Chemistry of Heterocyclic Compounds, Vol. 37, No. 2, 2001

FURAN AND THIOPHENE OXIMES: SYNTHESIS, REACTIONS, AND BIOLOGICAL ACTIVITY (REVIEW)*

E. Abele and E. Lukevics

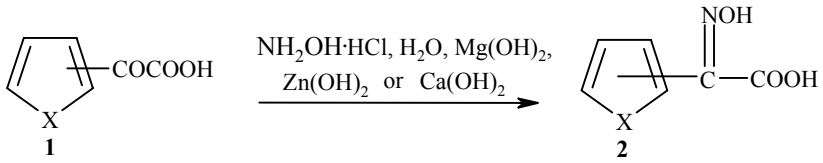
Data on methods for the production of furan and thiophene aldoximes, ketoximes, and amidoximes and their reactions are reviewed. The synthesis of new heterocycles from furan and thiophene oximes and the biological activity of derivatives of the oximes are discussed individually.

Keywords: oximes, thiophene, furan, biological activity.

1. SYNTHESIS OF FURAN AND THIOPHENE OXIMES

1.1. Synthesis of Aldoximes and Ketoximes

The classical method for the synthesis of furan oximes is based on the reaction of the aldehyde or ketone with hydroxylamine in the presence of $NaOH/H_2O$ [1], 2 N aqueous KOH/EtOH [2], K_2CO_3/EtOH [3], or NaOAc [4]. Magnesium, zinc, and calcium hydroxides are used as bases in the synthesis of the oximes. Thus, the reactions of furyl- and thienylglyoxalic acids **1** with $NH_2OH{\cdot}HCl$ in water in the presence of magnesium, zinc, or calcium hydroxide give 2-(2-hydroxyimino)acetic acids **2** containing 80-98% of the *syn* isomer [5].

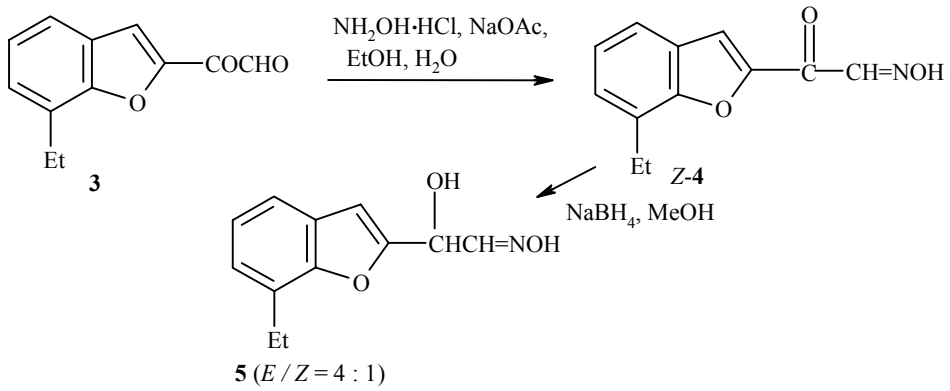


With $NH_2OH{\cdot}HCl$ in the presence of sodium acetate 2-(7-ethylbenzofuryl)glyoxal (**3**) gives the *Z*-isomer of 7-ethylbenzofuran-2-ylglyoxal oxime (**4**) as the only product. Reduction of oxime **4** with sodium borohydride leads to the formation of a mixture of the *E*- and *Z*-isomers of α-hydroxyaldoximes **5** [6].

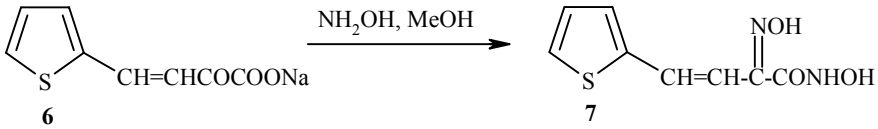
* Dedicated to Prof. L. I. Belen'kii in honor of his seventieth birthday.

Latvian Institute of Organic Synthesis, Riga; e-mail: abele@osi.lv. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 156-186, February, 2001. Original article submitted November 20, 2000.

0009-3122/01/3702-0141$25.00

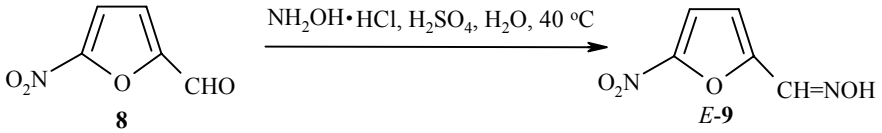


In the reaction of sodium 2-oxo-4-(2-thienyl)butenoate (**6**) with hydroxylamine, obtained from $NH_2OH·HCl$ and sodium methoxide, oxime of hydroxamic acid **7** was isolated as the main product with a yield of 51.8%. The increased reactivity of the salt of 2-oxo-4-(2-thienyl)butenoic acid compared with ethyl 2-oxo-4-phenylbutyrate in the reaction with hydroxylamine is due to the presence of the conjugated double bonds in the initial molecule and the difference in the structure of the thienyl group [7].

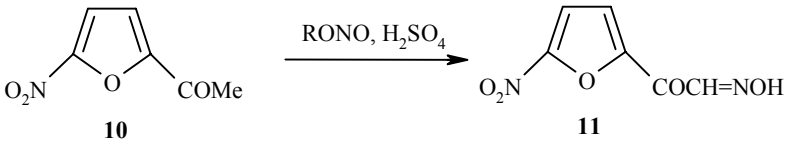


The methods were used successfully in the synthesis of α-furyl dioximes [8] and 2-acetyl-3,4-bis(hydroxymethyl)furan oximes [9].

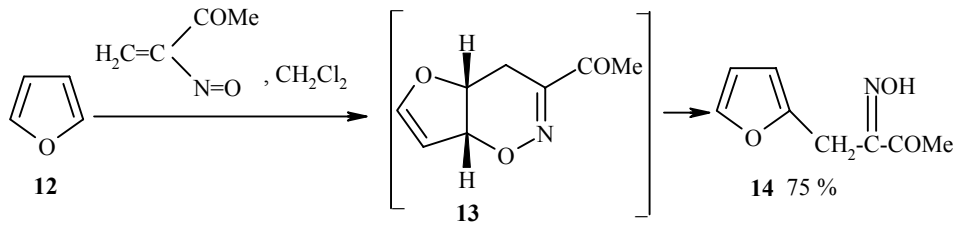
The synthesis of furan oximes in some cases can be realized in an acidic medium. For example, the *E*-isomer of 5-nitro-2-furancarbaldehyde (**9**) is obtained easily from 5-nitro-2-furancarbaldehyde (**8**) in the presence of $NH_2OH·HCl/H_2SO_4$ in water [10].



2-(5-Nitrofuran)glyoxaldehyde oxime (**11**) can be obtained by the reaction of 2-acetyl-5-nitrofuran (**10**) with alkyl nitrite in the presence of concentrated sulfuric acid [11].

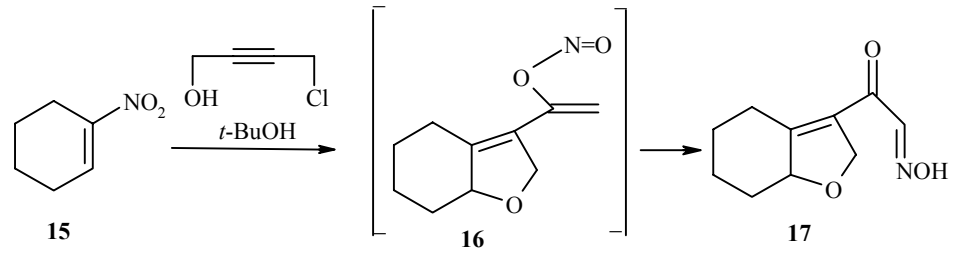


The unexpected formation of furan oxime **14** is observed in the cycloaddition of furan **12** to 3-nitrosobut-3-en-2-one. The intermediate of the reaction – 1,2-oxazine **13** – readily isomerizes to oxime **14** in two hours at room temperature [12].



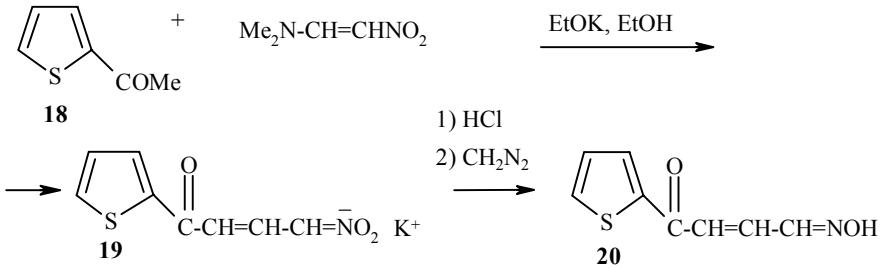
12 **13** **14** 75 %

In the presence of chlorobutynol and potassium *tert*-butoxide the cyclic nitroalkene **15** gives the derivative of dihydrofuran oxime **17**. The product **17** is formed through [1,3]-sigmatropic rearrangement of the intermediate vinyl nitrite **16** [13].



15 **16** **17**

In the presence of diazomethane in an acidic medium allylnitro derivatives are converted into the corresponding unsaturated ketoximes. For example, 2-acetylthiophene (**18**) and 2-dimethylamino-1-nitroethylene in a basic medium readily form the potassium salt of 4-nitro-1-(2-thienyl)-2-buten-1-one (**19**). Subsequent reaction of the intermediate **19** with concentrated hydrochloric acid and diazomethane gives 4-hydroxyimino-1-(2-thienyl)-2-buten-1-one (**20**) as the only product with a yield of 48% [14].

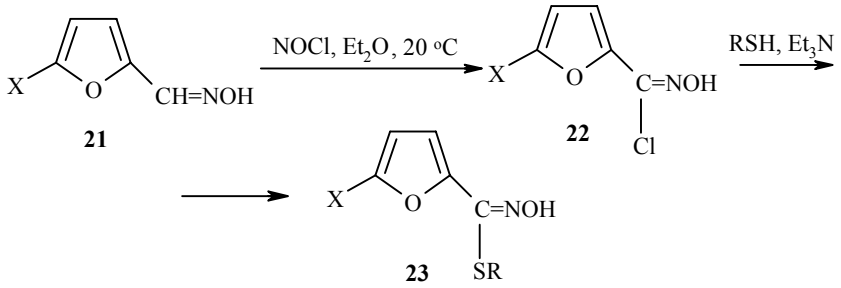


18 **19** **20**

5-Nitro-2-furancarbaldehyde *E*-oxime and 2-(2-nitrovinyl)furan are formed from 5-nitrofurancarbaldehyde and N-(1-furyl-2-nitroethyl)hydroxylamine by the Cope reaction under mild conditions. This oxime is formed through a nitrone intermediate [15].

1.2. Synthesis of Carbohydroximoyl Chlorides

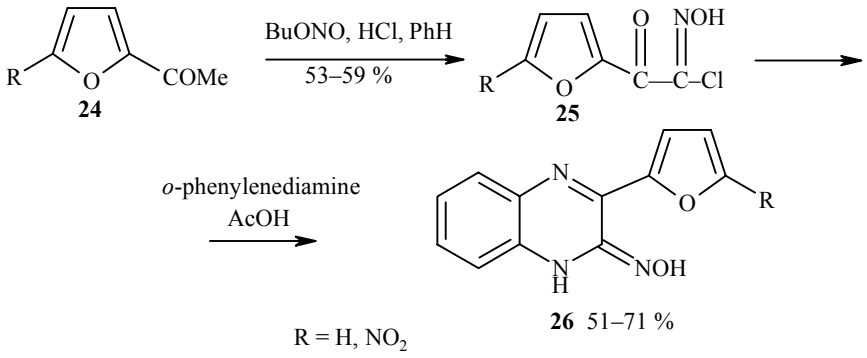
The most widely used method for the synthesis of 2-furancarbohydroximoyl chlorides is based on the action of nitrosyl chloride on oximes. Thus, the 5-derivatives of 2-furancarbohydroximoyl chlorides **22** were easily obtained by the reaction of the respective oximes **21** with $NOCl/Et_2O$. The products **22** are easily transformed into the corresponding sulfide derivatives of oximes **23** by reaction with thiols in the presence of triethylamine [16].



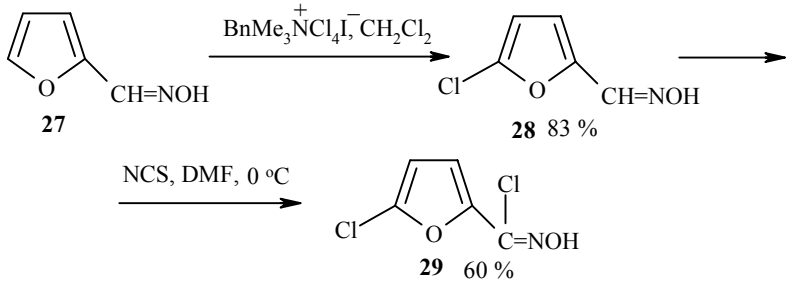
X = NO_2, 2-, 3- and 4-$NO_2C_6H_4$, R = Ph, CH_2Ph, CH_2 (2-furyl)

Derivatives of the fungicidal N-(N-methylcarbamoyl)furanacetimidoyl chloride were obtained by a similar method [17].

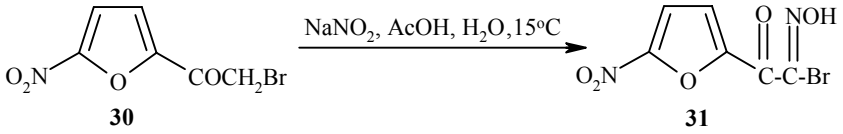
The derivatives of 2-acetylfuran **24** react readily with butyl nitrite in the presence of dry HCl and form the chlorine derivatives of glyoxal **25**. In the presence of *o*-phenylenediamine and acetic acid compounds **25** give 2-hydroxyimino-1,2-dihydroquinoxalines **26** [18, 19].



It is not possible to obtain the expected hydroximoyl chloride during the chlorination of 2-furancarbaldehyde oxime (**27**) with benzyltrimethylammonium tetrachloroiodate ($BnMe_3N^+ICl_4^-$), since the furan is readily halogenated in the ring. Instead a good yield of 5-chloro-2-furancarbaldehyde oxime **28** is obtained. Compound **28** is easily converted into the corresponding hydroximoyl chloride **29** merely by reaction with N-chlorosuccimide (NCS) in dimethylformamide [20].



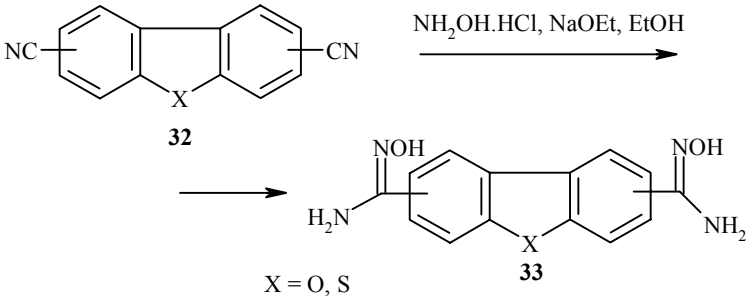
With $NaNO_2$/AcOH bromomethyl 5-nitro-2-furyl ketone (**30**) gives the 1-oxime of 5-nitro-2-furylglyoxyloyl bromide (**31**) as the only product. The product **31** is formed as a result of nitrosation of the active methylene group in ketone **30** [21].



30 **31**

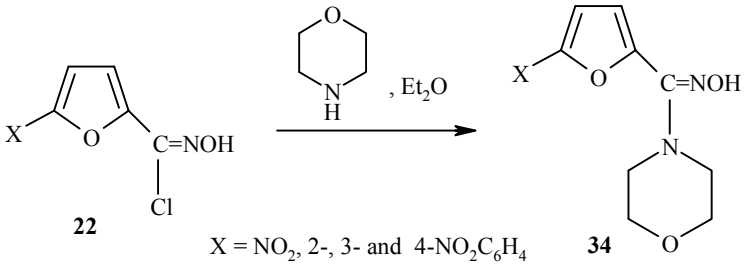
1.3. Furan and Thiophene Amidoximes

Furan and thiophene amidoximes have been known for more than 100 years [22]. These compounds are widely used as biologically active substances and are also used as heat-sensitive elements [23]. The eruptive characteristics of furan-2-amidoxime have been demonstrated [24]. These compounds are usually produced by the reaction of the respective nitriles with $NH_2OH{\cdot}HCl$ in the presence of KOH/EtOH [25, 26] or $NaHCO_3/MeOH/H_2O$ [27]. It was recently shown that derivatives of 2,8-di(N-hydroxyamidino)dibenzofuran and 3,7-di(N-hydroxyamidino)dibenzothiophene (**33**) can be synthesized by the reaction of the dinitriles (**32**) with hydroxylamine. The synthesized compounds were tested as agents against *Pneumocysis carinii* [28, 29].



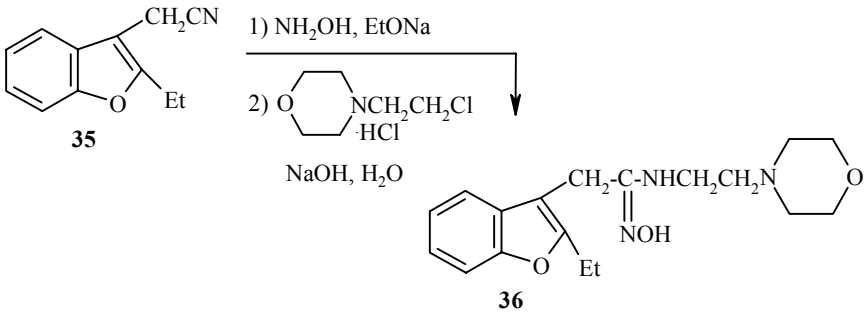
32 **33**

2-Furancarbomorpholide oximes **34** were obtained by the reaction of 2-furancarbohydroximidoyl chlorides **22** with morpholine in ether [16].



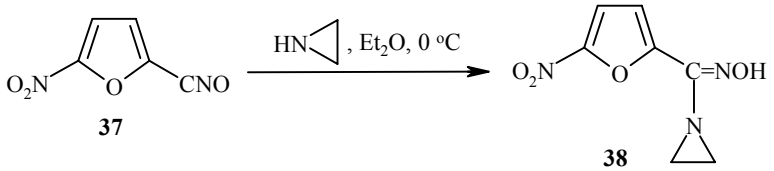
22 **34**

It was shown that it is possible to obtain derivatives alkylated at the amino group of the amidoxime [30]. For example, the reaction of 3-cyanomethyl-5-ethylbenzofuran (**35**) with $HN_2OH/EtONa$ and N-(2-chloroethyl)morpholine hydrochloride in aqueous sodium hydroxide leads to the N-alkylamidoxime **36** as the main product. Compound **36** exhibits strong antihypertonic activity.



35 **36**

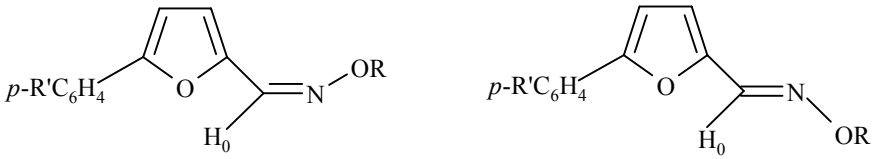
Not only carbohydroximoyl chlorides but also certain nitrile oxides react with secondary amines. Thus, the reaction of 5-nitro-2-furylnitrile oxide (**37**) with aziridine in ether at 0°C gives 1-(5-nitro-2-furoyl)aziridine oxime (**38**) with a yield of 80% [31, 32].



37 **38**

2. STRUCTURE OF FURAN AND THIOPHENE OXIMES

NMR spectroscopy is one of the most reliable methods for determining the structure of isomeric oximes. The classical method for determining the *E*,*Z*-isomerism of furan and thiophene oximes is comparison of the chemical shifts of the "aldehyde proton" (H_0) in both geometric forms. On account of the effect of the NOH group the signal of H_0 in the *Z*-isomers of 5-arylfurfural oximes **39** is shifted upfield by 0.4-0.5 ppm compared with the *E*-isomer [33, 34]. From analysis of the spin–spin coupling constants J_{H0H4} conclusions were reached about the preferred conformation of the side chain in relation to the plane of the furan ring in all the investigated isomers.



Z- **39** *E*- **39**

R = H, COMe; R' = H, Cl, Br, NO_2

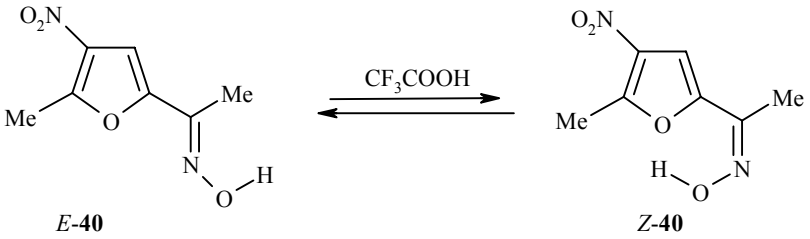
The geminal spin–spin coupling constants $J^{15}_{N–H0}$, the values of which are stereospecific (J = 14.0-17.5 Hz for the *Z*-isomers and J = 0.45-2.60 Hz for the *E*-isomers), were used successfully to determine the configuration [34, 35].

The ^1H, ^{13}C, and ^{15}N NMR spectra of the oximes of the 5-substituted furfurals [34] and 2-acetylfuran [36] were studied in detail. The spin–spin coupling constants between the protons of the ring and the oxime group were determined. Analysis of the ^1H–^1H spin–spin coupling constants with allowance for their stereospecificity shows that the *E*-isomers in the polar dimethyl sulfoxide have the *s-trans* while the *Z*-isomers have the *s-cis* conformation [37]. The signs of the straight and geminal ^{13}C–^{15}N spin–spin coupling constant were determined for the oxime of 5-trimethylsilylfurfural. After acidification of the solutions of the oximes of 2-acetylfuran and also with the introduction of halogens into the methyl group of 2-acetyl-5-nitrofuran oxime the content of the *Z*-isomer is increased.

The direct ^{13}C–^{13}C spin–spin coupling constants between the nuclei of the oxime carbon and the nearest carbon atom of the heterocyclic fragment were used to determine the configuration of the furan and thiophene rings [38]. The ^{13}C–^{13}C spin–spin coupling constants in the *E*-isomers (the unshared pair of the nitrogen atom is in the *cis* orientation to the interacting ^{13}C nuclei) are almost 15% greater than those in the *E*-isomer by 8-10 Hz.

Derivatives of 2-acetylthiophene oximes were investigated in detail by ^1H NMR [39]. The signal of the methyl group in the *Z*-isomers of these oximes is shifted by ~0.1 ppm upfield compared with the *E*-isomer. It was also shown that the isomers can be isolated by column chromatography. The rearrangement of the *E*- and *Z*-isomers of acetylthiophene oximes takes place with the formation of various amides (see 3.4). Conformational investigation of the dioximes showed that 2,5-diformylthiophene contains three isomers (*E*,*E*-, *Z*,*Z*-, and *Z*,*E*-) [40].

An increase in the proportion of the *E*-isomers is quite often observed when the *Z*-isomers of furan or thiophene oximes are stored or heated, but in some cases the opposite process, i.e., transformation of the *E*-isomer into the *Z*-isomer, is possible. Thus, the *Z*-isomer of 2-acetyl-5-methyl-4-nitrofuran (*Z*-**40**) is formed from the corresponding *E*-isomer *E*-**40** in the presence of trifluoroacetic acid [41]. The product *Z*-**40**, isolated by column chromatography, prove unstable and was reconverted into the *E* after two months.



E-**40** *Z*-**40**

The isomerism of the furan and thiophene oximes is easily established by means of the UV spectra [42] and by polarographic methods [43]. Urea forms a complex (1:1) only with the *Z*-isomer of 5-nitro-2-furancarbaldehyde oxime; the *E*-isomer does not form a complex under analogous conditions [44]. Only the *Z*-isomer of 2-furancarbaldehyde oxime forms a complex with Na_2PdCl_4. The complex separates from a solution in EtOH/EtOAc in the form of a precipitate [45].

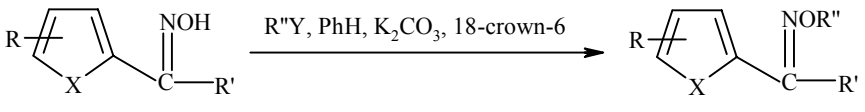
The structure of the furan and thiophene oximes has also been widely investigated by IR [46] and Raman spectroscopy [47, 48]; the dipole moments of the compounds were determined [49]. A detailed investigation of the mass spectra of furyl- and thienyl alkyl ketoximes and their O-ethers showed that unlike the aromatic ketoximes they are characterized by the formation of intense cations of the protonated nitriles [50].

3. REACTIONS OF FURAN AND THIOPHENE OXIMES

3.1. Synthesis of the Ethers of Furan and Thiophene Oximes

The classical methods for the production of the O-alkyloximes of furan and thiophene aldehydes and ketones are based on alkylation of the respective oximes by alkyl halides (or dialkyl sulfates) in the presence of sodium hydride in dimethylformamide [51], alkali-metal hydroxide in dimethyl sulfoxide [52], or sodium methoxide in methanol [53, 54]. Here nitrones are often formed during the alkylation of the oximes. Thus, the reaction of the oximes of furan and thiophene aldehydes with MeI/NaH in dimethylformamide leads to the formation of nitrones, i.e., the N-alkylation products [55, 56].

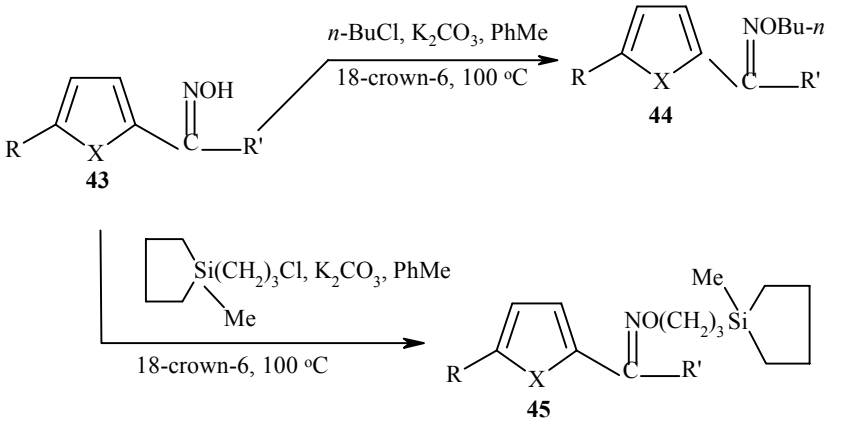
The use of phase-transfer catalysis in the synthesis makes it possible to alkylate the furan and thiophene oximes selectively. The alkylation of 2-furyl and 2-thienyl alkyl ketoximes **41** by alkyl and propargyl halides in solid K_2CO_3/18-crown-6/C_6H_6 at room temperature leads to the formation of the respective O-ethers **42** with yields of 32-74%. Nitrones are not formed under these conditions. An increase in the proportion of the *Z*-isomer is observed during the alkylation of sterically hindered ketoximes [57]:



41 **42**

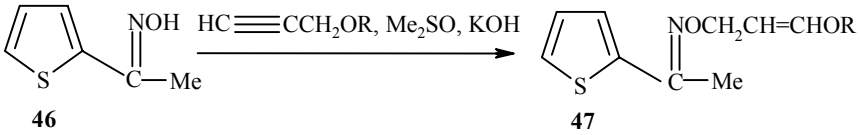
X = O, S; R = H, 5-Me, 5-Br; R' = Me, Et, *i*-Pr, $CHEt_2$; R" = Alk

Sterically hindered α-hydroxy- and α-methoxyketoximes in the phase-transfer catalyst system MeI/solid KOH/18-crown-6/C_6H_6 form the O-methyloximes of 2-methyl-1-(2-furyl)- and 2-methyl-2-methoxy-1-(2-thienyl)-1-propanones [58]. The phase-transfer catalysis method was also used in the synthesis of thiophene dioximes [59]. However, high yields of the alkylation products could only be obtained in cases where alkyl bromides and alkyl iodides were used as alkylating agents. In the presence of alkyl chlorides the alkylation products were obtained with low yields. We developed a convenient method for the synthesis of the O-ethers of furyl- and thienylketoximes **44** and **45** in the phase-transfer catalysis system alkyl chloride/solid K_2CO_3/18-crown-6/toluene at 100°C [60].

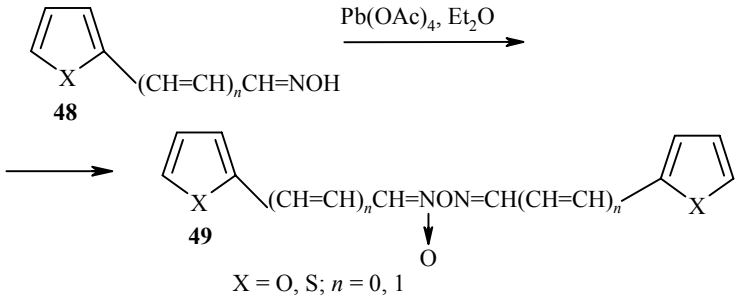


X = O, S; R = H, Me; R' = Me, *i*-Pr

Unsaturated O-ethers were obtained by the addition of oximes to propargyl ethers. For example, 2-acetylthiophene oxime (**46**) in the HC≡CCH_2OR/KOH/DMSO system at 110°C gives ethers **47** with yields of 9-12 % [61].

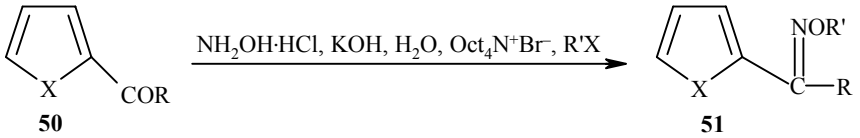


Aldoximes readily dimerize in the presence of lead tetraacetate. Thus, the reaction of the furan and thiophene aldoximes **48** with $Pb(OAC)_4/Et_2O$ leads to the respective N-oxides **49** as the main products with yields of 16-30% [62].



X = O, S; *n* = 0, 1

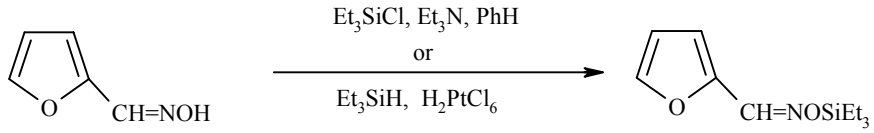
The O-ethers of furan and thiophene aldehyde and ketone oximes are also obtained from the corresponding carbonyl compounds. One method for the production of O-alkyloximes is based on the reaction of the ketones with the $NH_2OR{\cdot}HCl/Na_2CO_3/H_2O/MeOH$ system [63]. As a result of the limited number of O-alkylhydroxylamines (NH_2OR), however, it is less general in nature. We developed a new method stereoselective method for the synthesis of furan and thiophene O-alkyloximes **51** from the corresponding carbonyl compounds **50** in the phase-transfer catalysis system $NH_2OH{\cdot}HCl/KOH/H_2O/Oct_4N^+Br^-$ followed by treatment of the reaction mixtures with alkyl halides. Under these conditions the products **51** were obtained with yields of 32-79% and with good *E*-selectivity [64].



50 **51**

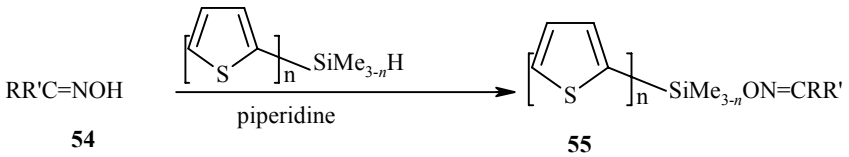
X = O, S; R = H, Me; R'X = MeI, EtI, $HC{\equiv}CCH_2Br$

Silyl ether of furfural oxime (**53**) was obtained by the reaction of furfural oxime (**52**) with triethylchlorosilane in the presence of triethylamine. The product **53** can also be obtained by heating oxime **52** with triethylsilane in the presence of H_2PtCl_6, but in this case side reduction reactions are observed [65]:



52 **53**

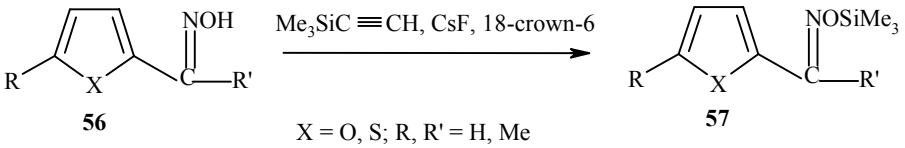
The thienyl-containing silyl ethers of oximes **55** are produced in the reaction of oximes **54** with thienylhydrosilanes in the presence of piperidine [66]:



54 **55**

R,R' = H, Me, Et; *n* = 1–3

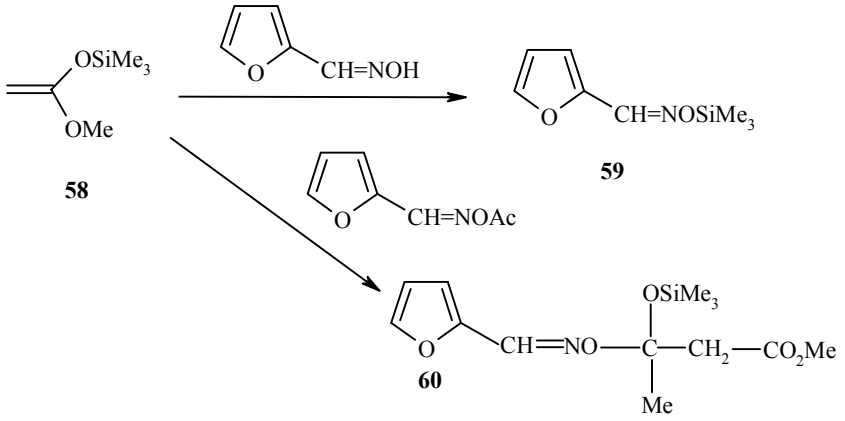
Furaldehyde and thiophenecarbaldehyde oximes **56** are readily silylated in the phase-transfer catalyst system trimethylsilylacetylene/CsF/18-crown-6/benzene at room temperature. The corresponding oxime silyl ethers **57** were obtained with yields of 40-84% [67]. The germylation of 2-acetylfuran oxime in the $Et_3GeC{\equiv}CPh/KF–Al_2O_3$/18-crown-6/benzene system proved ineffective, in contrast to the pyridine and aromatic oximes. The product in this case was only detected by mass spectrometry.



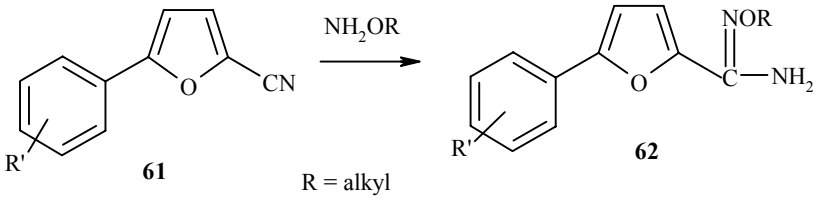
56 **57**

X = O, S; R, R' = H, Me

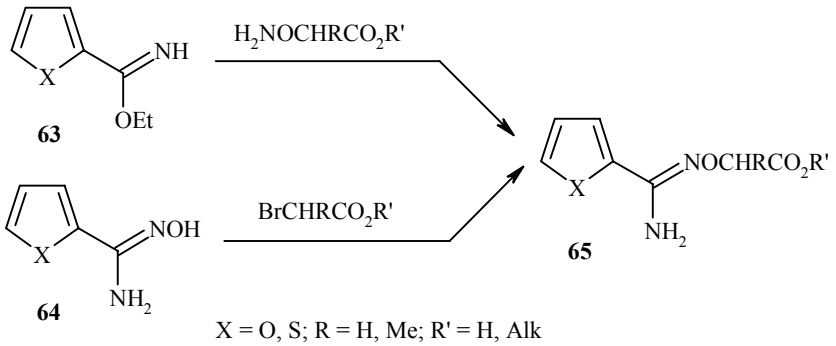
The silylated acetals of ketenes also react with oximes or oxime acetates. For example, the reaction of 2-furaldehyde oxime with 1-methoxy-1-trimethylsilyloxyethene (**58**) leads to the silylated oxime **59**.



The 2-furancarbaldehyde O-acetyloxime and alkene **58** give the silylated O-ether of oxime **60** [68]. O-ethers of furan amidoximes **62** were obtained by the reaction of the corresponding nitriles **61** with O-alkylhydroxylamines in the presence of KOH/EtOH or NaOMe/MeOH. The products **62** have strong antidepressant activity [69].

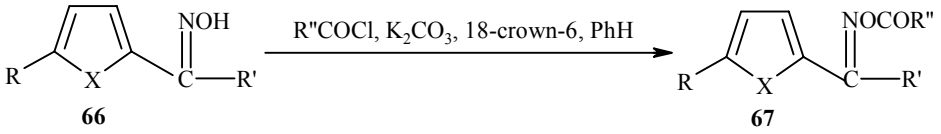


Ethers of furan and thiophene amidoximes **65** were obtained by the reaction of imines **63** with $H_2NOCHRCO_2R'$ or of oximes **64** with $BrCHRCO_2R'$. The alkylated amidoximes exhibit strong herbicidal activity [70].



The O-acyl derivatives of the furan and thiophene oximes were obtained by the acylation of the corresponding oximes by acid chlorides in the presence of pyridine [1, 71-74] or triethylamine [75]. Furan-containing aldoximes are acylated by acetic anhydride in the presence of pyridine, and the reaction is often accompanied by a Beckmann rearrangement [33, 76].

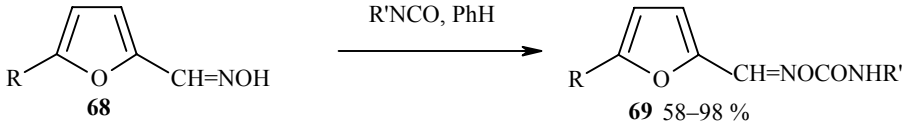
We realized the selective acylation of 2-furyl- and 2-thienylketoximes **66** in the phase-transfer catalyst system acyl chloride (R"COCl/solid K_2CO_3/18-crown-6/benzene at room temperature. Under these conditions the yield of the reaction products **67** amounted to 42-95%; the products of the Beckmann rearrangement were not formed [77]. The obtained O-acyloximes are easily transformed into the corresponding O-ethers in the phase-transfer catalyst system alkyl halide/solid KOH/18-crown-6/benzene [78].



66 **67**

X = O, S; R = H, Br; R' = Me, Et, *i*-Pr; R" = Me, Et, *t*-Bu, Ph

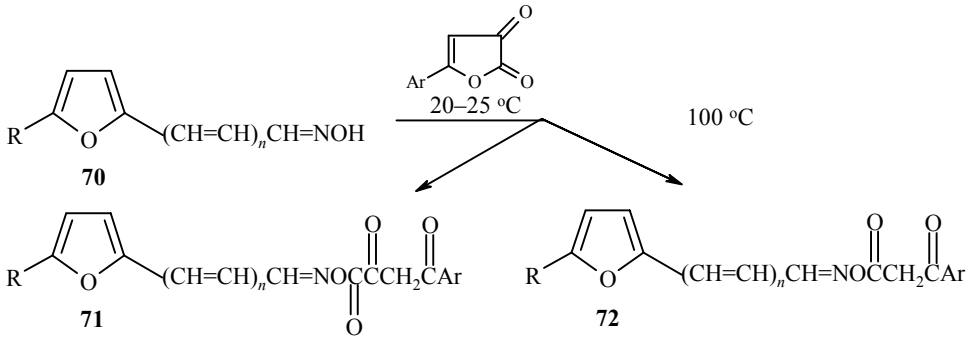
The furan and thiophene O-(alkyl(aryl)carbamoyl)oximes **69** were obtained by the reaction of the respective oximes **68** with alkyl and aryl isocyanates in benzene [79-81]. The products **69** were tested as pesticides [79].



68 **69** 58–98 %

R, R' = Alk, Ar

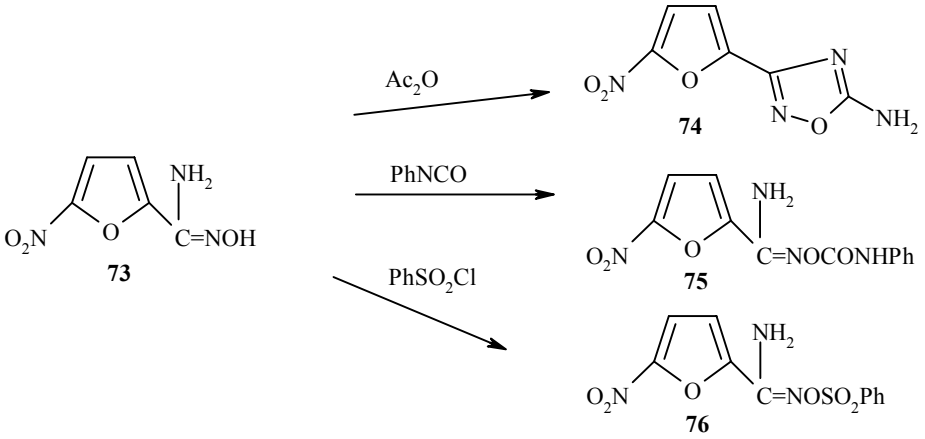
The O-acylated oximes **71** and **72** of the furan series were obtained by the reaction of oximes **70** and 5-aryl-2,3-dihydrofuran-2,3-diones at 20-25°C or 100°C respectively. The products **71** and **72**, isolated with yields of up to 94%, exhibit strong antimicrobial activity [82].



70 **71** **72**

R = H, NO_2; *n* = 0, 1

Acylated furan amidoximes were obtained by the reaction of the respective amidoximes with acid chlorides/K_2CO_3/acetone [83] or acetic anhydride [32]. However, the reaction of 5-nitro-2-furancarbamidoxime **73** with acetic anhydride gives the derivative of 1,2,4-oxadiazole **74** as the main product. The acylation products **75** and **76** were obtained by the reaction of oxime **73** with phenyl isocyanate or benzenesulfonyl chloride respectively [80].

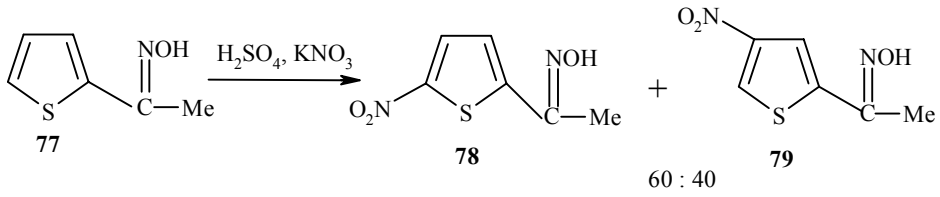


73 **74** **75** **76**

3.2. Reactions of the Oxime Groups and Rings

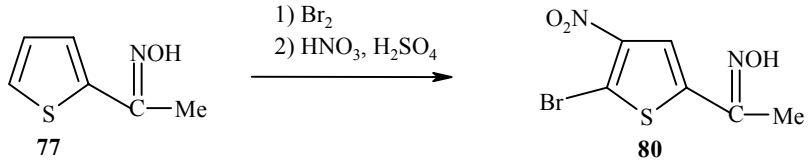
Advances in the chemistry of the derivatives of oximes were reviewed in [84]. The special features of the chemistry of furan and thiophene oximes will be examined further.

Derivatives of thiophene ketoximes are easily nitrated in the presence of conc. H_2SO_4/KNO_3. For example, during nitration 2-acetylthiophene oxime (**77**) gives a mixture of the oximes of 2-acetyl-4-nitrothiophene (**78**) and 2-acetyl-5-nitrothiophene (**79**) in a ratio of 40:60. 2-Propionylthiophene oxime is nitrated in a similar way. The products **78** and **79** were isolated in the pure form by fractional crystallization [85].



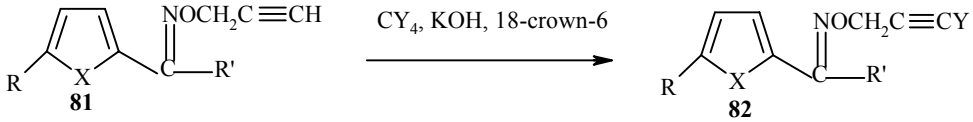
77 **78** **79**

The selective synthesis of oximes of 5-acetyl-2-halogeno-3-nitrothiophenes was described in a patent [86]. The reaction of 2-acetylthiophene oxime (**77**) with bromine and then with a mixture of sulfuric and nitric acids gives a good yield of 5-acetyl-2-bromo-3-nitrothiophene oxime (**80**).



77 **80**

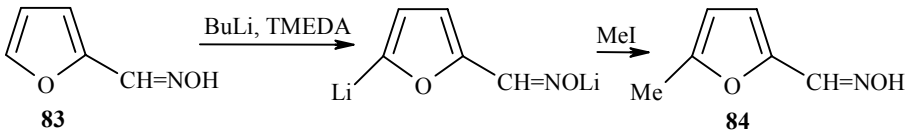
Halogenation of the propargyl ethers of furan and thiophene oximes **81** in phase-transfer catalyst systems CX_4 (X = Cl, Br)/solid KOH/18-crown-6 leads to the selective formation of O-(halogenopropargyl)oximes (**82**) with yields of up to 90%. Preliminary experiments showed that the optimum amount of carbon tetrabromide in relation to the substrate in the bromination of O-propargyloximes was 0.75 equivalent. This can be explained by disproportionation of the initially formed bromoform in the presence of alkali into carbon tetrabromide, which continues the reaction [87, 88].



81 **82**

X = O, S; Y = Cl, Br R = H, Br; R' = H, Me, Et

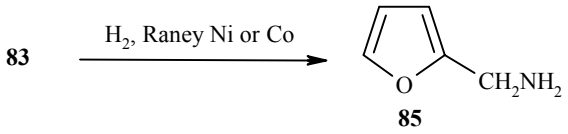
The synthetic possibilities of the dianion of furancarbaldehyde oxime in the production of 2,5-disubstituted furans were set out in [89, 90]. For example, the reaction of the *Z*-isomer of 2-furancarbaldehyde oxime (**83**) with butyllithium followed by treatment of the reaction mixture with methyl iodide leads to 5-methylfurancarbaldehyde oxime (**84**) with a yield of 95%.



83 **84**

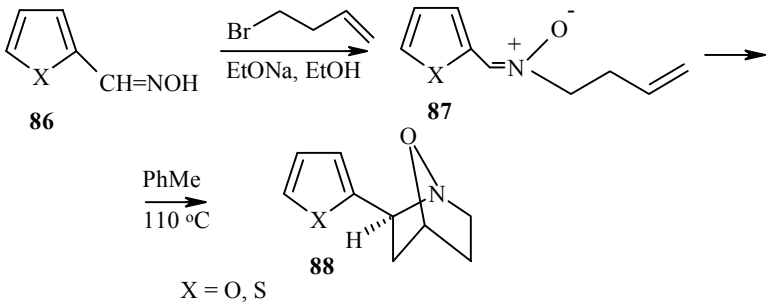
The dehydration of the oximes was described in [91]. Furan and thiophene oximes are readily transformed into the corresponding nitriles in the presence of $POCl_3$/DMF [92], DBU/MeCN [93], Ac_2O [94] or PhNCS [95], NaOMe/MeOH/DMF [55], or $CHCl_3$/60% aq. KOH/Oct_4NBr/PhMe [96].

It was shown that in the hydrogenation of 2-furancarbaldehyde oxime (**83**) in the presence of Raney nickel [97, 98] or cobalt [98] to the corresponding 2-furfurylamine (**85**) the Raney nickel exhibited the highest activity in the presence of 3% ammonia in ethanol. Under these conditions amine **85** was obtained with a yield of 51% [98].

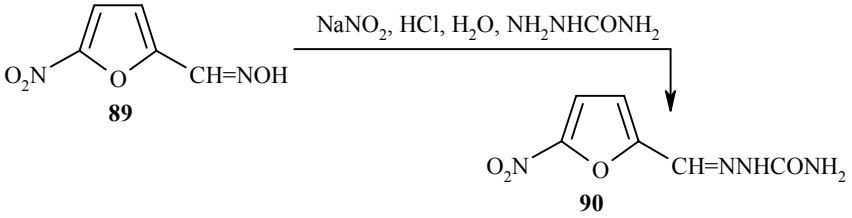


The reduction of the oxime derivatives of benzothiophene by the boron–pyridine complex gives derivatives of hydroxylamine [99]. The asymmetric reduction of the *E*- and *Z*-isomers of furyl ketoxime ethers by the chiral compounds of boron was used in the synthesis of certain optically active α-amino acids [100].

The reaction of the *Z*-isomers of 2-thiophene- and 2-furancarbaldehyde oximes **86** with 4-bromo-1-butene leads to the corresponding C-heteroaryl-N-3-butenylnitrones **87** with yields of 52-55%, while intramolecular thermocycloaddition of **87** leads to *exo-C*-2-furyl- and *exo-C*-thienyl-1-aza-7-oxabicyclo[2.1.1]heptanes **88** [101].



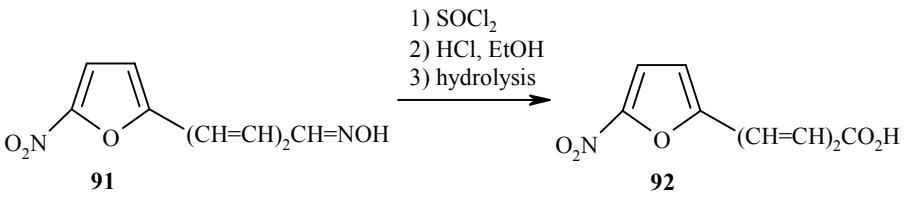
5-Nitro-2-furancarbaldehyde oxime (**89**) is readily transformed into 5-nitro-2-furancarbaldehyde semicarbazone (**90**) in the presence of HCl/$NaNO_2$ and a semicarbazide salt [102].



This reaction can also be realized in the $NH_2NHCONH_2$/H_2SO_4/HCl/EtOH system at 80-90°C [103].

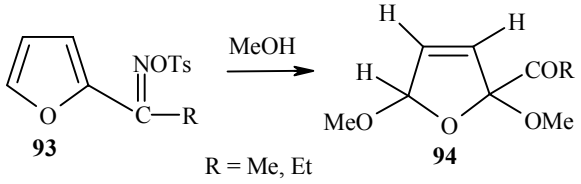
The synthesis of the Schiff base N-(5-amino-2-furfurylidene)-1-aminohydantoin from oxime **89** and of 1-aminohydantoin in the presence of sulfuric acid was described in the patent [104].

A method was developed for the production of derivatives of *trans*-ω-(5-nitro-2-furyl)polyenoic acids from ω-(5-nitro-2-furyl)polyene oximes. For example, the reaction of 5-(5-nitro-2-furyl)penta-2,4-dienal oxime (**91**) with thionyl chloride and HCl/EtOH followed by hydrolysis of the reaction mixture gives acid **92** with a yield of 85% [105].



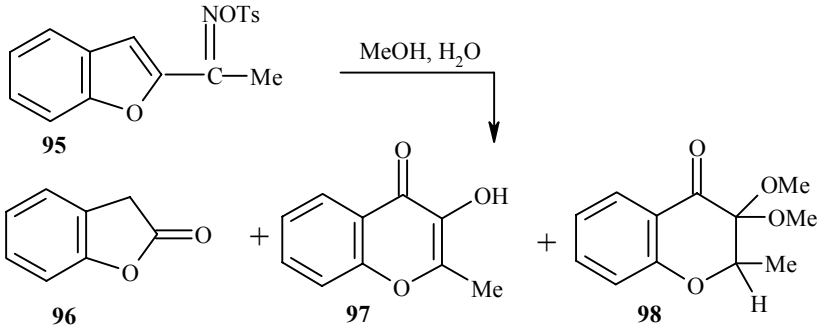
91 **92**

Investigation of the solvolysis of the O-*para*-toluenesulfonyloximes of furan ketones showed that the *Z*-isomers of the oximes are stable and do not undergo any changes at room temperature. The transformation of the *E*-isomers of the O-tosyloximes of furan ketones **93** to *cis*-4,5-dioxohexanal dimethyl acetals in an aqueous alcohol medium was described [1, 72, 106], but these results were later questioned. It was shown that the O-tosyloximes **93** give derivatives of 2,5-dimethoxy-2,5-dihydrofuran **94** in the presence of methanol [107, 108].



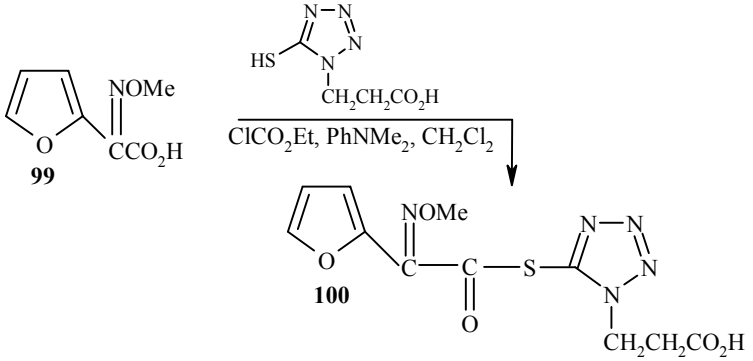
93 R = Me, Et **94**

In aqueous methanol benzofuran O-tosyloxime **95** gives a mixture of three products, i.e., 2-coumarone (**96**), 2-methyl-3-chromanol (**97**), and 2-methyl-3-chromanone diacetal (**98**) [72].



95 **96** **97** **98**

An interesting esterification of 2-furyl-2-methoxyiminoacetic acid (**99**) by tetrazolethiol in the $ClCO_2Et/PhNMe_2/CH_2Cl_2$ system was described in the patent [109]. The reaction resulted in the selective isolation of 1-(2-ethoxycarbonyl)tetrazol-5-yl 2-furyl-2-methoxyiminothioacetate (**100**) with a yield of 78%.

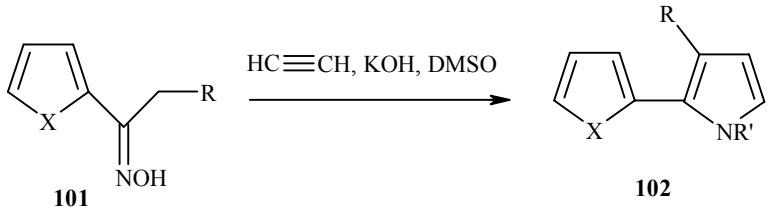


99 **100**

3.3. Synthesis of New Heterocycles from Furan and Thiophene Oximes

Advances in the synthesis of heterocyclic systems were reviewed in [110], and in the present section we will therefore dwell on specific reactions of furan and thiophene oximes.

One of the most interesting reactions of the oximes is the synthesis of pyrroles by the reaction of ketoximes with acetylenes in a basic medium (the Trofimov reaction). The synthetic possibilities of this reaction were set out in detail in the monographs [111-114]. A review on the synthesis of furyl- and thienylpyrroles was published recently [115]. Under classical conditions the synthesis of the pyrrole derivatives **102** from the corresponding furan and thiophene oximes **101** was conducted in an autoclave at 8-16 atm in the HC≡CH/KOH/DMSO system. The products **102** under these conditions were isolated with yields of up to 85%.

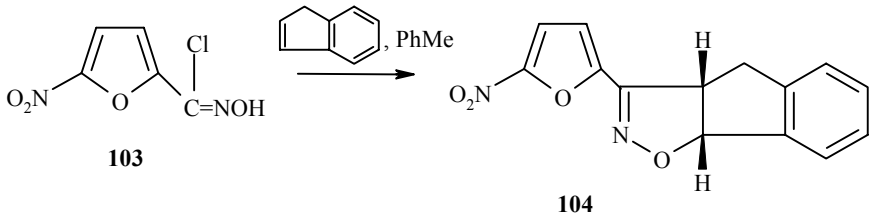


101 **102**

X = O, S; R = H, Me, Et; R' = H, CH=CH$_2$

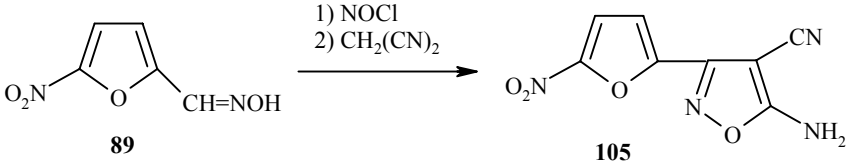
The synthesis of 2-(2-thienyl)- and 2-(3-thienyl)pyrroles was realized by a modified Trofimov reaction, i.e., by the addition of methyl 2-thienyl and methyl 3-thienyl ketoximes to methyl propiolate or dimethyl acetylenedicarboxylate [116]. The acetylene equivalent in similar syntheses was 1,2-dichloroethane [117] and vinyl chloride [115].

Furan carbohydroximoyl chlorides are readily converted into derivatives of isoxazolines in the presence of alkenes [20, 118, 119]. For example, 5-nitro-2-furanhydroximoyl chloride (**103**) and indene in boiling toluene form the thermal cyclic adduct **104** with a yield of 80% [120].



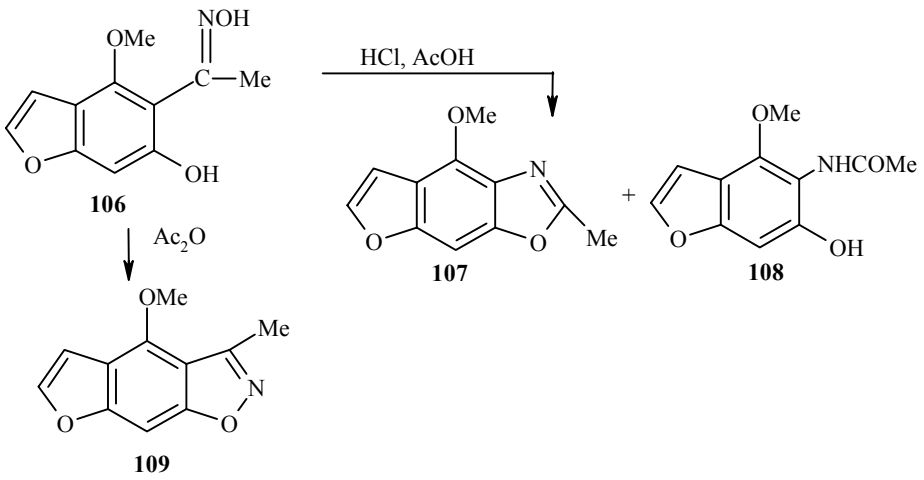
103 **104**

The synthesis of bactericidal 5-amino-4-cyano-3-(5-nitro-2-furyl)isoxazoles has been described [121]. Thus, the reaction of 5-nitrofurfural oxime (**89**) with nitrosyl chloride and cyclization of the intermediate with malononitrile gave isoxazole **105**.



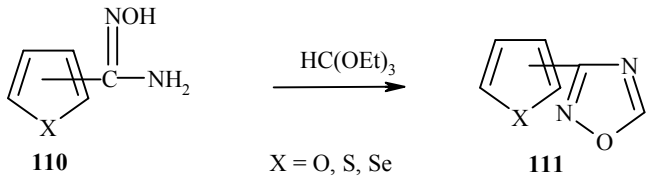
89 **105**

The synthesis and cyclization of visnaginone oxime (**106**) to the corresponding derivatives of benzoxazole **107** and benzisoxazole **109** were investigated in a fair amount of detail. It was shown that the reaction of oxime **106** in the presence of HCl in acetic acid led to a mixture of 4-methoxy-2-methylfuro[2,3-*f*]-benzoxazole (**107**) and anilide **108**. However, in acetic acid the product of the reaction of oxime **106** is 4-methoxy-3-methylfuro[3,2-*f*]benzisoxazole (**109**) [122].



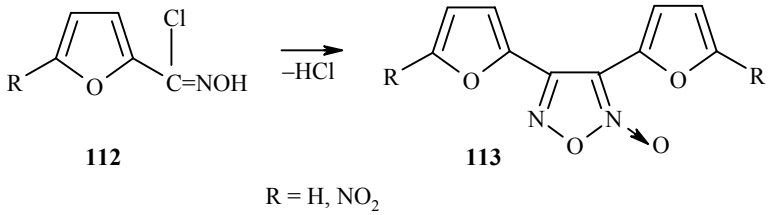
The analogous synthesis of 2,5,6-trimethylfuro[3,2-*f*]benzoxazole from 5-acetyl-6-methoxy-2,3-dimethylbenzofuran was realized in the presence of pyridine hydrochloride [123].

Oxadiazoles **111** were formed in the reaction of amidoximes **110**, obtained from the corresponding nitriles, with triethyl orthoformate [124].

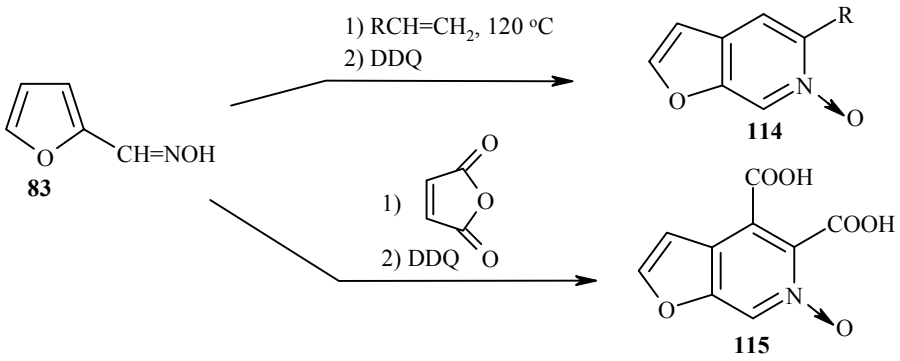


Similar transformations of furan and thiophene amidoximes into the respective 1,2,4-oxadiazoles are easily realized in the systems acyl chloride/$BF_3 \cdot OEt_2$/dioxane [125], acyl chloride/Ac_2O [126], $(EtO)_2CO$ [127], CH_3CHO/EtOH [128], and isopropenyl acetate/montmorillonite/KSF with microwave treatment [129].

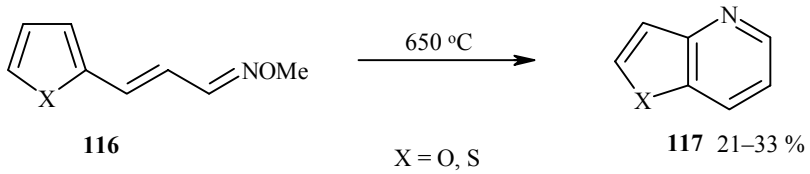
Chlorides of furanhydroxamic acids **112** dimerize in the presence of a base to 1,2,5-oxadiazole N-oxides **113**, which are formed through 2-furylnitrile oxides as intermediates [80].



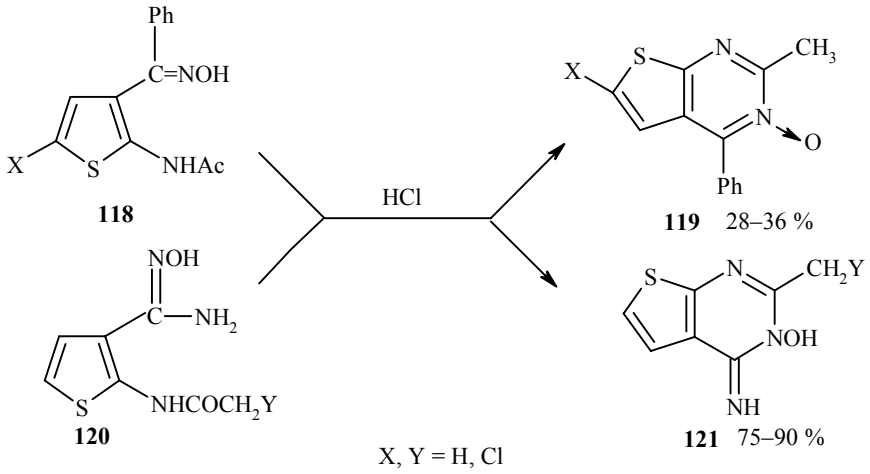
2-Furaldoxime was used as heterodiene in the Diels–Alder reaction. Thus, the reaction of oxime **83** with alkenes followed by treatment of the reaction mixtures with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gives the N-oxides of furo[2,3-*c*]pyridine **114** or **115** [130].



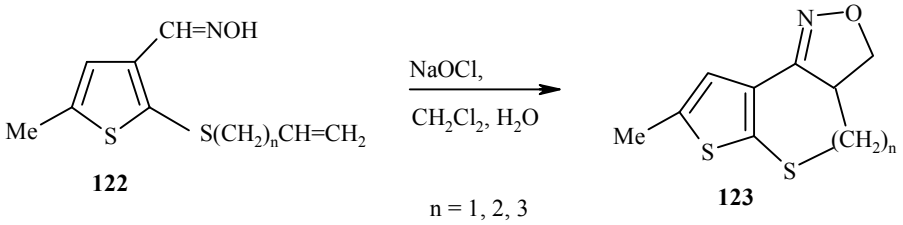
Furo[3,2-*b*]- and thieno[3,2-*b*]pyridines **117** were obtained by the pyrolysis of O-methyloximes of propenal **116** at 650°C. The products **117** are formed as a result of the cyclization of the iminyl radicals [131].



The synthesis and reactions of thieno[2,3-*d*]pyrimidine 3-oxides were examined in [132], where it was shown that oximes **118** readily undergo cyclization to thienopyrimidines **119** in the presence of HCl. Under analogous conditions amidoximes **120** give the heterocycles **121**.

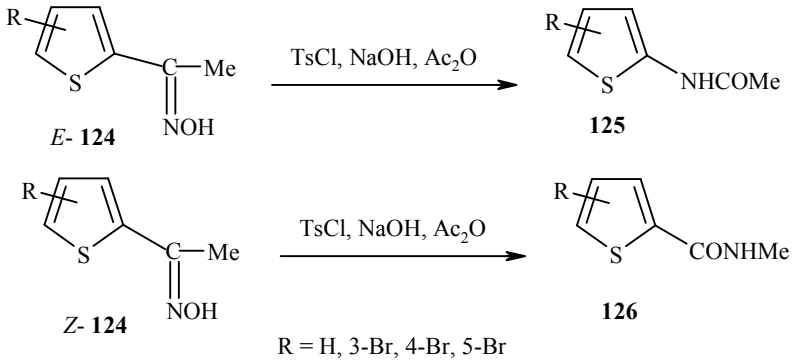


The synthesis of new tricyclic systems based on 2-alkenyl- or 2-alkynylthio-3-thiophenaldoximes has been described [133, 134]. For example, in the presence of sodium hypochlorite the thiophene oximes **122** give the tricyclic isoxazolines **123** as the main products.



3.4. Beckmann Rearrangement of Furan and Thiophene Oximes

The Beckmann rearrangement is one of the most characteristic reactions of oximes. The rearrangement of furan and thiophene oximes to the corresponding amides is usually conducted in the presence of phosphorus pentachloride in ether [135-137] or polyphosphoric acid in toluene [138]. The Beckmann rearrangement of furaldoxime to furamide in the presence of nickel and copper complexes is well known [139]. The rearrangement of the *E*- and *Z*-isomers of thiophene aldoximes leads to the formation of amides, while the *E*- and *Z*-isomers of thiophene ketoximes **124** under the conditions of Cymerman Craig [140] give amides **125** and **126** with yields of 87-96% [39, 141].

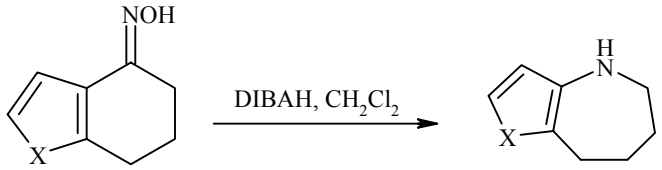


E- **124** **125**

Z- **124** **126**

R = H, 3-Br, 4-Br, 5-Br

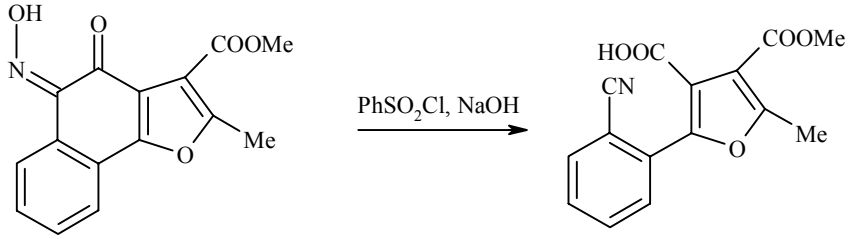
The Beckmann rearrangement of cyclic furan and thiophene ketoximes leads to the products from ring enlargement. Thus, 5,6,7,8-tetrahydrothieno[3,2-*b*]azepine and 5,6,7,8-tetrahydrofuro[3,2-*b*]azepine (**128**) were obtained from the respective heterocyclic oximes of cyclohexanone **127** in the presence of diisobutylaluminum hydride [142].



127 **128**

X = O, S

The analogous rearrangements of the oximes of thiophenocycloalkanones to the corresponding seven-membered and eight-membered heterocycles take place in the presence of polyphosphoric acid [143, 144] or benzenesulfonyl chloride in pyridine [145]. The Beckmann rearrangement also takes place readily in the O-benzenesulfonates of thiophene oximes in the presence of sodium acetate in aqueous methanol [146], in 8% aqueous sodium hydroxide [140], or under the influence of heat [147]. The treatment of 5-monooxime of 3-ethoxycarbonyl-2-methyl-4,5-dioxonaphtho[1,2-*b*]furan (**129**) with benzenesulfonyl chloride in an alkaline medium leads as a result of a Beckmann rearrangement of the second type to the formation of 5-(2-cyanophenyl)-3-methoxycarbonyl-2-methyl-4-furancarboxylic acid (**130**) with a yield of 80% [148].

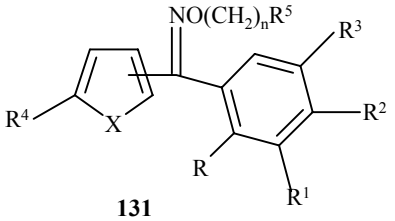


129 **130**

4. THE BIOLOGICAL ACTIVITY OF DERIVATIVES OF FURAN AND THIOPHENE OXIMES

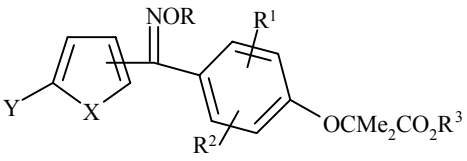
4.1. Action on the Cardiovascular System

The furyl- and thienylphenyl O-heteroaminoalkyloximes (**131**), obtained by the reaction of the respective oximes and chloropropyl derivatives of heterocyclic amines, exhibit antispasmodic and vasodilatory activity and are also characterized by cardiotropic effects [149-151]. Aminoethyloximes containing at least one thienyl radical exhibit coronary vasodilating activity [152]. The thiophene oximes **132** are used as agents that reduce the cholesterol level. For example, compound **132** (R-R^3 = H, at 3 × 25 mg/kg) reduces the cholesterol level in mice by 21.1% [153].



131

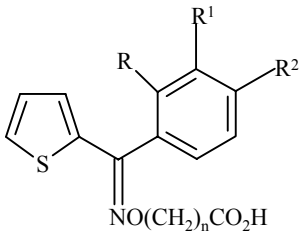
X = O, S; R^1–R^4 = H, Hal, Alk, R^5 = NH_2



132

X = O, S; Y= H, Alk; R–R^3 = H, Alk

The O-ethers of methoxyphenyl thienyl ketoximes **133**, obtained from the respective ketones, exhibited fairly high antiaggregation activity with reference to blood cells. The O-ethers **133** (with *n* = 2 or 3) were the most active [154].

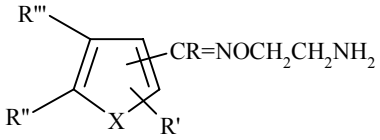


133

n = 2–4; R, R^1, R^2 = H, OMe

4.2. Sedative, Antidepressant, Tranquillizing, and Anticonvulsive Activity

O-(2-Aminoethyl)oximes of the furan and thiophene series **134**, produced from the respective oximes and 2-bromoethylamine hydrobromide, exhibited good antidepressant and sedative activity [155].

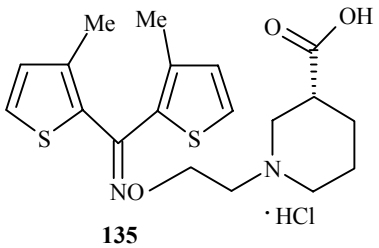


134

X = O, S; R–R''' = H, Alk

Derivatives of 5-phenyl-2-furamidoximes exhibited antidepressant activity in mice (25-50 mg/kg) [69]. The furan and thiophene ketones of the RCOQNR'R" [R = 2-furyl, 2- and 3-thienyl; Q = CHMe, $(CH_2)_3$; NR'R" = NMe_2, morpholino, 1-azepinyl) and their oximes have neuroleptic, tranquillizing, and analgesic activity [156].

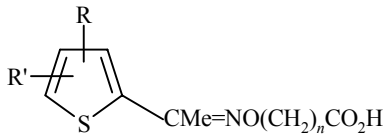
Derivatives of diaryloximes were investigated as anticonvulsants in the treatment of epilepsy. It was shown that ether of dithienyl ketoxime **135** has high activity [157].



135

4.3. Analgesic and Anti-inflammatory Activity

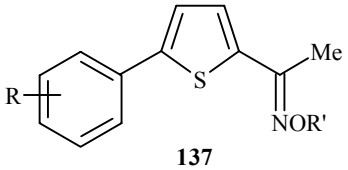
(α-Methyl-2-thienylideneaminooxy)alkanoic acids **136**, obtained by the reaction of the corresponding 2-acetylthiophene oximes with bromoacetic acid or by the reaction of ketones with O-substituted hydroxylamines [158], exhibited analgesic activity in the treatment of rheumatic diseases.



136

n = 1, 3; R, R' = H, Hal, Alk

The O-ethers of the oximes of benzoylthiophenes [159] and 2-benzofuranamidoximes [160] also have high analgesic and anti-inflammatory activity. Comparatively low anti-inflammatory and antidepressant activity was found in the O-alkyloximes of 2-acetyl-5-arylthiophenes **137** [161].



137

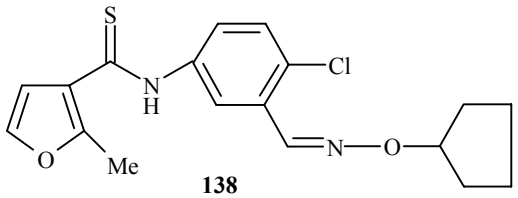
R = 4-Me, 4-CH_2CH_3, 4-$CHMe_2$, 3,4-Me_2;
R' = Alk, N-pyrrolidinoethyl, N-piperidinoethyl, N-morpholinoethyl

4.4. Cytotoxic, Antitumor, Antiviral, and Bactericidal Activity

The clearly defined cytotoxicity of the copper and cobalt complexes of 2-furancarbaldehyde oximes on the cells of L1210 lipoid leukemia with inhibition of the synthesis of DNA, RNA, and proteins was discovered recently [162, 163].

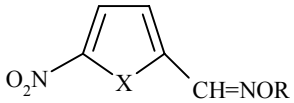
The derivatives of furan and thiophene oximes have been investigated little as antitumor agents. In tests on mice infected with leukemia L1210 the derivatives of the O-uraciloxime of 2-acetylthiophene showed low activity [164].

The antiviral activity of certain O-alkylated aromatic oximes, particularly the furan derivative **138**, against HIV-1 has been demonstrated [165].



138

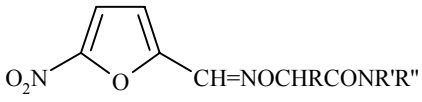
The derivatives of nitrofurans, including the nitro derivatives of furan oximes, were investigated as antibacterial agents. (One of the first papers relates to 1964.) Thus, it was established that the O-alkyl- and O-benzyloximes of the furan and thiophene series **139** have antibacterial activity against *Escherichia coli* [166].



139

X = O, S; R = CH_2CH_2OH, $PhCH_2$, PhCHMe, $PhCHMeCH_2$

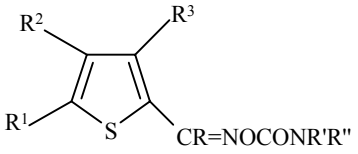
Further investigations showed that the derivatives of nitrofuran oximes were more effective as antibacterial agents [167, 168]. Derivatives of acid amides **140** exhibited strong antibacterial activity in suppressing the growth of *Mycobacterium tuberculosis* [169].



140

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

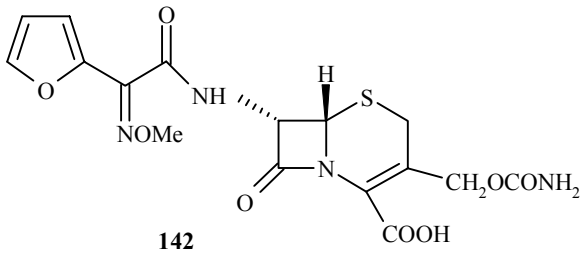
The strong antibacterial activity of derivatives of nitrofuran amidoximes has also been demonstrated [27, 170-174]. The 2-furan- and 2-thiophenamidoximes also exhibited activity against *Mycobacterium tuberculosis* in the absence of the nitro group [175]. Derivatives of the carbamates of furan oximes [176, 177] and thiophene oximes form a separate group. (For example, the O-derivatives of carbamates of thiophene oximes **141** have a wide spectrum of antibacterial and fungicidal activity.)



141

R^1–R^3, R–R" = H, Hal, Alk, Ar

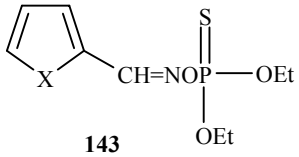
Thiophene oximes exhibited activity against infections caused by bacteria that produce β-lactamase [179] and also as microbicides in agrochemistry [180]. Furan and thiophene oxime fragments are present in cephalosporin antibiotics [181-187], among which cephuroxime (**142**) should be mentioned [188, 189].



142

4.5. Furan and Thiophene Oximes as Insecticides, Fungicides, Herbicides, Protozoicides, and Plant Growth Regulators

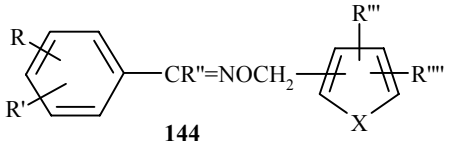
The O-alkyl and O-acyl derivatives of furan and thiophene oximes are widely used as insecticides. Thiophene O-carbamoyloximes have a broad spectrum of such activity [190-193]. Some compounds of this group exhibit pesticidal activity. The oxime derivatives of O,O-diethyl thiophosphates **143**, obtained from the oximes and $(EtO)_2P(S)Cl$ in the presence of triethylamine in acetone, exhibit appreciable activity in suppressing *Musca domestica* and *Tetranychus urticae* [194-196]



143

X = O, S

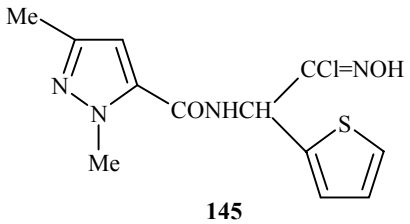
High insecticidal activity is exhibited by derivatives of oximes in which the furan or thiophene fragment is in an ether group [197, 198]. For example, the O-ethers of oximes **144** have been used against *Musca domestica*, *Prodenia lutura* and *Culex pipiens*.



144

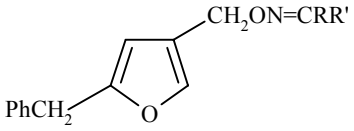
X = O, S; R, R' = H, Hal, Alk, *o*-Alk, R", R"" = Alk; R"' = H, Alk

In one of the first papers that examined the fungicidal activity of furan and thiophene oximes it was shown that 2-furancarbaldehyde oxime was a good fungicide and could be used as an antiseptic agent [199]. High fungicidal activity is exhibited by the 5-(3,4-dimethoxyphenyl), 5-(2,4-dichlorophenyl), 5-(4-chlorophenyl) [17, 200-201], and 5-(nitrophenyl) derivatives of the oximes of 2-furancarbaldehydes [202], the nitro derivatives of 2-furaldoximes [203] and 2-furamidoximes [25], and heterocyclic compounds containing fragments of furan and thiophene oximes (e.g., the inhibition of *Pseudomonas cubensis* by oxime **145** amounted to 100%) [204].



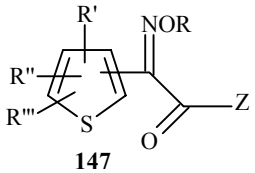
145

Thiophene O-carbamoyloximes obtained from the corresponding oximes and alkyl isocyanates or carbamoyl chlorides showed high pesticidal activity [205-208]. The oxime derivatives of furylmethyl ethers **146** [209] and 2-thienylacetic acids **147** [210] have been used as pesticides. Some of these compounds also exhibited insecticidal and fungicidal activity.



146

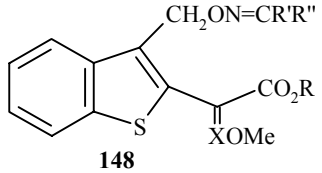
R, R' = Alk, Ar



147

R = Alk; R'–R'" = H, CN, Hal, Alk, Ar; Z = OAlk, NH_2

The ethers of benzothiophene oximes **148** were used as pesticides [211, 212].

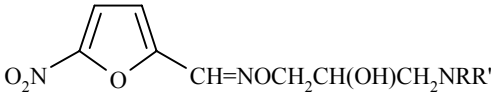


148

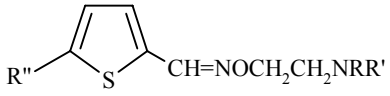
X = N, CH; R = Alk, R', R" = H, Alk

It was proposed to use derivatives of the O-alkyl derivatives of thiophene amidoximes as herbicides [70, 213, 214]. Some of these compounds, having phytohormonal activity, can be used as plant growth regulators.

The derivatives of nitrofuran aldoximes **149** have been used as antiprotozoa agents [215-218]. Thus, the O-aminoethyl derivatives of 2-thiophenecarbaldehydes **150**, obtained from the corresponding oximes and chloroethylamines in the presence of sodium methoxide, exhibit activity toward *Trichomonas foetus* [53].



149



150

R, R' = Alk, R" = H, NO_2

Certain O-ethers of furan [219, 220], 2,3-dihydrobenzofuran [221], and thiophene [220] oximes have found use as plant growth regulators.

REFERENCES

1. G. Ocskay and L. Vargha, *Tetrahedron*, **2**, 140 (1958).
2. K. Ishikawa, *Nippon Kagaku Zasshi*, **81**, 140 (1960).
3. N. I. Putokhin and V. S. Egorova, *Zh. Obshch. Khim.*, **18**, 1866 (1948).
4. Z. N. Nazarova and O. A. Chuprunova, *Zh. Obshch. Khim.*, **30**, 2825 (1960).
5. V. M. Clark, B. I. Gregory, and G. B. Webb, Ger. Pat. No. 2407909; *Chem. Abstr.*, **81**, 169431 (1974).

6. S. Jordan, R. E. Markwell, and B. S. Woolcott, *J. Chem. Soc. Perkin Trans. 1*, 928 (1978).
7. N. G. Panchenko and V. A. Slavinskaya, *Khim. Geterotsikl. Soedin.*, 1266 (1998).
8. S. A. Reed, C. V. Banks, and H. Diehl, *J. Org. Chem.*, **12**, 792 (1947).
9. Aktieselkabet Sadolin and Holmblad, Dan. Pat. No. 80973; *Chem. Abstr.*, **50**, 14811 (1956).
10. Sankyo Chemical Industries Co. Ltd., Jpn. Pat. No. 5935 (1964); *Chem. Abstr.*, **61**, 13283 (1964).
11. N. Saldabols, L. N. Alekseeva, S. Hillers, and A. Cimanis, USSR Inventor's Certificate No. 486669; *Chem. Abstr.*, **84**, 164595 (1976).
12. T. L. Gilchrist and T. G. Roberts, *J. Chem. Soc. Chem. Commun.*, 847 (1978).
13. E. Dumez, J. Rodriguez, and J. P. Dulcere, *Chem. Commun.*, 2009 (1999).
14. T. Severin, P. Adhikary, and I. Schnabel, *Chem. Ber.*, **102**, 1325 (1969).
15. H. K. Kim and P. M. Weintraub, *J. Org. Chem.*, **35**, 4282 (1970).
16. E. Jedlovska, J. Kovac, A. Piklerova, and P. Zalupsky, *Coll. Czech. Chem. Commun.*, **41**, 3085 (1976) (and references cited therein).
17. R. J. Alaimo, J. E. Gray, and G. M. Klein, US Pat. No. 4332735; *Chem. Abstr.*, **97**, 92122 (1982).
18. N. Saldabol, B. S. Velovich, L. N. Alekseeva, B. Brizga, and L. Kruzmetra, *Khim.-Farm. Zh.*, **3**, No. 9, 16 (1969).
19. N. O. Saldabol, A. Yu. Tsimanis, S. A. Giller, Yu. Yu. Popelis, L. N. Alekseeva, A. Ya. Zile, and A. K. Yalinskaya, *Khim.-Farm. Zh.*, **8**, No. 10, 12 (1974).
20. S. Kanemasa, H. Matsuda, A. Kamimura, and T. Kakinami, *Tetrahedron*, **56**, 1057 (2000).
21. H. B. Snyder, Jr., F. F. Ebetino, G. Gever, B. F. Stevenson, and A. Winterstein, *J. Heterocycl. Chem.*, **7**, 959 (1970).
22. F. Eloy and R. Leaners, *Chem. Rev.*, **62**, 155 (1962).
23. R. W. Henn, B. D. Wilson, and P. E. Woodgate, US Pat. No. 3794488; *Chem. Abstr.*, **81**, 71062 (1974).
24. G. A. Pearse, *Chem. Br.*, **20**, 30 (1984); *Chem. Abstr.*, **100**, 174565 (1984).
25. M. von Esch and W. R. Sherman, US Pat. No. 3097214; *Chem. Abstr.*, **59**, 13950 (1963).
26. N. Saldabol, V. Slavinskaya, J. Popelis, and I. Mazheika, *Khim. Geterotsikl. Soedin.*, 168 (2000).
27. F. Floy and C. J. Mirocha, US Pat. No. 1347874; *Chem. Abstr.*, **68**, 87139 (1968).
28. D. A. Patrick, J. E. Hall, B. C. Bender, D. R. McCurdy, W. D. Wilson, F. A. Tanious, S. Saha, and R. R. Tidwell, *Eur. J. Med. Chem.*, **34**, 575 (1999).
29. S. Wang, J. E. Hall, F. A. Tanious,, W. D. Wilson, D. A. Patrick, D. R. McCurdy, B. C. Bender, and R. R. Tidwell, *J. Med. Chem.*, **34**, 215 (1999).
30. A. Areschka and M. Descamps, British Patent No. 1508210; *Chem. Abstr.*, **89**, 163390 (1978).
31. T. Sasaki and T. Yoshioka, *Bull. Chem. Soc. Japan*, **40**, 2604 (1967).
32. T. Sasaki and T. Yoshioka, *Bull. Chem. Soc. Japan*, **42**, 556 (1969).
33. N. P. Kostyuchenko, A. F. Oleinik, T. I. Vozyakova, K. Yu. Novitskii, and Yu. N. Sheinker, *Khim. Geterotsikl. Soedin.*, 312 (1974).
34. Yu. Yu. Popelis, E. E. Liepin'sh, and E. Ya. Lukevits, *Khim. Geterotsikl. Soedin.*, 1172 (1985).
35. P. P. Solov'eva, Yu. N. Sheinker, A. F. Oleinik, and K. Yu. Novitskii, *Khim. Geterotsikl. Soedin.*, 890 (1975).
36. E. E. Liepin'sh and N. O. Saldabol, *Zh. Org. Khim.*, **27**, 521 (1981).
37. R. Wasylishen and T. Schaefer, *Can. J. Chem.*, **50**, 274 (1972).
38. L. B. Krivdin, G. A. Kalabin, R. A. Nesterenko, R. N. Nesterenko, and B. A. Trofimov, *Khim. Geterotsikl. Soedin.*, 709 (1985).
39. S. Conde, C. Corral, and J. Lissavetzky, *J. Heterocycl. Chem.*, **22**, 301 (1985).
40. B. Oussaid, J. P. Fayet, G. Pelletier, and B. Garrigues, *Bull. Soc. Chim. Belg.*, **101**, 969 (1992).
41. N. O. Saldabol, V. A. Slavinskaya, E. E. Liepin'sh, Yu. Yu. Popelis, and I. B. Mazheika, *Khim. Geterotsikl. Soedin.*, 1619 (1999).
42. R. F. Raffauf, *J. Am. Chem. Soc.*, **68**, 1765 (1946).

43. N. Tyutyulkov and D. Panaiotova, *Compt. Rend. Acad. Bulg. Sci.*, **11**, 201 (1958); *Chem. Abstr.*, **53**, 14781 (1959).
44. M. Mathew and G. J. Palenik, *J. Chem. Soc. Perkin Trans. 2*, 1033 (1972).
45. A. Bryson and F. P. Dwyer, *J. Proc. Roy. Soc. N. S. Wales*, **74**, 240 (1940); *Chem. Abstr.*, **35**, 3250 (1941).
46. R. Katritzky and J. M. Lagowski, *J. Chem. Soc.*, 657 (1959).
47. G. Schay, Gy. Varsanyi, and F. Dullien, *Acta Chim. Acad. Sci. Hung.*, **15**, 273 (1958).
48. F. Dullien, *Can. J. Chem.*, **35**, 1366 (1957).
49. K. E. Calderbank and R. J. W. Le Fevre, *J. Chem. Soc.*, 1462 (1949).
50. I. Mazeika, M. Gavars, A. P. Gaukhman, E. Abele, M. Shimanska, and E. Lukevics, *Latv. J. Chem.*, No. 1-2, 89 (1995).
51. A. van Zorge, Eur. Pat. 7679; *Chem. Abstr.*, **93**, 150119 (1980).
52. S. E. Korostova, L. N. Sobenina, A. I. Mikhaleva, R. N. Nesterenko, S. G. Shevchenko, V. B. Modonov, and R. I. Polovnikova, *Zh. Org. Khim.*, **24**, 2538 (1988).
53. F. Dalmas, M. Gasquet, P. Timon-David, N. Madadi. P. Vanelle, A. Vaille, and J. Maldonado, *Eur. J. Med. Chem.*, **28**, 23 (1993).
54. G. Ulrich and W. Raether, Ger. Pat. No. 2439629; *Chem. Abstr.*, **85**, 21082 (1976).
55. M. Alvarez, R. Granados, D. Mauleon, C. Minguillon, and M. Perez, *An. Quim. Ser. C*, **80**, 258 (1984).
56. R. Granados, D. Mauleon, and M. Perez, *An. Quim. Ser. C*, **79**, 275 (1983).
57. E. Abele, Yu. Polelis, E. Lukevits, M. Shimanska, and Yu. Gol'dberg, *Khim. Geterotsikl. Soedin.*, 18 (1994).
58. E. Abele, K. Rubina, R. Abele, J. Popelis, and E. Lukevits, *Latv. J. Chem.*, No. 3, 59 (1999).
59. S. J. Kirsch and H. Schelling, *J. Org. Chem.*, **44**, 3970 (1979).
60. E. Abele, R. Abele, K. Rubina, J. Popelis, I. Sleiksa, and E. Lukevics, *Synth. Commun.*, **28**, 2621 (1998).
61. B. A. Trofimov, A. I. Trofimov, A. I. Mikhaleva, R. N. Nesterenko, G. A. Kalabin, and O. A. Tarasova, *Zh. Org. Khim.*, **24**, 2618 (1988).
62. U. Pindur and B. Unterhalt, *Arch. Pharm. (Weinheim)*, **312**, 282 (1979).
63. H. Goda, M. Sato, H. Ihara, and C. Hirayama, *Synthesis*, 849 (1992).
64. E. Abele, R. Abele, J. Popelis, and E. Lukevics, *Org. Prep. Proc. Int.*, **32**, 153 (2000).
65. E. Ya. Lukevits and M. G. Voronkov, *Khim. Geterotsikl. Soedin.*, 36 (1965).
66. E. Lukevics, M. Dzintara, and O. A. Pudova, *Zh. Obshch. Khim.*, **53**, 2054 (1983).
67. E. Abele, K. Rubina, and E. Lukevics, *Latv. J. Chem.*, No. 1, 77 (2000).
68. Y. Kita, F. Iyoh, O. Tamura, Y. Y. Ke, T. Miki, and Y. Tamura, *Chem. Pharm. Bull.*, **37**, 1446 (1989).
69. S. S. Pelosi, Jr., US Pat. No. 3946049; *Chem. Abstr.*, **85**, 21083 (1976).
70. D. Farge, J. Leboul, Y. Le Goff, and G. Poiget, Ger. Pat. No. 2640484; *Chem. Abstr.*, **87**, 39141 (1977).
71. L. Vargha and F. Gonczy, *J. Am. Chem. Soc.*, **72**, 2738 (1950).
72. L. Vargha and G. Ocskay, *Acta Chim. Acad. Sci. Hung.*, **19**, 143 (1959) (and references cited therein).
73. P. Sohar, G. Varsanyi, L. Vargha, and G. Ocskay, *Acta Chim. Acad. Sci. Hung.*, **40**, 431, (1964).
74. L. Lang, G. Horvath, L. Vargha, and G. Ocskay, *Bull. Soc. Chim. France*, 2724 (1965).
75. T. Goto and S. Sakawa, *European Patent No.* 136640; *Chem. Abstr.*, **103**, 22474 (1985).
76. A. F. Oleinik, T. I. Vozyakova, N. I. Solov'eva, and K. Yu. Novitskii, *Khim. Geterotsikl. Soedin.*, 1026 (1975).
77. E. Abele, Yu. Popelis, M. Gavars, A. Gaukhman, M. Shimanska, and E. Lukevits, *Khim. Geterotsikl. Soedin.*, 886 (1994).
78. E. Abele, R. Abele, J. Popelis, and E. Lukevics, *Latv. J. Chem.*, No. 2, 61 (1998).
79. A. Krutosikova, V. Konecny, J. Kovac, and Spirkova, *Coll. Czech. Chem. Commun.*, **40**, 313 (1975).
80. T. Sasaki and T. Yoshioka, *Yuki Gosei Kagaku Kyokai Shi*, **25**, 665 (1967); *Chem. Abstr.*, **68**, 12789 (1968).

81. I. Castro, E. Lukevits, R. Pastrana, M. D. Gonzalez, and D. Popelis, *Sobre Deriv. Cana Azucar*, **18**, 36 (1984); *Chem. Abstr.*, **104**, 224792 (1986).
82. Yu. S. Andreichuk, D. D. Nekrasov, E. A. Kolevatova, and M. A. Trushule, *Khim.-Farm. Zh.*, **24**, 33 (1990).
83. M. von Eisch and A. J. Crovetti, US Pat. No. 3272833; *Chem. Abstr.*, **66**, 37761 (1967).
84. E. Abele and E. Lukevics, *Org. Prep. Proc. Int.*, **32**, 235 (2000).
85. B. P. Fabrichnyi, S. M. Kostrova, G. P. Gromova, and Ya. L. Gol'dfarb, *Khim. Geterotsikl. Soedin.*, 1483 (1973).
86. D. Mullem and L. Shuttleworth, UK Patent No. 2092128; *Chem. Abstr.*, **98**, 53678 (1983).
87. E. Abele, R. Abele, K. Rubina, Yu. Popelis, A. Gaukhman, and E. Lukevits, *Khim. Geterotsikl. Soedin.*, 1325 (1998).
88. E. Abele, K. Rubina, R. Abele, A. Gaukhman, and E. Lukevits, *J. Chem. Res. (S)*, 618 (1998).
89. D. J. Ager, *Tetrahedron Lett.*, **24**, 5441 (1983).
90. D. J. Ager, *J. Chem. Res. (S)*, 237 (1985).
91. W. Zhao, *Huahue Shiji*, **19**, 273 (1997); *Chem. Abstr.*, **127**, 330917 (1997).
92. H. Migulla and H. Paul, East Ger. Pat. No. 130148; *Chem. Abstr.*, **91**, 39306 (1979).
93. R. Cho, N. S. Cho, S. H. Song, and S. K. Lee, *J. Org. Chem.*, **63**, 8304 (1999).
94. S. Morikawa and S. Teratake, Jap. Pat. No. 7919963; *Chem. Abstr.*, **91**, 39301 (1979).
95. A. Obregia and C. V. Gheorghiu, *J. Prakt. Chem.*, **128**, 239 (1930); *Chem. Abstr.*, **25**, 1506 (1931).
96. E. Abele, R. Abele, and E. Lukevics, *Latv. J. Chem.*, No. 3, 63 (1999).
97. L. Beregi, *Magyar Kem. Folyoirat*, **56**, 257 (1950); *Chem. Abstr.*, **46**, 8000 (1952).
98. W. Reeve and J. Christian, *J. Am. Chem. Soc.*, **78**, 860 (1956).
99. G. S. Wayne, G. S. Lannoye, A. R. Haight, S. L. Parekh, W. Zhang, and R. R. Copp, *Heterocycles*, **53**, 1175 (2000).
100. S. Demir, *Pure Appl. Chem.*, **69**, 105 (1997).
101. Q. H. Chen, X. Z. Yu, T. Y. Zhang, and Z. B. Jia, *Acta Chim. Sinica. Engl. Ed.*, 176 (1989).
102. D. Nenitescu and C. Bucur, Ger. Pat. No. 1048590; *Chem. Abstr.*, **55**, 3614 (1961).
103. Z. Rybakow and J. Lange, Polish Patent No. 42394;*Chem. Abstr.*, **55**, 6496 (1961).
104. A. Swirska and J. Lange, Polish Patent No. 42189; *Chem. Abstr.*, **55**, 5533 (1961).
105. H. Ogawa and H. Sakaichi, *Synthesis*, 138 (1972).
106. L, Vargha and G. Ocskey, *Tetrahedron*, **2**, 151 (1958).
107. B. B. Greene and K. G. Lewis, *Tetrahedron Lett.*, 4759 (1966).
108. B. B. Greene and K. G. Lewis, *Aust. J. Chem.*, **21**, 1845 (1968).
109. Ssah. Chemical Industry Co. Ltd., Jpn. Pat. No. 81133285; *Chem. Abstr.*, **96**, 162708 (1982).
110. E. Abele and E. Lukevics, *Heterocycles*, **53**, 2285 (2000).
111. B. A. Trofimov, *Adv. Heterocycl. Chem.*, **51**, 177 (1990).
112. B. A. Trofimov and A. I. Mikhaleva, *Heterocycles*, **37**, 1193 (1994).
113. B. A. Trofimov and A. I. Mikhaleva, *Zh. Org. Khim.*, **32**, 1127 (1996).
114. B. A. Trofimov, *Pyrroles. Part Two: The Synthesis, Reactivity and Physical Properties of Substituted Pyrroles* (Ed. A. Jones), Wiley, New York (1992), p. 131.
115. S. E. Korostova, A. I. Mikhalev, and B. A. Trofimov, *Usp. Khim.*, **68**, 506 (1999).
116. G. A. Pinna, M. A. Pirisi, and G. Paglietti, *J. Chem. Res. (S)*, 210 (1993).
117. S. E. Korostova, R. N. Nesterenko, A. I. Mikhaleva, R. I. Polovnikova, and N. I. Golovanova, *Khim. Geterotsikl. Soedin.*, 901 (1989).
118. A. Krutosikova, J. Kovac, M. Dandarova, and M. Valenty, *Coll. Czech. Chem. Commun.*, **43**, 288 (1978).
119. R. S. Kusurkar, M. S. Wadia, D. K. Bhosale, S. S. Tavale, and V. G. Puranik, *J. Chem. Res. (S)*, 478 (1996).

120. T. Sasaki, T. Yoshioka, and Y. Suzuki, *Yuki Gosei Kagaku Kyokai Shi*, **27**, 998 (1969); *Chem. Abstr.*, **72**, 43542 (1970).
121. R. and L. Molecular Research Ltd., French Patent No. 2085655 (1972); *Chem. Abstr.*, **77**, 88474 (1972).
122. H. Hishmat, K. M. Khalil, N. M. A. El-Ebrashi, and M. N. M. Khodeir, *Z. Naturforsch.*, **33B**, 1491 (1978).
123. P. Demerseman, G. Colin, J. P. Lechartier, A. Cheutin, S. Combrisson, and R. Royer, *Bull. Soc. Chim. France*, 3601 (1969).
124. P. Dubus, B. Decroix, and P. Pastour, *Ann. Chim. (Paris)*, **10**, 331, (1975).
125. V. L. Narayanan, US Pat. No. 3976657; *Chem. Abstr.*, **85**, 192742 (1976).
126. A. A. Avetisiyan, G. S. Melikyan, and A. V. Galstiyan, *Arm. Zh. Khim.*, **36**, 738 (1983).
127. M. Descamps and A. Areschka, Ger. Pat. No. 2657902; *Chem. Abstr.*, **87**, 167874 (1977).
128. I. Saikawa, Jpn. Pat. No. 2822 (1967); *Chem. Abstr.*, **66**, 115715 (1967).
129. B. Uossaid, L. Moeini, B. Martin, D. Villemin, and B. Garrigues, *Synth. Commun.*, **25**, 1451 (1995).
130. S. Kusurkar and D. K. Bhosale, *Tetrahedron Lett.*, **32**, 3199 (1991) (and references therein).
131. C. L. Hickson and H. McNab, *Synthesis*, 464 (1981).
132. J. Fortea, *J. Prakt. Chem.*, **317**, 705 (1975).
133. M. M. Krayushkin, M. A. Kalik, E. Yu. Zvezdina, and V. S. Bogdanov, *Izv. Akad. Nauk. SSSR. Ser. Khim.*, 2837 (1991).
134. M. M. Krayushkin, M. A. Kalik, E. Yu. Zvezdina, L. G. Vorontsova, and M. G. Kurella, *Mendeleev Commun.*, 114 (1993).
135. C. Tsuchiya, *Nippon Kagaku Zasshi*, **82**, 1549 (1961); *Chem. Abstr.*, **59**, 2752 (1963).
136. O. Meth-Cohn and B. Narine, *Synthesis*, 133 (1980).
137. B. Unterhalt and H. J. Reinhold, *Arch. Pharm. (Weinheim)*, **308**, 346 (1975).
138. S. Deprets and G. Kitsch, *Eur. J. Org. Chem.*, 1353 (2000).
139. A. Bryson and F. P. Dwyer, *J. Proc. Roy. Soc. N. S. Wales*, **74**, 471 (1941); *Chem. Abstr.*, **35**, 4768 (1941).
140. J. Cymerman Craig and A. R. Naik, *J. Am. Chem. Soc.*, **84**, 3410 (1962).
141. A. Buzas and J. Teste, *Bull. Soc. Chim. France*, 359 (1960).
142. H. Cho, K. Murakami, H. Nakanishi, H. Isoshima, K. Hayakawa, and I. Uchida, *Heterocycles*, **48**, 919 (1998).
143. R. Martinez, M. E. L. Duran, C. L. Cortes, and J. Z. Gustavo Avila, *J. Heterocycl. Chem.*, **36**, 687 (1999).
144. R. Neidlein and N. Kolb, *Arch. Pharm. (Weinheim)*, **312**, 397 (1979).
145. B. P. Fabrichnyi, I. F. Shalavina, and Ya. V. Gol'dfarb, *Zh. Obshch. Khim.*, **31**, 1244 (1961).
146. V. P. Fabrichnyi, V. N. Bulgakova, and Ya. L. Gol'dfarb, *Khim. Geterotsikl. Soedin.*, 483 (1985).
147. M. Bastian, A. Ebnother, and E. Jucker, *Helv. Chim. Acta*, **34**, 283 (1971).
148. A. P. Stankyavichus, J. M. M. Stankyavichene, and P. B. Terent'ev, *Khim. Geterotsikl. Soedin.*, 1462 (1999).
149. P. Bessin, J. Laforest, and G. Thuillier, US Pat. No. 4207319; *Chem. Abstr.*, **93**, 220574 (1980).
150. G. Thuillier, J. Laforest, and P. Bessin, Ger. Pat. No. 2449205; *Chem. Abstr.*, **83**, 97004 (1975).
151. J. Laforest, Ger. Pat. No. 2922799; *Chem. Abstr.*, **93**, 180989; *Chem. Abstr.*, **92**, 180989 (1980).
152. J. Engel, A. Kleeman, F. Stroman, and K. Thiemer, Ger. Pat. No. 2851387; *Chem. Abstr.*, **91**, 74460 (1979).
153. J. Laforest, J. Bonnet, and P. Bessin, Ger. Pat. No. 2804981; *Chem. Abstr.*, **89**, 197323 (1978).
154. M. Varache-Lembege, A. Nuhrich, P. Renard, F. Duboudin, J. Vercauteren, and G. Devaux, *Arch. Pharm. (Weinheim)*, **328**, 417 (1995).
155. V. Philips' Gloeilampenfabrieken, Netherlands Patent No. 6810133; *Chem. Abstr.*, **72**, 121354 (1970).

156. L. A. Pons, M. F. Rodda, R. H. P. Marcy, and D. C. J. Duval, Ger. Pat. No. 2042504; *Chem. Abstr.*, **74**, 125485 (1971).
157. J. S. Knutsen K. E. Andersen, J. Lau, B. F. Lundt, R. F. Henry, H. E. Morton, L. Naerum, H. Peterson, H. Stephenson, P. D. Suzdak, M. D. B. Swedberg, C. Thomsen, and P. E. Sorensen, *J. Med. Chem.*, **42**, 3447 (1999).
158. J. van Dijk and J. M. A. Zwagemakers, Ger. Pat. No. 2016057; *Chem. Abstr.*, **74**, 12990 (1971).
159. Sankyo Co. Ltd., Jpn. Pat. No. 5970685; *Chem. Abstr.*, **101**, 110722 (1984).
160. J. P. Riffaud, C. Dupont, L. Rene, and R. Royer, *Eur. J. Med. Chem.-Chim. Ther.*, **17**, 577 (1982).
161. R. Shridhar, C. V. Reddy Sastry, S. C. Chaturvedi, R. Gurumurthy, P. P. Singh, C. Seshagiri Rao, and A. Y. Junnarkar, *Indian J. Chem.*, **23B**, 692 (1984).
162. H. Hall, K. F. Bastow, A. E. Warren, C. R. Barnes, and G. M. Bouet, *Appl. Organomet. Chem.*, **13**, 819 (1999).
163. H. Hall, C. C. Lee, G. Ibrahim, M. A. Khan, and G. M. Bouet, *Appl. Organomet. Chem.*, **11**, 565 (1997).
164. K. Matsumura, O. Miyashita, H. Shimadzu, and N. Hashimoto, Ger. Pat. No. 2841379; *Chem. Abstr.*, **91**, 39519 (1979).
165. W. G. Brouwer, Canadian Patent No. 2163175;*Chem. Abstr.*, **125**, 221559 (1996).
166. J. R. Nicolaus and E. Testa, British Patent No. 964721; *Chem. Abstr.*, **61**, 9467 (1964).
167. T. Sasaki, Jpn. Pat. No. 692722; *Chem. Abstr.*, **72**, 78854 (1970).
168. S. Ueno, E. Shimogo, T. Kawasaki, D. Immaru, and Y. Ossaka, Jpn. Pat. No. 7135064; *Chem. Abstr.*, **76**, 3711 (1972).
169. L. Kistaludy, L. Dancsi, A. Patthy, G. Fekete, and I. Szabo, Canadian Patent No. 1058195; *Chem. Abstr.*, **92**, 6399 (1980).
170. M. von Esch and A. J. Crovetti, US Pat. No. 3272828; *Chem. Abstr.*, **65**, 18560 (1966).
171. A. M. von Esch and A. J. Crovetti, US Pat. No. 3660390; *Chem. Abstr.*, **77**, 61794 (1972).
172. I. Saiwaka and T. Wada, Jpn. Pat. No. 9334 (1967); *Chem. Abstr.*, **68**, 95663 (1968).
173. I. Saiwaka and T. Wada, Jpn. Pat. No. 9335 (1967); *Chem. Abstr.*, **68**, 95664 (1968).
174. Norwich Pharmacal Co., Netherlands Patent No. 6500124; *Chem. Abstr.*, **64**, 8135 (1966).
175. G. Leandri, L. Maioli, and L. Ruzzier, *Boll. Sci. Fac. Chim. Ind. Bologna*, **15**, 57 (1957); *Chem. Abstr.*, **52**, 7291 (1958).
176. A. Kotani and S. Inamasu, Jpn. Pat. No. 7535113; *Chem. Abstr.*, **83**, 193063 (1975).
177. C. Seoh, *Yakhak Hoeji*, **17**, 167 (1973); *Chem. Abstr.*, **81**, 151867 (1974).
178. A. J. Crovetti and R. G. Stein, US Pat. No. 4061764; *Chem. Abstr.*, **88**, 100348 (1977).
179. S. N. Maiti, E. L. Setti, O. A. Phillips, A. V. N. Reddy, R. G. Micetich, R. Singh, F. Higastani, C. Kunugita, K. Nishida, and T. Uji, PCT Int. Appl. WO 9847895; *Chem. Abstr.*, **129**, 316092 (1998).
180. U. Heinemann, and S. Dutzmann, Ger. Pat. No. 19622354; *Chem. Abstr.*, **128**, 61422 (1998).
181. C. Humber, Ger. Pat. No. 2537558; *Chem. Abstr.*, **84**, 180253 (1976).
182. I. Gregory and D. M. Rogers, Ger. Pat. No. 2627212; *Chem. Abstr.*, **86**, 171478 (1977).
183. E. Ayres, Ger. Pat. No. 2744135; *Chem. Abstr.*, **89**, 43460 (1978).
184. H. O'Callaghan and M. Gregson, Ger. Pat. No. 2835288; *Chem. Abstr.*, **90**, 186982 (1979).
185. W. Foxton A. J. Pine, and G. B. Webb, UK Patent No. 2029823; *Chem. Abstr.*, **93**, 186382 (1980).
186. Biochemica Opos S. r. l., Jpn. Pat. No. 58167593; *Chem. Abstr.*, **100**, 138847 (1984).
187. K. H. Lee, Y. J. Yun, and K. D. Choe, *China Patent No.* 1199753; *Chem. Abstr.*, **132**, 279057 (2000).
188. D. Greenwood, N. J. Pearson, and F. O'Grady, *J. Antimicrob. Chemother.*, **2**, 337 (1976).
189. S. Lee, C. Sun, and H. P. Wang, *Chin. Pharm. J.*, **49**, 195 (1997).
190. T. Kay, British Patent No. 1273357; *Chem. Abstr.*, **77**, 61803 (1972).
191. T. Kay, S. African Patent No. 6907157; *Chem. Abstr.*, **76**, 14328 (1972).
192. S. Kishikawa, S. Maekawa, K. Matsui, and I. Aoshima, Jpn. Pat. No. 7502733; *Chem. Abstr.*, **83**, 73524 (1975).

193. E. Jedlovska, J. Kovak, A. Piklerova, and V. Konecny, *Chem. Zvesti*, **29**, 703 (1975).
194. R. G. Stein, A. J. Crovetti, and T. L. Crouch, Ger. Pat. No. 2262189; *Chem. Abstr.*, **79**, 66160 (1973).
195. J. Drabek, Z. Vesela, T. Sirota, J. Obertas, and M. Rupcik, Czech. Patent No. 141927; *Chem. Abstr.*, **77**, 88278 (1972).
196. Z. Vasela and S. Trchlik, Czech. Patent No. 152838; *Chem. Abstr.*, **81**, 105264 (1974).
197. T. Nishioka, A. Maehara, T. Mizutani, N. Itaya, I. Nakayama, and M. Hirao, Jpn. Pat. No. 8017323; *Chem. Abstr.*, **93**, 46404 (1980).
198. J. Bull, Ger. Pat. No. 2919816; *Chem. Abstr.*, **92**, 76273 (1980).
199. K. Murata and N. Kiriyama, *Rept. Osaka Municipal Research Inst. Domestic Sci.*, 17, 195 (1946); *Chem. Abstr.*, **41**, 4790 (1947).
200. R. J. Alaimo and J. E. Gray, US Pat. No. 4336199; *Chem. Abstr.*, 144752 (1982).
201. R. J. Alaimo and J. E. Gray, US Pat. No. 4339386; *Chem. Abstr.*, **97**, 182197 (1982).
202. V. Konecny and A. Krutosikova, Czech. Patent No. 169548; *Chem. Abstr.*, **88**, 169943 (1978).
203. J. Perronet and P. Girault, Ger. Pat. No. 2355424; *Chem. Abstr.*, **81**, 91334 (1974).
204. H. Suzuki, T. Mita, T. Takeyama, M. Hanaue, M. Nishikubo, and K. Yamagishi, Jpn. Pat. No. 02250869; *Chem. Abstr.*, **114**, 101988 (1991).
205. T. Kay, British Patent No. 1245397; *Chem. Abstr.*, **75**, 129654 (1971).
206. T. Kay, S. African Patent No. 7100299; *Chem. Abstr.*, **76**, 153578 (1972).
207. Imperial Chemical Industries Ltd., French Patent No. 2125659; *Chem. Abstr.*, **78**, 159411 (1973).
208. J. Crovetti and R. G. Stein, Ger. Pat. No. 2257062; *Chem. Abstr.*, **79**, 42332 (1973).
209. J. Bull, UK Patent No. 2053188; *Chem. Abstr.*, **95**, 80712 (1981).
210. H. Gayer, P. Gerdes, D. Kuhnt, S. Dutzmann, H. W. Dehne, and G. Haenssler, PCT Int. Appl. WO 9501973; *Chem. Abstr*., **124**, 29591 (1996).
211. S. Trah and F. Gantz, PCT Int. Appl. WO 9308183; *Chem. Abstr.*, **119**, 203277 (1993).
212. S. Trah, Ger. Pat. No. 19914756; *Chem. Abstr.*, **131**, 351229 (1999).
213. D. Farge, J. Leboul, Y. Le Goff, and G. Poiget, Ger. Pat. No. 2831983; *Chem. Abstr.*, **90**, 181591 (1979).
214. S. A. Philagro, Israeli Patent No. 55228; *Chem. Abstr.*, **99**, 175584 (1985).
215. U. Gebert and W. Raether, Ger. Pat. No. 2651084; *Chem. Abstr.*, **90**, 152184 (1979).
216. Hoechst A.G., Jpn. Pat. No. 7859660; *Chem. Abstr.*, **89**, 146903 (1978).
217. U. Gebert and W. Raether, Ger. Pat. No. 2516317; *Chem. Abstr.*, **87**, 39261 (1977).
218. U. Gebert and W. Raether, Ger. Pat. No. 2439629; *Chem. Abstr.*, **85**, 21082 (1976).
219. P. A. Bukowick, US Pat. No. 4002649; *Chem. Abstr.*, **86**, 139826 (1977).
220. H. Martin, US Pat. No. 4451286; *Chem. Abstr.*, **101**, 105791 (1984).
221. C. Rentzea, G. Reissenweber, K. H. Feuerherd, and J. Jung, Ger. Pat. No. 3213373; *Chem. Abstr.*, **100**, 68306 (1984).