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OXIMES OF FIVE-MEMBERED HETEROCYCLIC COMPOUNDS WITH TWO HETEROATOMS

2.* REACTIONS AND BIOLOGICAL ACTIVITY (REVIEW)

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Data on the reactions of oxazole, thiazole, pyrazole, and imidazole aldoximes, ketoximes, amidoximes, and their derivatives are reviewed. The synthesis of new heterocycles based on the oximes of five-membered heterocyclic compounds with two heteroatoms are considered separately. The principal results from investigation of the biological activity of the ethers of these oximes are also presented.

Keywords: imidazole, oxazole, oxime, pyrazole, thiazole, biological activity.

The oximes of five-membered heterocyclic compounds with two heteroatoms are widely used as intermediates in fine organic synthesis. We examined their methods of preparation and structural characteristics in [1]. In this article we discuss the reactions of oxazole, thiazole, pyrazole, and imidazole aldoximes, ketoximes, and amidoximes and their derivatives. Methods for the synthesis of new heterocyclic systems from derivatives of these oximes are described in a separate section. Some results from investigation of the biological activity of the ethers of these oximes are presented in the last section.

1. CHEMICAL TRANSFORMATIONS OF THE OXIMES OF FIVE-MEMBERED HETEROCYCLIC COMPOUNDS WITH TWO HETEROATOMS

1.1. Synthesis of the O-Derivatives of the Oximes

The principal method for the production of the ethers of isoxazoles is their alkylation with alkyl halides in the NaH/DMF system [2, 3]. The ethers of thiazole oximes are synthesized from the oximes and alkyl halides in the same system [4]. The reactions of the respective oximes with alkyl halides in the K_2CO_3/DMF [9], NaH/DMF [10], NaOH/DMF [11], or KOH/DMSO [12] systems have been used for the synthesis of the ethers of pyrazole (5, 6) and imidazole [7, 8] oximes. Ethers of pyrazolinone oximes **2** were obtained from the oximes **1** and Me_2SO_4 in the presence of triethylamine in water [13].

* For Communication 1, see [1].

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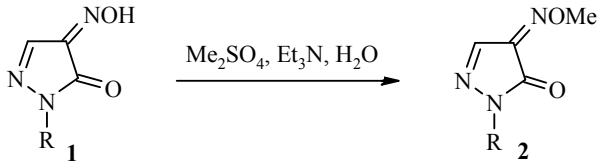
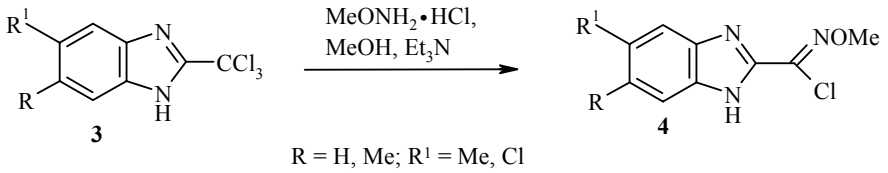
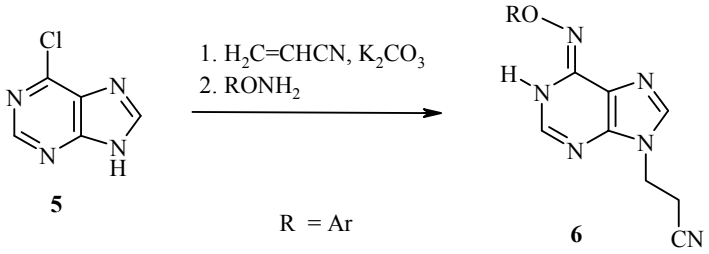


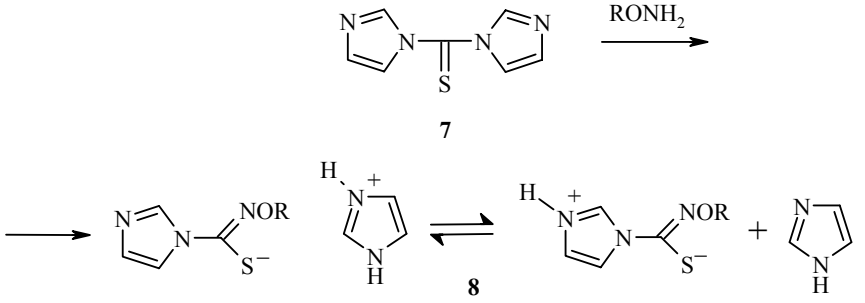
In addition, O-ethers of pyrazole and imidazole oximes were obtained from the carbonyl derivatives and O-alkyl derivatives of hydroxylamines (or their hydrochlorides) in MeOH/NaOAc [14], H_2O/NaOAc [15, 16], pyridine/EtOH [17], or Na_2CO_3/H_2O [18]. In the $MeONH_2 \cdot HCl/Et_3N$/MeOH system the trichloromethyl derivatives of benzimidazole **3** give good yields of the ethers **4** [19, 20].



The O-ethers of purine oximes **6** are readily formed from 6-chloropurine **5** with yields of 59-80% as a result of a two-stage process involving reaction of the cyanoethylation product with the O-alkyl derivatives [21].

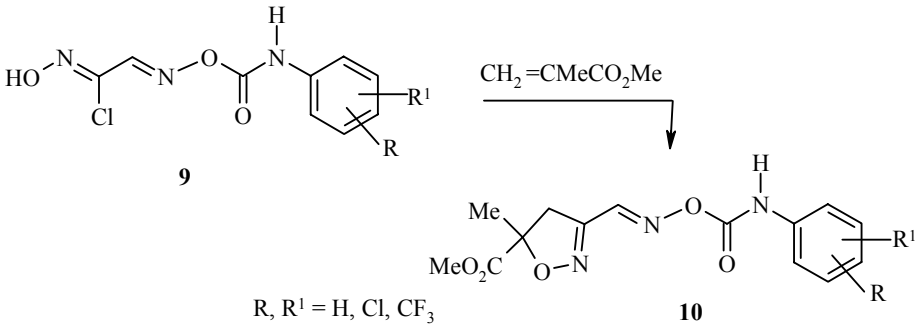


The N,N-thiocarbonyldiimidazole **7** and alkylhydroxylamines give quantitative yields of the salts of imidazole oxime ethers **8** [22].



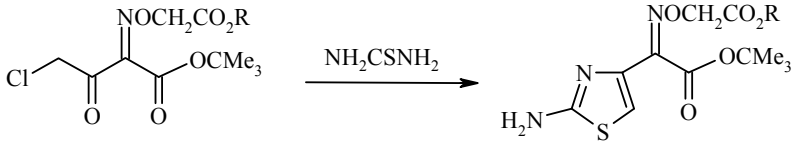
The synthesis of the O-ethers of imidazoline oximes from the respective 2-methylthioimidazolines and O-substituted hydroxylamines was described in [23].

The carbamoyl derivatives **10** are formed as a result of cyclocondensation of the oximes **9** with methyl methacrylate [24].



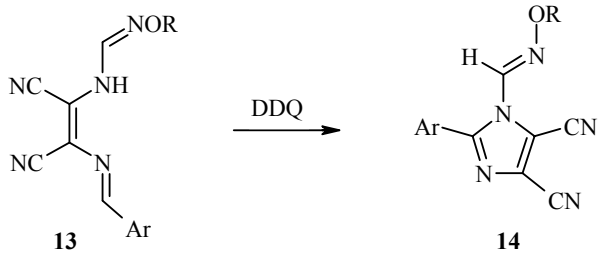
9 **10**

The O-ethers of thiazole oximes were obtained by the cyclization of the respective α-halo ketones containing an oxime O-ether fragment with derivatives or thiourea [25-52]. For example, the reaction of the ether **11** with thiourea in ether gives the ether of thiazole oxime **12** [31].



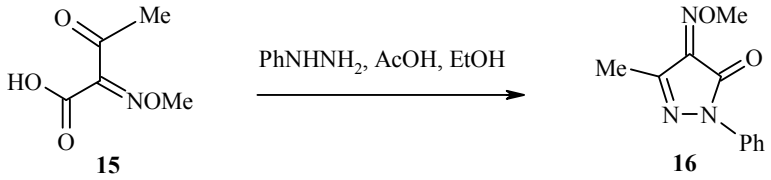
11 **12**

A series of papers were devoted to the synthesis of pyrazole and imidazole oxime ethers in cyclization reactions. Thus, the oximes **13** readily undergo cyclization in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and give the ethers **14** with yields of 61-83% [53].



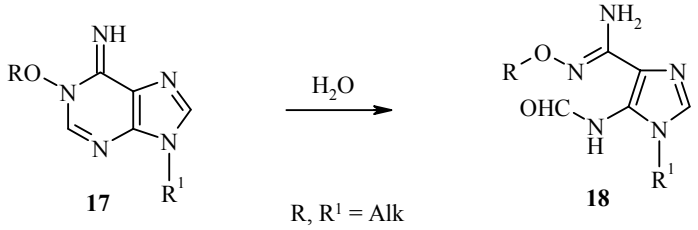
13 **14**

The reaction of ethyl 2-methoxyimino-3-oxobutyrate **15** and phenylhydrazine in acetic acid gives the pyrazolone oxime ether **16** with a yield of 48% [54].



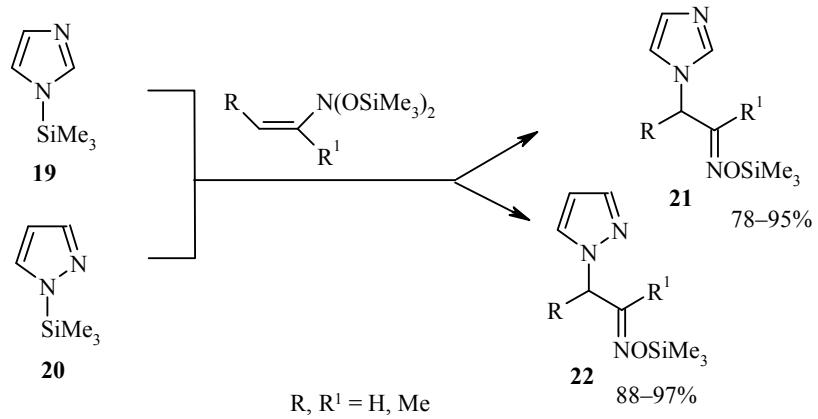
15 **16**

The ethers of imidazole oximes **18** are formed with good yields from 1-alkoxy-9-alkyladenines **17** by the Dimroth reaction in water [55-60].

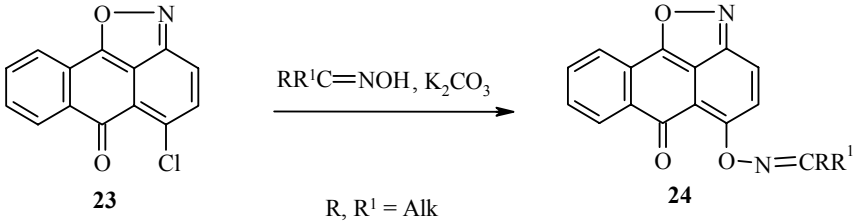


17 **18**

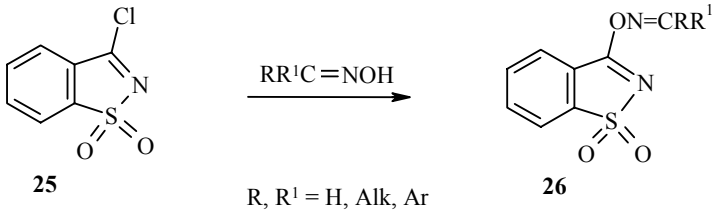
Silyl ethers of imidazole and pyrazole oximes **21** and **22** were obtained from the N-silylated heterocycles **19** or **20** and N,N-bis(silyloxy)enamines [61].



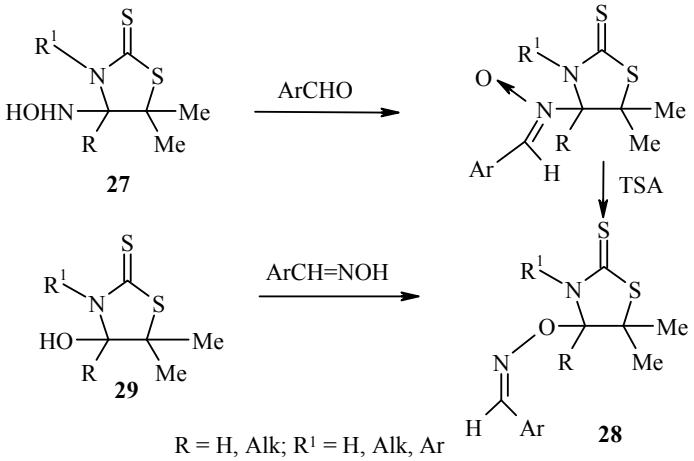
Ethers of another type **24** with an oxazole ring in the O-substituent are formed in the reaction of the oxazole **23** with ketoximes in the K_2CO_3/DMSO system at room temperature (yields 58-66%) [62].



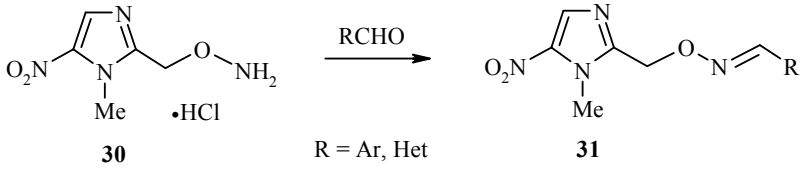
The benzoisothiazole compounds **25** and oximes readily give the fungicidal oxime ethers **26** [63, 64].



The reaction of 4-hydroxyaminothiazolidine-2-thiones **27** with aromatic aldehydes in the presence of 4-toluenesulfonic acid (TSA) gives oxime ethers **28** with yields of up to 90%. The reaction takes place through nitrone intermediates, which give the oximes in the presence of TSA. The reaction of the alcohols **29** with oximes and TSA also leads to the ethers **28** [65].



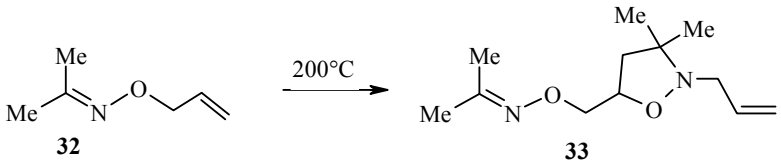
The imidazole oxime ethers **31** were obtained by the reaction of hydroxylamines **30** containing an imidazole fragment with aldehydes [66].



30 **31**

Ether derivatives of benzimidazole oximes were obtained in a similar way [67].

Ethers of similar type are also formed when acetone O-allyloxime **32** is heated at 200°C. As a result the ether **33** was obtained as the only product [68].

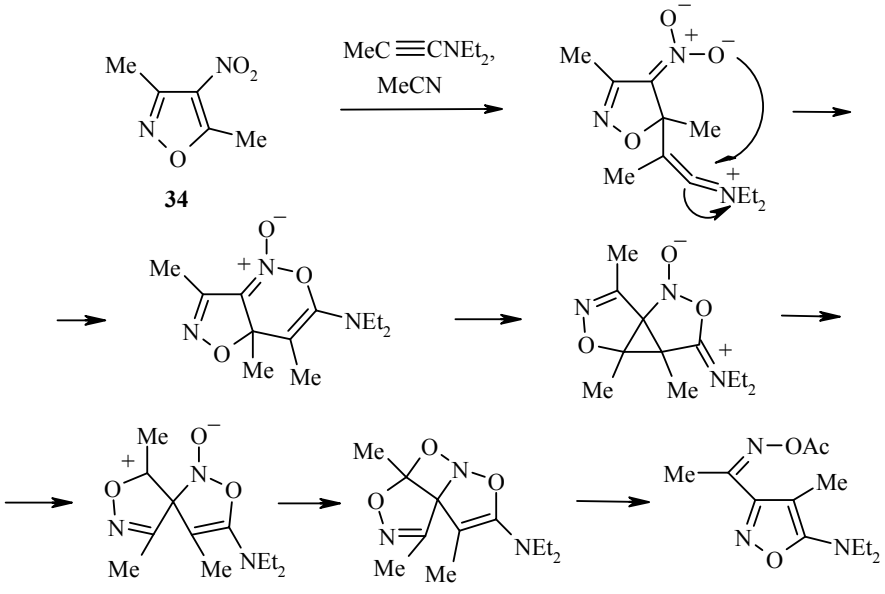


32 **33**

The acyl derivatives of benzisoxazole and isoxazole oxime ethers are synthesized smoothly from the corresponding oximes and acetic anhydride [69]. The synthesis of acyl derivatives of dihydroisoxazoles was described in [70].

The acyl derivatives of thiazole oximes are readily obtained from the corresponding oximes and AcCl [71] or acetic anhydride/K_2CO_3 [72]. The synthesis of O-carbamoyl derivatives of imidazothiazole oximes has also been described in the literature [73].

The acyl derivatives of imidazole and benzimidazole oximes are easily obtained from the corresponding oximes and AcCl/NaH/DMF [74] or RCOOH/DMAP/1-ethyl-3-(3-dimethylaminopropyl)carbodiimide [75].The chlorides of O-acylhydroxamic acids of imidazoline derivatives are obtained from the corresponding nitro derivatives and carboxylic acid chlorides in the presence of organic bases [76]. The synthesis of the carbamates of imidazole oximes was described in [77].

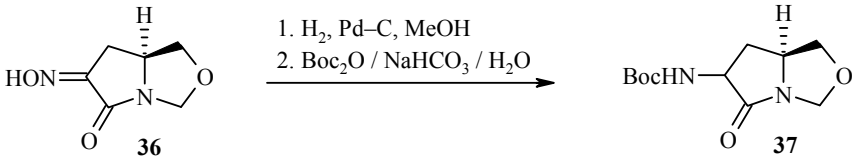


34 **35**

The rearrangement of 3,5-dimethyl-4-nitroisoxazole **34** in the presence of 1-diethylaminopropyne in acetonitrile gives the oxime acetate **35** with a yield of 23%. The structure of compound **35** was confirmed by X-ray crystallographic analysis [78].

1.2. Transformations of the Oxime Group

The reduction of the oxazole ketoxime **36** in the H_2/Pd–C/MeOH system followed by protection of the amino group results in the formation of the carbamates **37** with a yield of 54% [79].

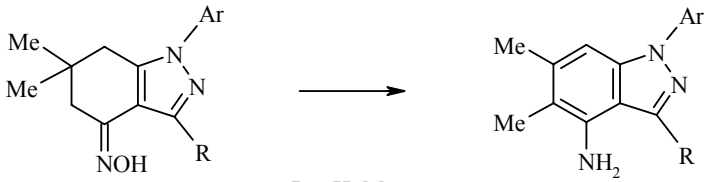


36 **37**

The reduction of oximes of the thiazole series to the corresponding amines was realized in the $Zn/NH_3/H_2O$ [80] and Zn/HCOOH/MeOH [81] systems. Imidazole and pyrazole oximes were reduced to the corresponding primary amine derivatives in the Zn/EtOH [82] and H_2/Pd–C/EtOH [83] systems. Hydrogenation of the amidoximes of imidazo[1,2-*a*]pyridines in the presence of Pd–C gave amidines [84].

The Beckmann rearrangement of thiazole ketoximes was realized in the presence of PCl_5 [85].

The reaction of 4-hydroxyimino-6,6-dimethyl-1-phenyl(or 2-pyridyl)-4,5,6,7-tetrahydroindazoles **38** with polyphosphoric acid takes place with migration of the methyl group and reduction of the oxime group to an amino group [86] leading to aromatization products **39**.

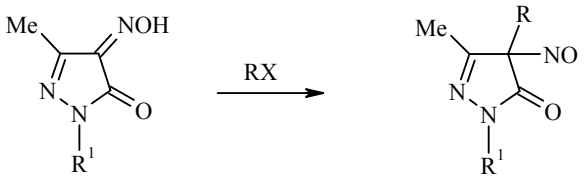


38 R = H, Me **39**

Imidazole, pyrazole, and benzisoxazole aldoximes are converted into nitriles in the presence of NBS/triethylamine [87], acetic anhydride [88], or PCl_3/Et_3N/MeCN [89]. The electrochemical oxidation of 4-hydroxyimino-2-pyrazolin-5-ones was investigated in detail in [90].

Purine-6-carbaldehyde oxime and MeCOSH form the corresponding thioaldehyde [91]. The reaction of 1-hydroxyimidazole-2-carbaldoxime 3-oxide and semicarbazide hydrochloride leads to the formation of the respective semicarbazone [92].

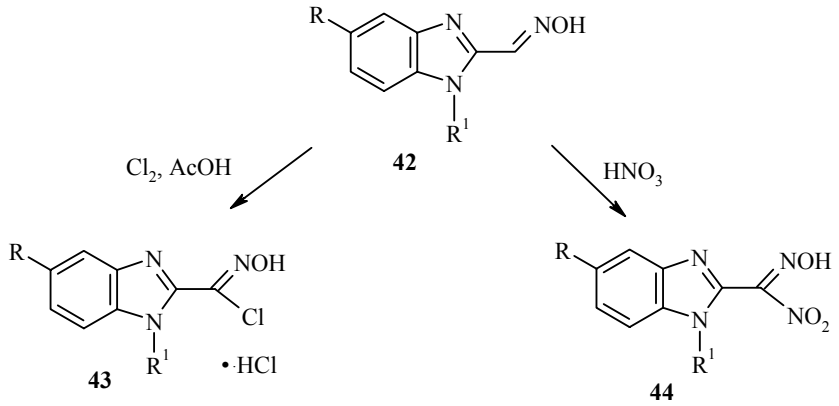
The only products from the reaction of 4-hydroxyimino-3-methyl-2-pyrazol-5-ones **40** with diazomethanes or alkyl halides are the 4-alkyl derivatives **41** [93].



40 R = Me, Et; R^1 = H, Ph **41**

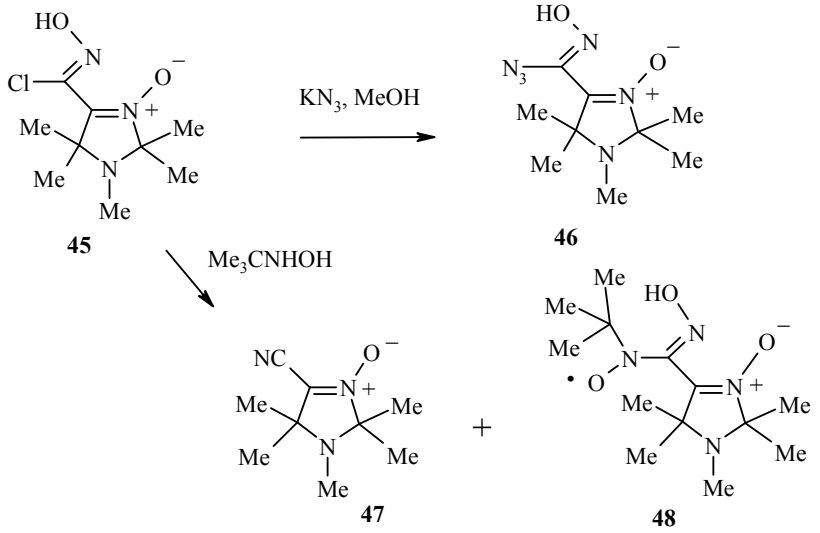
After treatment of the reaction mixtures with an aqueous solution of potassium carbonate pyrazole aldoximes and an excess of alkyl halides or dimethyl sulfate give nitrone derivatives [94].

The chlorination of 2-formyl-1-methylbenzimidazole oximes **42** with chlorine in glacial acetic acid leads to the hydroximoyl chlorides **43** with yields of up to 100%. The nitration of compound **42** gives the nitrolic acids **44** [95].



R = H, Me, NO_2; R^1 = H, Me

The reaction of the hydroximoyl chloride **45** with KN_3 in methanol leads to the azidooxime **46** with a quantitative yield. In the reaction of compound **45** with a twofold excess of *tert*-butylhydroxylamine the free radical **48** is formed in addition to the nitrile **47** [96].

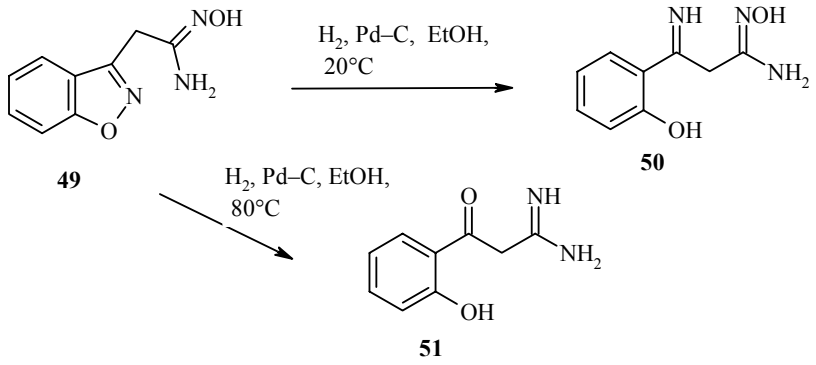


Deoximation of isothiazole aldoximes to the corresponding aldehydes was realized in 2N H_2SO_4 [97].

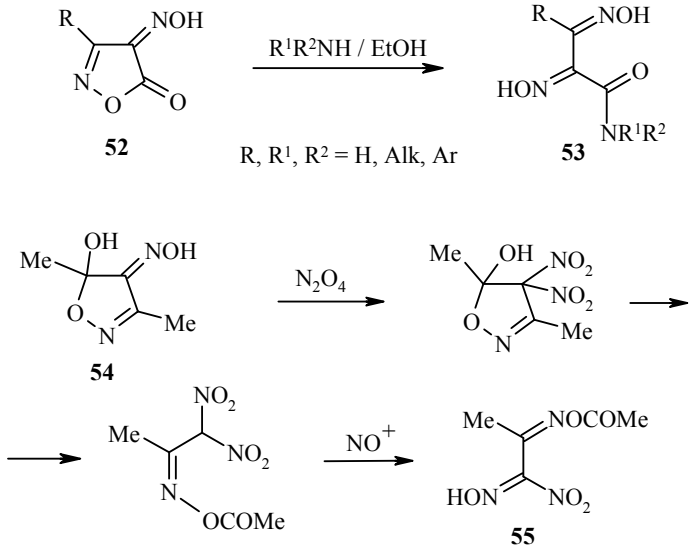
The reaction of the O-benzyl derivatives of imidazole oximes with KCN, NaOH, or MeONa also leads to unsaturated oximes [98].

1.3. Reactions Taking Place with Opening of the Heterocycle

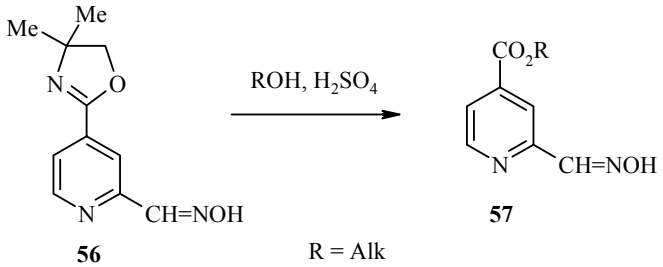
Reduction of benzisoxazole amidoxime **49** with 1 equiv. of hydrogen gave the oxime **50**. When the amount of hydrogen was increased (2 equiv.) at a higher temperature the ketone **51** was isolated as the only product [99].



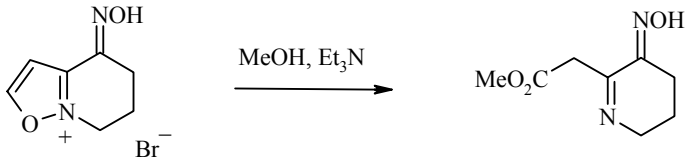
The reactions of 4-hydroxyimino-2-isoxazolin-5-ones **52** with amines give the oximes **53** [100]. The reaction of the oxime **54** with N_2O_4 leads to the formation of the dioxime **55** [101].



The 2-carbaldoximes of 4-alkoxycarbonylpyridines **57** are readily formed from the oxime **56** in the presence of alcohol and sulfuric acid [102].



In methanol in the presence of triethylamine the oxime salt **58** gives methyl (3-hydroxyimino-3,4,5,6-tetrahydropyridin-2-yl)acetate **59** with a yield of 52% [103].

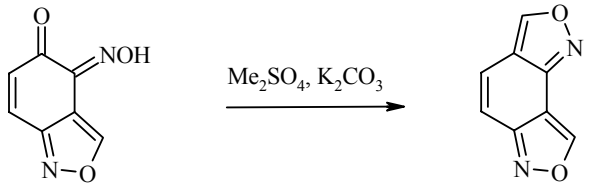


58 **59**

1.4. Synthesis of New Heterocyclic Systems from the Oximes of Five-Membered Heterocyclic Compounds with Two Heteroatoms

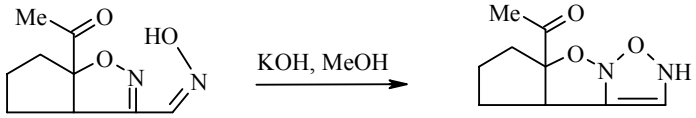
The latest advances in the synthesis of heterocyclic systems from oximes were reviewed in [104]. In this section the specific reactions of the oximes of five-membered heterocyclic compounds with two heteroatoms will be set out in greater detail.

The synthesis of dioxazole derivatives from oxazole or isoxazole oximes was set out in [105-108]. For example, in the Me_2SO_4/K_2CO_3/DMF system the oxime **60** gives the bisoxazole **61** [108].



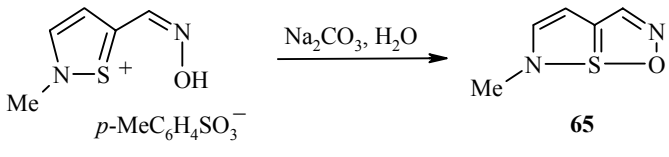
60 **61**

Intramolecular cyclization of the oxime **62** in the presence of alkali in methanol leads to isoxazolidino[2,3-*b*]-1,2,5-oxadiazoline **63** with a yield of 42% [109].



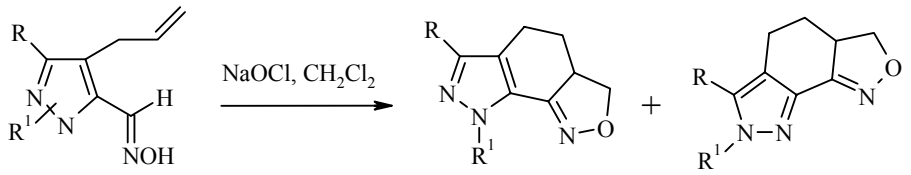
62 **63**

In aqueous sodium carbonate the *para*-toluenesulfonate of isothiazole oxime **64** gives the bicyclic product **65** with a yield of 87% [110].

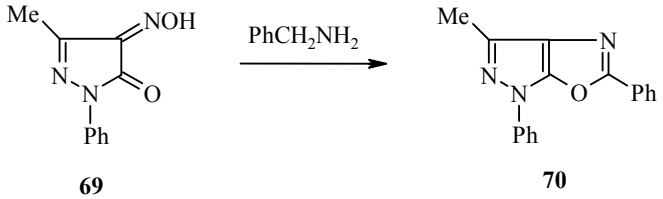


64 **65**

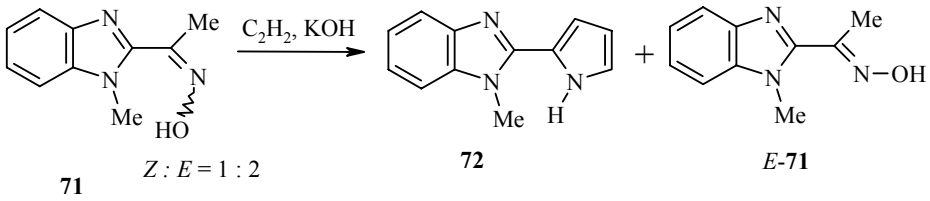
Heterocyclic systems containing an isoxazole and pyrazole (or imidazole) fragment were obtained successfully from pyrazole and imidazole oximes (111-114). Thus, the isomeric pyrazole oximes **66** and sodium hypochlorite form tricyclic derivatives of isoxazoline **67** and **68** with yields of up to 88% [114].



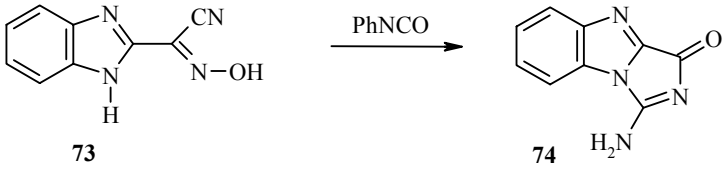
The reaction of 3-methyl-1-phenylpyrazole-4,5-dione monoxime **69** with benzylamine in ethanol leads to compound **70** with a yield of 69% [115].



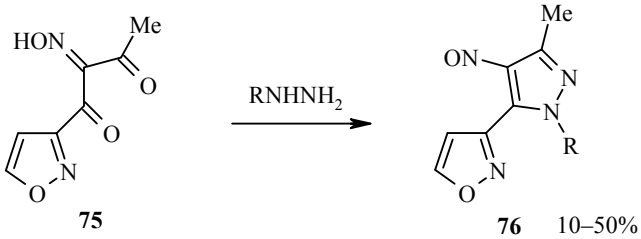
In the reaction of a mixture of the *anti* and *syn* isomers of 2-acetyl-1-methylbenzimidazole oxime **71** with acetylene in the KOH/DMSO system the pyrrole **72** is only formed from the *syn* isomer, and the *anti* isomer does not react under these conditions [116].



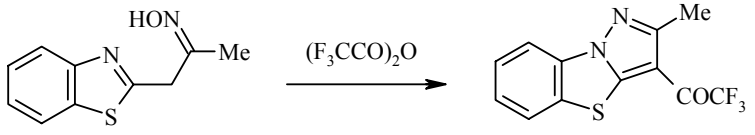
Benzimidazole oxime **73** and phenyl isocyanate form imidazo[1,5-*a*]benzimidazole **74** as the only product [117].



The isoxazole oxime **75** and substituted hydrazines give the nitroso derivatives of pyrazole **76** [118].

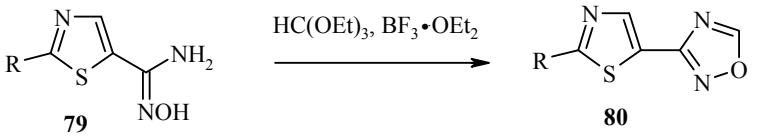


The reaction of (2-benzothiazolyl)acetone oxime **77** with an excess of trifluoroacetic anhydride gives the pyrazolo[5,1-*b*]benzothiazole **78** with a yield of up to 92% [119].



77 **78**

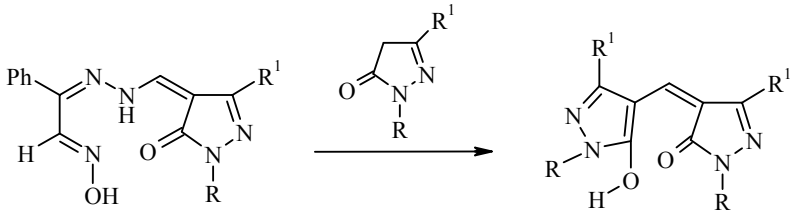
In the presence of BF_3 the thiazole amidoximes **79** and triethyl orthoformate form 1,2,4-oxadiazoles **80** [120].



79 **80**

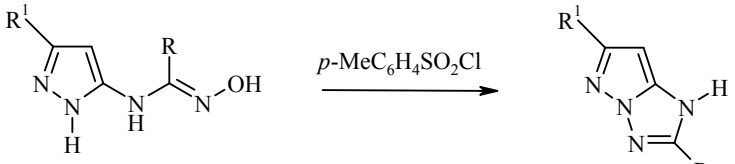
$R = NO_2, NH_2$

The reaction of the oximes **81** with pyrazolones leads to derivatives of dipyrazolylmethane **82** [121].



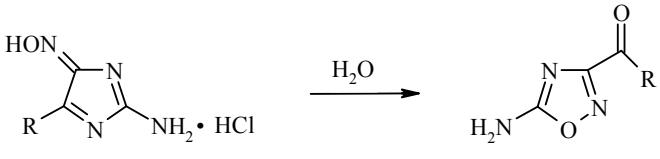
81 R, R^1 = Alk **82**

The pyrazolo[1,5-*b*][1,2,4]triazole system is synthesized easily from amidoximes containing a pyrazole ring [122-124]. Thus, the oximes **83** and tosyl chloride in tetrahydrofuran only form compounds of type **84** [122].



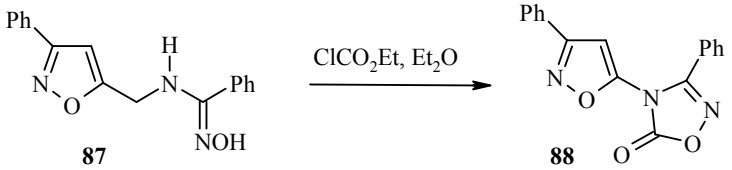
83 R, R^1 = Alk, Ar **84**

The synthesis of 1,2,4-oxadiazole derivatives from pyrazole [125], imidazole [125-127], and benzimidazole [128] amidoximes has been described in detail. 1,2,4-Oxadiazoles **86** were also obtained successfully from 4-hydroxyiminoimidazoles **85** in boiling water. The products **86** are clearly formed through hydrolytic opening of the imidazole ring followed by cyclization [129, 130].



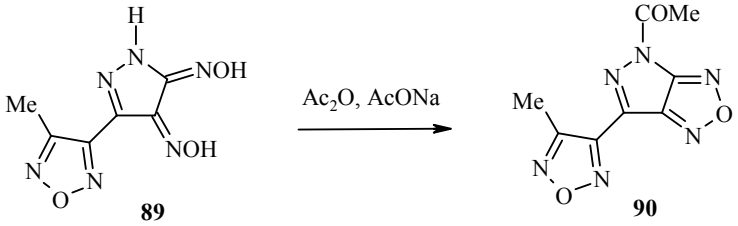
85 R = Alk **86**

The synthesis of furazans as a result of the rearrangement of isoxazole oximes (and also other oximes of 3-acyl-1,2-oxazoles) was described in detail in the review [131]. The reaction of the amidoxime **87** with $ClCO_2Et$ in ether leads to the formation of 1,2,4-oxadiazolone **88** [132].



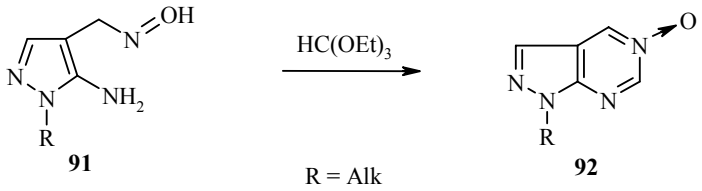
87 **88**

It was shown that the pyrazole dioxime **89** gives the pyrazolo[3,4-*c*]furazan derivative **90** with a yield of 70% when heated in acetic anhydride in the presence of sodium acetate [133, 134].



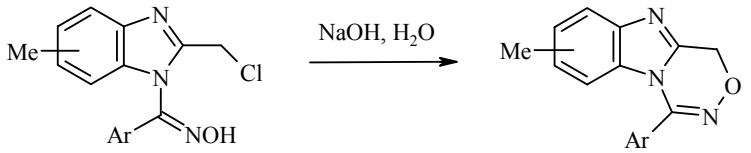
89 **90**

Several papers have been devoted to the synthesis of the imidazolopyrimidine [135, 136] and pyrazolopyrimidine [137] systems from the corresponding derivatives of imidazole and pyrazole oximes. For example, the reaction of the oximes **91** with ethyl orthoformate leads to pyrazolo[3,4-*d*]pyrimidines **92** [137].



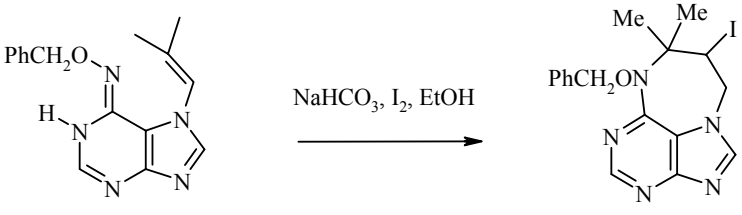
91 **92**

In an aqueous medium the benzimidazole oximes **93** are transformed into oxadiazino[4,5-*a*]-benzimidazoles **94** with yields of up to 99% [138].



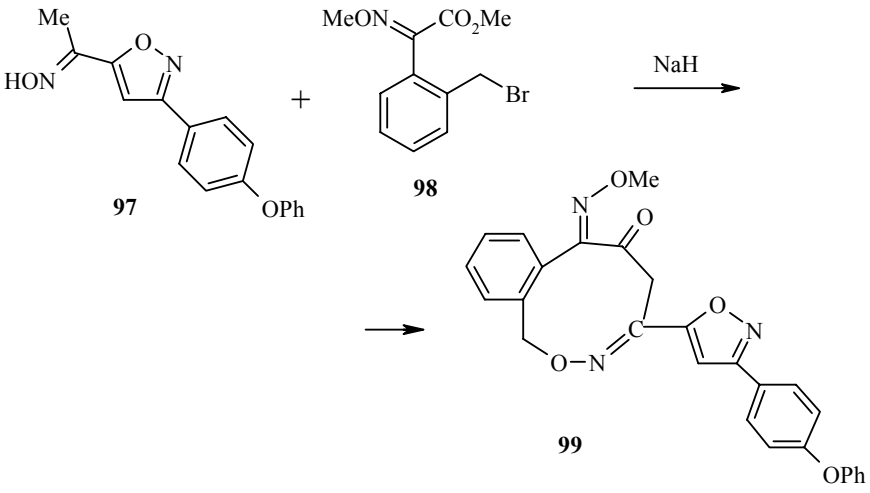
93 **94**

In the $NaHCO_3/I_2$/EtOH system the benzyl ether of purine oxime **95** gives the diazepine **96** with a yield of 75% [21].

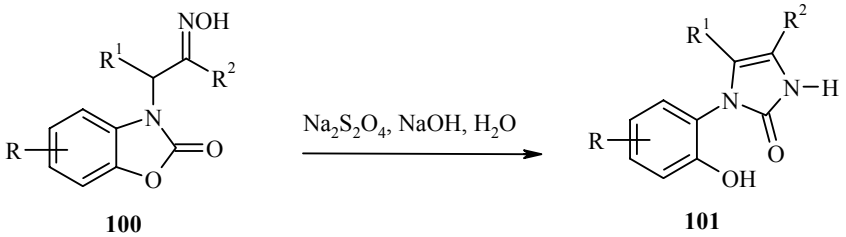


95 **96**

The 1,2-oxazonine ring **99** was obtained by cyclization of the two oximes **97** and **98** in the presence of NaH [139].

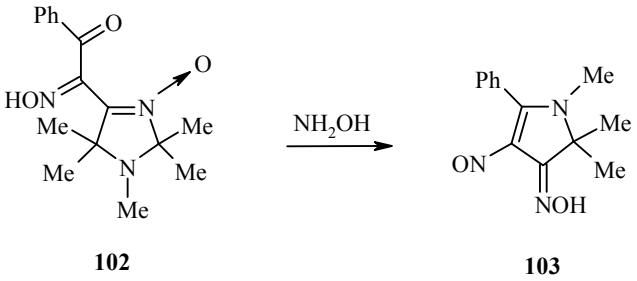


The reaction of benzoxazoline oximes **100** with $Na_2S_2O_4$ in 1% aqueous sodium hydroxide leads to the formation of the imidazolines **101** with yields of 50-89% [140].

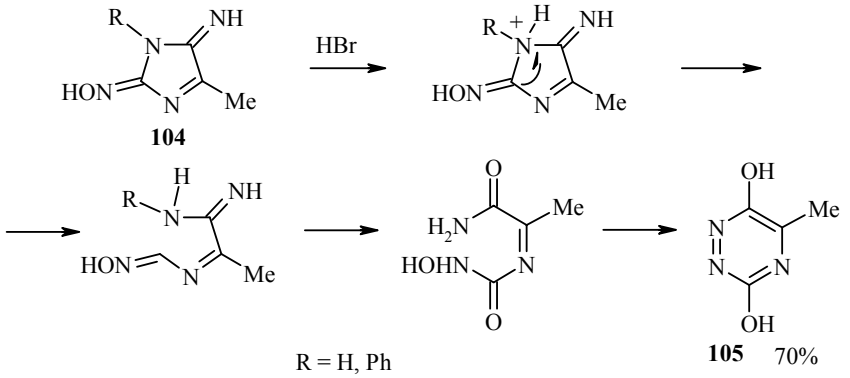


R = H, Hal, SO_2NH_2; R^1, R^2 = H, Me

The oxooximes of imidazolines **102** and hydroxylamine give the pyrroline **103** with a yield of 35%. The product **103** is formed through a recyclization stage [141].



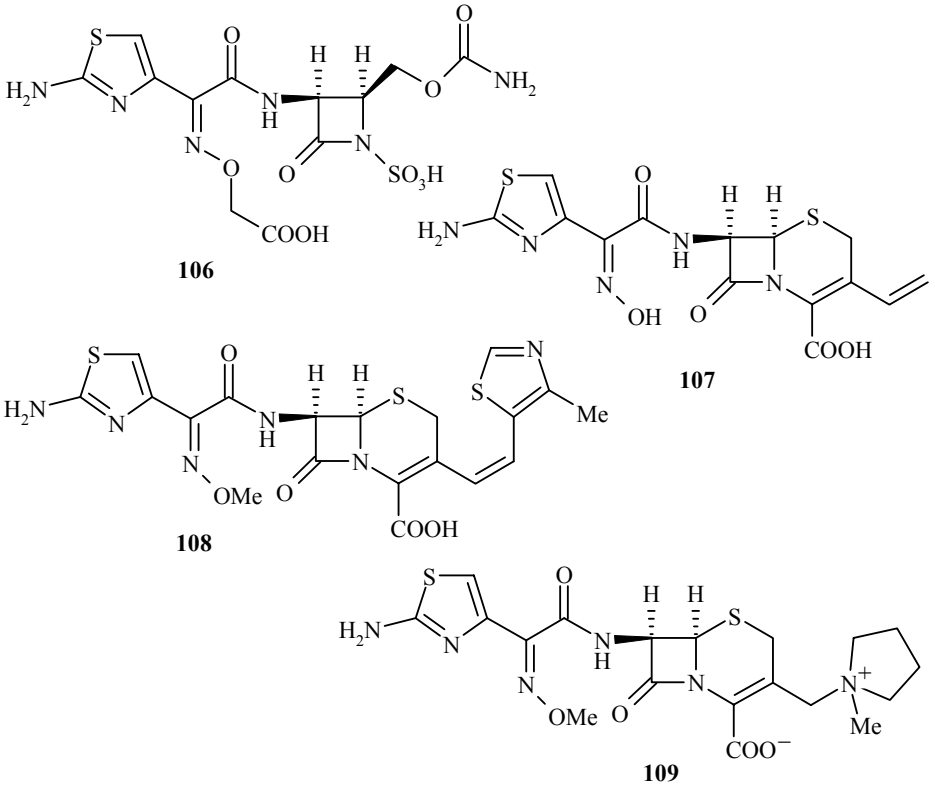
When the 2-hydroxyimino-5-iminoimidazolines **104** were heated with conc. HCl or HBr the recyclization product triazine **105** was isolated as the only product [142].

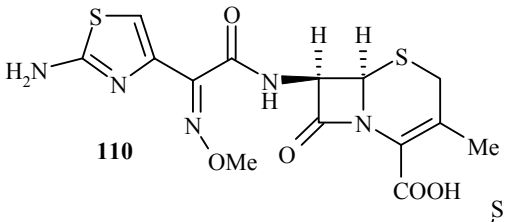


2. BIOLOGICAL ACTIVITY OF THE OXIMES OF FIVE-MEMBERED HETEROCYCLIC COMPOUNDS WITH TWO HETEROATOMS AND THEIR ETHERS

2.1. Bactericidal, Cytotoxic, Antitumor, and Antiviral Activity

Antibacterial agents based on thiazole, pyrazole and imidazole oximes – *Carumonam* **106**, *Cefdinir* **107**, *Celditoren* **108**, *Cefepime* **109**, *Cefetamet* **110**, *Cefixime* **111,** *Cefmenoxime* **112***, Cefodizime* **113**, *Cefoselis* **114,** *Cefotaxime* **115**, *Cefozopran* **116**, *Cefpirome* **117**, *Cefpodoxime Proxetil* **118**, *Cefquinome* **119**, *Ceftazidime* **120**, *Cefteram* **121**, *Ceftiofur* **122**, *Ceftizoxime* **123**, *Ceftriaxone* **124**, and *Cefuzonam* **125** have been widely used [143–145]. Apart from these widely used preparations it is necessary to mention the very extensive range of patents and publications devoted to thiazole oximes, which feature in the composition of cephalosporin antibiotics [146-219]. Apart from the thiazole oxime fragments cephalosporin antibiotics also include oxazole [220], isoxazole [221, 222], isothiazole [223, 224], selenazole [225], pyrazole [226-231], imidazole [232-240], and benzimidazole [241] fragments.





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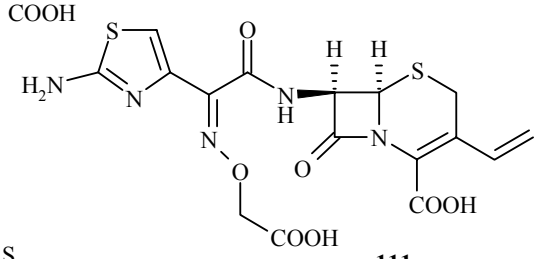

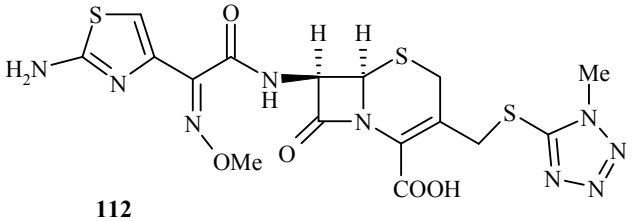

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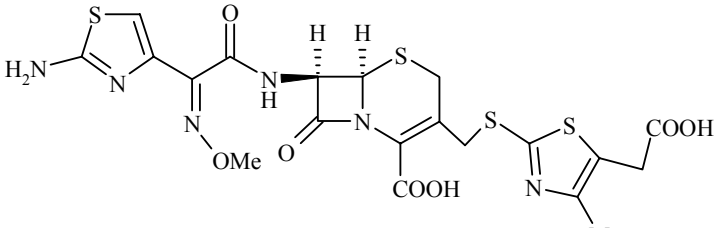

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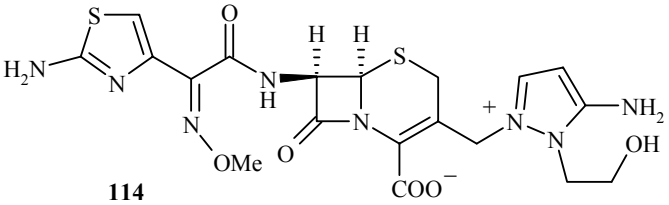

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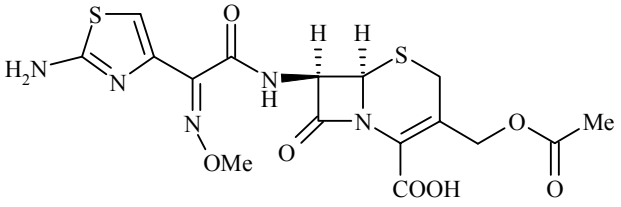

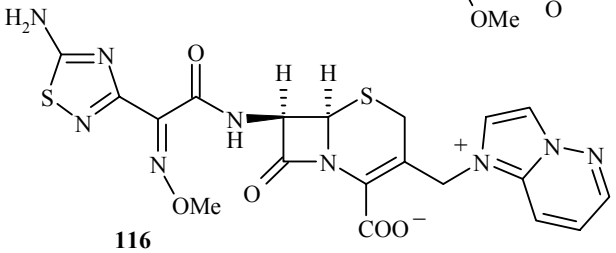

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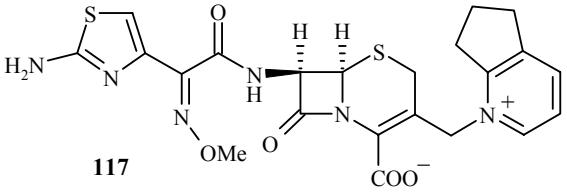

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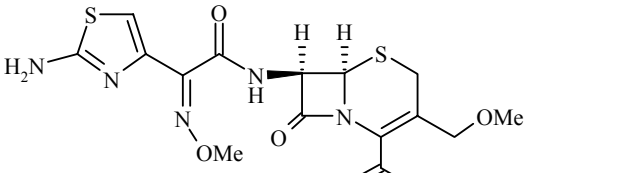

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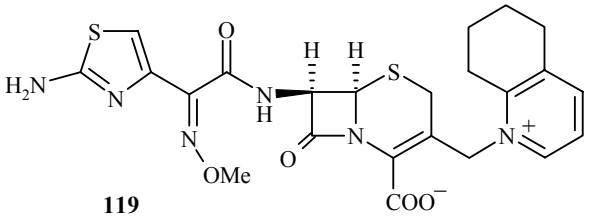

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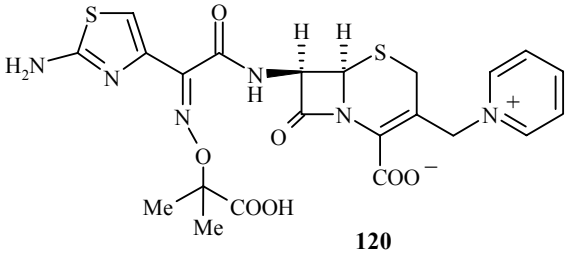

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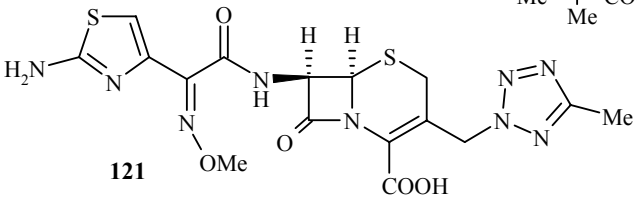

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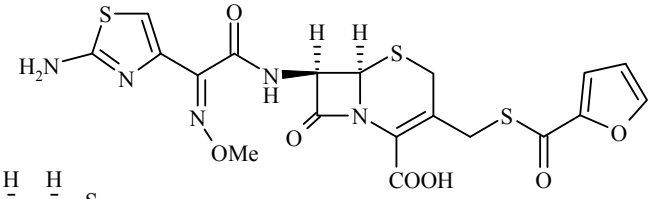

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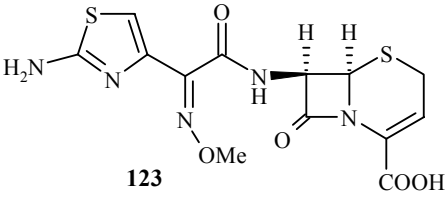

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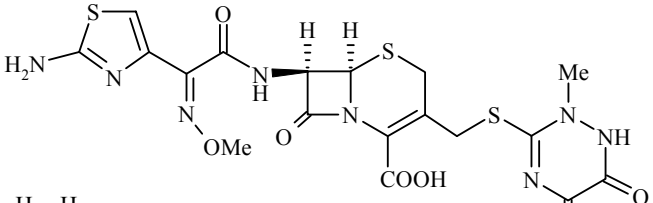

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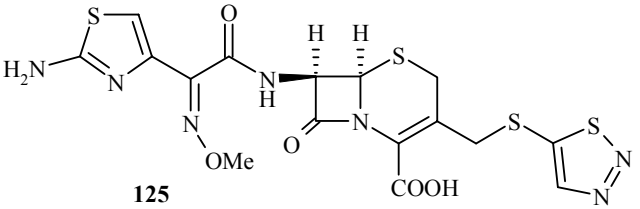
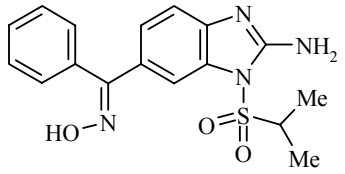


125

High antibacterial activity has also been demonstrated by benzoxazole [242], isoxazole [243, 244], thiazole [243, 244], pyrazole [243, 244], imidazole [243-245], and benzimidazole [249] oximes not containing cephalosporin fragments.

The O-ethers of pyrazole oximes have been investigated as cytotoxic and antitumor agents [250, 251].

Derivatives of the oximes of five-membered heterocyclic compounds with two heteroatoms have exhibited a wide range of antiviral activity. Among these compounds it is necessary to mention the O-ethers of isoxazoline oximes [252], N-(2-isoxazolin-3-ylmethyl)-2-alkoxyiminoacetamides [253], and pyrazole oxime ethers [254, 255]. The antiviral agent *Enviroxime* **126** has found widespread use [256].



126

In addition, imidazole oximes and their ethers have shown protozoacidal activity [257, 258].

2.2. The Action on the Cardiovascular System

Thiazole oximes have been proposed as agents against ischemic heart disease and are inhibitors of the aggregation of blood cells [259]. Oxazole [260-263], thiazole [263-265], and pyrazole [266, 267] oximes have been investigated in great detail as antidiabetic agents. Benzimidazole oximes were proposed as agents for the treatment of thrombocytic diseases [268, 269]. Pyrrolo[1,2-*c*]thiazole oximes were studied as antagonists of the factor for blood cell receptor activation [270].

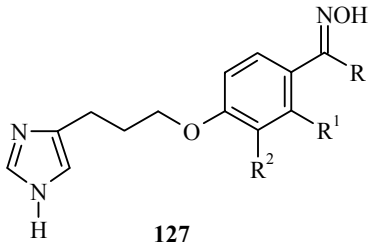
Imidazole oximes were proposed as thromboxane receptor antagonists and thromboxane synthase inhibitors [271].

It is also necessary to mention the vasodilatory action of derivatives of thiazole [272] and 4,5-dihydroisoxazole [273] oximes and the antihypertonic activity of thiazole [272] and imidazo[5,1-*c*]-1,2,4-oxadiazine [274] oximes.

2.3. Sedative, Antidepressant, and Anticonvulsive Activities

In the middle of the seventies investigations were carried out on pyrazole [275] and imidazole [276] amidoximes as sedatives and tranquillizers.

Recently imidazole oximes **127**, which are derivatives of the natural compound *Verongamine* **128**, were proposed as ligands in histamine H_3-receptors [277]. These compounds exhibited a wide range of activity in diseases of the central nervous system. O-Aminoalkyloximes of imidazolylphenones were investigated as agents for depression [17]. Purine oximes have been used against Alzheimer's disease [278]. Imidazole oximes (e.g., compound **129**) were used in the treatment of neurotraumatic and other diseases of the central nervous system [279, 280].



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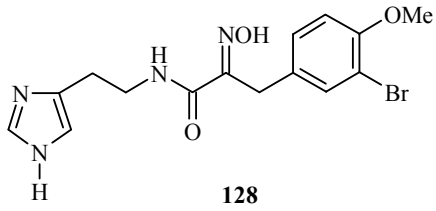

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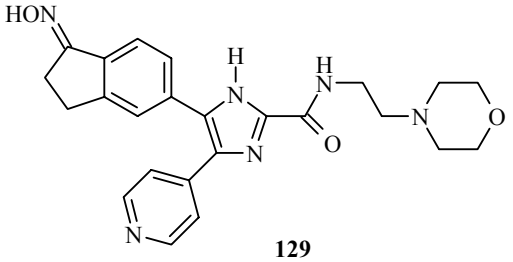
R, R^1, R^2 =H, Me, F, OMe

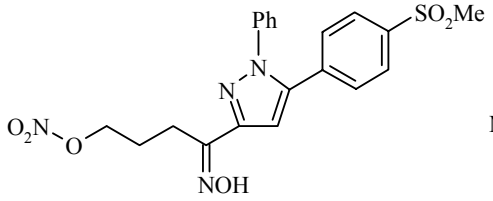


129

2.4. Analgesic and Anti-inflammatory Activities

The nitro derivatives of pyrazole amidoximes exhibited analgesic and psychotropic activity [281]. Pyrazole oximes (e.g., compound **130)** were investigated as cyclooxygenase-2 inhibitors. These compounds showed analgesic and anti-inflammatory activity [282].

Indazole oximes inhibit the activity of mitogen-activated proteinkinase (p38α). Among these compounds, used against inflammation and infection, it is necessary to mention the oxime **131** [283-285].



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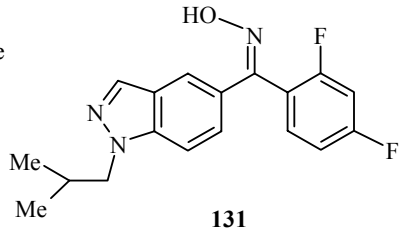
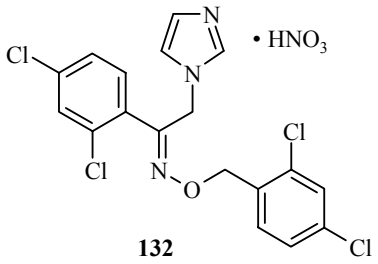


131

The oxime derivatives of 1,2-dihydro-2H-imidazo[4,5-*b*]quinolin-2-one exhibited high activity against allergy [286].

2.5. Oximes of Five-Membered Heterocyclic Compounds with Two Heteroatoms as Fungicides, Pesticides, Herbicides, and Insecticides

High fungicidal activity is exhibited by the oxime derivatives of oxazole [287], isoxazole [288-291], thiazole [292-297], benzothiazole [298-301], imidazole [302-322], benzimidazole [323], and pyrazole [324-338]. Among these compounds it is necessary to mention *Oxiconazole nitrate* **132** [302], which exhibits a wide range of fungicidal activity.



132

Pesticidal activity is exhibited by derivatives of isoxazole [339-342], benzisoxazole [343], thiazole [344], pyrazole [345-350], indazole [351], and 1,2-dithiole [352] oximes and also by 4-hydroxyimino-1-oxa-3-thiacyclopentanes [353].

The literature contains data on the herbicidal activity of isoxazole [354, 355], imidazole [356-358], pyrazole [359-371], and methylenedioxyphenyl oximes [372].

Pyrazole [373-378], imidazole [379-382], and dithiolane [383] oximes exhibited high insecticidal activity.

In addition, dithiolane [384] and isoxazole [385] oximes have been used as acaricides. The O-ethers of thiazole oximes exhibited biocidal activity [386]. Dioxolane oximes have been used in herbicidal antidotes [387].

2.6. Other Activities

Numerous publications have been devoted to the investigation of imidazole [388-400] and pyrazole [401] oximes as antidotes for poisoning by organophosphorus compounds.

Derivatives of imidazo[1,2-*a*]pyridine exhibit antiulcer activity [402]. Methylenedioxyphenyl oximes are used as agents against hepatitis [403, 404]. Imidazole oximes have exhibited diuretic activity [405]. Oxazole oximes and their O-ethers are inhibitors of fatty acid amide hydrolase [406]. Benzimidazole oximes exhibited $GABA_a$ receptor-modulator activity [407]. Isoxazole oximes containing 1-azabicyclo groups are used as muscarine ligands [408].

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