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SYNTHESIS, REACTIONS AND BIOLOGICAL ACTIVITY OF DERIVATIVES OF OXIMES OF SIX-MEMBERED OXYGEN HETEROCYCLES

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Abstract:
Literature data on the synthesis and structure of oximes of six-membered oxygen heterocycles with one heteroatom were reviewed. Synthesis of novel heterocycles from oximes of six-membered oxygen heterocycles was described. Biological activity of these oximes was also reviewed.

Keywords: oximes, six-membered oxygen heterocycles, pyranones, chromenones, xanthones, biological activity

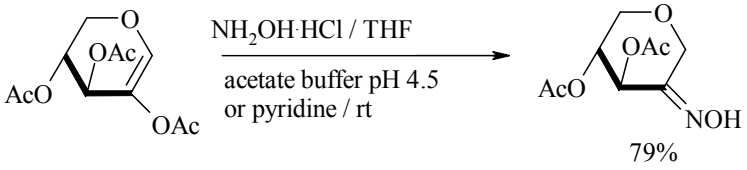
Introduction

The oximes of six-membered oxygen heterocycles with one heteroatom are widely used as intermediates in fine organic synthesis. In this review the principal methods for the production of aldoximes, ketoximes and amidoximes of six-membered oxygen heterocycles (such as, pyrans and their benzo analogues) and their derivatives are summarized. The principal methods for the investigation of the structure of the oximes of six-membered oxygen heterocycles are examined briefly with due regard to isomerism. The reactions and biological activity of the oximes of six-membered oxygen heterocycles will be examined in the last parts of the review. This work were carried out in continuation of serie of our reviews connected with synthesis, reactions and biological activity of heterocyclic oximes (such as, furan and thiophene oximes [Ia], indole and isatin oximes [Ib], pyridine oximes [Ic], pyrrole oximes [Id], quinoline oximes [Ie], oximes of five-membered heterocyclic compounds with two [If, Ig] and three [Ih, Ii] heteroatoms, oximes of six-membered heterocyclic compounds with two and three heteroatoms [Ij, Ik] and oximes of seven-membered heterocyclic compounds containing one [IIa] and two heteroatoms [IIb]).

1. SYNTHESIS OF OXIMES OF SIX-MEMBERED OXYGEN HETEROCYCLES

The classical method for the synthesis of oximes of six-membered oxygen heterocycles [III, IV] (such as, tetrahydropyran-4-one [V], 1-(tetrahydropyran-4-yl)ethanone [VI], 3-acetyl-3,4-dihydrochromen-2-one [VII] or 3-propionyl-chroman-2,4-dione [VIII] oximes) is based on the reaction of corresponding aldehydes or ketones with hydroxylamine hydrochloride in the systems EtOH / H_2O [IX], MeOH or EtOH / NaOAc [X-XIV], aq. EtOH / $NaHCO_3$ [XV, XVI], aq. EtOH /

K_2CO_3 [XVII, XVIII], MeOH / NaOMe [XIX], MeOH / Et_2NH [XX] or in the presence of pyridine in methanol or ethanol [XXI-XXV]. Oxime derived from o-xylal esters **2** was easily obtained from enol acetate **1** in the presence of hydroxylamine hydrochloride in acetate buffer (pH 4.5) or pyridine [XXVI]. Similarly, enamine **3** and thiones **5** in the presence of $NH_2OH \cdot HCl$ afforded corresponding oximes **4** [XXVII] and **6** [XXVIII, XXIX].



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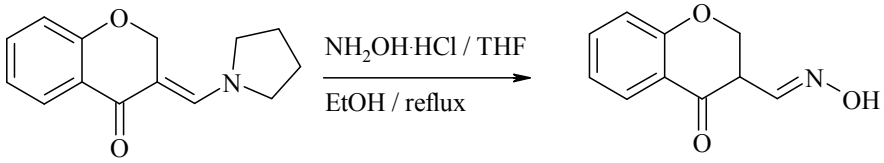

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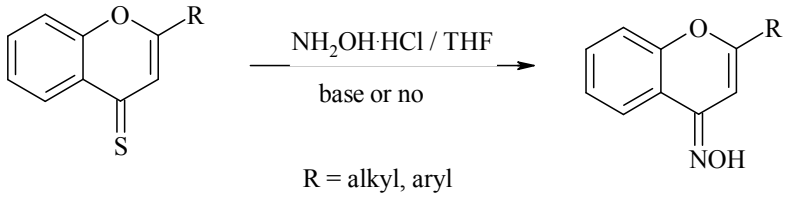
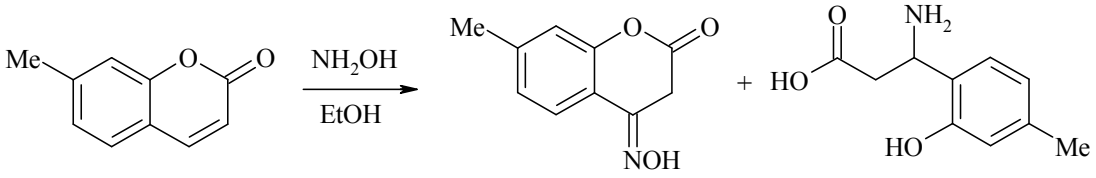


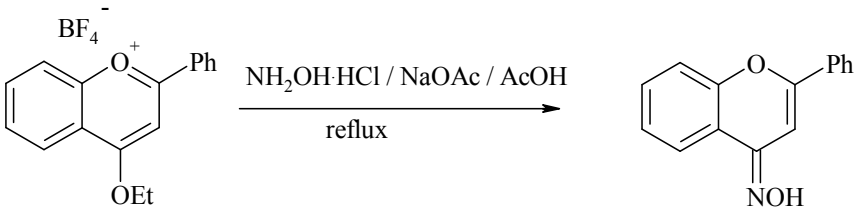
5 **6**

Treatment of 7-methylcoumarin (**7**) with hydroxylamine in ethanol afforded a mixture of 7-methyl-chroman-2,4-dione-4-oxime (**8**) and 3-amino-3-(2-hydroxy-4-methyl-phenyl)-propionic acid (**9**) [XXX].



7 **8** **9**

Some works were dedicated to synthesis of substituted chromen-4-one oximes from 4-hydroxy- [XXXI] or 4-ethoxypyrilium [XXXII] salts. Thus, interaction of 4-ethoxyflavylium tetrafluroborate (**10**) with $NH_2OH \cdot HCl$ in the presence of NaOAc in acetic acid afforded 2-phenyl-chromen-4-one oxime (**11**) in 81% yield [XXXII]. Treatment of sulfonium salt **12** with $NH_2OH \cdot HCl$ in the presence of pyridine leads to a mixture of sulfide **13** and oxime **14** (yield 38%) [XXXIII].



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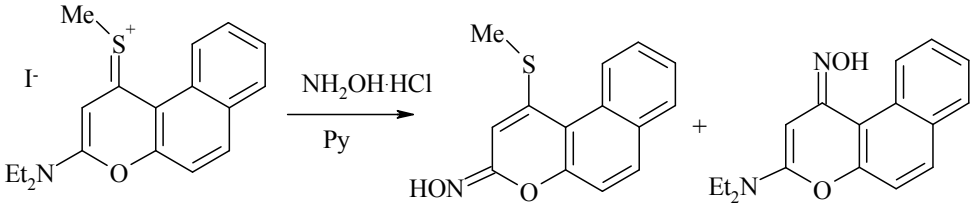
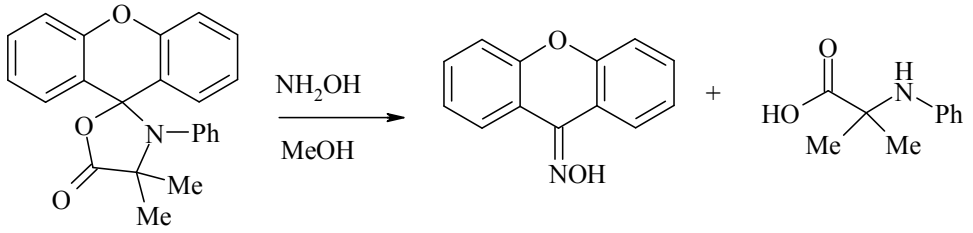


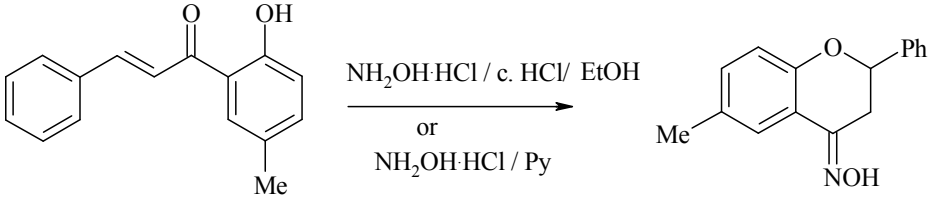
12 **13** **14**

Interestingly, that oxazolidine ring opening in 3'-phenyl-4',4'-dimethylxanthene-9-spiro-2'-oxazolidin-5'-one (**15**) in the presence of hydroxylamine in methanol at 60°C afforded xanthone oxime (**16**) and 2-methyl-2-phenylaminopropanoic acid (**17**) [XXXIV].

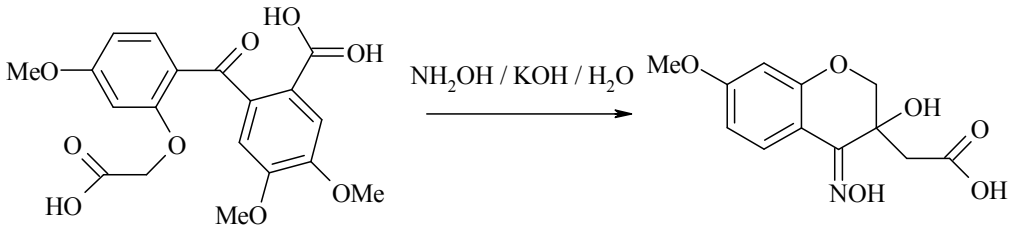


15 **16** **17**

Synthesis of oximes of six-membered oxygen heterocycles by cyclization aromatic ketone derivatives in the presence of hydroxylamine was described in three articles. Thus, treatment of chalcone derivative **18** in the system $NH_2OH \cdot HCl$ / conc. HCl or pyridine leads to 6-methyl-4-hydroxyiminoflavan **19** [XXXV]. Derivative of benzoic acid **20** in the system NH_2OH / KOH / H_2O afforded (3-hydroxy-4-hydroxyimino-7-methoxy-chroman-3-yl)-acetic acid (**21**) [XXXVI]. Beside this, tetrahydropyran-4-carbonitrile was readily transformed to corresponding pyran-4-amidoxime in the system $NH_2OH \cdot HCl$ / Na_2CO_3 / MeOH / H_2O at 70°C [XXXVII].

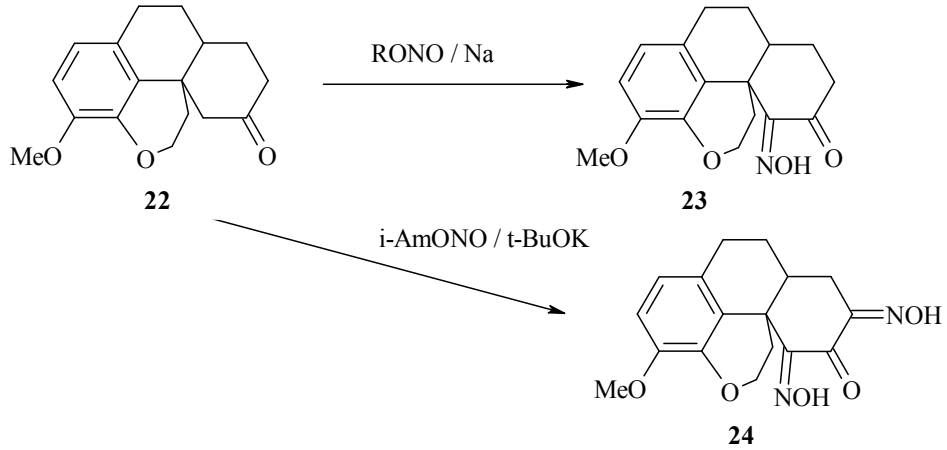


18 **19**

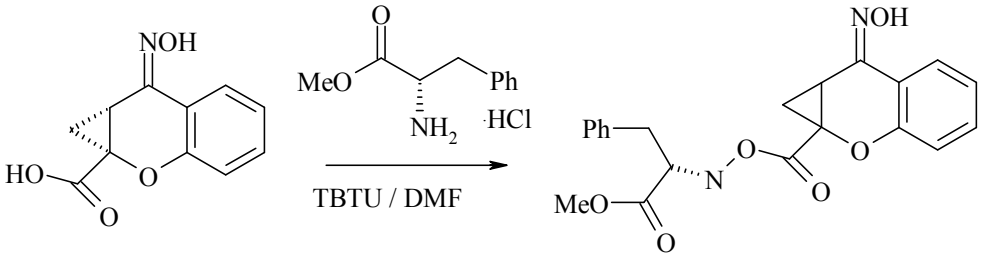


20 **21**

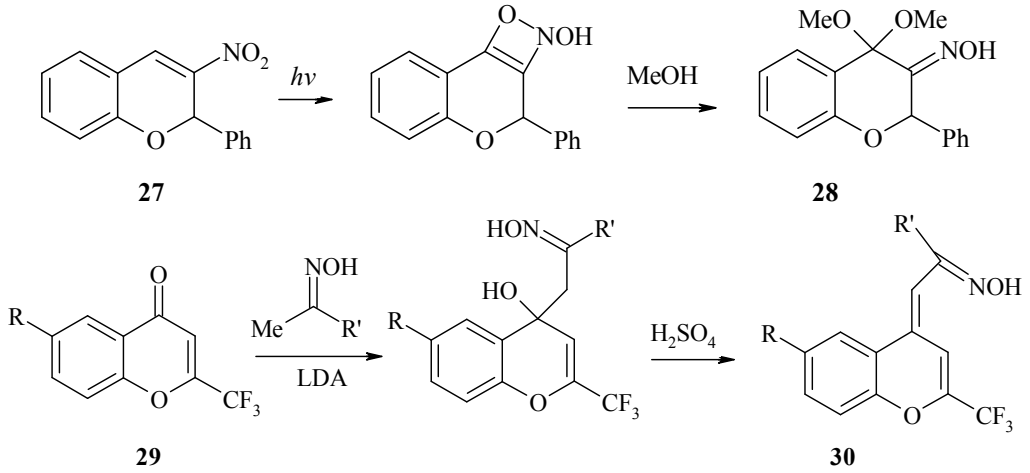
The second group of methods of synthesis of 6-methyl-chromano-3,4-dione-3-oxime [XXXVIII], 6-chloro-3-hydroxyimino-flavanone [XXXIX], 9-bromo-2-phenyl-pyrano[3,2-c]quinoline-3,4-dione-3-oxime [XL], 3,4-dihydro-3,5,6,7-tetramethylisocoumarin-4-one-1-oxime [XLI] and 2-benzo[1,3]dioxol-5-yl-5,7-dimethoxy-chroman-3,4-dione-3-oxime [XLII] is based on the reaction of corresponding heterocycles with nitrosating agents (for, example alkyl nitrites). Thus, treatment of polycycles (thelbenone and epi-thelbenone) **22** with alkyl nitrites in the presence of sodium leads to oximes **23** in low yield. However, using t-BuOK as base afforded dioximes **24** in 86-87 % yields [XVIII].



2,6-Anhydro-3-deoxy-4-C-hydroxyimino-D-mannonon-2-en-4-ulsonic acid was prepared by removing of acetyl protecting groups in the presence of LiOH / MeOH/ H_2O [XLIV]. Acetyl protecting groups also were removed in the presence of NH_3 / MeOH leading to (3S,4R,5R,6S)-6-[4-chloro-3-(4-ethoxy-benzyl)phenyl]-3,4,5-trihydro-tetrahydro-pyran-2-one oxime [XLV]. Oxime derivative bearing carboxylic acid group **25** was amidated using system L-phenylalanine methyl ester hydrochloride / O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) / i-Pr_2NEt / DMF without protection of oxime group and leading to amide **26** [XLVI].

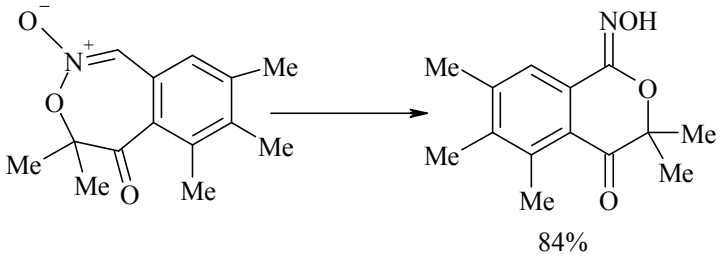


Synthesis of oxime derivatives of chromanone-3-one [XLVII] and pyrans [XLVIII, XLIX] were carried out from corresponding nitro compounds in the presence of reducing agents ($SnCl_2$ [XLVII, XLIX], Raney Ni / N_2H_4 or $NaBH_4$ / EtOH [XLVIII]). Nitro compound **27** undergo photoreaction in the presence of methanol leading to oxime **28** [L]. Finally, chromones **29** in the system LDA / R'CMe(NOH), after acidic workup, afforded oximes **30** [LI].



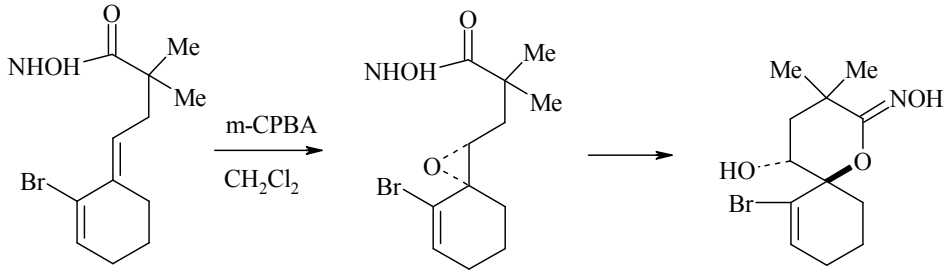
R = H, Me; R' = alkyl, Ph

Ring contraction of benzodiazepine-5(4H)-one derivative **31** to 3,4-dihydro-3,3,5,6,7-pentamethylisocoumarin-4-one 1-oxime **32** during a few days at ambient temperature was also described [XLI].

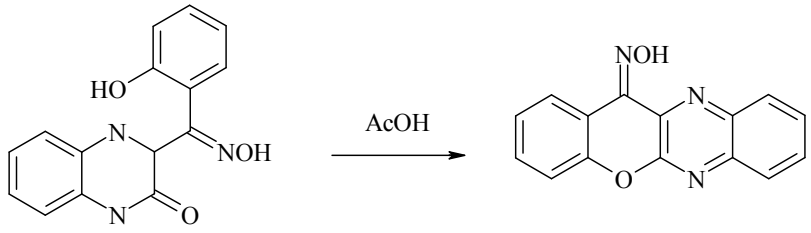


31 **32**

Large group of methods for the preparation of oximes of six-membered oxygen heterocycles is based on the cyclization reactions of different substrates. Thus, oxidative cyclization of hydroxamic acid **33** in the presence of m-CPBA / CH_2Cl_2 at room temperature afforded Z-lactone oxime **34** [LII]. Heating of (o-hydroxybenzoyl)-3-1H-quinoxalinone-2-oxime (**35**) in acetic acid leads to benzopyrano[1][2,3-b]quinoxalinone-12-oxime (**36**) in 50 % yield [LIII]. Recyclization of (2-dimethylamino-2H-chromen-2-yl)-(2-dimethylamino-2-methyl-chroman-4-yl)-methane in the presence of aqueous ethanolic solution of HCl and chloroform gives 1-(3,4-dihydro-[2,2']spirobichromen-4-yl)-propane-1,2-dione-1-oxime [XXV].

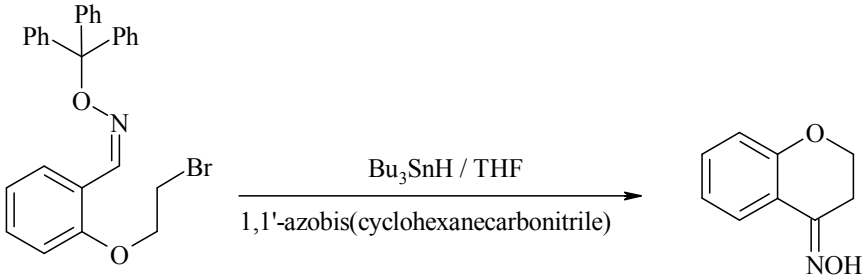


33 **34**



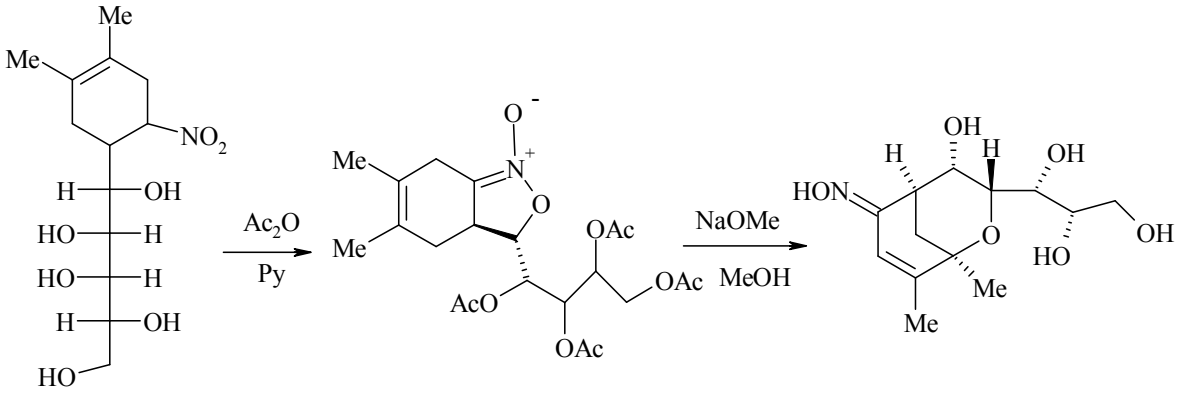
35 **36**

Radical cyclization of 2-(2-bromoethoxy)benzaldehyde O-(triphenylmethyl)oxime (**37**) in the system Bu_3SnH / i-Pr_2NEt / 1,1'-azobis(cyclohexanecarbonitrile) / THF afforded 2,3-dihydro-4H-1-benzopyran-4-one oxime (**38**) in 92 % yield [LIV].



37 **38**

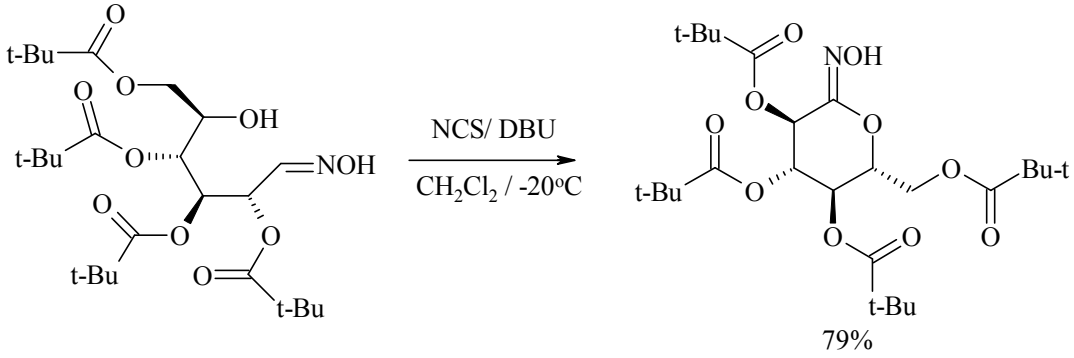
Multistep cyclization of (1S,2R,3S,4R)-1-(3,4-dimethyl-6-nitro-cyclohex-3-enyl)-pentane-1,2,3,4,5-pentaol (**39**) in the presence of Ac_2O / pyridine, followed by recyclization of an intermediate **40** in the presence of MeONa in MeOH, afforded oxime derivative of 2-oxa-bicyclo[3.3.1]non-7-en-6-one **40a** [LV].



39 **40** **40a**

Different oximes of six-membered oxygen heterocycles were obtained by cyclization of 5-hydroxypentanal oxime derivatives in the presence of MnO_2 / MeOH (then Na, NH_3) [LVI], activated MnO_2 / KH_2PO_4 / NaOH / H_2O [LVII], $NaIO_4$ / NaOAc / H_2O / EtOH [XIX], N-

chlorosuccinimide (NCS) / DBU [LVIII-LXIII] or 1-choro-2,5-pyrrolidinedione / DBU [LXIV]. For example, 2,3,4,6-tetra-O-pivaloyl-D-glucose oxime **42** was successfully prepared from 2,3,4,6-tetra-O-pivaloyl-D-gluconhydroximino-1,5-lactone **41** in the system NCS / DBU [LIX].

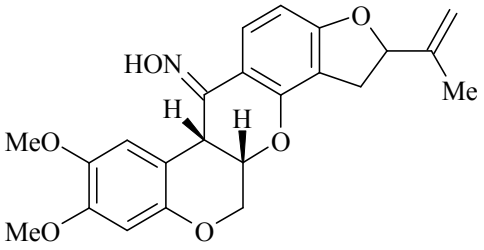


41 **42**

2. STRUCTURE

One of the most reliable method for determining of structure of the isomeric oximes of six-membered oxygen heterocycles with one heteroatom is NMR spectroscopy. The ^{1}H NMR spectra of oximes of pyranones [LXV], benzopyran-3(4H)-ones [XLVII], flavanones [Lb, LXVI,-LXVIII], benzopyrano[2,3-b]quinoxalinone [LIII] D-xylulose [XXVI] and derivatives of oximes of glucopyranose [LXI] have been investigated in details.

Structure of (5R,5R)-7-bromo-5-hydroxy-3,3-dimethyl-1-oxa-spiro[5,5]undec-7-en-2-one oxime [LII] and 1,2,12,12a-tetrahydro-8,9-dimethoxy-2-(1-methylethenyl)-[1]benzopyrano[3,4-b]furo[2,3-h][1]benzopyran-6(6H)-one oxime (**43**) [LXIX] was confirmed by X-ray crystallographic analysis.



43

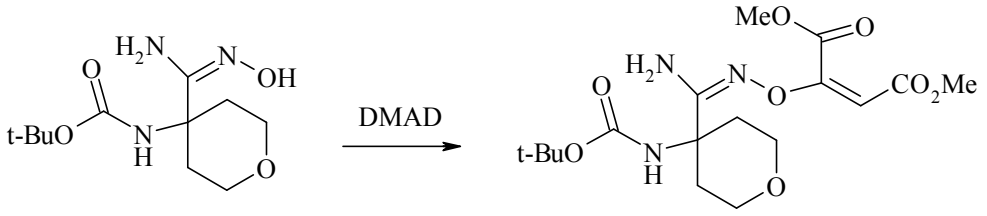
IR spectroscopy was also used to study the structure of 2,6-diaryltetrahydropyran-4-one O-benzyloximes [LXX], flavanone [Lb, LXVI] and benzopyrano[2,3-b]quinoxalinone [LIII] oximes, as well as, structure of derivatives of oximes of glucopyranose [LXI].

Interestingly, that E-isomer of (E)-2-deoxy-3,4,6-tri-O-pivaloyl-D-arabinohexonhydroximo-1,5-lactone in methylenechloride solution during 24h afforded Z-isomer [XVI]. Stereoselective synthesis of (E) and (Z)-2,3-dihydro-3(1,2,4-triazolyl)-4H-benzopyran-4-one oxime ethers were also described [LXXI]. Finally, enzymatic resolution of flavanone oximes using different lipases was recently presented [LXXII].

3. REACTIONS OF OXIMES OF SIX-MEMBERED OXYGEN HETEROCYCLES

3.1. Synthesis of O-alkyl derivatives of oximes

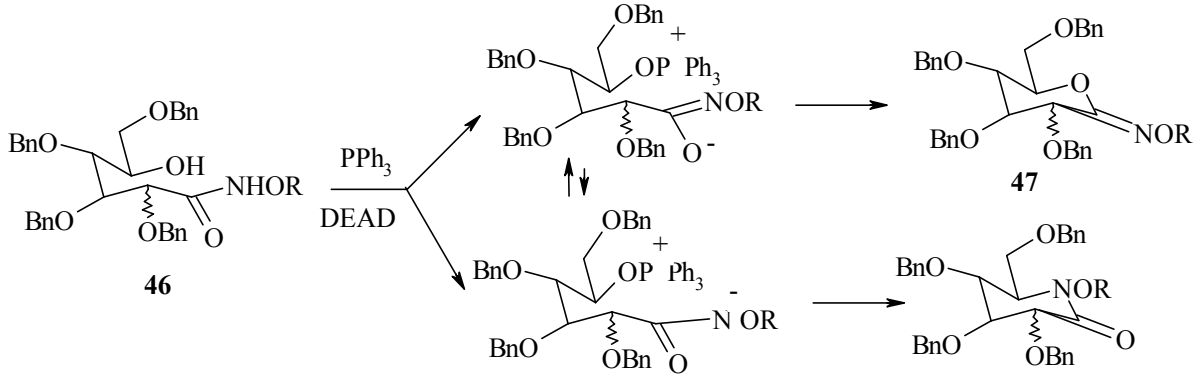
The principal method for the preparation of oxime O-ethers of six-membered oxygen heterocycles is alkylation of corresponding oximes with alkyl halides or dimethyl sulphate in the system K_2CO_3 / DMF [LXXI, LXXIII] or NaH / DMF [LXXIV] Activated hetaryl chlorides (4-chloropyrimidines) easily react with sodium salt of 2,2-dimethyltetrahydro-4-pyranone oxime without any transition metal catalyst affording corresponding O-ethers in yields up to 90% [LXXV]. Beside this, O-ethers of oximes of six-membered oxygen heterocycles are obtained from corresponding carbonyl compounds and O-alkyl derivatives of hydroxylamine in the MeOH [LXXVI] or in the system pyridinium p-toluenesulfonate (PPTS) / THF under microwave irradiation [LXXVII]. Reaction of oximes of substituted pyrans with dimethyl acetylenedicarboxylate (DMAD) in $CHCl_3$ [LXXVIIIa] or CH_2Cl_2 / Et_3N [LXXVIIIb] leads to oxime but-3-enedioic acid dimethyl ethers. Thus, treatment of amidoxime **44** with DMAD in $CHCl_3$ at 60°C leads selectively to oxime ether **45**.



44 **45**

Novel method for the synthesis of alkyl derivatives of sugar oximes by Au(I) catalyzed direct glycosylation of oximes by derivatives of 2-hex-1-ynylbenzoic acid tetrahydropyran-2-yl esters was also described [LXXIX].

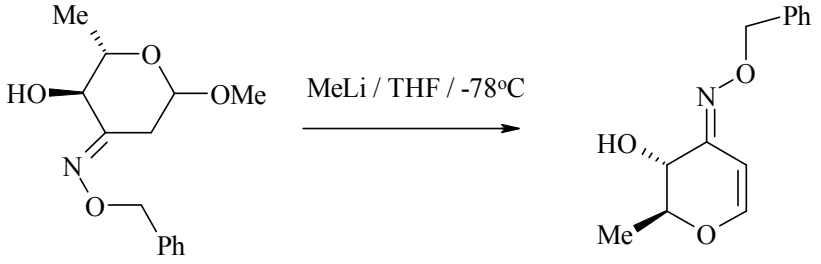
Synthesis of oxime O-alkyl ethers of different sugar derivatives from acyclic derivatives of 1N-benzyloxy-5-hydroxyhexanamide was presented in articles [LXXX-LXXXII]. Thus, treatment of N-alkoxyamines **46** with PPh_3 / diethyl azodicarboxylate (DEAD) / THF leads to a mixture oxime ethers **47** (yields up to 91 %) and tetrahydropyridones **48** (0-30%) [LXXX]. Proposed mechanism included deprotonation of NH of amides **46** by the reduced DEAD anion, followed by intramolecular alkylation, leading to products **47** and **48**.



R = alkyl

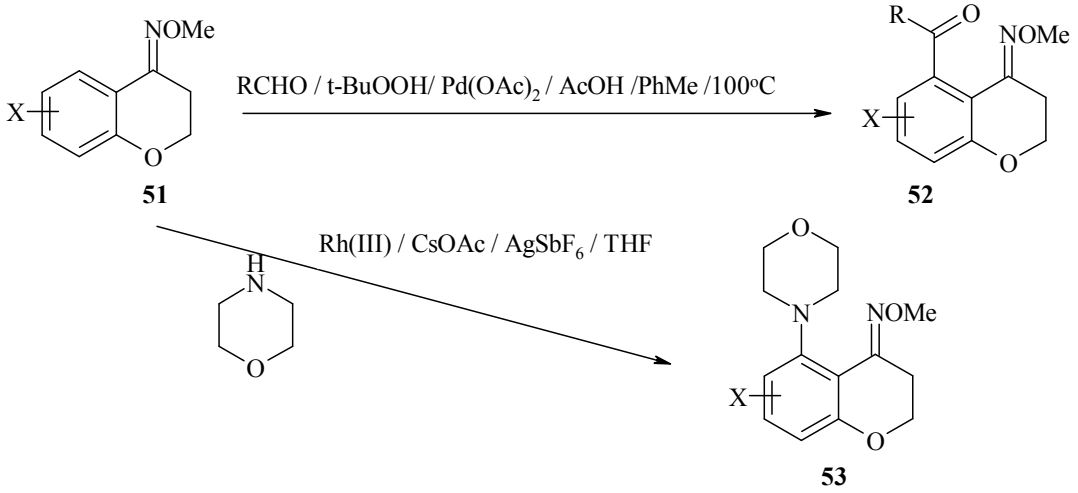
Some articles were dedicated to modification of oxime O-ethers of six-membered oxygen heterocycles. Thus, O-benzyloxime of methyl 2,6-dideoxy-α,β-L-erythrohexopyranosid-3-ulose

(**49**) in the presence of MeLi in THF at -78°C afforded O-benzyloxime of 1,5-anhydro-2,6-dideoxy-L-erythro-hex-1-en-3-ulose (**50**) in 51% yield [LXXXIII].



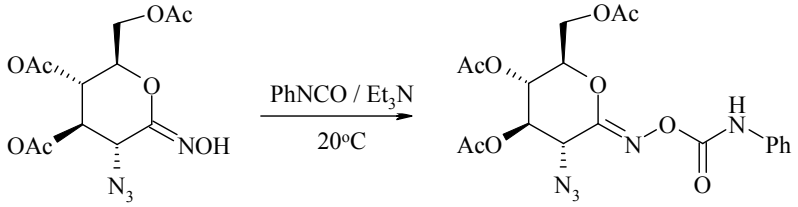
49 **50**

Palladium-catalyzed oxidative addition of aldehydes to oxime ethers were described in article [LXXXIV]. Thus, reaction 4-chromanone O-methyloximes (**51**) with aldehydes in the system t-BuOOH / $Pd(OAc)_2$ / AcOH / toluene afforded 5-acylated oxime ethers **52** [LXXXIV]. Rhodium(III)-catalyzed amination of C-H bonds in 4-chromanone O-methyloxime **51** in the system Rh(III) (for example, Cl(pentamethylcyclopentadieno)Rh(III)) / CsOAc / $AgSbF_6$ in THF at 60°C leads to amine **53** [LXXXV].



51 **52** **53**

Synthesis of acylated oximes of six-membered oxygen heterocycles from corresponding oximes was studied in the details in some works [XIX, LVII, LIX, LXXII, LXXXVI]. Oxime carbamates easily were prepared from oximes of six-membered oxygen heterocycles and alkyl or aryl isocyanates [LVIII, LXIII, LXXXVII]. For example, (Z)-O-(3,4,6-tri-O-acetyl-2-azido-2-deoxy-D-glucopyranosylidene)amino N-phenylcarbamate (**55**) was obtained in almost quantitative yield from oxime **54** and benzene isocyanate in the system Et_3N / diethylene oxide [LXIII].



91%

54 **55**

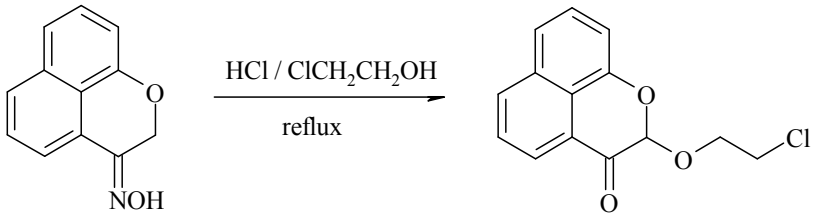
Selective deprotection of acetyl groups from O-(3'4',6,6'-penta-O-acetylchitobiosylidene)amino N-phenylcarbamate by NH_3 / MeOH leads selectively to O-(chitobiosylidene)amino N-phenylcarbamate. Oxime O-benzoyl group remain unprotected under these conditions [LVI].

Finally, silyl ether of chromanone oxime was successfully prepared in the system chromanone oxime/ t-butyldimethylchlorosilane / imidazole / CH_2Cl_2 at room temperature [LXXXVIII].

3.2. Transformation of oxime group in six-membered oxygen heterocycles

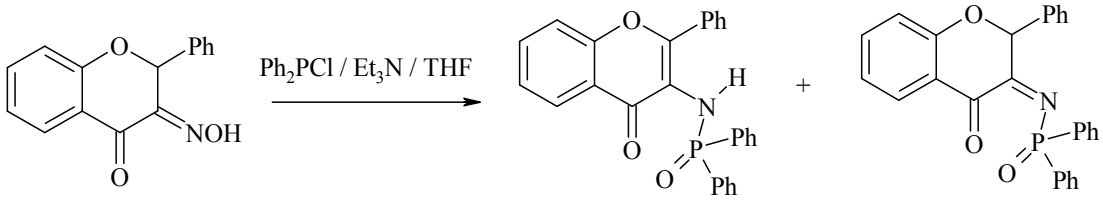
Hydrogenation of oximes (or O-ethers of oximes) of six-membered oxygen heterocycles to corresponding primary amines were easily realized in the systems 10% Pd/C / HBr / MeOH [LXXXIX], 10% Pd/C / MeOH / acid additives [XC], 10% Pd/C / NH_3 / MeOH [XCI], Raney nickel in EtOH or MeOH [XCII, XCIII]. Beside this, amine derivatives of six-membered oxygen heterocycles were obtained by the reduction of corresponding oximes in the systems $LiAlH_4$ / Et_2O / THF [XCIV], bis(2-methoxyethoxyaluminium hydride / PhMe [XCV], BH_3 / THF [XCVI], Zn / $MeCO_2Me$ [XCVII], Zn / NH_3 / NH_4OAc / H_2O [XCVIII] and $SnCl_2$ / AcOH [XCIX]. Reductive amidation of oximes of six-membered oxygen heterocycles to corresponding acetamides were described in some articles too [C, CI]. Synthesis of cyanochromones from corresponding aldoximes [CII] or aldehydes via aldoximes [CIII] was recently presented in literature.

Fragmentation of flavanone oximes and related compounds in the strongly acidic media (HCl or H_2SO_4) [CIV-CVI XLII] or in the presence of $Pb(OAc)_4$ in benzene [IV] afforded corresponding flavanones. Sometime synthesis of flavanones was accompanied by subsequent reactions. For example, treatment of naphtho[1,8-bc]pyran-3(2H)-one oxime (**56**) with HCl and ethylene chlorohydrin leads to 2-(2-chloro-ethoxy)-benzo[de]chromen-3-one (**57**) in 27% yield [CIV].



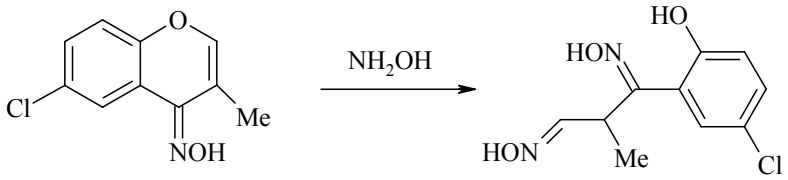
56 **57**

Treatment of 2-phenyl-3-hydroxyimino-4-chromanone (**58**) with diphenylphosphoryl chloride in the presence of Et_3N in THF at -45°C afforded mixture of tautomeric flavones **59** and **60** in overall yield 65% [CVII]. Reaction of xanthone oxime with N-phenylhydrazine gives xanthone phenylhydrazone [CVIII].

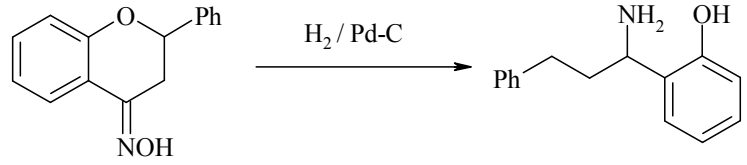


58 **59** **60**

Oximes of six-membered oxygen heterocycles readily undergo ring opening reaction leading to acyclic amine or oxime derivatives [LXXIII, CIX-CXII]. Thus, treatment of 6-chloro-3-methyl-chromen-4-one oxime (**61**) with hydroxylamine afforded dioxime **62** as single product [109]. Hydrogenation of 4-hydroxyiminoflavane (**63**) in the presence of Pd/C leads to 2-(1-amino-3-phenyl-propyl)-phenol (**64**) [CX].

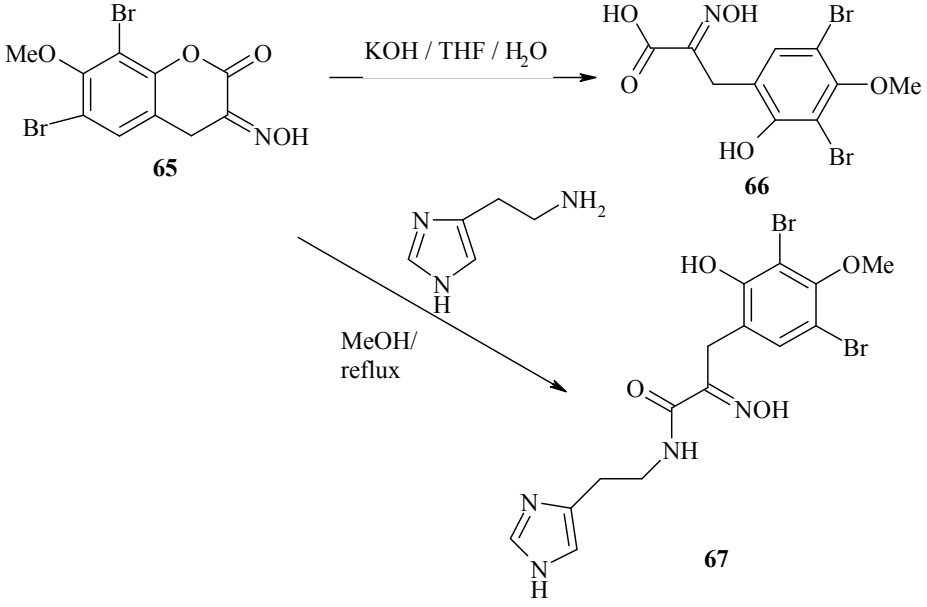


61 **62**

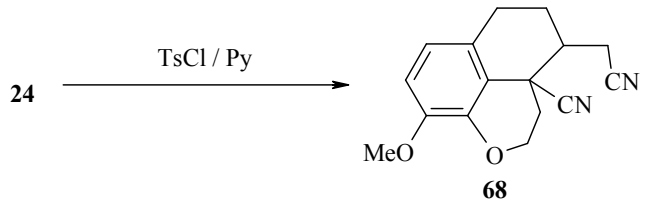


63 **64**

Ring opening of 5,8-dibromo-7-methoxy-3-hydroxyimino-3,4-dihydrocoumarin (**65**) with KOH in THF/ H_2O afforded oxime **66** in 98% yield [CXII]. However, reaction of oxime **65** with nucleophiles (for example, histamine) in MeOH leads to amide **67** in almost quantitative yield. Reaction of dioxime **24** with p-toluenesulfonyl chloride (TsCl) in pyridine gives dinitrile **68** in 30% yield [XLIV].



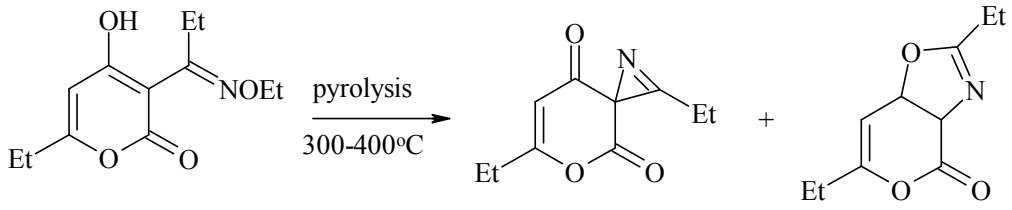
65 **66** **67**



68

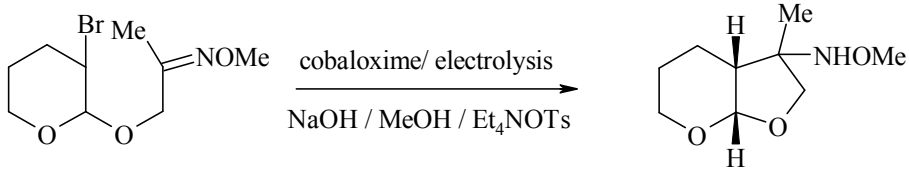
3.3. Synthesis of novel heterocyclic compounds from oximes of six-membered oxygen heterocycles

Recent advances in the synthesis of heterocyclic systems from oximes were described in reviews [CXIII, CXIV]. In this chapter specific reactions involving cyclization of oximes of six-membered oxygen heterocycles will be set out in details. Flash vacuum pyrolysis of oxime **69** at 300-400°C afforded a mixture of azirine **70** and oxazole **71** [CXV].



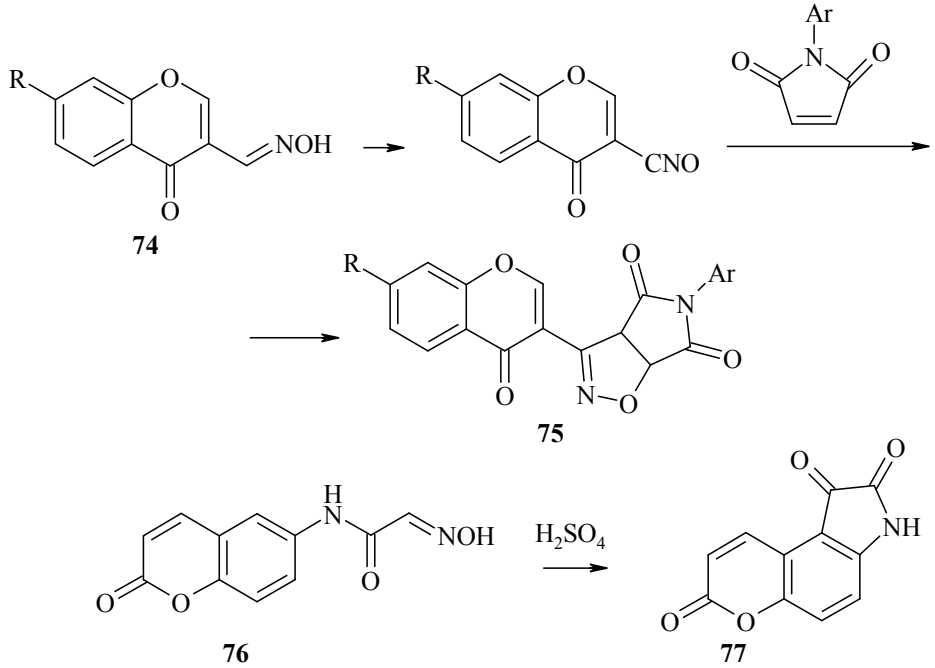
69 **70** **71**

Some works were dedicated to synthesis of five-membered heterocyclic compounds (such as furans [CXVI, CXVII], pyrroles [XLIX, CXVIII-CXX], imidazoles [CXXI, CXII], isoxazoles, oxazoles and oxadiazoles) from oximes of six-membered oxygen heterocycles. Thus, cobaloxime mediated radical cyclization of oxime ether **72** in the system NaOH / Et_4NOTs / MeOH under electrolysis conditions afforded tetrahydrofuran derivative **73** in 65% yield [CXVI].



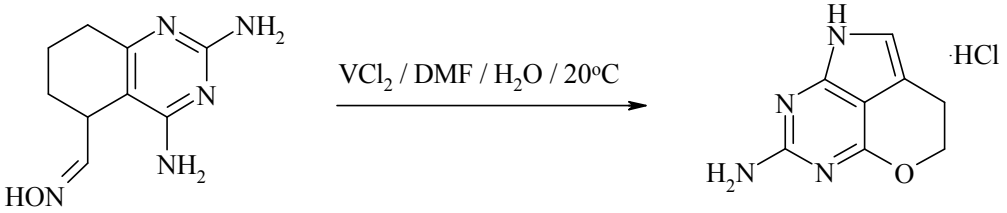
72 **73**

Addition of N-aryl maleimides to nitrile oxide, generated from oxime **74**, leads to addition products **75** [CXVIII]. Heating of oxime **76** in H_2SO_4 at 50°C (then at 90°C) afforded 1,2,7-trioxo-1,2,3,7-tetrahydropyrano[3,2-e]indole (**77**) in 70% yield. [CXIX, CXX].



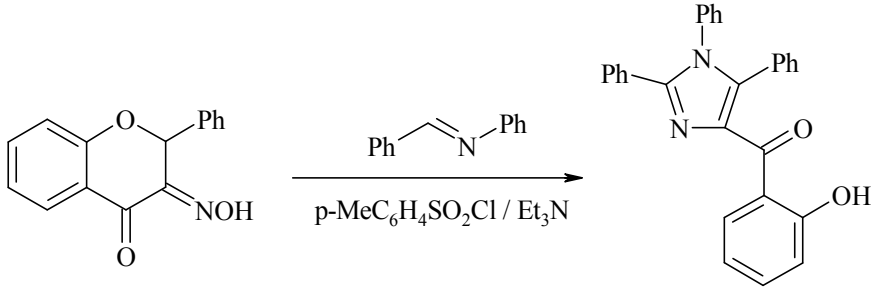
74 **75** **76** **77**

Novel pyrrole ring was also formed in the reaction of 2,4-diamino-6,7-dihydro-5H-pyrano[2,3-d]pyrimidine-5-carbaldehyde oxime (**78**) with aqueous solution of VCl_2 in DMF. Tricyclic product **79** was isolated in 20% yield [XLIX].



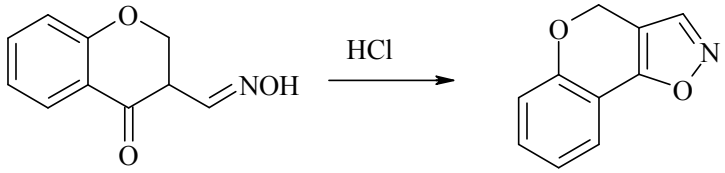
78 **79**

Two articles were dedicated to synthesis of imidazole derivatives from chromanone oxime derivatives. Thus, synthesis of 4,4-dimethyl-7-pentyl-9-benzyloxy-1H,4H-[1]benzopyrano[3,4-d]imidazole from 2,2-dimethyl-3-hydroxyimino-5-benzoyloxy-7-pentyl-4-chromanone in acidic (HCl) media was presented [CXXI]. Treatment of oxime **80** with N-phenyl-N-(phenylmethylidene)amine in the presence of p-toluenesulfonyl chloride / Et_3N / CH_2Cl_2 leads to polysubstituted imidazole **81**. Similarly oxime **80** in the system pyridine / p-toluenesulfonyl chloride afforded 2-(o-hydroxybenzoyl)-3-phenylimidazo[1,2-a]pyridine [CXXII].

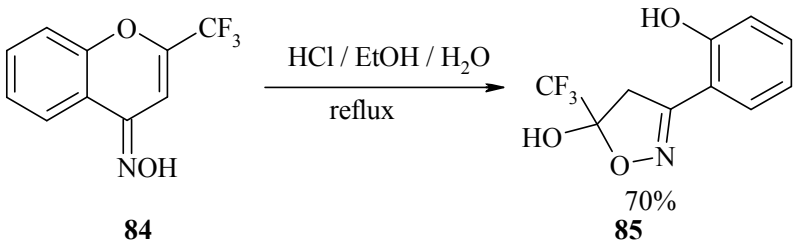


80 **81**

Synthesis of novel isoxazole ring by rearrangement of oximes of six-membered oxygen heterocycles (such as, pyranone or chromanone oximes) was widely presented in the literature [XXVII, XXIX, XXX, LI, CXXIII-CXXIX]. At first, 3-hydroxyiminomethylenechroman-4-one (**82**) in the presence of HCl afforded 4H-benzopyrano[1][3,4-d]isoxazole (**83**) [XXVII]. Interestingly, that 2-trifluoromethyl-4H-chromen-4-one oxime (**84**) in the similar conditions gives isoxazoline **85** in 70% yield [XXIX].

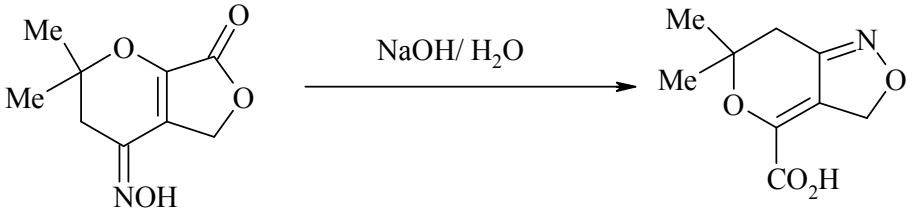


82 **83**



84 **85**

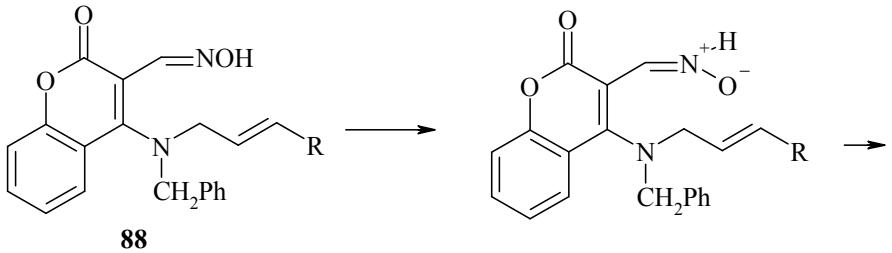
Pyran oxime derivative **86** undergo rearrangement to bicyclic isoxazoline **87** [CXXX]. Oxime **88** in different solvents (benzene, dioxane, MeCN, EtOH) afforded a mixture of two isoxazolines **89, 90** and diazepine **91** in yields up to 100% [CXXXI].



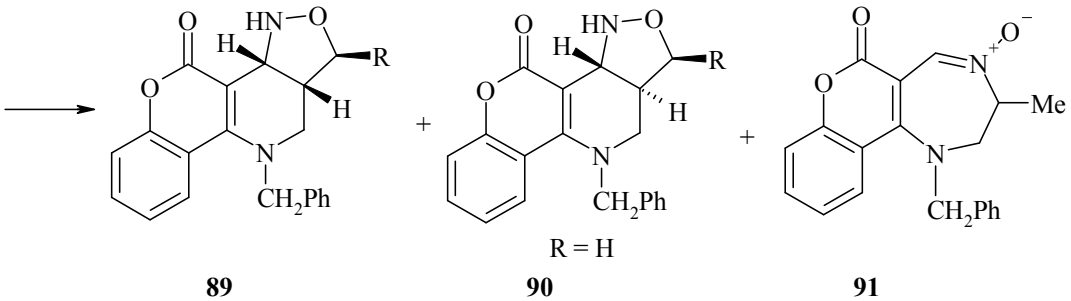
80%

86 **87**

Two works are connected with synthesis of oxazole derivatives from oximes of six-membered oxygen heterocycles. Thus, thermal rearrangement of oxime O-methyl ether **92** in the presence of phosphorous ylide afforded a mixture of oxazole **93** and oxazine **94** [CXXXII]. Reaction of pyran oxime ether **95** in refluxing o-dichlorobenzene afforded oxazole derivative **96** [LXXVIIIb].

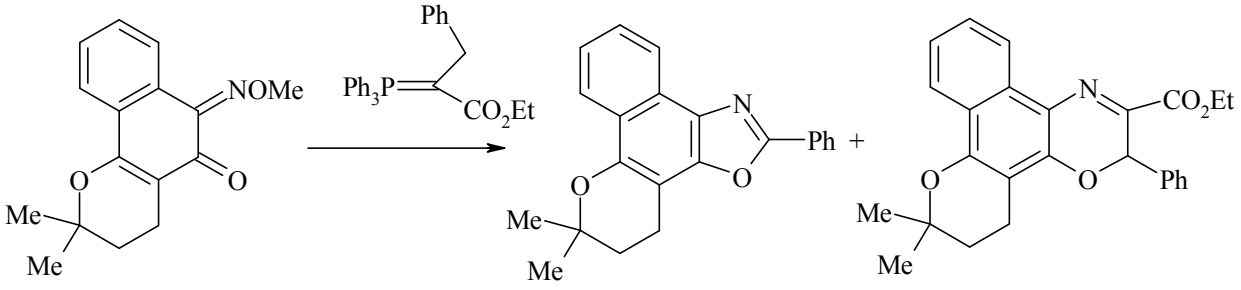


88

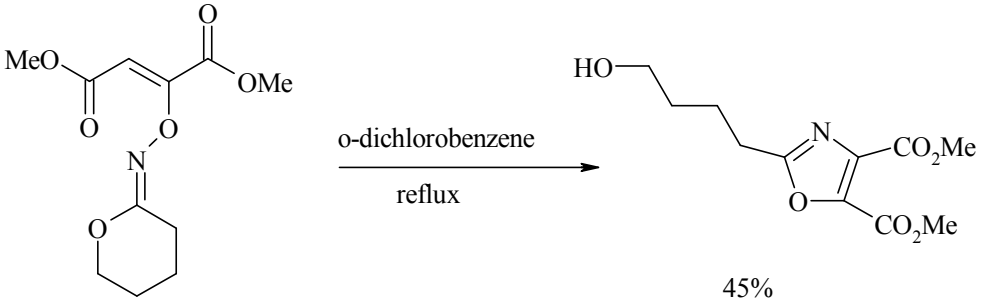


R = H

89 **90** **91**

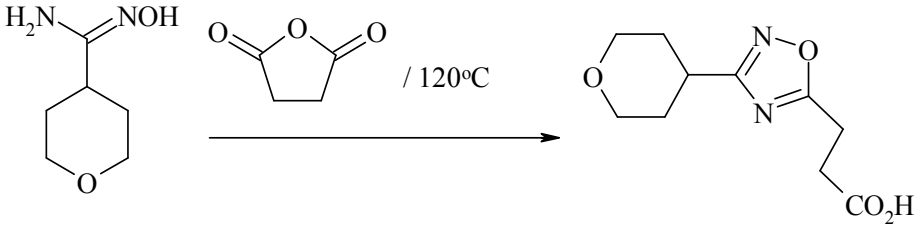


92 **93** **94**



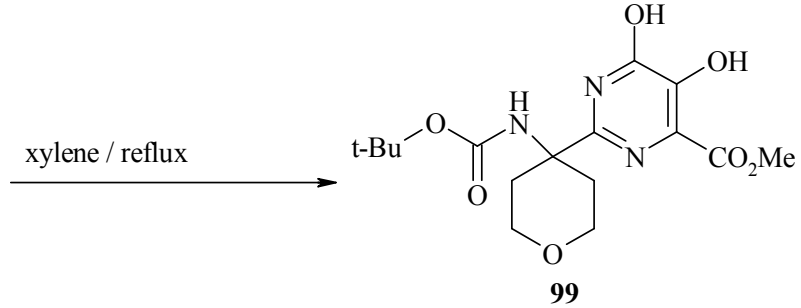
95 **96**

3-(3-Tetrahydro-2H-pyran-4-yl)-1,2,4-oxadiazol-5-yl)propionic acid (**98**) was prepared by addition of tetrahydrofuran-2,5-dione to amidoxime **97** at elevated temperature (120°C) [XXXVII].



97 **98**

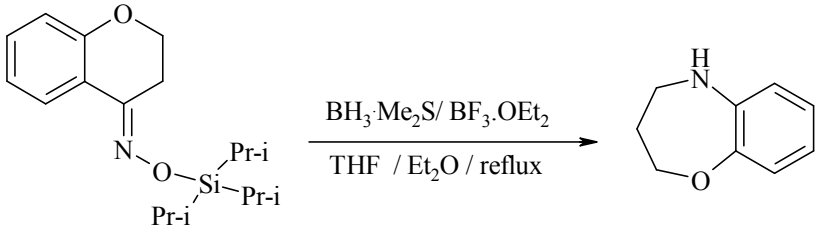
Some works were dedicated to synthesis of pyrimidine [LXXVIII, CXXXIII] and pyrazine [CXXI, CXXXIV] rings from oximes of six-membered oxygen heterocycles. Thus, heating of amidoxime O-ether **45** in xylene leads selectively to pyrimidine derivative **99** [LXXVIII].



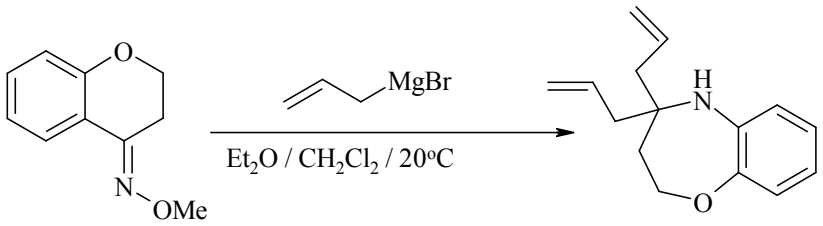
45 **99**

Beckmann type rearrangement of oximes of six-membered oxygen heterocycles to corresponding oxazepinones or oxazepines were successfully realized in the presence of PPA [CXXXV-CXXXVII], PCl_5 [CXXXVIII], H_2SO_4 [XLVIII], $LiAlH_4$ [CXXXIX] or diisobutylaluminium hydride [XXI, CXL]. Pyranone oxime tosylate in acidic conditions (HCl) also leads to oxazepinone [CXLI]. 4-Chromanone O-triisopropylsilyloxime (**100**) in the system $BF_3 \cdot OEt_2$ / $BH_3 \cdot Me_2S$ / THF / Et_2O at reflux leads to 2,3,4,5-tetrahydrobenzo[b][1,5]oxazepine (**101**) in 61 % yield [LXXXVIII]. Reaction of oxime O-

methyl ether **102** with an excess of allyl magnesium bromide in CH_2Cl_2 / Et_2O afforded diallylated oxazepine **103** in almost quantitative yield [CXLII].



100 **101**

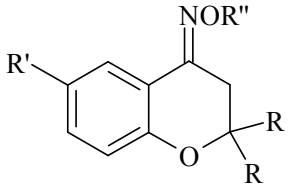


102 **103**

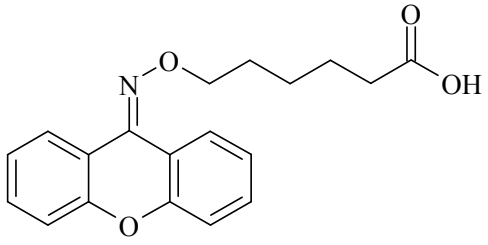
4. BIOLOGICAL ACTIVITY OF OXIMES OF SIX-MEMBERED OXYGEN HETEROCYCLES

4.1. The action on the cardiovascular system

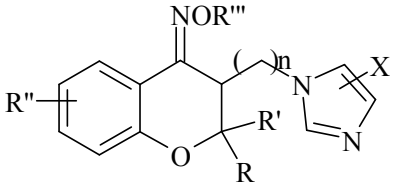
Benzopyranone oximes **104** exhibit the vasodilation activity [CXLIII]. Some works were dedicated to investigation of oximes of six-membered oxygen heterocycles as agents preventing or treatment of conditions connected with high concentration of cholesterol in the blood [CXLIV-CXLVI]. Xanthone oxime derivatives (for example, oxime ether **105)** were tested as aldose reductase inhibitors [CXLVII]. Oxime derivatives of 2-oxabicyclo[2,2,2]octane exhibit platelet antiaggregating activity [CXLVIII]. Finally, oximes **106** were tested as thromboxane A_1 antagonists. These compounds also showed antiplatelet activity [CXLIX].



104



105

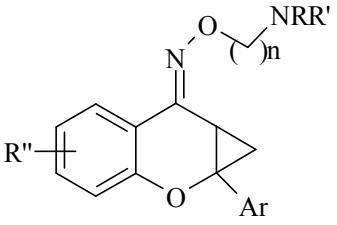


n = 0-4

106

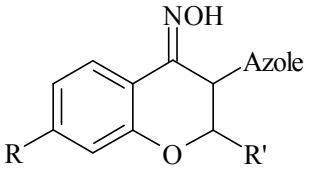
4.2. Action on central nervous system

In the 1995 CNS activity of oxime ethers of chromanone **107** was presented in the patent [CL]. 6-Fluoro-flavonoxime also was tested as potential CNS agent [CLI]. Beside this, high anticonvulsant activity of oxime derivatives of azolylchromanones **108** was described [CLII, CLIII]. 7-(Hydroxyimino)cyclopropa[b]chromanen-1a-carboxylates and related compounds showed high metabotropic glutamate receptor activity [XLVI, CLIV]. Oximes of six-membered oxygen heterocycles also exhibit allosteric modulator [CLV] and cannabinoid 1 receptor inverse agonist [XCVII] activities.



n =2-5; Ar = aryl

107

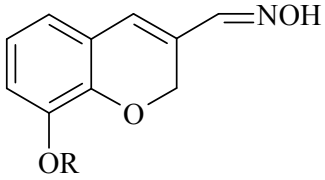


R, R' = H, Cl; Azole = 1-imidazolyl; 1-4-triazolyl

108

4.3. 5-Lipoxygenase inhibitors

Oximes of six-membered oxygen heterocycles (such as, oxime derivatives **109**) were tested as 5-lipoxygenase inhibitors [CLVI-CLIX]. These compounds exhibit a wide range of activity on the CNS, as well as, were used in the treatment of asthma, arthritis, psoriasis and allergy.

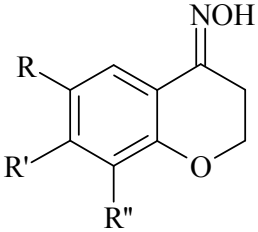


R = Ph, CH_2Ph

109

4.4. Diuretic activity

4-Chromanone oximes **110** were investigated as diuretic agent [CLX].

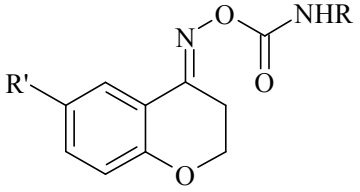


R= H, F, Cl; R' = Cl, Br; R" = H, Cl

110

4.5. Antisecretory activity

O-(Aminocarbonyl)oximes of benzopyranones (for oxample, compounds **111**) were studied as antisecretory agents (especially, gastric antisecretory agents) [LXXXVII, CLXI].

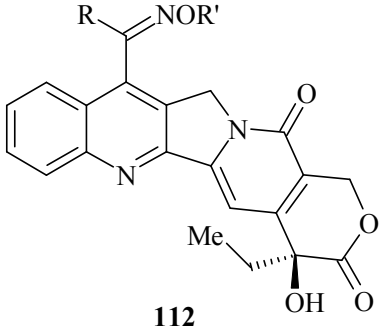


R = H, Me; R' = H, OMe

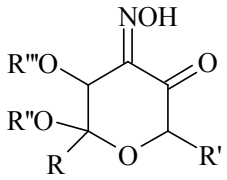
111

4.6. Anticancer, antiviral and antibacterial activities

Camptothecin **112** [CLXII, CLXIII], pyrone **113** [CLXIV] and isoflavone **114** [CLXV] oxime derivatives exhibit high anticancer activity**.** Beside this, cytotoxic and antiplatelet activities of flavone, isoflavone and xanthone oximes or oxime O-ethers were recently presented [CLXVI, CLXVII]. Chromanone oximes were proposed to possess antiviral activity against HIV-1 [CLXVIII]. Macrocyclic derivatives of xanthone oxime O-ethers were screened as potent inhibitor of hepatitis C serine protease inhibitors [CLXIX].

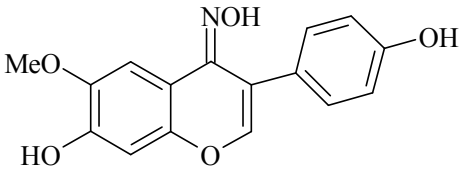


112



R, R'', R''' = alkyl;
R' = alkyl, aryl

113

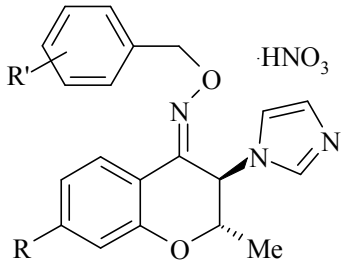


114

2,6-Diaryltetrahydropyran-4-one O-benzyloximes exhibit high antibacterial activity [LXX].

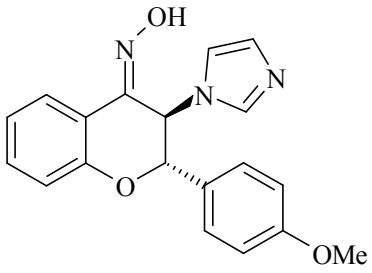
4.7. Oximes of six-membered oxygen heterocycles as fungicides, insecticides and herbicides

Derivatives of oximes of (Z)-3-azolyl-2-methylchromanone **115** [CLXX] and benzopyranone **116** [CLXXI], **117** [CLXXII] exhibit high fungicidal activity. Rotenone oxime O-ethers show high insecticidal activity [CLXXIII]. Beside this, different oximes of six-membered oxygen heterocycles were tested as herbicides [CLXXIV-CLXXVIII].

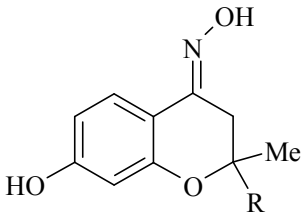


R = H, Cl; R' = Cl, F, Cl

115



116



R = alkyl

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4.8. Other activities of oximes of six-membered oxygen heterocycles

Chromanone oxime derivatives were used as inhibitors of protein kinases [CLXXIX], immunosuppressants [CLXXX] and tyrosylprotein sulfotransferase inhibitors [CLXXXI]. 1,5-Anhydro-3-(or 6-)-O-lauroyl-D-glucose oximes and related compounds were used as antioxidants and/or emulsifiers [CLXXXII]. Synthesis of model chymutin-like compounds [CLXXXIII] and chorismate mutase inhibitors [CLXXXIV], containing oximes of six-membered oxygen heterocycles, were described. Beside this, oximes of six-membered oxygen heterocycles were incorporated in the structure of derivatives of aflatoxin-B_1 [CLXXXV] and natural compounds isolated from *Moringa oleifera* [CLXXXVI].

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