Chemistry of Heterocyclic Compounds, Vol. 36, No. 3, 2000

STEROIDAL 1,2-OXAZOLES. SYNTHESIS AND BIOLOGICAL ACTIVITY. (REVIEW)

S. V. Drach, R. P. Litvinovskaya, and V. A. Khripach

Data on the synthesis and biological activity of isoxazole derivatives of steroids have been correlated.

Keywords: isoxazolylsteroids, isoxazolinylsteroids, biological activity.

Attention to steroid derivatives of oxazole is caused by the fact that these compounds proved to be interesting from the point of view of biological activity and moreover are convenient intermediates in the synthesis of numerous polyfunctional compounds [1,2]. A review was published comparatively recently devoted to steroidal 1,3-oxazoles [3].

The aim of the present review is to correlate the available information on methods of synthesis and on the biological activity of steroid derivatives of 1,2-oxazole (isoxazole). The latter may be divided provisionally into two types; compounds in which one of the steroid skeleton rings is condensed with the heterocycle, and steroids containing an isoxazole ring (or its derivatives) in the side-chain.

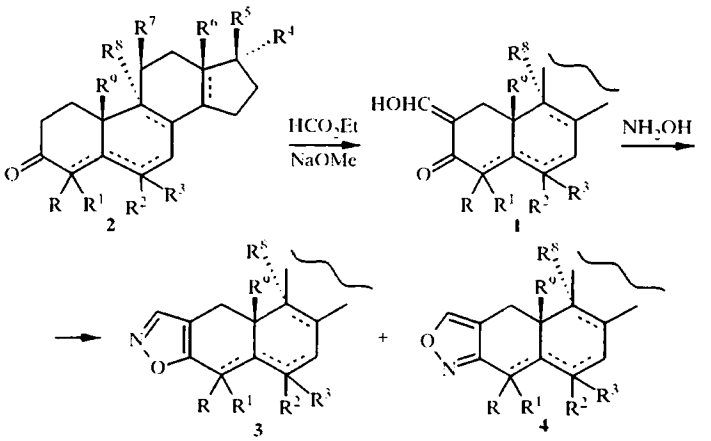
1. Synthesis of Steroidal Isoxazoles *via* α-Hydroxymethylene Ketones

Among the methods of synthesis of steroids condensed with isoxazole, one of the most important is the interaction of α-hydroxymethylene ketones with hydroxylamine. Compounds most studied up to the present time were obtained by this route, in which the $C_{(2)}$–$C_{(3)}$ bond of the steroid is common with the heterocycle [4-21]. The initial 2-hydroxymethylene-3-oxosteroids (**1**) may readily be synthesized by the condensation of 3-oxosteroids (**2**) with ethyl formate in the presence of sodium methylate (yields of compounds were 50-90%) [7,13-17].

A detailed study of the reaction of hydroxylamine with hydroxymethylene ketones of type **1** showed that it is possible to form [2,3-*d*]- and [3,2-*c*]isoxazoles **3** and **4** respectively [4]. The ratio of regiomers obtained in this way depends on the pH of the medium, the solvent used, and the temperature. In aqueous alcohol solution product **3** (8%) and product **4** (82%) are formed from 17β-hydroxy-2-hydroxymethylene-17α-methylandrostan-3-one, but in pyridine solution the yield was 91 and 6% respectively [4,18]. A high yield of [2,3-*d*]isoxazole **3** was achieved on carrying out the reaction with hydroxylamine hydrochloride in acetic acid, or alcohol solution in the presence of acetic acid [4,9,11,16,17,20]. It was noted that it was necessary to add sodium acetate when a tertiary hydroxyl group was present in the molecule of the initial compound. A dependence of the structure of formed product on the character of the acid component of the hydroxylamine salt used was detected [14]. On reacting 17β-hydroxyestra-4,9-dien-3-one with hydroxylamine sulfate [2,3-*d*]isoxazole was obtained but using hydrochloride [3,2-*c*]isoxazole predominated.

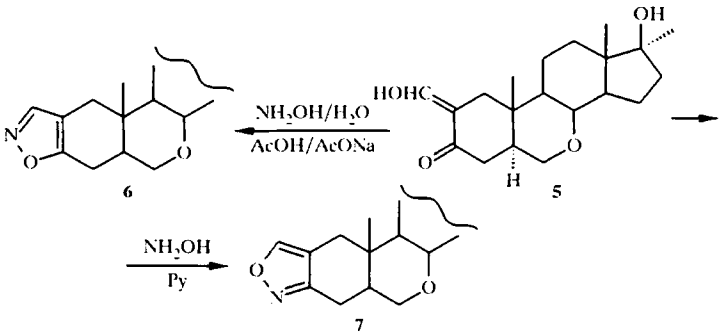
Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Minsk 220141; e-mail: litvin@ns.iboch.ac.by. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 291-314, March, 2000. Original article submitted January 11, 1999.

0009-3122/00/3603-0233$25.00©2000 KluwerAcademic/Plenum Publishers

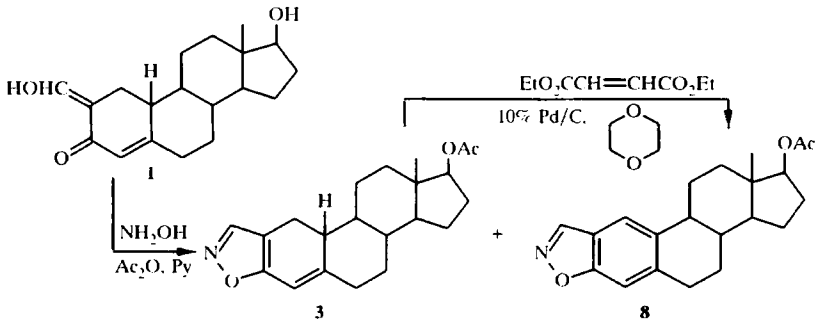


R = H, OH, Me; R^1 = H, Me; R^2 = H, Me; R^3 = H, Me; R^4 = H, Me, Et, $CH{=}CH_2$, $C{\equiv}CR^{10}$; R^5 = Me, OH, OMe, OAc, $OCOCH_2CH_2Ph$; R^4R^5 = O, OCH_2CH_2O; R^6 = H, Me; R^7 = H, OH; R^8 = H, F; R^9 = H, Me; R^{10} = Ph, C_6H_4F, 2-pyridyl, $C_6H_4NO_2$-4, $C_6H_4NMe_2$-4, $C_6H_4CF_3$-3

Analogous reactions were studied in a series of 7-oxa analogs of steroids [22]. The synthesis of the isomeric 7-oxaandrostanoisoxazoles was effected by the addition of hydroxylamine to 2-hydroxymethylene-7-oxaandrostan-3-one (**5**). The [2,3-*d*]isoxazole **6** is formed in aqueous acetic acid in the presence of sodium acetate, however in pyridine the regiomeric [3,2-*c*]isoxazole **7** was obtained.

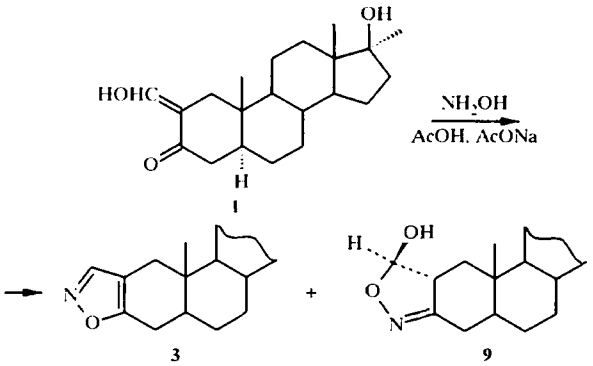


An unusual case of disproportionation of steroid derivatives was observed on using a similar method for the synthesis of [2,3-*d*]isoxazoles of the 19-norandrostane series [15].



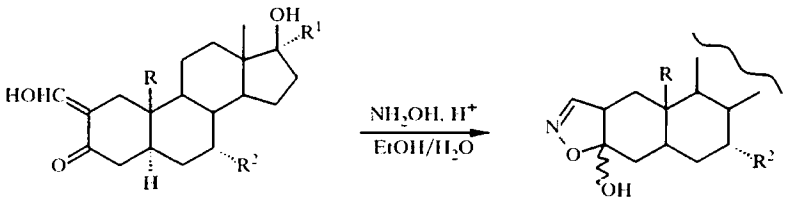
For example, on treating 2-hydroxymethylenestra-4-en-17β-ol-3-one **1** with hydroxylamine and subsequently acetylation, in addition to the desired isoxazole **3** (35% yield) isoxazole **8** was isolated, which is the A ring aromatization product (65% yield). An analogous A ring aromatization takes place under the action of ethyl maleate and 10% Pd/C in boiling dioxane on [2,3-*d*]isoxazoles of type **3** [23].

The addition of hydroxylamine to 2-hydroxymethylene-3-oxosteroid **1** in ethanol in the presence of sodium acetate was described in [4]. Together with the formation of the [2,3-*d*]steroidoisoxazole **3**, a small quantity (15% yield) of the [3,2-*c*]-5'-hydroxy-Δ^2-steroidoisoxazoline **9** was noted.



1 **3** **9**

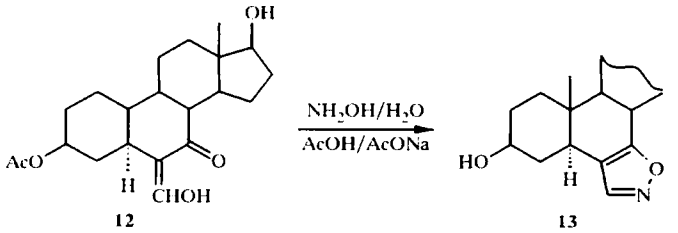
Isoxazoles **11**, regiomeric with product **9**, were synthesized from the 2-hydroxymethylene-3-ketones **10** and hydroxylamine on carrying out the reaction in neutral or weakly acidic aqueous alcohol solution [24, 25].



10 **11**

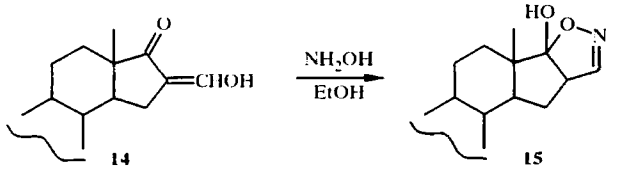
R = H, Me; R^1 = H, Me; R^2 = H, SEt

Only the [6,7-*d*]steroidoisoxazole **13** (45% yield) was obtained as a result of the interaction of the 6-hydroxymethylene-7-ketone **12** with an aqueous solution of hydroxylamine in acetic acid in the presence of sodium acetate [11].



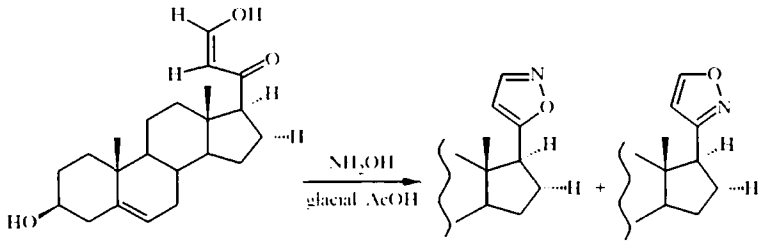
12 **13**

This method also proved to be convenient for the synthesis of certain isoxazolines condensed with the steroid molecule at the $C_{(16)}$–$C_{(17)}$ bond. Treatment of 16-hydroxymethylene-17-oxo derivatives **14** of androstane and estrane with hydroxylamine leads to [16,17-*d*]steroidoisoxazolines **15** in yields up to 70% [26, 27].



14 **15**

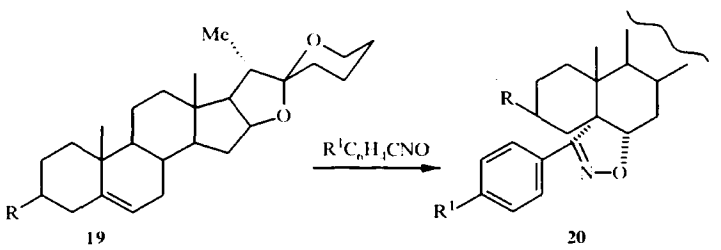
On condensing the 21-formyl derivative **16** (existing mainly in the keto-enol form) with hydroxylamine in glacial acetic acid in the presence of sodium acetate the 5'-substituted isoxazole **17** was obtained. Without sodium acetate a mixture of the 5'-and 3'-substituted isoxazoles **17** and **18** respectively was formed. Reaction of the 16,17-dehydro analog of compound **16** with hydroxylamine both in methanol and in glacial acetic acid, irrespective of the presence or absence of sodium acetate, leads only to the 16,17-dehydro analog of product **17** [28].



16 17 18

2. Synthesis of Steroidal Isoxazoles and Isoxazolines by the 1,3-Dipolar Cycloaddition Method

One of the important methods of synthesis of steroidal isoxazoles and their derivatives is the 1,3-dipolar cycloaddition of nitrile oxides to an unsaturated bond of the steroid molecule. 3'-Substituted [5α,6α-*d*]steroidoisoxazolines **20** were obtained as a result of such addition of aryl nitrile oxides to the spirost-5-ene derivative **19** [29]. The reaction was carried out in a benzene–ether mixture and the nitrile oxides were generated from the corresponding hydroxamic acid chlorides by the action of sodium hydroxide solution. Yields of products **20** were 64-90%, the highest yield being in the case of *p*-methoxybenzonitrile oxide. The formation of isomeric isoxazolinylsteroids was not observed.

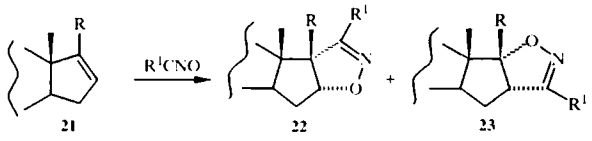


19 20

R = H, Cl, OH, OMe, OEt, OAc; R¹ = H, Me, Cl, OMe

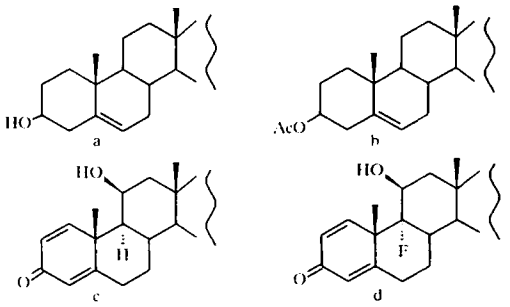
The 1,3-dipolar cycloaddition of nitrile oxides to Δ^{16}-steroids occurs ambiguously. The stereochemistry, the ratio of isomers, and the yields of the products formed depend both on the substituent at the $C_{(17)}$ atom and on the nature of the nitrile oxide used in the reaction and/or the solvent. Thus, the synthesis of 3'-substituted [17α,16α-*d*]steroidoisoxazolines **22** was effected in high yield (82-92%) by the cycloaddition of nitrile oxides to Δ^{16}-steroids **21a,b** (R = Ac; R' = Me, Ph, CO_2Et). The nitrile oxides were generated from hydroxamic acid halides [30, 31].

However the addition of carbethoxyformonitrile oxide to Δ^{16}-steroid **21b** (R = Ac) in ether proceeds slowly and leads to the [16α,17α-*d*] isomer **23b** (R' = $EtCO_2$) in 80% yield [32]. When R = $C(O)CH_2OH$ or $C(O)CH_2OAc$, and THF was used as solvent, the yield of product **23** reached 97% [33]. The formation of [16α,17α-*d*]steroidoisoxazolines **23c,d** (R' = H) in moderate yields (44-45%) was observed in the addition reaction of formonitrile oxide in anhydrous ether to 1,4,16-pregnatrienes **21c,d** [R = $C(O)CH_2OH$] or their 21-acetoxy derivatives [34].



21 22 23

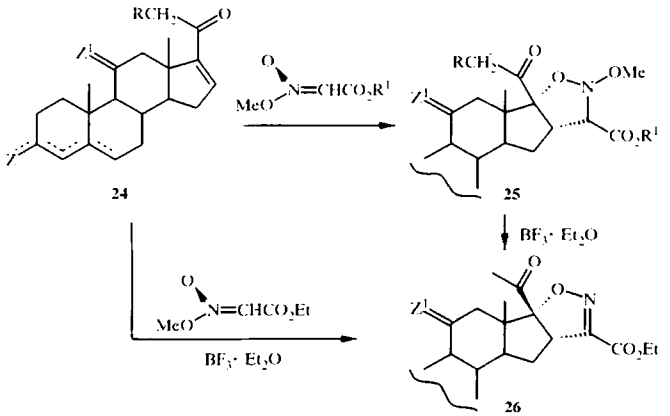
R = H, Ac, C(O)CH$_2$OH, C(O)CH$_2$OAc; R^1 = H, Me, Ph, CO$_2$Et



a b c d

In the case of the 1,3-dipolar cycloaddition of acetonitrile oxide (generated from acetylhydroxamoyl chloride and triethylamine in ether) to dehydropregnenolone acetate **21b** (R = Ac) in ether solution the regioisomeric addition products at the Δ^{16}-bond **22b** and **23b** were obtained in a ratio of 1 : 9 [35]. A mixture of [17α,16α-*d*]- and [16α,17α-*d*]androstenoisoxazolines **22b** and **23b** (R^1 = Me) was obtained in a ratio of 3 : 1 from acetonitrile oxide (obtained from nitroethane and phenyl isocyanate in benzene solution in the presence of triethylamine) and 3β-acetoxyandrosta-5,16-diene **21b** (R = H). The regiodirection in this case is opposite to that in the reaction with the acetyl derivative **21b** [36].

The authors of [37-41] investigated the addition of nitrone esters to Δ^{16}-steroids. For example the [16α,17α-*d*]steroidoisoxazoline **26** was obtained in 94% yield from 16-dehydropregnenolone acetate **24** (R = H; Z = H, OAc; Z^1 = H$_2$) and carbethoxymethanenitronic acid methyl ester in dichloromethane in the presence of boron trifluoride etherate [37, 38].



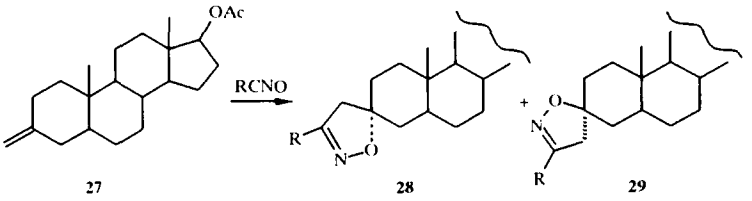
24 25 26

R = H, Me, CH$_2$OAc; R^1 = Me, Et; Z = O, OH, OAc; Z^1 = O, H$_2$

N-Methoxy[16α,17α-*d*]oxazole derivatives of pregnane **25** have been obtained in 65-80% yield by 1,3-dipolar addition of nitrone esters to 16-dehydro-20-oxosteroids **24** at high pressure (12-14 kbar) in polar organic solvents [39-41]. The reaction occurs regiospecifically, which was confirmed by the transformation of the obtained N-methoxyoxazole **25** (R = H, Z = OAc, Z^1 = H$_2$) into isoxazoline **26** in dichloromethane in the presence of trace amounts of boron trifluoride etherate.

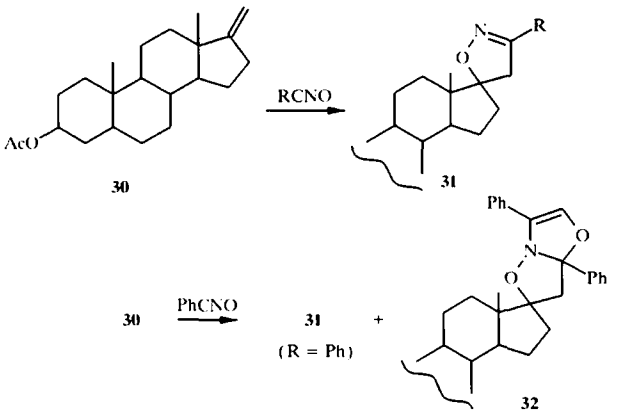
Treatment of 3- and 17-methylene derivatives of steroids with nitrile oxides gave 3- and 17-spiroisoxazolines [42-44]. The 3-methylene derivative **27** was obtained from the corresponding 3-oxosteroid by the Wittig reaction. Addition to compound **27** of methyl- and benzonitrile oxides (generated from the

corresponding hydroxamoyl chlorides and triethylamine in tetrahydrofuran at room temperature) gave a mixture (about 3 : 1) of the 3α- (**28**) and 3β-isomers (**29**) (R = Me, Ph) with the α-isomer predominating. On interacting the same 3-methylenesteroid **27** with ethoxycarbonylformo- and 2,4,6-trimethylbenzonitrile oxides only the 3α-isomer **28** (R = COOEt, $C_6H_2Me_3$-2,4,6, yields 60 and 25% respectively) was obtained [42]. The 3α-isomer **28** (R = CO_2Et) was formed in 39% yield [43] from the methylene derivative **27** and ethoxycarbonylformonitrile oxide in dioxane at 60°C during two days, but in the case of triphenylmethylnitrile oxide under the same conditions a mixture (1 : 1) of the two epimeric isoxazolines **28** and **29** (R = CPh_3) was obtained in 87% total yield [44].



R = Me, Ph, CO_2Et, $C_6H_2Me_3$-2,4,6, CPh_3

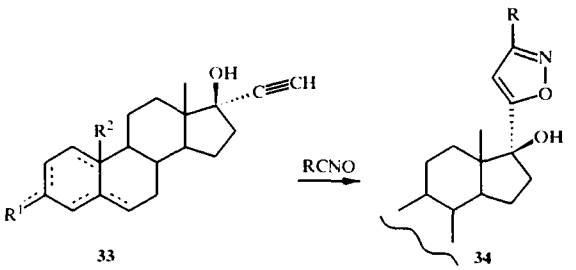
The addition of methyl-, benzo-, and 2,4,6-trimethylbenzonitrile oxides to 17-methylenesteroid **30** leads in each case to a single product, *viz.* the 3'-substituted 17-spiro-5'-(2-isoxazoline) **31** (60-70% yields). The nitrile oxide required was generated from the appropriate hydroxamoyl chloride by the action of triethylamine in tetrahydrofuran at room temperature or by boiling the required hydroxamoyl chloride in toluene.



R = Me, CO_2Et, $C_6H_2Me_3$-2,4,6

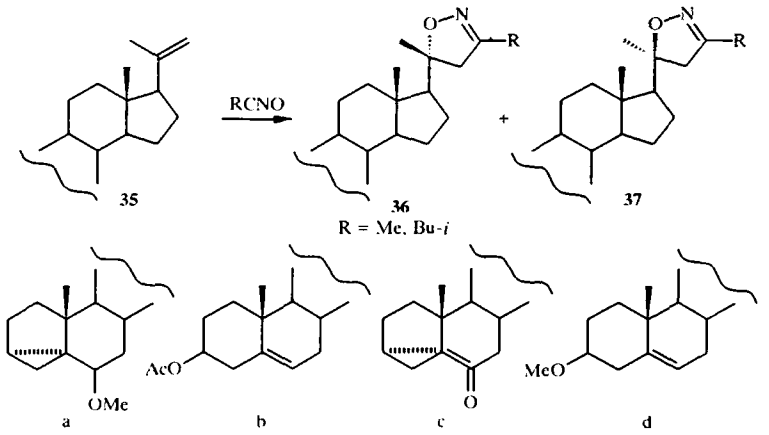
As a result of the reaction of the same steroid **30** with benzonitrile oxide at room temperature in addition to compound **31** (R = Ph, 70% yield) an insignificant quantity (5%) of the product of addition of two molecules of nitrile oxide **32** was formed. The stereochemistry of the adducts was not shown by the authors. Attempts to synthesize compounds of type **32** from steroidal isoxazoles obtained from other nitrile oxides were not successful [42].

1,3-Dipolar cycloaddition of nitrile oxides may also occur at an unsaturated bond of the steroid side chain with the formation of isoxazoles or isoxazolines containing a steroid residue as a substituent. The isoxazoles **34** were obtained in yields up to 80% by the action of various nitrile oxides on the 17α-ethynyl-17β-hydroxysteroids **33** [45, 46].



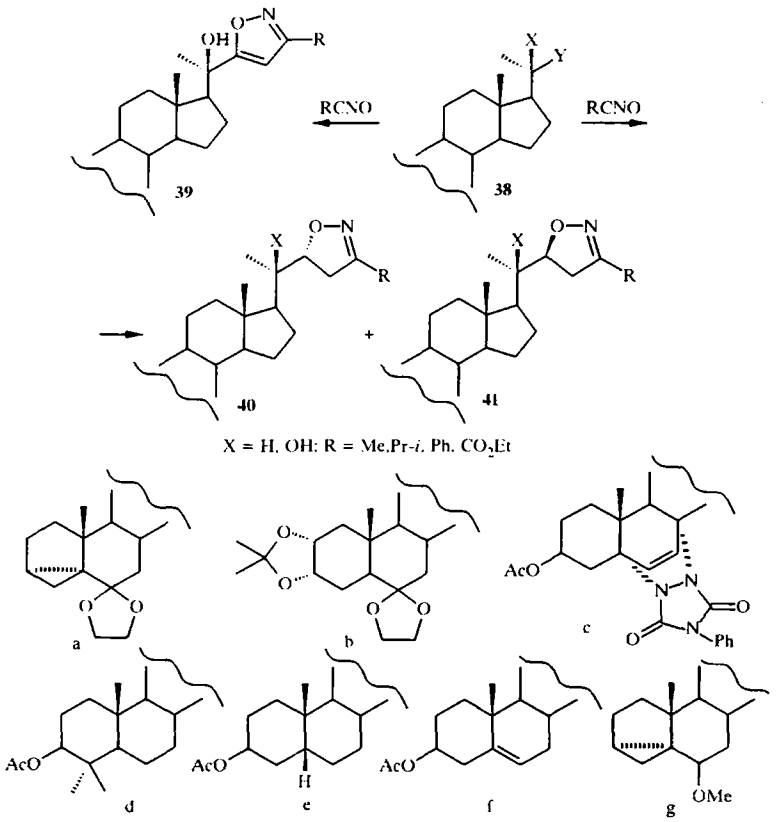
R = Me, Ph, CO_2Et; R^1 = O, OH, OMe; R^2 = H, Me

In the case of $\Delta^{20(22)}$-steroids **35** a mixtures of the stereoisomeric isoxazolines **36** and **37** were obtained.



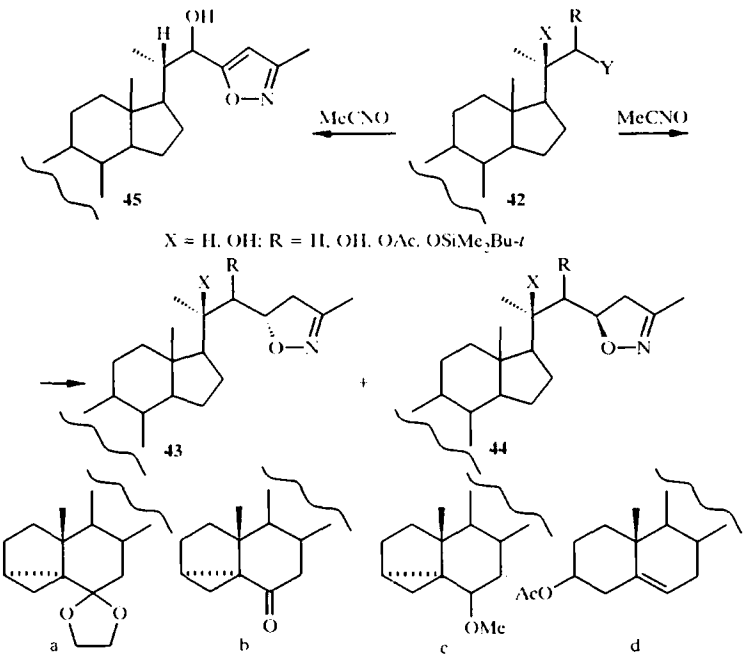
The addition proceeds regioselectively and with a significant degree of stereoselectivity. The ratio **36** : **37** was 3 : 1, i. e. the epimer formed preferentially is the product of attack by nitrile oxide at the double bond at the sterically less hindered side (the α-side of the steroid). The result of the reaction depends on the character of the substituent R of the nitrile oxide. For example, when R = 2-Pr no cycloaddition products were detected [47, 48].

On reacting the acetylenic derivative **38f** (X = OH, Y = C≡CH) in tetrahydrofuran or ether with aceto- or isobutyronitrile oxide the substituted isoxazoles **39f** were obtained in yields up to 60% [49, 50].



In the case of the olefins **38** (X = H, OH, Y = CH=CH_2) only one regiomer of the substituted isoxazoline is formed as a mixture of 5'-(*R*)- and 5'-(*S*)-epimers **40** and **41** the ratio of which (from 1.5 : 1 to 6 : 1) depends in this case not only on the structure of the nitrile oxide used as the dipole, but also on the structure of the cyclic part of the actual steroidal compound [47, 51-58].

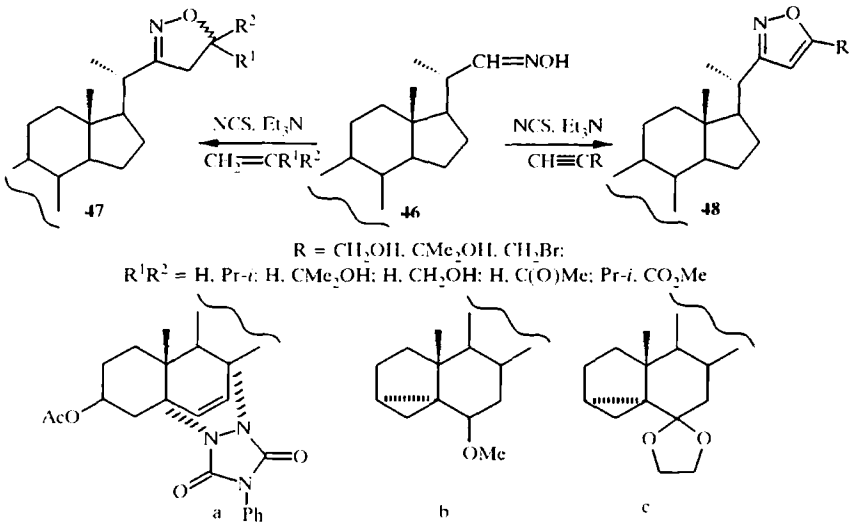
The addition of nitrile oxides to Δ^{21}-steroids takes place regioselectively but the stereoselectivity depends essentially on the nature of the substituent in the position α to the double bond. The interaction of (20*S*,22*S*)-22-hydroxy-23-enes **42a,b** (R = OH, Y = CH=CH_2) with acetonitrile leads to the 5'-epimeric isoxazolines **43** and **44** (ratio 4.5 : 1) in 87-89% yield. The preferred formation of the *threo*-isomer **44** proved to be unexpected. On reacting the (20*S*,22*S*)-22-acetoxy derivatives **42a,b** (R = OAc, Y = CH=CH_2) practically no stereoselectivity was observed for the process and the two epimeric isoxazolines were formed in equal quantities. On protecting the hydroxyl function by a bulky substituent (R = $OSiMe_2Bu$-*t*) the reaction became stereoselective and only the (22*R*,5'*S*)-diastereomer was obtained. However the yields of the products were low [59, 60].



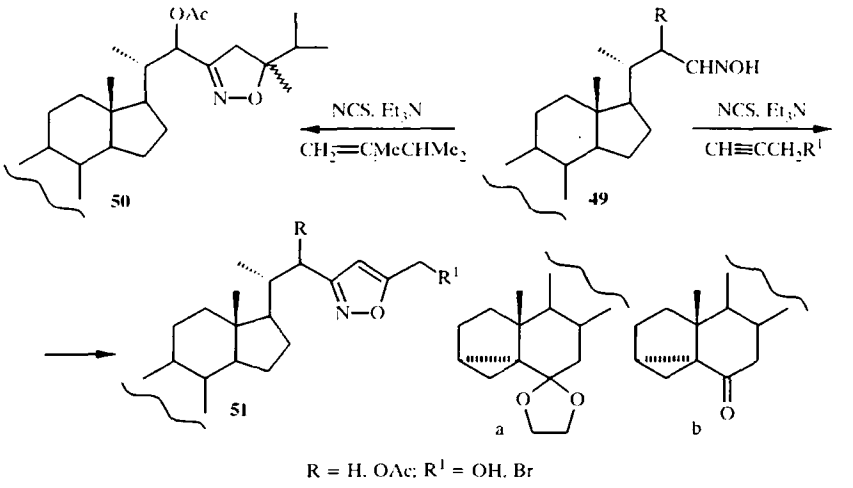
Addition of acetonitrile oxide to the (20*S*,22*R*)-isomer of **42a,b** (R = OH, X = H, Y = CH=CH_2) occurred regioselectively, as in the case of the (22*S*)-epimer, with the preferential formation of the (22*S*,5'*S*)-isomer but the degree of selectivity was reduced and the ratio of *threo* : *erythro* products **43** : **44** was 2 : 1. The preferred formation of the *threo*-isomer when using (20*S*,22*R*)-22-acetoxy-23-ene **42** (R = OAc, X = H, Y = CH=CH_2) as dipolarophile was noted [59, 61].

Investigation of the interaction of β-hydroxyolefins **42c,d** (R = H, X = OH, Y = CH=CH_2) with acetonitrile oxide showed that this leads to the formation of one regiomer as a mixture of the two 5'-epimers **43** and **44** (R = H, X = OH) in a ratio of 1 : 1 [62].

The isoxazoles **45** were obtained from the acetylenic alcohols **42c** (R = H, X = H, Y = C≡CH) and acetonitrile oxide (65-78% yield) [63]. On using steroidal $C_{(22)}$- and $C_{(23)}$-nitrile oxides as dipole in the 1,3-dipolar cycloaddition reaction with olefins the compounds regioisomeric to that described above were obtained. 1,1-Substituted ethylenes were the dipolarophiles in this case. The reaction of the $C_{(22)}$-steroidal nitrile oxides generated from the oximes **46a,b** with olefins (allyl alcohol, 2-methyl-3-buten-2-ol, methyl vinyl ketone, 3-methyl-1-butene, methyl 2-isopropylacrylate) led in each case to a mixture (1 : 1) of epimers **47a,b** (64-84% yield) [64,65]. The isoxazoles **48a,c** were obtained by addition to an acetylenic derivative (propargyl bromide, propargyl alcohol, 2-methyl-3-butyn-2-ol) (85-98% yield) [66, 67].

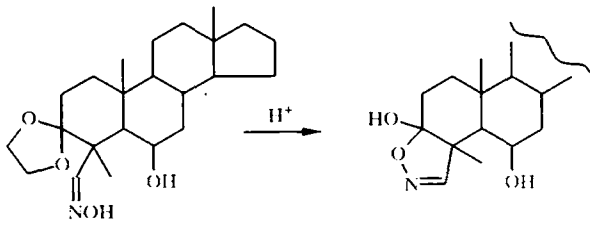


The interaction of the $C_{(23)}$-nitrile oxide, generated from oxime **49**, having an oxygen-containing substituent in the α-position to the nitrile oxide group, with 2,3-dimethyl-1-butene leads to the isoxazoline **50** (yield 70-78%). The cycloaddition proceeds regioselectively but no stereoselectivity was observed in the reaction. Interaction of the same nitrile oxide with propargyl alcohol or bromide leads to the cycloadducts **51** (83-95% yield) [68, 69].



3. Other Methods of Synthesis of Steroidal Isoxazoles

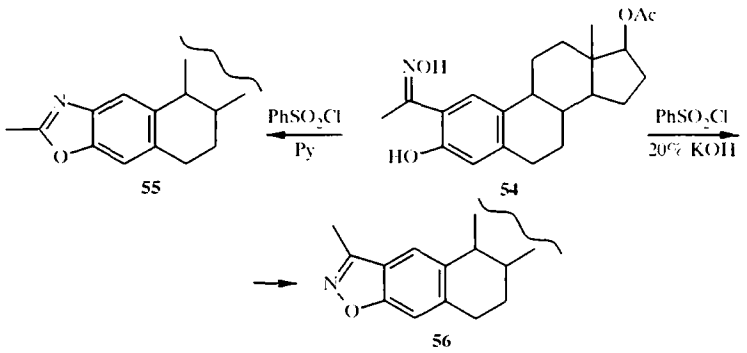
Study of aldoximes showed that acidic treatment of 3,3-ethylenedioxy-4α-aldoxime **52a** leads to a mixture of isoxazolines **53** isomeric at $C_{(3)}$, but the use of the 4β-oximino derivative **52b** under the same conditions enables only the corresponding 3β,4β-isomer of **53** to be obtained [70].



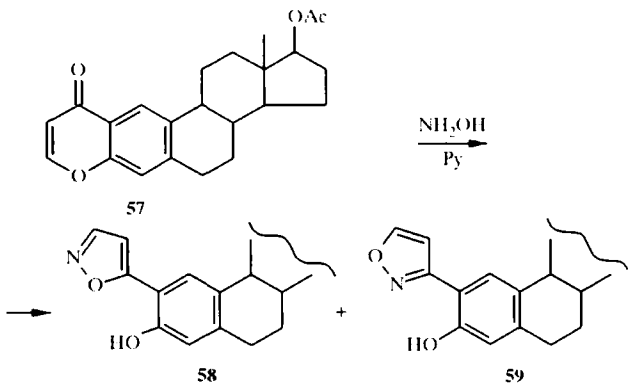
52a,b 53

a 4α-CH=NOH, 6α-OH; b 4β-CH=NOH, 6β-OH

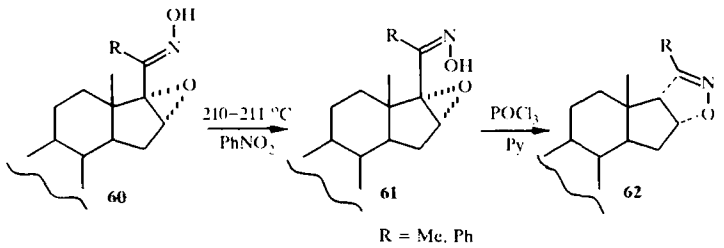
Reaction of the β-hydroxy oxime **54** with benzene- or toluenesulfonyl chloride in pyridine leads to the 2'-methylsteroid **55**. If the reaction was carried out in a dilute aqueous solution of potassium hydroxide, the main product was the 3'-methylsteroidisoxazole **56** [71, 72].



Treatment of compound **57** with hydroxylamine in pyridine leads to a mixture of the regiomeric 2-isoxazolylsteroids **58** and **59** [72].

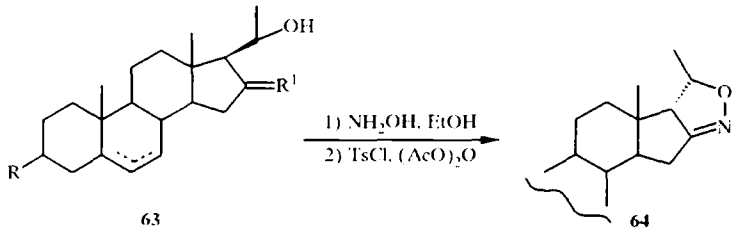


On boiling 20-oximes of 16α,17α-epoxysteroids **60** in nitrobenzene their isomers **61** were formed which under the action of phosphorus oxychloride in pyridine gave the [17α,16α-*d*]steroidoisoxazolines **62** [73].



R = Me, Ph

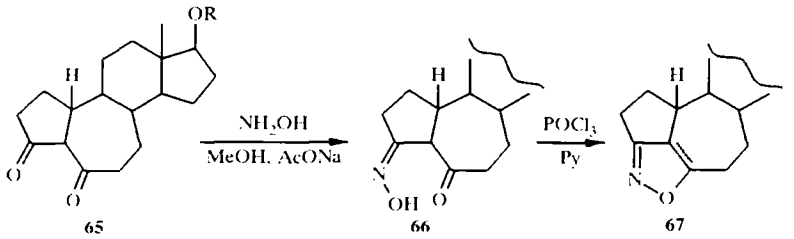
Reaction of 20-hydroxy-16-oxosteroids **63** (R^1 = O) with hydroxylamine in alcohol and subsequent Beckmann rearrangement of the resulting 16-oximes **63** (R^1 = NOH) under the action of *p*-toluenesulfonyl chloride or acetic anhydride gave steroido[16,17-*c*]isoxazolines **64** (85% yield). Cyclization of the oximes occurred with reversal of the configuration at $C_{(20)}$ [74].



63 64

R = α-AcO, β-AcO; R^1 = O, NOH

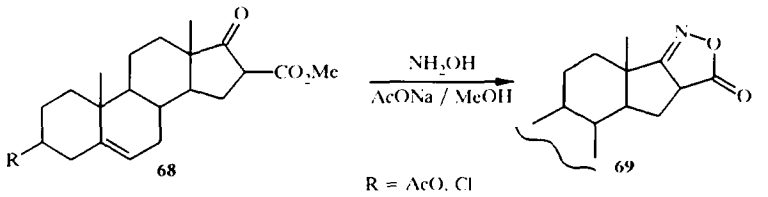
A mixture of *syn*- and *anti*-3-hydroxyimino-6-oxosteroids **66** was obtained from the 3,6-dioxo derivatives of the A-nor-B-homoestrane **65** and hydroxylamine in methanol in the presence of sodium acetate. Isomerization of the latter in formic acid and subsequent cyclization under the action of phosphorus oxychloride in pyridine led to [3,5,6-*cd*]isoxazoles **67** in about 40% yield [75, 76].



65 66 67

R = H, Ac, CHO

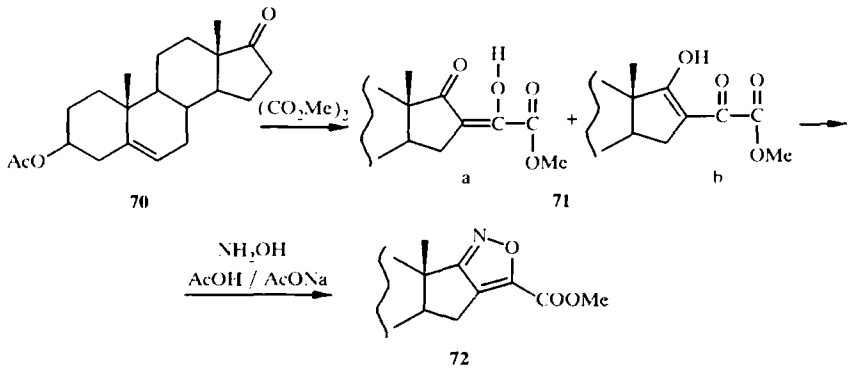
On boiling 16-methoxycarbonylandrost-5-en-17-ones **68** with hydroxylamine in methanol in the presence of sodium acetate, the steroidoisoxazolines **69** were synthesized in 51-52% yield [77].



68 69

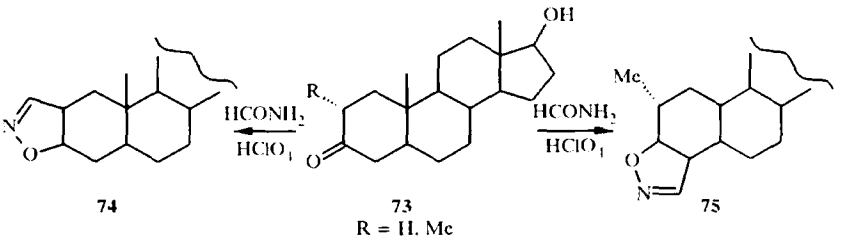
R = AcO, Cl

A mixture of tautomers **71a,b** in which compound **71a** predominated was obtained in 65% yield from 3β-acetoxyandrostane **70** with dimethyl oxalate in the presence of sodium methylate in pyridine. Reaction of compound **71a,b** with hydroxylamine hydrochloride in acetic acid in the presence of sodium acetate led to the steroidoisoxazole **72** [78].



70 71 72

A method has been developed to obtain compounds containing the isoxazoline ring which consists of the interaction of steroidal ketones with formamide in the presence of perchloric acid. In particular [2,3-*d*]steroidoisoxazoline **74** was obtained from dihydrotestosterone **73** (R = H) under these conditions in one stage [79-81].

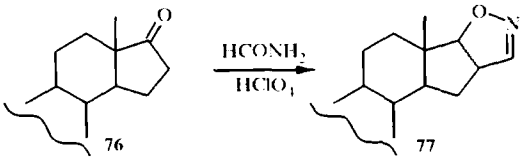


74 **73** **75**

R = H, Me

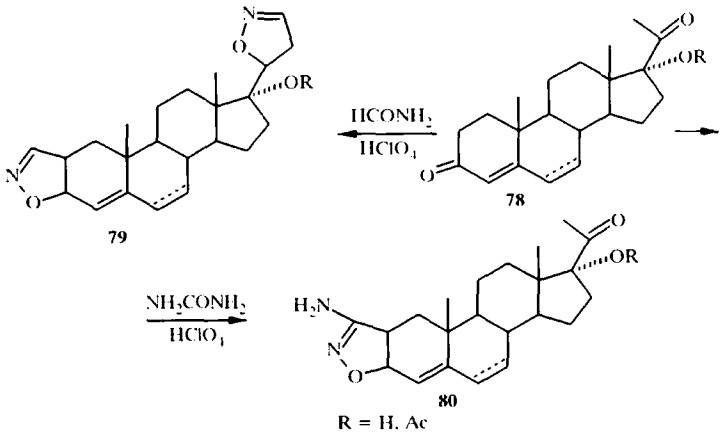
When there is a substituent in position 2 in the molecule of a 3-oxosteroid (R = Me), the isoxazoline grouping is added at the $C_{(3)}$–$C_{(4)}$ bond of ring A and leads to [4,3-*d*]steroidoisoxazoline **75**.

[16,17-*d*]Steroidoisoxazolines **77** were obtained from the 17-oxosteroids **76** under analogous conditions.



76 **77**

It is important to note that the method indicated differs favorably from previous methods since it does not require specially preformed starting keto steroids. The application of this method to the progesterone derivative **78** enabled compounds with two isoxazoline rings **79** to be obtained (yields about 40%).

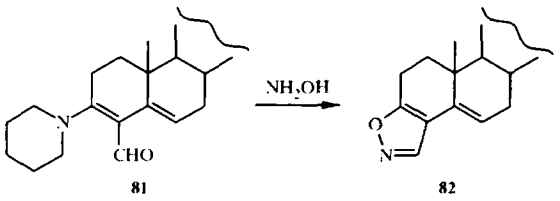


79 **78** **80**

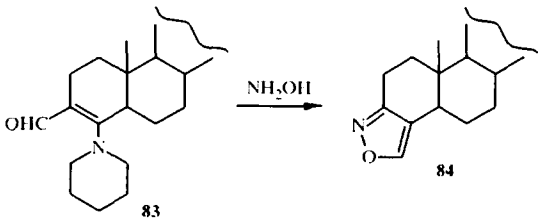
R = H, Ac

The derivatives **78** react somewhat differently with urea. In an aprotic solvent (such as β-methylnaphthalene) in the absence of acid catalysts only one urea molecule reacts with a steroid molecule even under forcing conditions with the formation of the 5'-amino[2,3-*d*]steroidoisoxazoline **80** in 30% (R = H) or 54% yield (R = OAc), i. e., the acyl group at position 17 does not react.

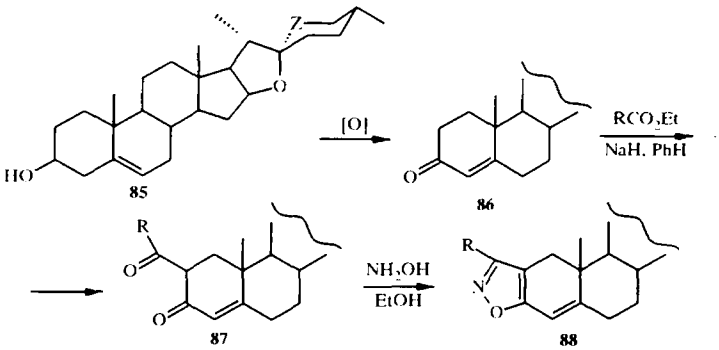
3-Enamines of 4-formyltestosterone **81** react with hydroxylamine forming [4,3-*d*]isoxazoles of the type of **82** [82].



When using the 4-enamino-3-formylsteroids **83** the [3,4-*c*]steroidoisoxazoles **84** regiomeric with compound **82** were obtained.

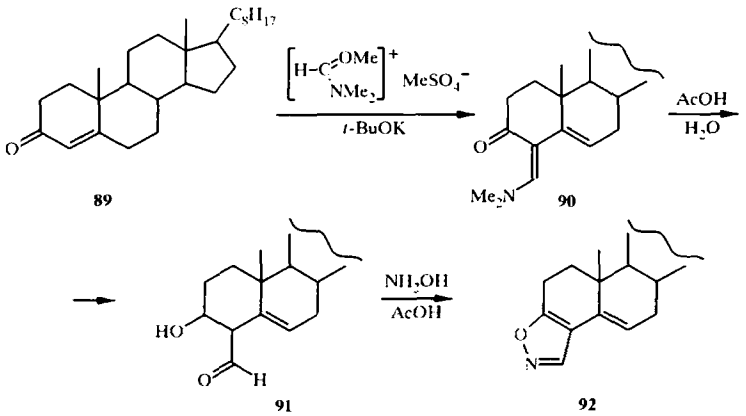


A method of synthesizing 3'-substituted [2,3-*d*]steroidoisoxazoles has been developed from 3-hydroxysteroids using diosgenin and solasodine as examples [83-85]. Oppenauer oxidation of the 3-hydroxy-Δ^5-steroids **85** leads to the 3-oxo-Δ^4 derivative **86**, reaction of which with ethyl formate, ethyl trifluoroacetate, or diethyl oxalate in benzene in the presence of sodium hydride gave the 2-acyl-substituted derivatives **87**. The action of hydroxylamine in boiling alcohol on the latter gave derivatives of diosgenin and solasodine **88** containing a 3'-substituted isoxazole ring (60-70% yields).



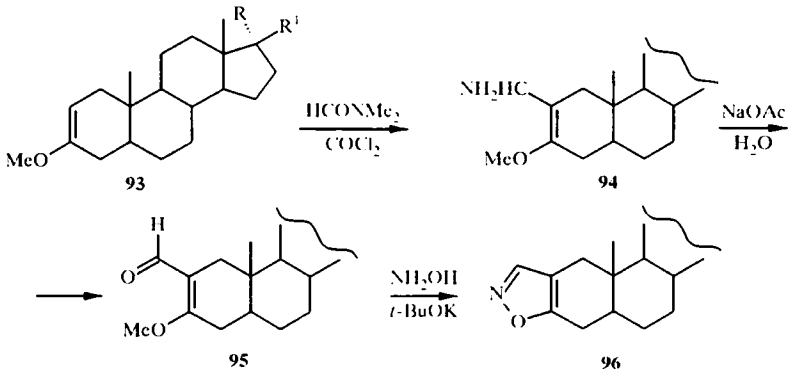
R = H, CF_3, CO_2Et; Z = O, NH

Conversion of 3-oxo-Δ^4-steroids into [4,3-*d*]steroidoisoxazoles has also been described in [86], where the ability of certain salts of dimethylformamide to react with carbanions was used.



The carbanion obtained by treating cholest-4-en-3-one **89** with seven equivalents of potassium *t*-butylate in tetrahydrofuran was converted by the action of methasulfate derivatives of dimethylformamide into 4-dimethylaminomethylenecholest-5-en-3-one **90**. Hydrolysis of the latter with aqueous acetic acid led to the 4-formyl derivative **91**. Reaction of compound **91** with hydroxylamine in acetic acid gave isoxazole **92** (62% yield).

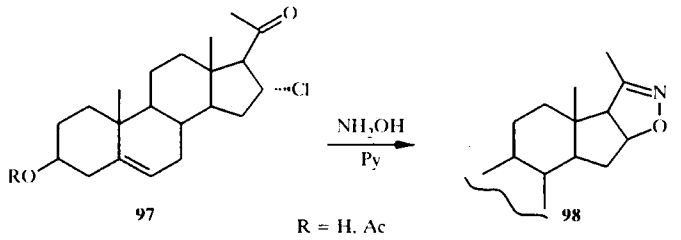
An approach to the synthesis of [2,3-*d*]steroidoisoxazoles was also developed from 3-methoxy-2-ene derivatives of androstenolone **93** [87]. Treatment of the latter with the Vilsmeier reagent (synthesized from dimethylformamide and phosgene), with subsequent hydrolysis of the resulting iminium salt **94** with aqueous sodium acetate gave compound **95**. Subsequent interaction of the resulting 2-formyl derivatives **95** with hydroxylamine in alkaline medium gave the isoxazoles **96**.



93 94 95 96

R = H, Me; R¹ = OH, OAc

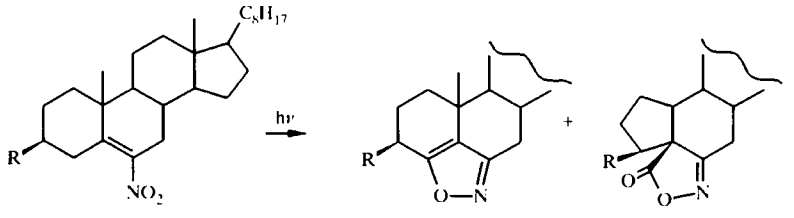
The corresponding 3'-isoxazolino[16,17-*d*]methylandrostanes **98** were obtained in high yield by the interaction of 16α-chloro derivatives of pregnane **97** with hydroxylamine in pyridine [88].



97 98

R = H, Ac

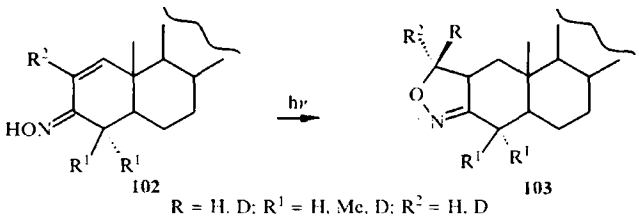
Cases of the formation of steroidal isoxazoles on photochemical irradiation of a series of steroid molecules have been described. Irradiation of 6-nitrocholestanes **99** in hexane, dioxane, or acetic acid with a medium pressure mercury lamp led to [6,5,4-*cd*]cholestenoisoxazoles **100** in 6-53% yield and A-norcholestanoisoxazolines **101** (when carrying out the reaction in acetic acid) in 2-5% yield, together with other products [89, 90].



99 100 101

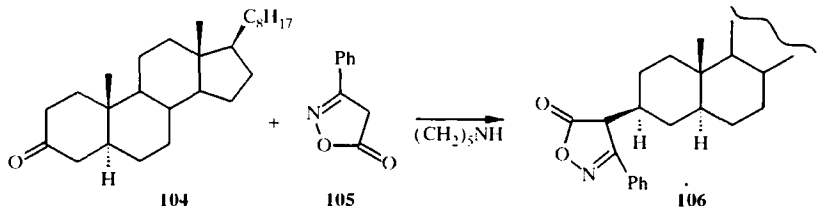
R = H, OAc

When investigating the photoconversions of the 3-ketoximes **102** a mixture of their *Z*- and *E*-isomers was subjected to irradiation in methanol or benzene (and also in their deuterated forms) by a medium pressure mercury lamp in an atmosphere of nitrogen. The yield of [3,2-*c*]steroidoisoxazolines **103** was 18-20% [91].



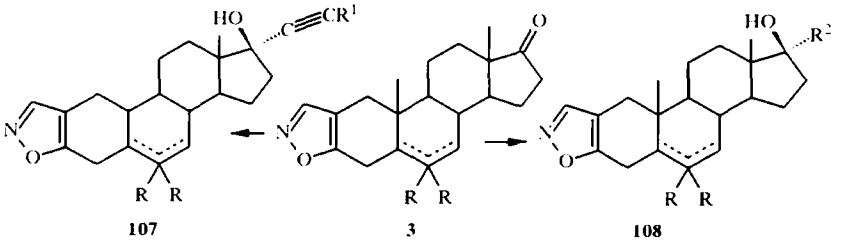
R = H, D; R^1 = H, Me, D; R^2 = H, D

By condensing cholestan-3-one **104** by the Knoevenagel reaction with the 4-substituted isoxazolinone **105** in ethanol in the presence of catalytic quantities of piperidine, and subsequent reduction of the resulting product with sodium borohydride, the steroidal isoxazolinone **106** was synthesized in 47% yield [92].



New functionalized steroidal isoxazoles have been synthesized by the interaction of keto steroids with organometallic compounds using the high stability of the isoxazole ring under the reaction conditions. The steroidal 17-acetylenes **107** were obtained by the ethynylation of 17-oxo[2,3-*d*]steroidoisoxazoles **3** with a mixture of trifluoromethylacetylene and ethylmagnesium bromide in dry tetrahydrofuran [93].

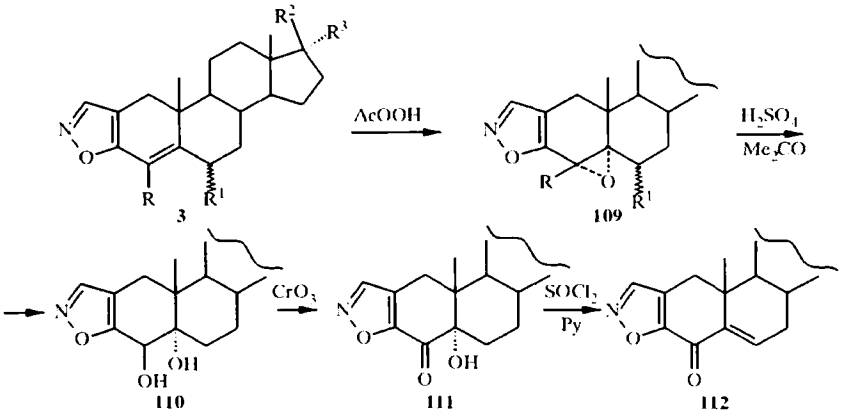
The method was developed using other organometallic compounds, containing zirconium in particular [94]. A large selection of new [2,3-*d*]steroidoisoxazoles **108** (yields up to 85%) were synthesized by reaction of the 17-oxosteroid **3** (R = H) with arylzirconium tributylates.



R = H, Me; R^1 = H, CF_3; R^2 = 2'-furyl, 3'-thienyl, $C_6H_4R^3$;
R^3 = H, 2'-OH, 4'-F, 4'-Me, 4'-OMe

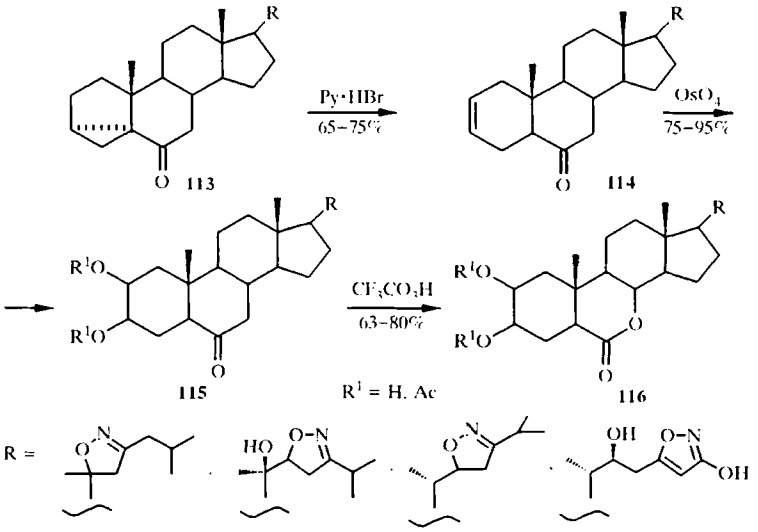
A series of 4,5-epoxy[2,3-*d*]steroidoisoxazoles **109** was obtained by treating Δ^4-compounds **3** with peracetic or perphthalic acids in benzene [10, 95-100]. The yield of the required epoxide was not great (about 30%), however conducting the reaction in chloroform or dichloromethane with permaleic or *m*-chloroperbenzoic acid in the presence of small quantities of pyridine enabled the yield of 4,5-epoxy[2,3-*d*]steroidoisoxazole to be increased to 80-90%.

The corresponding 4β,5α,17β-trihydroxy[2,3-*d*]steroidoisoxazole **110** was obtained in 76% yield on breaking the 4α,5α-epoxide **109** (R = R^1 = R^3 = H; R^2 = OH) with an aqueous acetone solution of sulfuric acid. Oxidation of compound **110** with chromic anhydride leads to the 4-oxoalcohol **111**, which was converted into the Δ^5-4-ketone **112** on treatment with thionyl chloride in pyridine [95].



R = H, Me; R^1 = H, Me; R^2 = H, C≡CH, Me, OH, $CH=CH_2$, OCOMe;
R^3 = H, OH, alkyl, OAc, R^2R^3 = OCH_2CH_2O

The stability of the heterocycle of 17- and 20-isoxazolinyl- and 22-isoxazolylsteroids enabled reactions to be carried out which were connected with the introduction of functionality characteristic of brassinosteroids into rings A and B.



The 6-ketones **113** were subjected to isomerization into the Δ^2-6-ketones **114** by the action of pyridinium bromide in boiling DMF. *Cis* hydroxylation of the Δ^2-bond by the action of osmium tetroxide in acetone in the presence of N-methylmorpholine N-oxide led to the 2α,3α-diols **115**. Introduction of the lactone function into ring B with the formation of the B-homo-7-oxa-6-ketone **116** was effected by Bayer–Williger oxidation with trifluoroperacetic acid [58, 96].

Biological testing of the isoxazole derivatives of the steroids described above showed that they possess various forms of biological activity depending on their structure. The data on biological activity are summarized in Table 1.

TABLE 1. Biological Activity of Steroidal Isoxazoles

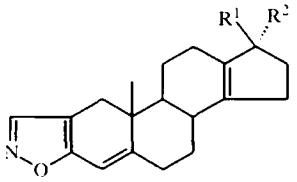
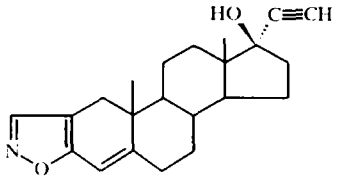
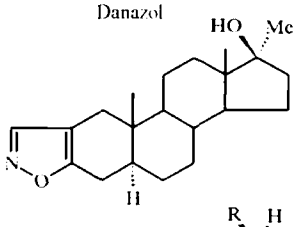
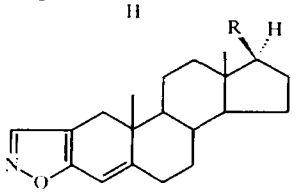
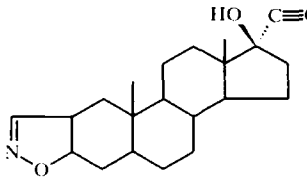
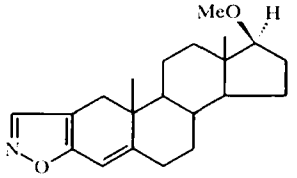
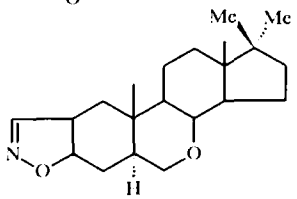
Structural formula	Substituent	Activity	References
1	2	3	4
	$R^1 = H$, $R^2 = OAc$; $R^1 = R^2 = Me$	Androgenic, equal to 1/5 activity of testosterone	[5]
 Danazol		Testosterone inhibitor	[102, 103]
		Endocrine	[4]
	R = β-OAc, β-OH	Anabolic - androgenic	[11]
		Estrogenic	[93]
		Enzyme inhibitor	[8]
		Antigonado-tropic	[22]

TABLE 1 (continued)

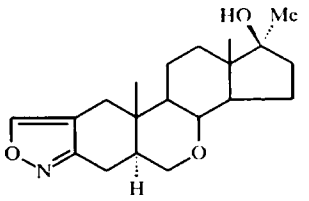
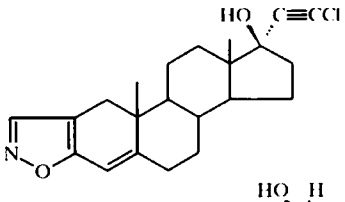
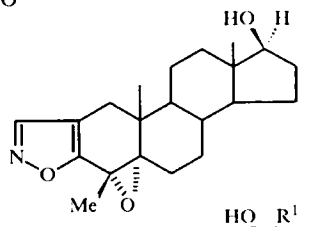
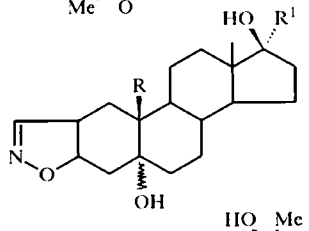
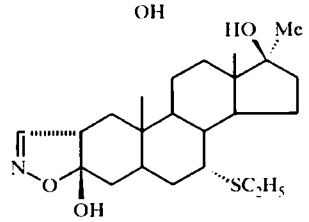
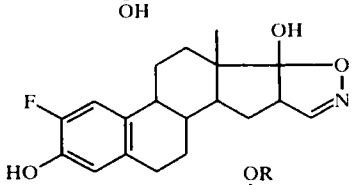
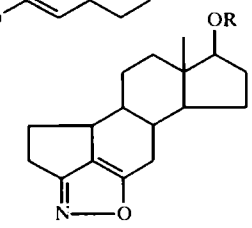
1	2	3	4
		Antigonado-tropic	[22]
		Abortive agent	[104]
		Contraceptive	[97]
	R = H, Me R¹ = H, Me, Et, CH=CH₂	Depresses gonadotropin of the hypophysis	[24]
		Myotropic, anabolic	[25]
		Reduces cholesterol content, estrogenic	[27]
	R = H, Ac, formyl	Anabolic	[75] [76]

TABLE 1 (continued)

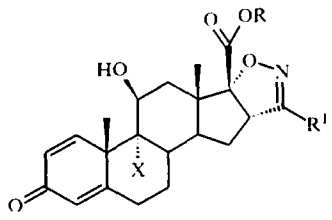
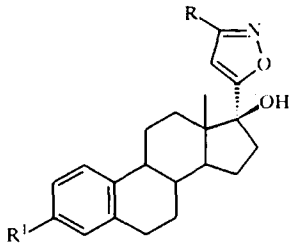
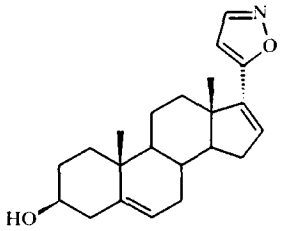
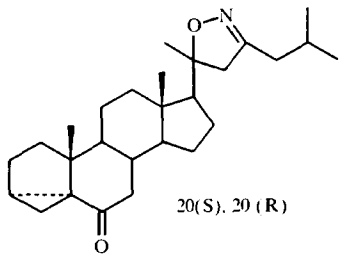
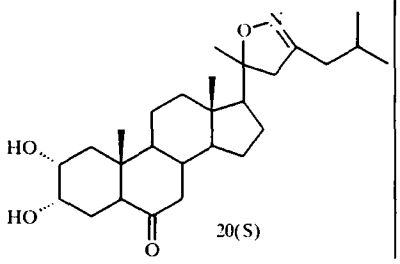
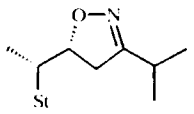
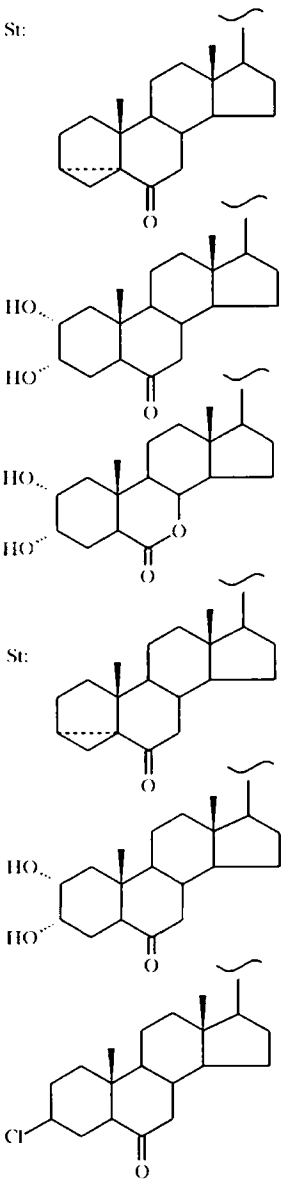
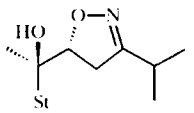
1	2	3	4
	R = H, Ac R^1 = H, CO_2Et X = H, F	Anti-inflammatory	[33] [34]
	R = Ph, Me, CO_2Et, R^1 = OH, OMe	Antiovulatory	[45]
		Potential inhibitor of cytochrome P-450	[28]
 20(S), 20 (R)		Growth stimulant	[105]
 20(S)		Growth stimulant	[105]

TABLE I (continued)

1	2	3	4
		Growth stimulant	[105] [106] [107]
		Growth stimulant	[105]

REFERENCES

1. A. A. Akhrem and Yu. A. Titov, *Usp. Khim.*, **36**, 745 (1967).
2. A. V. Kamernitzky and A. M. Turuta, *Heterocycles*, **7**, 547 (1977).
3. C. Camoutsis, *J. Heterocycl. Chem.*, **33**, 539 (1996).
4. A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, D. K. Phillips, G. O. Potts, A. Arnold, A. L. Beyler, and R. O. Clinton, *J. Med. Chem.*, **6**, 1 (1963).

5. E. Caspi and D. M. Piatak, *Can. J. Chem.*, **41**, 2294 (1963).
6. R. O. Clinton and A. J. Manson, US Pat. 3135743; *Chem. Abstr.*, **61**, 5730 (1964).
7. P. J. Palmer, *J. Chem. Soc.*, No. 7, 3901 (1963).
8. J. C. Babcock and J. A. Campbell, US Pat. 3980638; *Chem. Abstr.*, **86**, 43912 (1977).
9. F. Winternitz, C. Menou, and E. Arnal, *Bull. Soc. Chim. France*, 505 (1960).
10. R. G. Christiansen, Ger. Pat. 2855091; *Chem. Abs.*, **92**, 6812 (1980).
11. E. Caspi and D. M. Piatak, *Chem. Ind.*, 1984 (1962).
12. R. O. Clinton, US Pat. 3515735; *Chem. Abstr.*, **73**, 45694 (1970).
13. T. Nambara, K. Shimada, S. Iwamura, M. Mori, and M. Nokubo, *Chem. Pharm. Bull.*, **21**, 2474 (1973).
14. A. A. Shishkina, T. I. Ivanenko, V. M. Rzheznikov, and K. K. Pivnitskii, *Khim.-farm. Zh.*, **8**, No. 1, 7 (1976).
15. P. Ruggieri, C. Gandolfi, and U. Guzzi, *Tetrahedron Lett.*, No. 50, 4603 (1965).
16. V. Kumar and A. B. Todaro, *Synthesis*, No. 6, 523 (1992).
17. S. Giacopello, M. E. Deluca, and A. M. Seldes, *Z. Naturforsch. B*, **47**, 891 (1992).
18. E. Marchetti and P. Donini, *Gazz. Chim. Ital.*, **91**, 1133 (1961).
19. P. J. Dharam and R. Y. Mange, Indian Pat. 166480; *Chem. Abstr.*, **117**, 49006 (1992).
20. M. A. Viswamitra, R. Radhakrishnan, J. Bandekar, and G. R. Desiraju, *J. Am. Chem. Soc.*, **115**, 4868 (1993).
21. L. H. Briggs, J. P. Bartley, and P. S. Rutledge, *J. Chem. Soc. C*, No. 11, 2115 (1971).
22. R. W. Guthrie, R. W. Kierstead, and R. A. Le Mahieu, US Pat. 3869467; *Chem. Abstr.*, **83**, 43609 (1975).
23. P. Ruggieri, C. Gandolfi, and U. Guzzi, *Tetrahedron Lett.*, No. 2, 205 (1966).
24. R. G. Christiansen and J. C. Collins, Ger. Pat. 3018903; *Chem. Abstr.*, **95**, 25400 (1981).
25. H. Kaneco, K. Nakamura, J. Jamato, and M. Kurokawa, *Chem. Pharm. Bull.*, **17**, 11 (1969).
26. K. Bruckner, K. Irmsher, F. Werder, K.-H. Bork, and H. Mets, *Chem. Ber.*, **94**, 2897 (1961).
27. D. Bertin and L. Nedelec, US Pat. 3629245; *Chem. Abstr.*, **76**, 86006 (1972).
28. Y. Ling, I. Li, Y. Liu, K. Kato, G. T. Klus, and A. Brodie, *J. Med. Chem.*, **40**, 3297 (1997).
29. A. U. Siddiqui, A. H. Siddiqui, and T. S. Ramian, *J. Indian Chem. Soc.*, **69**, 282 (1992).
30. W. Fritsch, G. Seidl, and H. Ruschig, *Liebigs Ann. Chem.*, **677**, 139 (1964).
31. U. Stache, W. Fritsch, and H. Ruschig, *Liebigs Ann. Chem.*, **685**, 228 (1965).
32. G. W. Moersch, E. L. Wittle, and W. A. Neuklis, *J. Org. Chem.*, **40**, 1272 (1965).
33. T. Kwon, A. S. Heiman, E. T. Oriaku, K. Yoon, and H. J. Lee, *J. Med. Chem.*, **38**, 1048 (1995).
34. M. Khalil, M. F. Maponya, D.-H. Ko, Z. You, E. T. Oriaku, and H. J. Lee, *Med. Chem. Res.*, No. 6, 52 (1996).
35. A. Ius, C. Parini, G. Sportoletti, G. Vecchio, and G. Ferrara, *J. Org. Chem.*, **36**, 3470 (1971).
36. T. Kametani, H. Furuyuma, and T. Honda, *Heterocycles*, **19**, 357 (1982).
37. I. S. Levina, E. I. Mortikova, and A. V. Kamernitzky, *Synthesis*, No. 8, 562 (1974).
38. A. V. Kamernitzky and I. S. Levina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 5, 1139 (1980).
39. A. V. Kamernitzky, I. S. Levina, and E. M. Mortikova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 8, 1924 (1977).
40. A. V. Kamernitzky, I. S. Levina, E. I. Mortikova, and B. S. El'yanov, *Tetrahedron Lett.*, No. 37, 3235 (1975).
41. I. S. Levina, A. V. Kamernitzky, E. I. Mortikova, B. S. El'yanov, and V. M. Zhulin, Authors Certificate USSR 491625; *Byull. Izobret.*, No. 42, 60 (1975).
42. C. Parini, S. Colombi, A. Iric, R. Longhi, and G. Vecchio, *Gazz. Chim. Ital.*, **107**, 559 (1977).
43. J. Kalvoda and H. Kaufmann, *J. Chem. Soc., Chem. Commun.*, No. 6, 209 (1976).
44. H. Kaufman and J. Kalvoda, *J. Chem. Soc., Chem. Commun.*, No. 6, 210 (1976).
45. H. Laurent, *Rev. Soc. Quim. Mex.*, **13**, 218A, (1969).
46. A. A. Akhrem, F. A. Lakhvich, and V. A. Khripach, *Zh. Obshch. Khim.*, **45**, 2572 (1975).
47. A. V. Baranovsky, R. P. Litvinovskaya, and V. A. Khripach, *Zh. Org. Khim.*, **26**, 1274 (1990).

48. N. I. Garbuz, G. P. Yankovskaya, A. V. Baranovsky, R. P. Litvinovskaya, and V. A. Khripach, *Khim. Prir. Soedin.*, No. 3, 391 (1994).
49. A. A. Akhrem, V. A. Khripach, F. A. Lakhvich, M. I. Zavadskaya, O. A. Drachenova, and I. A. Zorina, *Dokl. Akad. Nauk SSSR*, **297**, 364 (1987).
50. A. A. Akhrem, V. A. Khripach, F. A. Lakhvich, M. I. Zavadskaya, O. A. Drachenova, and I. A. Zorina, *Zh. Org. Khim.*, **25**, 2120 (1989).
51. A. I. Verenich, A. A. Govorova, N. M. Galitskii, A. V. Baranovskii, R. P. Litvinovskaya, and V. A. Khripach, *Zh. Struk. Khim.*, No. 5, 152 (1992).
52. R. K. Tkhaper, I. G. Reshetova, and A. V. Kamernitzky, *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 11, 2646 (1991).
53. R. K. Tkhaper, I. G. Reshetova, A. V. Kamernitzky, and R. P. Litvinovskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 4, 969 (1991).
54. A. A. Akhrem, V. A. Khripach, R. P. Litvinovskaya, A. V. Baranovsky, M. I. Zavadskaya, A. N. Kharitonovich, E. V. Borisov, and F. A. Lakhvich, *Zh. Org. Khim.*, **25**, 1901 (1989).
55. V. A. Khripach, R. P. Litvinovskaya, A. V. Baranovsky, and A. A. Akhrem, *Dokl. Akad. Nauk SSSR*, **318**, 597 (1991).
56. V. Khripach, R. Litvinovskaya, A. Baranovsky, and S. Drach, *Tetrahedron Lett.*, **31**, 7065 (1990).
57. V. Khripach, V. Zhabinskii, and R. Litvinovskaya, in: *Brassinosteroids: Chemistry, Bioactivity and Application*, H. G. Gulter, T. Yokota, and G. Adam (editors), Am. Chem. Soc., Washington (1991), p. 43.
58. V. A. Khripach, R. P. Litvinovskaya, and S. V. Drach, *Zh. Org. Khim.*, **29**, 717 (1993).
59. R. P. Litvinovskaya, S. V. Drach, and V. A. Khripach, *Mendeleev Commun.*, No. 6, 215 (1995).
60. R. P. Litvinovskaya, V. A. Tereshko, S. V. Drach, and V. A. Khripach, *Zh. Obshch. Khim.*, **66**, 859 (1996).
61. R. P. Litvinovskaya, A. S. Lyakhov, A. A. Govorova, S. V. Drach, and V. A. Khripach, *Bioorg. Khim.*, **23**, 147 (1997).
62. V. A. Khripach, R. P. Litvinovskaya, S. V. Drach, and E. A. Ermolenko, *Zh. Org. Khim.*, **34**, 1037 (1998).
63. V. A. Khripach, V. N. Zhabinskii, V. K. Ol'khovik, M. I. Zavadskaya, O. A. Drachenova, and N. B. Khripach, *Zh. Org. Khim.*, **32**, 841 (1996).
64. R. P. Litvinovskaya, H. V. Koval', and V. A. Khripach, *Khim. Geterotsikl. Soedin.*, No. 2, 267 (1998).
65. V. A. Khripach, V. N. Zhabinskii, and A. I. Kotyatkina, *Zh. Org. Khim.*, **29**, 1569 (1993).
66. V. A. Khripach, V. N. Zhabinskii, and A. I. Kotyatkina, *Zh. Org. Khim.*, **29**, 1573 (1993).
67. R. P. Litvinovskaya, N. V. Koval', and V. A. Khripach, *Zh. Org. Khim.*, **33**, 1522 (1997).
68. R. P. Litvinovskaya, S. V. Drach, and V. A. Khripach, *Zh. Org. Khim.*, **33**, 201 (1997).
69. V. A. Khripach, V. N. Zhabinskii, and N. D. Pavlovskii, *Zh. Org. Khim.*, **34**, 59 (1998).
70. J. M. Midgley, J. E. Parkin, and W. B. Whalle, *J. Chem. Soc. D*, No. 13, 789 (1970).
71. L. A. Maldonado and P. Crabbe, *Chem. Ind.*, No. 35, 1146 (1970).
72. P. Crabbe, L. A. Maldonado, and I. Sanchez, *Tetrahedron*, **27**, 711 (1971).
73. L. I. Klimova and N. N. Suvorov, *Zh. Obshch. Khim.*, **34**, 1357 (1964).
74. S. Noguchi, M. Imanishi, and K. Morita, *Chem. Pharm. Bull.*, **12**, 1189 (1964).
75. Roussel-UCLAF, Fr. Pat. 1780; *Chem. Abstr.*, **59**, 14061 (1963).
76. Roussel-UCLAF, Belg. Pat. 624199; *Chem. Abstr.*, **60**, 12083 (1964).
77. A. U. Siddiqui, D. Ramesh, Y. Satyanarayana, M. Srinivas, and A. H. Siddiqui, *Org. Prep. Proced. Int.*, **25**, 356 (1993).
78. A. H. Siddiqui, Y. Satyanarayana, M. Srinivas, and K. Rajeshwar, *J. Indian Chem. Soc.*, **69**, 846 (1992).
79. L. N. Volovel'skii, N. V. Popova, and I. P. Fal'ko, Authors Certificate USSR 447402; *Byull. Izobret.*, No. 39 (1974).
80. L. N. Volovel'skii, N. V. Popova, M. Ya. Yakovleva, and V. G. Khukhryanskii, *Zh. Obshch. Khim.*, **45**, 2090 (1975).
81. L. N. Volovel'skii, I. B. Skachek, and I. I. Kuz'menko, *Khim. Prir. Soedin.*, No. 2, 168 (1979).
82. J. R. Housley, Brit. Pat. 1287271; *Chem. Abstr.*, **77**, 152462 (1972).

83. G. S. Khatamkulova, M. I. Goryaev, and M. P. Irismetov, *Izv. Akad. Nauk KazSSR, Ser. Khim.*, No. 4, 71 (1974).
84. M. P. Irismetov and M. I. Goryaev, *Trud. Inst. Khim. Nauk, Akad. Nauk KazSSR*, **52**, 17 (1980).
85. M. P. Irismetov, M. I. Goryaev, and G. Yu. Tsvetkova, *Zh. Obshch. Khim.*, **46**, 1407 (1976).
86. H. Chanh and J. Sylvestre, *Bull. Soc. Chim. France*, No. 10, 3586 (1971).
87. D. Burn, G. Cooley, J. W. Ducler, B. Ellis, D. M. Kirk, and V. Petrow, *Tetrahedron Lett.*, No. 13-14, 733 (1964).
88. Y. Sato and H. Kaneko, *Steroids*, **5**, 279 (1965).
89. J. T. Pinhey, E. Rizzardo, and G. C. Smith, *Aust. J. Chem.*, **31**, 113 (1978).
90. J. T. Pinhey, E. Rizzardo, and G. C. Smith, *Aust. J. Chem.*, **31**, 97 (1978).
91. H. Suginome, K. Macoto, O. Toshiharu, J. Shinji, O. Takashi, S. Hisanori, and F. Akio, *J. Chem. Soc. Perkin Trans. 1*, No. 4, 427 (1992).
92. J. Boivin, S. Huppe, and S. Z. Zard, *Tetrahedron Lett.*, **37**, 8735 (1996).
93. R. G. Christiansen, US Pat. 4055562; *Chem. Abstr.*, **88**, 121545 (1978).
94. V. Kumar and M. R. Bell, *Heterocycles*, **29**, 1773 (1989).
95. H. C. Neumann, G. O. Potts, W. T. Ryan, and F. W. Stonner, *J. Med. Chem.*, **13**, 948 (1970).
96. R. P. Litvinovskaya, A. V. Baranovsky, and V. A. Khripach, *Zh. Org. Khim.*, **33**, 1350 (1997).
97. R. G. Christiansen, Can. Pat. 1125278; *Chem. Abstr.*, **97**, 216572 (1982).
98. R. G. Christiansen, US Pat. 4160027; *Chem. Abstr.*, **91**, 211680 (1979).
99. K. O. Gelotte and J. Chester, US Pat. 4755595; *Chem. Abstr.*, **110**, 115182 (1989).
100. W. E. Jones and R. S. Andrews, Eur. Pat. 154476; *Chem. Abstr.*, **105**, 60813 (1986).
101. R. O. Clinton and A. J. Manson, Brit. Pat. 1123770; *Chem. Abstr.*, **85**, 108895 (1976).
102. G. Nathansohn, G. Winters, and E. Testa, US Pat. 3459740; *Chem. Abstr.*, **71**, 102135 (1969).
103. T. Tamaya, N. Furuta, T. Motoyama, S. Boku, Y. Ohono, and H. Okada, *Acta Endocrinol.*, **88**, 190 (1978).
104. J. F. Shi, Q. J. Liao, and F. Xu, *Yaoxue Xuebao*, **23**, 860 (1988).
105. R. P. Litvinovskaya, S. V. Drach, A. V. Baranovsky, V. A. Strel'tsova, and V. A. Khripach, *Vestsi Akad. Navuk Belarus, Ser. Biyal. Navuk*, No. 2, 49 (1996).
106. V. A. Khripach, R. P. Litvinovskaya, S. V. Drach, and V. A. Strel'tsova, Authors Certificate USSR 1786807; *Byull. Izobret.*, No. 3, 321 (1996).
107. V. A. Khripach, R. P. Litvinovskaya, S. V. Drach, and V. A. Strel'tsova, Authors Certificate USSR 174755; *Byull. Izobret.*, No. 26, 72 (1992).