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PYRIDINE OXIMES: SYNTHESIS, REACTIONS, AND BIOLOGICAL ACTIVITY. (REVIEW)

E. Abele, R. Abele, and E. Lukevics

Data on methods for the production of pyridine aldoximes, ketoximes, amidoximes, and their derivatives and their reactions are reviewed. The synthesis of new heterocycles from pyridine oximes is discussed separately. The principal results of research into the biological activity of the oximes are presented.

Keywords: oximes, pyridine, biological activity.

Pyridine oximes are widely used as intermediates in fine organic synthesis. In the present work we consider the principal methods for the production of pyridine oximes and their reactions. Methods for the synthesis of new heterocyclic systems from derivatives of these oximes are considered under a separate heading. The principal methods used for investigation of the structure of pyridine oximes with due regard to their isomerism are briefly examined. The main pathways for the selective production of the *E*- and *Z*-isomers of the oximes and their O-ethers are described. The last section contains the results from investigation of the biological activity of the derivatives of pyridine oximes.

1. SYNTHESIS OF PYRIDINE OXIMES

1.1 Synthesis of Pyridine Aldoximes and Ketoximes

The classical method for the synthesis of pyridine oximes is based on the reaction of the aldehyde or ketone with hydroxylamine in methanol [1] or with hydroxylamine hydrochloride in ethanol [2], isopropyl alcohol [3], pyridine [4], NaOH/EtOH/H_2O [5, 6], Na_2CO_3/EtOH/H_2O [7, 8], NaOMe/MeOH [9], $NaHCO_3$/MeOH [10], NaOAc/MeOH [11], NaOAc/H_2O [12], or Na/EtOH [13]. By a modification of these methods it is possible to obtain the pyridine ketoximes **2** from the corresponding nitriles **1**. Thus, the reaction of the nitrile **1** with Grignard reagents (RMgBr) followed by reaction with $NH_2OH \cdot HCl$ leads to the formation of the oximes **2** [14, 15]. The pyridine oxime **5** was obtained by a five-stage synthesis from the bipyridyl derivative **4** [16, 17]. The reactions of pyridine nitriles in the H_2/Pd–C/HCl/H_2O/$NH_3OH \cdot HSO_4$ system also lead to pyridine aldoximes [18].

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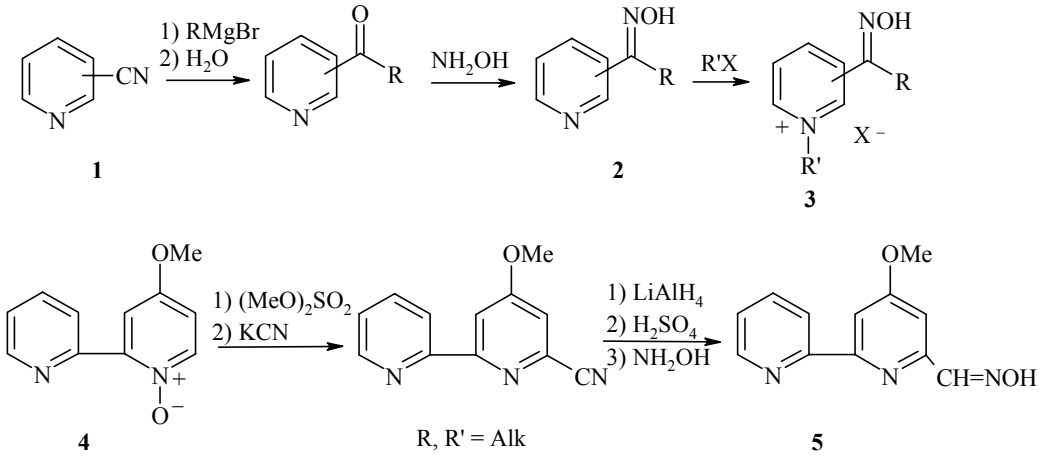
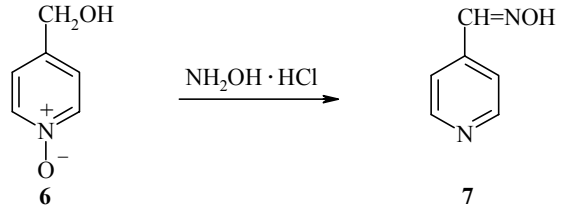
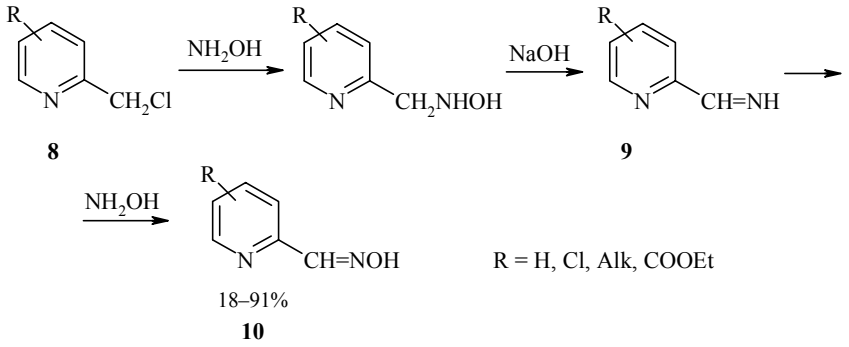


In reaction with alkyl (or aryl) halides under neutral conditions pyridine oximes form quaternary salts [e. g., the salt **3**] [15]. The synthesis of the salts of pyridine oximes has been widely described in a series of papers [19-30]. These compounds are used as antidotes for poisoning by organophosphorus compounds [29] and as micellar catalysts [30].

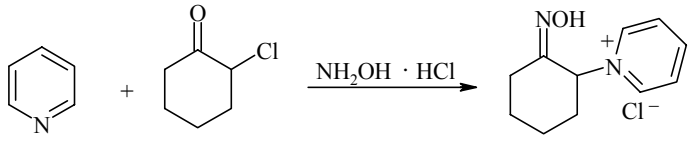
The 4-pyridine aldoxime (**7**) is produced by the reaction of 4-hydroxymethylpyridine N-oxide (**6**) with hydroxylamine [31].



The 2-pyridine aldoximes **10** are readily formed in the reaction of the respective chloromethylpyridines **8** in the $NH_2OH{\cdot}HCl/NaOH/{\cdot}H_2O/EtOH$ system. The products **10** are formed through the aldimine intermediate **9** [32]. The 3- and 4-pyridine aldoximes were obtained similarly [33].

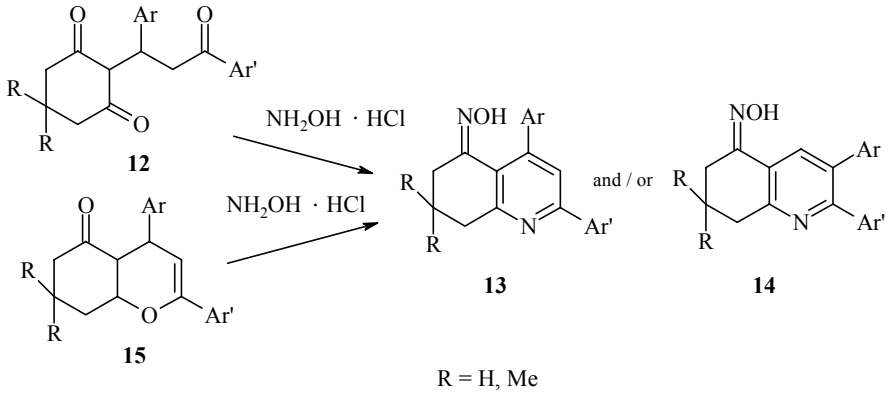


Among the methods for the synthesis of pyridine oximes it is necessary to mention the three-component synthesis of 2-pyridiniocyclohexanone oxime (**11**) from 2-chlorocyclohexanone and hydroxylamine hydrochloride in pyridine [34]. 3-(4-Pyridyl)-2-cyclohexen-1-one was obtained similarly [35].



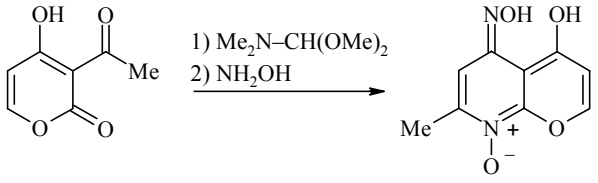
11

2-(3-Oxopropyl)cyclohexanone-1,3-diones **12** undergo cyclization in the presence of hydroxylamine hydrochloride with the formation of the tetrahydroquinoline oximes **13** and **14** in a ratio of ~1:1. The oximes **13** and **14** are also formed during the recyclization of tetrahydrochromenes **15** [36].



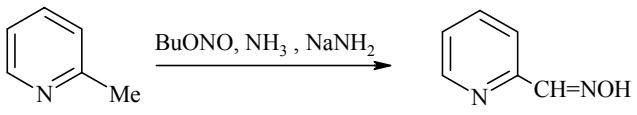
R = H, Me

A two-stage synthesis of 4-hydroxy-5-hydroxyimino-7-methyl-5H-pyrano[2,3-*b*]pyridine (**17**) was described in [37]. The reaction of the ketone **16** with $Me_2NCH(OMe)_2$ and hydroxylamine gives the oxime **17** as the only product.

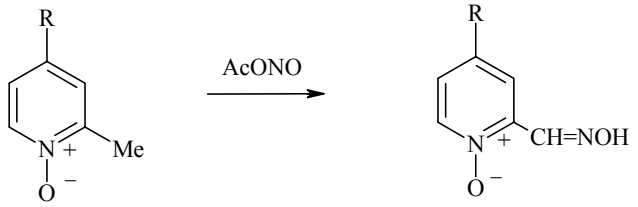


16 **17**

A series of methods for the synthesis of pyridine oximes are based on the nitrosation of pyridine derivatives. For example, 2-picoline (**18**) in the $NaNH_2/NH_3$/BuONO system gives the aldoxime **19** with a yield of 75% [38, 39]. The analogous nitrosation of picoline N-oxides **20** with acetyl nitrite gives the oxime derivatives **21** as the main products [40]. The following systems have also been used as nitrosating agents in the synthesis of pyridine oximes: BuONO/EtOH/MeONa [41], BuONO/EtOH/Na [42], *t*-BuONO/ THF/BuLi (or *tert*-BuOK) [43], amyl nitrite [44], amyl nitrite/KNH_2 (or $NaNH_2$)/NH_3 [45, 46], $NaNO_2$/HCl [47], and $NaNO_2$/AcOH [48].

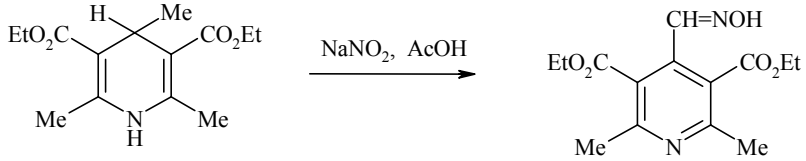


18 **19**



20 **21**

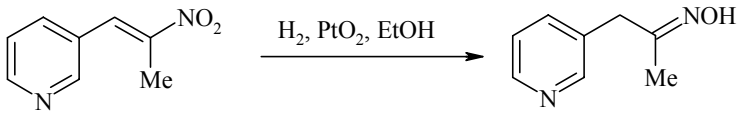
The unexpected aromatization of 1,4-dihydropyridine **22** during nitrosation in the presence of sodium nitrite in acetic acid leads to the formation of the pyridine oxime **23** as the main product [49].



22 **23**

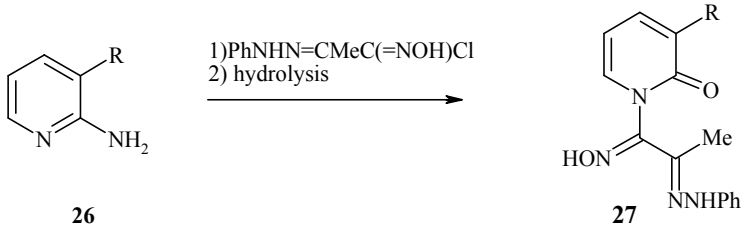
4-Pyridine aldoxime was obtained successfully by the oxidation of 4-methylpyridine with oxygen at the surface of V–Mo oxide catalysts at 460-480°C in the presence of hydroxylamine [50].

Hydrogenation of the nitro derivative **24** at PtO_2 in ethanol leads to the formation of the oxime **25** with a yield of 27% [51].

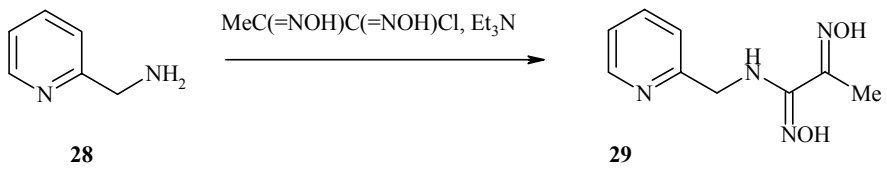


24 **25**

The reaction of 2-aminopyridines **26** with the oxime PhNHN=CMeC(=NOH)Cl gives the pyridones **27** with yields of 87-90% [52]. The reaction of the oxime MeC(=NOH)C(=NOH)Cl with 2-aminomethylpyridine (**28**) in the presence of triethylamine leads to the dioxime **29** with a yield of 77% [53]. Fungicidal pyridine derivatives of 2-hydroxyimino(alkoxyimino)-3-(acylhydrazino)butyric acids were obtained similarly [54].



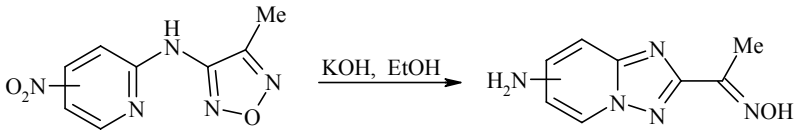
26 **27**



28 **29**

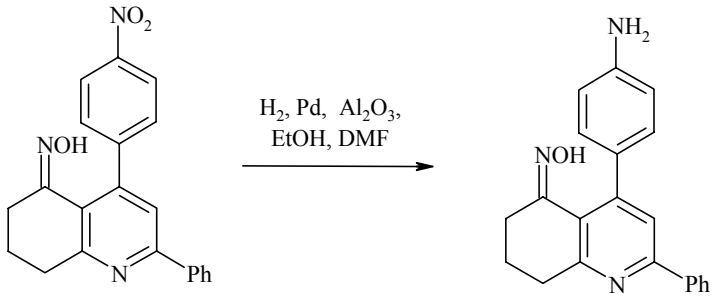
R = H, Me

The rearrangement of 1,2,5-oxadiazoles **30** in the presence of potassium hydroxide in ethanol leads to the formation of 2-acetyl-6(8)-amino-1,2,4-triazolo[1,5-*a*]pyridine oximes **31** with yields of 32-68% [55].

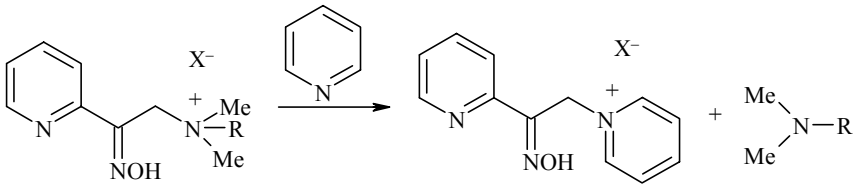


30 **31**

The transformations of some pyridine oximes into others have also been described. Thus, the selective hydrogenation of 4-(4-nitrophenyl)-5-oxo-2-phenyl-5,6,7,8-tetrahydroquinoline (**32**) oxime using the complex of palladium(II) with 4-(2-pyridylazo)resorcinol gives the oxime amino derivative **33** as the only product [56].



32 **33**

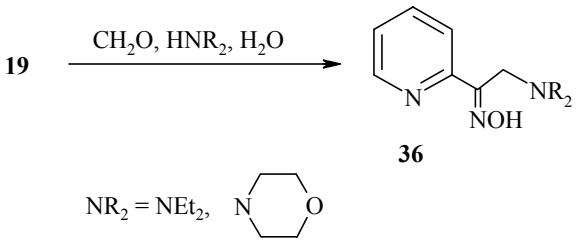


34 **35**

R = Alk; X = Br, NO_3

In the presence of pyridine the quaternized amino derivatives of pyridine oximes **34** give N-[2-hydroxyimino-2-(2-pyridyl)ethyl]pyridinium bromide (**35**) [57].

The 2-pyridine aldoxime (**19**) is readily aminomethylated by formalin in the presence of a secondary amine, leading to 2-(1'-hydroxyiminoethyl-2'-dialkylamino)pyridines **36** with yields of 52-63% [58].

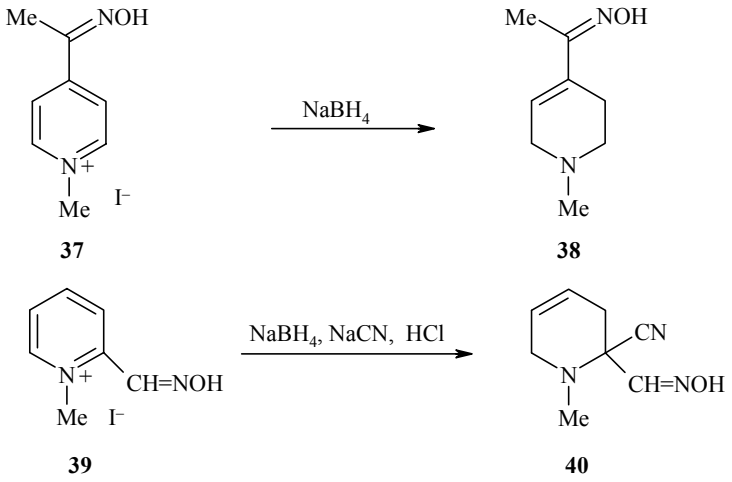


36

NR_2 = NEt_2,

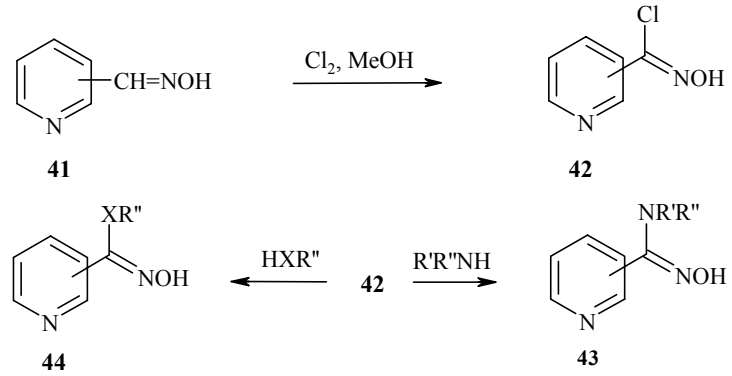
Several papers have been devoted to the synthesis and characteristics of the oximes of tetrahydropyridines [59-61]. For example, the reduction of the quaternized oxime **37** with sodium borohydride leads to the formation of 1,2,3,6-tetrahydropyridine oxime **38** [62]. Reduction of the salt of 2-pyridine

aldoxime **39** with sodium borohydride in the presence of NaCN/HCl gives 2-cyano-1-methyl-1,2,3,6-tetrahydropyridine 2-aldoxime (**40**) with a yield of 71% [63].



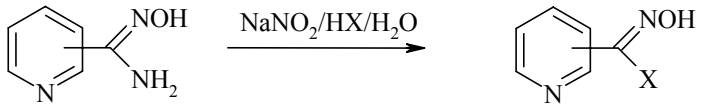
1.2. Synthesis of Pyridine Amidoximes, Hydroximoyl Chlorides and Their Derivatives

Pyridine amidoximes have been known for more that 100 years [64]. These compounds are usually produced by the reactions of pyridine nitriles with $NH_2OH \cdot HCl$ in the presence of $Na_2CO_3/EtOH/H_2O$ [65-67] or $Na_2CO_3/EtOH$ [68]. The synthesis of hydroxamoyl chlorides and amidoximes from the corresponding pyridine aldoximes was described in several papers. For example, the pyridine aldoximes **41** are readily chlorinated with chlorine in methanol and form pyridine hydroximoyl chlorides **42** with yields of up to 82% [69-71]. The reactions of hydroximoyl chlorides **42** with various amines or ammonia give the pyridine aldoximes **43** as the main products [70, 72, 73]. The reaction of the oximes **42** with nucleophilic compounds of sulfur and oxygen leads to the formation of pyridinehydroximates or thiohydroximates **44** [70, 72]. 4-Pyridinecarbaldehyde amidoxime was obtained similarly [74]. The intermediate in the reactions of the oximes **42** described above is the pyridine nitrile oxide (Py–CNO), generated from the hydroxamoyl chlorides in the presence of a base, and this reacts readily with nucleophilic reagents forming the products **43** and **44**.



R'R"NH = NH_3, $NH_2C_6H_4$, NH_2OH, $HNEt_2$; X = O, S; R" = Alk, Ph

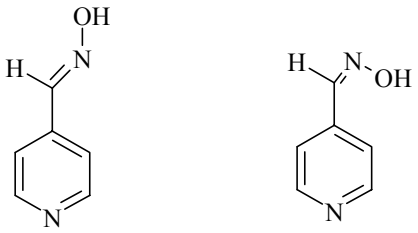
Under diazotization conditions ($NaNO_2/H_2O/HX$, X = Cl, Br) the pyridine amidoximes **45** give the pyridine hydroximoyl chlorides (or bromides) **46** with yields of 48-88% [75].



45 **46**

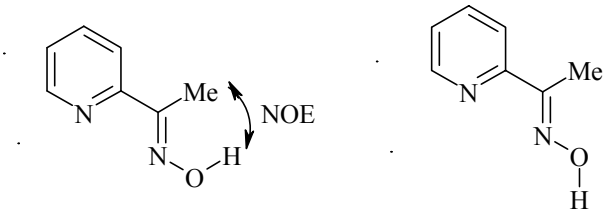
2. THE STRUCTURE OF PYRIDINE OXIMES

One of the most reliable methods for determination of the structure of isomeric pyridine oximes is NMR spectroscopy. The oxime group in pyridine oximes has a descreening effect, and the downfield signals of the "aldehydic proton" of the pyridine oxime **7** were therefore assigned to the *E*-isomer, while the analogous upfield signals were assigned to the *Z*-isomer [76, 77]. In the *Z*-isomer the signals in the pyridine ring are descreened. In [77] the two isomers of the oxime **7** were studied in detail. The *E*- and *Z*-isomers of these oximes are distinguished by their melting points: *E*-**7** 165-167°C, *Z*-**7** 132-133°C.



E-**7** *Z*-**7**

The configuration of the oximes and of the 2-acetylpyridine oxime (**47**), in particular, was established by NOE ^{1}H NMR spectroscopy – by determining the influence of the Overhauser effect. It should be noted that the conformation of the oxime **47a** has a strong NOE, in contrast to structure **47b**, which does not have such an effect [78].



s-cis-**47a** *s-trans*-**47b**

There are data in the literature on the ^{1}H NMR spectroscopy of the oximes of the N-oxides of pyridine aldehydes [79] and N-alkoxypyridine aldehydes [80].

The isomeric hydrochlorides of 3-pyridine amidoxime were separated by chromatography on plates of silica gel with alcohol, acetone, NH_4OH, and water in ratios of 70:5:10:15 as eluant [81]. The isomers of 2-pyridine amidoxime are easily separated on account of the different solubility in benzene [82]. It should be noted that only the *Z*-isomer of phenyl 2-pyridyl ketoxime forms a complex with Fe(II) [83]. Pyridine aldoximes and ketoximes also form complexes with Ni(II) [84-87], Fe(II) and Fe(III) [87-89], Zn(II) [85], Co(II) [85, 90], Co(III) [91], Cu(I) and Cu(II) [85, 86, 92-94], Pd(II) [95], Pb(II) [89], Ru(III) [89], Re(VII) [96], Au(III) [89],

U(VI) [87, 89, 95], rare-earth elements [97], and Me_3B [98]. Pyridine amidoximes form complexes with Ni(II) [99, 100], Fe(III) [100], Co(II) [100, 101], Cu(II) [102], Cd(II) [100], Hg(II) [100], Ag(I) [100], Pd(II) [100, 103], Pb(II) [100], and U(VI) [100, 104] ions.

The structure of the pyridine oximes is confirmed by the data from extensive investigations into the kinetics of the hydrolysis of methylpyridine ketoximes in sulfuric acid [105] and the hydrolysis of the O-ethers of pyridine ketoximes catalyzed by Ni(II), Zn(II), or Cu(II) ions [106-109].

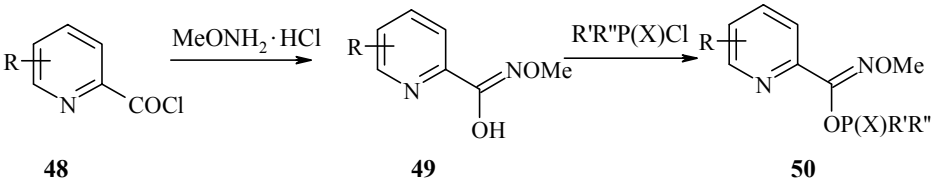
The structure of oximes of the Py–CR=NOH type (Py = pyridine, R = H, Me, Ph, NH_2) [110], the oximes of (pyridinemethylene)aminoacetophenones [111], and the cyclic aggregates of α,β-unsaturated pyridine ketoximes [112] was recently investigated by X-ray crystallographic analysis.

The structure of pyridine oximes has been investigated by UV [113-121] and IR [121-124] spectrometry, mass spectrometry [125-127], and polarography [128-131]. The thermodynamic dissociation constants [132] were also determined by spectrometry, the molecular orbitals for pyridine aldoximes were calculated by semiempirical methods [133], and the possibility of photochemical isomerization of the *E*-oximes of 4-pyridinecarbaldehyde was demonstrated [134].

3. REACTIONS OF PYRIDINE OXIMES

3.1. Synthesis of the Ethers of Pyridine Oximes

The principal methods for synthesis of the O-ethers of pyridine oximes are based on the O-alkylation of hydroxylamines (or their hydrochlorides) with carbonyl derivatives [135] in ethanol [136-138], pyridine [139], or the Na_2CO_3/EtOH [140], pyridine/MeOH [141], or pyridine hydrochloride/pyridine [142, 143] systems. The acetals of pyridine ketones and O-alkoxyhydroxylamines form the corresponding O-ethers of the oximes [144]. The N-methoxypyridinecarboximidoyl phosphates **50** were obtained by the two-stage reaction of the corresponding pyridinecarbonyl chlorides **48**. At the first stage of the reaction of the chloride **48** with $NH_2OMe \cdot HCl$ the ethers **49** are formed. The reaction of the pyridines **49** with $(EtO)_2P(S)Cl$ in acetonitrile gives good yields of the phosphates **50**, which exhibit high insecticidal activity [145].

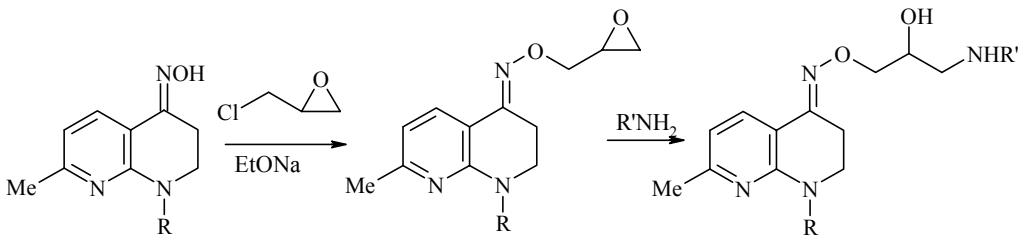


48 **49** **50**

R = H, Hal, NO_2, CF_3, Alk; R',R" = AlkO, AlkS, Ph, PhO; X = O, S

The reactions of the respective oximes with alkyl halides (or dimethyl sulfate [73]) in the Na/EtOH [146], KOH/MeOH [147], NaH/DMF [148], EtONa/EtOH [149], K_2CO_3/MeCN [150], and NaI/Et_3N/Me_2CO [151] systems were widely used in the synthesis of O-ethers of pyridine oximes.

The synthesis of the oxime ethers of naphthiridines **53** (potential antihypertonic agents) was described in [152, 153]. The reaction of naphthiridine oximes **51** with epichlorohydrin in the EtONa/EtOH/PhMe system leads to the epoxides **52** with yields of 36-72%. Opening of the epoxide ring with nucleophilic amines leads to the ethers **53** with yields of 29-65%.

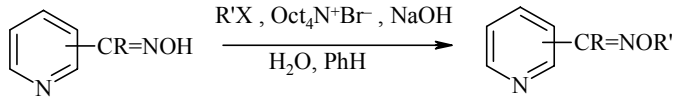


51 **52** **53**

R = Alk, Bn; R' = Alk

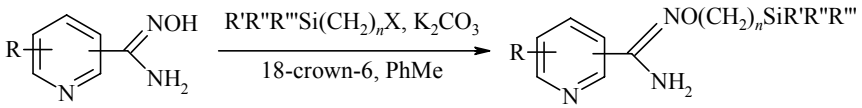
By phase-transfer catalysis (PTC) it is possible to realize the selective alkylation of pyridine oximes. The high effectiveness of the alkyl halide (RX, X = Br, I)/10% aq. NaOH/$Oct_4N^+Br^-$/PhH system in the alkylation of pyridine oximes **54** was demonstrated in [154, 155]. Under the given conditions the respective O-ethers were isolated with yields of 14-86%.

The alkyl bromide (RBr)/aq. NaOH/$PhCH_2NEt_3^+Cl^-$/CH_2Cl_2 [156], RBr/2N aq. NaOH/$Bu_4N^+Br^-$/CH_2Cl_2 [157], or RCl/solid KOH/solid KI/18-crown-6/PhH [158] PTC systems were used in the synthesis of O-ethers from pyridine oximes. The pyridine amidoximes **56** were also alkylated by silicon-containing alkyl halides [R'R"R'"$Si(CH_2)_nX$] in the solid K_2CO_3/18-crown-6/PhMe system. The reaction products **57** (yields 33-79%) exhibited high cytotoxicity [159].



54 **55**

R = H, Ph; R' = Alk

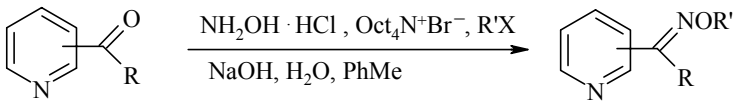


56 **57**

R = H, Me; R', R", R'" = Alk; *n* = 1, 3; X = Br, I

Pyridine oximes were O-methylated under the conditions of three-phase catalysis in the presence of polymer-fixed onium salts [160].

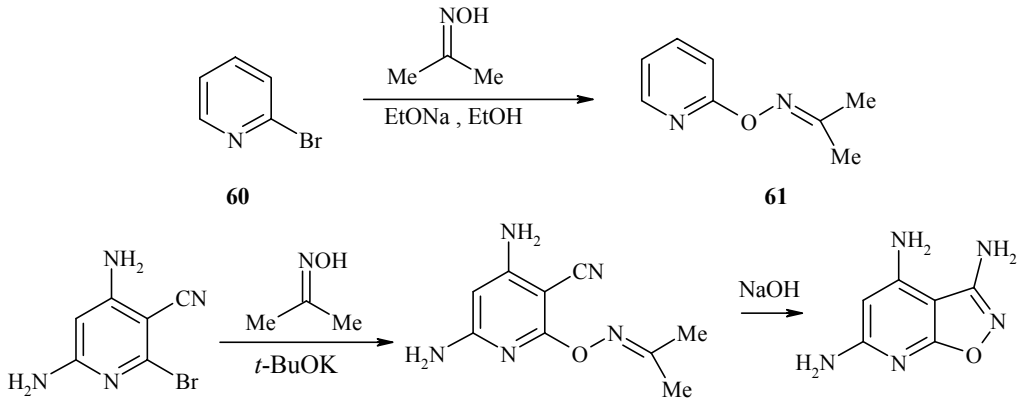
A new single-stage method was developed for the *E*-stereoselective synthesis of the O-ethers of pyridine aldoximes and ketoximes **59** from the carbonyl compounds **58** in the $NH_2OH{\cdot}HCl$/25% aq. KOH/$Oct_4N^+Br^-$/PhMe system [161].



58 *E*-**59**

R = H, Me; R' = Alk; X = Br, I

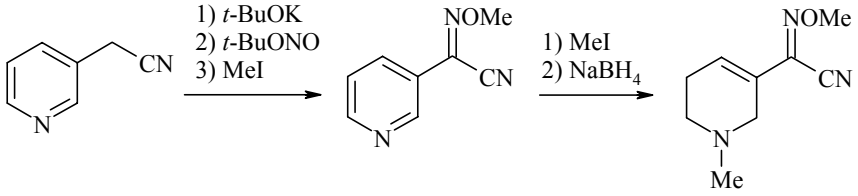
The publications [162-164] were devoted to the synthesis of the ethers of pyridine-containing oximes by arylation of the oximes of halopyridines. For example, the arylation of acetone oxime by 2-bromopyridine (**60**) in the presence of NaOEt/EtOH gives acetone O-(2-pyridyl)oxime **61** [163]. The analogous reaction of acetone oxime with 4,6-diamino-2-bromo-3-cyanopyridine (**62**) in the presence of *t*-BuOK leads to the formation of the ether **63** with a yield of 60%. Cyclization of the oxime derivative **63** in the presence of aqueous sodium hydroxide gives isoxazolo[5,4-*b*]pyridine-3,4,6-triamine **64** (yield 29%) [164].



60 **61** **62** **63** **64**

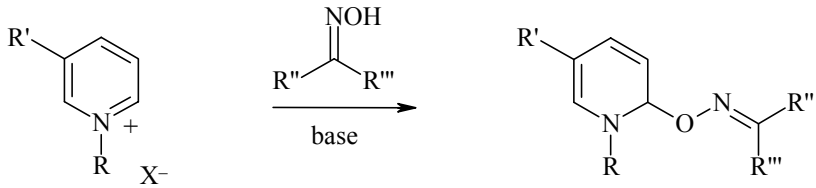
It is also necessary to mention the possibility of using ethylene carbonate in the synthesis of oxime ethers. For example, in the presence of $AcNMe_2$ pyridine oximes and ethylene carbonate give good yields of the respective O-2-hydroxyethyloximes [165].

The oxime O-methyl ether **66** was obtained with a yield of 86% from the corresponding nitrile **65** in the *t*-BuOK/*t*-BuONO/THF system with subsequent treatment of the reaction mixture with methyl iodide. The ether **66** is easily quaternized (MeI) and reduced further to the 1,2,5,6-tetrahydropyridine derivative **67** [166].



65 **66** **67**

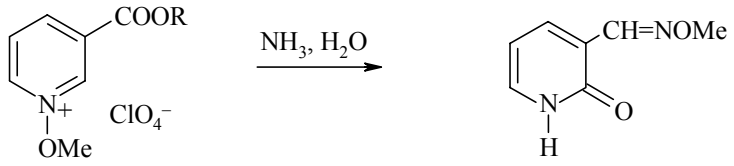
The pyridinium salts **68**, containing electron-withdrawing groups at position 3, react with aliphatic oximes under basic conditions and give the oxime ethers of dihydropyridine **69** as the main products [167].



68 **69**

R = Alk; R' = CN, MeNHCO, Bn_2SO_2, Me_2NSO_2; R", R''' = Alk

The rearrangement of 3-substituted N-methoxypyridinium salts **70** in aqueous ammonia leads to the formation of 2-methoxyiminomethyl-2-pyridone **71** with a yield of up to 35% [168, 169].

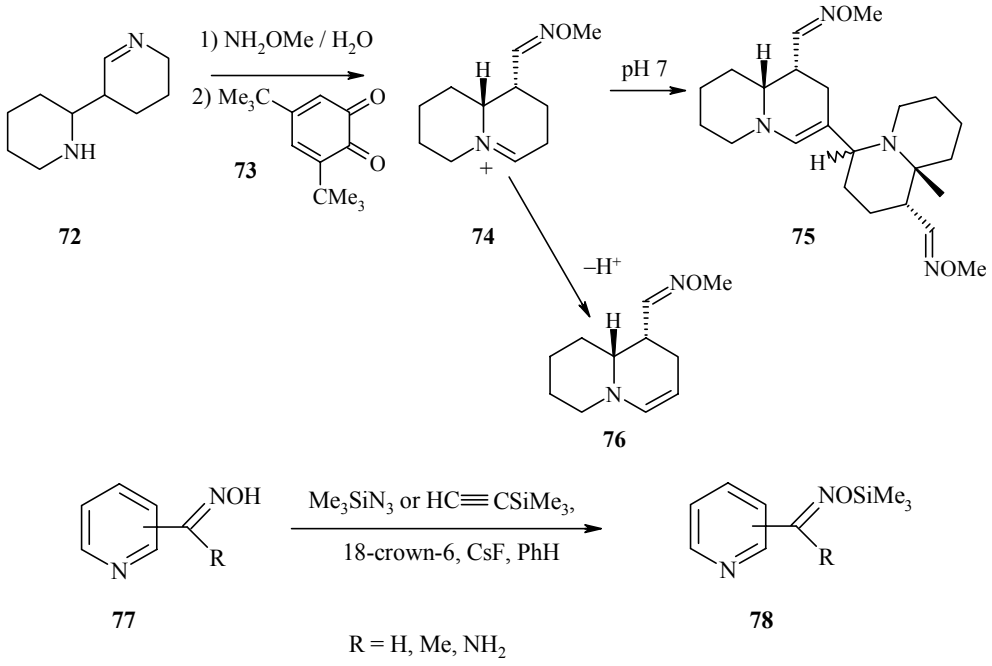


70 **71**

R = H, Me, NH_2

The synthesis of the oxime derivatives of quinolizine from tetrahydroanabasine **72** was described in [170]. The reaction of compound **72** with NH_2OMe in water and then with the quinone **73** gives the cyclic imine salt **74**, which is readily transformed into the quinolizine **76** or dimerizes to the product **75**.

O-Trimethylsilyloximes of pyridine amidoximes were obtained by boiling the respective oximes with hexamethyldisilazane in the presence of catalytic amounts of trimethylchlorosilane [123, 127]. Recently we developed two new PTC methods for synthesis of the silyl ethers of pyridine oximes. For example, the oximes **77** are easily silylated in the two-phase $HC{\equiv}CSiMe_3$/CsF/18-crown-6/benzene [171] and Me_3SiN_3/CsF/18-crown-6/benzene systems. The oxime silyl ethers **78** were isolated with yields of up to 100%.



72 **73** **74** **75** **76**

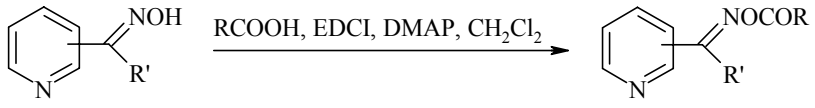
77 **78**

R = H, Me, NH_2

Fungicidal O-triethylstannyl ethers of pyridine aldoximes were obtained by the stannylation of oximes with chlorostannanes in the presence of sodium methoxide [172]. Pyridine O-dimethylarsine oximes were obtained from the oximes and Me_2NAsMe_2 [173].

The O-acyl derivatives of pyridine oximes [174, 175] were obtained by acylation of the respective oximes with acetic anhydride [176], acid chlorides/Et_3N [178], and $AcOCH{=}CMe_2$/DBU [179] or of the oximate anions with *p*-nitrophenyl acetate [180]. Syntheses of acyl derivatives of pyridine oximes by acylation of the oximes with carboxylic or amino acids in the presence of a carbodiimide derivative are known [181-184].

For example, the oximes **79** are easily acylated by acids (RCOOH) in the 4-dimethylaminopyridine (DMAP)/3-(dimethylaminopropyl)-1-ethylcarbodiimide (EDCI)/CH_2Cl_2 system and give good yields of the acyl derivatives **80** [184].



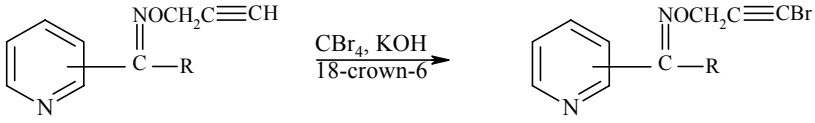
79 **80**

R = Alk, Py; R' = H, Me

3.2. Reactions of the Oxime Groups and Rings

Recent advances in the chemistry of oxime derivatives were reviewed in [185]. Features of the chemistry of pyridine oximes will mostly be presented in this section.

The bromination of propargyl ethers of pyridine oximes **81** in the PTC system CBr_4/solid KOH/18-crown-6 leads to the selective formation of the O-(bromopropargyl)oximes **82** with yields of up to 64%. Preliminary experiments had shown that the optimum amount of carbon tetrabromide during the bromination of O-propargyloximes is 0.75 equivalent in relation to the substrate. This can be explained by disproportionation of the initially formed bromoform in the presence of alkali into carbon tetrabromide, which then reacts further [186, 187].

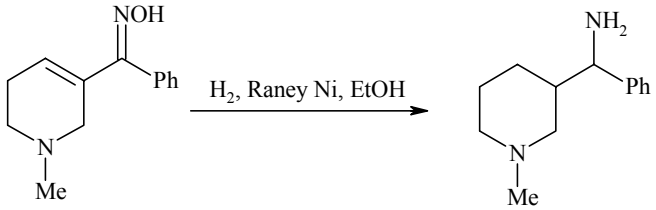


81 **82**

R = H, Me

The dehydration reactions of oximes were described in the review [188]. Pyridine aldoximes are readily converted into the corresponding nitriles in the presence of $NaOH/Me_2SO$ [189, 190], Ac_2O [191], Ac_2O/OH^- [192], hexachlorocyclotriphosphazatriene [193], or $CHCl_3$/60% aq. KOH/Oct_4NBr/PhMe [194]. 3-Pyridylamidoxime gives a mixture of amide and nitrile during oxidation with hydrogen peroxide in the presence of Fe(III) complexes of porphyrins [195]. The N-oxides of O-acylated pyridine aldoximes also form pyridine nitriles in the presence of sulfonyl chlorides [196].

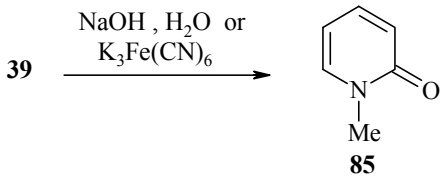
The hydrogenation of pyridine ketoximes to the corresponding primary pyridine amines was conducted in the presence of $PdCl_2$/AcOH [197], $PdCl_2$/HCl [198] or Pd–C/MeOH/HCl [199] [200]. Sometimes reduction of the pyridine ring is observed during hydrogenation. For example, the hydrogenation of 3-benzoyl-1-methyl-1,2,5,6-tetrahydropyridine (**83**) over Raney nickel gave a mixture of isomers of 3-(1-aminobenzyl)-1-methylpiperidine **84** with an overall yield of 63% [201].

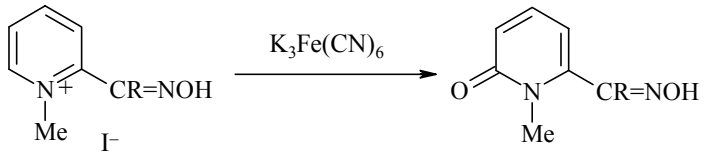


83 **84**

Pyridine oximes are also reduced to primary amines by polarography [202, 203] or with zinc in acetic acid [204], trifluoroacetic acid [205], and $NH_3/H_2O/EtOH$ [206]. 4-Pyridine amidoxime was reduced to the corresponding amidine in the presence of $Ru_3(CO)_{12}/CO$ [207]. During the oxidation of pyridine amidoximes with $K_3[Fe(CN)_6]$ at pH 12 the formation of the corresponding pyridine acid and NO was observed [208]. 3-(4-Pyridyl)aniline was obtained from 3-(4-pyridyl)-2-cyclohexanone oxime in the acetic anhydride/H_3PO_4 system [209].

In the presence of sodium hydroxide [210] or $K_3Fe(CN)_6$ [211] the 2-pyridine aldoxime salt **39** gave N-methyl-α-pyridone **85** as the main product. Oxidation of the ketoximes **86** with $K_3Fe(CN)_6$ led to the formation of the oxime derivatives of pyridones **87** [211].

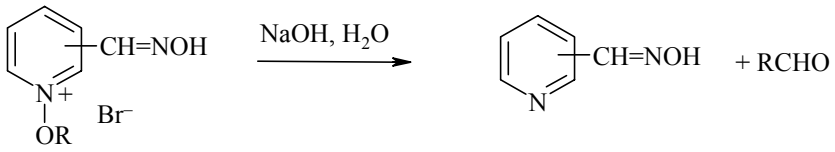




86 **87**

R = Me, Et, Bn, Ph

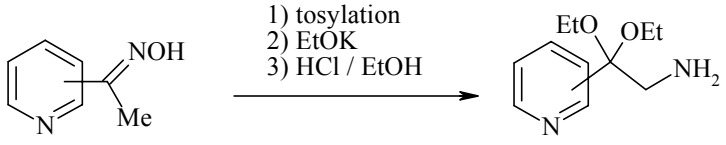
In a basic medium the oximes of 1-alkoxypyridinecarbaldehydes **88** eliminate the aldehydes **90** and give the oximes **89** [212]. The action of Ac_2O/OH^- on the oximes of N-methoxypyridinecarbaldehydes leads to products of the MeON=CRCH=CR'CH=CHOAc type (R, R' = H or CN) from opening of the pyridine ring [192].



88 **89** **90**

R = Alk

Tosylation of the oximes of acetylpyridines **91** and subsequent treatment of the reaction mixtures with potassium ethoxide and then with HCl/EtOH lead to 2,2-diethoxy-2-pyridylethylamines **92** with yields of 53-92% [213].



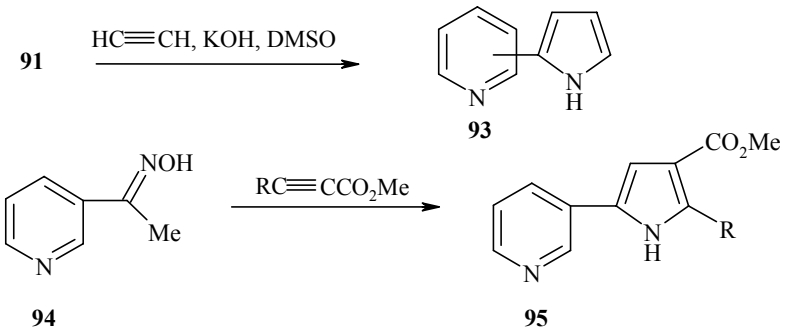
91 **92**

In [214] the principal production paths and the reactions (methylation, nitration, acylation, and reduction) of 4-hydroxy-7-methyl-5-hydroxyimino-5H-pyrano[2,3-*b*]pyridine 8-oxide were presented.

3.3. Synthesis of New Heterocyclic Systems from Pyridine Oximes

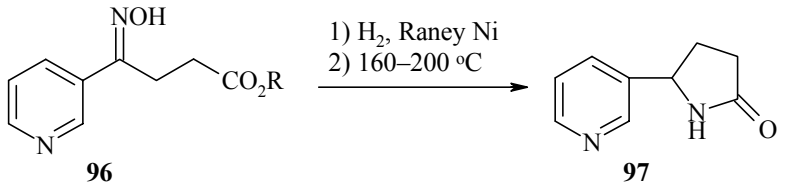
The latest advances in the synthesis of heterocyclic systems from oximes were reviewed in [215]. In this section the specific reactions of pyridine oximes will be discussed in greater detail.

One of the most interesting reactions of oximes is the synthesis of pyrroles by the reaction of ketoximes with acetylenes in a basic medium (the Trofimov reaction). The synthetic potentialities of this reaction have been set out in numerous reviews and monographs [216-219]. Under the classical conditions the synthesis of derivatives of pyrrole **93** from pyridine ketoximes **91** was carried out in an autoclave at 12-14 atm in the HC≡CH/KOH/DMSO system at 80-85°C. Under these conditions the products **93** were isolated with yields of 42-80% [220]. At higher pressures (16-25 atm) and temperatures 2-pyridyl-1-vinylpyrroles were isolated as the main products [221]. The reaction of 3-acetylpyridine oxime **94** with the esters of alkynoic acids ($RC{\equiv}CCO_2Me$) gives 2,3-substituted 5-(3-pyridyl)-1H-pyrroles **95** [222]. The formation of these products takes place through the corresponding O-vinyloximes as intermediates.



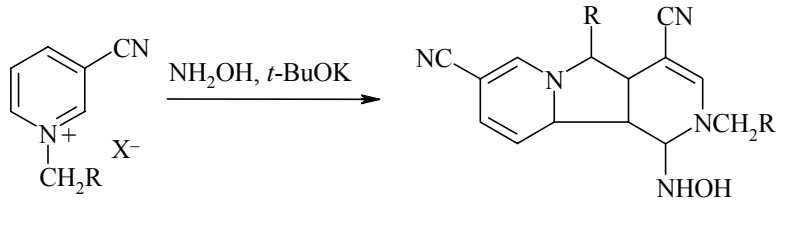
R = H, CO_2Me

5-(3-Pyridyl)-2-pyrrolidone (**97**) was obtained successfully from γ-hydroxyimino-γ-(3-pyridyl)butyrate esters **96** by hydrogenation over Raney nickel followed by thermal cyclization of the intermediate amine [223].



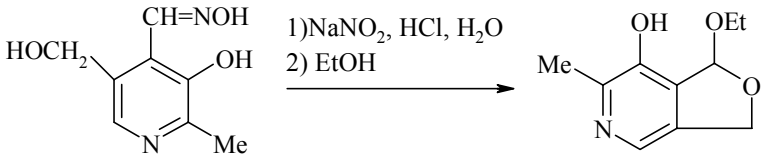
R = Alk

The synthesis of tricyclic derivatives of dipyrido[1,2-*a*:3',4'-*c*]pyrroles **99** was realized in one stage from the salts of pyridine nitriles **98** in the NH_2OH/*t*-BuOK/CH_2Cl_2 system [224]. The formation of these products goes through the intermediate amidoxime salts.



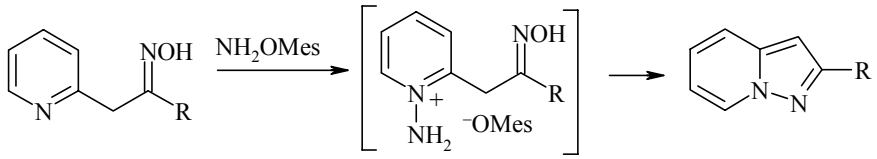
R = Ar; X = Cl, Br, I

In the $NaNO_2/HCl/H_2O$ system the oxime of 4-formyl-3-hydroxy-5-(hydroxymethyl)-2-methylpyridine (**100**) gives the hydrochloride of 6-methyl-1,3-dihydrofuro[3,4-*c*]pyridin-7-ol (**101**) [12].



100 **101**

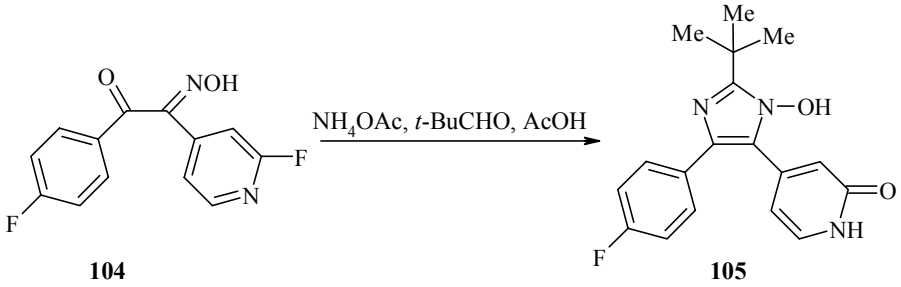
Derivatives of pyrazole [225] and imidazole were also obtained successfully from pyridine oximes. For example, pyrazolo[1,5-*a*]pyridines **103** are readily formed (with yields of up to 80%) from the oximes **102** and O-mesitylsulfonylhydroxylamine in chloroform [226].



102 **103**

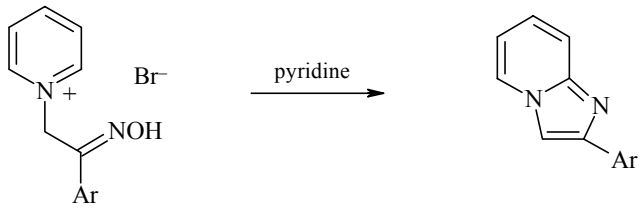
R = H, Ph

Several papers have been devoted to the synthesis of N-hydroxyimidazoles [227, 228] and 2- or 3-imidazoline 3-oxides [229] from pyridine oximes. For example, the reaction of the ketoxime **104** with *t*-BuCHO/NH_4OAc/AcOH gives the imidazole **105** with a yield of 49% [228].

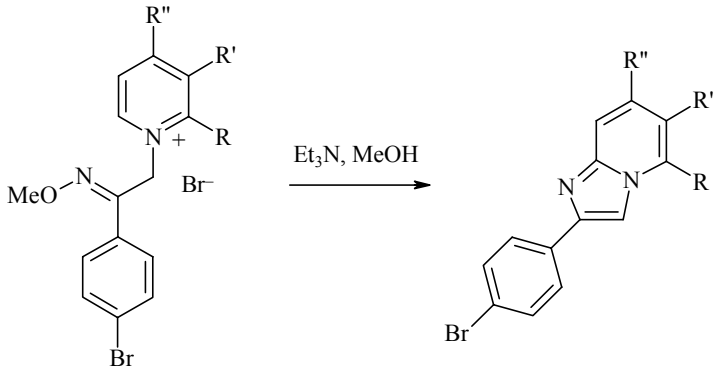


104 **105**

Pyridine oximes are good starting compounds for the production of imidazo[1,2-*a*]pyridines [230-234]. Thus, in the presence of a tertiary amine the salts of oximes **106** or the oxime ethers **107** form imidazo[1,2-*a*]pyridines **108** and **109** respectively with yields of up to 96% [231, 232].



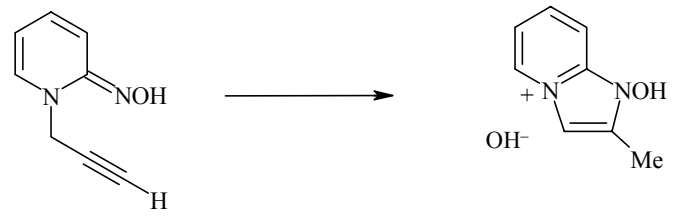
106 **107**



108 **109**

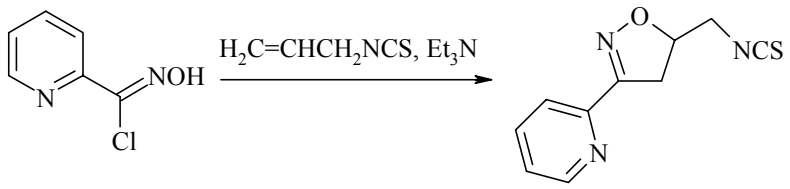
R-R" = H, Alk

Thermal cyclization of the hydroxyiminopyridine **110** leads to the formation of the imidazopyridine **111** [234].

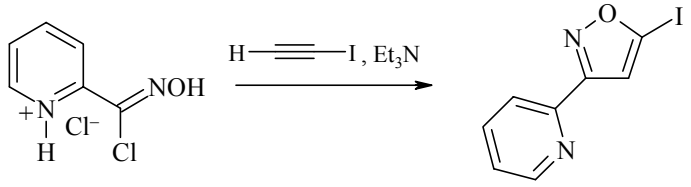


110 **111**

A series of methods have been described for the synthesis of isoxazole derivatives from pyridine oximes. Pyridine aldoximes in the presence of $NaOCl/Et_3N$ or amidoximes in the presence of $NaNO_2/HCl/H_2O$ and Et_3N give the respective nitrile oxides (see section 1.2), which enter readily into cycloaddition with alkenes and alkynes. For example, the reaction of the oxime **112** in the alkene/$NaOCl/Et_3N/CH_2Cl_2$ system leads to the formation of the fungicidal isoxazoline **113** [235]. Under analogous conditions the oxime **114** and iodoethane give derivatives of 5-iodoisoxazole **115** with a yield of 90% [236].

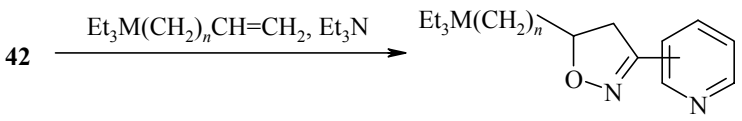


112 **113**



114 **115**

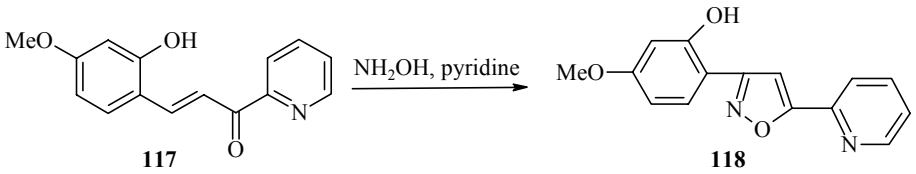
The 1,3-dipolar cycloaddition of nitrile oxides, produced from the oximes, to unsaturated stannanes and germanes was reviewed in [237]. The reaction of hydroximoyl chlorides **42** with vinyl- or allylsilanes (or the germanes) gives the 2-isoxazolines **116** with yields of 42-73% [238].



116

M = Si, Ge; n = 0, 1

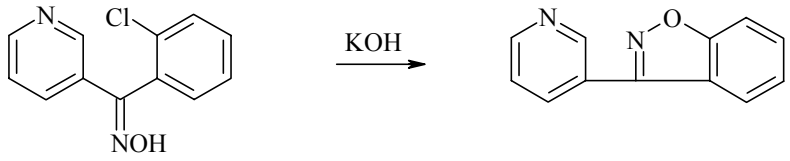
Sometimes pyridine chalcones in reaction with hydroxylamine form isoxazoles instead of the expected oximes. For example, 1-(2-hydroxy-4-methoxyphenyl)-3-(2-pyridyl)-1-propanone (**117**) in the hydroxylamine/pyridine/ethanol system gives 3-(2-hydroxy-4-methoxyphenyl)-5-(2-pyridyl)-1,2-oxazole (**118**) with a yield of 77% [239].



117 **118**

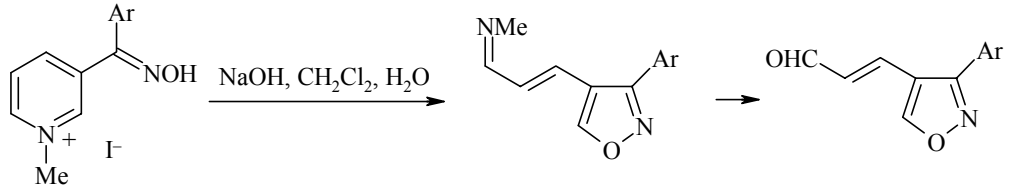
Similarly, 5-acetyl-4-aryl-6-methyl-3,4-dihydro-2(1H)-pyridones give isoxazolo[5,4-*b*]pyridin-6(7H)-ones [240]. In the presence of hydroxylamine cyanomethylpyridines and pyridine β-dicarbonyl compounds ($PyCOCH_2COR$) are converted into 5-amino-3-(pyridyl)isoxazoles [241, 242] or 3,5-disubstituted isoxazoles [243] respectively.

When heated in ethylene glycol monomethyl ether in the presence of potassium hydroxide 3-(2-chlorobenzoyl)pyridine oxime forms 3-(2-1H-pyridinon-3-yl)-1,2-benzisoxazole (**120**). The product **120** was also obtained from 5H-[1]benzopyrano[2,3-*b*]pyridin-5-one in the $NH_2OH{\cdot}HCl$/ /KOH/EtOH system [244].



119 **120**

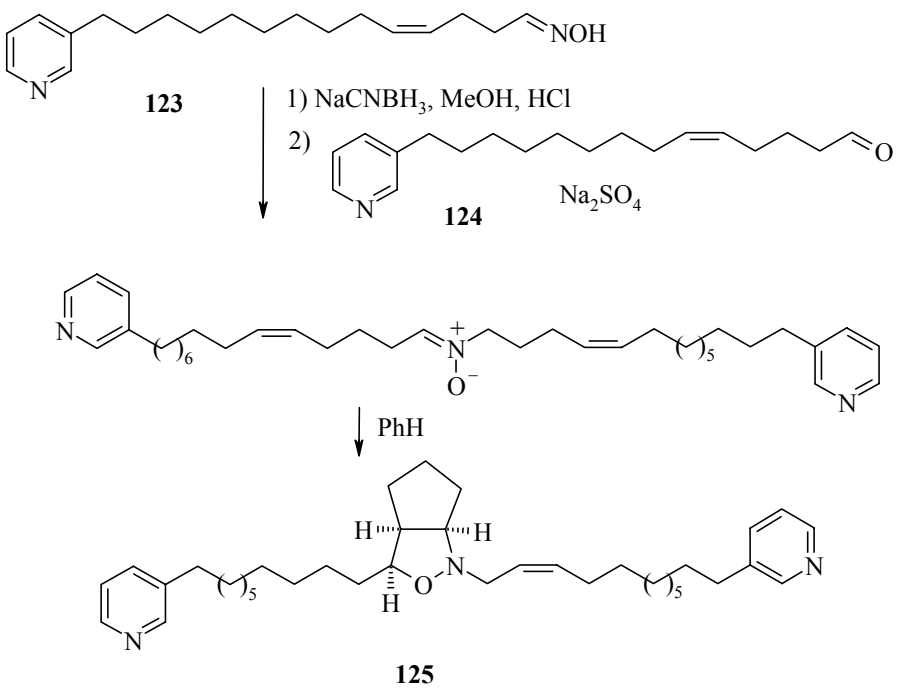
The quaternized pyridine oximes **121** undergo cyclization in a basic medium with the formation of the isoxazole acrylaldehydes **122**, and the reaction takes place through opening of the pyridine ring [245].



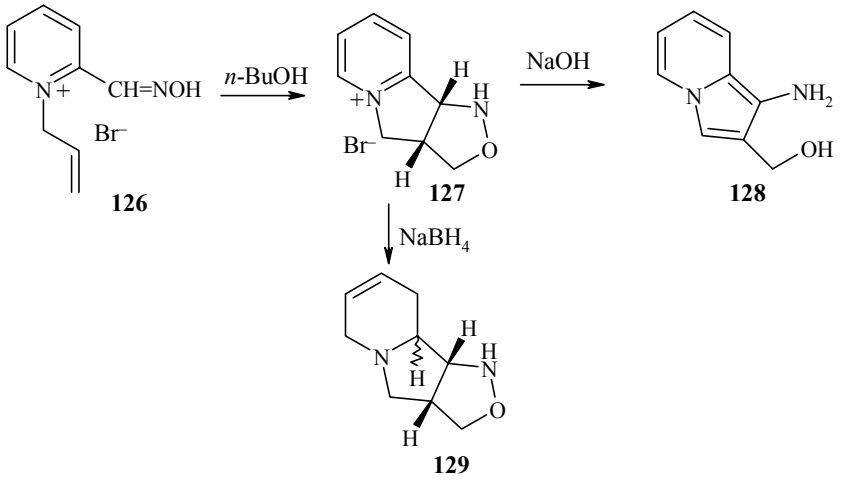
121 **122**

Ar = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$

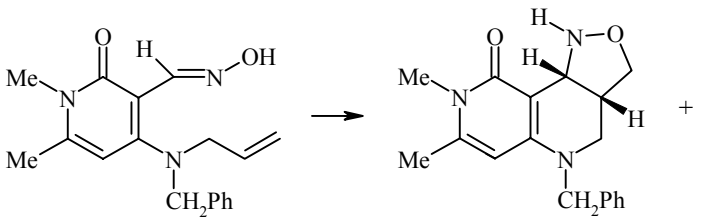
The three-stage synthesis of the cytotoxic alkaloid pyrinodemin A **125** was described by the authors of [246]. Thus, reduction of the oxime **123** with $NaCNBH_3$ in methanol followed by reaction with the aldehyde **124** and thermal cyclization of the intermediate leads to the product **125**.



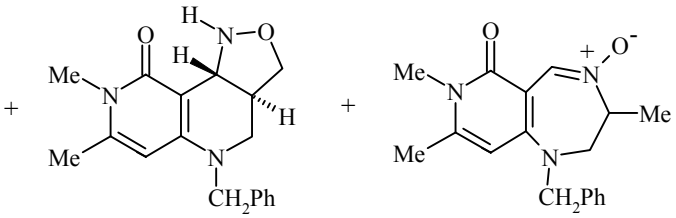
The 1,2-prototropy of oximes and the generation of the corresponding nitrones were described in [247]. For example, the pyridine oxime **126** gives the isoxazoline **127** when boiled. The unstable cyclic adduct **127** is easily transformed into the indolizine **128** (yield 62%) in an alkaline medium or is reduced ($NaBH_4$) to the tricyclic product **129** (yield 60%).



Thermal cyclization of the *E*-isomer of the oxime **130** in benzene leads to the formation of two isomeric isoxazolines **131** and **132** and the N-oxide **133** (yields 76, 14, and 8% respectively). However, the cyclization of the oxime **130** in ethanol gives only the product **131** with a 93% yield [247].



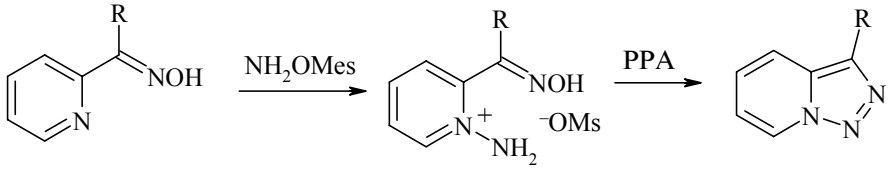
130 **131**



132 **133**

The synthesis and reactions of the oxazole derivatives of pyridine oximes were described in [248].

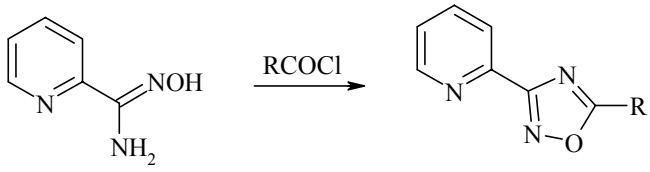
The synthesis of triazoles from pyridine oximes was realized in [226, 249]. For example, the reaction of the oximes **134** with O-mesitylsulfonylhydroxylamine and then with polyphosphoric acid (PPA) leads to triazolo[1,5-*a*]pyridines **135** with yields of 63-76% [226].



134 **135**

R = H, Me, Ph

Derivatives of biologically active oxadiazoles were obtained from pyridine amidoximes [250-255]. Reactions leading to the synthesis of pyridine-containing 1,2,4-oxadiazoles usually include acylation of the amidoximes with acetic anhydride [256] or acyl chlorides [257-259] followed by thermal cyclization. For example, 2-pyridineamidoxime (**136**) and acyl chlorides give the oxadiazoles **137** with yields of 27-70% [259].

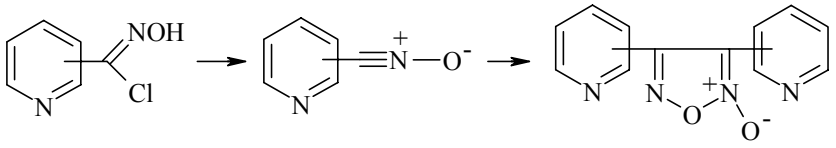


136 **137**

R = Me, NMe_2

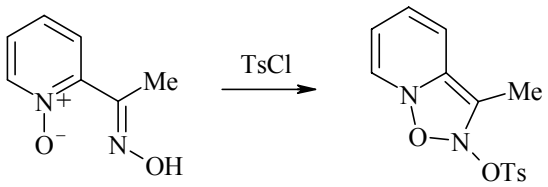
3-Pyridyl-1,2,4-oxadiazoles were also obtained by the reaction of pyridine amidoximes with aldehydes in acetic acid [260].

Pyridine nitrile oxides, obtained from hydroximoyl chlorides **138**, readily dimerize to the furoxans **139** on standing [72] or in the presence of a base [261].



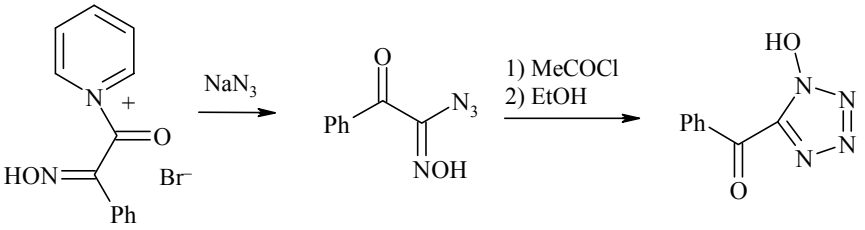
138 **139**

During tosylation the *E*-oxime of 2-acetylpyridine 1-oxide (**140**) gives the 1,2,5-oxadiazole **141** as the only product, and in the presence of tosyl chloride the *Z*-isomer of the oxime **140** forms the corresponding O-tosyloxime [262].



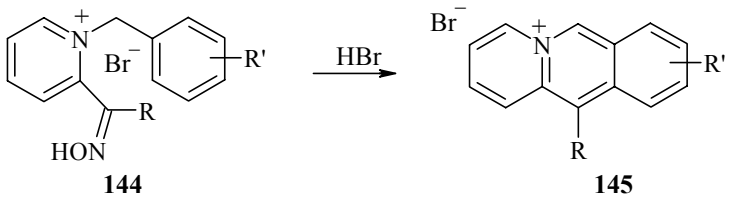
140 **141**

5-Benzoyl-1-hydroxytetrazole (**143**) was obtained from the oxime **142** in reaction with sodium azide and then with acetyl chloride and ethanol. The product **143** is formed through benzoyl azidooxime as intermediate [263].

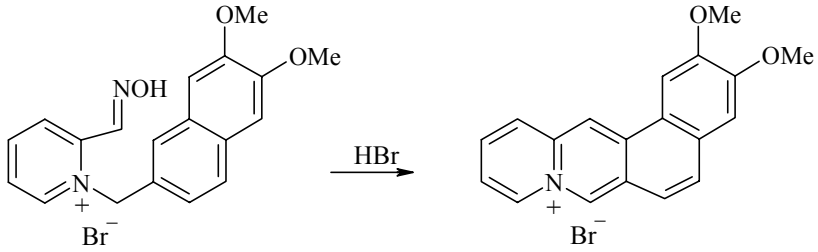


142 **143**

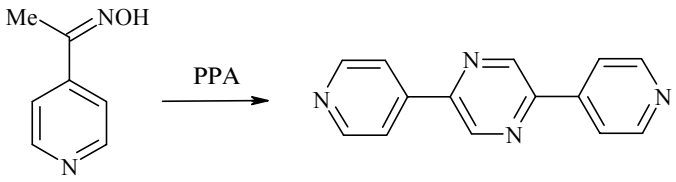
Pyridine oximes have been used successfully in the synthesis of derivatives of acridizine [264, 265], benzoquinolizine [266], naphthoquinolizine [267], and thienonaphthiridine [268]. For example, the oxime salt **144** readily undergoes cyclization in 48% aqueous HBr with the formation of derivatives of acridizine **145** with yields of 21-99% [264]. Naphtho[1,2-*b*]quinolizine **147** was obtained under similar conditions from the pyridine oxime salt **146** with a yield of 45% [267].



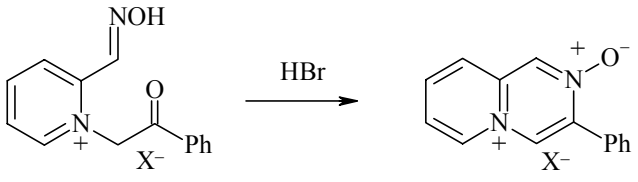
R = H, Me; R' = H, Me, OMe



In the presence of polyphosphoric acid 4-acetylpyridine oxime dimerizes with the formation of the pyridazine **149** [44].

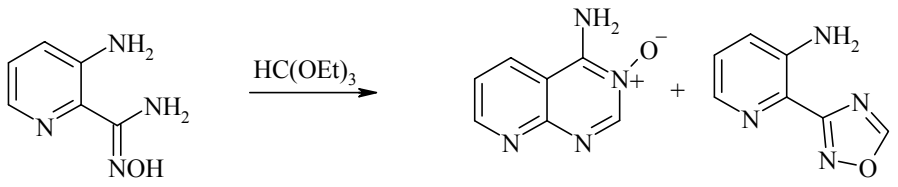


In concentrated hydrobromic acid the pyridine oxime salt **150** is transformed into 3-phenyl-3-azaquinolizinium 2-oxide **151** with a yield of 85% [269].

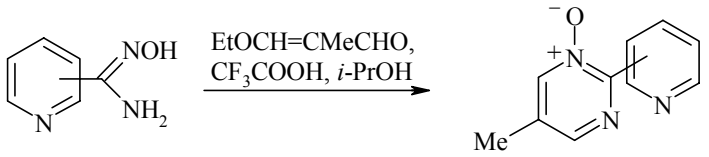


X = Br, picryl

A series of papers have been devoted to the synthesis of derivatives of pyrimidine from pyridine amidoximes [270-273]. In boiling triethyl orthoformate 2-amino-3-pyridylamidoxime (**152**) gives a mixture of 4-aminopyrido[2,3-*b*]pyrimidine 3-oxide (**153**) (yield 89%) and 1,2,4-oxadiazole (**154**) (yield 1.3%) [270]. In the 3-ethoxy-2-methylpropenal/CF_3COOH/isopropanol system the pyridine amidoximes **155** give 5-methyl-2-pyridylpyrimidine 1-oxides **156** with yields of 65-83% [272, 273].

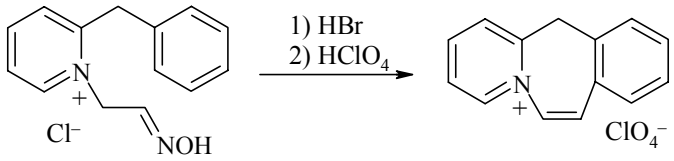


152 **153** **154**

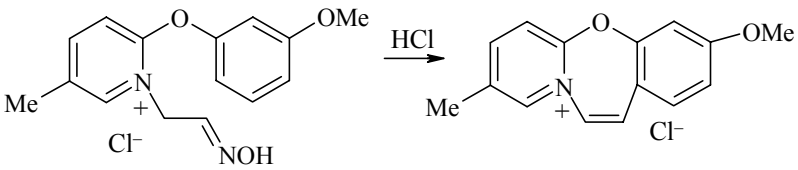


155 **156**

The synthesis of seven-membered heterocyclic compounds was also realized from the salts of pyridine oximes. In 48% aqueous hydrobromic acid 1-(2-hydroxyiminoethyl)-2-benzylpyridinium chloride (**157**) undergoes cyclization with the formation of the salt **158** with a yield of 81%. The cyclization of the oxime **159** to the oxazepine **160** was also realized in an acidic medium (HCl) [266].



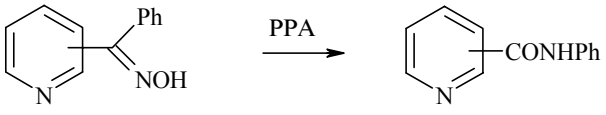
157 **158**



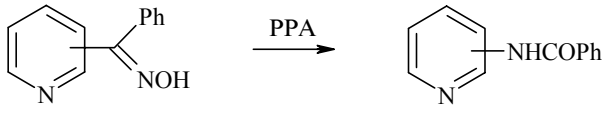
159 **160**

3.4. Beckmann Rearrangement of Pyridine Oximes

The Beckmann rearrangement is one of the most characteristic reactions of oximes. The rearrangements of pyridine oximes into the corresponding amides has usually been conducted in the presence of PCl_5 in THF [274], P_2O_5 in phosphoric acid [275], $SOCl_2/CHCl_3$ [5, 276], or HCOOH [277]. The *E*- and *Z*-isomers of pyridine oximes rearrange with the formation of various amides [44, 278]. Rearrangement of the *E*- and *Z*-oximes of pyridine ketoximes **161** gives the amides **162** and **163** respectively.

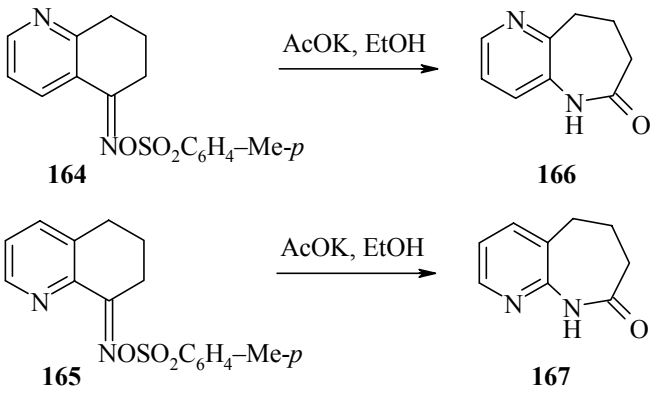


E-**161** **162**



Z-**161** **163**

The synthesis of the azepines **166** and **167** was realized successfully as a result of the Beckmann rearrangement of the oxime tosylates **164** and **165** respectively in the AcOK/EtOH/H_2O system [279].



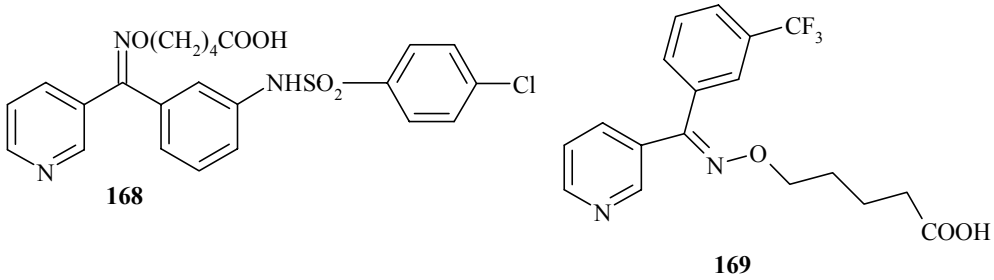
164 **166**

165 **167**

4. THE BIOLOGICAL ACTIVITY OF DERIVATIVES OF PYRIDINE OXIMES

4.1. Action on the Cardiovascular System

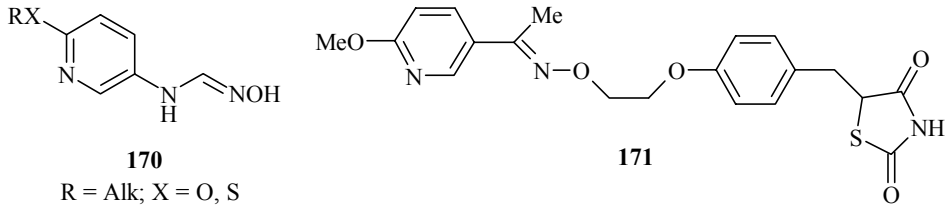
A broad spectrum of activity of pyridine oximes on the cardiovascular system has been investigated. Pyridine oximes (Py–CX=NOH; Py = pyridyl, X = halogen) and their salts have been proposed as agents against ischemic heart disease and are inhibitors of the aggregation of blood cells [280-283]. It is necessary to mention the oxime phenylsulfonamide derivative **168** [284] and ridogrel **169** in particular [285].



168

169

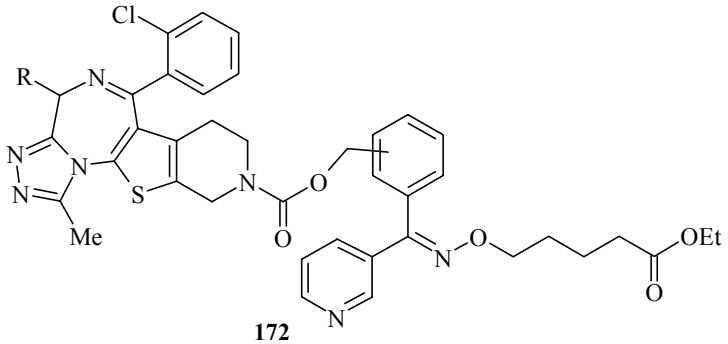
Pyridine oximes {e.g., **170** [286]} have been proposed as cerebro- or cardiovascular agents [287, 288] and cardiotonics [289, 290]. The O-ethers of pyridine hydroximoyl chlorides [291, 292], amidoximes [293, 294], or ketoximes [295, 296] can be used as antidiabetic agents. For example, the ether **171** reduces the blood glucose level in mice by 49.3% at a dose of 1 mg/kg perorally [295].



170
R = Alk; X = O, S

171

Several papers have been devoted to study of the ethers of pyridine oximes [e.g., **172**] as antagonists of the factor in the activation of blood cell receptors and as thromboxane synthetase inhibitors [297-299]. These compounds were proposed as agents against allergy, ischemic heart disease, inflammation, thrombosis formation, and treatment of psoriasis.



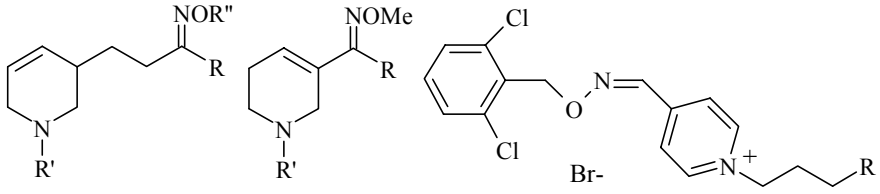
172

R = H, Me

It is necessary to mention the vasodilator [300-302] and antihypertonic [303, 304] activity of pyridine oxime derivatives. These compounds have also been used as agents reducing the blood sugar level [305].

4.2. Sedative, Antidepressant, and Antispasmodic Activity

Derivatives of pyridine ketoximes have been investigated as antidepressants [306, 307] and tranquillizers [308]. The N-oxides of pyridine O-alkyloximes were tested as agents for the control of neurotic reactions [309]. The ability to bind sigma receptors was recently discovered in tetrahydropyridine oximes **173**. Compounds **173** were tested as antidepressants in psychoses and as anti-inflammatory agents [310]. Antispasmodic activity was detected in the oxime derivatives of tetrahydropyridines [311], and they are moreover muscarine receptor agonists [166, 312-315]. Oxime derivatives of 1,2,5,6-tetrahydropyridine were studied as agents for the treatment of dementia [316]. Among agents against Alzheimer's disease it is necessary to mention the ethers **174**. Quaternized derivatives of pyridine oximes are allosteric modulators of muscarine receptors [317].



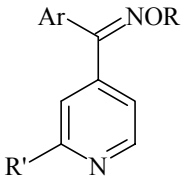
173 **174** **175**

173 R = Alk, Ar; R' = Alk; R" = H, Alk, CH_2Ph;

174 R = H, Alk, CN, Cl, F; R' = H, Alk; **175** R = Alk, Ar

4.3. Analgesic and Anti-inflammatory Activity

Derivatives of pyridine aldoximes [318] and O-substituted tetrahydropyridine oximes [319] have exhibited analgesic activity. Papers [320-322] were devoted to the study of pyridine oximes as anti-inflammatory agents. For example, the ethers of arylpyridine oximes **176** have anti-inflammatory and antiasthmatic activity [322]. In addition, the oxime ethers of 1-pyridyl-3-pentanone [323] and pyridyl phenyl ketones [324] exhibited antihistamine or spasmolytic activity.



176

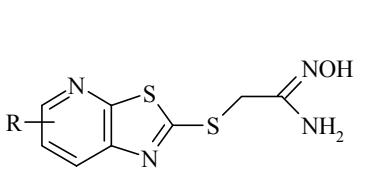
R = H, Alk, COAlk; R' = Alk, CO_2Alk, $CON(Alk)_2$, $CSN(Alk)_2$, CN, NO_2, OAlk, $S(O)_n$Alk, n = 0–2

Derivatives of 1,2,5,6-tetrahydropyridine oximes [325-328] and the salts of bispyridinium oximes [329, 330] displayed high activity on choline receptors. These compounds can be used both as agents lowering body temperature and as analgesics.

4.4. Cytotoxic, Antiviral, and Bactericidal Activity

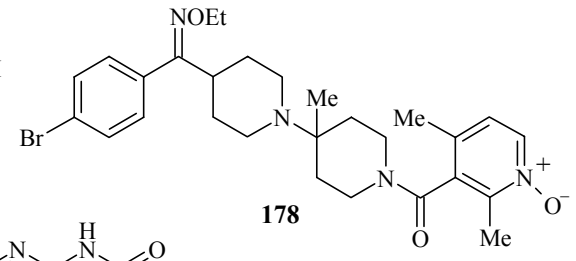
Derivatives of pyridine oximes have been studied little as cytotoxic and antiviral agents. Recently it was shown that silicon-containing pyridine oximes have high cytotoxicity on HT-1080 (human fibrosarcoma) and MG-22A (mouse hepatoma) strains (see section 3.1) [159].

Oxime derivatives of thiazolo[5,4-*b*]pyridine **177** exhibit activity against *influenza B-Mass* virus [331]. Among the antiviral agents should be mentioned the oxime derivatives of pyridine **178** [332] and naphthiridine **179** [333], which exhibit high activity against HIV-1.



177

R = H, Cl, Br



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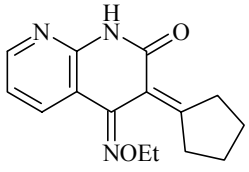
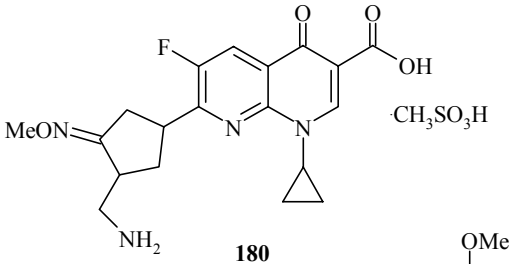


179

Pyridine aldoximes [334], oximes of 2-[2-(5-nitro-2-furyl)vinyl]-5-acetylpyridine [335], 2-(pyridyloxymethylphenyl)-2-alkoxyimino-N-alkylacetamides [336], and amidoximes [337, 338] have bactericidal activity. Recently it was shown that the oximes of naphthiridine have a broad spectrum of

antibacterial activity [339-343]. Among these compounds it is necessary to mention hemifloxacin mesylate **180**. Bactericidal activity was exhibited by the natural compounds *caerulomycin A* **181** and *collismycin A* **182** [344] and their analogs [345].



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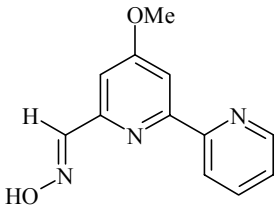

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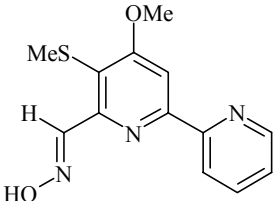
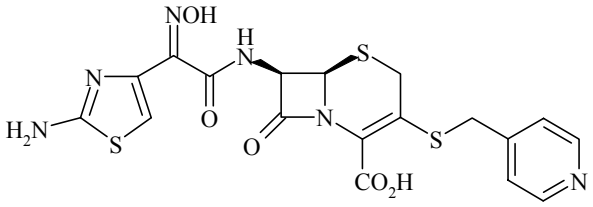


182

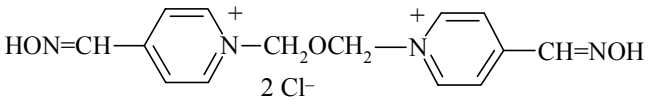
Fragments of pyridine oximes enter into the structure of certain cephalosporin antibiotics [346-350], and the oxime **183** can be cited as an example.



183

4.5. Pyridine Oximes as Antidotes for Poisoning by Organophosphorus Compounds

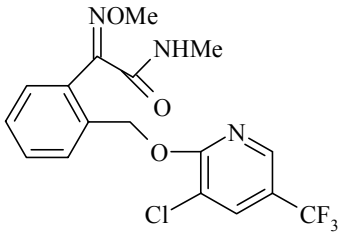
Numerous publications have been devoted to investigation of pyridine oximes as antidotes against poisoning by organophosphorus compounds [29, 351-358]. The mechanism of the action of the oximes was discussed in detail in the review [359]. The high activity of pyridine aldoximes [360-398], ketoximes [399, 400], amidoximes [401], and their salts should be noted. The ethers of pyridine [402, 403] and bispyridine oximes [404-426] have been widely investigated as inhibitors of acetylcholineesterase. The product obidoxime (toxogonin) **184** has received the widest application.



184

4.6. Pyridine Oximes as Fungicides, Pesticides, Herbicides, and Acaricides

Pyridine oxime derivatives have high fungicidal activity [157, 427-450]. For example, compound **185** shows 100% control over *Sphaerotheca fulginea* at 500 ppm [430]. The oxime ethers **186** (>90% control over *Plasmopara viticola* at 100 g/ha [442]) and **187** (>95% control over *Phytophthora infestans*, *Erysiphe graminis*, and *Puccinia recondita* at 100 ppm [450]).



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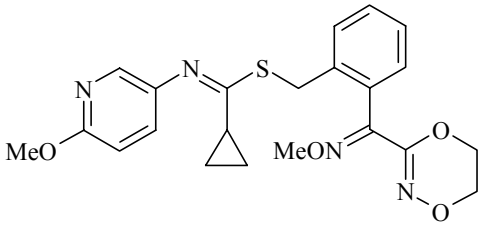

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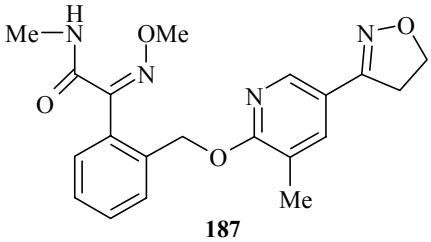
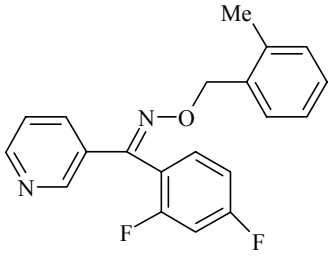


187

Pyridine oximes are widely used as herbicides [1, 451-462]. It is necessary to mention the oxime **188**, which inhibits *Eshinochloa crus-galli* in rice fields [459].



188

Pyridine oximes and their ethers also have pesticidal [463-467] and acaricidal [468] activity.

4.7. Other Activities

Derivatives of 3-pyridine aldoxime are used as agents against hepatitis [469, 470]. Pyridine oxime derivatives also exhibited antiulcer activity [471]. They are inhibitors of fatty acid hydroxylase [472], 5-lipoxygenase [473], modulators of p38 MAP kinase [474], and antiandrogens [475].

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