INTRAMOLECULAR HYDRIDE SHIFT IN SOME STEROID HYDROXY ALDEHYDES AND HYDROXY KETONES*

A. KASAL and A. TRKA

Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6

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A number of steroid γ- and δ-hydroxy aldehydes and γ- and δ-hydroxy ketones was prepared. These substances were exposed to alkalies in the presence of deuterium oxide and the reaction products were analysed by mass spectrometry. The intramolecular hydride transfer was detected in the case of δ-hydroxy carbonyl substrates only.

In an earlier paper[1] in which we reported on the formation of γ- and δ-lactones during Oppenauer oxidation of dihydroxysteroids we presented proof of an intramolecular hydride ion rearrangement during oxidation. This hydride ion transfer was interpreted as an isomerization of the intermediary aldehydo-ketone (intramolecular Tishchenko reaction) or even of the hydroxy carbonyl derivative (intramolecular Meerwein–Pondorff-Oppenauer reaction). It seemed that the last mentioned reaction takes place with the δ- but not with the γ-hydroxy carbonyl substrates. In this paper we report on the attempts at redox isomerization of several additional γ- and δ-hydroxy carbonyl derivatives.

For the preparation of starting hydroxy aldehydes the reduction of corresponding lactones with some of the reducing reagents (sodium, diborane, boranes, complex hydrides) came into consideration. We found that in boiling benzene or toluene a practically quantitative reduction of lactones *I*, *III*, *V*, *VII*, *XII* and *XIV* may be achieved with tri-tert-butoxylithium aluminum hydride[2]. It was observed that lactone *IX* is stable in the presence of this reagent, even for prolonged reaction times. Chromatography of crude products on silica gel thin layers showed that in no case did a detectable reduction of the corresponding hemiacetal to diol or triol take place. In the IR spectra of the products (except for compound *VIII*) no absorption for the aldehyde group could be detected (see Table I). In all the ^{1}H-NMR spectra of the products the signals of the —OCHO— grouping were present in the 4·8 to 5·6 ppm region. However, they show that the substances are not of uniform configuration

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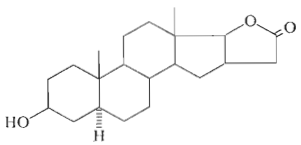
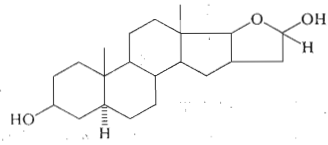


I



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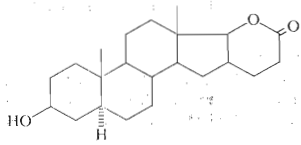

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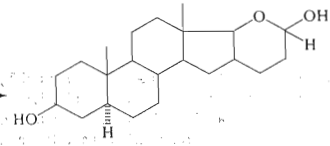

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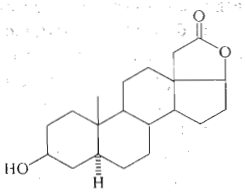

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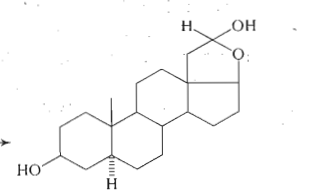

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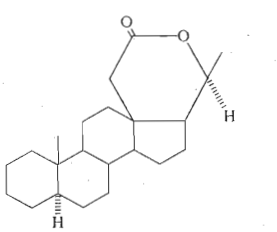

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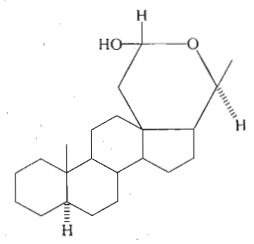

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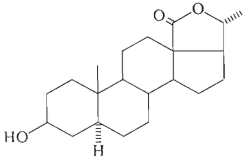
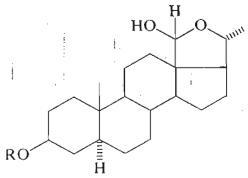
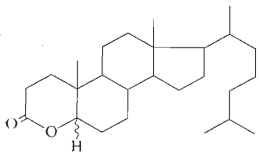


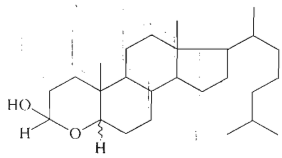
IX



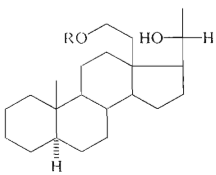
X, R = H
XI, R = Ac



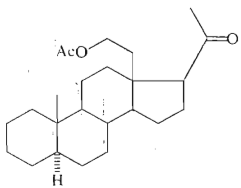
XII, 5α-H
XIV, 5β-H



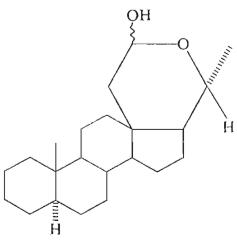
XIII, 5α-H
XV, 5β-H



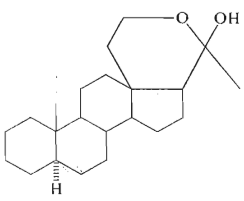
XVI, R = H
XVII, R = Ac



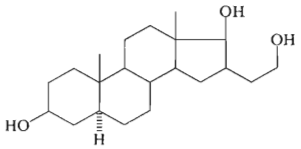
XVIII



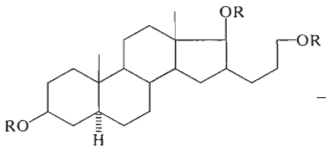
XIX



XX

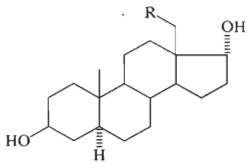


XXI → *XXII*



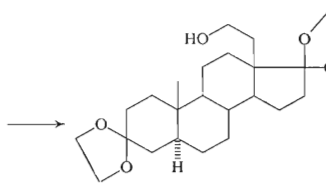
XXIII, R = H
XXV, R = Ac

XXIV, R = H
XXVI, R = Ac

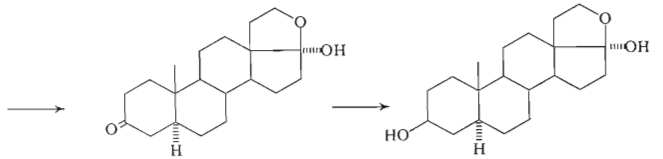


XXVII, R = CN
XXVIII, R = $CONH_2$

XXIX, R = $COOCH_3$
XXX, R = $CONH_2$



XXXI → *XXXII*



XXXIII *XXXIV*

of the newly introduced asymmetry centre; this fact is probably due both to the small stereospecificity of the reduction itself, and to the working-up method and the manipulation[3].

The required hydroxy ketones or their derivatives *XVIII*, *XX*, *XXII*, *XXIV* were prepared by oxidation of diols in which the primary hydroxyl group was temporarily protected by tritylation or acetylation. An alternative route was employed for the preparation of 3β,18α-dihydroxy-18-homo-5α-androstan-17-one (*XXXIV*) which was prepared from 18-cyano-5α-androstan-3β,17α-diol[4] (*XXVII*). Alkaline hydrolysis, esterification with diazomethane and oxidation with chromium trioxide in pyridine gave diketo ester *XXIX*. The reduction of the methoxycarbonyl group in compound *XXIX* to a hydroxymethyl group was carried out with lithium alu-

TABLE I

Frequencies and Integrated Intensities of the (C=O) Bands of Carbonyl Derivatives

Compound[a]	*VIII*[b,c]	*XXII*	*XXIV*	*XXXIV*[b]
ν_{max}	1 710	1 738	1 738	1 730
B^d	2 225	6 243	9 319	3 496
ν_{max}	—	1 726	1 727	1 721
B^c	—	5 882	3 056	888

[a] The spectra were measured in tetrachloromethane unless otherwise stated. The integrated intensities are given in $cm^{-2}\,l\,mol^{-1}$ and the wave numbers in cm^{-1}; if necessary, the bands were submitted to numerical separation by the method of damped least squares method. In the spectra of compounds *II*, *IV*, *VI*, *XIII*, *XV*, *XIX*, *XX* and *XXXVII* no adsorption bands of either the free or hydrogen bonded carbonyl group were found. The spectra were compared with those of 5α-pregnan-18-al (ν(C=O) 1 726 cm^{-1}, B^d 10988) and 5α-androstan-3β-ol-17-one (ν(C=O) 1 742 cm^{-1}, B^d 13940); [b] The spectrum was measured in chloroform; [c] in the spectrum measured in tetrachloromethane ($c = 5 \cdot 10^{-4}$ mol) absorption bands at 1717 and 3617 cm^{-1} were found; [d] integrated intensity of the free carbonyl group; [e] Integrated intensity of the intramolecularly hydrogen bonded carbonyl group.

minum hydride after preliminary protection of both keto groups in the form of ethylenedioxy derivatives. Acid cleavage of diketal *XXXI* under standard conditions gave predominantly monoketal *XXXII* (IR spectrum: 1705 cm^{-1}, mass spectrum: 362 (M^+)) for the further cleavage of which more drastic conditions had to be used. The fact that the 17-keto group is masked in 18-hydroxymethyl-5α-androstane-3,17--dione in a hemiacetal grouping enabled partial reduction of this substance with complex hydride, under formation of diol *XXXIV*.

The IR spectra of hydroxy ketones used in this paper show that the 18-substituted derivatives occur predominantly (*XXXIV*) or totally (*XX*, *XXXVII*) in hemiacetal form. In 16β-hydroxyalkyl-5α-androstan-17-ones (*XXII*, *XXIV*) the proportion of the hemiacetal form is negligible, but the intramolecular hydrogen bond plays a more important role (see Table I). The behaviour of 3-hydroxy-4-nor-3,5-seco-cholestan-5-one (*XXXV*) in solution has been described earlier[3].

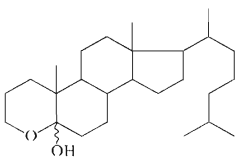
TABLE II

Relative Occurrence of Deuterated Species of Hydroxycarbonyl Derivatives

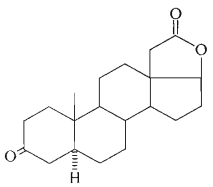
Oxygen-containing groups in positions	Substances	d_0	d_1	d_2	d_3	d_4	d_5	d_6
16b, 17	*II*[a,b,g]	0	3	97	0	—	—	—
	XXII[d]	10	90	0	0	—	—	—
16c, 17	*IV*[a]	12	25	56	7	—	—	—
	XXIV[a]	17	55	15	13	—	—	—
17, 18a	*VI*[b,f]	7	24	69	0	0	—	—
	XXXIV[a]	0	18	82	0	0	—	—
18a, 20	*VIII*[b,g]	4	2	4	8	18	31	33
	XIX[b,g]	0	0	4	11	25	35	25
	XX[c,f]	0	1	10	33	31	17	7
18, 20	*XI*[c,g]	100	0	0	0	0	—	—
	XXXVII[c,g]	5	13	16	29	37	—	—
3, 5	*XIII*[b,f]	2	7	56	7	28	—	—
	XV[b,f]	17	17	61	4	1	—	—
	XXXV[b,e]	0	2	12	36	50	—	—

[a] The substance gives a strong molecular signal and the product was analysed directly; [b] the product was analysed after oxidation to the corresponding lactone; [c] the product was reduced with lithium aluminum hydride and then oxidized according to Jones to lactone; [d] the product was converted to trimethylsilyl ether and then analysed; [e] the yield of the lactone in the oxidation of the product according to Jones is 23%; [f] the yield of the lactone is 80%; [g] the yield of the lactone is over 90%.

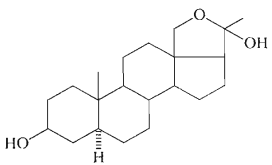
For the proof of the intramolecular character of the possible redox reaction a method[5] was used consisting in the exchange of hydrogen atoms in α-positions to the carbonyl group. Attempts at redox isomerisation of hydroxycarbonyl substances were carried out by heating with alkaline alumina[6] containing deuterium oxide. When intramolecular redox equilibrium is attained between the carbinol and the carbonyl group, the number of deuterium atoms entering into the molecule corresponds to the number of hydrogen atoms in α-positions to both oxygen functions. This number was determined on the basis of the mass spectra of the products or of their trimethylsilyl ethers, or from the products of subsequent



XXXV



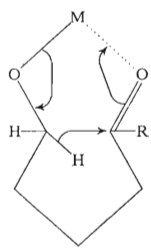
XXXVI



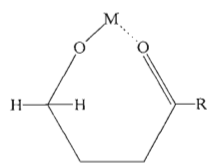
XXXVII

oxidation, which were compared with the mass spectra of corresponding non-deuterated standards (Table II). The method was also checked on substrates from the preceding study[1] where the hydride ion shift was proved preparatively (cases *XI*, *XIX*, *XX*). If the products of deuteration of both redox isomers were used for the measurement, the method afforded reliable results. From Table II it follows that the intramolecular hydride shift has been proved in all δ-hydroxy aldehydes and δ-hydroxy ketones tested, but it was not proved in any γ-hydroxycarbonyl derivative mentioned here. A lesser aptitude of γ-hydroxycarbonyl derivatives to undergo a redox reaction under the given conditions cannot be explained only by differing stability of the corresponding cyclic hemiacetals: in this group substance *XXII* does not undergo

redox isomerization either, even though this substance exists at 35°C in solution to about 50% in the open form; it is probable[7] that at the temperature of the reaction the proportion of the open form will be still higher. We believe that the difference between the reactivity of δ- and γ-hydroxycarbonyl derivatives depends on the steric arrangement of the centres probably reacting in the assumed[8] intermediary type *A* or *B*: the conformation of the first somewhat resembles that of medium-size rings in which the 1,5-hydride shift is common[9]. 1,4-Shifts of the hydride ion are less frequent [10]. The fact that such a migration does not take place between the atoms $C_{(18)}$ and $C_{(20)}$ in substances *X* and *XXXVII*, but that it does take place, even though unwillingly, in the corresponding aldehydo-ketone (ref.[1]), may be explained by supposing that an electronic factor is operative in the intermediate of the Tishchenko reaction, which facilitates the splitting off of the hydride ion.



A



B

EXPERIMENTAL

The melting points were measured on a Kofler block and they are not corrected. Analytical samples were dried over phosphorus pentoxide at 50°C/0·2 Torr. Optical rotation and infrared spectra were measured in chloroform, unless stated otherwise. ^{1}H-NMR spectra were measured in chloroform, unless stated otherwise, on a Varian HA-100 (100 MHz) instrument. The chemical shifts are given in δ-scale (ppm). The mass spectra were measured on an AEI 902 spectrometer. For the chromatography and the isolation of hemiacetals absolute ether was used. Numerical separation of the bands in the IR spectra was carried out on a Hewlett-Packard 9830 apparatus.

3β,17β-Dihydroxy-16β-ethyl-5α-androstan-16b-al, Hemiacetal (*II*)

From a solution of the lactone of 3β,17β-dihydroxy-5α-androstan-16β-ylacetic acid[11] (300 mg, *II*) 30 ml of the azeotropic mixture was distilled off. After addition of tri-tert-butoxylithium aluminum hydride the mixture was refluxed for one hour, then cooled and poured into a solution of sodium potassium tartrate (about 150 ml). The product was extracted with chloroform and the extract dried by filtration through a bed of sodium sulfate. The solvent was evaporated under

reduced pressure and the product crystallized from acetone–heptane. M.p. 208–217°C, $[\alpha]_D^{20}$ +60° (*c* 1·0, pyridine); IR spectrum: 3370, 1056, 1037, 1018, 1001 and 952 cm^{-1}; ^{1}H-NMR: 0·65 (s, 18-H), 0·79 (s, 18-H), 3·42 (mt, 3-H), 4·12 (d, J = 9·4 Hz, 17-H), 5·59 (d, J = 4·5 Hz, 16b-H) ppm. For $C_{21}H_{34}O_3$ (334·4) calculated 75·40% C, 10·25% H; found: 75·19% C, 10·27% H.

3β,17β-Dihydroxy-16β-propyl-5α-androstan-16c-al, Hemiacetal (*IV*)

In a similar manner the lactone of 3β,17β-dihydroxy-5α-androstan-16β-yl-propionic acid[12] (330 mg, *III*) was converted to substance *IV*, m.p. 148–152°C (acetone), $[\alpha]_D^{20}$ +63° (*c* 1·5, pyridine); IR spectrum (nujol): 3300, 1135, 1104, 1072, 1042, 1000 cm^{-1}; ^{1}H-NMR (pentadeuteriopyridine): 0·83 and 0·84 (s, 18-H and 19-H), 3·66 (mt, 3-H), 3·89 (d, J = 9 Hz, 16-H) and 5·52 (mt, 16c-H) ppm. For $C_{22}H_{36}O_3$ (348·5) calculated: 75·81% C, 10·41% H; found: 75·50% C, 10·55% H.

3β,17β-Dihydroxy-18-homo-5α-androstan-18a-al, Hemiacetal (*VI*)

Similarly as above the lactone of 3β,17β-dihydroxy-5α-androstan-18-carboxylic acid[4] (55 mg, *V*) was converted to compound *VI*, m.p. 160–167°C (acetone and heptane), $[\alpha]_{20}^{D}$ +4° (*c* 1·3, pyridine); IR spectrum: 3625, 1119, 1089, 1040, 1008 cm^{-1}; ^{1}H-NMR spectrum (hexadeuteriodimethyl sulfoxide): 0·72 (s, 19-H), 5·37 (mt, 18a-H) ppm. For $C_{20}H_{32}O_3$ (304·5) calculated: 78·89% C, 10·60% H; found: 78·60% C, 10·84% H.

20α-Hydroxy-18-homo-5α-pregnan-18a-al, Hemiacetal (*VIII*)

Similarly, the lactone of 20α-hydroxy-5α-pregnan-18-carboxylic acid[1] (*VII*, 130 mg) was converted to substance *VIII*, m.p. 163–166°C (acetone), $[\alpha]_D^{20}$ +52° (*c* 2·0, pyridine); IR spectrum: 3600, 1171, 1105, 1098, 1062, 1046 and 1015 cm^{-1}. ^{1}H-NMR: 0·76 (s, 19-H), 1·14 (d, J = 6·5 Hz, 21-H), 3·11 (s, OH), 3·83 (q, J = 6·5 Hz, 20-H) and 4·83 (dd, J = 10 and 2 Hz, 18a-H) ppm. For $C_{22}H_{36}O_2$ (332·5) calculated: 79·46% C, 10·91% H; found: 79·31% C, 10·72% H.

4-Oxa-5β-cholestan-3ξ-ol (*XV*)

4-Oxa-5β-cholestan-3-one[13] (*XIV*) was reduced under the above given conditions for 20 minutes. The product was chromatographed on a thin layer of silica gel (10% of ether in benzene, detection with morin in aqueous acetone, elution with ether). M.p. 103–106°C, $[\alpha]_D^{20}$ +14° (*c* 2·0, pyridine); ^{1}H-NMR spectrum: 0·67 (s, 18-H), 0·84 (s, 19-H), 0·87 (d, J = 6 Hz, 26 and 27-H), 0·91 (d, J = 6·6 Hz 21-H), 3·30 and 3·83 (mt, 5-H) and 4·73 and 5·30 (mt, 3-H) ppm; (deuteriopyridine); 0·66 (s, 18-H), 0·79 (s, 19-H), 0·89 (d, J = 6 Hz, 26 and 27-H). 0·93 (d, J = 6·5 Hz, 21-H), 3·27 and 4·04 (mt, 5-H), 4·83 and 5·46 (mt, 3-H) ppm. For $C_{26}H_{46}O_2$ (390·6) calculated: 79·94% C, 11·87% H; found: 79·97% C, 11·86% H.

4-Oxa-5α-cholestan-3α-ol (*XIII*)

Similarly, 4-oxa-5α-cholestan-3-one[13] (*XII*, 58 mg) was converted to dihydroderivative[13] *XIII* (46 mg) which after crystallization from acetone and heptane melted at 190–193°C (literature gives 188–190°C).

Attempt at Reduction of Lactone of 3β,20β-Dihydroxy-5α-pregnan-18-oic Acid

A solution of lactone[14] *IX* (50 mg) in 15 ml of xylene was concentrated by azeotropic distillation to half its volume, then mixed with 150 mg of tri-tert-butoxylithium aluminum hydride and

refluxed for 3 hours. After the conventional work-up a product was obtained the IR spectrum of which was identical with that of the starting compound.

18a-Acetoxy-18-homo-5α-pregnan-20β-ol (*XVII*)

A solution of 18a,20β-dihydroxy-18-homo-5α-pregnane[1] (*XVI*, 80 mg) in 90% aqueous acetic acid (20 ml) was refluxed for 50 minutes, concentrated *in vacuo* and the product (55 mg) isolated from the unreacted product (25 mg) by thin layer chromatography on silica gel (50% ether in benzene, $R_F = 0{\cdot}70$). M.p. 115–117°C (acetone, water); $[\alpha]_D^{20}$ 0° (*c* 0·9); ^{1}H-NMR spectrum: 0·80 (s, 19-H), 1·15 (d, $J = 6$ Hz, 21-H), 2·04 (s, $COCH_3$), 3·77 (mt, 20-H) and 4·34 (mt, $W_{1/2} = 42$ Hz, 18a-H_2) ppm. For $C_{24}H_{40}O_3$ (376·6) calculated: 76·55% C, 10·71% H; found: 76·46% C, 10·62% H.

18-Acetoxy-18-homo-5α-pregnan-20-one (*XVIII*)

Hydroxy ketone *XVII* (55 mg) was oxidized according to Jones to give a crude product melting at 94–96°C (51 mg), which after crystallization from aqueous acetone had m.p. 98–99°C, $[\alpha]_D^{20}$ +65° (*c* 0·9); IR spectrum (CCl_4): 1741, 1238, 1036 and 1706 cm^{-1}. ^{1}H-NMR spectrum: 0·81 (s, 19-H), 2·02 (s, $OCOCH_3$), 2·20 (s, 21-H), 3·60 (ddd, $J = 10$, 10 and 6 Hz, 18a-H), 4·03 (mt, 18a-H) ppm. For $C_{24}H_{38}O_3$ (374·5) calculated: 76·96% C, 10·23% H; found: 80·05% C, 10·31% H.

3β,16b-Dihydroxy-16β-ethyl-5α-androstan-17-one (*XXII*)

A suspension of 16β-ethyl-5α-androstan-3β,16b,17β-triol[15] (*XXI*, 200 mg) and triphenylmethyl chloride (500 mg) in pyridine (4 ml) was heated at 105°C for 3 hours, under exclussion of moisture. The mixture was evaporated in a vacuum and the residue dissolved in 3 ml of acetone and oxidized with Jones's reagent at room temperature. After 6 minutes' standing it was diluted with an aqueous solution of potassium hydrogen carbonate and the product was extracted with ether, the extract washed with a saturated sodium chloride solution and dried by filtration through a bed of sodium sulfate. After evaporation of the filtrate the residue was heated with 30 ml of acetic acid and 3 ml of water for 10 minutes, then cooled and concentrated *in vacuo*. The product was precipitated with water (20 ml) and filtered off under suction. The precipitate was dissolved in acetone, stirred with 1 g of silica gel, and the suspension dried in a vacuum. The dry material was transferred onto a column of silica gel (30 ml) and eluted with 50% of ether in benzene (50 ml). Dihydroxy ketone *XXII* (150 mg) was thus obtained which was crystallized from acetone and heptane, m.p. 181–183°C, $[\alpha]_D^{20}$ +83° (*c* 1·3, pyridine). ^{1}H-NMR (pentadeuteriopyridine): 0·86 (s, 18- and 19-H), 3·60 (mt, 3-H) and 3·76 (mt, 16b-H) ppm. IR spectrum (KBr): 1738 and 1047 cm^{-1}. For $C_{21}H_{34}O_3$ (334·5) calculated: 75·40% C, 10·25% H; found: 75·18% C, 10·13% H.

3β,16c-Dihydroxy-16β-propyl-5α-androstan-17-one (*XXIV*)

In a similar manner 16β-propyl-5α-androstan-13β,16c,17β-triol (*XXIII*, 160 mg) was converted to the corresponding dihydroxy ketone which was purified by chromatography on silica gel thin layers (25% of ether in benzene, detection with morin in acetone, R_F 0·25). The product (102 mg, m.p. 155–178°C) was crystallized from acetone and heptane, m.p. 180–185°C, $[\alpha]_D^{20}$ +65° (*c* 1·2, pyridine); IR spectrum: 1728, 3615 and 1038 cm^{-1}; ^{1}H-NMR (pentadeuteriopyridine): 0·82 (s, 19-H), 0·79 (s, 18-H), 3·70 (t, $J = 6$ Hz, 16c-H), 3·55 (mt, 3-H) ppm. For $C_{22}H_{36}O_3$ (348·5) calculated: 75·81% C, 10·41% H; found: 75·68% C, 10·36% H.

3β,16c-Diacetoxy-16β-propyl-5α-androstan-17-one (*XXVI*)

Acetylation of substance *XXIV* with acetic anhydride in pyridine afforded a diacetate, m.p. 141–144°C (methanol), $[\alpha]_D^{20}$ +73° (*c* 0·7); CD spectrum (methanol): λ_{max} 306 nm ($\Delta\varepsilon$ +3·94); IR spectrum: 1730 and 1248 cm^{-1}; ^{1}H-NMR: 0·86 (s, 19-H), 0·91 (s, 18-H), 2·04 and 2·02 (s, CH_3COO), 4·05 (t, J = 6·5 Hz, 16c-H) ppm. For $C_{26}H_{40}O_5$ (432·6) calculated: 72·19% C, 9·32% H; found: 72·16% C, 9·37% H.

3β,16c,17β-Trihydroxy-16β-propyl-5α-androstane (*XXIII*)

A solution of the lactone of 3′-(3β,17β-dihydroxy-5α-androstan-16β-yl)propionic acid[12] (2 g) in tetrahydrofuran (50 ml) was refluxed with lithium aluminum hydride (about 0·5 g). After 4 hour's refluxing the excess reagent was decomposed with a saturated sodium sulfate solution and the mixture saturated with anhydrous sodium sulfate. Inorganic material was then filtered off and the filtrate concentrated in a vacuum; the residue melted at 229–231°C (benzene, 1·3 g), $[\alpha]_D^{20}$ +9° (*c* 0·7, pyridine); ^{1}H-NMR (pentadeuteriopyridine): 0·70 and 0·78 (s, 18- and 19-H), 3·71 (t, J = 6·5 Hz, 16c-H), 3·63 (d, J = 10 Hz, 17-H), 4·40 (mt, 3-H) ppm; mass spectrum: *m/e* 350 (M^+); For $C_{22}H_{38}O_3$ (350·5) calculated: 75·38% C, 10·93% H; found: 74·93% C, 10·94% H.

3β,16c,17β-Triacetoxy-16β-propyl-5α-androstane (*XXV*)

Acetylation of triol *XXIII* (70 mg) with acetic anhydride in pyridine at room temperature afforded triacetate *XXV*, m.p. 127–129°C (methanol), $[\alpha]_D^{20}$ +15° (*c* 1·3), ^{1}H-NMR: 0·78 (s, 18-H), 0·83 (s, 19-H), 2·00, 2·02 and 2·06 (s, CH_3COO), 4·01 (t, J = 6·5 Hz, 16c-H), 4·66 (d, J = 10 Hz, 17-H) and 4·68 (mt, 3-H) ppm. For $C_{28}H_{44}O_6$ (476·6) calculated: 70·55% C, 9·30% H; found: 70·48% C, 9·31% H.

Methyl Ester of 3,17-Dioxo-5α-androstan-18-carboxylic Acid (*XXIX*)

3β,17α-Dihydroxy-18-cyano-5α-androstane[4] (*XXVII*, 1·4 g) was refluxed in a solution of 7·3 g of potassium hydroxide in 40 ml of methanol for 100 h. The mixture was diluted with water (about 100 ml) and evaporated in a vacuum to about half its volume. After acidification with hydrochloric acid the mixture was extracted with chloroform, the extract washed with water, dried over sodium sulfate and evaporated. The residue was dissolved in methanol and mixed with an ethereal diazomethane solution. After 10 minutes the volatile material was evaporated under reduced pressure and the residue oxidized with chromium trioxide (6 g) in pyridine (70 ml). After 48 hours the mixture was poured into a solution of potassium hydrogen carbonate and the product extracted with ether. The extract was washed with dilute hydrochloric acid, water, and potassium hydrogen carbonate solution, and dried. After evaporation the residue was dissolved in a mixture of benzene and ether (10 : 1) and filtered through a silica gel column. The purified product (0·9 g) melted at 100–103°C, $[\alpha]_D^{20}$ +98° (*c* 1·1). IR spectrum: 1742 and 1710 cm^{-1}; ^{1}H-NMR spectrum: 1·06 (s, 19-H), 3·63 (s, OCH_3) ppm. For $C_{21}H_{30}O_4$ (346·4) calculated: 72·80% C, 8·73% H; found: 72·71% C, 8·69% H.

Amide of 3β,17α-Dihydroxy-5α-androstan-18-carboxylic Acid (*XXVIII*)

When crude 3β,17α-dihydroxy-5α-androstan-18-carboxylic acid from the preceding experiment was extracted with chloroform a precipitate was formed between the aqueous and the chloroform layers. The precipitate was separated by filtration and the solid material dissolved in excess chloro-

form, dried by filtration over sodium sulfate and crystallized from a mixture of benzene and chloroform. M.p. 269—272°C, IR spectrum (KBr): 3200, 1670, 1625 and 1045 cm^{-1}. For $C_{20}H_{33}NO_3$ (335·9) calculated: 71·60% C. 9·91% H. 4·18% N; found: 71·28% C, 9·90% H, 4·06% N.

Amide of 3.17-Dioxo-5α-androstan-18-carboxylic Acid (*XXX*)

Oxidation of diol *XXVIII* with chromium trioxide in pyridine and conventional working up of the reaction mixture gave diketone *XXX*, m.p. 281—283°C, $[\alpha]_D^{20}$ +120° (*c* 1·1, chloroform with 10% of methanol); IR spectrum (KBr): 1705, 1695, 1665, 3270 cm^{-1}; mass spectrum: 331 *m/e* (M^+), 313 ($M^+ - H_2O$), 273 (base peak, $M^+ - CH_2CONH_2$); ^{1}H-NMR spectrum (Polysol): 0·92 (s, 19-H), 7·83 (mt, NH_2) ppm. For $C_{20}H_{29}NO_3$ (331·4) calculated: 72·47% C, 8·82% H, 4·23% N; found: 72·49% C, 8·66% H, 4·27% N.

3,3 : 17,17-Bisethylenedioxy-18-homo-5α-androstan-18a-ol (*XXXI*)

Diketo ester *XXIX* (53 mg), *p*-toluenesulfonic acid (40 mg) and 10 ml of ethylene glycol were refluxed in toluene (50 ml) for 6 h, using a Dean-Stark separator. The mixture was diluted with benzene, washed with a potassium hydrogen carbonate solution and water, dried and evaporated in a vacuum. The end of the reaction was checked by thin layer chromatography in 25% ether in benzene. The R_F value of the starting compound was 0·22 and that of the product 0·33. The crude diketal was refluxed with lithium aluminum hydride in dioxan for 5 h. The reaction mixture was decomposed by pouring it into a solution of sodium potassium tartrate and the product was purified by thin layer chromatography on silica gel (50% of ether in benzene, R_F 0·51). Yield, 40 mg of a product melting at 116—124°C, which after crystallization from acetone and heptane had m.p. 136—139°C; mass spectrum: *m/e* 406 (M^+), 307 and 281. For $C_{24}H_{38}O_5$ (406·6) calculated: 70·90% C, 9·42% H; found: 70·66% C, 9·53% H.

3-Oxo-17,17-ethylenedioxy-18-homo-5α-androstan-18a-ol (*XXXII*)

a) Diketal *XXXI* (20 mg) was mixed with a solution of *p*-toluenesulfonic acid (20 mg) in acetone (1·5 ml). After 18 h standing at 20°C the solution was diluted with 50 ml of benzene, concentrated *in vacuo* to one tenth of its volume, washed with a potassium hydrogen carbonate solution and water, dried over sodium sulfate and concentrated in a vacuum. The residue was purified by thin layer chromatography on silica gel (ether, R_F 0·50, 10 mg), m.p. 164—166°C. Mass spectrum: *m/e* 362 (M^+), 301, 300, 263 and 206; IR spectrum (KBr): 3400, 3580, 1705, 1215, 1145, 1138, 1072 and 1048 cm^{-1}.

b) A solution of diketal *XXXI* (60 mg) in 6 ml aqueous acetic acid (85%) was heated at 85°C for 1 h, then diluted with water (10 ml) and concentrated to half its volume. The product was extracted with benzene and separated by silica gel thin layer chromatography (50% ether in benzene, double development). The main product (35 mg) had m.p. 164—166°C, undepressed with the sample prepared as above. The more polar admixture (15 mg) was identical with compound *XXXII*.

18a-Hydroxy-18-homo-5α-androstan-3,17-dione (*XXXIII*)

a) A solution of diketal *XXXI* (60 mg) in 5 ml of acetic acid and 1 ml of water was refluxed for 4 h, then diluted with 15 ml of water and concentrated in a vacuum to half its volume. The product was extracted with ether, the extract concentrated and the residue chromatographed

on a silica gel thin layer with 50% ether in benzene (double development, detection with morin in aqueous acetone). The product (36 mg) melted at 181–183°C (ether)., $[\alpha]_D^{20}$ +62° (pyridine, *c* 0·8). IR spectrum (KBr): 1711, 3360, 1052 and a negligible band at 1735 cm^{-1}; mass spectrum: 318 *m/e* (M^+), 374 *m/e* (M^+ – 44, base peak); ^{1}H-NMR spectrum: 1·02 (s, 19-H), 3·77 (mt, 18-H) ppm. For $C_{30}H_{30}O_3$ (318·4) calculated: 75·43% C, 9·50% H; found: 75·18% C, 9·57% H.

b) Compound *XXXII* (15 mg) was refluxed with dilute acetic acid (80%; 5 ml) for 4 hours and the mixture was worked up as under *a*). Yield, 6 mg of a substance identical with that from the above experiment.

3β,18a-Dihydroxy-18-homo-5α-androstan-17-one (*XXXIV*)

From a solution of hydroxydione *XXXIII* (25 mg) in toluene (10 ml) about 5 ml of solvent were distilled off, the mixture was cooled, and tri-tert-butoxylithium aluminum hydride (90 mg) added. The mixture was allowed to stand at room temperature for 50 minutes and poured into a solution of Seignett salt and extracted with ether. Thin layer chromatography on silica gel (50% of ether in benzene, double development) gave 18 mg of compound *XXXIV*, m.p. 174 to 177°C (benzene), $[\alpha]_D^{20}$ +41° (*c* 0·8, pyridine). ^{1}H-NMR spectrum: 0·80 (s, 19-H), 3·60 (mt, 3-H) and 3·73 (mt, 18a-H) ppm. IR spectrum: 3615, 3600, 1730, 1077, 1055, 1039 cm^{-1}; mass spectrum: 320 *m/e* (M^+). For $C_{20}H_{32}O_3$ (320·5) calculated: 74·95% C, 10·07% H; found: 74·68% C, 9·88% H.

Isomerization of Hemiacetals

Alkaline alumina was prepared by stirring 40 g of neutral alumina with 100 ml of a 2% aqueous potassium hydroxide solution, the solvent was removed by filtration and alumina was dried, without washing, at 120°C for 8 hours. This product was deactivated with deuterium oxide (10 ml). The tested hemiacetal (1 to 2 mg), alkaline alumina (0·5 g) and xylene (2 ml) were introduced into a 20 ml ampule, air was removed with nitrogen and the ampule sealed and heated in a boiling xylene bath. After 8 hours the mixture was cooled, inorganic material was removed by filtration through a bed of sodium sulfate and washed with absolute ether. The organic solution (about 20 ml) was washed with 1 ml of water, dried and evaporated. The residue was analysed either directly by mass spectrometry (Table II, method *a*), or it was oxidized to lactone (method *b*) or reduced by boiling with a lithium aluminum hydride solution in tetrahydrofuran, and then oxidized (method *c*) or it was converted to trimethylsilyl derivative and analysed as such (method *d*). Oxidations were carried out in acetone with Jones reagent, trimethylsilyl derivatives were prepared by dissolving 1 mg of compound in 0·1 ml of a mixture containing 0·07 ml of pyridine, 0·01 ml of trimethylsilyl chloride and 0·02 ml of hexamethyldisilazan; after 18 h the solution was introduced in to the spectrometer cell. The spectra were evaluated after comparison with the spectra of undeuterated authentic samples.

Lactone of 3-Oxo-17β-hydroxy-5α-androstan-18-carboxylic Acid (*XXXVI*)

Hydroxy lactone *V* (10 mg) was oxidized in acetone with Jones reagent at room temperature. The conventional work-up afforded a product which was purified by silica gel thin-layer chromatography and crystalization from acetone and heptane, m.p. 176–178°C (6 mg). IR spectrum: 1711, 1769, 1191, 1180 cm^{-1}. Mass spectrum: 316 (M^+), 245 and 244 *m/e*.

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