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INDOLE AND ISATIN OXIMES: SYNTHESIS, REACTIONS, AND BIOLOGICAL ACTIVITY*. (REVIEW)

E. Abele, R. Abele, O. Dzenitis, and E. Lukevics

Data on methods for the production of isatin and indole aldoximes, ketoximes, and amidoximes and their reactions are reviewed. Individual syntheses of new heterocycles from indole and isatin oximes are discussed. The principal results from investigation of the biological activity of derivatives of the oximes are also presented.

Keywords: isatin, indole, oximes, biological activity.

Indole and isatin oximes are widely used as intermediates in fine organic synthesis. In the present article the methods for the production of isatin and indole oximes and their reactions are discussed. Methods for the synthesis of new heterocyclic systems from derivatives of these oximes are considered under a separate heading. The principal methods used to investigate the structure of isatin and indole oximes with regard to their isomerism are also briefly examined. The principal methods for the selective production of the *E*- or *Z*-isomers and their O-ethers are also presented. The last chapter contains results from investigation of the biological activity of derivatives of indole and isatin oximes.

1. SYNTHESIS AND STRUCTURE OF INDOLE AND ISATIN OXIMES

1.1. Synthesis of Indole Oximes

The classic method for the synthesis of indole oximes is based on the reaction of an aldehyde or ketone with hydroxylamine hydrochloride in the presence of 10% aqueous NaOH [1], NaOH–EtOH [2], NaOAc–*n*-PrOH–H_2O [3], NaOAc–dioxane [4], Na_2CO_3–H_2O [5], or Na_2CO_3–EtOH–H_2O [6].

By a modification of this method it is possible to obtain the mono- or dioximes of 1,2-bis(3-indolyl)glyoxal (**1**). Thus, the reaction of the diketone **1** with one equivalent of $NH_2OH·HCl$ in the presence of pyridine in ethanol leads to a mixture of the *anti*-monoxime **2** (yield 54%) and the *syn*-monoxime **3** (yield 38%). The use of a 10-fold excess of hydroxylamine hydrochloride leads to 1,2-bis(3-indolyl)-1,2-bis(hydroxyimino)ethane (**4**) selectively with a yield of 71%. The compounds exhibited high antimicrobial activity [7].

* Dedicated to Prof. S. Gronowitz on his 75th birthday.

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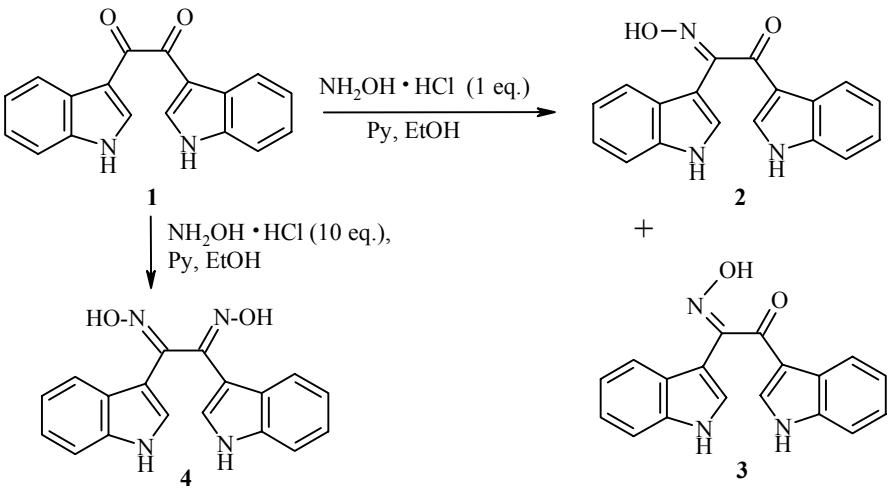
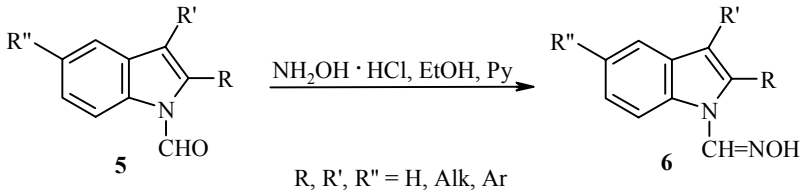
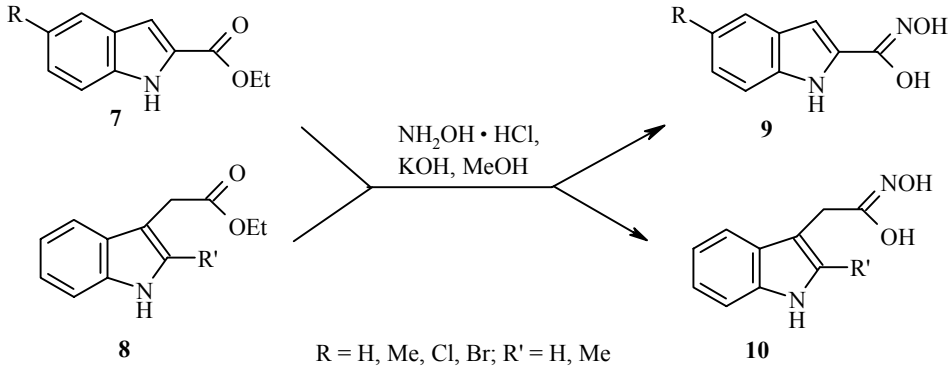


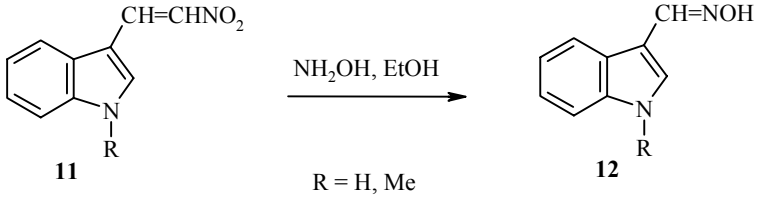
N-Formylindoles **5** also form the respective oximes **6** in the hydroxylamine hydrochloride–ethanol–pyridine system. However, the yields of the products in this case are low (2-14%) [8].



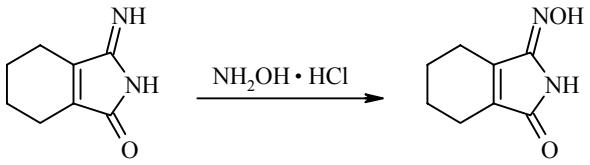
The indolylhydroxamic acids **9** and **10** were obtained successfully from the corresponding esters of indolecarboxylic acids **7** and **8** in reaction with hydroxylamine hydrochloride in the presence of potassium hydroxide in methanol [9].



The reaction of 3-nitrovinylindoles **11** with hydroxylamine in ethanol leads to the aldoximes **12** with yields of 35-61%. The products **12** may be formed through dissociation of the intermediate products from nucleophilic addition of hydroxylamine to nitrovinylindole [10].

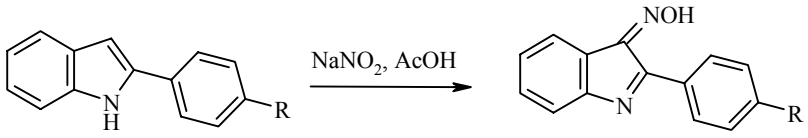


Isoindole oximes have been produced successfully from the corresponding imines. For example, the keto imine **13** and hydroxylamine hydrochloride in cellosolve form Δ^8-hexahydro-1-hydroxyimino-3-oxoisoindole (**14**) as the only product [11].



13 **14**

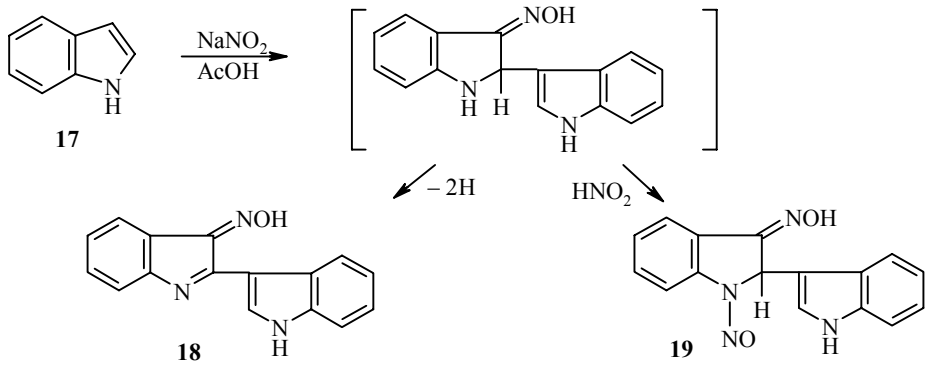
A series of methods for the synthesis of indole oximes have been based on the nitrosation of indole derivatives. For example, 2-arylindoles **15** and sodium nitrite in acetic acid give the oximes **16** with yields of up to 100% [12, 13]. Similar products were also obtained from 2,3-unsubstituted indoles [14]. Ethyl nitrite [15], butyl nitrite [16], and isonitrosoacetone [17] have also been used as nitrosating agents in the synthesis of indole oximes.



15 **16**

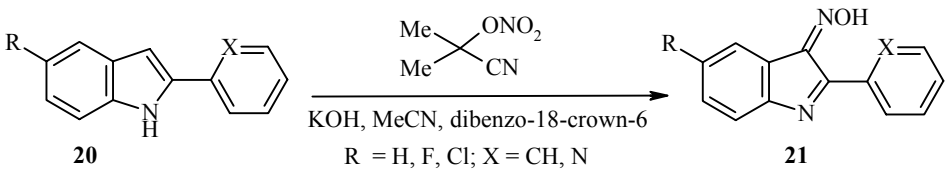
R = H, Bn, CH_2Bn

The nitrosation of indole **17** and benzindoles in the presence of sodium nitrite and acetic acid has been investigated by several authors [18-20]. It was shown that the reaction with indole leads to the formation of two products **18** and **19** in a ratio that depends on the reaction temperature. Thus, compound **18** is mainly formed at room temperature, while compound **19** is formed at 10°C.



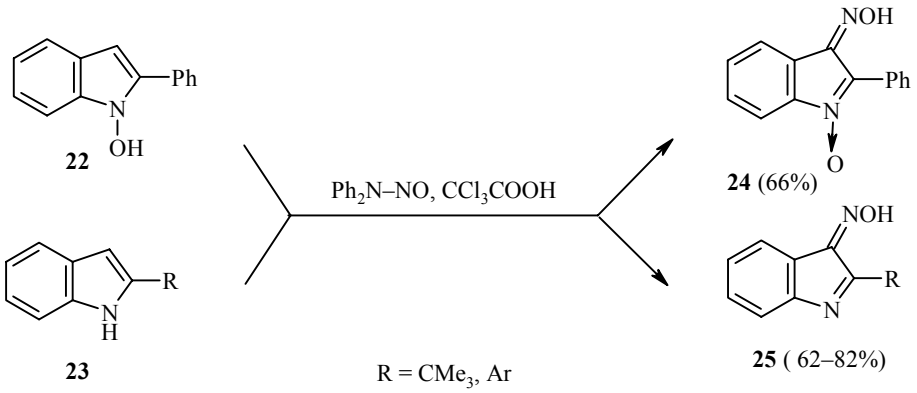
17 **18** **19**

A phase-transfer synthesis of the 3-hydroxyimino derivatives **21** from 2-arylindoles **20** was realized successfully in a system containing 2-cyano-2-propyl nitrate, potassium hydroxide, dibenzo-18-crown-6, and acetonitrile. Under these conditions the oximes **21** were isolated as the main products with yields of 54-72% [21].

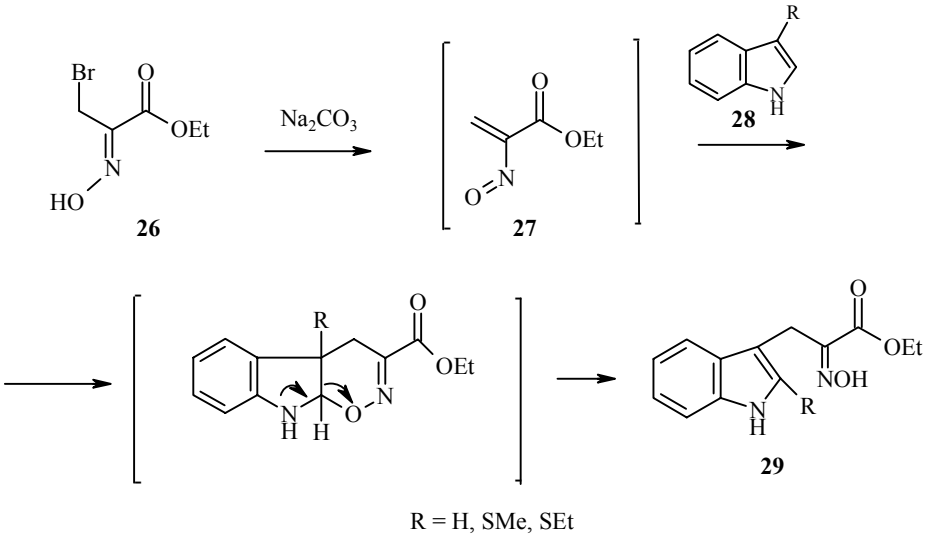


20 R = H, F, Cl; X = CH, N **21**

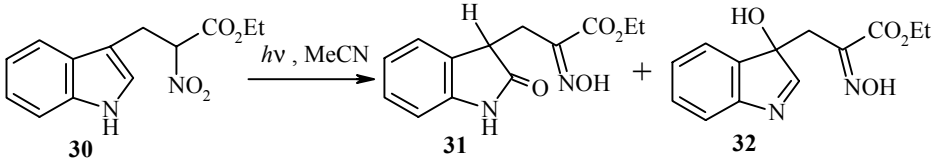
The successful use of N-nitrosodiphenylamine as nitrosating agent should also be mentioned [22]. In the $Ph_2NNO – CCl_3COOH – CH_2Cl_2$ system the indoles **22** and **23** are easily converted into the corresponding oximes **24** or **25** [23].

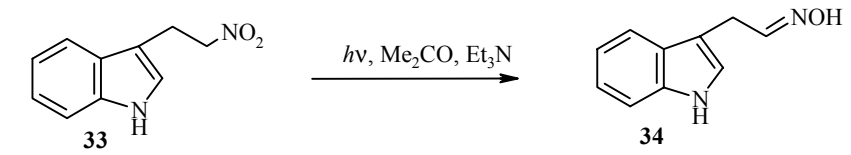


Cycloaddition of the nitrosoalkene **27**, obtained from the oxime **26** and sodium carbonate, leads to the selective formation of indole oximes **29** with yields of up to 74%. In the case of 3-alkylthioindoles migration of the alkylthio group to position 2 is observed [24-27].

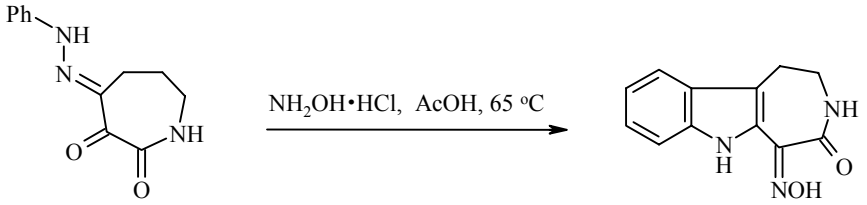


Indole oximes were successfully produced by the photochemical reaction of the nitro derivatives in acetone or acetonitrile. For example, ethyl α-nitro-β-(3-indolyl)propionate (**30**) gives a mixture of the two oximes **31** (yield 50%) and **32** (traces) [28]. Exposure of 3-(2-nitropropyl)indole **33** to a mercury lamp (500 W) in acetone leads to the formation of the oxime **34** with a yield of 41% [29].

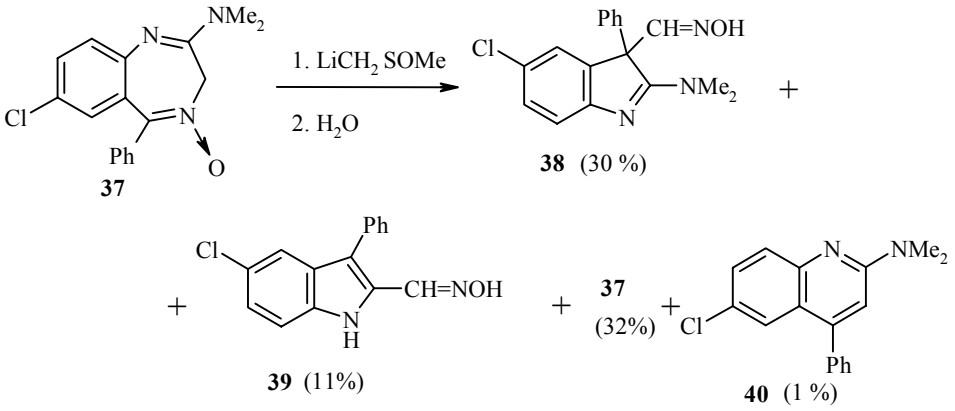




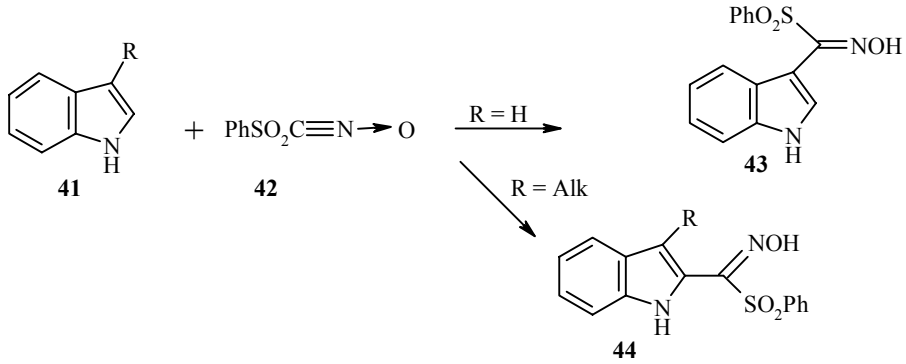
An interesting method was developed for the synthesis of 1,2-dioxo-1H,2,3,4,5-tetrahydroazepino-[4,4-*b*]indole (**36**) from the hydrazone **35** in reaction with hydroxylamine hydrochloride and acetic acid [30].



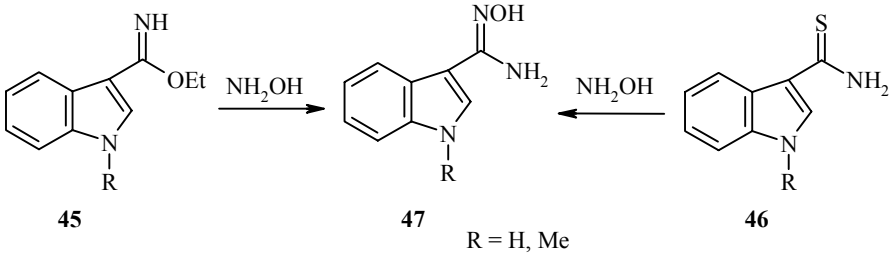
Derivatives of the indole oximes **38** and **39** can also be obtained by the rearrangement of 7-chloro-2-dimethylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (**37**) in the presence of lithiodimethyl sulfoxide. In addition to the oximes **38** and **39**, the reaction mixture contained the regenerated initial compound **37** and traces of the quinoline **40** [31].



The reaction of derivatives of indole **41** with phenylsulfonylnitrile oxide (**42**) gives the sulfonyloximes **43** or **44** as main products with yields of 11-82%. The oximes are formed through isoxazole intermediates [32].



Indole amidoximes were obtained by two methods. The indole imidic esters **45** and hydroxylamine hydrochloride in the presence of sodium carbonate in a water–dioxane mixture gave the indole amidoximes **47** with yields of 75-80% [33, 34]. The amidoximes **47** were also obtained successfully from the thioamides of 3-indolecarboxylic acids **46** in the $NH_2OH{\cdot}HCl - K_2CO_3 - H_2O$ – EtOH system or dioxane. However, the yields under these conditions were not greater than 30-32% [34].

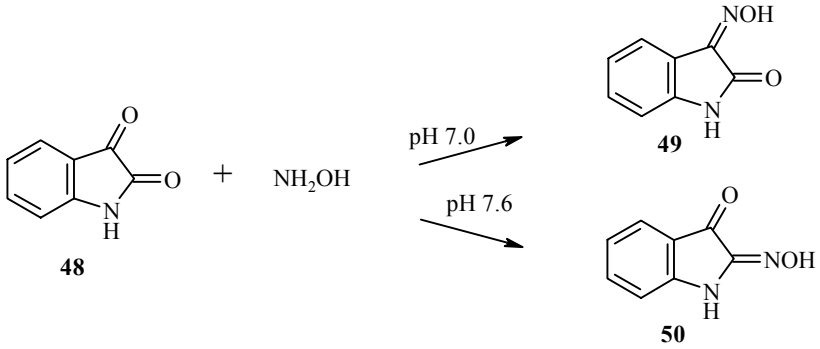


45 **47** **46**

R = H, Me

1.2. The Synthesis of Isatin Oximes

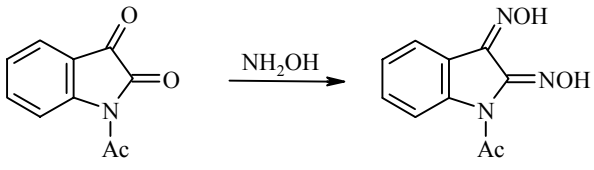
The main group of methods for the synthesis of isatin oximes is based on the reaction of isatin derivatives and hydroxylamine hydrochloride in water or alcohol [35-38]. An interesting method for the synthesis of isatin oximes was described in [39]. It was found that isatin (**48**) in the $NH_2OH–Na_2CO_3–EtOH–H_2O$ system at pH 7.0 gives isatin 3-oxime (**49**) selectively. However, if the pH is increased to 7.6 the formation of isatin 2-oxime (**50**) is observed.



48 **49** **50**

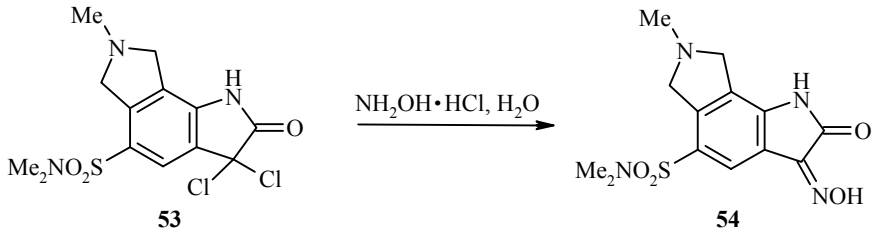
Isatin 2-oxime was also obtained by the reaction of isatin O-methyl ether with hydroxylamine [40].

N-Acetylisatin dioxime (**52**) is formed readily by the reaction of the N-acetylisatin (**51**) with hydroxylamine [41].



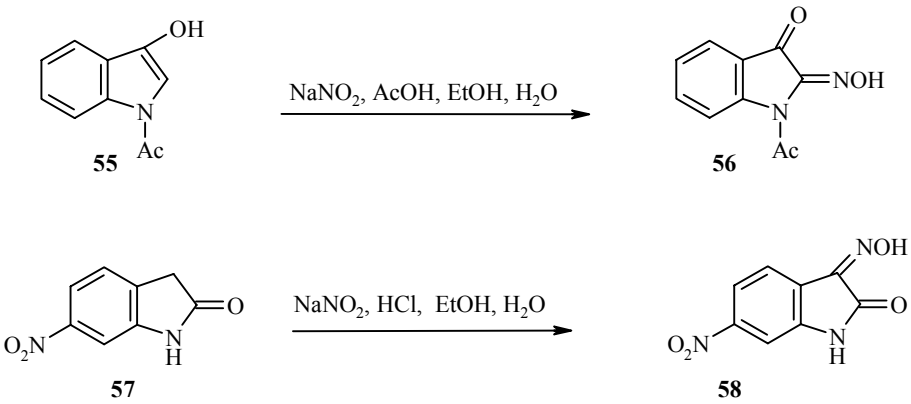
51 **52**

An interesting method was recently described for the synthesis of the dimethylsulfonamide derivative of isatin 3-oxime **54** from the 3,3-dichlorooxindole **53** in the presence of aqueous hydroxylamine hydrochloride. Under the given conditions the product **54** was obtained with a yield of 57% [42].



53 **54**

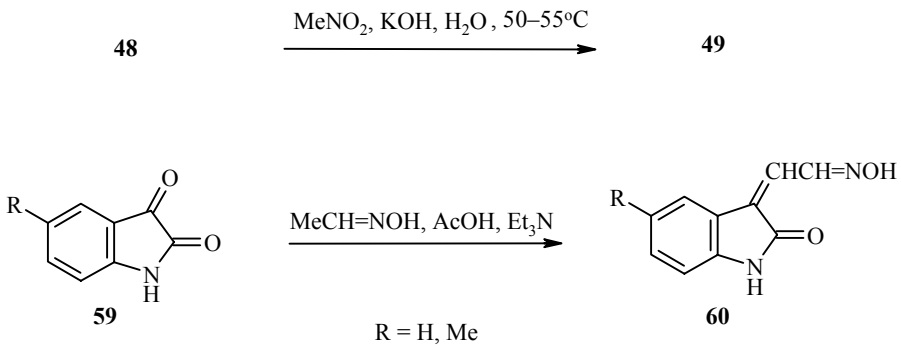
Several methods for the synthesis of isatin oximes were based on the nitrosation of indole derivatives. Thus, 1-acetylindoxyl (**55**) in the $NaNO_2$ – AcOH – EtOH – H_2O system gives 1-acetylisatin 2-oxime (**56**) with a yield of 63% [43]. Under similar conditions 6-nitrooxindole (**57**) gives 6-nitroisatin **58** with a yield of 91% [44].



55 **56**

57 **58**

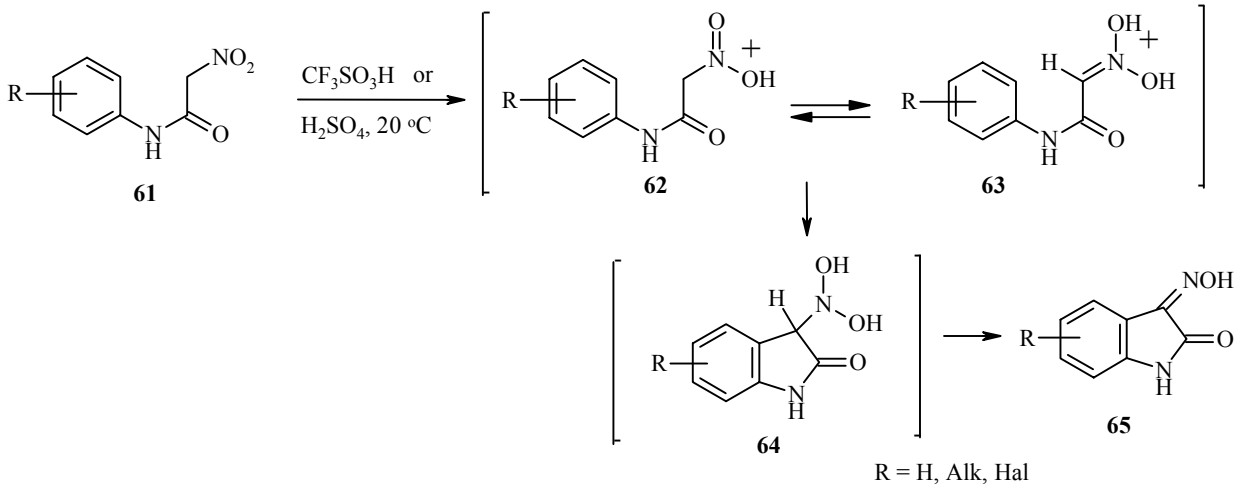
The reaction of isatin **48** and nitromethane in the presence of a 50% solution of potassium hydroxide leads to the formation of 3-isatin oxime **49** [45]. It is interesting that the reaction of the isatins **59** with acetaldoxime in the presence of acetic acid gives the oximes **60** as the main products [17].



48 **49**

59 **60**

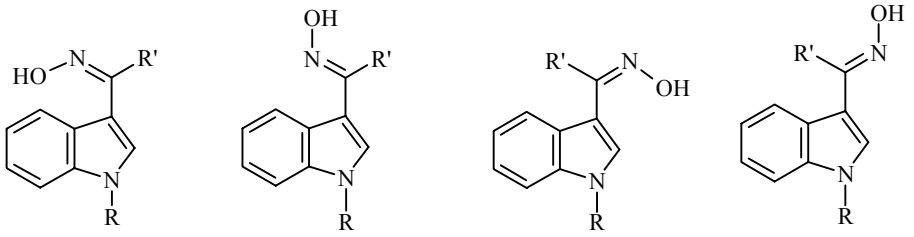
In the presence of trifluoromethanesulfonic acid or sulfuric acid the nitroacetanilides **61** are converted into the corresponding isatinic acids with yields of 42-89%. The intermediates of this reaction (the salts **62** and **63**) easily undergo cyclization to oxindole derivatives **64**, the dehydration of which gives the oximes **65** [46-50]. Polyphosphoric acid was also used successfully for this reaction [51].



1.3. The Structure of Indole Oximes

One of the most reliable methods for determination of the structure of isomeric indole oximes is NMR spectroscopy. In [52] the stereochemistry of the oximes of 3-indolecarbaldehyde, 3-acetylindole, hydroxymethyl 3-indolyl ketone, and their derivatives was studied in detail. The oximes of 3-indolecarbaldehyde were studied in greatest detail. In the spectrum of this compound, dissolved in CD_3OD, there are singlets at 7.72 ppm and 8.29 ppm and multiplets in the region of 7.05-7.85 ppm. After heating or storage additional signals are observed in the spectrum in the form of singlets at 7.43 and 8.32 ppm and a multiplet at 8.05 ppm. The singlets at 8.29 and 7.43 ppm correspond to the C-2 protons of the indole ring, since in solution in $DC(O)N(CD_3)_2$ the signals are split on account of coupling with the NH proton of the indole ring with spin–spin coupling constants of 3.5-4.0 Hz. The signals of the aldehyde are observed at 8.32 and 7.72 ppm (in CD_3OD), and the difference in the chemical shifts of these signals $\Delta\delta$ is 0.6 ppm. Since the proton of the aldehyde group in the *syn* isomers of the oximes is shifted by 0.6-0.7 ppm downfield compared with the *anti* isomer, it was concluded that the initial oxime is in the *anti* form. Thus, the *anti*-oxime of 3-indolecarbaldehyde in solution gradually isomerizes to the *syn* isomer. The equilibrium ratio of the isomers of this oxime is established by heating the *anti* isomer in CD_3OD at 60°C for 2 h, and the ratio of the *syn* and *anti* isomers amounts to 47:53.

The usual *syn*,*anti* isomerism for indole ketoximes is supplemented by the possibility of a different mutual arrangement of the double bonds, i.e., *s-cis* and *s-trans* isomerism [53]. Thus, for the oximes **66** it is basically possible for four isomers to exist:



s-trans-anti-**66** *s-trans-syn*-**66** *s-cis-anti*-**66** *s-cis-syn*-**66**

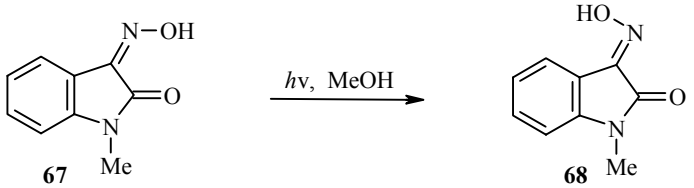
According to the ^1H NMR spectra, the oximes of 3-acylindoles have the *s-trans* conformation and exist in the form of the *syn* isomers. The structure of the *s-trans-syn*-oxime of 3-acetyl-1-methylindole was confirmed by X-ray crystallographic analysis [53, 54]. Recently the structure of the *cis* isomer of 1-methyl-3-

indolecarbaldehyde oxime, the *trans* isomer of 1-methyl-5-methoxy-3-indolecarbaldehyde oxime [55], and ethyl *trans*-α-hydroxyimino-β-[2-(α,α-dimethylallyl)-3-indolyl]propionate [56] was investigated by X-ray crystallographic analysis.

The stereochemical structure of the oximes of 3-acetyl-2-methylindoles was investigated by ^{1}H and ^{13}C NMR methods and also by UV and IR spectroscopy [57]. In the ^{13}C NMR spectra the so-called γ-effect, due to the effect of the hydroxyl group, appears. This effect is stronger, the larger the number of protons at the investigated carbon atom and the closer the steric γ substituent. It was shown on the basis of the spectral data that the oximes of 3-acyl-2-methylindoles exist in the form of a mixture of two isomeric forms with a preponderance of the *s-trans-syn* isomer. The fraction of the *anti* form increases (to 25-35%) with increase in the size of the alkyl radical in the oxime group [57].

The structure of the indole oximes has also been investigated comprehensively by mass spectrometry [58] and IR spectroscopy [59].

It should be noted that N-methylisatin 3-oxime (**67**) is transformed into the isomeric oxime **68** (yield 35%) when irradiated by a mercury lamp (100 W) in methanol. Isatin 2-oxime does not isomerize under similar conditions [60].



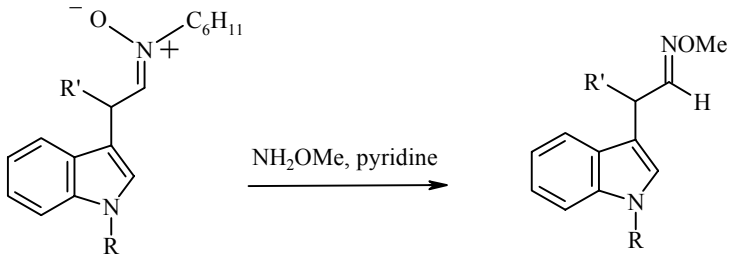
67 **68**

The characteristics of the ^{1}H and ^{13}C NMR spectra for some isatin oximes are given in [61]. The structure of isatin oximes has also been investigated by UV spectroscopy [62, 63] and polarography [64, 65]. The ability of isatin oximes to form characteristic colored complexes with metal ions should also be noted [66-68].

2. THE REACTIONS OF INDOLE AND ISATIN OXIMES

2.1. Synthesis of the Ethers of Indole and Isatin Oximes

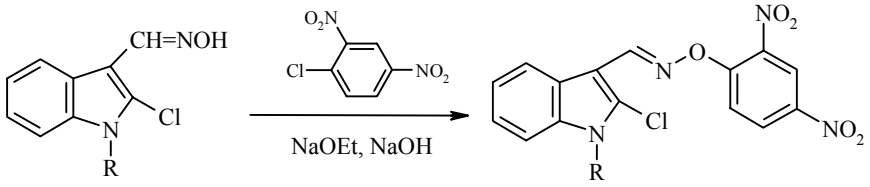
The main group of methods for the synthesis of the O-ethers of indole and isatin oximes is based on the reaction of the O-alkyl derivatives of hydroxylamines with carbonyl derivatives in the presence of sodium carbonate [69], ethanol–pyridine [70], or *p*-toluenesulfonic acid–ethanol [71]. The reaction of the indole nitrones [69] with O-methylhydroxylamine in pyridine gives the methyl ethers of indole oximes **70** with yields of up to 75% [72].



69 **70**

R, R' = H, Me

The synthesis of the O-aryl derivatives of indole oximes **72** as potential insecticides and nematocides was realized successfully with 2,4-dinitrochlorobenzene as arylating agent. Thus, in the 2,4-dinitrochlorobenzene–sodium ethoxide–sodium hydroxide system at room temperature the oximes **71** give the O-ethers **72** with yields of 95-98% [73].

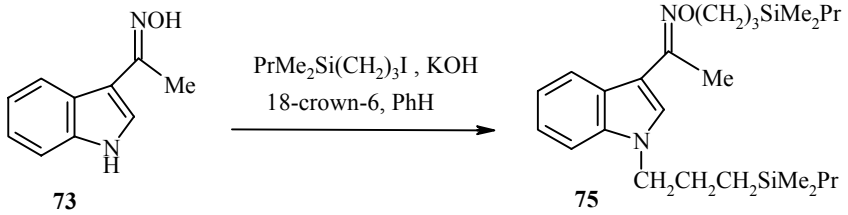


71 **72**

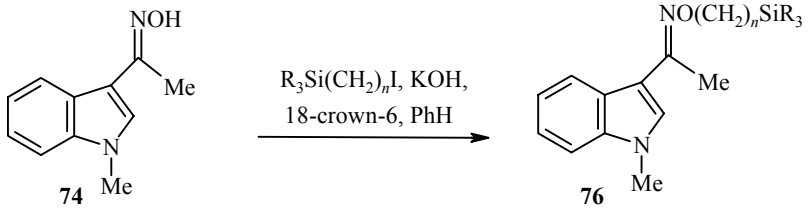
R = Me, Et, Ph

The sodium salt of isatin 3-oxime was also alkylated successfully in DMF [74].

With phase-transfer catalysis it is possible to alkylate indole oximes successfully with silicon-containing alkyl iodides. Thus, in the system containing alkyl iodide, solid potassium carbonate, 18-crown-6, and benzene the indole oximes **73** and **74** give the O-ethers **75** or **76** with yields of up to 38% [75].



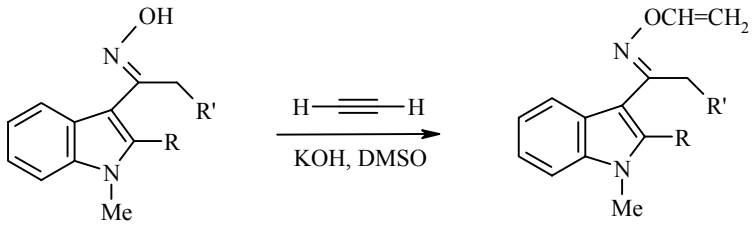
73 **75**



74 **76**

$R_3Si(CH_2)_nI$ = *n*-$PrMe_2Si(CH_2)_3I$, $MeEt_2SiCH_2CH_2Si(Me_2)CH_2I$

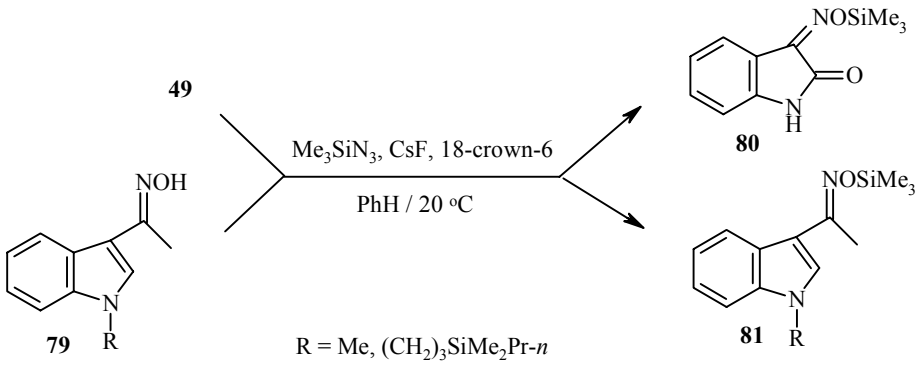
The O-vinyl derivatives of indole oximes **78** were obtained by the addition of acetylene to the oximes **77** in the presence of potassium hydroxide in DMSO at 40-70°C [76].



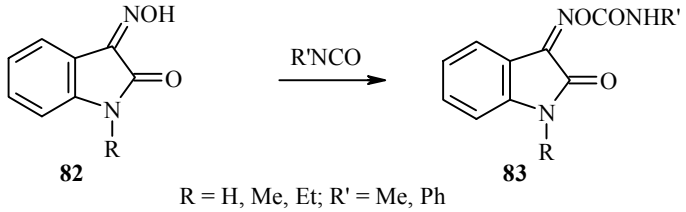
77 **78**

R = H, Me; R' = H, Me, $CHMe_2$

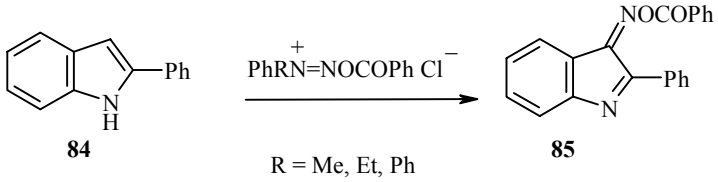
The indole **79** and isatin **49** oximes are readily silylated in the two-phase system containing Me_3SiN_3, CsF, 18-crown-6, and benzene. The silyl ethers of oximes **80** and **81** were isolated with yields of up to 100% [77].



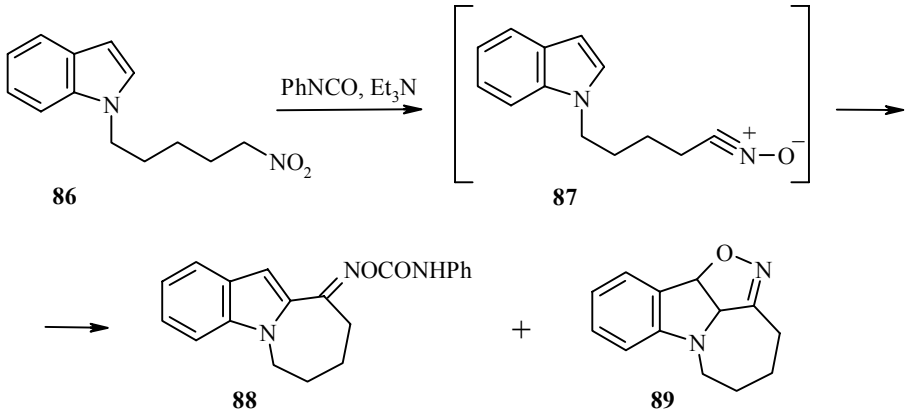
O-Acyl derivatives of indole and isatin oximes [78] were obtained successfully by acylation of the respective oximes by acid anhydrides [33]. The carbamoyl derivatives of indole [79] and isatin [80] oximes were obtained by the reaction of the respective oximes with alkyl or aryl isocyanates. For example, the reaction of the oximes **82** with isocyanates gave the carbamoyl derivatives **83**, which have antiviral activity, as the main products [80].



The reaction of 2-phenylindole (**84**) with benzoyloxydiazonium chloride in chloroform led to the formation of the O-benzoyl oxime derivative **85**, which was isolated with a yield of up to 86% [81].

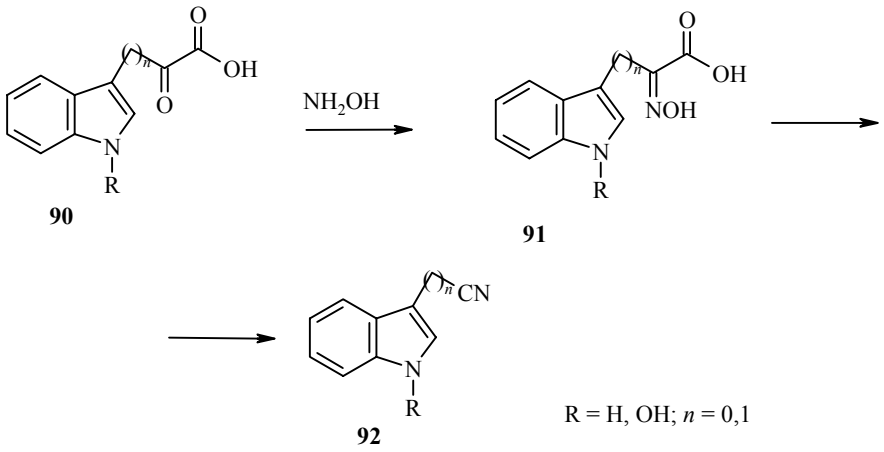


In the presence of catalytic amounts of triethylamine the ω-nitroalkylindole **86** and phenyl isocyanate give the tricyclic acylated oxime **88** (yield 20%) and the tetracyclic cycloadduct **89** (yield 20%). The products **88** and **89** are formed through the intermediate nitrile oxime **87** [82].



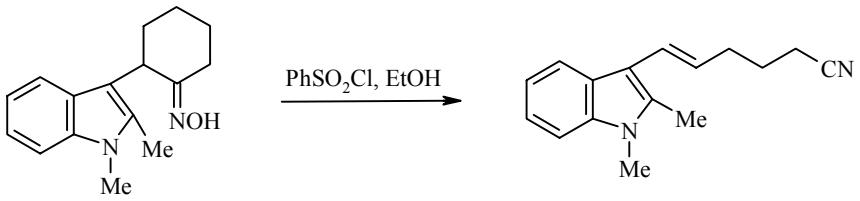
2.2. The Reactions of Indole Oxime Groups and Rings

One of the characteristic reactions of indole oximes is dehydration. Indole aldoximes are usually converted readily into the corresponding nitriles in the presence of acetic anhydride [83-85], acetic anhydride and triethylamine [86], $Me_2N^+=CHCl\ ^-SO_3H$ [87], copper salts [88], and phosphonitrile chlorides [89] or by biochemical methods [90-93]. Indole aldehydes are converted successfully into nitriles by the action of $NH_2OH{\cdot}HCl$ – HCOOH [94], $NH_2OH{\cdot}HCl$ – NaOAc – AcOH [95], or $NH_2OH{\cdot}HCl$ – NaOAc – EtOH [95]. The formation of nitriles in these cases occurs through aldoximes as intermediates. In boiling methanol [96] or in water [97] the oximes of α-keto acids **91**, obtained from compounds **90** and hydroxylamine, give the corresponding nitriles **92** with yields of up to 60%.



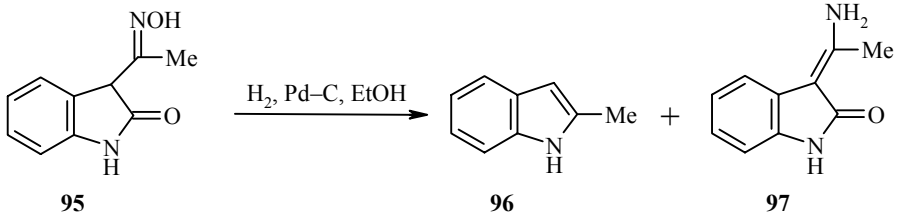
90 **91** **92**

It is interesting that the ketoxime **93** in the presence of benzenesulfonyl chloride gives 1,2-dimethyl-3-(5-cyano-1-pentenyl)indole (**94**) with a yield of 81% as the only product [98].



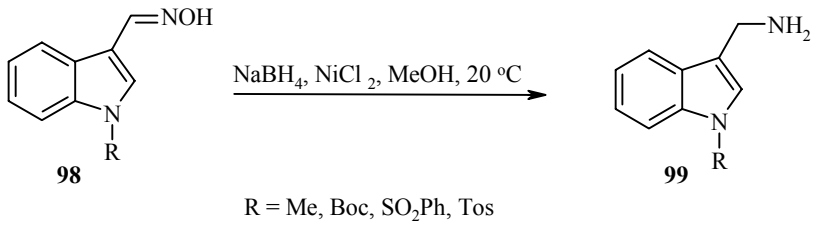
93 **94**

The hydrogenation of indole oximes has been described in several papers. The hydrogenation of indole ketoximes in the presence of Pd–C [99] or PtO_2 [100] usually leads to the formation of the corresponding amines or hydroxylamines. However, the hydrogenation of 3-acetyloxyindole oxime **95** in the presence of palladium on carbon in ethanol gives a mixture of 2-methylindole (**96**) (21%) and 3-(α-aminoethylidene) oxindole (**97**) (66%) [101].

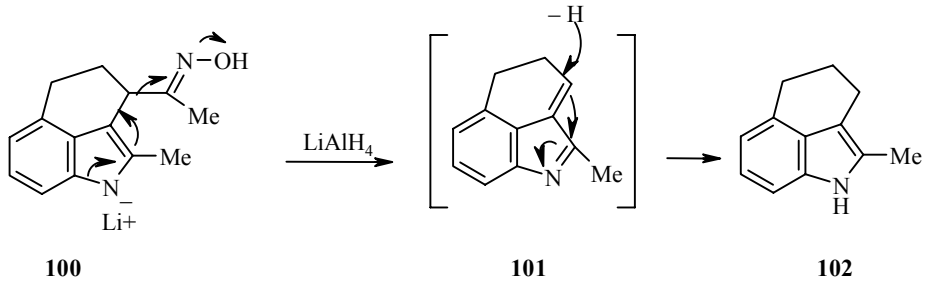


95 **96** **97**

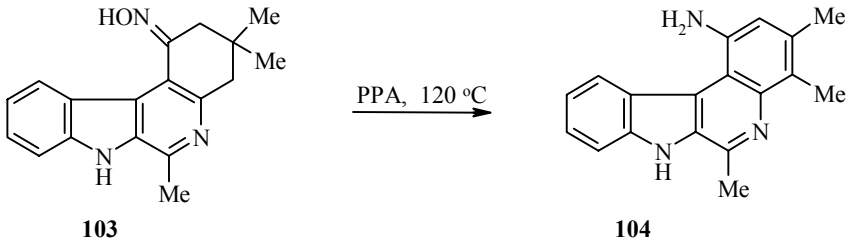
The reduction of indole aldoximes **98** with sodium borohydride in the presence of $NiCl_2 \cdot 6H_2O$ in methanol leads to the respective amines **99** with yields of 67-82% [102].



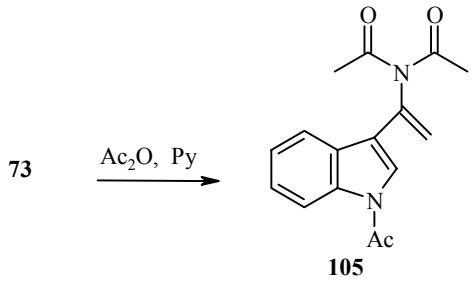
Similar indole amino derivatives were also obtained in the presence of BH_3 in tetrahydrofuran [103] or aluminum amalgam in ether [104]. However, the reduction of the oxime **100** with lithium aluminum hydride leads to the formation of 2-methyl-1,3,4,5-tetrahydrobenzo[*c*,*d*]indole (**102**) as the only product. In these cases the product **102** is formed through the intermediate indolenine **101** [105].



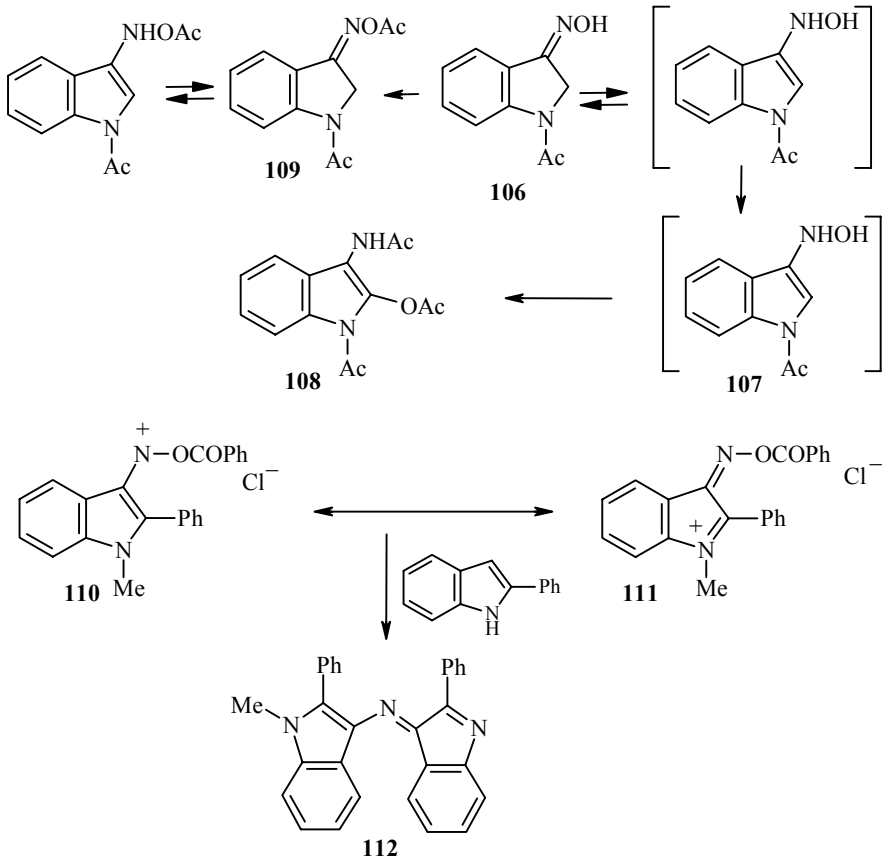
It is interesting that the oxime **103** in the presence of polyphosphoric acid gives 1-amino-3,4,6-trimethylindolo[2,3-*c*]quinoline (**104**) with a yield of 50% [106].



The synthesis of the enamides of indole oximes was described by the authors of [107]. For example, 3-acetylindole oxime **73** in the presence of acetic anhydride and pyridine gives N-[(1-acetyl-3-indolyl)vinyl]diacetamide (**105**) with a yield of 28%.



In the presence of acetic anhydride N-acetylindoxyl oxime (**106**) gives a mixture of N-acetyl-3-acetylamino-2-acetoxyindole (**108**) and N-acetylindoxyl acetyloxime (**109**). In the tautomeric form in an acidic medium the oxime **106** probably rearranges to the aminoindole **107**. The rearrangement product **107** is acylated with the formation of compound **108** [108].

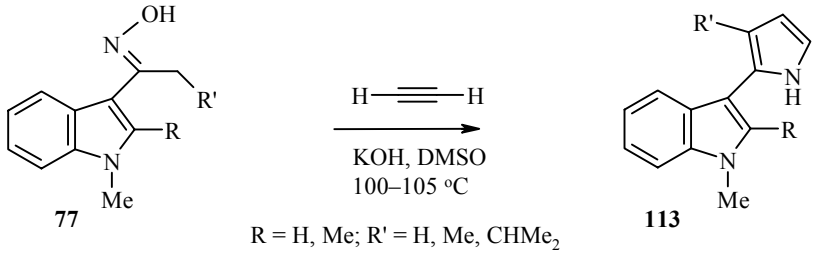


It was shown that the salts of imines (the tautomeric forms **110** and **111**) in reaction with 2-phenylindole give the dimer **112** as the main product [109].

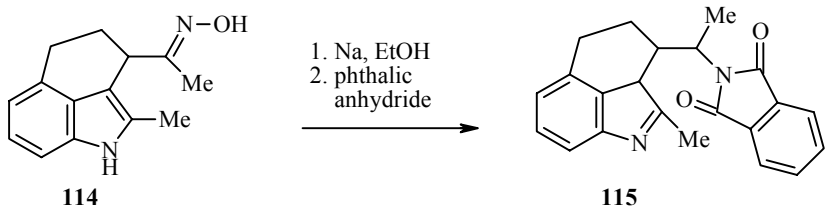
2.3. Synthesis of New Heterocycles from Indole Oximes

Advances in the synthesis of heterocyclic systems from oximes are summarized in the review [110], and in this section therefore we will dwell only on the specific reactions of indole oximes.

The cycloaddition of ketoximes to acetylenes (the Trofimov reaction [111-114]) has been used in the synthesis of pyrroloindoles. Thus, the reaction of indole ketoximes **77** with acetylene in DMSO at 100-105°C gives 3-(2-pyrrolyl)indoles **113** with yields of 29-36% [76].

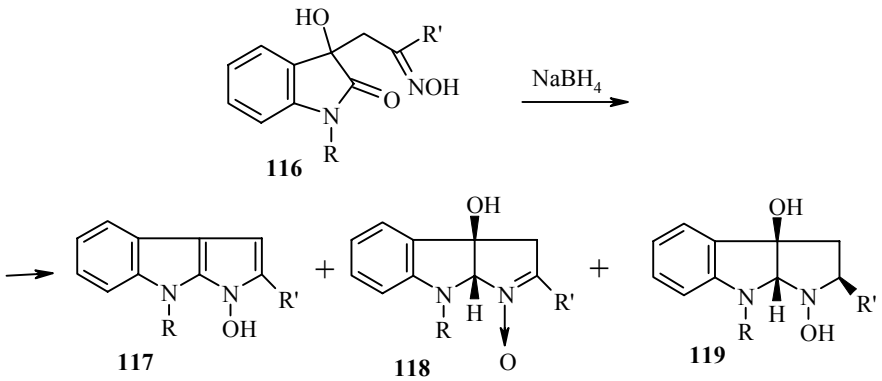


The reaction of the oxime **114** with sodium in the presence of phthalic anhydride leads to the formation of the phthalimide derivative **115** as the only product [105].



114 **115**

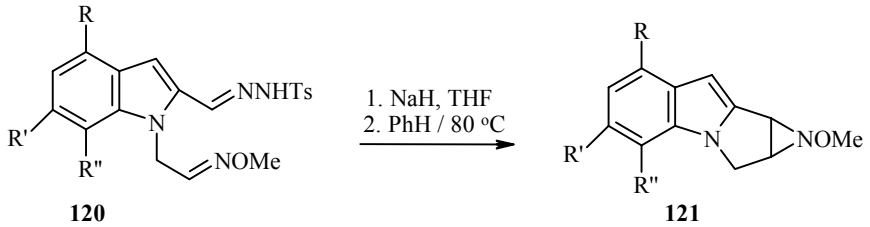
The reduction of oxindole oximes **116** with sodium borohydride gives a mixture of three pyrrolo[2,3-*b*]-indoles **117**-**119**. At -10°C the indoles **117** are the main products. At higher temperatures, however, the products **118** and **119** are formed [115].



116 **117** **118** **119**

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

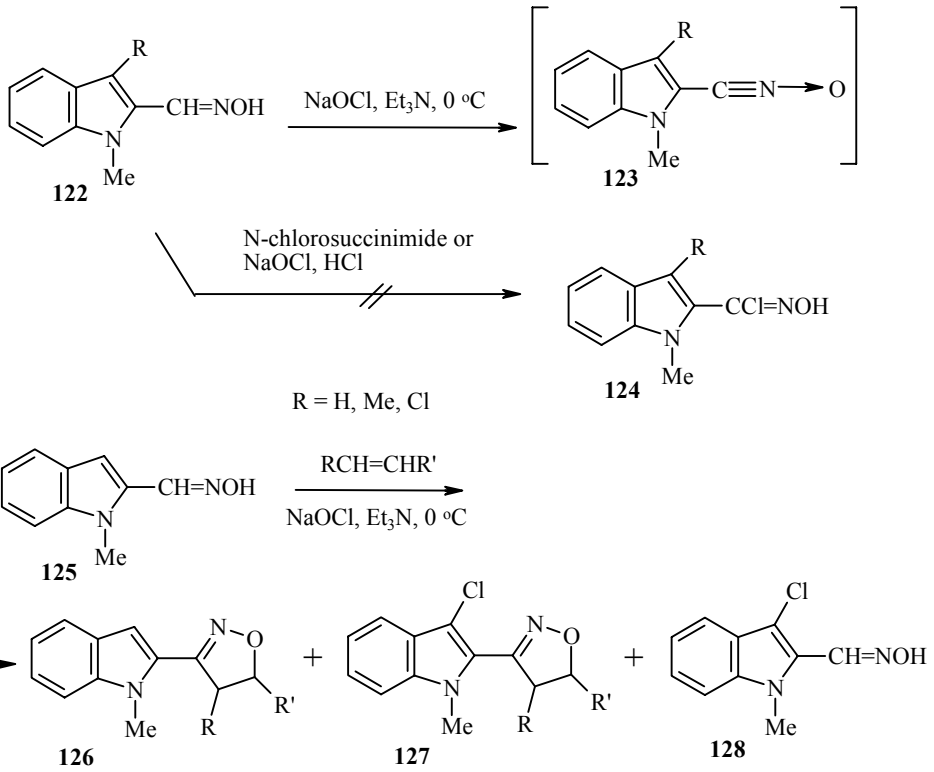
In the presence of sodium hydride in tetrahydrofuran followed by cyclization in boiling benzene the methyl ethers **120**, containing a tosylhydrazone group, are converted into aziridinopyrrolo[1,2-*a*]indoles **121** with yields of 61-67% [116].



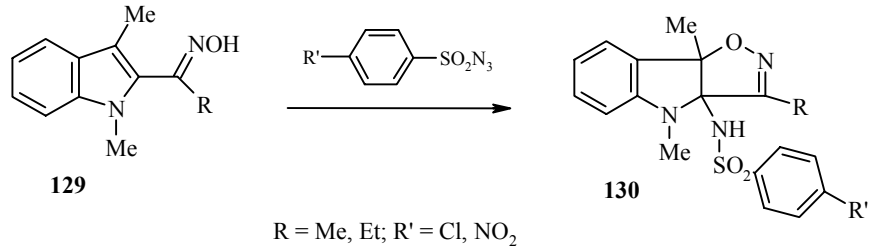
120 **121**

R = H, Br; R' = H, OMe; R'' = H, OBn

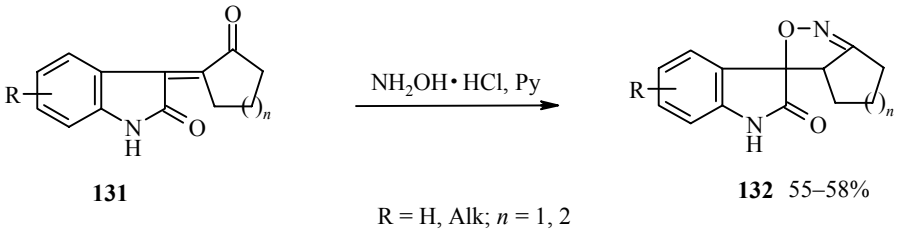
A series of methods have been described for the synthesis of isoxazole derivatives from indole oximes. In the presence of sodium hypochlorite and triethylamine the indole oximes **122** give the corresponding nitrile oxides **123**. In the case of indole oximes the chloro oximes **124** cannot be isolated in the pure form on account of their instability. The nitrile oxides obtained from aldoximes are easily transformed into isoxazolines and isoxazoles in the presence of alkenes or alkynes. For example, the reaction of the oxime **125** in the system containing alkene, sodium hypochlorite, triethylamine, and methylene chloride leads to the formation of a mixture of two isoxazolines **126** and **127** (yields up to 45%) and the chlorinated oxime **128** [117, 118].



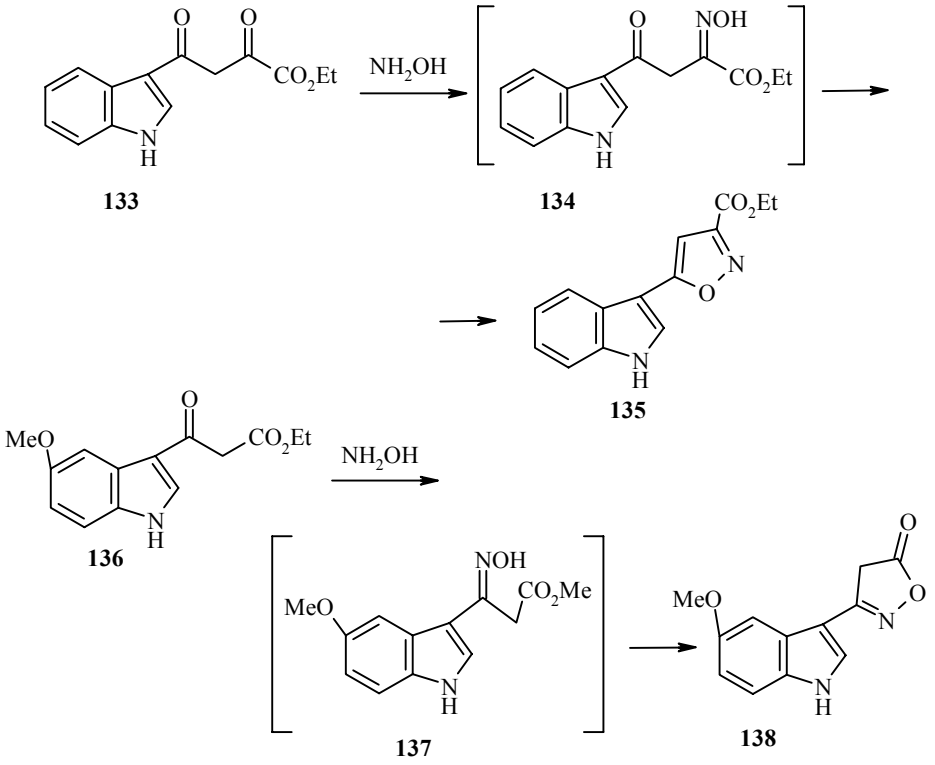
The reaction of 2-acyl-1,3-dimethylindole oximes **129** with the azides of arenesulfonic acids gives good yields of dihydroisoxazolo[4,5-*b*]indoles **130** [119].



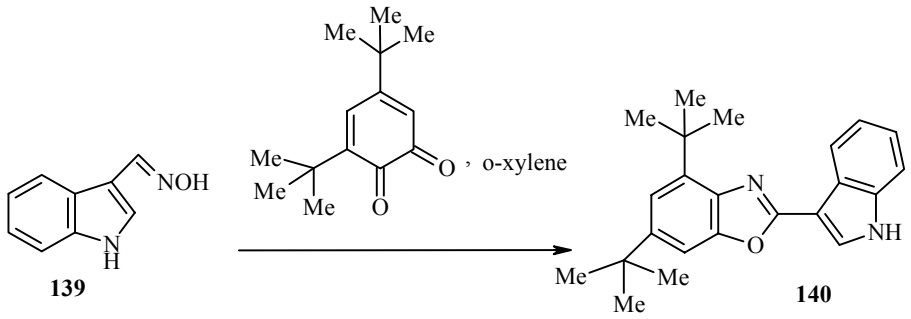
A similar synthesis of oxazole derivatives from indole oximes was described in [120-123]. The isoxazolines **132** were also obtained successfully from the corresponding ketones **131** in the presence of hydroxylamine hydrochloride and pyridine. The products **132** are formed through the oximes as intermediates [124].



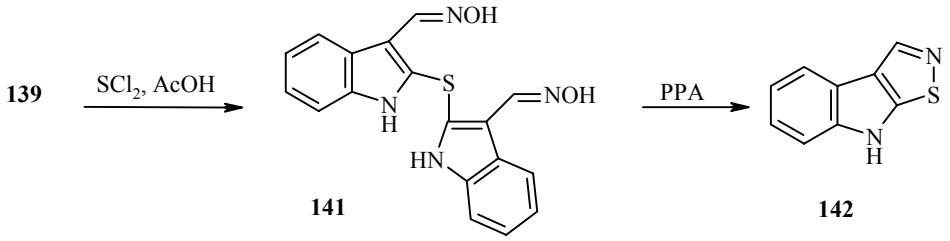
The action of hydroxylamine on ethyl 4-(3-indolyl)-2,4-butanedioate (**133**) in the presence of pyridine gave the isoxazoline **135** with a yield of 66%. The reaction takes place through the oxime **134**, which undergoes cyclization to the product **135** during the reaction [125]. Under similar conditions the oxime **137**, produced *in situ* from the keto ester **136** and $NH_2OH \cdot HCl$ in the presence of pyridine, gives 3-(5-methoxy-1H-3-indolyl)-4H-isoxazolin-5-one **138** with a yield of 50% [126].



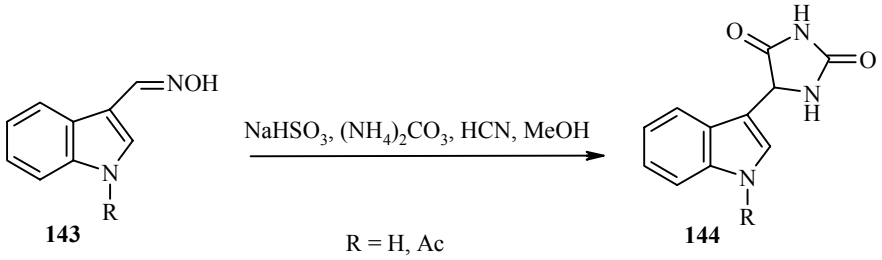
The thermal reaction of the indole aldoxime **139** and 3,5-di-*tert*-butyl-1,2-benzoquinone in boiling xylene gives the benzoxazole **140** with a yield of 37% [127].



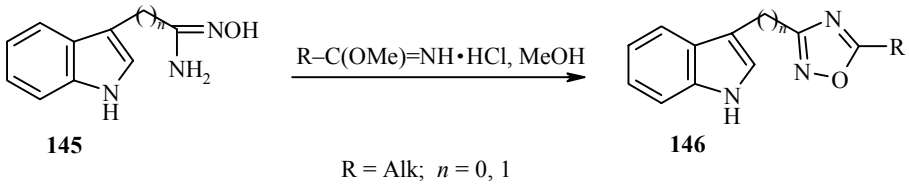
A two-stage method was developed for the synthesis of isothiazolo[5,4-*b*]indole (**142**) from 3-indolecarbaldehyde oxime. The reaction of the oxime **139** with sulfur dichloride in acetic acid gives the sulfide **141** with a yield of 67%. In the presence of polyphosphoric acid the intermediate **141** undergoes cyclization to the tricyclic product **142** (yield 18%) [128].



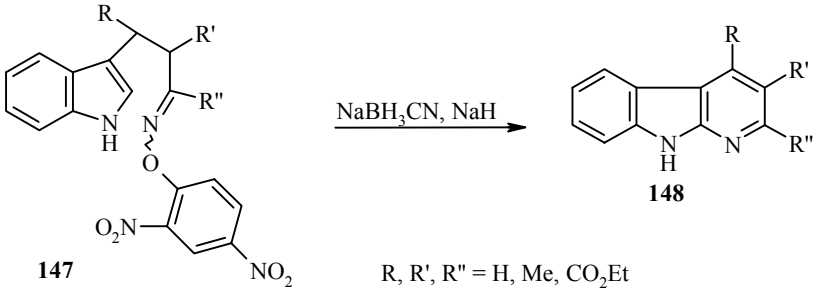
A convenient synthesis for the indole derivatives of hydantoins **144** with yields of up to 59% in the sodium bisulfite–hydrogen cyanide–ammonium carbonate–methanol system was proposed in [129, 130].



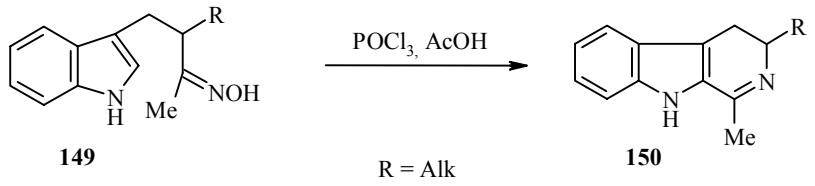
The condensation of indole amidoximes **145** with the hydrochlorides of methyl imidic esters in methanol leads to the formation of 3,5-disubstituted 1,2,4-oxadiazoles **146** with yields of up to 58% [33]. Indole derivatives of oxadiazoles have been proposed for the treatment of migraine [131] and schizophrenia [132].



Indole oximes are widely used in the synthesis of α-, β-, and γ-carbolines. The synthesis of α-carbolines **148** is easily realized with yields of 45-72% from the O-2,4-dinitrophenyloximes of β-(3-indolyl) ketones **147** in the $NaBH_3CN$–sodium hydride–1,4-dioxane system [133].

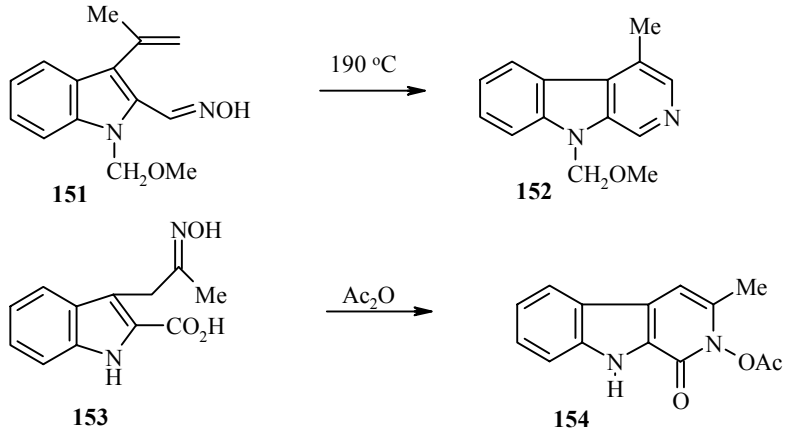


The synthesis of the β-carbolines **150** was realized successfully by cyclization of the oximes **149** in the presence of phosphorus oxychloride in acetic acid [134]. Similar syntheses of carbolines were also realized in the presence of phosphorus pentachloride [135-137] or polyphosphoric esters [138].



149 **150**

β-Carbolines were obtained by thermal cyclization of the oximes of 3-substituted 2-indolecarbaldehydes. For example, the oxime **151** in *o*-dichlorobenzene at 190°C gives the carboline **152** with a yield of 81% [139, 140]. 3-Methyl-β-carboline **154** was obtained by the cyclization of the oxime **153** in boiling acetic anhydride [141].

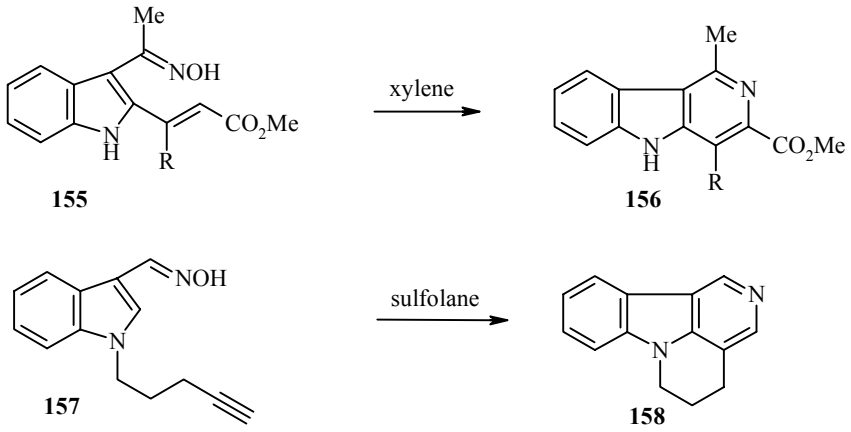


151 **152**

153 **154**

A method was also developed for the synthesis of the β-carboline alkaloid 17α,21-epoxyapovincaminate by the cyclization of carboline oximes [142].

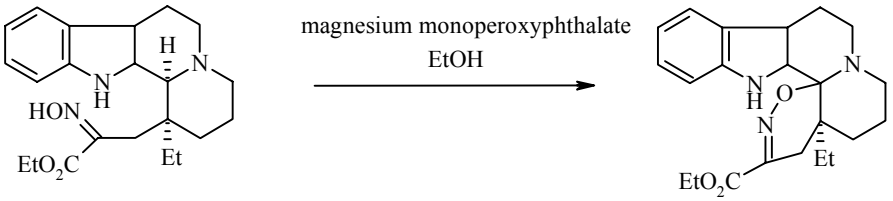
Derivatives of γ-carbolines were also obtained successfully by the cyclization of oxime derivatives. Boiling of the oximes **155** in xylene gives the γ-carbolines **156** with yields of 51-55% [143]. A method was developed for preparation of the tetracyclic carboline alkaloids isocanthine, isocanthin-6-one, 1-methylisocanthine, and 1-methylisocanthin-3-one by an intramolecular hetero-Diels–Alder reaction. For example, the oxime **157** in sulfolane at 285°C gives isocanthine with a yield of 8% [144].



155 **156**

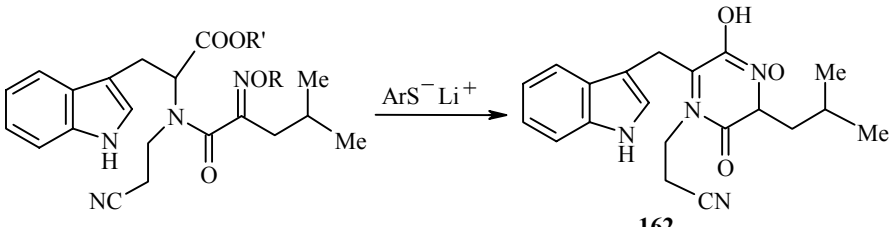
157 **158**

Several papers have been devoted to the synthesis of five-membered oxazine derivatives – vincalkaloids [145-148]. In the presence of magnesium monoperoxyphthalate in acetic acid the oxime **159** gives the five-membered heterocycle **160** as the only product.



159 **160**

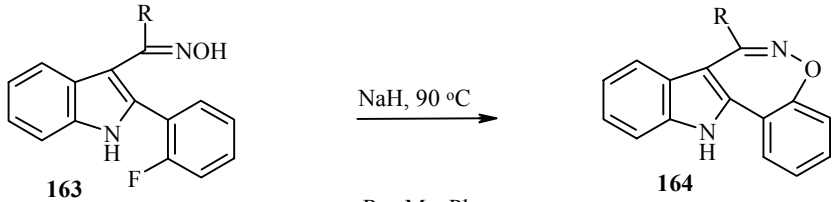
The cyclization of oxime derivatives **161** to the corresponding pyrazine N-oxides **162** was realized successfully in the presence of lithium arenethiolates (lithium 2-benzimidazolethiolate and 2-naphthalenethiolate) [149]. A similar cyclization of oximes was also realized successfully in the presence of dicyclohexylcarbodiimide [150, 151].



161 **162**

R = H, CH_2CH_2CN; R' = Me, CH_2Ph

In the presence of sodium hydride in DMF the oximes of 3-acyl-2-(2-fluorophenyl)indoles **163** give 1H-indolo[3,2-*b*]benzoxazepines **164** with yields of 33-51% [152].

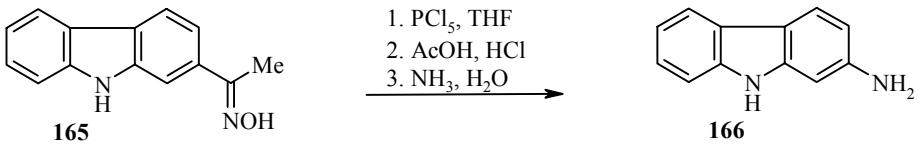


163 **164**

R = Me, Ph

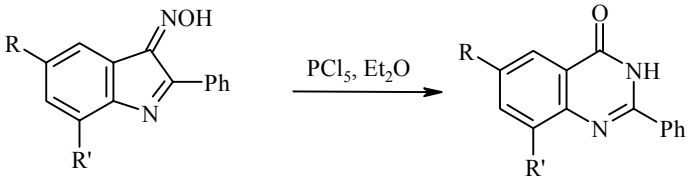
2.4. Beckmann Rearrangement of Indole Oximes

The Beckmann rearrangement is one of the most characteristic reactions of oximes. The rearrangements of indole ketoximes to the corresponding amides are usually carried out in the presence of acetic acid [153] or of HCl in acetic anhydride [154]. A simple method was developed for the synthesis of 2-aminocarbazole (**166**), based on the Beckmann rearrangement of oxime of 2-acetylcarbazole (**165**) in the presence of phosphorus pentachloride in tetrahydrofuran, followed by hydrolysis of the intermediate (HCl–AcOH and NH_4OH) [155].



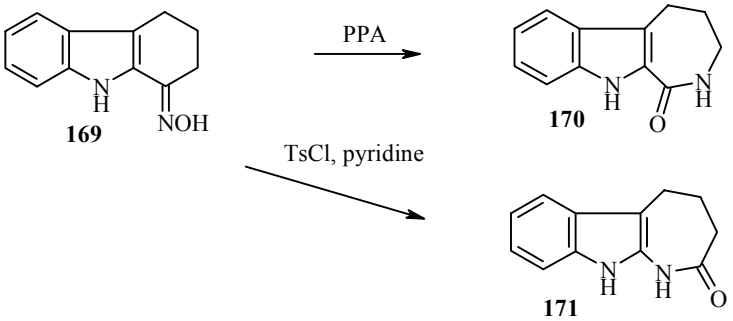
165 **166**

The reaction of the oximes of 2-arylindoles **167** with phosphorus pentachloride in ether leads to the formation of 2-phenylquinazolones **168** [156].



167 **168**

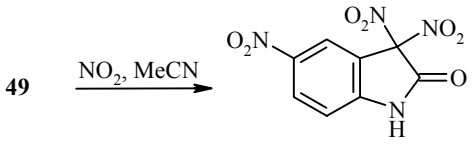
Selective methods were developed for the production of 3,4,5,10-tetrahydroazepino[3,4-*b*]indol-1(2H)-one (**170**) and 3,4,5,10-tetrahydroazepino[2,3-*b*]indol-2(1H)-one (**171**) by Beckmann rearrangement. Thus, in polyphosphoric acid at 100-110°C the oxime **169** gives the azepine **170** with a yield of 72%. However, the reaction of the oxime **169** in the presence of *p*-toluenesulfonyl chloride (TsCl) in pyridine gives the lactam **171** as main product with a yield of 25% [157].



169 **170** **171**

2.5. Reactions of Isatin Oximes

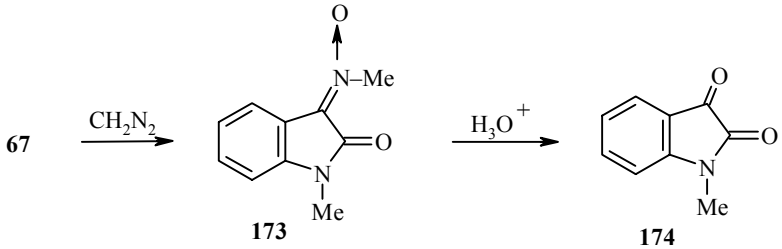
Isatin 3-oxime (**49**) is readily nitrated by NO_2 in warm acetonitrile and gives 3,3,5-trinitrooxindole (**172**) with a yield of 72% [158].



172

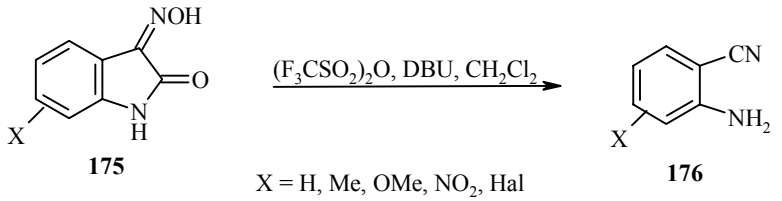
The reduction of isatin oximes with lithium aluminum hydride under various conditions was studied in detail by the authors in [159]. For example, isatin 2-oxime (**50**) is reduced by lithium aluminum hydride in dioxane at 101°C and gives a mixture of indole (14%), the initial oxime **50** (11%), and traces of indigo.

N-Methylisatin 3-oxime **67** reacts with diazomethane with the formation of the nitrone **173**. The oxime **67** reacts in a similar way with MeI–MeONa. Hydrolysis of the nitrone with mineral acids gives 1-methylisatin **174** with a yield of 87% [37, 160].



173 **174**

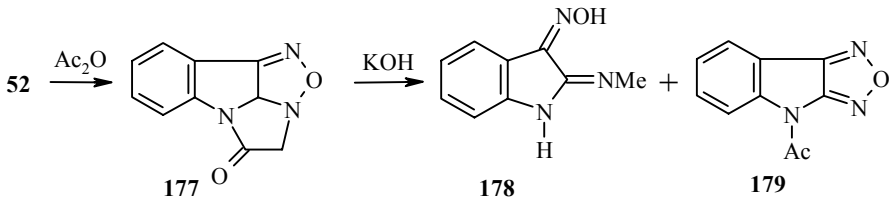
A series of reactions of isatin oximes were based on opening of the five-membered ring in these compounds by various reagents. 2-Substituted benzonitriles were isolated as the main products. In the reaction of isatin 3-oximes **175** with trifluoromethanesulfonic anhydride in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 2,6-lutidine derivatives of 2-aminobenzonitriles **176** are formed with yields of up to 80% [161].



175 **176**

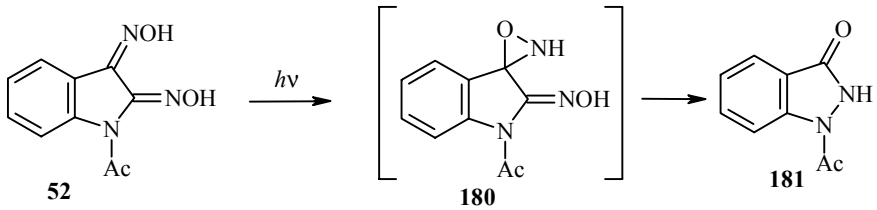
Similar 2-aminobenzonitriles from isatin 3-oximes were also obtained in the presence of triphenylphosphine or Ph_3P=CHR (R = CO_2Me, CO_2Et, or COPh) [162]. At increased temperature the formation N,N'-di(*o*-cyanophenyl)urea is also observed [166]. However, the reaction of isatin 3-oxime with phosphorus pentachloride in benzene gives 2-isocyanatobenzonitrile with a yield of 90% [168, 169]. It is also known that isatin 2-oxime rapidly decomposes during fusion with the formation of isatin, ammonia, and 2,4-dihydroxyquinazoline.

Isatin oximes have been used in the synthesis of new heterocyclic compounds. When boiled in acetic anhydride 1-acetylisatin dioxime (**52**) gives 2-oxo-1,2-dihydro-10H-imidazo[1,2-*a*]-1,2,5-oxadiazolo[3,4-*b*]-indole (**177**) with a yield of 31%. In the presence of potassium hydroxide in a mixture of methanol and water (1:1) compound **177** gives the oxime **178** (yield 45%) and 1-acetyl-1,2,5-oxadiazolo[3,4-*b*]indole (**179**) (yield 8%) [41].



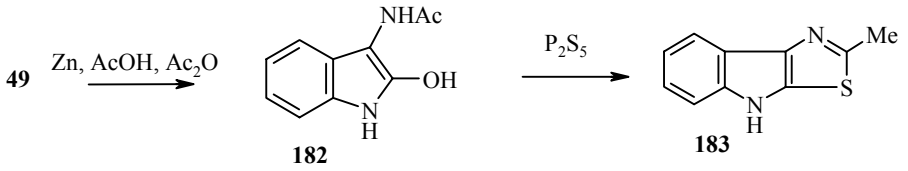
177 **178** **179**

Irradiation of the dioxime **52** with a mercury lamp in methanol gives N-acetylindazolone (**181**) with a yield of 10%. The product **181** is formed through the intermediate hydroxyaziridine **180** [60].

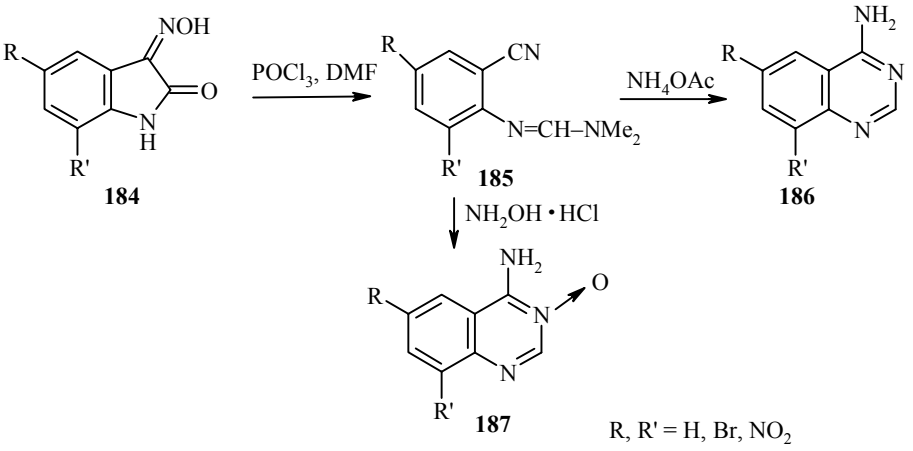


52 **180** **181**

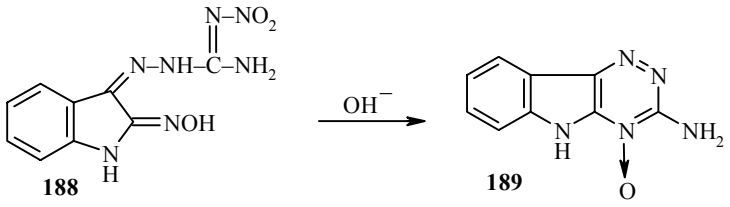
The synthesis of 2-methylindolo[3,2-*d*]thiazole (**183**) was realized in two stages from isatin 3-oxime; reduction of the oxime **49** with zinc dust in acetic acid followed by treatment of the intermediate **182** with phosphorus pentasulfide in xylene gives the tricyclic product with a yield of 56% [170].



In the presence of the Vilsmeier reagent (DMF–phosphorus oxychloride) the isatin oximes **184** form N,N-dimethyl-N'-(*o*-cyanophenyl)formamidines **185**. Treatment of compounds **185** with ammonium acetate gives 4-aminoquinazolines **186** with yields of 71-80%. However, 4-aminoquinazoline 3-oxides **187** are formed in the reaction of formamidines **185** with hydroxylamine hydrochloride (yields 80-94%) [171].



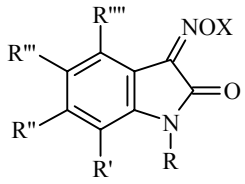
The synthesis of 3-amino-1,2,4-triazino[5,6-*b*]indole N-oxide (**189**) by alkaline cyclization of the 3-nitroguanylhydrazone of isatin 2-oxime **188** has been described [172].



3. THE BIOLOGICAL ACTIVITY OF DERIVATIVES OF INDOLE AND ISATIN OXIMES

3.1. Action on the Cardiovascular System

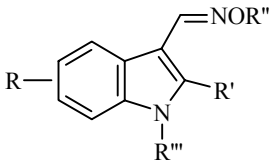
The broad spectrum of activity of isatin oximes acting on the cardiovascular system has been investigated. The isatin oximes **190** have been proposed as agents against migraine and for coronary and ischemic heart disease, arteriospasm, cardiac arrhythmia, hypertension, and other disorders [173].



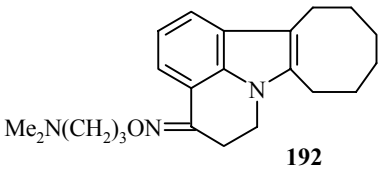
190

X = H, Alk, Ar, Ac, CH_2CN; R = H, Alk, Ar;
R–-R"" = H, Hal, Alk, Ar, NO_2, CN, CF_3, SO_2NH_2

The 3-indolecarbaldehyde oximes **191** exhibit antiarrhythmic activity [174]. Hypotensive activity has been found in tetracyclic derivatives of indole oximes [175]. For example, at 200 mg/kg the oxime **192** lowers blood pressure in rats by 28%.



191



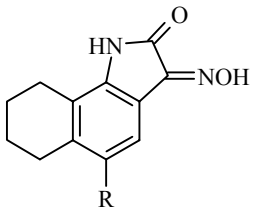
192

R = H, Alk, OH, Hal, NO_2, NH_2; R' = Hal, OH, SH, NH_2; R" = H, Alk, Ac; R'" = H, Alk, Ar

3-Alkanoyl-1-*tert*-aminoalkylindole oximes have vasoconstrictive activity [176]. The blocking action of indole O-(3-alkylamino-2-hydroxypropyl)oximes on β-adrenoreceptors has also been investigated [177].

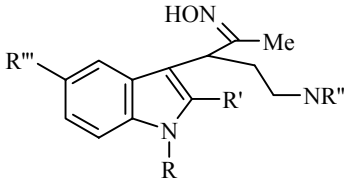
3.2. Antidepressant, Tranquillizing, and Anticonvulsive Activity

A series of papers have been devoted to the study of indole [178] and isatin [69, 179-187] oximes as agents affecting the central nervous system. The anticonvulsive activity of isatin oximes **193** should be noted [188, 189].



193

R = H, NO_2, SO_2NH_2,
SO_2NHMe, SO_2NMe_2



194

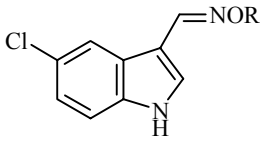
R = Alk, Ar; R' = H, Me; R" = Me, Et;
R'" = H, Cl, OMe

The oximes of indole aminoketones **194** exhibited high antidepressant and analgesic activity [190]. Indole and carbazole amidoximes [ROCHC'C(=NOH)NH_2, R = indolyl, carbazolyl; R' = H, Me) can also be used as antidepressants [191].

The oxime derivatives of β-carbolines [192] and furo[3,2-*b*]indoles [193] exhibited good psychotropic activity. The antidepressant activity and antagonism with amphetamine in 3-indolecarbaldehyde oxime were investigated [194].

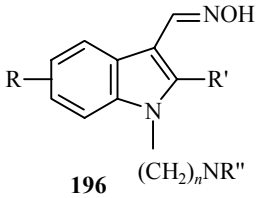
3.3. Analgesic and Anti-inflammatory Activity

The oxime derivatives of 5-chloroindole **195** [195] and 1-aminoalkylindoles **196** [196] exhibited high analgesic and anti-inflammatory activity.



195

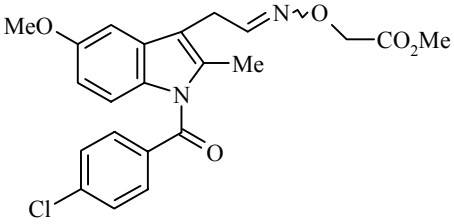
R = H, COMe, COPh



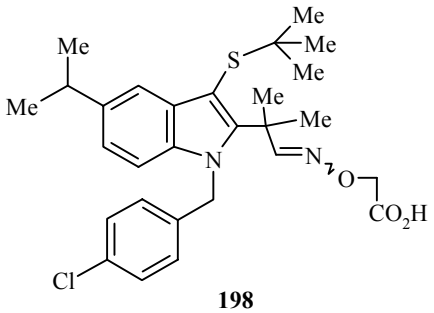
196

R = H, Alk, Hal, OAlk; R' = H, Alk, Ar, Hal; NR'' = N_3, NH_2, azetidinyl, morpholinyl, piperidinyl, pyrrolidinyl, piperazinyl, thiamorpholinyl; *n* = 2–6

A series of papers were devoted to study of the carboxylates of indole oxime ethers as inhibitors of the biosynthesis of leukotriene [70, 197, 198] or prostaglandins [199, 200]. All these compounds have been proposed as anti-inflammatory agents, and the oxime ethers **197** and **198** were mentioned as some of the most active.



197

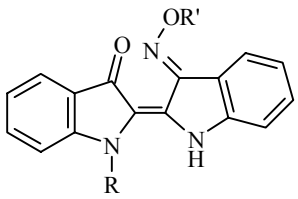


198

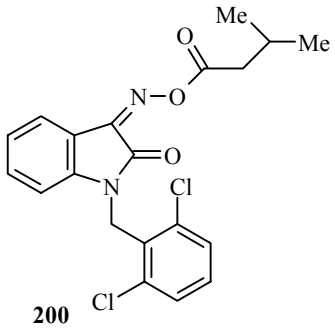
The oxime derivatives of indoline [201, 202], isoindole [203], and isatin [204] also have antiinflammatory and antiasthmatic activity.

3.4. Antitumor, Antiviral, and Bactericidal Activity

Clearly defined antileukemia activity was recently discovered in the oxime derivatives of indirubin **199** [205]. Derivatives of indole oximes (including the oxime **200**, as the most active) were investigated as inhibitors of telomerase and displayed high antitumor activity [206].

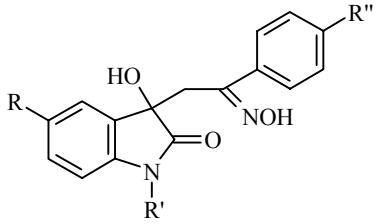


199 R, R' = H, Alk



200

Isatin 3-oxime also displayed activity against HIV-1 [207] and polio virus [208]. Antiviral activity was found in carbamoyl derivatives of indole 3-oxime **83** [80]. High antibacterial activity was exhibited by the oxime derivatives of mitomycin antibiotics [209]. The broad spectrum of antimicrobial activity in the oxime derivatives of 2-indolinone **201** should be mentioned [210].



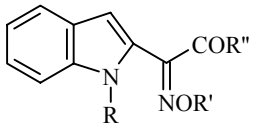
201

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

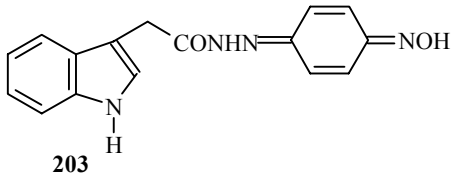
The high activity of isatin 3-oxime against *Mycobacterium tuberculosis* has been described [211]. Indole oxime fragments are present in cephalosporin antibiotics [212].

3.5. Indole Oximes as Fungicides and Plant Growth Regulators

High fungicidal activity is exhibited by the oxime derivatives of 2-substituted indoles **202** [213] and 3-substituted indoles **203** [214].



202



203

R, R' = Alk; R" = OAlk, SAlk, NHAlk, $NAlk_2$

3-Indolylacetaldehyde oxime also displays fungicidal activity [215] and is used as a plant growth regulator [216].

3.6. Other Activity

Coumarin derivatives of isatin oximes are used as fluorescent agents in medicine [217]. The antidote activity of isatin 3-oxime during intoxication by organophosphorus compounds should also be mentioned [218].

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