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OXIMES OF SEVEN-MEMBERED HETEROCYCLIC COMPOUNDS CONTAINING TWO HETEROATOMS

E. Ābele

Latvian Institute of Organic Synthesis, 21 Aizkraukles Street, Rīga, LV-1006, Latvia,
e-mail: abele@osi.lv

Literature data concerning the synthesis and structure of diazepane, oxazepane and thiazepane oximes were reviewed. Synthesis of novel heterocycles from the oximes of seven-membered heterocycles containing two heteroatoms was described. Biological activity of oximes of seven-membered heterocycles with two heteroatoms was also reviewed.

Key words: *oxime, diazepane, oxazepane, thiazepane.*

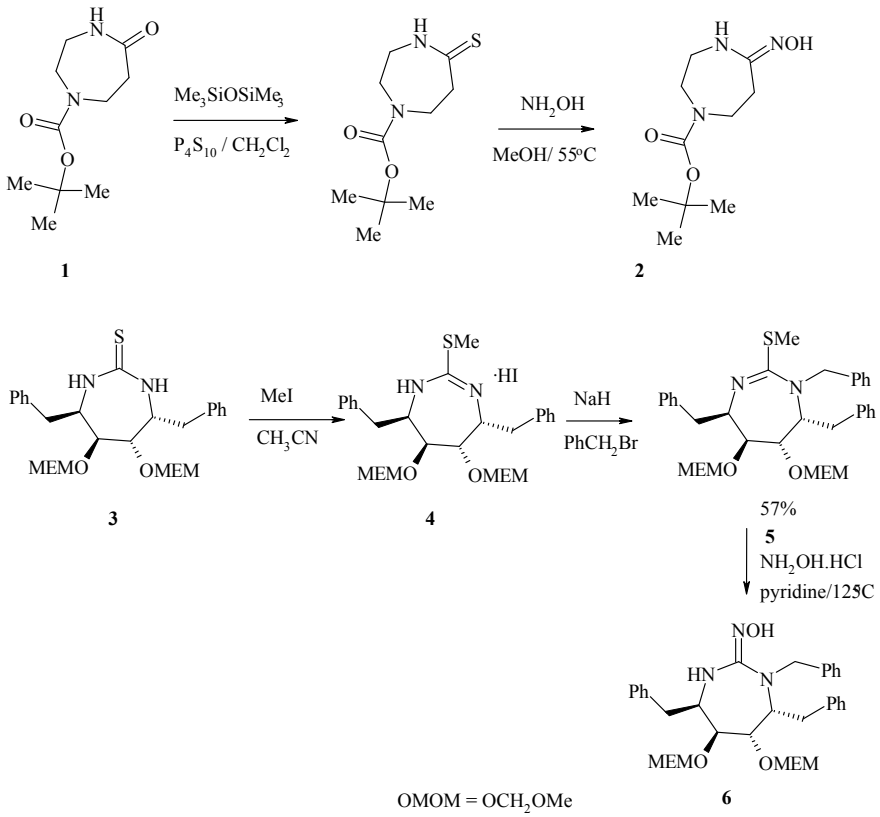
INTRODUCTION

The oximes of seven-membered heterocyclic compounds containing two heteroatoms are widely used as intermediates in fine organic synthesis. In this review, the principal methods for the production of diazepane, oxazepane and thiazepane aldoximes, ketoximes and amidoximes and their derivatives are summarized. The principal methods for the investigation of the structure of the oximes of seven-membered heterocyclic compounds with two heteroatoms are examined briefly. The reactions and biological activity of the oximes of seven-membered heterocyclic compounds with two heteroatoms will be presented.

1. SYNTHESIS OF OXIMES OF SEVEN-MEMBERED HETEROCYCLIC COMPOUNDS CONTAINING TWO HETEROATOMS

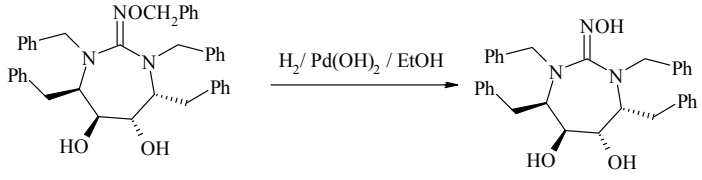
1.1. Synthesis of diazepane oximes

The classical method for the synthesis of 1,3- and 1,4-diazepane [1] oximes is based on the reaction of diazepane ketones with hydroxylamine hydrochloride in the presence of Na_2CO_3 / EtOH [2], aqueous $NaHCO_3$ / *i*-PrOH [2, 3], aqueous NaOH [4] or pyridine in ethanol / MS 4 Å [5]. 1,4-Diazepane oximes **2** were obtained in the two-step reaction from Boc-protected 1,4-diazepanone **1** in the presence of P_4S_{10} / hexamethyl disiloxane and then by treatment with hydroxylamine in methanol [6]. Similarly, 1,3- [7] and 1,4-diazepane [8] oximes are obtained from the corresponding methylated thiones. Thus, treatment of thione **3** with methyl iodide affords methyl sulfide **4.** Interaction of compound **4** with benzyl bromide in the presence of NaH / DMF affords sulfide **5**. Further interaction of diazepane **5** with hydroxylamine hydrochloride leads to formation of oxime **6**, the yield being 81% [7].



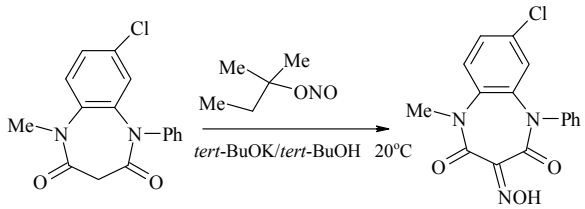
1 **2** **3** **4** **6**

Interestingly, that the oxime of 1,3-diazepane **8** can be prepared by the reductive debenzylation of corresponding oxime ether **7** in the system H_2 / $Pd(OH)_2$ / EtOH at 25 °C[7].



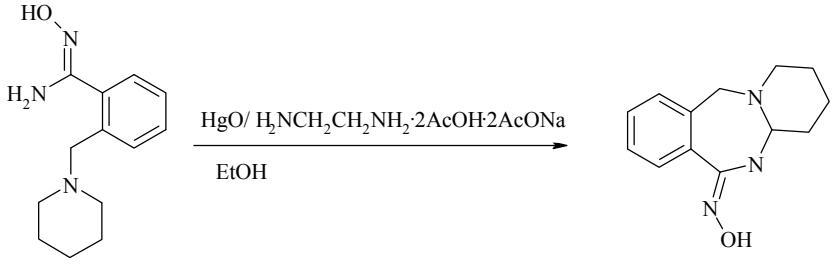
7 **8**

1,4-Diazepane oximes are successfully obtained also by the nitrosation of 1,4-diazepane derivatives. As nitrosation agents *tert*-AmylONO/ *tert*-BuOK / *tert*-BuOH [9] and 3-methylbutyl nitrite / *tert*-BuOK / PhMe / THF [10] are used. Thus, reaction of 1-phenyl-5-methyl-8-chloro-1,2,4,5-tetrahydro-2,4-dioxo-3H-1,5-benzodiazepine **9** with *tert*-amyl nitrite in the presence of *tert*-BuOK in *tert*-BuOH affords oxime **10** in 85% yield [9].

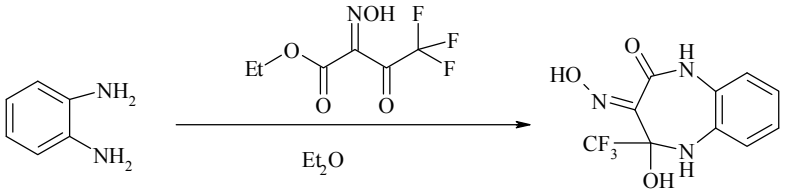


9 **10**

Treatment of (*Z*)-2-piperidinomethyl benzamidoxime (**11**) with ethylenediaminetetraacetic acid disodium salt in ethanol in the presence of HgO leads to formation of the oxime of benzodiazepinone **12** in 75% yield [11]. Reaction of benzene-1,2-diamine (**13**) and 4,4,4-trifluoro-2-[(*Z*)-hydroxyimino]-3-oxobutyric acid ethyl ester in diethyl ether affords oxime **14** in 80% yield [12].



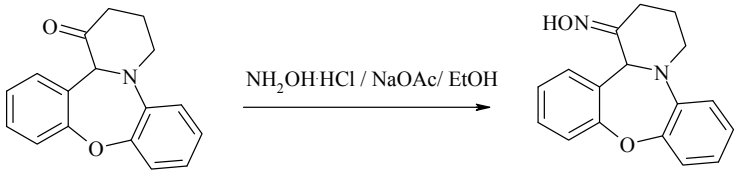
11 **12**



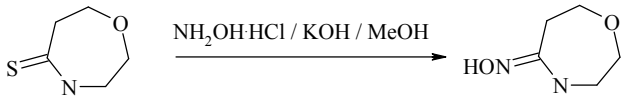
13 **14**

1.2. Synthesis of oxazepane oximes

Synthesis of 1,3- and 1,4-oxazepane oximes have been described in some articles [13-17]. Thus, interaction of oxepane ketone **15** with hydroxylamine hydrochloride in the presence of NaOAc/ EtOH leads to oxepane oxime **16** [13]. Similarly thiones (for example, compound **17**) are converted to corresponding oximes (e.g., compound **18**) in the system *hydroxylamine hydrochloride / base (aqueous KOH or pyridine)* [14].

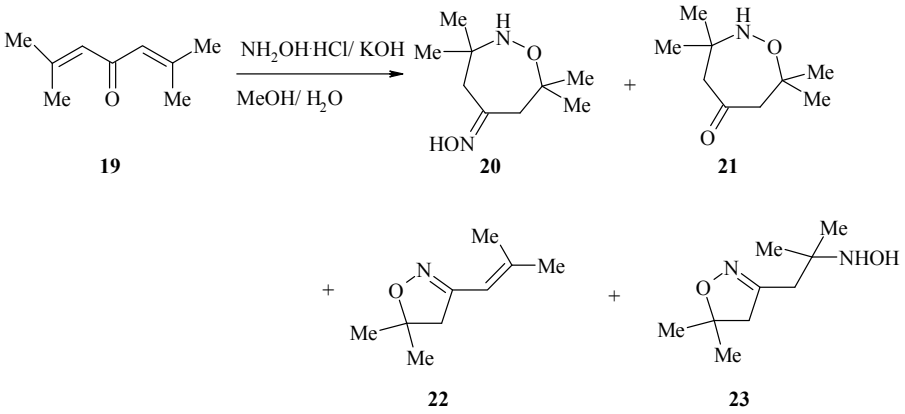


15 **16**



17 **18**

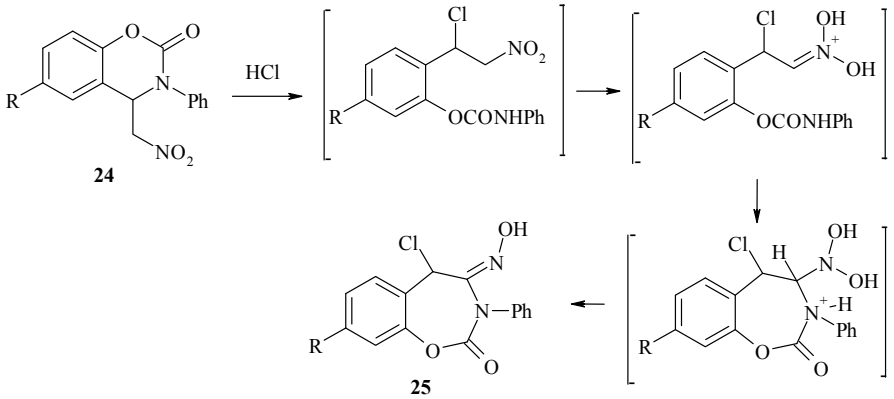
Reactions of hydroxylamine as an ambident nucleophile with 2,6-dimethyl-2,5-heptadien-4-one (**19**) was studied in details in the article [16]. For example, treatment of the compound **19** with $NH_2OH·HCl$ in the system KOH / MeOH / H_2O at room temperature leads to formation of a mixture of *E*-isomer of 1,2-oxazepane oxime **20**, oxazepanone **21** and two isoxazolines **22** and **23**.



19 **20** **21**

22 **23**

The treatment of oxazinones **24** with HCl gives colourless crystalline oximes **25** in 32 or 35% yield. The conversion of compound **24** to oxime **25** involves the loss of OH-group and the incorporation of chlorine atom [17].



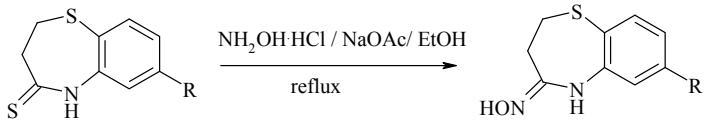
24

25

R = H, Cl

1.2. Synthesis of thiazepane oxime

Synthesis of 2,3-dihydro-5H-benzo[b][1,4]thiazepin-4-one oximes **27** was carried out from 2,3-dihydro-1,5-benzothiazepin-4(5H)-thiones **26** in the system *hydroxylamine hydrochloride / NaOAc / EtOH* [18].



26

83-94 %

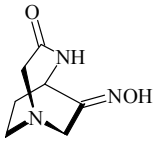
27

R = H, Cl

2. STRUCTURE

One of most reliable methods for determining of structure of the isomeric oximes of seven-membered heterocyclic compounds containig two heteroatoms is NMR spectroscopy. The ^{1}H NMR spectra of oximes of diazepane [5, 8, 12], oxazepane [17] and thiazepane [18] have been investigated in details.

However, only the structure of 1,4-diaza-6-(hydroxyimino)bicycle[3.2.2]-nonan- 3-one (**28**) has been determined using X-ray crystallographic analysis [5].



28

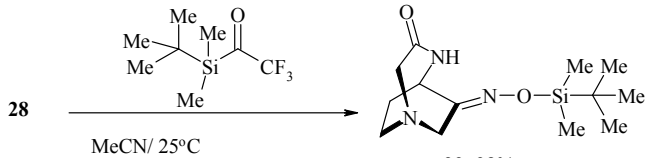
IR spectroscopy was also used to study the structure of diazepane and oxazepane oximes [8].

3. REACTIONS OF SEVEN-MEMBERED HETEROCYCLIC COMPOUNDS WITH ONE HETEROATOM

3.1. Synthesis of O-alkyl derivatives of oximes

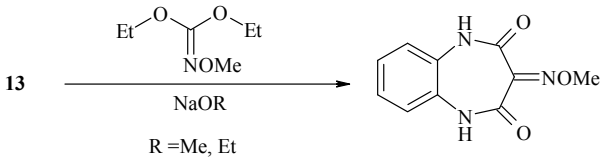
3.1.1. O-Ethers of diazepane oximes

The main method for the preparation of O-ethers of azepane oximes is alkylation of the corresponding oximes with alkyl halides in the systems *NaH / Bu_4NI / THF* [7] and *NaH / DMF* [19]. Synthesis of oxime silyl ether **29** was carried out from oxime **28** and N-methyl-N-*tert*-butyldimethylsilyl-1,1,1-trifluoroacetamide in acetonitrile at room temperature [5].



28 MeCN/ 25°C **29** 98%

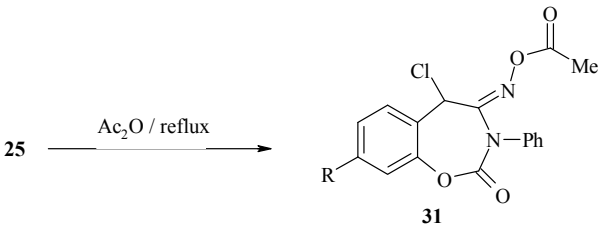
Reaction of *o*-phenylenediamine (**13**) with diethyl methoxyiminomalonate in the presence of sodium methylate [20] or sodium ethylate [21] leads to formation of 1,5-dihydrobenzo[b][1,4]diazepine-2,3,4-trione 3-(O-methyloxime (**30**) in yield up to 76%.



13 NaOR, R =Me, Et **30**

3.1.2. O-Esters of oxazepane oxime

Refluxing oxazepane oximes **25** in acetic anhydride affords corresponding O-acetyloximes **31** in 78–80 % yields [17].

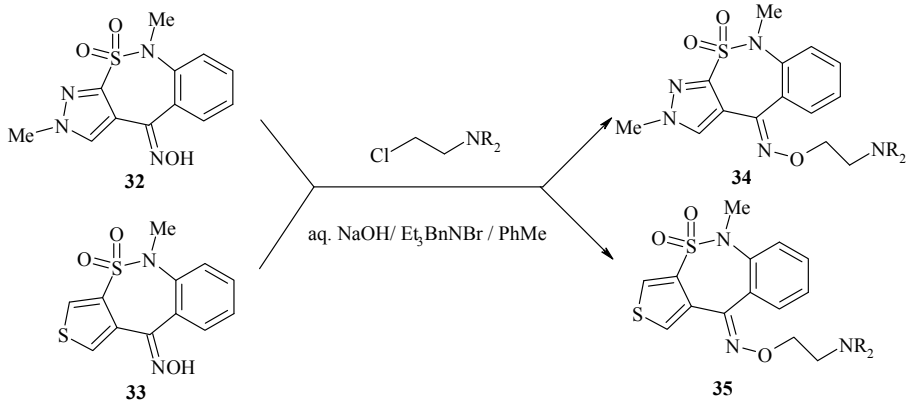


25 Ac_2O / reflux **31**

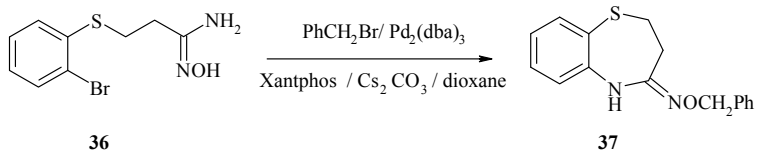
R = H, Cl

3.1.3. O-Ethers of thiazepane oximes

Phase transfer catalytic method has been used in the synthesis thiazepine oxime O-ethers. Thus, treatment of oximes **32** and **33** with $R_2NCH_2CH_2Cl$ in the two phase system *aqueous NaOH / Et_3BnNBr / toluene* at reflux gives corresponding oxime O-ethers **34** and **35** in yields up to 94 % [22].

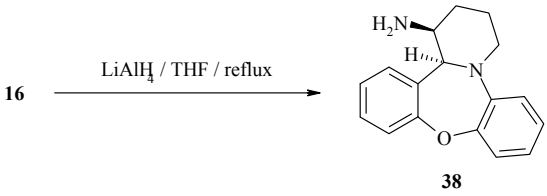


We have recently described novel palladium-catalyzed method of synthesis of 1,4-thiazepine O-benzyloxime **37** in the system *oxime* **36** / *benzyl bromide / $Pd_2(dba)_3$ / Xantphos / Cs_2CO_3 /dioxane* [23].

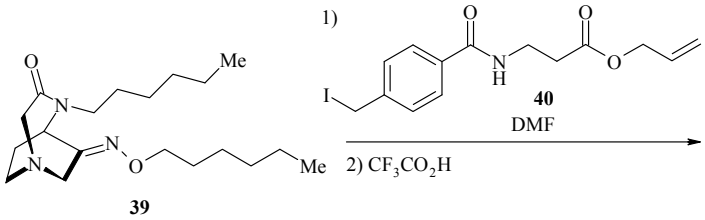


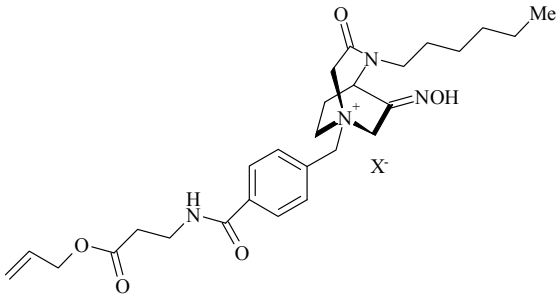
3.2. Transformation of oxime group

Reduction of 3,4-dihydro-2H,13bH-9-oxa-4a-azatribenzo[a,c,e]-cycloheptен-1-one oxime **16** with $LiAlH_4$ in refluxing THF affords amine **38** as single product [1].



The functionalization of oxime ether **39** by quaternization with iodide **40** in DMF, followed by deprotection of oxime O-hexyl ether group, leads to formation of ammonium salt **41** [5].





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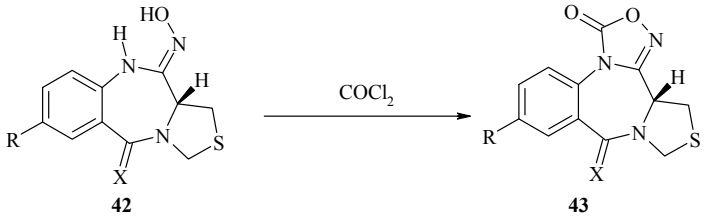
3.3. Synthesis of novel heterocyclic compounds from oximes of seven-membered heterocycles with one heteroatom

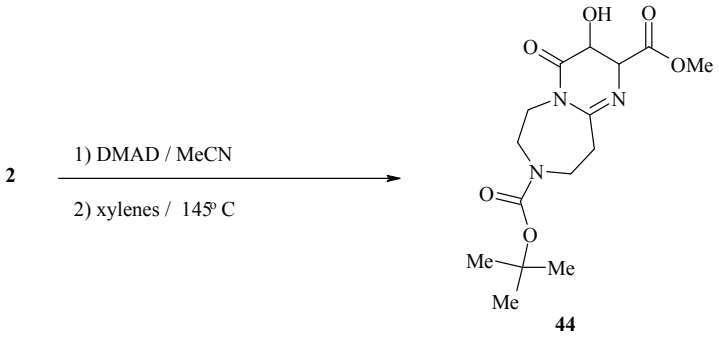
Recent advances in the synthesis of heterocyclic systems are described in reviews [23, 24]. In this chapter, the specific reactions involving cyclization of oximes of seven-membered heterocyclic compounds with two heteroatoms will be set out in details. Thus, the treatment of 11-hydroxyimino-5*H*-thiazolo[4,3-*c*][1,4]benzodiazepines **42** with phosgene in refluxing toluene affords oxadiazole derivatives **43** 61–75% yields [25].



42 **43**

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

Addition of oxime **2** to dimethyl acetylenedicarboxylate (DMAD) in MeCN, followed by thermal cyclization of intermediate in xylenes at 145 ^{o}C, leads to bicycle **44** in 19% yield [6].



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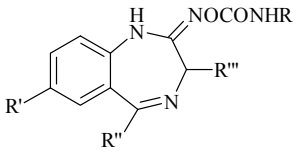
4. BIOLOGICAL ACTIVITY OF OXIMES OF SEVEN-MEMBERED HETEROCYCLIC COMPOUNDS WITH ONE HETEROATOM

4.1. The action on the cardiovascular system

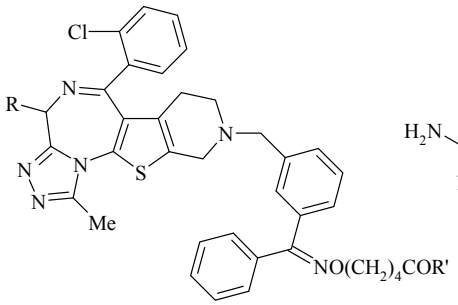
The first investigation of carbamoyloxyimino-1,4-benzodiazepines **45** as the agents improving blood circulation was published in 1981 [26]. More recently

diazepine oximes **46** as platelet activating factor (PAF) receptor antagonists with tromboxane synthase inhibitor (TxSI) activity were presented in the chemical literature [27–29]. Beside this, 1,4-diazepane oxime derivatives of type **47** were used as factor Xa inhibitors [30]. All these compounds showed high activity on the different diseases of cardiovascular system (for example, myocardial infarction, deep vein thrombosis).



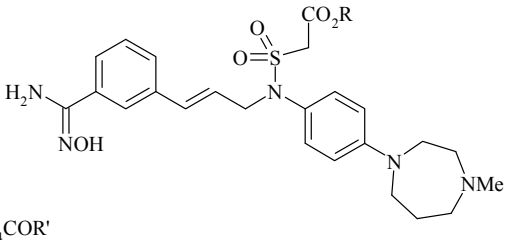
R = aryl; R′ = Cl, Br, NO_2, CF_3; R″ = Ph, pyridyl; R‴ = H, alkyl

45



R = H, Me; R′ = O-alkyl, N-alkyl

46

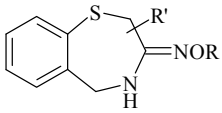


R = alkyl

47

4.2. Action on the central nervous system

Derivatives of thiophene or pyrazole-fused 1,2-benzothiazine **34** and **35** [22] and 1,4-benzothiazine oximes **48** [31] exhibit high activity on central nervous system.



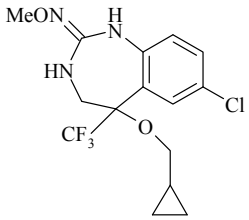
R, R' = H, alkyl

48

Derivatives of 1,3-diazacycloalkyl oximes, including 1,3-diazepine oximes, were found to possess muscarinic properties [32].

4.3. Antiviral and antibacterial activity

Azepine oxime derivatives **49** [19], **7** and **8** [6] were tested as antiviral agents against HIV-1. Thus, oxime **8** showed an inhibition constant of 42 n*M* for HIV protease. Interestingly, that oxime **7** is a weak inhibitor of HIV protease (K_1 = 3 μ*M*). The presence of a larger group such as benzyloxy group has a dramatic effect on its binding to the active site of HIV protease [6]. Oximes of benzo-, naphtho- and quinolino-1,4-thiazepines were tested *in vitro* for anti-bacterial and antifungal activity [18].



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Acknowledgement

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R E F E R E N C E S

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DIVUS HETEROATOMUS SATUROŠU SEPTIŅLOCEKĻU HETEROCIKLISKO SAVIENOJUMU OKSĪMI

E. Ābele

K O P S A V I L K U M S

Apkopoti literatūras dati par diazepāna, oksazepāna un tiazepāna oksīmu sintēzi un struktūru. Apkopoti dati par jaunu heterociklu sintēzi no septiņlocekļu heterociklisko savienojumu ar diviem heteroatomiem oksīmiem. Darba pēdējā nodaļā apkopoti dati par septiņlocekļu heterociklisko savienojumu, kas satur divus heteroatomus, oksīmu bioloģisko aktivitāti.

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