Ch. Camoutsis* and S. Nikolaropoulos

University of Patras, School of Health Sciences, Department of Pharmacy,
Laboratory of Pharmaceutical Chemistry, Patras, Greece

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The present review considers new useful heterocyclosteroids which contain five-membered heterocyclic systems, namely, isoxazoles, isoxazolines and isoxazolidines, condensed to the cyclopentanoperhydrophenanthrene skeleton, in different positions of the molecule, with changes in their physiological activity and the appearance of new interesting biological properties. Literature coverage for the review includes publications up to the end of 1996.

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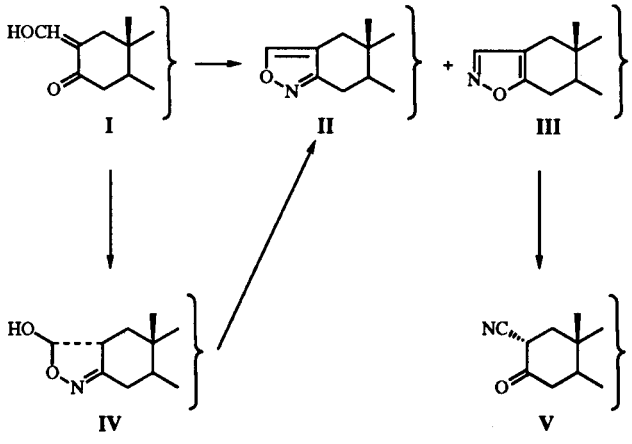
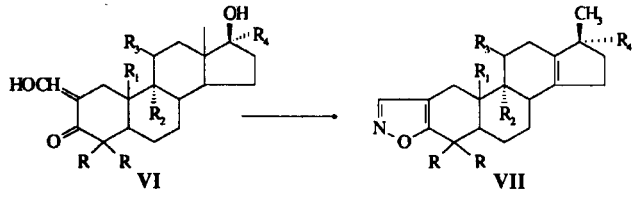
Steroidal Isoxazoles.

Steroids containing an isoxazole ring can be obtained by a great variety of methods. The main method of synthesis of compounds of this class is the condensation of the 2-hydroxymethylene-3-ketosteroids **I** with hydroxylammonium chloride to afford a mixture of isomeric [3,2-*c*]- **II** and [2,3-*d*]isoxazoles **III** [1-5]. When the reaction is carried out under mild conditions in addition to these products up to 15% of 5'-hydroxy[3,2-*c*]-2'-isoxazolines **IV** are formed, which are converted into **II** on heating with acetic anhydride [4,6,7]. On treating the reaction products with sodium methoxide, the [3,2-*c*]-derivatives **II** remain unchanged, but the [2,3-*d*]-derivatives **III** are quantitatively converted into 2α-cyano-3-ketosteroids **V**, a process which allows mixtures **II** and **III** to be separated [1-5,7].



The rate of formation of **II** and **III** is dependent on the *p*H of the medium, the solvent and the temperature. In a weakly alkaline medium, *e.g.* in alcoholic solution containing an excess of sodium acetate a mixture of isomeric isoxazoles is usually formed [1,4,5]. When the reaction is carried out in aqueous alcohol [4,8-13] or in glacial acetic acid [4,7,13-15] isomer **III** is formed preferentially, since in pyridine solution the main product is isomer **II** [3,10,11,14].

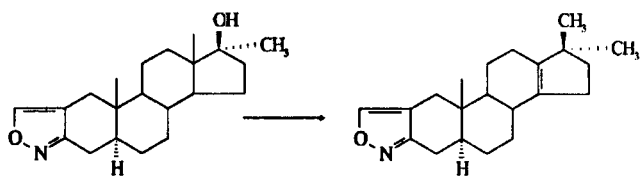
When a hydroxymethylene ketone **VI** containing a tertiary hydroxyl at $C_{(17)}$ is introduced into the reaction, in glacial acetic acid, acid-catalyzed dehydration of tertiary alcohols takes place to yield 17,17-dialkyl-18-norsteroido-13-eno[2,3-*d*]isoxazole **VII** [4,13,16,17].



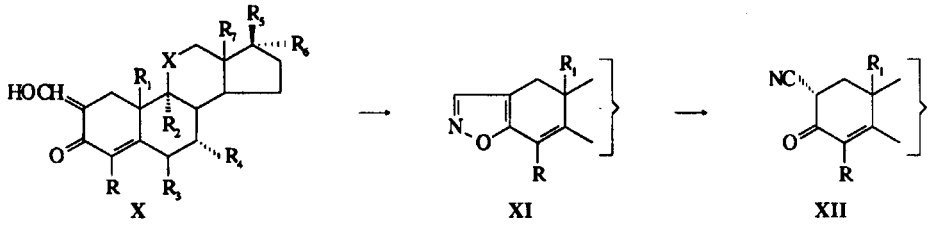
R = H	$R_1 = CH_3$	$R_2 = H$	$R_3 = H$	$R_4 = CH_3$	Δ^4
R = H	$R_1 = H$	$R_2 = H$	$R_3 = H$	$R_4 = CH_2CH_3$	Δ^4
R = H	$R_1 = CH_3$	$R_2 = F$	$R_3 = OH$	$R_4 = CH_3$	Δ^4
R = H	$R_1 = CH_3$	$R_2 = H$	$R_3 = H$	$R_4 = CH_3$	5a-H
$R = CH_3$	$R_1 = CH_3$	$R_2 = H$	$R_3 = H$	$R_4 = CH_3$	Δ^5

In order to prevent dehydration when the 2-hydroxymethylene-3-ketosteroid contains a tertiary hydroxyl group, it was found necessary to employ the addition of sodium acetate so that the condensation was carried out under mildly acidic conditions [4].

Similarly, by acid-catalyzed dehydration of tertiary alcohols, the 17,17-dimethyl-18-norandrost-13-eno-[3,2-*c*]isoxazole (**IX**) is also formed on boiling a solution of 17β-hydroxy-17α-methylandrostano[3,2-*c*]isoxazole (**VIII**) and 3*N* ethereal hydrochloride solution in glacial acetic acid [4,5].

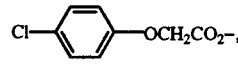
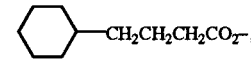


Unsaturated 2-hydroxymethylene-3-ketosteroids **X** with a Δ^4 double bond or two $\Delta^{4,6}$ double bonds are converted into the corresponding androst-4-eno[2,3-*d*]isoxazoles [1,4,8,12,13,16-33] and androst-4,6-dieno[2,3-*d*]isoxazoles **XI** [4,8,13,18]. In both of these cases the steroidal-[2,3-*d*]isoxazoles were the sole products of these reactions. Their structures were demonstrated by their ready conversion to 2α-cyano-3-ketosteroids **XII** [1-5,7,8,13,-18-20,23-25,31].



R = H, CH_3, C_2H_5 R_1 = H, CH_3 R_2 = F R_3 = H, α-CH_3, =CH_2 R_4 = CH_3

R_5 = OH, OCH_3, $OCOCH_3$, $OCOC_2H_5$, OC_3H_7, $COCH_3$, $CH(OH)CH_3$,

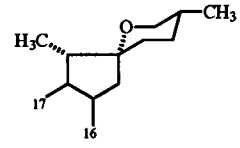
$COCH_2OH$,  ,  , OC_2H_5,

$COCH_2OCOCH_3$, $OCO(CH_2)_5CH_3$, $OCO(CH_2)_9CH_3$, $O(CH_2)_4CH_3$,

$O(CH_2)_5CH_3$, 2-$AcOC_6H_4O$

R_6 = H, CH_3, C_2H_5, C≡CH, OH, C_3H_7, C≡CCF_3, C≡CBr, C≡CCl, C≡CR (R=Ph, Subst. Ph, 2-Pyridinyl, 2-thienyl),

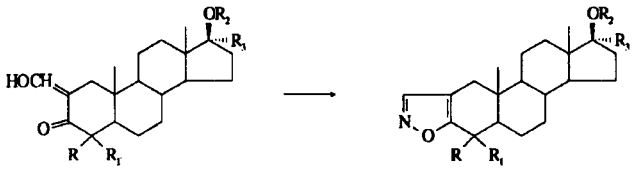
CH_2=CH, CH_2CH=CH_2, C≡$CHCH_3$,

CH≡CCH_2 

R_7 = CH_3, C_2H_5

X = CH_2, C=O, CHOH, $\Delta^{9(10)}$

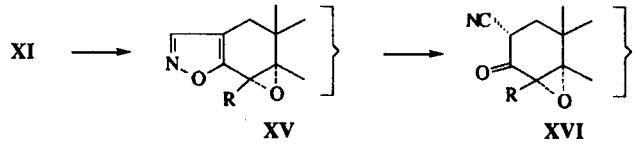
The same products are also formed from the 4,4-*gem*-dialkyl-2-hydroxymethylene-3-ketosteroids **XIII**. Apparently the 4,4-dialkyl group sterically hinders the nucleophilic attack of hydroxylamine at the 3-position to such an extent that under the experimental conditions the steroidal[2,3-*d*]isoxazole **XIV** is formed exclusively [4,12,13,18,34].



XIII XIV

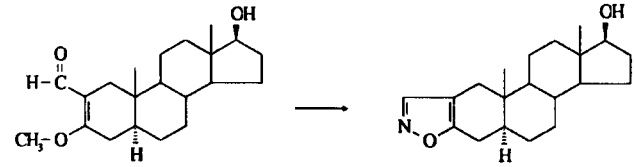
$R = CH_3$	$R_1 = CH_3$	$R_2 = H$	$R_3 = H$	Δ^5
$R = CH_3$	$R_1 = CH_3$	$R_2 = H$	$R_3 = C{\equiv}CH$	Δ^5
$R = CH_3$	$R_1 = CH_3$	$R_2 = H$	$R_3 = CH_3$	Δ^5
$R = CH_3$	$R_1 = CH_3$	$R_2 = CH_3$	$R_3 = H$	Δ^5
$R = C_2H_5$	$R_1 = C_2H_5$	$R_2 = H$	$R_3 = CH_3$	Δ^5
$R = CH_3$	$R_1 = CH_3$	$R_2 = H$	$R_3 = H$	5a-H
$R = CH_3$	$R_1 = CH_3$	$R_2 = H$	$R_3 = CH_3$	5a-H
$R:R_1 = (CH_2)_5$		$R_2 = H$	$R_3 = CH_3$	Δ^5
$R:R_1 = (CH_2)_6$		$R_2 = H$	$R_3 = CH_3$	Δ^5

Epoxidation of steroidal[2,3-*d*]isoxazoles **XI** with *m*-chloroperbenzoic acid or peracetic acid gave the corresponding 4α,5α-epoxy-derivatives **XV** which by cleavage afforded the 2α-cyano-4α,5α-epoxy-3-ketosteroids **XVI** [24,25,35-42].



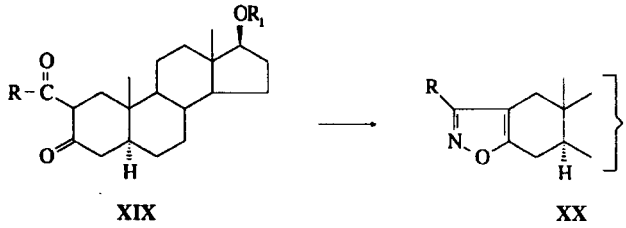
XV XVI

Another path for the production of [2,3-*d*]isoxazoles consists in the reaction of 2-formyl-3-methoxyandrost-2-en-17β-ol (**XVII**) with hydroxylammonium chloride [43].



XVII XVIII

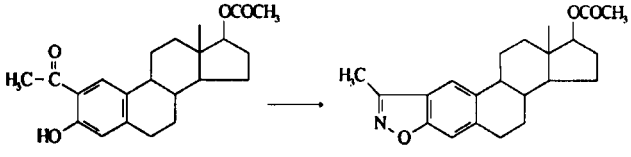
Isoxazolosteroids containing alkyl substituents in position 3' of the isoxazole ring were synthesized on the basis of the corresponding β-diketones by condensation of 2-acyl-3-ketosteroids **XIX** with hydroxylammonium chloride [4,13,18].



XIX XX

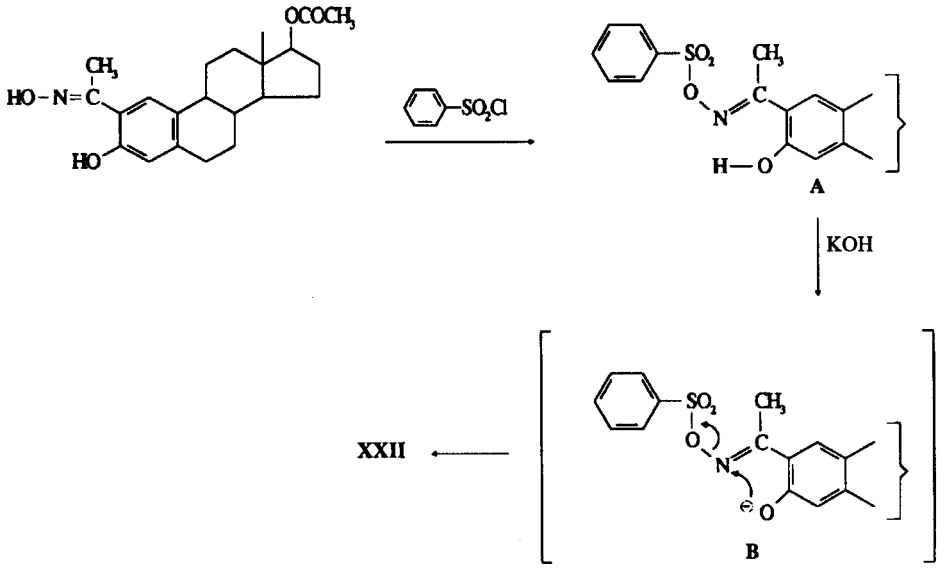
$R = CH_3$	$R_1 = H$
$R = CH_3$	$R_1 = COCH_3$
$R = CH_3CH_2CH_2$	$R_1 = H$
$R = CH_3CH_2CH_2$	$R_1 = Ph\text{-}CO$

Similarly the acetylestradiol **XXI**, after condensation with hydroxylamine in the presence of benzenesulfonyl or *p*-toluenesulfonyl chloride in dilute potassium hydroxide, gave the 3'-methylbenzisoxazole **XXII** [44,45].



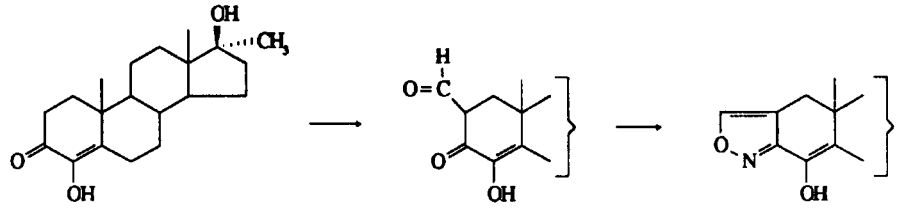
XXI XXII

According to the reaction mechanism the formation of **XXII** proceeds by the following scheme.



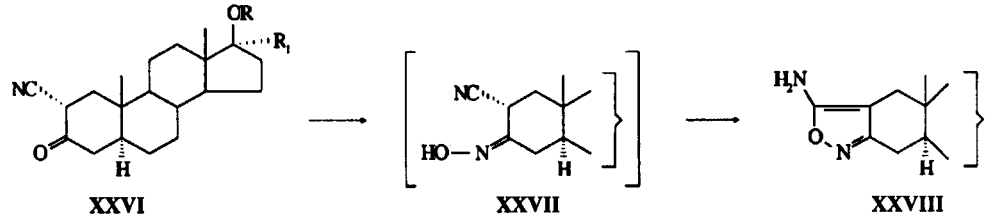
In a strongly alkaline medium the C-3 phenoxide anion **B** displaces the benzenesulfonate to afford the methylbenzisoxazole **XXII** [45].

An isoxazolo-derivative of structure **II** was obtained by formylation of 17α-methyl-4,17-dihydroxyandrost-4-en-3-one (**XXIII**) with ethyl formate and sodium methoxide in pyridine followed by treatment with hydroxylammonium chloride in ethanol [46].



XXIII **XXIV** **XXV**

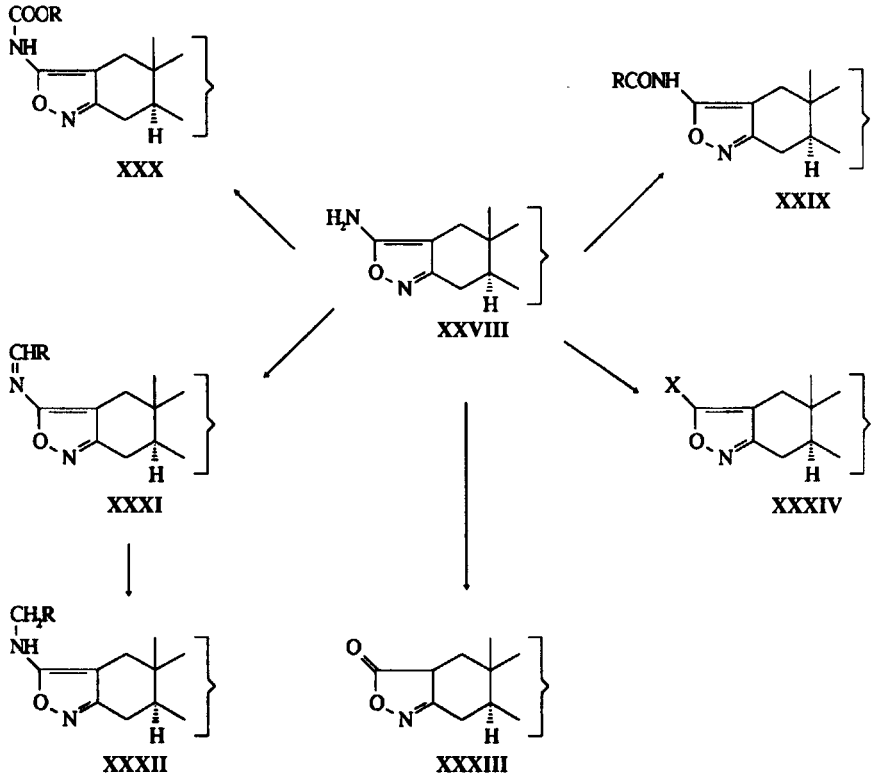
A series of 5'-amino-substituted steroido[3,2-*c*]isoxazoles was obtained by condensation of 2α-cyano-3-ketosteroids **XXVI** with hydroxylammonium chloride in a pyridine or an ethanol solution [5,47,48].



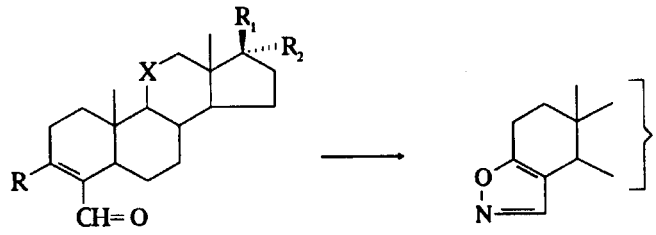
XXVI **XXVII** **XXVIII**

R = H R1 = H
R = H R1 = CH_3

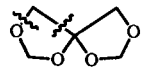
Acylation of the 5'-amino group with acyl chlorides or ethyl chlorocarbonate gives the corresponding acylates **XXIX**, (R = alkyl) and urethanes **XXX**, (R = OC_2H_5) [49]. Condensation with aldehydes gives Schiff bases **XXXI** which are reduced by sodium tetrahydroborate to the corresponding 5'-alkylamino-derivatives **XXXII**. Deamination by hydrolysis of **XXVIII** with mineral acids leads to the 5'-isoxazolinones (**XXXIII**). Diazotization in hydrochloric or hydrobromic acid allows the corresponding halo-derivatives **XXXIV** to be obtained [49].



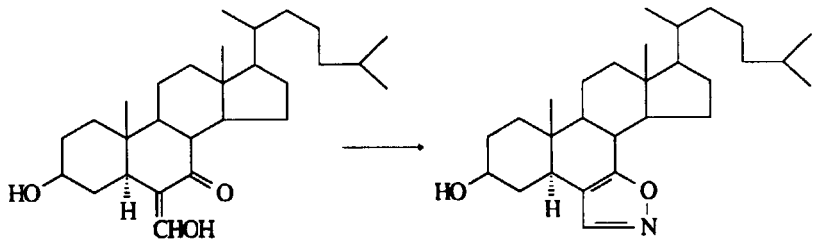
Isoxazole derivatives condensed with the steroids in positions 3,4 were obtained by reaction of 4-formyl-3-hydroxysteroids **XXXV** (R = OH) [21,50-52] or 4-formyl-3-piperidine **XXXV** (R = $C_5H_{10}N$) with hydroxylammonium chloride [53].



XXXV XXXVI

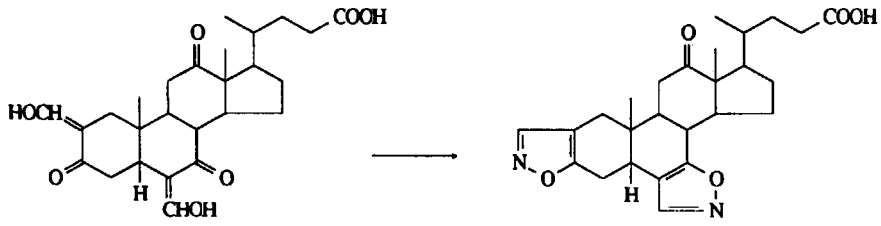
R = OH	$R_1 = C_8H_{17}$	$R_2 = H$	$X = CH_2$	Δ^5
R = OH	R_1 = OH	$R_2 = H$	$X = CH_2$	Δ^1, 5a-H
R = OH	R_1 = OH	$R_2 = CH_3$	$X = CH_2$	Δ^1, 5a-H
R = OH	R_1,R_2 = 		X = C=O	Δ^1, 5a-H
R = OH	$R_1 = COCH_2OH$	R_2 = OH	X = C=O	Δ^1, 5a-H
R = OH	$R_1 = t$-Bu	$R_2 = H$	$X = CH_2$	Δ^5
$R = C_5H_{10}N$	$R_1 = COCH_2CH_3$	$R_2 = H$	$X = CH_2$	Δ^5
$R = C_5H_{10}N$	$R_1 = COCH_2CH_3$	$R_2 = H$	$X = CH_2$	$\Delta^{5,9(11)}$

Similarly the 6-hydroxymethylene-7-ketocholestanol (**XXXVII**) gave a [6,7-*d*]isoxazole derivative **XXXVIII** [16].

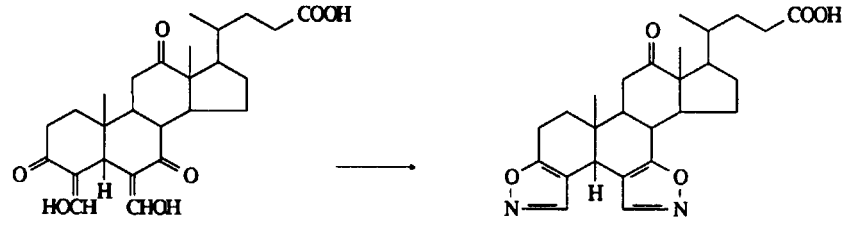


XXXVII XXXVIII

Under the same conditions the 2,6-dihydroxymethylene-3,7,12-triketocholanic acid (**XXXIX**) and 4,6-dihydroxymethylene-3,7,12-triketocholanic acid (**XLI**) afforded the [2,3-*d*][6,7-*d*]diisoxazoles **XL** and [4,3-*d*]-[6,7-*d*]diisoxazoles **XLII** correspondingly [54].

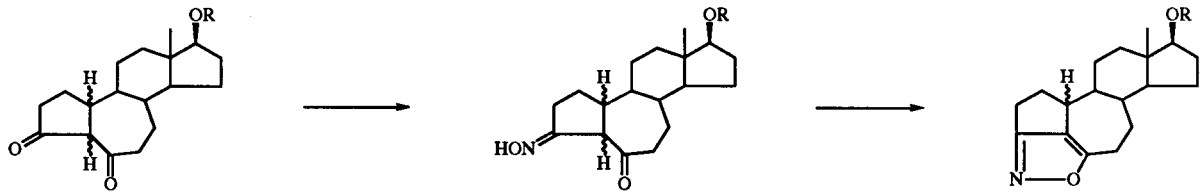


XXXIX XL



XLI XLII

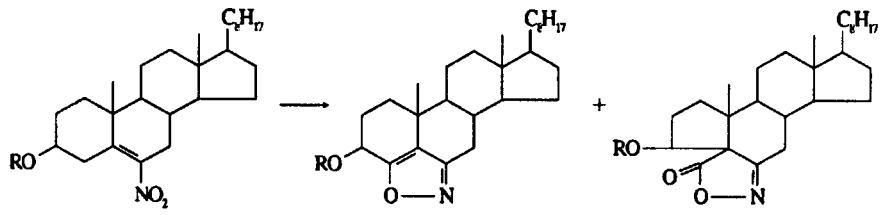
Steroidal isoxazoles simultaneously fused to the 3,5 and 6 positions of the A and B rings of the steroid nucleus were prepared by the reaction of the 17β-acetoxy-3,6-dioxo-*A*-nor-*B*-homo-5ξ,10ξ-estrane (**XLIII**) with hydroxylammonium chloride in a pyridine solution in the presence of phosphoryl chloride at -10° to 10°, *via* the intermediate formation of an 3-oximino derivative **XLIV** [55-56].



XLIII XLIV XLV

R = H, $COCH_3$

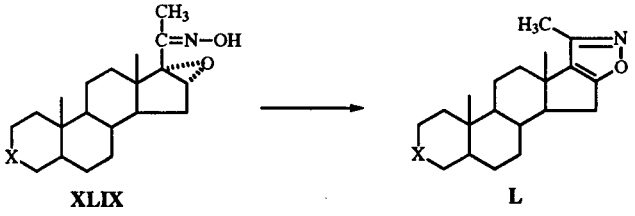
Irradiation of 3β-acetoxy-6-nitrocholest-5-ene and 6-nitrocholest-5-ene (**XLVI**) gave the cholestenoisoxazoles **XLVII** fused to the 4,5 and 6 positions of the A and B rings of the steroid nucleus and A-nor-cholestenol-[6,5-*c*]isoxazolin-5-one (**XLVIII**) [57].



XLVI XLVII XLVIII

R = H, $COCH_3$

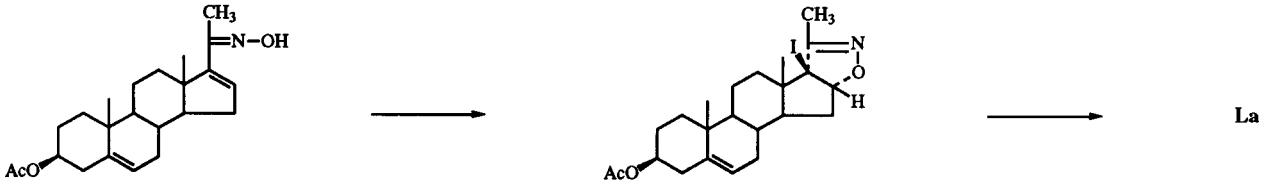
Dehydration of oxime of the acetate of 16α,17α-epoxy-3β-hydroxypregn-5-en-20-one (**XLIX**) with phosphoryl chloride in pyridine afforded the acetate of androst-5-en-3β-ol[17,16-*d*]-3'-methylisoxazole (**L**) [58].



XLIX **L**

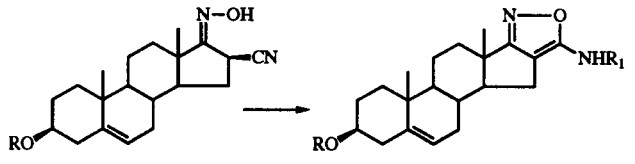
a. X = $CHOCOCH_3$, Δ^5
b. X = CHOH, Δ^5
c. X = C=O, Δ^4

The same compounds were formed by dehydroiodination, by silver acetate in a solution of glacial acetic acid, of 3β-acetoxy-17β-iodo-5-androstene[17α,16α-*d*]-3'-methylisoxazoline (**LII**), prepared by heating the oxime of pregna-5,16-dien-3β-acetoxy-20-one (**LI**) with lead tetraacetate and iodine in a solution of benzene containing 1% water [59].



LI **LII** **La**

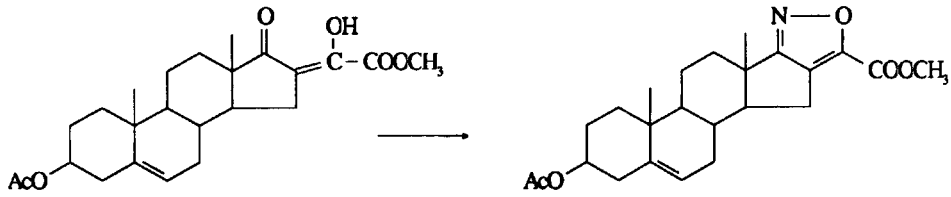
Treatment of 16β-cyanoandrost-5-en-3β-ol-17-one oxime (**LIII**) with methanolic potassium hydroxide at room temperature gave the androsteno[17,16-*c*]isoxazoles **LIV** [60].



LIII **LIV**

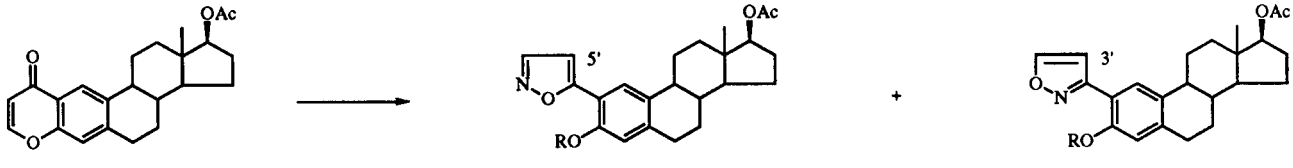
R = R_1 = H
R = R_1 = $COCH_3$

Androsteno[17,16-*c*]isoxazoles were also prepared by cyclization of the steroidal glyoxalate **LV** with hydroxylamine hydrochloride [61].



LV LVI

Treatment of [3,2-*b*]-γ-pyrone-estra-1,3,5(10)-trien-17β-olacetate (**LVII**) with hydroxylamine hydrochloride in pyridine solution, followed by acetylation leads to a mixture of isomeric 3,17β-dihydroxy-2-(5'-isoxazolyl)-estra-1,3,5(10)-triene-3,17-diacetate (**LVIIIb**) and 3,17β-dihydroxy-2-(3'-isoxazolyl)estra-1,3,5(10)-trien-3,17-diacetate (**LIXb**) separated by fractional crystallization [44-45].

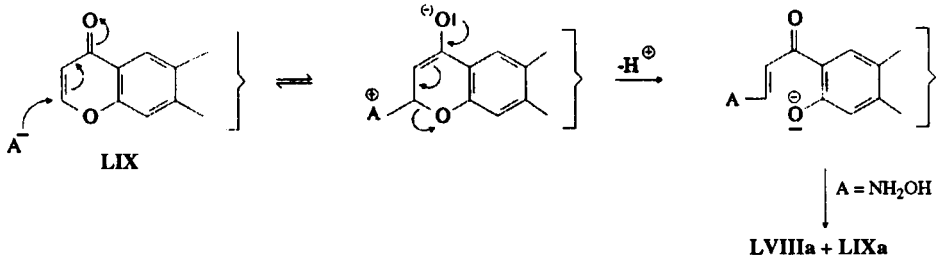


LVII LVIII LIX

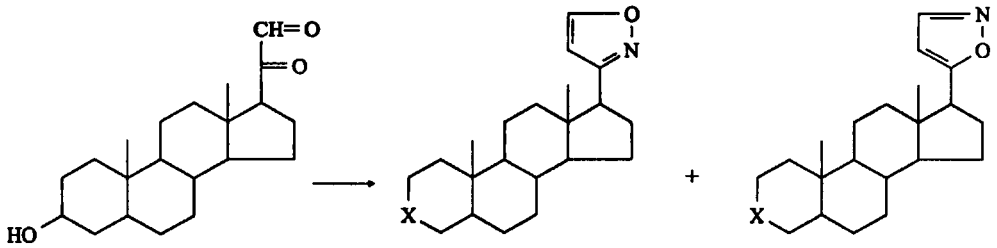
a. R = H
b. R = $COCH_3$

a. R = H
b. R = $COCH_3$

From the reaction mechanism view point the formation of isomeric **LVIIIa** and **LIXa** can be rationalized as indicated in the scheme. The 5'-isoxazolyl derivative **LVIIIa** would result from initial attack by the nitrogen atom of hydroxylamine on the γ-pyrone ring, since an inital attack by the oxygen atom should be favored to give the 3'-isoxazolyl derivative **LIXa** [45].



When 3β-hydroxy-21-formylpregn-5-en-20-one (**LX**) was allowed to react with hydroxylamine hydrochloride in acetic acid a mixture of 17β-(3-isoxazolyl)-5-androsten-3β-ol acetate (**LXI**) and 17β-(5-isoxazolyl)-5-androsten-3β-ol acetate (**LXII**) was obtained, which were separated on thin layer and by vapor phase chromatography [62].

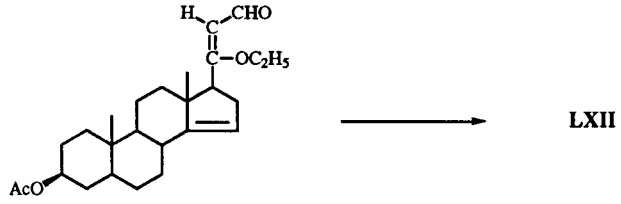


LX LXI LXII

a. X = CHOCOCH$_3$, Δ^5
b. X = CHOH, Δ^5
c. X = CO, Δ^4

On the other hand, the reaction of 3β-hydroxy-21-formylpregn-5-en-20-one (**LX**) with hydroxylamine hydrochloride in glacial acetic acid, buffered with sodium acetate, yielded only the 17β-(5-isoxazolyl)-5-androsten-3β-ol (**LXII**). Evidently, the *p*H of the reaction media has great influence in determining the products formed [62].

Compounds of structure **LXII** were also prepared from 3β-acetoxy-20-ethoxy-21-formyl-17β-pregna-14,20-diene (**LXIII**) with hydroxylamine hydrochloride [63,64].

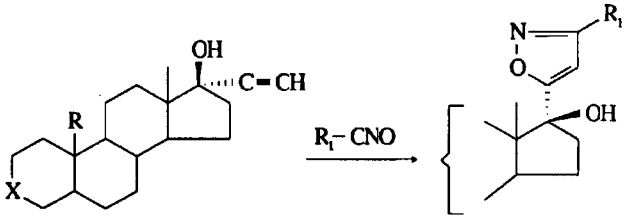


LXIII

Δ^5, 5α-H

LXII

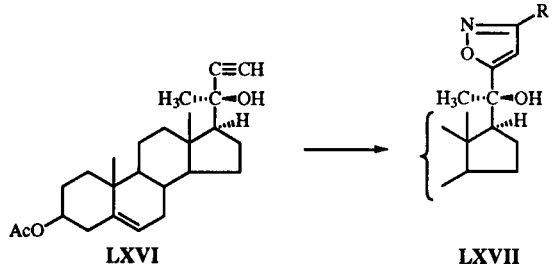
The isomeric 17α-(5-isoxazolyl)steroids **LXV** have been obtained by 1,3-dipolar cycloaddition of nitrile oxides to 17β-hydroxy-17α-ethynylsteroids **LXIV** [65-68].



LXIV LXV

X = CHOCH$_3$		R_1 = CH$_3$	$\Delta^{1,3,5(10)}$
X = CHOCH$_3$		R_1 = Ph	$\Delta^{1,3,5(10)}$
X = CHOCH$_3$		R_1 = COOH	$\Delta^{1,3,5(10)}$
X = CHOCH$_3$		R_1 = COOC$_2$H$_5$	$\Delta^{1,3,5(10)}$
X = CHOH		R_1 = Ph	$\Delta^{1,3,5(10)}$
X = CHOH		R_1 = COOC$_2$H$_5$	$\Delta^{1,3,5(10)}$
X = CO	R = H	R_1 = Ph	Δ^4
X = CO	R = H	R_1 = COOC$_2$H$_5$	Δ^4
X = CO	R = CH$_3$	R_1 = CH$_3$	Δ^4
X = CO	R = CH$_3$	R_1 = Ph	Δ^4
X = CHOH	R = CH$_3$	R_1 = CH$_3$	Δ^5

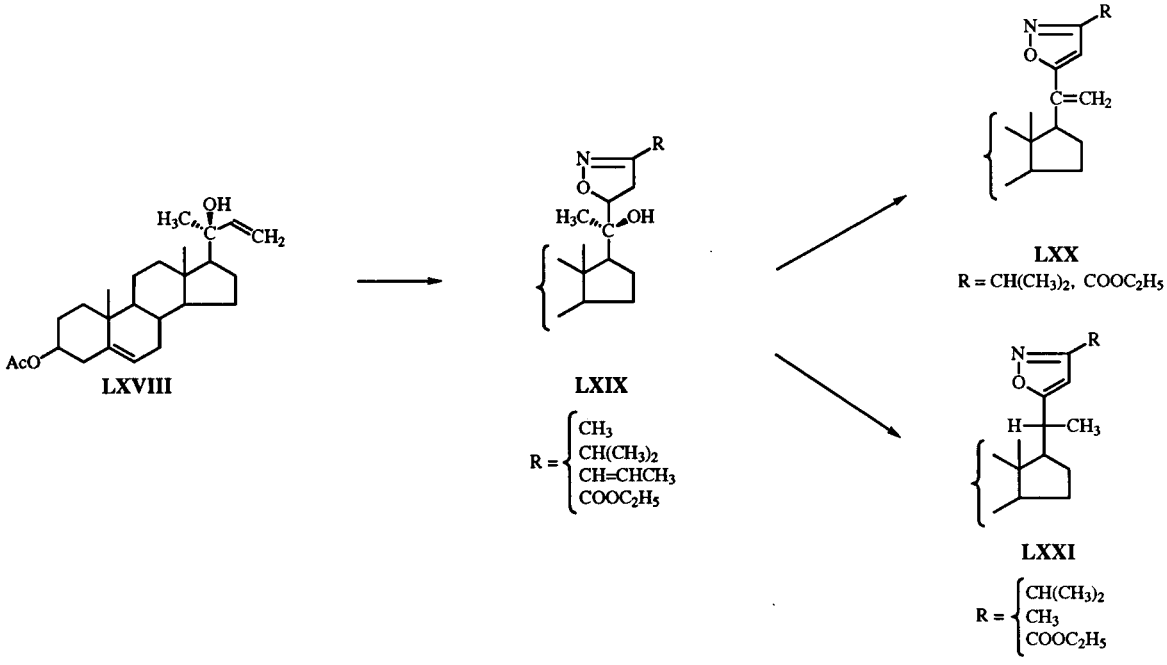
By a similar reaction the steroidal 20*R*-(3-alkylisoxazol-5-yl) **LXVII** were formed including the reaction of the steroidal acetylenes **LXVI** with alkylnitrile oxides [69,70].



LXVI LXVII

R = CH$_3$, CH(CH$_3$)$_2$

1,3-Dipolar cycloaddition of nitrile oxides to steroidal olefines **LXVIII** proceeds regio- and stereoselectively to give (20*R*)-20-hydroxy-20-isoxazolinyl pregnenols **LXIX** [71,72], which after dehydration by thionyl chloride in dimethylformamide at room temperature gave the substituted isoxazolylpregnenols **LXX** [73] since by dehydration upon treatment with trifluoroacetic acid in refluxing nitromethane in the presence of lithium perchlorate, the (20*R*)-isoxazolylpregnenols (**LXXI**) were obtained stereoselectively [74,75].



LXVIII

LXIX

R = CH3, CH(CH3)2, CH=CHCH3, COOC2H5

LXX

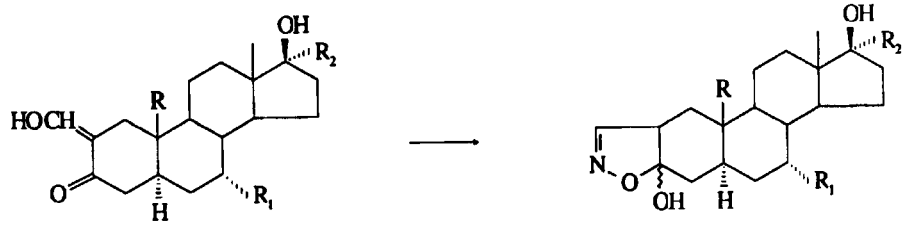
R = CH(CH3)2, COOC2H5

LXXI

R = CH(CH3)2, CH3, COOC2H5

Steroidal Isoxazolines.

Attachment of the isoxazoline ring to steroids can be brought about by condensation of hydroxylamine with steroid ketones of suitable structure. Thus, the reaction of 2-hydroxymethylene-3-ketosteroids **LXXII** with hydroxylamine hydrochloride gave the steroido[2,3-*d*]-5'-hydroxy-$\Delta^{2'}$-isoxazolines **LXXIII**, [7,76].

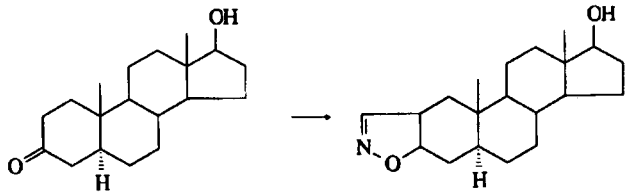


LXXII

LXXIII

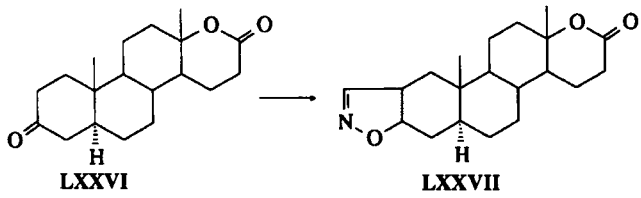
R = H, CH_3
R_1 = SCH_2CH_3
R_2 = H, CH_3, C_2H_5, $CH=CH_2$, C≡CH

Steroidal [2,3-*d*]isoxazolines were also formed by cyclocondensation of steroidal ketones **LXXIV** with formamide in the presence of 50% perchloric acid at 140° [77,78].



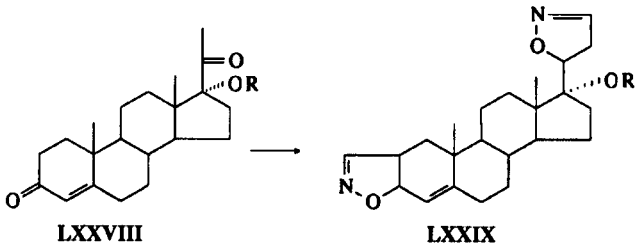
LXXIV **LXXV**

The reaction proceeds analogously with dihydrotestololactone **LXXVI** leading to 5α-dihydrotestololactono[2,3-*d*]-isoxazoline **LXXVII** [78].



LXXVI **LXXVII**

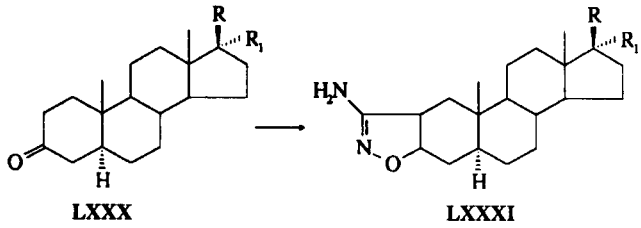
Similarly, the 17α-hydroxy- and 17α-acetoxyprogesterone **LXXVIII** gave the corresponding bisisoxazolines **LXXIX** [79].



LXXVIII **LXXIX**

R = H, $COCH_3$

A series of 3'-amino-substituted steroidoisoxazolines of the structure **LXXXI** was obtained by cyclization of oxosteroids **LXXX** with urea in methylnaphthalene at 200-210°, or with thiurea in dioxane or acetic acid in the presence of perchlorate and sulphuric acid [79,80].

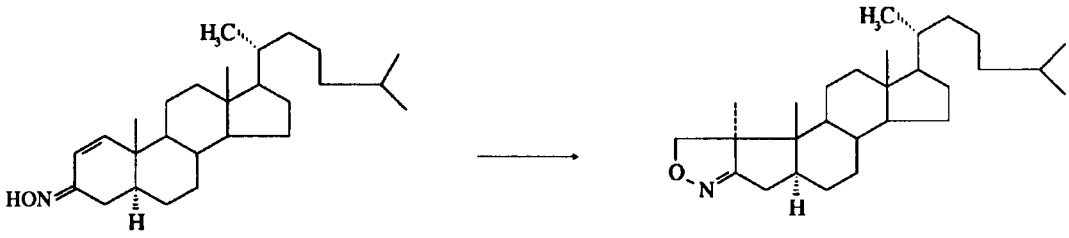


LXXX **LXXXI**

R = $COCH_3$ R_1 = OH
R = OH R_1 = H

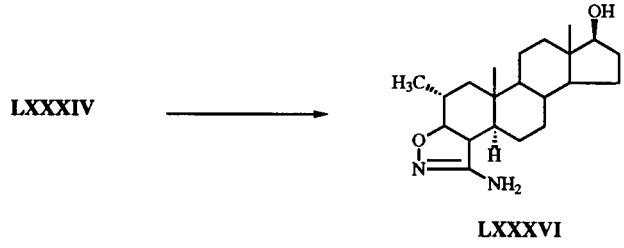
The isomeric steroido[3,2-*c*]isoxazolines were obtained by reaction of 2-hydroxymethylene-3-ketosteroids with hydroxylamine hydrochloride. When the reaction takes place under mild conditions, in addition to [3,2-*c*]- and [2,3-*d*]isoxazoles, the steroido[3,2-*c*]-5'-hydroxy-$\Delta^{2'}$-isoxazoline **IV** [4,6,7] is formed, as described in the chapter on isoxazoles.

Irradiation of cholest-1-en-3-one oxime (**LXXXII**) in benzene-acetic acid gave the isoxazoline **LXXXIII** [81].

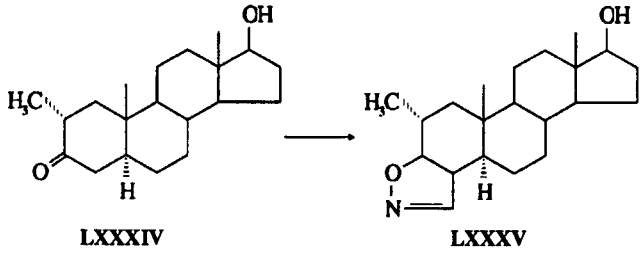


LXXXII LXXXIII

Cyclocondensation of steroidal ketones having a substituent at $C_{(2)}$, as in the case of 2α-methyldihydrotestosterone (**LXXXIV**), with formamide in the presence of 50% perchloric acid at 140°, the isoxazoline ring is constructed at $C_{(3)}$-$C_{(4)}$ of ring A with formation of 2α-methyl-17β-hydroxy-5α-androstano[4,3-*d*]isoxazoline **LXXXV** [78].



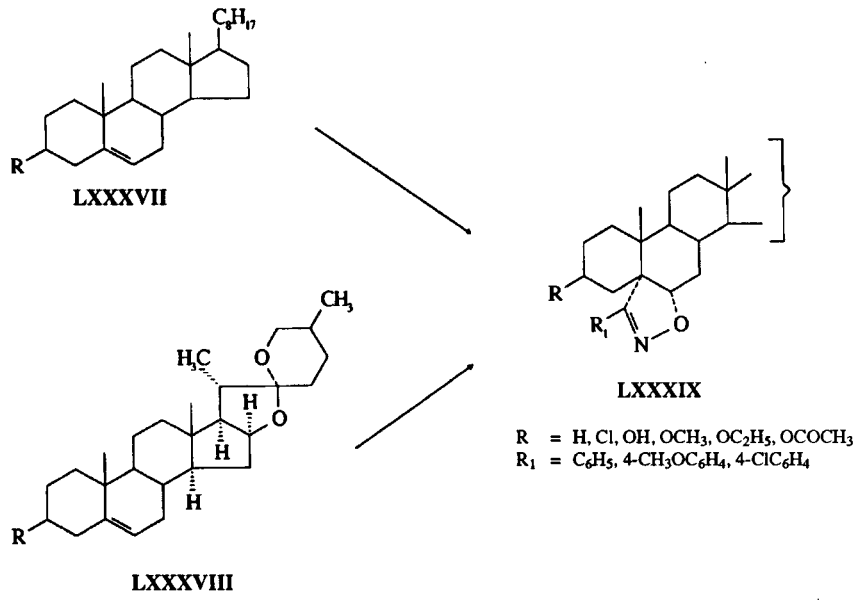
LXXXIV LXXXVI



LXXXIV LXXXV

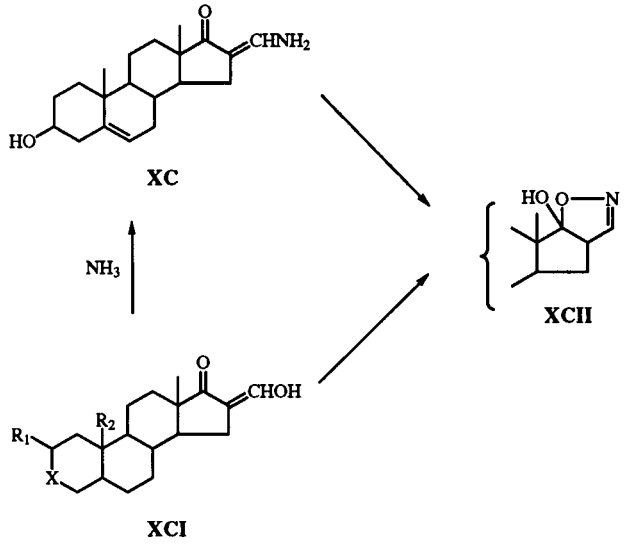
Compounds of the structure **LXXXV** with an amino group in position 3' were obtained from the 2α-methyldihydrotestosterone (**LXXXIV**) by the same procedure as for the preparation of 3'-amino-substituted steroidoisoxazolines **LXXXI** [80].

1,3-Dipolar cycloaddition of aryl nitrile oxides to 5-cholestenes **LXXXVII** and (25*R*)-5-spirostenes **LXXXVIII** gave the isoxazoline derivatives **LXXXIX** [82,83].

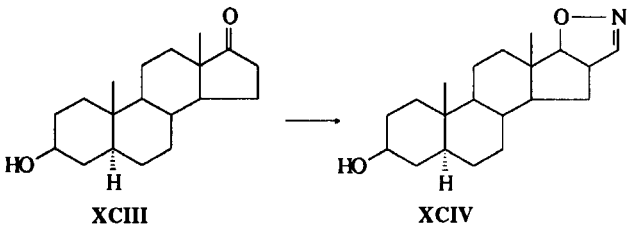


Isoxazoline derivatives condensed with the steroids in positions, 16,17 were obtained by condensation of the 16-methylenamino-17-ketosteroids **XC** [84] or 16-hydroxymethylene-17-ketosteroids **XCI** [84-87] with hydroxylamine hydrochloride, to yield the [16,17-*d*]isoxazoline derivatives **XCII**.

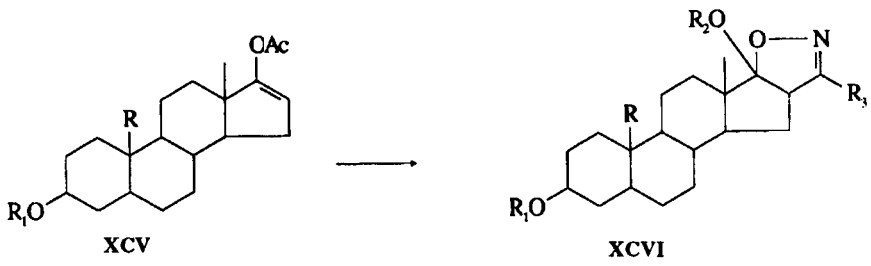
Steroidal[16,17-*d*]-2'-isoxazolines **XCIV** were also formed by cyclocondensation of 17-ketosteroids **XCIII** with formamide in the presence of 50% perchoric acid at 140° [78].



R_1 = H	X = CHOH	R_2 = CH_3	Δ^5
R_1 = H	X = C=O	R_2 = CH_3	Δ^4
R_1 = H	X = CHOH	R_2 = H	Δ^5
R_1 = H	X = $CHOCH_3$		$\Delta^{1,3,5(10)}$
R_1 = H	X = C=O	R_2 = CH_3	$\Delta^{1,4}$
R_1 = H	X = C=O	R_2 = CH_3	$\Delta^{4,6}$
R_1 = F	X = CHOH		$\Delta^{1,3,5(10)}$
R_1 = H	X = $CHOC_2H_5$		$\Delta^{1,3,5(10)}$

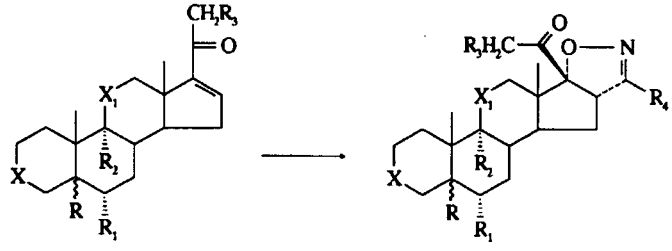


Another pathway for the preparation of compounds of similar structure consists in the 1,3-dipolar cycloaddition of Δ^{16}-17-acetoxysteroids **XCV** and Δ^{16}-20-ketosteroids **XCVII** with the appropriate hydroxamoyl chlorides in the presence of triethylamine or nitrile oxides to afford the steroido[16,17-*d*]-2'-isoxazolines **XCVI** [88] and steroido[16α,17α-*d*]-2'-isoxazolines **XCVIII** [89-92] correspondingly.

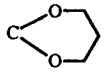


XCV XCVI

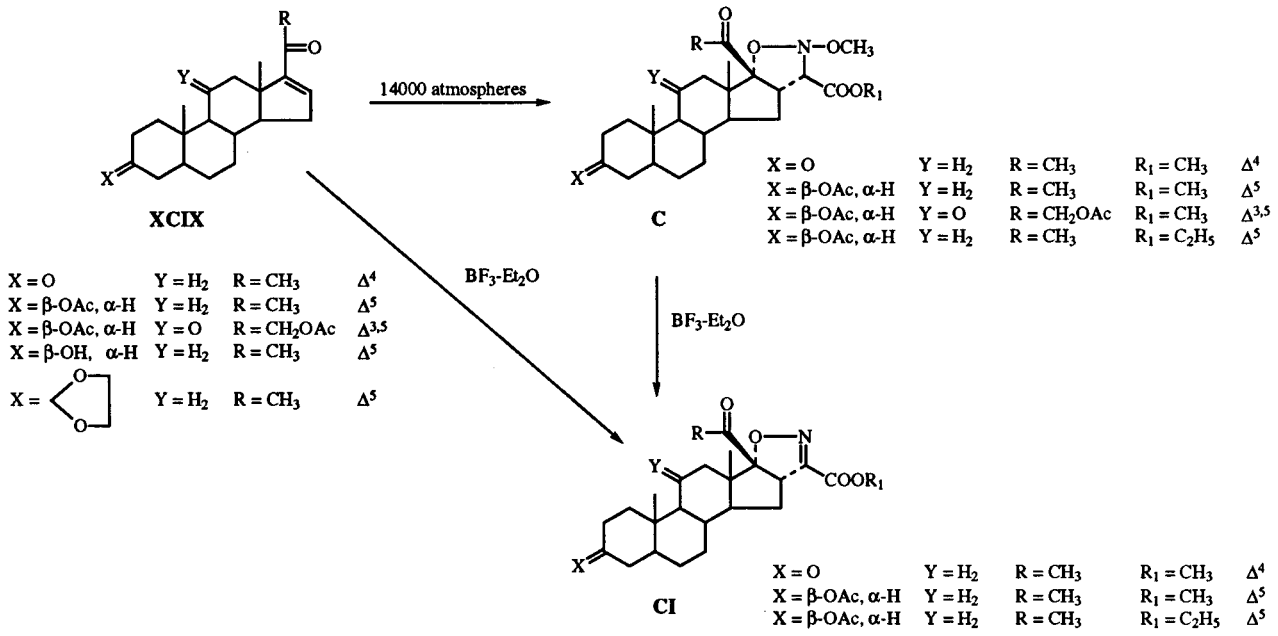
$R = CH_3$	$R_1 = H$	$R_2 = H$	$R_3 = COOH$
$R = CH_3$	$R_1 = COCH_3$	$R_2 = COCH_3$	$R_3 = COOC_2H_5$
$\Delta^{1,3,5(10)}$	$R_1 = CH_3$	$R_2 = H$	$R_3 = COOH$
$\Delta^{1,3,5(10)}$	$R_1 = CH_3$	$R_2 = COCH_3$	$R_3 = COOC_2H_5$



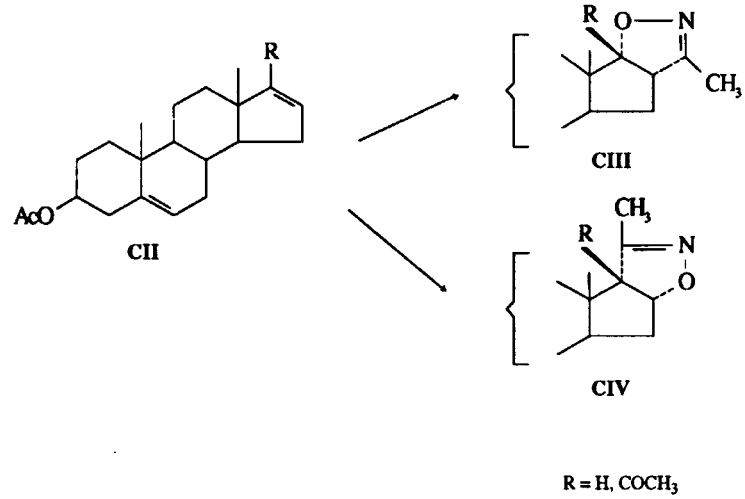
XCVII XCVIII

X	X_1	R	R_1	R_2	R_3	R_4	Δ
CO	CHOH	–	H	H	OAc	CH_3	1,4
CO	CHOH	–	CH_3	F	OAc	CH_3	4
	CHOH	OH	CH_3	H	OAc	CH_3	–
$CHOCOCH_3$	CH_2	–	H	H	H	CH_3	5
CO	CH_2	–	CH_3	H	H	CH_3	4
CO	CHOH	–	H	F	OAc	CH_3	1,4
CO	CH_2	–	CH_3	H	H	C_6H_5	4
$CHOCOCH_3$	CH_2	–	H	H	H	C_6H_5	5
CO	CHOH	–	H	H	OAc	Cl	1,4
CO	CHOH	–	H	H	OAc	$COOC_2H_5$	1,4
$CHOCOCH_3$	CH_2	–	H	H	H	$COOC_2H_5$	5
$CHOCOCH_3$	CH_2	β-H	H	H	H	$COOC_2H_5$	–
CO	CH_2	–	CH_3	H	H	$COOC_2H_5$	4
CO	CHOH	–	H	H	OAc	COOH	1,4
CO	CH_2	–	CH_3	H	H	COOH	4
$CHOCOCH_3$	CH_2	β-H	H	H	H	COOH	–
CHOH	CH_2	–	H	H	H	COOH	5
CO	CH_2	–	H	H	H	COOH	5

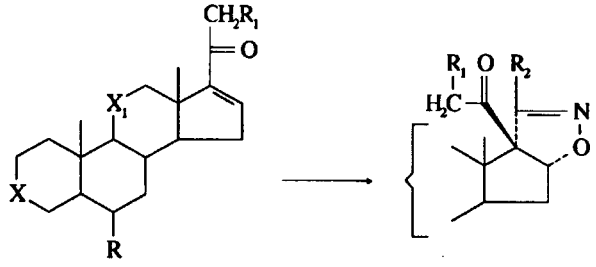
16-Dehydro-20-ketosteroids **XCIX** of the pregnane series enter into cycloaddition reactions with nitronic esters ($R_1O_2CH=N(O)-OCH_3$), to give, depending on the reaction conditions, either steroido[16α,17α-*d*]-2'-isoxazolidines **C** [93,94] at high pressures of about 14000 atmospheres, which are converted to isoxazolines **CI** on treatment with boron trifluoride etherate, or steroido-[16α,17α-*d*]-2'-isoxazolines **CI** (catalysis: Lewis acids) [95,96].



By study of 1,3-dipolar cycloaddition of nitrile oxides to unsaturated systems, initially it was long believed that such cycloaddition to an asymmetric ene system resulted in only one of the two possible isomers **CIII** namely that in which the oxygen of the nitrile oxide is bonded to the most heavily substituted carbon atom of the asymmetric double bond, "normal addition". Recently, however, a few instances have been reported in which the other possible isomer, arising from "inverse addition", was also formed. The results can only be explained by the fact that during the reaction the oxygen of the reactant, in this case acetonitrile oxide, attaches to both C_{17} and C_{16} of the steroid to form two different isoxazoline rings, **CIII** and **CIV** [97,98].



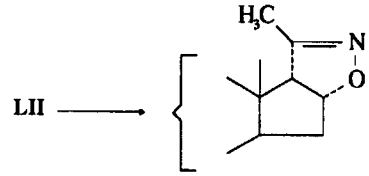
By the same procedure as for the preparation of steroido[16α,17α-*d*]-2'-isoxazolines **XCVIII**, German chemists have reported the formation of isomeric steroido[17α,16α-*d*]-2'-isoxazolines **CVI**, as a result of 1,3-dipolar cycloaddition, "inverse addition", of aceto-, benzo- [99] and ethyl oxalate nitrile oxides [100] to 16-dehydro-20-ketopregnenes.



CV **CVI**

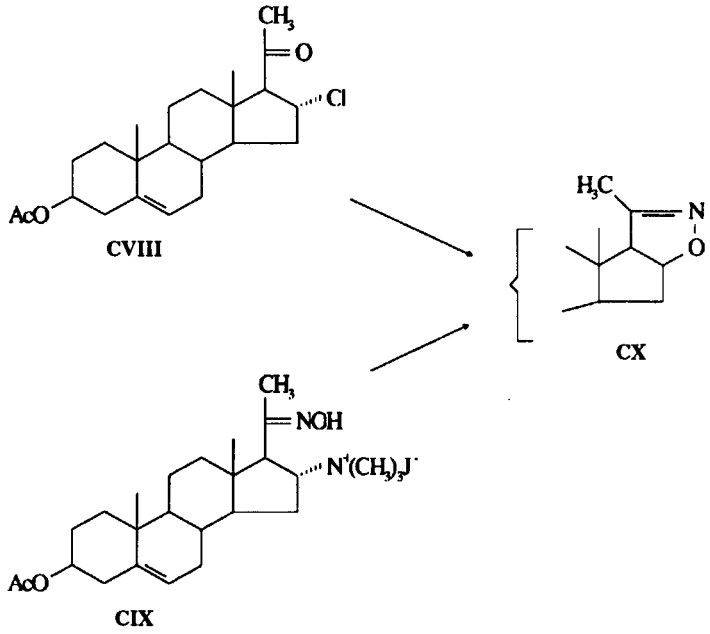
X	X_1	R	R_1	R_2	Δ
CHOAc	CH_2	H	H	CH_3	5
CHOH	CH_2	H	H	CH_3	5
CHOAc	CH_2	CH_3	H	CH_3	5
CHOH	CH_2	CH_3	H	CH_3	5
CO	CH_2	H	H	CH_3	4
CO	CO	H	H	CH_3	4
CO	CO	H	OH	CH_3	4
CO	CH_2	CH_3	H	CH_3	4
CHOAc	CH_2	H	H	C_6H_5	5
CHOH	CH_2	H	H	C_6H_5	5
CHOAc	CH_2	CH_3	H	C_6H_5	5
CHOH	CH_2	CH_3	H	C_6H_5	5
CO	CH_2	H	H	C_6H_5	4
CO	CO	H	H	C_6H_5	4
CO	CO	H	OH	C_6H_5	4
CO	CH_2	CH_3	H	C_6H_5	4
CHOAc	CH_2	H	H	$COOC_2H_5$	5
CHOH	CH_2	CH_3	H	$COOC_2H_5$	5
CO	CH_2	H	H	$COOC_2H_5$	4
CO	CH_2	CH_3	H	$COOC_2H_5$	4
CHOH	CH_2	H	H	COOH	5
CO	CH_2	H	H	COOH	4
CO	CH_2	CH_3	H	COOH	4

Heating compound **LII** with pulverized zinc in glacial acetic acid afforded the compound, of similar structure, 3β-acetoxy-5-androsteno[17α,16α-*d*]-3'-methyl-2'-isoxazoline (**CVII**) [59].

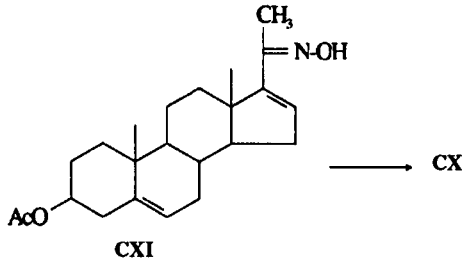


CVII

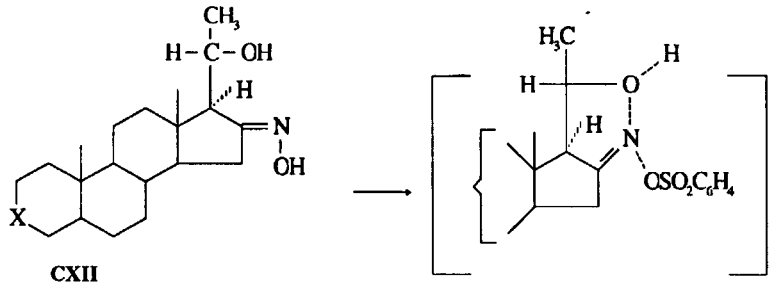
3'-Methylandrosteno[17,16-*d*]isoxazolines **CX** are also formed in high yield in the formation of oximes of 3β-acetoxy-16α-chloropregnenone (**CVIII**) and in low yield in the treatment of the trimethylammonium iodide derivative **CIX** with 3% potassium hydroxide [101].



The same compound **CX** was obtained by irradiation of *anti*-16-dehydropregnenolone oxime 3-acetate (**CXI**) with unfiltered uv light in benzene and tetrahydrofuran [102].

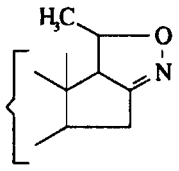


Under Beckmann rearrangement conditions, on treatment with tosyl chloride or acetic anhydride in pyridine, the oximes of 16-keto-20α-hydroxysteroids **CXII** are converted into steroido[16,17-*c*]-2'-isoxazolines **CXIII**. The most probable mechanism is cyclization from the *anti*-forms of the initial oxime with retention of the $C_{(20)}$ configuration [103].



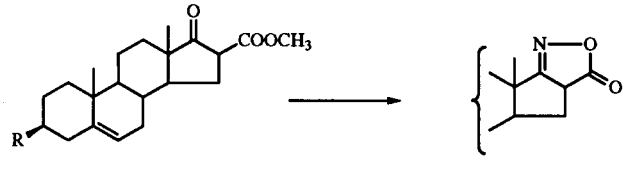
CXII

a. X = CHOH, Δ^5
b. X = CHOCOCH$_3$, Δ^5
c. X = CO, Δ^4



CXIII

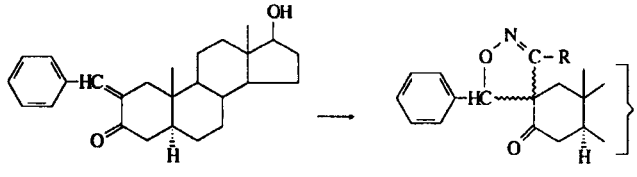
The isomeric androsteno[17,16-*c*]-2'-isoxazolin-5'-ones **CXV** were obtained by cyclization of 3β-acetoxy- and 3β-chloro-5-androsten-16-carbomethoxy-17-one **CXIV** with hydroxylamine hydrochloride [104].



CXIV

R = OCOCH$_3$, Cl

CXV



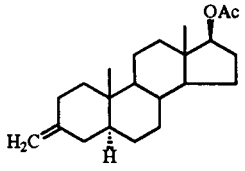
CXVI

CXVII

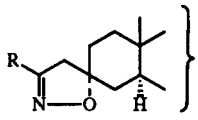
R = CH$_3$, C$_6$H$_5$

In a manner similar to that described for the synthesis of isoxazoline derivatives **XCVI** and **XCVIII** the 2-benzylidene-5α-androstan-17β-ol-3-one (**CXVI**) gave the 2-spiroisoxazolines **CXVII** [5α-androstan-17β-ol-3-one]-2-spiro-4'-[3'-methyl-5'-phenyl-Δ^2-isoxazoline] and [3',5'-diphenyl-Δ^2-isoxazoline] derivative [99].

1,3-Dipolar additions of nitrile oxides, generated *in situ* from the corresponding hydroxamoyl chlorides by addition of a catalytic amount of triethylamine or by thermal generation at the boiling point of the solvent, to 3-methylene-5α-androstan-17β-yl acetate (**CXVIII**) gave the steroido-3-spiro-5'-(3'-substituted-Δ^2-isoxazolines) **CXIX** and **CXX** [105-107]. Depending upon the nitrile oxide, one or more derivatives were found which were isolated by column chromatography.

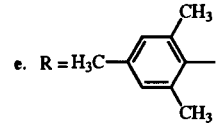


CXVIII

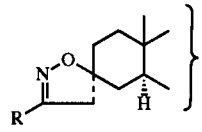


CXIX

a. R = CH_3
b. R = C_6H_5
c. R = $COOC_2H_5$
d. R = COOH



f. R = Ph_3C



CXX

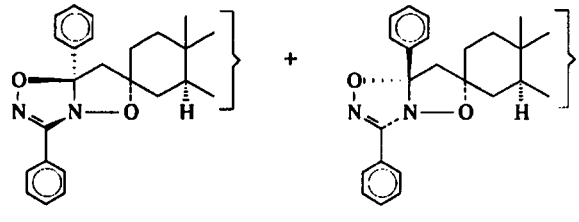
a. R = CH_3
b. R = C_6H_5
f. R = Ph_3C

In the case of addition, of aceto-, benzo- and triphenylacetonitrile oxides to 3-methylenesteroid **CXVIII**, two stereoisomeric mono-adducts, steroido-3(*R*)-spiro-5'-(3'-substituted-Δ^2-isoxazolines) **CXIXa-b,f** and steroido-3(*S*)-spiro-5'-(3'-substituted-Δ^2-isoxazolines) **CXXa-b,f** were obtained, originating from α or β attack on the double bond [107].

The C=N bond of steroido-3(*R*)- and 3(*S*)-spiro-5'-(3'-phenyl-Δ^2-isoxazolines) **CXIXb** and **CXXb** undergo further cycloaddition with only benzonitrile oxide to give the bis-adducts steroido-3-spiroisoxazolidine[2,3-*d*]oxadiazolines **CXXI-CXXIV**. Attempts to synthesize "mixed" bis-adducts by further reaction of benzonitrile oxide with isoxazolines from other nitrile oxides, met with failure. In the bis-adducts the oxygen of the benzonitrile oxide was linked to the carbon of the isoxazoline C=N double bond [107].

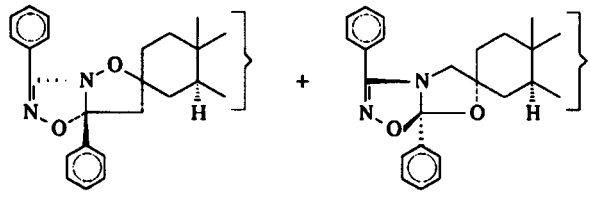
The steroidal isoxazolines **CXIXb** and **CXXb** gave two isomeric bis-adducts each, the stereochemistry of which were determined from circular dichroism and by x-ray diffraction [108].

CXIXb ⟶



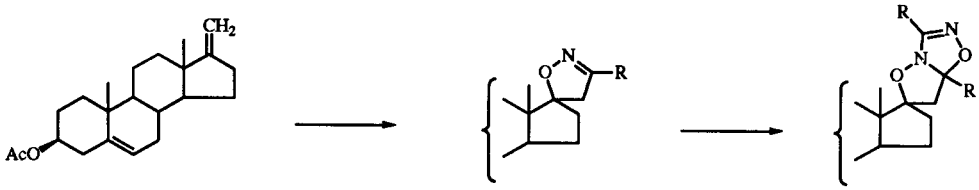
CXXI **CXXII**

CXXb ⟶

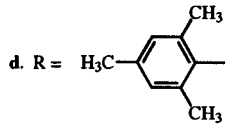


CXXIII **CXXIV**

In the same way, 17-methylene-5-androsten-3β-yl acetate (**CXXV**) with nitrile oxides gave 3β-acetoxy-5-androsten-17-spiro-5'-(3'-substituted-Δ^2-isoxazolines) **CXXVI**. From the addition of benzonitrile oxide to 17-methylenesteroid **CXXV** only two products were obtained: one mono-adduct **CXXVIb** and the bis-adduct **CXXVII** which was also produced by addition of benzonitrile oxide to the isolated **CXXVIb** [107].

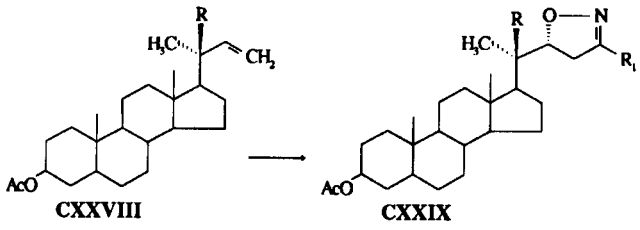


CXXV **CXXVI** **CXXVII**

a. R = CH_3
b. R = C_6H_5
c. R = $COOC_2H_5$
d. R = 

b. R = C_6H_5

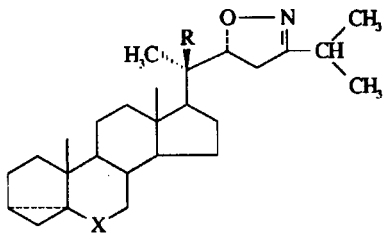
20-Isoxazolinylsteroids of the structure **CXXIX** were prepared by 1,3-dipolar cycloaddition of nitrile oxides to Δ^{22}-steroids **CXXVIII** [71,72,109].



CXXVIII **CXXIX**

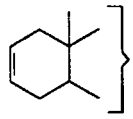
a. R = OH, R_1 = CH_3, $CH(CH_3)_2$, $CH{=}CHCH_3$, $COOC_2H_5$ Δ^5
b. R = H, R_1 = $CH(CH_3)_2$, 5β-H

Similarly the 6-methoxy- or 6-keto-(22*R*)-20-(3-isopropylisoxazolin-5-yl)-3α,5-cyclo-5α-pregnanes **CXXX** were obtained [110-113]. By treatment of 6-keto-derivatives **CXXXb** with pyridine hydrobromide, and subsequent *cis* hydroxylation of the obtained 5α-pregn-2-en-6-one derivative (**CXXXI**) with OsO_4, the (22*R*)-20-(3-isopropylisoxazolin-5-yl)-5α-pregnan-2α,3α-dihydroxy-6-one (**CXXXII**) was obtained [112].

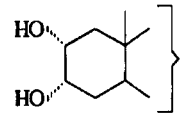


CXXX

a. X = $CHOCH_3$, R = H
b. X = CO, R = H
c. X = $CHOCH_3$, R = OH

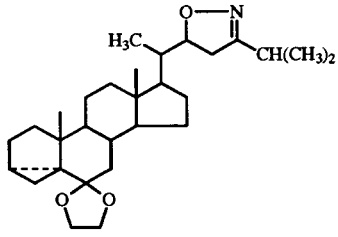


CXXXI

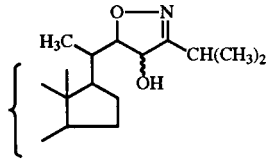


CXXXII

Hydroxylating 20-isoxazolylsteroids 22*R*- and 22*S*-**CXXXIII** with lithium diisopropylamide and trimethyl borate in tetrahydrofuran-hexamethylphosphoramide at -78° followed by *tert*-butyl peroxide in triethylamine gave 20*S*, 22*R*, 23*R*-**CXXXIV** and 20*S*, 22*S*, 23*S*-**CXXXIV** [114].

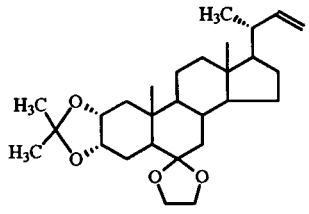


CXXXIII

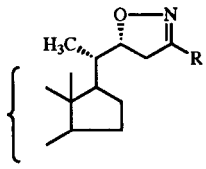


CXXXIV

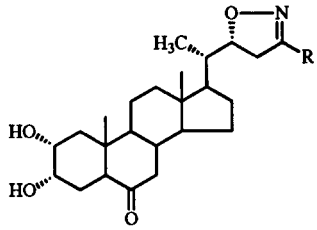
The cyclization of the protected 2α,3α-dihydroxy-6-oxoallyl derivative **CXXXV** with an alkylnitrile oxide (RCN→O) (R=CH_3, $CH(CH_3)_2$) by 1,3-dipolar addition gave the isoxazoline **CXXXVI** which after deprotection to 2α,3α-dihydroxy-6-oxoisoxazoline derivative **CXXXVII** afforded the isoxazoline derivative **CXXXVIII** by lactonization [115].



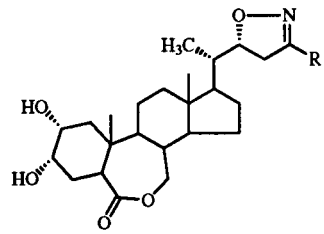
CXXXV



CXXXVI
R = CH_3, $CH(CH_3)_2$

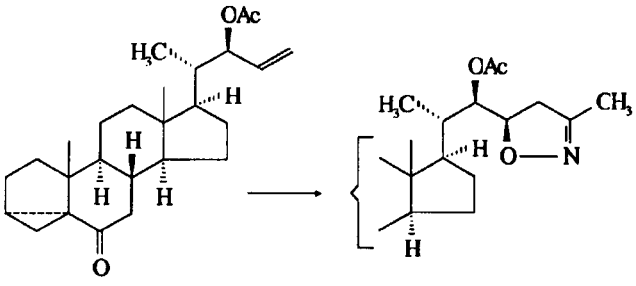


CXXXVII
R = $CH(CH_3)_2$



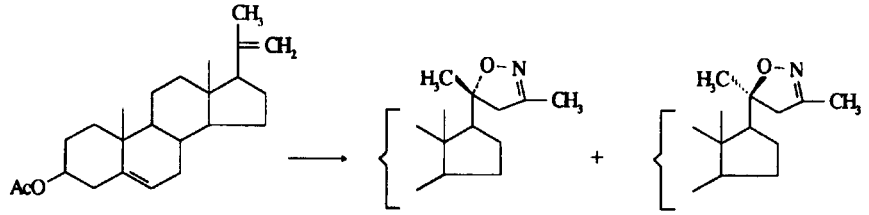
CXXXVIII
R = $CH(CH_3)_2$

In the same way, the Δ^{23}-steroid **CXXXIX** with acetonitrile oxide ($CH_3CN\rightarrow O$) gave the (22*R*)-22-acetoxy-22-(3-methylisoxazolin-5-yl)-3α,5-cyclo-23-nor-5α-cholestan-6-one (**CXL**). Determination of the absolute configuration and molecular structure of the major cycloaddition product **CXL** was accomplished by X-ray crystallography [116].



CXXXIX **CXL**

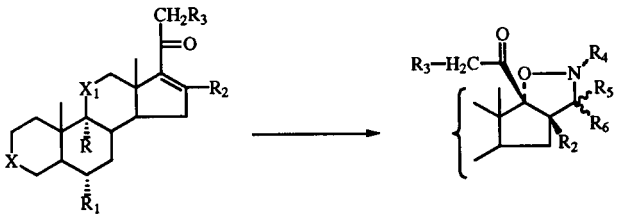
1,3-Dipolar cycloaddition of acetonitrile oxide to the $\Delta^{20(22)}$-pregnene olefin (**CXLI**) in chloroform containing pyridine and *N*-chlorosuccimide, which proceeds regio- and stereoselectively, gave a mixture of the 20*R*-isomer **CXLII** and the 20*S*-isomer **CXLIII** with predominant formation of the 20*R*-isomer [117].



CXLI **CXLII** **CXLIII**

Steroidal Isoxazolidines.

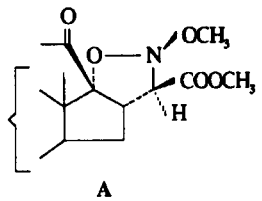
Derivatives of a completely hydrogenated isoxazole ring, which are reported in the literature, are condensed only with the ring D of the steroidal system. The title compounds, steroido[16α,17*a*-*d*]tetrahydro-1',2'-isoxazoles **CXLV**, were formed regiospecifically, as a mixture of stereoisomers, possibly *N*-invertomers, by high pressure induced 1,3-dipolar cycloaddition of nitronic acids to 16-dehydro-20-oxosteoids **CXLIV** in a polar organic solvent, *e.g.* dichloromethane [93,94,118-121].



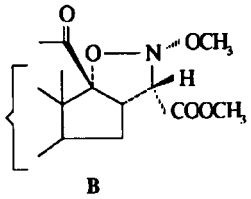
CXLIV CXLV

X = CHOCOCH$_3$, CHOH, CO, 
X_1 = CH_2, CO, CHOH, CHCl
R = H, Cl, F
R_1 = H, CH_3, F
R_2 = H, CH_3
R_3 = H, OH, OAc
R_4 = CH_3, OCH_3, $C_6H_5CH_2$
R_5 = H, $COOCH_3$, $COOC_2H_5$, 4-$NO_2C_6H_4$, 4-ClC_6H_4
R_6 = H
Δ = 1,4, 3, 4, 5, 3,5, 9(10)

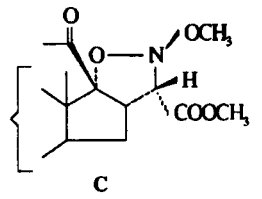
Most dipolarophiles **CXLIV** react with nitronic acids to form two stereomeric pairs **A**, **B** and **C**, **D**, respectively. Taking into account the regiospecifity of cycloaddition preferential rear side attack of the dipole, the compounds obtained can be expected to be the stereoisomers only at C-3' and the *N*-atoms. Hence four partial structure **A-D** can be suggested for the cycloadducts [93].



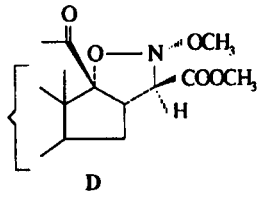
A



B

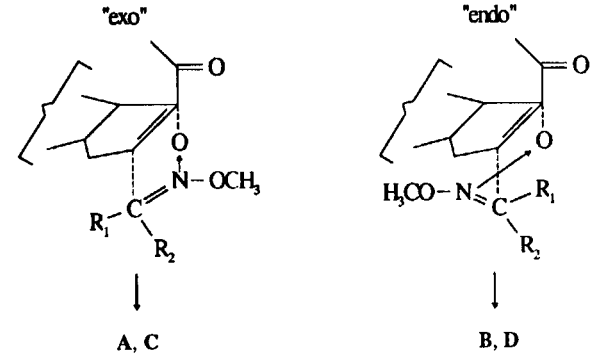


C

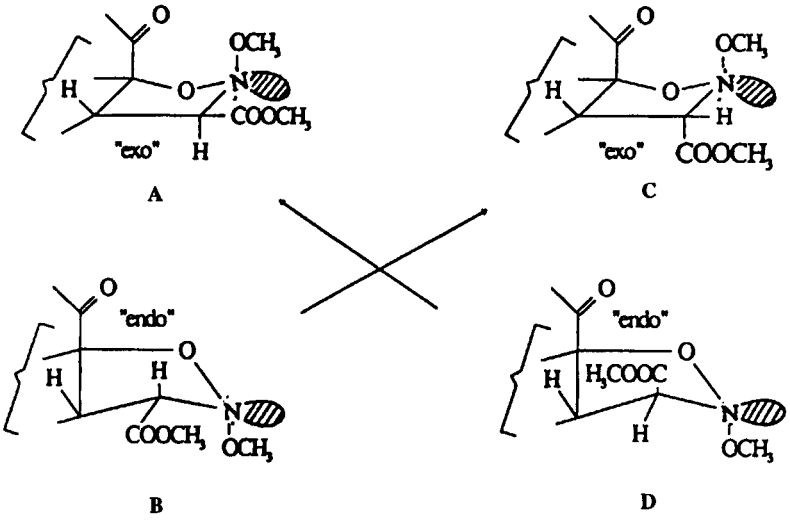


D

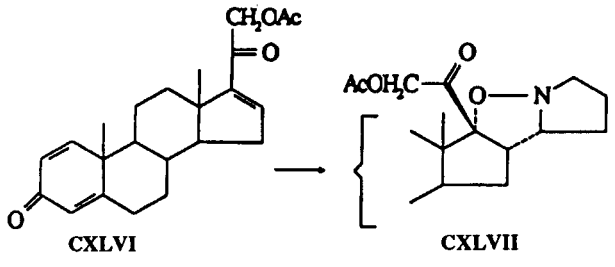
As one can see these structures represent all possible isomers at C-3' and *N*-atoms and are related as follows: **A**, **B** and **C**, **D** are diastereomeric pairs, **A**, **C** and **B**, **D** are C-3' epimeric pairs, **A**, **D** and **B**, **C** are nitrogen invertomers. These isomerization results lead to the conclusion that stereomeric pairs **A**, **B** and **C**, **D** are not epimeric, at C-3' or nitrogen invertomeric, but diastereomeric ones, arising from the two modes, "exo-endo" type of the dipolarophile approach to the dipole [93].



The transformation of unstable isomers to stable forms (**B-C, D-A**) proceeds as a simultaneous nitrogen inversion and isoxazolidine ring conformational change (nE—E^n) [93].

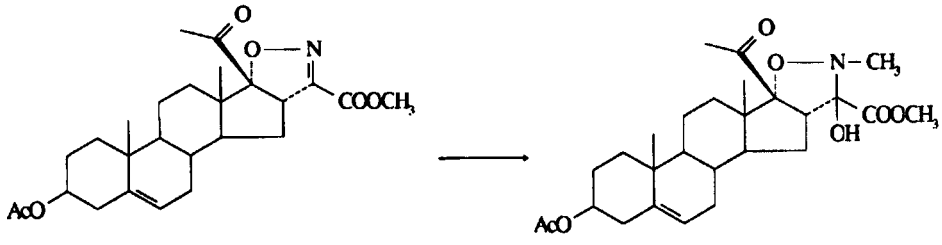


Similarly, 1,3-dipolar cycloaddition of pyrroline *N*-oxide to 1,4,16-pregnatriene-3,20-dione-21-ol acetate (**CXLVI**) produced the pregn-1,4-dien-3-one-21-acetoxy-2',3'-trimethylene[16α,17α-*d*]isoxazolidine (**CXLVII**) [121].



CXLVI **CXLVII**

The 3'-carbomethoxypregn-5-en-3β-ol-20-one[16α,17α-*d*]-2'-isoxazoline acetate (**CXLVIII**) by treatment with methyl fluosulfonate was converted *via* the intermediate step of the ammonium salt, which is decomposed by alkali, to the corresponding 2'-methyl-3'-hydroxy-3'-carbomethoxypregn-5-en-3β-ol-20-one[16α,17α-*d*]-1',2'-isoxazolidine (**CXLIX**) [94,96].



CXLVIII **CXLIX**

Biological Activity of Steroidal Isoxazoles, Isoxazolines, Isoxazolidines and Their Derivatives.

It is noted that attachment of an isoxazole ring to the steroid skeleton brings about interesting changes in the activity of the initial steroids. The most interesting compounds were the steroidal[2,3-*d*]isoxazoles of the androstane series, which proved to be very active when tested for myotrophic activity [4,13], determined by the growth response of the levator muscle, anabolic activity [1,4,11,18], by nitrogen retention, low androgenic activity [1,4,11,13,18], by the gain in weight of the ventral prostate, and in addition they have estrogenic activity [4,8], determined by vaginal cornification, all in rats.

The most interesting member of the isoxazole series in terms of the separation of anabolic and androgenic activities was 17β-hydroxy-17α-methylandrostano[2,3-*d*]isoxazole. It was 0.25 as anabolic, 0.43 as myotrophic and 0.11 as androgenic as testosterone propionate when compared parenterally. Furthermore, this steroid was 9.7 times as anabolic, 2 times as myotrophic and 0.24 times as androgenic as methyltestosterone when compared orally [4].

The completely saturated products always have greater activity than their Δ^4- and $\Delta^{4,6}$-analogous [4].

It was found the 17β-hydroxy-17α-methylandrost-4-eno[2,3-*d*]isoxazole to be 0.10-0.33 as anabolic 0.50 to equally as myotrophic and 0.10-0.20 as androgenic as testosterone propionate when compared parenterally. In addition this steroid was approximately 1.2 times as anabolic, equally as myotrophic and 0.10 as androgenic as methyltestosterone when given orally [4]. Similarly, this compound shows about 25-50% of the myotrophic activity of testosterone acetate upon subcutaneous administration in mice while having an androgenic activity of only about 1/3 that of testosterone acetate, it is about 1/4 as active as testosterone acetate in nitrogen retention studies [13].

The 17β-hydroxy-17α-methylandrost-4,6-dieno-[2,3-*d*]isoxazole exhibited approximately 0.1 the anabolic and androgenic activities of 17β-hydroxy-17α-methyl-androstano[2,3-*d*]isoxazole on parenteral administration [4].

When the 17α-alkyl group of the above isoxazole series was larger than methyl, a decrease in these activities was noted. Also, the introduction of additional 4,4-dimethyl-, 6α-methyl- and 3'-alkyl-substituents on the androstano-isoxazole molecule lead to minimal nyotrophic activity [4].

In the 19-nor series, 19-nor-17β-hydroxy-17α-methyl-androst-4-eno[2,3-*d*]isoxazole proved to be the most interesting. It was found to be progestational equal in activity to progesterone intramuscularly, and at least as active as Ethisterone when given orally, highly active both anabolically and myotrophically, and in addition has a low degree of androgenic and estrogenic activities. The latter response, however, is atypical since considerable mucification and leucocytic infiltration accompany cornifying effects on the vaginal epithelium [4,8].

The isomeric isoxazolo[3,2-*c*] derivatives, 17β-hydroxy-17α-methylandrostano[3,2-*c*]isoxazole [1,5], and 4,17-dihydroxy-17α-methylandrost-4-eno-[3,2-*c*]isoxazole [46], showed potential anabolic activity [1,46], significant myotrophic activity [5] and low androgenic activity [1,5], but contrary to the corresponding [2,3-*d*] analogs these compounds were found to exhibit a lower order of activity. The first compound has found practical application as an anabolic agent under the name of *Andro-isoxazole* [122-126].

Steroido[2,3-*d*]isoxazoles **XI** ($R = R_2 = R_3 = R_4 = H$, $R_1 = R_7 = CH_3$, $X = CH_2$, $R_5 = OH$, $R_6 = C{\equiv}CCF_3$), has estrogenic activity in rats at 50 mg/kg/day (s.c.) 3 times daily [12], since compounds of similar structure **XI** ($R = R_2 = R_3 = R_4 = R_6 = H$, $R_1 = R_7 = CH_3$, $R_5 = OCH_3$, $X = CH_2$) are useful as steroid enzyme inhibitors [23].

17α-Ethinyl-17β-hydroxyandrost-4-eno[2,3-*d*]isoxazole, *danazol* (**XI**, $R = R_2 = R_3 = R_4 = H$, $R_1 = R_7 = CH_3$, $X = CH_2$, $R_5 = OH$, $R_6 = C{\equiv}CH$, $\Delta = 4$), in tests on mice, rats, rabbits and dogs was an orally active pituitary gonadotropin inhibitor devoid of estrogenic and progestational activity. *Danazol* had weak inpeded androgenic activity and was also shown to have antiandrogenic, antiprogestational and antiestrogenic activity. Toxicological studies established the safety of *danazol and* metabolic studies established that *danazol* is the active steroid [127].

The affinity of norgestrel[2,3-*d*]isoxazole and its halo derivatives to progesterone, estrogen and androgen receptors was determined [30].

Similarly, the binding activity of 17β-hydroxy-6-methylandrost-4-eno[2,3-*d*]isoxazole and 17β-hydroxy-17α–ethynyl-6-methylandrost-4-eno[2,3-*d*]isoxazole to progesterone receptor was examined [31].

During investigations on steroidal[2,3-*d*]isoxazoles, 17β-acetoxyandrost-4-eno[2,3-*d*]isoxazole and 17,17-dimethyl-19-norandrost-4,13-dieno[2,3-*d*]isoxazole were found to have tumor-inhibiting properties [16,17].

4α,5α-Epoxy-derivatives of steroido[2,3-*d*]isoxazoles of the structure **XV** ($R = R_1 = R_7 = CH_3$, $R_2 = R_3 = R_4 = R_6 = H$, $R_5 = OH$, $X = CH_2$) had a minimum 100% ED of 500 mg/kg in rats when tested for interceptive activity orally at day 10 of pregnancy [40].

The 17β-dihydroxy-5α-androstan-1,3-dieno[4,3-*d*]isoxazole (**XXXVI**, $R_1 = OH$, $R_2 = H$, $X = CH_2$, Δ^1, 5α-H) was exhibited anabolic and antiandrogenic activity [50].

Steroidal isoxazoles of the structure **XLV** (R = H) can be used in the treatment of protein anabolism [55] and for its testosterone-like activity [56].

Steroidal 17α-(3-substituted-5-isoxazolyl) derivatives **LXV** have hypocholesteremic and antifertility activity [65] but lack androgenic, anabolic, estrogenic and antiovulatory activity [66].

Estreno[2,3-*d*]dihydroisoxazoldiols **LXXIII** possessed pituitary gonadotropin inhibiting and anabolic activities [76].

17β-Hydroxy-17α-methylandrostano[3,2-*c*]-5'-hydroxy-2'-isoxazolines **IV** have pituitary-inhibiting, anabolic and myotrophic activity [6].

The 5'-hydroxy-2'-isoxazolino[16,17-*d*]androstanes and -19-norandrostanes **XCII** showed strong anabolic and reduced androgenic activity [86]. The same isoxazoline derivatives of 2-fluoroestrone was hypocholesterolemic in the female rat at 50 microg/kg daily, but estrogenic only at 10 mg/rat [87].

Pregnano[16α,17α-*d*]isoxazolines of the structure **XCVIII** are useful for fertility control pregnancy maintenance, and as antiinflammatory, antibacterial, antiviral and antifungal agents, are claimed [92].

The pregnano[16α,17α-*d*]isoxazolines of the structure **CXLV** were active as topical antiinflammatory agents in mice [120,121]. In fact the most potent compound **CXLV**

(X = C=O, X_1 = CHOH, R = F, R_1 = R_2 = R_5 = R_6 = H, R_3 = $OCOCH_3$, R_4 = CH_3, Δ = 1,4) was considerably more potent than the standard, betamethazone 17-valerate. It is interesting to note that in this [16α,17α-*d*]isoxazolidine series the introduction of the fluorine at C_9 doubles the topical potency of the 2'-methyl compound **CXLV** (X = C=O, X_1 = CHOH, R = R_1 = R_2 = R_5 = R_6 = H, R_3 = $OCOCH_3$, R_4 = CH_3, Δ =1,4) but has no effect upon the 2'-benzyl analogue **CXLV** (X = C=O, X_1 = CHOH, R = R_1 = R_2 = R_5 = R_6 = H, R_3 = $OCOCH_3$, R_4 = $CH_2C_6H_5$, Δ = 1,4) [121].

The hexacyclic compound **CXLVII** was, however, inactive at the highest dose derived; presumably, interaction of ring D and the substituents at 16α and 17α with some biological receptor is hindered by the bulk of the pyrrolidine ring [121].

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