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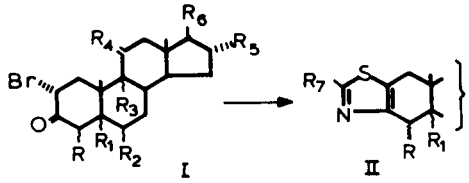
In order to discover new useful steroids in which the cyclopentanoperhydrophenanthrene system is condensed with various heterocyclic rings, many new compounds are continually being synthesized and tested for physiological action. The thiazole, isothiazole, thiazoline and thiazolidine ring condensed on several positions of the steroidal skeleton, has shown great interest due to the physiological properties. Literature coverage for this review includes publications which appear from 1946 to the 1980's.

J. Heterocyclic Chem., 18, 1485 (1981).

Steroido[3,2-*d*]thiazoles.

Compounds of this class, with an H or a CH_3, C_6H_5, OC_2H_5, NH_2, NHC_6H_5, $NHCH_2CH{=}CH_2$ and SH substituted at the 2', were synthesized by treatment of the 2α-bromo-3-ketosteroids (I) with thioformamide (1-5), thioacetamide (1-6), thiobenzamide (1), xanthogenamide (1), thiourea (2-3, 7-10), *N*-phenyl- (2-3), *N*-allylthiourea (2-3) and ammonium dithiocarbamate (11) in alcoholic solution.

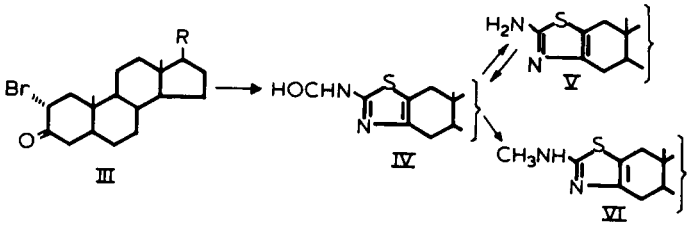
The compounds prepared are listed in Table I.



I II

The characteristic specific rotary powers and ultraviolet spectra of the above thiazoles are listed in Tables II and III, respectively.

When the reaction of the 2α-bromo-3-ketosteroids (III) with thiourea was performed in dimethylformamide the corresponding 2'-formamidothiazolosteroids (IV) were formed, which were converted into 2'-aminothiazolosteroids (V) after hydrolysis with dilute sulfuric acid or alcoholic potassium hydroxide (12).



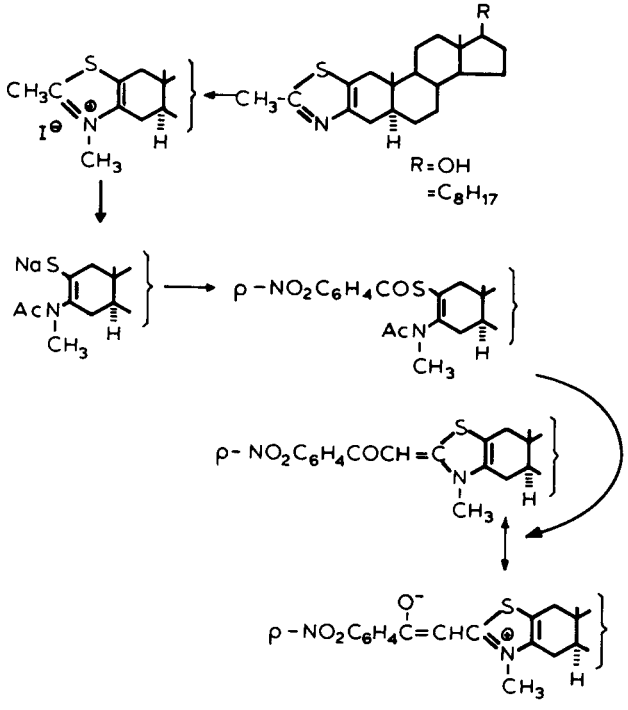
III IV V VI

a, R = $OCOCH_3$
b, R = C_8H_{17}

2'-Formamidothiazolosteroids (IV) also were obtained by the reaction of the 2'-aminothiazolosteroids (V) with dimethylformamide at reflux temperature or with formyl acetic anhydride at room temperature (12).

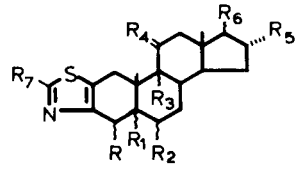
Furthermore, the 2'-formamidothiazolosteroids (IVb) on reduction with lithium aluminium hydride produced the 2'-methylaminothiazolosteroids (VI) (12).

The 2',3'-dihydrothiazoles have been prepared by thermal rearrangement of the thiolesters, according to the following equation (13).



On treating the 1α,2α-epoxy-3-ketosteroids (VII) with thiourea in boiling methanol, a mixture of 2'-aminothiazolo-1α-hydroxysteroids (VIII) and bis(3-ketosteroid-1-en-2-yl)sulfides (IX) were obtained (14).

Table I



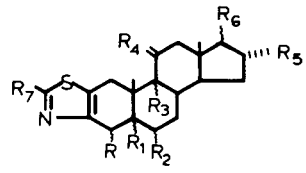
R	R_1	R_2	R_3	R_4	R_5	R_6	R_7	References
H	α-H	H	H	H_2	H	β-OH α-H	H	1,5
Δ^4	-	H	H	H_2	H	β-OH α-H	H	1
α-CH_3	α-H	H	H	H_2	H	β-OH α-H	H	1
H	α-H	H	H	H_2	H	β-OH α-C_2H_5	H	1
H	α-H	α-CH_3	H	H_2	H	β-OH α-H	H	1
Δ^4	-	Δ^6, CH_3	H	H_2	H	β-OH α-CH_3	H	1
Δ^4, Cl	-	H	α-F	O	H	β-OH α-CH_3	H	1
Δ^4, Br	-	H	α-F	O	H	β-OH α-CH_3	H	1
Δ^4	-	α-F	H	β-OH α-H	H	β-OH α-H	H	1
H	α-H	H	H	H_2	H	β-OH α-H	CH_3	1,5
Δ^4	-	H	H	H_2	H	β-OH α-H	CH_3	1
α-CH_3	α-H	H	H	H_2	H	β-OH α-H	CH_3	1
H	α-H	H	H	H_2	H	β-OH α-C_2H_5	CH_3	1,6
H	α-H	α-CH_3	H	H_2	H	β-OH α-H	CH_3	1
Δ^4	-	Δ^6, CH_3	H	H_2	H	β-OH α-CH_3	CH_3	1
Δ^4, Cl	-	H	α-F	O	H	β-OH α-CH_3	CH_3	1
Δ^4, Br	-	H	α-F	O	H	β-OH α-CH_3	CH_3	1
Δ^4	-	α-F	H	β-OH α-H	H	β-OH α-H	CH_3	1
H	α-H	H	H	H_2	H	β-OH α-H	OC_2H_5	1
Δ^4	-	H	H	H_2	H	β-OH α-H	OC_2H_5	1
α-CH_3	α-H	H	H	H_2	H	β-OH α-H	OC_2H_5	1
H	α-H	H	H	H_2	H	β-OH α-C_2H_5	OC_2H_5	1
H	α-H	α-CH_3	H	H_2	H	β-OH α-H	OC_2H_5	1
Δ^4	-	Δ^6, CH_3	H	H_2	H	β-OH α-CH_3	OC_2H_5	1
Δ^4, Cl	-	H	α-F	O	H	β-OH α-CH_3	OC_2H_5	1
Δ^4, Br	-	H	α-F	O	H	β-OH α-CH_3	OC_2H_5	1
Δ^4	-	α-F	H	β-OH α-H	H	β-OH α-H	OC_2H_5	1
H	α-H	H	H	H_2	H	β-OH α-H	C_6H_5	1

Table I, continued

Δ^4	-	H	H	H_2	H	β-OH α-H	C_6H_5	1
α-CH_3	α-H	H	H	H_2	H	β-OH α-H	C_6H_5	1
H	α-H	H	H	H_2	H	β-OH α-C_2H_5	C_6H_5	1
H	α-H	α-CH_3	H	H_2	H	β-OH α-H	C_6H_5	1
Δ^4	-	Δ^6, CH_3	H	H_2	H	β-OH α-CH_3	C_6H_5	1
Δ^4, Cl	-	H	α-F	O	H	β-OH α-CH_3	C_6H_5	1
Δ^4, Br	-	H	α-F	O	H	β-OH α-CH_3	C_6H_5	1
Δ^4	-	α-F	H	β-OH α-H	H	β-OH α-H	C_6H_5	1
H	α-H	H	H	H_2	H	β-OH α-CH_3	H	2,3,4,5
H	α-H	H	H	H_2	H	β-OH α-CH_3	CH_3	2,3,4,5,6
H	α-H	H	H	H_2	H	β-OH α-CH_3	NH_2	2,3
H	α-H	H	H	H_2	H	β-OH α-CH_3	$NHCH_2CH=CH_2$	2,3
H	α-H	H	H	H_2	H	β-OH α-CH_3	NHC_6H_5	2,3
H	α-H	H	H	H_2	H	β-C_8H_{17} α-H	H	3
H	α-H	H	H	H_2	H	β-C_8H_{17} α-H	CH_3	3
H	α-H	H	H	H_2	H	β-C_8H_{17} α-H	NH_2	3,7
H	α-H	H	H	H_2	H	β-C_8H_{17} α-H	$NHCH_2CH=CH_2$	3
H	α-H	H	H	H_2	H	β-C_8H_{17} α-H	NHC_6H_5	3
H	α-H	H	H	H_2	H	β-OH α-H	NH_2	8
H	α-H	H	H	H_2	H	β-$OCOCH_3$ α-H	NH_2	8
H	α-H	H	H	H_2	H	β-$OCO(CH_2)_2CH_3$ α-H	NH_2	8
H	α-H	H	H	H_2	H	β-$OCO(CH_2)_2COOH$ α-H	NH_2	8
H	α-H	H	H	H_2	H	β-$OCOC_6H_5$ α-H	NH_2	8
H	α-H	H	H	H_2	H	β-$OCOCH=CHC_6H_5$ α-H	NH_2	8
Δ^4	-	H	H	H_2	H	β-OH α-H	NH_2	9
Δ^4	-	H	H	O	H	$=CHCOOCH_3$	NH_2	10
Δ^4	-	H	H	O	CH_3	Bismethylenedioxy	SH	11
Δ^4	-	H	H	O	CH_3	Bismethylenedioxy	H	11
Δ^4	-	H	H	β-OH α-H	CH_3	Bismethylenedioxy	H	11
Δ^4	-	H	H	β-OH α-H	CH_3	β-$COCH_2OH$ α-OH	H	11

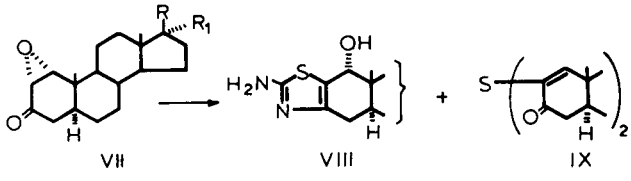
Esterification of compounds belonging to reference 1 produced the acetate, propionate, butyrate, cyclopropionate and benzoate derivatives.

Table II



R	R_1	R_4	R_5	R_6	R_7	$[\alpha]_D$	References
H	α-H	H_2	H	β-OH α-CH_3	H	+48.8° +33°	2,3 4
						+33°, +37°, +37°	5
H	α-H	H_2	H	β-OH α-CH_3	CH_3	+35.6° +47°	2,3 4
						+47°, +42°, +44°	5
H	α-H	H_2	H	β-OH α-CH_3	NH_2	+45°	2,3
H	α-H	H_2	H	β-OH α-CH_3	$NHCH_2CH{=}CH_2$	+50.5°	2,3
H	α-H	H_2	H	β-OH α-CH_3	NHC_6H_6	+46°	2,3
H	α-H	H_2	H	β-C_8H_{17} α-H	CH_3	+52.9° (c = 0.81, chloroform)	3
H	α-H	H_2	H	β-C_8H_{17} α-H	NH_2	+64.4° (c = o.496) +58.3° (c = 0.78, chloroform)	7 3
H	α-H	H_2	H	β-C_8H_{17} α-H	$NHCH_2CH{=}CH_2$	+57.4° (c = 1.03, chloroform)	3
H	α-H	H_2	H	-β-C_8H_{17}	NHC_6H_5	+62.9° (c = 0.99, chloroform)	3
H	α-H	H_2	H	β-OH α-H	NH_2	+67.8° ±0.2° (1% 95% ethanol)	8
H	α-H	H_2	H	β-OH α-H	H	+91°	5
H	α-H	H_2	H	β-OH α-H	CH_3	+64°	5
H	α-H	H_2	H	β-OH α-C_2H_5	CH_3	+36°	6
Δ^4	-	H_2	H	β-OH	NH_2	-100 (dioxan)	9
H	α-H	O	H	=CHCOOCH$_3$	NH_2	+150 (chloroform)	10
H	α-H	O	CH_3	BMD	SH	+72° (c = 0.6, chloroform)	11
H	α-H	O	CH_3	BMD	H	+121° (c = 0.5, chloroform)	11
H	α-H	β-OH	CH_3	BMD	H	+60° (c = 0.62, chloroform)	11
H	α-H	β-OH	CH_3	β-$COCH_2OH$	H	+150° (c = 0.43, chloroform)	11

BMD = Bismethylenedioxy



VII VIII IX

a, R = $COCH_3$, R_1 = H

b, R = $OCOCH_3$, R_1 = H

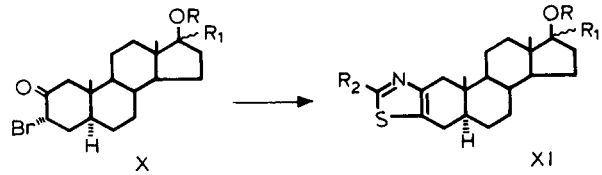
c, R = βCH_3 / $\alpha OCOCH_3$, R_1 = H

d, R = $COCH_3$, R_1 = $OCOCH_3$

Steroido[2,3-*d*]thiazoles.

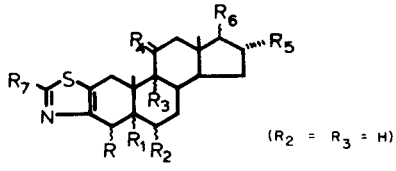
Steroido[2,3-*d*]thiazoles were also obtained on the basis of the corresponding α-haloketones. In the condensation of 3α-bromo-2-ketosteroids (X) with thioformamide, thioacetamide or thiobenzamide, in alcoholic solution [2,3-*d*]-thiazoles (XI) are obtained which contain hydrogen, methyl or phenyl substituents in position 2′ of the thiazole ring (15).

The compounds prepared are listed in Table IV.



X XI

Table III



R	R_1	R_4	R_5	R_6	R_7	λ max (ethanol)	mμ (logε)	ε	λ max (chloroform)	References
H	α-H	H_2	H	β-OH	H	251	(3.64)		2.75, 3.00-3.05, 6.40	2,3
				α-CH_3		252	(3.61)			4
						252	(3.61)		3.01, 6.47 (very short) (1)	5
H	α-H	H_2	H	β-OH	CH_3	253	(3.72)		2.76, 6.40	2,3
				α-CH_3		254	(3.76)			4
						254	(3.76)		3.07 (ms), 6.39 (w) (1)	5
H	α-H	H_2	H	β-OH	NH_2				2.76, 2.86, 2.94, 6.25, 6.57	2,3
				α-CH_3						
H	α-H	H_2	H	β-OH	$NHCH_2CH{=}CH_2$	266	(3.93)		2.76, 2.90, 6.07	2,3
				α-CH_3					6.27, 6.49	2,3
H	α-H	H_2	H	β-OH	NHC_6H_5	298	(4.21)		2.76, 2.90, 3.06, 6.19, 6.48	
				α-CH_3					6.64 (1)	2,3
H	α-H	H_2	H	βC_8H_{17}	CH_3				6.12, 6.41 (1)	3
H	α-H	H_2	H	β-C_8H_{17}	NH_2				2.82-3.02, 6.13-6.25, 6.1,	
				α-H					6.53 (1)	3
H	α-H	H_2	H	β-C_8H_{17}	$NHCH_2CH{=}CH_2$				2.92, 6.07, 6.30, 6.49	3
				α-H						
H	α-H	H_2	H	β-C_8H_{17}	NHC_6H_5				2.93, 6.21, 6.50, 6.67	3
				α-H						
H	α-H	H_2	H	β-OH	H	252	(3.69)			5
				α-H						
H	α-H	H_2	H	β-OH	CH_3	254	(3.74)		3.06 (ms), 6.40 (ms) (1)	5
				α-H						
H	α-H	H_2	H	β-OH	CH_3	254-256	(3.71)			6
				α-C_2H_5						
H	α-H	H_2	H	β-OH	NH_2	263		7000		8
				α-H						
Δ^4		H_2	H	β-OH	NH_2	264.5		7470		9
				α-H						
H	α-H	O	CH_3	BMD	SH	248, 327,		11200,	3-3.2, 3.7, 5.88, 6.23,	11
						333,		13200,		
						246, 293		13600 (3),		
								20000,		
								10600 (4)		
H	α-H	O	CH_3	BMD	H	271 (2)		8400	5.88, 6.1, 6.5, 9.06	11
H	α-H	β-OH	CH_3	BMD	H	263		9680 (3)	2.75, 3, 6.1, 6.5, 9.08	11
		α-H								
H	α-H	β-OH	CH_3	β-$COCH_2OH$	H	263		8500 (3)	3-3.1, 5.8, 6.15, 6.52	11
		α-H		α-OH						
H	α-H	H_2	H	β-C_8H_{17}	NHCOH	285	(3.94) (2)			12
				α-H						
H	α-H	H_2	H	β-$OCOCH_3$	NHCOH	280	(4.10)			12

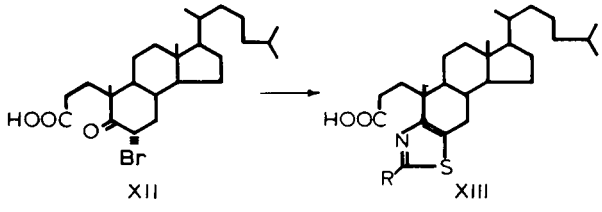
(1) Potassium bromide. (2) Chloroform. (3) Methanol. (4) Methanol-sodium hydroxide.
BMD = Bismethylenedioxy.

Table IV

R	R_1	R_2	Reference
H	H	H	15
$COCH_3$	H	H	15
COC_6H_5	H	H	15
H	β-CH_3	H	15
$COCH_2CH_3$	β-CH_3	H	15
	β-CH_3	H	15
H	α-CH=CH_2	H	15
$COCH_3$	α-CH=CH_2	H	15
$CO(CH_2)_4CH_3$	α-CH=CH_2	H	15
H	α-C_2H_5	H	15
$COCH_2CH_3$	α-C_2H_5	H	15
	α-C_2H_5	H	15
H	H	CH_3	15
$COCH_3$	H	CH_3	15
COC_6H_5	H	CH_3	15
H	α-CH_3	CH_3	15
$COCH_2CH_3$	α-CH_3	CH_3	15
	α-CH_3	CH_3	15
H	α-CH=CH_2	CH_3	15
H	α-C_2H_5	CH_3	15
H	H	C_6H_5	15
$COCH_3$	H	C_6H_5	15
COC_6H_5	H	C_6H_5	15
H	α-CH_3	C_6H_5	15
$COCH_2CH_3$	α-CH_3	C_6H_5	15
	α-CH_3	C_6H_5	15
H	α-CH=CH_2	C_6H_5	15
H	α-C_2H_5	C_6H_5	15

Steroido[5,6-*d*]thiazoles.

Thiazole derivatives condensed with the steroidal frame skeleton in positions 5 and 6 were obtained by reaction of 6α-bromo-3,5-seco-4-norcholestan-5-on-3-oic acid (XII) with thioacetamide or thiosemicarbazide in ethanol (16).



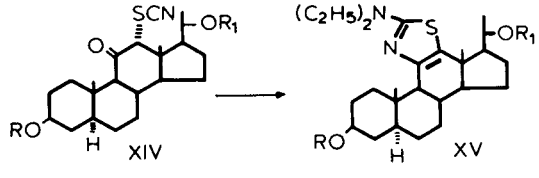
XII XIII

a, R = CH_3

b, R = $NHNH_2$

Steroido[11,12-*d*]thiazoles.

The reaction of 12α-thiocyanato-11-ketosteroids (XIV) with secondary amines in boiling dioxane leads to the [11,12-*d*]thiazole derivatives (XV) (17).



XIV XV

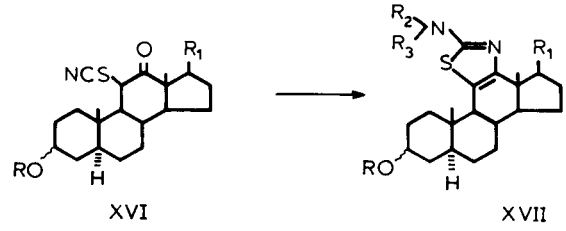
R = R_1 = $COCH_3$

a, R = R_1 = $COCH_3$

Refluxing 2'-diethylaminothiazolo[11,12-*d*]-5α-pregn-11-ene-3β,20β-diacetate with potassium carbonate in aqueous methanol gave the corresponding dihydroxy compound (XVb).

Steroido[12,11-*d*]thiazoles.

In an analogous manner to the synthesis of steroido-[11,12-*d*]thiazoles the reaction of 11β-thiocyanato-12-keto-steroids (XVI) with secondary amines produced the [12,11-*d*]thiazoles (XVII) (18-19).

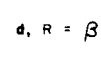


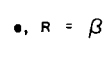
XVI XVII

a, R = α-$COCH_3$, R_1 = $CH(CH_3)CH_2CH_2COOCH_3$

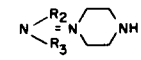
b, R = α-$COCH_3$, R_1 = $CH(CH_3)CH_2CH_2COOCH_3$

c, R = α-$COCH_3$, R_1 = $CH(CH_3)CH_2CH_2COOCH_3$

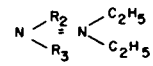
d, R = β-H, R_1 = 

e, R = β-$COCH_3$, R_1 = 

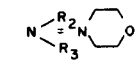
a, R = α-$COCH_3$, R_1 = $CH(CH_3)CH_2CH_2COOCH_3$

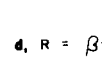
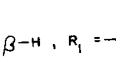


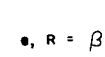
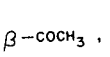
b, R = α-$COCH_3$, R_1 = $CH(CH_3)CH_2CH_2COOCH_3$



c, R = α-$COCH_3$, R_1 = $CH(CH_3)CH_2CH_2COOCH_3$

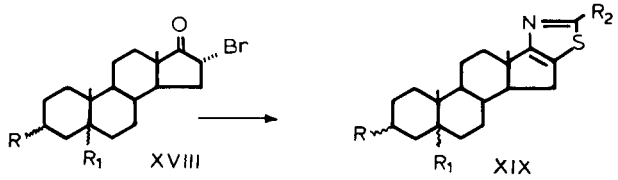


d, R = β-H, R_1 =  , 

e, R = β-$COCH_3$, R_1 =  , 

Steroido[17,16-*d*]thiazoles.

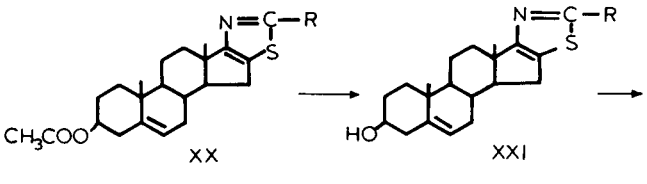
The usual method for the synthesis of the title compounds involves the reaction of 16α-bromo-17-ketosteroids (XVIII) with thioacetamide or thiourea in boiling alcohol (12,20-23). When the reaction of XVIII with thiourea takes place in dimethylformamide, the 2'-formamido-thiazolosteroids are formed (12).



XVIII XIX

The compounds prepared are listed in Table V.

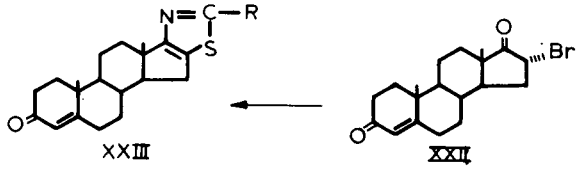
Saponification of 3β-acetoxythiazolosteroids (XX) followed by Oppenauer oxidation afforded thiazolo-4-en-3-one derivatives (XXIII) (20-23), which were also obtained by reaction of 16α-bromo-3,17-dione (XXII) (22) with thioacetamide or thiourea.



XX XXI

a, R = CH_3
b, R = NH_2

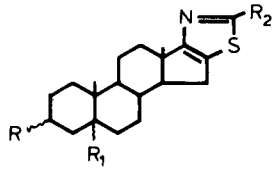
a, R = CH_3
b, R = NH_2



XXIII XXII

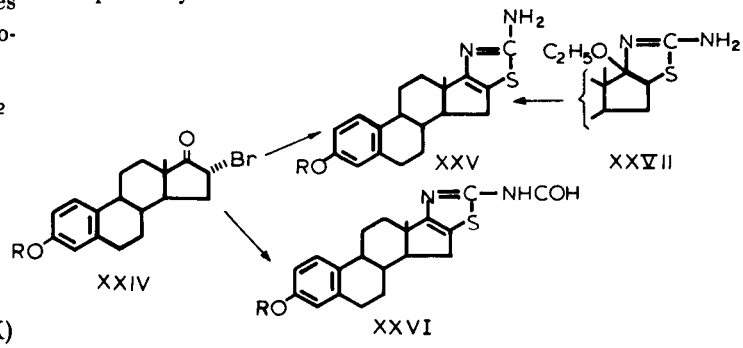
a, R = CH_3
b, R = NH_2
c, R = $NHCOCH_3$

Table V



Compound	R	R_1	R_2	References
XIXa	β-$OCOCH_3$	α-H	NHCOH	12
XIXb	β-$OCOCH_3$	β-H	NHCOH	12
XIXc	α-$OCOCH_3$	α-H	NHCOH	12
XIXd	H	α-H	NHCOH	12
XIXe	β-$OCOCH_3$	Δ⁵	NHCOH	12
XIXf	H	α-H	NH_2	12
XIXg	β-OH	α-H	NH_2	12
XIXh	β-$OCOCH_3$	Δ⁵	NH_2	12
XIXi	β-OH	Δ⁵	NH_2	20,21,22
XIXk	β-$OCOCH_3$	Δ⁵	$NHCOCH_3$	20,21,22
XIXl	β-OH	Δ⁵	CH_3	20,21,22,23
XIXm	β-$OCOCH_3$	Δ⁵	CH_3	20,21,22,23

Similarly 16α-bromoestra-1,3,5(10)-trien-17-one (XXIV) is converted by heating with thiourea in boiling alcohol (24) or in dimethylformamide (12) to 2'-amino-(XXV) or to 2'-formamidothiazoloestra-1,3,5(10),16-tetraene (XXVI), respectively.

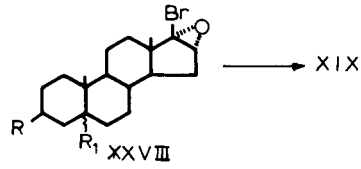


XXV XXVII XXIV XXVI

R = CH_3 R = $COCH_3$

Alternatively XXV can be obtained by treatment of 3-methoxy-2'-amino-4'-ethoxy-4',5'-dihydrothiazolo[1-7,16-*d*]-estra-1,3,5(10)triene (XXVII) with aqueous sodium hydroxide (24).

A plausible pathway for the conversion of XXVIII to XIX is a concerted process involving ring opening of the epoxide by thiourea at C-16 with the expulsion of bromide and the formation of an acyclic intermediate (12).



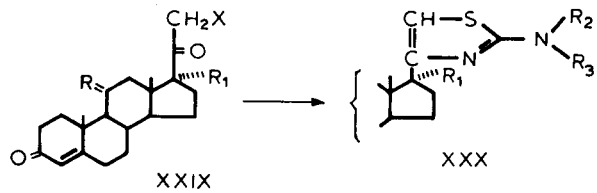
XXVIII XIX

a, R = $OCOCH_3$, R_1 = α-H, R_2 = NHCOH
b, R = H, R = α-H, R_2 = NHCOH

a, R = $OCOCH_2$
b, R = H

Steroido[20,21-*d*]thiazoles.

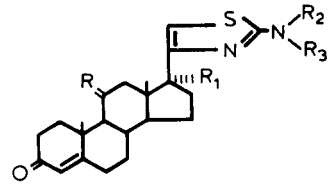
The standard method for the preparation of the 2'-amino- or 2'-N-substituted aminosteroido[20,21-*d*]thiazoles (XXX) involves the condensation of thiourea or its N-substituted derivatives with 21-substituted-20-ketosteroids (XXIX) in several solvents, such as acetone, ethanol or anhydrous dimethylformamide (12,25-30).



XXIX XXX

X = Cl, Br, J, OSO_2CH_3, $OSO_2C_6H_4CH_3$, OH

Table VI

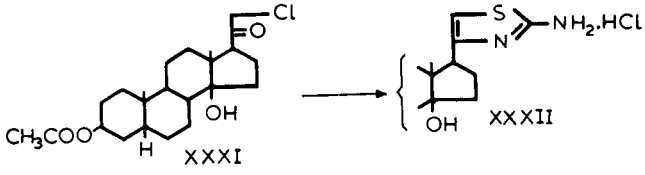


R	R_1	R_2	R_3	mp (bp °C)	Yield (%)	$[\alpha]_D$ (chloroform)	λ max (ethanol) mμ	(log ε)	References
H_2	OH	H	H	226	94.4	+61.69 (c = 0.2378)	242.5 ~ 245	(4.24)	27
H_2	OH	H	CH_3	227	97.5	+105.4 (c = 0.8126)	243.2 ~ 244.3	(4.30)	27
H_2	OH	H	C_2H_5	211	88.7	+102 (c = 0.9831)	242.5 ~ 244.5	(4.09)	27
H_2	OH	H	C_3H_7	184	92.8	+105.2 (c = 1.077)	242.3 ~ 245	(4.07)	27
H_2	OH	H	*iso*-C_3H_7	187.5	92.8	+109.9 (c = 1.0159)	242.3 ~ 245	(4.29)	27
H_2	OH	H	C_4H_9	153.5	96.5	+96.4 (c = 1.0195)	241.5 ~ 243.5	(4.32)	27
H_2	OH	H	*sec*-C_4H_9	139	89.6	+100.5 (c = 0.932)	243.2 ~ 244.2	(4.29)	27
H_2	OH	H	C_6H_5	247	96.4	+98 (c = 0.400)	239.8 ~ 242 289 ~ 292	(4.21) (4.20)	27
H_2	OH	H	4-$CH_3OC_6H_4$	195	92.5	+103.4 (c = 0.847)	241.5 ~ 242.5 296	(4.28) (4.25)	27
H_2	O	H	4-$C_2H_5OC_6H_4$	185	92.5	+100.2 (c = 0.600)	241 ~ 242.5 296 ~ 298	(4.24) (4.22)	27
H_2	OH	H	4-$CH_3C_6H_4$	217	89.7	+102.4 (c = 0.629)	240 ~ 242 293 ~ 296	(4.16) (4.25)	27
H_2	OH	H	2-$CH_3C_6H_4$	213.5	83.3	+102.4 (c = 0.688)	240 ~ 242.5 293 ~ 296	(4.10) (3.87)	27
H_2	OH	H	4-ClC_6H_4	202	85.5	+81.1 (c = 0.073) (a)	239.8 ~ 241.8 297 ~ 300	(4.16) (4.29)	27
H_2	OH	H	2-ClC_6H_4	210	98.1	+58.1 (c = 0.206) (a)	238.5 ~ 241.5 293 ~ 295.5	(4.16) (4.07)	27
H_2	OH	H	3-ClC_6H_4	204	92	+131.1 (c = 0.240) (a)	240.5 ~ 242.5 296 ~ 298	(3.85) (3.89)	27
H_2	OH	H	2,3-$Cl_2C_6H_3$	243	86.2	+81.8 (c = 0.397) (a)	236 ~ 237 296 ~ 299	(3.97) (3.89)	27
H_2	OH	H	2,5-$Cl_2C_6H_3$	223	95.6	+102.6 (c = 0.336) (a)	236.5 ~ 238.5 293.5 ~ 295.5	(4.05) (3.95)	27
H_2	OH	CH_3	C_6H_5	185	96.1	+109 (c = 0.785)	240.5 ~ 242.5 295	(4.40) (3.99)	27
H_2	OH	C_2H_5	C_6H_5	151	96.2	+114.5 (c = 1.612)	239.3 ~ 241.8 295 ~ 296	(4.41) (4.41)	27
H_2	OH	H		219	83.5	+79 (c = 0.3275)	242 ~ 244	(4.25)	27
O	OH	H	H	250	91	+163.1 (c = 0.309)	240.5 ~ 242	(4.35)	27
O	OH	H	CH_3	243	90	+171.6 (c = 0.802)	239	(4.26)	27
O	OH	H	C_6H_5	247	89	+11.7 (c = 0.323)	264	(3.77)	27
O	OH	CH_3	C_6H_5	214	86.5	+141 (c = 1.031)	241.5 295 ~ 296	(4.37) (3.79)	27
H_2	H	H	CH_3	219	83.9	+132.7 (c = 0.662)	242.5	(4.24)	27
H_2	H	H	C_6H_5	226	81.8	+111.4 (c = 0.984)	241 ~ 243 295 ~ 298	(4.16) (3.65)	27
H_2	H	C_2H_5	C_6H_5	144	93.1	+123.5 (c = 0.945)	241 ~ 242 296 ~ 299	(4.51) (3.39)	27

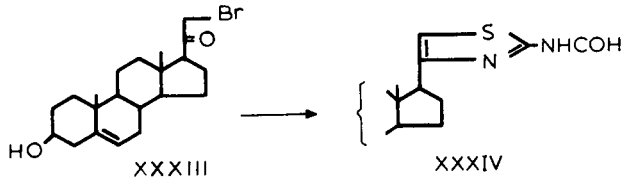
(a) *N,N*-Dimethylformamide.

The compounds prepared and their melting points, yields, specific rotary powers and ultraviolet spectra are listed in Table VI.

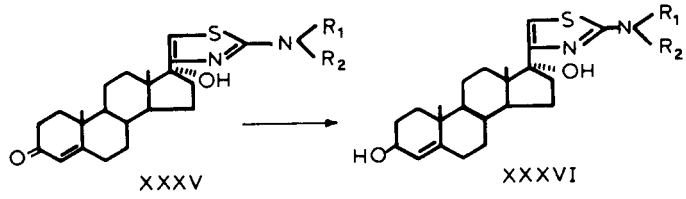
Similarly 3β, 14-dihydroxy-17β-(2'-amino-4'-thiazolyl)-5β,14β-androstane-3-acetate hydrochloride (XXXII) was prepared (30).



It has been reported that the reaction of 21-bromo-3β-hydroxy-5-pregnen-20-one (XXXIII) with thiourea in refluxing dimethylformamide yielded the 2′-formamidothiazolo[20,21-*d*]pregna-5,20-dien-3β-ol (XXXIV) (12).

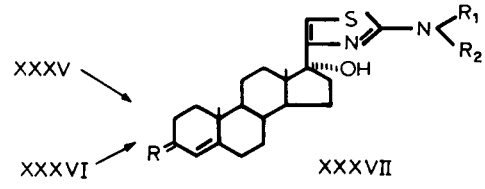


Reduction of 17α-hydroxy-17β-(2′-alkylamino- or 2′-arylamino- or 2′-*N*,*N*-alkylamino)-4′-thiazolyl)androst-4-ene-3-one (XXXV) with sodium borohydride in dioxane or dioxane-methanol (1:1) and subsequent purification by chromatography through acid-washed alumina yielded a sole product which corresponds to 3β,17α-diol (XXXVI). (31-32).



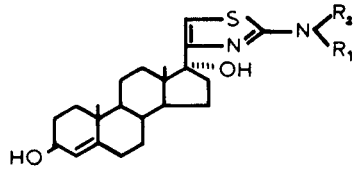
The compounds prepared and their melting points, yields, specific rotary powers and ultraviolet spectra are listed in Table VII.

Compounds XXXV and XXXVI after the action of succinic anhydride in pyridine yielded *N*- and 3β-*O*-succinate (XXXVII), while the aliphatic amino derivatives of XXXVI produce 3β-*O*,*N*-disuccinate (31,33).



The compounds prepared and their melting points, yields, specific rotary powers and ultraviolet spectra are listed in Table VIII.

Table VII



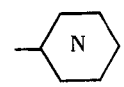
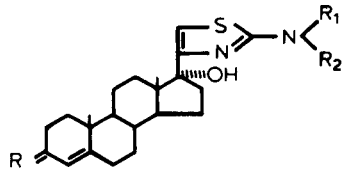
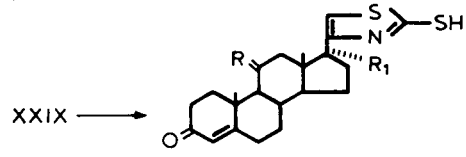
R_1	R_2	mp °C	Yield	$[\alpha]_D$ (chloroform)	λ max (ethanol) (mμ)	(log ε)	References
H	H	240.5	85	+16.69 (c = 0.1716)	259 ~ 260	(3.50)	31
H	CH_3	216	90.9	+10.81 (c = 0.248)	261 ~ 264	(3.57)	31
H	C_2H_5	222.5	95	+47.61 (c = 0.294)	264 ~ 266	(3.82)	31
H	C_3H_7	202	70	+76.87 (c = 0.576)	265.3 ~ 266.2	(3.92)	31
H	*iso*-C_3H_7	218	85	+62.76 (c = 0.415)	266 ~ 267	(3.75)	31
H	C_4H_9	161	70	+37.20 (c = 0.532)	262 ~ 265	(3.81)	31
H	C_6H_5	199	88.8	+43.74 (c = 0.901)	295.5	(4.23)	31
H		212	80	39.09 (c = 0.024)	264.5 ~ 265.7	(3.76)	31
H	2-$CH_3C_6H_4$	192	60	+43.03 (c = 1.162)	293 ~ 294	(4.00)	31
H	4-$CH_3C_6H_4$	202	82.3	+18.94 (c = 1.162)	295.5 ~ 2965	(4.06)	31
H	3-ClC_6H_4	209	79	+79.36 (c = 0.794)	298 ~ 299	(4.27)	31
					254	(3.81)	
C_2H_5	C_6H_5	214	73.3	+58.73 (c = 0.794)	260.5	(3.72)	31
					295 ~ 298	(3.82)	

Table VIII



R	R_1	R_2	mp °C	Yield	$[\alpha]_D$ (chloroform)	λ max (ethanol) (mμ)	(log ε)	References
O	$COCH_2CH_2COOH$	H	217	70.5	-57.73 (c = 0.433)	242 ~ 243	(4.14)	31
α-H						227.5 ~ 228	(4.37)	31
β-$OCOCH_2CH_2COOH$	$COCH_2CH_2COOH$	CH_3	142	61.2	+133.33 (c = 0.075)	235.2 ~ 235.8	(4.37)	
						243.5 ~ 244	(4.21)	
						275 ~ 276.5	(3.98)	
α-H								
β-$OCOCH_2CH_2COOH$	H	4-$CH_3C_6H_4$	176	65.2	+49.32 (c = 1.774)	293.5 ~ 294.5	(3.24)	31
α-H								
β-$OCOCH_2CH_2COOH$	H	2-$CH_3C_6H_4$	182	70	+70.54 (c = 0.283)	290.5 ~ 292	(4.06)	31

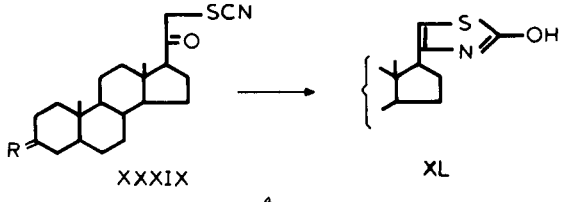
The reaction of XXIX with ammonia and carbon disulphide in ethanol leads to a 2'-mercaptoderivative (XXXVIII) (25).



XXIX

a, R = H_2, R_1 = H
b, R = O, R_1 = OH

Similarly 2'-hydroxy derivatives (XL) were prepared by treatment of 21-thiocyanato-20-ketosteroids (XXXIX) with concentrated hydrochloric acid in boiling 2-propanol (25).

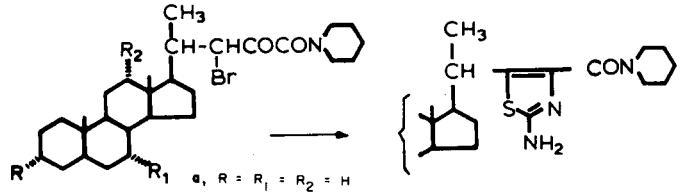


XXXIX XL

a, R = O, Δ^4
b, R = α-H, β-OH, Δ^5

Steroido[23,22-*d*]thiazoles.

The treatment of the 22-bromo-23-ketocholanic acid piperidylamides (XLI) with thiourea in boiling alcohol yielded 2'-amino-5'-(20-ternocholanyl)-4'-thiazolecarboxylic acid piperidylamides (XLIIa-e) (34).

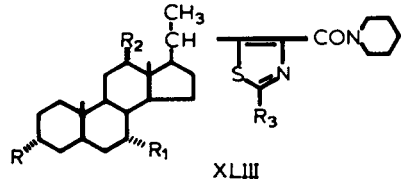


XLI XLII

a, R = R_1 = R_2 = H
b, R = OH, R_1 = R_2 = H
c, R = $OCOCH_3$, R_1 = R_2 = H
d, R = R_1 = $OCOCH_3$, R_1 = R_2 = H
e, R = R_1 = R_2 = $OCOCH_3$

Benzylation and acetylation of XLIIa and XLIId afforded the corresponding *N*-Benzyl-(XLIIIa) and *N*-acetoxy-derivatives (XLIIIb) (34).

Furthermore, treatment of XLIIa and XLIIe with concentrated hydrochloric or hydrobromic acid and BuONO respectively, produced the 2-Cl-(XLIIIc) and 2-Br-compounds (XLIIId) (34).



XLIII

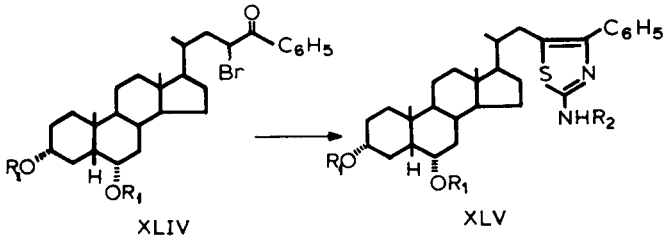
a, R = R_1 = R_2 = OH, R_3 = $NHCH_2C_6H_5$
b, R = R_1 = $OCOCH_3$, R_2 = H, R_3 = $NHCOCH_3$
c, R = R_1 = R_2 = OH, R_3 = Cl
d, R = R_1 = R_2 = $OCOCH_3$, R_3 = Br

Steroido[24,23-*d*]thiazoles.

As starting substance for the preparation of the above thiazoles the 24-phenyl-23-bromo3α,6α-diacetoxy-5β-

cholane-24-one (XLIV) was chosen, which condensed with thiourea in boiling ethanol (35).

Tosylation of XLVc and heating with potassium acetate in aqueous dimethylformamide of the XLVd, yielded a mixture of two products XLVIa and XLVIb. Acetylation of the reaction mixture led to the 3β-acetoxy-Δ⁴-steroid (XLVIb) which was converted into the 3β-hydroxy-Δ⁴-steroid (XLVIa) (35).



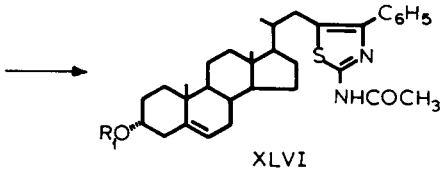
XLIV XLV

a, $R_1 = R_2 = COCH_3$

b, $R_1 = COCH_3$, $R_2 = H$

c, $R_1 = H$, $R_2 = COCH_3$

d, $R_1 = Ts$, $R_2 = COCH_3$

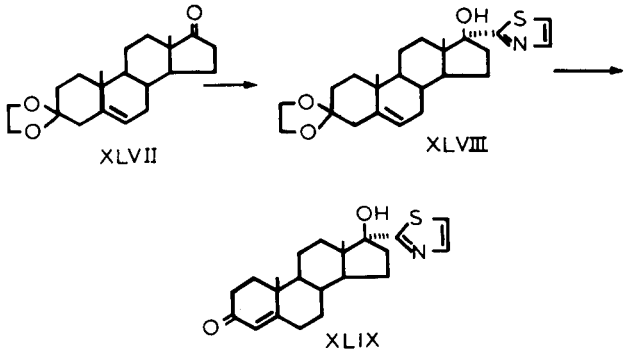


XLVI

a, $R_1 = H$

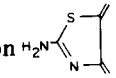
b, $R_1 = COCH_3$

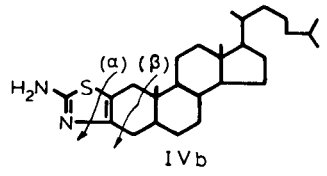
Steroidal thiazoles in which the heterocyclic ring is not condensed with the steran skeleton have been reported by Yoneno (36). Starting with 3,3-ethylenedioxy-17-oxo-5-androstene (XLVII) by treatment with lithium and 2-bromothiazole obtained the 3,3-ethylenedioxy-17α-(2-thiazolyl)-17β-hydroxy-5-androstene (XLVIII) which with acetic acid produced the final product, 3-oxo-17α-(2-thiazolyl)-17β-hydroxy-4-androstene (XLIX).



XLVII XLVIII XLIX

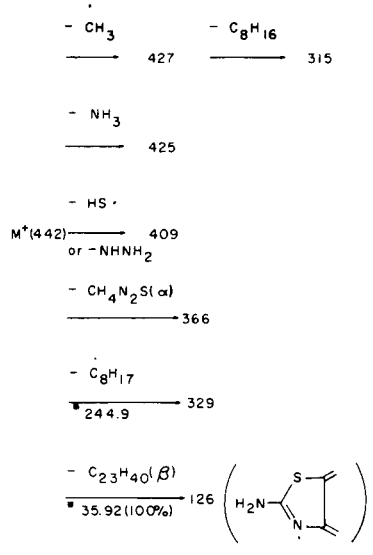
Mass Spectra of Aminothiazolosteroids (12).

The base peak (100%) of compound IVb occurred at m/e 126 corresponding to the ion  . A metastable peak at m/e 35.92 shows that this peak (m/e 126) arises directly from M^+, path β. The molecular ion m/e 442, has a medium intensity. Further fragmentation of compound IVb is shown in Scheme 1.



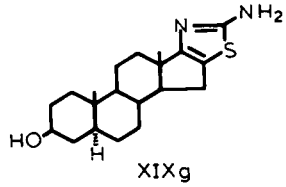
IVb

Scheme 1



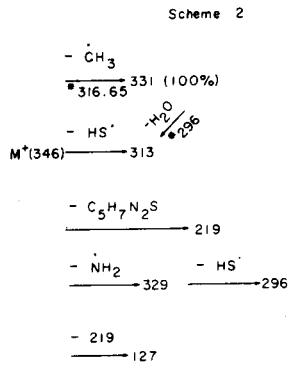
$C_{28}H_{46}N_2S$ (MW 442)

The spectrum of XIXg (R = β-OH, R_1 = α-H, R_2 = NH_2) reveals a peak (100%) at m/e 331, which originates by the loss of $\cdot CH_3$ from M^+, as it is shown from m* at m/e 316.65. The molecular ion at m/e 346 is rather abundant (50% based on the base peak). The most interesting fragmentation peaks are shown in Scheme 2.



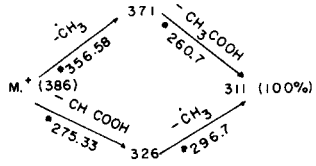
XIXg

Scheme 2

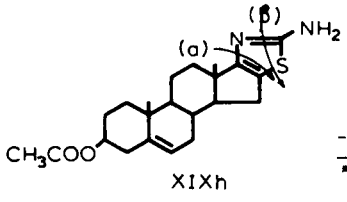


$C_{20}H_{30}N_2OS$ (MW 346)

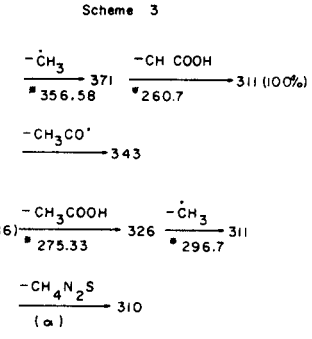
The possible pathways for the formation of the base peak (100%) at m/e 311 of the compound XIX (R = β-$OCOCH_3$, R_1 = Δ^5, R_2 = NH_2) are shown below.



Further, the ion (M^{+}-60) 326 possibly arises from M^{+} by the loss of $S{=}\dot{C}{-}NH_2$, m/e 60, path β (Scheme 3). Further fragmentation peaks are shown in Scheme 3.

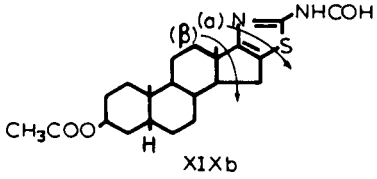


Scheme 3

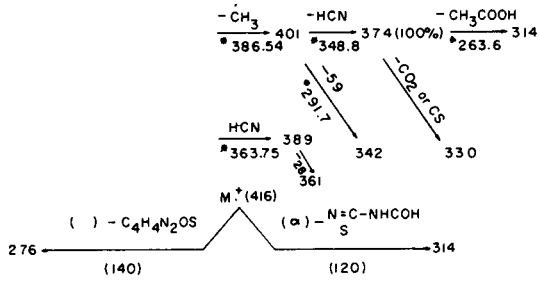


$C_{22}H_{30}N_2O_2S$ (MW 386)

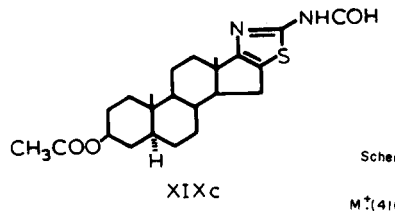
The peaks of the fragmentation of the formamidothiazolosteroids XIXb (R = β-$OCOCH_3$, R_1 = β-H, F_2 = NHCOH), XIXc (R = α-$OCOCH_3$, R_1 = α-H, R_2 = NHCOH, XIXd (R = H, R_1 = α-H, R_2 = NHCOH) and XXXIV are presented in Schemes 4-7.



Scheme 4



$C_{23}H_{32}N_2O_3S$ (MW 416)

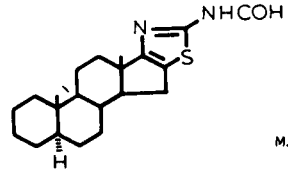


Scheme 5

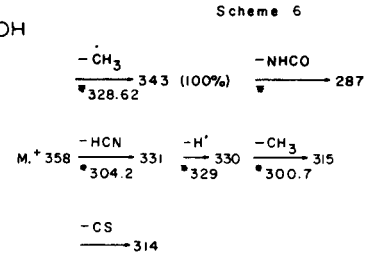
M.+(416)

$C_{23}H_{32}N_2O_3S$ (MW 416)

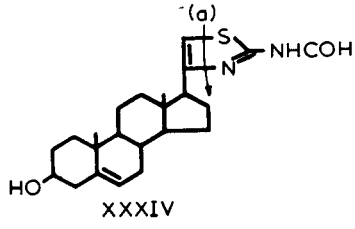
The fragmentation of this compound is similar to that of XIX (R = β-$OCOCH_3$, R_1 = α-H, R_2 = NHCOH), except for the observed peak intensities. The base peak (100%) is at m/e 401 (M^{+}-·CH_3).



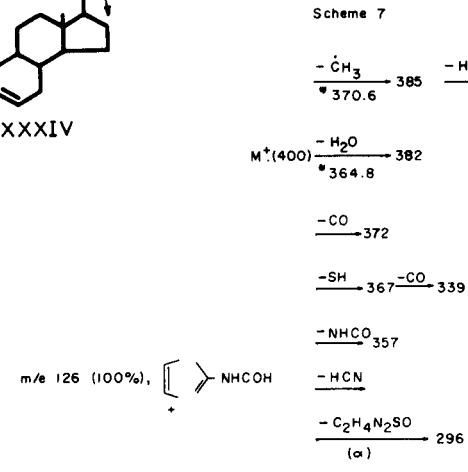
Scheme 6



$C_{21}H_{30}N_2OS$ (MW 358)



Scheme 7

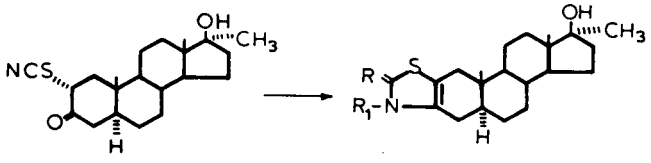


$C_{23}H_{32}N_2O_2S$ (MW 400)

Steroidal Thiazolines.

Steroido[3,2-*d*]thiazolines.

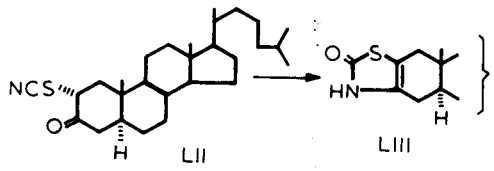
Condensation of 2α-thiocyanatoandrostan-3-one (L) with *o*-toluidinehydrochloride in boiling ethanol produced a 2-androsten[3,2-*d*]thiazoline (37). By this method various *N*-substituted derivatives (LI) were obtained.



L LI

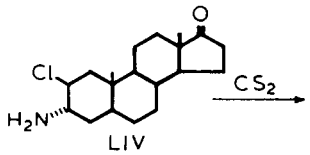
a, R = NH, R_1 = C_6H_5
b, R = NH, R_1 = o-$CH_3C_6H_4$
c, R = NH, R = p-$CH_3C_6H_4$
d, R = NH, R_1 = o-$CH_3OC_6H_4$
e, R = NH, R_1 = p-$CH_3OC_6H_4$
f, R = NH, R_1 = p-ClC_6H_4
g, R = N(CH$_2$CH$_2$)$_2$O, R_1 = H

When the 2α-thiocyanatocholestan-3-one (LII) was heated in dioxane containing aqueous hydrochloric acid, cyclization took place to give oxothiazoline (LIII) (38).

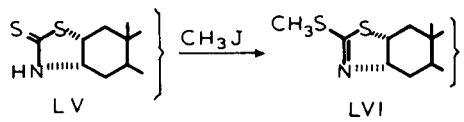


LII LIII

Campbell and Craig (39) reported the synthesis of 2'-thioxo-2β,2', 3β,3'-tetrahydro-5α-androst-2-eno[3,2-*d*]-thiazol-17-one. Starting from 3α-amino-2β-chloro-5α-androstan-17-one (LIV), which on treatment with carbon disulfide followed by methylation afforded LVI.

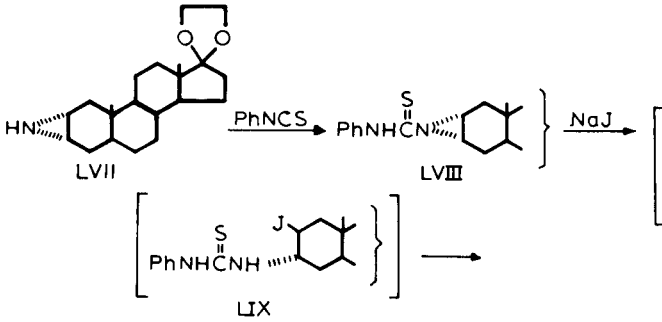


LIV

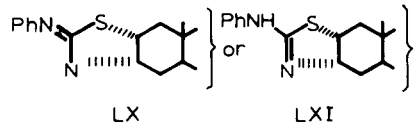


LV LVI

The same authors (39) describe an alternate route to the synthesis of thiazolines from the α-aziridine which involved *N*-thioacyclation with phenylisothiocyanate.



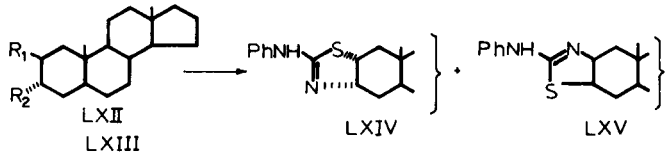
LVII LVIII LIX



LX LXI

α-Aziridine (LVII) with phenylisothiocyanate produced an unstable thiocarbamoyl aziridine (LVIII). Ring expansion of LVIII by sodium iodide in acetone produced by trans-diazial ring opening, the 2β-iodo-compound (LIX) which cyclized to the thiazolidine (LX) or its tautomer (LXI).

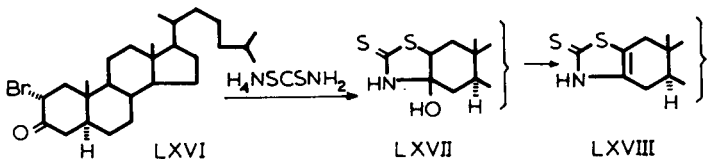
The *vic*-iodoisothiocyanates inseparable mixture (1:7) (LXII) and (LXIII) derived from 5α-androst-2-ene reacts with aniline in the dark, forming compounds LXIV and LXV in a ratio 1:6, which are separated by p]c (40).



LXII LXIII LXIV LXV

R_1 = J, R_2 = NCS
R_1 = NCS, R_2 = J

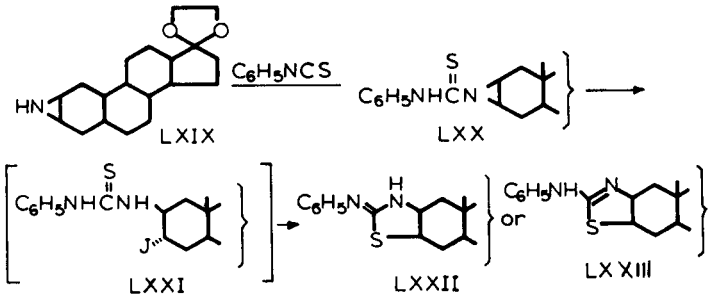
2α-Bromo-cholestan-3-one (LXVI) in condensation with ammonium dithiocarbamate formed cholestanothioxothiazolidine (LXVII), the dehydration of which yielded the corresponding cholestanothioxothiazoline (LXVIII) (41).



LXVI LXVII LXVIII

Steroido[2,3-*d*]thiazolines.

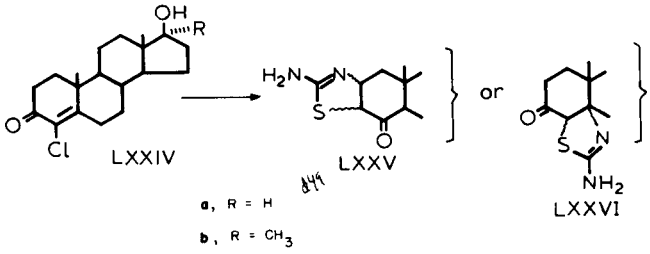
The reaction of 2β,3β-dihydro-5α-androst-2-eno[2,3-β]-azirin-17-one ethylene acetal (LXIX) with phenylisothiocyanate produced an unstable thiocarbamoyl aziridine (LXX), which was transformed by sodium iodide *via* the 3α-iodointermediate (LXXI) into the 2β,3β-thiazolidine (LXXII) or its tautomer (LXXIII) (39).



LXIX LXX LXXI LXXII LXXIII

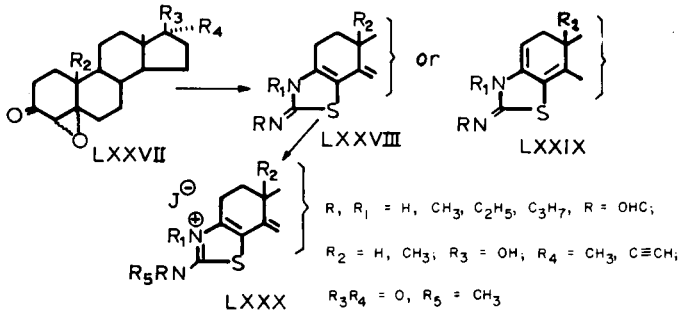
Treatment of the 4-chloro-Δ^4-3-ketosteroids (LXXIV) with thiourea produced compounds LXXV or LXXVI. It is

not known whether the compounds possess [2,3-*d*] or [4,5-*d*] structure (9).

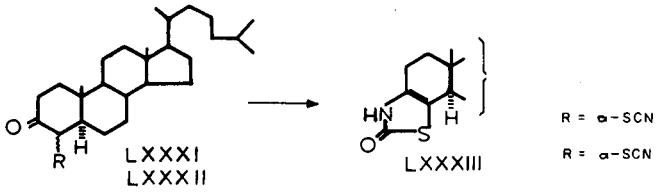


Steroido[3,4-*d*]thiazolines.

Thiazolines derivatives condensed with the steroidal skeleton in position C-3, C-4 are formed by treatment of 4ζ,5ζ-epoxyandrostanes (LXXVII) with thiourea or *N,N*-substituted thiourea (42). Quartenary salts were obtained by the action of methyliodide on LXXVIII or LXXIX.

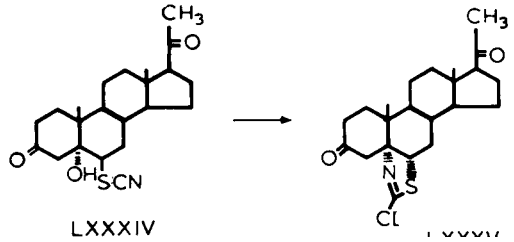


Column chromatography for separation of the mixture 4α-thiocyanato- (LXXXI) and 4β-thiocyanatocholestan-3-one (LXXXII) by alumina led to the isolation of the 2'-oxo[3,4-*d*]thiazoline (LXXXIII) (38).



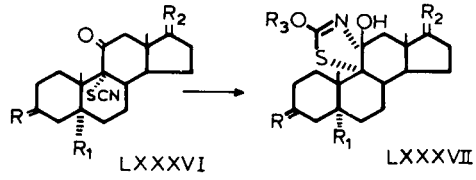
Steroido[5,6-*d*]thiazolines.

Passing of dry hydrogen chloride gas in a cooled suspension of 5α-hydroxy-6β-thiocyanato-5α-pregnane-3,20-dione (LXXXIV) in acetic acid produced, 2'-chlorothiazolino[5,6-*d*]-5α-pregnane-3,20-dione (LXXXV)(43-44).



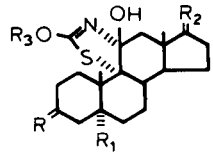
Steroido[11,9-*d*]thiazolines.

The 9α-thiocyanato-11-keto-steroids (LXXXVI) were suitable starting material for the preparation of 2'-ethoxy- or 2'-methoxythiazolino[11α,9α-*d*]steroids (LXXXVII). Treatment of LXXXVI with aqueous methanolic or ethanolic potassium carbonate produced LXXXVII (45-46).



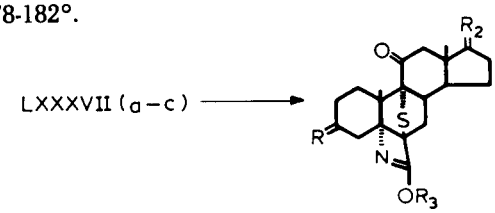
The compounds prepared are presented in Table IX.

Table IX



No.	R	R_1	R_2	R_3
a.	O	Δ^4	O	CH_3
b.	O	Δ^4	β-$COCH_2OH$ α-H	CH_3
c.	O	Δ^4	β$COCH_2OCOCH_3$ α-OH	CH_3
d.	O	Δ^4	O	C_2H_5
E.	O	Δ^4	β-OH	CH_3
f.	O	Δ^4	O	CH_3 Δ_1
g.	β-OH α-H	Δ^4	β-OH α-H	CH_3
h.	O	α-H	O	CH_3

The 2'-methoxythiazolino[11α,9α-*d*]steroids (LXXXVIIa-c) were isomerized to 2'-methoxy-5',6'-dihydro-4'*H*-1',3'-thiazino[4',5',6':5α,10,9α]steroids (LXXXVIII) upon refluxing in a methanolic solution or fusing at 178-182°.



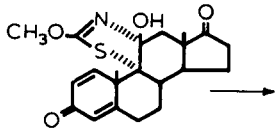
a, R = R_2 = O, R_3 = CH_3
b, R = O, R_2 = β$COCH_2OH$ α OH, R_3 = CH_3
c, R = O, R_2 = β$COCH_2OCOCH_3$ α OH, R_3 = CH_3

This rearrangement involves the rupture of the C-N bond at C-11 of the thiazole ring and the reattachment of the nitrogen bearing function to C-5 with the resultant for-

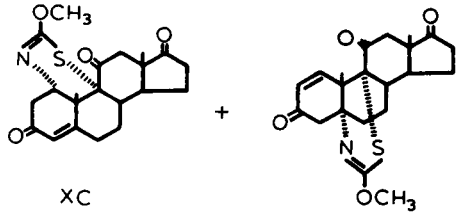
mation of the dihydrothiazine ring.

This isomerization takes place in the presence of an α,β-unsaturated keto-system. This requirement becomes apparent by the refractoriness of 2′-methoxythiazolino-[11α,9α-*d*]-Δ^4-androstene-3ζ,11β,17β-triol during prolonged refluxing with methanol (46).

Isomerization of LXXXIX produced three compounds, which were separated by chromatography on alumina producing a major XC, and a minor product XCI as well as the initial material (46).



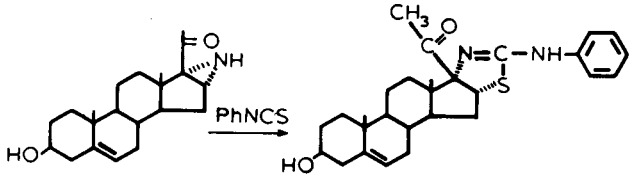
LXXXIX



XC XCI

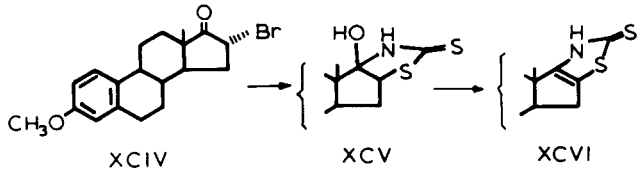
Steroido[17,16-*d*]thiazolines.

The synthesis of 2′-anilino(16α,17α)thiazolino[17,16-*d*]-pregn-5-en-3β-ol-20-one (XCIII) can be effected by the action of phenylisothiocyanate on the 16α,17α-imino-pregn-5-en-3β-ol-20-one (XCII) (47).



XCII XCIII

16α-Bromo-3-methoxyestra-1,3,5(10)-triene-17-one (XCIV) in condensation with ammonium dithiocarbamate formed estratrienothiazolidine (XCV) the dehydration of which produced the corresponding thiazoline (XCVI) (41).



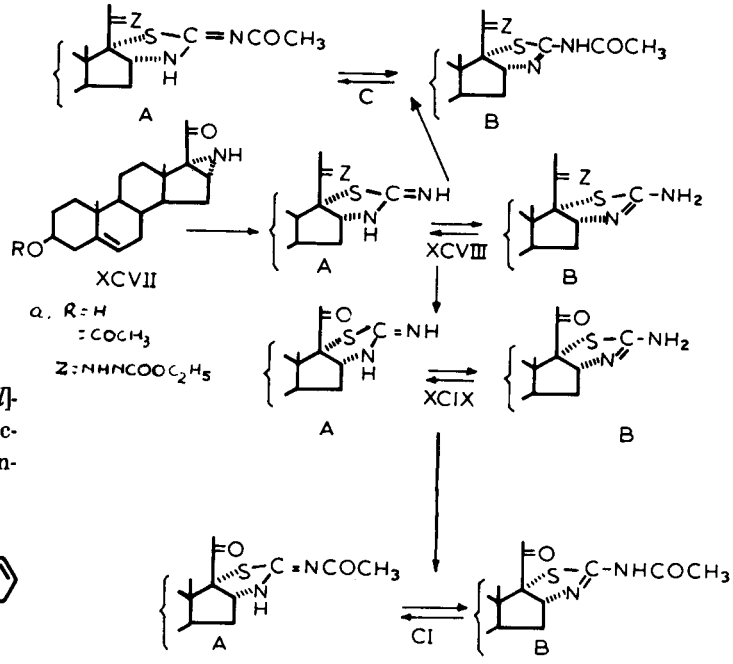
XCIV XCV XCVI

Steroido[16,17-*d*]thiazolines.

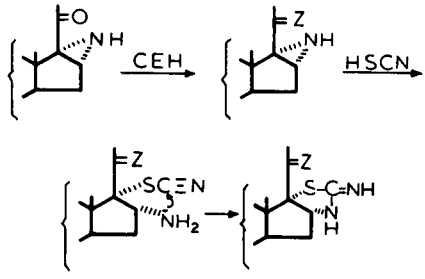
Derivatives of [16,17-*d*]thiazolines were prepared by reaction of 16α,17α-epimino-20-ketosteroids with thiocyanic acid (XCVII) (48) and their 20-carbethoxyhydrazides (CII) with thioacetic acid (49), or thiocyanic acid (50).

The reaction of 16α,17α-epimino-20-ketosteroids with pyridine thiocyanate in the presence of carbethoxyhydrazine proceeds readily at room temperature and it's practically complete in 30 minutes to afford the 2′-amino-[16α,17α-*d*]thiazoline-20-carbethoxyhydrazone (XCVIII), which after heating in an aqueous methanol hydrogen chloride solution yields 20-ketone (XCIX).

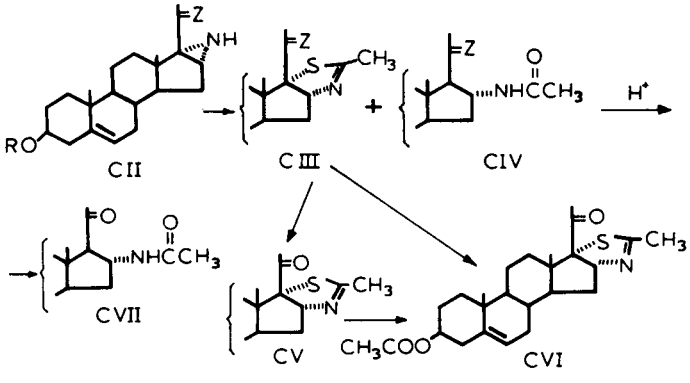
An increase in the reaction time leads to the formation of the thiazoline (XCVIIIA)HSCN salt. Because of the high reactivity of the aminothiazoline grouping selective acetylation of XCVIIIA and XCIXA took place in the *N*-acetates CA and CIA respectively. When the reaction time was increased, under the same conditions, the diacetates CB and CIB were formed (48).



The reaction is realized *via* a number of intermediate steps, one of which is the formation of the 16α,17α-epimino-20-carbethoxy hydrazone. The latter undergoes *cis*-opening with a rupture of the 17-C-N bond, the insertion of SCN group from the α-region of the molecule, and the cyclization of the formed addition product. The ease of cyclization is apparently caused by the *cis*-arrangement of the reacting groups.



In contrast, the reaction of 16α,17α-epiminopregnenolone-3,*N*-diacetate with thioacetic acid yields a complex mixture of products, since the reaction of 16α,17α-epiminopregnenolone-20-carbethoxyhydrazone (CII) with thioacetic acid gave mainly two products: 2'-methylpregn-5-en-3β-ol-20-one[16α,17α-*d*]thiazoline 20-carbethoxyhydrazone (CIII) and 16α-acetylaminopregn-5-en-3β-ol-20-one 20-carbethoxyhydrazone (CIV) (49).



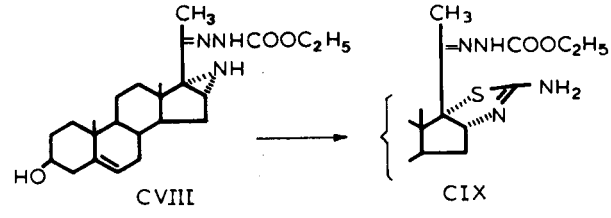
In an aqueous methanol solution the carbethoxyhydrazones (CIII) and (CIV) yield the ketones CV and CVII respectively.

The reaction is sensitive to very small changes in conditions.

Generally an alkaline or acidic medium during treatment favors the formation of CIV. It may be assumed that formation of both reaction products proceeds through one and the same intermediate. The following mechanism may be proposed to explain the observed course of the reaction. The protonated form of the aziridine, under the influence of the hydrazone fragment undergoes cis-scission with the introduction of a $SCOCH_3$ ion at the 17 position to form a 17α-thioacetate-16α-amine. Allowing for the tendency of systems with cis-oriented substituents to undergo acyl migration an intermediate stage such as C, has been postulated, that stabilizes itself by forming the thiazoline (CIII) and the 16α-acetylamine (CIV). In confirmation it may be said that the formation of the C type intermediate both in the acid-catalyzed acyl migration of S-acetylthioamides and in the acid hydrolysis of thiazolines is kinetically demonstrated.

Formation of a thiazoline in this reaction is possible only if the principle of *cis*-scission of the aziridine is observed; therefore, the location of the heteroatoms and the α-configuration of the heterocyclic ring must be assigned by analogy with the above described heterocyclizations that occur under the same conditions (48).

20-Carbethoxyhydrazone (CVIII) reacts extremely readily with thiocyanic acid producing the 2'-aminothiazoline (CIX) (50).

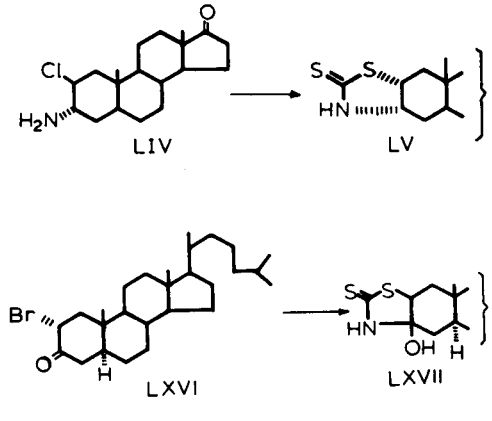


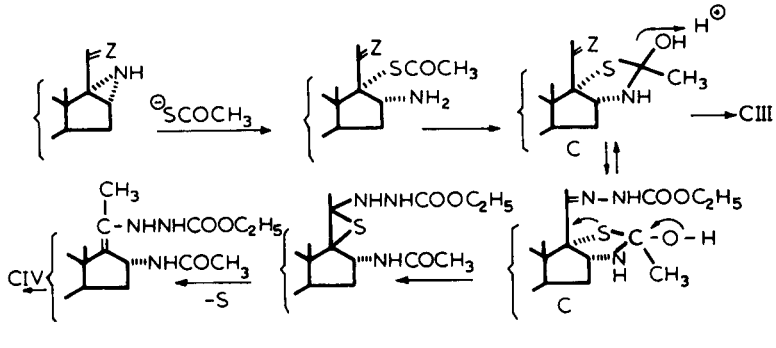
The mechanism for the *cis* opening of 16α,17α-epimino-20-ketosteroids in the presence of a reagent for the CO group, assumes, that the formation of 16α,17α-epiminosteroid 20-carbethoxyhydrazones is the step preceding the *cis* opening of the aziridine.

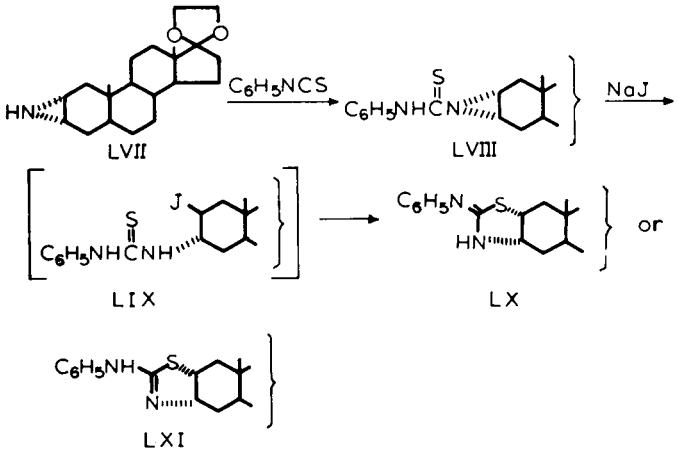
Steroidal Thiazolidines.

Steroido[3,2-*d*]thiazolidines.

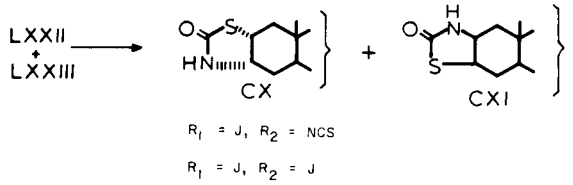
The introduction of the thioxothiazolidine (LV and LXVII) and phenyliminothiazolidine (LX) groupings in the 2,3-position of cholestane (41) and androstane (39) series has been presented in the thiazoline chapter.



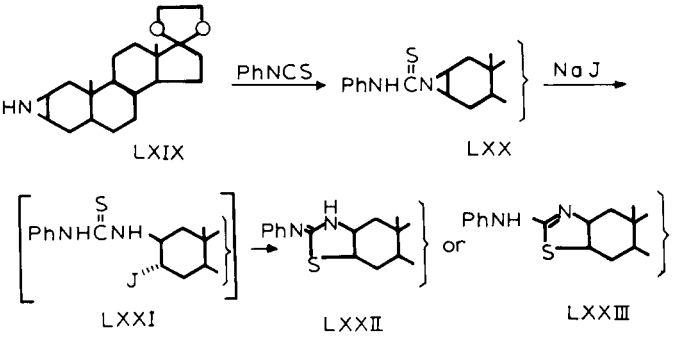




A mixture of androstanethiazolidine-2-ones (CX) and (CXI) in a ratio 1:6.3 separated by plc were formed by heating of the *vic*-isothiocyanates (LXII) and (LXIII) under reflux in the dark with anhydrous methanol in tetrachloroethylene (40).

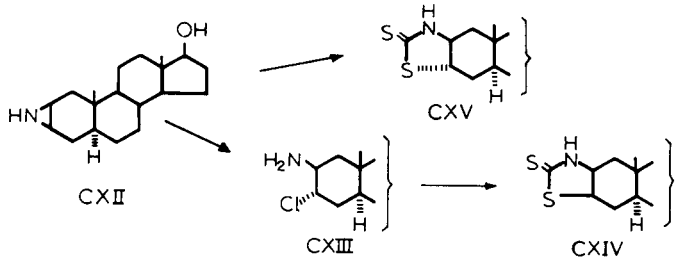


In the thiazoline chapter the synthesis of 2′-phenyliminoandrostan[2β,3β-*d*]thiazolidine (LXXII) (39) has been presented.

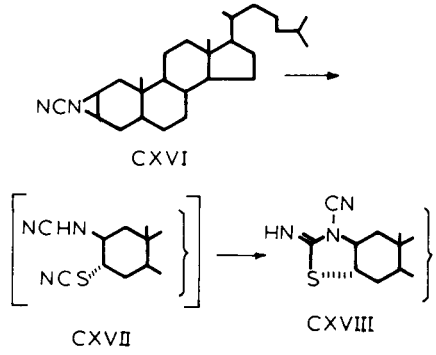


The preparation of 2′-oxoandrostan[2β,3β-*d*]thiazolidine (CXI) was also reported above.

Steroido[2,3-*d*]thiazolidines having a thioxo-group at 2′-position were prepared by Ponsold and Preibsch (51). Thus in the reaction of 3α-chloro-2β-amino-5α-androstan-17β-ol (CXIII) with carbon disulfide and alkali the 17β-hydroxy-2′-thioxo-2′,3′,4′α,5′α-tetrahydro-5α-androstan-2-eno[2β,3β-*d*]thiazole (CXIV) was obtained. Its isomer 17β-hydroxy-2′-thioxo-2′,3′,4′α,5′β-tetrahydro-5α-androst-2-eno[2β,3α-*b*]thiazole (CXV) was also prepared from 2β,3β-imino-5α-androstan-17β-ol (CXII) by the same method.

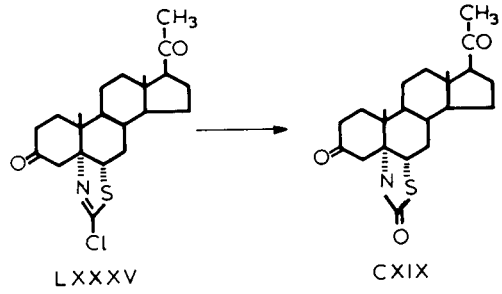


The nucleophilic action of HSCN on 2β,3β-(cyanoimino)cholestan (CXVI) produced the 2′-imino-3′-cyanothiazolidino[2β,3α-*d*]cholestan (CXVIII), by ring closure of the intermediate 2β-(cyanoimino)-3α-thiocyanatocholestan (CXVII) (52).



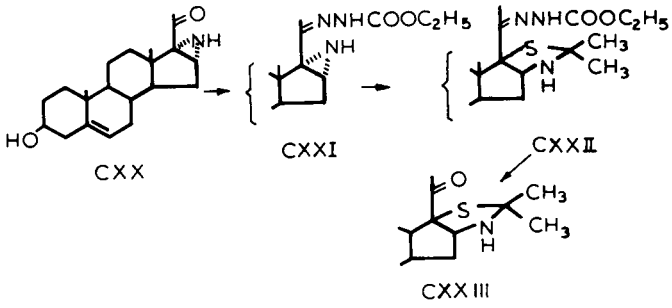
Steroido[5,6-*d*]thiazolidines.

The 2′-chloro[5α,6α-*d*]thiazolidine (LXXXV) on treatment with zinc dust in acetic acid was transformed into 2′-oxothiazolidine (CXIX) (43).



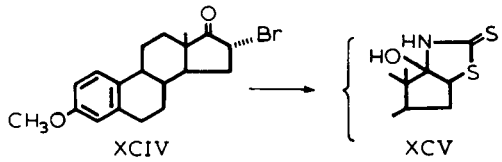
Steroido[16,17-*d*]thiazolidines.

The synthesis of 20-ketosteroid[16α,17α-*d*]-fused to 1,3-thiazolidine was described by Kamernitskii and his coworkers (53). Thus the treatment of 20-carbethoxyhydrazone (CXXI) with hydrogen sulfide in acetone-dioxan afforded 2′,2′-dimethyl-(3β-hydroxy-20-ethoxycarbonylhydrazone-5-pregneno[16α,17α-*d*]-1′,3′-thiazolidine (CXXII), which is cleaved to the free carbonyl compound (CXXIII) with dilute hydrochloric acid in methanol-acetone.



Steroido[17,16-*d*]thiazolidines.

2'-Thioxo-estrathiazolidines (XCV) have been presented in the thiazoline chapter.



Spirothiazolidines.

Saturated 3-ketosteroids (CXXIV) reacted with β-mercaptoethylamine in ethanol, pyridine (54) or in benzene in the presence of *p*-toluenesulphonic acid (55) at room temperature to form steroid-3,2'-spirothiazolidines (CXXV), the acetylation of which afforded the *N*-acetyl-derivatives.

The compounds prepared are listed in Table X.

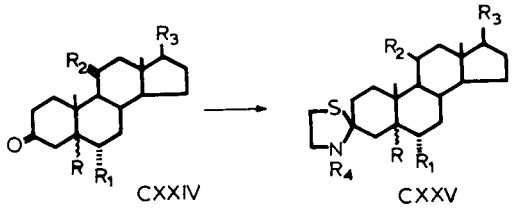
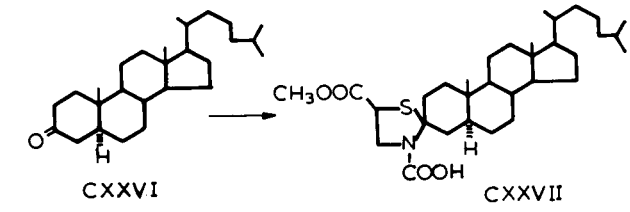


Table X

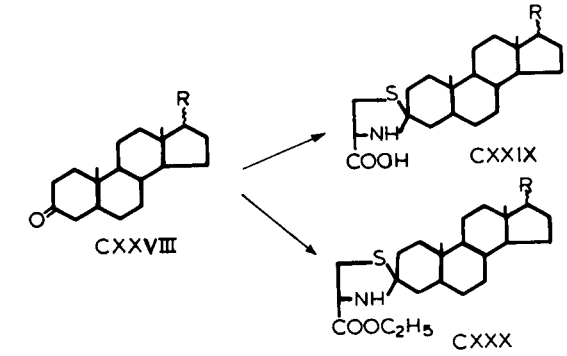
R	R_1	R_2	R_3	R_4	Reference
α-H	H	H_2	C_8H_{17}	H	53,54
β-H	H	H_2	C_8H_{17}	H	53
α-H	H	H_2	C_8H_{17}	$COCH_3$	53,54
Δ^4	OH	H_2	$OCOCH_3$	H	53
Δ^4	$OCOCH_3$	H_2	$OCOCH_3$	H	53
Δ^5	OH	H_2	β-$COCH_3$ α-OH	H	53
Δ^5	H	O	$COCH_3$	H	53

Cholestan-3,2'-spirothiazolidine was also prepared by introduction of hydrogen sulfide in an alcoholic solution of cholestane and ethylenimine (54).

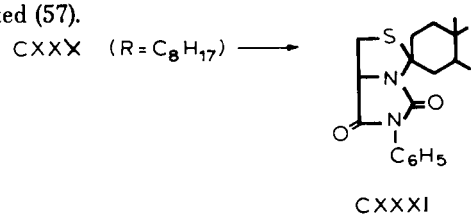
Condensation of 3-cholestanone (CXVI) with cysteine followed by acetylation and diazomethane methylation led to the compound CXXVII (55).



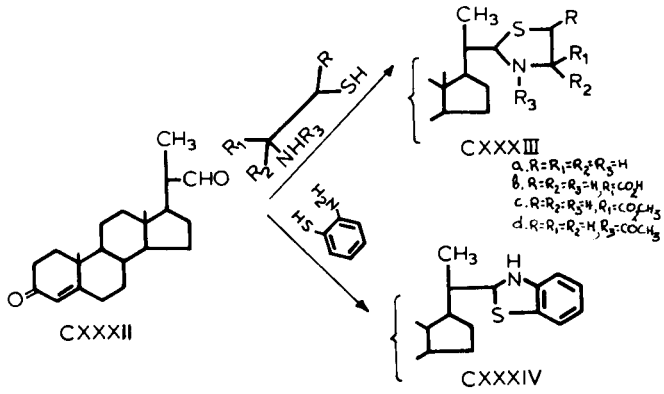
When an alcoholic solution of 3-ketosteroids was added to an aqueous alcoholic solution of L(+)-cysteine hydrochloride or L(+)-cysteine ethyl ester hydrochloride buffered with potassium acetate, spiro[steroid-3,2'-thiazolidines-4'-carboxylic acid] (CXXIX) and spiro[steroid-3,2'-thiazolidines-4'-carboxylic acid ethyl ester] (CXXX) were formed (56-57).



Treatment of spiro[cholestan-3,2'-thiazolidine-4'-carboxylic acid ethyl ester] (CXXX) R = C_8H_{17}) with phenylisocyanate the *N*-phenylhydantoin (CXXXI) was isolated (57).



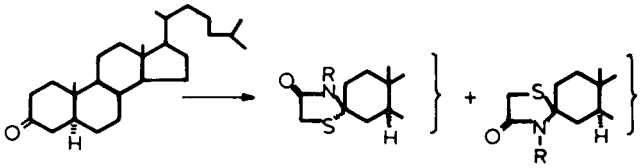
Spiro(steroid)thiazolidines attached to the steroidal side chain were prepared by bringing 3-oxo-pregn-4-ene-20β-carboxaldehyde (CXXXII) to react with various aminothiols (58).



Acetylation of CXXXIIIa produced the *N*-acetyl-derivative CXXXIIId.

Spirothiazolidinones.

Cyclocondensation of 5α-cholestan-3-one (CXXXV) with thioglycolic acid and ammonium carbonate (55) produced two diastereoisomers CXXXVIa and CXXXVIIa of the 4-thiazolidinone.



CXXXV CXXXVI CXXXVII

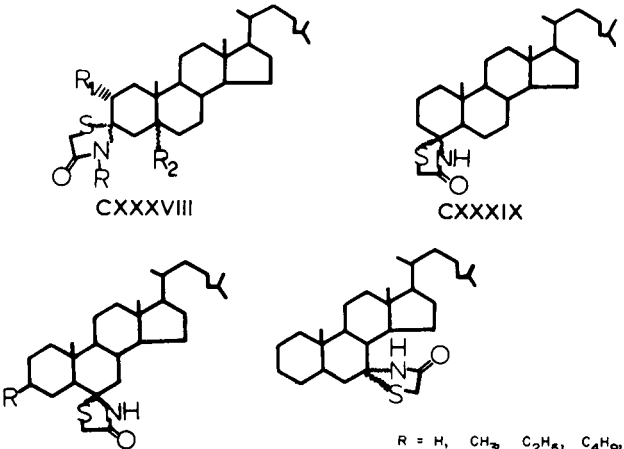
a, R = H
b, R = CH_3
c, R = C_2H_5
d, R = C_4H_9
e, R = $C_6H_5CH_2$
f, R = $COCH_3$
g, R = $COCH_2CH_3$
h, R = COC_6H_5
i, R = C_6H_5

a, R = H
b, R = CH_3
c, R = $COCH_3$

Alkylation or acylation of CXXXVIa produced compounds (XXXVIb-h) whereas the epimer CXXXVIIa produced only (XXXVIIb-c) due to steric hindrance (59).

Compounds (XXXVIe and XXXVIi were also prepared by cyclocondensation of CXXXV with thioglycolic acid and RNH_2 (R = $C_6H_5CH_2$, C_6H_5) (59).

Similarly spirothiazolidinones CXXXVIII, CXXXIX, CXL and CXLI were prepared (60).



CXXXVIII CXXXIX

CXL

R = H, $OCOCH_3$

CXLI

R = H, CH_3, C_2H_5, C_4H_9, $C_6H_5CH_2$, C_6H_5, $COCH_3$, COC_2H_5, COC_6H_5

R_1 = H, $(CH_3)_2CHCH_2CH_2$

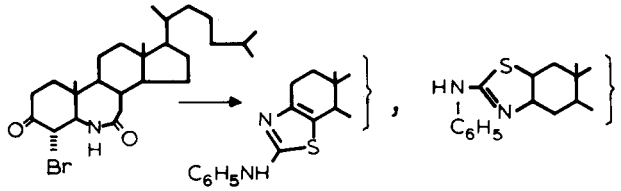
R_2 = α-H, β-H

The compounds formed, exist in two possible steric modifications since the thiazolidine ring is at a right angle to the plane of the steroid nucleus. Consequently an isomer can be considered to have the sulphur atom of the heterocyclic ring above the plane of the nucleus while the sulphur atom of the second isomer would be below the plane of the nucleus (57).

Spiro[cholestanethiazolidin]ones CXXXVIa and CXXXVIIa isomerized under acidic, basic and thermal conditions, whereas *N*-alkyl derivatives CXXXVIb-d and CXXXVIIb did not isomerize under basic conditions (61).

Modified Steroidal Aminothiazoles.

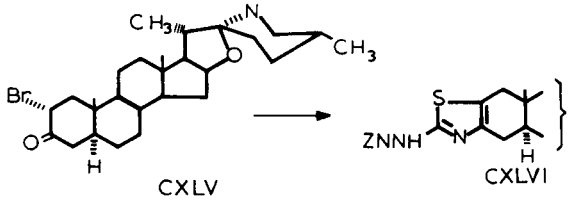
The attachment of an aminothiazole ring to the modified cyclopentanoperhydrophenanthrene system was effected by the reaction of bromoketone (CXLII) with *N*-phenylthiourea producing 2′-phenylaminothiazolo-[3,4-*d*]-6-aza-B-homo-5α-cholestan-7-one (CXLIII) (62).



CXLII CXLIII CXLIV

This compound must be assigned an angular structure CXLIII instead of the linear structure CXLIV (62).

Cyclocondensation of the bromosolasodane (CXLV) with $ZNNHC(S)NH_2$ [Z = cyclopentylidene, $NO_2C_6H_4CH$, $(C_6H_5)_2C$, $C_6H_5CH{=}CHCH$, $C_6H_5CH{=}CHCCH_3$, decahydronaphthylidene, $((CCH_3)_2NCO)C_6H_4CH$, HOC_6H_4CH] produced the corresponding aminothiazole derivative (CXLVI) (63).



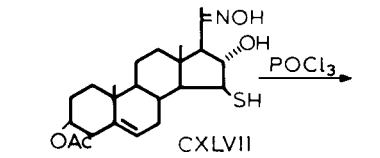
CXLV CXLVI

Reaction of CXLV with thiourea afforded the 2′-amino-thiazolo[3,2-*d*]solasodane (63).

Steroidal Isothiazoles.

Steroido[17,16-*d*]isothiazoles.

The Beckmann rearrangement of 3β-acetoxy-16β-mercapto-17α-hydroxy-5-pregnen-17-one oxime (CXLVII) upon the action of phosphorus oxychloride gives 3β-acetoxy-17α-hydroxy-3′-methylisothiazolino[17,16-*d*]androst-5-ene (CXLVIII) which on dehydration leads to androsteno-[17,16-*d*]isothiazole derivative (CXLIX) (20,64-65), according to the following equation.



CXLVII

CXLVIII CXLIX

Biological Activity of Thiazole-steroids and Their Derivatives.

The broad spectrum of the physiological activity of steroids in which a cyclopentanoperhydrophenanthrene system is condensed with thiazolium or thiazoline ring has drawn the attention of the medicinal chemists to this class of steroids.

The study from the biological aspect of the alkaloids of the steroid series which show interesting physiological activity, showed that many of them, such as cardiac glycosides interact specifically at the cardiotonic steroid binding site of Na^+, K^+-AT face.

Biological tests showed that the 17β-hydroxyandrostano[3,2-*d*]thiazoles (II) possessed anabolic, antigonatotropic and antiestrogenic activity (1). Similar structure compounds showed anabolic, androgeno-activity (2,4-6), lowering the blood pressure of mammals (8) and antiinflammatory activity 0.5 times that of hydrocortisone (11). Aminothiazoles of the structure VIII, have also showed antiinflammatory activity (14). 2'-Aminothiazolo[3,2-*d*]-5α-cholest-2-ene (V) and 2'-aminothiazolo[17,16-*d*]androsta-5,16-dien-3β-ol acetate (XX, R = NH_2) were tested for antimicrobial activity (12).

The cholestan-aminothiazole had no antimicrobial activity against any of the organisms which were tested, while androsten-aminothiazole showed moderate activity. The microorganisms used and the doses for testing are reported below.

Compound (a)

Organism	V	XX (R = NH_2)
Escherichia coli	NI	NI
Pseudomonas aeruginosa	NI	NI
Streptococcus ugalactiae	NI	250
Streptococcus mutans	NI	62.5
Streptococcus aureus	NI	NI
Corynebacterium sp.	1000	62.5
Norcardia asteroides	NI	125
Candida albicans	NI	250
Saccharomyces arevisiae	NI	625

(a) NI stands for not inhibitory at 1000 mg/ml; dilutions tested (mg/ml) 1000, 500, 250, 125, 62.5, 31.25, 15.625, 7.8125.

Compounds of the structure XI are useful as anabolic-androgenic agents (15).

Steroido[12,11-*d*]thiazoles (XVII) produce antigestagenic activity (18).

2'-Substituted thiazolo[17,16-*d*]steroids of the androstanes used as controlling agents for menopausal illnesses, progesterone antagonists, and for hypergonadism control (22-23).

The 3-methoxy-2'-aminothiazolo[17,16-*d*]estra-1,3,5(10),16-tetraene has an important inhibiting action on the hypophysis and is particularly effective for the treatment of the hypophysis overloaded with FSH, caused by castration or menopause (24).

The 17β-(2-substituted-4-thiazolyl)-4-androsten-3-one series (XXX, XXXVIII-XXXIX) have a digitalis-like regulating effect on cardiac arrhythmia and also have hypotensive and pituitary-inhibitory properties (25). In opposite, Shaub and Weiss (26) have reported that in 17β-(2-amino-4-thiazolyl)-4-androsten-3-one derivatives, no activity of significant interest was observed.

However, Japanese workers (27-29, 31-33) have studied the pharmacological properties of 17β-[2-aklylamino- (or 2-arylamino- or 2-*N*,*N*-alkylarylamino-) thiazolyl]androst-4-en-3β,17α-diol and 17β-[2-alkylamino- (or 2-arylamino-or 2-*N*,*N*-alkylarylamino)-4-thiazolyl]androst-4-en-3-one derivatives and found that some of these have digitalis-like properties.

The analogue 17β-(2'-amino-4'-thiazolyl)-5β,14β-androstane-3β,14-diol 3-acetate hydrochloride (XXXII) showed no inotropic activity (30).

The ternorcholanylthiazoles (XLII-XLIII) are useful because of their regulatory effect on the cardiovascular system and their antihormonal activity. They act as antihypotensive agents (34).

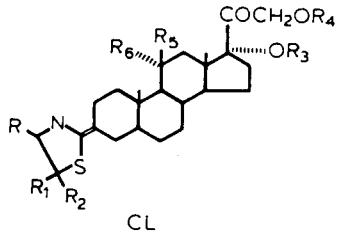
Steroidal thiazolines of the structure LI have showed, anabolic activity (37).

The attempts, so far recorded, to synthesize steroido-[3,4-*d*]-(2'-imino-3'-substituted) thiazolines (LXXVIII) exhibiting contraceptive and antilipogenic activity have met with success, and their quaternary salts (LXXX) possessed antibacterial activity (42).

Steroido-thiazolidine CXXXIIIb was found to possess c-AMP phosphodiesterase inhibitory properties in a minimum inhibitory concentration of 50 mg/ml when tested in vitro by a maximal dose of 100 mg/ml (58).

3β-Acetoxy-3'-methylisothiazolo[17,16-*d*]androsta-5,16-diene (CXLI) is an anti-corpus luteum substance (65).

Transient pro-drug forms of androstane CL, 4,5-didehydro CL, and 1,2,4,5-tetradehydro CL (R_3, R_4 = H, alkyl, R_3R_4 = CR_7R_8, R_7R_8 = alkyl, aryl, cycloalkyl, R_5 = OH, R_6 = H, R_5R_6 = O) were useful in alleviating inflammatory conditions. Compounds CL also were suitable for



CL

topical or oral administration and were efficiently metabolized by the skin or by the gastrointestinal wall in a non-toxic fashion (66).

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