The Participation of 3,5-Cyclosteroids in Aromatization Reactions

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The preparation of 6β,7β-dihydroxy-3α,5-cycloandrostan-17-one and 2β,17β-diacetoxy-6α-hydroxy-3α,5-cycloandrostane and their reaction with hydrobromic acid in acetic acid is described. They both afford the corresponding 4-methylestratriene accompanied by, in the case of the former, an anthrasteroid and in the case of the latter, 17β-acetoxy-5α-androst-2-en-6-one and the related 2- and 3-bromo-6-ones.

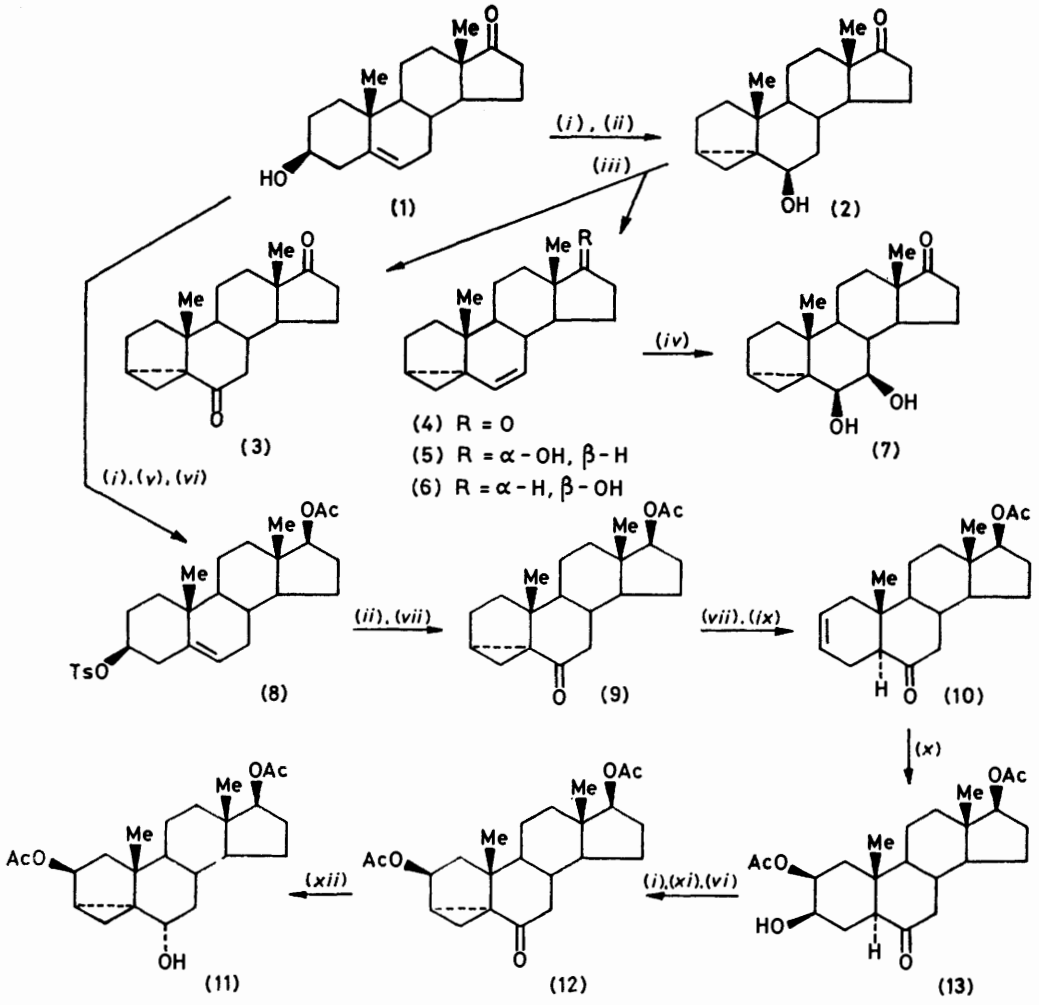
THE participation of the steroidal 3α,5-cyclopropane ring in the delocalization of a carbocation is well-documented.[1] We have now examined the participation of this system in the developing carbocation associated with the dienol–benzene type of rearrangement. The dienol–benzene aromatization of steroids that contain two double bond equivalents and a carbocation source, by reaction with hydrobromic acid and acetic acid, is a fairly general process.[2] The rearrangement is limited by the ease with which a C-5 carbocation may be generated, by the presence of electron-withdrawing substituents at C-6 and C-11 and by methyl substitution on ring A (*e.g.* at C-4). In these circumstances alternative reactions including different aromatizations, may occur.[3] The 3α,5-cyclopropane ring is known to participate in solvolytic reactions at C-6 [1] and we have noted its involvement in the epoxidation of a 6,7-olefin.[4] 6β,7β-Dihydroxy-3α,5-cycloandrostan-17-one (7) and 2β,17β-diacetoxy-6α-hydroxy-3α,5-cycloandrostane (11) were examined as substrates. The reaction of 2β,6α-dihydroxy-3α,5-cyclocholestane with aqueous sulphuric acid has been studied previously.[5a] The products were identified as cholest-5-ene-2α,3β-diol, 5β-cholest-2-ene-5,6α-diol and the C-5 epimeric cholest-2-en-6-ones. No aromatic products were detected. By contrast the cleavage of unsubstituted 3α,5-cyclosteroids with hydrogen chloride affords [5b] 3-methyl-A-norsteroids.

RESULTS AND DISCUSSION

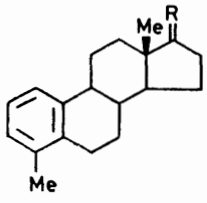
The substrates were prepared from dehydroisoandrosterone (1) as shown in Scheme 1. Some by-products accompanied the dehydration of the alcohol (2) by alumina.[4] These were the 17α-alcohol (5) [identified by oxidation to the 17-ketone (4)], the 17β-alcohol (6) [6] [identified by reduction of the 17-ketone (4)], and the 6,17-dione (3) [7] [identified by oxidation of the 6β-alcohol (2)]. Their formation is unexceptional.[8] Suprisingly the product of osmylation of the 6-ene (4) was the 6β,7β-diol. The magnitude of the H-7–H-8 (11 Hz) and H-6–H-7 (3 Hz) coupling constants together with the relative positions of these and the 19-methyl resonances compared with the unsubstituted 6β-hydroxy-3α,5-cyclosteroid were indicative of the stereochemistry. As in the case of hydride reduction of the 6-ketone (12), the 3α,5-cyclopropane ring, has directed attack to the β-face. The 6β,7β-diol was obtained previously by the microbiological hydroxylation of (2).[9] The preparation of 2β,17β-diacetoxy-6α-hydroxy-3α,5-cycloandrostane (11) *via* 2β,17β-diacetoxy-3β-hydroxyandrostan-6-one (13) [10] followed the route established in the cholestane series.[5]

Reaction of 6β,7β-dihydroxy-3α,5-cycloandrostan-17-one (7) with hydrobromic acid in glacial actic acid gave predominantly 4-methylestra-1,3,5(10)-trien-17-one (14) [11] accompanied by some anthrasteroid (15).[11] It is interesting to note that even in this case in which the substituents are on ring B, a ring A aromatic steroid predominates. Under the same conditions 2β,17β-diacetoxy-6α-hydroxy-3α,5-cycloandrostane (11) gave 17β-acetoxy-4-methylestra-1,3,5(10)-triene (16) as the major aromatic steroid and a small amount of a second unidentified aromatic compound. The non-aromatic products were identified as 17β-acetoxy-5α-androst-2-en-6-one (10) [12] and the bromo-ketones (17), (18), and (19).

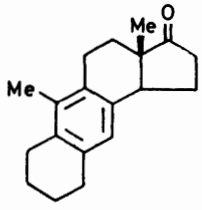
Analysis of the ^{13}C n.m.r. spectra of the bromo-ketones (17) and (18) (see Table) suggested that the bromine atoms were located at C-2 in (17) and at C-3 in (18). Particularly significant were the downfield shifts of the C-1, C-2, and C-3 resonances in (17) and the C-2, C-3, and C-4 resonances in (18) compared to 17β-acetoxy-5α-androstan-6-one (20). An authentic sample of 17β-acetoxy-2α-bromo-5α-androstan-6-one (17) was prepared from the 2-en-6-one (10) [12] *via* the 3-α-bromo-2β-ol. The 3α-bromine atom was hydrogenolysed with tri-n-butyltin hydride and the 2β-alcohol then converted to its methanesulphonate. Nucleophilic substitution of the latter with lithium bromide gave the 2α-bromosteroid. In (18) the 5-H proton resonance appeared at δ 2.82 (q, *J* 5 and 9 Hz) deshielded by a 1–3-diaxial interaction with the 3α-bromine atom. An authentic sample of the 3α-bromosteroid was prepared by treatment of the corresponding 3β-toluene-*p*-sulphonate (21) with lithium bromide. In this preparation, the 3α-bromo-steroid (18) was accompanied by some of the 3β-bromo-epimer (22). Epimerization of the 3α-isomer could be brought about by refluxing it with lithium bromide in methyl ethyl ketone. The toluene-*p*-sulphonate (21) was obtained by hydroboronation and oxidation of the olefin (8). The third bromo-ketone was tentatively identified as 17β-acetoxy-2β-bromo-5β-androstan-6-one (19). It differed from the known 17β-acetoxy-3-bromoandrostan-6-ones.[13] The *cis*-A/B fusion was indicated by the magnitude of the circular dichroism curve ($\Delta\varepsilon_{297} - 3.21$) [14] and by the low-field shift of the C-19 resonance.[15] The position of the carbon-13 resonances of the ring-A atoms and the



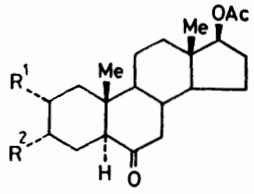
SCHEME 1 (*i*), TsCl,pyridine; (*ii*), NaOAc,H_2O; (*iii*), Al_2O_3,xylene; (*iv*), OsO_4; (*v*), $NaBH_4$,MeOH; (*vi*) Ac_2O,pyridine; (*vii*), CrO_3, acetone; (*viii*), HI,HOAc; (*ix*), Li_2CO_3,LiBr,DMF; (*x*), AgOAc,HOAc,I_2,H_2O; (*xi*), KOBu^t,Bu^{t}OH; (*xii*), LiAl(OBu^t)$_3$H,THF



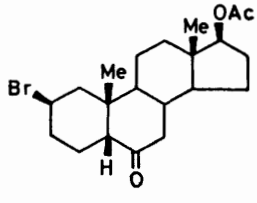
(14) R = O
(16) R = α-H, β-OAc



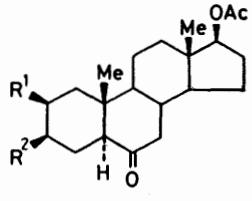
(15)



(17) R^1 = Br, R^2 = H
(18) R^1 = H, R^2 = Br
(20) R^1 = R^2 = H



(19)



(21) R^1 = H, R^2 = OTs
(22) R^1 = H, R^2 = Br
(23) R^1 = Ac, R^2 = H

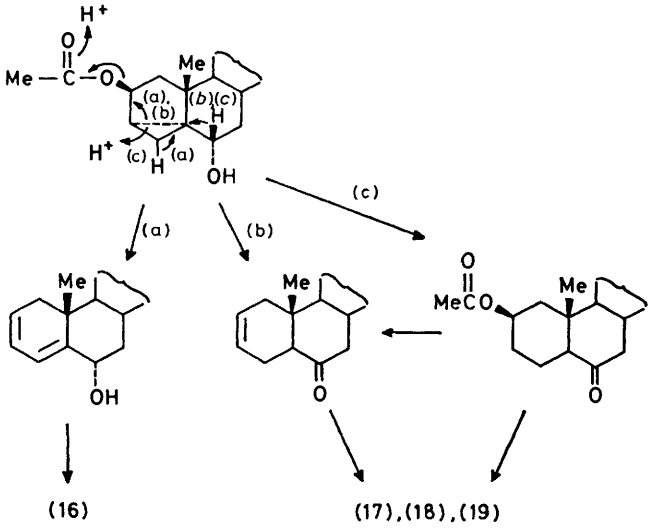
multiplicity of the C*H*Br resonance suggested that it was an equatorial 2β-substituent.

The formation of both the aromatic and non-aromatic steroids may be rationalized by participation of the cyclopropane ring in the solvolytic displacement of the

^{13}C N.m.r. signals of the 6-keto-steroids (in $CDCl_3$, p.p.m. from $SiMe_4$)

Carbon atom	Compound (20)	(17)	(18)	(19)
1	28.1	49.4	32.3	47.2
2	20.6	48.4	29.4	46.3
3	25.1	36.3	52.9	36.6
4	20.5	22.1	30.1	23.5
5	58.7	57.2	53.3	59.4
6	211.6	210.4	210.8	213.1
7	46.2	46.0	46.0	42.3
8	37.6	37.3	37.6	37.1
9	54.2	53.8	53.8	40.6
10	41.6	44.6	41.4	42.3
11	21.4	20.7	20.6	20.6
12	36.5	36.9	36.4	36.6
13	43.0	43.0	43.0	43.0
14	51.2	51.0	51.1	51.1
15	23.2	23.2	23.2	23.2
16	27.4	27.3	27.4	27.4
17	82.2	82.1	82.2	82.1
18	12.0	12.1	12.1	12.0
19	13.0	13.5	13.3	27.5
Me	21.0	21.1	21.1	21.1
CO	170.7	171.0	171.0	171.0

2β-acetate (see Scheme 2). Whereas the aromatic compounds may arise through the formation of a dienol, the ketonic products may arise through the 2-en-6-one (10) (pathway b). An alternative pathway (c) may involve the opening of the cyclopropane ring to form the 2β,17β-diacetoxyandrostan-6-one (23). In an attempt to distinguish between these possibilities both the steroids (10) and (23) were treated with refluxing hydrobromic acid in



SCHEME 2

glacial acetic acid. However, both gave the same mixture of 2- and 3-bromosteroids as obtained from the cyclosteroid. The formation of the 2β- and 3α-bromo-ketones represent the *trans*-addition of HBr to a Δ^2-olefin. In the case of the former, subsequent nucleophilic displacement by bromide ion affords the 2α-epimer, whilst the diaxial interaction between the 2β-bromine atom and the C-10 angular methyl group provides a driving force for the isomerization at C-5 to afford the *cis*-A/B ring junction. A similar pathway may arise from the initial formation of a C-6 carbocation.

EXPERIMENTAL

General experimental details have been described previously.[16]

Dehydration of 6β-*Hydroxy*-3α,5-*cycloandrost*-17-*one*.—The steroid [4] (5 g) in xylene (100 ml) was heated under reflux with alumina (grade 1) (15 g) for 20 h. The mixture was filtered and the solvent evaporated to afford an oil which was chromatographed on silica. Elution with 5% ethyl acetate–light petroleum gave 3α,5-cycloandrost-6-en-17-one which crystallized from light petroleum as needles (1.56 g), m.p. 135—136 °C (lit.,[4] 136—137 °C). Elution with 10% ethyl acetate–light petroleum gave 3α,5-cycloandrost-6-en-17α-ol (100 mg) which crystallized from light petroleum as needles, m.p. 110—112 °C; $\nu_{max.}$ 3 380, cm^{-1}; δ 0.43 (1 H, m), 0.72 (3 H, s, 18-H), 0.90 (3 H, s, 19-Me), 3.70 (1 H, d, *J* 6 Hz, 17-H), 5.15 (1 H, dd, *J* 3 and 10 Hz, 7-H), and 5.54 (1 H, d, *J* 10 Hz, 6-H).

3α,5-Cycloandrost-6-en-17β-ol (200 mg) was obtained on further elution with 10% ethyl acetate–light petroleum. It crystallized from aqueous ethanol as needles, m.p. 137—139 °C, $[\alpha]_D$ −49° (*c* 0.2) (lit.,[6] 137—138 °C, $[\alpha]_D$ −55°) (Found: C, 83.5; H, 10.3. Calc. for $C_{19}H_{28}O$: C, 83.8; H, 10.3%), $\nu_{max.}$ 3 320, 3 060, and 3 020 cm^{-1}; δ 0.43 (1 H, m), 0.77 (3 H, s, 18-H), 0.88 (3 H, s, 19-Me), 3.62 (1 H, t, *J* 8 Hz, 17-H), 5.14 (1 H, dd, *J* 3 and 10 Hz, 7-H), and 5.45 (1 H, d, *J* 10 Hz, 6-H). Further elution with 10% ethyl acetate–light petroleum gave 3α,5-cycloandrostane-6,17-dione (210 mg) which crystallized from actone–light petroleum as needles, m.p. 187—189 °C, $[\alpha]_D$ +120° (*c* 0.2) (lit.,[7] 182—183 °C, $[\alpha]_D$ +113°) (Found: C, 80.0; H, 9.1. Calc. for $C_{19}H_{26}O_2$: C, 79.8; H, 9.1%); $\nu_{max.}$ 1 730 and 1 690 cm^{-1}; δ 0.07 (1 H, t, *J* 4 Hz), and 0.84 and 0.97 (both 3 H, s, 18- and 19-Me). The starting material (1.8 g) was eluted with 15% ethyl acetate–light petroleum.

Inter-relationship of the By-products.—(*a*) 3α,5-Cycloandrost-6-en-17α-ol (50 mg) in acetone (5 ml) was treated with the 8N chromium trioxide reagent at room temperature. Methanol was then added, the solution poured into water, and the steroid recovered in ethyl acetate to afford 3α,5-cycloandrost-6-en-17-one which was identified by its n.m.r. spectrum.

(*b*) 3α,5-Cycloandrost-6-en-17-one (500 mg) in methanol (50 ml) was treated with sodium borohydride (200 mg) at room temperature for 1 h. The solution was poured into water and the steroid recovered in ethyl acetate to afford 3α,5-cycloandrost-6-en-17β-ol (440 mg), identical (n.m.r., i.r. and m.p.) to the sample described above.

(*c*) 3α,5-Cyclo-6β-hydroxyandrostan-17-one (350 mg) in acetone (20 ml) was treated with the 8N chromium trioxide reagent. Methanol was added and the solution poured into water. The product was recovered in ethyl acetate to afford 3α,5-cycloandrostane-6,17-dione (330 mg), identical (n.m.r., i.r.) to the material described above.

2β,17β-*Diacetoxy*-3α,5-*cycloandrostan*-6-*one*.— 2β,17β-Diacetoxy-3β-hydroxyandrostan-6-one [10] was converted to its 3β-*toluene*-p-*sulphonate* with toluene-*p*-sulphonyl chloride in pyridine. The derivative crystallized from acetone–light

petroleum as needles, m.p. 177—179 °C, $[\alpha]_D$ −21.7° (*c* 0.2) (Found: C, 64.2; H, 7.2. $C_{30}H_{40}O_8S$ requires C, 64.3; H, 7.1%); $\nu_{max.}$ 1 735, 1 710, and 1 600 cm^{-1}; δ 0.76 (3 H, s, 18-Me), 0.87 (3 H, s, 19-Me), 1.99, (6 H, s, Ac), 2.40 (3 H, s, Ar-*Me*), 4.48 (2 H, m, 3- and 17-H), 5.07 (1 H, m, 2-H), and 7.28 and 7.71 (each 2 H, d, *J* 8 Hz, Ar-H). The toluene-*p*-sulphonate (650 mg) was added to a solution of potassium t-butoxide [from potassium (200 mg) in t-butyl alcohol (15 ml)] which was then heated under reflux for 30 min. The solution was poured into water, acidified with dilute hydrochloric acid, and the steroid recovered in chloroform. The solvent was evaporated to give an oil which, as shown by the n.m.r. spectrum, was a mixture of mono- and di-acetates. It was re-acetylated with acetic anhydride in pyridine overnight, to afford 2β,17β-*diacetoxy*-3α,5-*cycloandrostan*-6-*one* (320 mg) which crystallized from light petroleum as needles, m.p. 160—162°, $[\alpha]_D$ −28.6° (*c* 0.2) (Found: C, 71.1; H, 8.20. $C_{23}H_{32}O_5$ requires C, 71.3; H, 8.25%); $\nu_{max.}$ 1 730 and 1 690 cm^{-1}; δ 0.80 (3 H, s, 18-Me), 0.99 (3 H, s, 19-Me), 1.95 and 1.98 (each 3 H, s, OAc), 4.57 (1 H, t, *J* 8 Hz, 17-H), and 5.30 (1 H, m, 2-H).

2β,17β-*Diacetoxy*-6α-*hydroxy*-3α,5-*cycloandrostane*.— The above ketone (200 mg) in dry tetrahydrofuran (10 ml) was treated with lithium tris-(t-butoxy)aluminium hydride (400 mg) for 1 h at 0 °C. Ice was added and the product recovered in chloroform to afford the 6α-*alcohol* (200 mg) which crystallized from acetone–light petroleum as needles, m.p. 150—152 °C, $[\alpha]_D$ +16.7° (*c* 0.2) (Found: C, 70.7; H, 8.6. $C_{23}H_{34}O_5$ requires C, 70.8; H, 8.7%); $\nu_{max.}$ 3 555 and 1 720 cm^{-1}; δ 0.79 (3 H, s, 18-Me), 0.92 (3 H, s, 19-Me), 1.98 (6 H, s, 2 Ac), 3.80 (1 H, dd, *J* 4 and 11 Hz, 6-H), 4.52 (1 H, t, *J* 8 Hz, 17-H), 5.20 (1 H, m, 2-H).

Reactions with Hydrobromic Acid.—(*a*) 6β,7β-Dihydroxy-3α,5-cycloandrostan-17-one (200 mg) in glacial acetic acid (4 ml) and 48% hydrobromic acid (0.5 ml) was heated under reflux for 10 min. The solution was cooled, poured into aqueous sodium hydrogencarbonate, and the steroids recovered in ethyl acetate and chromatographed on silica. Elution with 1% ethyl acetate–light petroleum gave the anthrasteroid (15) (40 mg) which crystallized from acetone–light petroleum as prisms, m.p. 135—138 °C, $[\alpha]_D$ +122° (*c* 0.2) (lit.,[11] 138—140 °C, $[\alpha]_D$ +142°) (Found: C, 84.9; H, 8.9. Calc. for $C_{19}H_{24}O$: C, 85.1; H, 9.0%); $\nu_{max.}$ 1 740 cm^{-1}; δ 1.10 (3 H, s, 18-Me), 2.10 (3 H, s, Ar-*Me*), and 6.81 (1 H, s, Ar-H). Elution with 2% ethyl acetate–light petroleum gave 4-methylestra-1,3,5(10)-trien-17-one (60 mg), which crystallized from acetone as prisms, m.p. 185—187 °C, $[\alpha]_D$ +139° (lit.,[11] 184—186 °C), identical with an authentic sample.

(*b*) 2β,17β-Diacetoxy-6α-hydroxy-3α,5-cycloandrostane (200 mg) in glacial acetic acid (4 ml) and 48% hydrobromic acid (0.5 ml) were refluxed for 15 min. The solution was cooled and poured into aqueous sodium hydrogencarbonate. The steroids were recovered in ethyl acetate and chromatographed on silica. Elution with 3% ethyl acetate–light petroleum gave 17β-acetoxy-4-methylestra-1,3,5(10)-triene (54 mg) which crystallized from acetone–light petroleum as needles, m.p. 178—181 °C, $[\alpha]_D$ +39° (*c* 0.2) (lit.,[11] 188 °C, $[\alpha]_D$ +38°) identified by comparison (n.m.r.) with authentic material. Subsequent fractions gave a small amount of a gummy aromatic (δ 7.0, m, Ar-H) product. Elution with 4% ethyl acetate–light petroleum gave a mixture (n.m.r.) of 17β-acetoxyandrost-2-en-6-one and 17β-*acetoxy*-3α-*bromo*-5α-*androstan*-6-*one* (22 mg). The latter was purified by crystallization from light petroleum as needles, m.p. 195—198 °C, $[\alpha]_D$ −11.4° (*c* 0.2) (Found: C, 61.2; H, 7.3. $C_{21}H_{31}O_3Br$ requires C, 61.3; H, 7.5%); $\nu_{max.}$ 1 730 and 1 705 cm^{-1}; δ 0.75, 0.80, and 2.00 (each 3 H, s, 18- and 19-Me and OAc) 2.82 (1 H, q, *J* 5 and 9 Hz, 5-H), and 4.65 (2 H, m, 3- and 17-H). Chromatography of the mother-liquors on silica impregnated with silver nitrate gave 17β-acetoxy-5α-androst-2-en-6-one, identified by its n.m.r. spectrum. Elution with 5% ethyl acetate–light petroleum gave 17β-*acetoxy*-2α-*bromo*-5α-*androstan*-6-*one* (9 mg) which crystallized from acetone as needles, m.p. 246—249°, $[\alpha]_D$ −31.4° (*c* 0.1) (Found: C, 61.4; H, 7.5. $C_{21}H_{31}O_3Br$ requires C, 61.3; H, 7.5%); $\nu_{max.}$ 1 745 and 1 725 cm^{-1}; δ 0.80 (6 H, s, 18- and 19-Me), 2.01 (3 H, s, OAc), 4.13 (1 H, m, 2-H), and 4.61 (1 H, t, *J* Hz, 17-H). Further elution with 5% ethyl acetate–light petroleum gave 17β-*acetoxy*-2β-*bromo*-5β-*androstan*-6-*one* (10 mg) which crystallized from ethyl acetate as needles, m.p. 227—229 °C, $[\alpha]_D$ −130° (*c* 0.2) (Found: C, 51.45; H, 7.4. $C_{21}H_{31}O_3Br$ requires C, 61.3; H, 7.5%); $\nu_{max.}$ 1 730 and 1 695 cm^{-1}; δ 0.79 (3 H, s, 18-Me), 0.90 (3 H, s, 19-Me), 2.00 (3 H, s, 17-OAc), 4.06 (1 H, m, $W_{\frac{1}{2}}$ 26 Hz 2-H), and 4.58 (1 H, t, *J* 8 Hz, 17-H).

(*c*) 17β-Acetoxy-5α-androst-2-en-6-one (200 mg) in glacial acetic acid (2 ml) was refluxed with 48% hydrobromic acid (1 ml) for 15 min and worked up as above. Chromatography on silica and elution with 4% ethyl acetate–light petroleum gave 17β-acetoxy-3α-bromo-4α-androstan-6-one (50 mg) identified by its n.m.r. and m.p. Elution with 5% ethyl acetate–light petroleum gave first 17β-acetoxy-2α-bromo-5α-androstan-6-one (74 mg) and then 17β-acetoxy-2β-bromo-5β-androstan-6-one (50 mg), both of which were identified by n.m.r., i.r., and m.p.

(*d*) 2β,17β-Diacetoxy-5α-androstan-6-one (236 mg) in glacial acetic acid (2 ml) and 48% hydrobromic acid (1 ml) were refluxed for 15 min and worked up as above. Chromatography on silica gave 17β-acetoxy-3α-bromo-5α-androstan-6-one (37 mg), 17β-acetoxy-2α-bromo-5α-androstan-6-one (52 mg), and 17β-acetoxy-2β-bromo-5β-androstan-6-one (33 mg), which were identified by their i.r. and n.m.r. spectra.

Hydroboronation of 17β-*Acetosy*-3β-p-*tolylsulphonyloxyandrost*-5-*ene*.—Borane in tetrahydrofuran (6.8ml of 1M soln.) was added dropwise under nitrogen to a stirred ice-cold solution of 17β-acetoxy-3β-*p*-tolylsulphonyloxyandrost-5-ene (1.36 g) in dry tetrahydrofuran (27 ml). The solution was allowed to warm to room temperature over 1 h. 2M Sodium hydroxide (3.4 ml) and then 1.8M hydrogen peroxide (3.8 ml) were added and the solution was stirred for 2 h. Sodium chloride was added to saturate the aqueous layer and the tetrahydrofuran layer then separated. The solution was concentrated and ethyl acetate was added. The solution was then washed with water and brine, and dried. The solvent was evaporated and the residual gum (1.34 g) dissolved in acetone (50 ml) and treated with an excess of 8N chromium trioxide. Water (200 ml) was added and the steroids were recovered in ethyl acetate. The solvent was evaporated to afford 17β-*acetoxy*-3β-p-*tolylsulphonyloxy*-5α-*androstan*-6-*one* (930 mg) which crystallized from acetone–light petroleum as needles, m.p. 156—158 °C, $[\alpha]_D$ −21.8° (*c* 0.2) (Found: C, 66.4, H, 7.7. $C_{28}H_{38}O_6S$ requires C, 66.8; H, 7.75%); $\nu_{max.}$ 1 730, 1 710, and 1 600 cm^{-1}; δ 0.71 (3 H, s), 0.75 (3 H, s) (18- and 19-Me), 1.98 (3 H, s, OAc), 2.39 (3 H, s, Ar-*Me*), 4.45 (2 H, m, 3- and 17-H), and 7.27 and 7.72 (each 2 H, d, *J* 8 Hz, Ar-H). Preparative layer chromatography of the mother-liquors gave 3β-p-*tolylsulphonyloxy*-5α-*androstane*-6-17-*dione* which

crystallized from acetone–light petroleum as needles, m.p. 177—179 °C, $[\alpha]_D$ +39° (*c* 0.2) (Found: C, 68.1; H, 7.5. $C_{26}H_{34}O_5S$ requires C, 68.0; H, 7.6%); $\nu_{max.}$ 1 733, 1 697, and 1 598 cm^{-1}; δ 0.72 and 0.81 (each 3 H, s, 18- and 19-Me), 2.38 (3 H, s, Ar-Me), 4.32 (1 H, m, 3-H), and 7.25 and 7.71 (each 2 H, d, *J* 8 Hz, Ar-H).

Reaction of 17β-Acetoxy-3β-p-tolylsulphonyloxy-5α-androstan-6-one with Lithium Bromide.—The steroid (500 mg) in butanone (12.5 ml) was heated with lithium bromide (135 mg) under reflux for 2 h. Ethyl acetate was added to the solution, which was then washed with water, dried, and the solvents evaporated to afford a gum. Chromatography on silica and elution with 5% ethyl acetate–light petroleum gave 17β-acetoxy-3α-bromo-5α-androstan-6-one (220 mg) identical (n.m.r., i.r., and m.p.) to the material described above. Elution with 10% ethyl acetate–light petroleum gave 17β-acetoxy-3β-bromo-5α-androstan-6-one (70 mg) which crystallized from acetone–light petroleum as prisms, m.p. 185—186 °C, $[\alpha]_D$ −19.4° (*c* 0.3) (lit.,[13] 184—186 °C, $[\alpha]_D$ −21°) (Found: C, 61.3; H, 7.5. Calc. for $C_{21}H_{31}O_3Br$: C, 61.3; H, 7.5%); $\nu_{max.}$ 1 730 and 1 705 cm^{-1}; δ 0.80 (6 H, s, 18- and 19-Me), 1.99 (3 H, s, OAc), 3.92 (1 H, m, 3-H), and 4.61 (1 H, t, *J* 8 Hz, 17-H).

Epimerization of the 3α-Bromo-ketone. The 3α-bromo-ketone (65 mg) in butanone (2 ml) containing lithium bromide (16 mg) was refluxed for 2 h. The solution was worked up as above and the product chromatographed on silica. Elution with 4% ethyl acetate–light petroleum gave the starting material (40 mg). Further elution with 5% ethyl acetate–light petroleum gave 17β-acetoxy-3β-bromo-5α-androstan-6-one (20 mg), identified by its n.m.r. spectrum.

17β-Acetoxy-3α-bromo-2β-hydroxy-5α-androstan-6-one.—*N*-Bromosuccinimide (2.1 g) was added to a solution of 17β-acetoxy-5α-androst-2-en-6-one (3 g) in dioxan (150 ml) containing perchloric acid (30 ml, 0.5M). The solution was stirred in the dark for 2 h at room temperature. Aqueous sodium sulphite (10%) was added until no blue colour was obtained with potassium iodide–starch paper. The solution was poured into water and the steroids were recovered in ether. The solvent was evaporated to give *17β-acetoxy-3α-bromo-2β-hydroxy-5α-androstan-6-one* (2.5 g) which crystallized from acetone as needles, m.p. 225—227 °C, $[\alpha]_D$ +32.4 (*c* 0.2) (Found: C, 59.1; H, 7.2. $C_{21}H_{31}O_4Br$ requires C, 59.0; H, 7.3%); $\nu_{max.}$ 3 410, 1 730, and 1 685 cm^{-1}; δ 0.77 (3 H, s, 18-Me), 0.93 (3 H, s, 19-Me), 1.98 (3 H, s, OAc), 2.77 (1 H, dd, *J* 11 and 1.5 Hz, 5-H), 4.22 (2 H, m, 2- and 3-H), and 4.57 (1 H, t, *J* 8 Hz, 17-H).

17β-Acetoxy-2β-hydroxy-5α-androstan-6-one.—The above bromo-steroid (1.7 g) in dry benzene (100 ml) was treated with tri-n-butyltin hydride (3.4 ml) and azobisisobutyronitrile (100 mg) under reflux for 5 min. Water was added and the solvent was evaporated to give a residue which was chromatographed on silica. Elution with 30% ethyl acetate–light petroleum gave *17β-acetoxy-2β-hydroxy-5α-androstan-6-one* (800 mg) which crystallized from acetone–light petroleum as needles, m.p. 201—202 °C, $[\alpha]_D$ −37° (*c* 0.2) (Found: C, 72.3; H, 9.3. $C_{21}H_{32}O_4$ requires C, 72.4; H, 9.2%); $\nu_{max.}$ 3 460, 1 730, and 1 690 cm^{-1}; δ 0.77 (3 H, s, 18-Me), 0.97 (3 H, s, 19-Me), 1.98 (3 H, s, OAc), 4.10 (1 H, m, 2-H), and 4.58 (1 H, t, *J* 8 Hz, 17-H). The *2β,17β-diacetate*, prepared with acetic anhydride in pyridine, crystallized from acetone–light petroleum as needles, m.p. 204—206 °C, $[\alpha]_D$ −18° (*c* 0.1) (Found: C, 70.7; H, 8.7. $C_{23}H_{34}O_5$ requires C, 70.8; H, 8.7%); $\nu_{max.}$ 1 730 and 1 702 cm^{-1}; δ 0.80 (3 H, s, 18-Me), 0.92 (3 H, s, 19-Me), 2.00 (3 H, s, 17-OAc), 2.01 (3 H, s, 2-OAc), 4.61 (1 H, t, *J* 8 Hz, 17-H), and 5.08 (1 H, m, 2-H). The *2β-methanesulphonate*, prepared with methanesulphonyl chloride in pyridine, crystallized as needles from acetone–light petroleum, m.p. 157—159 °C, $[\alpha]_D$ −36° (*c* 0.2) (Found: C, 62.1; H, 7.9. $C_{22}H_{34}O_6S$ requires C, 62.0; H, 8.0%); $\nu_{max.}$ 1 720 and 1 700 cm^{-1}; δ 0.80 (3 H, s, 18-Me), 0.94 (3 H, s, 19-Me), 2.01 (3 H, s, OAc), 2.96 (3 H, s, OSO_2Me), 4.61 (1 H, t, *J* 8 Hz, 17-H), and 5.04 (1 H, m, 2-H).

17β-Acetoxy-2α-bromo-5α-androstan-6-one.—The above methanesulphonate (50 mg) in dry tetrahydrofuran (2 ml) was heated under reflux for 1 h with lithium bromide (200 mg). Water was added and the steroids were recovered in ethyl acetate. The solvent was evaporated and the residue chromatographed on silica. Elution with 4% ethyl acetate–light petroleum gave a mixture of olefins (n.m.r.) (29 mg). Elution with 5% ethyl acetate–light petroleum gave 17β-acetoxy-2α-bromo-5α-androstan-6-one (5 mg) identical (n.m.r.) to the material obtained previously.

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