STEROIDS. XIII*

16-Substituted Steroids

By

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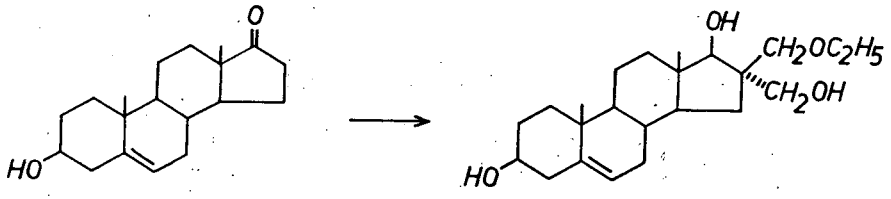
A short survey is given of the investigations concerning the preparation and examination of 16-substituted androstane, estrone and pregnane derivatives, respectively, carried out in recent years in the authors' laboratory.

The present work aimed *inter alia* at the elaboration of simple synthetic methods for the preparation of various 16-substituted steroids. Pregna-5,16-dien-3β-ol-20-one and 17-ketosteroids were used as starting materials.

For this purpose the reaction of 17-ketosteroids with formaldehyde was examined. Instead of the expected hydroxymethylation reaction androst-5-en-3β-ol-17-one (I) transformed under energetic conditions to 16β-ethoxymethyl-16α-hydroxymethyl-androst-5-ene-3β,17β-diol (II) [1].



I *II*

Fig. 1

In case of estrone-3-ethers (III) the 16,16-bis-hydroxymethyl-17-ketone derivative (IV) was the main product [2].

We have elucidated the mechanism and the steric course of the reaction, as well as the route of formation of the by-products.

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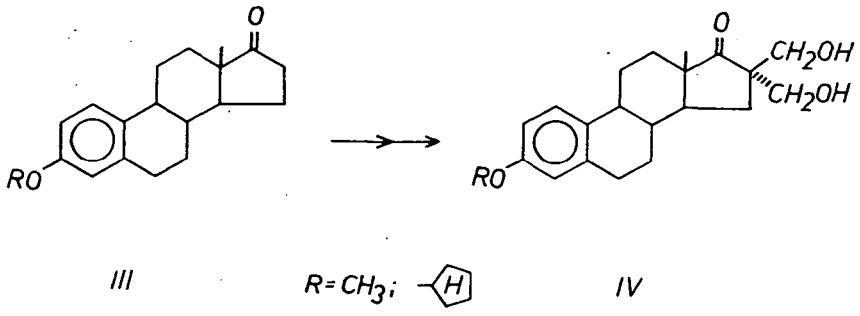


Fig. 2

Starting with androst-5-en-3β-ol-17-one, androst-4-en-3,17-dione, 19-nor-androst-4-en-3,17-dione, estra-1,3,5(10)-trien-3-ol-17-one (herefrom estrone) and estrone-3-ether, respectively, the corresponding 16-hydroxymethylene derivatives were prepared. It was found that the reduction with complex metal hydrides of these 16-substituted-17-ketosteroids gave mixtures of at least two isomeric products [3, 4]. The emergence of isomeric products is explained by the appearance of the new centers of asymmetry at C-16 and C-17.

Since on basis of literary data [5] reduction of the 17-keto group affords, apart from a few exceptions [6], stereoselectively the 17β-hydroxy group, the isomeric products must differ in the configuration of the C-16 carbon atom.

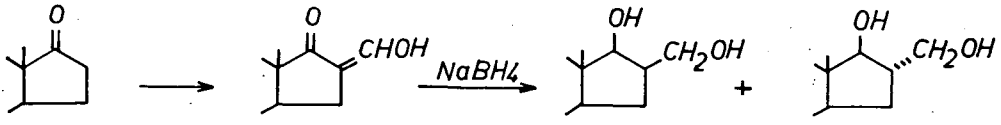


Fig. 3

In determining the configuration of the C-16 carbon atom an exact chemical method was to be sought, which can be generalized for α,γ-disubstituted steroids, as well.

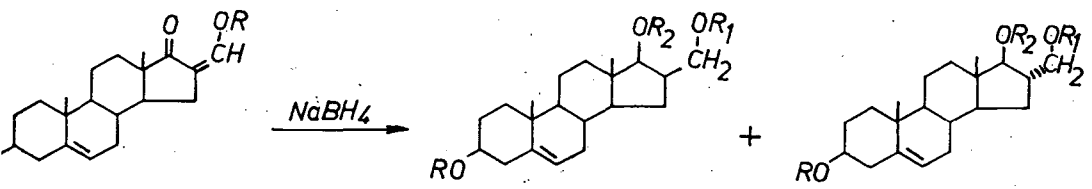
The phenomenon of neighbouring group participation recognized with alicyclic systems [7] was found to be suitable to solve the problem.

This new method of determination of the configuration was employed for 16α- and 16β-hydroxymethylandrost-5-ene-3β,17β-diols (VI, VII). 16-Hydroxymethylen-androst-5-en-3β-ol-17-one (V) prepared according to RUZIČKA [8] and the corresponding diacetate (Va), respectively, gave on reduction with sodium borohydride in alcohol solution the two isomeric 16-hydroxymethyl derivates (VI, VII) as main products.

The chromatographically separated isomers were converted to 16α- and 16β-(*p*-toluenesulfonyloxymethyl)-androst-5-ene-3β,17β-diol diacetate (VIb VIIb).

The two isomeric tosylate-diacetate derivatives (VIb VIIb) were subjected to alcoholysis.

16α-(*p*-Toluenesulfonyloxymethyl)androst-5-ene-3β,17β-diol diacetate (VIIb)



V R=H

Va. R=Ac

VI

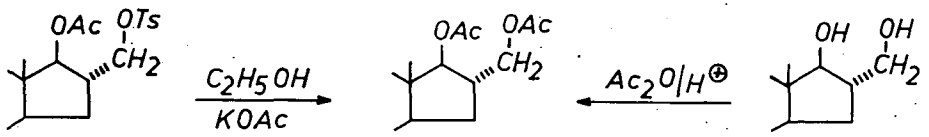
VII

	R	R_1	R_2
VI, VII	H	H	H
a.	Ac	H	H
b.	Ac	Ts	Ac
c.	Ac	Ac	Ac
d.	Ac	Ac	Ts
e.	Ac	Ac	H
f.	Ac	H	Ac
g.	H	Ts	H

Fig. 4

transformed with potassium acetate in abs. alcohol to 16α-acetoxymethyl-androst-5-ene-3β,17β-diol diacetate (VIIc) by S_N2 replacement of the *p*-toluenesulfonyl group, which was also prepared from the parent compound (VII) by acetylation and identified.

On the other hand, solvolysis of 16β-(*p*-toluenesulfonyloxymethyl)androst-5-ene-3β,17-diol diacetate (VIb) in abs. alcohol and in the presence of potassium acetate afforded cyclic acetoxonium ion VIII, which then transformed to the stable orthoester (IX). The cyclic orthoester (IX) was isolated from the reaction mixture and identified with the product obtained from 16β-hydroxymethylandrost-5-en-3β,17β-diol-3-acetate (VIa) with triethyl orthoacetate [3, 9].



VIIb. VIIc. VII

Fig. 5

The latter reaction involving a neighbouring group participation, which can be characterized by the general symbol (AcO-6), could proceed only if the steric orientation of the 16-*p*-toluenesulfonyloxymethyl group was *cis* with respect to the 17β-acetoxy group, *i.e.* it was also a β-substituent.

The supposed intermediary cyclic acetoxonium ion could be isolated in form of the crystalline fluoroborate salt by treatment of the cyclic orthoester (IX) with boron trifluoride etherate.

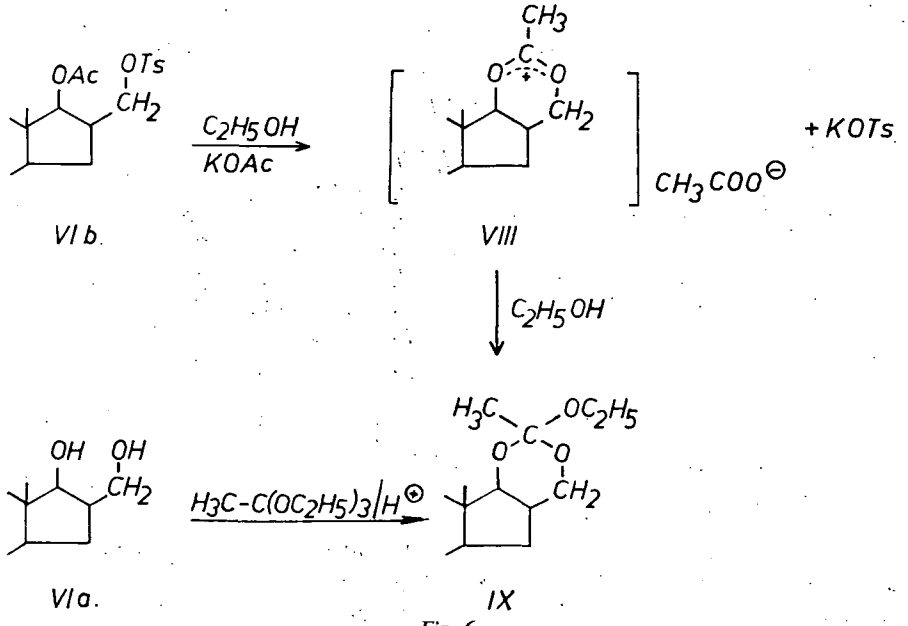
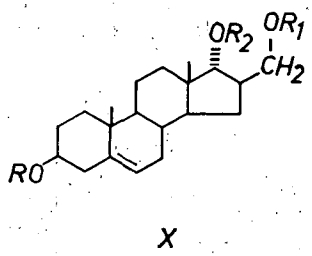


Fig. 6

In the meantime, CORBELLINI *et al.* [4] established the configuration of 16α- and 16β-hydroxymethyl-androst-5-ene-3β-17β-diol (VI, VII) through the corresponding 16α- and 16β-aminomethyl derivatives of known configuration with the same result.

The chromatographic purification of the reduction product of 16-hydroxymethyleneandrost-5-en-3β-ol-17-one (V) revealed the presence of a third isomer, which was also isolated, in addition to the isomeric 16α- and 16β-hydroxymethyl main products (VI, VII). As the 16β,17β (VI) and 16α,17β (VII) isomers of already proved configuration were the main products of the reduction, this third stereoisomeric modification might only be either of the remaining two possible variations, *i.e.* 16β,17α (X) and 16α,17α. In order to establish the configuration of the third isomeric modification by means of the neighbouring group participation method, the mixed *p*-toluenesulfonate-acetate ester (Xb) of the compound was prepared and subjected to solvolysis in alcohol in the presence of potassium acetate. The reaction gave the triacetate (Xc) of the starting compound without formation of the orthoester by neighbouring group participation. On the basis of the reaction the new isomer must be the 16β,17α-derivative (X).

The 16β,17α steric structure rendered probable by the solvolysis reaction was proved by the neighbouring group participation method. Accordingly, 3β-acetoxy-16β-acetoxymethyl-17α-(*p*-toluenesulfonyloxy)androst-5-ene (Xd) was prepared and



X

X	R	R_1	R_2
a.	Ac	H	H
b.	Ac	Ts	Ac
c.	Ac	Ac	Ac
d.	Ac	Ac	Ts
e.	Ac	Ac	H
f.	Ac	H	Ac

Fig. 7

treated with aqueous acetic acid in the presence of potassium acetate, when, probably through acetoxonium ion (XII), 16β-acetoxymethylandrost-5-ene-3β,17β-diol diacetate (VIc) of known configuration resulted.

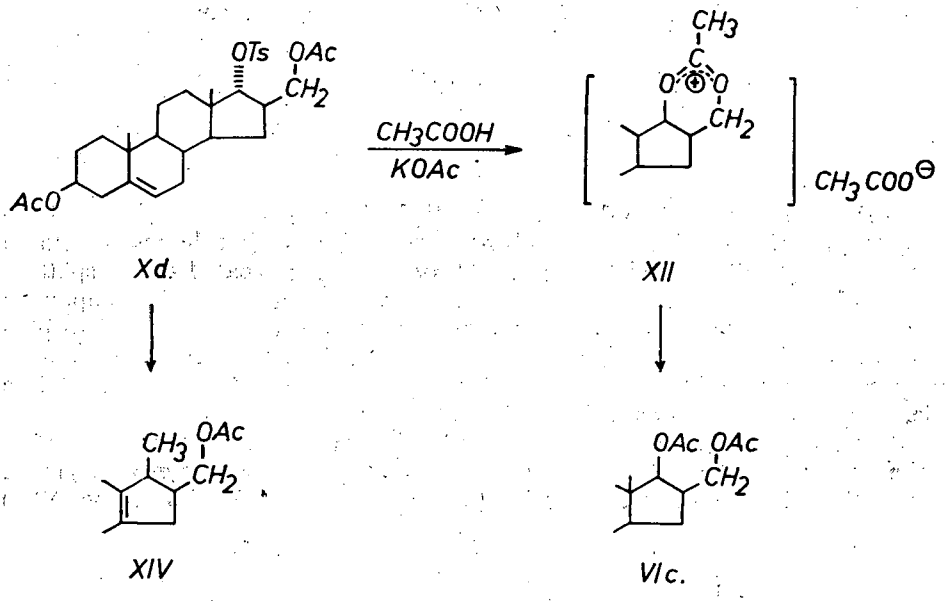


Fig. 8

Efforts were made to prepare also the fourth member, of the series of four isomeric 16-hydroxymethyl-17-hydroxyandrost-5-ene-3β-ol derivatives possible, three of which (VI, VII, X) have already been discussed in the foregoing.

Starting with 16α-acetoxymethylandrost-5-en-3β,17β-diol-3-acetate (VIIe) of

already proved configuration 3β-acetoxy-16α-acetoxymethyl-17β-(*p*-toluenesulfonyloxy)androst-5-ene (VIId) was prepared. The compound VIId was subjected to acetolysis with aqueous acetic acid in the presence of potassium acetate. Under these conditions the 17β-*p*-toluenesulfonyl group was split with participation of the neighbouring 16α-acetoxymethyl group, the process being characterizable by the symbol (AcO-6), to give the fourth isomer of 16α,17α steric structure (XIc).

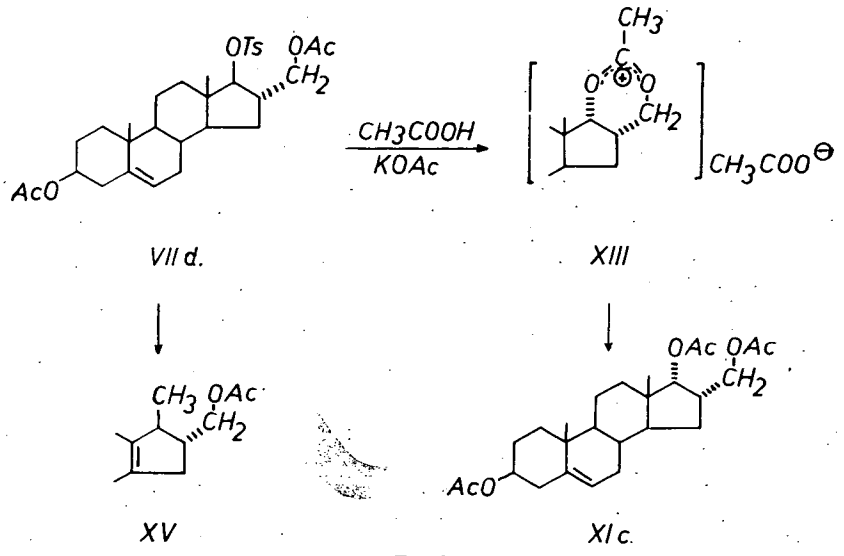


Fig. 9

In the case of 3β-acetoxy-16β-acetoxymethyl-17α-(*p*-toluenesulfonyloxymethyl)-androst-5-ene (Xd) and 3β-acetoxy-16α-acetoxymethyl-17β-(*p*-toluenesulfonyloxy) androst-5-ene-(VIId) the neighbouring acetoxy group participated in the splitting of the *p*-toluenesulfonyl group by means of an S_Ni process. In both cases (compounds Xd and VIId) WAGNER—MEERWEIN rearrangement, too, was experienced to proceed to a small extent, to give compounds XIV and XV. However, neighbouring group participation must have been the faster process, as the triacetate derivatives (VIc, XIc) were obtained as main products.

The WAGNER—MEERWEIN rearrangement became the predominant reaction in the case when the C-16 carbon atom did not bear the acetoxymethyl group. Thus in the solvolysis of 3β-acetoxy-17β-(*p*-toluenesulfonyloxy)androst-5-ene (XVI)

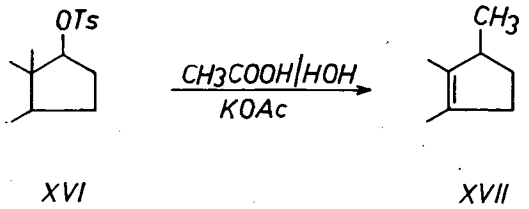


Fig. 10

the replacement of the C-17 *p*-toluenesulfonyl group did not occur at all and the rearrangement product (XVII) was obtained.

The triacetates of the isomeric 16-hydroxymethyl-17-hydroxyandrost-5-ene-3β-ols (VIc, XIc) underwent deacetylation and subsequent stereospecific acyl migration processes during chromatography on alkaline aluminium oxide column. Compounds VIIc and Xc underwent selective deacetylation to give 3,17-diacetates (VIIf, Xf).

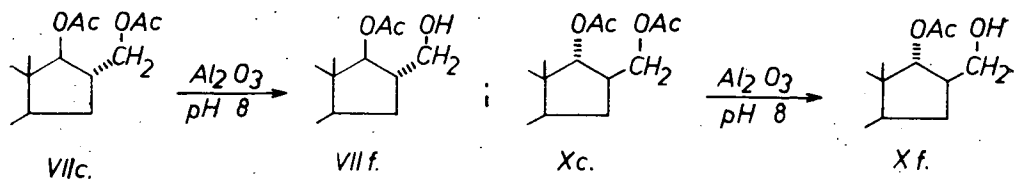


Fig. 11

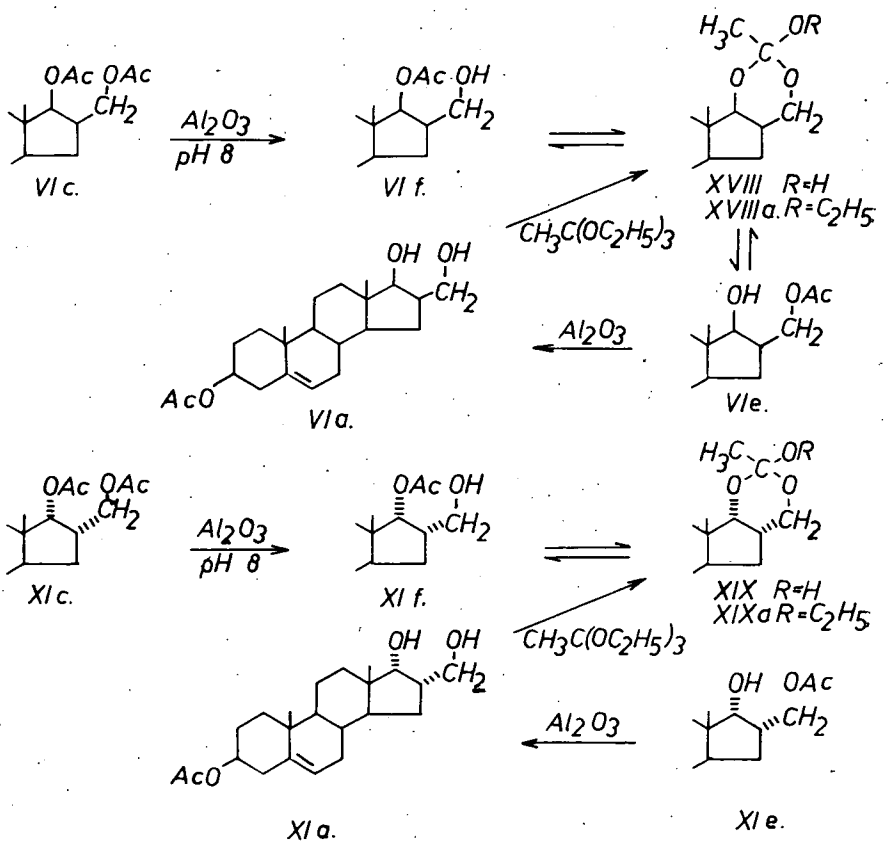


Fig. 12

In the case of the *cis* 16β,17β (VIc) and 16α,17α (XIc) isomers the removal of the acetyl group from the primary hydroxyl was followed by secondary acyl migration to the primary hydroxyl liberated in the preceeding step and a further deacetylation at this site. Thus the reaction gave compounds VIa and XIa containing free hydroxyl groups at the ring D.

Cyclic ortho-acid derivatives (XVIII, XIX) were supposed to be the intermediary products of the acyl migration. Acidic and alkaline hydrolysis of cyclic orthoesters (XVIIIa, XIXa) obtained from XIa and VIa, respectively, and triethyl orthoacetate resulted in the above two pair of acetates (VIe, XIe, VIf, XIf).

Beside the stereospecific acyl migration reaction occurring with the *cis* 16β,17β (VIc) and 16α,17α (XIc) isomers, as well as the absence of this reaction with the *trans* 16α,17β (VIIc) and 16β,17α (Xc) isomers, the following reaction was found to prove the configuration of these compounds: the mixed *p*-toluenesulfonate-acetate esters (VIb, XIb) transformed in aqueous alkaline medium by means of a neighbouring group participation characterizable by the general symbol ($0^{(-)}-4$) to cyclic oxetane derivatives (XX, XXI), while under the same conditions the *trans* 16α,17β (VIIb) and 16β,17α (Xb) isomers underwent hydrolysis [10].

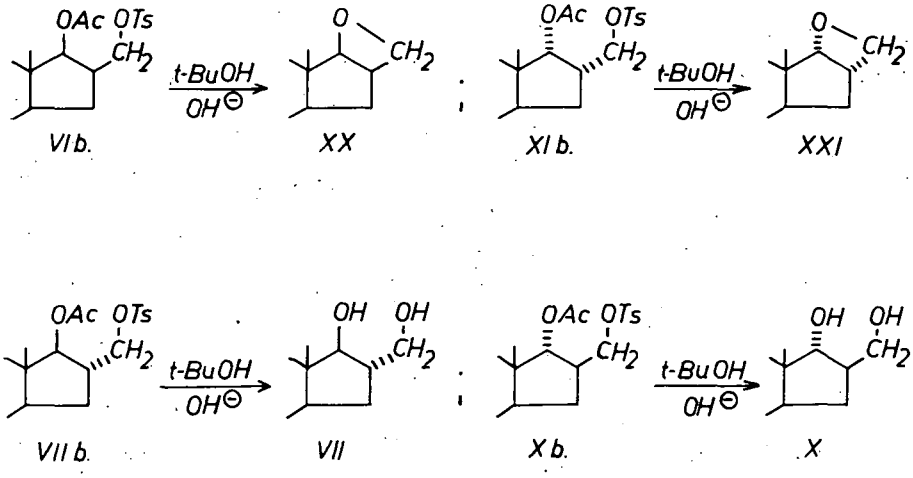


Fig. 13

With the four 16-hydroxymethyl-17-hydroxy isomers of proved steric structure in hand, we succeeded in elucidating the steric structure of some further 16-substituted steroids containing other substituents.

With the products of MANNICH reaction of 17-ketosteroids [12] it was experienced that reduction with sodium borohydride of the 16-piperidinomethyl hydrochloride derivative (XXII) gave two isomeric products (XXIII, XXIV). These were actually 16-isomers, as was proved by a transformation of the 16-tosyloxymethyl isomers (VIg, VIIg) which did not affect the center of asymmetry [14].

Since the isomerization may proceed in the ketone phase only, the isomerization in alkaline medium of various ketone bases of known steric structure originating from different reactions was examined [11]. It was found that the 16β-substituted

ketone (XXVI) obtained from the 16-methylene derivative (XXV) by addition of piperidine [13] undergoes isomerization to the corresponding 16α derivative (XXVII), while the reverse reaction could not be induced.

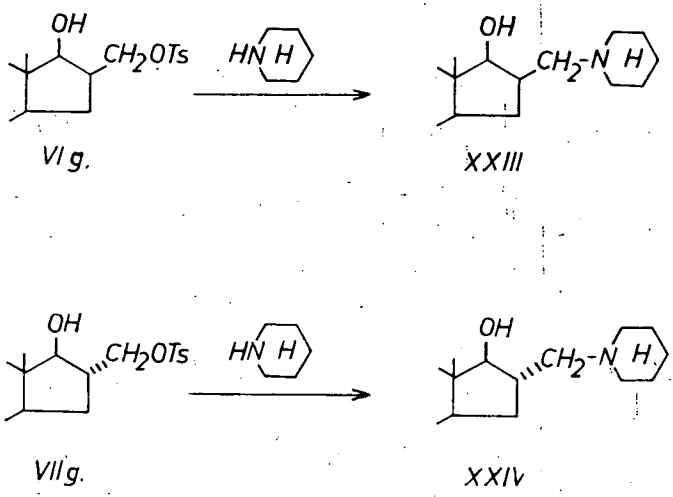


Fig. 14

The ketone base (XXVII) isolated from the product of the MANNICH reaction contains a 16α-substituent [13]. Since it is incapable of isomerization, the 16β-isomer can appear in the reduction of the MANNICH salts only if it was present originally in the mixture, that is to say the MANNICH reaction of 17-ketosteroids is not a stereo-

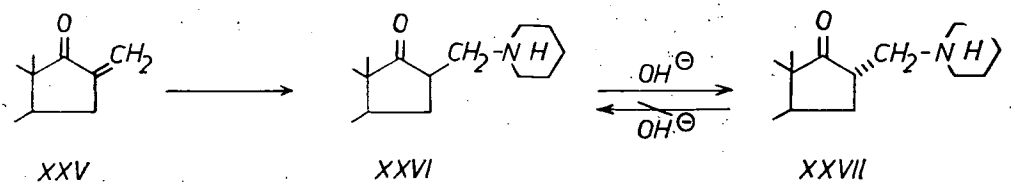


Fig. 15

selective process, but it affords a mixture of isomers, of which the 16β-derivative transforms *via* a stereospecific isomerization to the corresponding 16α derivative during the alkaline workup of the reaction mixture.

In the following a survey is given of our results in the field of pregnane derivatives.

As it is known from literature, several effective 16-substituted pregnane derivatives have been prepared and described. Therefore we examined the transformation of 3β-acetoxy-pregna-5,16-dien-20-one (XXVIII) available from diosgenine or solasodine by degradation to various 16-substituted pregnane derivatives. Particular attention was given to examining the addition of hydrogen cyanide to the C_{16}—C_{17} double bond as well as to the stereochemistry of the resulting 16-nitrile

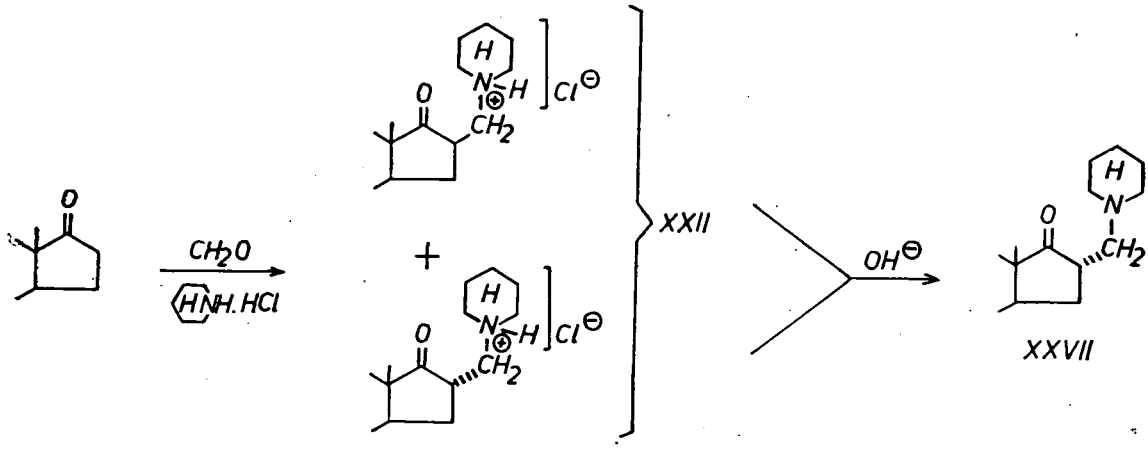
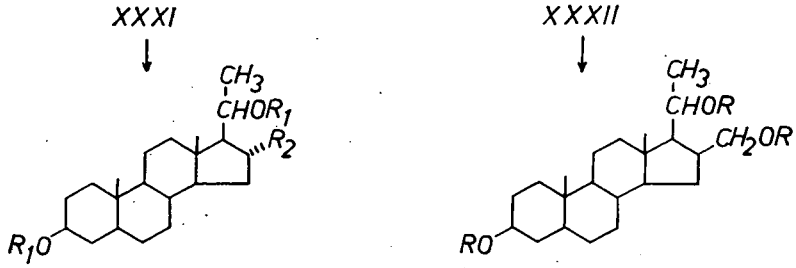
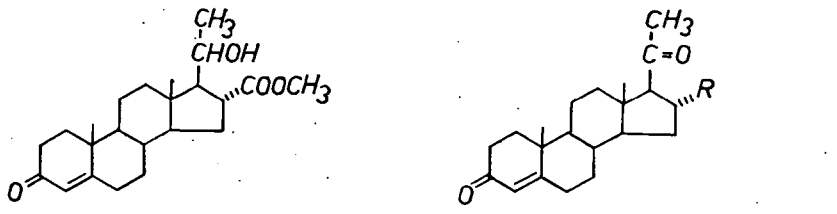


Fig. 16



		R_1	R_2
XXXIV	a.	Ac	COOH
	b.	Ac	$COOCH_3$
	c.	H	CH_2OH
	d.	H	$CH_2OCOC_6H_5$
	e.	H	$COOCH_3$

		R
XXXIII	a.	H
	b.	Ac



XXXVI	a.	$COOCH_3$
	b.	CH_2OH
	c.	CH_2Cl
	d.	$CH_2OCOC_6H_5$

Fig. 17

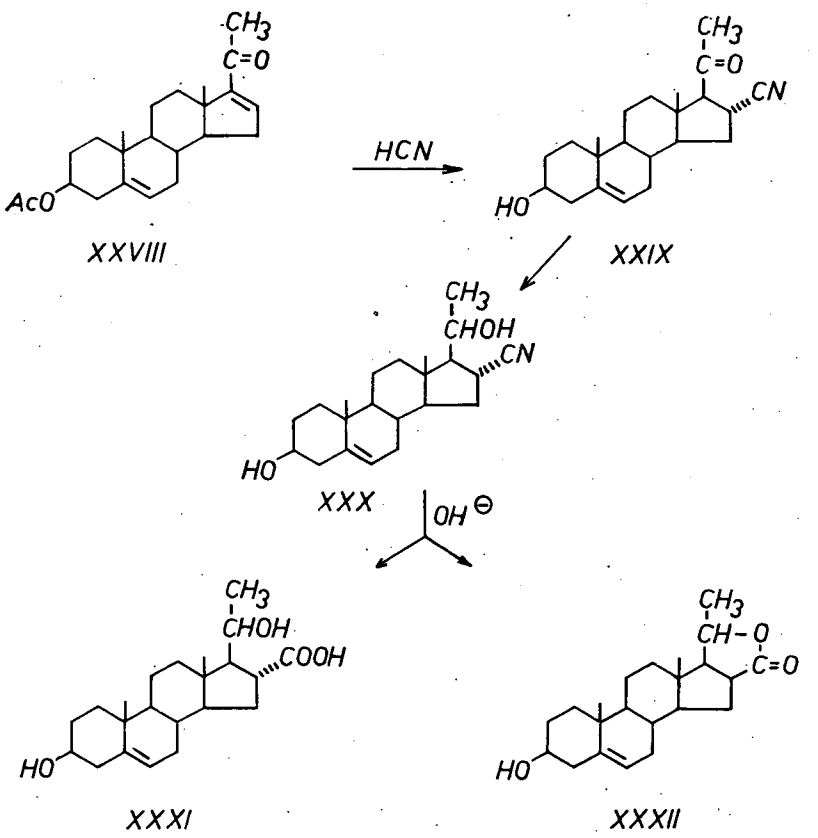


Fig. 17

and the products available therefrom by alkaline hydrolysis [15—30]. 3β-Hydroxy-16α-cyanopregn-5-en-20-one (XXIX) was prepared by the method of ROMO [15], MAZUR and CELLA [17]. The compound (XXX) was reduced and subjected to alkaline hydrolysis to give two isomeric 16-carboxylic acids, one of them in form of a lactone (XXXI, XXXII), respectively. From these the 16-hydroxymethyl, acetoxymethyl, benzoyloxymethyl, chloromethyl and methoxycarbonyl derivatives of pregnenediol, pregnenolone and progesterone (XXXIII—XXXVI), respectively, were prepared [31].

In addition, in order to obtain various 6,16-disubstituted pregnane derivatives a number of 5,6- and 16,17-epoxides were synthesized (XXXVII—XLIII) and their steric structure examined [32].

Experiments on dehydrogenation of pregnane derivatives by means of various quinones were also made. Depending on the steroid molecule, the quinone reagent, and the experimental conditions, the reaction gave different unsaturated compounds (XLIV—XLIX) [33].

A procedure was elaborated for the transformation of solasodine (XLIXa) by epoxidation (L) of the diacetate (XLIXb), followed by ring-opening with hydro-

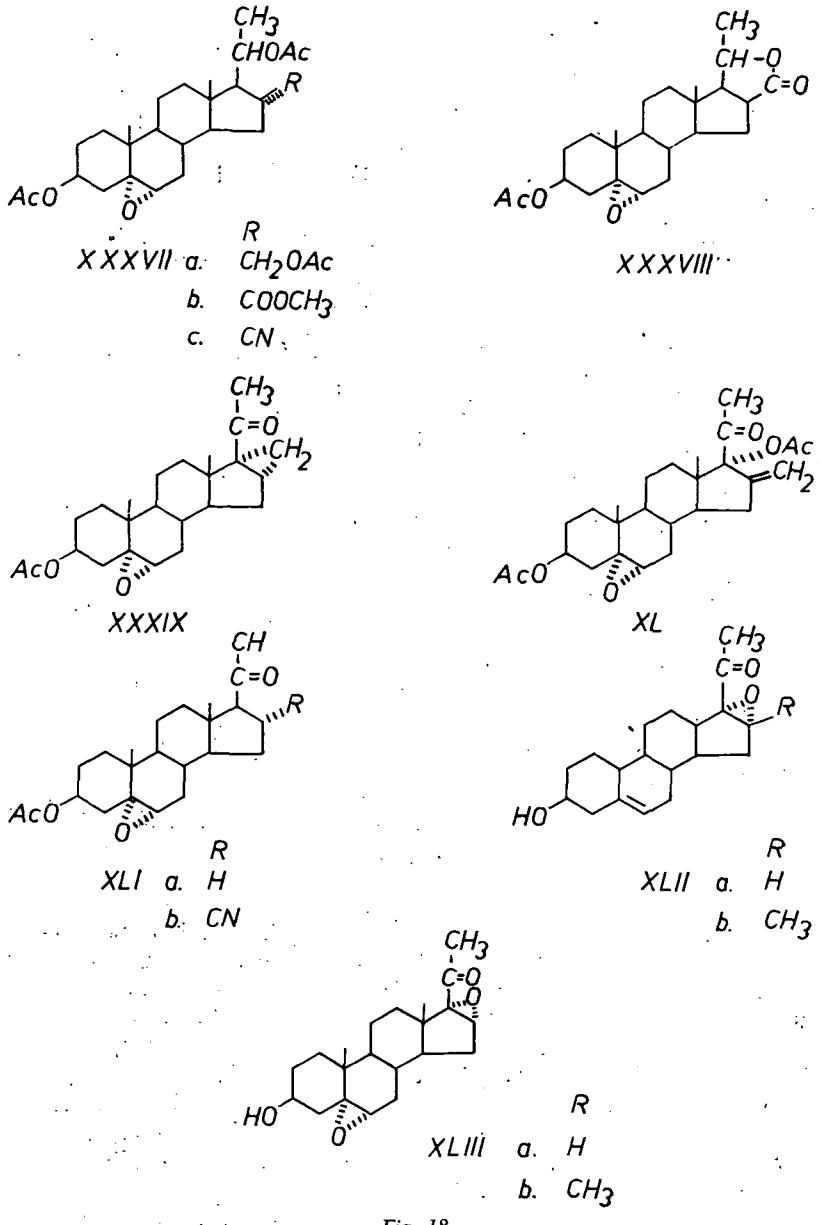


Fig. 18

chloric acid and oxidation of the side-chain by known method. This way 3β-acetoxy-6-chloropregna-5,16-dien-20-one (LII) was obtained [34].

In the foregoing we have reported the alkaline hydrolysis of 3β,20β-dihydroxy-16α-cyanopregn-5-ene (XXX), which gave 16α-carboxylic acid (XXXI) and 16β-

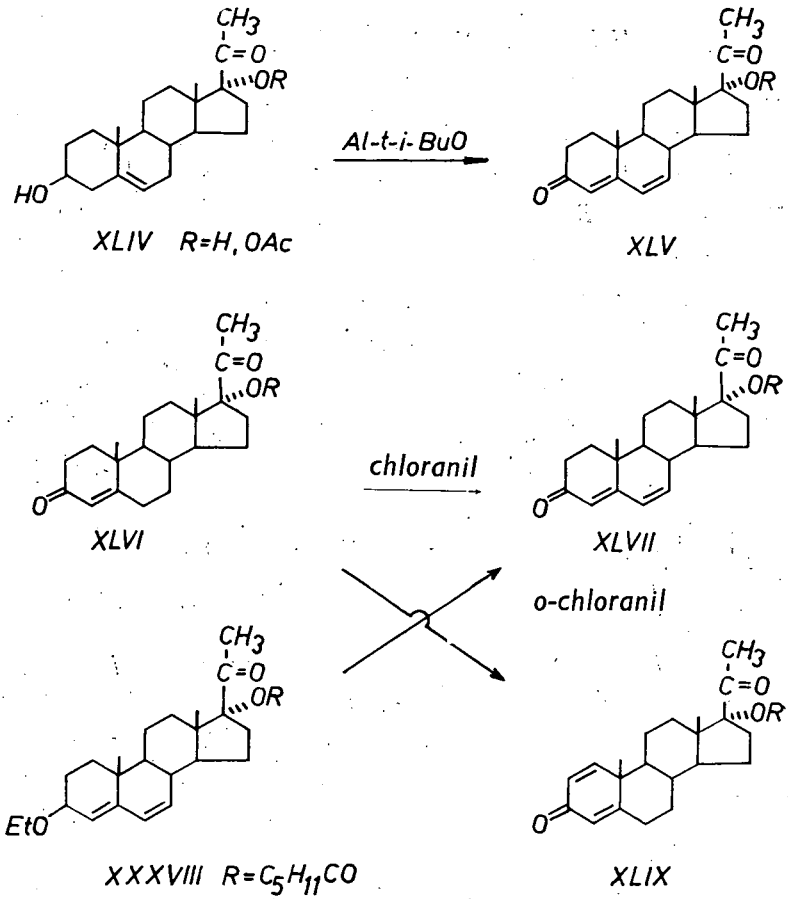


Fig. 19

lactone (XXXII). Several publications deal with the isomerization [15—31, 37, 38] and since our further investigations required a knowledge of the stereochemistry of the reaction proceeding at ring D of pregnane derivatives, a thorough examination of the problems was undertaken [34 — 36, 39].

We pointed out that the isomerization occurred during the alkaline hydrolysis of the nitrile (XXX) in a phase of the hydrolysis, when the molecule still contains nitrogen, as the end-products do not interconvert into one another under alkaline conditions.

One of the intermediary products of the reaction, a 16α-carboxamide (LIII) could be isolated and its structure was proved by synthesis. The hydrolysis of this carboxamide afforded the same products as that of the parent nitrile (XXX).

On the contrary, hydrolysis of the 20-ketonitrile (XXIX) gave the 17α (*iso*)-pregnane derivative (LIV) [17]. Starting with this compound the isomeric 16β-

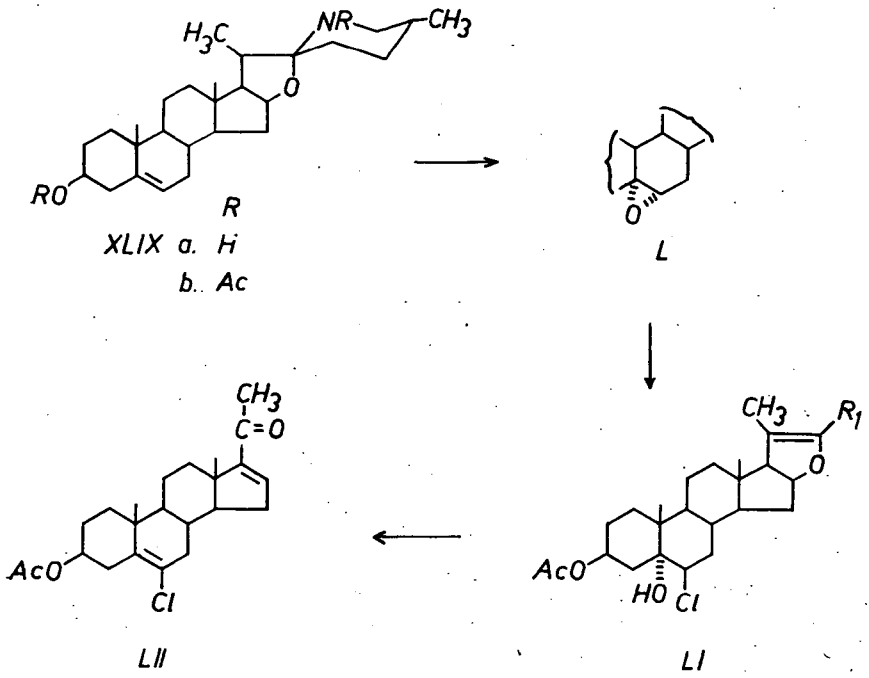

H3C
NR
CH3
O
RO
R
XLIX a. H
b. Ac
L
CH3
R1
O
AcO
HO
Cl
LI
CH3
C=O
AcO
Cl
LII

Fig. 20

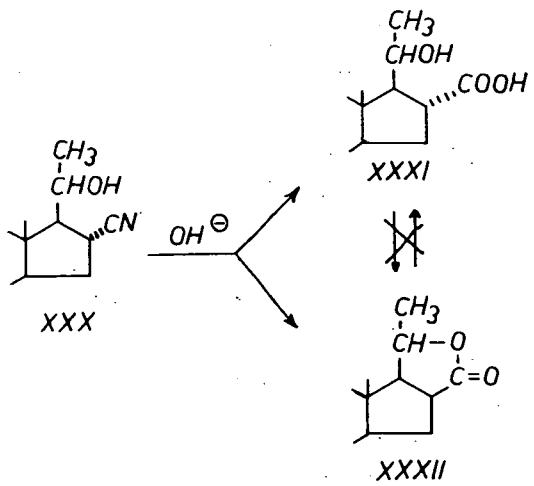

CH3
CHOH
CN
XXX
OH⊖
CH3
CHOH
COOH
XXXI
CH3
CH–O
C=O
XXXII

Fig. 21

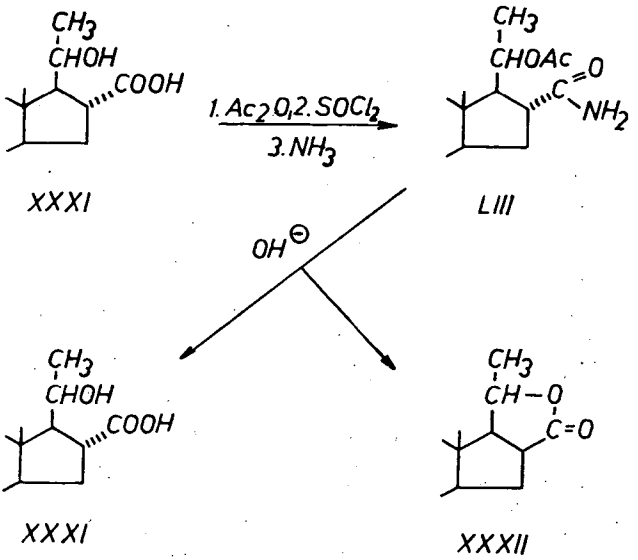

CH3
CHOH
COOH
XXXI
1. Ac2O, 2. SOCl2
3. NH3
CH3
CHOAc
C=O
C
NH2
LIII
OH⊖
CH3
CHOH
COOH
XXXI
CH3
CH—O
C=O
XXXII

Fig. 22

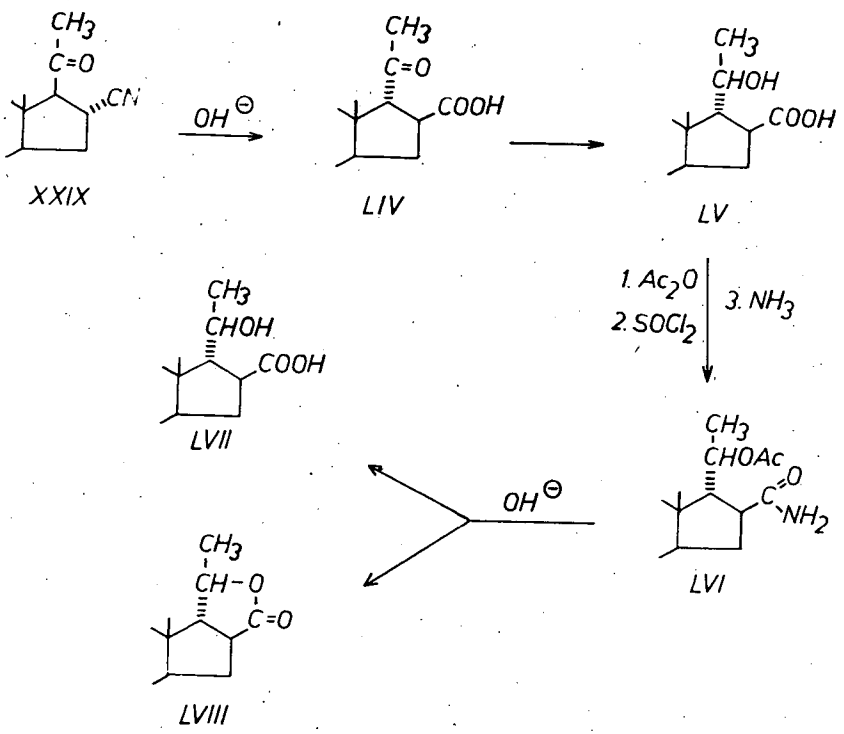

CH3
C=O
CN
XXIX
OH⊖
CH3
C=O
COOH
LIV
CH3
CHOH
COOH
LV
1. Ac2O
2. SOCl2
3. NH3
CH3
CHOH
COOH
LVII
CH3
CHOAc
C=O
C
NH2
LVI
OH⊖
CH3
CH—O
C=O
LVIII

Fig. 23

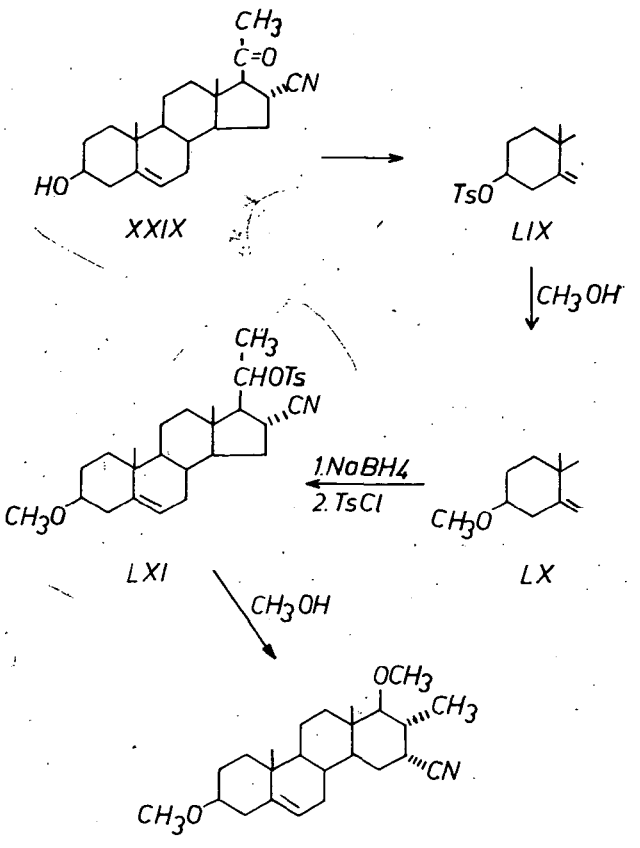


Fig. 24

carboxamide (LVI) could be synthesized, which similarly to the 16α-epimer gave two products (LVII, LVIII) on alkaline hydrolysis.

Since the 20-ketonitrile (XXIX) transforms rapidly to the 17α-derivative without isomerization at the C_{16} carbon atom, the 20-ol affords two isomeric products (XXX, XXXI) at a slower rate, moreover the amide acetate of the 17α-20-ol (LVI), too, undergoes isomerization on alkaline hydrolysis to give two products (LVII, LVIII), the conclusion was drawn that the C_{20}-hydroxyl group affects the reaction by means of neighbouring group participation. In order to screen the effect, attempts were made to prepare the 20-methoxy-nitrile and to examine its hydrolysis. Starting with the 3-tosyloxy derivative (LIX) the 3-methoxy compound (LX) was obtained by methanolysis. Reduction and subsequent tosylation afforded the 3-methoxy-20-tosyloxy derivative (LXI), which, treated with methanol, resulted however, in the D-homoderivative (LXII), probably *via* a WAGNER—MEERWEIN rearrangement.

In another approach to the synthesis of the 20-methoxy derivative (LXII), the reduced 3-methoxy derivative (LXa) was treated with diazomethane in the presence

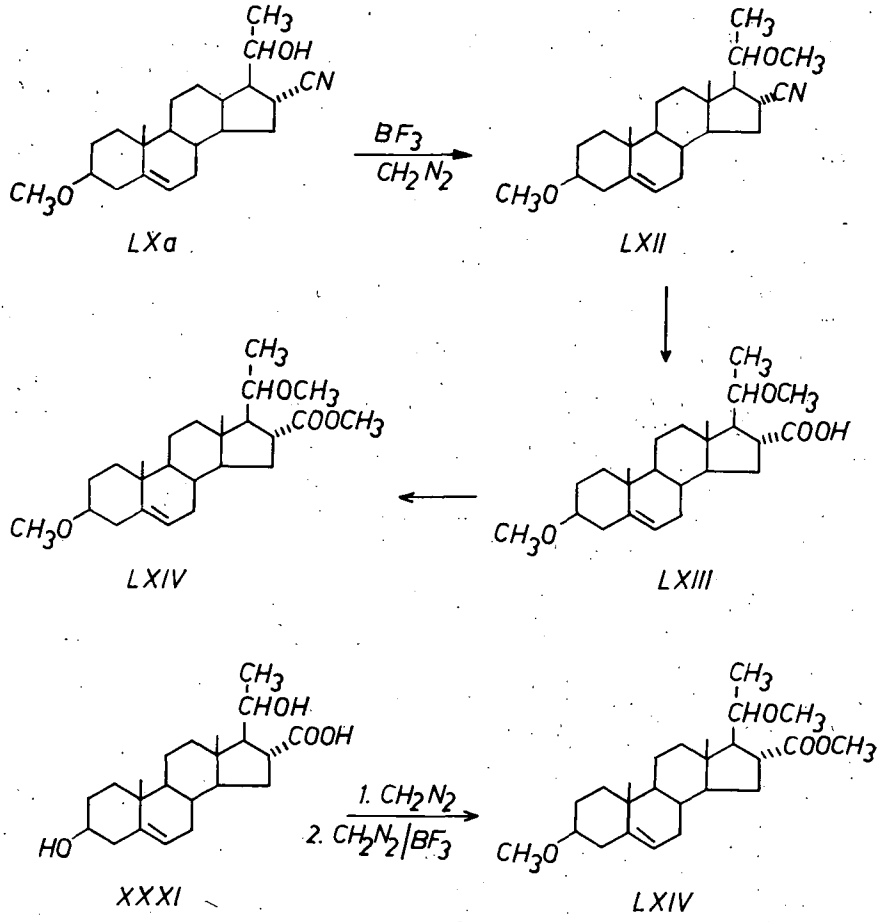


Fig. 25

of boron trifluoride, according to KASAL [40] and thus the 3,20-dimethoxy derivative (LXII) was obtained. Alkaline hydrolysis of the latter gave, after a long reaction time, a carboxylic acid (LXIII) only, the identification of this compound by synthesis in form of the methyl ester (LXIV) is in progress.

* * *

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СТЕРОИДЫ XIII

Стероиды, Замещенные в Позиции 16

И. Вейс-Винце, Г. Шнейдер, М. Халмош, Й. А. Сабо, К. Ковач

Авторы дали краткий обзор о своих результатах, которых достигли в последних годах в области синтеза и исследования 16-замещенных стероидов в ряде андростана, эстрона и прегнана.