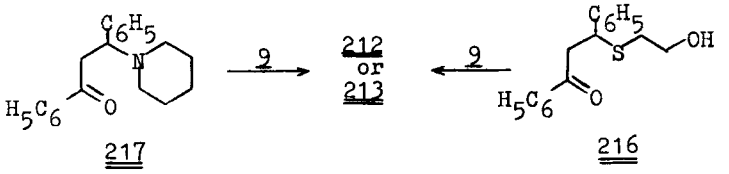
Scheme 73

These reactions were studied for the first time in the case of the synthesis of 4,6-diaryl-3-cyanopyridine-2(1*H*)-thiones.[33,141,142] Also a series of 4,6-dihetaryl-3-cyanopyridine-2(1*H*)-thiones has been obtained.[40] Later, α,β-unsaturated carbonyl compounds were used in the synthesis of 4,5,6-trisubstituted 3-cyanopyridine-2(1*H*)-thiones.[143-145] The reaction course depends on the nature of the catalyst and on the reaction conditions. The use of sodium alkoxides in boiling ethanol or methanol results in the formation of substituted 3-cyanopyridine-2(1*H*)-thiones **211**.[33,40,142-145] When **209** are treated with **9** in ethanol in the presence of an equimolar amount of base at 20 °C, tetrahydropyridines are formed.[146-152] The organic base plays a role both as a catalyst and as a stabilizing agent; thiones can be isolated as the corresponding stable salts. Thus, hydropyridines have been isolated and characterized as the salts **212** and **213**. The substituted 3,4-dihydropyridine-2(1*H*)-thiones **214** are formed upon acidification of their salts **213** with HCl. The compounds **214** are relatively stable and oxidize to 3-cyanopyridine-2(1*H*)-thiones **211** in organic solvents and to pyridyl sulfides **215** in the presence of atmospheric oxygen.



Scheme 74

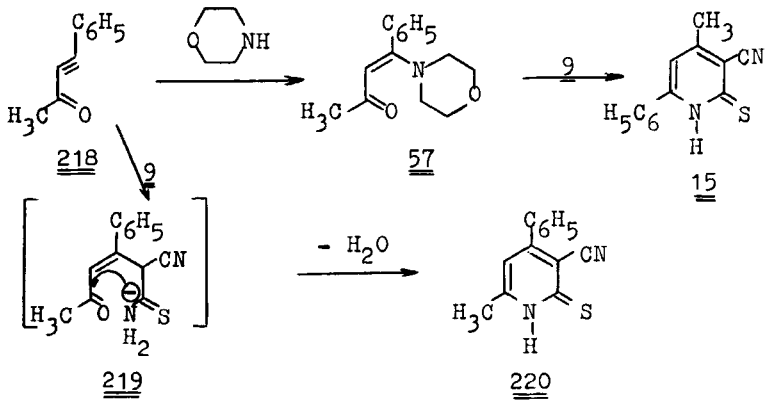
In some instances, 2-mercaptoethanol **216** has been used as a stabilizer interfering with the oxidation of **211** to the disulfides **215**.[141] This allowed the synthesis of the hydropyridines **212–214** from an adduct of chalcone **216** and cyanothioacetamide **9**.[153] In a similar manner, the compounds **212–214** have been synthesized from reaction products of chalcone and piperidine **217**.[146] However, these methods are lengthy and offer no improvement in the synthesis of the hydropyridines **212–214** and the pyridinethiones **211**. Nevertheless, the application of **216** as an antioxidant is appropriate in the given reactions.



Scheme 75

There is evidence that the condensation of α,β-unsaturated ketones with **9**, compared to that of 1,3-dicarbonyl compounds, proceeds more regioselectively. Thus, interaction of 1-(3- and 4-pyridinyl)-1-butene-3-ones with **9** led to derivatives of 3,4- and 4,4-dipyridyls only.[13]

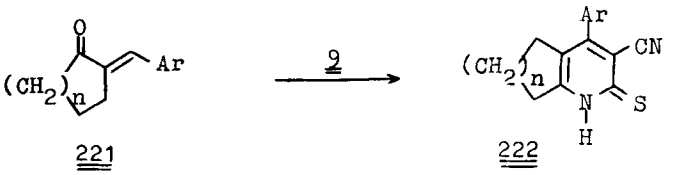
The literature contains only one example of the application of acetylenic carbonyl compounds in the synthesis of substituted 3-cyanopyridine-2(1*H*)-thiones.[154] From acetylphenylacetylene, 6-methyl-4-phenyl-3-cyanopyridine-2(1*H*)-thione **220** and 4-methyl-6-phenyl-3-cyanopyridine-2(1*H*)-thione **15** were obtained readily and with high regioselectivity. Evidently, formation of the Michael adduct **219** occurs first, the subsequent intramolecular cyclization of which results in the formation of pyridine **220**.



Scheme 76

Carried out in the presence of morpholine this reaction gives a mixture of the (*E*,*Z*)-isomers of the β-enamino ketone **57**, the condensation of which with **9** yields the pyridine **15**. Also in the synthesis of annelated 3-cyanopyridine-2(1*H*)-thiones

unsaturated carbonyl compounds have been used. Interaction of 2-arylidenepentane-(hexane)-2-thiones **221** with **9** proceeds with formation of the 4-aryl-5,6-polymethylene-3-cyanopyridine-2(1*H*)-thiones **222**.[155]

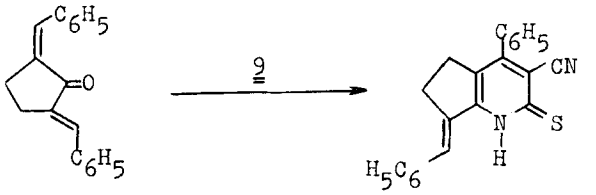


221 **222**

n = 1, 2; Ar = C_6H_5, 4-ClC_6H_4

Scheme 77

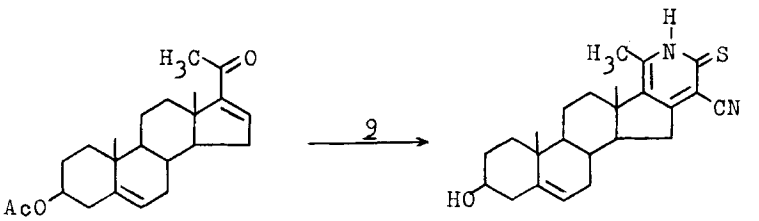
The condensation of 2,5-dibenzylidenecyclopentanone **223** with **9** takes place upon heating in ethanol in the presence of sodium ethoxide. This method has been used for the synthesis of the pyridinethione **224**.[156]



223 **224**

Scheme 78

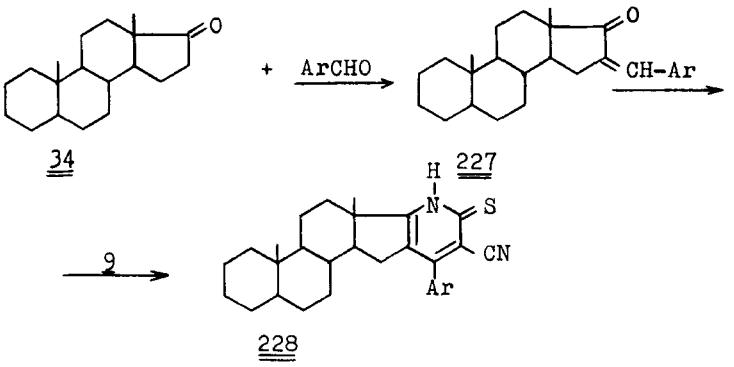
The steroid derivative **226** has been obtained under similar conditions.[157] The condensation is accompanied by the hydrolysis of an acetoxy group of the starting steroid **225**.



225 **226**

Scheme 79

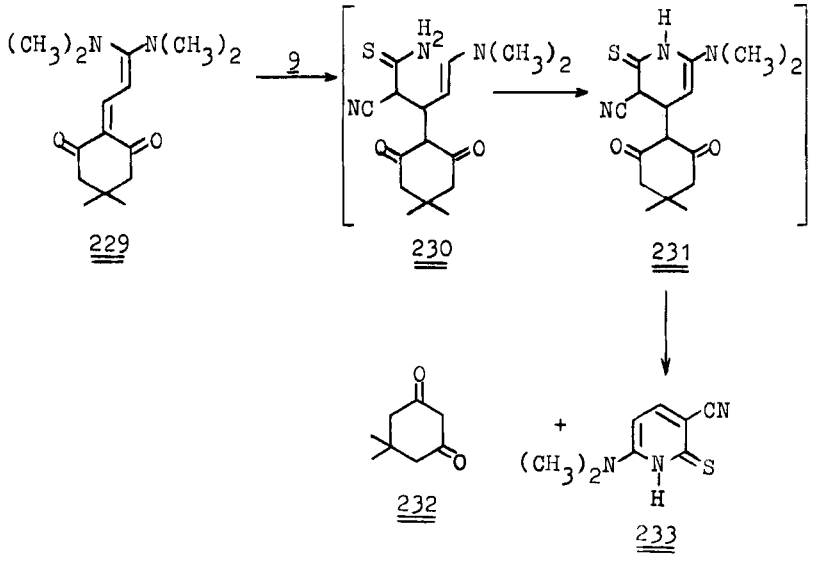
Condensation of 5β-androstan-17-one **34** with aromatic aldehydes and subsequent interaction of the so obtained arylideneketones **227** with **9** result in the formation of 4-arylpyridinethiones condensed with a steroid fragment **228**.[157]



Ar = C_6H_5, 3-FC_6H_4, 2-C_4H_3O, 3-C_5H_4N

Scheme 80

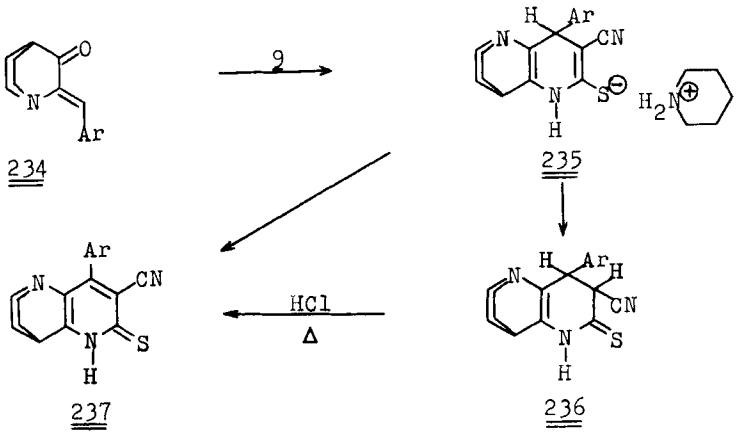
The interaction of the keto diene **229** with **9** is of particular interest.[158] Two intermediates, i.e. first **230** and then **231**, are supposed to form. Elimination of dimedone **232** gives rise to 6-dimethylamino-3-cyanopyridine-2(1*H*)-thione **233**.



Scheme 81

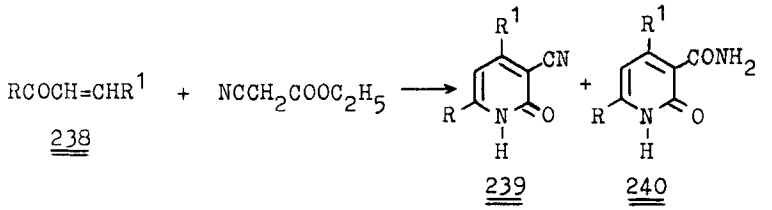
The application of α,β-unsaturated carbonyl compounds in the synthesis of 3-cyanopyridine-2(1*H*)-thiones permits one to obtain, depending on the reaction conditions, their hydro analogs which can be used in the synthesis of annelated hydropyridines; this is of particular importance in the synthesis of specific physiologically active substances.[159,160]

It is interesting to note in this context the annelation of the 2-arylidene-3-oxoquinuclidines **234** to the 4-aryl-3-cyano-5,8-ethano-5,6,7,8-tetrahydro-1,5-naphthyridine-2(1*H*)-thiones **237**.[160] The reaction proceeds via salts of the 1,4-dihydropyridines **235** and the 3,4-dihydropyridinethiones **236**.



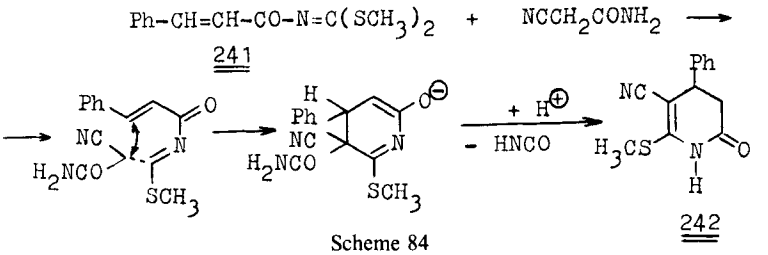
Scheme 82

α,β-Unsaturated carbonyl compounds have been used for a long time and rather extensively in the synthesis of 3-cyanopyridin-2(1*H*)-ones.[15-17] One example of recent work will be presented here.[161] Condensation of the unsaturated ketone **238** with cyanoacetic ester results in the formation of a mixture of 3-cyano- and 3-carbamoylpyridin-2(1*H*)-one, **239** and **240**.



Scheme 83

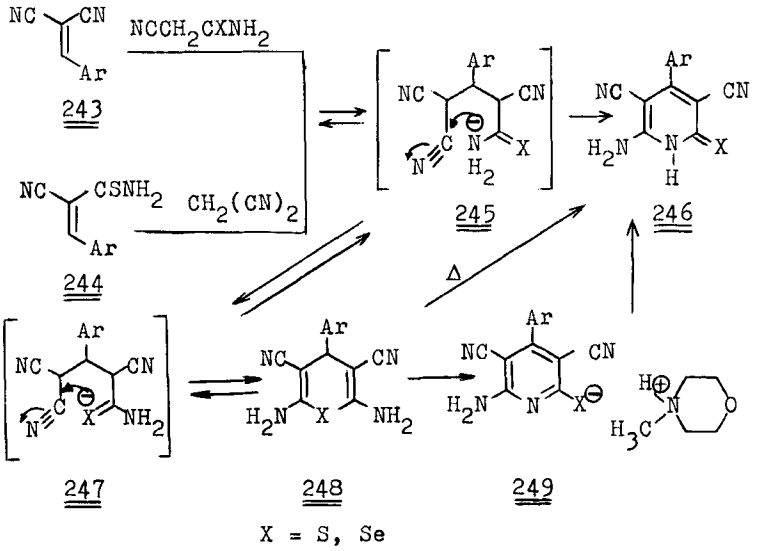
If a reactive dithiomethylene group is present in the α,β-unsaturated carbonyl compound, the condensation changes its course with elimination of methanethiol.[162] A hydropyridone **242** is form in high yield.



Scheme 84

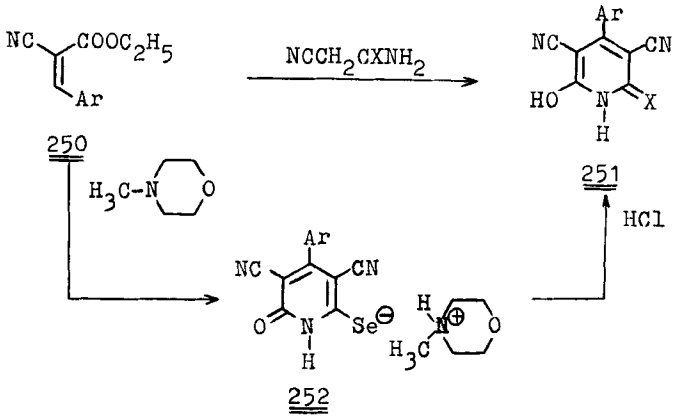
2.2.4. Synthesis from α,β-unsaturated nitriles The strategy of the synthesis of 3-cyanopyridine-2(1*H*)-thiones and -selenones from α,β-unsaturated nitriles and cyanothio(seleno)acetamide **9** and **10** amounts to the construction of δ-cyano thio-(seleno)amides and the subsequent intramolecular closure of a pyridine ring. The

starting materials are arylidenemalononitriles and **9** and **10**. The interaction of **243** or **244** with **9**, **10** or malononitrile in a Michael reaction may serve as examples. Subsequent intramolecular cyclization of the adducts **245** leads to the 3-cyanopyridine-2(1*H*)-thiones and -selenones **246**.



Scheme 85

According to this procedure in boiling ethanol different 6-amino-4-aryl(hetaryl)-3,5-dicyanopyridine-2(1*H*)-thiones and -selenones **246** have been obtained in the presence of organic bases.[163-173] 4-Aryl-6-hydroxy-3,5-dicyanopyridine-2(1*H*)-thiones and -selenones **251** have been synthesized from arylidenecyanoacetic esters **250** and **9** or **10** in a similar way.[173-175] In a case where pyridineselenones were the intermediates the corresponding *N*-methylmorpholine salts **252** were isolated.[173]

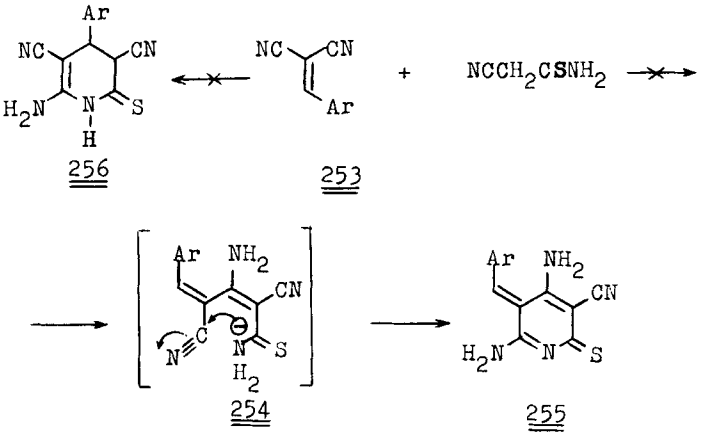


Scheme 86

It has been found that the formation of **246** proceeds by recyclization of the corresponding thio(seleno)-pyrans **248**.[168-170,172] The recyclization takes place via salts of pyridinethiones and -selenones **249**, which have been liberated and characterized in a number of cases.[169-173]

Thus, the formation of **246** and **248** may be considered as a consequence of the ambident behavior of the thio(seleno)amide fragment in the intermediates **245** and **247**, depending upon the conditions. Under conditions of kinetic control formation of the thio(seleno)pyrans **248** was observed. Under conditions of thermodynamic control the pyridinethiones and -selenones **246** are formed. Overall, the oberved transformations are in keeping with reversibility of all stages except the formation of the pyridinethiones and -selenones **246**.

Simultaneously with the work of refs.[163,164,167] Egyptian scientists, [174,176] described the interaction of the arylidenemalononitriles **253** with **9** under thermodynamic control with formation of the 5-arylidenepyridinethiones **255**.

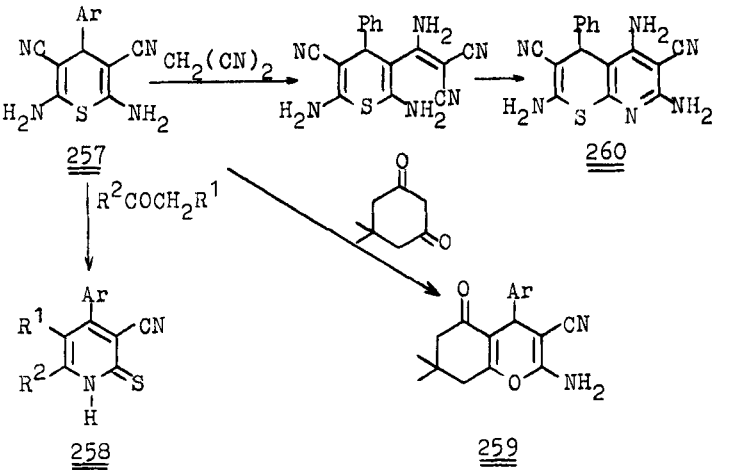


Scheme 87

These results have been presented in reviews.[6,9] The authors of these reports[6,9,174,176] believe that the interaction of the arylidenemalononitriles **253** with **9** proceeds via intermediate **254** with subsequent cyclization to the 5-arylidenepyridinethione **255**. In their opinion, interaction of **9** with one of the nitrile groups of the arylidenemalononitrile **253** with participation of a methylene group prevails over the Michael reaction. However, an analysis of the spectra and X-ray data of the conversion products of α,β-unsaturated nitriles has shown that it is the Michael reaction which prevails in all cases of similar transformations.[163,164,167] The final products of such interactions are always 6-amino-4-aryl-3,5-dicyanopyridine-2(1*H*)-thiones and -selenones **246** only, and not 5-arylidenepyridinethiones **255** as erroneously claimed in refs.[6,9,174,176] The reaction of (1-amino-2,2,2-trichloroethylidene)malononitrile with **9** has also been presented incorrectly.[177] In a number of cases the thiopyran structure **248** has been attributed to pyridinethiones **246**.[178] The structure of the thiones and selenones formed from **253** and

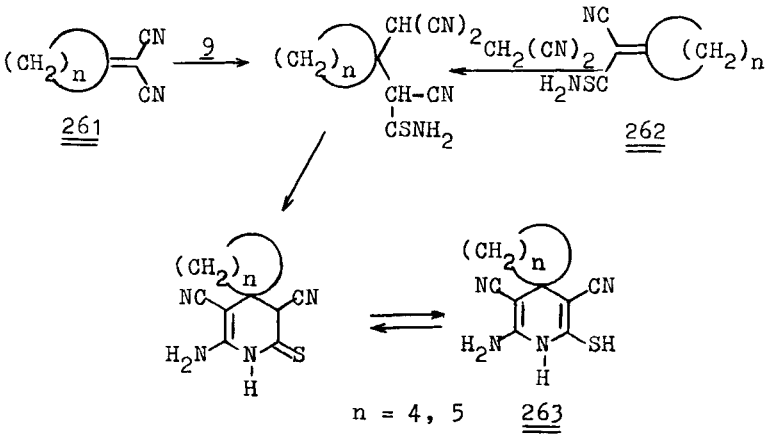
9 or **10**, respectively, have been unequivocally proven by X-ray analysis.[168-170] The formation of 3,4-dihydropyridinethiones **256** as claimed in ref.[179] has not been corroborated by significant additional work.

Pyridinethiones **258**,[180] tetrahydro-4*H*-benzo[*b*]pyrans **259**,[180] and azinothiopyrans **260**[181] have been obtained from the thiopyrans **257**.



Scheme 88

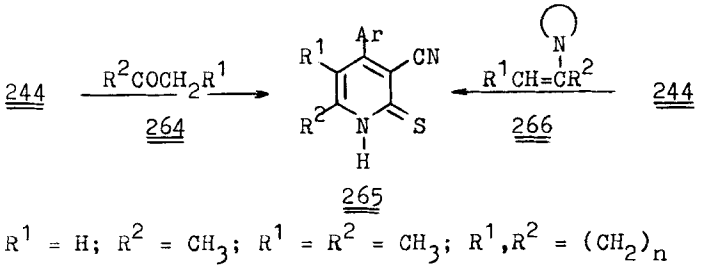
The one-stage condensation of cyclopentamethylenemalononitrile **261** and of its thioamide **262** with methylene active nitriles yields the spirodihydropyridines **263**.[182]



Scheme 89

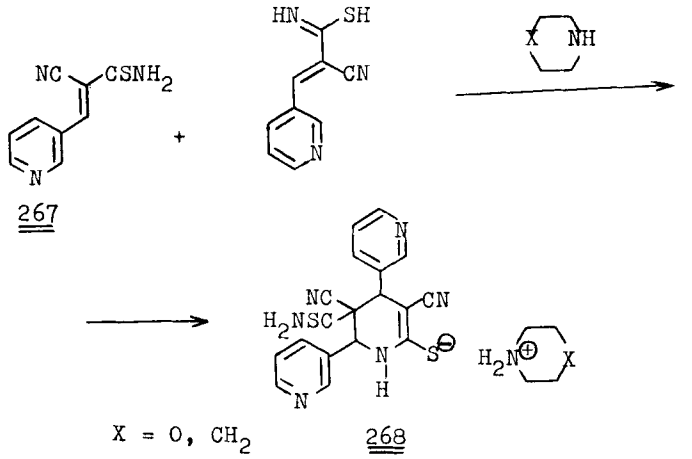
In the synthesis of 3-cyanopyridine-2(1*H*)-thiones and their hydro analogs, reactions of arylidenecyanothioacetamides **244** with α-methylene(methyl)carbonyl compounds or their enamines have found wide application. Depending on the structure of the carbonyl

compound and the reaction conditions, the reaction can be stopped both at the stage of the hydropyridinethiones and of the pyridine-2(1*H*)-thiones. The monocarbonyl compounds **264** acetone and methyl ethyl ketone, as well as cycloalkanones interact with **244** with formation of the substituted 4-aryl-3-cyanopyridine-2(1*H*)-thiones **265**.[164,167,183-190] In this case attempts to isolate hydropyridinethiones fail as a rule. Analogous results were obtained with the enamines **266** and cyclohexanone.[164,167,183,184,186] However, with the enamines **266** the reactions take place under milder conditions and in the absence of basic catalysts. Moreover, increased yields were noted.



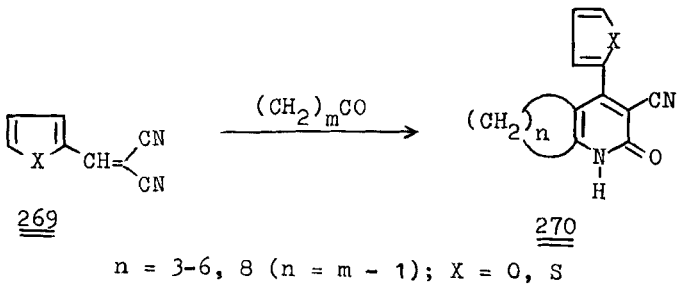
Scheme 90

In the case of methyl ethyl ketone, the reaction is highly regioselective with formation of the more substituted 4-aryl-5,6-dimethyl-3-cyanopyridine-2(1*H*)-thione. These methods allowed the preparation of the 4-aryl(furyl,pyridyl)pyridinethiones **265** in high yields. Nevertheless, these reactions have some limitations. In the case of the interaction of pyridinylidenecyanothioacetamide **267** with cyclopentanone or cyclohexanone in the presence of an equimolar amount of base, the reaction changes its course and results in the formation of pyridine-2-thiolate salts **268**.[164] Thus, cyclic ketones with their relatively low CH-acidity do not react with **267**. Under these conditions, the cyclodimerization of **267** in a Diels-Alder reaction prevails over the Michael reaction.



Scheme 91

Hetarylidenemalononitriles **269** react with cycloalkanones to form condensed 3-cyanopyridine-2(1*H*)-ones **270**.[190]

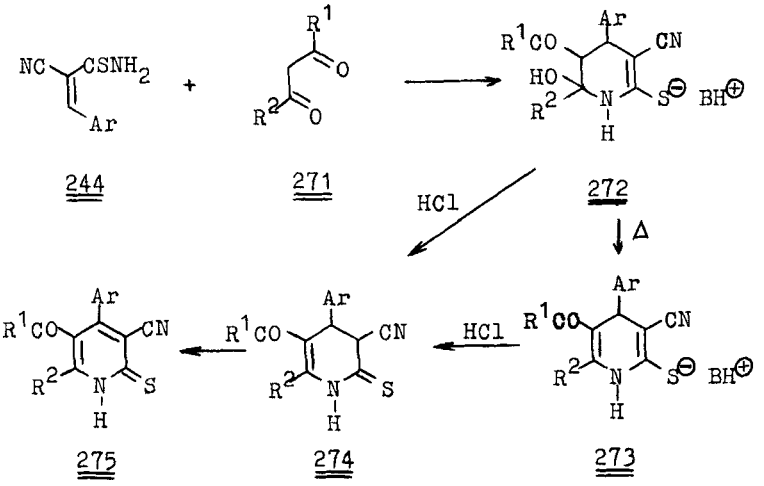


269 270

n = 3-6, 8 (n = m - 1); X = O, S

Scheme 92

Analogous reactions of β-dicarbonyl compounds have been studied.[141,147,167,183,186,189,191-197] Unlike monocarbonyl derivatives, reaction of 1,3-dicarbonyl compounds **271** or their enamines with arylidenecyanoacetamides **244** proceeds with the formation of substituted 3-cyanohydropyridine-2(1*H*)-thiones or their salts.[141,147,167,183,189-196] It is also possible to isolate the tetrahydropyridine-2-thiolates **272** the subsequent dehydration of which results in the 1,4-dihydropyridine-2-thiolates **273**.

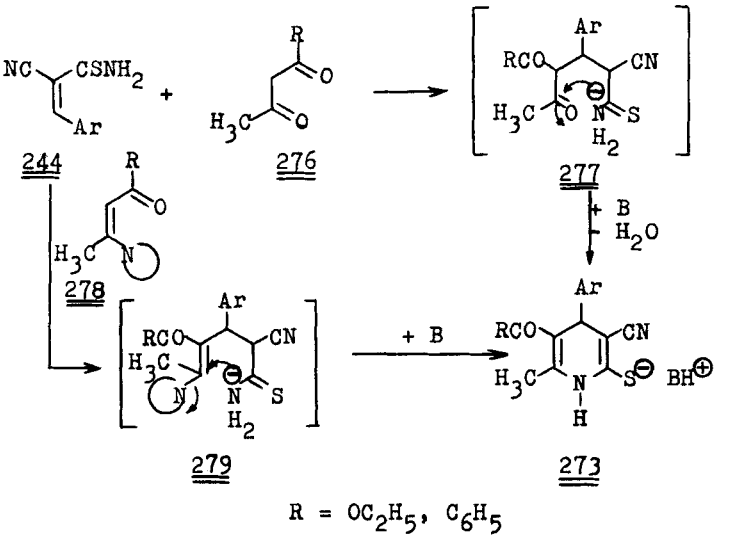


244 271 272 273 274 275

Scheme 93

Upon acidification of the salts **272** and **273** the 3,4-dihydro-3-cyanopyridine-2(1*H*)-thiones **274** were obtained which dehydrogenize in solution to the pyridine-2(1*H*)-thiones **275** in low yields.

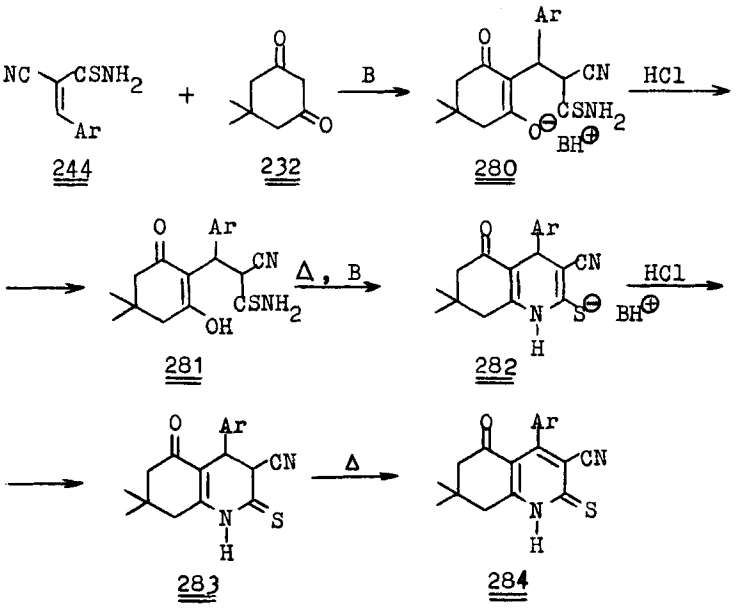
As in the case of enamines of monocarbonyl compounds, β-enaminocarbonyl derivatives interact with arylidenecyanothioacetamides **244** in the absence of basic catalysts and with formation of 1,4-dihydropyridine-2-thiolates. Ref.[193] defines the regiochemistry of reactions of **244** with unsymmetric 1,3-dicarbonyl compounds **276** or their enamines.



Scheme 94

It has been established that the regiochemistry of these reactions is determined by the relative reactivity of the carbonyl groups in the transition state, e.g. **277**. In this particular case only 5-benzoyl(ethoxycarbonyl)pyridine-2-thiolates **273** are formed. In the case of the enamines **278** the reaction proceeds probably through intermediate **279** towards the pyridinethiolates **273**.

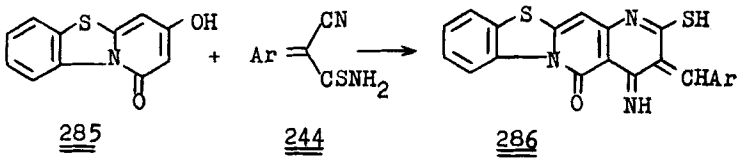
Important information concerning the mechanism of the interaction of 1,3-dicarbonyl compounds with **244** is given in refs.[164,195] The introduction of a cyclic 1,3-dicarbonyl compound, dimedone **232**, permitted to isolate and study the Michael adducts as the salts **280**. Subsequent acidification of **280** leads to the formation of the adducts **281**. Upon heating of **280** in ethanol or of **281** in the presence of organic bases the quinoline-2-thiolates **282** are formed. The latter when acidified transform to hydroquinoline-2(1*H*)-thiones **283**, when heated in ethanol to the quinoline-2(1*H*)-thiones **284**.



Scheme 95

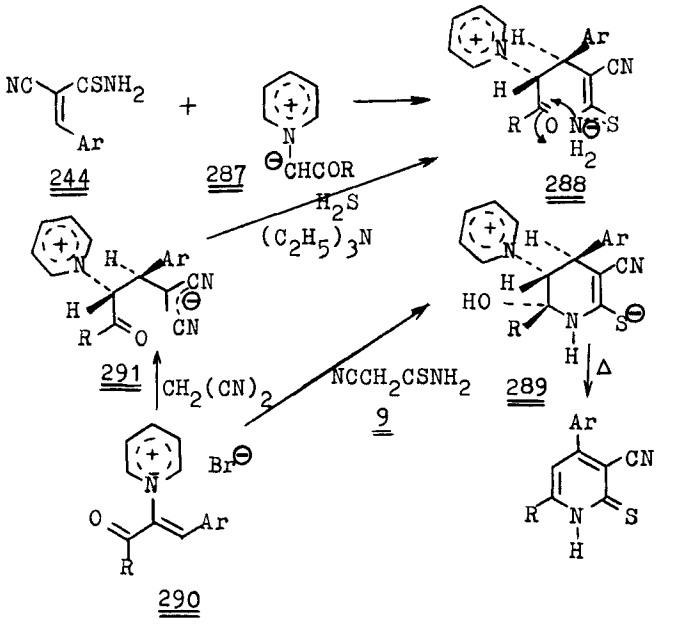
Thus, it was found that the formation of pyridine-2(1*H*)-thiones from arylidenecyanothioacetamides **244** and 1,3-dicarbonyl compounds takes place via the corresponding Michael adduct.

As an exception from the scheme suggested, the reaction of the benzothiazolone **285** with **244** results in the condensed system **286**.[198]



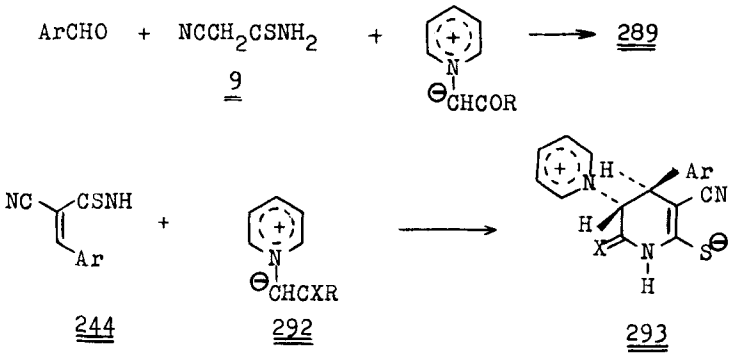
Scheme 96

Until recently, the stereochemistry of the reaction of carbonyl compounds with **244** was practically unknown. Published reports[199–203] point out that pyridine ylides are convenient reagents for the investigation of the stereochemistry of reactions relating to the formation of pyridine-2(1*H*)-thiones. The reaction of **244** with pyridine ylides **287** proceeds with the formation of betainic 3,4-*trans*-1,2,3,4-tetrahydropyridine-2-thiolates **289**. It has been found that the high stereoselectivity of these reactions is due to the stereoselective addition of the pyridine ylides to **244**. The subsequent cyclization of the adducts **288** occurs with preservation of the *trans*-arrangement of the hydrogen atoms in **289**.[202,203]



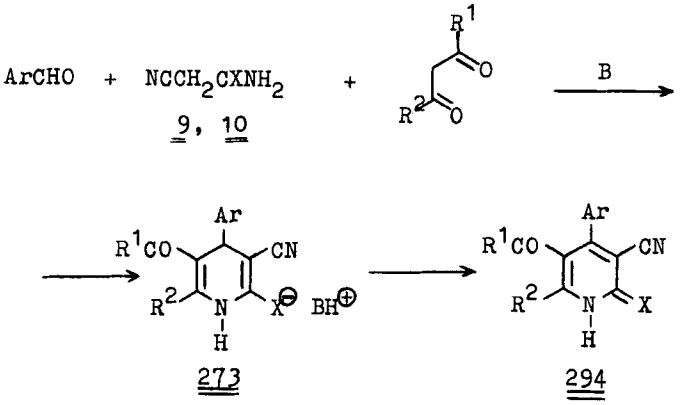
Scheme 97

Tetrahydropyridines **289** have been obtained from the styrylpyridine salts **290** and **9** in high yield.[200] By changing the structure of the CH-acid it was possible to isolate and study adduct **291** which is formed by interaction of the (*E*)-isomer **290** with malononitrile. The subsequent interaction of the *trans*-adduct **291** with hydrogen sulfide proceeds with formation of the *trans*-tetrahydropyridine **289** which in turn gives the pyridine-2(1*H*)-thione upon boiling in AcOH in the presence of ammonium acetate. Based on this study of the stereochemical aspects of the abovementioned reactions, a simpler method for the synthesis of **289** has been developed without isolation of the unsaturated compounds **244** or **290**.[203] The condensation of aldehydes, **9**, and pyridine ylides is stereoselective and yields the tetrahydropyridines **289**.



Scheme 98

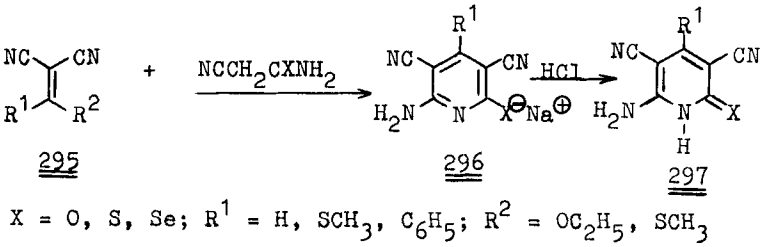
2-Oxo(thio)tetrahydropyridine-6-thiolates **293** have been prepared in high yield by condensation of **244** with pyridine ylides **292**. However, more interesting, from a practical point of view, is the synthesis of substituted 3-cyanopyridine-2(1*H*)-thiones and -selenones by the ternary condensation of aldehydes, cyanothio(seleno)acetamide **9** or **10** and 1,3-dicarbonyl compounds in the presence of excess organic base.[147,191,192]



Scheme 99

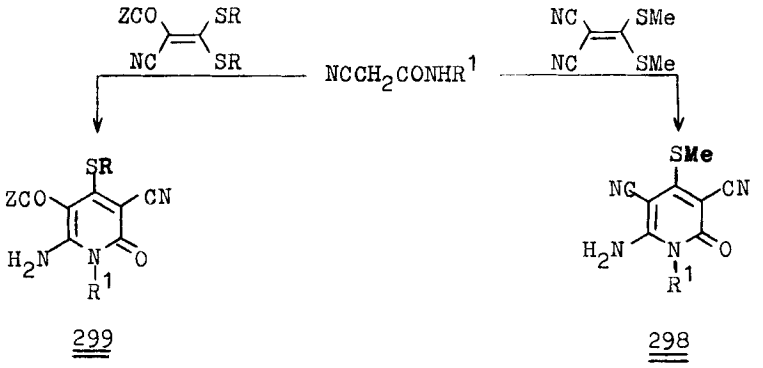
Compounds **273**, when oxidized by atmospheric oxygen in an acid medium, undergo dehydrogenation with formation of the pyridines **294**.

In the synthesis of 3-cyanopyridine-2(1*H*)-thiones and -selenones, the unsaturated nitriles **295**, containing a nucleofugal group in the β-position, have found application.[204–206] When unsaturated nitriles interact with **9** or **10** in the presence of sodium ethoxide, the sodium salts of pyridine-2-thiolates(selenolates) **296** are obtained within high yield.



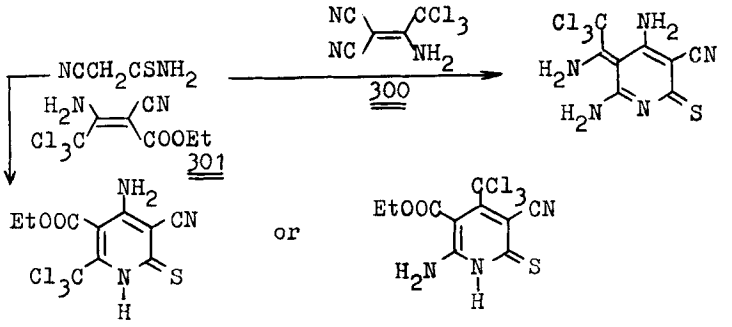
Scheme 100

Acidification of **296** with HCl leads to the pyridine-2(1*H*)-thiones and -selenones **297**. 3-Cyanopyridin-2(1*H*)-ones **298** and **299** have been prepared in a similar way.[207]



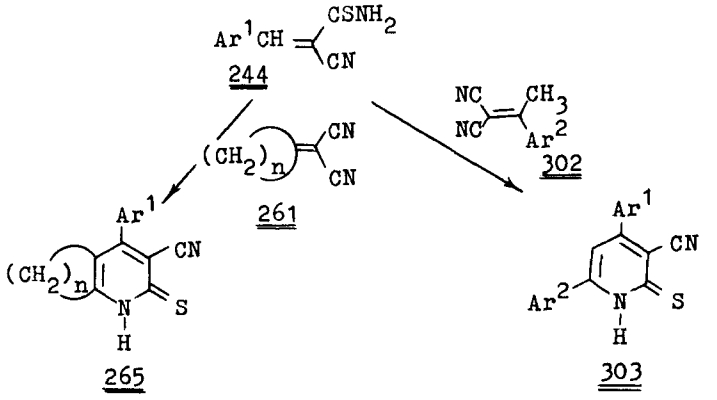
Scheme 101

In the case of the nitriles **300** and **301** the reaction takes another course.[177]



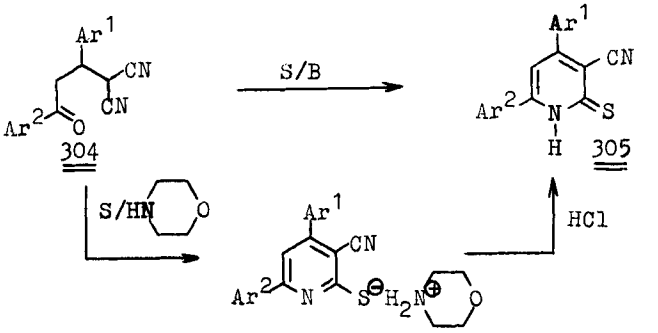
Scheme 102

The unsaturated nitriles **261** and **302** have also been allowed to react with arylidenecyanothioacetanilides **244**. In hot ethanol the 3-cyanopyridine-2(1*H*)-thiones **265** and **303** form in the presence of organic bases.[208]



Scheme 103

2.2.5. δ-Keto nitriles in the synthesis of 3-cyanopyridine-2(1H)-thiones δ-Keto nitriles, accessible by reaction of α,β-unsaturated ketones with malononitrile, have been successfully used in the synthesis of 4,6-diaryl-3-cyanopyridine-2(1*H*)-thiones. It has been found that the interaction of δ-keto nitriles **304** with elemental sulfur gives a high yield of pyridine-2(1*H*)-thiones **305** upon heating in ethanol and in the presence of organic bases.[33,209–212] The introduction of an equimolar amount of morpholine into the reaction leads to the formation of the morpholine salts **306** the acidification of which results in the pyridinethiones **305**.

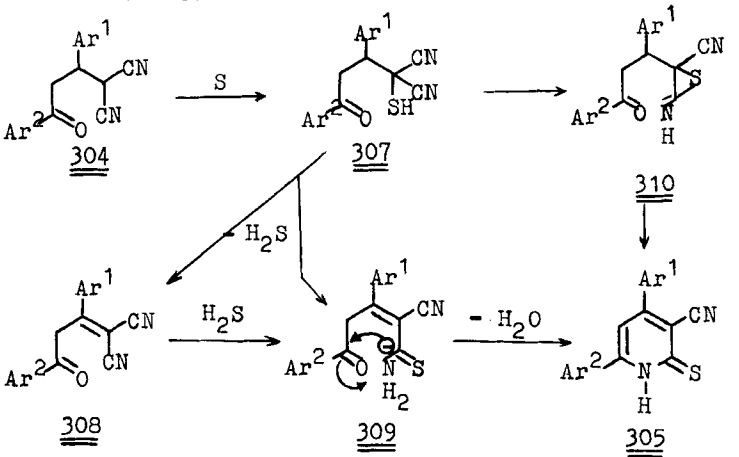


304 **305** **306**

Ar^1, Ar^2 = C_6H_5, 4-FC_6H_4, 4-ClC_6H_4, 2-C_4H_3S

Scheme 104

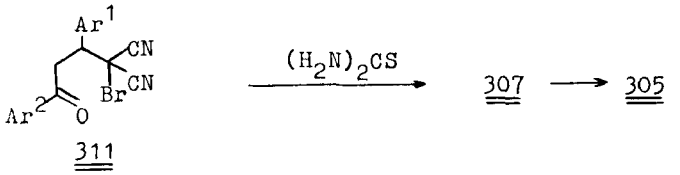
A study of the paths of formation of 3-cyanopyridine-2(1*H*)-thiones from **304** showed that the general scheme of this reaction may be presented as follows: first thiolation of an α-carbon atom and formation of intermediate **307**, the elimination of hydrogen sulfide, followed by its addition to one of the nitrile groups of the unsaturated nitrile **308** with final formation of the δ-keto thioamide **309**. Subsequent intramolecular condensation leads to the 3-cyanopyridine-2(1*H*)-thione **305**.



304 **307** **310** **308** **309** **305**

Scheme 105

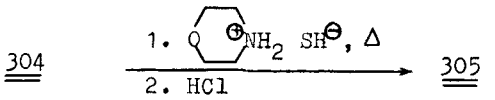
3-Cyanopyridine-2(1*H*)-thiones **305** could also be formed via the thiirane **310** which could just as well result from the intramolecular cyclization of **307**. The role of intermediates in this process leading to pyridine-2(1*H*)-thiones has been proven experimentally.[212] The probability of the formation of 3-cyanopyridine-2(1*H*)-thiones **305** via **307** has been suggested by the reaction of (α-bromo-δ-oxoalkyl)malononitriles **311** with thiourea.



311

Scheme 106

An organic base may be a carrier of hydrogen sulfide in these reactions. This has been confirmed by the synthesis of 3-cyanopyridine-2(1*H*)-thiones **305** from δ-keto nitriles **304** and morpholine hydrosulfide[34] or hydrogen sulfide.[146]

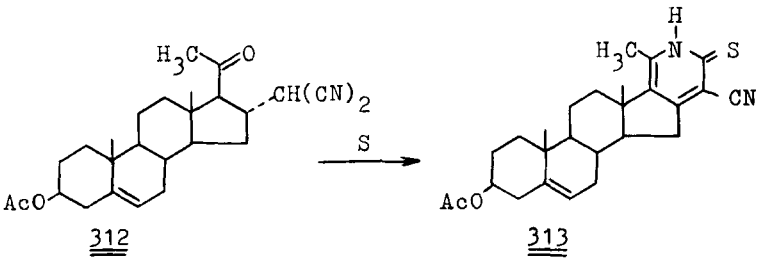


304 305

Scheme 107

For the synthesis of 4,6-diaryl-3-cyanopyridine-2(1*H*)-thiones, also δ-keto nitriles and Lawesson's reagent have been used.[11,213] However, the yield is somewhat lower in this case. Taking into consideration that Lawesson's reagent is less readily available than sulfur its application is justified for other methods leading to the substitution of an oxygen atom in pyridin-2(1*H*)-ones by sulfur.

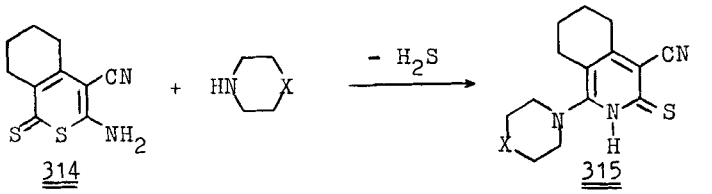
The δ-keto nitrile **312** and elemental sulfur form the pyridinethione **313** annelated with a steroid ring system.[214]



312 313

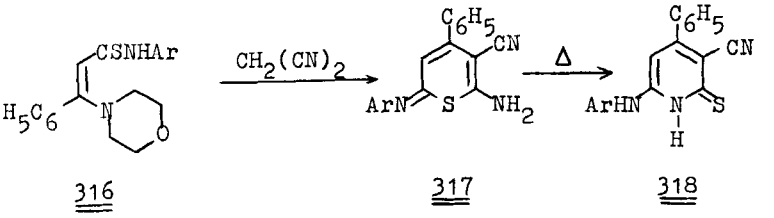
Scheme 108

2.2.6. Recyclization and other methods In the synthesis of substituted 3-cyanopyridine-2(1*H*)-thiones and -selenones, recyclizations of sulfur(selenium)-containing heterocycles —thiopyrans, selenopyrans, isothiazoles, 1,3-dithiacyclohexenes, have been found useful. 6-Amino-3,4-tetramethylene-2-thioxo-5-cyanopyran **314** recyclizes to 3-cyano-4,5-tetramethylenepyridine-2(1*H*)-thione **315** upon treatment with organic bases.[215]



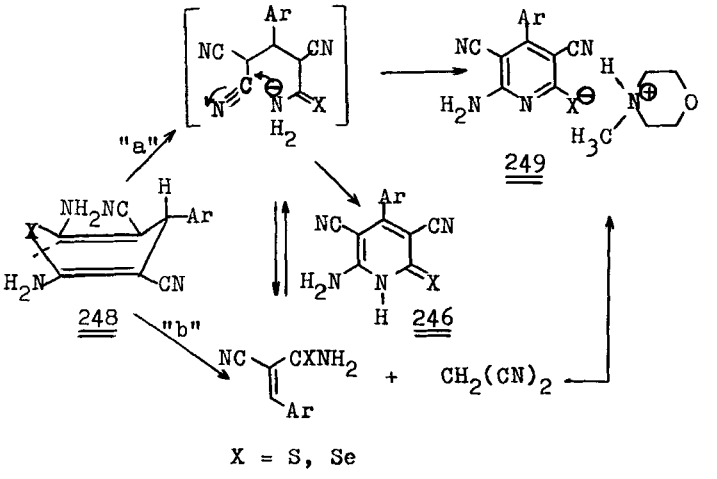
Scheme 109

Ref.[216] presents an original method of synthesis of substituted 3-cyanopyridine-2(1*H*)-thiones. Interaction of the β-enamino thioamides **316** with malononitrile yielded the substituted thiopyrans **317** under kinetic control conditions. Upon heating with an organic base under thermodynamic control conditions the thiopyrans **317** undergo transformation to 3-cyano-pyridine-2(1*H*)-thiones **318**.



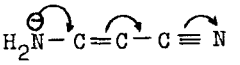
Scheme 110

It is also appropriate to consider the recyclization of **248** to derivatives of 3-cyano-pyridine-2(1*H*)-thiones and -selenones **246** already mentioned in Section 2.2.4. According to physico-chemical analysis and X-ray diffraction studies the thio(seleno)pyran ring in **248** possesses a flattened boat conformation with an equatorial aryl substituent in position 4.[165,168-170,172]



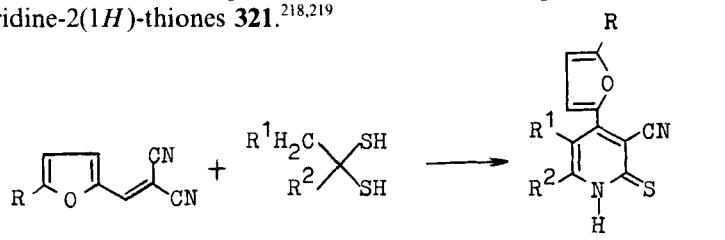
Scheme 111

Full p,π-conjugation in the enamino nitrile is possible with the involved groups in a common plane. The above mentioned factors as well as the steric congestion in **248** with voluminous electron-acceptor substituents, interfere with free inversions of ring bonds and with inversions of ring substituents as well as with the transitions to extreme conformations upon temperature increase. Upon heating **248** cannot decrease its strain by conformational transitions, therefore the weakest bond of the ring (dash marked) cleaves and the subsequent transformation of the 3-cyanopyridine-2(1*H*)-thiones and -selenones **246** follows path "a" or "b". Evidently, similar recyclization steps could be invoked for the transformation of the thiopyrans **314** and **317** to the pyridinethiones **315** and **318** described in refs.[215,216]



Scheme 112

Under thermodynamic control enamino nitriles of 1,3-dithiacyclohexenes suffer ring transformation leading to substituted 3-cyanopyridine-2(1*H*)-thiones.[164,184,185,217-221] Recyclizations of this type were first observed in the reaction of 2-furfurylidenemalononitrile **319** with 1,1-dithiols **320**. Attempts to isolate an expected 1,3-dithiacyclohexane, as shown in the example of interaction of benzylidenemalononitrile with 1,1-dithiols, failed.[222] The main products of this exothermic process were the 4-(2-furyl)-3-cyanopyridine-2(1*H*)-thiones **321**.[218,219]

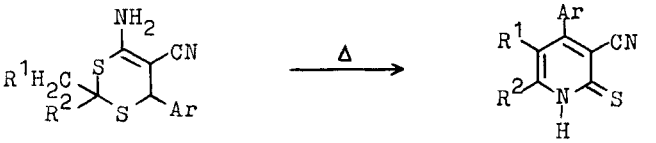


319 **320** **321**

R^1 = H, R^2 = CH_3; R^1 = R^2 = CH_3; R^1,R^2 = $(CH_2)_3$; R^1,R^2 = $(CH_2)_4$; R = H, Ar

Scheme 113

Later it was shown that substituted 3-cyanopyridine-2(1*H*)-thiones are also formed from the corresponding 1,3-dithiacyclohexenes **322**.[184,185,217,220,221]

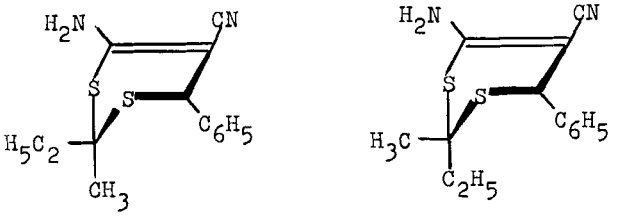


322 **265**

Scheme 114

The regiochemistry of this recyclization has been much studied in the case of the 2,2-dialkyl-6-aryl-1,3-dithia-4-cyclohexenes **322**.[184,185] Formally, the recyclization is accompanied by elimination of hydrogen sulfide and two hydrogen atoms. The course

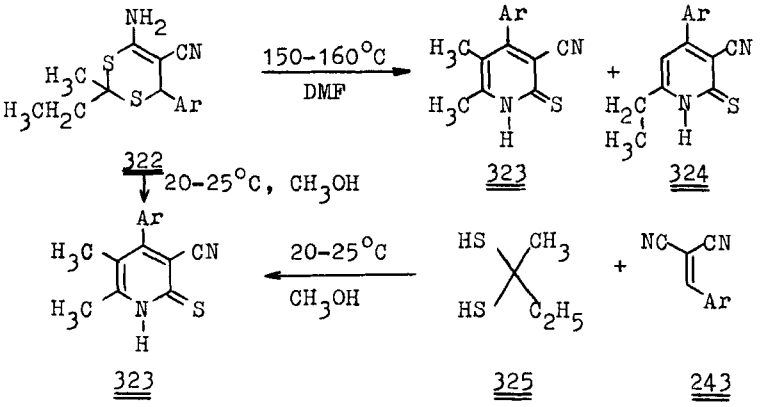
of the reaction is determined by the structure of the starting 1,3-dithiacyclohexenes. The most stable conformation of substituted 1,3-dithiacyclohexenes is the half-chair. Considering the high intensity and the position (2187–2194 cm^{-1}) of the C≡N absorption in their IR spectra one can assume strong conjugation between the nitrile and the amino group and, hence, a rather rigid system of atoms connected with the $C^4=C^6$ double bond. In addition, in the system under discussion, interlocking of an aromatic nucleus with a cyano group is observed which hinders free rotation along the axes of the C^5–CN and C^6–Ph bonds, much alike the abovementioned 4*H*-thio(seleno)pyrans. This is also corroborated by the fact that the NMR spectra of the 2,2-dimethyl-1,3-dithia-4-cyclohexene **322** (R^1 = H, R^2 = Me) contain one singlet due to the C^6H proton and two singlets due to the axial and equatorial methyl group, respectively. All proton signals of the 2-methyl-2-ethyl-1,3-dithia-4-cyclohexenes **322A, B** are doubled due to a different degree of steric screening in the stereoisomers **A** and **B**.



322-A 322-B

Scheme 115

A pseudoequatorial arrangement of the ethyl group is known to be favored. It is possible to obtain isomers which only differ with respect to the pseudoaxial and pseudoequatorial position of the substituent in position 2 of **322A, B**. Their mutual conformational transition is impossible in this case. For these reasons the reaction conditions have a profound effect on the regiochemistry of transformations of the 1,3-dithiacyclohexene **322**. Upon recyclization of **322** in DMF at 150–160 °C a mixture of the 3-cyanopyridine-2(1*H*)-thiones **323** and **324**, with predominance of the more highly substituted **323**, is formed.



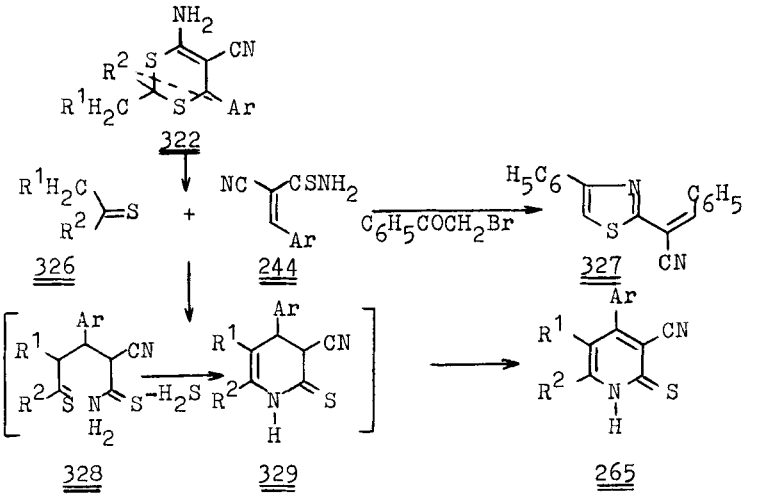
323 323 324

323 325 243

Scheme 116

Recyclization of **322** in methanol at 20–25 °C leads to the most substituted **323**. It has been found that, parallel to the formation of **323**, interaction of arylidenemalononitrile **243** with 2,2-butanedithiol **325** occurs. In this manner the regioselectivity of the recyclization and its dependence on the structure of the starting 1,3-dithia-4-cyclohexenes has been determined.

To establish the mechanism of the recyclization, an X-ray diffraction study of 4-amino-6-phenyl-5-cyano-2-cyclohexanespiro-1,3-dithia-4-cyclohexene has been carried out.[221] The atoms S^1 and C^2 in the central heterocycle lie in different planes relative to the planar fragment, i.e. the heterocycle has a deformed half-chair conformation which may be considered as intermediate between a chair and a twist-boat. The bond length S^1–C^6 is very close to the standard value, the bond S^1–C^2 shorter, and the bond S^3–C^2 longer than the standard value of a S–C_{sp^3} bond. The C^4=C^5 double bond and the adjacent four atoms are coplanar. The plane of the planar trigonal nitrogen atom of the amino group is almost coplanar with the planar S^3–C^4=C^5–C^6 unit, which is due to the fully developed p,π-conjugation in the enamino nitrile fragment. It could thus be concluded that the 1,3-dithia-4-cyclohexenes **322** are conformationally rigid. As a consequence heating of **322** leads to the rupture of the weakest bonds S^1–C^6 and S^3–C^2 (dash marked) which leads to cyclohexanethiones or acyclic thioketones **326** and arylidenecyanothioacetamides **244**.[184,221]

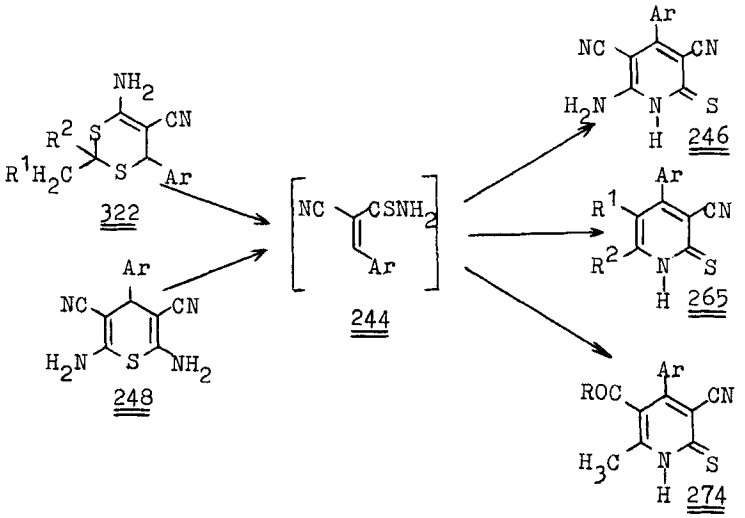


Scheme 117

Thermolysis of 1,3-dithia-4-cyclohexene **322** (R^1, R^2 = $(CH_2)_2$) yields cyclohexanethione.[221] Attempts to isolate benzylidenecyanothioacetamides **244** failed. However, the presence of amide **244** is confirmed by the formation of 1-(4-phenyl-2-thiazolyl)-2-phenyl-1-cyanoethylene **327** upon addition of phenacyl bromide to the reaction mixture.

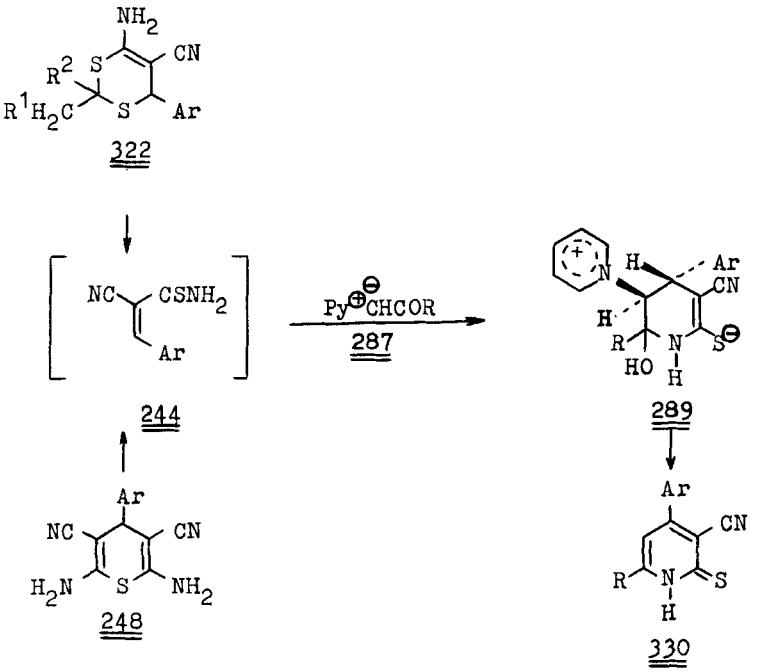
Subsequent reaction steps consist of interaction of the thioketones **326** and the arylidenecyanothioacetamides **244** followed by formation of the Michael adducts **328**. Elimination of hydrogen sulfide from **328** and dehydrogenation of the dihydropyridine-2(1*H*)-thione **329** result in the formation of the 3-cyanopyridine-2(1*H*)-thiones **265**. This reaction scheme is supported by the formation of the pyridinethione **265** (Ar = Ph, R^1, R^2 = $(CH_2)_2$) from cyclohexanethione and benzylidenecyanothioacetamide.[184,221]

With the aim of elucidating the mechanism of the recyclization of 4*H*-thiopyrans **248** and 1,3-dithiacyclohexenes **322** cross-recyclizations with different CH-acids, α-methylene ketones, 1,3-dicarbonyl compounds and their enamines, cyanoacetic ester and malononitrile have been studied.[147-149] The cycloelimination of the heterocycles **248** and **322** with formation of the amides **244** and malononitrile or thioketones, respectively, occurs under thermodynamic control. Subsequent competitive reactions of **244** with malononitrile or carbonyl compounds lead to the formation of the substituted 3-cyanopyridine-2(1*H*)-thiones **246**, **265**, and **274**.



Scheme 118

In order to study the mechanism and stereochemistry of transformations of the heterocycles **248** and **322**, their reactions with pyridine ylides **287** have been investigated.[223] It was established that these transformations have common intermediates, the arylidenecyanothioacetamides **244** which react stereoselectively with pyridine ylides to form the 3,4-*trans*-1,2,3,4-tetrahydropyridine-2-thiolates **289**.



R = CH_3, C_6H_5, cyclopropyl

Scheme 119

Upon heating of **289** with ammonium acetate in acetic acid the corresponding pyridine-2(1*H*)-thiones **330** have been obtained.

On the basis of these results it was noted that **248** and **322** possess common features of their stereo- and electronic structures, namely:

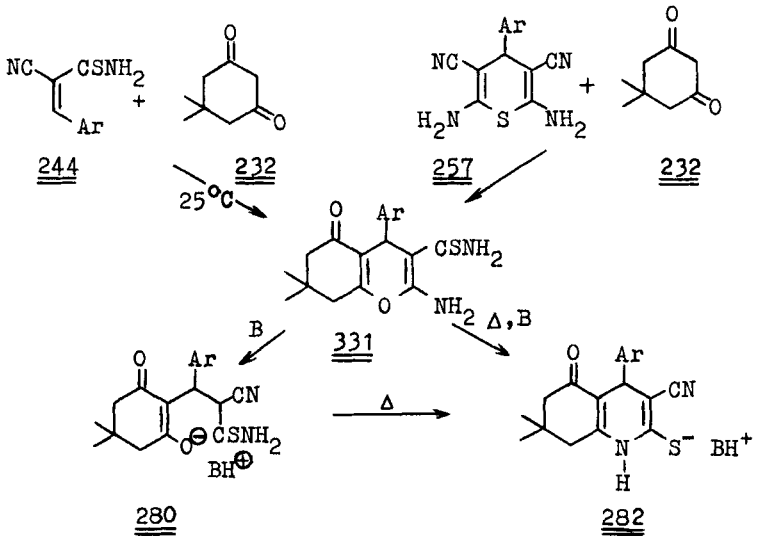
— they contain a coplanar enaminonitrile fragment with a highly developed system of *p*,π-conjugation;

— they are partially hydrogenated;

— their rings are sterically crowded with bulky electron-acceptor substituents;

— they are overall nonplanar.

These properties cause their thermodynamic instability. As the enthalpy increases, they cannot decrease their energy by profound conformational transitions and instead undergo cycloelimination involving the weakest bonds. Moreover, the reaction products are similar in containing an exocyclic double bond in position 2. On the strength of these generalized results, the conversion of heterocyclic enaminonitriles to pyridines with an exocyclic double bond has been called degenerate.[223] In ref.[224] it was found that under conditions of kinetic control arylidenecyanothioacetamides **244** react with dimedone to form the substituted pyrans **331**.

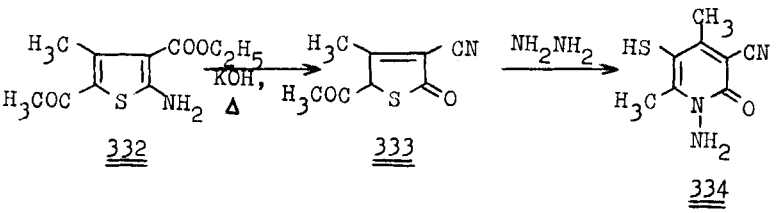


Scheme 120

As noted earlier (see Section 2.2.4.), similar pyrans have been prepared from the thiopyrans **257**.[180]

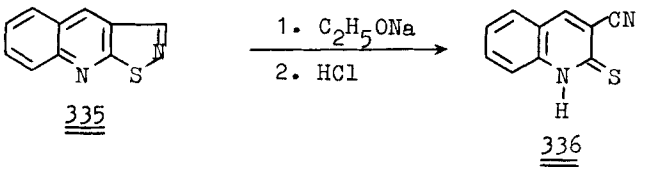
In the presence of bases **331** undergo recyclizations with the formation of **280** which, upon heating in ethanol, cyclize to the quinolinethiolates **282** which have also been obtained in one stage without isolation of the salts **280** by heating of the reagents in ethanol in the presence of bases. Comparing these data with the results given in Section 2.2.4 one notes that the cause of the large variety of reaction paths of arylidenecyanothioacetamides **244** and carbonyl compounds in the ambident behavior of the thioamide fragment in the adducts **280** depending on the reaction conditions.

Derivatives of 3-cyanopyridine can also be obtained by recyclization of substituted five-membered heterocycles. Thus, successive recyclization of the substituted thiophene **332** to the thienone **333** by heating in the presence of alkali and then, upon treatment of the latter with hydrazine, to the 3-cyano-2-pyridone **334** has been described in ref.[225]



Scheme 121

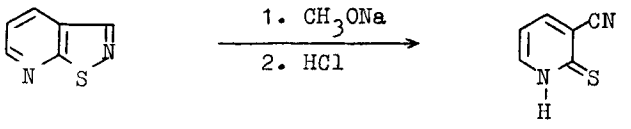
The synthesis of 3-cyanopyridine-2(1*H*)-thiones is also possible by recyclization of isothiazolopyridines.[226,227] Thus, isothiazoloquinoline **335** forms 3-cyanoquinoline-2(1*H*)-thione **336**.[226]



335 336

Scheme 122

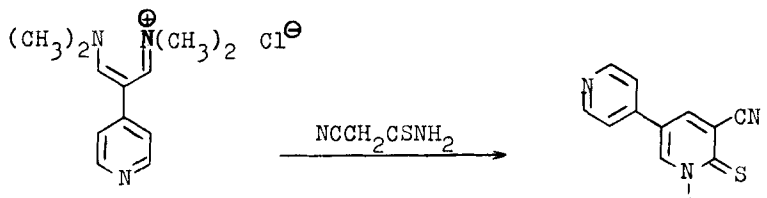
The recyclization of isothiazolopyridine **337** to 3-cyanopyridine-2(1*H*)-thione **338** proceeds in a similar way.[228]



337 338

Scheme 123

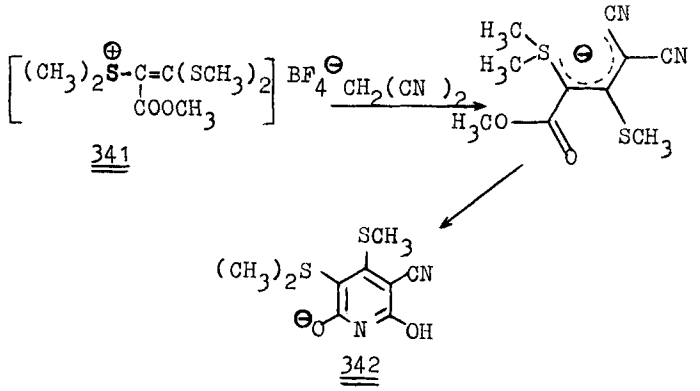
The original method of synthesis of the 3-cyanopyridine-2(1*H*)-thione **340** displaying cardiotonic activity started from the quarternary diamine salt **339**.[20]



339 340

Scheme 124

The application of the salt **341** in the reaction with malononitrile leads to the betaine **342**.[8]

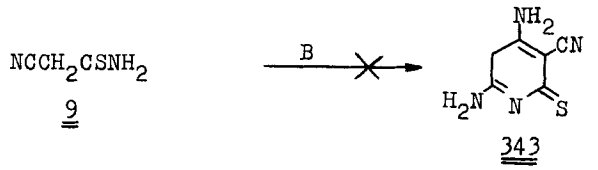


341

342

Scheme 125

In refs.[229-231] the possibility of the synthesis of 3-cyanopyridine-2(1*H*)-thiones and -selenones by dimerization of cyanothio(seleno)acetamide **9** and **10** has been shown. Initially, the product of the dimerization of **9** in basic medium was considered to possess structure **343**.[229,230]

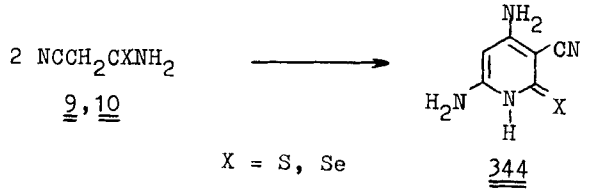


9

343

Scheme 126

Spectroscopic and X-ray diffraction studies showed that the products of the dimerization of cyanothio(seleno)acetamides **9** and **10** are 4,6-diamino-3-cyanopyridine-2(1*H*)-thione and -selenone **344**,[231] respectively.



9, 10

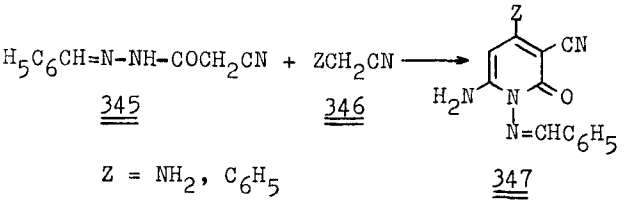
X = S, Se

344

Scheme 127

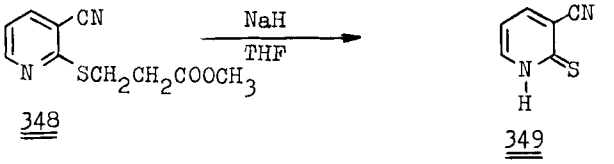
These data show that **344** in the solid state as well as in solution exist exclusively as 3-cyanopyridine-2(1*H*)-thione and -selenone, while the chemical arguments in favor of structure **343**, reported in refs.,[229,230] are incorrect.

A synthesis of the 3-cyano-2-pyridone **347** by condensation of the cyanoacetic acid derivatives **345** and **346** also belongs in this context.[232]



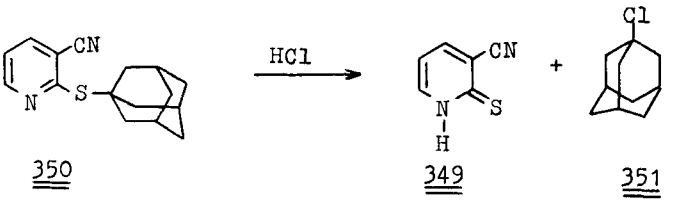
Scheme 128

There are additional methods for the synthesis of 3-cyanopyridine-2(1*H*)-thiones; they involve cleavage of 2-alkylthio-3-cyanopyridine-2(1*H*)-thiones.[227,233] Reduction of **348** by sodium hydride in THF leads to 3-cyanopyridine-2(1*H*)-thione **349**.[227]



Scheme 129

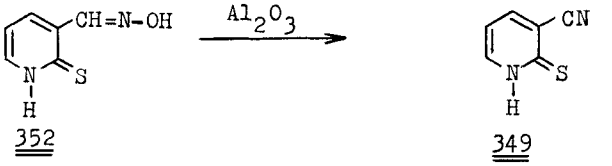
The electrophilic cleavage of 2-adamantylthio-3-cyanopyridine **350** in concentrated HCl proceeds unconventionally.[233] Regioselective rupture of an S–Ad bond occurs and 3-cyanopyridine-2(1*H*)-thione **349** and 1-chloroadamantane **351** are formed.



Scheme 130

This unexpected result is probably not so much due to the bulk of the adamantyl group but rather to its electronic characteristics.

Compound **349** has also been obtained by heating of oxime **352** with aluminum oxide in dry toluene.[228]



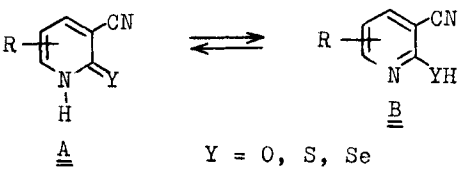
Scheme 131

3. PHYSICO-CHEMICAL PROPERTIES OF 3-CYANOPYRIDINE-2(1*H*)-THIONES AND -SELENONES

Physical and chemical investigations have been carried out to chart the structures, reactivity, and regio- and stereospecific transformations and for the conformational analysis of substituted 3-cyanopyridine-2(1*H*)-thiones and -selenones.

3.1. Ultraviolet Spectroscopy

UV spectroscopy is widely used for the study of the structure of 3-cyanopyridine-2(1*H*)-thiones and -selenones in combination with other methods of physico-chemical analysis. The nitrile group manifests itself as a chromophore with an absorption band the maximum of which lies within the hard-to-study spectral region (below 1600 Å), but, when joined to the pyridine-2(1*H*)-thione(selenone) system, it makes a definite contribution to the overall absorption pattern. In the UV spectra of 3-cyanopyridine-2(1*H*)-thiones and -selenones, several absorption peaks are usually observed. On the basis of a comparison of the spectral data of different pyridine-2(1*H*)-thiones with those of heterocycles containing the fragment NH–C=S it was found that the absorption maximum in the region 300–400 nm is not representative of the pyridinethione tautomeric form.[14,24,28,33,38,45-48,183,217,218,234,235] Thus, in the UV spectra of 4,6-diaryl-3-cyanopyridine-2(1*H*)-thiones there are three to four absorption maxima, hence the absorption maximum at 305–321 nm corresponding to the π–π^* transition is characteristic of the thione form **A** (Table 1).[33]



Scheme 132

Table 1. UV spectra of 4,6-diaryl-3-cyanopyridine-2(1*H*)-thiones **305** in ethanol

Ar^1	Ar^2	λ_{max}, nm (log ε)
C_6H_5	C_6H_5	288 (4.47), 245 (4.26), 315 (4.35), 418 (3.70)
2-FC_6H_4	C_6H_5	247 (4.04), 310 (4.27), 418 (3.54)
2-ClC_6H_4	C_6H_5	246 (4.19), 308 (4.44), 416 (3.66)
4-FC_6H_4	C_6H_5	245 (4.06), 306 (4.24), 419 (3.48)
4-ClC_6H_4	C_6H_5	245 (4.16), 305 (4.43), 418 (3.68)
4-BrC_6H_4	C_6H_5	250 (4.22), 312 (4.57), 419 (3.89)
4-$CH_3OC_6H_4$	C_6H_5	282 (4.26), 320 (4.46), 416 (3.68)
C_6H_5	4-$CH_3C_6H_4$	245 (4.05), 305 (4.33), 420 (3.59)
C_6H_5	4-FC_6H_4	290 (4.22), 244 (4.03), 315 (4.12), 416 (3.45)
C_6H_5	4-$CH_3OC_6H_4$	255 (4.12), 316 (4.53), 418 (3.84)

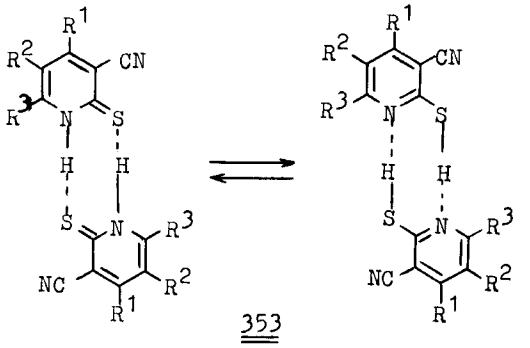
Table 2. UV absorption maxima of 4-furyl-3-cyanopyridine-2(1*H*)-thiones **321** in ethanol

R	n	λ_{max}, nm (log ε)
H	3	237 (4.11), 264 (4.14), 316 (4.35), 462 (3.23)
H	4	236 (4.07), 266 (4.13), 316 (4.32), 460 (3.25)
2,4-$Cl_2C_6H_3$	4	245 (4.05), 276 (4.11), 349 (4.01), 458 (3.15)
3,4-$Cl_2C_6H_3$	4	242 (4.29), 282 (4.20), 348 (4.37), 454 (3.20)

An analogous character of the UV spectrum in the region 316–349 nm is observed for 4-(2-furyl)-3-cyanopyridine-2(1*H*)-thiones.[218] In this case, the long-wave maximum in the region 454–462 nm is somewhat displaced bathochromically compared with the 4,6-diaryl-3-cyanopyridine-2(1*H*)-thiones **305** which is in keeping with the more intensive color of furylpyridinethiones (Table 2).

Upon change from a protic solvent (ethanol) to an aprotic one (dioxane), the tautomeric equilibrium does not change and remains displaced towards the pyridine-2(1*H*)-thione **A**. This is evident from the UV spectra of substituted 4-aryl-3-cyanopyridine-2(1*H*)-thiones[38,45,46,217,235] (Tables 3 and 4).

From this it follows that 3-cyanopyridine-2(1*H*)-thiones, as well as other substituted pyridine-2(1*H*)-thiones,[14,234] are present in the solution as the dimers **353**. The stability of **353** is governed by the strength of the hydrogen bonds as well as by extraneous influences.[234]



353

Scheme 133

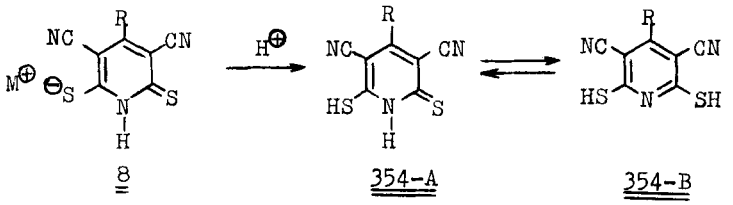
Table 3. UV absorption maxima of 4-aryl-5,6-polymethylene-3-cyanopyridine-2(1*H*)-thiones **222** in dioxane

Ar	n	λ_{max}, nm (log ε)
C_6H_5	1	258 (4.22), 320 (3.81), 438 (2.94)
4-ClC_6H_4	1	263 (4.42), 333 (4.46), 435 (3.71)
3-BrC_6H_4	1	258 (4.19), 320 (3.98), 442 (3.28)
C_6H_5	2	254 (4.12), 345 (4.14), 426 (3.45)
3-FC_6H_4	2	259 (4.18), 316 (4.10), 427 (3.25)
4-FC_6H_4	2	264 (4.22), 314 (4.14), 428 (3.47)
4-ClC_6H_4	2	257 (4.11), 315 (4.12), 428 (3.39)
4-BrC_6H_4	2	254 (4.06), 314 (4.20), 430 (3.51)
4-$CH_3C_6H_4$	2	260 (3.84), 312 (3.79), 424 (3.06)

Table 4. UV absorption maxima of substituted 4-aryl-3-cyanopyridine-2(1*H*)-thiones **265** in dioxane

Ar	R^1	λ_{max}, nm (log ε)
C_6H_5	H	262 (3.60), 314 (3.64), 421 (2.93)
3-FC_6H_4	H	259 (4.24), 314 (4.26), 426 (3.59)
4-FC_6H_4	H	265 (3.96), 317 (3.92), 426 (3.22)
4-ClC_6H_4	H	324 (4.00), 349 (4.01), 458 (3.15)
4-BrC_6H_4	H	311 (4.08), 428 (3.28), 480 (4.17)
2-C_4H_3O	H	236 (3.68), 268 (3.62), 317 (4.13), 450 (3.13)
C_6H_5	CH_3	280 (3.88), 317 (3.76), 428 (3.00)
4-ClC_6H_4	CH_3	258 (3.97), 318 (3.96), 430 (3.24)
4-BrC_6H_4	CH_3	260 (4.16), 319 (3.84), 428 (2.93)
4-$CH_3OC_6H_4$	CH_3	261 (4.35), 313 (4.36), 422 (3.60)
4-$C_2H_5OC_6H_4$	CH_3	316 (4.40), 422 (3.63)

UV spectroscopy has been successfully used to determine the thione-thiol equilibrium in 4-alkyl-3,5-dicyano-pyridine-2(1*H*)-6-thiolates **8**. The UV spectra of **8** in methanol contain five absorption maxima; one of these, at 342–344 nm, is characteristic of compounds containing an NH–C=S fragment.[28] Upon protonation of **8** the tautomeric equilibrium **354A** ⇄ **354B**, like the previous one, is displaced towards the 6-thiolpyridine-2(1*H*)-thione **354A** (Table 5).



Scheme 134

Table 5. UV absorption maxima of 4-alkyl-3,5-dicyanopyridine-2(1*H*)-thiolates **8** in methanol

R	M	λ_{max}, nm (log ε)
CH_3	NH_4	208 (4.37), 221 (4.30), 298 (4.32), 343 (4.25), 415 (4.14)
CH_3	K	208 (4.49), 221 (4.40), 298 (4.42), 416 (4.30)
CH_3	$C_5H_{13}N$	208 (4.39), 221 (4.31), 298 (4.31), 344 (4.28), 415 (4.18)
C_2H_5	Na	208 (4.49), 221 (4.30), 299 (4.34), 344 (4.30), 416 (4.20)
C_2H_5	$C_5H_{13}N$	208 (4.41), 221 (4.35), 298 (4.29), 343 (4.27), 418 (4.11)
C_3H_7	NH_4	208 (4.43), 222 (4.35), 299 (4.30), 343 (4.20), 415 (4.17)
C_3H_7	C_5H_6N	207 (4.51), 222 (4.43), 297 (4.43), 343 (4.40), 415 (4.25)
C_3H_7	$C_5H_{13}N$	208 (4.44), 223 (4.37), 298 (4.39), 343 (4.39), 415 (4.26)
C_6H_{13}	NH_4	208 (4.37), 222 (4.31), 298 (4.31), 342 (4.31), 414 (4.19)
C_6H_{13}	K	208 (4.37), 223 (4.31), 298 (4.35), 344 (4.34), 415 (4.22)

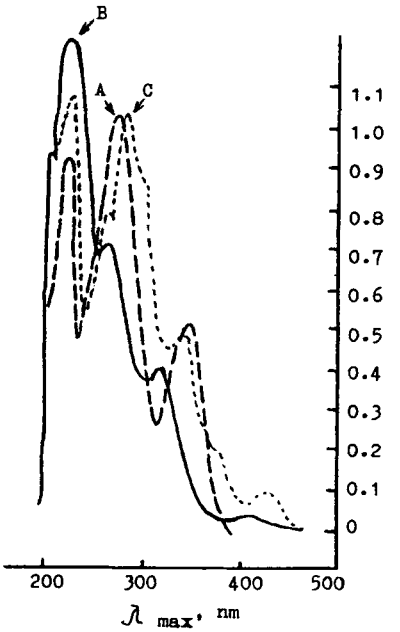


Figure 1. UV spectra of 6-methyl-4,5-tetramethylene-3-cyanopyridin-2(1H)-one (**A**), -thione (**B**) and -selenone (**C**) **23** in ethanol.

The UV spectra of 3-cyanopyridine-2(1*H*)-selenones are similar to those of the corresponding thiones.[24,58] However, on going from pyridin-2(1*H*)-ones to pyridine-2(1*H*)-thiones and -selenones, a displacement of the absorption maxima towards longer wavelengths occurs (Figure 1).

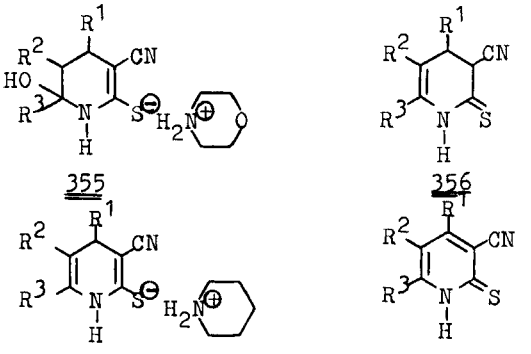
Probably these differences are connected with the decreased polarization of the C=Y (Y = O, S, Se). In the selenium-containing pyridines the equilibrium is also displaced towards the pyridine-2(1*H*)-selenone **23A**.

23-A 23-B

Y = O, S, Se

Scheme 135

It has been shown that the maximum absorption wavelengths increase upon going from hydrogenated pyridinethiolates **355** to hydrogenated thiones **356** and from dihydropyridinethiolates **357** to the corresponding thiones **358** (285–290 nm for **355**, 325–330 nm for **357**, 346–350 nm for **356**, 400–420 nm for **358**).[45,146,147]



355 356

357 358

R^1 = C_6H_5, 4-ClC_6H_4, 4-FC_6H_4, 4-Py;
R^2 = H, $COOC_2H_5$, $COCH_3$; R^3 = CH_3, C_6H_5

Scheme 136

These changes in the UV spectra reflect the extent of conjugation in the systems concerned.

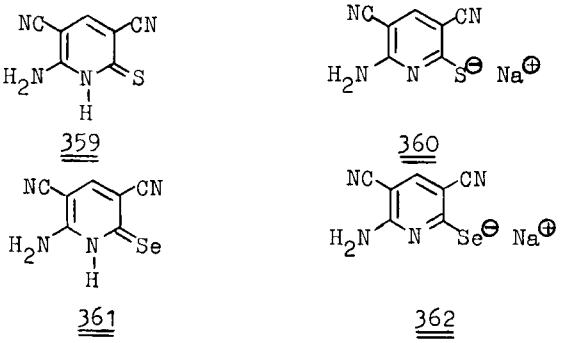
3.2. *Infrared Spectroscopy*

IR spectroscopy is widely used for the study of the structure of 3-cyanopyridine-2(1*H*)-thiones and -selenones. The IR spectra confirm that substituted 3-cyanopyridine-2(1*H*)-thiones and -selenones, excluding some hydrogenated analogs, exist in the thione (selenone) tautomeric form **A**. By correlation of the spectral data of 3-cyanopyridine-2(1*H*)-thiones with those of standard compounds containing an NH–C=S fragment it has been established that the C=S absorption band is of medium intensity and manifests itself in the region of 1158–1208 cm^{-1}.[25,28,49,141,194,204] The position of the C=S absorption band is significantly influenced by substituents in position 6. Thus, in the IR spectra of salts of 4-alkyl-3,5-dicyanopyridine-2(1*H*)-6-thiols **8** and the corresponding pyridine-thiones, the vibration frequency of the C=S group decreases to 1158–1177 cm^{-1}.[28] This is also suggested by the position of the absorption band of cyano groups in positions 3 and 5 (Table 6).

Table 6. IR absorption bands of C≡N and C=S groups of 4-alkyl-3,5-dicyanopyridine-2(1*H*)-thiolates **8**

		ν, cm^{-1} (KBr)	
R	M	C≡N	C=S
CH_3	NH_4	2200	1162, 1179
C_2H_5	NH_4	2210	1160, 1176
C_3H_7	NH_4	2210	1158, 1175
C_6H_{13}	NH_4	2210	1160, 1176
C_2H_5	Na	2200	1159, 1165
C_2H_5	H	2200	1160, 1177

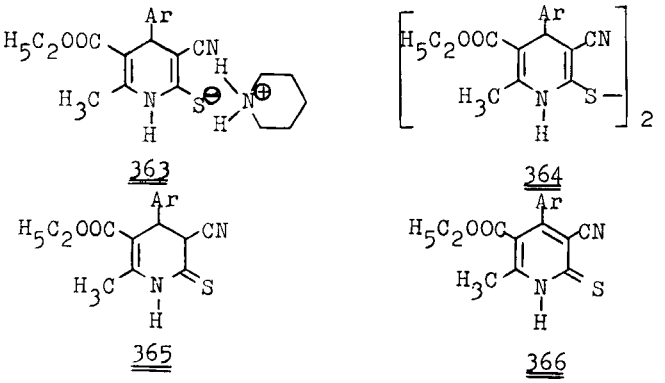
IR spectroscopy, in combination with other methods, has been used successfully to determine regularities in the redistribution of electronic density in 5-amino-3,5-dicyanopyridine-2(1*H*)-thiones, -selenones, and their salts **359–362**.[204]



Scheme 137

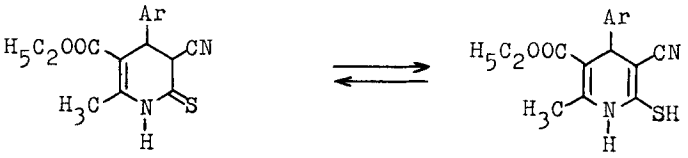
In the IR spectrum of pyridinethione **359**, two absorption bands of similar intensity are present at 2206 and 2230 cm^{-1}, corresponding to C^5–CN and C^3–CN, respectively. The C=S absorption lies around 1220 cm^{-1}. Upon salt formation such as in **360** the C=S absorption disappears and the CN absorptions shift to 2200 and 2221 cm^{-1}. The 2200 cm^{-1} absorption is of increased intensity due to stronger conjugation in the thiolato nitrile fragment NC–C=C–S^-. The wavenumber decrease of the C^3–CN band of **360** amounts to $\Delta\nu$ 30 cm^{-1}. A similar situation is observed in the IR spectra of the selenium-containing pyridines **361** and **362**. However, the wavenumber decrease of the C^3–CN band of **362** is less substantial and amounts to $\Delta\nu$ 13 cm^{-1} which may be explained by the larger radius of the Se atom. Therefore its ionization affects the character of the conjugation in the NC–C=C–Se^- fragment to a lesser degree.

IR spectroscopy has also been used for stereochemical investigations of 3-cyanopyridine-2(1*H*)-thiones as well as of their hydrogenated analogs and salts.[146,183,191–193] The IR spectra of the pyridinethiones and their derivatives **363–366** have been investigated.



Scheme 138

Here the absorption bands corresponding to the valence vibrations of the cyano groups are observed at 2166–2182 cm^{-1} in the salts **363**, at 2200–2203 cm^{-1} in the disulfides **364**, at 2250–2267 cm^{-1} in the 3,4-dihydropyridines **365**, and at 2232–2240 cm^{-1} in the pyridinethiones **366**. Thus, the cyano groups absorption wavenumbers increase with decreasing conjugation in the fragment N–C(S)–C–CN of **363–366**. A similar dependence of CN absorptions has been described in ref.[193]



365-A 365-B

Scheme 139

According to IR data the hydrogenated 3-cyanopyridine-2(1*H*)-thiones **365A**, unlike the pyridine-2(1*H*)-thiones **366**, exist in chloroform solutions in tautomeric equilibrium with the thiols **365B**. The tautomeric equilibrium in this case more precisely involves the *cis*-3,4-dihydropyridine-2(1*H*)-thiones **365**.[193]

The position of the tautomeric equilibrium **A** ⇄ **B** has been determined by analysis of the high-wavenumber region of the IR spectra of pyridine-2(1*H*)-thiones (3150–3300 cm^{-1}), corresponding to the characteristic absorption of the NH group.[25,49,141,146,147,191–193,204]

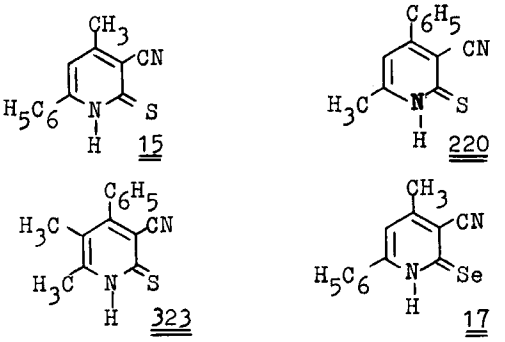
3.3. NMR Spectroscopy

In the study of the structure and tautomerism of 3-cyanopyridine-2(1*H*)-thiones and -selenones NMR spectroscopy has found the most extensive application. According to ^{1}H and ^{13}C NMR spectroscopy 3-cyanopyridine-2(1*H*)-thiones and -selenones exist in the tautomeric form **A**. The signal of the NH proton under standard conditions (DMSO-d_6, 25 °C) is a broad singlet in the region δ 8–14 ppm. This chemical shift is practically unaffected by substituents on the pyridine ring. With 4,6-diaryl-3-cyanopyridine-2(1*H*)-thiones the ^{1}H signal of the NH group is found in the region 14.00–14.30 ppm.[33,210] A similar situation is observed in the NMR spectra of 4-aryl-6-alkyl-,[218,235] 4-aryl-5,6-polymethylene-,[217,218] 6-alkyl-4,5-polymethylene-3-cyanopyridine-2(1*H*)-thiones,[45,46] 4,6-diaryl-3-cyanopyridine-2(1*H*)-selenones,[24] and other derivatives of 3-cyanopyridine-2(1*H*)-thiones and -selenones.[24,25,47–49,141,146,147,191,192,194] The NMR spectra allow also an almost unambiguous determination of the position of the substituents on the pyridine ring (Table 7 and 8).

Table 7. ^{1}H NMR spectra of substituted 4-(2-furyl)-3-cyanopyridine-2(1*H*)-thiones **321** in DMSO-d_6 (δ, ppm)

R	n	NH (s)	Furyl protons C^5H (q)	Furyl protons C^3H (q)	Furyl protons C^4H (q)	Alkyl protons (m)	J, Hz
H	3	13.94	8.02	7.44	6.78	2.96, 2.81, 2.04 (t)	$J_{3,4}$ = 3.7 $J_{3,5}$ = 0.8 $J_{4,5}$ = 2.0
H	4	13.91	7.93	7.08	6.60	2.72, 2.38, 1.59	$J_{3,4}$ = 3.6 $J_{3,5}$ = 0.9 $J_{4,5}$ = 1.8

The ^{1}H signals of alkyl substituents in position 4 or 6 of the pyridine ring appear downfield from those of 5-alkyl substituents (see Table 7).[38,46] By correlating the spectral characteristics of the isomeric pyridinethiones **15** and **220** with those of the pyridinethione **323** it is possible to establish the structures of **15**, **17**, and **220** and thus the direction of the condensation of benzoylacetone with cyanothio(seleno)acetamide **9** and **10**.[38]



Scheme 140

Table 8. ^{1}H NMR spectra of substituted 4-aryl-3-cyanopyridine-2(1*H*)-thiones **265** in DMSO-d_6 (δ, ppm)

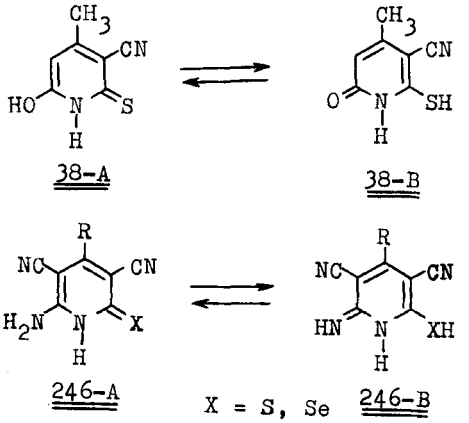
Ar	R^1	NH (s)	Arom. protons (m)	H^5 (s)	Alkyl protons (s)
C_6H_5	H	13.93	7.53	6.75	2.40
3-FC_6H_4	H	13.87	7.42	6.77	2.40
4-FC_6H_4	H	13.90	7.49 (d), 7.33 (d)	6.72	2.40
4-ClC_6H_4	H	13.89	7.55	6.69	2.39
4-BrC_6H_4	H	13.91	7.67 (d), 7.49 (d)	6.69	2.39
2-C_4H_3O	H	13.94	7.97 (q), 7.60 (q), 6.75 (q)	6.95	2.38
C_6H_5	CH_3	13.93	7.40		2.40, 1.74
4-ClC_6H_4	CH_3	13.95	7.54 (d), 7.29 (d)		2.42, 1.74
4-BrC_6H_4	CH_3	13.93	7.70 (d), 7.24 (d)		2.44, 1.74
4-$CH_3OC_6H_4$	CH_3	13.85	7.21 (d), 7.05 (d)		3.80, 2.42, 1.76
4-$C_2H_5OC_6H_4$	CH_3	13.88	7.20 (d), 7.02 (d)		4.05 (q), 2.37, 1.77, 1.35 (t)

Table 9. ^{1}H NMR spectra of 6-aryl-3-cyanopyridine-2(1*H*)-thiones **12** ($R^1 = R^2 = H$; $R^3 = Ar$; X = S) in DMSO-d_6 (δ, ppm)

Ar	NH (s)	C^4H (d)	C^5H (d)	$^3J_{4,5}$	Arom. protons (m)
C_6H_5	14.02	8.06	7.07	7.5	7.4, 7.8
4-ClC_6H_4	14.09	8.10	7.13	7.8 ($^3J_{5,4}$)	7.54 (d), 7.80 (d)
4-BrC_6H_4	13.96	8.12	7.12	7.7 ($^3J_{5,2}$)	7.62 (d), 7.74 (d)
4-$CH_3OC_6H_4$	13.94	8.04	7.03	7.6 ($^3J_{5,5}$)	7.08 (d), 7.49 (d), 3.84 (s) (CH_3)
3,4-$Cl_2C_6H_3$	14.08	8.14	7.08	7.5	7.54, 7.89
3-C_5H_4N	14.11	8.16	7.13	7.9	7.54 (C^5H), 8.16 (q) (C^4H), 8.70 (q) (C^6H), 8.90 (s) (C^2H)

In monosubstituted 3-cyanopyridine-2(1*H*)-thiones, the coupling constants of the pyridine protons are practically identical with those of other pyridines and the picolines. The constants $^3J_{4,5}$ of 6-aryl(alkyl)-3-cyanopyridine-2(1*H*)-thiones and -selenones lie in the range 7.5–7.9 Hz (see Table 9) which is characteristic of pyridine and 2-picoline.[25,49,236] The chemical shifts of C^4H and C^5H are practically unaffected by substituents in a pyridine ring.

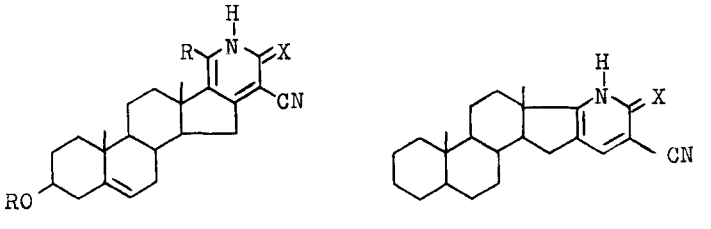
NMR spectroscopy has also been used to study the tautomeric equilibria of the 3-cyanopyridine-2(1*H*)-thiones and -selenones **38**, **69**, **246**, and **313**, substituted with OH and NH_2.[114,163,204]



Scheme 141

It has been found that **38** are in a tautomeric equilibrium with prevalence of the thione form **38A**.[114] In the case of the amino derivatives **246** the tautomeric equilibrium is completely displaced towards the thione **246A**.[163,204] ^{1}H and ^{13}C NMR spectroscopy has

found application in the study and determination of the structure of the steroid annelated 3-cyanopyridine-2(1*H*)-thiones and -selenones **36** and **313**.[57,157]



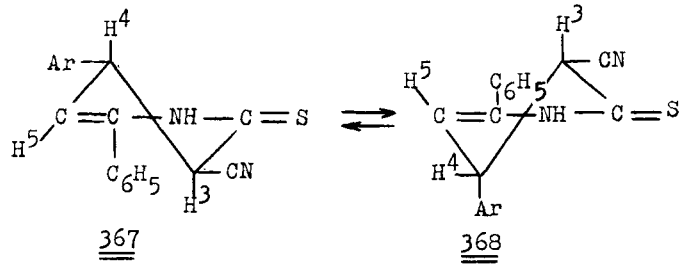
313 36

313-A ⇌ 313-B 36-A ⇌ 36-B

Scheme 142

Thus, it has been possible to determine the direction of the annelation reaction and to trace the influence of the conformationally rigid steroid skeleton on the character of the transformation.[57,157] According to ^{1}H and ^{13}C NMR spectroscopy **36** and **313** are present in DMSO-d_6 solutions in the thiono tautomeric form **36A** and **313A**, respectively. Typical are the NH proton and the C=S C_{sp^2} carbon signals.[193,210]

However, the application of ^{1}H and ^{13}C NMR spectroscopy is of greatest importance in the study of the structure of hydrogenated pyridinethiones and their salts.[147,164,183,191-193] Based on ^{1}H NMR it has been found that 3,4-dihydropyridine-2(1*H*)-thiones exist as mixtures of the *cis*- and *trans*-stereoisomers **367** and **368**.[146]



367 368

Scheme 143

The $^{3}J_{3,4}$ value of 11–12 Hz in one isomer of **367** suggests a *trans*-diaxial position of H^3 and H^4. In the *cis*-isomer **368** $^{3}J_{3,4}$ equals 6 Hz. In this case both isomers are in dynamic equilibrium.

NMR spectroscopy has been used in much the same way for the determination of the three-dimensional structure of 3-cyano-3,4-dihydropyridine-2(1*H*)-thiones containing electron-withdrawing groups in position 5.[147,183,191,193]

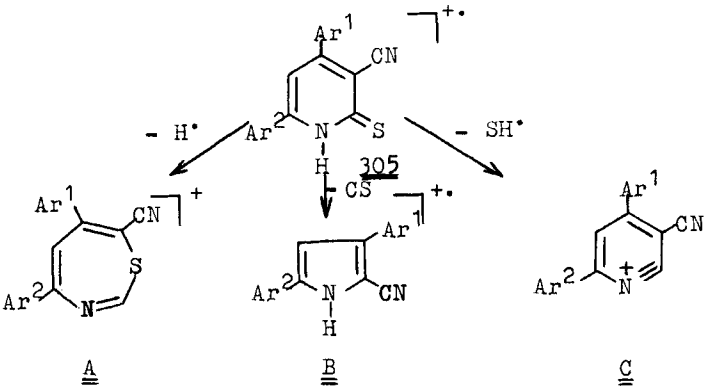
Table 10. Mass spectra (*m/z*, I%) of 4,6-diaryl-3-cyanopyridine-2(1*H*)-thiones **305**

Ar^1	Ar^2	$M^{+\cdot}-H^{\cdot}$	$M^{+\cdot}-CS$	$M^{+\cdot}-HS^{\cdot}$
C_6H_5	C_6H_5	287 (91)	244 (6)	255 (22)
2-FC_6H_4	C_6H_5	305 (40)	262 (11)	273 (7)
2-ClC_6H_4	C_6H_5	321 (29)	278 (9)	289 (6)
4-BrC_6H_4	C_6H_5	367 (43)	323 (7)	334 (6)
4-$CH_3OC_6H_4$	C_6H_5	317 (24)	274 (5)	285 (3)
C_6H_5	4-$CH_3C_6H_4$	301 (37)	258 (3)	269 (6)
C_6H_5	4-$CH_3OC_6H_4$	317 (34)	274 (18)	285 (4)
C_6H_5	4-FC_6H_4	305 (47)	262 (7)	273 (4)
4-ClC_6H_4	2-C_4H_3S	327 (25)	284 (12)	295 (7)
4-BrC_6H_4	2-C_4H_3S	372 (92)	329 (3)	340 (< 3)
C_6H_5	2-C_4H_3S	293 (40)	250 (< 3)	261 (5)

3.4. Mass Spectrometry

A characteristic property seen in the mass spectra of substituted pyridine-2(1*H*)-thiones is their relatively high stability against electron impact. In the mass spectra of the 4,6-diaryl-3-cyanopyridine-2(1*H*)-thiones **305** the molecular ion is responsible for the base peak while the relative intensities of the fragment peaks lie in the range 24.1–62.5%.[34] However, one mode of fragmentation of the molecular ion pyridinethione **305** involves the loss of hydrogen atoms $H^{\cdot}$ which leads to the formation of a stable thiazepine structure (**A**), isoelectronic with the cycloheptatrienyl cation (Table 10).

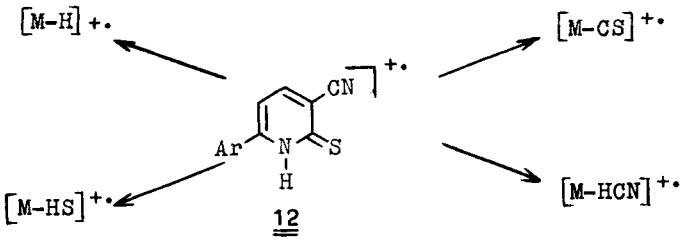
The other fragmentations of the molecular ion take place by elimination of $CS^{\cdot}$ (**B**) and by loss of an $HS^{\cdot}$ moiety (**C**). In the case of the halogen derivatives additional ion peaks of medium intensity and corresponding to elimination of $Hal^{\cdot}$ and HHal (Hal = F, Cl) from $M^{+\cdot}$ are observed.



Scheme 144

A somewhat different picture is seen in the mass spectra of the 6-aryl-3-cyanopyridine-2(1*H*)-thiones **12** (R^1 = R^2 = H; R^3 = Ar; X = S).[49] The mass spectra of **12** are

characterized by molecular ion base peaks and high stability against electron impact, W_m 44.1 and 51.5%. In addition to the loss from $M^{+\cdot}$ of $H^{\cdot}$, $CS^{\cdot}$, and $HS^{\cdot}$ elimination of HCN is observed.



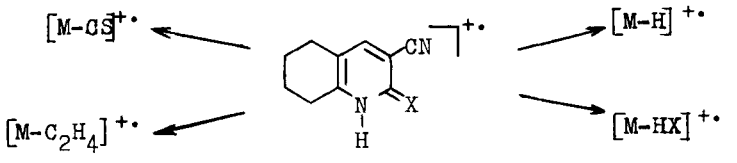
12

Ar = C_6H_5, 3-C_5H_4N

Scheme 145

A similar fragmentation scheme of 4-methyl(trifluoromethyl)-6-phenyl-3-cyanopyridine-2(1*H*)-thione is described in ref.[41]

The fragmentation of $M^{+\cdot}$ of 5,6-tetramethylene-3-cyanopyridine-2(1*H*)-thione and -selenone **26** also involves loss of $H^{\cdot}$, $HS^{\cdot}$, $HSe^{\cdot}$, and $CS^{\cdot}$.[25]



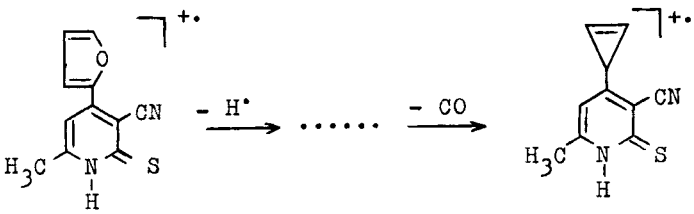
26

X = S, Se

Scheme 146

In the latter case elimination of $CSe^{\cdot}$ from $M^{+\cdot}$ occurs. Besides, the elimination of C_2H_4 from a cyclohexane moiety is observed for **26**.

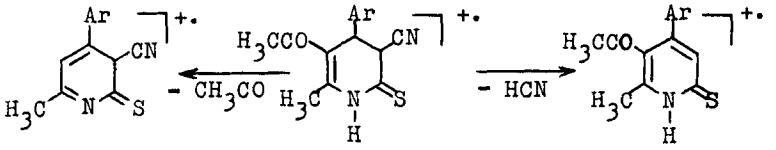
The distinctive features of the mass spectral disintegration of $M^{+\cdot}$ of 4-(2-furyl)-3-cyanopyridine-2(1*H*)-thione **321** are elimination of CO and $H^{\cdot}$ and the formation of the cation of 4-(3-cyclopropenyl)pyridine-2(1*H*)-thione **369**.



321 369

Scheme 147

The hydrogenated pyridinethiones **274** show less stability against electron impact (7–8%).[183]



220 **274** **275**

Scheme 148

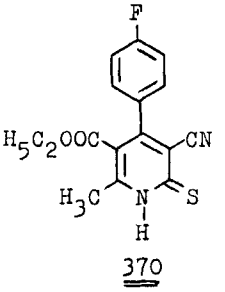
The main pathways in the fragmentation of the molecular ion are competitive elimination of HCN and of $CH_3CO^{\cdot}$ with formation of the possible structures **220** and **275**. The dehydrogenation of the pyridinethiones **274** under electron impact is less pronounced and the corresponding peaks amount to only 10% of the intensity of $M^{+\cdot}$.

Mass spectrometry has been used for the determination of the structure of 6-adamantyl-3-cyanopyridine-2(1*H*)-thione and -selenone, their alkyl derivatives,[50,51] and other substituted 3-cyanopyridine-2(1*H*)-thiones.[163]

3.5 X-Ray Diffraction Analysis

The structure of pyridine-2(1*H*)-thione was first studied by the photographic method.[237] It was found with a certain degree of accuracy that the heterocycle has a planar structure with a C=S bond length of 1.68(2) Å. On the basis of these data the conclusion was made that the molecule in the crystal is chiefly in the tautomeric form of pyridinethione and not of pyridinethiol. Subsequent X-ray diffraction[238–245] and neutron diffraction investigations confirmed the presence of the thione form in the solid state. It was found that in pyridine-2(1*H*)-thione the pyridine ring is flat while the mean lengths of the C–N and C–C bonds in it deviate slightly from the mean values of the corresponding bonds in unsubstituted pyridine.[246]

X-Ray diffraction investigations also proved that substituted 3-cyanopyridine-2(1*H*)-thiones and -selenones in the solid state exist in the thione and selenone forms (**A**), respectively. Thus, an X-ray analysis of 6-methyl-4-(4-fluorophenyl)-3-cyano-5-ethoxycarbonylpyridine-2(1*H*)-thione **370** has been carried out.[247]



370

Scheme 149

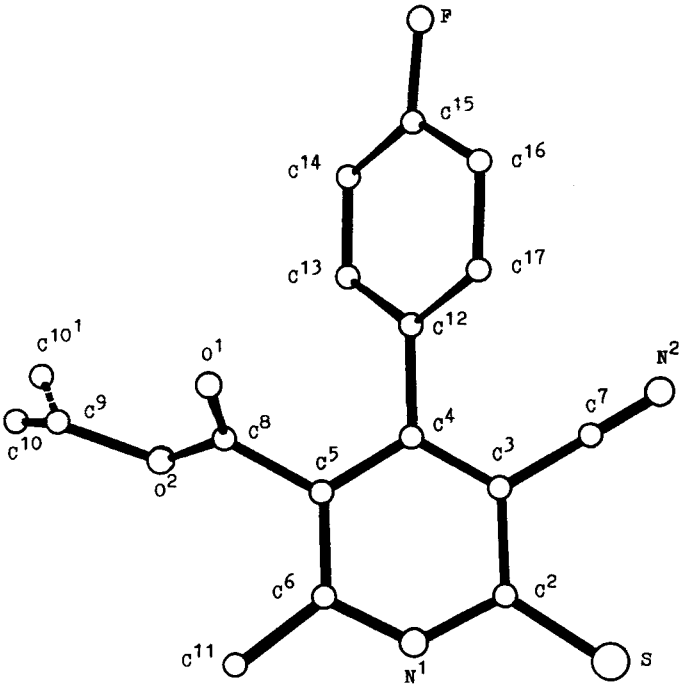


Figure 2. Structure of 6-methyl-4-(4-fluorophenyl)-3-cyano-5-ethoxycarbonylpyridine-2(1*H*)-thione **370**.

The pyridine ring of **370** is approximately planar (the positions of the atoms deviate from the ring plane no more than 0.021(4) Å) (Fig. 2, Tables 11 and 12).

The decreased intramolecular distances, S . . . C^7 3.040(4); C^7 . . . C^{12} 2.872(5); C^7 . . . C^{17} 2.964(6); C^8 . . . C^{12} 2.921(5); C^8 . . . C^{13} 3.017(6); O^1 . . . C^{12} 3.055(5) and C^8 . . . C^{11} 3.008(5) Å (the sums of the van-der-Waals radii of the atom pairs S/C, C/C and O/C being equal to 3.50, 3.40, and 3.22 Å, respectively[248]), squeeze the atoms S, C^7,

Table 11. Bond lengths d (Å) of **370**

Bond	d	Bond	d
N^1-C^2	1.378(5)	C^8-O^1	1.197(5)
C^2-S	1.660(4)	C^8-C^2	1.307(5)
C^2-C^3	1.434(5)	O^2-C^9	1.530(7)
C^3-C^4	1.383(5)	C^9-C^{10}	1.343(10)
C^3-C^7	1.427(5)	C^9-C^{10^1}	1.231(10)
C^4-C^5	1.403(5)	C^{12}-C^{13}	1.385(5)
C^4-C^{12}	1.495(5)	C^{13}-C^{14}	1.386(6)
C^5-C^6	1.383(5)	C^{14}-C^{15}	1.377(6)
C^5-C^8	1.483(5)	C^{15}-F	1.369(4)
C^6-N^1	1.364(5)	C^{15}-C^{16}	1.349(6)
C^6-C^{11}	1.489(6)	C^{16}-C^{17}	1.386(6)
C^7-N^2	1.150(5)	C^{17}-C^{12}	1.386(5)

Table 12. Valence angles ω (degrees) of **370**

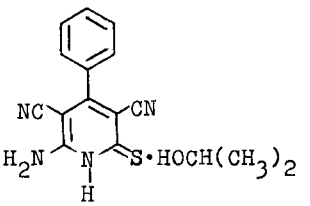
Angle	ω	Angle	ω
$C^2N^1C^6$	126.6(3)	$C^5C^8C^1$	124.6(4)
$N^1C^2C^3$	113.3(3)	$C^5C^8C^2$	112.0(3)
N^1C^2S	120.5(3)	$O^1C^8O^2$	123.4(4)
SC^2C^3	126.2(3)	$C^8O^2C^9$	115.7(4)
$C^2C^3C^4$	122.5(3)	$O^2C^9C^{10}$	109.9(6)
$C^2C^3C^7$	115.9(3)	$O^2C^9C^{101}$	100.9(9)
$C^4C^3C^7$	121.6(3)	$C^4C^{12}C^{13}$	120.4(3)
$C^3C^4C^5$	119.4(3)	$C^4C^{12}C^{17}$	120.4(3)
$C^3C^4C^{12}$	119.7(3)	$C^{17}C^{12}C^{13}$	119.2(4)
$C^5C^4C^{12}$	120.8(3)	$C^{12}C^{13}C^{14}$	120.8(4)
$C^4C^5C^6$	119.8(3)	$C^{13}C^{14}C^{15}$	117.2(4)
$C^4C^5C^8$	120.2(3)	$C^{14}C^{15}F$	117.5(4)
$C^6C^5C^8$	119.8(3)	$C^{16}C^{15}F$	118.4(4)
$C^5C^6N^1$	118.2(3)	$C^{14}C^{15}C^{16}$	124.1(4)
$C^5C^6C^{11}$	126.4(3)	$C^{15}C^{16}C^{17}$	117.9(4)
$C^{11}C^6N^1$	115.4(3)	$C^{16}C^{17}C^{12}$	120.7(4)
$C^3C^7N^2$	177.8(4)		

and C^8 and (to a lesser degree) C^{11} and C^{12} out of the heterocyclic plane by 0.073(1), −0.125(4), 0.149(4), −0.020(5) and −0.026(4) Å, respectively. This steric congestion also twists the substituents out of the heterocyclic plane: the dihedral angle with the Ar plane is 51.2° while that with the ethoxycarbonyl group plane is 123.5°.

The length of the C^2=S bond of 1.660(4) Å is increased compared to the standard C=S bond length of 1.610(9) Å (in thioacetaldehyde) and equals that in pyridine-2(1*H*)-thione.

It may be supposed that an intermolecular hydrogen bond between the N^1 atom of the heterocycle of one molecule and the oxygen atom of the carbonyl group of a second molecule is formed in the crystal with a glide plane (N^1 . . . O^1 3.052(4); N^1 . . . H 0.84(4); N . . . O^1 2.39(4) Å; the angle N^1–H . . . O^1 is 136.1(3)°) between the two molecules.

An X-ray analysis of **371** has been accomplished. As illustrated in Fig. 3 and Tables 13 and 14 with the molecular parameters of thione **371** and 2-propanol, **371** crystallizes as a complex with 2-propanol.



371

Scheme 150

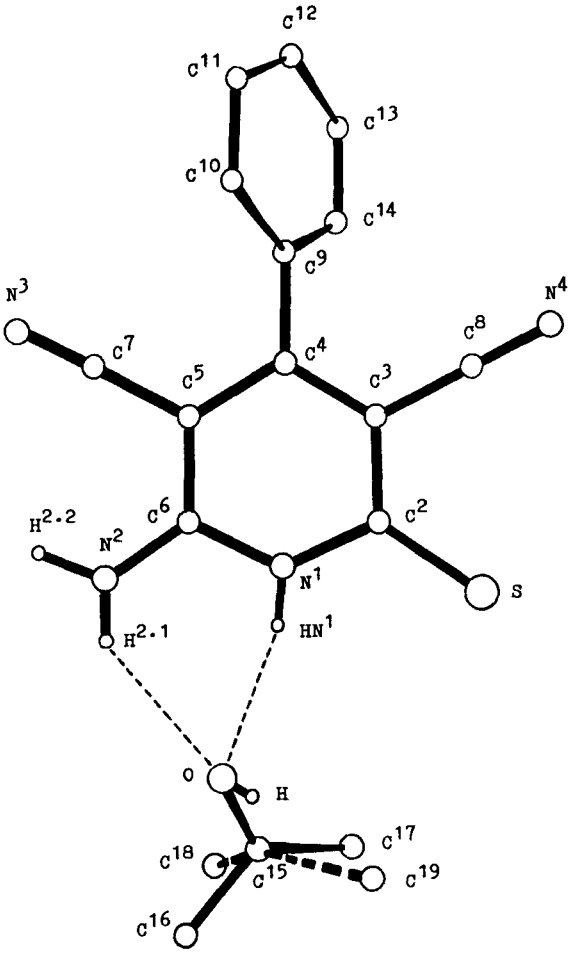


Figure 3. 6-Amino-4-phenyl-3,5-dicyanopyridine-2(1*H*)-thione **371** and disordered isopropanol of crystallization connected with the former by hydrogen bonds.

The molecular structure of **371** is characterized by the presence of a C=S double bond and a planar heterocyclic system. The atoms C^3 and C^6 deviate slightly from the mean plane of the heterocycle (by 0.026(4) and 0.019(4) Å, respectively). The pyridine ring has an only slightly non-planar structure, even in 6-methyl-4-(4-fluorophenyl)-3-cyano-5-ethoxycarbonylpyridine-2(1*H*)-thione **370** with additional voluminous substituents.

The non-planarity of the pyridine ring is caused by the short intramolecular contacts S . . . C^8 3.047(5); C^8 . . . C^9 2.889(6); C^8 . . . C^{14} 3.121(7); C^7 . . . C^9 2.919(6); C^7 . . . C^{10} 3.114(7), and C^7 . . . N^2 2.842(6) Å, leading to displacement of the atoms S, C^7, C^8, C^9, and N^2 out of the heterocyclic plane by −0.105(1), −0.032(5), 0.210(5), −0.105(4), and 0.021(4) Å, respectively. These steric interactions twist the benzene ring out of the heterocyclic plane by 58.5°.

Table 13. Bond lengths d (Å) of **371** · $HOCH(CH_3)_2$

Bond	d	Bond	d
N^1–C^2	1.373(6)	C^8–N^4	1.144(6)
C^2–S	1.666(5)	C^9–C^{10}	1.392(7)
C^2–C^3	1.418(6)	C^{10}–C^{11}	1.382(7)
C^3–C^4	1.376(6)	C^{11}–C^{12}	1.363(8)
C^3–C^8	1.436(7)	C^{12}–C^{13}	1.388(8)
C^4–C^5	1.396(6)	C^{13}–C^{14}	1.378(7)
C^4–C^9	1.487(6)	C^{14}–C^9	1.394(7)
C^5–C^6	1.402(6)	C^{15}–O	1.475(8)
C^5–C^7	1.438(6)	C^{15}–C^{16}	1.534(11)
C^6–N^1	1.351(6)	C^{15}–C^{17}	1.369(17)
C^6–N^2	1.335(6)	C^{15}–C^{18}	1.030(36)
C^7–N^3	1.146(6)	C^{15}–C^{19}	1.592(15)

Also here the C^2=S bond length of 1.666(5) Å exceeds the standard C=S bond length of 1.610(9) Å (in thioacetaldehyde) and corresponds to the C=S bond length of 1.660(4) Å in the pyridinethione **370**.[247] On the other hand, it is slightly shorter than the C=S double bond of pyridine-2(1*H*)-thione. The elongation of the C=S bond in complexed **371** relative to the standard value 1.610(9) Å is probably due to a redistribution of electron density in this molecule caused by participation of C^2 in conjugation with the double bond C^3=C^4 as well as with the unshared electron pair of N^1. In **371** the bond lengths C^2–N^1 and N^1–C^6 of 1.373(6) and 1.351(6) Å, respectively, are shorter than the standard value for an ordinary C_{sp^2}–N bond of 1.426(12) Å (the sum of the valence angles at the planar-trigonal atom N^1 is 359.8°) and close to the mean values in pyridine.[246] The endocyclic C–C single bond lengths of 1.418(6) and 1.396(6) Å, respectively, are less than the standard value of a C_{sp^2}–C_{sp^2} bond, i.e. 1.476 Å, with corresponding lengthening of

Table 14. Valence angles ω (degrees) of **371** · $HOCH(CH_3)_2$

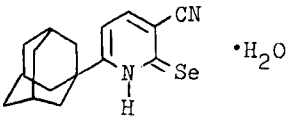
Angle	ω	Angle	ω
$C^6N^1C^2$	126.8(4)	$C^5C^7N^3$	177.8(5)
$N^1C^2C^3$	114.2(4)	$C^3C^8N^4$	177.8(5)
N^1C^2S	119.4(3)	$C^4C^9C^{10}$	121.5(4)
SC^2C^3	126.4(3)	$C^4C^9C^{14}$	119.9(4)
$C^2C^3C^4$	122.6(4)	$C^{10}C^9C^{14}$	118.6(4)
$C^2C^3C^8$	116.0(4)	$C^9C^{10}C^{11}$	121.0(5)
$C^8C^3C^4$	121.2(4)	$C^{10}C^{11}C^{12}$	119.3(5)
$C^3C^4C^5$	118.8(4)	$C^{11}C^{12}C^{13}$	121.1(5)
$C^3C^4C^9$	120.7(4)	$C^{12}C^{13}C^{14}$	119.6(5)
$C^9C^4C^5$	120.5(4)	$C^{13}C^{14}C^9$	120.3(5)
$C^4C^5C^6$	120.5(4)	$OC^{15}C^{16}$	106.3(6)
$C^4C^5C^7$	122.3(4)	$OC^{15}C^{17}$	123(1)
$C^7C^5C^6$	117.2(4)	$OC^{15}C^{18}$	124(2)
$C^5C^6N^1$	116.9(4)	$OC^{15}C^{19}$	104.2(7)
$C^5C^6N^2$	125.5(4)	$C^{16}C^{15}C^{19}$	114.3(8)
$N^2C^6N^1$	117.5(4)	$C^{17}C^{15}C^{18}$	103(3)

C=C double bonds to 1.376(6) and 1.402(6) Å, respectively. As a whole, the endocyclic C–C distances in the pyridine ring of **371** are rather close to the corresponding range of bond lengths in pyridine, 1.378–1.393 Å.[246]

The coordination plane of the planar-trigonal atom N^2 (the sum of the valence angles is 357°) is approximately coplanar with the heterocyclic plane (the dihedral angle is 17.9°) which is favorable for p,π-interaction of the unshared electron pair of this atom with the π-system of the heterocycle. This conjugation causes a sharp decrease of the C^6–N^2 bond length to 1.335(6) Å.

In the crystal of the complex of **371** with propanol a fully developed system of hydrogen bonds in which all active hydrogen atoms participate is operative.

In ref.[249] the structure of 6-(1-adamantyl)-3-cyanopyridine-2(1*H*)-selenone **372** has been studied. Fig. 4 shows a general view of **372**, crystallizing from the reaction mixture as the monohydrate.



372

Scheme 151

The pyridine ring of **372** is approximately planar: the atoms C^3 and C^6 lie outside the plane of the four other atoms of the ring. The ring bond lengths **372** (N^1–C^2 1.37(1); C^2–C^3 1.43(2); C^3–C^4 1.37(2); C^5–C^6 1.38(2), and C–N 1.34(1) Å) are close to those of 3-cyanopyridine-2(1*H*)-thiones.

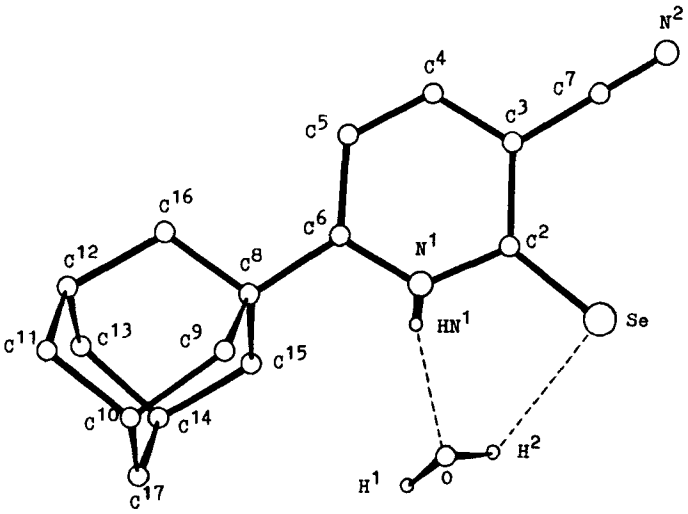


Figure 4. Selenone **372** and water of crystallization connected with the former by hydrogen bonds.

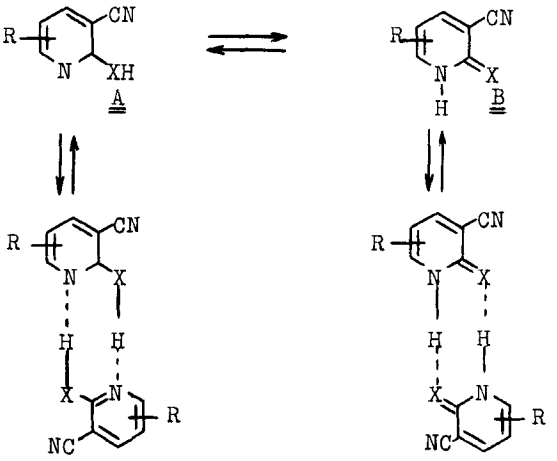
The C^2=Se bond length is 1.80(1) Å. The short distance Se . . . C^7 of 3.18(1) Å squeezes Se and C^7 out of the $N^1C^2C^3$ and $C^2C^3C^4$ planes by −0.11 and 0.20 Å, respectively. The deformation of the valence angles SeC^2C^3 and $C^7C^3C^2$ is less pronounced.

The adamantyl substituent is oriented in such a way that the atoms C^5 and C^6 are in a hidden position (the torsional angle $C^5C^6C^8C^{18}$ is equal to 10(3)°). In the crystal each selenone molecule is bound to a molecule of water of crystallization.

4. CHEMICAL PROPERTIES OF 3-CYANOPYRIDIN-2(1*H*)-ONES, -THIONES, AND -SELENONES

3-Cyanopyridin-2(1*H*)-ones, -thiones, and -selenones are bifunctional compounds with two reactive groups. These are the conjugated cyano group for which addition reactions[250] are characteristic and the amide (thioamide, selenoamide) group with an endocyclic nitrogen atom the reactivity of which is determined by a tautomeric equilibrium, the effect of substituents on the pyridine ring, and the reaction conditions.

3-Cyanopyridine-2(1*H*)-thiones and -selenones as well as their oxygen-containing analogs[234] in solution are in tautomeric equilibrium between the lactim (**A**) and the lactam (**B**) form.[251-253]

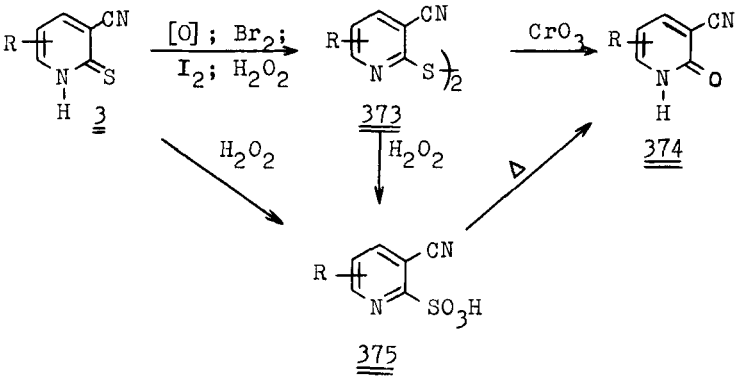


Scheme 152

On one hand, this equilibrium stabilizes the compounds: they exist predominant in the dimeric form held together by hydrogen bonds. On the other hand, this equilibrium requires the presence of a mobile hydrogen atom in the amide or thio(seleno)amide group.

4.1. Reactions of Amide and Thio(seleno)amide Groups with an Endocyclic Hydrogen Atom

4.1.1. Oxidation Characteristic of 3-cyanopyridine-2(1*H*)-thiones **3** is their ability to enter into oxidation-reduction reactions with the endocyclic nitrogen atom at the expense of the thioamide group. In refs.[33,53,141,145,149,156,254,255] it has been noted that these compounds are oxidized in solution by atmospheric oxygen to the disulfides **373**. The compounds **373** are obtained on a preparative scale from the corresponding **3** with iodine in the presence of bases.[33,141] Hydrogen peroxide, sodium nitrite, and bromine may also be used as oxidants.[149,255,256]

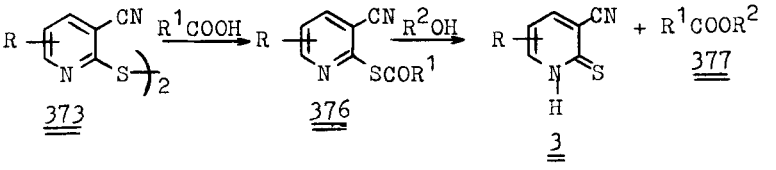


Scheme 153

The 2,2-bis(3-cyano-2-pyridyl) disulfides **373** can be further oxidized under more forcing conditions. For example, chromium trioxide oxidizes **373** to the 3-cyanopyridin-2(1*H*)-ones **374**.[156,255]

4,6-Dimethyl-3-cyanopyridine-2-sulfonic acid **375** is formed from 4,6-dimethyl-3-cyanopyridine-2(1*H*)-thione with excess hydrogen peroxide.[255] It is likely that the reaction proceeds via the corresponding disulfides. The 2-pyridinesulfonic acids **375** are hydrolyzed to the corresponding 3-cyanopyridin-2(1*H*)-ones **374** upon heating.

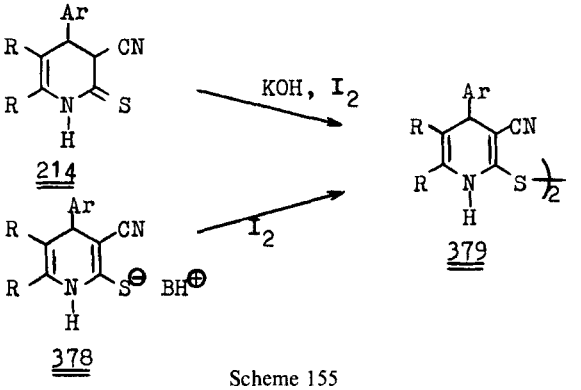
The disulfides **373** have been used in the synthesis of the thiolesters **376**. Compounds **376**, as well as 2-pyridinethiones without ring substituents are subject to intramolecular transformations.[257-259] It is precisely this circumstance which explains their recent successful use for the synthesis of the esters **377** and, also, of macrocyclic lactams.



Scheme 154

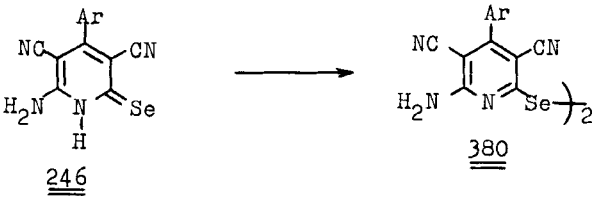
In the presence of triphenylphosphine **373** are acylated by carboxylic acids with formation of the acylthiopyridines **376**. Subsequent interaction of **376** with alcohols gives high yields of the esters **377**.[257]

In a number of refs.[147,191,192] the oxidation of the 3,4-dihydropyridine-2(1*H*)-thiones **214** and their salts to the hydrogenated disulfides **379** are described.



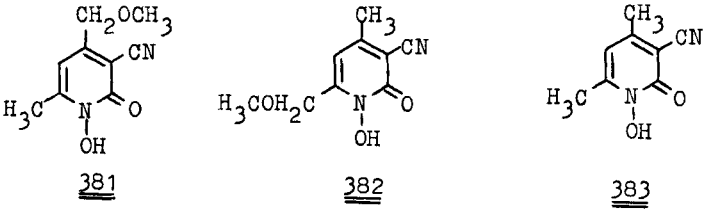
Scheme 155

As in the case of pyridine-2(1*H*)-thiones **214** and **378** are easily oxidized in solution by atmospheric oxygen to the corresponding disulfides **379**. Compounds **379** have been prepared by treatment of **214** and **378** with iodine. Pyridine-2(1*H*)-selenones are also oxidized with ease. However, data concerning the redox properties of pyridine-2(1*H*)-selenones are practically non-existent, except ref.[172] describing the synthesis of the diselenide **380** from 3-cyanopyridine-2(1*H*)-selenone **246** (X = Se).



Scheme 156

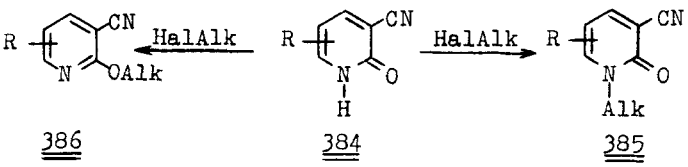
Oxidations of 3-cyanopyridin-2(1*H*)-ones leading to the formation of *N*-oxides have been studied. Thus, from 4,6-disubstituted 3-cyanopyridin-2(1*H*)-ones and hydrogen peroxide the hydroxamic acids **381–383** have been obtained in yields of 31, 28, and 36%, respectively.[260]



Scheme 157

4.1.2. Alkylation In the synthesis of pyridine derivatives 2-alkoxy(alkylthio, -seleno)-pyridines have found wide application. The syntheses of these compounds are based on the alkylation of pyridin-2(1*H*)-ones, -thiones, and -selenones with alkyl halides and on the interaction of 2-halopyridines with alkanethiolates. Methyl iodide, ethyl iodide, phenacyl bromides, bromides and chlorides of esters and amides of carboxylic acids, chloroacetonitrile, bromonitromethane, allyl bromide, and cyclohexyl bromide have been widely used as alkyl halides. Alcohols, DMF, DMSO, benzene, chloroform, water, etc. have been used as solvents.

The tautomeric equilibrium involving the amide moiety leads to the situation that 3-cyanopyridin-2(1*H*)-ones **384** are alkylated both at the nitrogen and the oxygen atom with formation of the pyridones **385**, the pyridines **386**, or mixtures of both.

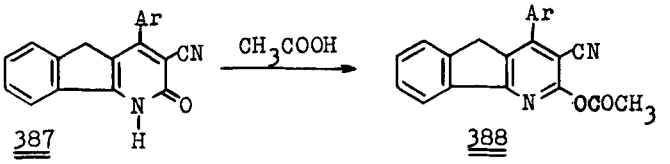


Scheme 158

With alkyl halides in ethanol in the presence of potassium hydroxide the alkyl derivatives **385** are formed in 24–89% yield.[261,262] In acetonitrile in the presence of potassium hydroxide a mixture of **385** and **386** in 28 and 42% yield, respectively, was obtained.[261] The alkylation of 4,5-tetramethylene-3-cyanopyridin-2(1*H*)-ones in DMF/KOH proceeds similarly.[45]

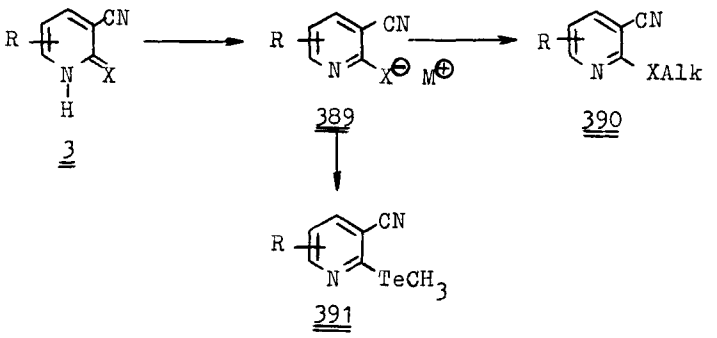
The interaction of alkyl halides with the sodium or potassium salts of 3-cyanopyridin-2(1*H*)-ones leads to the corresponding 2-alkoxy derivatives **386**.[263–268] The same products are obtained by alkylation in the presence of acids, in DMF in the presence of sodium hydride, as well as by alkylation in acetone, acetonitrile, or ethyl acetate.[261,269–273] Alkoxy derivatives of 3-cyanopyridines are also formed when diethyl sulfate is used as the alkylating agent in the presence of potassium carbonate.[261,271–273]

Acylation of the pyridones **387** with acetic acid yielded the esters **388**.[262]



Scheme 159

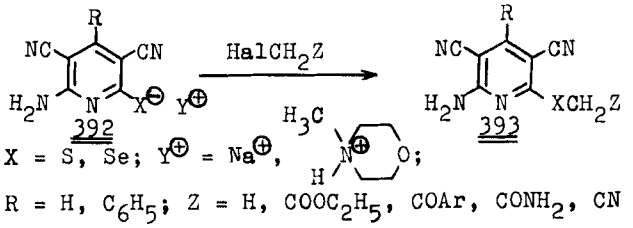
In refs.[4,7,24,26,37,38,40,45,46,49–52,54,57,114,155,157,159,163,170,173,185,204,209,214,217–220,232,274–280] it was shown that in contrast to pyridin-2(1*H*)-ones *N*-alkylation of 3-cyanopyridine-2(1*H*)-thiones and -selenones is unimportant in the presence of base and the corresponding 2-alkylthio(seleno)pyridines were formed. The initially formed salts **389** are alkylated at the chalcogen atom to yield **390**.



M = Na, K; X = S, Se, Te

Scheme 160

The alkylation of the sodium salt of pyridine-2-tellurolate with methyl iodide leads to 2-methyltelluropyridine **391**.[26] The sodium salts of a number of substituted pyridine-2-thiolates and pyridine-2-selenolates have been isolated prior to the alkylation reaction.[170,173,204]

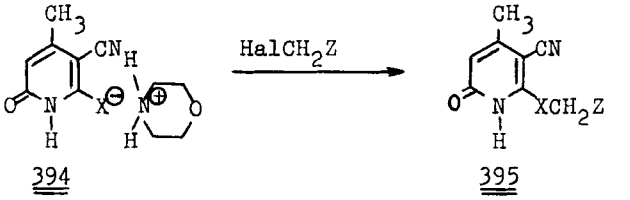


X = S, Se; $Y^{\oplus}$ = $Na^{\oplus}$, ;

R = H, C_6H_5; Z = H, $COOC_2H_5$, COAr, $CONH_2$, CN

Scheme 161

It has been shown that in the presence of several nucleophilic centres in the salts **392** alkylation occurs at the chalcogen atom with formation of **393**.[204] The alkylation of the morpholinium salts of 4-methyl-6-oxo-3-cyanopyridine-2(1*H*)-thiolate(selenolate) **394**[114,146] with different alkyl halides and the effect of the solvent on the regiochemistry of this reaction have been studied.

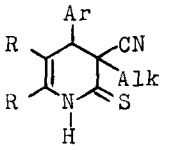


X = S, Se; Z = H, CN, COAr, $COOC_2H_5$

Scheme 162

Independent of the nature of the solvent the reaction proceeds with formation of the 2-alkylthio(seleno)pyridines **395**.

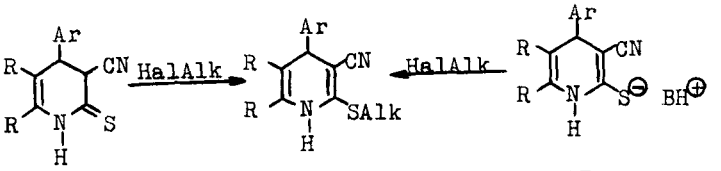
The alkylation of 3,4-dihydropyridine-2(1*H*)-thiones and their salts has been investigated. Initially, it was wrongly stated that the alkylation of 3,4-dihydropyridine-2(1*H*)-thiones in basic medium leads to 3-alkyl-3-cyanodihydropyridine-2(1*H*)-thiones **396**.[281,282]



396

Scheme 163

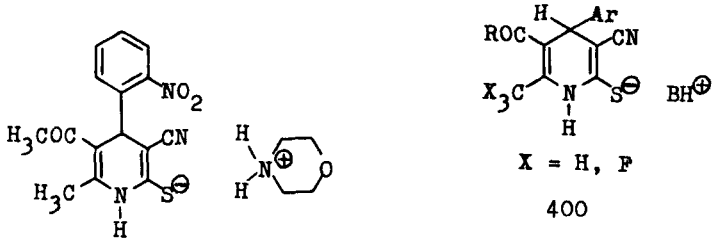
However, later work showed that the alkylation of 3,4-dihydropyridine-2(1*H*)-thiones with alkyl halides in a basic medium and the alkylation of the salts **397** proceed with formation of the 2-alkylthio-1,4-dihydropyridines **398**.[150,152,164,183,195,283]



398 **397**

Scheme 164

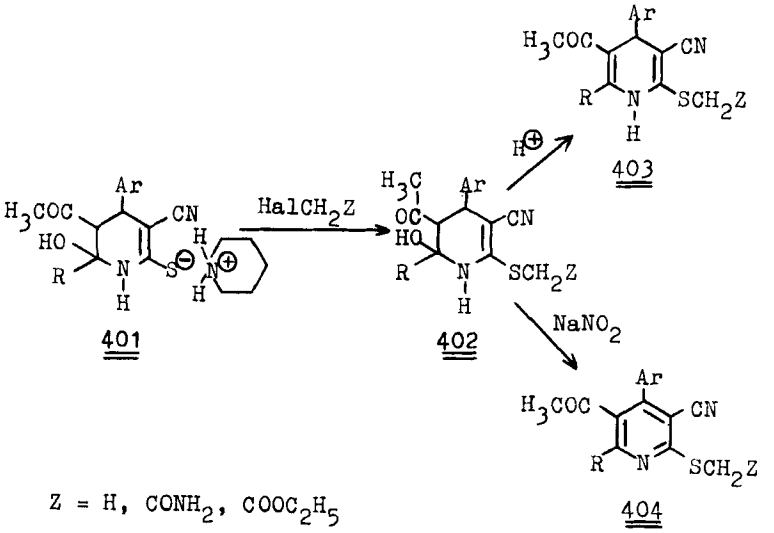
In refs.[164,183,193,284] it has been noted that the partial localization of the negative charge on the sulfur atom is the deciding factor for the regiochemistry of the alkylation of **397**. By X-ray diffraction analysis it has been found that the sulfur atom carries the formal negative charged in morpholinium 5-acetyl-3-cyano-1,4-dihydro-6-methyl-4-(2-nitrophenyl)-2-pyridinethiolate **399**.[284] In subsequent work[183,193] the X-ray diffraction data were correlated with spectroscopic data and the results obtained confirmed by chemical transformations of the salts **400**.



399 **400**

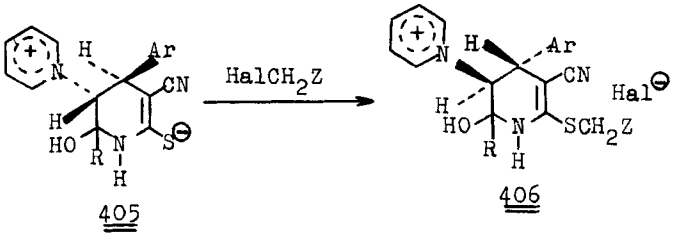
Scheme 165

The alkylation of tetrahydropyridine-2-thiolates **401** and the sense of the dehydration and dehydrogenation of the alkylation products **402** have been investigated.[152] It was shown that the alkylation of **401** proceeds with conservation of the starting material's conformation to yield the 2-alkylthiotetrahydropyridines **402** which eliminate water in acid medium to form the 2-alkylthio-1,4-dihydropyridines **403**. In the presence of sodium nitrite aromatization occurs and the 2-alkylthiopyridine **404** is formed.



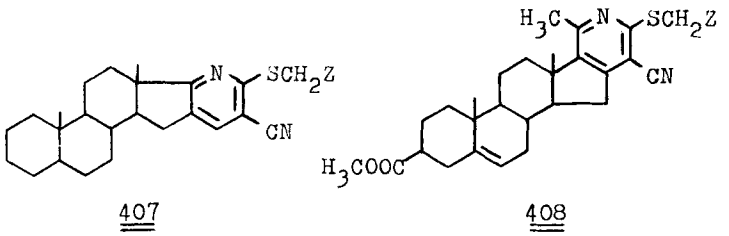
Scheme 166

The alkylation of the betaines **405** with alkyl halides proceeds with high regioselectivity in much the same way with conservation of conformation.[202] The 6-alkylthiotetrahydropyridines **406** are formed with the *trans*-pseudoaxial position of the hydrogen atoms H^3 and H^4 and the *trans*-pseudoequatorial position of the substituents Py^+ and Ar preserved.



Scheme 167

This knowledge of the regio- and stereochemistry of alkylations of pyridinethiones and -selenones was applied in the synthesis of the difficultly accessible steroid annelated 2-alkylthiopyridines **407** and **408**.[57,157] In this case, conservation of the conformation of the steroid skeleton is observed.

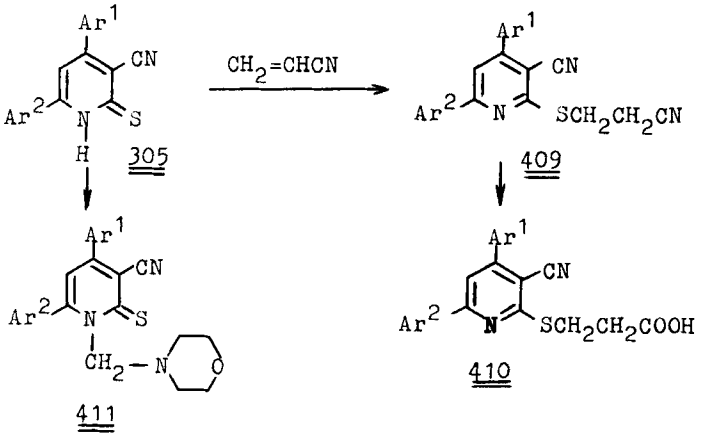


407 408

Scheme 168

Using optically active alkyl halides the authors of ref.[285] established that the alkylation of pyridine-2(1*H*)-thione proceeds according to an S_N2 mechanism with Walden inversion at the asymmetric carbon atom.

4.1.3 Addition reactions In the presence of base 4,6-diaryl-3-cyanopyridine-2(1*H*)-thiones **305** add to electron-deficient double bonds with formation of 2-alkylthio-3-cyanopyridine-2(1*H*)-thiones **409**. The compounds **409** are used for the synthesis of 2-(3-cyano-2-pyridylthio)propionic acids **410**.[286]

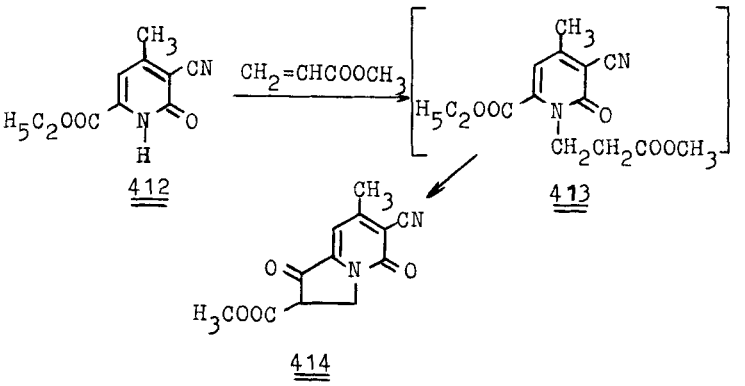


305 409 411 410

Scheme 169

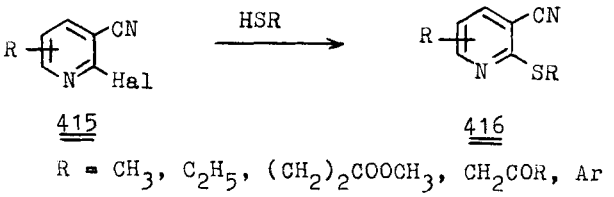
In the Mannich reaction *N*-alkylamino-3-cyanopyridine-2(1*H*)-thiones **411** are formed from the substituted 3-cyanopyridine-2(1*H*)-thiones **305**.

The *N*-alkylpyridone **413** is an intermediate in the addition of the 3-cyanopyridin-2(1*H*)-one **412** to the C=C double bond of methyl methacrylate.[287] Subsequent Dieckmann condensation results in the formation of the corresponding indolizine **414**.



Scheme 170

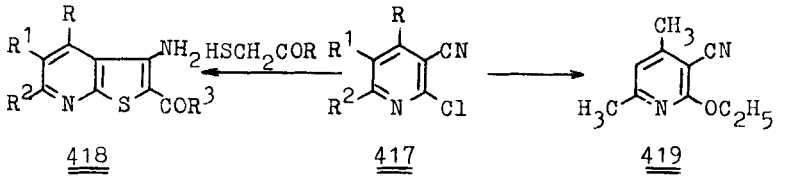
4.1.4 Miscellaneous methods for the synthesis of O-, S- and N-substituted 3-cyanopyridines 2-[Alkyl(aryl)thio]pyridines **416** have been obtained by interaction of 2-halopyridines **415** with alkane- or arenethiols in the presence of base.[227,288-291]



Scheme 171

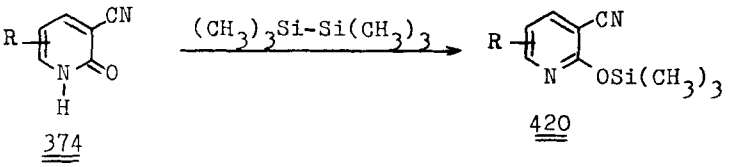
The reaction is complicated in some cases by the formation of pyridin-2(1*H*)-ones and 2-alkoxypyridines as by-products and a corresponding decrease of the yield of **416**.

Upon treatment of 2-chloro-3-cyanopyridines **417** with esters of thioglycolic acid the substituted 3-aminothieno[2,3-*b*]pyridines **418** have been synthesized.[288,292] With R = R^2 = CH_3 and R^1 = H the 4,6-dimethyl-2-ethoxy-3-cyanopyridine **419** can be isolated as a by-product together with the corresponding thienopyridine **418**.



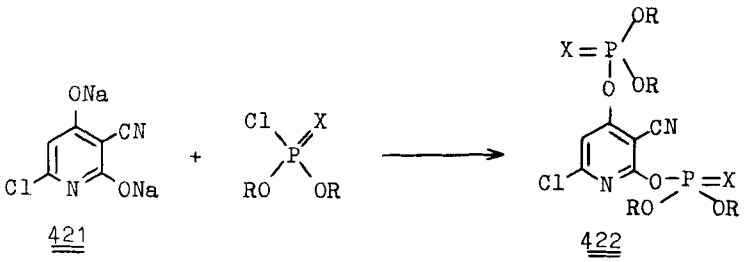
Scheme 172

Starting from 3-cyanopyridin-2(1*H*)-ones organosilicon compounds have been synthesized. Interaction of the 3-cyanopyridin-2(1*H*)-ones **374** with hexamethyldisilazane results in the formation of the 2-trimethylsiloxy-3-cyanopyridines **420** in a yield of 89–97%.[293]



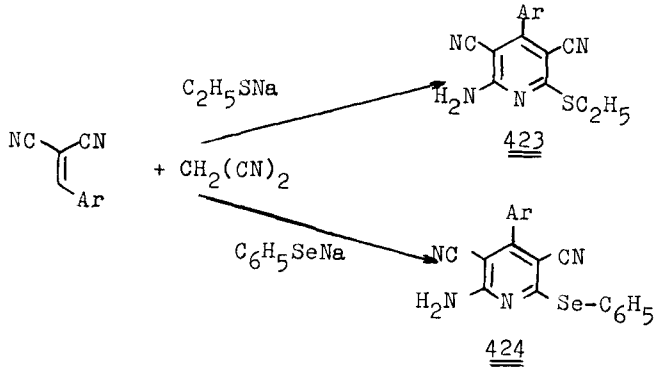
Scheme 173

The phosphorylated 3-cyanopyridines **422** have been prepared by interaction of the disodium salt of 2,5-dihydroxy-6-chloro-3-cyanopyridine **421** with dialkylhalophosphates and -thiophosphates.[294]



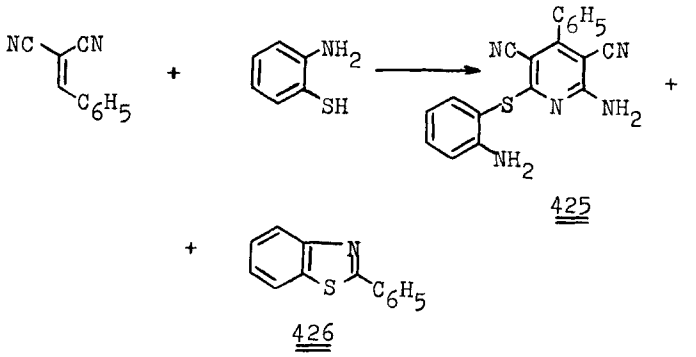
Scheme 174

In addition, there is a variety of pathways to 2-alkyl(aryl)thio(seleno)pyridines by cyclization of acyclic nitriles with alkyl(aryl)thiols(selenones) in the presence of base.[11,295-299] 6-Amino-4-aryl-3,5-dicyano-2-ethylthiopyridines **423** have been synthesized from arylidenemalononitriles, malononitrile, and sodium ethanethiolate in ethanol.[295,296]



Scheme 175

The interaction of arylidenemalononitriles and malononitrile with sodium benzeneselenolate proceeds in ethanol in a similar way with the formation of **424**.[299] In ref.[298] describing the interaction of benzylidenemalononitrile with 2-mercaptoaniline, the formation of a sulfur-containing analog of **424** as a by-product was noted. The benzothiazole **426** was isolated together with **425**.

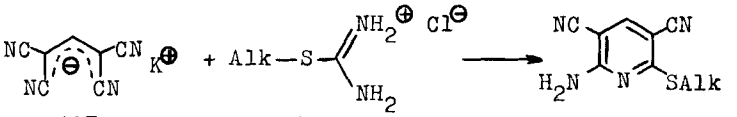


425

426

Scheme 176

2-Alkylthiopyridines have been obtained by treatment of the thiouronium salts **428** with potassium tetracyanopropenide **427**.[297] Variation of the substituents in **428** permits the synthesis of various 2-alkylthiopyridines **429**.

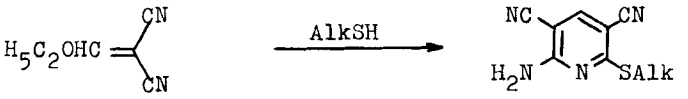


427 428 429

Alk = CH_3, C_2H_5, $CH_2C_6H_5$

Scheme 177

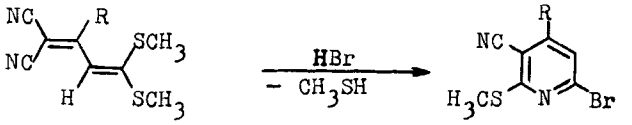
However, it was already shown in preceding work[300] that **429** can be obtained in a simpler way, from ethoxymethylenemalononitrile **430** and alkanethiolates.



430 429

Scheme 178

Reaction of 4,4-bis(methylthio)buta-1,3-diene-1,1-dicarbonitrile **431** with hydrogen bromide leads to the pyridine **432**.[301]



431 432

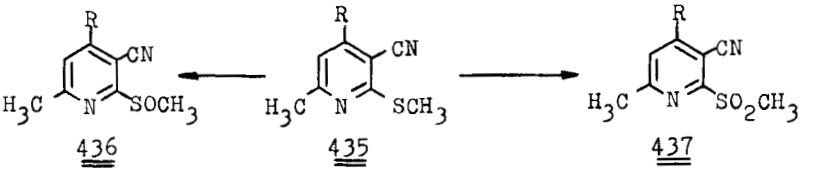
Scheme 179

S-Alkyl derivatives of 3-cyano-4-quinolones **434** are formed by intramolecular condensation of **433**.[302]

433 **434**

Scheme 180

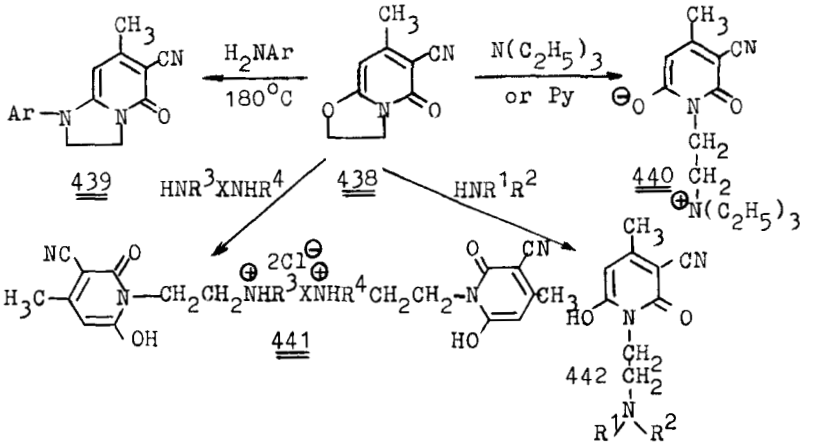
The *S*-methyl derivatives **435** can be oxidized to the sulfoxides **436** and the sulfones **437**; the latter have been shown to exhibit cardiotonic activity in dogs.[280]



436 **435** **437**

Scheme 181

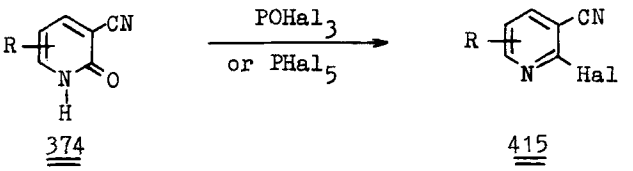
In ref.[303] reactions of 6-cyano-2,3-dihydro-7-methyloxazolo[3,2-*a*]pyridin-5(*H*)-one **438** with different amines have been studied. It was shown that the reaction direction depends on the structure of the amine. The 3-cyano-2-pyridones **439–442**, substituted at the ring nitrogen atom, are formed.



439 **438** **440** **441** **442**

Scheme 182

4.1.5. Nucleophilic attack on a carbonyl group 3-Cyanopyridin-2(1*H*)-ones **374** have found wide application in the synthesis of 2-halo-3-cyanopyridines **415**.[62,63,66,133,161,250,267,271-273,304-316]

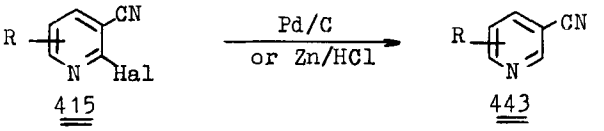


374 415

Scheme 183

Phosphorus oxybromide and phosphorus pentabromide have been used to prepare 2-bromo-3-cyanopyridines.[310,317]

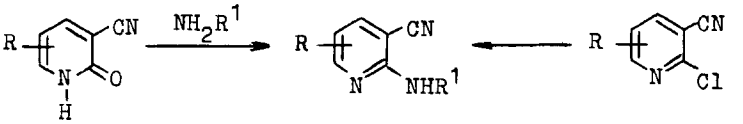
3-Cyanopyridines with a free position 2 **443** have been obtained by dehalogenation of 2-halo-3-cyanopyridines **415** with palladium on carbon or zinc and hydrochloric acid.[310,318]



415 443

Scheme 184

The quantity of work concerning the synthesis of 2-halo-3-cyanopyridines is great which may be explained by their broad use in nucleophilic substitutions leading to different classes of compounds. From 2-halo-3-cyanopyridines various 2-substituted pyridines have been prepared.[304,319,320] Thus, the 2-amino-3-cyanopyridines **444** have been obtained from both 3-cyanopyridines **374**[263,265,266] and 2-chloro-3-cyanopyridines **415** (Hal = Cl).[62,63,264,267,269,304,307,313,316,321]

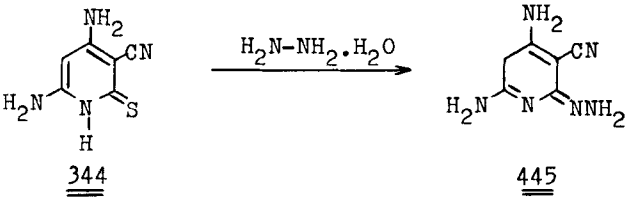


374 444 415

R^1 = C_2H_5, C_3H_7, C_6H_5, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$

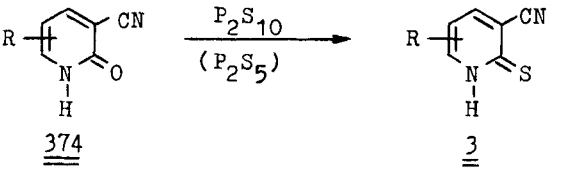
Scheme 185

As an example of the substitution of thioamide sulfur the reaction of 3-cyanopyridine-2(1*H*)-thione **344** (X = S) with hydrazine in ethanol to yield **445** can be cited.[230]



Scheme 186

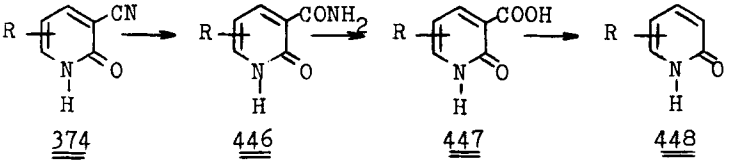
3-Cyanopyridin-2(1*H*)-ones **374** are subject to substitution reactions leading to the formation of the 3-cyanopyridine-2(1*H*)-thiones **3**.[6,28,190,322,323]



Scheme 187

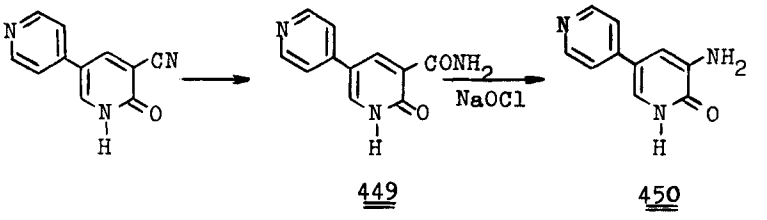
4.2. Reactions of the Nitrile Group

3-Cyanopyridin-2(1*H*)-ones and -thiones take part in standard reactions characteristic of compounds containing a nitrile group.[250] One such reaction is the hydrolysis of the nitrile group[324] in acid or alkaline medium. The nitrile group of 3-cyanopyridin-2(1*H*)-ones can be hydrolyzed to an amide group **446**,[67,82,325-329] under more severe conditions to a carboxyl group **447**.[65,85,263,309,330-341] The reaction can be followed by decarboxylation.[65,85,263,309,336,339] Pyridones with a vacant position 2 **448** are obtained directly from 3-cyanopyridin-2(1*H*)-ones **374** by acid hydrolysis.[64,76,77,342-346]



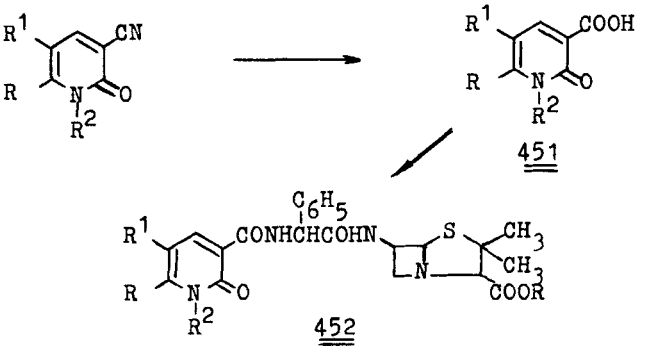
Scheme 188

Upon treatment of 3-carbamoylpyridin-2(1*H*)-one **449** with sodium hypochlorite 3-aminopyridin-2(1*H*)-one **450**,[67] exhibiting cardiotonic activity, has been obtained.



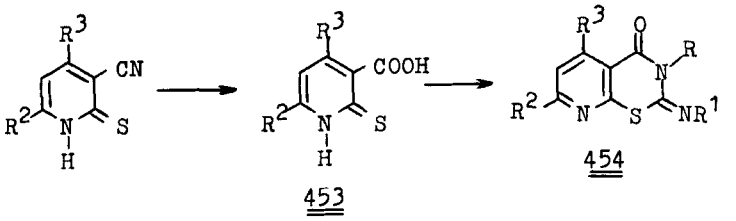
Scheme 189

Pyridonecarboxylic acids **451** are used in the synthesis of the ampicillin derivatives **452**.[337,339]



Scheme 190

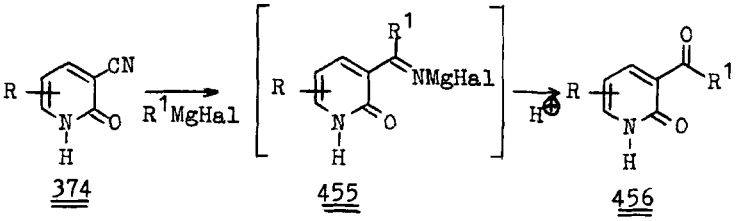
Acid hydrolysis of 6-methyl-3-cyanopyridine-2(1*H*)-thione has been utilized in the synthesis of 6-methylthieno[2,3-*b*]pyridine.[347] Pyrido[3,2-*e*]-1,3-thiazin-4-ones **454**, possessing an antidepressive effect on the nervous system, have been obtained from 2-mercaptonicotinic acid **453** according to the following scheme:[348]



Scheme 191

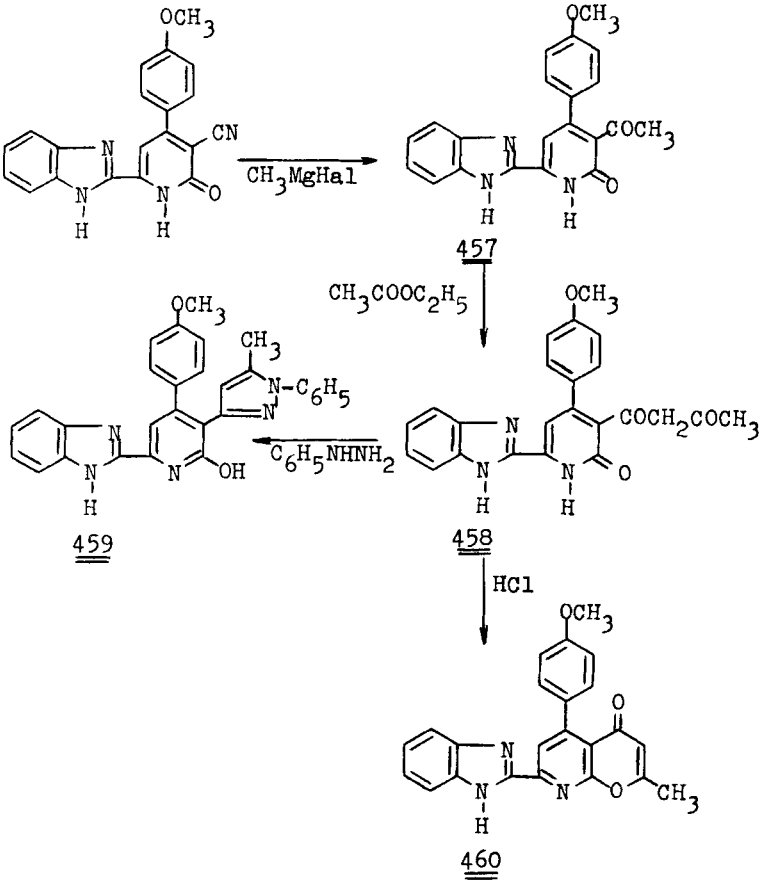
The nitrile group of 3-cyanopyridine-2(1*H*)-thiones reacts with nucleophiles such as ammonia. Thus, partial aqueous ammonolysis of the nitrile group yields the corresponding nicotinic acid amides. The reaction has been used in the synthesis of hydrogenated isomers of nicotinamide.[349]

3-Cyanopyridin-2(1*H*)-ones have been used in the synthesis of the pyridyl ketones **456** via the *N*-magnesio ketimines **455**.[161,264-269,309,350-353]



Scheme 192

By treatment of 3-acetyl-2-pyridone **457** with ethyl acetate the pyridonylacetone **458**, useful for the synthesis of different heterocyclic systems such as **459** and **460**, is formed.[251]

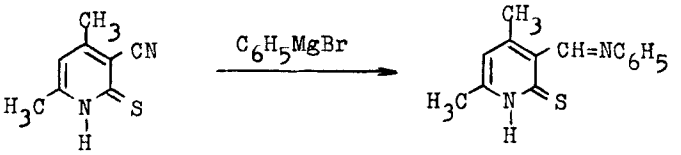


Scheme 193

The transformations of 3-cyano-2-pyridines may also follow other direction. For example, the pyridone **461** adds a Grignard agent to its $C^3=C^4$ double bond to form **462**.[265]

Scheme 194

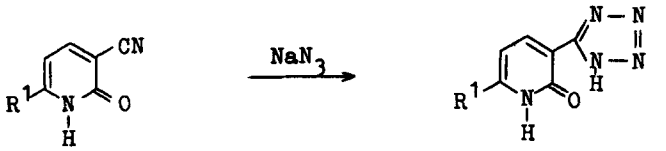
The reaction of 3-cyanopyridine-2(1*H*)-thiones with phenylmagnesium bromide is quite remarkable. Brief heating of 4,6-dimethyl-3-cyanopyridine-2(1*H*)-thione **50** (X = S) with phenylmagnesium bromide results in the formation of the Schiff base **463**.[354]



50 463

Scheme 195

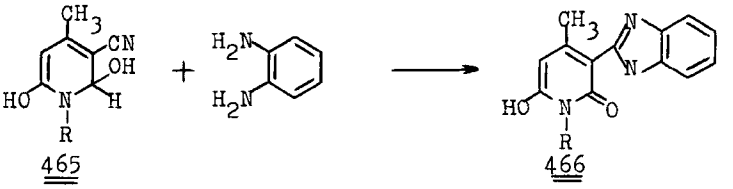
6-Alkyl-1,2-dihydro-2-oxo-3(1*H*)-tetrazol-5-ylpyridines **464**, of certain interest as antidiabetic agents, have been obtained from 6-alkyl-3-cyanopyridin-2(1*H*)-ones **12** and sodium azide.[355]



12 464

Scheme 196

Upon condensation of *o*-phenylenediamine with 2,6-dihydroxy-3-cyanopyridines **465** in the usual way 3-(2-benzimidazolyl)-6-hydroxy-2-pyridones **466** are formed in the presence of polyphosphoric acid.[356,357]

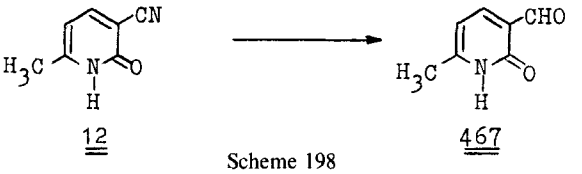


465 466

R = H, CH_3, C_2H_5

Scheme 197

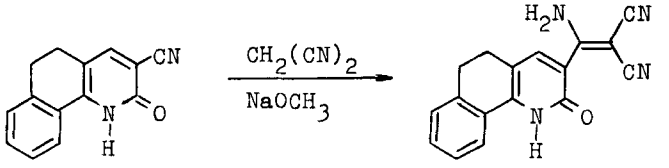
6-Methyl-3-cyanopyridin-2(1*H*)-one **12** (R^1 = R^2 = H; R^3 = CH_3; X = O) forms 6-methyl-3-formylpyridin-2(1*H*)-one **467** after subsequent treatment with hexamethyldisilane (HMDS) and diisobutylaluminumhydride (DIBAH) in toluene.[358]



12 467

Scheme 198

Derivatives of 3-cyanopyridin-2(1*H*)-ones react with CH acids. Addition of malononitrile to the nitrile group of **468** in the presence of sodium methoxide leads to 3-(1,1-dicyano-2-aminoethylene)naphthopyridone **469**.[359]

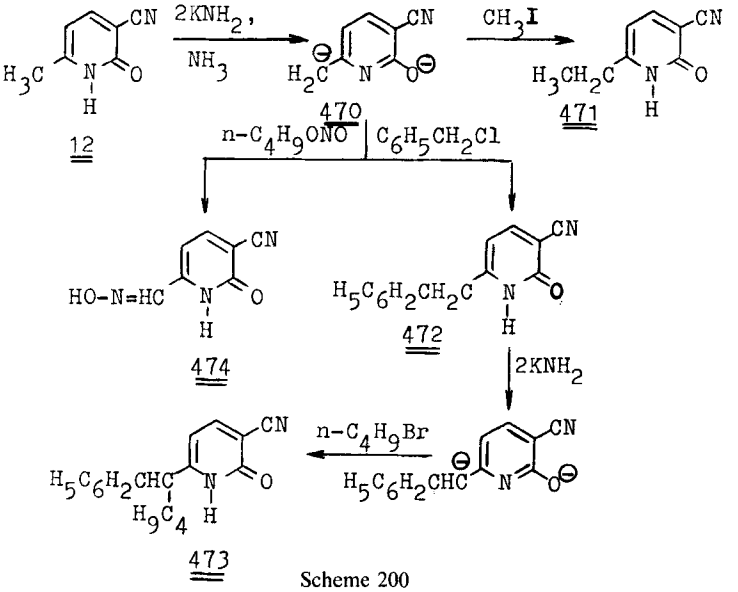


468 469

Scheme 199

4.3. Reactions with Participation of other Substituents on the Pyridine Ring

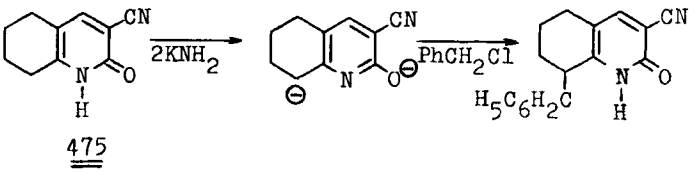
Alkyl substituted 3-cyanopyridin-2(1*H*)-ones can suffer deprotonation of methyl or α-methylene groups. The anions formed may then act as nucleophilic reagents. The reactions of 6-methyl-3-cyanopyridin-2(1*H*)-one **12** ($R^1 = R^2 = H$; $R^3 = CH_3$; X = O) with different electrophilic reagents in the presence of 2 mol sodium amide in liquid ammonia have been studied.[360,361] The dianion **470** is alkylated selectively with haloalkanes with the formation of alkylpyridones such as **471** and **472** which in turn can be alkylated at a methylene group with the formation of tertiary alkylpyridones such as **473**.[360] When **470** interacts with butyl nitrite the aldoxime **474** is formed.[361]



12 470 471 474 472 473

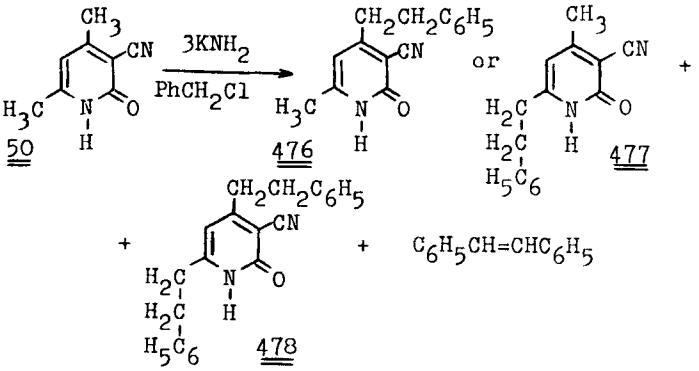
Scheme 200

5,6-Tetramethylene-3-cyanopyridin-2(1*H*)-one **475** is alkylated in position 8 in a similar way.[360]



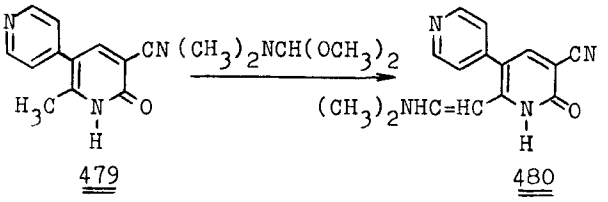
Scheme 201

Alkylation of 4,6-dimethyl-3-cyanopyridin-2(1*H*)-one **50** (X = O) with benzyl chloride in the presence of 3 mol sodium amide leads to a mixture of two substituted 3-cyanopyridin-2(1*H*)-ones, either **476** or **477** and **478**, in a yield of 35% each.[360]



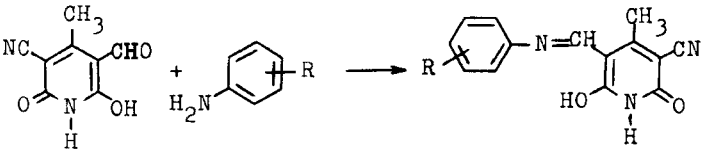
Scheme 202

6-(2-Dimethylaminoethenyl)pyridone **480** has been obtained from pyridone **479** and *N*,*N*-dimethylformamide dimethylacetal.[362]



Scheme 203

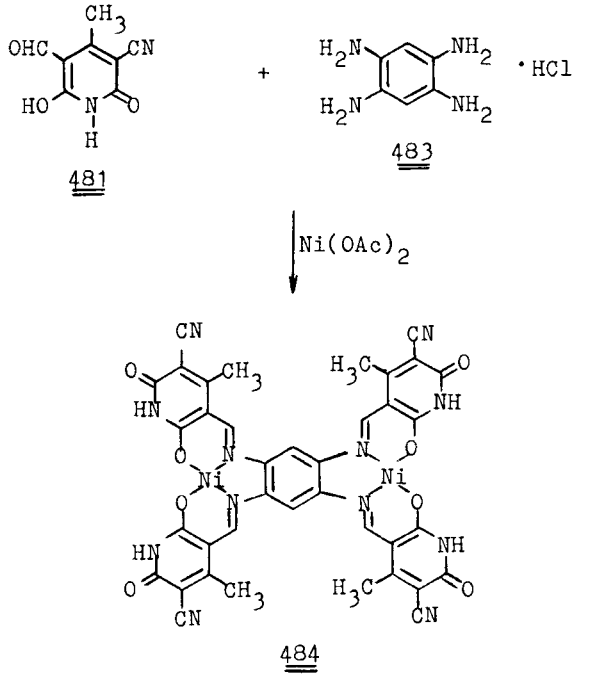
The reactions of 5-formyl-3-cyanopyridin-2(1*H*)-one **481** with aromatic amines have been studied. The 5-pyridylazomethines **482** thus formed have been patented as pigments.[363-365]



481 482

Scheme 204

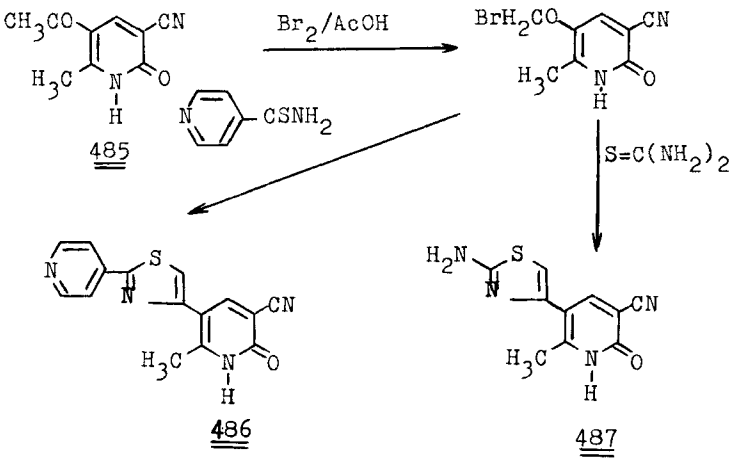
In the presence of nickel(II) acetate the corresponding nickel complexes could be isolated.[364-366] Thus, the azomethine pigment **484** has been obtained by condensation of 5-formylpyridine **481** with 1,2,4,5-tetraaminobenzene in the presence of nickel(II) acetate.[365]



481 483 484

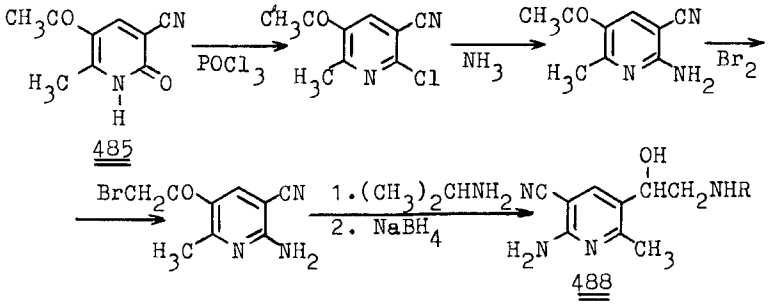
Scheme 205

The presence in the pyridones **485** of an acetyl group in position 5 allows their use in the synthesis of the 5-(4-thiazolyl)-2-pyridones **486** and **487**, exhibiting cardiotonic activity.[92,367]



Scheme 206

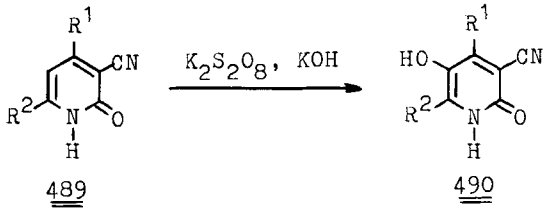
The pyridone **485** has also been used in the synthesis of the growth factor **488**.[368]



Scheme 207

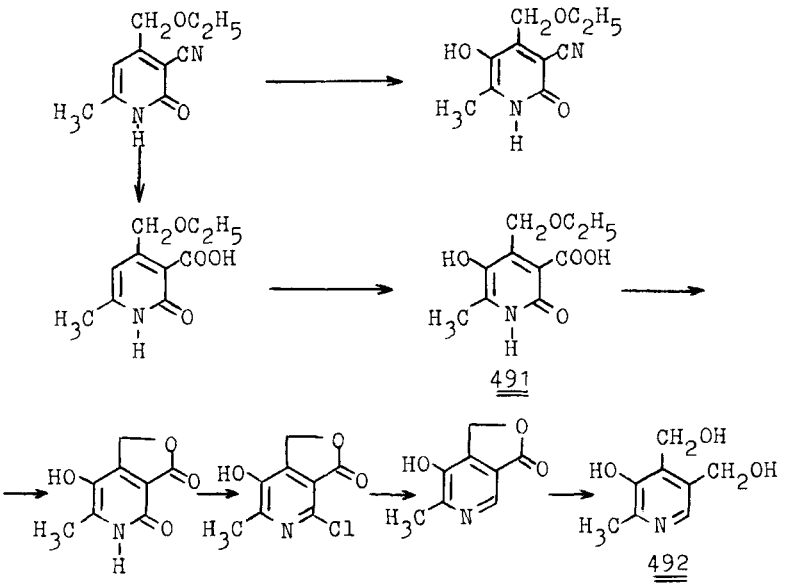
4.4. Reactions Involving Pyridine Ring Carbon Atoms

Reactions involving the vacant ring positions of 3-cyanopyridin-2(1*H*)-ones have been widely used. Hydroxylation of the substituted 3-cyanopyridin-2(1*H*)-ones **489** with potassium persulfate in alkaline medium yields the substituted 5-hydroxy-3-cyanopyridin-2(1*H*)-ones **490**.[341,369,370]



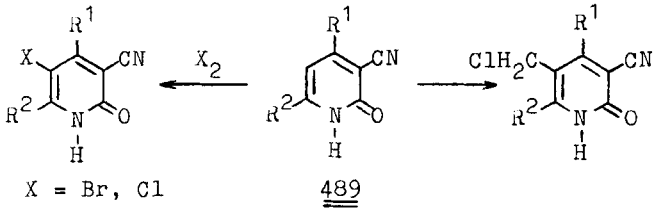
Scheme 208

5-Hydroxy-6-methyl-3-carboxy-4-ethoxymethylenepyridin-2(1*H*)-one **491** has been used in a synthesis of vitamin B_6 **492**.[332,340,341,370]



Scheme 209

Brominations,[310] chlorinations,[371] and chloromethylations[328] of 3-cyanopyridin-2(1*H*)-ones **489** are also known.

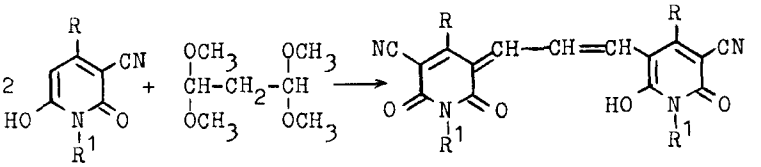


Scheme 210

5-Nitro-3-cyanopyridin-2(1*H*)-ones are obtained by nitration of 3-cyanopyridin-2(1*H*)-ones.[372-378] Nitric acid is generally used as nitrating agent. The sulfonation of 3-cyanopyridin-2(1*H*)-ones to the corresponding 5-sulfonic acids proceeds in a similar way.[379]

Of considerable practical interest are 6-hydroxy-4-alkyl-3-cyanopyridin-2(1*H*)-ones by virtue of their use in the synthesis of dyes.[380–385]

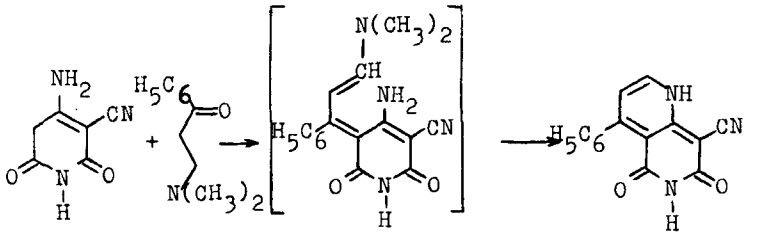
The 3-cyanopyridin-2(1*H*)-one derivatives **495**, obtained by condensation of malonic aldehyde tetraacetal **494** with **493**, have claimed use in photography as antifogging agents in silver halide emulsions.[386,387]



493 494 495

Scheme 211

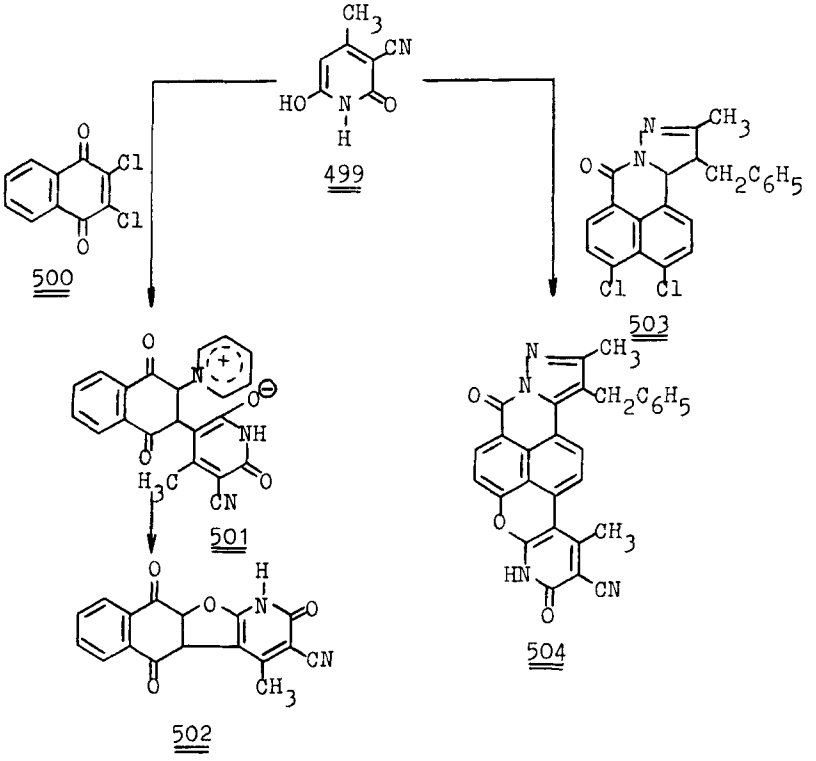
6-Hydroxy-3-cyanopyridin-2(1*H*)-ones are also used in the synthesis of annelated heterocyclic systems.[99] Interaction of 4-amino-3-cyanopyridine-2,6-dione **496** with 3-dimethylamino-1-phenyl-2-propanone **497** results in the formation of 3-cyanonaphthyridinedione **498**.



496 497 498

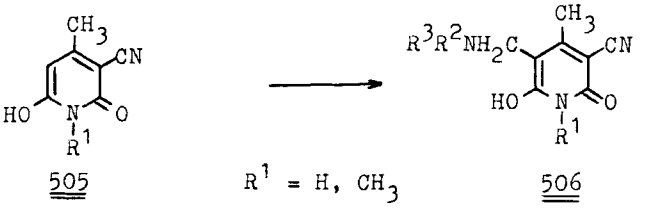
Scheme 212

2,3-Dichloronaphthoquinone **500** and the dichloropyrazolopyrimidine **503** react with the pyridone **499** to form different condensed systems where the pyridine ring is directly annelated with furan **502**[388] or pyran **504**.[389] From the reaction of **500** with **499** in ethanol in the presence of pyridine the zwitterion **501** has been isolated and characterized.[388]



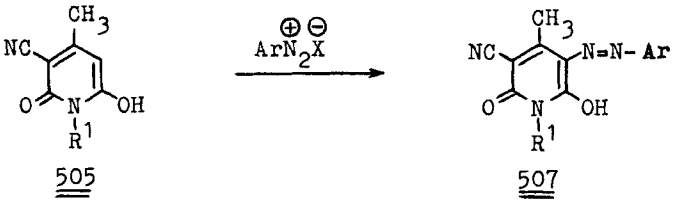
Scheme 213

It has been noted that the 6-hydroxy-3-cyanopyridin-2(1*H*)-ones **505** form the 5-(alkylaminomethyl)-pyridines **506** when subjected to Mannich conditions.[390]



Scheme 214

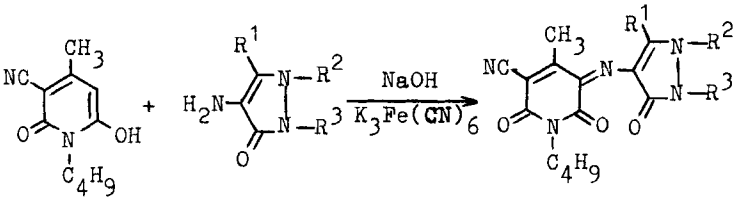
The pyridones **505** couple with diazonium salts to form the azo dyes and pigments **507**.[391-397]



505 507

Scheme 215

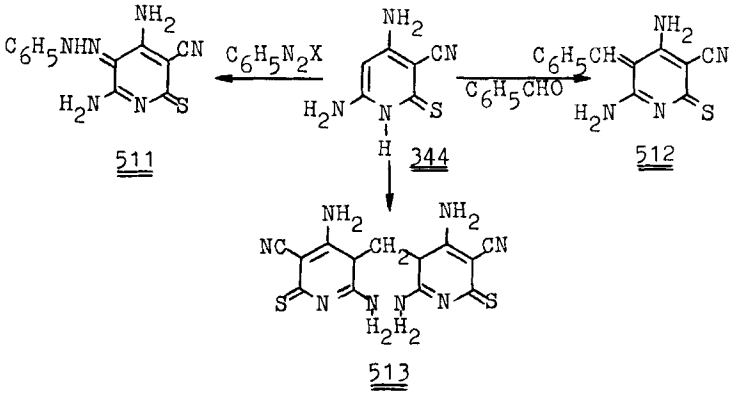
When 1-butyl-6-hydroxy-4-methyl-3-cyanopyridin-2(1*H*)-one **508** reacts with a 4-aminopyrazolone **509** in water in the presence of NaOH, followed by oxidation with potassium ferricyanide in aqueous sodium hydrogen carbonate, compound **510** is formed.[398]



508 509 510

Scheme 216

The authors of refs.[229,230] have studied the chemical properties of 4,6-diamino-3-cyanopyridine-2(1*H*)-thione **344** (X = S), among other things a number of reactions involving the vacant position 5 of **344**; the latter result in the formation of the azo compounds **511** and the condensation products **512** and **513**.



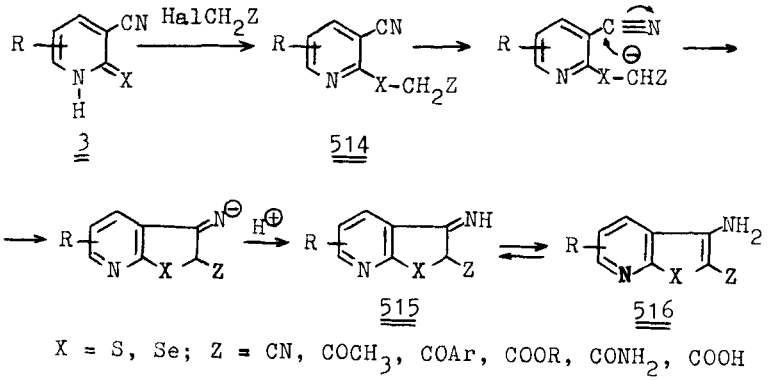
511 344 512 513

Scheme 217

4.5. Synthesis of Furo(Thieno, Selenopheno)[2,3-b]pyridines and then, on Their Basis, Condensed Heterocycles

3-Cyanopyridin-2(1*H*)-ones, -thiones, and -selenones are bifunctional compounds. As a rule, in the synthesis of condensed heterocyclic compounds, modification of both functional groups (amide and nitrile) occurs; these groups take part in the formation of the new ring.

One of these important reactions is the synthesis of substituted 3-aminofuro(thieno, selenopheno)[2,3-*b*]pyridines by the Thorpe–Ziegler reaction. This reaction may be presented as follows:[4]



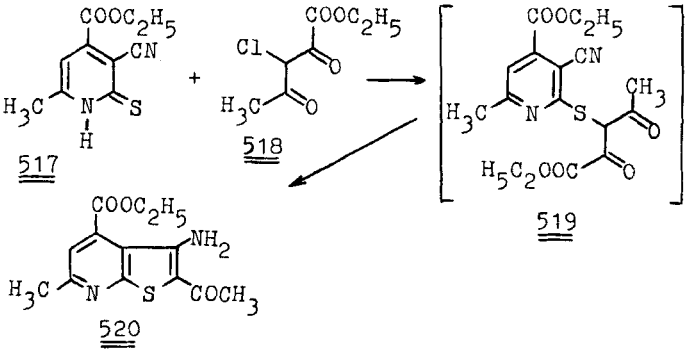
Scheme 218

The direction of the cyclization and its ease are determined by the relative mobility of the hydrogen atoms of the methylene group as well as by the electrophilic character of the nitrile group. The reaction may be catalyzed by both bases and acids. Bases promote the deprotonation of the methylene group. The greater the electronegativity of the substituent Z the faster is the cyclization proceeds. It has been quantitatively determined that the rate of the cyclization of **514** to **516** decreases, depending on the electronegativity of Z, in the following order: NO_2 > ArCO > CN > $CO_2C_2H_5$ > $CONH_2$ > H. Esters of α-haloacetic acids (Z = CO_2CH_3, $CO_2C_2H_5$), the corresponding amides (Z = $CONH_2$, CONHR), chloro- and bromoacetic acid (Z = COOH), α-halo ketones (Z = $COCH_3$, COC_6H_5), chloroacetonitrile (Z = CN), and other compounds have been used as the halogen derivatives $HalCH_2Z$.

Vicinal hydroxy nitriles react with halogen derivatives of methylene active compounds with formation of 2-alkoxypyridines **514**. Cyclization of the latter under Thorpe conditions leads to 3-aminofuro[2,3-*b*]pyridines **516**.[4,268,399,400] The cyclization occurs upon heating of the *O*-alkyl derivatives for several minutes in the presence of sodium ethoxide.[400,401] In some cases the reactions are carried out without isolation of the 2-alkoxy-3-cyanopyridines **514**, thus yielding the furopyridines **516** directly in a yield of 60–95%.[400,402,403] The presence of bulky substituents in position 6 of the pyridone promotes *O*-alkylation.

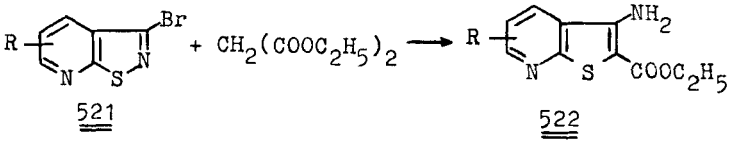
The synthesis of 3-amino-2-Z-thieno(selenopheno)[2,3-*b*]pyridines is carried out in ethanol or DMF. Alkali metal alkoxides, aqueous alkali metal hydroxides, and organic bases (diethylamine, triethylamine, morpholine) have been used as catalysts. The tautomeric equilibrium **515** ⇄ **516** is completely displaced towards the amino form **516**. This method has been used to obtain a number of 3-aminothiophenes and -selenophenes, annelated with a pyridine, quinoline, or isoquinoline ring, as well as with a steroid skeleton or other systems.[4,7,11,21,24,26,37,38,40,41,45,47,49-53,57,114,155,157,160,163,164, 172,185,197,204,211,212,214,217-220,227,274-279,404-409]

In the synthesis of 3-amino-2-Z-thieno[2,3-*b*]pyridines, 2-halo derivatives of 1,3-dicarbonyl compounds have been used. By alkylation of 6-methyl-3-cyano-4-ethoxycarbonylpyridine-2(1*H*)-thione **517** with **518**, followed by hydrolysis of intermediate **519**, and finally cyclization according to Thorpe, 3-amino-2-acetyl-6-methyl-4-ethoxycarbonylthieno[2,3-*b*]pyridine **520** has been synthesized.[43,44]



Scheme 219

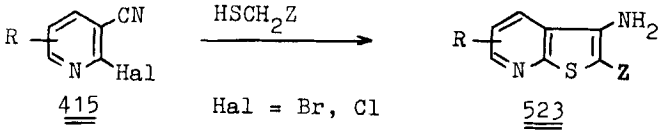
3-Aminothieno[2,3-*b*]pyridines have been prepared by recyclization of the 3-bromoisothiazolo[5,4-*b*]pyridines **521**.[410] When **521** interact with malonic ester in the presence of base 3-amino-2-ethoxycarbonylthieno[2,3-*b*]pyridines **522** are formed.



Scheme 220

3-Aminothieno[2,3-*b*]pyridines have also been obtained by treatment of 2-halo-3-cyanopyridines with methylene active thiols in the presence of base.[288,411-417]

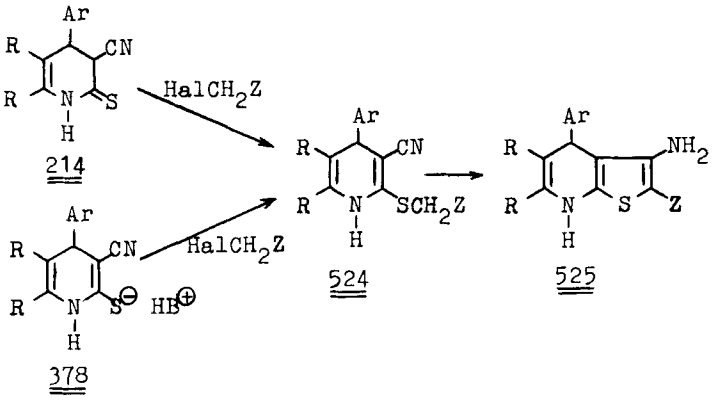
Reaction of 3-cyano-2-halopyridines **415** with alkanethiols leads to 3-aminothieno-[2,3-*b*]pyridines **523** in yields of up to 90%.[105,417]



415 523

Scheme 221

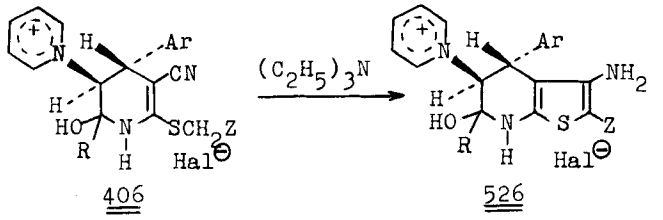
From 3-cyano-3,4-dihydropyridine-2(1*H*)-thiones **214** or their salts **378** the hydrogenated 3-aminothieno[2,3-*b*]pyridines **525** have been obtained.[152,159,167,183,193,195,283]



214 524 525 378

Scheme 222

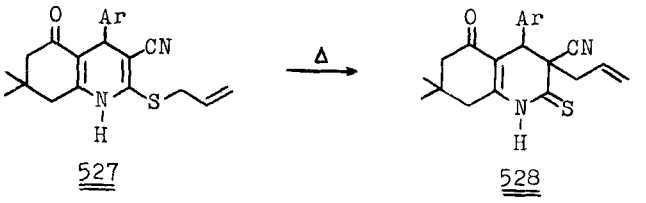
The synthesis of **525** can be carried out in one stage without isolation of the 2-alkylthiopyridines **524** in the presence of excess base. Starting from the salts **406** the hydrogenated 3-aminothieno[2,3-*b*]pyridines **526** have been synthesized.[418] The *trans*-relationship of Ar and Py^+ does not change during this reaction.



406 526

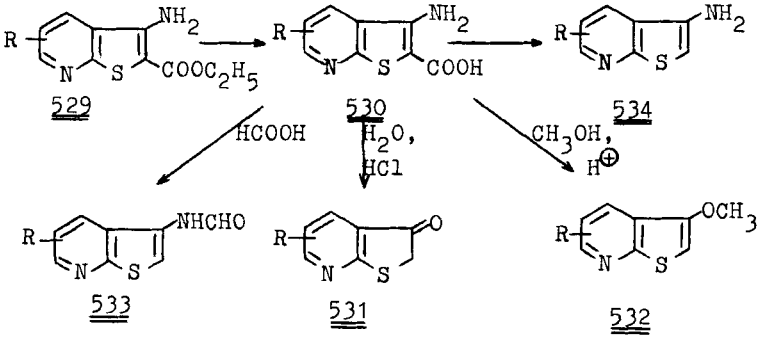
Scheme 223

Reactions of the 2-allylthioquinolines **527** under thermodynamic control proceed in a characteristic way. When **527** are heated in organic solvents or in the solid state a [3,3]-sigmatropic rearrangement, not cyclization to the corresponding thienoquinoline, occurs with migration of the allyl group to position 3 of the pyridine ring leading to the thiones **528** in high yields.[419]



Scheme 224

From 3-amino-2-Z-thieno[2,3-*b*]pyridines different derivatives can be obtained. 3-Aminothieno[2,3-*b*]pyridines with an ethoxycarbonyl or carboxyl function in position 2 are of substantial interest in this respect.[21,274,288,404,408,420,421] 3-Amino-2-ethoxycarbonylthieno[2,3-*b*]pyridine **529** hydrolyzes in the presence of base to 3-aminothieno-[2,3-*b*]pyridine-2-carboxylic acid **530**, stable in the crystalline state.

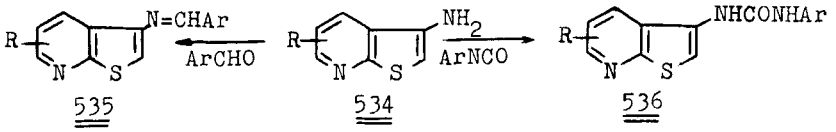


Scheme 225

The acids **530** can also be prepared in one step from the corresponding pyridinethiones and α-haloacetic acids.[274,408] The compounds **530** are used for the synthesis of 3-substituted thieno[2,3-*b*]pyridines. Thus, their decarboxylation has been studied under a variety of conditions. Compounds **530**, when boiled in water in the presence of hydrochloric acid, are subject not only to decarboxylation, but also to oxidative deamination with formation of the 3-oxo-4,6-dimethyl-2,3-dihydrothieno[2,3-*b*]pyridines **531**. With methanol as the solvent, the decarboxylation taking place upon heating of the acidified reaction mixture is followed by condensation to 3-methoxy-4,6-dimethylthieno-[2,3-*b*]pyridines **532**.[404] With formic acid as the catalyst the decarboxylation leads to 3-formylamino-4,6-dimethylthieno[2,3-*b*]pyridines **533**.[421]

3-Amino-4,6-dimethylthieno[2,3-*b*]pyridines **534** have been obtained by decarboxylation of **530** in absolute ethanol at 60–70 °C in the presence of acetic acid.[404] However, use of phosphoric acid yields better results. In this case **534** is formed in close to quantitative yields.[274] 3-Aminothieno[2,3-*b*]pyridine has also been obtained by reduction of 3-nitrothieno[2,3-*b*]pyridine;[422] however, the yield is much lower than that of the decarboxylation procedure.

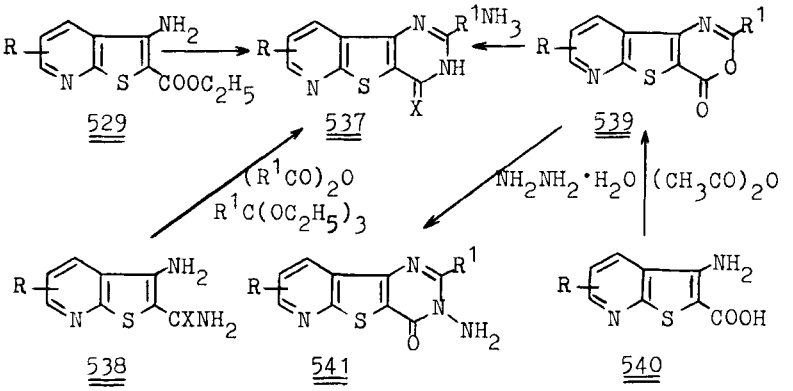
3-Aminothieno[2,3-*b*]pyridines **534** possess the characteristic properties of aromatic amines. They react with aromatic aldehydes to form the Schiff bases **535**. Their reaction with isocyanates results in the formation of the ureas **536**.[41,274]



Scheme 226

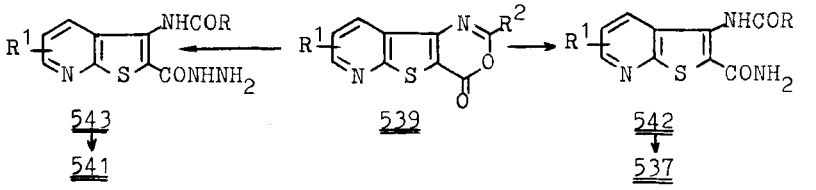
3-Aminothieno(selenopheno)[2,3-*b*]pyridines are used to prepare condensed heterocycles. Many of the syntheses described so far had biologically active compounds as their aim.

4-Oxo(thio)pyrido[2′,3′:5,4]thieno[2,3-*d*]pyrimidines **537** have been synthesized from **529** by different methods: condensation of the esters **529** with formamide, treatment of the amides **538** with orthoformate, acylation with acetic anhydride and subsequent intramolecular condensation.[288,404,415,421,423-426] Pyrido[2′,3′:5,4]thieno[2,3-*d*]oxazine-4-ones **539**,[423,424] obtained from the 3-amino-2-carboxythieno[2,3-*b*]pyridines **540** and acetic anhydride, have been used in the synthesis of 4-oxopyrido[2′,3′:5,4]thieno-[2,3-*d*]pyrimidines.



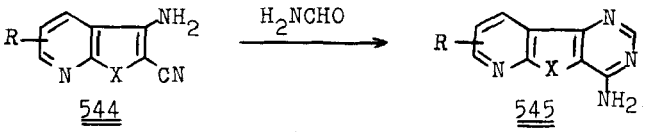
Scheme 227

Compounds **541** have been synthesized by condensation of the oxazinones **539** with hydrazine hydrate.[424] It was first shown in ref.[274] that the formation of the annelated heterocycles **537** and **541** from **539** occurs via the intermediates **542** and **543**, respectively.



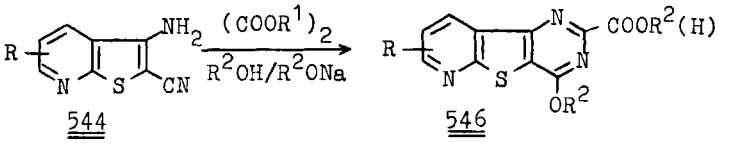
Scheme 228

Condensation of the 3-amino-2-cyanothieno(selenopheno)[2,3-*b*]pyridines **544** with formamide gives high yields of the annelated pyrimidines **545**.[24,26,41,45,46,49,185,217-219,279,404,409,427] Many of the abovementioned reactions have also been used in the synthesis of new selenium-containing heterocyclic systems.



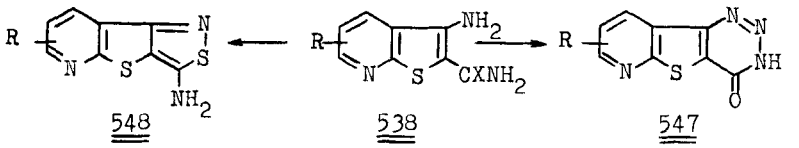
Scheme 229

Condensation of the 3-amino-2-cyanothieno[2,3-*b*]pyridines **544** (X = S) with dialkyl oxalates in the presence of sodium alkoxides leads to the 4-alkoxypyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimido-2-carboxylates **546**.[427-429]



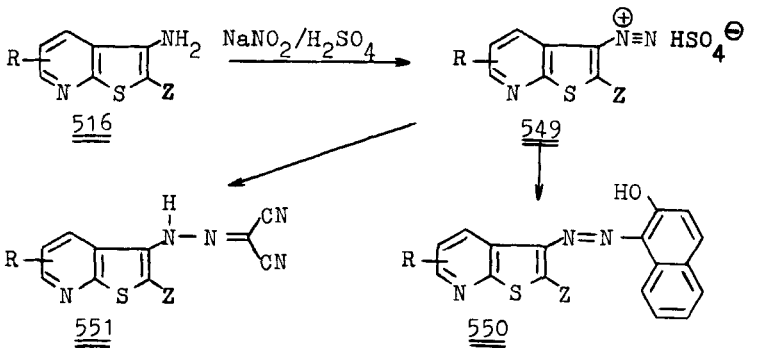
Scheme 230

3-Amino-2-carbamido(thiocarbamido)thieno[2,3-*b*]pyridines **538** have been used for the preparation of the annelated triazines **547**.[423]



Scheme 231

Condensed 3-aminothieno[2,3-*b*]pyridines, like aromatic amines, can be diazotized with sodium nitrate in glacial acetic acid in the presence of concentrated sulfuric acid. The diazonium salts **549** couple with 2-naphthol with formation of the azo dyes **550**. The azo compounds **550**, useful as indicators, undergo pH dependent color changes.[185,217]



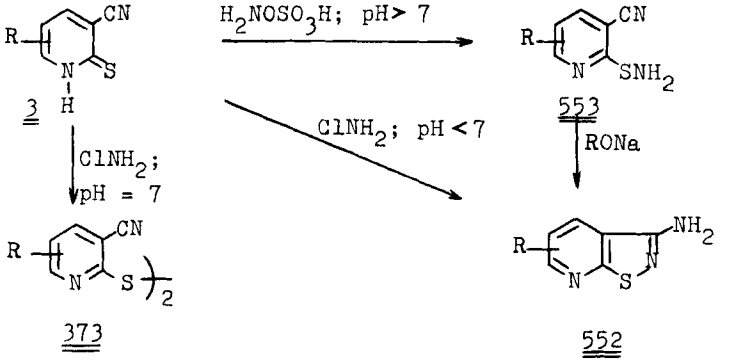
Scheme 232

The diazonium salts **549** also react with CH-acids to form **551**.[217]

4.6. Synthesis of Isothiazolo[5,4-b]pyridines and Other Condensed Pyridines

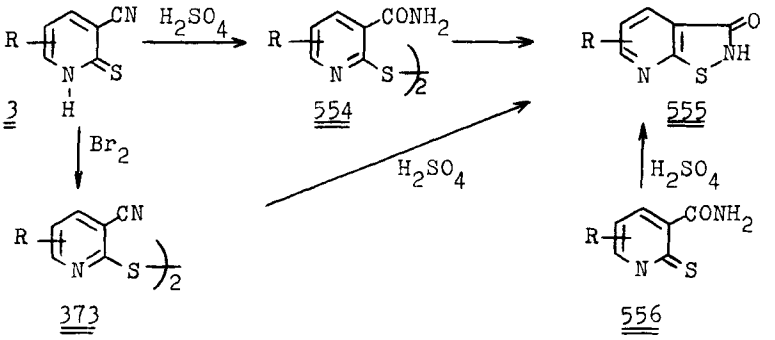
3-Cyanopyridine-2(1*H*)-thiones react with chloramine, sulfamic acid,[430,431] sulfuric acid, and bromine[256,432] as well as with hydroxylamine[433] and ammonia in the presence of oxidants to form isothiazolopyridines.[434]

This reaction depends on the reaction conditions, the pH of the medium, and the character of the aminating agent.[430] With chloramine as the reagent the 2,2′-bis(3-cyanopyridyl) disulfides **373** are formed at pH 7; with pH < 7 the 3-aminothiazolo[5,4-*b*]pyridines **552** form directly. At pH 7 **373** forms in a mixture of sulfamic acid and the corresponding 3-cyanopyridine-2(1*H*)-thione. However, at pH > 7 the 2-aminothio-3-cyanopyridines **553** are obtained; **553** cyclize to the corresponding isothiazolopyridines **552** upon heating in ethanol in the presence of sodium ethoxide.



Scheme 233

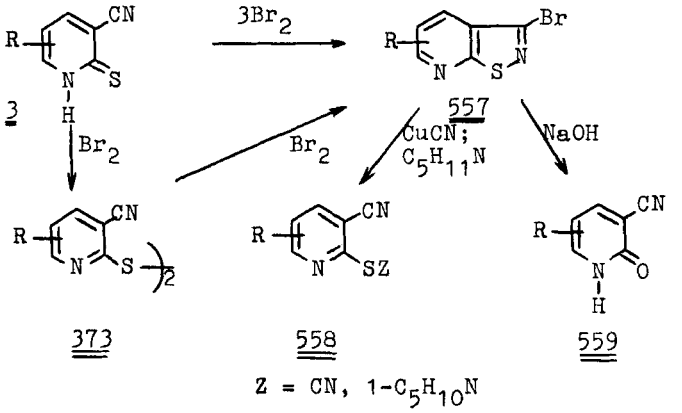
The synthesis of 3-oxo derivatives of isothiazolo[5,4-*b*]pyridines from 3-cyanopyridine-2(1*H*)-thiones by heating in sulfuric acid is of practical importance.[256,432]



Scheme 234

The 3-oxoisothiazolo[5,4-*b*]pyridines **555** have been obtained from the disulfides **373** as well as from the 3-carbamoylpyridine-2(1*H*)-thiones **556**.[256] The authors of ref.[256] showed that the conversion of 3-cyanopyridine-2(1*H*)-thiones to **555** proceeds via intermediate **373**. However, in earlier work[432] presenting this synthesis for the first time it was shown that the 2,2-bis(3-carbamoylpyridyl) disulfide **554** is the intermediate. Evidently, **556** is oxidized to **554** and subsequent intramolecular cyclization results in the formation of **555**. The isothiazolopyridine **555** is formed in a similar manner from **373** via its hydrolysis to **554** with subsequent intramolecular cyclization.

3-Cyanopyridine-2(1*H*)-thiones, when heated in dry chloroform with excess bromine, form 3-bromoisothiazolo[5,4-*b*]pyridines **557**.[256,410] The reaction probably involves intermediate **373**. Compounds **557** are used in the synthesis of substituted pyridines.[256,410]

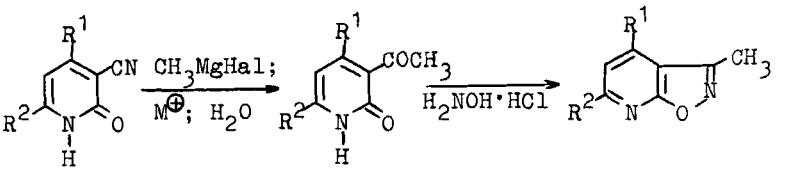


373 558 559

Scheme 235

When reacting with nucleophilic reagents the isothiazolopyridines **557** open their isothiazole ring with formation of the pyridines **558** and **559**.

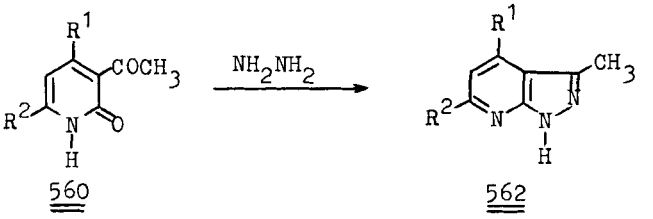
The isoxazolopyridines **561** have been obtained by treatment of the 3-acetylpyridin-2(1*H*)-ones **560** with hydroxylamine hydrochloride in acetic acid.[161,264]



489 560 561

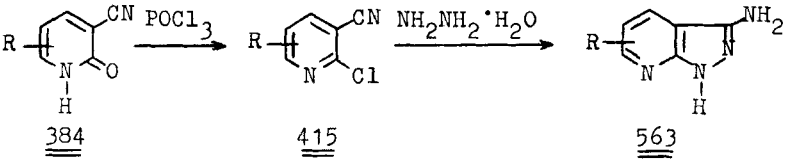
Scheme 236

Treatment of **560** with hydrazine leads to the 3-methylpyrazolo[5,4-*b*]pyridines **562**.[161]



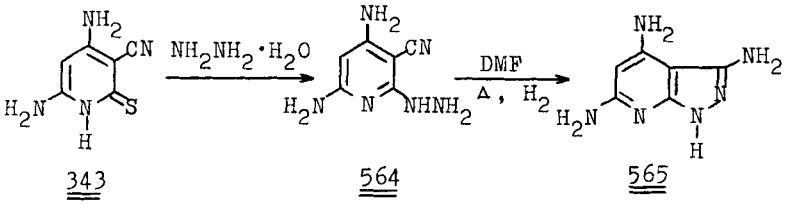
Scheme 237

3-Aminopyrazolopyridines can be obtained from both pyridines and pyridinethiones. It has been shown that the reaction of 2-halo-3-cyanopyridines with hydrazine hydrate proceeds with formation of the 3-aminoisopyrazolopyridines **563** which are used as thrombosis inhibitors[312] and as intermediate in the synthesis of azo dyes.[311]



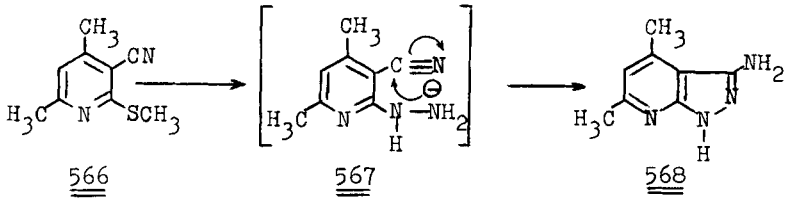
Scheme 238

The reaction of 4,6-diamino-3-cyanopyridine-2(1*H*)-thione **343** with hydrazine hydrate leads to the 2-hydrazinopyridine **564** which then cyclizes to 3-aminoisoxazolopyridine **565** upon hydrogenation in hot DMF.[229]



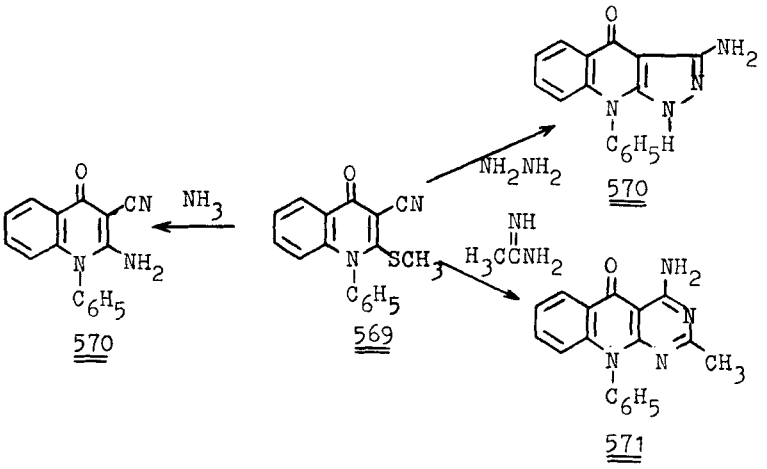
Scheme 239

The reaction of 4,6-dimethyl-2-methylthio-3-cyanopyridine **566** with hydrazine gives 3-amino-4,6-dimethylpyrazolo[5,4-*b*]pyridine **568**.[255] Probably this reaction proceeds as a nucleophilic substitution via the intermediate **567**.[435]



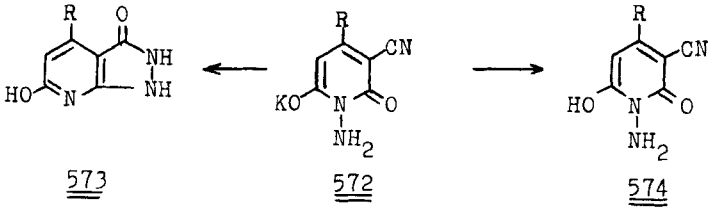
Scheme 240

This reaction has been studied in more detail in the case of 1-phenyl-2-methylthio-3-cyano-4-oxoquinoline **569**.[436] When **569** was allowed to react with ammonia the amine **570** was formed. The difficultly accessible heterocyclic systems **571** and **572** could be conveniently obtained by treatment of **569** with hydrazine and acetamide, respectively.



Scheme 241

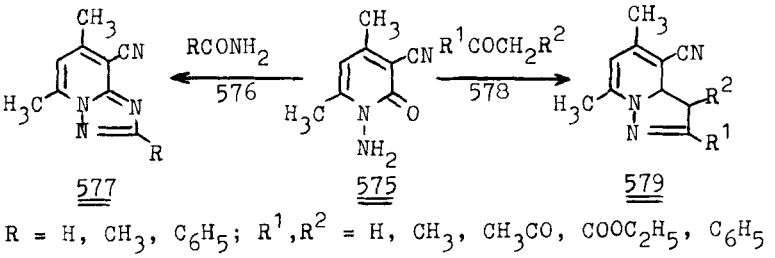
1-Amino-3-cyano-2-pyridones possess a considerable synthetic potential.[437-440] Treatment of the pyridinethiolates **572** (R = CF_3, $CO_2C_2H_5$), i.e. with a strong electron acceptor group at C^4, with dilute hydrochloric or acetic acid, causes cyclization to the pyrazolopyridinones **573**. The pyridinolates **572** on the other hand, yield the 6-hydroxy-3-cyanopyridones **574**.[437]



Scheme 242

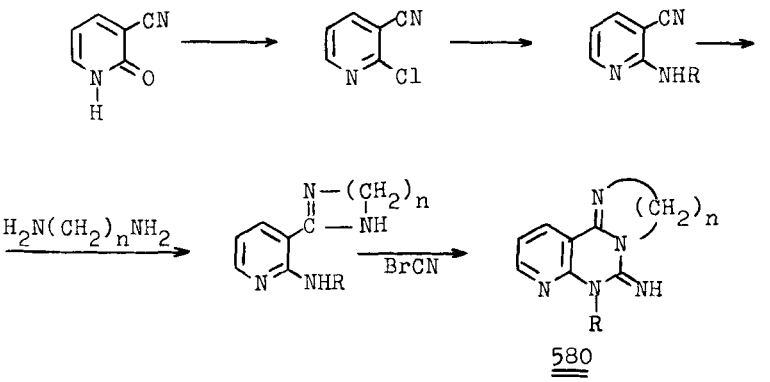
When the aminopyridones **575** react with amides **576** 1,2,4-triazolo[1,5-*a*]pyridines **577** are formed in high yield. The reaction is carried out by heating in DMF in the presence of catalytic amounts of anhydrous zinc chloride.[439]

Use of the ketones **578** in this reaction leads to the pyrazolo[1,5-*a*]pyridines **579**.[440] This allows the introduction of different substituents in positions 2 and 3 of **579**; polycondensated nitrogen-containing heterocyclic systems are obtained.



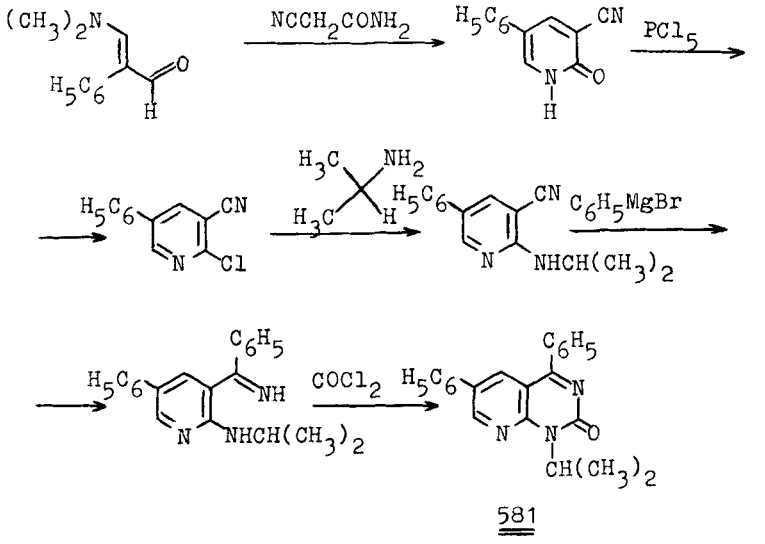
Scheme 243

3-Cyanopyridin-2(1*H*)-ones have been used in the synthesis of the iminopyrido[3,2-*e*] pyrimidines **580**[313]



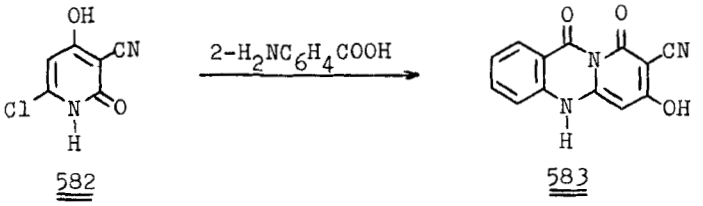
Scheme 244

and the 1,2-dihydropyrido[2,3-*d*]pyrimidines **581**.[62]



Scheme 245

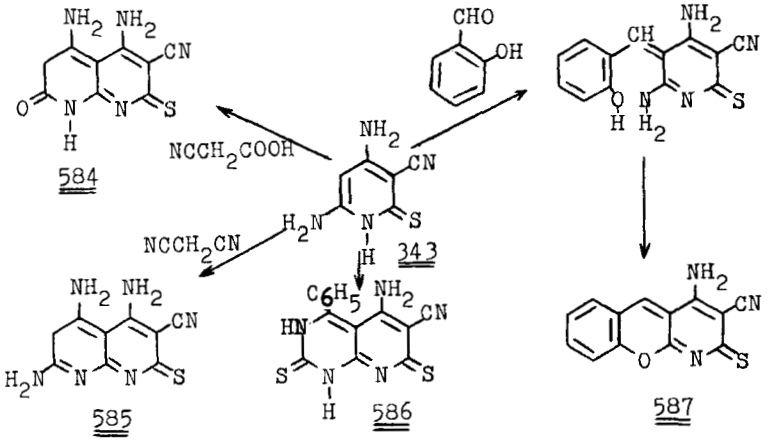
When 6-chloro-3-cyanopyridin-2(1*H*)-one **582** is treated with *o*-aminobenzoic acid substitution of the chlorine occurs with formation of the annelated pyridone **583**.[441]



582 583

Scheme 246

In analogy with the abovementioned reactions, 4,6-diaminopyridinethione **343** is useful in the synthesis of the condensed systems **584–587**.[229,230]



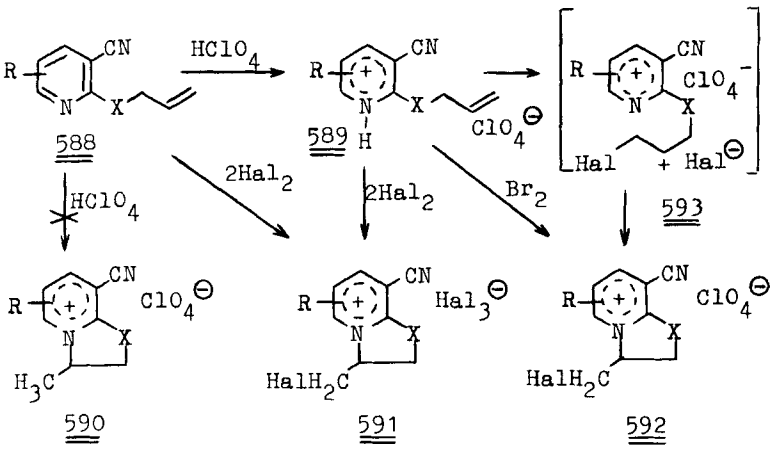
584 343 585 586 587

Scheme 247

4.7. Synthesis and Stereochemistry of Thiazolo(Selenazolo)[3,2-a]pyridinium Salts

The 2-allylthio(seleno)pyridines **588** and the 2-[2-cyclohexen-1-ylthio(seleno)]pyridines **595**, obtained from 3-cyanopyridine-2(1*H*)-thiones or -selenones and allyl halides, have been found to be convenient reagents for the synthesis of thiazolo(selenazolo)[3,2-*a*]-pyridinium salts.[25,49,53,54,172,204,205,231,442–444]

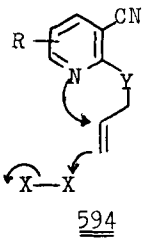
The reactions of **588** with electrophilic reagents (chlorine, iodine, bromine, perchloric acid) can take different directions, depending on the nature of the electrophile. The reaction of **588** with perchloric acid leads to the pyridinium perchlorates **589**, not to the thiazolo(selenazolo)[3,2-*a*]pyridinium salts **590**. This can be explained by the relatively high basicity of the pyridine ring.[25] The perchlorates **589** do not cyclize to **590** under more severe conditions such as boiling in acetic acid. However, when **588** react with two equivalents of bromine or iodine a highly regioselective heterocyclization occurs with formation of the thiazolo(selenazolo)pyridinium trihalides **591**.



Scheme 248

The compounds **591** are formed from **589** with bromine or iodine in acetic acid at 25 °C. Reaction with one equivalent of bromine at 90–100 °C results in the formation of the perchlorates **592**.[25]

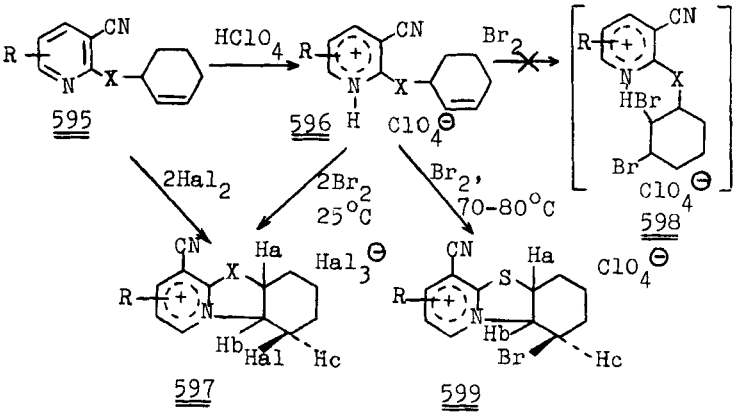
The quaternization of **588** to **591** is an electrophilic process. The electrophilic character of the quaternization is obvious in the case of the formation of **591** and **592** from **589**. Here the quaternization proceeds as an intramolecular electrophilic substitution of a proton by a carbocation via the intermediate **593**.[25] The high acidity of the reaction medium prevents an alternative quaternization by addition and subsequent nucleophilic substitution. The quaternization of **588** and **591** is assumed to be a concerted process;[25] the electrophilic attack on the allylic double bond of **588** and the quaternization occur synchronously via intermediate **594**.



Scheme 249

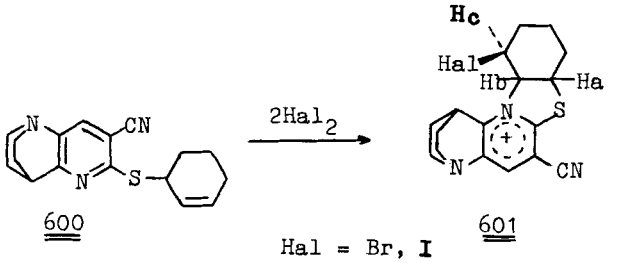
However, the electrophilic quaternization of allylthio(seleno)pyridines does not permit an analysis of the stereochemistry of this reaction. In order to refine this picture the reactions of 2-[2-cyclohexen-1-ylthio(seleno)]pyridines **595** with different electrophilic reagents have been studied, and the structures of the so formed annelated pyridinium salts investigated.[445,446] The reactions of **595** with bromine, iodine, or perchloric acid proceed in different directions. The reaction of **595** with perchloric acid, like that of **588**, leads to the corresponding pyridinium perchlorates **596**. The reaction of **595** with two

moles of halogen gives the thiazolo(selenazolo)[3,2-*a*]pyridinium trihalides **597**. The triiodides **597** (Hal = I) are always formed independently of the added amount of iodine. The corresponding quaternized azines **597** have also been obtained by bromination of **596** in acetic acid at 25 °C. The direction of this reaction depends on the temperature and includes the possibility of quaternization by the nucleophilic mechanism via intermediate **598**. When **596** are brominated in acetic acid at 70–80 °C the benzothiazolo[3,2-*a*]pyridinium perchlorates **599** are formed.



Scheme 250

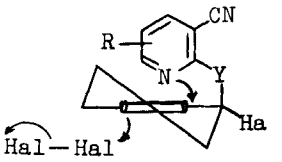
According to the NMR and X-ray diffraction data of 4-iodo-6,8-dimethyl-9-cyano-1,2,4,4a,10a-hexahydrobenzothiazolo[3,2-*a*]pyridinium triiodide[445,446] the electrophilic quaternization of **595** to **597** is a highly stereoselective process. The protons H_a and H_b have a *cis*-configuration and the protons H_b and H_c *trans*-configuration. The same stereochemistry was observed in the reactions of the quinuclidinopyridines **600** with halogens which lead to the difficultly accessible annelated heterocycles **601**.[447]



Scheme 251

X-Ray diffraction analysis of **600** showed that the nitrogen atom of the pyridine ring is in close contact with the C=C double bond of the cyclohexene moiety.[447] It is the closeness of these reaction centres which favors this synchronous process with a high degree of stereoselectivity. The high stereoselectivity involving the two proton systems H_a, H_b and H_b, H_c is probably due to the transition state **602** and determined by the synchronous effects of a donor (the electron pair of the pyridine nitrogen atom) and an

acceptor (the halogen molecule) on the π-electrons of the multiple bond of the cyclohexene moiety.

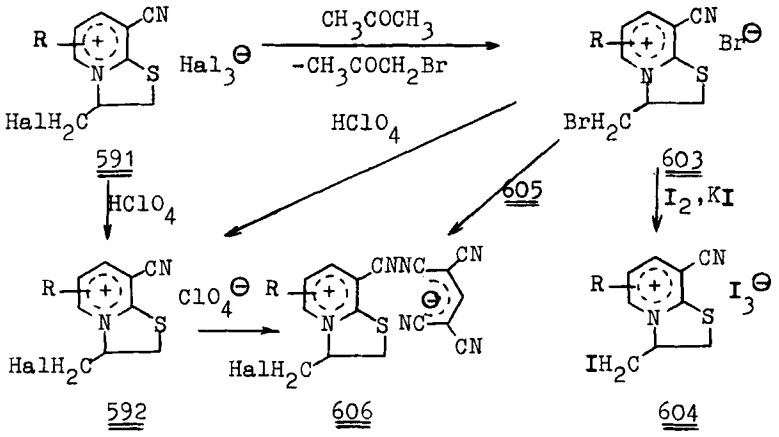


602

Scheme 252

The donor and the acceptor affect the π-electrons of the double bond from transoid positions. The position of proton H_a is firmly locked in the transition state while the protons H_b and H_c are coplanar with the planar part of the cyclohexene system. The subsequent electrophilic rupture of the multiple bond and the electrophilic quaternization occur synchronously; during this process the protons H_b and H_c move into *trans*-positions opposite to the transoid orientation of the donor and the acceptor. Thus, the intramolecular electrophilic quaternization of 2-cyclohexen-2-ylthio(seleno)pyridines proceeds as a synchronous *trans*-quaternization with *cis*-annelation to yield a hexahydrobenzothiazolo(selenazolo)[3,2-*a*]pyridinium salt.

Reactions of the quaternized azines **591** and **597** which affect the anionic part of the molecule have also been studied.[25,49,53,443] When the tribromides **591** react with acetone the bromides **603** and bromoacetone are formed. The corresponding triiodides are more stable. They do not react with acetone under similar conditions. The tribromides and triiodides **591** react with perchloric acid to form the perchlorates **592**. The bromides **603** reacts with iodine and potassium iodide with formation of the triiodides **604**. However, it has been found that the 1,1,3,3-tetracyanopropenide anion is the most active in this anion exchange. The perchlorates **592** and the bromides **603** react with sodium 1,1,3,3-tetracyanopropenide **605** with displacement of perchlorate or bromide, respectively, and formation of the 1,1,3,3-tetracyanopropenylide of thiazolo[3,2-*a*]pyridinium **606**.[25,445]

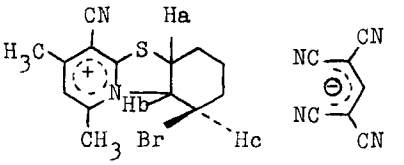


Scheme 253

The capacity to displace anions from thiazolo(selenazolo)[3,2-*a*]pyridinium salts depends on the nature of the anion, especially its basicity. The reactivity changes in the following order:[25]

$$(NC)_2CCHC(CN)_2^- > ClO_4^- > I^- > Br^-$$

A similar order of anion exchange is observed in a series of benzothiazolo(selenazolo)-[3,2-*a*]pyridinium salts **607**.[445,448]



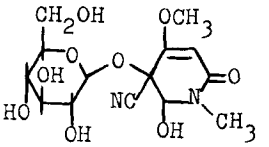
607

Scheme 254

By NMR spectroscopy and X-ray diffraction analysis of **607** it was found that the stereochemistry of the heterocyclic cation is not affected by the anion exchange.

5. CERTAIN ASPECTS OF PRACTICAL APPLICATION

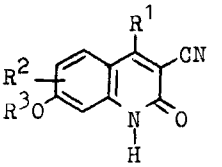
In addition to some practical uses noted in the previous chapters, useful biologically active compounds have been developed on the basis of 3-cyanopyridin-2(1*H*)-ones. Several of them, for instance *N*-methyl-4-methoxy- and *N*-methyl-4-amino-3-cyano-2-pyridones, with an effect on fermentative activity, have been isolated from green plants.[326,449-451] A new type of glycoside **608** has been isolated from plants and characterized.[451]



608

Scheme 255

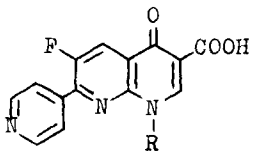
Substituted 3-cyanoquinolin-2(1*H*)-ones have found wide application as enzyme substrates in the determination of glycosides in clinical analysis.[452]



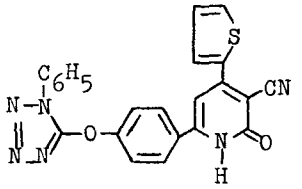
609

Scheme 256

Not only 3-cyanopyridin-2(1*H*)-ones, but also their derivatives have been proposed as active ingredients of fungicidal and antimicrobial preparations.[315,453] Thus, 6-aryl-4-(furyl)- and 6-aryl-4-(thienyl-2)-3-cyanopyridin-2(1*H*)-ones display antimicrobial and fungicidal activity.[454] High antibactericidal activity against *Staphylococcus aureus 209 P C-1* and *Escherichia coli NIHF C-2* has been demonstrated *in vitro* for **610** (R = C_2H_5, CH_2CH_2F, $CH{=}CH_2$), obtained from 6-(4-pyridyl)-3-cyanopyridin-2(1*H*)-one in several steps.[455] The most active against *Pseudomonas aeruginosa 12* is the naphthyridone **610** (R = cyclopropyl). The pyridone **611** is active against *Staphylococcus aureus S-A*.[456]



610



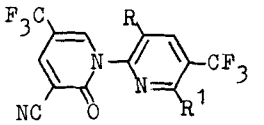
611

Scheme 257

5-Nitro-2-chloro-3-cyanopyridine, obtained from the corresponding pyridone, when used in a dose of 500 mg prevents the development of *Pythium ultimum* more effectively than tetramethylthiuram disulfide.[457] 5-Nitro-2-pyrrolidino-3-cyanopyridine is an insecticide active against *Phisfabae* and *Megoura vicia*.[457]

Phosphorylated 3-cyanopyridines in a concentration of 0.001% are lethal for *Musca domestica*.[294] Also active acaricides have been found among the abovementioned pyridones.

The dipyridyls **612** exhibit insecticidal activity against German cockroaches.[458]



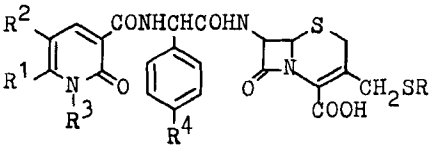
612

R = F, Cl; R^1 = H, F, Cl

Scheme 258

Among the 3-cyanopyridin-2(1*H*)-ones as well as among the substituted nicotinic acids derived from the herbicides suitable as plant growth regulators have been found.[332-334,459] *N*-Substituted 4,6-dimethyl-3-carboxy-2-pyridones have been patented as growth regulators of plants and as nematocides.[332,334]

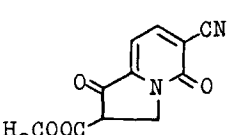
Starting from 3-cyanopyridin-2(1*H*)-ones a series of pharmaceutical preparations have been developed. Bactericides derived from ampicillin and inhibiting *Staphylococcus aureus* in a dose of 0.39 mg/kg show promise.[337,339] Analogous derivatives of cephalosporic acid **613** synthesized from 3-cyanopyridin-2(1*H*)-ones are used as bactericides against Gram positive and Gram negative bacteria.[460]



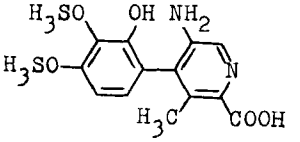
613

Scheme 259

3-Cyanopyridin-2(1*H*)-ones have been used in the synthesis of the antitumor compounds **614** and **615**.[287,461]



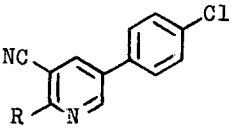
614



615

Scheme 260

Some 2-substituted 3-cyanopyridines exhibit moderate antitubercular activity.[320] The possibility of the use of 3-cyanopyridin-2(1*H*)-ones in antiinflammatory preparations has been studied on several examples. 5-(4-Chlorophenyl)-3-cyanopyridin-2(1*H*)-ones[462] and their derivatives **616** substituted in position 2[463] are used as antiinflammatory agents in a dose of 0.5–150 mg/kg.



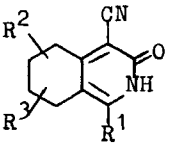
616

R = OH, OCH_2COOH, $(CH_3)_2NCH_2CH_2NH$

Scheme 261

2,6-Dihydroxy-3-carbamoyl-4-methylpyridine, formed by hydrolysis of the corresponding 3-cyanopyridin-2(1*H*)-one, exhibits antiinflammatory and sedative activity.[326]

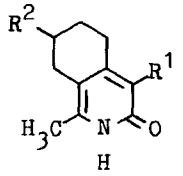
Among the 3-cyanopyridin-2(1*H*)-ones also the effective cardiotonics **617** have been found.[464–467] Compound **617** (R^1 = CH_3; R^2 = 4-pyridyl; R^3 = H) in a dose of 0.1 mg/kg causes in dogs a blood pressure decrease of 8.7% and a heart rate increase of 27.6%.[465]



617

Scheme 262

A substantial cardiotonic activity is also displayed by **618**, obtained in a number of cases from **617**.[342]

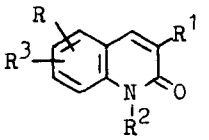


618

R^1 = H, Hal, NO_2, CH_3CO; R^2 = H, CH_3, CH_3O, C_6H_5, 2-, 4-Py

Scheme 263

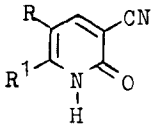
A large group of hetarylquinolin-2(1*H*)-ones **619** possesses inotropic effects.[468]



619

Scheme 264

Together with the condensed systems **618** and **619** the 5,6-disubstituted 3-cyanopyridin-2(1*H*)-ones **620** have been patented as cardiotonics.[81,86-89,92-94,362,367,469-477]



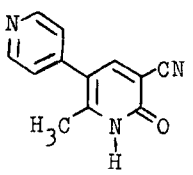
620

Scheme 265

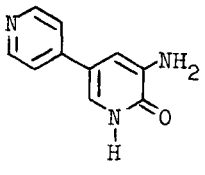
Because of the large number of compounds of this type this review only discusses the most typical and active ones.

In a series of 5-(4-thiazolyl)pyridin-2(1*H*)-ones[89,92,367] the most pronounced cardiotonic activity was shown by 5-[2-(4-pyridyl)4-thiazolyl]-6-methyl-3-cyanopyridin-2(1*H*)-one[92] which, administered in a dose of 10^{-5} g/ml, increases the contraction of the left artery of guinea pigs by 116% *in vitro*.

The 6-substituted 5-(4-pyridyl)-3-cyanopyridin-2(1*H*)-ones **620** (R = 4-pyridyl) have recently attracted much interest as cardiotonics. The most useful are milrinone **621** and its analogs.[83,362,470,472-476] The cardiotonic **621** and its analog amrinone **622** possess a high inotropic effect with insignificant side effects.[67,472-474]



621

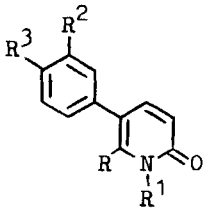


622

Scheme 266

The pyridones **620** (R = 4-pyridyl; $R^1 = C_4H_7OCH_2$)[477] and **620** (R = 4-pyridyl; $R^1 = CH(OH)OCH_3$),[87] administered in a dose of 10^{-4} mol, cause increased contraction of the papillary muscles in guinea pigs *in vitro* by 44 and 72%, respectively. Substitution with a cyclopropyl group in position 6 increases the activity. Thus, **620** (R = 4-pyridyl; R^1 = cyclopropyl) in a dose of 10^{-5} mol increases the contraction of the papillary cardiac muscles in guinea pigs by 117%.[86]

High cardiotonic activity was also observed with 5-phenyl substituted pyridones **623**, obtained by hydrolysis of the corresponding 3-cyanopyridin-2(1*H*)-ones.[85,344]



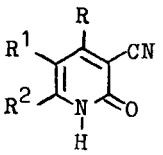
623

Scheme 267

5-(4-Hydroxyphenyl)-6-methylpyridin-2(1*H*)-one **623** (R = CH_3; $R^1 = R^2 = H$; R^3 = OH) increases the strength of the papillary muscles and the contraction of the right artery in cats by 86 and 77%, respectively, at a dose of 10 mg/ml.[344]

6-Methyl-5-(4-methylsulfinylphenyl)pyridin-2(1*H*)-one **623** (R = CH_3; $R^1 = R^2$ = H; $R^3 = NOCH_3$), administered *in vitro* in doses of 30, 100, and 300 mg/kg, increases the strength of the systole in dogs by 43 and 153% with relatively small changes in the cardiac rhythm and the blood pressure.[85].

A significant increase of the strength of the contractions of the heart in anesthetized dogs was caused by the 5-substituted 3-cyanopyridin-2(1*H*)-ones **620** (R = pyrimidyl, pyrazinyl, pyridazinyl; R^1 = H).[68] The pyridones **12** (X = O) and their salts have been proposed as cardiotonics.[478]

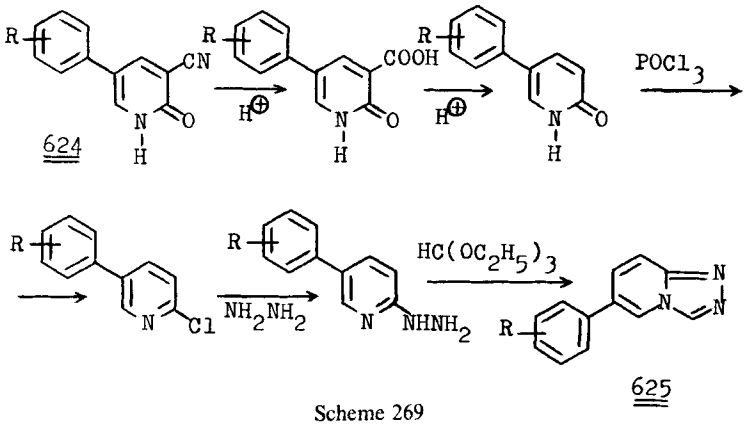


12

Scheme 268

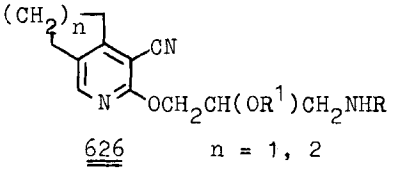
The administration of **12** (R = R^1 = R^2 = CH_3; X = O) to guinea pigs in a dose of 10^{-4} mol alters the isometric contractions and heart beats (ejections of the artery) by about 100.4 and 12.8%, respectively.[88]

In some cases derivatives of 3-cyanopyridin-2(1*H*)-ones have been used in the synthesis of antihypertonic agents. Thus, the substituted 6-phenyl-1,2,4-triazolo-[4,3-*a*]pyridines **625** exhibiting antihypertonic activity have been obtained in several steps from the substituted 5-phenyl-3-cyanopyridin-2(1*H*)-ones **624**.[65]



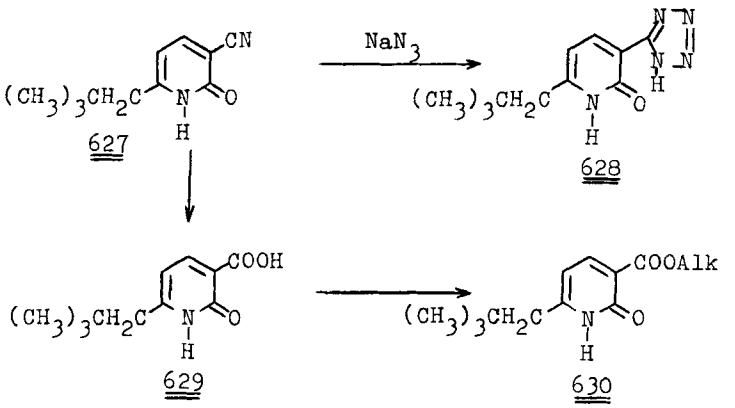
Scheme 269

Pyridyloxolypropanolamines are also used as antihypertonics **626**.[479]



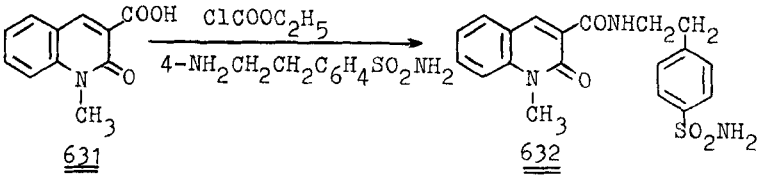
Scheme 270

A large number of derivatives of 6-(2,2-dimethylpropyl)pyridin-2(1*H*)-one **627–630** have found use as antibiotics.[335,338,355,480]



Scheme 271

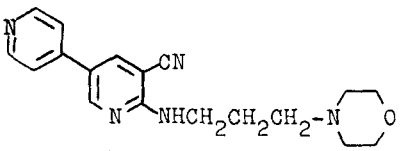
The sulfonamide **632**, obtained from the quinoline **631** exhibits an antidiabetic effect.[481]



631 632

Scheme 272

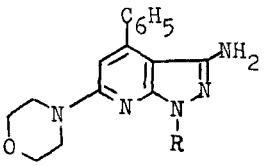
2-Aminoalkylamino-5-(4-pyridyl)-3-cyanopyridine **633** with a tonic, vaso- and bronchodilative, and antiallergic effect exhibits a broad spectrum of activity.[481]



633

Scheme 273

A 1-molar solution of 1*H*-pyrazolo[2,4-*b*]pyridine **634**, prepared from 6-hydroxy-4-phenyl-3-cyanopyridin-2(1*H*)-one, inhibits thrombosis by 50%.[312]

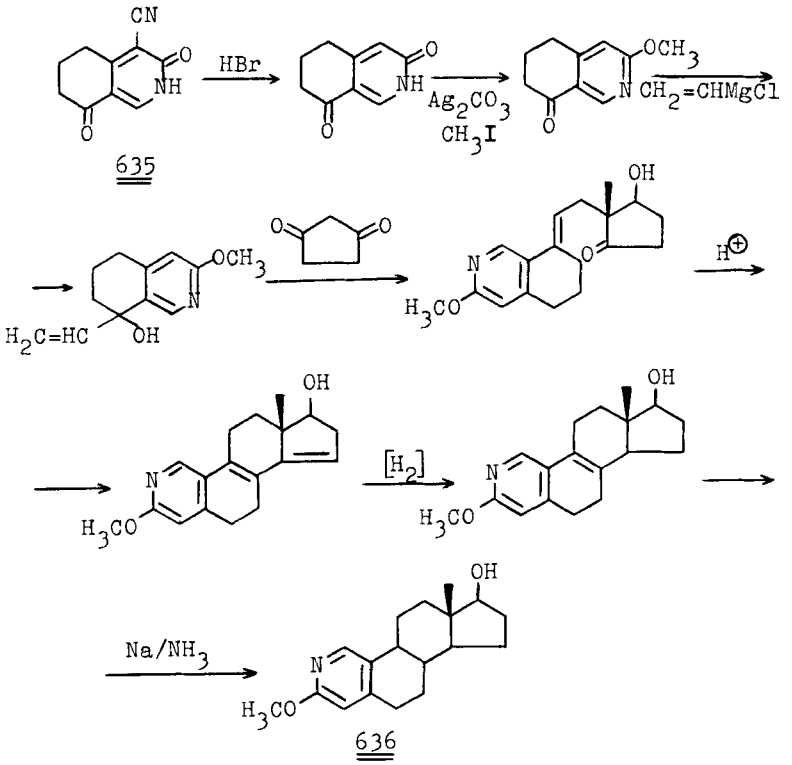


634

Scheme 274

Scattered examples of the application of 3-cyanopyridin-2(1*H*)-ones in the synthesis of antagonists of β-adrenoceptics,[482] antispastic,[390] and anthelminthic[66] compounds, and inhibitors of gastric acid secretion,[483] as well as of the active constituent of an anticoccidiosis preparation for warm-blooded species are known.[384]

The synthesis of (±)-2-azaestradiol **636** from 2,5,6,7-tetrahydro-4-cyanopyridine-3,8-dione **635** according to the following scheme is of considerable interest:[345,346]

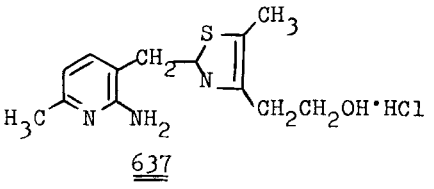


635

636

Scheme 275

As mentioned earlier, 3-cyanopyridin-2(1*H*)-ones are used in the synthesis of vitamin B_6.[310,340,341] An intermediate for the synthesis of the new heterovitamin B_1 is 6-methyl-3-cyanopyridin-2(1*H*)-one **637**.[316]



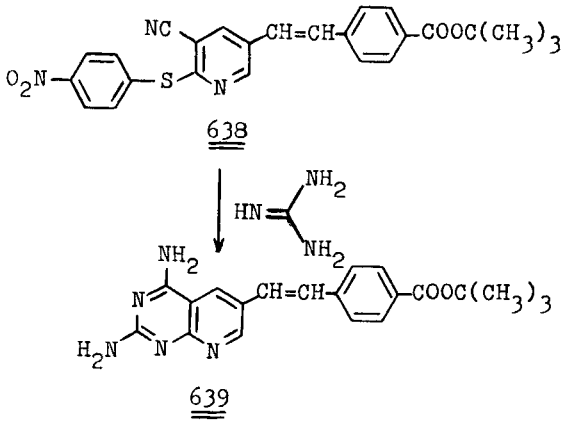
637

Scheme 276

3-Cyanopyridine-2(1*H*)-thiones and their derivatives have found wide application in different areas of biologically active substances, antioxidants, and other practically important compounds.[4,7,11,409] Among the substituted 3-cyanopyridine-2(1*H*)-thiones and their derivatives substances possessing insecticidal, acaricidal, and nematocidal activity have been discovered.[432] In addition, among the thienopyridines bactericides

have been found.[484] Substituted 2-arylthio-3-cyanopyridines have been patented as herbicides, defoliants, and desiccants.[289,290]

Another example is the preparation of the folic acid analogs **639** from substituted 2-[(4-nitrophenyl)thio]pyridines **638**.[485]



Scheme 277

Many 3-cyano-3,4-dihydropyridine-2(1*H*)-thiones and their salts possess cardiovascular activity.[148,151,152] Annelated pyridines obtained from 3-cyanopyridine-2(*1*H)-thiones show different types of physiological activity.[227,254,348,406,486–488] Disulfides derived from 3-cyanopyridine and complexes of 3-cyanopyridine-2(1*H*)-thiones are used as antioxidants.[489–493] A number of pigments have been prepared from 3-aminothieno]2,3-*b*] pyridines.[405,420,431,492,493]

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