The Reaction of Some 1α,2α- and 2α,3α-Methylene Steroids with Hydrobromic Acid

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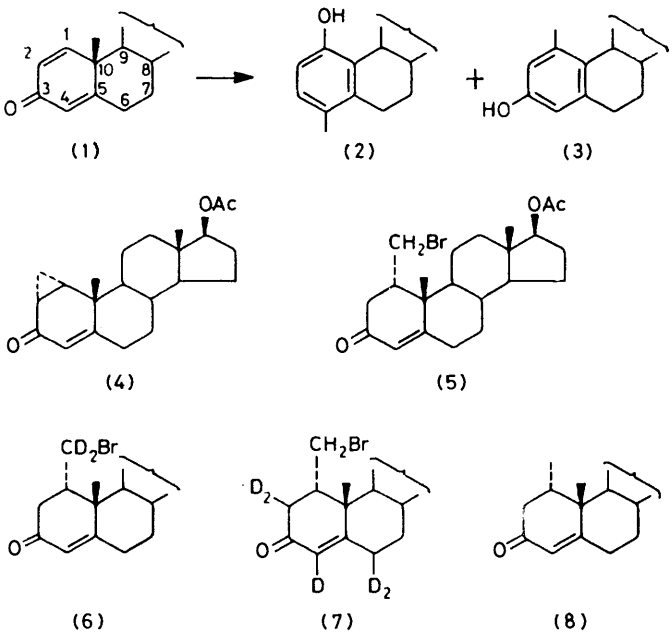
Treatment of 17β-acetoxy-1α,2α-methyleneandrost-4-en-3-one under the conditions of the dienone–phenol rearrangement affords 17β-acetoxy-1α-bromomethylandrost-4-en-3-one rather than a phenol. The corresponding 3α-alcohol gave a 1α-bromomethyl-3,5-diene rather than an aromatic compound. 2α,3α-Methyleneandrost-5-ene-4,17-dione also gave a 2α-bromomethylandrost-5-ene-4,17-dione rather than a phenol.

THE acid-catalysed dienone–phenol rearrangement of steroids, (1) to (2) or (3), has been the subject of a number of studies.[1] The orientation of the phenols which are formed, varies markedly with the substituents which are attached to the dienone (*e.g.* a 4-methyl,6-ketone or a $\Delta^{6,7}$-olefin). These results have been rationalized in terms of two paths:—one involving the migration of the 9,10-bond to C-5 and a spiran intermediate which leads to '*para*' phenols of type (2) and the other involving the migration of the C-10 methyl group to C-1 which leads to '*meta*' phenols of the type (3). The effect of a 1,2-methylene group as a double-bond equivalent on the reactions of an androst-4-en-one under the typical conditions (HBr, acetic acid) of the dienone–phenol rearrangement has not been examined. A range of products may be envisaged depending upon whether protonation of the unsaturated ketone induces rearrangement of the 9,10-bond to C-5 before cyclopropane ring opening or not. Cleavage of the cyclopropane ring might occur in several ways giving either an A-homosteroid, a methylated aromatic steroid, or a bromomethyl compound. Reaction of 17β-acetoxy-1α,2α-methylene-5α-androstan-3-one with HCl or HI at room temperature affords the 1-chloromethyl or 1-iodomethyl steroid [2a] whilst the preparation and reactions of some 6,7-disubstituted 3-oxo-1α,2α-methylene-Δ^4-steroids [2b] including the selective 6,7-ring-opening of 1α,2α;6β,7β-dimethylene-3-oxo-Δ^4-steroids have been studied.[2c] The acid-catalysed cleavage of the cyclopropane ring in some 3-hydroxy-1,2-methylene steroids has also been examined.[2d]

17β-Acetoxy-1α,2α-methyleneandrost-4-en-3-one (4) was prepared [3] by the addition of dimethylsulphoxonium methylide [4] to 17β-acetoxyandrost-1,4,6-trien-3-one followed by partial hydrogenation of the Δ^6-olefin. The failure of the methylide to add under similar conditions to the 1,4-dien-3-one may be due to the easier formation of the 1,3,5-trien-3-olate anion compared to the enolization of the 1,4,6-trien-3-one. The anion would not react with the methylide. Treatment of the 17β-acetoxy-1α,2α-methyleneandrost-4-en-3-one (4) with hydrobromic acid in glacial acetic acid gave the 1α-bromomethyl steroid (5) in 83% yield together with its 17β-alcohol. The latter was readily re-acetylated. The structure of these products was established as follows. The presence of bromine followed from the analytical and mass spectral data whilst the u.v., i.r., and n.m.r. spectra revealed the existence of the Δ^4-3-one ($\lambda_{max.}$ 245 nm; $\nu_{max.}$ 1 680 cm^{-1}; δ 5.75, 1 H, s). The location of the bromine atom in the γ-position relative to the carbonyl group was established by regeneration of the



cyclopropane ring on treatment with potassium t-butoxide. Repetition of the reaction with 17β-acetoxy-1α,2α-[$^2H_2$]methyleneandrost-4-en-3-one and with 17β-acetoxy-1α,2α-methyleneandrost-4-en-3-one in deuterium bromide and [$^2H_4$]acetic acid gave two deuterium-labelled steroids, (6) and (7). Whilst compound (6) lacked signals at δ 3.20 (1 H, t, *J* 10 Hz) and 3.67 (1 H, d of t, *J* 2.5 and 10 Hz) compound (7) lacked signals at δ 2.98 (1 H, dd, *J* 2.5 and 17 Hz) and δ 2.68 (1 H, d of q, *J* 2.5, 5, and 17 Hz). Analysis of the 220 MHz ^1H n.m.r. spectra of these (see Table) together with careful spin-decoupling experiments indicated the presence of a O=C·CH_2·CH(CH_2Br)C– grouping affording a distinction between an A-homo- and a bromomethyl steroid. Structure (5) was confirmed by reduction with zinc in acetic acid which gave 17β-acetoxy-1α-methylandrost-4-en-3-

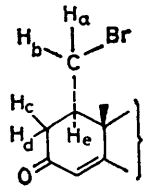
one (8) (1-Me, δ 0.95, d, J 7 Hz) [2,*] and 17β-acetoxy-1α,2α-methyleneandrost-4-en-3-one. Thus the 1α,2α-methylene bridge has, rather surprisingly, blocked the dienone–phenol rearrangement.

Androsta-2,5-diene-4,17-dione (9) reacts with hydrobromic acid in glacial acetic acid to give 4-hydroxy-1-methylestra-1,3,5(10)-trien-17-one (10) by methyl migration from C-10 to C-1.[5] The effect of a 2α,3α-methylene group was examined in this case. 5α-Hydroxy-2α,3α-methyleneandrostane-4,17-dione (11) was prepared by the addition of dimethylsulphoxonium methylide to 5α-hydroxyandrost-2-ene-4,17-dione.[6] The α-configuration of the methylene group was assigned from the known mode of attack [7] of the methylide. Further evidence for the stereochemistry of the addition was obtained by reduction of the dione with lithium aluminium hydride to afford a triol (12) in which the 19-H_3 n.m.r. signal showed a significant (Δδ 0.24) downfield shift compared to the parent ketone. Hence, typical of the hydride reduction of 4-ketones, reduction has proceeded from the α-face to afford a β-alcohol.

N.m.r. spectra of 1α-bromomethyl steroids (5), (6), and (7)

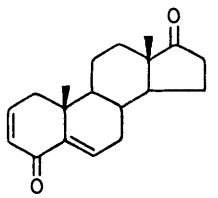
Proton	Chemical shift	Multiplicity	Coupling constants (Hz)	Spin decoupling experiments
H_a	3.67 [a]	d of t	J_{ab} 10; J_{ae} 2.5; J_{ad} 2.5	Irradiation at δ 3.20 collapsed this to a triplet, J 2.5 Hz; irradiation at δ 2.68 and 2.38 collapsed this to quartets, J 10 and 2.5 Hz.
H_b	3.20 [a]	t	$J_{ba} = J_{be} = 10$	Irradiation at δ 3.67 and 2.38 collapsed this to a doublet, J 10 Hz.
H_c	2.98	d of d	J_{cd} 17; J_{ce} 2.5	Irradiation at δ 2.68 collapsed this to a doublet, J 2.5 Hz; irradiation at 2.38 collapsed this to a doublet, J 17 Hz.
H_d	2.68 [b]	d of q	J_{dc} 17; J_{de} 5; J_{da} 2.5	Irradiation at δ 3.20 collapsed this to a quartet, J 17 and 5 Hz; irradiation at δ 2.98 collapsed this to a quartet J 5 and 2.5 Hz; irradiation at δ 2.38 collapsed this to a quartet J 17 and 2.5 Hz.
H_e	2.38 [b]	m	Unresolved	

[a] Absent in (6). [b] Absent in (7).



Unfortunately the 4-H and 17-H proton resonances overlapped. However in the diacetate (13) they were separate and the 4-H signal now appeared as a singlet (δ 4.90). Consequently the 4α-H and the 3-H have a dihedral angle of *ca.* 90° indicative of a 2α,3α-methylene substituent and a 3β-hydrogen atom.

Dehydration of 5α-hydroxy-2α,3α-methyleneandrostane-4,17-dione with thionyl chloride gave the corresponding Δ^5-olefin (14). Treatment of both the 5α-alcohol (11) and the Δ^5-olefin (14) with hydrobromic acid in glacial acetic acid afforded 2α-bromomethylandrost-5-ene-4,17-dione (15). The presence of the bromomethyl group was established by a two-proton doublet at δ 3.38 (J 5 Hz) in the n.m.r. spectrum. This resonance was absent from the spectrum of the corresponding deuteriated compound which was obtained by treating 5α-hydroxy-2α,3α-[$^2H_2$]methyleneandrostane-4,17-dione with hydrobromic acid in glacial acetic acid. When the 2α-bromomethyl-4-ketone (15) was treated with potassium t-butoxide, the cyclopropane ring was regenerated. However the product was the non-conjugated 2α,3α-methyleneandrost-6-ene-4,17-dione (16) [6-H and 7-H, δ 5.71 and 5.98 J 11 Hz; u.v. $\lambda_{max.}$ 209 nm (ε 870)]. This compound could also be obtained from 2α,3α-methyleneandrost-5-ene-4,17-dione (14) on treatment with potassium t-butoxide in tetrahydrofuran. The 2α-bromomethylandrost-5-ene-4,17-dione (15) was also formed in 88% yield by treating the 6-ene (16) with hydrobromic acid in glacial acetic acid.



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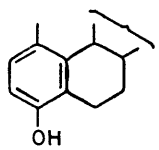

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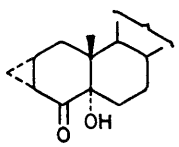

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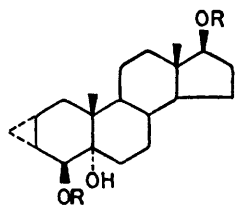
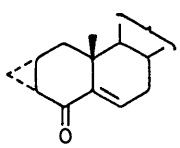


(12) R = H
(13) R = Ac



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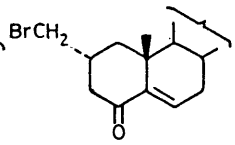

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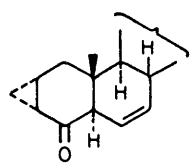

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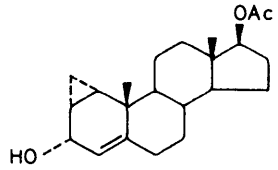
Molecular models suggest that the relative stability of the non-conjugated 2α,3α-methyleneandrost-6-ene-4,17-dione compared to the conjugated isomer, may be

* We thank Professor R. Wiechert for sending us spectral data for this compound.

attributed to the interaction of the cyclopropane ring with ring B in the conjugated isomer and also to the interaction between C-1 and C-11 in the latter. The models also suggest that the 6-ene possesses a trans A/B ring junction in which both the 5-H and the 8-H subtend a dihedral angle of *ca.* 90° with the olefinic hydrogen atoms leading to a lack of coupling between these centres. Thus the 2α,3α-methylene bridge has also blocked the dienone–phenol rearrangement.

Consequently the effect of the 1α,2α-methylene bridge as a potential double-bond equivalent on the dienol–benzene rearrangement was also examined. Reduction of the unsaturated ketone (4) with lithium aluminium tri-t-butoxy hydride gave two epimeric alcohols (17) and (18). The stereochemistry of the alcohols was assigned from their n.m.r. spectra. Examination of Dreiding models showed that a 1α,2α-methylene substituent forces ring A to adopt a boat conformation in which (*a*) there is a diaxial interaction between a 3β-substituent and C-19 and (*b*) there is a dihedral angle of *ca.* 90° between the 3β-H and the 4-H and of 15° between the 3α-H and the 4-H. The 19-H_3 resonance in the β-alcohol (18) appeared at lower field (Δδ 0.18 p.p.m.) than in the α-epimer (17) whilst in the β-alcohol (18) $J_{3H:4\text{-}H}$ was 5 Hz and in the α-alcohol (17) $J_{3H:4\text{-}H}$ was 0 Hz. The major product of the reduction was the α-alcohol (17) in which the reagent has attacked the molecule from the β-face of the molecule in contrast to the reaction in the absence of the 1α,2α-methylene bridge.



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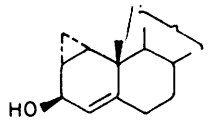

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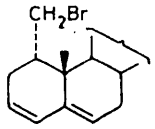

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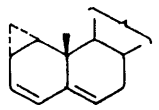

(20)

Treatment of the 1α,2α-methylene-3α-alcohol (17) with hydrobromic acid in glacial acetic acid again gave no aromatic material. The major product (60%) was 17β-acetoxy-1α-bromomethylandrosta-3,5-diene (19). This compound showed triple maxima in the u.v. spectrum characteristic of a $\Delta^{3,5}$-diene ($\lambda_{max.}$ 229, 236, 244 nm).[8] The ^1H n.m.r. spectrum showed signals for a CH_2Br group (δ 3.04, 1 H, t, *J* 11 Hz and δ 3.52, 1 H, d of q, *J* 1.5, 3, and 11 Hz) analogous to those in the ^1H n.m.r. spectrum of 17β-acetoxy-1α-bromomethylandrost-4-en-3-one (5). These signals were absent in the deuteriated sample which was prepared from 17β-acetoxy-3α-hydroxy-1α,2α-[$^2H_2$]methyleneandrost-4-ene. The coupling pattern was consistent with the presence of the system $CH_2CH(CH_2Br)C$. When the reaction was carried out at room temperature in acetone, the product of dehydration (20) was obtained along with (19). The dehydration product, which retained the cyclopropane ^1H n.m.r. resonances (δ 0.15) and had three olefinic proton resonances (δ 5.30, 5.57, and 5.85), was also obtained by treatment of the alcohol with toluene-*p*-sulphonic acid in acetic anhydride. However treatment of 17β-acetoxy-1α,2α-methyleneandrosta-3,5-diene (20) with HBr in glacial acetic acid at 50 °C gave only intractable material. The results may be rationalized by the formation of a C-3 carbocation from the 17β-acetoxy-3α-hydroxy-1α,2α-methyleneandrost-4-ene (17) which may react in two ways. Loss of a proton from C-6 affords the diene. On the other hand cleavage of the cyclopropane ring affords a 1α-bromomethylandrosta-2,4-diene. The 2,4-diene then isomerizes to the more stable 3,5-diene. Thus under the normal conditions of the steroidal dienone–phenol and dienol–benzene rearrangement, a 1α,2α- or 2α,3α-methylene substituent blocks the aromatization reaction.

EXPERIMENTAL

General experimental details have been described previously.[9]

Reaction of 17β-*Acetoxy*-1α,2α-*methyleneandrost*-4-*en*-3-*one* (4) *with Hydrobromic Acid.*—The steriod (4)[3] (200 mg) in glacial acetic acid (2 ml) was heated under reflux with 48% hydrobromic acid (0.5 ml) for 15 min. The solution was cooled and poured into aqueous sodium hydrogen carbonate and the steroid was recovered in ethyl acetate. The products were purified by p.l.c. on silica in 30% ethyl acetate–light petroleum. The band R_F 0.29 gave 17β-*acetoxy*-1α-*bromomethylandrost*-4-*en*-3-*one* (5) (167 mg) which recrystallized from acetone–light petroleum as needles, m.p. 138—140 °C (lit.,[10] m.p. 144—145 °C), $[\alpha]_D$ +76° (*c* 0.2) (Found: C, 62.4; H, 7.3. Calc. for $C_{22}H_{31}BrO_3$: C, 62.4; H, 7.3%), $\lambda_{max.}$ 245 nm (ε 141 55); $\nu_{max.}$ 1 730, 1 680, and 1 610 cm^{-1}; δ(220 MHz) 0.87 (3 H, s, 18-H), 1.37 (3 H, s, 19-H), 2.07 (3 H, s, OAc), 2.68 (1 H, d, q, *J* 2.5, 5 and 17 Hz, 2-H), 2.98 (1 H, d, d *J* 2.5 and 17-Hz, 2-H), 3.20 (1 H, t, *J* 10 Hz, 1′-H) 3.67 (1 H, d, t, *J* 2.5 and 10 Hz, 1′-H), 4.62 (1 H, t, *J* 8 Hz, 17-H), and 5.75 (1 H, s, 4-H). The starting material (14 mg) was obtained from the band R_F 0.18. Elution of the band at R_F 0.07 gave 1α-bromomethyl-17β-hydroxyandrost-4-en-3-one (29 mg) as an oil, $\lambda_{max.}$ 3 450, 1 665, and 1 610 cm^{-1}; δ(90 MHz) 0.81 (3 H, s, 18-H), 1.35 (3 H, s, 19-H), 2.71 (1 H, m, 2-H), 2.86 (1 H, m, 2-H), 3.12 (1 H, t, *J* 10 Hz, 1′-H) 3.63 (2 H, m, 1′- and 17-H), and 5.72 (1 H, s, 4-H). The oil was acetylated with acetic anhydride in pyridine to afford the acetate (5), identified by its m.p. and n.m.r. spectra. The above experiment was repeated with 17β-acetoxy-1α,2α-[$^2H_2$]-methyleneandrost-4-en-3-one (200 mg) to afford 17β-acetoxy-1α-bromo[$^2H_2$]methylandrost-4-en-3-one (150 mg) which crystallized from acetone–light petroleum as needles, m.p. 138—141 °C, δ(220 MHz) 0.86 (3 H, s, 18-H), 1.36 (3 H, s, 19-H), 2.06 (3 H, s, OAc), 2.67 (1 H, dd, *J* 5 and 17 Hz, 2-H), 2.96 (1 H, dd, *J* 2.5 and 17-Hz, 2-H), 4.62 (1 H, t, *J* 8 Hz, 17-H), and 5.75 (1 H, s, 4-H).

1α-Bromo[$^2H_2$]methyl-17β-hydroxyandrost-4-en-3-one (20 mg) had δ 0.81 (3 H, s, 18-H), 1.37 (3 H, s, 19-H), 2.65 (1 H, dd, *J* 5 and 17 Hz, 2-H), 2.98 (1 H, dd, 2.5 and 17 Hz

2-H), 3.68 (1 H, t, *J* 8 Hz 17-H), and 7.78 (1 H, s, 4-H). A solution of 17β-acetoxy-1α,2α-methyleneandrost-4-en-3-one (140 mg) in [$^2H_4$]acetic acid (1.5 ml) was heated under reflux with deuteriobromic acid (0.5 ml) for 15 min. Deuterium oxide (1 ml) was added to the cooled solution which was then cautiously poured onto solid potassium carbonate. The pH of the solution was adjusted to 7 with [$^2H_4$]acetic acid and the products were extracted with ethyl acetate. The steroids were purified by preparative layer chromatography on silica in 30% ethyl acetate–light petroleum. 17β-Acetoxy-1α-bromomethyl[2,2,4,6,6-$^2H_5$]androst-4-en-3-one had *m/e* 429 (M^+); δ 0.84 (3 H, s, 18-H), 1.37 (3 H, s, 19-H), 2.04 (s, OAc) 3.12 (1 H, t, *J* 10 Hz, 1′-H), and 3.60 (1 H, d, d, *J* 2.5 and 10 Hz, 1′-H).

Reaction of the Bromo-ketone (5) *with Potassium t-Butoxide*.—A solution of 17β-acetoxy-1α-bromomethylandrost-4-en-3-one (50 mg) in tetrahydrofuran (5 ml) was heated under reflux with potassium t-butoxide (100 mg) for 1 h. Dilute hydrochloric acid was added to the mixture and the products were extracted with ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and water and dried over sodium sulphate. The solvent was evaporated to afford 17β-acetoxy-1α,2α-methyleneandrost-4-en-3-one (4) (30 mg) which was identified by its n.m.r. and i.r. spectra.

Reduction of the Bromo-ketone (5) *with Zinc*.—The bromoketone (5) (30 mg) in glacial acetic acid (2 ml) was heated under reflux with zinc dust (100 mg) for 1 h. The solution was poured into aqueous sodium hydrogen carbonate and extracted with ethyl acetate to afford a gum which was chromatographed on silica. Elution with 7% ethyl acetate–light petroleum gave 17β-acetoxy-1α-methylandrost-4-en-3-one (8) (13 mg) which crystallized as needles from aqueous methanol, m.p. 133—137 °C, $[\alpha]_D$ +86° (*c* 0.2) (lit.,[2,5] 139—140 °C) (Found: C, 76.5; H, 9.2. Calc. for $C_{22}H_{32}O_3$: C, 76.7; H, 9.3%), $\lambda_{max.}$ 243 nm (ε 6 880); $\nu_{max.}$ 1 730, 1 660, and 1 615 cm^{-1}; δ 0.85 (3 H, s, 18-H), 0.95 (3 H, d, *J* 7 Hz, 1-CH_3), 1.30 (3 H, s, 19-H), 2.04 (3 H, s, OAc), 4.60 (1 H, t, *J* 8 Hz, 17-H), and 5.70 (1 H, s, 4-H). Elution with 10% ethyl acetate–light petroleum gave 17β-acetoxy-1α,2α-methyleneandrost-4-en-3-one (10 mg) identified by its i.r., and n.m.r. spectra and m.p.

5α-*Hydroxy*-2α,3α-*methyleneandrostane*-4,17-*dione* (11).—Dimethylsulphoxonium methylide was prepared from trimethylsulphoxonium iodide (1 g) in dimethyl sulphoxide (10 ml) and sodium hydride (155 mg). A solution of 5α-hydroxyandrost-2-ene-4,17-dione [6] (500 mg) in dimethylsulphoxide (20 ml) was added and the mixture was stirred at room temperature for 5 h under nitrogen. The mixture was poured into saturated sodium chloride and the product recovered in chloroform. Evaporation of the solvent gave a gum which was chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave 5α-*hydroxy*-2α,3α-*methyleneandrostane*-4,17-*dione* (320 mg) (11) which crystallized from acetone as prisms, m.p. 228—229 °C, $[\alpha]_D$ +30° (*c* 0.2) (Found: C, 75.8; H, 9.0. $C_{20}H_{28}O_3$ requires C, 76.0; H, 8.9%), $\nu_{max.}$ 3 430, 1 735, and 1 670 cm^{-1}; δ 0.79 (3 H, s, 18-H) and 0.88 (3 H, s, 19-H). The above procedure was repeated with [$^2H_9$]trimethylsulphoxonium iodide in [$^2H_6$]-dimethyl sulphoxide to afford 5α-hydroxy-2α,3α-[$^2H_2$]-methylene[16,16-$^2H_2$]androstane-4,17-dione (*m/e* 320).

2α,3α-*Methylene*-4β,5α,17β-*trihydroxyandrostane* (12).—A solution of 5α-hydroxy-2α,3α-methyleneandrostane-4,17-dione (200 mg) in tetrahydrofuran (40 ml) was treated with lithium aluminium hydride (100 mg) at room temperature for 30 min. Ethyl acetate and then saturated sodium chloride were carefully added. The upper organic layer was separated and the solvent evaporated. The residue was dissolved in ethyl acetate and washed with saturated sodium chloride and water and then dried over sodium sulphate. The solvent was evaporated to afford 2α,3α-*methylene*-4β,5α,17β-*trihydroxyandrostane* (140 mg) (12) which crystallized from ethyl acetate as plates, m.p 230—234 °C, $[\alpha]_D$ +4° (*c* 0.1) (Found: C, 75.0; H, 10.0. $C_{20}H_{32}O_3$ requires C, 75.0; H, 10.0%), $\nu_{max.}$ 3 560 and 3 400br cm^{-1}; δ([$^2H_6$]acetone) 0.47 (2 H, m, cyclopropane), 0.74 (3 H, s, 18-H), 1.13 (3 H, s, 19-H), 2.47 and 2.77 (singlets, removed on washing with ^2H_2O), and 3.48 (2 H, m, 4- and 17-H). The 4β,17β-*diacetate*, prepared with acetic anhydride in pyridine, crystallized from ethyl acetate–light petroleum as needles, m.p. 194—197 °C, $[\alpha]_D$ +12° (*c* 0.15) (Found: C, 71.0; H, 8.8. $C_{24}H_{36}O_5$ requires C, 71.3; H, 8.9%, $\nu_{max.}$ 3 520, 1 730, and 1 720 cm^{-1}; δ 0.62 (2 H, m, cyclopropane), 0.75 (3 H, s, 18-H), 1.02 (3 H, s, 19-H), 1.98 and 2.01 (each 3 H, s, OAc), 4.55 (1 H, t, *J* 8 Hz, 17-H), and 4.90 (1 H, s, 4-H).

Dehydration of 5α-*Hydroxy*-2α,3α-*methyleneandrostane*-4,-17-*dione* (11).—A solution of the steroid (100 mg) in dry pyridine (10 ml) was cooled to −20 °C and freshly redistilled thionyl chloride (0.5 ml) was added dropwise with stirring. The mixture was stirred at −20 °C for 30 min and then allowed to warm up to room temperature during a further 30 min. The solution was cooled to 0 °C and ice was added. It was then poured into dilute hydrochloric acid and the steroid extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid, water, and aqueous sodium hydrogen carbonate, and then dried over sodium sulphate. The solvent was evaporated to afford 2α,3α-*methyleneandrost*-5-*ene*-4,17-*dione* (14) (90 mg) which crystallized from acetone–light petroleum as needles, m.p. 153—155 °C, $[\alpha]_D$ −97° (*c* 0.2) (Found: C, 80.9; H, 8.7. $C_{20}H_{26}O_2$ requires, C, 80.5; H, 8.7%), $\lambda_{max.}$ 243 nm (ε 10 217); $\nu_{max.}$ 1 740, 1 675, and 1 625 cm^{-1}; δ 0.50 (2 H, m, cyclopropane), 0.81 (3 H, s, 18-H), 1.02 (3 H, s, 19-H), and 6.65 (1 H, m, 3-H).

Reaction of 5α-*Hydroxy*-2α,3α-*methyleneandrostane*-4,17-*dione* (11) *with Hydrobromic Acid*.—The steroid (11) (200 mg) in glacial acetic acid (1 ml) and 48% hydrobromic acid (1 ml) were heated under reflux for 15 min. The solution was poured into aqueous sodium hydrogen carbonate and the steroids were recovered in ethyl acetate and chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave 2α-*bromomethylandrost*-5-*ene*-4,17-*dione* (15) which crystallized from acetone–light petroleum as prisms, m.p. 166—168 °C, $[\alpha]_D$ +5° (*c* 0.3) (Found: C, 63.4; H, 7.2. $C_{20}H_{27}BrO_2$ requires C, 63.3; H, 7.1%), $\lambda_{max.}$ 241 nm (ε 8 150); $\nu_{max.}$ 1 735, 1 675, and 1 620 cm^{-1}; δ 0.90 (3 H, s, 18-H), 1.01 (3 H, s, 19-H), 3.38 (2 H, d, *J* 5 Hz, 2′-H), and 6.52 (1 H, q, *J* 2 and 5 Hz, 6-H). The experiment was repeated with 2α,3α-[$^2H_2$]methylene-5α-hydroxy[16,16-$^2H_2$]androstane-4,17-dione to afford 2α-[$^2H_2$]bromomethylandrost-5-ene-4,17-dione, δ 0.90 (3 H, s, 18-H), 1.01 (3 H, s, 19-H), and 6.52 (1 H, q, *J* 2 and 5 Hz, 6-H).

Reaction of 2α,3α-*Methyleneandrost*-5-*ene*-4,17-*dione* (14) *with Hydrobromic Acid*.—The steroid (25 mg) in glacial acetic acid (1 ml) and 48% hydrobromic acid (1 ml) were heated under reflux for 15 min. The products were recovered as above to afford 2α-bromomethylandrost-5-ene-4,17-dione (13 mg) which was identified by its n.m.r. spectrum.

Reaction of 2α,3α-*Methyleneandrost*-6-*ene*-4,17-*dione* (16)

with Hydrobromic Acid.—The steroid (40 mg) in glacial acetic acid (1 ml) and 48% hydrobromic acid (1 ml) were heated under reflux for 15 min. The products were recovered as above to afford 2α-bromomethylandrost-5-ene-4,17-dione (45 mg) which was identified by its n.m.r. spectrum.

Reaction of 2α-Bromomethylandrost-5-ene-4,17-dione (15) *with Potassium t-Butoxide.*—The bromoketone (15) (80 mg) in tetrahydrofuran (5 ml) was heated under reflux with potassium t-butoxide (100 mg) for 30 min. Water was added to the cold solution which was then extracted with ethyl acetate. The organic extract was washed with water, dried over sodium sulphate, and evaporated to afford *2α,3α-methyleneandrost-6-ene-4,17-dione* (16) (50 mg) which crystallized from ethyl acetate as prisms, m.p. 198—200 °C, $[\alpha]_D$ −36° (*c* 0.15) (Found: C, 80.6; H, 8.7. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.7%), $\lambda_{max.}$ 209 (ε 872); $\nu_{max.}$ 3 070, 3 040, 1 735, and 1 685 cm^{-1}; δ 0.84 (3 H, s, 18-H), 0.89 (3 H, s, 19-H), and 5.71 and 5.98 (1 H, each, d, *J* 11 Hz, 6- and 7-H). Treatment of 2α,3α-methyleneandrost-5-ene-4,17-dione (35 mg) in dry tetrahydrofuran (4 ml) with potassium t-butoxide (50 mg) under the same conditions, gave 2α,3α-methyleneandrost-6-ene-4,17-dione (16) (30 mg) identical to the material described above.

Reduction of 17β-Acetoxy-1α,2α-methyleneandrost-4-en-3-one (4).—A solution of the steroid (4) (1 g) in dry tetrahydrofuran (40 ml) containing lithium tri-t-butoxyaluminium hydride (1.5 g) was heated under reflux for 1½ h. Brine was added and then the steroids were recovered in ethyl acetate and chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave *17β-acetoxy-3β-hydroxy-1α,2α-methyleneandrost-4-ene* (150 mg) which crystallized from light petroleum as needles, m.p. 65—67 °C $[\alpha]_D$ +42° (*c* 0.2) (Found: C, 76.8; H, 9.2. $C_{22}H_{32}O_3$ requires C, 76.7; H, 9.3%); $\nu_{max.}$ 3 270, 1 740, and 1 660 cm^{-1}; δ 0.41 (2 H, m, cyclopropane), 0.80 (3 H, s, 18-H), 1.21 (3 H, s, 19-H), 1.98 (3 H, s, OAc), 4.24 (1 H, d, *J* 5 Hz, 3-H), 4.52 (1 H, t, *J* 8 Hz, 17-H), and 5.20 (1 H, d, *J* 5 Hz, 4-H). Further elution with 15% ethyl acetate–light petroleum gave *17β-acetoxy-3α-hydroxy-1α,2α-methyleneandrost-4-ene* (680 mg) which crystallized from acetone–light petroleum as thick blades, m.p. 158—160 °C; $[\alpha]_D$ +87° (*c* 0.1) (Found: C, 76.8; H, 8.7. $C_{22}H_{32}O_3$ requires C, 76.7; H, 9.3%), $\nu_{max.}$ 3 500, 3 075, 1 720, and 1 655 cm^{-1}; δ 0.35 (2 H, m, cyclopropane), 0.79 (3 H, s, 18-H), 1.03 (3 H, s, 19-H), 1.97 (3 H, s, 17-OAc), 4.88 (2 H, m, 3- and 17-H), and 4.98 (1 H, s, 4-H).

Reaction of 17β-Acetoxy-3α-hydroxy-1α,2α-methyleneandrost-4-ene (17) *with Hydrobromic Acid.*—(*a*) The steroid (17) (200 mg) in glacial acetic acid (4 ml) was treated with hydrobromic acid (0.5 ml) at 50 °C for 15 min. The solution was cooled and poured into aqueous sodium hydrogen carbonate. The steroids were recovered in ether. The extract was washed with aqueous sodium hydrogen carbonate and water and dried. The solvent was evaporated *in vacuo* below 30 °C to afford a gum which was purified by preparative layer chromatography. *17β-Acetoxy-1α-bromomethylandrosta-3,5-diene* (19) (140 mg) crystallized from light petroleum as needles, m.p. 94—96 °C, $[\alpha]_D$ −38° (*c* 0.2) (Found: C, 64.5; H, 7.6. $C_{22}H_{31}BrO_2$ requires C, 64.9; H, 7.6%), $\lambda_{max.}$ 229 (ε 21 900), 236 (ε 23 080), and 244 nm (ε 15 980); $\nu_{max.}$ 3 010 and 1 730 cm^{-1}; δ(220 MHz) 0.83 (3 H, s, 18-H), 1.09 (3 H, s, 19-H), 2.05 (3 H, s, 17-OAc), 3.04 (1 H, t, *J* 11 Hz, 1′-H), 3.52 (1 H, d, q, *J* 1.5, 3 and 11 Hz, 1′-H), 4.62 (1 H, t, *J* 81 Hz, 17-H), 5.46 (2 H, m, 3- and 6-H), and 5.85 (1 H, d, d, *J* 2 and 11 Hz, 4-H). The above experiment was repeated with 17β-acetoxy-1α,2α-[$^2H_2$]methylene-3α-hydroxyandrost-4-ene (100 mg) to afford 17β-acetoxy-1α-[$^2H_2$]bromomethylandrosta-3,5-diene, δ(220 MHz), 0.83 (3 H, s, 18-H), 1.09 (3 H, s, 19-H), 2.04 (3 H, s, 17-OAc), 4.62 (1 H, t, *J* 8 Hz, 17-H), 5.46 (2 H, m, 3- and 6-H), and 5.85 (1 H, dd, *J* 2 and 11 Hz, 4-H).

(*b*) 17β-Acetoxy-3α-hydroxy-1α,2α-methyleneandrost-4-ene (100 mg) in acetone (5 ml) was treated with 48% hydrobromic acid (0.5 ml) at room temperature for 1 h. Water was added and the product was recovered in ether. N.m.r. showed the product to be a mixture of 17β-acetoxy-1α-bromomethylandrosta-3,5-diene and 17β-acetoxy-1α,2α-methyleneandrosta-3,5-diene. The mixture was chromatographed on silica gel impregnated with silver nitrate (10%). Elution with 1% ethyl acetate–light petroleum gave *17β-acetoxy-1α,2α-methyleneandrosta-3,5-diene* (20) which crystallized from ethanol as plates, m.p. 116—118 °C, $[\alpha]_D$ +22° (*c* 0.2) (Found: C, 81.4; H, 9.3. $C_{22}H_{30}O_2$ requires C, 81.0; H, 9.2%); $\lambda_{max.}$ 238 (ε 4 252), $\nu_{max.}$ 1 735 and 1 655 cm^{-1}; δ 0.15 (1 H, m, cyclopropane), 0.82 (3 H, s, 18-H), 1.09 (3 H, s, 19-H), 2.00 (3 H, s, 17-OAc), 4.57 (1 H, t, *J* 8 Hz, 17-H), 5.30 (1 H, t, *J* 3 Hz, 6-H), 5.57 (1 H, d, *J* 10 Hz, 4-H), and 5.85 (1 H, d, m, *J* 10 Hz, 3-H).

Dehydration of 17β-Acetoxy-3α-hydroxy-1α,2α-methyleneandrost-4-ene.—The steroid (17) (400 mg) in acetic anhydride (16 ml) was treated with toluene-*p*-sulphonic acid (800 mg) at room temperature for 3 min. Ether was added and the solution was washed with water and dried over sodium sulphate. The solvents were evaporated *in vacuo* to afford a solid which was chromatographed on silica. Elution with 3% ethyl acetate–light petroleum gave 17β-acetoxy-1α,2α-methyleneandrosta-3,5-diene (240 mg) which was identical to the sample described above.

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