Steroidal Oxazoles, Oxazolines, and Oxazolidines

Charalambos Camoutsis
University of Patras, School of Health Sciences,
Department of Pharmaceutical Chemistry,
Patras, Greece

Received February 20, 1996

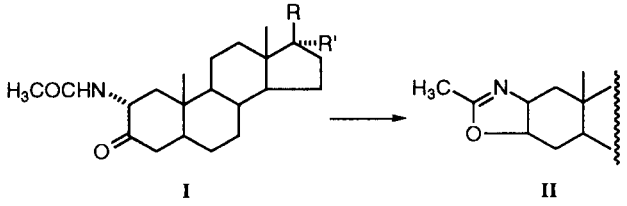
Dedicated to the memory of Professor Nicholas Alexandrou

In recent years the interest of this investigator has been attracted to a series of new compounds in which a cyclopentanoperhydrophenanthrene system is condensed with various heterocyclic rings. As was to be expected, the addition of heterocycles to steroids often leads to a change of their physiological activity and the appearance of new interesting biological properties. Since the numerous data on the synthesis and properties of the steroidal oxazoles, oxazolines, and oxazolidines are scattered, this stimulated us to write the present review, in which the literature published up to the end of 1994 is systematized.

J. Heterocyclic Chem., **33**, 539 (1996).

Steroidal Oxazoles.

The intramolecular cyclization of the 2α-acetamido-3-ketosteroids **I**, by the use of sulphuric acid, gave the 2′-methylsteroidal[2,3-*d*]oxazoles **II** [1].

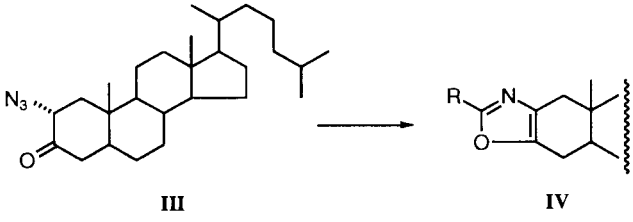


I **II**

R = OH, $OCOCH_3$, C_8H_{17}

R' = H, CH_3

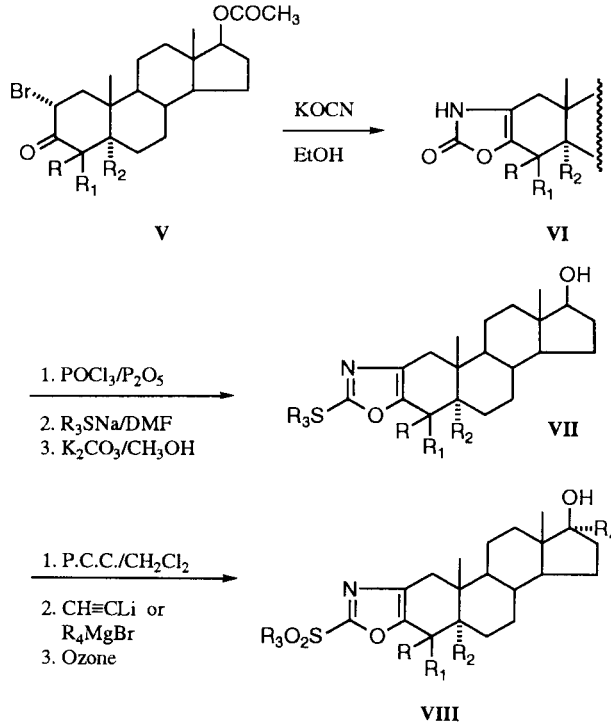
A simpler method for the preparation of compounds of similar structure involves the reaction of the 2α-azido-cholestane-3-one (**III**) with acyl halides in the presence of triphenylphosphine [2].



III **IV**

R = CH_3, C_6H_5

Compounds of similar structure with an alkylsulfonyl group in position 2′ were prepared by cyclocondensation of the 2α-bromo-5α-androstan-3-one (**V**) with KOCN in ethanol. The resulting 2′,3′-dihydro-2′-oxoandrost-2-eno-[2,3-*d*]oxazole (**VI**) was converted in four steps to **VIII** [3,4].



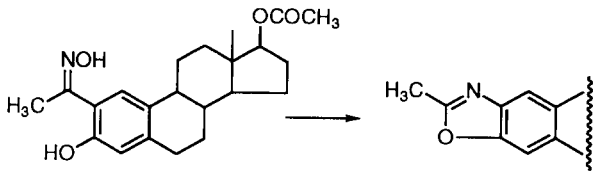
V **VI** **VII** **VIII**

R-R_2 = H; R_1-R_2 = bond; R = H, CH_3;

R_3 = CH_3, C_2H_5, C_3H_7, $CH(CH_3)_2$;

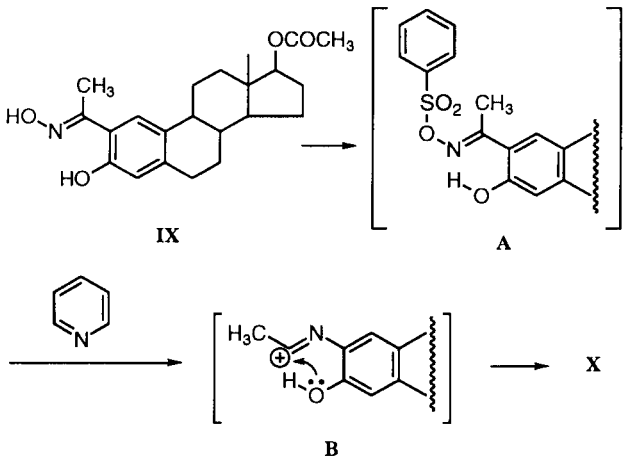
R_4 = H, CH_3, C_2H_5, vinyl, C≡CH

2′-Methyl[2,3-*d*]benzoxazole of the estrane series was obtained by reaction of oxime **IX** with benzenesulfonyl chloride or *p*-toluenesulfonyl chloride in pyridine [5,6].



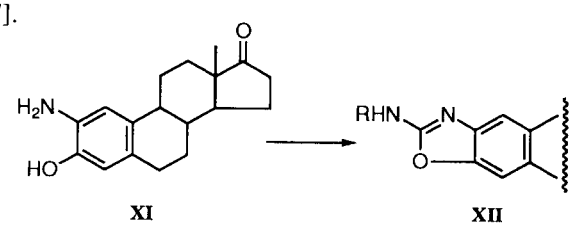
IX X

According to the reaction mechanism, in weakly basic pyridine medium, the benzenesulfonate ester **A** of the oxime **IX**, by a Beckmann rearrangement **A→B** before attack by the phenolic hydroxyl at C-3, gave the benzoxazole **X** [6].



IX A B X

It is possible to produce compounds of similar structure by cyclocondensation of 2-amino-3-hydroxyestra-1,3,5-(10)-trien-17-one **XI** with the appropriate isothiocyanate derivatives in the presence of dicyclohexylcarbodiimide [7].



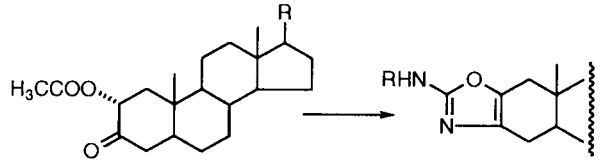
XI XII

R = cyclo-C_6H_{11}, $CH_2C_6H_5$, C_6H_5,

m-$CH_3C_6H_4$, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$,

p-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4

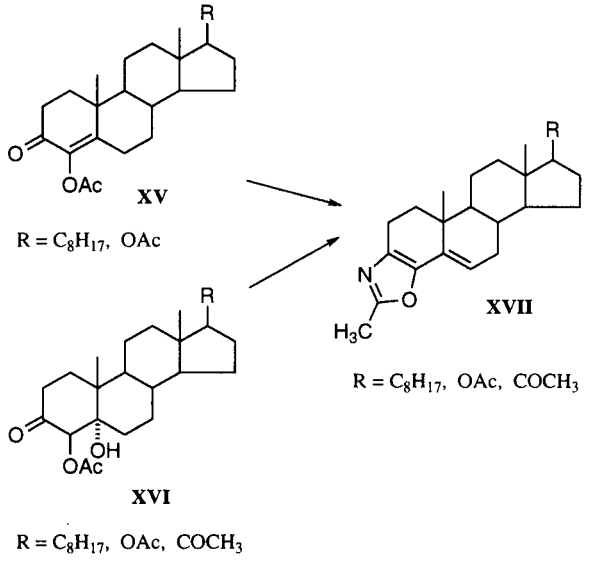
The isomeric 2′-methylsteroidal[3,2-*d*]oxazoles **XIV** were prepared by the reaction of 2α-acetoxy-3-ketosteroids with ammonium acetate in acetic acid [1,8].



XIII XIV

R = $OCOCH_3$, C_8H_{17}

By a similar reaction 2′-methylsteroidal[3,4-*d*]oxazoles of androstanes, cholestanes and progesterone were obtained, including the interaction of vicinal ketoacetates with ammonium acetate in acetic acid [8].



XV

R = C_8H_{17}, OAc

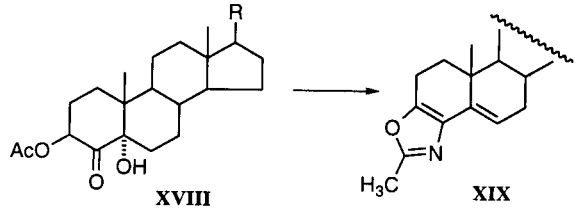
XVII

R = C_8H_{17}, OAc, $COCH_3$

XVI

R = C_8H_{17}, OAc, $COCH_3$

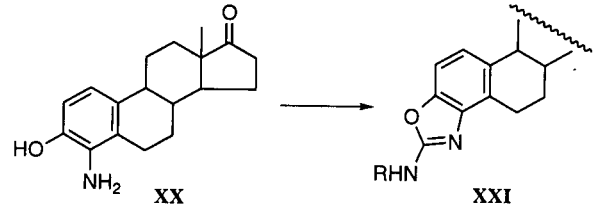
In contrast, the 3β-17-diacetoxy-5α-hydroxy-4-androstanone and 3β-acetoxy-5α-hydroxy-4-cholestanone under the same conditions gave the isomeric compounds 2′-methyl[4,3-*d*]oxazoles **XIX** [8].



XVIII XIX

R = OAc, C_8H_{17}

Similar compounds of the estrane series were obtained from the 4-amino-3-hydroxyestra-1,3,5(10)-trien-17-one (**XX**), by the same procedure as for the preparation of 2′-methyl[2,3-*d*]benzoxazoles **XII** [7].



XX XXI

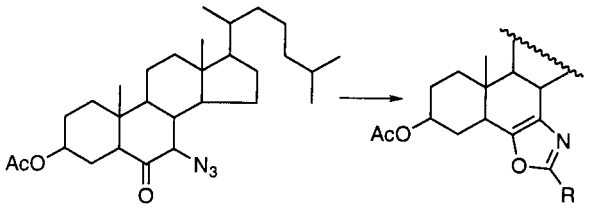
R = cyclo-C_6H_{11}, $CH_2C_6H_5$, C_6H_5,

m-$CH_3C_6H_4$, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$,

p-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4

The azidosteroid ketones with an equatorial azide group can be transformed with triphenylphosphine and several acyl halides to oxazolosteroids in an easily understandable

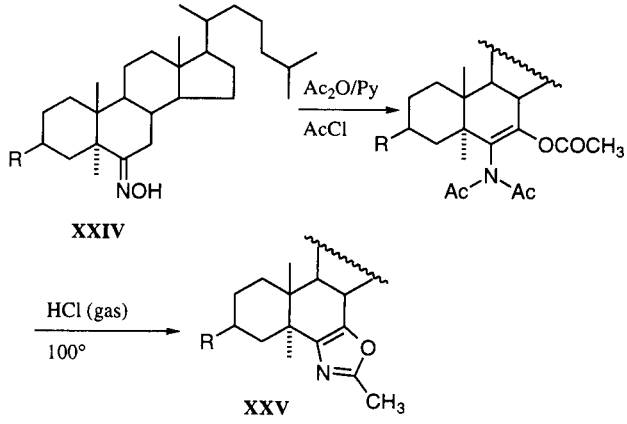
manner. Indeed, by treating 3β-acetoxy-7β-azido-cholestan-6-one with acyl halides in the presence of triphenylphosphine the corresponding 2′-substituted steroidal[7,6-*d*]oxazoles **XXIII** were formed, whereas the same reaction with the 7α-epimer proceeds without cyclization, yielding the 7α-amido group [2].



XXII **XXIII**

R = CH_3, C_6H_5, $CH_2C_6H_5$, $COOCH_2CH_3$

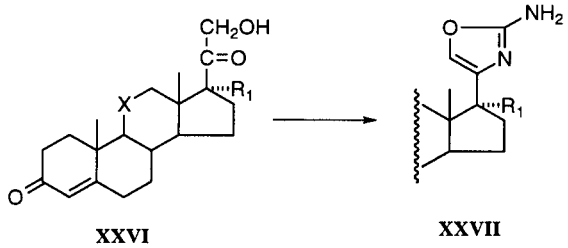
Reaction of 3β-cholestan-6-one oxime (**XXIV**) in dry pyridine-acetic anhydride with acetyl chloride followed by cyclization with dry hydrogen chloride (gas) provided the isomeric oxazoles **XXIII**, 2′-methyl-5α-cholestan-[6,7-*d*]oxazoles and the deoximation product, 5α-cholestan-6-one [9].



XXIV **XXV**

R = $OCOCH_3$, Cl

The reaction of the 20-oxo-21-hydroxy side chain of corticosteroids **XXVI** with cyanamide in methanolic aqueous ammonia gave the 17β-(2-aminooxazol-4-yl)-steroids **XXVII** [10].



XXVI **XXVII**

X = CH_2, R_1 = H

X = CO, R_1 = OH

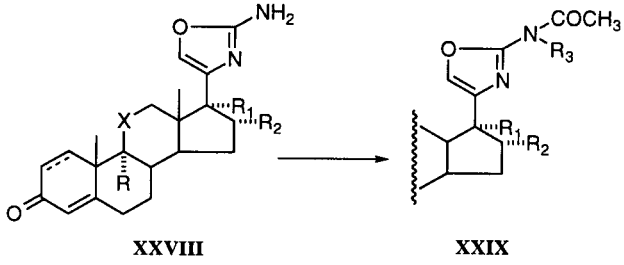
X = β-CHOH, R_1 = OH

X = CO, R_1 = OH, Δ^1

X = β-CHOH, R_1 = OH, Δ^1

X = CO, R_1 = OH, 3,3-ethylenedioxy, Δ^5

Acetylation of the 17β-(2-aminooxazol-4-yl)steroids **XXVIII** with acetic anhydride under nitrogen gave the mono- and diacetylated compounds **XXIX** [11]. Spectroscopic and physicochemical studies showed that the acetylation takes place only at the exocyclic N [12].



XXVIII **XXIX**

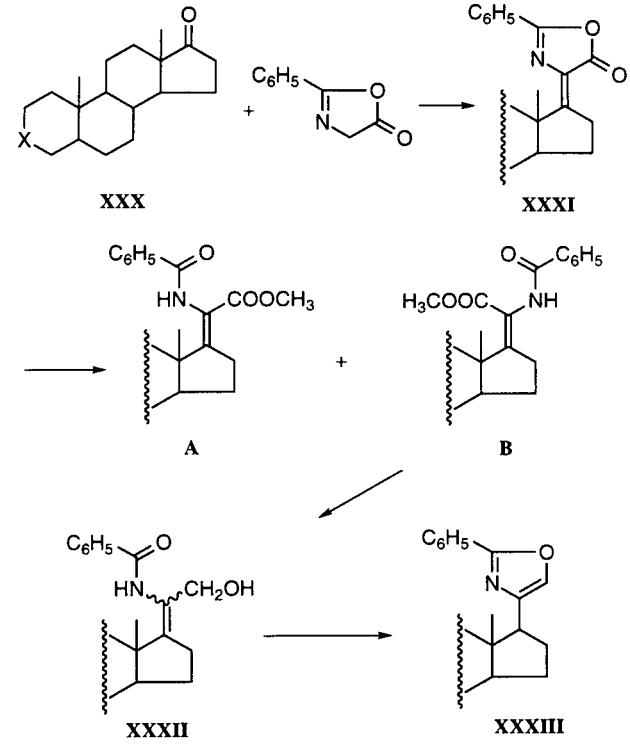
X = CH_2, C=O, β-CHOH

R = H, F

R_1 = H, OH

R_2 = H, CH_3

R_3 = $COCH_3$



XXX **XXXI**

A **B**

XXXII **XXXIII**

X	Δ
β-CHOH	5

4

4, 9(11)

CH_3OC 1, 3, 5(10)

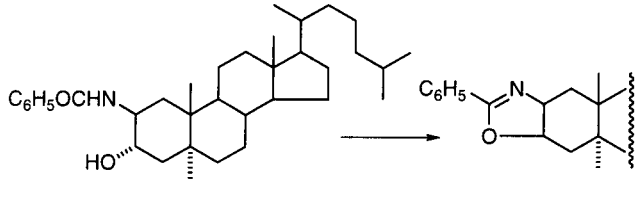
C=O 4

C=O 4, 9(11)

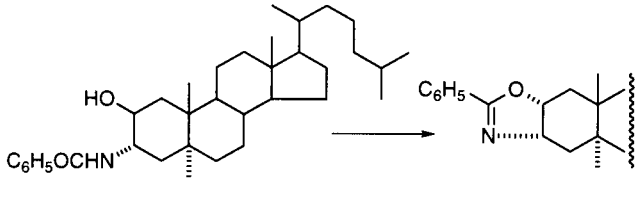
A new method of preparation of the 17β-(2-phenyl-1,3-oxazol-4-yl)steroids (**XXXIII**) consists in the condensation of the 17-oxosteroids **XXX** with 5-phenyloxazolin-2-one with titanium tetrachloride in the presence of pyridine to give the steroidal azalactones **XXXI**, which were cleaved by sodium methoxide to yield isomeric compounds **A** and **B**. The latter after reduction to the corresponding compounds **XXXII** followed by cyclization with hydrochloric acid, yielded the steroidal oxazoles [13].

Steroidal Oxazolines.

The reaction of the vicinal *trans*-hydroxyamides with thionyl chloride and then washing with alkali gives the [2,3-*d*] and [3,2-*d*]oxazolines. So, the 2β-benzamido-3α-hydroxycholestane (**XXXIV**) and 3α-benzamido-2β-hydroxycholestane (**XXXVI**) after treating with thionyl chloride yield the 2′-phenylcholestan[2β,3β-*d*]oxazoline (**XXXV**) and 2′-phenylcholestan[3α,2α-*d*]oxazoline (**XXXVII**) correspondingly [14].

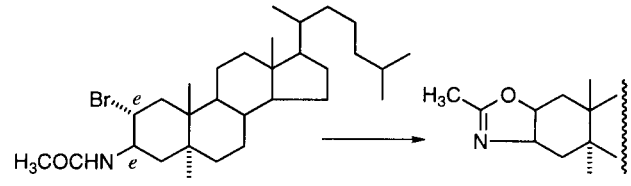


XXXIV **XXXV**

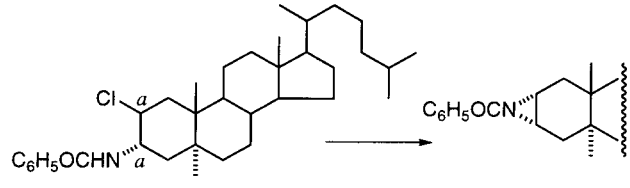


XXXVI **XXXVII**

In the case of the vicinal haloamides only these, with diequatorial configuration of the halide and amide groups, cyclized into an oxazoline in alkaline solution, whereas the diaxial *trans*-haloamides under the same conditions of cyclization yield aziridines because the internal displacement of halide takes place by the amide nitrogen atom instead of the displacement by amide oxygen. For example, 2α-bromo-3β-acetylamidocholestane (**XXXVIII**) in strong alkali gives 2′-methylchlolestan[3β,2β-*d*]oxazoline (**XXXIX**) [15], whereas the 2β-chloro-3α-benzamidocholestane **XL** gives 2α,3α-aziridine **XLI** [16].



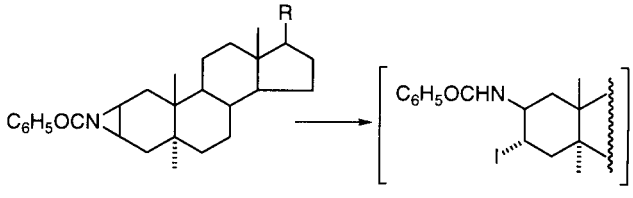
XXXVIII **XXXIX**



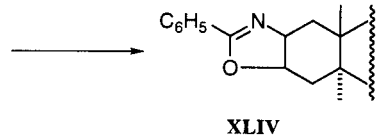
XL **XLI**

However, the [3α,2α-*d*]oxazolines **XXXVII** were prepared by the heating of diaxial haloamides **XL** with sodium bicarbonate in a mixture ethanol-chloroform-acetone for two weeks [17].

Treatment of 2β,3β-(*N*-benzoylimino)steroids **XLII** with sodium iodide in acetone gave, by *trans*-diaxial ring opening, the transient 2β-benzamido-3α-iodosteroids **XLIII** which spontaneously cyclized to the 2′-phenylsteroido[2β,3β-*d*]oxazolines **XLIV** [17,18].

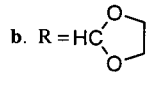


XLII **XLIII**



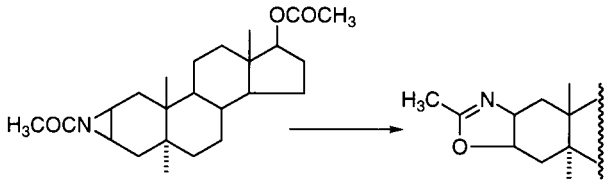
XLIV

a. R = C_8H_{17}

b. R = 

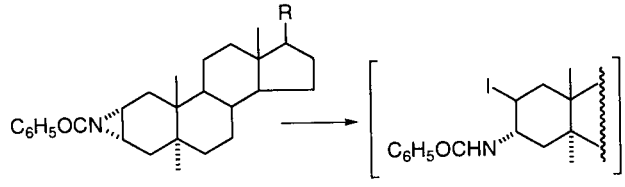
The same oxazoline **XLIVb** was afforded by heating of the 2β,3β-aziridine **XLIIb** to 200° for two hours [18].

Under the same conditions the reaction of the 17β-acetoxy-3β-acetylimino-5α-androstane (**XLV**) with sodium iodide gave 17β-acetoxy-2′-methyl-5α-androstano[2β,-3β-*d*]oxazoline (**XLVI**) [19].

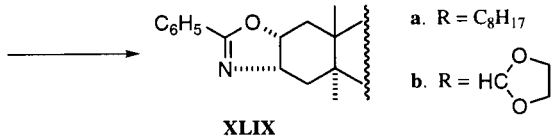


XLV XLVI

In an analogous manner to the above synthesis of oxazolines **XLIV** the 2α,3α-(*N*-benzoylimino)steroids **XLVII** gave the oxazolines **XLIX** *via* the 3*a*-benzamido-2β-iodosteroids **XLVIII** [18].



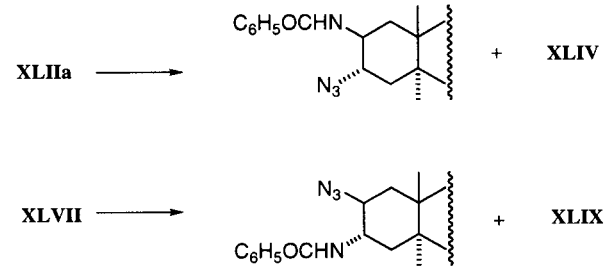
XLVII XLVIII



XLIX

On carrying out the reaction of 2α,3α-benzoyliminocholestane (**XLVIIα**) with boron trifluoride etherate in the absence of the external nucleophile the [3α,2α-*d*]oxazoline **XLIX** is formed [17].

The same oxazolines **XLIV** and **XLIX** of the cholestane series were obtained by reaction of 2β,3β- and 2α,3α-benzoyliminocholestane, **XLIIα** and **XLVIIα** with sodium azide in dimethyl sulfoxide [20].



XLIIa → + XLIV

XLVII → + XLIX

Steroidal oxazolines in which the heterocycle is condensed with ring A of the steroid in positions 3 and 4 were prepared from the reaction of 3α,4α-epoxynitrocholest-5-ene **L** with acrylonitrile or phenyl cyanide in the presence of trifluoride etherate [21,22].

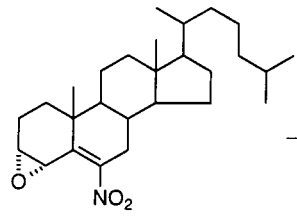
Steroidal oxazolones of type **LIV** can be obtained by the reaction of phenylurethane **LIII** with ammonium acetate in glacial acetic acid or with methanesulfonic acid in toluene [8,23].

Oxazolinethione **LVIα** of the estrane series were prepared by cyclocondensation of 2-amino-3-hydroxyestra-1,3,5(10)-trien-17-one (**LV**) with carbon disulfide and alkali, which after alkylation yielded the oxazolinethiones **LVIb-e** [24].

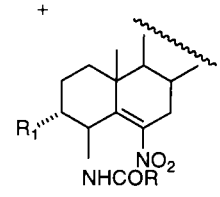
LI

R = CH=CH$_2$

R = C$_6$H$_5$



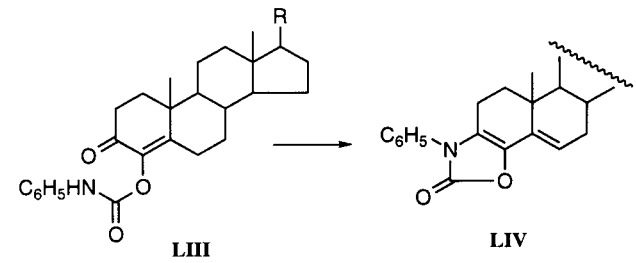
L



LII

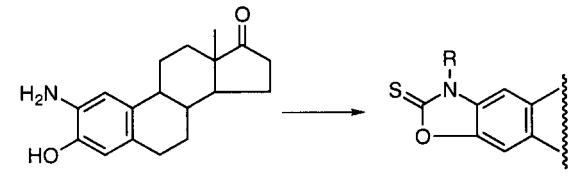
R = CH=CH$_2$, R$_1$ = OH

R = C$_6$H$_5$, Δ^3



LIII LIV

R = C_8H_{17}, $COCH_3$



LV LVI

R

a. H

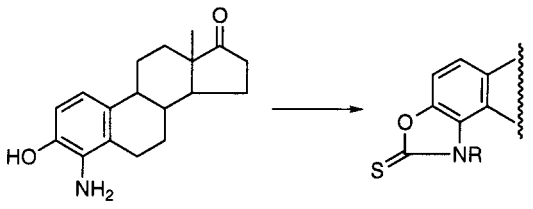
b. CH_3

c. $Me_2NCH_2CH_2$

d. CH_2CH_2N

e. CH_2CH_2NO

By the same reaction the isomeric oxazolinethiones **LVIII** were prepared from 4-amino-3-hydroxyestra-1,3,5(10)-trien-17-one (**LVII**) [24].



LVII LVIII

R

a. H

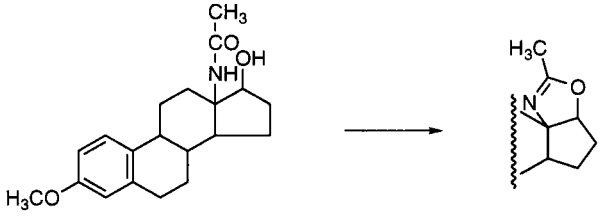
b. CH_3

c. $Me_2NCH_2CH_2$

d. CH_2CH_2N

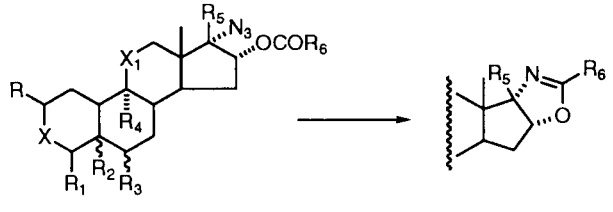
e. CH_2CH_2N

Steroidal derivatives with an oxazoline ring in positions 13 and 17 of estrane were prepared by treatment of the 13-acetylamino derivative of estradiol **LIX** with methanolic hydrogen chloride, conditions under which *cis*-acylaminoalcohols usually undergo N → O acyl migration, to give directly the oxazoline **LX** [25].

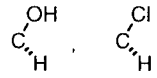


LIX LX

20-Ketosteroidal[17α,16α-*d*]oxazolines have been studied much more. The general method of synthesis of the compounds of this class includes the acetylation of 16α-hydroxy-17α-azides followed by cyclization after reduction of the azide formed [26-40].



LXI LXII

$X_1 = CH_2$, C=O, 

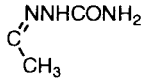
R = H, Br

R_1 = H, Br

R_2 = α-H

R_3 = H, CH_3, α-CH_3, CHO

R_4 = H, Br, Cl, F

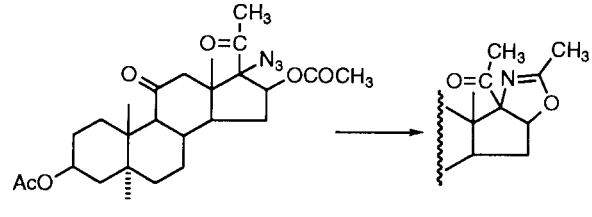
R_5 = $COCH_3$, $COCH_2OH$, $COCH_2OAc$, 

$COCH_2O_2CCH_2CH_2COOH$

R_6 = H, CH_3, C_2H_5, C_3H_7, C_4H_9, C_6H_5

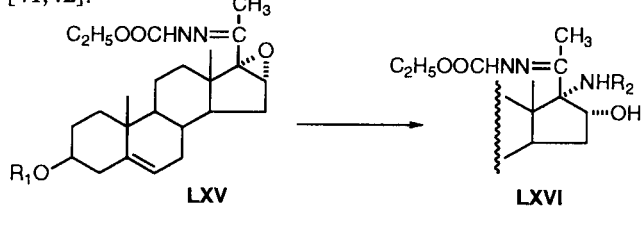
Δ = 4, 5, 1,4, 3,5, 4,6, 9(11), 1,3,5(10)

In an analogous manner the 3,16-diacetate (**LXIII**) of 17β-azido-5α-pregnane-3β,16β-diol-11,20-dione, gave the 2′-methyloxazolino[17β,16β-*d*]-3β-acetoxy-5α-pregnane-11,20-dione (**LXIV**) [26].

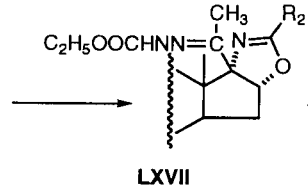


LXIII LXIV

Also, the oxazolines **LXII** are obtained by cyclocondensation, with acetic anhydride in acetic acid and subsequent hydrolysis, of 16α-hydroxy-17α-amino-20-ethoxycarbonylhydrazonopregnanes **LXVI**, prepared from 16α,-17α-epoxy-20-ethoxycarbonylhydrazonopregnanes **LXV**, after treating with ammonia gas or primary amines in pyridine or dimethylformamide at room temperature [41,42].



LXV LXVI



LXVII LXII

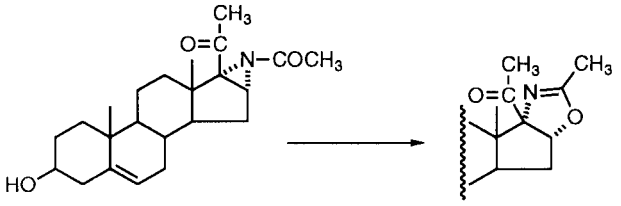
$R_1 = R_2 = H$

$R_1 = COCH_3$, $R_2 = H$

$R_1 = H$, $R_2 = CH_3$

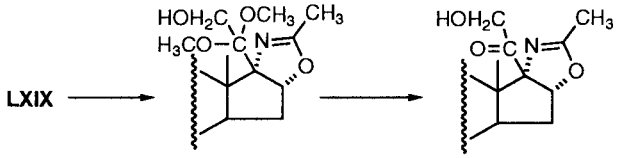
$R_1 = H$, $R_2 = CH_2C_6H_5$

On heating, 16α,17α-acetyliminopregn-5-en-3β-ol-20-one (**LXVIII**) with sodium iodide in diglyme the pregn-5-en-3β-ol-20-one[17α,16α-*d*]-2′-methyloxazoline (**LXIX**) is obtained [43].



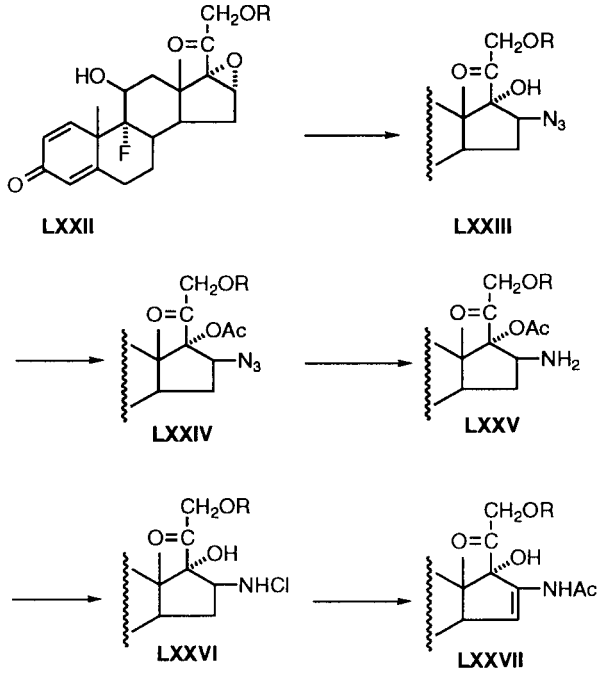
LXVIII **LXIX**

When the [17α,16α-*d*]oxazolines of 20-ketosteroids were treated with (diacetoxyiodo)benzene in methanolic sodium hydroxide at 20° the ketals **LXX** yielded which underwent successive ketal hydrolysis to give the 20-keto-21-hydroxyoxazolines **LXXI** [44,45].

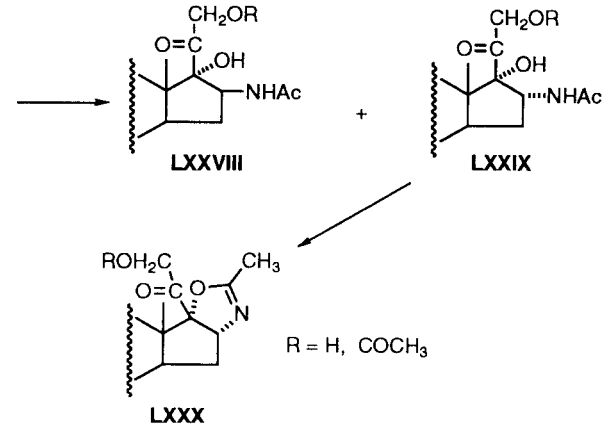


LXX **LXXI**

The isomeric 2′-methyl[16α,17α-*d*]oxazolines of 20-ketosteroids with a nitrogen atom at C-16 were obtained by two methods. The first of these consists in a multistep process, starting from 16α,17α-epoxy-20-ketosteroid **LXXII** as depicted by the following scheme [46].

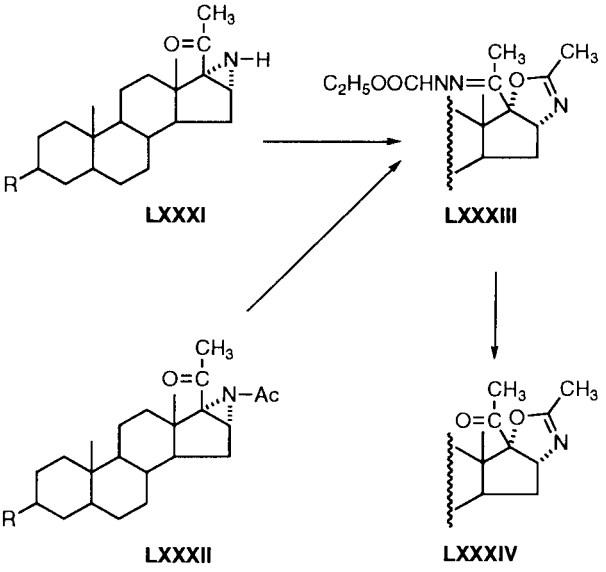


LXXII **LXXIII** **LXXIV** **LXXV** **LXXVI** **LXXVII**



LXXVIII **LXXIX** **LXXX**

According to the second method the compounds mentioned are prepared through the 16α,17α-epimino or 16α,17α-acetylepimino-20-ketosteroids **LXXXI** and **LXXXII**. Both 16α,17α-epimine **LXXXI** and its *N*-acetate **LXXXII** easily react with acetic acid at 20° in the presence of carbethoxyhydrazine to give the oxazoline 20-carbethoxyhydrazone **LXXXIII** [47-50]. The same result is observed when *N*-acetate **LXXXII** is heated for a short time with pyridine thiocyanate or acetate in the presence of carbethoxyhydrazine [48,49,51]. The hydrazone protection was removed by hydrolysis with aqueous methanolic hydrogen chloride solution at 20°.



LXXXI **LXXXIII** **LXXXII** **LXXXIV**

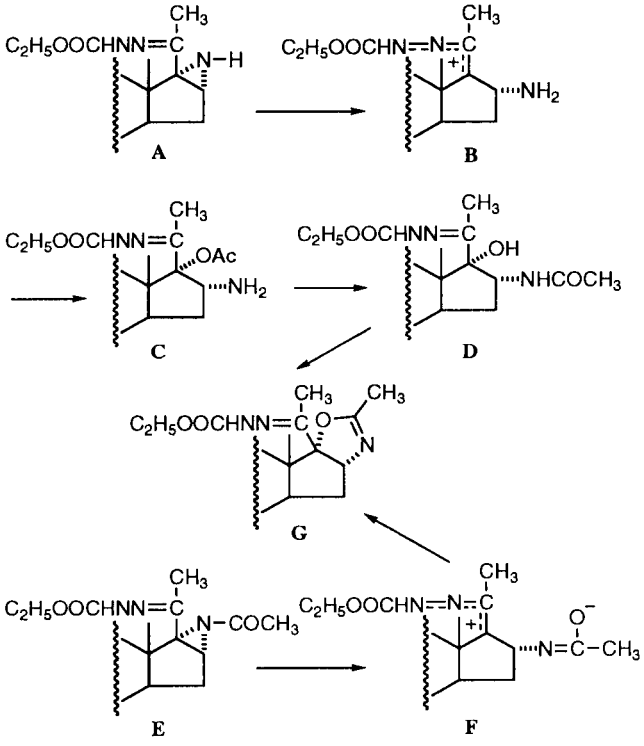
a. R = OH, Δ^5

b. R = OAc, Δ^5

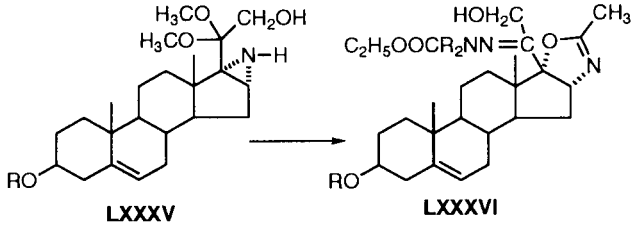
c. R = C=O, Δ^5

A check of the reaction course reveals that it proceeds *via* a number of consecutive steps. The first step is the formation of 20-carbethoxyhydrazone 16α,17α-epimine. This is confirmed by the fact that epimine is inert toward acetic acid in the absence of a reagent on the CO group.

The hydrazone grouping formed exerts the determining influence on the reactivity and direction of opening of the aziridine ring by facilitating the rupture of the C-N bond α to the hydrazone fragment. The resulting cation **B** can be stabilized in two ways depending on the substitution at nitrogen and the reagent. In the case of the reaction of 16α,17α-epimine **A** with acetic acid the 17-center is apparently attacked by acetate ion, with subsequent acyl migration and intramolecular cyclization of the 16α-acetylamine **D**. In contrast to this, the reaction of *N*-acetylepimine **E** proceeds through an intramolecular attack of the acyl group of the aziridine [48].



Similarly, *cis* cleavage of the aziridine ring of 16α,17α-epimino-20,20-dimethoxypregnenolone (**LXXXV**) by acetic acid in the presence of carbethoxyhydrazine gave the oxazoline **LXXXVIa** which after acetylation afforded the oxazoline **LXXXVIb** [52].

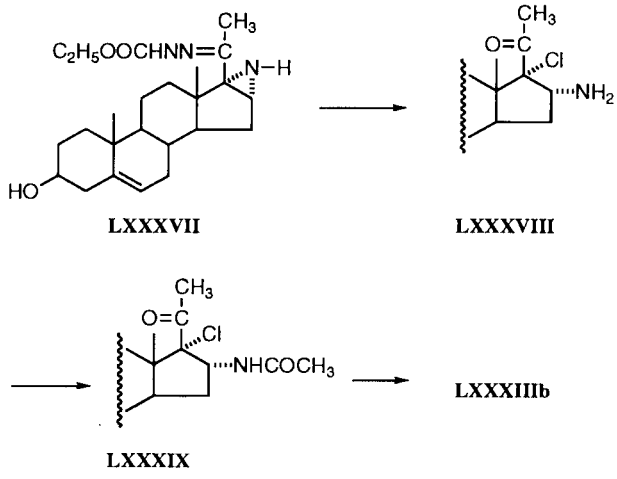


LXXXV **LXXXVI**

a. R = R_2 = H, R_1 = Ac

b. R = R_1 = R_2 = Ac

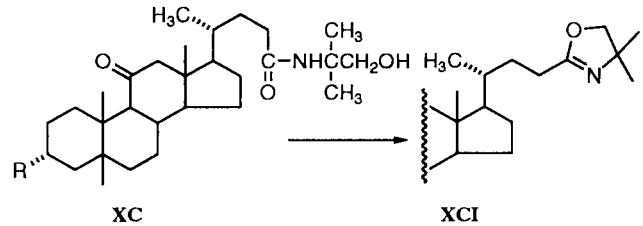
When the 16α,17α-epiminopregnenolone 20-carboethoxyhydrazone (**LXXXVII**) is refluxed for a short time with concentrated hydrochloric acid in methanol solution the epimino ring undergoes *cis*-opening, accompanied by removal of the hydrazone protection to give the 17α-chloro-16α-aminopregn-5-en-3β-ol-20-one (**LXXXVIII**), which after acelylation, by reaction with carboethoxyhydrazine in acetic acid leads to the oxazoline **LXXXIIIb** [53].



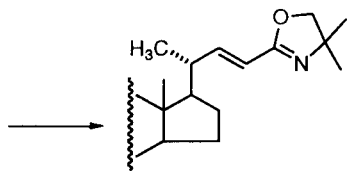
LXXXVII **LXXXVIII**

LXXXIX **LXXXIIIb**

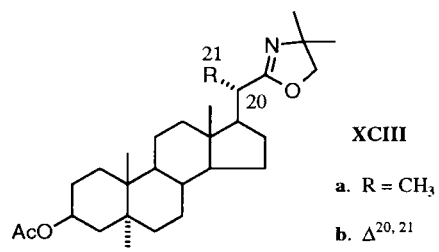
23-Oxazolinylsteroids **XCI** were prepared by cyclization of 23-amidosteroids **XC** with thionyl chloride in tetrahydrofuran [54-56] or with boric acid in xylene [57-59]. The oxazoline derivatives by treatment with benzeneseleninic acid in a mixture of tetrahydrofuran-pyridine gave unsaturated derivatives **XCII** with an α double bond at C-22 [57]. Similarly, the 20-oxazolinylsteroids **XCIII** were prepared [57].



XC **XCI**



XCII R = OH, $OCOCH_3$

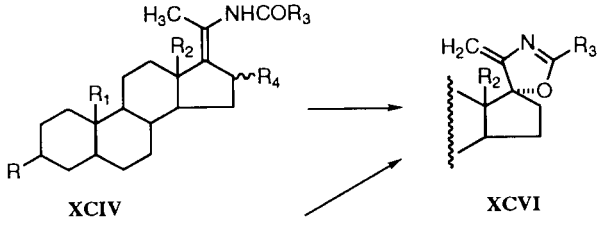


XCIII

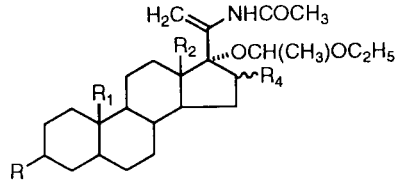
a. R = CH_3

b. $\Delta^{20,21}$

Steroidal 17-spirooxazolines are prepared by different methods analogously to the starting compounds. Thus, the treatment of alkylaminosteroids **XCIV** with *m*-chloroperbenzoic acid gave spirooxazoline **XCVI** [60,61], since the treatment of the steroidenamide **XCV** with *p*-toluenesulfonic acid hydrate [62] or the Vilsmeyer reagent gave the spirooxazolines **XCVI** [63].



XCIV **XCVI**



XCV

R = H, $OCOCH_3$

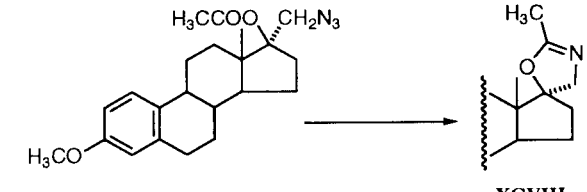
R_1 = H, alkyl, haloalkyl, alkyl containing O or N functional group

R_2 = alkyl

R_3 = H, alkyl, halo, hydroxy and/or oxo-functions in A, B and/or C rings, phenyl, phenylalkyl

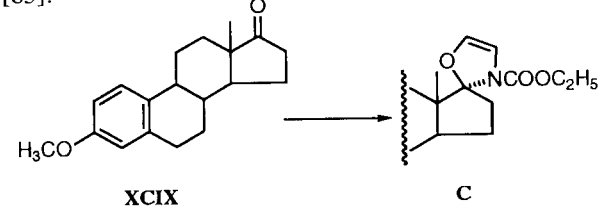
R_4 = H, alkyl

Treatment of (azidomethyl)estratriene **XCVII** with triphenylphosphine in benzene gave spirooxazoline **XCVIII** [64].

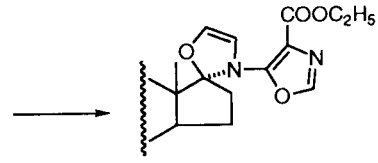


XCVII **XCVIII**

Another path for the preparation of the spirooxazolines consists in the reaction of estrane methyl ether **XCIX** with the ethyl ester of lithium isocyanoacetic acid to afford the 4′′-(4-ethoxycarbonyl-5-oxazolyl)-3-methoxy-1,3,5(10)-estratrien-17β(→1′)-spiro-5′-Δ^2-oxazoline **CI** [65].

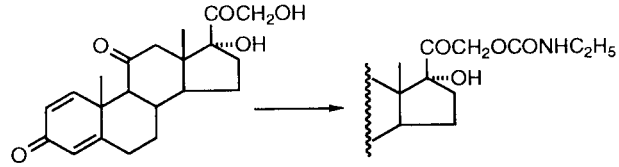


XCIX **C**

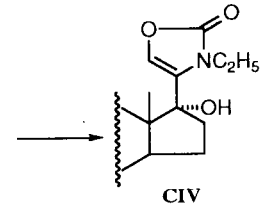


CI

In the reaction of prednisone with ethyl isocyanate, instead of the expected 21-carbamate **CIII** a product of its cyclization was obtained, the [20,21-*d*]oxazolone **CIV** [66].

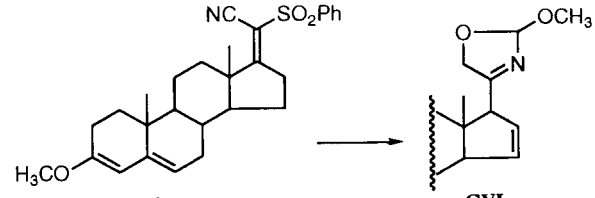


CII **CIII**



CIV

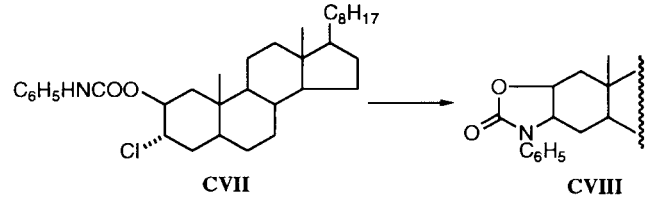
Condensation of (isocyanomethylene)androstadiene **CV** with formaldehyde and methanol in benzene containing aqueous sodium hydroxide and $PhCH_2N^+Et_3OH^-$ gave the 17β-(2-methoxyoxazolin-4-yl)steroid **CVI** [67].



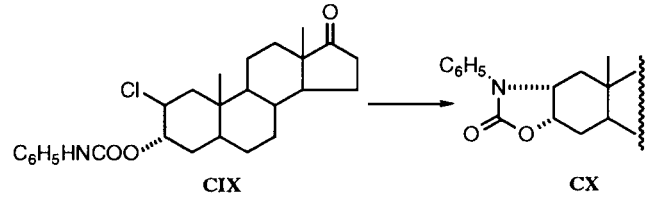
CV **CVI**

Steroidal Oxazolidines.

Steroidal derivatives containing a completely hydrogenated oxazole ring attached with the A ring have been prepared by cyclization of vicinal *trans*-chlorourethanes in a boiling ethanolic solution of potassium hydroxide [68].

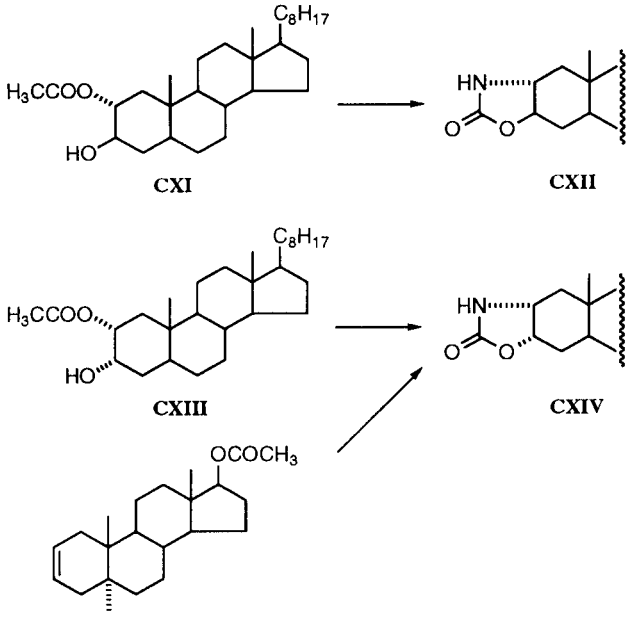


CVII **CVIII**



CIX **CX**

Curtius degradation of 2α-carbomethoxycholestan-3β-ol (**CXI**) and 2α-carbomethoxycholestan-3α-ol (**CXIII**) afforded the [2α,3β-*d*]- **CXII** and [2α,3α-*d*]oxazolidinone **CXIV** [69] which was also prepared from the reaction of 17β-acetoxy-5α-androst-2-ene **CXV** with silver cyanide and iodine [70].

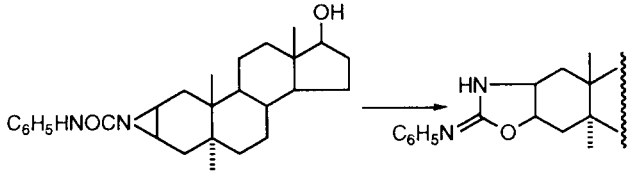


CXI **CXII**

CXIII **CXIV**

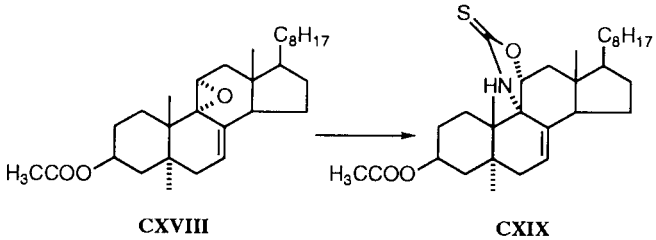
CXV

[2β,3β-*d*]Oxazolidines of the androstane series with a phenylimino group at position 2′ yielded **CXVII** by treatment of *N*-phenylcarbamoyl-2β,3β-imino-17β-hydroxy-5α-androstane (**CXVI**) with sodium iodide in acetone [19].



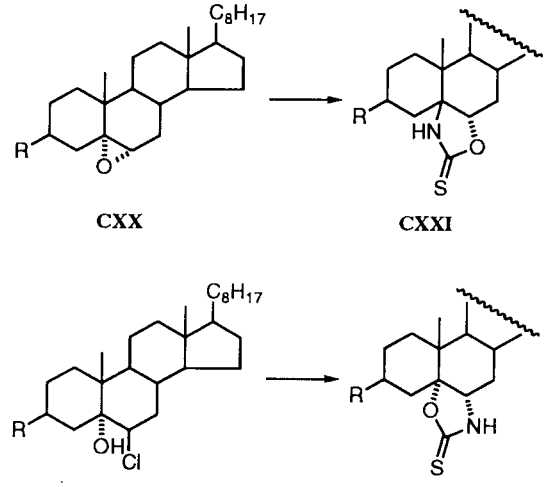
CXVI **CXVII**

In preparing the oxazolidines attached to rings B and C the epoxysteroids have been used as starting materials. Thus, the action of thiocyanic acid on 9α,11α-epoxide of the ergostane series leads to a [9α,11α-*d*] derivative of oxazolidine **CXIX**. Its formation apparently includes the *cis*-axial-equatorial opening of the epoxide ring [71].



CXVIII **CXIX**

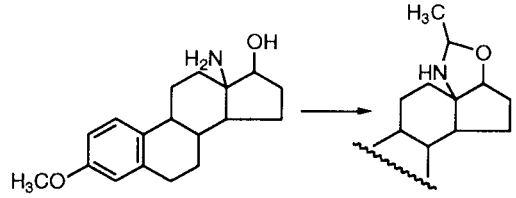
Similarly, the reaction of 5α,6α-epoxycholestanes **CXX** with allyl isothiocyanate in the presence of aluminum chloride gave cholestano[5β,6α-*d*]oxazolidine-2′-thiones **CXXI** [72] since the reaction of 6β-chloro-5α-hydroxycholestane (**CXXII**) with potassium isothiocyanate in dimethylformamide gave the cholestano[6α,5α-*d*]-2′-thiooxazolidine (**CXXIII**) [73].



CXX **CXXI**

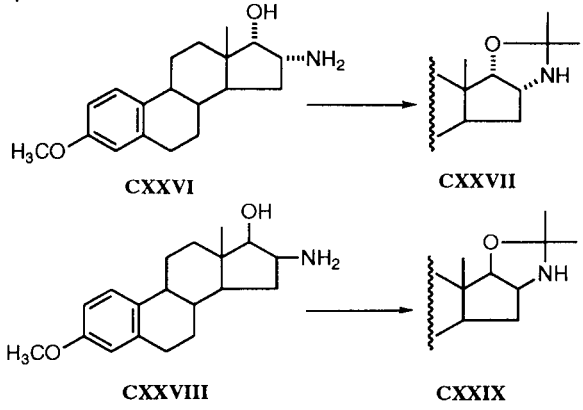
CXXII **CXXIII**

The addition of the oxazolidine ring at positions 13 and 17 to estrane was obtained by refluxing the 13-amino-18-norestradiol-3-methyl ether **CXXIV** with acetaldehyde in benzene [25].



CXXIV **CXXV**

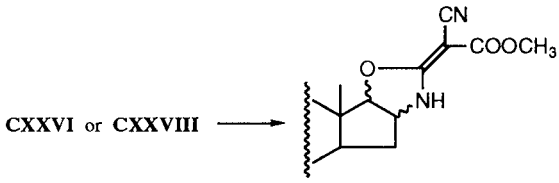
In order to prepare steroidal 2′,2′-dialkyloxazolidines the condensation of vicinal hydroxyamines with ketones has often been used. Thus, the condensation of 16α,17α-hydroxyamines **CXXVI** and 16β,17β-hydroxyamines **CXXVIII**, with ketones yielded the epimeric 2′,2′-dimethyl[16α,17α-*d*]- **CXXVII** and 2′,2′-dimethyl[16β,-17β]oxazolidines **CXXIX** of the estrane series [74-76].



CXXVI **CXXVII**

CXXVIII **CXXIX**

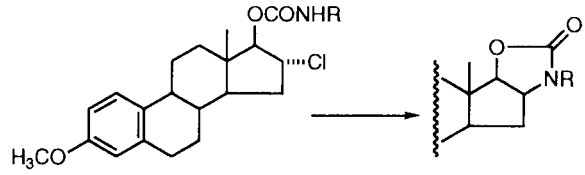
The reaction of hydroxyamines **CXXVI** and **CXXVIII** with activated ketene thioacetals gave the corresponding oxazolidines **CXXX** [77].



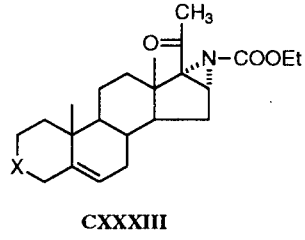
CXXX

In a manner similar to that described for the synthesis of phenyloxazolidino[3β,4β-*d*]steroids **CVIII** the phenyl- and ethyloxazolidino[16β,17β-*d*]estra-1,3,5(10)trien-3-yl methyl ether (**CXXXII**) were prepared [68].

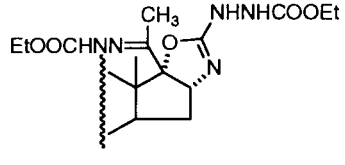
[16α,17α-*d*]Oxazolidines of 20-ketosteroids were prepared by intramolecular isomerization of 16α,17α-*N*-carboethoxyepiminopregnenolone (**CXXXIII**) [78]. Thus, the epiminopregnenolone **CXXXIII** undergoes stereospecific ring cleavage in acetic acid containing carboethoxyhydrazine to give oxazoline **CXXXIV** and oxazolidinone **CXXXV** in a 3:1 ratio. The rate-determining step is the formation of the 20-carboethoxyhydrazone. The 20-carboethoxyhydrazone of [16α,17α-*d*]oxazolidine **CXXXV**, under conditions of removing the hydrazone protection, converts to oxazolidinone **CXXXVIa** which undergoes Oppenauer oxidation to yield Δ^4-3-ketone **CXXXVIc**.



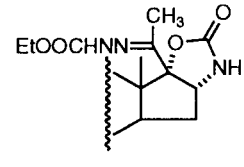
CXXXI **CXXXII**



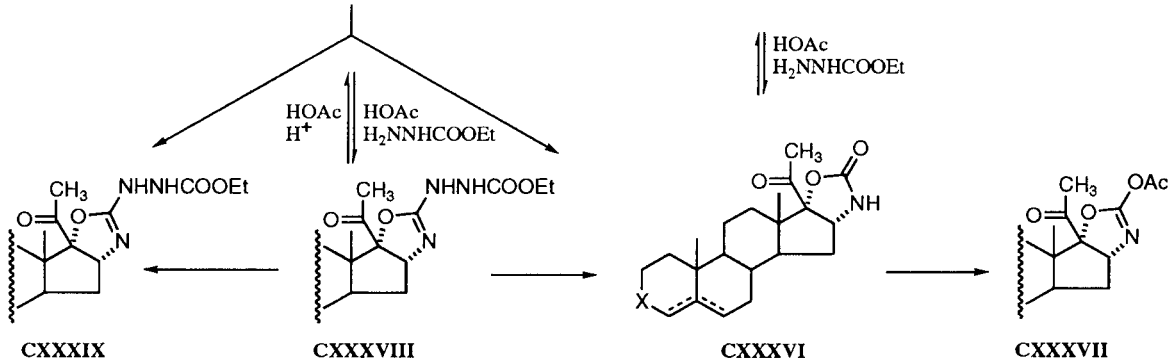
CXXXIII



CXXXIV



CXXXV



CXXXIX **CXXXVIII** **CXXXVI** **CXXXVII**

X = C(OH)H

a. X = C(OH)H, Δ^5

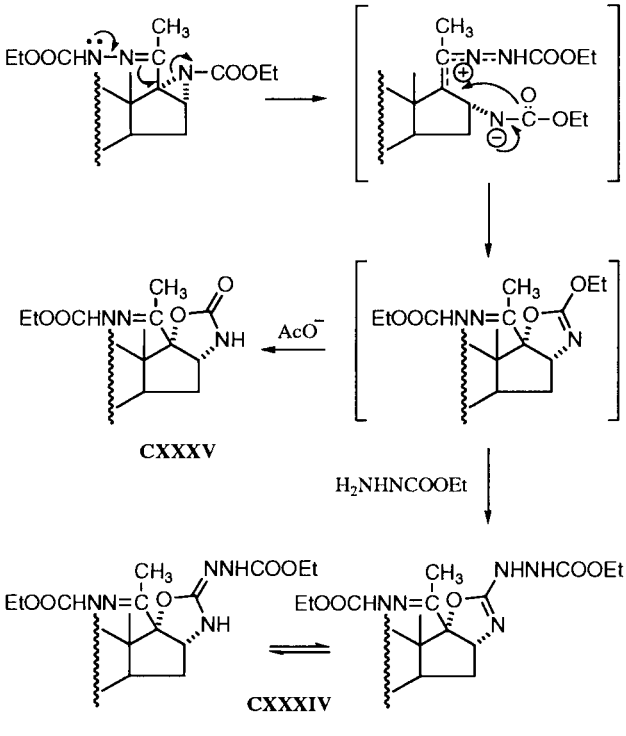
b. X = C(OCOCH3)H, Δ^5

c. X = C=O, Δ^4

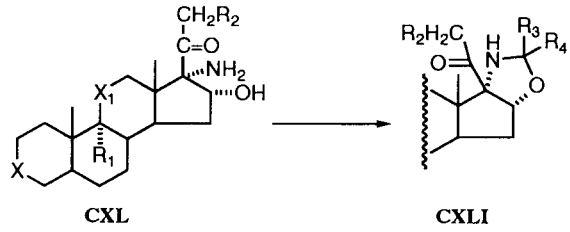
X = C(OCOCH3)H

Heating of oxazolidinone **CXXXVIa** with acetic anhydride in the presence of sodium acetate leads to enol acetate **CXXXVII**. This acetylation apparently occurs as a consequence of a shift in the tautomeric equilibrium towards the enol.

The formation of 20-carboethoxyhydrazones **CXXXIV** and **CXXXV** under the reaction conditions occurs independently, since they do not mutually convert into each other. The first step is the attack of carboethoxyhydrazine on the 20-keto group. The hydrozone fragment formed facilitates cleavage of the 17-C-N bond which is accompanied by intramolecular nucleophilic cyclization of the substituent at the nitrogen atom. The reaction does not stop at the formation of the 2′-ethoxyoxazoline which may react further by two independent pathways: 1) condense with a second carboethoxyhydrazine molecule with the formation of **CXXXIV** or 2) undergo attack by the acetate anion with the loss of ethyl acetate and formation of oxazolidinone **CXXXV**. The predominant process is condensation with carboethoxyhydrazine.



The main method of synthesis of isomeric [17α,16α-*d*]-oxazolidines of 20-ketosteroids is the condensation of the 16α-hydroxy-17α-aminosteroids with an aldehyde or ketone [30,38,79-84]. The reaction may take place in the presence of water or under anhydrous conditions. Because, the reaction of the amino alcohols with acetone leads to low yields, in contrast to the corresponding reaction with aldehydes, the acetone dimethylacetal in dimethylformamide and *p*-toluenesulfonic acid was used.



CXL **CXLI**

X =  , C=O

R_1 = H, F

X_1 = CH_2,  , C=O

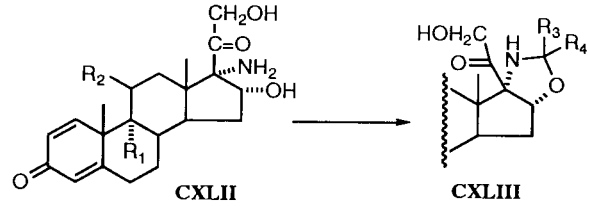
R_2 = H, OH, CH_3COO, BzO

R_3 = H, CH_3, C_6H_5

R_4 = H, CH_3

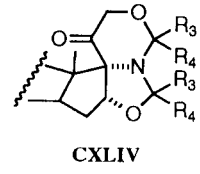
Δ = 1,4; 5; 1,4,9(11)

The condensation of 17α-amino-16α-hydroxysteroids with an hydroxyl group at C-21 gives a mixture of [17α,-16α-*d*]oxazolidine **CXLIII** and [17α,16α-*d*]oxazolidino-[3′,4′-*c*]-2*H*-tetrahydro-1,3-oxazin-5′′-one **CXLIV** [38,-79,80].



CXLII **CXLIII**

+



CXLIV

R_1 = F

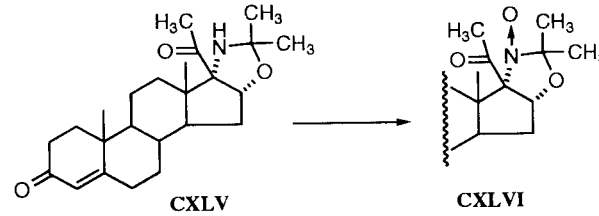
R_2 = H, OH

R_3 = H, CH_3

R_4 = H, CH_3

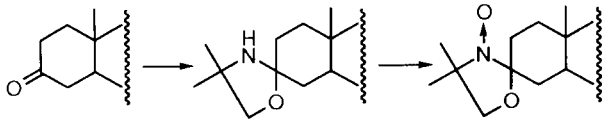
Δ = 9(11)

Spin-labelled 2′,2′-dimethyl[17α,16α]oxazolidino-pregn-4-en-3,20-dione **CXLVI** with a long-lived iminoxyl radical, was prepared by the oxidation of the oxazolidine with *m*-chloroperbenzoic acid [82].



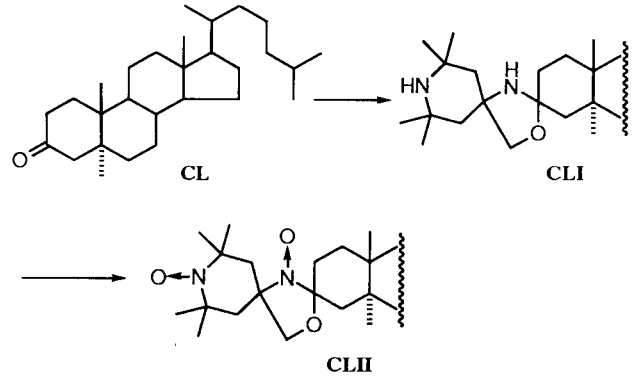
CXLV **CXLVI**

Refluxing a toluene solution, of 3-ketosteroids of the cholestane, androstane and D-homo-17α-azaandrostane series containing an excess of 2-amino-2-methylpropan-1-ol and a trace of *p*-toluenesulfonic acid monohydrate for several hours led to the corresponding 3-spiro-2′-[4′,4′-dimethyl-2′-oxazolidines] **CXLVIII**, which after oxidation with *m*-chloroperbenzoic acid afforded the *N*-oxyl derivatives **CXLIX** [85-90].



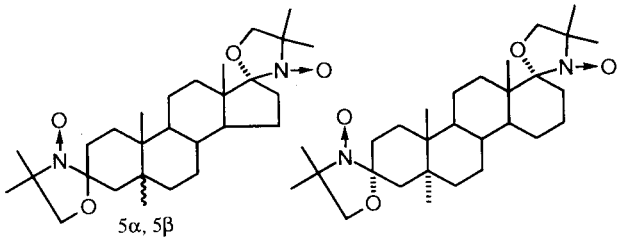
CXLVII **CXLVIII** **CXLIX**

Similarly, condensation of 4-amino-4-(hydroxymethyl)-2,2,6,6-tetramethylpiperidine with 5α-cholestan-3-one gave the 3-dispiro[oxazolidinepiperidine]cholestane (**CXLI**), which upon oxidation with *m*-chloroperbenzoic acid gave the corresponding dinitroxide **CLII** [90].



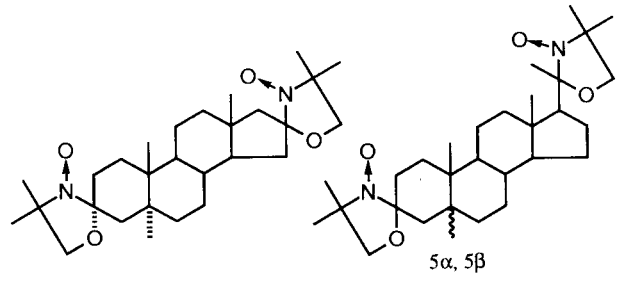
CL **CLI** **CLII**

Steroidal diketones as 5α- and 5β-androstane-3,17-dione, D-homo-5α-androstane-3,17-dione, 5α-androstane-3,16-dione, 5α- and 5β-pregnane-3,20-dione with 2-amino-2-methylpropan-1-ol gave the corresponding 3,17-dispiro-, 3,17α-dispiro-, 3,16-dispiro[4′,4′-dimethyl-2′-oxazolidines] and 2′-[3-spiro(4′,4′-dimethyl-2′-oxazolidine)pregn-5α-20-yl]-4′,4′-dimethyloxazolidine which with *m*-chloroperbenzoic acid afforded the dinitroxide derivatives **CLIII-CLVI** [91].



5α, 5β

CLIII **CLIV**

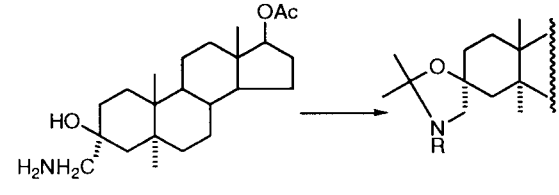


5α, 5β

CLV **CLVI**

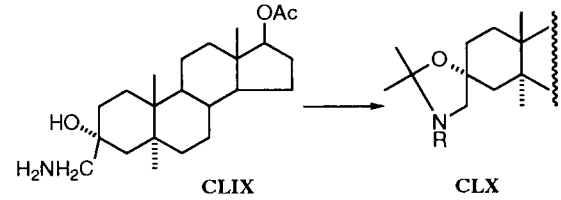
The synthesis of the spin heterocyclic drugs seems to be attractive for the investigation of the mechanism of their physiological action. Their use not only allows monitoring their distribution in a living being but also permits ESR measurements of their complexes with corresponding receptors [82].

The reaction of 17β-acetoxy-3β-hydroxy-3α-(aminomethyl)-5α-androstane (**CLVII**) and its 3α-hydroxy-3β-(aminomethyl) epimer **CLIX** with acetone afforded the epimers 3-spirooxazolidines **CLVIII** and **CLX** [92].



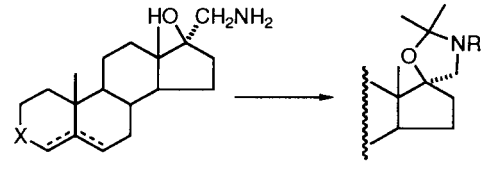
CLVII **CLVIII**

R = H, $COCH_3$



CLIX **CLX**

R = H, $COCH_3$



CLXI **CLXII**

a. X = CHOH, R = H, Δ^5

b. X = CHOH, R = $COCH_3$, Δ^5

c. X = $CHOCOCH_3$, R = $COCH_3$, Δ^5

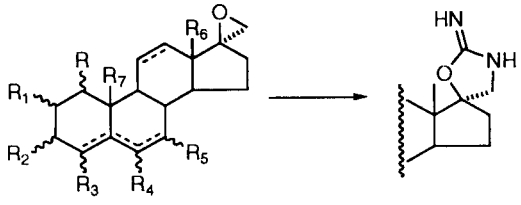
d. X = C=O, R = $COCH_3$, Δ^4

e. X = $CHOCOCH_3$, R = C_2H_5, Δ^5

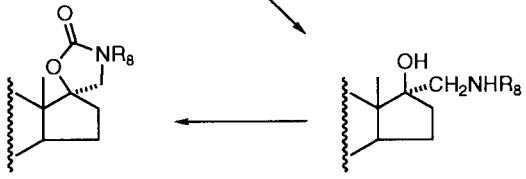
f. X = C=O, R = C_2H_5, Δ^4

Analogous results are also obtained with 17β-hydroxy-17α-(aminomethyl)steroids. 17β-Hydroxy-17α-(aminomethyl)steroids of androst-5-ene series are converted. into 17-spiro[androstane-17-yl-5′-oxazolidine] derivatives **CLXII**. The *N*-acetyl derivatives **CLXII c-d** can then be reduced to the corresponding *N*-ethyloxazolidines **CLXIIe-f** [93,94].

On the other hand, the cyclocondensation of the 17β-hydroxy-17α-(aminoalkyl)steroids **CLXIV**, obtained by the ring cleavage of steroidal 17-spirooxiranes **CLXIII** with alkylamines, with diethyl carbonate afforded the substituted steroidal 17s-spiro-5′-[2′-oxo-3′-alkyloxazolidones] **CLXV** [95-100], whereas the reaction of steroidal 17-spirooxiranes **CLXIII** ($R = R_1 = R_3 = R_4 = R_5 = H$, $R_6 = R_7 = CH_3$, $R_2 = OH$, Δ^5) with guanidine yielded the 17s-spiro-5′-[2′-iminooxazolidinone] **CLXVI** [101].



CLXIII **CLXVI**



CLXV **CLXIV**

R = H, alkylthio, alkenylthio, aralkylthio, acylthio

R_1 = H, CH_3, $(CH_3)_2$, $=CH_2$, cyclopropylidene

R_2 = OH, F, =O, $EtOCO_2$, =NOH, $=NOCH_3$, $=NOCH_2CH=CH_2$

R_3 = H, CH_3

R_4 = H, cyclopropylidene

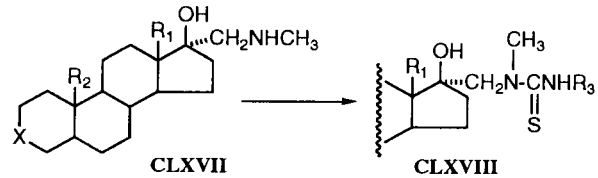
R_5 = H, Et, SH, alkylthio, alkenylthio, aralkylthio, acylthio

R_6 = H, C_{1-4} alkyl

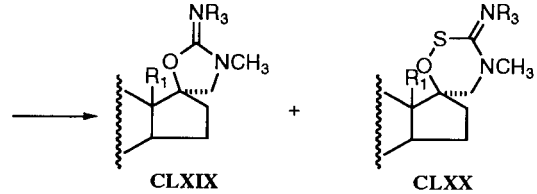
R_7 = H, CH_3

R_8 = H, CH_3, C_2H_5, $CH(CH_3)_2$, $CH_2=CHCH_2$, $(MeO)_2P(O)CH_2$

In contrast, when the 17β-hydroxy-17α-aminomethylsteroids (**CLXVII**) react with isothiocyanates the steroidal thioureas **CLXVIII** are formed, which after cyclocondensation in pyridine containing iodine the 17s-spiro-5′-[2′-imino-3′-methyloxazolidinones] **CLXIX** substituted in imino group are yielded with simultaneous formation of spirooxathiazines **CLXX** [102].



CLXVII **CLXVIII**



CLXIX **CLXX**

a. X = CHOH, $R_1 = R_2 = CH_3$, Δ^5

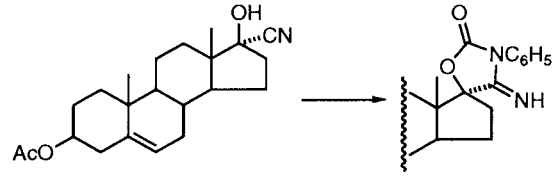
b. X = $CHOCH_3$, $R_1 = CH_3$, $\Delta^{2,5(10)}$

c. X = $CHOCH_3$, $R_1 = CH_3$, $\Delta^{1,3,5(10),8}$

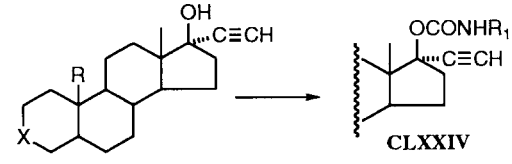
d. X = $CHOCH_3$, $R_1 = C_2H_5$, $\Delta^{2,5(10)}$

e. R_3 = CH_3, 2,6-$(CH_3)_2C_6H_3$, $PhCH_2$, $PhCHCH_3$, Bz

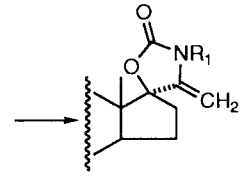
The reaction of 3β,17β-dihydroxy-17α-cyanoandrost-5-ene-3-acetate (**CLXXI**) with phenyl isocyanate led to the corresponding oxazolidinone **CLXXII** with an imino group in position 4′ [103].



CLXXI **CLXXII**



CLXXIII **CLXXIV**



CLXXV

a. X = CHOH, R = CH_3, $R_1 = C_6H_5$, Δ^5

b. X = CHOAc, R = CH_3, $R_1 = C_6H_5$, Δ^5

c. X = CHOH, R = CH_3, $R_1 = C_2H_5$, Δ^5

d. X = C=O, R = H, $R_1 = CH_3$, C_6H_5, Δ^4

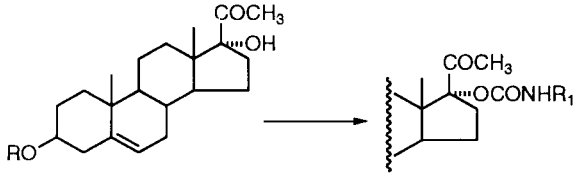
e. X = C=O, R = H, $R_1 = C_2H_5$, Δ^4

f. X = C=O, R = CH_3, $R_1 = C_3H_7$, Δ^4

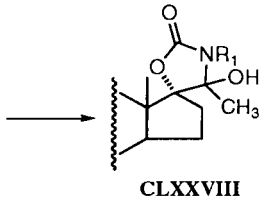
g. X = $CHOCH_3$, $\Delta^{1,3,5(10)}$, $R_1 = C_2H_5$, C_6H_5

Steroids, which have an ethynyl group at C-17 instead of a cyano group, with alkyl or aryl isocyanates gave oxazolidinones **CLXXV** with an exocyclic methylene group in position 4′, *via* formation of steroidal carbamates **CLXXIV** [103-108].

By the same reaction the 3β,17α-dihydroxypregn-5-en-20-one (**CLXXVI**, R = H) with isocyanates in the presence of sodium hydroxide and the 3β,17α-dihydroxypregn-5-en-20-one 3-formate (**CLXXVI**, R = CHO) with isocyanates in the presence of *N*-methylmoropholine as the catalyst, the oxazolidinone spiro systems **CLXXVIII** stereoisomeric at C-17 of the steroid nucleus were produced [103].



CLXXVI **CLXXVII**



CLXXVIII

a. R = H, R_1 = C_6H_5

b. R = H, R_1 = *m*-ClC_6H_4

c. R = H, R_1 = *p*-ClC_6H_4

d. R = H, R_1 = *m*-$CH_3C_6H_4$

e. R = H, R_1 = *p*-$CH_3C_6H_4$

f. R = H, R_1 = C_2H_5

g. R = CHO, R_1 = C_6H_5

h. R = CHO, R_1 = *o*-ClC_6H_4

i. R= CHO, R_1 = *m*-ClC_6H_4

j. R = CHO, R_1 = *o*-$CH_3C_6H_4$

k. R = CHO, R_1 = *m*-$CH_3C_6H_4$

l. R = CHO, R_1 = *p*-$CH_3C_6H_4$

m. R = CHO, R_1 = α-naphthyl

n. R = $COCH_3$, R_1 = C_6H_5

o. R = $COCH_3$, R_1 = *m*-ClC_6H_4

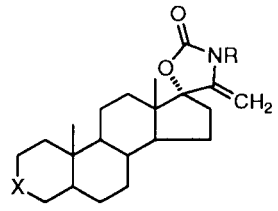
p. R = $COCH_3$, R_1 = *p*-ClC_6H_4

q. R = $COCH_3$, R_1 = *m*-$CH_3C_6H_4$

r. R = $COCH_3$, R_1 = *p*-$CH_3C_6H_4$

s. R = $COCH_3$, R_1 = C_2H

The treatment of 3-acetate derivatives **CLXXVIII**, **n-p**, **r-s** with phosphorus oxychloride in pyridine gave the exocyclic methylene oxazolidinone **CLXXIXa-e**. *N*-Butyl and *N*-allyl derivatives **CLXXIXf-g** were also prepared from the reaction of the steroidal formates **CLXXVI** (R = CHO) with *n*-butyl and allyl isocyanates respectively, without a base as catalyst, whereas the 17α-hydroxyprengn-4-ene-3,20-dione by heating with aryl isocyanates in the presence of *N*-methylmorpholine afforded also the exocyclic methylene oxazolidinones **CLXXIX** [103].



CLXXIX

a. X = $CHOCOCH_3$, R = C_6H_5, Δ^5

b. X = $CHOCOCH_3$, R = *m*-ClC_6H_4, Δ^5

c. X = $CHOCOCH_3$, R = *p*-ClC_6H_4, Δ^5

d. X = $CHOCOCH_3$, R = *p*-$CH_3C_6H_4$, Δ^5

e. X = $CHOCOCH_3$, R = C_2H_5, Δ^5

f. X = OCHO, R = *n*-C_4H_9, Δ^5

g. X = OCHO, R = $CH_2CH{=}CH_2$, Δ^5

h. X = C=O, R = C_6H_5, Δ^4

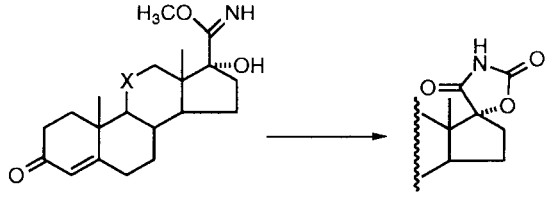
i. X = C=O, R = *o*-ClC_6H_4, Δ^4

j. X = C=O, R = *m*-ClC_6H_4, Δ^4

k. X = C=O, R = *p*-ClC_6H_4, Δ^4

l. X = C=O, R = *m*-$CH_3C_6H_4$, Δ^4

Substitution of the exocyclic methylene group by oxygen in oxazolidine derivatives **CLXXIX**, the steroid-17-spiro-5′-oxazolidine-2′,4′-diones yielded **CLXXXI** which are prepared by cyclization of steroidal hydroxyimidates **CLXXX** with alkyl chlorocarbonates [109].

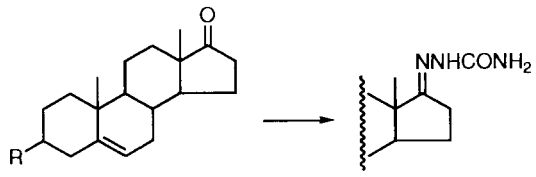


CLXXX **CLXXXI**

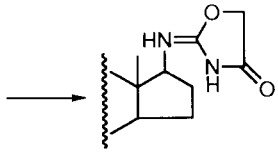
X = CH_2

X = CO

Steroidal oxazolidinones of the structure **CLXXXIV** are prepared from the corresponding steroidoketones **CLXXXII** by conversion to the semicarbazone **CLXXXIII** and subsequent cyclocondensation with chloroacetic acid in acetic acid [110].



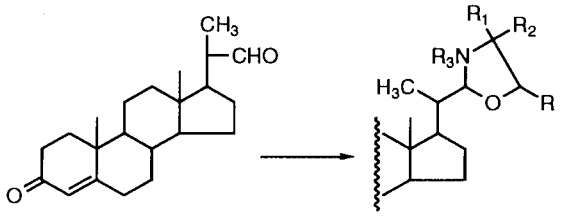
CLXXXII CLXXXIII



CLXXXIV

R = OH, $OCOCH_3$, OCH_3, OC_2H_5, Cl

20- and 21-Oxazolidinyl steroids are prepared from the reaction of 20- and 21-steroidal aldehydes with substituted 2-aminoethanol. So, the cyclocondensation of 3-oxopregn-4-en-20β-carboxaldehyde **CLXXX** with substituted 2-aminoethanol gave the 2′-(3-oxopregn-4-en-20-yl)oxazolidines **CLXXXVI**. The methylation of **CLXXXVI** (R = C_6H_5, R_1 = H, R_2 = R_3 = CH_3) with methyl iodide afforded the 2′-(3-oxopregn-4-en-20-yl)-3′,3′,4′-trimethyl-5′-phenyloxazolide [111].

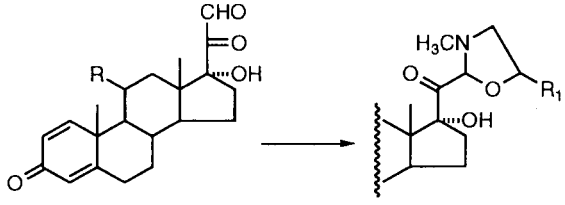


CLXXXV CLXXXVI

R = R_1 = R_2 = H

R_3 = H, CH_3, C_2H_5, CH_2CH_2OH, C_6H_5

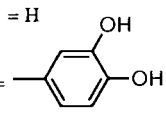
Similarly, the 11β,17α-dihydroxy-3,20-dioxopregn-1,4-dien-21-al (**CLXXXVII**) by heating with 2-methylaminoethanol yielded the 11β,17α-dihydroxy-17-[(3-methyl-2-oxazolidinyl)carbonyl]androst-1,4-dien-3-one (**CLXXXVIII**) [112].



CLXXXVII CLXXXVIII

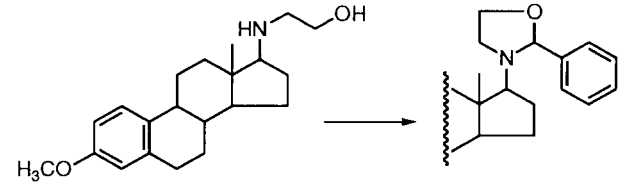
a. R = OH, R_1 = H

b. R = H, R_1 =



The same reaction of prednisolone-21-aldehyde with (-)-epinephrine gave the 17α-hydroxy-17-[(3-methyl-5-(3,4-dihydroxyphenyl)-2-oxazolidinyl)carbonyl]androst-1,4-dien-3-one (**CLXXXVIII**) [112].

Cyclization of 17β-(2-hydroxyethylamino)-3-methoxy-$\Delta^{1,3,5(10)}$-estrane (**CLXXXIX**) with benzaldehyde in the presence of *p*-toluenesulfonic acid gave the 3-methoxy-17β-(2-phenyl-3-oxazoldinyl)-$\Delta^{1,3,5(10)}$-estrane (**CXC**) [113].



CLXXXIX CXC

Biological Activity of Steroidal Oxazoles, Oxazolines, Oxazolidines and Their Derivatives.

The steroidal oxazoles, oxazolines and oxazolidines in which the heterocyclic ring is condensed with a substituent on the steroid skeleton have drawn the attention of the medicinal chemists, to this class of steroids, due to physiological properties of the above compounds.

Biological tests showed that the steroidal methanosulfonyl heterocycles of the structure **VIII** CR = R_1 = R_2 = H, R_3 = CH_3, R_4 = C≡CH) that Ih/18h relative binding affinity ratio = 17 in the *in vitro* rat prostate androgen receptor competition assay [3,4].

The 2′-substituted amino-17-oxoestra-α(10)-4-dieno-[2,3-*d*]oxazole (**XII**) and estra-1,5(10)-dieno[4,3-*d*]oxazole (**XXI**) derivatives, after testing *in vitro* for anabolic-catabolic activities by measuring their effects on the activity of bovine pancreatic ribonuclease, possessed the same anabolic-catabolic activities as the parent steroidal hormone [7]. Similarly, the estratrienooxazolinethiones of the structure **LVI** and **LVIII** were tested *in vitro* for effect on bovine pancreatic Rnase activity, and all possessed weak anabolic activities except **LVI** (R = H) and **LVIII** (R = 2-morpholinoethyl) which possessed mild catabolic activity [24].

Compounds of the structure **XXVII** and **XXIX** were effective local antiinflammatory agents and were devoid of corticoid behavior; **XXIXa** (X = β-CHOH, R = F, R_1 = OH, R_2 = CH_3, R_3 = H, Ac, R_4 = F) and **XXIXb** (X = β-CHOH, R = F, R_1 = OH, R_2 = CH_3, R_3 = Ac) possessed the highest antiinflammatory activity, and **XXIXa** were inactive on prostaglandin synthesis *in vitro*. Compound **XXVII** (X = CO, R_1 = OH) showed some inhibitory activity and decreased oxygen consumption, whereas **XXIX** (X = CO, R = R_2 = R_3 = H, R_1 = OH) stimulated prostaglandin production and oxygen consumption. It was

proposed that antiinflammatory activity was due to an antioxidant effect [11].

Steroido[17α,16α-*d*]oxazolines **LXII** showed antiinflamatory [32,33,37] glucocorticoid [32] and strong progestational activity [39]. Compounds of similar structure are also useful as hormone-like agents [37] and their water-soluble esters **LXII** (R_5 = $COCH_2O_2CCH_2COOH$) protected mice from anaphylactic shock at 22 mg/kg (ED_{50} i.p.) *vs.* 35.5 and 143 mg/kg, respectively, for prednisolone hemisuccinate and hydrocortisone hemisuccinate [40].

Steroido[17α,16α-*d*]oxazolidines **CXLI** possessed antiflammatory [79] and gestagenic activity [83] whereas these compounds, without an O-containing functional group in position 21 showed excellent progestational activity [38].

Steroidooxazolidinooxazines of the structure **CXLIV** also have antiinflammatory activity [79].

The 11β,21-dihydroxy-3,20-dioxo-9α-fluoro-2′-methyl-1,4-pregnadieno[16α,17α-*d*]oxazoline 21-acetate was 10 times as active as hydrocortisone as an antiinflammatory and also had glucocorticoid activity, increasing rat liver glycogen from a value of 1-2 to 17-18 at a dose of 50γ [46].

Steroidal oxazolidinone of the structure **CXIV** showed antiestrogenic and anabolic activity [70].

Some of the bile acid oxazoline derivatives **XCI** alter the activity of bacterial 7-dehydroxylases *in vivo*, and inhibit the growth of certain anaerobic bacteria in pure culture [54].

Spiro[androstane-17-yl-5′-oxazolidine] derivatives **CLXII**, were tested for aldosterone antagonistic activity in the andrenalectomized rat, at a dose of 800 mcg/kg, but none of the compounds displayed appreciable antagonistic activity [94].

In contrast, the 17s-spiro-5′-(2′-oxo-3′-alkyloxazolidines) **CLXV** and the 17s-spiro-5′-(2′-alkylimino-3′-methyloxazolidinones) **CLXIX** showed diuretic [95,96,98] antialdosterone activity [95-99,102], antiandrogenic activity[97] and antiminelarcorticoid activity [100].

17-Spirooxazolidinones of structure **CLXXV**, of the estrane series had about 1/300th the estrogenic activity of estradiol. The substituted compounds of the androsterone series possessed only a low order of activity in all assays studied, whereas the corresponding compounds of the 19-norandrosterone series proved to be of the most interest. Furthermore, in the progestational assay the above 19-norandrosterone compounds showed good activity [107].

The 11β,17α-dihydroxy-17-[(3-methyl-2-oxazolidinyl)carbonyl]androsta-1,4-dien-3-one (**CLXXXVIIIa**) produced approximately the same response in the thymus and granuloma decrease at 1.2 mg (total, s.c. for 3 days) as the saturated hydrocortisone produced at 4.8 mg in adrenalectomized female rats. The 17α-hydroxy-17-[(3-methyl-5-(3,4-dihydroxyphenyl)-2-oxazolidinyl)carbamoyl]androsta-1,4-dien-3-one (**CLXXXVIIIb**) was inactive in the thymolytic assay but exhibited 34% of hydrocortisone activity in the adrenal suppression assay in female rats administered a total dose of 20 mg over 10 days [112].

REFERENCES AND NOTES

[1] G. Ohta, K. Koshi and K. Obata, *Chem. Pharm. Bull.*, **16**, 1487 (1968).

[2] A. Wollach and E. Zbiral, *Tetrahedron*, **32**, 1289 (1976).

[3] J. P. Mallamo, G. M. Pilling, J. R. Wetzel, P. J. Kowalczyk, M. R. Bell, R. K. Kullnig, F. H. Batzold, P. E. Juniewicz and R. C. Winneker, *J. Med. Chem.*, **35**, 1663 (1992).

[4] J. P. Mallamo and J. R. Wetzel, US Patent 5,134,135 (1992); *Chem. Abstr.*, **117**, 212789y (1992).

[5] L. A. Maldonado and P. Crabbe, *Chem. Ind.*, 1146 (1970).

[6] P. Crabbe, L. A. Maldonado and I. Sanchez, *Tetrahedron*, **27**, 711 (1971).

[7] El-Sebaii, A. Ibrahim, A.-Moshen M. E. Omar, N. S. Habib, O. M. AboulWafa and J. Bourdais, *J. Heterocyclic Chem.* **19**, 761 (1982).

[8] B. Fürer, S. Julia and C. P. Papantoniou, *Bull. Soc. Chim. France*, 3407 (1966).

[9] Shafiullah and J. A. Ansari, *Synth. Commun.*, **13**, 419 (1983).

[10] G. Rapi, M. Ginanneschi and M. Chelli, *J. Chem. Soc., Perkin Trans. I*, 1999 (1975).

[11] G. Rapi, M. Chelli, M. Ginanneschi, L. Zilletti, S. Franchi-Micheli, A. Meli and G. Volterra, *Eur. J. Med. Chem.-Chim. Ther.*, **20**, 277 (1985).

[12] G. Rapi, M. Ginanneschi, M. Chelli and A. Boicelli, *J. Chem. Soc., Perkin Trans. I*, 249 (1978).

[13] S. Solyom, K. Szilagyi and L. Toldy, *Liebigs Ann. Chem.*, 153 (1987).

[14] K. Ponsold and B. Häfner, *Chem. Ber.*, **98**, 1487 (1965).

[15] K. Ponsold and H. Groh, *Chem. Ber.*, **98**, 1009 (1965).

[16] K. Ponsold and D. Klemm, *Chem. Ber.*, **99**, 1502 (1966).

[17] G. Drefahl, K. Ponsold and D. Klemm, *J. Prakt. Chem.*, **38**, 168 (1968).

[18] M. M. Campbell, R. C. Craig, A. C. Boyd, I. M. Gilbert, R. T. Logan, J. Redpath, R. G. Roy, D. S. Savage and T. Sleigh, *J. Chem. Soc., Perkin Trans. I*, 2235 (1979).

[19] K. Ponsold and W. Preibsch, *Chem. Ber.*, **104**, 1752 (1971).

[20] K. Ponsold and D. Klemm, *Chem. Ber.*, **105**, 2654 (1972).

[21] Shafiullah, A. Shakir and M. Rafiuddin, *Indian J. Chem.*, **24B**, 662 (1985).

[22] Shafiullah, M. R. Ansari, S. Hussain and S. A. Ansari, *J. Indian Chem. Soc.*, **67**, 907 (1990).

[23] S. Julia and C. P. Papantoniou, *Bull. Soc. Chim. France*, 3410 (1966).

[24] A.-Moshen M. E. Omar and O. M. AboulWafa, *J. Pharm. Sci.*, **71**, 983 (1982).

[25] D. B. R. Johnston, F. S. Waksmunski, T. B. Windholz and A. A. Patchett, *Chimia*, **22**, 84 (1968).

[26] G. Nathansohn, G. Winters and A. Vigevani, *Gazz. Chim. Ital.*, **95**, 1338 (1965).

[27] F. Winternitz and Ch. R. Engel, *Steroids*, 805 (1965).

[28] G. Nathansohn and G. Winters, Netherlands Appl. 6,605,174 (1966); *Chem. Abstr.*, **66**, 65758k (1967).

[29] G. Nathansohn and G. Winters, Netherlands Appl. 6,605,375 (1966); *Chem. Abstr.*, **66**, 65748g (1967).

[30] G. Nathansohn, G. Winters and E. Testa, *J. Med. Chem.*, **10**, 799 (1967).

[31] K. Ponsold, B. Schönecker and I. Pfaff, *Chem. Ber.*, **100**, 2957 (1967).

[32] G. Nathansohn and G. Winters, British Patent 1,077,393 (1967); *Chem. Abstr.*, **68**, 114866w (1968).

[33] G. Nathansohn, G. Winters and E. Testa, British Patent 1,119,081 (1968); *Chem. Abstr.*, **69**, 97015u (1968).

[34] G. Nathansohn, G. Winters and E. Testa, British Patent 1,119,082 (1968); *Chem. Abstr.*, **69**, 97004q (1968).

[35] G. Nathansohn, G. Winters and E. Testa, British Patent 1,119,083 (1968); *Chem. Abstr.*, **69**, 97003p (1968).

[36] G. Nathansohn, G. Winters and V. Aresi, *Steroids*, 383 (1969).

[37] G. Nathansohn, G. Winters and E. Testa, US Patent 3,459,740 (1969); *Chem. Abstr.*, **71**, 102135f (1969).

[38] G. Nathansohn and G. Winters, German Offen. 1,921,778 (1969); *Chem. Abstr.*, **72**, 55773w (1970).

[39] G. Nathansohn, G. Odasso, P. De Ruggeri and U. Guzzi, French Demande, 2,007,755 (1976); *Chem. Abstr.*, **73**, 35632s (1970).

[40] G. Nathansohn and G. Winters, French Demande 2,481,279 (1980); *Chem. Abstr.*, **96**, 143176e (1980).

[41] Gruppo Lepetit S.p.A., Belg. BE 891,242 (1982); *Chem. Abstr.*, **97**, 182737d (1982).

[42] G. Winters, *Synthesis*, 281 (1984).

[43] K. Ponsold and B. Schönecker, East German Patent 64,716 (1968); *Chem. Abstr.*, **71**, 50381m (1969).

[44] A. V. Kamernitzky, A. M. Turuta, T. M. Fadeeva, A. A. Korobov, A. I. Terekhina and T. I. Gritsina, *Khim. Prir. Soedin.*, 735 (1984).

[45] A. V. Kamernitzky, A. M. Turuta, T. M. Fadeeva and Z. I. Istomina, *Synthesis*, 326 (1985).

[46] G. Nathansohn, German Offen. 2,132,104 (1972); *Chem. Abstr.*, **76**, 99932j (1972).

[47] D. Kal´sines, A. V. Kamernitzky and A. M. Turuta, USSR Patent 509,601 (1976); *Chem. Abstr.*, **84**, 180476a (1976).

[48] D. Kal´sines, A. V. Kamernitzky and A. M. Turuta, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1838 (1976).

[49] A. V. Kamernitzky, D. Kal´sines and A. M. Turuta, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2090 (1977).

[50] A. V. Kamernitzky and A. M. Turuta, *Heterocycles*, **7**, 547 (1977).

[51] A. V. Kamernitzky, A. M. Turuta, T. M. Fadeeva and Z. I. Istomina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2138 (1984).

[52] A. V. Kamernitzky, A. M. Turuta and Z. I. Istomina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2608 (1986).

[53] A. V. Kamernitzky, D. Kal´sines, A. M. Turuta and T. M. Fadeeva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2128 (1977).

[54] B. I. Cohen, P. S. May, C. K. McSherry and E. H. Mosbach, *Steroids*, **40**, 701 (1982).

[55] M. Une, B. I. Cohen and E. H. Mosbach, *J. Lipid Res.*, **25**, 407 (1984).

[56] E. H. Mosbach, N. K. N. Ayengar and C. K. McSherry, US Patent 4,460 509 (1984); *Chem Abstr.*, **101**, 211558e (1984).

[57] D. H. R. Barton, W. B. Motherwell, J. Wozniak and S. Z. Zard, *J. Chem. Soc., Perkin Trans. 1*, 1865 (1985).

[58] D. H. R. Barton, S. Z. Zard and J. Wozniak, German Offen. DE 3,536,880 (1986); *Chem. Abstr.*, **105**, 115287c (1986).

[59] S. Tu and X. Qing, *Zhongguo Yaoke Daxue Xuebao*, **19**, 116 (1988).

[60] D. H. R. Barton, W. B. Motherwell and S. Z. Zard, *Nouv. J. Chim.*, **6**, 295 (1982).

[61] D. H. R. Barton, W. B. Motherwell and S. Z. Zard, French Demande FR 2,493,324 (1982); *Chem. Abstr.*, **97**, 182739f (1982).

[62] V. H. Van Rheenen, European Patent Appl. EP 153,001 (1985); *Chem. Abstr.*, **105**, 60816s (1986).

[63] N. Carruthers and S. Garshasb, PCT Int. Appl. WO 91 08,218 (1991); *Chem. Abstr.*, **115**, 183661b (1991).

[64] M. Huebner and K. Ponsold, *Z. Chem.*, **22**, 186 (1982).

[65] G. Haffer, R. Wiechert and G. A. Hoyer, *Chem. Ber.*, **107**, 2405 (1974).

[66] H. D. Brown, A. R. Matzuk, D. R. Hoff and L. H Sarett, *J. Org. Chem.*, **27**, 961 (1962).

[67] A. M. Van Leusen and A. M. Van Leusen, European Patent Appl. EP 123,736 (1984); *Chem. Abstr.*, **102**, 149625q (1984).

[68] K. Ponsold and P. Grosse, German Offen. 1,924,168 (1970); *Chem. Abstr.*, **73**, 35634u (1970).

[69] A. Pavia and F. Winternitz, *Bull. Soc. Chim. France*, 3104 (1969).

[70] K. Sasaki, Japan Patent 70 06,530 (1970); *Chem. Abstr.*, **73**, 15117z (1970).

[71] Y. Ueda and E. Mossettig, *Steroids*, 361 (1963).

[72] Shafiullah and H. Ishrat, *Acta Chim. Hung.*, **125**, 611 (1988).

[73] M. S. Ahmad and Z. Alam, *Indian J. Chem., Sect. B*, **27B**, 486 (1988).

[74] B. Schönecker and K. Ponsold, *Z. Chem.*, **11**, 148 (1971).

[75] B. Schönecker and K. Ponsold, East German Patent 108,289 (1974); *Chem. Abstr.*, **83**, 10597c (1975).

[76] B. Schönecker and K. Ponsold, *Tetrahedron*, **31**, 1113 (1975).

[77] B. Schönecker, *Z. Chem.*, **22**, 186 (1982).

[78] Z. I. Istomina and A. M. Turuta, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2318 (1979).

[79] G. Nathansohn and G. Winters, German Offen. 1,965,963 (1970); *Chem. Abstr.*, **74**, 100292t (1971).

[80] G. Winters, M. Cannas and G. Nathansohn, *Ann. Chim. (Rome)*, **62**, 803 (1972).

[81] J. D. Lewis, B. D. Cameron, D. R. Hawkins, L. F. Chasseaud and E. R. Franklin, *Arzneim.-Forsch.*, **25**, 1646 (1975).

[82] A. V. Kamernitzky, A. J. Terekhina and I. V. Vesela, *Indian J. Chem.*, **15B**, 99 (1977).

[83] A. I. Terekhina, I. V. Vesela, A. V. Kamernitzky and L. I. Lisitsa, *Khim.-Farm. Zh.*, **11**, 97 (1977).

[84] S. V. Lindeman, V. E. Shklover, Yu. T. Struchkov, I. V. Vesela and A. V. Kamernitzky, *Biorg. Khim.*, **9**, 1412 (1983).

[85] J. F. W. Keana, S. B. Keana and D. Beetham, *J. Am. Chem. Soc.*, **89**, 3055 (1967).

[86] T. B. Marriot, G. B. Birrell and O. H. Griffith, *J. Am. Chem. Soc.*, **97**, 627 (1975).

[87] J. A. Nelson, S. Chou and T. A. Spencer, *J. Am. Chem. Soc.*, **97**, 648 (1975).

[88] K. Metzner and L. Lebertini, *Tetrahedon Letters*, 81 (1975).

[89] D. L. Smith and T. A. Spencer, *J. Heterocyclic Chem.*, **16**, 807 (1979).

[90] J. F. W. Keana and R. J. Dinerstein, *J. Am. Chem. Soc.*, **93**, 2808 (1971).

[91] E. K. Metzner, L. J. Libertini and M. Calvin, *J. Am. Chem. Soc.*, **99**, 4500 (1977).

[92] J. B. Jones and P. Price, *J. Chem. Soc. D*, 1478 (1969).

[93] H. Heusser, P. T. Herzig, A. Fürst and P. A. Plattner, *Helv. Chim. Acta*, **44**, 1093 (1950).

[94] A. K. Sharma, N. J. Doorenbos and N. S. Bhacca, *J. Pharm. Sci.*, **60**, 1677 (1971).

[95] S. Solyom, L. Toldy, K. Szilagyi, I. Schafer, E. Szondy, J. Borvendeg and I. Hermann, German Offen. 2,811,101 (1978); *Chem. Abstr.*, **90**, 121876g (1979).

[96] S. Solyom, L. Toldy, K. Szilagyi, I. Schafer, E. Szondy, J. Borvendeg and I. Hermann, German Offen. 2,912,835 (1979); *Chem. Abstr.*, **92**, 147042y (1980).

[97] S. Solyom, K. Szilagyi and L. Toldy, *Steroids*, **35**, 361 (1980).

[98] K. Szilagyi, S. Solyom, L. Toldy, I. Schafer, E. Szondy, J. Borvendeg and I. Hermann, European Patent Appl. EP 31,591 (1981); *Chem. Abstr.*, **96**, 6946s (1982).

[99] S. Solyom and L. Toldy, *Int. Conf. Chem. Biotechnol. Biol. Act. Nat. Prod. [Proceedings], 1st*, **2**, 120 (1981).

[100] S. Solyom, L. Toldy, G. Szilagyi, I. Schafer and E. Szondy,

Hung. Teljes HU 34,221 (1985); *Chem. Abstr.*, **103**, 215644u (1985).

[101] D. N. Kirk and M. A. Wilson, *J. Chem. Soc. C*, 414 (1971).

[102] S. Solyom, Z. Zubouvics and L. Toldy, *Acta Chim. Akad. Sci. Hung.*, **100**, 89 (1979).

[103] A. P. Leftwick, *Tetrahedron*, **26**, 321 (1970).

[104] N. R. Easton, D. R. Cassady and R. D. Dillard, *J. Org. Chem.*, **27**, 2927 (1962).

[105] K. Sisido, K. Hukuoka, M. Tuda and H. Nozaki, *J. Org. Chem.*, **27**, 2663 (1962).

[106] P. J. Stoffel and A. J. Speziale, *J. Org. Chem.*, **28**, 2814 (1963).

[107] E. Farkas and J. A. Swallow, *J. Med. Chem.*, **7**, 739 (1964).

[108] G. W. Moersch and P. L. Creger, *J. Heterocyclic Chem.*, **2**, 207 (1965).

[109] M. Ginanneschi, M. Chelli, A. Papini and G. Rapi, *Steroids*, **55**, 501 (1990).

[110] A. H. Siddiqui, R. K. Rao, V. U. Rao and M. Srinivas, *J. Indian Chem. Soc.*, **68**, 243 (1991).

[111] Y. Golander, E. Breuer and S. Sarel, *Arch. Pharm.*, **312**, 192 (1979).

[112] E. J. Agnello and P. R. Farina, *J. Med. Chem.*, **15**, 363 (1972).

[113] V. R. Zepter, H. Greiner and M. Schreiber, *J. Prakt. Chem.*, **312**, 1175 (1970).