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OXIMES OF SIX-MEMBERED HETEROCYCLIC COMPOUNDS WITH TWO AND THREE HETEROATOMS. II.* REACTIONS AND BIOLOGICAL ACTIVITY (REVIEW)

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Data on the reactions of pyridazine, pyrimidine, pyrazine, triazine, oxazine, thiazine, oxadiazine, and thiadiazine aldoximes, ketoximes, and amidoximes and their derivatives are reviewed. The synthesis of new heterocycles based on the oximes of six-membered heterocyclic compounds with two and three heteroatoms is considered separately. The principal results of research into the biological activity of these oximes and their ethers are also presented.

Keywords: oxadiazine, oxazine, oxime, pyrazine, pyridazine, pyrimidine, thiadiazine, thiazine, triazine.

The oximes of six-membered heterocyclic compounds with two and three heteroatoms are widely used as intermediates in fine organic synthesis. Their production methods and structural features were examined in the review [1]. In this article we discuss the reactions of pyridazine, pyrimidine, pyrazine, triazine, oxazine, thiazine, oxadiazine, and thiadiazine aldoximes, ketoximes, and amidoximes and their derivatives. Methods for the synthesis of new heterocyclic systems from the derivatives of these oximes are considered in a separate section. In the last section some results from investigation of the biological activity of the ethers of these oximes are considered.

1. CHEMICAL TRANSFORMATIONS OF THE OXIMES OF SIX-MEMBERED HETEROCYCLIC COMPOUNDS WITH TWO AND THREE HETEROATOMS

1.1. Synthesis of the O-Derivatives of the Oximes

1.1.1. O-Ethers of Pyridazine Oximes

The principal method for the production of the ethers of pyridazine oximes is alkylation by alkyl halides in the NaH/DMF system [2]. In addition, the O-ethers of pyridazine oximes were obtained from the carbonyl derivatives and hydrochlorides of the O-alkyl derivatives of hydroxylamines in the presence of sodium acetate in methanol [3].

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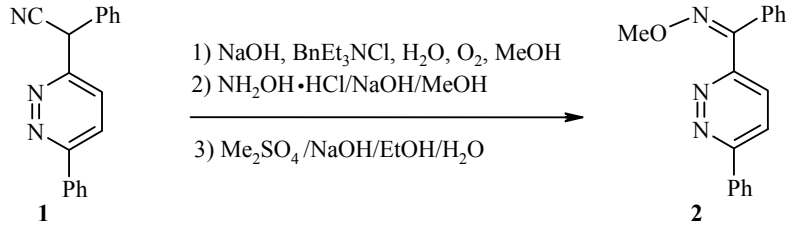
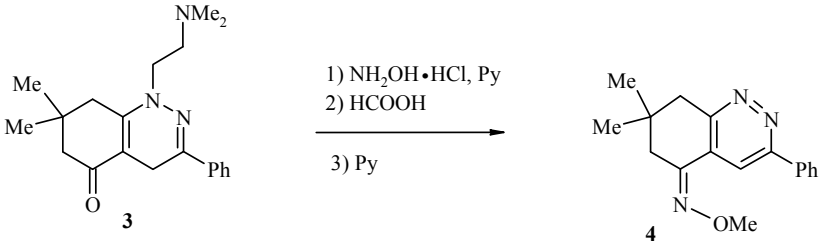
A three-stage method was developed for the synthesis of O-ether derivatives of the pyridazine ketoxime **2** from the nitrile **1** [4]. The reaction mechanism involves oxidative hydrolysis of the initial nitrile to the ketone followed by synthesis of the oxime ether **2** under the conditions of phase-transfer catalysis.



1 **2**

The O-methyloxime of 7,7-dimethyl-3-phenyl-7,8-dihydro-6H-cinnolin-5-one (**4**) was obtained in the reaction of the 2-dimethylamino derivative **3** in the hydroxylamine hydrochloride/pyridine system followed by reaction with formic acid and pyridine. The reaction results in aromatization of the pyridazine ring [5].

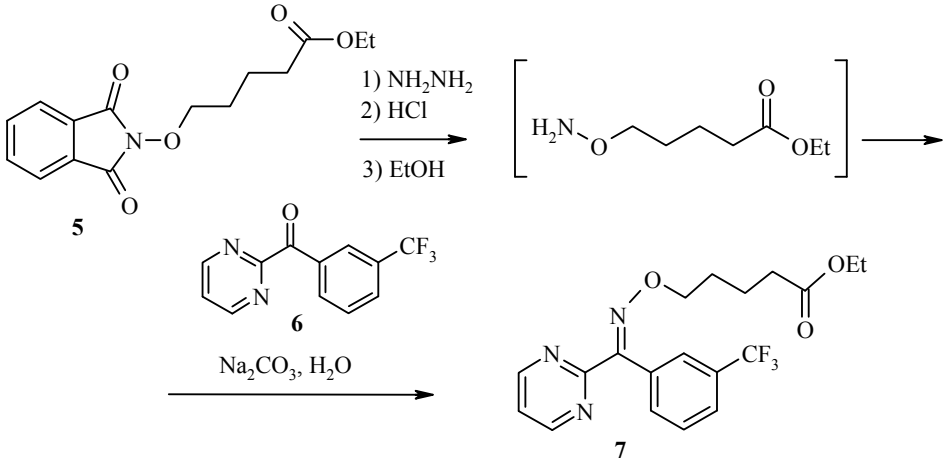


3 **4**

The O-acetyloxime of 5-chloro-2-hydroxypyridazine-3-carbaldehyde was obtained from the corresponding oxime and acetic anhydride [6]. A method was also developed for the synthesis of ethers of pyridazine oximes from the dichloro derivatives of pyridazines and various oximes in the NaH/DMF or NaOH/acetone systems [7].

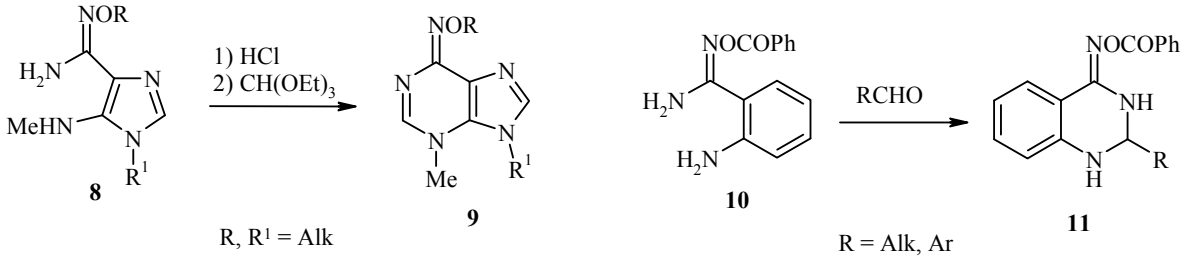
1.1.2. O-Ethers of Pyrimidine Oximes

The O-ethers of pyrimidine oximes are usually obtained from the oximes and alkyl halides in the K_2CO_3/MeCN [8] or NaH/DMF [9] systems. The literature also contains information about the synthesis of pyrimidine oxime ethers from the corresponding carbonyl compounds and O-alkoxyhydroxylamines [2, 10, 11]. For example, the reaction of the phthalimide derivative **5** with hydrazine and then with hydrochloric acid leads to the formation of the O-alkylhydroxylamine, which readily condenses with the pyrimidine ketone **6** in the presence of an aqueous solution of Na_2CO_3 and gives the O-alkyloxime **7** [2].



5 **6** **7**

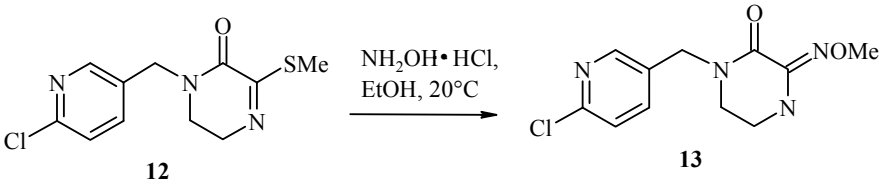
Cyclization of the O-ethers of imidazole amidoximes **8** with triethyl orthoformate in the presence of hydrochloric acid gives the adenine O-alkyloximes **9** [12, 13]. A similar reaction of the amine **10** with aldehydes leads to the ethers **11** [14].



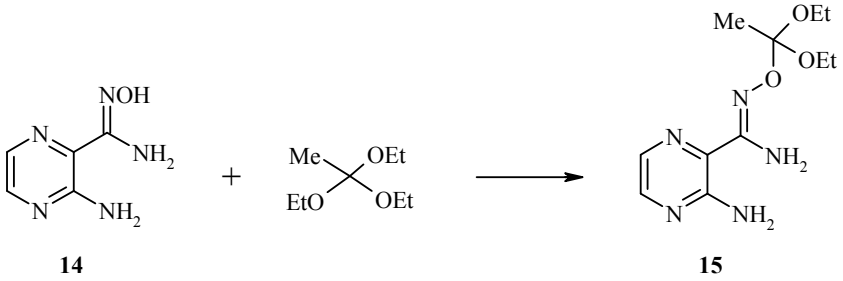
O-Acylated pyrimidine oximes were also obtained from the corresponding oximes and acid chlorides or anhydrides [15-18].

1.1.3. O-Ethers of Pyrazine Oximes

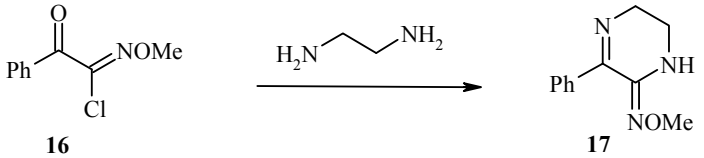
The chief method for the production of O-ethers of pyrazine and quinoxaline oximes is based on alkylation of the oximes with alkyl halides in the presence of sodium hydride [19, 20] or sodium isopropoxide in 2-propanol [21]. O-Ethers of pyrazine oximes were also obtained from carbonyl derivatives and the hydrochlorides of O-methylhydroxylamines in the presence of $NaHCO_3$ in aqueous ethanol [22]. The literature contains one example of the synthesis of the 3-methyloxime of 1-[(6-chloropyridin-3-yl)methyl]piperazine-2,3-dione (**13**) by nucleophilic substitution of the methylthio group in the derivative of 3-methylthio-5,6-dihydropyrazin-2-one **12** [23].



It is interesting that the action of heat on a mixture of 2-aminopyrazine-3-carboxamide oxime (**14**) with triethyl orthoacetate leads to the formation of the ether **15** with a yield of 53% [24].



Cyclization of the hydroximoyl chloride derivative **16** with ethylenediamine results in the formation of the O-methyloxime of 3-phenyl-5,6-dihydro-2(1H)-pyrazinone (**17**) [25].

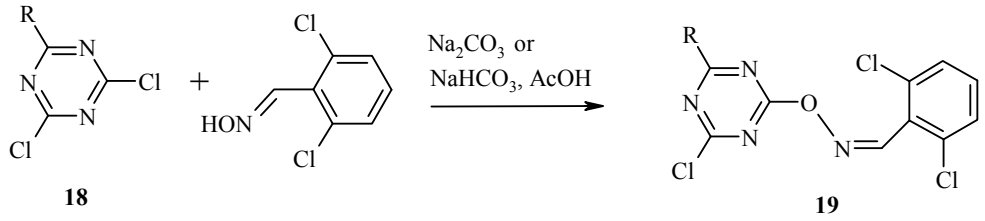


The synthesis of O-acyl derivatives of pyrazine and quinoxaline oximes is realized by acylation of the oximes in the presence of acetic anhydride [26, 27] or by the use of alkyl isocyanates [28, 29].

1.1.4. O-Ethers of 1,2,4- and 1,3,5-Triazine Oximes

The O-methyl ethers of 1,2,4-triazine oximes were obtained by alkylation of the oximes in the presence of NaH in DMF [30]. The O-acetyl derivatives of 1,2,4-triazine oximes were produced in the oxime/acetic anhydride/pyridine/benzene system [31].

The reactions of 2,4-dichlorotriazine derivatives **18** with 2,6-dichlorobenzaldoxime in an aqueous solution of Na_2CO_3 or $NaHCO_3$ give the O-ethers **19** [32]. The ether derivatives of triazine oximes are used as photoactive agents [33].

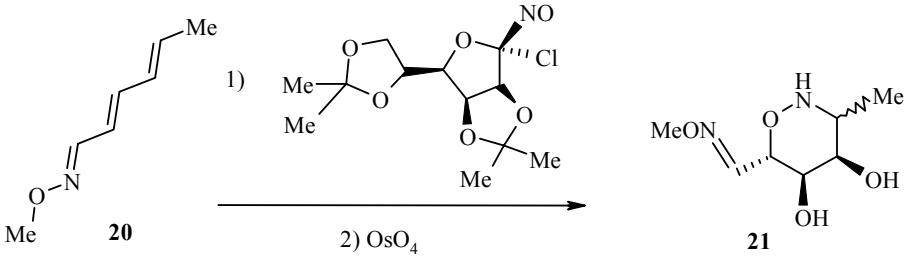


R = NH_2, NHEt, NHPh

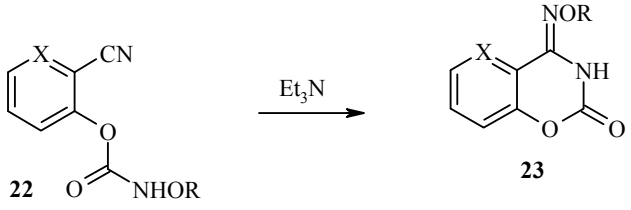
O-Acylated 1,3,5-triazine oximes were obtained from the corresponding oximes and chlorides [34] or acid anhydrides [35, 36].

1.1.5. O-Ethers of 1,2-, 1,3-, and 1,4-Oxazine and 1,4-Thiazine Oximes

O-Ethers of 1,2-oxazine oximes were obtained from carbonyl derivatives and the hydrochlorides of O-methylhydroxylamines in the presence of $NaHCO_3$ in aqueous ethanol [37]. Cyclization of the O-methyl oxime of hexa-2,4-dienal (**20**) in the presence of a chiral chloronitroso dienophile in chloroform followed by oxidation (with OsO_4) gives the 1,2-oxazine O-methyloxime **21** [38, 39].

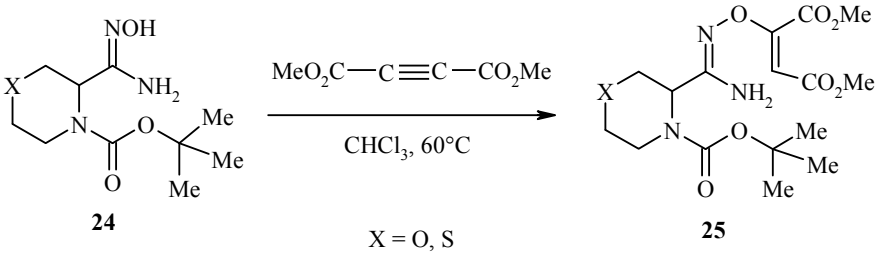


Cyclization of derivatives of acylated *o*-cyanophenols **22** in the presence of triethylamine leads to the ethers of 1,3-oxazine oximes **23** [40, 41].



X = CH, N; R = Alk

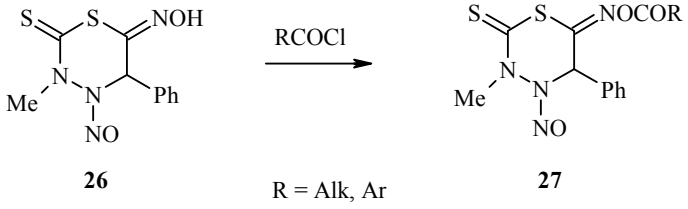
The addition of dimethyl acetylenedicarboxylate to derivatives of morpholine or 1,4-thiazine oximes **24** gives the oxime ethers **25** as the only products [42].



O-Acetyl derivatives of morpholine oximes were obtained in the oxime/acyl chloride/ethyl acetate system or in chloroform [43, 44].

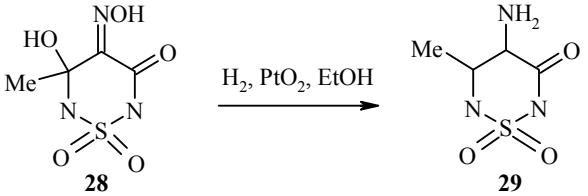
1.1.6. O-Ethers of 1,3,4-Thiadiazine Oximes

The acylation of 6-hydroxyimino-3-methyl-4-nitroso-5-phenyltetrahydro-1,3,4-thiazine-2-thione (**26**) in the acyl chloride/pyridine/acetonitrile system gives 16-72% yields of the acylated oximes **27** [45, 46].

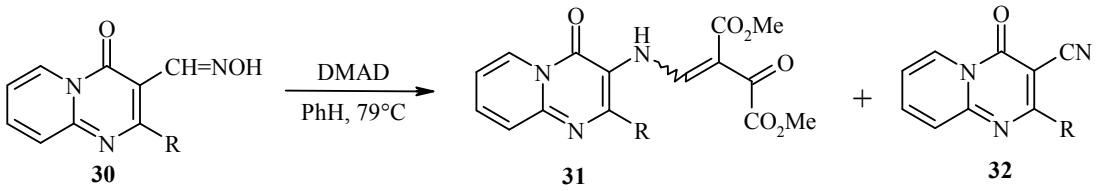


1.2. Transformations of the Oxime Group

Pyridazine ketoximes and their O-ethers are easily reduced to the corresponding amines in the presence of $LiAlH_4$ in diethyl ether [47, 48] or in the H_2/PtO_2 system [49]. Hydrogenation of uracil oximes in the presence of nickel catalysts also leads to the corresponding amines [50]. The reduction of 1,2,4-triazole ketoximes in the presence of baker's yeast leads to secondary triazole alcohols [51]. The synthesis of the respective hydroxylamines [52] or amines [53, 54] is easily realized by the reduction of 1,2- and 1,3-oxazine ketoximes in the presence of $NaCNBH_3$ [52] or $LiAlH_4$ [54]. Hydrogenation of the oxime group of 1,2-thiazine ketoximes in the presence of Raney nickel in acetic acid gives primary amines [55]. However, the hydrogenation of the 1,2,6-thiazine oxime **28** on PtO_2 leads to the product **29**. Thus, in this reaction reduction of the alcohol group in the thiadiazine ring is observed in addition to hydrogenation of the oxime group [56].



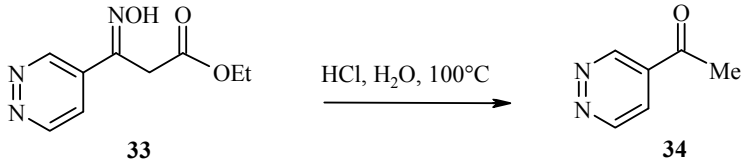
Pyrimidine aldoximes are converted into nitriles in the presence of $Ac_2O/SOCl_2$ [57], PPh_3 [58], or $POCl_3$ [59, 60]. It is interesting that the reaction of derivatives of pyrido[1,2-*a*]pyrimidine aldoximes **30** with dimethyl acetylenedicarboxylate leads to a mixture of enamines **31** (yields up to 84%) and nitriles **32** [61]. In boiling acetic anhydride in the presence of sodium acetate quinoxaline aldoximes form nitriles [62].



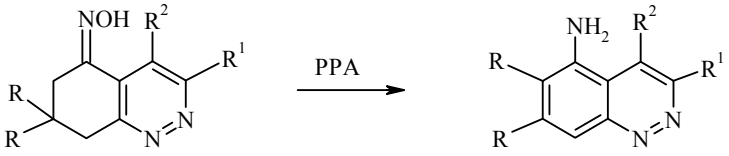
30 **31** **32**

R = OBn, OEt; DMAD – dimethyl acetylenedicarboxylate

The action of heat on the pyrazine oxime **33** in an aqueous solution of HCl leads to the ketone **34** as a result of deoximation followed by decarboxylation of the ester group [63]. Aromatization of 5,6,7,8-tetrahydrocinnoline oximes **35** to aminocinnolines **36** as a result of a Semmler–Wolff rearrangement was realized in the presence of PPA [5].



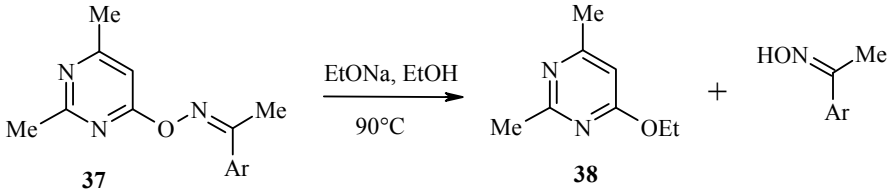
33 **34**



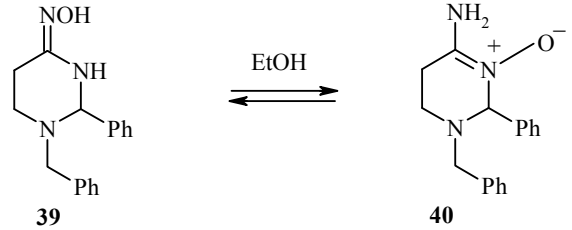
35 **36**

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

Hydrolysis of the pyrimidine oxime ethers **37** in the presence of sodium ethoxide gives the ethers **38** [64]. The reversible isomerization of 1,2-disubstituted 4-hydroxyiminohexahydropyrimidines was described in [65]. Thus, in alcohols the oxime **39** isomerizes to the nitrone **40**. In aprotic solvents, however, the reverse process, i.e., the transformation of compound **40** to the oxime **39**, is observed [65]. In the presence of trivalent iron nitrate the pyrimidine ketoximes are converted into nitro derivatives [66].



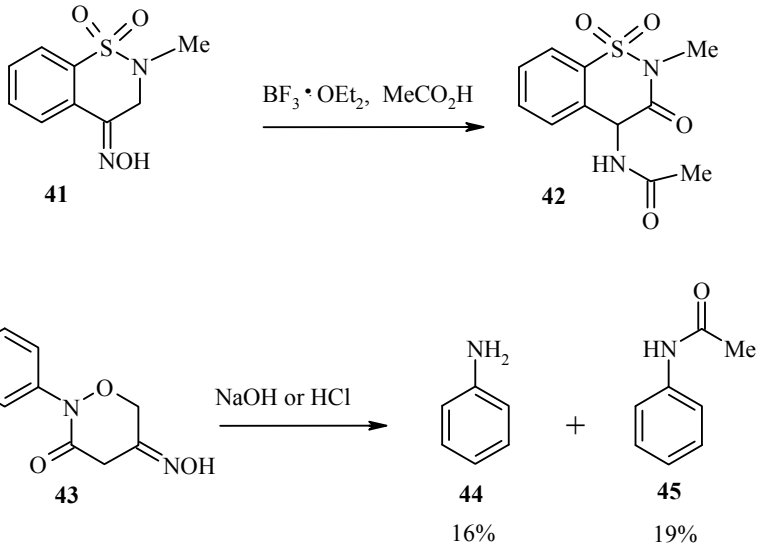
37 **38**



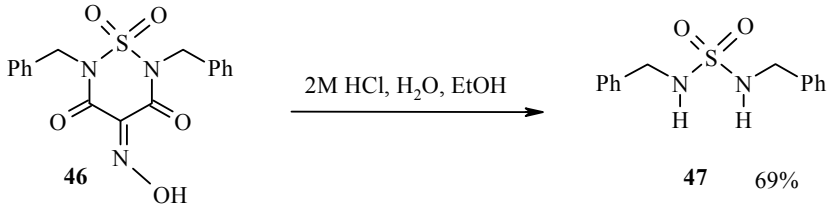
39 **40**

The deoximation of quinoxaline aldoximes in the $NaNO_2/H_2SO_4$ [67] and $NaNO_2/HCl/H_2O$ [68] systems and the Beckmann rearrangement of thiazine ketoximes in the $LiAlH_4$/ether system [69] are also represented in the chemical literature.

In the presence of $BF_3 \cdot OEt_2$ in acetic acid the oximes of 1,2-thiazin-3-one **41** rearrange to the amide **42** [70]. In aqueous alkali or in hydrochloric acid the 1,2-oxazine oxime **43** forms aniline **44** and N-acetylaniline **45** [71].



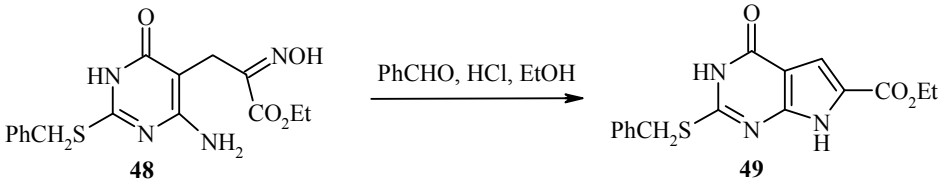
In a boiling water–ethanol solution of hydrochloric acid the 1,2,6-thiadiazine oxime **46** gives N,N-dibenzylsulfamide **47** with a yield of 69% [72].

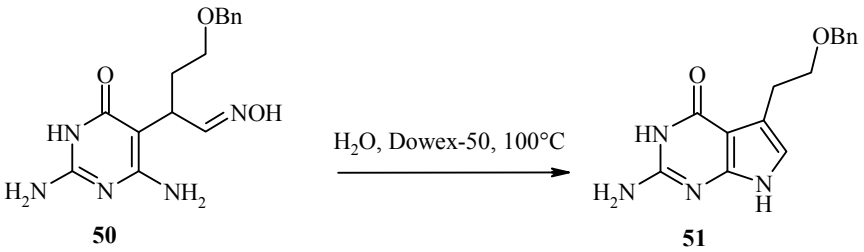


1.3. Synthesis of New Heterocyclic Systems from the Oximes of Six-Membered Heterocyclic Compounds with Two and Three Heteroatoms

Recent advances in the synthesis of heterocyclic systems from oximes were summarized in the reviews [73, 74]. In this section specific cyclization reactions of the oximes of six-membered heterocyclic compounds with two and three heteroatoms will be set out in greater detail.

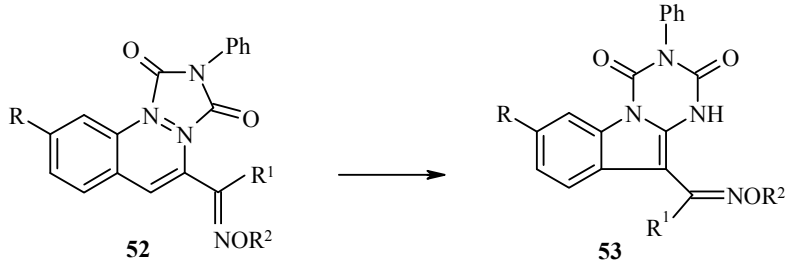
Several papers have been devoted to the synthesis of new heterocyclic systems containing a pyrrole or indole ring. In the reaction of the pyrimidone oxime **48** with hydrochloric acid in the presence of benzaldehyde the derivative of 4,7-dihydropyrrolo[2,3-*d*]pyrimidine **49** is formed with an 81% yield [75]. The similar reaction of the oxime **50** in the presence of Dowex-50 resin in water leads to the formation of the product **51** with a 71% yield [76].





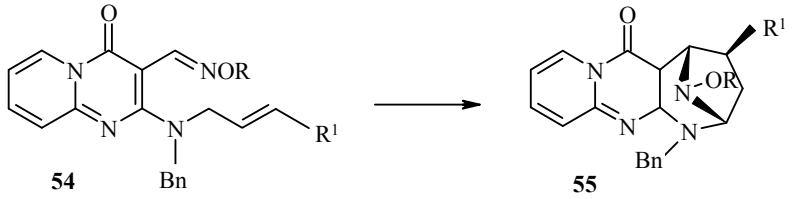
50 **51**

The photoinduced rearrangement of derivatives of cinnoline oximes **52** leads to the indole derivative **53** [77]. In the thermic reaction of pyrido[1,2-*a*]pyrimidine aldoximes **54** in *o*-dichlorobenzene tetracyclic derivatives of pyrrolidine **55** were isolated as the main products [78].



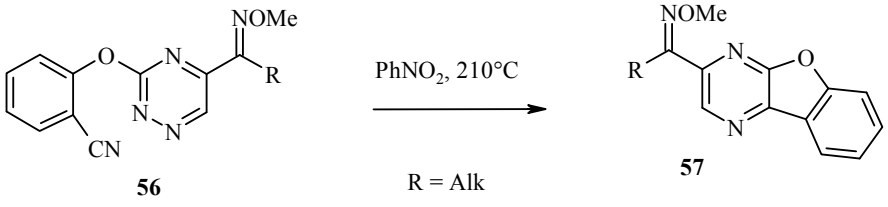
52 **53**

R = H, Cl, OMe; R^1, R^2 = Alk



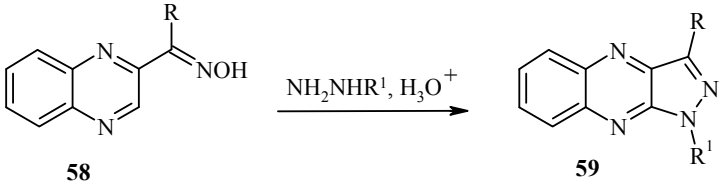
54 **55**

As a result of an intramolecular Diels–Alder reaction 1,2,4-triazine ketoxime **56** is converted into the oxime derivative benzo[*b*]furo[2,3-*b*]pyrazine **57** [30].

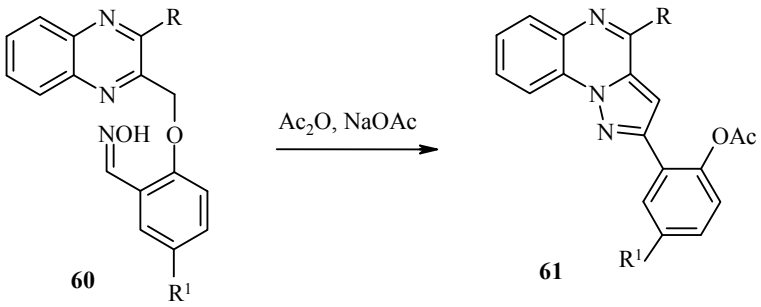


56 **57**

The 1H-pyrazolo[3,4-*b*]quinazoline system **59** is obtained (with yields of 62-86%) from the quinoxaline oximes **58** and hydrazine derivatives in an acidic medium [79, 80]. Cyclization of the oximes **60** in acetic anhydride in the presence of sodium acetate leads to pyrazolo[1,5-*a*]quinoxalines **61** with yields of 41-58% [80].

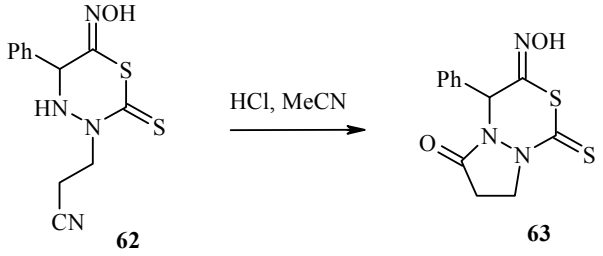


58 **59**

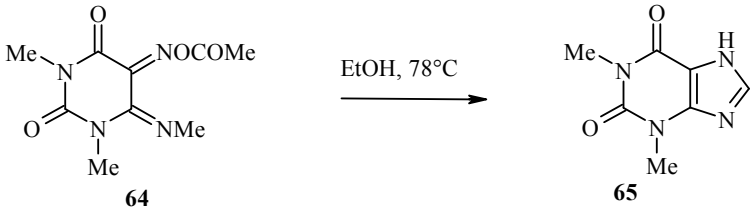


R = Me, Ph; R^1 = H, Br

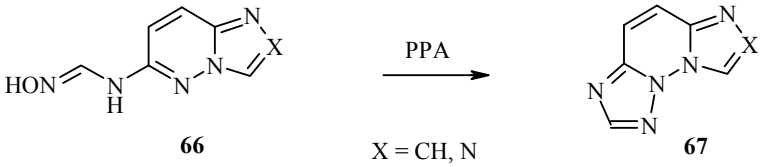
Cyclization of 1,3,4-thiadiazine-3-propionitrile **62** in the presence of hydrochloric acid in acetonitrile gives the oxime derivative of pyrazolo[1,2-*c*][1,3,4]thiadiazine **63** [46].



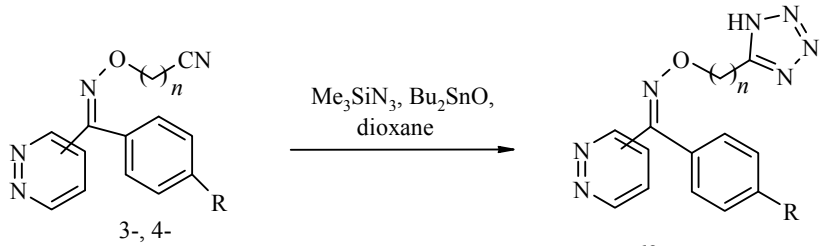
A series of papers were devoted to the synthesis of heterocycles containing an imidazole ring from the oxime derivatives of uracil [81-84], pyrimidine [85], and 1,2,6-thiadiazine [86]. Thus, the cyclization of 5-acetyloxyimino-4-methyliminouracil (**64**) in boiling ethanol gives theophylline **65** [83].



The cyclization of pyridazine [87] and pyrimidine [88] formamidoximes in the presence of dehydrating agents (e.g., PPA) leads to the formation of a new triazole ring. For example, the reaction of the oximes **66** with PPA at 70-80°C leads to the tricyclic products **67** [87].



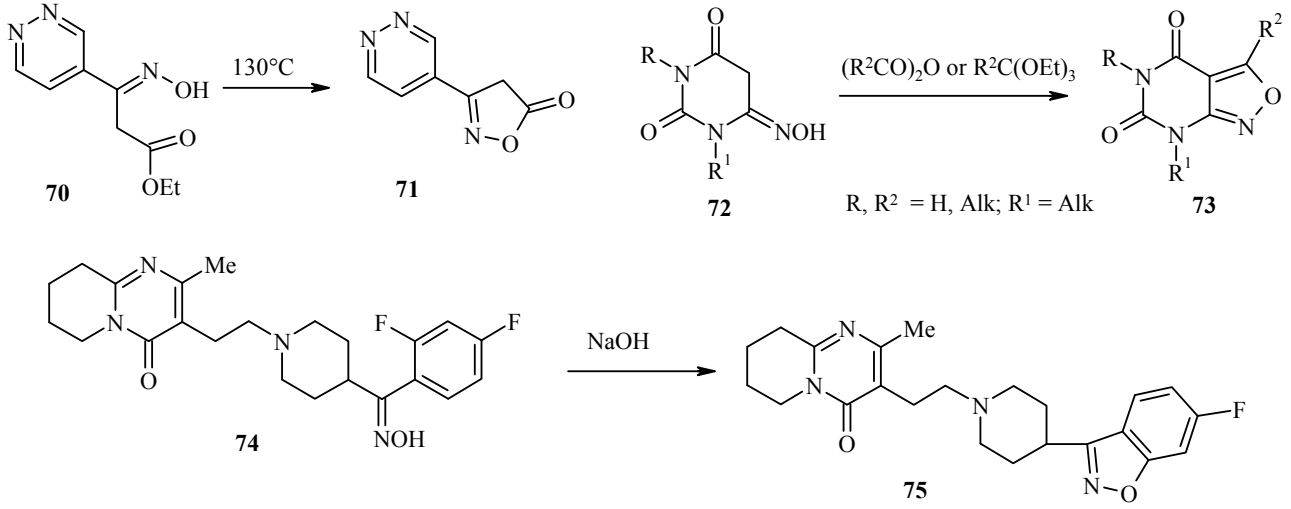
In the Me_3SiN_3/Bu_2SnO/dioxane system the O-(*ω*-cyanoalkyl)oximes **68** give tetrazolyl derivatives of pyridazine oximes **69**, which are used as inhibitors of aldose reductase [89].



68 **69** 44–83%

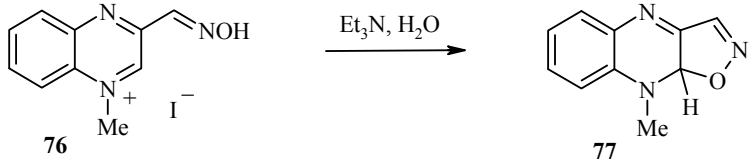
n = 5, 6; R = H, Cl, OMe

The production of compounds containing an isoxazole ring from pyridazine [63], pyrimidine [90-93], cinnoline, and pyrazine oximes [94-98] has been described widely in the literature. Thus, heating of ethyl 3-hydroxyimino-3-pyridazin-4-ylpropionate (**70**) to 130°C gives the isoxazol-5-one derivative **71** [63]. The reaction of pyrimidine oximes **72** with acid anhydrides or orthoesters at 140°C leads to the formation of isoxazolo[3,4-*d*]pyridines **73** [92]. It is interesting that the cyclization of the *o*-fluorine-containing oxime **74** in an alkaline medium leads to the 1,2-benzoxazole **75** [93].



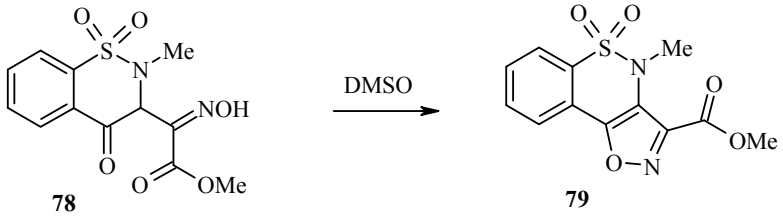
70 **71** **72** **73** **74** **75**

In water in the presence of catalytic amounts of triethylamine the oxime salt **76** gives the derivative of dihydroisoxazolo[4,5-*b*]quinoxaline **77** with an 86% yield [99].



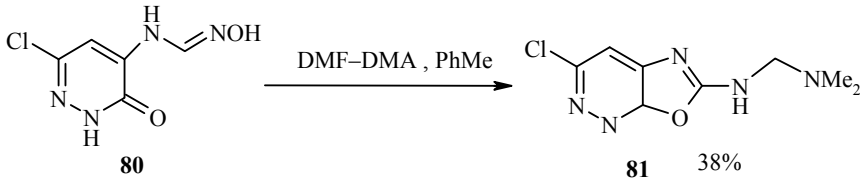
76 **77**

When heated in DMSO the 1,2-benzothiazine oxime **78** forms the isoxazolo[4,5-*c*][1,2]benzothiazine derivative **79** [100].



78 **79**

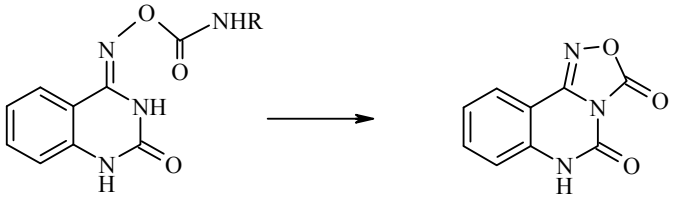
6-Chloro-2-(N,N-dimethylaminomethylamino)oxazolo[5,4-*c*]pyridazine (**81**) was obtained successively by the cyclization of formamidoxime **80** in the presence of DMF dimethyl acetal in boiling toluene [101].



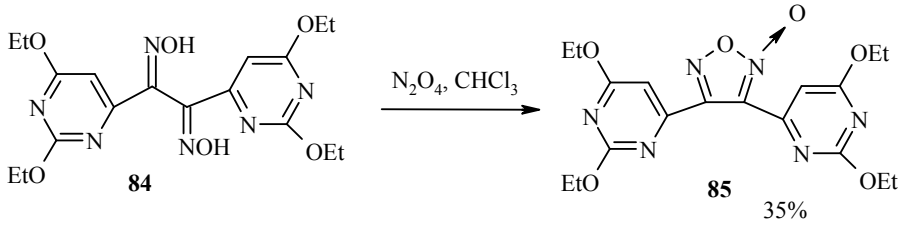
80 **81** 38%

DMF–DMA – DMF dimethyl acetal

1,2,4-Oxadiazole derivatives of pyridazine oximes were obtained from amidoximes in the presence of an acylating agent [102, 103]. A series of papers were devoted to the production of 1,2,4-oxadiazole derivatives of pyrimidine from pyrimidine oximes [16, 104-107]. Thus, the action of heat on the oxime ethers **82** at the melting point leads to oxadiazolinoquinazoline **83** [107]. The synthesis of bis(pyrimidyl)furoxane **85** was realized by the oxidation of bis(pyrimidine) glyoxime **84** in the presence of N_2O_4 in chloroform [108].

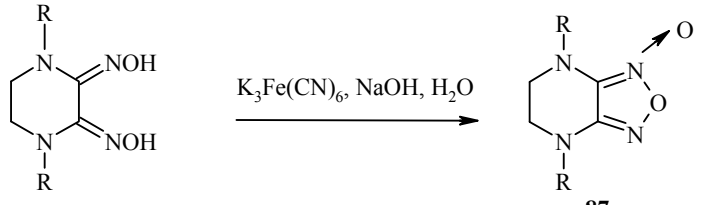


82 R = Me, Et, Ph **83**



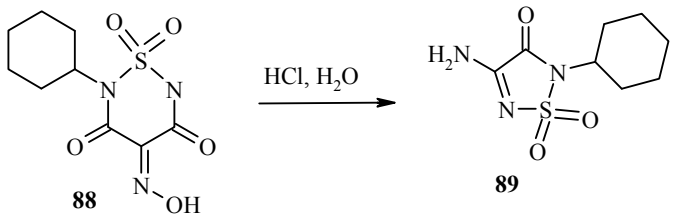
84 **85** 35%

The synthesis of 1,2,4-oxadiazole derivatives of pyrazines from pyrazine oximes is also widely represented in the literature [24, 27, 109-113]. The reaction of the dioxime **86** with $K_3Fe(CN)_6$ in aqueous alkali gives furoxano[3,4-*b*]piperazines **87** with yields of 72-98% [114].

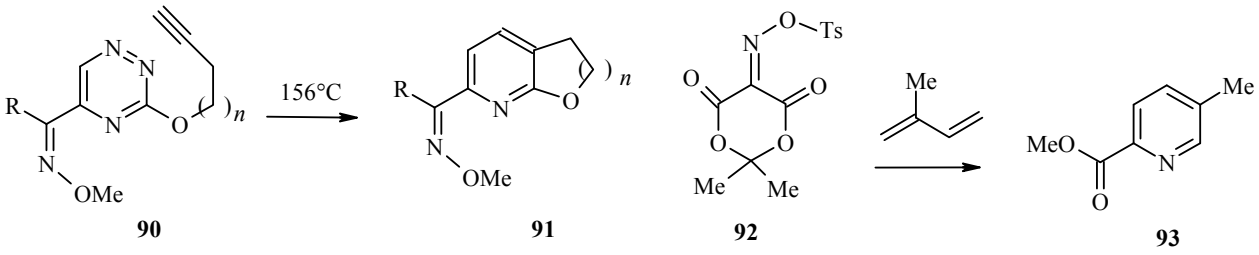


86 R = Alk **87**

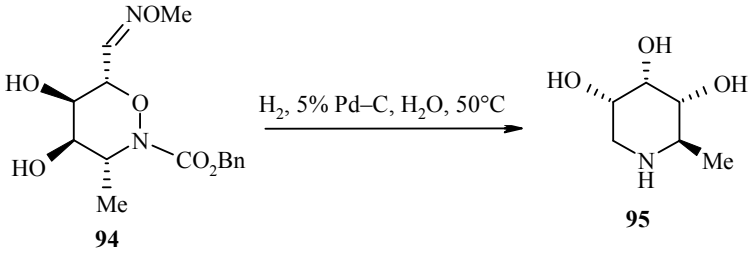
The O-acylated 1,2,4-triazine [115, 116] and 1,3,5-triazine [34] amidoximes are easily transformed into 1,2,4-oxadiazole derivatives of triazines. 1,3,4-Thiadiazine oximes in a basic medium [46] and 1,2,6-thiadiazine oximes in an acidic medium [72] are converted into thiadiazoles. For example, the action of heat on the oxime **88** in concentrated hydrochloric acid gives 4-amino-2-cyclohexyl-3-oxo-2,3-dihydro-1,2,5-thiadiazole 1,1-dioxide (**89**) with a 71% yield [72].



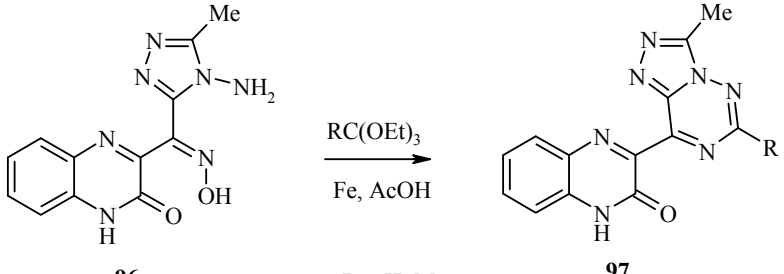
An intramolecular Diels–Alder reaction with the O-methyl ether of the triazine oxime **90** at 156°C gives the pyridine oxime **91** [30]. [4+2] Cycloaddition of 2-methyl-1,3-butadiene to the oxime **92** leads to the formation of methyl 5-methylpyridine-2-carboxylate.

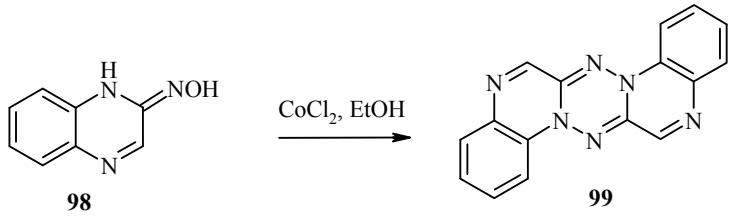


The hydrogenation of the methyl ether of 1,2-oxazine oxime **94** in the presence of 5% palladium on carbon in water gives the piperidine derivative **95** with a yield of 71% [39].



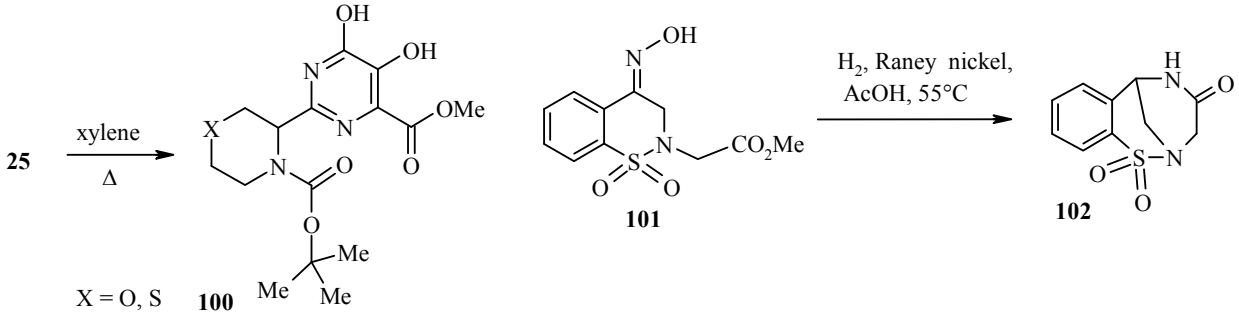
The action of heat on the quinoxaline oxime **96** and orthoester in acetic acid in the presence of iron powder leads to the formation of the new 1,2,4-triazine ring **97** [96]. In boiling toluene in the presence of $CoCl_2$ the quinoxaline oxime **98** gives the tetrazine **99** [118].



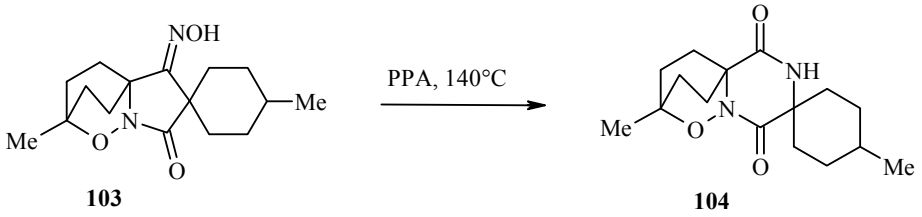


In boiling xylene the morpholine oxime ether **25** forms the pyrimidine derivative **100** with a yield of 54% [42].

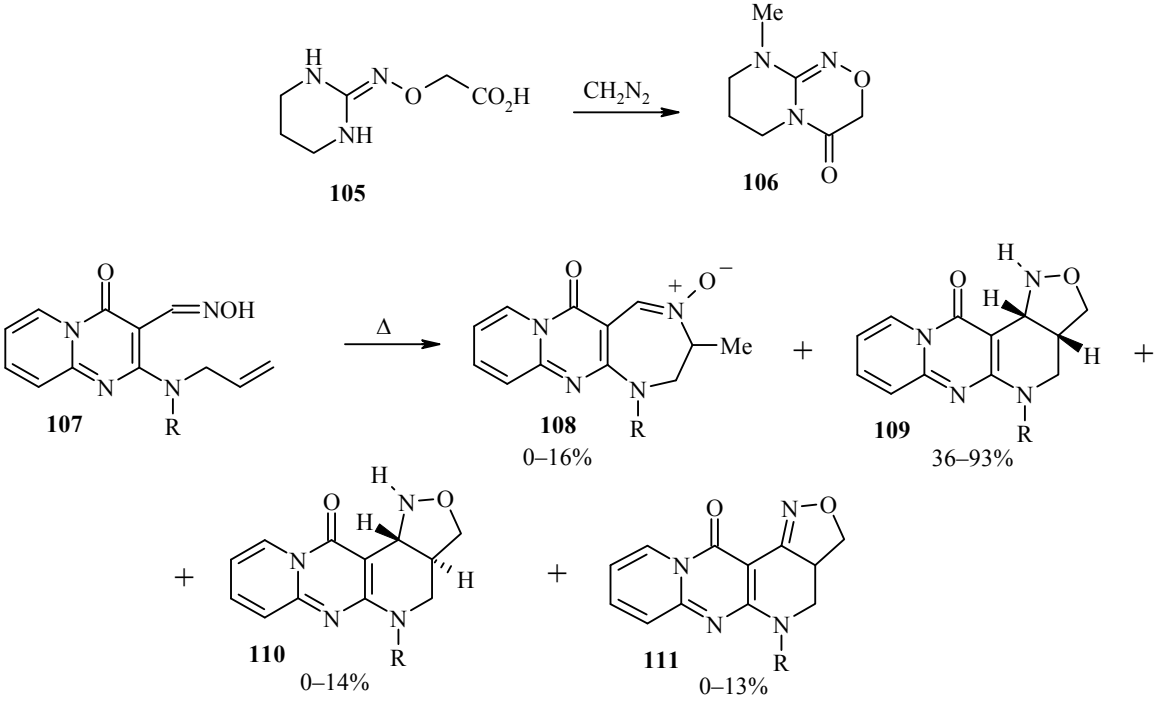
Hydrogenation of the 1,2-thiazine oxime **101** in the presence of Raney nickel in acetic acid gives 1,2,5-benzothiadiazocine 1,1-dioxide **102** with a yield of 73% [119].



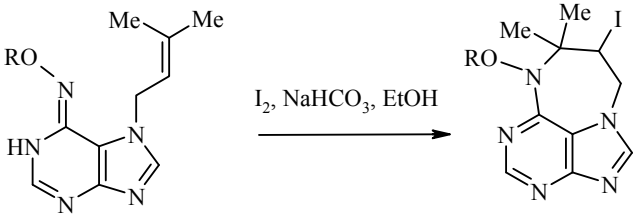
The Beckmann rearrangement of the 1,2-oxazine oxime **103** in PPA at 140°C leads to a derivative of pyrazino[1,2-*b*][1,2]oxazine **104** [120].



It is interesting that in the presence of diazomethane the acid **105** gives 9-methyl-6,7,8,9-tetrahydropyrimido[2,1-*c*][1,2,4]oxadiazin-4-one (**106**) as the only product [121].



The action of heat on the pyrido[1,2-*a*]pyrimidine oxime in various solvents (ethanol, benzene, or acetonitrile) leads to the formation of a mixture of products **108-111** [122]. The diazepine ring in compound **113** is also formed as a result of cyclization of the purine oxime **112** in the $I_2/NaHCO_3/EtOH$ system at room temperature [123].



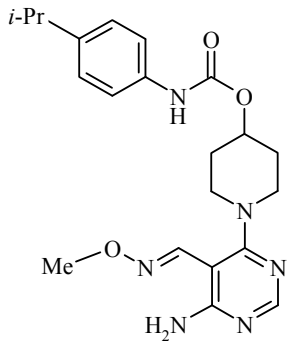
112 R = Alk **113**

2. BIOLOGICAL ACTIVITY OF THE OXIMES OF SIX-MEMBERED HETEROCYCLIC COMPOUNDS WITH TWO AND THREE HETEROATOMS AND THEIR O-ETHERS

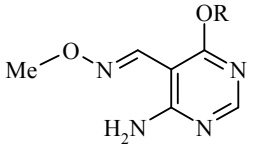
2.1. Bactericidal, Anticancer, and Antiviral Activity

Antibacterial agents based on cephalosporin antibiotics, including the O-substituted oximes cefuroxime, cefotaxime, ceftriaxone, ceftazidime, etc. have found widespread use [124-126]. Derivatives of the oximes of pyridazine [127, 128], pyrazine [129], quinoxaline [130, 131], piperazine [132-141], 1,2,4-triazine [142, 143], 1,4-oxathiane [144], and 1,3,4-thiadiazine [145] also exhibit high antibacterial activity.

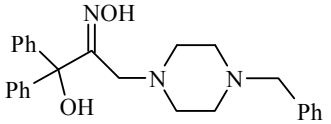
Derivatives of acetylformamidoxime, containing piperazine fragments, were investigated as cytotoxic agents on the cell lines of lymphocyte leucosis and Jensen's sarcoma. However, these compounds did not exhibit high activity [146]. The anticancer and antiproliferative activity of the O-ethers of pyrimidine oximes (e.g., compounds **114** and **115**) have been widely investigated [147-155]. The piperazine oxime **116** showed high activity on the cancer cells of human sarcoma [156]. The anticancer activity in the oximes of (quinazolin-4-yl)aminophenylethanone [157], the O-ethers of 1,4-dioxin aldoximes [158], and pyrazine diazohydroxides [159] should also be mentioned. Our investigations showed that 4-(3,4-dihydro-2H-[1,3]thiazino[3,2-*a*]benzimidazol-3-yloxy)-N-hydroxybutyroamidine (**117**) exhibits high cytotoxicity in mouse hepatoma cells (MG-22A).



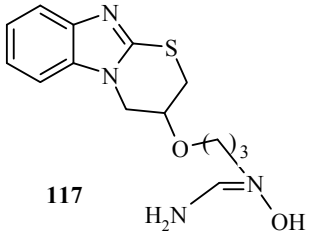
114



115 R = heteryl

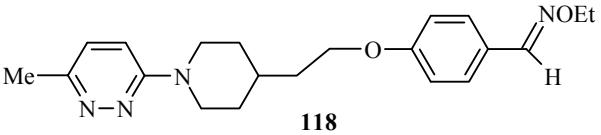


116

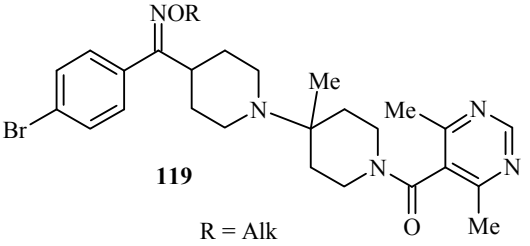


117

Derivatives of the oximes of six-membered heterocyclic compounds with two heteroatoms displayed a broad range of antiviral activity. Among these compounds it is necessary to mention O-(4-quinazolinyl)oxime ethers [160, 161], the O-ether of pyridazine oxime **118** [162], and 1,2- and 1,4-oxazine oximes [163]. The high antiviral activity of the O-ethers of pyrimidine oximes **119** against HIV-1 was also discovered [164, 165]. Various pyrazine oximes displayed antitubercular activity [166, 167]. In addition trypanocidal activity was found in the O-ethers of piperazine amidoximes [168], and antimalarial activity was found in purine oximes [169].



118

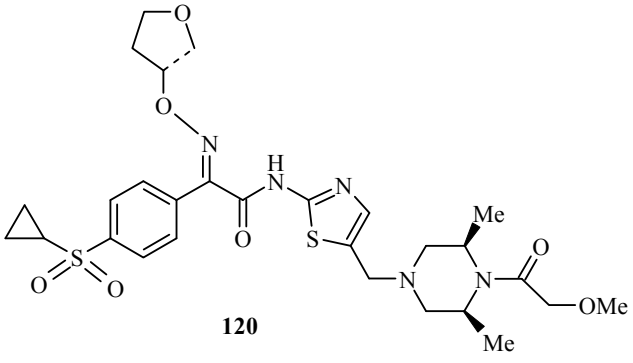


119

R = Alk

2.2. Action on the Cardiovascular System

Piperazine oximes and their O-ethers, among which it is necessary to mention the derivative **120**, were studied as agents that activate glucokinase [170]. These compounds can be used in the treatment of diabetes. Piperazine oximes also displayed high cholesterol-lowering and lipid-lowering activity [171].



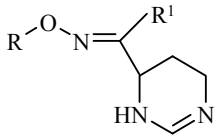
120

The vasodilatory activity of pyrimidine oximes [172], the hypotensive activity of piperazine oximes [173], and the antiarrhythmic activity of 2-(pyrimidylthio)acetamidoximes [174] should be mentioned. Diazine formamidoximes were studied as agents for the treatment of cerebrovascular diseases [175]. Piperazine [176] and 1,4-thiadiazine [177] oxime O-ethers are α- and β-adrenoblockers respectively, and piperazine oximes have cardiovascular activity [178].

2.3. Action on the Central Nervous System

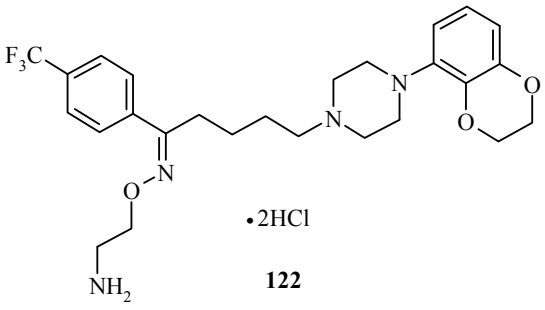
Investigations of the ethers of piperazine [179] and pyrimidine [180] ketoximes as sedative and psychotropic agents were conducted in the middle of the seventies of the twentieth century. The sedative and anticonvulsive activity of the oxime derivatives of barbiturates was also described in the literature [181].

The action of the O-ethers of tetrahydropyrimidine oximes **121** on muscarinic receptors was investigated. These compounds were used for the treatment of Alzheimer's disease [182-185]. Several papers have been devoted to the investigation of piperazine oximes as neurokinin antagonists; these compounds are used in the treatment of diseases of the central nervous system [186-189]. Oxime derivatives containing 1,4-benzodioxin and piperazine fragments (e.g., compound **122**) have also shown high activity in the treatment of diseases of the central nervous system [190, 191].



121

R, R^1 = H, Alk

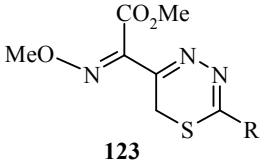


• 2HCl

122

2.4. Analgesic Activity

Piperazine ketoximes [192] and amidoximes [193] showed high analgesic activity, while the O-ethers of 1,2,4-thiadiazine oximes **123** exhibited anesthetic activity [194].



123

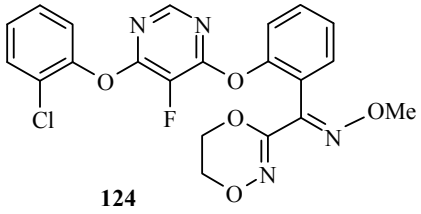
R = heteryl

2.5. Anti-inflammatory Activity

High anti-inflammatory activity was exhibited by piperazine ketoximes [195] and O-acylated derivatives of 1,4-dioxin oximes [196].

2.6. Pesticidal Activity

The fungicide with pyrimidine and 1,4,2-dioxazine rings *Fluoxastrobin* **124** has been widely used [124-126]. In addition to this widely used product it is necessary to mention the very wide range of patents and publications devoted to the fungicidal activity of oxime derivatives of pyridazine [197, 198], pyrimidine [199-211], quinazoline [212], pyrazine [213], 1,3,4-triazine [214], 1,3-oxazine [215], morpholine [216], and 1,4,2-dioxazine [217-224].



124

Pesticidal activity is exhibited by derivatives of the oximes of pyrimidine [225-227], 1,4-dithiane [228], 1,4-oxazine [229], and 1,4,2-dioxazine [230, 231].

In the literature there are data on the herbicidal activity of pyrimidine [232-253], pyrazine [19], 1,4-benzoxazine [254], and 1,2,6-thiadiazine [255] oximes and the O-ethers of chlorine-substituted 1,3,5-triazine oximes [32]. 1,3-Thiazine [256], pyrimidine, and 1,4,2-dioxazine [257] oximes have shown high insecticidal activity.

In addition, pyrimidine oximes are used as acaricides [258], while 1,3,5-triazine oximes are used as plant growth regulators [259].

2.7. Other Activities

Pyrimidine [260-262] and morpholine [263] oximes were investigated as antidotes for poisoning by organophosphorus compounds.

Derivatives of α-hydroxyiminopyrazineacetonitriles have shown antiulcer activity [264]. Quinoxaline oximes reduce the amount of serotonin in the blood in mice [265]. Various pyrimidine oximes are antagonists of cholecystokinin or gastrin [266] and inhibit various protein kinases [267]. Pyridazine oxime ethers inhibit phosphodiesterase IV [268], while 1,2,4-tetrazine oximes inhibit cysteine kinase [269]. Various ethers of diazine oximes inhibit serine protease selectively [270]. The oximes of 4-amino-6-arylaminopyrimidine-5-carboxaldehydes are dual inhibitors of protein tyrosine kinases EGFR and ErB-2 [271]. The oximes of 1-aryl-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one are agonists of dopamine D_4 receptors [272].

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