OXIMES OF SEVEN-MEMBERED HETEROCYCLIC COMPOUNDS CONTAINING ONE HETEROATOM

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Literature data on the synthesis and structure of azepane, oxepane and thiepane oximes were reviewed. Synthesis of novel heterocycles from oximes of seven-membered heterocycles containing one heteroatom were described. Biological activity of oximes of seven-membered heterocycles with one heteroatom was also reviewed.

**Key words**: *oxime, azepane, thiepane, oxepane.*

INTRODUCTION

The oximes of seven-membered heterocyclic compounds containing one heteroatom are widely used as intermediates in fine organic synthesis. In this review, the principal methods for the preparation of azepane, thiepane and oxepane 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 one heteroatom are examined briefly with regard to isomerism. The reactions and biological activity of the oximes of seven-membered heterocyclic compound containing one heteroatom will be examined in the second part of the review.

1. SYNTHESIS OF OXIMES OF SEVEN-MEMBERED HETEROCYCLIC COMPOUNDS WITH ONE HETEROATOM

### 1.1. Synthesis of azepane oximes

The classical method for the synthesis of azepane oximes is based on the reaction of azepane ketones with hydroxylamine hydrochloride in the presence of different bases [1], aqueous or aqueous methanolic solution of NaHCO$_3$ [2, 3] or pyridine in methanol or ethanol [4–6]. Azepane oximes **2** have been obtained in the two-step reaction from the acid **1** in the presence of polyphosphoric acid (PPA) and hydroxylamine hydrochloride [6].


R = COOH, OH, NO$_2$, OMe, Cl
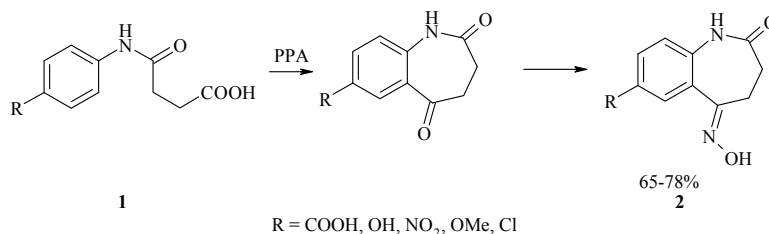
Hexahydro-2H-azepin-2-thione has been easily transformed to the oxime of perhydro-2-azepinone in the system $NH_2OH \cdot HCl$ / $NaHCO_3$ / MeOH / PhH [7]. Cyclic enol ether **3** in the system $NH_2OH \cdot HCl$ / $NaHCO_3$ / MeOH leads to formation of oxime of azepinone **4** as single product [8].
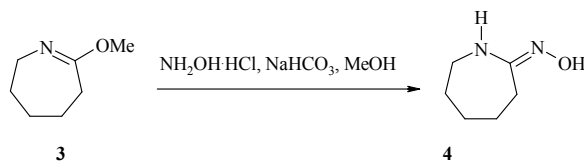
3-Oxime of 4-(phenylhydrazino)azepan-2,3-dione (**6**) has been prepared in two steps by amination of morpholine derivative **5** in the presence of phenyl-hydrazine and hydroxylamine hydrochloride [9]. Interaction of enamine **7** with hydroxylamine hydrochloride affords oxime derivative **8** in 50% yield [10].
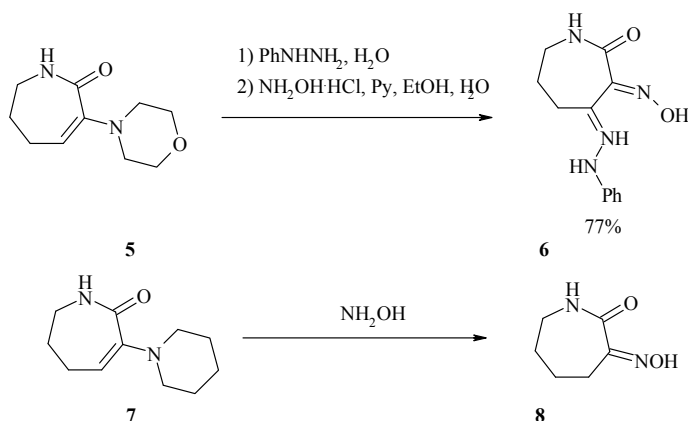

Azepane oximes have been successfully obtained also by the nitrosation of side chain of azepane derivatives. As nitrosation agents $NaNO_2$ / H_2O / AcOH [11], BuONO / KHMDS (potassium bis(trimethylsilyl)amide)/ THF [12], BuONO / KHMDS / PhMe [13], *tert*-BuONO / *tert*-AmONa / PhH / PhMe [14], *tert*-BuONO / *tert*-BuOK / PhMe [15], *tert*-BuONO / *tert*-BuOK / CHCl₃ / PhMe [16], *iso*-AmONO / HCl [4, 17] and *iso*-AmONO / LiHMDS / THF [18] are used.
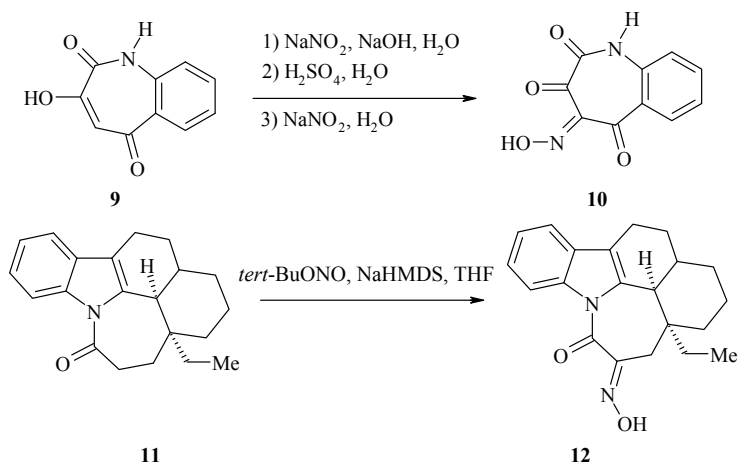
Interesting is the fact that the reaction of 2,5-dihydrobenzo[f]azepin-2,5-dion-3-ol (**9**) in the system $NaNO_2$ / NaOH (then $2M$ aqueous solution of H_2SO_4) leads to formation of 4-oxime of 1H-benzo[b]azepin-2,3,4,5-tetraone (**10**) [19]. Nitrosation of CH_2 group is the key step in the preparation of alkaloid (+)-vincamine. Thus, the reaction of azepine derivative **11** with *tert*-butyl nitrite in the presence of NaHMDS (sodium bis(trimethylsilyl)amide) in THF afforded a mixture of *E*- and *Z*-isomers of oxime **12** in 65% yield [20].

Derivatives of imidazoline or hexahydropyrimidine **13** in the presence of trifluoromethanesulfonic acid undergo cyclization to bicyclic azepine oximes **14** in 62 and 90% yields [21]. Cyclization of amidoximes **15** in the presence of Hg(II) salts yields bicyclic amidines **16** [22].

13   14

n = 1, 2

15   16

R = H, Ph
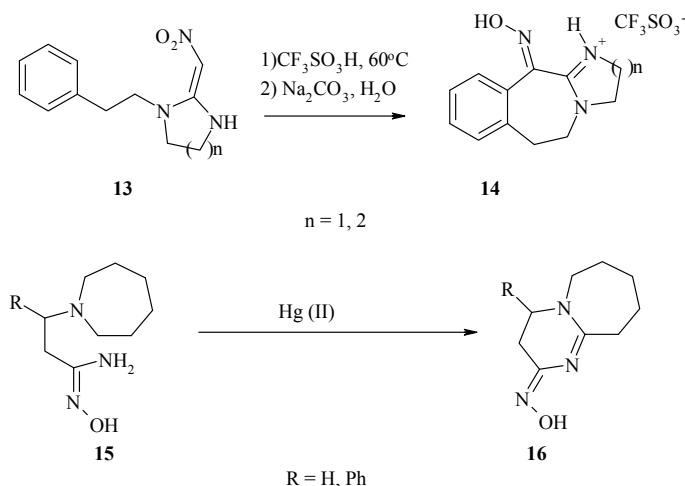
1.2. Synthesis of oxepane oximes

Some methods have been dedicated to the synthesis of oxepane oximes [23]. Thus, interaction of oxepane ketones with hydroxylamine hydrochloride in the presence of NaOAc/ EtOH [24] or pyridine/ EtOH leads to formation of oxepane oximes [25].
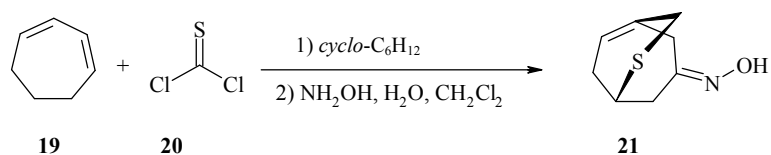
1.3. Synthesis of thiepane oximes

Thiepane oximes typically have been obtained by treatment of the corresponding carbonyl compounds with hydroxylamine [26, 27] or hydroxylamine hydrochloride [28, 29]. Synthesis of this class of compounds has been also successfully carried out by two-step reaction starting from the ester **17**. Thus, cyclocondensation of the ester **17** in the presence of sodium ethylate and then reaction with hydroxylamine afforded thiepane oxime **18** [30].


17   18
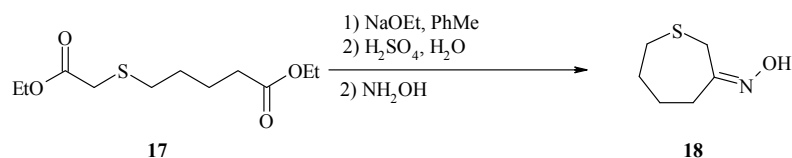
The interesting synthesis of oxime of 2-thiabicyclo[3,2,2]non-5-en-3-one (**21**) without separation of intermediates is described in patent [31]. Reaction of

1,3-cycloheptadiene (**19**) with thiophosgene (**20**) in cyclohexane, with the subsequent treatment of reaction mixture with hydroxylamine in methylene chloride, leads to formaton of oxime **21** as single product.


Thiepane oximes have been also obtained by the nitrosation of thiepane alkyl derivatives in the systems BuONO / EtONa / EtOH [32, 33], PentylONO / HCl / Et$_2$O [34] or *iso*-AmONO / HCl / Et$_2$O [35].

Hydrogenation of 4-nitro-2,3-dihydrobenzo[*b*]thiepine 1,1-dioxide (**22**) in the presence of 10% Pd/C in dioxane affords oxime **23** in 68% yield [36]. The interaction of nitro derivatives **24** with trifluoromethanesulfonic acid leads to formation of the intermediate salts **25**. Methanolysis of salts **25** gives benzo-thiepane oximes **26** in 70–83% yields [37].
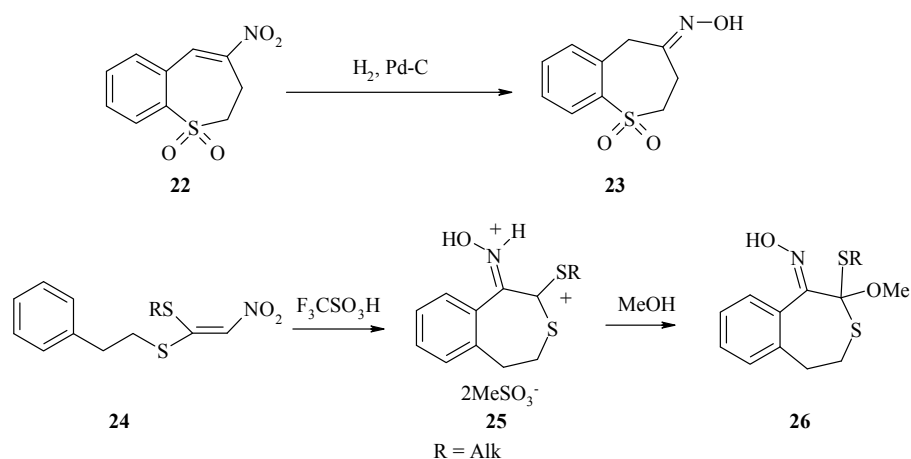
2. STRUCTURE

One of the most reliable methods for determination of the structure of the isomeric oximes of seven-membered heterocyclic compounds containing one heteroatom is the NMR spectroscopy. The ^{1}H NMR spectra of oximes of azepane [18, 21, 37–39] and thiepane [40] have been investigated in details.
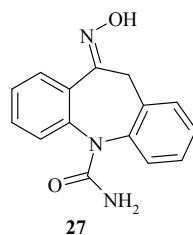
However, only the structure of 10-(hydroxyimino)-10,11-dihydrodibenz[b,f]-azepin-5-carboxamide has been determined by the X-ray crystallographic analysis. Compound **27** undergoes crystallizations forming dimeric structure.

Torsion angle C(11)–C(10)–N(10)–O(10) in dimeric crystals of the compound **27** was –0.3(5) or –1.4(4)°. The asymmetric dimer of compound **27** crystallizes with four molecules of ethanol [41].

IR spectroscopy has been also used to study the structure of azepane [4] and thiepane [32] oximes.

The irradiation of *E*-isomer of 10-(hydroxyimino)-10,11-dihydrodibenz[b,f]-azepin-5-carboxamide (Sunset CPT lamp, >290 nm) in the system *acetonitrile – water* leads to formation of the *Z*-isomer[41].

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

3.1. Synthesis of O-alkyl derivatives of oximes
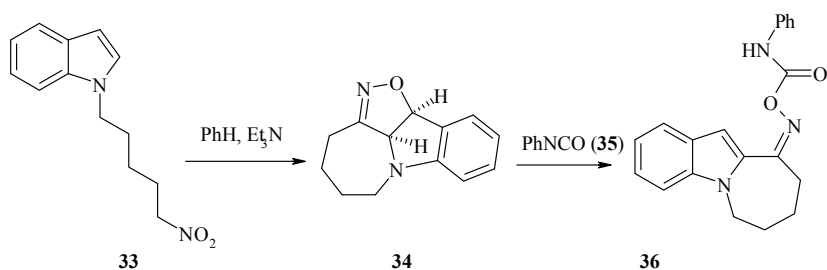
3.1.1. O-Ethers of azepane oximes

The principal method for the preparation of O-ethers of azepane oximes is the alkylation of the corresponding oximes with alkyl halides in the system K_2CO_3 / Me_2CO [42]. Beside this O-ethers of azepane oximes are obtained from the corresponding carbonyl compounds and O-alkyl derivatives of hydroxyl-amine in the presence of pyridine in methanol [43], pyridine in ethanol [9] or sodium acetate in acetic acid [44]. Reaction of oxime of azepan-2-one with dimethyl acetylenedicarboxylate (DMAD) in acetonitrile gives a mixture of *E*- and *Z*-isomers of oxime ethers **28** and **29** in the ratio 8:1 [45].
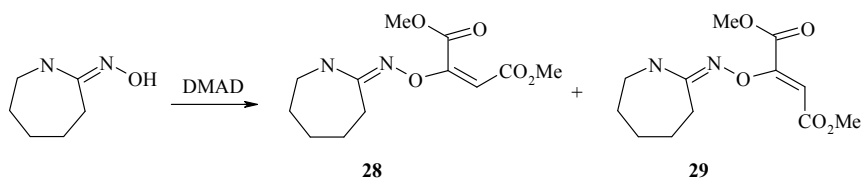
Synthesis of O-acyl derivatives of azepane oximes have been studied in details in two articles [37, 41]. Thus, interaction of oxime **30** with tetra-hydrofuran-2,5-dione (**31**) in the system *pyridine / CH₂Cl₂* at 20 °C affords the acyl derivative **32** in 48% yield [41].
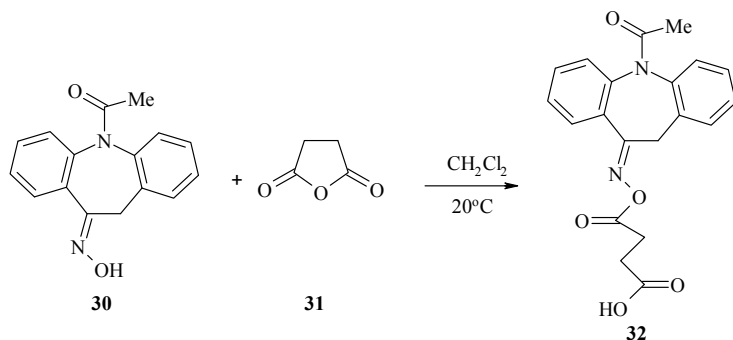

Thermal reaction of the nitro derivative **33** in benzene in the presence of triethylamine gives four-cyclic intermediate **34**. The subsequent reaction of this compound with phenyl isocyanate (**35**) leads to formation of O-acyl derivative of azepane oxime **36** in 20% yield [37].
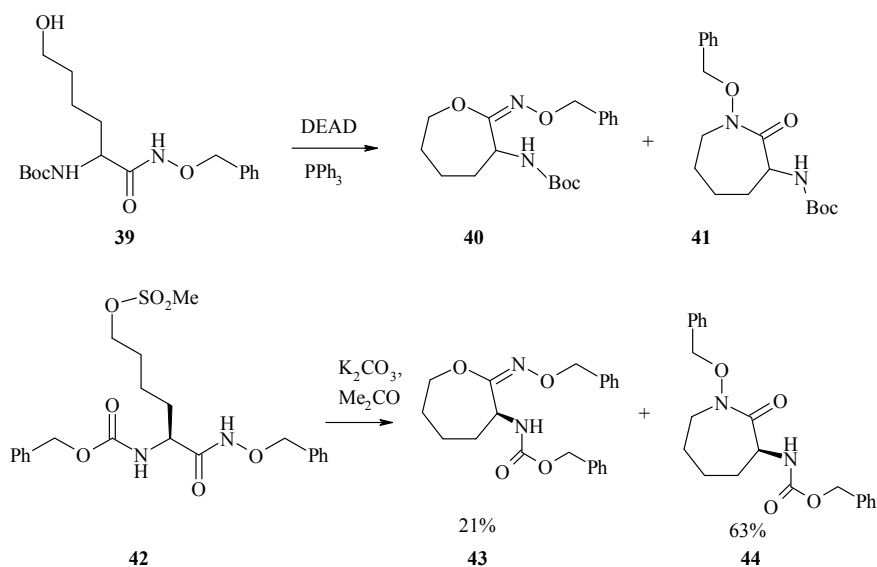
3.1.2. O-Ethers of oxepane oximes

O-Ethers of oxepane oximes have been obtained from the corresponding oximes in the system *alkyl halide / NaNH₂ / PhH* [46]. Ring opening / oximation reaction of 4-methyl-4-pentyl-3,8-dioxabicyclo[3.2.1]octan-1-ol (**37**) by potassium acetate in methanol with subsequent reaction with methoxyamine hydrochloride affords 3-hydroxy-6-methoxyimino-2-methyl-2-penthyloxepane (**38**) in 92% yield [47].
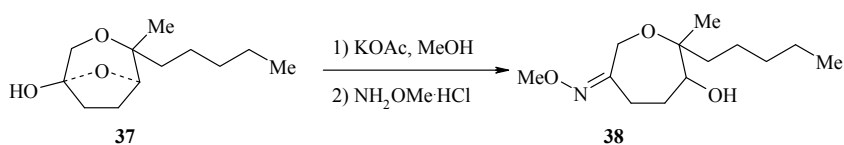
Reaction of O-benzyl hydroxylamine **39** with diethyl azodicarboxylate (DEAD) and triphenylphosphine gives a mixture of isomeric oxepane O-benzyl oximes **40** (yield of the *E*-isomer 22%, of the *Z*-isomer 13%) and of azepane **41** (yield 43%) [48]. The treatment of the sulfonate **42** with K₂CO₃ in acetone affords a mixture of ether of oxepine oxime **43** and azepan-2-one **44** [49].

Radical oxidation of the steroid derivative **45** with lead tetraacetate in the presence of calcium carbonate and iodine leads to formation of a mixture of O-methyloxime **46** and macrocyclic compound **47** [50].

45 **46** **47**
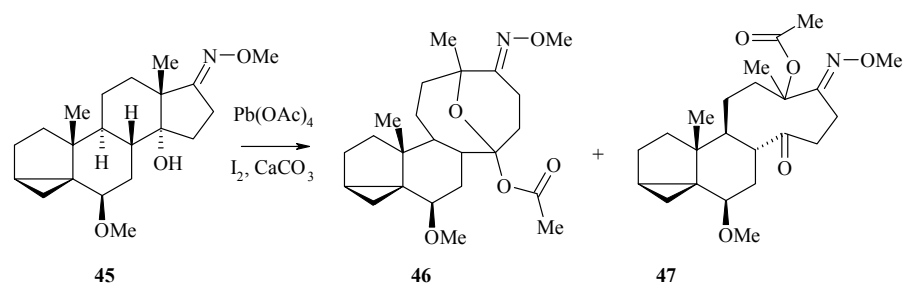
3.1.3. O-Ethers of thiepane oximes

Some works have been dedicated to the synthesis of acyl derivatives of thiepane oximes [51–53]. For example, dibenzothiepin-10-one oxime **48** and acetic anhydride in the presence of pyridine at room temperature gives the corresponding acetate **49** in 86% yield [53].

48 **49**
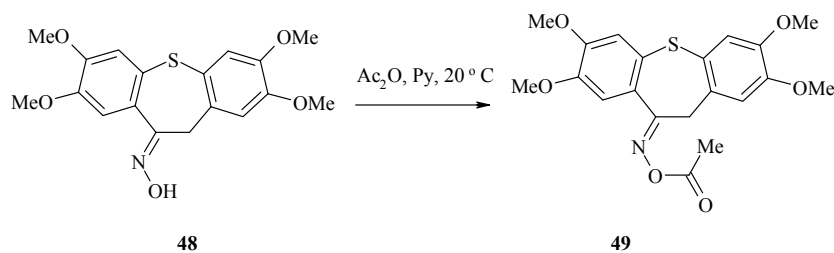
3.2. Transformation of oxime group

Hydrogenation of azepane oximes to the corresponding primary amines have been easily realized in the systems 10% Pd/C/MeOH [54], 10% Pd / C / EtOH / HCl / H$_2$O [18, 55] or 10% Pd/C/EtOH [13]. Reductive amidation of the azepane oximes or oxime acetates is described in some articles [1, 12, 56].

50 **51**

52 **53**
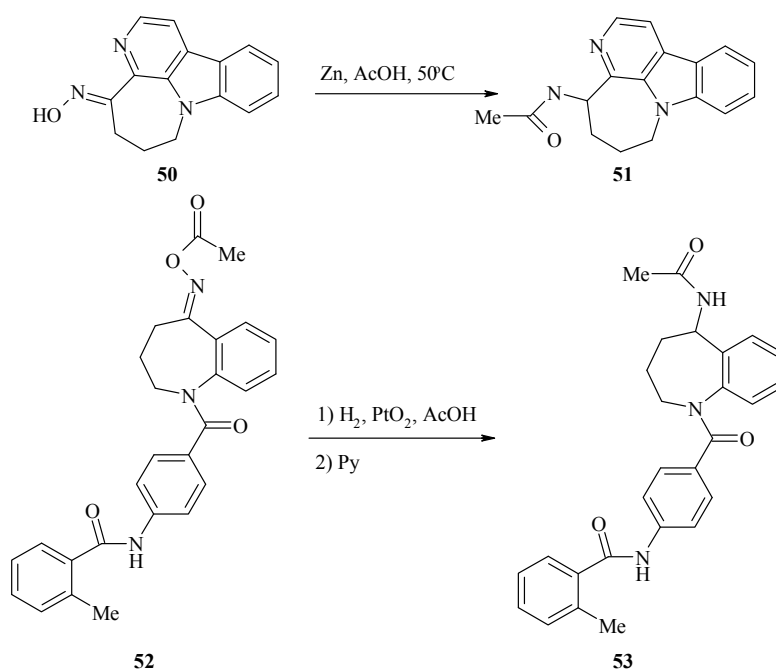
Thus, the reaction of the four-cyclic derivative of azepane oxime **50** with zinc dust afforded acetamide **51** in 87% yield [1]. Hydrogenation of O-acetyloxime **52** in the presence of catalytic amounts of PtO_2 in acetic acid and pyridine leads to formation of amide **53** in 44% yield [56].

Alkaloid (+)-vincamin **55** has been obtained recently by the two-step reaction from azepane oxime **12**. Thus, deoximation of compound **12** in the s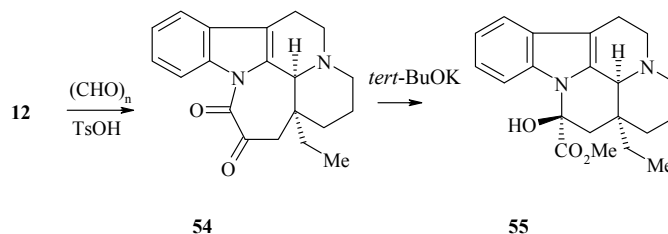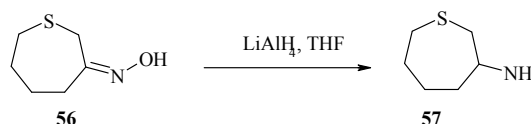ystem *paraform / TsOH / AcOH* gives ketone **54**. Subsequent reaction of the compound **54** with potassium *tert*-butoxide gives (+)-vincamine **55** in 40% yield [56].

Thiepane oxime **56** has been easily transformed to the corresponding amine **57** by reduction with $LiAlH_4$ in tetrahydrofuran [57].

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

The recent advances in the synthesis of heterocyclic systems have been described in the reviews [58, 59]. In this chapter, specific reactions involving cyclization of oximes of seven-membered heterocyclic compounds containing one heteroatom will be set out in details.

Some works have been dedicated to the synthesis of five-membered heterocyclic compounds (such as furans, isoxazoles and oxazoles) from oximes of seven-membered heterocyclic compounds with one heteroatom. Thus, interaction of azepine oxime ether **58** with a mixture of formic and phosphoric acids at 60 °C affords 5,7-dihydro-6H-[1]benzofuro[3,2-*d*][1]benzazepin-6-one (**59**) in the yields up to 74% [44].

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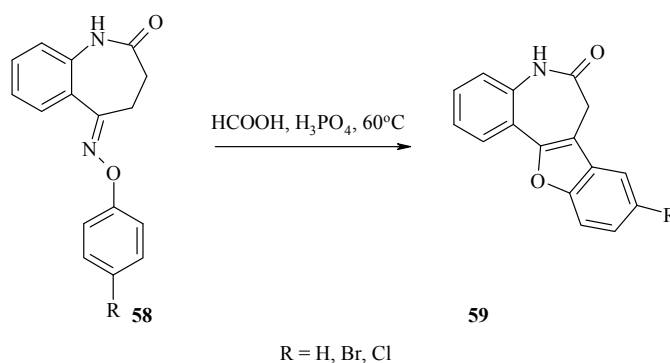
The treatment of 3,4-dihydro-4-hydroxymethylen-[1]benzothiepin-5(2H)-one (**60**) with hydroxylamine hydrochloride in acetic acid leads to formation of a mixture of isoxazolines **61** and **62**. Formation of product **61** (yield 4%) proceeds via the oxime intermediate [60]. Reaction of thiepine oxime **63** with butyllithium and then with ethyl acetate afforded isoxazoline **64** as single product [61].
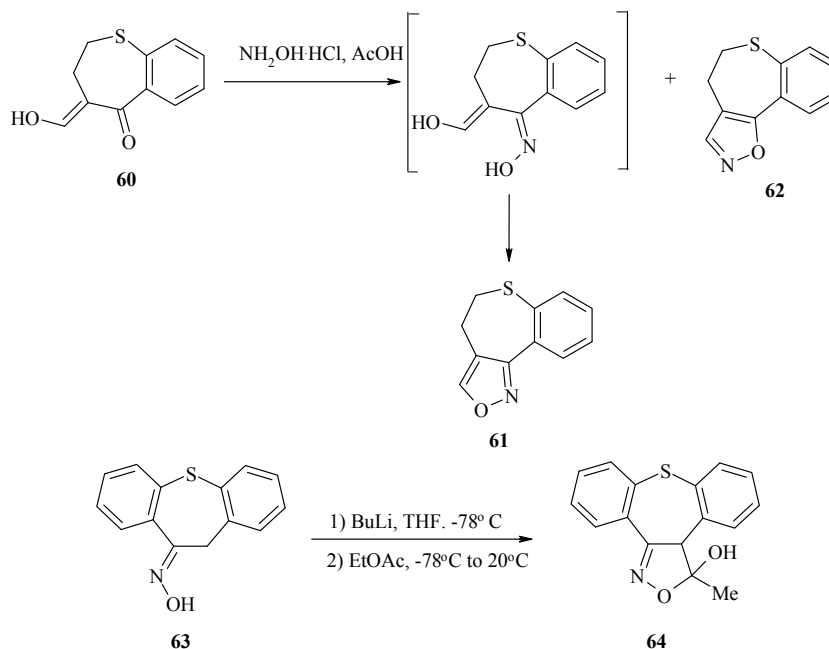
Thermal recyclization of O-ether of oxepane oxime **65** in the refluxing *o*-dichlorobenzene gives oxazole **66** in 41% yield [62].
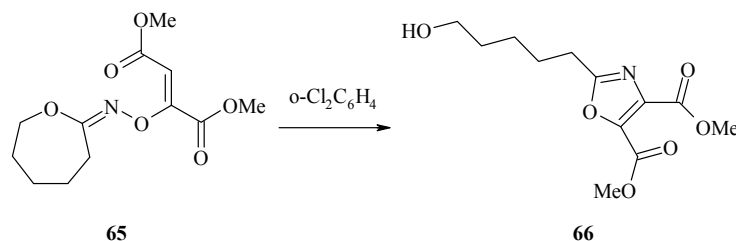
The cyclization of adducts of addition of DMAD to the derivative of azepan-2-one oxime gives different products. Thus, thermal reaction of *E*-isomer of azepine oxime **28** affords a mixture of pyrimidone **67** and 1,2,4-oxadiazole **68**

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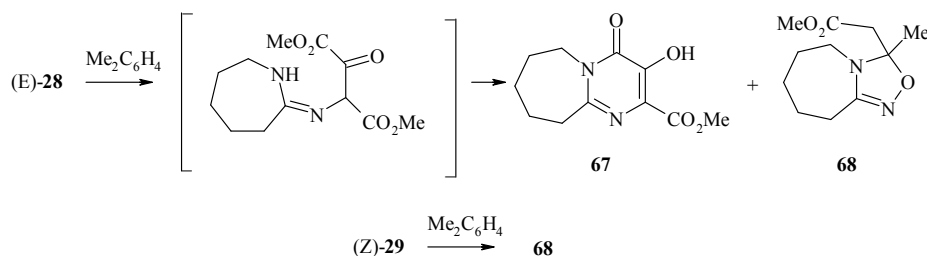
(in ratio 7:3) as result of 1,3-rearrangement of compound **28**. However, *Z*-isomer **29** under similar conditions gives only oxadiazole **68** [63].

The rearrangement of O-ether of azepane oxime **69** leading to formation of 1,2,3,4-tetrahydrochromeno[3,4-b]pyridin-5-one (**74**) has been investigated in the article [64]. Mechanism of this reaction includes the acidic hydrolysis of oxime **69** to imine salts **70** with subsequent alcoholysis to oxolactam intermediate **71**. Product of cyclization of oxolactam **72** in trifluoroacetic acid affords benzofuroazepine **73** in 95% yield. However, intermediate **71** under the alcoholysis conditions gives pyridocoumarin **74** in 69% yield.
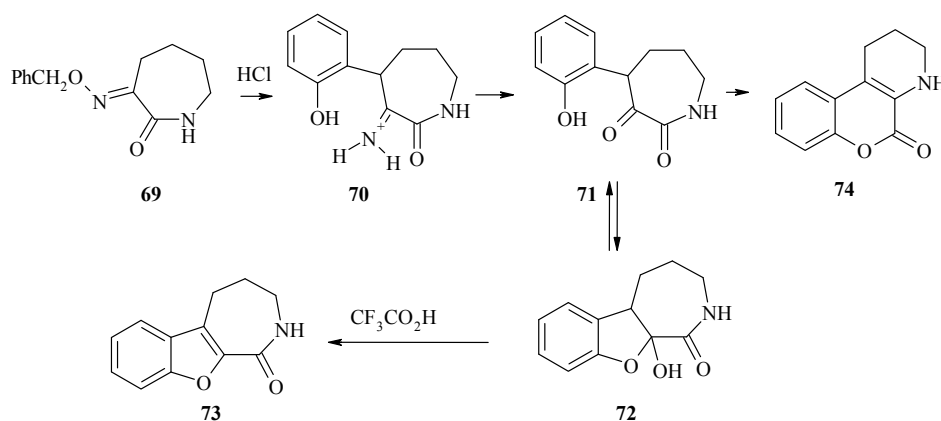
Synthesis of indolonaphthyridines, e.g. alkaloid apotacamine, from oximes of azepinocarbolines by ring contraction has been studied in two works [14, 65]. The reaction of oxime **75** with ethoxyethanol in the presence of alkali with subsequent acidic hydrolysis has been found to lead to the formation of indolonaphthyridine **76** [14]. Similar reaction of oxime **77** with concentrated H_2SO_4 affords apotacamine **78** in 42% yield [65].
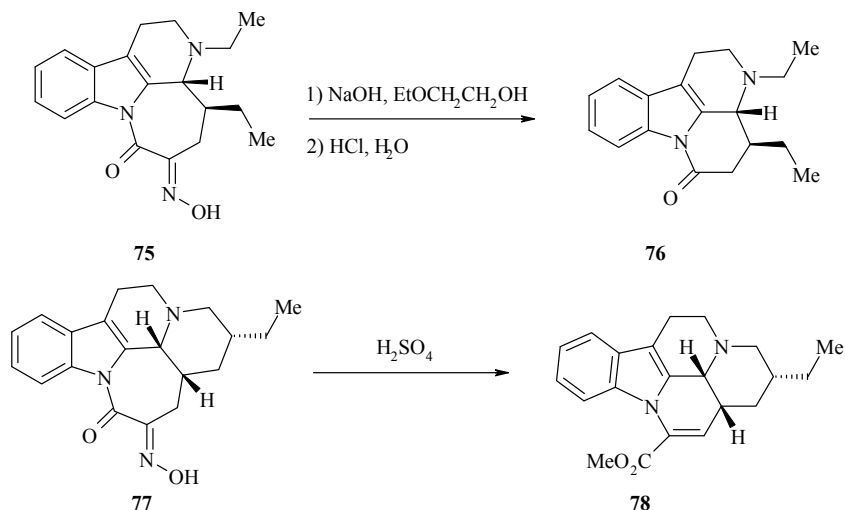
Novel four step method of synthesis of the novel heterocyclic system oxazinoazepines from 4-oximes of azepin-4,5-diones has been described [4].
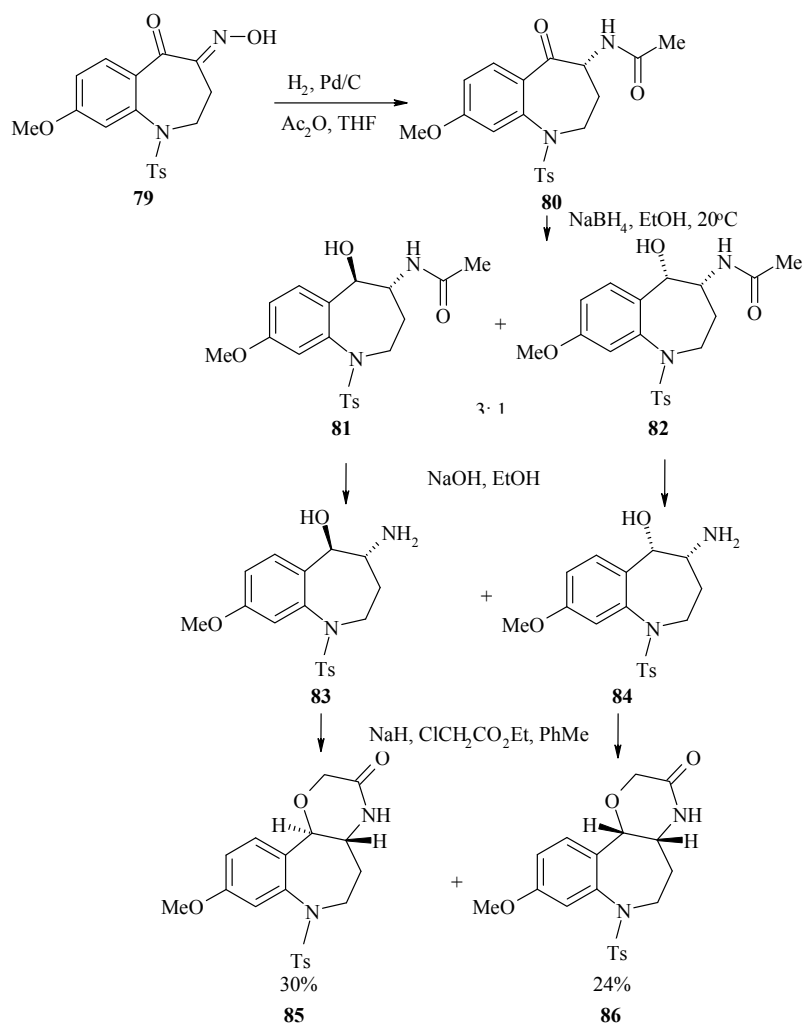
Thus, the reductive amidation of oxime **79** leads to formation of amide **80**. Reduction of this amide **80** with sodium borohydride in ethanol affords diastereomeric carbinols **81** and **82,** which have been separated using the column chromatography. Hydrolysis of amide groups in compounds **81** and **82** gives the amines **83** and **84,** correspondingly. Final products **85** and **86** have been obtained by the cyclization of amines **83** and **84** in the system NaH / PhMe at 80°.

Beckmann rearrangement of azepine [6, 66, 67] and oxepine [23] oximes to corresponding cyclic amides has been successfully realized in the presence of PPA [23, 66, 67] or SOCl$_2$ [6]. Thus, the reaction of azepine oxime **87** in thionyl chloride gives 8-nitro-1,3,4,6-tetrahydrobenzo[b][1,4]diazocin-2,5-dione (**88**) in 80% yield [6]. Oxime of 4,5-dihydrobenzo[b]oxepin-3-one (**89**) and PPA at 90°C afforded selectively the derivative of 1,4-oxazocine **90** [23].
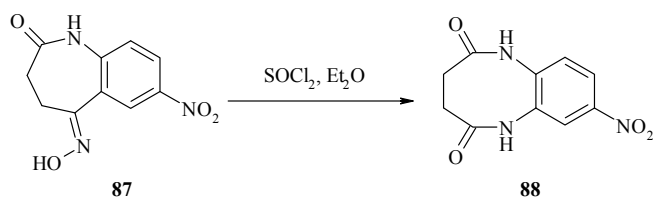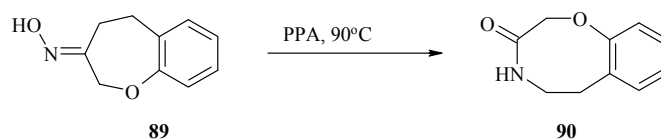
4. BIOLOGICAL ACTIVITY OF OXIMES OF SEVEN-MEMBERED HETEROCYCLIC COMPOUNDS WITH ONE HETEROATOM

4.1. The action on the cardiovascular system

The first investigation of azepine amidoxime **91** as hypertensive agent has been carried out more than fifty years ago [68]. Oxepine oximes **92** have been shown to exhibit high hypertensive activity [69].
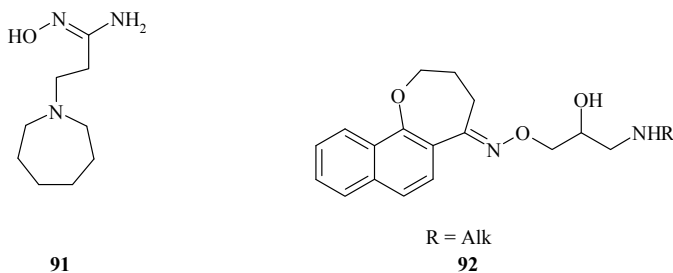
Azepine oximes have been also used in the treatment of diabetes of types 1 and 2 [70]. Beside this, the derivatives of azepan-3-oxime have been used as potentiators of 6-hydroxytryptophan. These compounds exhibit a wide range of activities on the blood circulatory system [71].

4.2. Action on central nervous system

At the end of the sixties the results of investigation of antidepressive activity of oxepine and thiepine oximes **93** have been described in patent [72]. Beside this, the high anticonvulsant activity of dibenzazepine oxime derivatives **94** has been presented [41]. Azepine oximes show also high activity on muscarinic receptors [73].
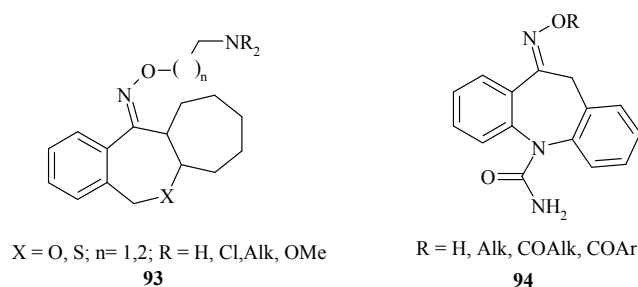
4.3. Analgesic activity

Oximes of azabicycloalkanones, including azepine derivatives, exhibit high analgesic activity [74].

4.4. Diuretic activity

Potassium salt of azepine oxime **95** was investigated as the diuretic agent [38].

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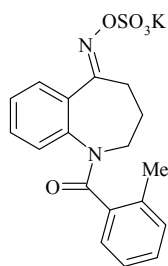
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4.5. Antiviral activity

Azepine oxime derivatives **96** and **97** have been tested as the antiviral agents against HIV-1 [75-77]. Among these oximes, the compound **98** possessed $IC_{50} = 0.06$ μM against HIV-1. Azepine oxime derivative **99** has been screened as the potent inhibitor of vesicular stomatitus virus G protein movement in the plasma membrane [78].

X = H, NH₂, CN, OH, Cl; R = H, Alk
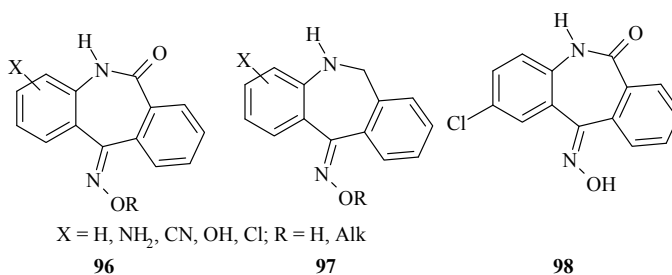
96   **97**   **98**
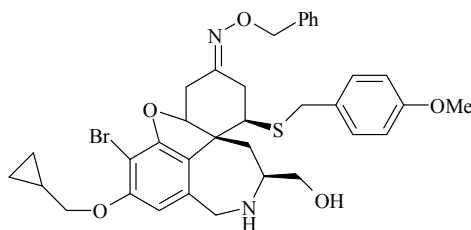
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4.6. Oximes of azepine and thiepine as fungicides, insecticides and nematocides

The derivatives of oximes of thiepine [31] and azepine [79] exhibit high fungicidal and insecticidal activity. Beside this, azepine oximes (for example, compound **100**) have been tested as nematocides [80, 81].
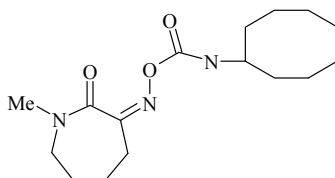
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VIENU HETEROATOMU SATUROŠU SEPIŅLOCEKĻU
HETEROCIKLISKO SAVIENOJUMU OKSĪMI

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

Apkopoti literatūras dati par azepāna, oksepāna un tiepāna oksīmu sintēzi un struktūru, kā arī dati par jaunu heterociklu sintēzi no septiņlocekļu heterociklisko savienojumu ar vienu heteroatomu oksīmiem. Darba pēdējā nodaļā apkopoti dati par septiņlocekļu heterociklisko savienojumu ar vienu heteroatomu oksīmu bioloģisko aktivitāti.

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