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SYNTHESES OF SOME 3β-ACETOXY-5-HYDROXY-STEROIDS CONTAINING DIFFERENT SUBSTITUENTS AT POSITION 17

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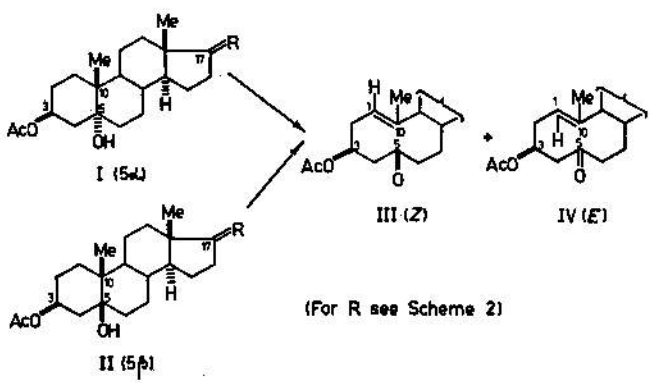
A number of 3β-acetoxy-5-hydroxy-steroids in the 5α (A/B-*trans*) and 5β (A/B-*cis*) series, containing different substituents at C(17) (I and II, a—e), have been synthesized according to the general reaction sequence (Scheme 2) involving conversion of 3β-acetoxy- or 3β-hydroxy-5-olefinic steroids (V) to the corresponding 5α, 6α- and 5β, 6β-epoxy compounds (VI and VII) by means of peracids (the β-epoxides (VII) being also obtainable indirectly from (V) via the α-epoxides (VI); Scheme 4), followed by reductive opening of the oxirane ring in these epoxides with lithium aluminium hydride and acetylation of the 3-hydroxyl group in the resulting 3β, 5α- and 3β, 5β-diols (VIII and IX). The ^{1}H-NMR spectra of these compounds and of other intermediates, such as 5α-androstane-3β,5,6β-triol 3,6-diacetate (XIIId) and triacetate (XIVd), are discussed.

In order to study the effect of configuration at C(5) and the influence of remote substituents (i.e. „long range" effects) on the ease and stereochemical course of the oxidative 5,10-fragmentation of 5-hydroxy-steroids (I and II, Scheme 1), a reaction which involves cleavage of the C(5)—C(10) bond and formation



Scheme 1

of ten-membered ring containing (*Z*)- and (*E*)-1(10)-olefinic 5,10-seco-steroid derivatives (III and IV)[1–3], 5α- and 5β-alcohols (I and II) with different substituents (R) at C(17) were required as substrates.

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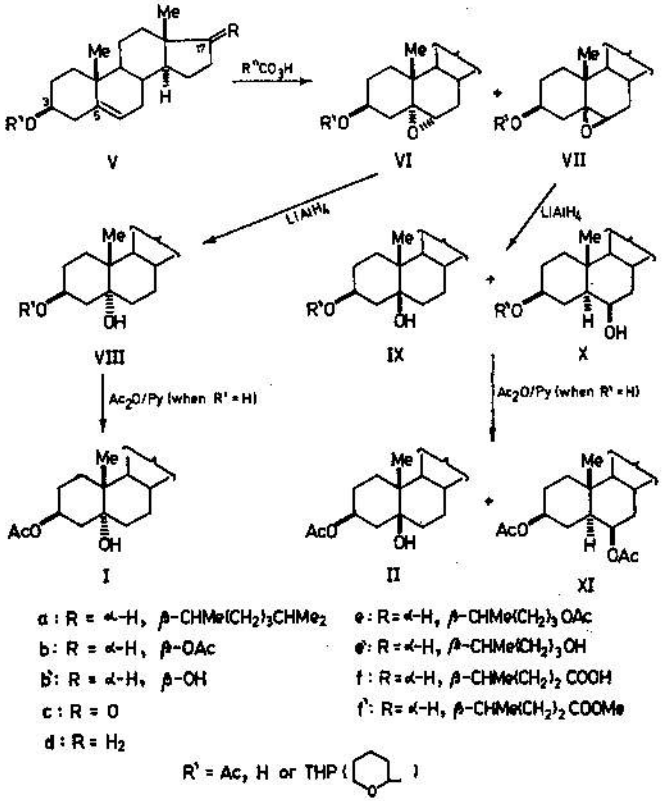
The following 17-substituted and 17-unsubstituted 3β-acetoxy-5-hydroxy--steroids (I and II, Scheme 2) were considered to be convenient substrates for the investigation of this type of fragmentation:

— In the 5α (i.e. A/B-*trans*) series (I): 5α-cholestane-3β,5-diol 3-acetate (Ia), 5α-androstane-3β,5,17β-triol 3,17-diacetate (Ib), 3β,5-dihydroxy-5α-androstan-17-one 3-acetate (Ic), 5α-androstane-3β,5-diol 3-acetate (Id), 5β-cholane--3β,5,24-triol 3,24-diacetate (Ie);

— In the 5β (i.e. A/B-*cis*) series (II): 5β-cholestane-3β,5-diol 3-acetate (IIa), 5β-androstane-3β,5,17β-triol 3,17-diacetate (IIb), 3β,5-dihydroxy-5β-androstan-17-one 3-acetate (IIc), 5β-androstane-3β,5-diol 3-acetate (IId).

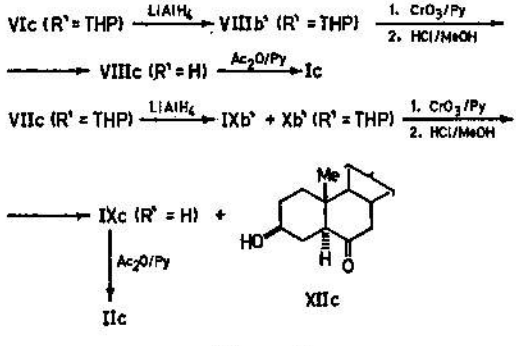


Scheme 2

With the exception of 5β-cholestane-3β,5-diol 3-acetate (IIa), which was obtained from 4β,5-epoxy-5β-cholestan-3β-ol acetate by lithium aluminium hydride reduction and subsequent acetylation of the 3β-hydroxyl group, all the alcohols mentioned above were synthesized according to the reaction sequences outlined in Scheme 2. Epoxidation of the 3β-acetoxy- or 3β-hydroxy-5-olefinic steroids (V, R' = Ac or H) with peracids (monoperphthalic or 3-chloroperbenzoic acid) afforded in high yield the corresponding 5α,6α- and 5β,6β-epoxy compounds (VI and VII, R' = Ac or H), which were separated and subjected to reduction

with lithium aluminium hydride*. In the case of the α-epoxides (VI, R' = Ac or H), the reductive opening of the oxirane ring was regioselective [i.e. attack of hydride took place exclusively at C(6)][4] and gave as only product the 3β,5α-diols (VIII, R' = H), which were converted by acetylation of the 3β-hydroxyl group to the corresponding 3β-acetoxy-5α-hydroxy-steroids (I). In contrast to the α-epoxides (VI, R' = Ac or H), the 5β,6β-epoxy compounds (VII, R' = Ac or H) were not reduced regioselectively by lithium aluminium hydride [attack of hydride taking place at both C(6) and C(5)][4], but afforded mixtures of the 3β,5β-diols (IX, R' = H) and the isomeric 3β,6β-dihydroxy-5α-steroids (X, R' = H) (in variable ratios depending upon the epoxide reduced), from which the required 5β-alcohols, either as the 3β,5β-diols (IX, R' = H) or (upon acetylation) as the final 3β-acetoxy-5β-hydroxy compounds (II), could be separated by column chromatography and/or crystallization.

In the synthesis of 3β,5-dihydroxy-5α-androstan-17-one 3-acetate (Ic) and 3β,5-dihydroxy-5β-androstan-17-one 3-acetate (IIc), the 3β-hydroxyl group in the 5α,6α- and 5β,6β-epoxy-17-ketones (VIc and VIIc, R' = H) was first protected by conversion to the 3β-(2'-tetrahydropyranyl)oxy group (VIc and VIIc, R' = THP). Lithium aluminium hydride effected reductive opening of the oxirane ring in these epoxides (Scheme 3) as desribed above (for the epoxy compounds

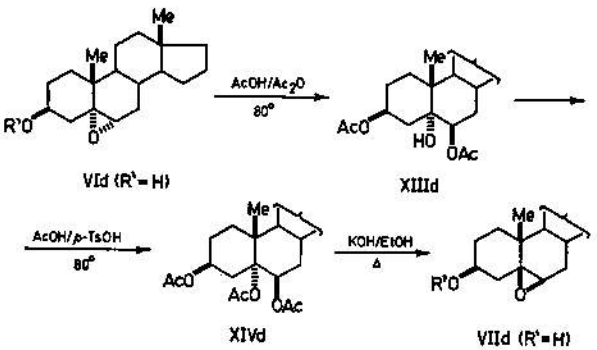


Scheme 3

VI and VII with the 3β-acetoxy- or 3β-hydroxyl group), and reduced also the 17-oxo group to the 17β-hydroxyl group, so that the α-epoxide (VIc, R' = THP) was converted to the 5α,17β-diol (VIIIb', R' = THP), and the β-epoxide (VIIc, R' = THP) to a mixture of 5β,17β-diol (IXb', R' = THP) and 6β,17β-diol (Xb', R' = THP). Reoxidation to 17-one followed by deetherification at C(3) afforded, in the case of the 5α-alcohol (VIIIb', R' = THP, Scheme 3), the 17-oxo-3β,5α-diol (VIIIc, R' = H), which was acetylated to give the required 3β-acetoxy-17-oxo--5α-ol (Ic). The same procedure (i.e. reoxidation and deetherification) applied to the mixture of the 5β- and 6β-alcohols (IXb' + Xb', R' = THP, Scheme 3) gave 17-oxo-3β,5β-diol (IXc, R' = H) and 3β-ol-6,17-dione (XIIc, which were separated by column chromatography, and the diol (IXc, R' = H) converted by acetylation to the required 3β-acetoxy-17-oxo-5β-ol (IIc).

* The α-epoxides (VI) were usually the major products of epoxidation of olefins (V) with peracids.

5,6β-Epoxy-5β-androstan-3β-ol (VIId, R' = H), necessary for the synthesis of 5β-androstane-3β,5-diol 3-acetate (IId), could not be obtained in sufficiently high yield by direct epoxidation (with peracids) of 5-androsten-3β-ol (Vd, R' = = H). Therefore, it was prepared, as shown in Scheme 4, from the corresponding 5α,6α-epoxide (VId, R' = H) [which was obtained as the major product of direct epoxidation of (Vd, R' = H)], by opening of the oxirane ring by means of acetic acid - acetic anhydride, followed by acetylation of the 5α-hydroxyl group in the so formed 3β,5α,6β-triol 3,6-diacetate (XIIId), and reclosure of the oxirane ring, but now as the 5β,6β-epoxide, by treatment of the triacetate (XIVd) with ethanolic potassium hydroxide (XIVd→VIId, R' = H)*.



Scheme 4

It is of interest to note (Scheme 5) that, whereas in 5-androstane-3β,5,6β--triol 3,6-diacetate (XIIId) the NMR resonance signal of the equatorial α-proton at C(6) (which holds a β-acetoxyl group) is centered normally at δ 4.76, upon acetylation of the axial 5α-hydroxyl group, i.e. in 5α-androstane-3β,5,6β-triol triacetate (XIVd), this 6α-proton is deshielded by the 5α-acetate carbonyl and its signal is displaced downfield by about 1.2 ppm, its position being at δ 5.93. The same difference in the position of the chemical shift of the equatorial α-proton at C(6) is also observed (Scheme 5), as reported and explained previously[5] and now confirmed, in the case of 5α-cholestane-3β,5,6β-triol 3,6-diacetate (XIIIa) (normal position) and its 5α-acetate ester (XIVa)** (downfield displacement). Besides, the resonance signal of the equatorial α-proton of the $H_2C(4)$ group is similarly displaced downfield (Scheme 5) by the axial 5α-acetoxyl group (again deshielding effect of the 5-acetate carbonyl), its position being at δ 2.85—2.87 in the triacetates (XIVa) and (XIVd), whereas in the corresponding 5α-ols (XIIIa) and (XIIId) it lies within the methylene envelope in the absorption region δ 1—1.8.

The opposite situation regarding the signal of the axial α-proton at C(3) (which also bears a β-acetoxyl group), namely its normal position (δ 4.75—4.76)

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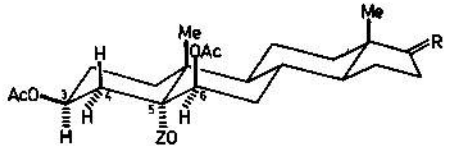
* Other 5β,6β-epoxy steroids (VII) could also be obtained from the corresponding α-epoxides (VI) by this reaction sequence (Scheme 4).

** The 5α-cholestane-3β,5,6β-triol 3,6-diacetate (XIIIa)[6] and triacetate (XIVa)[7] were prepared in the same way as described below (see Experimental) for the corresponding 5α-androstane derivatives (XIIId) and (XIVd). Complete NMR data of these compounds are given in Experimental.

when the axial 5α-substituent is acetoxyl (in XIVa and XIVd) and considerable downfield displacement (δ 5.20—5.21) when this substituent is 5α-hydroxyl (in XIIIa and XIIId), has been discussed previously[8] (Scheme 5).

Due to the influence of the axial 5α-hydroxyl group, in the ^{1}H-NMR spectra of the 3β,5α-diols (VIII, R' = H) and their 3-acetates (I), the resonance of the axial 3α-proton is, as expected[8], displaced downfield (relative to the 3α-proton signal of the corresponding 5α-unsubstituted compounds), and is located at about δ 4.1 in the diols (VIII) and δ 5.15—5.2 in the 3-acetates (I), with a half-band width ($W/2$) of 18—22 Hz[8] (see Experimental). In the 3β,5β-diols (IX, R' = H) and their 3-acetates (II), the chemical shift of the equatorial 3α-proton is not



XIII : Z = H
XIV : Z = Ac
a : R = β-CHMe(CH$_2$)$_3$CHMe$_2$, H
d : R = H$_2$

^{1}H-NMR Chemical Shifts (in δ ppm values)			
Compound	$H_{\alpha-ax}$-C(3) [a]	$H_{\alpha-eq}$-C(6) [b]	$H_{\alpha-eq}$-C(4)
XIIIa	5.20	4.75	c)
XIVa	4.75	5.92	2.85 [d]
XIIId	5.21	4.76	c)
XIVd	4.76	5.93	2.87 [d]

a) m, W/2 18–20 Hz.
b) m, W/2 4.5–5 Hz.
c) Position not detectable, since within the methylene envelope, in the region δ 1–1.8.
d) dxd, $J_{gem} \sim 14$ Hz, $J_{3ax,4eq}$ 4–5 Hz.

Scheme 5

markedly affected by the equatorial 5β-hydroxyl group[8], its position being normal with respect to the 3α-proton signal in the corresponding 5β-unsubstituted compounds, i.e. in the region δ 4.15—4.2 for the diols (IX) and δ 5.15—5.3 for the 3-acetates (II), with a half-band width ($W/2$) of 7—8 Hz[8] (see Experimental).

In the 5α,6α-epoxides (VI, R' = H or Ac) the 6β-proton signal is a doublet situated at δ 2.90—2.96, J = 3.5—4 Hz[9]; in the 5β,6β-epoxides (VII, R' = H or Ac) the 6α-proton resonates also as doublet, but at lower field (δ 3.03—3.15) and with a smaller coupling constant (J = 2.5—3 Hz)[9]*. When R' = H, the signal of the 3α-proton is located at about δ 3.9 for the α-epoxides (VI) and δ 3.7

* For complete NMR data of 5,6-epoxy steroids (VI) and (VII) see Experimental.

for the β-epoxides (VII); when R' = Ac, this 3α-proton resonates in the region of δ 4.9—5.05 for the α-epoxides (VI) and δ 4.8 for the β-epoxides (VII); in all cases the half-band width ($W/2$) is 18—22 Hz, indicating that in the β-epoxides (VII) the 3α-proton is also axially oriented. When compared to the respective 5α-unsubstituted compounds, it can be seen that the 3α-proton signal in the 3β--hydroxy- and 3β-acetoxy 5α,6α-epoxides (VI, R' = H and Ac) is displaced downfield by 0.2—0.3 ppm[9a]; however, this is not so in the case of the 3β-hydroxy and 3β-acetoxy 5β,6β-epoxides (VII, R' = H and Ac), where the 3α-proton, being axial, resonates at higher field (by about −0.2 to −0.4 ppm) than the equatorial 3α-proton in the corresponding 3β-hydroxy- and 3β-acetoxy 5β-unsubstituted compounds.

According to our results, the downfield increment value (Δ ppm) for the signal position of the angular methyl group protons at C(19) due to the 5β-hydroxyl group should be 0.02—0.00 ppm[8] (instead of the reported value of 0.08 ppm[10]), and that due to the 5β,6β-epoxy group 0.04 ppm[9,11]; the 5α,6α-epoxy group causes an upfield displacement of the signal of the angular methyl protons at C(18), the increment being −0.04 ppm[9]. With these increment values and those due to other substituents, given previously[10,11], a good agreement between the calculated and observed chemical shifts for the methyl protons as C(18) and C(19) (of the steroid compounds described in this paper) were obtained (see Experimental).

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EXPERIMENTAL*

Melting points are uncorrected. Optical rotations were measured at 20° in $CHCl_3$ solution, unless stated otherwise. ^{1}H-NMR spectra were obtained at 100 MHz with a Varian HA-100-D spectrometer in $CDCl_3$ solution, using TMS as internal standard; chemical shifts are reported in δ (ppm) values, and splittings (i.e. coupling constants J) in Hz (abbreviations: s — singlet d — doublet, t — triplet, q — quartet, m — multiplet, b— broad). IR spectra were determined on a Perkin-Elmer instrument, Model 337; ν_{max} are given in cm^{-1} units. Silica gel (0.05—0.2 mm) was used for preparative column chromatography. The separation of products was monitored by thin-layer chromatography on silica gel G (Stahl) with benzene-ethyl acetate (9:1, 7:3 or 1:1), detection being affected with 50% aqueous sulfuric acid. Light petroleum refers to the fraction boiling at 40—60°.

Syntheses of 3β-acetoxy-5-hydroxy-steroids (I *and* II)**.

5α-Cholestane-3β,5-diol 3-acetate (Ia). — This compound, m.p. 185°[13], was prepared (according to Scheme 2) from cholesterol (Va, R'=H), via 5,6α-epoxy-5α-cholestan-3β-ol (VIa, R'=H) and 5α-cholestane-3β,5-diol (VIIIa, R'=H), as described previously[3]. (NMR data for (Ia) and (VIIIa, R'=H) were given before[8]).

5β-Cholestane-3β,5-diol 3-acetate (IIa). — This alcohol, m.p. 80—81°[14], was obtained by the lithium aluminium hydride reduction of 4β,5-epoxy-5β-cholestan-3β-ol acetate, followed by 3-acetylation of the resulting 5β-cholestane-3β,5-diol (IXa, R'=H), as reported in the literature[14]. (NMR data for (IIa) and (IXa, R'=H) have been described previously[8]).

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** All known compounds had optical rotations in agreement with those reported in the literature. (For additional melting point and optical rotation values (of known steroid compounds described in this paper), with bibliographical data up to 1961, see reference 12).

5α-Androstane-3β,5,17β-triol 3,17-diacetate (Ib). — This hydroxy steroid, m.p. 181—182°[15], was synthesized (Scheme 2) from 3β-acetoxy-5,6α-epoxy-5α-androstan-17-one (VIc, R'=Ac), via 5α-androstane-3β,5,17β-triol (VIIIb', R'=H), according to published procedure[15]. IR (KBr) of (Ib): 3460, 1740, 1715, 1245 (b), 1030; NMR of (Ib): 0.78 (Me—18, s), 1.01 (Me—19, s), 2.01 and 2.05 (AcO at C-3 and C-17, two s), 4.64 (HC-17, t, J=7.5 Hz), 5.22 (HC-3, bm, $w/2$=22 Hz).

5β-Androstane-3β,5,17β-triol 3,17-diacetate (IIb). — A solution of 3β-acetoxy-5,6β-epoxy-5β-androstan-17-one (VIIc, R'=Ac)[16,17],* (11.1 g) in anh. diethyl ether (320 ml) was reduced with lithium aluminium hydride (4.5 g) in anh. diethyl ether (250 ml) (reflux 7 hours), to give, after the usual work up (hydrolysis at 0° by dropwise addition of water and 2*N* sulfuric acid), a mixture of products (IXb'+Xb', R'=H) which was acetylated with acetic anhydride (50 ml) in dry pyridine (100 ml) at room temperature for 48 hours. The resulting mixture was worked up in the usual way, i.e. treated portionwise at 0° with methanol (70 ml), concentrated in vacuo to a small volume, poured into crushed ice-water (150 g) containing conc. HCl (70 ml), the white solid filtered off, washed with water and dried. Recrystallization from methanol afforded 5β-androstane-3β,5,17β-triol 3,17-diacetate (IIb) (6.21 g, 49.4%), m.p. 138—139°, $[\alpha]_D$=+42.4° (c=0.95); IR (KBr): 3540, 3440, 3330, 1730, 1720, 1250 (b), 1040; NMR: 0.78 (Me-18), 0.99 (Me-19, s), 2.04 and 2.08 (AcO at C-3 and C-17, two s), 4.67 (HC-17, t, J=8 Hz), 5.27 (HC-3, m, $w/2$=8 Hz). (Found: C, 70.27; H, 9.35%. $C_{23}H_{36}O_5$ (392.52) requires: C, 70.37; H, 9.24%).

Saponification of this 5β-alcohol (100 mg) with 5% methanolic potassium hydroxide (5 ml) at room temperature gave 5β-androstane-3β,5,17β-triol (IXb', R'=H), which was recrystallized from methanol (67 mg, 85.3%), m.p. 206—208°, $[\alpha]_D$=+28.8° (c=0.69); IR (KBr): 3400, 1050. (Found: C, 73.77; H, 10.28%. $C_{19}H_{32}O_3$ (308.45) requires: C, 73.98; H, 10.46%).

3β,5-Dihydroxy-5α-androstan-17-one 3-acetate (Ic). — A solution of 3β-acetoxy-5,6α-epoxy-5α-androstan-17-one (VIc, R'=Ac)[16,17],** (8.00 g) in methanol (670 ml) was saponified for one hour at room temperature with 5% methanolic potassium hydroxide (40 ml); the resulting reaction mixture was neutralized with AcOH, concentrated in vacuo to a small volume and treated with water, affording, as precipitate, 3β-hydroxy-5,6α-epoxy-5α-androstan-17-one (VIc, R'=H) (6.92 g, 98.4%), which was recrystallized from acetone-methanol (6.40 g, 91.5%), m.p. 228—230°[18,19]; IR (KBr): 3400, 1730, 1060, 1025[19]; NMR: 0.82 (Me-18, s), 1.09 (Me-19, s), 2.95 (HC-6, d, J=3.8 Hz), 3.90 (HC-3, $w/2$=22 Hz)[19].

To a solution of this epoxy-alcohol (6.20 g) in dry benzene (550 ml), freshly distilled dihydropyrane (18 ml) and *p*-toluenesulfonic acid (140 mg) were added and the mixture left at room temperature for 2—3 hours. After washing with aqueous $NaHCO_3$ and water, drying (Na_2SO_4) and removal (in vacuo) of benzene, 3β-[(tetrahydro-2*H*-pyran-2-yl)oxy]-5,6α-epoxy-5α-androstan-17-one (VIc, R'=THP) was obtained (7.24 g, 91.6%), m.p. 151—154° (from acetone-methanol); IR (CCl_4): 1740, 1025. This product (6.99 g), in dry diethyl ether (200 ml), was reduced with 1.8 g of lithium aluminium hydride suspended in dry diethyl ether (120 ml); after refluxing for 2 hours, the ice-cooled reaction mixture was hydrolyzed with the calculated amount of water, filtered, washed with water, dried (Na_2SO_4) and evaporated (in vacuo) to dryness, affording 3β-[(tetrahydro-2*H*-pyran-2-yl)oxy]-5α-androstan-17β-ol (VIIIb', R'=THP) (7.00 g, 99.1%), m.p. 153—155° (from acetone); IR (KBr): 3450, 1015. This ether (6.83 g), without further purification, was dissolved in dry pyridine (70 ml) and oxidized by addition (of this solution), at room temperature, to a stirred pyridine solution of CrO_3-pyridine complex [prepared by careful, portionwise addition of chromic anyhdride (6.8 g) to stirred pyridine (70 ml), which was kept at 15—18° by external cooling (ice bath)]. After standing for 36 hours (at room temperature), the mixture was decanted and filtered, the precipitate washed well with methylene chloride, and the combined filtrates washed with several portions of a saturated aqueous solution of cupric sulfate (until no more change in color occurred) and with water. After drying (Na_2SO_4) and removal (in vacuo) of solvent, the crude product was hydrolyzed for 30 minutes at room temperature with a solution of conc. HCl (16 ml) in methanol (120 ml); the resulting mixture was diluted with water, the precipitate filtered off, washed with water (until neutral) and air-dried. In this way, 3β,5-dihydroxy-5α-androstan-17-one (VIIIc, R'=H) was obtained (4.13 g, 77.5%), which was recrystallized from acetone-methanol (3.70 g, 69.4%), m.p. 276—278°[15,16,20]; IR (KBr): 3480, 3400, 1730, 1030.

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* This 3β-acetoxy-5β,6β-epoxide (VIIc, R'=Ac), m.p. 184—185°[16,17], and its 5α,6α-diastereomer (VIc, R'=Ac), m.p. 222°[16,17], were obtained by epoxidation of 3β-acetoxy-5-androsten-17-one (Vc, R'=Ac) with monoperphthalic acid[16]. ^{1}H-NMR data of these epoxides are given below.

** See preceding footnote.

Acetylation of this diol (3.40 g) with acetic anhydride (25 ml) in pyridine (50 ml) at room temperature for 12 hours gave (after the usual work up, as described above in *Synthesis of IIb*) 3β,5-dihydroxy-5α-androstan-17-one 3-acetate (Ic) (3.70 g, 95.6%), double m.p. 152—154° and 164—166° (from acetone-methanol)[16,20,21]; IR (KBr): 3480, 3410, 1740, 1720, 1265, 1245, 1025; NMR: 0.87 (Me-18, s), 1.05 (Me-19, s), 2.01 (AcO-3, s), 5.15 (HC-3, bm, $w/2=20$ Hz)[21].

3α,5-*Dihydroxy*-5β-*androstan*-17-*one* 3-*acetate* (IIc). — A solution of 3β-acetoxy-5,6β--epoxy-5β-androstan-17-one (VIIc, R'=Ac)[16,17] (10.08 g) in methanol (240 ml) was saponified with 5% methanolic potassium hydroxide (40 ml) at room temperature for one hour, to give (after working up as described above in *Synthesis of Ic*) 3β-hydroxy-5,6β-epoxy-5β-androstan--17-one (VIIc, R'=H) (8.56 g, 96.6%), m.p. 161—162° (from methanol)[16,22]; IR (KBr): 3560, 3400, 1730, 1060, 1030; NMR: 0.84 (Me-18, s), 1.02 (Me-19, s), 3.10 (HC-6, d, $J=2.5$ Hz), 3.70 (HC-3, bm, $w/2=22$ Hz)[19].

This epoxy-alcohol (8.24 g) in dry benzene (700 ml) was treated with dihydropyrane (30 ml) and *p*-toluenesulfonic acid (250 mg) at room temperature for 3 hours, affording (after working up as described above in *Synthesis of Ic*) 3β-[(tetrahydro-2*H*-pyran-2-yl)oxy]-5,6β-epoxy--5β-androstan-17-one (VIIc, R'=THP) (10.50 g, ≃100%), m.p. 112—113° (from acetone--methanol); IR (KBr): 1735, 1025. Reduction of this product (9.40 g) in dry diethyl ether (400 ml) with lithium aluminium hydride (2.25 g) in dry diethyl ether (100 ml) (reflux 2—3 hours) gave (after working up as described above in *Synthesis of Ic*) a mixture of products (IXb'+Xb', R'= =THP), which was oxidized with CrO_3 in pyridine and hydrolyzed with HCl-methanol as described above (in *Synthesis of Ic*). The acid solution, after hydrolysis, was concentrated (in vacuo), extracted with several portions of methylene chloride, and these were washed with aqueous NaHCO, and water, dried (Na_2SO_4) and evaporated (in vacuo) to dryness, leaving an oily residue which was chromatographed on silica gel (440 g). Elution with benzene-diethyl ether (68:32) gave 2.62 g (35.3%) of 3β,5-dihydroxy-5β-androstan-17-one (IXc, R'=H), m.p. 182.5—183.5° (from acetone-methanol); IR (KBr): 3500, 3470, 1738, 1090, 1050; NMR: 0.88 (Me-18, s), 0.99 (Me-19, s), 4.23 (HC-3, m, $w/2=8$ Hz). (Found: C, 74.48; H, 9.76%. $C_{19}H_{30}O_3$ (306.43) requires: C, 74.47; H, 9.87%).

Elution with diethyl ether afforded 3β-hydroxy-5α-androstane-6,17-dione (XIIc) (3.39 g, 46%), m.p. 177—178° (from methanol)[20]; IR (KBr): 3450, 1740, 1720, 1055; NMR: 0.79 (Me-19, s), 0.88 (Me-18, s), 3.60 (HC-3, bm, $w/2=18$ Hz).

Acetylation of 3β,5-dihydroxy-5β-androstan-17-one (IXc, R'=H) (2.50 g) with acetic anhydride (25 ml) in dry pyridine (50 ml) at room temperature for 60 hours and working up of the resulting mixture as described above (in *Synthesis of IIb*), afforded 3β,5-dihydroxy-5β-androstan-17-one 3-acetate (IIc) (2.644 g, 93%), m.p. 154—155° (from acetone-methanol), $[\alpha]_D=+118°$ ($c=0.74$); IR (KBr): 3570, 3520, 1740, 1265, 1245, 1215, 1160, 1015; NMR: 0.88 (Me-18, s), 1.02 (Me-19, s), 2.09 (AcO-3, s), 5.26 (HC-3, m, $w/2=8$ Hz). (Found: C, 72.65; H, 9.38%. $C_{21}H_{32}O_4$ (348.47) requires: C, 72.38; H, 9.26%).

5α-*Androstane*-3β,5-*diol* 3-*acetate* (Id). — A solution of 3β-acetoxy-5-androsten-17-one (Vc, R'=Ac) (20.0 g) and hydrazine hydrate (80 ml of 85%) in ethylene glycol (400 ml) was heated one hour at 100° (temperature of the reaction mixture) with magnetic stirring, whereupon the starting material was completely converted to its hydrazone. The flask was cooled to room temperature and 75 g of potassium hydroxide (pellets) were added portionwise through the reflux condenser, which was then removed and the bath temperature raised slowly and carefully until the temperature inside the flask had reached 200° (about 2 hours) and most of the volatile material had distilled. The condenser was then reconnected (air cooling) and the temperature in the flask maintained at 200—210° for 5 hours. The reaction mixture was cooled and poured into crushed ice-water (about 1000 g) and conc. HCl (50 ml) with vigorous stirring. The precipitate was filtered off, thoroughly washed with water and air-dried. 5-Androsten-3β-ol (Vd, R'=H) was thus obtained, which after recrystallization from methanol (13.06 g, 78.6%) had m.p. 133—134°[23], $[\alpha]_D=-48°$ ($c=0.89$, MeOH)[23]; IR (KBr): 3400, 3240 1050 (d), 950, 810; NMR:, 0.74 (Me-18, s), 1.04 (Me-19, s), 3.75 (HC-3, q, $J=7$ Hz), 5.42 (HC-6, m, $w/2=10$ Hz). (Found: C, 83.27; H, 11.14%. $C_{19}H_{30}O$ (274.43) requires: C, 83.15; H, 11.02%).

To a stirred solution of this olefinic alcohol (4.48 g) in diethyl ether (300 ml) 3-chloroperbenzoic acid (3.45 g) was added portionwise at 20°. After two hours the reaction mixture was filtered (if necessary), washed with aqueous $NaHCO_3$ and water (until neutral), dried (Na_2SO_4) and evaporated to dryness under reduced pressure, to give a mixture of 5α,6α- and 5β,6β-epoxides (VId+VIId, R'=H), which was twice recrystallized from methanol, affording, pure 5,6α-epoxy--5α-androstan-3β-ol (VId, R'=H), m.p. 154—155°[24–26], $[\alpha]_D=-85°$ ($c=0.78$, MeOH)[25,26]; IR (KBr): 3420, 1050; NMR: 0.66 (Me-18, s), 1.06 (Me-19, s), 2.91 (HC-6, d, $J=4$ Hz), 3.87 (HC-3, bm, $w/2=22$ Hz)[26]. (Found: C, 78.61; H, 10.36%. $C_{19}H_{30}O_2$ (290.43) requires: C, 78.57; H, 10.41%).

This α-epoxide (2.972 g) in dry diethyl ether (160 ml) was reduced with lithium aluminium hydride (700 mg) in dry diethyl ether (40 ml) (reflux 3 hours), to give (after hydrolysis at 0° with water and 2*N* sulfuric acid, followed by the usual work up) 5α-androstane-3β,5-diol (VIIId, R'=H) (2.85 g, 95.2%),m.p. 199—200° (from methanol)[24], $[\alpha]_D = +24°$ ($c=0.98$); IR (KBr): 3620, 3420, 3320, 1050; NMR: 0.70 (Me-18, s), 0.98 (Me-19, s), 4.08 (HC-3, bm, $w/2=20$ Hz)[27]. (Found: C, 77.83; H, 10.77%. $C_{19}H_{32}O_2$ (292.45) requires: C, 78.03; H, 11.03%).

A solution of this diol (2.056 g) in pyridine (30 ml) and acetic anhydride (15 ml) was left at room temperature for 6 hours and then poured into crushed ice-water (500 g) containing conc. HCl (35 ml). The separated product was filtered off, washed with water and air-dried. 5α-Androstane-3β,5-diol 3-acetate (Id) (2.236 g, 95.1%) was thus obtained, and was recrystallized from acetone-methanol (1.927 g, 81.9%), m.p. 160—161°[24], $[\alpha]_D = -16°$ ($c=0.82$); IR (KBr): 3480, 1750, 1720, 1280, 1260, 1040; IR (CCl_4): 3600, 3460, 1740, 1720, 1240, 1030; NMR: 0.68 (Me-18, s), 0.99 (Me-19, s), 1.98 (AcO-3, s), 5.17 (HC-3, bm, $w/2=20$ Hz). (Found: C, 75.33; H, 10.32%. $C_{21}H_{34}O_3$ (334.48) requires: C, 75.40; H, 10.25%).

5β-*Androstane*-3β,5-*diol* 3-*acetate* (IId). — A solution of the above described (in *Synthesis of Id*) 5,6α-epoxy-5α-androstan-3β-ol (VId, R'=H) (5.96 g) in glacial acetic acid (120 ml) and acetic anhydride (20 ml) was heated at 80° for 5 hours and then concentrated in vacuo (to about 20 ml). After cooling, crystalline 5α-androstane-3β,5,6β-triol 3,6-diacetate (XIIId) separated (7.63 g, 94.7%), m.p. 185.5° (from methanol)[28,29], $[\alpha]_D = -80.2°$ ($c=1.15$)[29]; IR (CCl_4):3600, 3470, 1730, 1710, 1260, 1240, 1025; NMR: 0.74 (Me-18, s), 1.18 (Me-18, s), 2.01 and 2.07 (AcO at C-3 and C-6, two s), 4.76 (HC-6, m, $w/2=5$ Hz), 5.21 (HC-3, bm, $w/2=20$ Hz)[29]. (Found: C, 70.15; H, 9.34%. $C_{23}H_{36}O_5$ (392.52) requires: C, 70.37; H, 9.24%).

This diacetate (6.90 g) and *p*-toluenesulfonic acid (250 mg) in glacial acetic acid (90 ml) were heated at 80° for 4 hours, The mixture was then poured into ice-cold water and the precipitate extracted with diethyl ether. The ethereal layer was washed with aqueous $NaHCO_3$ and water, dried (Na_2SO_4) and evaporated to dryness under reduced pressure, affording 5α-androstane-3β,5,6β-triol triacetate (XIVd) (7.46 g, 97.7%), m.p. 166—167° (from methanol), $[\alpha]_D = -69°$ ($c=1.2$); IR (KBr): 1740, 1245—1225 (t), 1215, 1035—1015 (t); NMR: 0.73 (Me-18, s), 1.23 (Me-19, s), 2.01 and 2.09 (AcO at C-3, C-5 and C-6, two singlets, the former corresponding to three H and the latter to six H), 2.87 (Hα C-4, d×d, $J_{gem}=14$ Hz, $J_{3,4}=4.5$ Hz), 4.76 (HC-3, bm, $w/2=20$ Hz), 5.93 (HC-6, m, $w/2=5$ Hz). (Found: C, 68.88; H, 8.96%. $C_{25}H_{38}O_6$ (434.55) requires: C, 69.09; H, 8.81%).

A solution of this triacetate (7.02 g) in absolute ethanol (300 ml) was treated with potassium hydroxide pellets (10 g), and then refluxed for 6 hours. It was neutralized with acetic acid, concentrated in vacuo, diluted with water and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), evaporated (in vacuo) to dryness, and the oily residue (3.54 g, 75.5%) chromatographed on silica gel (180 g). Elution with benzene diethyl ether (9:1) gave 5,6β-epoxy-5β-androstan-3β-ol (VIId, R'=H) (3.04 g, 64.8%), m.p. 182—183° (from methanol)[26], $[\alpha]_D = -17.2°$ ($c=1.0$)[26]; IR (KBr): 3420, 1050; NMR 0.69 (Me-18, s), 1.00 (Me-19, s), 3.08 (HC-6, d, $J=3$ Hz), 3.70 (HC-3, bm, $w/2=20$ Hz)[26]. (Found: C, 78.38; H, 10.62%. $C_{19}H_{30}O_2$ (290.43) requires: C, 78.57; H, 10.41%).

A solution of this epoxy-alcohol (6.26 g) in anh. diethyl ether (350 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1.50 g) in diethyl ether (50 ml) and the mixture refluxed for 6 hours. After hydrolysis at 0° with water and 2*N* sulfuric acid, followed by the usual work up and evaporation oa solvent, the residue obtained was recrystallized from acetone, affording 5α-androstane-3β,6β-diol (Xd, R'=H) (2.03 g, 32.2%), m.p. 193°[30], $[\alpha]_D = -17°$ ($c=0.91$)[30]; IR (KBr): 3420, 1040, 1018; NMR: 0.72 (Me-18, s), 1.03 (Me-19, s), about 3.65 (HC-3, bm, $w/2=22$ Hz), 3.80 (HC-6, m, $w/2=5$ Hz)[27,30]. (Found: C, 77.80; H, 10.76%. $C_{19}H_{32}O_2$ (292.45) requires: C, 78.03; H, 11.03%).

The mother liquors from the above described crystallization were chromatographed on silica gel (200 g). Elution with benzene-diethyl ether (75:25) afforded 5β-androstane-3β,5-diol (IXd, R'=H) (2.23 g, 35.4%),m.p. 153—154° (from acetone-methanol), $[\alpha]_D = +20°$ ($c=1.03$); IR (KBr): 3360, 1110, 1060, 985; NMR: 0.69 (Me-18, s), 0.94 (Me-19, s), 4.15 (HC-3, m, $w/2=8$ Hz). (Found: C, 77.93; H, 11.11%. $C_{19}H_{32}O_2$ (292.45) requires: C, 78.03; H, 11.03%). Elution with diethyl ether gave a further amount (1.78 g) of 5α-androstane-3β,6β-diol (Xd, R'=H) (the total yield being 3.81 g, i.e. 60.4%).

A solution of 5β-androstane-3β,5-diol (IXd, R'=H) (1.96 g) in pyridine (30 ml) containing acetic anhydride (15 ml) was allowed to stand for 65 hours at room temperature. The mixture was then poured into a mixture of ice (150 g) and conc. HCl (30 ml), and the white precipitate was filtered off, washed with water and air-dried. Recrystallization from acetone-methanol gave 5β-androstane-3β,5-diol 3-acetate (IId) (2.05 g, 91.5%), m.p. 90—91°, $[\alpha]_D = +38°$ ($c=0.51$);

IR (KBr): 3580, 1740, 1230, 1040; NMR: 0.68 (Me-18, s), 0.96 (Me-19, s), 2.04 (AcO-3, s), 5.23 (HC-3, m, $w/2=7$ Hz). (Found: C, 75.56; H, 10.36%. $C_{21}H_{34}O_3$ (334.48) requires: C, 75.40; H, 10.25%).

5α-*Cholane*-3β,5,24-*triol* 3,24-*diacetate* (Ie). — Into a solution of 3β-hydroxy-5-cholen--24-oic acid (Vf, R'=H)* (50 g) in absolute methanol (150 ml), 1.5 g of gaseous HCl was introduced and the mixture heated on a water bath for 15 minutes. It was then cooled to 0°, and the separated 3β-hydroxy-5-cholen-24-oic acid methyl ester (Vf', R'=H) (51.3 g, 98.9%) filtered off and recrystallized from methanol (47.36 g, 91.3%), m.p. 140—142°[31],$[\alpha]_D=-43°$ ($c=0.95$)[31]; IR (KBr): 3480, 1710, 1065, 860, 795; NMR: 0.68 (Me-18, s), 0.92 (Me-21, d, $J=6$ Hz), 1.00 (Me-19, s), 3.52 (HC-3, bm, $w/2=22$ Hz), 3.66 (MeO at C-24, s), 5.36 (HC-6, d, $J=5$ Hz). (Found: C, 77.07; H, 10.32%. $C_{25}H_{40}O_3$ (388.57) requires: C, 77.27; H, 10.38%).

To a solution of this methyl ester (12.50 g) in diethyl ether (50 ml), 174 ml of an ethereal solution of monoperphthalic acid (containing 0.07 g/ml of peracid) was added and the resulting mixture left overnight at room temperature. The precipitate (*o*-phthalic acid) was removed by filtration, the filtrate washed successively with aqueous solutions of KI, $Na_2S_2O_3$ and $NaHCO_3$, and then with water, dried (over Na_2SO_4) and evaporated to dryness under reduced pressure, affording 3β-hydroxy-5,6α-epoxy-5α-cholan-24-oic acid methyl ester (VIf', R'=H), which was recrystallized from acetone-methanol (11.86 g, 91.1%), m.p. 98°, $[\alpha]_D=-50.9°$ ($c=1.00$); IR (KBr): 3420, 1735, 1190, 1170—1155 (d), 1060, 1040, 965; NMR: 0.61 (Me-18, s), 0.90 (Me-21, d, $J=6$ Hz), 1.05 (Me-19, s), 2.90 (HC-6, d, $J=4$ Hz), 3.66 (MeO at C-24, s), about 3.88 (HC-3, bm, $w/2=20$ Hz). (Found: C, 74.25; H, 9.70%. $C_{25}H_{40}O_4$ (404.57) requires: C, 74.21; H, 9.97%).

This epoxy-ester (10 g) in diethyl ether (250 ml) was reduced with lithium aluminium hydride (2.7 g) in diethyl ether (200 ml) (reflux 9 hours), to give (after hydrolysis at 0° with water and 2*N* sulfuric acid, and the usual work up) 5α-cholane-3β,5,24-triol (VIIIe', R'=H) (9.17 g, 98%), m.p. 208—209°, which was recrystallized from acetone (8.26 g, 88.3%), m.p. 213°, $[\alpha]_D=+21.8°$ ($c=0.90$, MeOH); IR (KBr): 3380, 1065, 1045, 1030; NMR (DMSO): 0.61 (Me-18, s), 0.88 (Me-19, s, and Me-21, d), 3.32 (H_2C-24, t, $J=7.5$ Hz), 3.83 (HC-3, bm, $w/2=20$ Hz). (Found: C, 76.02; H, 11.24%. $C_{24}H_{42}O_3$ (378.58) requires: C, 76.14; H, 11.18%).

A solution of this triol (4.58 g) in pyridine (90 ml) and acetic anhydride (45 ml) was left at room temperature for 12 hours. After the usual work up (as in *Synthesis of IIb*), the crystalline solid obtained was recrystallized from methanol, to give 5α-cholane-3β,5,24-triol 3,24-diacetate (Ie) (5.31 g, 94.9%), m.p. 155—156°, $[\alpha]_D=+2°$ ($c=0.93$); IR (KBr): 3455, 1735, 1705, 1265, 1245, 1225, 1025; NMR: 0.64 (Me-18, s), 0.91 (Me-21, d, $J=6$ Hz), 0.98 (Me-19, s), 1.98 and 2.02 (AcO at C-3 and C-24, two s), 4.02 (H_2C-24, t, $J=7$ Hz), 5.15 (HC-3, bm, $w/2=22$ Hz). (Found: C, 72.56; H, 10.14%. $C_{28}H_{46}O_5$ (462.65) requires: C, 72.69; H, 10.02%).

^{1}H-NMR data of related compounds.

5α,6α-*Epoxy steroids* (VI). — 5,6α-Epoxy-5α-cholestan-3β-ol (VIa, R'=H), m.p. 142—143°[3,12,13,18]; NMR: 0.62 (Me-18, s), 0.87 (Me-21, Me-26 and Me-27, d, $J=6$ Hz), 1.05 (Me-19, s), 2.92 (HC-6, d, $J=4$ Hz), about 3.90 (HC-3, bm, $w/2=22$ Hz) (see also ref. 9b).

5,6α-Epoxy-5α-cholestan-3β-ol acetate (VIa, R'=Ac), m.p. 96—97°[12,13]; NMR: 0.60 (Me-18, s), 0.85 (Me-21, Me-26 and Me-27, d, $J=6$ Hz), 1.08 (Me-19, s), 2.00 (AcO-3, s), 2.90 (HC-6, d, $J=4$ Hz), 4.97 (HC-3, bm, $w/2=22$ Hz).

3β-Acetoxy-5,6α-epoxy-5α-androstan-17-one (VIc, R'=Ac), m.p. 222°[16,17,22b]; NMR: 0.80 (Me-18, s), 1.12 (Me-19, s), 2.01 (AcO-3, s), 2.96 (HC-6, d, $J=4$ Hz), about 5.05 (HC-3, bm, $w/2=20$ Hz).

5,6α-Epoxy-5α-androstan-3β-ol acetate (VId, R'=Ac), m.p. 115—116°[26,29a]; NMR: 0.64, (Me-18, s), 1.06 (Me-19, s), 1.98 (AcO-3, s), 2.89 (HC-6, d, $J=4$ Hz), 4.93 (HC-3, sextet, $w/2=24$ Hz) (see also ref. 29a).

5β,6β-*Epoxy steroids* (VII). — 5,6β-Epoxy-5β-cholestan-3β-ol (VIIa, R'=H), m.p. 129—131°[12,13,22a,22c]; NMR: 0.64 (Me-18, s), 0.85 (Me-21, Me-26 and Me-27, d, $J=6$ Hz), 1.00 (Me-19, s), 3.10 (HC-6, d, $J=2.5$ Hz), 3.70 (HC-3, bm, $w/2=20$ Hz).

5,6β-Epoxy-5β-cholestan-3β-ol acetate (VIIa, R'=Ac), m.p. 110—112°[12,13,22a,22c]; NMR: 0.65 (Me-18, s), 0.86 (Me-21, Me-26 and Me-27, d, $J=6$ Hz), 1.01 (Me-19, s),2.02 (AcO-3, s), 3.08 (HC-6, d, $J=2.5$ Hz), 4.78 (HC-3, bm, $w/2=20$ Hz) (see also ref. 9b).

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* This acid had m.p. 232—234°[12,31b]; IR (KBr): 3350, 1695, 1285, 1200, 1055, 840, 800; NMR ($CDCl_3$+DMSO): 0.67 (Me-18, s), 0.92 (Me-21, d, $J=6$ Hz), 0.99 (Me-19, s), 3.40 (HC-3, bm, $w/2=22$ Hz), 5.30 (HC-6, d, $J=5$ Hz).

3β-Acetoxy-5,6β-epoxy-5β-androstan-17-one (VIIc, R'=Ac), m.p. 184—185°[16,17,22a,22c]; NMR: 0.88 (Me-18, s), 1.05 (Me-19, s), 2.05 (AcO-3, s), 3.15 (HC-6, d, J=2.8 Hz), 4.82 (HC-3, bm, $w/2$=18—20 Hz).

5,6β-Epoxy-5β-androstan-3β-ol acetate (VIId, R'=Ac), m.p. 82°; IR (CCl_4): 1740, 1245, 1040; NMR: 0.72 (Me-18, s), 1.00 (Me-19, s), 1.98 (AcO-3, s), 3.03 (H C-6, d, J=2.5 Hz), about 4.83 (HC-3, bm, $w/2$=22 Hz). (Found: C, 75.50; H, 9.54%. $C_{21}H_{32}O_3$ (332.47) requires: C, 75.86; H, 9.70%).

Acetate esters. — 5-Androsten-3β-ol acetate (Vd, R'=Ac), m.p. 95—97° (MeOH)[23,32], $[\alpha]_D=-78°$ (c=1.01), was obtained from the corresponding alcohol (Vd, R'=H; see *Synthesis of Id*) by acetylation with Ac_2O-pyridine at 20° in the usual way; IR (KBr): 1740, 1250, 1045, 825; NMR: 0.72 (Me-18, s), 1.03 (Me-19, s), 2.01 (AcO-3, s), 4.60 (HC-3, bm, $w/2$=22 Hz), 5.39 (HC-6, d, J=5 Hz).

5α-Androstane-3β,6β-diol diacetate (XId), m.p. 82—83°, $[\alpha]_D=-56°$ (c=1.06), was obtained from the corresponding diol (Xd, R'=H; see *Synthesis of IId*) by acetylation with Ac_2O-pyridine at 20°, in the usual way; IR (KBr): 1730 (d), 1250, 1230, 1040, 1020; NMR: 0.73 (Me-18, s), 1.02 (Me-19, s), 1.99 and 2.02 (AcO-3 and AcO-6, two s), 4.70 (HC-3, bm, $w/2$=22 Hz), 4.93 (HC-6, q, J=3.5 Hz). (Found: C, 73.30; H, 9.54%. $C_{23}H_{36}O_4$ (376.52) requires: C, 73.36; H, 9.64%).

5α-Cholestane-3β,5,6β-triol 3,6-diacetate (XIIIa), m.p. 164—166°[6-12]; NMR: 0.68 (Me-18, s), 0.88 (Me-21, Me-26 and Me-27, d, J=6 Hz), 1.17 (Me-19, s), 2.02 and 2.07 (AcO-3 and AcO-6, two s), 4.75 (HC-6, m, $w/2$=4 Hz), 5.20 (HC-3, bm, $w/2$=20 Hz) (see also Scheme 5 and ref. 5).

5α-Cholestane-3β,5,6β-triol triacetate (XIVa), m.p. 149—150°[7,12]; NMR: 0.69 (Me-18, s), 0.85 (Me-21, Me-26 and Me-27, d, J=6 Hz), 1.19 (Me-19, s), 2.01 and 2.08 (AcO at C-3, C-5 and C-6, two singlets, the first corresponding to three H and the second — at lower field — to six H), 2.85 (HC-4, d×d, J_{gem}=14 Hz, $J_{3,4}$=4.5 Hz), 4.75 (HC-3, bm, $w/2$=20 Hz), 5.92 (HC-6, m, $w/2$=4.5 Hz) (see also Scheme 5 and ref. 5).

ИЗВОД

СИНТЕЗЕ НЕКИХ 3β-АЦЕТОКСИ-5-ХИДРОКСИ-СТЕРОИДА КОЈИ САДРЖЕ РАЗЛИЧИТЕ СУПСТИТУЕНТЕ У ПОЛОЖАЈУ 17

ЉУБИНКА ЛОРЕНЦ, ЗОРКА МАКСИМОВИЋ, РИСТО БОЖИНОВ, ВЛАДА ПАВЛОВИЋ, ИВАН ЈУРАНИЋ и МИХАИЛО Љ. МИХАИЛОВИЋ

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Синтетизовани су неки 3β-ацетокси-5-хидрокси-стероиди из 5α (A/B-*trans*) и 5β (A/B-*cis*) серије који садрже различите супституенте у положају 17 (I и II, a—e), према општем реакционом поступку (схема 2) који обухвата прво трансформацију 3β-ацетокси- или 3β-хидрокси-5-олефинских стероида (V) у одговарајућа 5α,6α- и 5β,6β-епокси-једињења (VI и VII) помоћу перкиселина (а β-епоксиди (VII) се могу добити и индиректно из (V) преко α-епоксида (VI); схема 4), затим редуктивно отварање оксиранског прстена у овим епоксидима помоћу литијум-алуминијум-хидрида и најзад ацетиловање 3-хидроксилне групе у тако посталим 3β,5α- односно 3β,5β-диолима (VIII и IX). Разматрани су и ^{1}H-NMR спектри ових једињења а и других интермедијера, нпр. 5α-андростан-3β,5,6β-триол-3,6-диацетата (XIIId) и одговарајућег триацетата (XIVd).

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