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EFFECT OF 17-SUBSTITUENT IN BASE-CATALYZED EQUILIBRATION OF STEROIDAL 2β,3β-DISUBSTITUTED 6-KETONES

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Relative stability of 5α- and 5β-isomers in the series of 2β,3β-disubstituted 6-ketosteroids was established by ORD analysis and preparative separation of mixtures obtained on base-catalyzed equilibration. The equilibrium was found to be influenced by the character of the $C_{(17)}$-substituent; introduction of an oxygen function (a keto group or hydroxyl) results in a marked change in the equilibrium constant as compared with the equilibrium constants of compounds lacking any substituent or bearing a cholestane side chain, a methylene or a nitrate group at this position. The effect of the substitution at $C_{(17)}$ cannot be explained in terms of conformational transmission or by simple transmission of polar effects.

During the course of an investigation[1] how the antisclerotization activity of steroidal 2β,3β-dihydroxy 6-ketones may be influenced by the structure of the 17-side chain, we found that the character of the side chain is also reflected in the composition of the mixture of 5α- and 5β-isomers resulting from the base-catalyzed equilibration of these ketones.

First observation of this kind was made on 2β,20β-diacetoxy-3β-hydroxy-5α-pregnan-6-one[2] which, on hydrolysis with potassium hydrogen carbonate in boiling methanol, practically does not change its configuration at $C_{(5)}$. On the other hand, an analogous treatment of 2β-acetoxy-3β-hydroxy-5α-androstan-6,17-dione[3] leads to a mixture of 5α- and 5β-isomeric 6-ketones. In an attempt to find out which factors are responsible for the observed differences, we investigated the base-catalyzed equilibration of a series of 2β,3β-dihydroxy 6-ketones using aqueous–methanolic solution of potassium carbonate at 33·5°C and examined the dependence of the equilibration constant on the character of the $C_{(17)}$-substituent. The composition of the equilibrium mixtures was determined by means of ORD measurements; in several cases these determinations were parallelled by preparative separation. Starting material for the preparation of 5α- and 5β-isomeric 2β,3β-dihydroxyandrostan-6-ones *Vb* and *VI* was 6β-hydroxy-3α,5-cyclo-5α-androstan-17-one (*I*) (refs[5,6]) which

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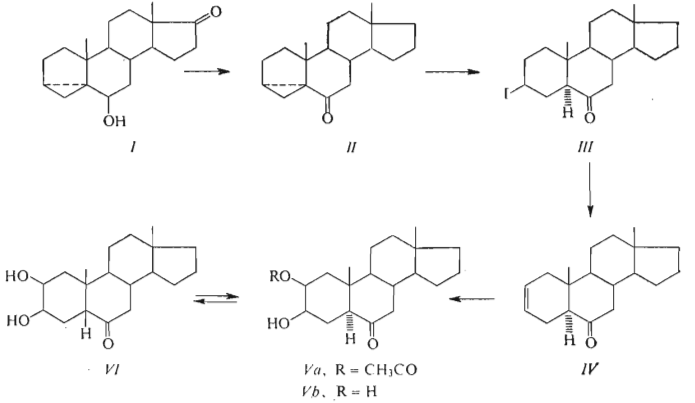
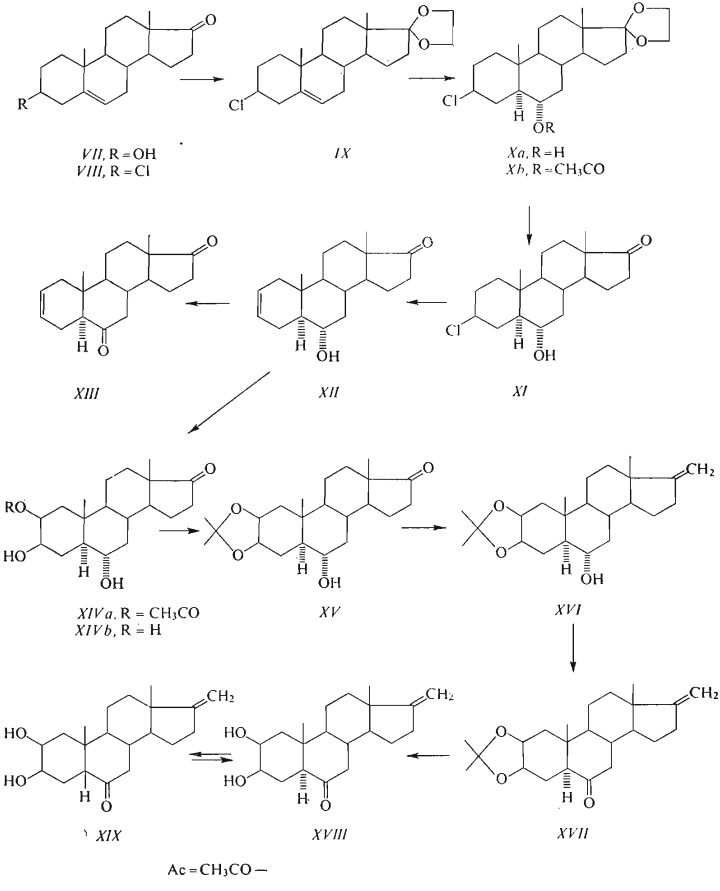
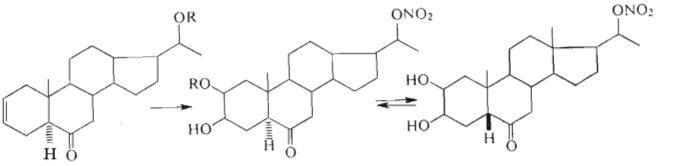
after Wolff–Kishner reduction followed by chromium trioxide–pyridine complex oxidation yielded the known[5,7] 3α,5-cyclo-5α-androstan-6-one (*II*). The ketone *II* was treated with hydriodic acid in acetic acid solution to give 3β-iodo derivative *III* in 56% yield; the latter compound afforded Δ^2-olefin *IV* on heating with lithium carbonate and lithium bromide in dimethylformamide solution. *cis*-Hydroxylation of the derivative *IV* with iodine and silver acetate in wet acetic acid[8] resulted in the formation of 2β-acetoxy-3β-hydroxy-5α-androstan-6-one (*Va*). Under mild alkaline conditions, *i.e.* on treatment with potassium hydrogen carbonate at 33°C, the latter compound yielded 2β,3β-dihydroxy-5α-androstan-6-one (*Vb*), whereas base-catalyzed equilibration of the 5α-isomer *Vb*, using potassium carbonate in boiling methanol, gave a mixture of 5α- and 5β-isomeric 6-ketones *Vb* and *VI* in an approximate ratio of 2 : 3. The configuration at $C_{(5)}$ of the ketones *Vb* and *VI* was allotted on the grounds of their chromatographic properties and their ORD curves[1-4,8]: the 5α-isomer is less polar and has a lower negative molecular amplitude ($a = -66$) as compared with the 5β-isomer ($a = -161$). Configurations at $C_{(5)}$ of other 2β,3β-dihydroxy 6-ketones, described in the present paper, were established in the same manner. In the preparation of 5α- and 5β-isomeric 2β,3β-dihydroxy-17-methyleneandrostan-6-ones *XVII* and *XVIII* we set out from 3β-hydroxy-5-androsten-17-one (*VII*) which on treatment with phosphorus oxychloride gave the 3β-chloro derivative *VIII*, the preparation of which in several ways is reported in literature[9-11]. In order to protect the 17-keto group in the 3β-chloro derivative, the latter was converted to the ethylenedioxy derivative *IX* which by hydroboration with gaseous diborane in tetrahydrofuran gave 3β-chloro-17-ethylenedioxy-5α-androstan-6α-ol (*Xa*) in 79% yield. The



formation of 6α-derivative is in line with the *cis*-addition of the reagent occurring preferentially from the less hindered side of the molecule[12]. The alcohol *Xa* was characterized as the acetate *Xb*. Acid hydrolysis of the ketal *Xa* provided the 17-ke-



tone *XI* which on heating with chinoline eliminated hydrogen chloride to afford a mixture of olefins (Δ^2-olefin presumably accompanied by the Δ^3-compound) from which the desired Δ^2-olefin could be isolated by means of chromatography on silica gel impregnated with silver nitrate. The structure of Δ^2-olefin *XII* for the preponderant component was proved by converting it to the known[3,5,13] 5α-androst-2-en-6,17-dione (*XIII*) on oxidation with chromium trioxide–pyridine complex. The unsaturated compound *XII* was *cis*-hydroxylated[8] to 2β-acetoxy-3β,6α-dihydroxy-5α-androstan-17-one (*XIVa*) which yielded the triol *XIVb* on acid hydrolysis. The triol *XIVb* was converted smoothly to 2β,3β-isopropylidene derivative *XV* which, after application of the Wittig reaction, afforded the 17-methylene derivative *XVI* in 89% yield. Oxidation of the latter compound with chromium trioxide–pyridine complex gave the 6-keto derivative *XVII* the mild acid hydrolysis[1] of which resulted in the formation of 2β,3β-dihydroxy-17-methylene-5α-androstan-6-one (*XVIII*). Base-catalyzed equilibration of the 5α,6-ketone *XVIII* with potassium carbonate in boiling methanol furnished a mixture of 5α- and 5β-isomeric 6-ketones *XVIII* and *XIX* in approximately 2 : 3 ratio. ORD curves of both isomeric ketones *XVIII* and *XIX* show a negative Cotton effect which is considerably stronger for the 5β-derivative ($a = -77$ and -182 for *XVIII* and *XIX*, respectively). For the preparation of 5α- and 5β-isomeric 2β,3β,20β-trihydroxypregnan-6-one 20-nitrates (*XXIb* and *XXII*), the starting substance 20β-acetoxy-5α-pregn-2-en-6-one (*XXa*) (ref.[4]) was saponified with potassium carbonate in boiling methanol to 20β-alcohol *XXb* which was treated with concentrated nitric acid and acetic anhydride at -5 to -10°C to yield the 20-nitrate *XXc* in 73% yield. The latter compound was then converted to 2β-acetoxy-3β,20β-dihydroxy-5α-pregnan-6-one 20-nitrate (*XXIa*) from which 2β,3β,20β-trihydroxy-5α-pregnan-6-one 20-nitrate (*XXIb*) could be prepared on mild alkaline hydrolysis using potassium hydrogen carbonate in methanol at 37°C. More vigorous conditions, *i.e.* boiling with potassium carbonate in methanol, led to a mixture of 5α- and 5β-isomeric 6-ketones *XXIb* and *XXII* in an approximate proportion of 2 : 3. The ORD curves of both isomeric ketones *XXIb* and *XXII* exhibit a negative Cotton effect which, again, is much stronger for 5β- than for the 5α-isomer ($a = -60$ and -167 for the 5α-isomer *XXIb* and 5β-isomer *XXII*, respectively).

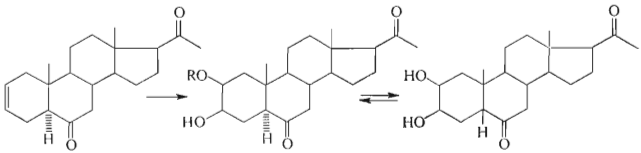


XXa, R = CH_3CO
XXb, R = H
XXc, R = NO_2

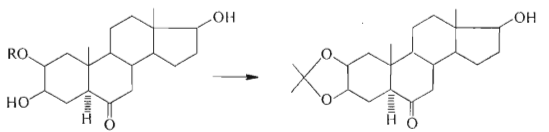
XXIa, R = CH_3CO
XXIb, R = H

XXII

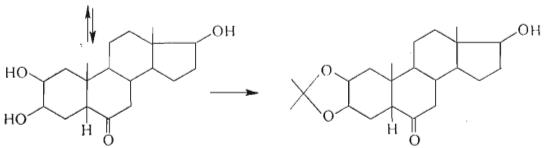
The starting material for the synthesis of 5α- and 5β-isomeric 2β,3β,17β-trihydroxyandrostan-6-ones *XXVIb* and *XXVII* was 2β-acetoxy-3β,17β-dihydroxy-5α-androstan-6-one (*XXVIa*)[3] which on hydrolysis with potassium carbonate in methanol at room temperature gave a mixture of 5α- and 5β-isomeric 6-ketones *XXVIb* and *XXVII*. The triol *XXVIb* has been prepared recently[3] in our laboratory by a different procedure. The ORD curves of both 5α- and 5β-isomeric 6-ketones show a picture analogous with the preceding cases: again, the negative value of the 5β-isomer *XXVII* ($a = -157$) is considerably larger than that of the 5α-isomer *XXVIb* ($a = -93$). The isomers *XXVIb* and *XXVII* were used for the preparation of their respective isopropylidene derivatives *XXIX* and *XXVIII*. Similarly as in the parent compounds, the negative value of the Cotton effect is larger in the case of the 5β-derivative *XXIX* ($a = -148$) than that of the 5α-isomer *XXVIII* ($a = -100$). 2β,3β-Dihydroxy-5β-pregnan-6,20-dione (*XXV*) along with the earlier reported[2] 2β,3β-dihydroxy-



XXIII *XXIVa*, R = CH_3CO *XXV*
XXIVb, R = H



XXVIa: R = CH_3CO *XXVIII*
XXVIb: R = H



XXVII *XXIX*

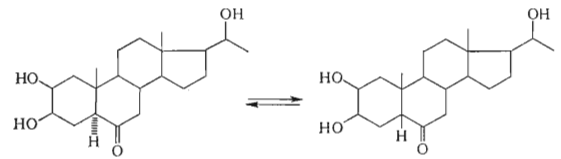
5α-pregnan-6,20-dione *XXIVb* was prepared by alkaline saponification of 2β-acetoxy-3β-hydroxy-5α-pregnan-6,20-dione(*XXIVa*) using potassium hydrogen carbonate in boiling methanol. Owing to the presence of the 20-keto group, the 5α-isomer *XXIVb* exhibits a strong positive Cotton effect ($a = +82$) whereas only a weaker negative Cotton effect ($a = -42$) is characteristic of the isomer *XXV*, the mutual relalion of both values and the higher polarity of the dione *XXV* being in line with the general behavior of both stereoisomeric types[1-4,8]. 2β,3β,20β-Trihydroxy-5β-pregnan-6-one (*XXXI*) was prepared by base catalyzed equilibration of the known[2] 2β,3β,20β-trihydroxy-5α-pregnan-6-one (*XXX*) using potassium carbonate in methanol at 37°C. The ORD curve of the 5β-ketone *XXXI* shows a negative Cotton effect with a molecular amplitude of $a = -167$.

The compounds studied were equilibrated at 33·5°C in aqueous–methanolic medium in the presence of potassium carbonate. The equilibrium was reached both from 5α- and from 5β-isomers. The equilibrium constants K (5α-isomer⇄5β-isomer) were determined by the ORD method[16,17]. The results listed in Table I are average values from three experiments. In several cases, the equilibration was performed in the same medium at 87°C and the equilibrated mixtures separated by column chromatography on silica gel. Also in these cases, the equilibrium was achieved starting both from 5α- and 5β-isomers. The results are as follows:

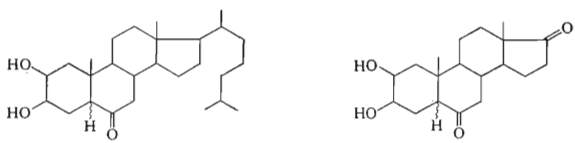
Compound	*Vb, VI*;	*XXXII, XXXIII*;	*XVIII, XIX*;	*XXXIV, XXXV*
Substituent at $C_{(17)}$	—	$-C_8H_{17}$	$=CH_2$	$=O$
$K^{5\alpha/5\beta}$	1·31	1·50	1·44	1·80

Owing to the higher temperature used, the equilibrium constants thus obtained are somewhat higher than those obtained at 33·5°C, however, the direction of the influence on the equilibrium constant, characteristic of structural changes in the side chain, remains preserved. In the case of the 20-keto derivative, the 17β-oriented side chain might be suspected of giving rise to a limited amount of the 17α-isomer. The presence of such a compound could render the ORD method inapplicable to the desired purpose owing to the diametrically different course of the ORD curve with opposed sign of the Cotton effect in 17α-pregnan-20-one type as compared with its 17β-isomer[14]. In order to gain the necessary information as to whether or not such isomerisation occurs, 3β-hydroxy-5α-pregnan-20-one was subjected to the action of potassium carbonate under the conditions used in the 5α⇄5β-equilibration experiments. Since the ORD curve of the ketone tested remained practically unaltered ($a = +178$ and $+168$ before and after the treatment), it was obvious that no significant inversion proceeds at $C_{(17)}$; the legitimacy of the application of the ORD method

was thus shown to be beyond doubt. The results summarized in Table I show that for compounds lacking any substituent at $C_{(17)}$ or bearing a cholestane side chain, a methylene or a nitrate group at this position, the relative proportion of 5α- and 5β-isomers is approximately 1 : 1. On the other hand, introduction of oxygen function (a keto group or hydroxyl) results in a marked change in the equilibrium constant, whereby the effect is of opposite direction for the keto group than for the hydroxyl: in the compounds with a keto group at $C_{(17)}$ or $C_{(20)}$, the equilibrium constant is shifted toward the 5β-isomer, whereas in compounds substituted with a hydroxyl at $C_{(17)}$ or $C_{(20)}$, the 5α-isomer prevails in the equilibrium mixture.



XXX *XXXI*



XXXII 5α H
XXXIII 5β H

XXXIV 5α H
XXXV 5β H

DISCUSSION

The conformation analysis predicts greater thermodynamic stability for unsubstituted 6-oxo-5α-cholestane derivatives. The proof of this prediction was given by equilibration experiments[15]. Also in the equilibrium mixture of various 3β-substituted cholestan-6-ones the thermodynamically more stable 5α-isomer preponderates, in agreement with an assumption made on the basis of analogy with the simple models[16]. It has been established[17,18] for certain 3α-substituted 6-cholestanones that the 5α-isomers are more stable than could be expected from the above analogy[16]. This fact was explained by the presence of electrostatic interactions between the 3α-substituent and the 6-keto group. The presence of an additional substituent in the 2-position essentially influences the equilibria in the 6-ketosteroids. Introduction

of a 2β-substituent into a 3β-substituted 6-ketone results in a shift of the equilibrium toward the 5β-isomer, owing to a strong 1,3-diaxial interaction between the 2β-substituent and 10β-methyl in the 5α-isomer[1,8,19]. A shift of the equilibrium exclusively towards the 5β-isomer was encountered in 2β,3α-disubstituted 6-ketosteroids[4,20]. This fact was explained by the existence of two strong 1,3-diaxial interactions, partly between the 2β-substituent and 10β-methyl and partly between the 3α-substituent and 5α-hydrogen. As follows from the results summarized in Tables I and II, the equilibrium of 2β,3β-disubstituted 6-ketosteroids is also influenced by the character of the substituent at $C_{(17)}$. Explanation on the basis of the known concepts by a steric mechanism appears impossible. Conformational transmission[21–24] as a transmission of conformation deformation caused by an unsaturated group, can be ruled out since introduction of a methylene group into the 17-position (*XVIII*, *XIX*) does not alter the equilibrium constant as compared with the unsubstituted compounds *Vb* and *VI*. Moreover, there does exist a difference in equilibrium constants between 17-methylene (*XVIII*, *XIX*) and 17-keto (*XXXIV*, *XXXV*) substituted derivatives, though both 17-substituents are practically equivalent from the point of view of conformational transmission. This absence of conformational transmission is in line with a similar observation of other authors[25–28] that conformational transmission is not operative in epimerisation at asymmetric centers adjacent to a keto group located either in the A-ring or in the side chain.

The above observations cannot be explained by a transmission of the inductive effect either. Two facts are not compatible with such an interpretation. The values of the equilibrium constants of the compounds *XXIb*, *XXII* substituted at $C_{(20)}$

TABLE I

Equilibrium Constants of Base Catalyzed Isomerization (5α ⇄ 5β) of Some 6-Ketosteroids at 33·5°C

5α,5β-Isomer	Substituent at $C_{(17)}$	λ, nm	$K_{5\beta/5\alpha}$ [a]
Vb, *VI*	—	310	1·08
XXXII, *XXXIII*	$-C_8H_{17}$	310	0·94
XVIII, *XIX*	$=CH_2$	310	0·93
XXXIV, *XXXV*	=O	316	1·31
XXIVb, *XXV*	$-COCH_3$	314	7·06
XXVIb, *XXVII*	—OH	310	0·13
XXX, *XXXI*	$-CH(OH)CH_3$	310	0·14
XXIb, *XXII*	$-CH(ONO_2)CH_3$	310	1·04
XXVIII, *XXIX*	—OH, 2β,3β-isopropylidenedioxy	313	0·56

[a] Maximal deviation of individual measurements from the values listed did not exceed 10%.

with a strongly polar nitrate group are practically identical with those of compounds *Vb, VI* lacking any substituent at $C_{(17)}$. A second inconsistence appears to be the fact that the 20-keto group causes a much larger shift in the equilibrium towards the 5β-isomer than the 17-keto group as compared with the 17-unsubstituted derivative, although the inductive effect must decrease with increasing distance. The same order in magnitude of the effect of 17- and 20-keto groups on a distant reaction center was observed previously by Bodor[29] in the investigation of the substitution rate in 3-oxo-4-chloro-4-androstene and pregnene derivatives. Bodor[29] rationalized this observation by operation of the field effect. Such an interpretation, however, cannot be applied to the effect of polar 17-substituents in our case. Also according to this theory, introduction of the 20β-nitrate group should exert a definite effect on the equilibrium which, however, is not the case (Table I). Also the opposed influence of 17β- and 20β-hydroxyl groups as compared with 17- and 20-keto groups is difficult to explain either by inductive or by field effect.

Slight shift of the equilibrium toward the 5β-isomer (Table I), which was observed in the case of the 2β,3β-isopropylidenedioxy derivative *XXVIII* (as compared with the free 2β,3β-dihydroxy derivative *XXVIb*), can be explained by considerable crowding of one methyl from the isopropylidene grouping with both the angular methyl group and 4β-hydrogen. Owing to ridigity of the system, the crowding cannot be relieved by bending away of the respective groupings. On the other hand, the *syn*-diaxial interaction between the 2β-hydroxyl and the angular methyl in the 2β,3β-diol can be relieved owing to free rotation of the 2β-hydroxyl group. Consequently, the situation appears to be less favorable for the 5α-isomer in the isopropylidene derivative.

The question of solvation effects, certainly of interest in this connection, could not be pursued owing to poor solubility of the respective compounds in suitable solvents.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Unless stated otherwise, optical rotations were measured in chloroform. The infrared spectra were measured on a Zeiss UR 10 spectrophotometer, ultraviolet spectra on a CF 4 (Optica Milano) spectrophotometer and ORD measurements on a Jasco Model ORD/UV-5 spectropolarimeter. The identity of samples prepared by different routes was checked by mixture-melting point determination and by infrared spectra. The analyses of compounds *VI, XIVb, XIX, XXV* and *XXXI* gave constantly lower values.

3α,5-Cyclo-5α-androstan-6-one (*II*)

The solution of 6β-hydroxy-3α,5-cyclo-5α-androstan-17-one (*I*, ref.[5,6], 3·79 g) in triethylene glycol (209 ml) was treated with hydrazine hydrate (22·8 ml, 80%) and solid potassium hydroxide (6·08 g) and heated in an open flask. The temperature was allowed to rise to 140°C and the mixture was refluxed at this temperature for 30 minutes whereupon the condenser was removed until the temperature reached 200°C and refluxing was then continued for 3 hours. The mixture was then cooled, poured into water and the product extracted with ether. The ethereal extract was washed with water, dried with sodium sulfate and the solvent evaporated *in vacuo*. The oily residue (3·8 g) was dissolved in pyridine (80 ml) and the solution added to a stirred chromium trioxide (2·7 g)–pyridine (30 ml) complex at 0°C. After standing at room temperature for 48 hours

the reaction mixture was diluted with ether, washed with water, 5% hydrochloric acid, 5% potassium hydrogen carbonate and water, dried with sodium sulfate and the solvent evaporated *in vacuo*. After repeated crystallization from methanol the residue (3·15) g afforded 2·5 g of the ketone *II*, m.p. 122—123·5°C, $[\alpha]_D^{22}$ +31°, (*c* 0·1); literature[5] reports m.p. 122—122·5°C, $[\alpha]_D$ +34·5° (ethanol). Infrared spectrum (chloroform): 1 679 cm^{-1}. For $C_{19}H_{28}O$ (272·4) calculated: 83·77% C, 10·36% H; found: 83·64% C, 10·44% H.

3β-Iodo-5α-androstan-6-one (*III*)

A solution of the ketone *II* (2·5 g) in acetic acid (175 ml) was treated with 57% hydriodic acid (5 ml) and allowed to stand at room temperature for 48 hours. The mixture was poured into ice and extracted with ether. The ethereal extract was washed with water, 5% potassium hydrogen carbonate, 3% sodium thiosulfate, and water, dried with sodium sulfate and the solvent evaporated *in vacuo*. The residue (3·3 g) afforded after recrystallization from ethanol 2·1 g of the iodo derivative *III*, m.p. 160—164°C, $[\alpha]_D^{22}$ +31° (*c* 0·3). Infrared spectrum (tetrachloromethane): 1 716 cm^{-1}. For $C_{19}H_{29}IO$ (403·3) calculated: 56·57% C, 7·24% H, 31·44% I; found: 56·92% C, 7·05% H, 30·79% I.

5α-Androst-2-en-6-one (*IV*)

The suspension of the iodo ketone *III* (2·1 g), lithium carbonate (2·1 g) and lithium bromide (2·1 g) in dimethylformamide (23·8 ml, 1% of water) was heated in nitrogen atmosphere at 120°C for 1 hour. The reaction mixture was allowed to cool, diluted with light petroleum–benzene (1 : 1), inorganic salts were filtered off, the filtrate was washed with water, dried with sodium sulfate and the solvent evaporated *in vacuo*. The residue (1·54 g) was chromatographed on a column of silica gel (70 g) in benzene–light petroleum (7 : 3) to afford 255 mg of the olefine *IV*, which was crystallized from methanol, m.p. 68—72°C, $[\alpha]_D^{22}$ +71° (*c* 0·5). Infrared spectrum (tetrachloromethane): 3065, 3025, 1713, 1658 cm^{-1}. Ultraviolet spectrum (heptane): λ_{max} 221 nm ($\log \varepsilon$ 3·32), λ_{max} 273 nm ($\log \varepsilon$ 2·44). For $C_{19}H_{28}O$ (272·4) calculated: 83·77% C, 10·36% H; found: 83·04% C, 10·31% H.

2β-Acetoxy-3β-hydroxy-5α-androstan-6-one (*Va*)

A stirred solution of the olefin *IV* (1·4 g) in tetrahydrofuran (15 ml), acetic acid (151 ml) and water (2·45 ml) was treated with silver acetate (2·1 g) and pulverized iodine (1·3 g) was added portionwise over a period of 5 minutes. The temperature was raised to 55°C and the stirring continued for 3 h. After cooling, the reaction mixture was passed through a small sodium chloride column, the latter washed with hot ethyl acetate and the filtrate evaporated *in vacuo*. The residue was dissolved in ethyl acetate, the solution washed with water, 5% potassium hydrogen carbonate, water, 3% sodium thiosulfate and water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (1·8 g) was repeatedly recrystallized from ethyl acetate–heptane to afford 525 mg of the monoacetate *Va*, m.p. 213—218°C, $[\alpha]_D^{22}$ +9° (*c* 0·2). Infrared spectrum (chloroform): 3590, 1729, 1711, 1250, 1070 cm^{-1}. For $C_{21}H_{32}O_4$ (348·5) calculated: 72·38% C, 9·26% H; found: 72·57% C, 9·54% H.

2β,3β-Dihydroxy-5α-androstan-6-one (*Vb*)

A solution of the monoacetate *Va* (350 mg) in methanol (35 ml) was treated with aqueous potassium hydrogen carbonate solution (280 mg in 3·5 ml) at 37°C for 23 h. After concentrating to one third of the volume the reaction mixture was poured into water and the product extracted

with chloroform. The extract was washed with water, over sodium sulfate and the solvent evaporated *in vacuo*. The residue (330 mg) afforded after repeated crystallization from ethyl acetate–heptane 205 mg of the diol *Vb*, m.p. 178—180°C, $[\alpha]_D^{24}$ —52° (*c* 0·1). Infrared spectrum (chloroform): 3615, 1708 cm^{-1}. ORD (*c* 0·1, 24°C): $[\Phi]_{260}$ +3483°, $[\Phi]_{275}$ +4128°, $[\Phi]_{285}$ +3022°, $[\Phi]_{296}$ ±0°, $[\Phi]_{305}$ —2709°, $[\Phi]_{311}$ —3806°, $[\Phi]_{317}$ —3032°, $[\Phi]_{335}$ —1161°, $[\Phi]_{400}$ —260°, a = —79. ORD (methanol, *c* 0·1, 25°C): $[\Phi]_{260}$ +3332°, $[\Phi]_{277}$ +3675°, $[\Phi]_{280}$ +3087°, $[\Phi]_{293}$ ±0°, $[\Phi]_{300}$ —1862°, $[\Phi]_{305}$ —2891°, $[\Phi]_{310}$ —2670°, $[\Phi]_{325}$ —1323°, $[\Phi]_{400}$ —150°, a = = —66. For $C_{19}H_{30}O_3$ (306·4) calculated: 74·47% C, 9·87% H; found: 74·06% C, 10·02% H.

2β,3β-Dihydroxy-5β-androstan-6-one (*VI*)

A solution of the ketone *Vb* (150 mg) in methanol (15 ml) was treated with aqueous potassium carbonate solution (75 mg in 1·5 ml) and refluxed in nitrogen atmosphere for 8 hours. After concentrating *in vacuo* to one third of the volume the reaction mixture was poured into water and the product extracted with chloroform. The extract was washed with water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (150 mg) was chromatographed on silica gel (20 g) in benzene–ethyl acetate (4 : 1). The product which was eluted first (65 mg) afforded after crystallization from ethyl acetate–heptane 55 mg of the 5α-isomer *Vb*, m.p. 178 to 180°C, $[\alpha]_D^{22}$ —50° (*c* 1·0).

The second fraction (85 mg) was crystallized from ethyl acetate–heptane to afford 75 mg of the 5β-isomer *VI*, m.p. 167—169°C, $[\alpha]_D^{22}$ —104° (*c* 0·5). Infrared spectrum (chloroform): 3600, 3560, 3430, 1698 cm^{-1}. ORD (methanol, *c* 0·1, 25°C): $[\Phi]_{260}$ +6574°, $[\Phi]_{274}$ +7719°, $[\Phi]_{280}$ +6872°, $[\Phi]_{294}$ ±0°, $[\Phi]_{305}$ —6773°, $[\Phi]_{350}$ —8366°, $[\Phi]_{325}$ —5777°, $[\Phi]_{350}$ —2390°, a = —161. For $C_{19}H_{30}O_3$ (306·4) calculated: 74·47% C, 9·87% H; found: 72·33% C, 9·84% H.

3β-Chloro-5-androsten-17-one (*VIII*)

To a solid 3β-hydroxy-5-androsten-17-one (*VII*; 50 g) phosphorus oxychloride (60 ml) was added dropwise under stirring at 0°C and the reaction mixture was allowed to stand at room temperature for 20 h. The mixture was then poured on ice, the solid was collected by suction and dissolved in ether. The ethereal solution was washed with 5% potassium hydrogen carbonate, water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The oily residue (40 g) was crystallized from ethanol to yield 15 g of the ketone *VIII*, m.p. 152—156°C. The chromatography of the mother liquor on silica gel (350 g) in benzene–light petroleum (1 : 1) afforded a further 15 g of the ketone *VIII*, m.p. 153—155·5°C. The sample for analysis was crystallized from ethanol, m.p. 156—157°C, $[\alpha]_D^{22}$ +17·5° (*c* 1·0) literature[9] reports m.p. 155—157°C, $[\alpha]_D$ +14° and[10] m.p. 154°C, $[\alpha]_D$ +14·6°. Infrared spectrum (chloroform): 1734, 1668 cm^{-1}. For $C_{19}H_{27}ClO$ (306·9) calculated: 74·35% C, 8·96% H, 11·58% Cl; found: 73·99% C, 8·77% H, 11·49% Cl.

3β-Chloro-17-ethylenedioxy-5-androstene (*IX*)

A mixture of the ketone *VIII* (15 g), *p*-toluenesulfonic acid (500 mg), ethylene glycol (70 ml) and benzene (700 ml) was refluxed for 52 hours. After cooling the reaction mixture was treated with 0·1% potassium hydroxide, the benzene layer was washed with water, dried over anhydrous potassium carbonate and evaporated *in vacuo*. After recrystallization from ethanol the residue (16 g) afforded 14·5 g of the derivative *IX*, m.p. 149—151·5°C, $[\alpha]_D^{23}$ —78° (*c* 1·1). Infrared spectrum (chloroform): 1668 cm^{-1}. For $C_{21}H_{31}ClO_2$ (350·9) calculated: 71·87% C, 8·90% H, 10·10% Cl; found: 71·88% C, 8·79% H, 10·09% Cl.

3β-Chloro-17-ethylenedioxy-5α-androstan-6α-ol (*Xa*)

Gaseous diborane, which was prepared by portionwise adding of sodium borohydride (4·9 g) to a solution of boron trifluoride etherate (28 g) in diglyme (100 ml), was passed through a solution of the olefin *IX* (3 g) in tetrahydrofuran (200 ml) under stirring in nitrogen atmosphere for 30 minutes. The reaction mixture was allowed to stand in nitrogen atmosphere for 2 hours at room temperature, cooled to 0°C and under stirring treated with 140 ml of the solution, prepared from 10% aqueous potassium hydroxide solution (108 ml) and 30% hydrogen peroxide (72 ml). After 1 hour the reaction mixture was diluted with ether, the ethereal layer was washed with water, dried over sodium sulfate and evaporated *in vacuo*. The residue (3 g) afforded after repeated crystallization from ethanol 1·5 g of the derivative *Xa*, m.p. 167—167·5°C. The chromatography of the mother liquor on silica gel (100 g) in benzene–ether (95:5) gave a further 1 g of the derivative *Xa*, m.p. 166—167°C. The analytical sample was crystallized from ethanol, m.p. 167—167·5°C, $[\alpha]_D^{23}$ +18° (*c* 1·0). Infrared spectrum (chloroform): 3615 cm^{-1}. For $C_{21}H_{33}ClO_3$ (368·9) calculated: 68·36% C, 9·01% H, 9·61% Cl; found: 68·63% C, 9·06% H, 9·69% Cl.

6α-Acetoxy-3β-chloro-17-ethylenedioxy-5α-androstane (*Xb*)

The alcohol *Xa* (135 mg) was acetylated with acetic anhydride (1·4 ml) in pyridine (6 ml) for 16 h at room temperature. Usual working up yielded 130 mg of the acetate *Xb*, which was crystallized from ethanol, m.p. 206—208°C, $[\alpha]_D^{23}$ +47° (*c* 1·0). Infrared spectrum (tetrachloromethane): 1738, 1244 cm^{-1}. For $C_{23}H_{35}ClO_4$ (411·0) calculated: 67·21% C, 8·58% H, 8·63% Cl; found: 67·94% C, 8·57% H, 8·81% Cl.

3β-Chloro-6α-hydroxy-5α-androstan-17-one (*XI*)

p-Toluenesulfonic acid (13 g) was added to a solution of the derivative *Xb* (13 g) in methanol (700 ml). The mixture was left at room temperature for 3 hours, concentrated *in vacuo* to one third of the volume, poured into water and the product taken up in ether. The ethereal extract was washed with 5% potassium hydrogen carbonate, water, dried over sodium sulfate and evaporated *in vacuo*. The residue (11 g) afforded after crystallization from heptane–chloroform 6·5 g of the ketone *XI*, m.p. 179—181°C, $[\alpha]_D^{22}$ +132° (*c* 0·8). Infrared spectrum (chloroform): 3615, 1733 cm^{-1}. For $C_{19}H_{29}ClO_2$ (324·9) calculated: 70·24% C, 8·99% H, 10·92% Cl; found: 69·90% C, 9·05% H, 11·13% Cl.

6α-Hydroxy-5α-androst-2-en-17-one (*XII*)

A solution of the derivative *XI* (6·3 g) in freshly distilled quinoline (90 ml) was refluxed in nitrogen atmosphere for 1 hour. After cooling the reaction mixture was diluted with water and the product taken up in ether. The ethereal extract was washed with 10% sulfuric acid, 5% potassium hydrogen carbonate, water, dried over sodium sulfate and evaporated *in vacuo*. The residue (5·3 g) was chromatographed on 20% silver nitrate-silica gel (600 g) in benzene–acetone (99 : 1) to give a fraction containing a mixture of the olefin *XII* and a less polar impurity (3 g), followed by a fraction of pure olefin *XII* (1·8 g) m.p. 172—174°C (from acetone), $[\alpha]_D^{23}$ +172° (*c* 0·7). Infrared spectrum (chloroform): 3615, 1734, 1659 cm^{-1}. For $C_{19}H_{28}O_2$ (288·4) calculated: 79·12% C, 9·78% H; found: 78·69% C, 9·59% H.

5α-Androst-2-en-6,17-dione (*XIII*)

A solution of the alcohol *XII* (50 mg) in pyridine (2 ml) was added to a chromium trioxide (20 mg)–pyridine (1 ml) complex and the mixture left at room temperature for 20 h. The mixture was

poured into water, the product taken up in ether and the ethereal extract was washed with 5% hydrochloric acid, 5% potassium hydrogen carbonate and water, dried over sodium sulfate and evaporated *in vacuo*. The residue (45 mg) was crystallized from ethanol to afford 20 mg of the dione *XIII*, m.p. 193—194°, $[\alpha]_D^{22}$ +123° (*c* 1·0) in accordance with literature[3,5,13].

2β-Acetoxy-3β,6α-dihydroxy-5α-androstan-17-one (*XIVa*)

A solution of the Δ^2-derivative *XII* (1·8 g) in acetic acid (108 ml) and water (1·8 ml) was treated with silver acetate (2·75 g), and pulverized iodine (1·7 g) was added portionwise under stirring. Stirring was then continued at 50°C for 3 h. The insoluble material was removed by filtration through a small sodium chloride column, and the filtrate was concentrated *in vacuo*. The residue was dissolved in chloroform, the chloroform solution was washed with water, 5% potassium hydrogen carbonate, water, 3% sodium thiosulfate, water, dried over sodium sulfate and evaporated *in vacuo*. The residue (1·8 g) was crystallized from ethyl acetate to give 1·55 g of the monoacetate *XIVa*, m.p. 225—228°C, $[\alpha]_D^{25}$ +110° (*c* 1·1). Infrared spectrum (chloroform): 3590, 1732, 1250 cm^{-1}. For $C_{21}H_{32}O_5$ (364·5) calculated: 69·20% C, 8·85% H; found: 68·81% C, 8·56% H.

2β,3β,6α-Trihydroxy-5α-androstan-17-one (*XIVb*)

A solution of the monoacetate *XIVa* (600 mg) in chloroform (3·5 ml)–methanol (35 ml) was treated with concentrated hydrochloric acid (0·6 ml) at 30°C for 20 h. After concentrating to one third of the volume the reaction mixture was poured into water and the product was taken up in chloroform. The chloroform extract was washed with water, dried over sodium sulfate and evaporated *in vacuo*. The residue (500 mg) was recrystallized from tetrahydrofuran–heptane to give 400 mg of the triol *XIVb*, m.p. 246—250°C, $[\alpha]_D^{22}$ +123° (*c* 0·8, ethanol). Infrared spectrum (nujol): 3300, 1748, 1731 cm^{-1}. For $C_{19}H_{30}O_4$ (322·4) calculated: 70·77% C, 9·38% H; found: 69·34% C, 9·20% H.

6α-Hydroxy-2β,3β-isopropylidenedioxy-5α-androstan-17-one (*XV*)

The suspension of the triol *XIVb* (1·1 g) in acetone (200 ml) was treated with *p*-toluenesulfonic acid (140 mg) and the mixture was agitated at room temperature for 90 minutes. Anhydrous potassium carbonate (500 mg) was added and the mixture was agitated for 15 minutes. The mixture was then passed through a small sodium sulfate column and the filtrate was concentrated *in vacuo*. The residue (1·3 g) afforded after recrystallization from acetone–heptane 1·05 g of the derivative *XV*, m.p. 176—178°C, $[\alpha]_D^{21}$ +127° (*c* 0·8). Infrared spectrum (chloroform): 3615, 1744, 1045 cm^{-1}. For $C_{22}H_{34}O_4.1\,C_3H_6O$ (420·6) calculated: 71·38% C, 9·58% H; found: 71·14% C, 9·34% H.

2β,3β-Isopropylidenedioxy-17-methylene-5α-androstan-6α-ol (*XVI*)

To a solution of bromobenzene (9 ml) in ether (300 ml) lithium (1·08 g) was added and the mixture was refluxed for 7 hours in nitrogen atmosphere. Triphenylmethylphosphonium iodide (27 g) was added and the mixture agitated at room temperature for 3 hours. Then a solution of the ketone *XV* (1·8 g) in ether (60 ml)–dioxane (60 ml) was added dropwise over a period of 10 minutes in nitrogen atmosphere and the reaction mixture was agitated for 90 minutes at room temperature. Ether was distilled off, replaced by dioxane (210 ml) and refluxed for 10 h. After cooling the mixture was diluted with water and the product taken up in chloroform–ether. The extract was washed with 5% hydrochloric acid, 5% potassium hydrogen carbonate, water, dried over sodium sulfate and evaporated *in vacuo*. The oily residue (13 g) was chromatographed on silica gel (280 g) in ben-

zene to furnish an oil (4 g) in which the 17-methylene derivative was accompanied by triphenylphosphine oxide. This mixture was rechromatographed on silica gel (450 g) in light petroleum–acetone (9 : 1) to yield 1·67 g of the derivative *XVI*, which was crystallized from heptane, m.p. 170—172°C, $[\alpha]_D^{21}$ +69° (*c* 0·7). Infrared spectrum (chloroform): 3615, 3065, 1655, 880 cm^{-1}. For $C_{23}H_{36}O_3$ (360·5) calculated: 76·62% C, 10·07% H; found: 76·12% C, 10·23% H.

2β,3β-Isopropylidenedioxy-17-methylene-5α-androstan-6-one (*XVII*)

The hydroxy derivative *XVI* (1 g) was dissolved in pyridine (30 ml) and oxidized with chromium trioxide (1 g)–pyridine (30 ml) complex at room temperature for 15 hours. Usual workup and crystallization from methanol gave the ketone (600 mg), m.p. 225—228°C, $[\alpha]_D^{22}$ +26° (*c* 0·3). Infrared spectrum (chloroform): 3065, 1708, 1657, 1049, 880 cm^{-1}. For $C_{23}H_{34}O_3$ (358·5) calculated: 77·05% C, 9·56% H; found: 76·66% C, 9·50% H.

2β,3β-Dihydroxy-17-methylene-5α-androstan-6-one (*XVIII*)

The suspension of the ketone *XVII* (210 mg) in methanol (100 ml) was treated with 3·5 ml of dilute hydrochloric acid (1 : 4) and the mixture stirred at room temperature for 90 min. After concentrating to one third of the volume the reaction mixture was poured into water and the product taken up in chloroform. The chloroform extract was washed with 5% potassium hydrogen carbonate, water, dried over sodium sulfate and evaporated *in vacuo*. The residue (195 mg) afforded after repeated crystallization from ethyl acetate–heptane 120 mg of the diol *XVIII*, m.p. 182—184°C, $[\alpha]_D^{25}$ —50° (*c* 0·1). Infrared spectrum (chloroform): 3615, 3065, 1708, 1656, 886 cm^{-1}. ORD (*c* 0·1, 24°C:) $[\Phi]_{265}$ +5772, $[\Phi]_{272}$ +5994°, $[\Phi]_{280}$ +5439°, $[\Phi]_{295}$ ±0°, $[\Phi]_{305}$ —3589°, $[\Phi]_{311}$ —4810°, $[\Phi]_{317}$ —4181°, $[\Phi]_{350}$ —888°, *a* = —108. ORD (methanol, *c* 0·1, 25°C): $[\Phi]_{250}$ +3299°, $[\Phi]_{268}$ +3690°, $[\Phi]_{279}$ +3082°, $[\Phi]_{293}$ ±0°, $[\Phi]_{302}$ —3450°, $[\Phi]_{305}$ —4050°, $[\Phi]_{310}$ —3725°, $[\Phi]_{320}$ —2450°, $[\Phi]_{400}$ —100°, *a* = —77. For $C_{20}H_{30}O_3$ (318·4) calculated: 75·43% C, 9·50% H; found: 75·66% C, 9·46% H.

2β,3β-Dihydroxy-17-methylene-5β-androstan-6-one (*XIX*)

A solution of the diol *XVIII* (150 mg) in methanol (15 ml) was treated with aqueous potassium carbonate solution (75 mg in 1·5 ml) and the mixture was refluxed in nitrogen atmosphere for 7 h. After concentrating to one third of the volume the reaction mixture was poured into water and the product taken up in chloroform. The chloroform extract was washed with water, dried over sodium sulfate and evaporated *in vacuo*. The residue (150 mg) was chromatographed on silica gel (20 g) in benzene–ethyl acetate (4 : 1). The less polar fraction (75 mg) afforded after crystallization from ethyl acetate–heptane 48 mg of the 5α-isomer *XVIII*, m.p. 182—184°C, $[\alpha]_D^{22}$ —49° (*c* 1·0). The second fraction (85 mg) gave after recrystallization from ethyl acetate–heptane 73 mg of the 5β-isomer *XIX*, m.p. 183—185°C, $[\alpha]_D^{25}$ —209 (*c* 0·1). Infrared spectrum (chloroform): 3420, 3070, 1699, 1657, 888 cm^{-1}. ORD (*c* 0·1, 24°C): $[\Phi]_{245}$ +7418°, $[\Phi]_{270}$ +9430°, $[\Phi]_{274}$ +10235°, $[\Phi]_{280}$ +9488°, $[\Phi]_{297}$ ±0°, $[\Phi]_{310}$ —8280°, $[\Phi]_{317}$ —9660°, $[\Phi]_{325}$ —7245°, $[\Phi]_{400}$ —1150°, *a* = —199. ORD (methanol, *c* 0·1, 25°C): $[\Phi]_{240}$ +6893°, $[\Phi]_{260}$ +8465°, $[\Phi]_{272}$ +9493°, $[\Phi]_{278}$ +8949°, $[\Phi]_{294}$ ±0°, $[\Phi]_{305}$ —7015, $[\Phi]_{310}$ —8707°, $[\Phi]_{317}$ —8333°, $[\Phi]_{400}$ —1088°, *a* = —182. For $C_{20}H_{30}O_3$ (318·4) calculated: 75·43% C, 9·50% H; found: 73·29% C, 9·28% H.

20β-Hydroxy-5α-pregn-2-en-6-one (*XXb*)

The suspension of 20β-acetoxy-5α-pregn-2-en-6-one (*XXa*, ref.[2], 2·3 g) in methanol (200 ml) was treated with aqueous potassium carbonate solution (2·3 g in 10 ml) and the mixture re-

fluxed for 8 h. After concentration to one third of the volume the reaction mixture was poured into water and the product taken up in ether. The ethereal extract was washed with water, dried over sodium sulfate and evaporated *in vacuo*. The residue (2·15 g) was chromatographed on silica gel (200 g) in benzene–ether (95 : 5) to give the starting acetate *XXa* (550 mg) followed by the alcohol *XXb* (1·4 g) which was crystallized from acetone–heptane m.p. 147·5°—148°C, $[\alpha]_D^{18}$ +1·6° (*c* 1·0). Infrared spectrum (chloroform): 3605, 1707, 1657, 1087 cm^{-1}. For $C_{21}H_{32}O_2$ (316·5) calculated: 79·69% C, 10·19% H; found: 79·66% C, 10·16% H.

20β-Hydroxy-5α-pregn-2-en-6-one 20-nitrate (*XXc*)

The alcohol *XXb* (3 g) in chloroform (60 ml), was added to a solution prepared at —15°C from acetic anhydride (18 ml) and nitric acid (4·2 ml) and the reaction mixture was allowed to stand at —10°C for 1 hour. The mixture was poured into cold water and the product taken up in chloroform. The chloroform extract was washed with 5% potassium hydrogen carbonate, water, dried over sodium sulfate and evaporated *in vacuo*. The residue (4·2 g) was repeatedly crystallized from methanol to yield 2·5 g of the nitrate *XXc*, m.p. 139—141·5°C, $[\alpha]_D^{19}$ +0·4° (*c* 0·8). Infrared spectrum (chloroform): 1708, 1625, 1276, 864, 1652 cm^{-1}. For $C_{21}H_{31}NO_4$ (361·5) calculated: 69·49% C, 8·64% H, 3·87% N; found: 69·60% C, 8·50% H, 4·26% N.

2β-Acetoxy-3β,20β-dihydroxy-5α-pregnan-6-one 20-nitrate (*XXIa*)

To a solution of Δ^2-derivative *XXc* (2 g) in acetic acid (294 ml) and water (4·62 ml) silver acetate (7·44 g) and pulverized iodine (2·2 g) were subsequently added under stirring. The reaction mixture was then stirred at 50°C for 3 h. The insoluble material was removed by filtration through a small sodium chloride column and the filtrate concentrated *in vacuo*. The residue was dissolved in ethyl acetate, the solution was washed with 5% potassium hydrogen carbonate, water, 3% sodium thiosulfate, water, dried over sodium sulfate and evaporated *in vacuo*. After chromatography on silica gel (200 g) in benzene–acetone (gradient elution) the residue (3 g) afforded the monoacetate *XXIa* (995 mg) which was crystallized from methanol, m.p. 233—236°C (with decomp.), $[\alpha]_D^{18}$ +4·6° (*c* 1·0, methanol). Infrared spectrum (chloroform): 3590, 1727, 1710, 1624, 1277, 1258, 1243 cm^{-1}. For $C_{23}H_{35}NO_7$ (437·5) calculated: 63·13% C, 8·00% H, 3·20% N; found: 62·81% C, 7·82% H, 3·35% N.

2β,3β,20β-Trihydroxy-5α-pregnan-6-one 20-nitrate (*XXIb*)

A solution of the monoacetate *XXIa* (160 mg) in methanol (15 ml) was treated with an aqueous potassium hydrogen carbonate solution (150 mg in 2 ml) and the mixture was kept at 37°C for 47 h. After concentrating to one third of the volume the reaction mixture was poured into water, the separated product was collected by suction and dissolved in chloroform. The chloroform extract was washed with water, dried over sodium sulfate and evaporated *in vacuo*. The residue (145 mg) was crystallized from aqueous methanol to yield 100 mg of the diol *XXIb*, m.p. 228 to 232°C (decomp.), $[\alpha]_D^{22}$ —8·2° (*c* 0·1, methanol). Infrared spectrum (nujol): 3525, 3390, 1689, 1611, 1280 cm^{-1}. ORD (methanol, *c* 0·1, 25°C): $[\Phi]_{235}$ +2400°, $[\Phi]_{243}$ +616°, $[\Phi]_{250}$ +1231°, $[\Phi]_{265}$ +2831°, $[\Phi]_{273}$ +3262°, $[\Phi]_{276}$ +3262°, $[\Phi]_{280}$ +2954°, $[\Phi]_{294}$ ±0°, $[\Phi]_{301}$ —1908°, $[\Phi]_{305}$ —2708°, $[\Phi]_{310}$ —2524°, $[\Phi]_{313}$ —2524°, $[\Phi]_{320}$ —1723°, $[\Phi]_{345}$ —616°, $a = -60$. For $C_{21}H_{33}NO_6$ (395·5) calculated: 63·77% C, 8·41% H, 3·55% N; found: 63·24% C, 8·35% H, 3·35% N.

2β,3β,20β-Trihydroxy-5β-pregnan-6-one 20-nitrate (*XXII*)

A solution of the monoacetate *XXIa* (500 mg) in methanol (100 ml) was treated with an aqueous potassium carbonate solution (250 mg in 5 ml) and the mixture was refluxed for 4 hours. After concentrating to one third of the volume the reaction mixture was poured into water, the separated product was collected by suction, washed with water, dissolved in methanol and ethyl acetate and evaporated *in vacuo*. The residual substance (440 mg) was chromatographed on silica gel (40 g) in benzene–ethyl acetate (gradient elution) to give two separate fractions. Crystallization of the first fraction from aqueous methanol yielded 120 mg of the diol *XXIb*, m.p. 228—232°C (decomp.), $[\alpha]_D^{22}$ —8° (*c* 1·0, methanol). Crystallization of the second fraction from methanol afforded 155 mg of diol *XXII*, m.p. 221—222·5°C, $[\alpha]_D^{22}$ —74° (*c* 0·1, methanol). Infrared spectrum (chloroform): 3610, 3565, 1702, 1277, 1624, 1045 cm^{-1}. ORD (methanol, *c* 0·06, 26°C): $[\Phi]_{232}$ +6690°, $[\Phi]_{242}$ +3344°, $[\Phi]_{250}$ +4630°, $[\Phi]_{265}$ +7331°, $[\Phi]_{267}$ +8295°, $[\Phi]_{270}$ +8231°, $[\Phi]_{280}$ +7395°, $[\Phi]_{295}$ ±0°, $[\Phi]_{303}$ —5916°, $[\Phi]_{310}$ —8360°, $[\Phi]_{319}$ —7588°, $[\Phi]_{330}$ —4501°, $[\Phi]_{355}$ —2058°, $[\Phi]_{400}$ —1157°, *a* = —167. For $C_{21}H_{33}NO_6.1\ CH_4O$ (427·5) calculated: 61·80% C, 8·72% H, 3·28% N; found: 61·83% C, 8·34% H, 3·15% N.

2β-Acetoxy-3β-hydroxy-5α-pregnane-6,20-dione (*XXIVa*)

A solution of 5α-pregn-2-en-6,20-dione (*XXIII*, ref.[4], 3·7 g) in acetic acid (400 ml) and water (6·5 ml) was treated subsequently with silver acetate (5·65 g) and pulverized iodine (3·3 g) with stirring. The stirring was then continued at 50°C for 3 h. The insoluble material was removed by filtration through a small sodium chloride column and the filtrate concentrated *in vacuo*. The residue was dissolved in chloroform, the solution was washed with 5% potassium hydrogen carbonate, water, 3% sodium thiosulfate, water, dried over sodium sulfate and the solvent evaporated *in vacuo*. Recrystallization of the residue (3·1 g) from ethyl acetate gave 1·28 g of the acetate *XXIVa*, m.p. 236—243°C. Crystallization of the mother liquor from ethyl acetate–light petroleum gave an additional 550 mg of the acetate *XXIVa*, m.p. 235—241°C. The analytical sample was crystallized from ethyl acetate, m.p. 239—243°C, $[\alpha]_D^{24}$ +73° (*c* 0·9). Infrared spectrum (chloroform): 3590, 1730, 1708, 1250 cm^{-1}. For $C_{23}H_{34}O_5$ (390·5) calculated: 70·74% C, 8·78% H; found: 70·49% C, 8·69% H.

2β,3β-Dihydroxy-5β-pregnane-6,20-dione (*XXV*)

A solution of the monoacetate *XXIVa* (500 mg) in methanol (50 ml) was treated with aqueous potassium hydrogen carbonate solution (150 mg in 1·25 ml) and the mixture was refluxed for 2 h. After concentrating to one third of the volume the reaction mixture was poured into water and the product extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate and evaporated *in vacuo*. The residue (470 mg) was chromatographed on silica gel (70 g) in benzene–ethyl acetate (1 : 1). The less polar fraction was recrystallized from ethyl acetate–heptane to afford 150 mg of 2β,3β-dihydroxy-5α-pregnane-6,20-dione (*XXIV*)[2], m.p. 193—194°C, $[\alpha]_D^{22}$ +49·5° (*c* 0·9). ORD (methanol, *c* 0·1, 25°C): $[\Phi]_{250}$ —3077°, $[\Phi]_{265}$ —4163°, $[\Phi]_{275}$ —3489°, $[\Phi]_{286}$ ±0°, $[\Phi]_{290}$ +2896°, $[\Phi]_{300}$ +3620°, $[\Phi]_{306}$ +4751°, $[\Phi]_{311}$ +3892°, $[\Phi]_{314}$ +3982°, $[\Phi]_{317}$ +4073°, $[\Phi]_{320}$ +3846°, $[\Phi]_{400}$ +724°, *a* —82. Crystallization of the second fraction from ethyl acetate–heptane gave 280 mg of the dione *XXV*, m.p. 154—155°C, $[\Phi]_D^{24}$ —18° (*c* 0·6). Infrared spectrum (chloroform): 3600, 1701, 1360, 3560, 3440 cm^{-1}. ORD (methanol, *c* 0·01, 26°C): $[\Phi]_{250}$ —582°, $[\Phi]_{260}$ —1307°, $[\Phi]_{275}$ ±0°, $[\Phi]_{285}$ +2323°, $[\Phi]_{290}$ +2904°, $[\Phi]_{295}$ +2614°, $[\Phi]_{306}$ ±0°, $[\Phi]_{314}$ —1146°, $[\Phi]_{320}$ —1307°, $[\Phi]_{325}$ —871°, $[\Phi]_{400}$ —290°, *a* —42. For $C_{21}H_{32}O_4$ (348·5) calculated: 72·38% C, 9·26% H; found: 69·67% C, 9·22% H.

2β,3β,17β-Trihydroxy-5α-androstan-6-one (*XXVIb*) and 2β,3β,17β-Trihydroxy-5β-androstan-6-one (*XXVII*)

A solution of 2β-acetoxy-3β,17β-dihydroxy-5α-androstan-6-one (*XXVIa*, ref.[3], 750 mg) in methanol (110 ml) was treated with aqueous potassium carbonate solution (550 mg in 10 ml) at room temperature for 20 h. After concentrating to one third of the volume the reaction mixture was poured into water, the solid was collected by suction and washed with water. The filtrate was extracted with ethyl acetate, the extract washed with water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue was combined with the still moist product obtained by filtration, methanol and ethyl acetate were added and the solvent was evaporated *in vacuo*. The residue (700 mg) gave after chromatography on silica gel (75 g, the product was dissolved in methanol, c. 5 g of silica gel added to the solution and the solvent evaporated *in vacuo*) in benzene–ethyl acetate (the gradient elution) two separated fractions. The less polar one afforded after recrystallization from ethyl acetate 325 mg of the isomer *XXVIb*, m.p. 238—245°C, $[\alpha]_D^{22}$ —5° (methanol, *c* 0·9); the literature[3] reports m.p. 231—235°C, $[\alpha]_D^{20}$ —4° (methanol, *c* 0·9) ORD (methanol, *c* 0·1, 25°C): $[\Phi]_{335}$ —1093°, $[\Phi]_{320}$ —2404°, $[\Phi]_{313}$ —3497°, $[\Phi]_{310}$ —3570°, $[\Phi]_{305}$ —3715°, $[\Phi]_{300}$ —2258°, $[\Phi]_{293}$ ±0°, $[\Phi]_{280}$ +4662°, $[\Phi]_{274}$ +5245°, $[\Phi]_{269}$ +5318°, $[\Phi]_{240}$ +4881°, *a* —90. Crystallization of the second fraction from ethyl acetate gave 295 mg of the isomer *XXVII* m.p. 226—229°C, $[\alpha]_D^{25}$ —92° (methanol, *c* 0·2). Infrared spectrum (nujol): 3370, 1674, 1687, 1705, 1055 cm^{-1}, ν(CO) 1706 cm^{-1} in dioxane). ORD (methanol, *c* 0·2, 25°C): $[\Phi]_{400}$ —971°, $[\Phi]_{350}$ —2233°, $[\Phi]_{325}$ —5438°, $[\Phi]_{315}$ —7185°, $[\Phi]_{310}$ —7768°, $[\Phi]_{304}$ —5826°, $[\Phi]_{294}$ ±0°, $[\Phi]_{285}$ +5341°, $[\Phi]_{272}$ +7962°, $[\Phi]_{260}$ +6797°, *a* —157. For $C_{19}H_{30}O_4$ (322·4) calculated: 70·77% C, 9·38% H; found: 70·92% C, 9·69% H.

17β-Hydroxy-2β,3β-isopropylidenedioxy-5α-androstan-6-one (*XXVIII*)

A solution of the diol *XXVIb* (100 mg) in acetone (20 ml) was treated with *p*-toluenesulfonic acid (10 mg) and the mixture was agitated at room temperature for 2 hours. Solid potassium carbonate (20 mg) was added and the mixture agitated for 15 minutes. The mixture was then passed through a sodium sulfate column and the filtrate was concentrated *in vacuo*. Crystallization of the residue (100 mg) from methanol afforded 55 mg of the derivative *XXVIII*, m.p. 244—246°C, $[\alpha]_D^{20}$ —2° (*c* 1·0). Infrared spectrum (chloroform): 3610, 1708, 1247, 1050 cm^{-1}. ORD (*c* 0·1, 25°C): $[\Phi]_{260}$ +5539°, $[\Phi]_{275}$ +5974°, $[\Phi]_{285}$ +4670°, $[\Phi]_{298}$ ±0°, $[\Phi]_{304}$ —2498°, $[\Phi]_{306}$ —2770°, $[\Phi]_{313}$ —3992°, $[\Phi]_{320}$ —2770°, $[\Phi]_{335}$ —1032°, $[\Phi]_{375}$ —163°, *a* —100. For $C_{22}H_{34}O_4$ (362·5) calculated: 72·89% C, 9·45% H; found: 72·77% C, 9·29% H.

17β-Hydroxy-2β,3β-isopropylidenedioxy-5β-androstan-6-one (*XXIX*)

A solution of the diol *XXVII* (100 mg) in acetone (20 ml) was treated with *p*-toluenesulfonic acid (10 mg) and the mixture was agitated at room temperature for 2 h. The same workup as in the case of the preparation of the compound *XXVIII* gave 130 mg of an oil which which was chromatographed on two plates of silica gel (20 × 20 cm) in benzene–ethyl acetate (3 : 7). The corresponding zones were collected, eluted with ether and the solvent evaporated *in vacuo*. Crystallization of the residue (100 mg) from aqueous methanol afforded 75 mg of the derivative *XXIX*, m.p. 173—175°C, $[\alpha]_D^{20}$ —56° (*c* 0·6). Infrared spectrum (chloroform): 3605, 1703 cm^{-1}. ORD (*c* 0·1, 25°C): $[\Phi]_{265}$ +6832°, $[\Phi]_{275}$ +7494°, $[\Phi]_{285}$ +6281°, $[\Phi]_{298}$ ±0°, $[\Phi]_{308}$ —5620°, $[\Phi]_{313}$ —6612°, $[\Phi]_{318}$ —7273°, $[\Phi]_{325}$ —5730°, $[\Phi]_{350}$ —2094°, $[\Phi]_{400}$ —992°, *a* —148. For $C_{22}.H_{34}O_4.1\ CH_4O$ (394·5) calculated: 70·02% C, 9·71% H; found: 69·52% C, 9·59% H.

The Equilibration of 17β-Hydroxy-2β,3β-isopropylidenedioxy-5α-androstan-6-one (*XXVIII*) and Its 5β-Isomer *XXIX*

A solution of the derivative *XXVIII* (150 mg) in methanol (15 ml) was treated with an aqueous potassium carbonate solution (75 mg in 1·5 ml) and the mixture was refluxed in nitrogen atmosphere for 7 h (water bath, 88°C). After concentrating to one third of the volume *in vacuo* the reaction mixture was poured into water and the product extracted with chloroform. The chloroform extract was washed with water, dried over sodium sulfate and evaporated *in vacuo*. The residue (150 mg) afforded after crystallization from methanol 125 mg of the 5α-isomer *XXVIII*, m.p. 244—244·5°C, $[\alpha]_D^{22}$ —2·5° (*c* 1·0).

The 5β-Isomer *XXIX* (150 mg) was equilibrated by the same manner as *XXVIII*. The crude product (145 mg) afforded after crystallization from methanol 129 mg of the 5α-isomer *XXVIII*, m.p. 243—245°C, $[\alpha]_D^{22}$ —2° (*c* 1·0).

2β,3β,20β-Trihydroxy-5β-pregnan-6-one (*XXXI*)

A solution of 2β,3β,20β-trihydroxy-5α-pregnan-6-one (*XXX*, ref.[2], 330 mg) in methanol (50 ml) was treated with an aqueous potassium carbonate solution (115 mg in 2 ml) and left at 37°C for 60 h. After concentrating to one third of the volume the reaction mixture was poured into water, the product collected by suction and washed with water. The filtrate was extracted with chloroform, the extract washed with water, dried over sodium sulfate and evaporated *in vacuo*. The residue was combined with the still moist product obtained by filtration, methanol and ethyl acetate were added and the solution was evaporated *in vacuo*. The residue (300 mg) gave after chromatography on silica gel (40 g) in benzene–ethyl acetate (gradient elution) two fractions. The less polar one was crystallized from ethyl acetate–heptane to give 110 mg of the 5α-isomer *XXX*, m.p. 241—244°C, $[\alpha]_D^{22}$ —18° (methanol, *c* 0·1). ORD (methanol, *c* 0·1, 24°C): $[\Phi]_{260}$ +6487°, $[\alpha]_{272}$ +7085°, $[\Phi]_{279}$ +6213°, $[\Phi]_{293}$ ±0°, $[\Phi]_{300}$ —3924°, $[\Phi]_{305}$ —5559°, $[\Phi]_{310}$ —5287°, $[\Phi]_{311}$ —5450°, $[\Phi]_{314}$ —4960°, $[\Phi]_{375}$ —763°, *a* —126. Recrystallization of the second fraction from ethyl acetate afforded 90 mg of the 5β-isomer *XXXI*, m.p. 219—221°C, $[\alpha]_D^{26}$ —96° (methanol, *c* 0·1). Infrared spectrum (nujol): 3525, 3410, 3270, 1697, 1731 cm^{-1}. ORD (methanol, *c* 0·1, 26°C): $[\Phi]_{260}$ +7010°, $[\Phi]_{271}$ +8141°, $[\Phi]_{275}$ +8141°, $[\Phi]_{282}$ + 6784°, $[\Phi]_{294}$ ±0°, $[\Phi]_{304}$ —6784°, $[\Phi]_{310}$ —8593°, $[\Phi]_{320}$ —7236°, $[\Phi]_{350}$ —2488°, $[\Phi]_{400}$ —1131°, *a* —167. For $C_{21}H_{34}O_4$ (350·5) calculated: 71·96% C, 9·78% H; found: 70·71% C, 9·46% H.

The Equilibration of 2β,3β-Dihydroxy-5α-androstane-6,17-dione (*XXXIV*) and Its 5β-Isomer *XXXV*

A solution of the diol[3] *XXXIV* (150 mg) in methanol (15 mg) was treated with an aqueous potassium carbonate solution (75 mg in 1·5 ml) as in the case of *XXVIII*. After evaporating the chloroform solution *in vacuo*, the residue (150 mg) was chromatographed on silica gel (20 g) in benzene–ethyl acetate (gradient elution) to give two fractions. The less polar one was crystallized from ethyl acetate–heptane to furnish 46 mg of the 5α-isomer *XXXIV*, m.p. 243—244·5°C, $[\alpha]_D^{22}$ +66° (*c* 1·0) in accordance with literature[3]. The second fraction (84 mg) yielded after recrystallization from ethyl acetate–heptane 55 mg of the 5β-isomer *XXXV*, m.p. 214—216°C, $[\alpha]_D^{22}$ —14·5° (*c* 1·0) in accordance with the literature[3].

The 5β-isomer (150 mg) was equilibrated in the same manner. Chromatography of the crude product (150 mg) on silica gel afforded 63 mg of the 5α-isomer *XXXIV* and 83 mg of the 5β-isomer *XXXV*.

The Equilibration of 2β,3β-Dihydroxy-5α-cholestan-6-one (*XXXII*) and Its 5β-Isomer *XXXIII*

A solution of the diol *XXXII* (ref.[1]) (100 mg) in methanol (10 ml) was treated with an aqueous potassium carbonate solution (50 mg in 1 ml) and the mixture was refluxed in nitrogen atmosphere for 7 h (water bath, 88°C). The reaction mixture was worked up as in the case of *XXXIV*. The residue (100 mg) gave after chromatography on silica gel (10 g) in benzene–ethyl acetate (gradient elution) 38 mg of the 5α-isomer *XXXII*, m.p. 213—215°C (ethyl acetate–heptane), $[\alpha]_D^{22}$ +4° (*c* 1·0) and 57 mg of the 5β-isomer *XXXIII*, m.p. 178—180°C (ethyl acetate–heptane), $[\alpha]_D^{22}$ —56° (*c* 1·0) (ref.[1]).

The 5β-isomer *XXXIII* was equilibrated by the same manner. The crude product (100 mg) was chromatographed on silica gel to give 35 mg of the 5α-isomer *XXXII* and 55 mg of the 5β-isomer *XXXIII*.

The Equilibration of 5α- and 5β-Isomeric 6-Ketones *Vb*, *VI*; *XXXII*, *XXXIII*; *XVIII*, *XIX*; *XXXIV*, *XXXV*; *XXIVb*, *XXV*; *XXVIb*, *XXVII*; *XXIb*, *XXII*; *XXVIII*, *XXIX*

A solution of the ketone (10 mg) in methanol (2 ml) was treated with an aqueous potassium carbonate solution (5%, 0·1 ml) and the reaction mixture was left at 33·5°C for 88 h (only in the case of the compounds *XXIIIb* and *XXIV* the reaction mixture was allowed to stand for 176 hours because of the lesser solubility of these compounds). The reaction mixture was then poured into water and the product extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated *in vacuo* at 25°C. The composition of the equilibrium mixtures was then determined by measuring the molecular rotations of the methanolic solutions of the mixtures and of the pure isomers at the chosen wave length (Table I).

ORD curves 2β,3β-*Dihydroxy*-5α-*androstane*-6,17-*dione* (XXXV); (methanol, *c* 0·172, 25°C): $[\Phi]_{400}$ +1023°, $[\Phi]_{330}$ +3627°, $[\Phi]_{316}$ +6138°, $[\Phi]_{310}$ +5906°, $[\alpha]_{297}$ ±0°, $[\Phi]_{290}$ —2976°, $[\Phi]_{278}$ —5115°, $[\Phi]_{270}$ —4743°, $[\Phi]_{230}$ —2976°, a = +112·5. 2β,3β-*Dihydroxy*-5β-*androstane*-6,17-*dione* (XXXVI); (methanol, *c* 0·075, 25°C): $[\Phi]_{400}$ ±0°, $[\Phi]_{350}$ ±0°, $[\Phi]_{327}$ +151°, $[\Phi]_{320}$ +516°, $[\Phi]_{316}$ +688°, $[\Phi]_{313}$ +387°, $[\Phi]_{311}$ ±0°, $[\Phi]_{300}$ —1548°, $[\Phi]_{298}$ —1720°, $[\Phi]_{295}$ —1591°, $[\Phi]_{290}$ —2064°, $[\Phi]_{275}$ —473°, $[\Phi]_{240}$ ±0°, a = +27·5. 2β,3β-*Dihydroxy*-5α-*cholestan*-6-*one* (XXXIII)[1]; (methanol, *c* 0·1, 20°); $[\Phi]_{450}$ —290°, $[\Phi]_{306}$ — 3570°, $[\Phi]_{310}$ —3310°, $[\Phi]_{270}$ +5710°, $[\Phi]_{245}$ +5060°, $[\Phi]_{230}$ +5650°, a = —93. 2β,3β-*Dihydroxy*-5β-*cholestan*-6-*one* (XXXIV)[1]; (methanol, *c* 0·1, 20°): $[\Phi]_{400}$ —1130°, $[\Phi]_{310}$ —9010°, $[\Phi]_{274}$ +9630°, $[\Phi]_{234}$ +6440°, $[\Phi]_{218}$ +7570°, a = —186.

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