Some Alternative Pathways leading to the Aromatization of Ring A of Steroids

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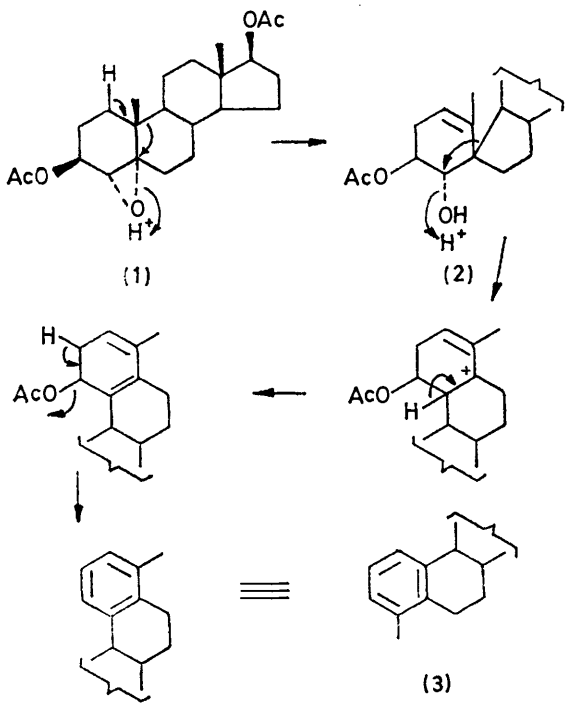
In contrast to 3β,17β-diacetoxy-4,5-epoxyandrostanes, 3β,17β-diacetoxy-4,5-epoxyoestrane undergoes aromatization in hydrobromic acid–glacial acetic acid without the intervention of a spiro-intermediate. Under these conditions 3β,17β-diacetoxy-4α,5α-epoxy-2,2-dimethylandrostane gave a small amount of an aromatic steroid, possibly 17β-acetoxy-2,3,9-trimethyloestratriene, together with 17β-acetoxy-2,2-dimethylandrost-5-en-4-one and 17β-acetoxy-2,2-dimethylandrost-4-en-3-one. 3β,17β-Diacetoxy-4,5-epoxy-4-methylandrostanes gave 17β-acetoxy-1,4-dimethyloestratriene by a pathway involving a C-10 to C-1 methyl migration, together with 17β-acetoxy-4-methylandrost-4-en-3-one; 17β-acetoxy-3,4-dimethyloestratriene was a minor product.

TREATMENT of 3-acetoxy-4,5-epoxyandrostanes with hydrobromic acid in glacial acetic acid affords [1] 4-methyloestratrienes (3) *via* a spiro-intermediate (2) rather than by methyl migration. In the 19-norsteroids aromatization by this spirodiene pathway could compete with a pathway involving simple eliminations without rearrangement whilst in the 2,2-dimethyl- and 4-methylandrostanes the spirodiene pathway is blocked by the methyl substituents. In this paper we describe the reactions of these 3-acetoxy-4,5-epoxy-steroids with hydrobromic acid in glacial acetic acid.

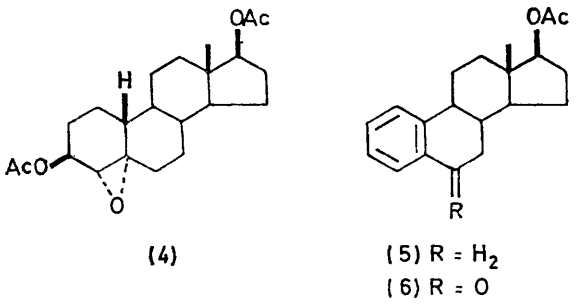
3β,17β-Diacetoxy-4α,5α-epoxyoestrane (4) was prepared from 19-nortestosterone acetate [2] by reduction with sodium borohydride to form 17β-acetoxy-3β-hydroxyoestr-4-ene. This was acetylated and then epoxidized with *m*-chloroperbenzoic acid. Surprisingly epoxidation of the alcohol followed by acetylation gave the same rather than the epimeric epoxide implying a conformation of ring A in which the hydroxy-group lies in the plane of the olefin and is thus unable to exert a stereochemical control over the direction of approach of a reagent to the olefin. The stereochemistry of the epoxide was assigned on the basis of its n.m.r. spectrum. The C-4 proton resonance appears at τ 7·12 characteristic of the α-epoxides.[3] In the isomeric 17β-acetoxy-4β,5β-epoxy-3β-hydroxyoestrane [4] the C-4 proton resonance appears at τ 6·87, *J* 4 Hz. Although the C-4 proton

[1] D. Baldwin and J. R. Hanson, *J.C.S. Perkin I*, 1972, 1889.
[2] J. A. Hartman, *J. Amer. Chem. Soc.*, 1955, **77**, 5151.
[3] D. J. Collins, J. J. Hobbs, and S. Sternhell, *Tetrahedron Letters*, 1963, 623.
[4] T. Nambara, H. Hosoda, T. Anjyo, M. Yamauchi, and J. Mohri, *Chem. and Pharm. Bull.* (*Japan*), 1972, **20**, 287.

resonance is a singlet in the corresponding 3β,17β-diacetoxy-4α,5α-epoxyandrostane,[1] it appears as a doublet, J 1·5 Hz, in both the epoxyoestrane and the 3-deuteriated epoxyoestrane. In the oestrane series the C-10 proton can have a W type relationship with a C-4β proton. In



SCHEME 1



this conformation there is a dihedral angle of approximately 90° between the C-3α and C-4β protons accounting for the absence of coupling between these protons. Treatment of the epoxide with hydrobromic acid in glacial acetic acid gave 17β-acetoxyoestra-1,3,5(10)-triene (5).[5]

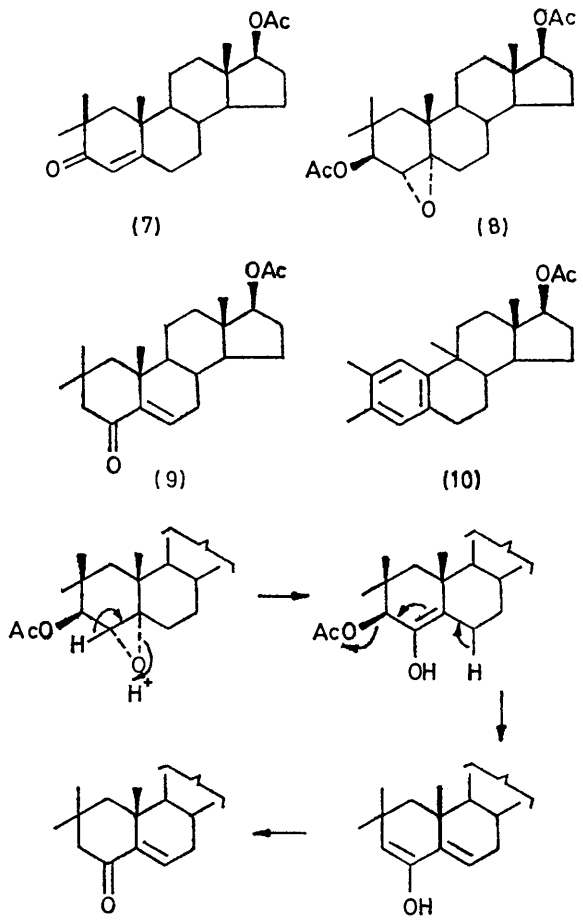
The pathway involving a spiro-intermediate may be distinguished from routes involving elimination without rearrangement by examining the aromatization of 3α-deuterio-3β,17β-diacetoxy-4α,5α-epoxyoestrane. A pathway involving a spiro-intermediate and rearrangement will lead to a 1-deuterio-oestratriene whilst other routes would afford a 3-deuterio-product. The deuteriosteroid was prepared by reduction of 19-nortestosterone acetate with sodium borodeuteride followed by acetylation and epoxidation. It was then aromatized by brief treatment with hydrobromic acid in glacial acetic acid. The site of deuteriation in the aromatic product was established by oxidation of the deuteriated and non-deuteriated 17β-acetoxyoestra-1,3,5(10)-trienes to the C-6 ketones (6) using chromium trioxide in glacial acetic acid.[6] The C-6 carbonyl group deshields the C-4 proton relative to the other aromatic protons. The C-4 proton resonance then appeared as a doublet at τ 1·99, J 8 Hz, coupled to C-3. In the deuteriated product this doublet collapsed to a singlet and hence the deuterium atom was located at C-3. Consequently aromatization in this case did not proceed through a spiro-intermediate in contrast to the route taken by the androstanes. Although in the spiro-intermediate (2) there is a release of the C-1–C-11 interaction, this does not outweigh the ease with which the C-5 carbonium ion may be discharged by the loss of the C-10 proton.

In order to shed some light on other pathways that might compete with the spirodiene aromatization, we then examined the reaction of some steroids bearing methyl groups at sites of proton loss such as C-2 and C-4. 17β-Acetoxy-2,2-dimethylandrost-4-en-3-one (7) was prepared[7] by the kinetically controlled methylation of testosterone with methyl iodide and potassium t-butoxide followed by acetylation. Reduction of the ketone with sodium borohydride gave the 3β-alcohol which was then acetylated and epoxidized with *m*-chloroperbenzoic acid to afford 3β,17β-diacetoxy-4α,5α-epoxy-2,2-dimethylandrostane (8). The C-4 proton resonance appeared at τ 7·15 as expected for this stereochemistry[3] but the coupling constant, $J_{3\alpha:4\beta}$ 2 Hz, suggested that ring A exists in a skew conformation to relieve the C-2–C-10 methyl interactions. This steroid was treated with hydrobromic acid in glacial acetic acid. The ketonic products were 17β-acetoxy-2,2-dimethylandrost-5-en-4-one (9) and 17β-acetoxy-2,2-dimethylandrost-4-en-3-one (7). The former showed $\lambda_{max.}$ 246 nm (ε 7000) [17β-acetoxyandrost-5-en-4-one, 241 nm (ε 6100)[8]]. The n.m.r. spectrum contained a multiplet, τ 3·41, assigned to the β-proton of an αβ-unsaturated ketone (the C-6 proton). The compound exchanged four deuterium atoms on treatment with sodium deuterioxide in deuterium oxide.

A minor aromatic product was tentatively assigned the structure 17β-acetoxy-2,3,9-trimethyloestra-1,3,5(10)-triene (10). The n.m.r. spectrum showed two tertiary aliphatic *C*-methyl resonances (τ 9·20 and 9·05) and two aromatic *C*-methyl resonances (7·90 and 7·80) together with two aromatic singlet proton resonances (3·32 and 3·16). In the mass spectrum the base peak was at *m/e* 325 corresponding to the loss of a methyl group from C-9 and the formation of a stable benzylic radical ion. The formation of this aromatic steroid may be rationalized by the formation of a C-5 carbonium ion, and then a C-9

[5] E. Hecker, *Chem. Ber.*, 1962, **95**, 977.
[6] R. C. Cambie and T. D. R. Manning, *J. Chem. Soc.* (*C*), 1968, 2602.
[7] L. Nedelac, method quoted by H. Laurent and R. Wiechert in ' Organic Reactions in Steroid Chemistry,' eds. J. Fried and J. A. Edwards, van Nostrand Reinhold, New York, 1972, p. 92.
[8] G. A. Boswell, *J. Org. Chem.*, 1968, **33**, 3699.

to C-5 transannular hydride shift followed by a C-10 to C-9 methyl shift. Aromatization of ring A by a methyl

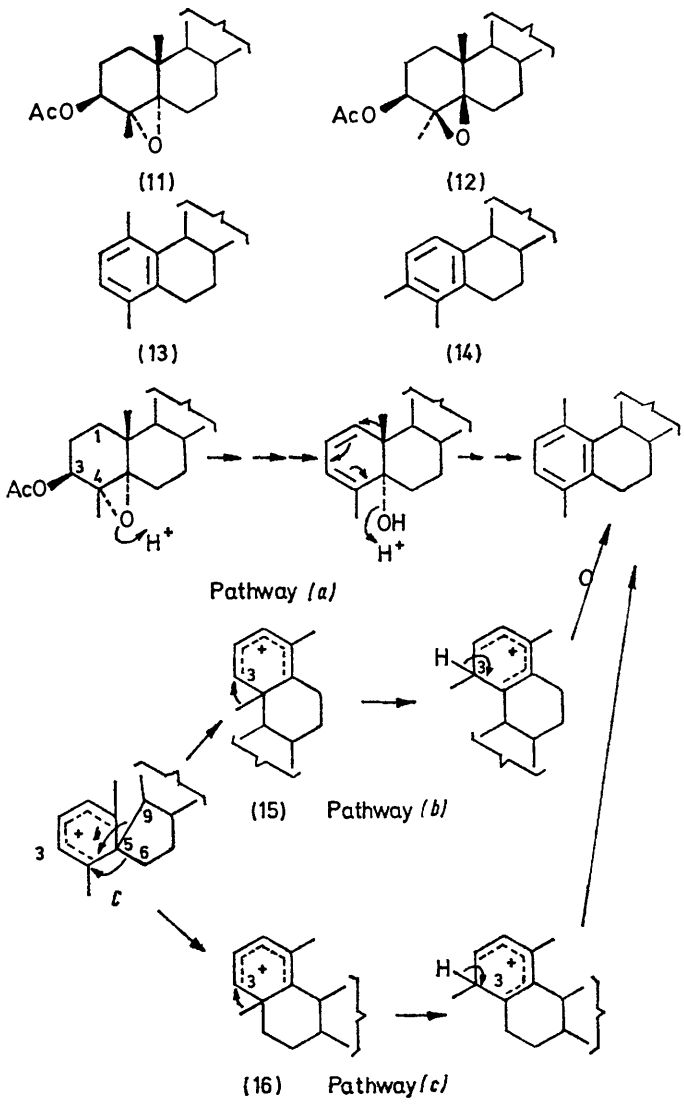


SCHEME 2

shift from C-2 to C-3 and by dehydration then follows. The formation of 17β-acetoxy-2,2-dimethylandrost-5-en-4-one may involve the Δ^4-enol of a C-4 ketone in an elimination reaction (see Scheme 2). The formation of 17β-acetoxy-2,2-dimethylandrost-5-en-4-one as a ketonic product contrasts with the formation of testosterone acetate from the 3β,17β-diacetoxy-4,5-epoxyandrostanes perhaps reflecting the differing conformations of the acetoxy-epoxides. In a skew conformation of ring A arising from the relief of the C-2–C-10 diaxial methyl group interaction, a 3β-acetoxy-group can take up a pseudo-axial configuration and as a neighbouring group can participate in stabilizing a C-5 carbonium ion. This could facilitate on the one hand a hydride transfer from C-9 on the α-face of the molecule and on the other hand the elimination reactions to form the androst-5-en-4-one.

17β-Acetoxy-4-methylandrost-4-en-3-one [9] was reduced with sodium borohydride to form the 3β-alcohol which was acetylated and then epoxidized with *m*-chloroperbenzoic acid to give 3β,17β-diacetoxy-4α,5α-epoxy-4β-methylandrostane (11). Alternatively the 3β-alcohol was epoxidized and then acetylated in which case the 4β,5β-epoxide (12) was the major product. Both these acetoxy-epoxides gave 17β-acetoxy-1,4-dimethyloestra-1,3,5(10)-triene (13) [10] as the major aromatic steroid together with 17β-acetoxy-4-methylandrost-4-en-3-one as the ketonic product on treatment with hydrobromic acid in glacial acetic acid. Surprisingly 17β-acetoxy-3,4-dimethyloestra-1,3,5(10)-triene (14) [11] was obtained as a minor product. The aromatic steroids were identified by comparison with authentic material.

There are a number of pathways which could account for the formation of 17β-acetoxy-1,4-dimethyloestra-1,3,5(10)-triene. In one pathway (*a*) there is a C-10 to



SCHEME 3

C-1 methyl migration. In the other pathways the C-4 methyl group may become an angular substituent in (15) or (16) which can be formed from the spiro-intermediate

[9] N. A. Atwater, *J. Amer. Chem. Soc.*, 1957, **79**, 5315; F. Sondheimer and Y. Mazur, *ibid.*, p. 2906.

[10] H. Dannenberg and H. G. Neumann, *Annalen*, 1961, **646**, 148.

[11] P. Bey, F. Lederer, and G. Ourisson, *Chem. and Pharm. Bull. (Japan)*, 1965, **13**, 1140.

either by migration of the C-5–C-9 bond [pathway (*b*)] or by migration of the C-5–C-6 bond [pathway (*c*)]. The methyl group may then migrate to C-3 [≡ C-1 in pathway (*b*)] and subsequent proton loss may then afford an aromatic product. These pathways may be distinguished by deuterium labelling. If the 1,4-dimethyloestratriene were formed from a 4-deuteriomethyl steroid by pathways (*a*) or (*c*) then a C-4 deuteriomethyloestratriene would result whilst pathway (*b*) would produce a C-1 deuteriomethyloestratriene. Secondly formation of the 1,4-dimethyloestratriene from a 3-deuterio-steroid by pathway (*a*) would involve retention of deuterium whilst pathways (*b*) and (*c*) would involve its loss.

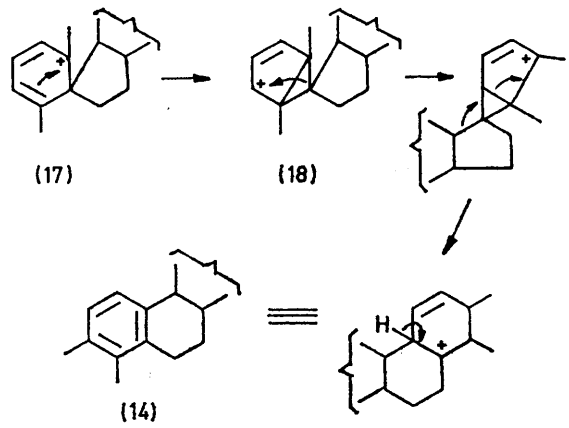
3α-Deuterio-3β,17β-diacetoxy-4α,5α-epoxy-4-methylandrostane was prepared from 17β-acetoxy-4-methylandrost-4-en-3-one by reduction with sodium borodeuteride, acetylation, and epoxidation. Brief treatment (to avoid exchange on the aromatic ring) of the deuterio-steroid with hydrobromic acid in glacial acetic acid gave 17β-acetoxy-1,4-dimethyloestra-1,3,5(10)-triene which retained deuterium on the aromatic ring (n.m.r. integral 1·1H instead of 2H). Secondly 3β,17β-diacetoxy-4α,5α-epoxy-4β-[$^2H_3$]methylandrostane was prepared from 17β-acetoxy-4-[$^2H_3$]methylandrost-4-en-3-one and treated with hydrobromic acid in glacial acetic acid to give a deuteriomethyloestratriene. The aromatic methyl resonances in the n.m.r. spectrum were assigned by comparison with 1- and 4-methyloestratrienes and by the marked effect of a C-6 ketone on the position of the resonance due to the C-4 methyl group (see Table).

Aromatic *C*-methyl proton resonances for 1- and 4-methyloestratrienes

	τ Values	
	1-Me	4-Me
17β-Acetoxy-1-methyloestratriene	7·70	
17β-Acetoxy-4-methyloestratriene		7·84
17β-Hydroxy-1,4-dimethyloestratriene	7·69	7·77
17β-Acetoxy-1-methyloestratrien-6-one	7·60	
17β-Acetoxy-4-methyloestratrien-6-one		7·35
17β-Acetoxy-1,4-dimethyloestratrien-6-one	7·64	7·43

In the deuteriated product, which was purified as the crystalline 17β-alcohol, the resonance corresponding to the C-4 methyl group at τ 7·67 was absent. Consequently the aromatic steroid contained a C-4 deuteriomethyl group. A pathway involving an overall C-10 to C-1 methyl group migration as in (*a*) is compatible with these results. The formation of the 3,4-dimethyloestratriene was less readily understood. It could arise by a series of methyl shifts or by a pathway involving a 1,4-sigmatropic rearrangement of the bicyclo[3.1.0]-hexenyl cation (18) formed from the spiro-carbonium ion (17).[12] Unfortunately it could not be isolated from the experiments using the deuteriated steroids.

In conclusion, we have shown that alternative pathways from steroidal acetoxy-epoxides to oestratrienes exist and that these can depend on the substitution of ring A.



EXPERIMENTAL

General experimental details have been described previously.[13]

17β-*Acetoxy*-3β-*hydroxyoestr*-4-*ene*.— 19-Nortestosterone acetate [2] (4·3 g) in methanol (200 ml) was treated with sodium borohydride (1·0 g) at 0° for 1 h. The solution was acidified with glacial acetic acid (3 ml) and poured into water. The solution was extracted with ethyl acetate and the extract was washed with water, dried ($MgSO_4$), and the solvent evaporated under reduced pressure. 17β-*Acetoxy*-3β-*hydroxyoestr*-4-*ene* (2·95 g) crystallized from acetone–light petroleum as needles, m.p. 109—111°, $[\alpha]_D^{20}$ +31° (*c* 0·3) (Found: C, 75·3; H, 9·5. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·5%), $\nu_{max.}$ 3350br, 1725, 1615, and 1245 cm^{-1}, τ 9·17 (3H, s, 18-H_3), 7·96 (3H, s, 17-OAc), 5·83 (1H, m, 3-H), 5·38 (1H, t, *J* 8 Hz, 17-H), and 4·60 (1H, s, 4-H).

3β,17β-*Diacetoxy*-4α,5α-*epoxyoestrane* (4).—17β-Acetoxy-3β-hydroxyoestr-4-ene (2·3 g) in benzene (50 ml) was treated with *m*-chloroperbenzoic acid (2·6 g) at room temperature overnight. The solution was diluted with ethyl acetate, washed thoroughly with aqueous iron(II) sulphate, dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and dried ($MgSO_4$). The solvent was evaporated under reduced pressure, and the residue dissolved in pyridine (10 ml) and treated with acetic anhydride (2·3 ml) at room temperature overnight. The solution was poured into dilute hydrochloric acid and the product was recovered in ethyl acetate. Chromatography on alumina gave, in the fractions eluted with 5% ethyl acetate–light petroleum, 3β,17β-*diacetoxy*-4α,5α-*epoxyoestrane* (4) (622 mg) which crystallized from acetone–light petroleum as plates, m.p. 153—155°, $[\alpha]_D^{20}$ −16° (*c* 0·2) (Found: C, 70·15; H, 8·3. $C_{22}H_{32}O_5$ requires C, 70·2; H, 8·6%), $\nu_{max.}$ 1725 cm^{-1}, τ 9·17 (3H, s, 18-H_3), 7·97 (3H, s, 17-OAc), 7·93 (3H, s, 3-OAc), 7·12 (1H, d, *J* 1·5 Hz, 4-H), 5·39 (1H, t, *J* 8 Hz, 17-H), and 5·04 (1H, m, 3-H).

Alternatively 3β,17β-diacetoxyoestr-4-ene [2] was treated as above with *m*-chloroperbenzoic acid to afford the 4α,5α-epoxide which was identical (m.p., $[\alpha]_D$, i.r., and n.m.r.) with the material prepared above.

Reaction of 3β,17β-*Diacetoxy*-4α,5α-*epoxyoestrane with Hydrobromic Acid in Acetic Acid*.—The epoxide (525 mg) was treated with 48% hydrobromic acid (1·05 ml) in glacial acetic acid (5 ml) and heated under reflux for 25 min. The solution turned blue and then red over 25 min. The solution was poured into aqueous sodium hydrogen carbonate

[12] R. B. Woodward and R. Hoffmann, 'The Conservation of Orbital Symmetry,' Verlag-Chemie, Weinheim, 1970, p. 138.
[13] J. R. Hanson and T. D. Organ, *J. Chem. Soc.* (*C*), 1970, 513.

and the product was recovered in ether. Chromatography on alumina gave, in the fractions eluted with 2·5% ethyl acetate–light petroleum, 17β-acetoxyoestra-1,3,5(10)-triene (5) (120 mg) which crystallized from light petroleum as needles, m.p. 119—121°, $[\alpha]_D^{20}$ +46° (*c* 0·2) (lit.,[5] m.p. 120—121°, $[\alpha]_D^{25}$ +52°) (Found: C, 80·8; H, 8·5. Calc. for $C_{20}H_{26}O_2$: C, 80·5; H, 8·8%), τ 9·17 (3H, s, 18-H_3), 8·01 (3H, s, 17-OAc), 5·40 (1H, t, *J* 8 Hz, 17-H), and 3·04 (4H, m, ArH), $\nu_{max.}$ 1735, 1240, and 740 cm^{-1}.

17β-*Acetoxyoestra*-1,3,5(10)-*trien*-6-*one* (6).—17β-Acetoxyoestra-1,3,5(10)-triene (700 mg) in glacial acetic acid (35 ml) was treated with a solution of chromium trioxide (350 mg) in water (2·5 ml) at 70° for 3 h. Methanol was then added. The solution was poured into water and neutralized with sodium hydrogen carbonate. The steroid was recovered in ethyl acetate and chromatographed on alumina. Elution with 50% ether–light petroleum gave 17β-*acetoxyoestra*-1,3,5(10)-*trien*-6-*one* (6) (73 mg) which crystallized from acetone–light petroleum as prisms, m.p. 219—221°, $[\alpha]_D^{20}$ −25° (*c* 0·2) (Found: C, 77·2; H, 7·7. $C_{20}H_{24}O_3$ requires C, 76·9; H, 7·7%), $\nu_{max.}$ 1730, 1675, and 1600 cm^{-1}, τ 9·19 (3H, s, 18-H_3), 8·00 (3H, s, 17-OAc), 5·30 (1H, t, *J* 8 Hz, 17-H), 2·57 (3H, m, 1—3-H), and 1·99 (1H, d, *J* 8 Hz, 4-H).

3β,17β-*Diacetoxy*-3-*deuterio*-4α,5α-*epoxyoestrane*.— 19-Nortestosterone acetate [2] (4·9 g) in dry ether (50 ml) and methan[^{2}H]ol (10 ml) was treated with sodium borodeuteride (1·1 g) at 0° for 1 h. The solution was acidified with glacial acetic acid (5 ml) and poured into water (200 ml). The product was recovered in ethyl acetate. The crude deuteriosteroid (4·8 g) was treated with acetic anhydride (5 ml) in pyridine (25 ml) at room temperature for 24 h. The solution was poured into dilute hydrochloric acid and the product recovered in ethyl acetate. 3β,17β-Diacetoxy-3-deuterio-oestr-4-ene (3·3 g) crystallized from acetone as plates, m.p. 128—130°, *m/e* 361, $\nu_{max.}$ 2160w (C–D) cm^{-1}, n.m.r.; no resonance at τ 4·79. The steroid (3·2 g) in benzene (75 ml) was treated with *m*-chloroperbenzoic acid (3·6 g) at room temperature overnight. The solution was diluted with ethyl acetate, washed thoroughly with iron(II) sulphate, dilute hydrochloric acid, and aqueous sodium hydrogen carbonate, dried, and evaporated. 3β,17β-Diacetoxy-3-deuterio-4α,5α-epoxyoestrane (2 g) crystallized from acetone–light petroleum as plates, m.p. 152—154°, $[\alpha]_D$ −12 (*c* 0·3), $\nu_{max.}$ 2140w (C–D) cm^{-1}, *m/e* 377, n.m.r.; no resonance at τ 5·04.

Reaction of 3β,17β-*Diacetoxy*-3-*deuterio*-4α,5α-*epoxyoestrane with Hydrobromic Acid in Acetic Acid*.—The steroid (950 mg) in glacial acetic acid (10 ml) and 48% hydrobromic acid (2 ml) was heated to reflux and then immediately cooled. The solution was poured into aqueous sodium hydrogen carbonate and the product was recovered in ether. Chromatography on alumina gave, in the fractions eluted with 4% ether–light petroleum, 17β-acetoxy-3-deuterio-oestra-1,3,5(10)-triene (160 mg), which crystallized from methanol as needles, m.p. 119—121°, $[\alpha]_D^{20}$ +50° (*c* 0·25), *m/e* 299, $\nu_{max.}$ 2250w (C–D) cm^{-1}, n.m.r.; the resonance at τ 2·99 was a 3-proton multiplet.

Oxidation as above gave 17β-acetoxy-3-deuterio-oestra-1,3,5(10)-trien-6-one, m.p. 220—222°, *m/e* 313, n.m.r.; the resonance at τ 2·0 (1H, s, 4-H) was a singlet rather than a doublet and the resonance at 2·53 was a 2-proton multiplet.

17β-*Acetoxy*-2,2-*dimethylandrost*-4-*en*-3-*one* (7).— 17β-Hydroxy-2,2-dimethylandrost-4-en-3-one, prepared according to the method of Nedelac,[7] had m.p. 188—190°, $[\alpha]_D^{20}$ +72° (*c* 0·3) (lit.,[7] m.p. 190°, $[\alpha]_D$ +49°). The 17β-*acetate* (7), prepared with acetic anhydride in pyridine, crystallized from acetone as needles, m.p. 168—170°, $[\alpha]_D^{20}$ +43° (*c* 0·3) (Found: C, 76·6; H, 9·45. $C_{23}H_{34}O_3$ requires C, 77·05; H, 9·6%), $\nu_{max.}$ 1735, 1675, and 1625 cm^{-1}, τ 9·2 (3H, s, 18-H_3), 8·94, 8·88, and 8·76 (each 3H, s, 2α- and 2β-Me, 19-H_3), 8·00 (3H, s, 17-OAc), 5·43 (1H, t, *J* 8 Hz, 17-H), and 4·35 (1H, s, 4-H).

17β-*Acetoxy*-3β-*hydroxy*-2,2-*dimethylandrost*-4-*ene*.— The foregoing acetate (1·1 g) in methanol (70 ml) was treated with sodium borohydride (250 mg) at 0° for 1 h. The solution was acidified with glacial acetic acid and poured into water. The product was recovered in ethyl acetate. 17β-*Acetoxy*-3β-*hydroxy*-2,2-*dimethylandrost*-4-*ene* (980 mg) crystallized from acetone as needles, m.p. 155—157°, $[\alpha]_D^{20}$ +13° (*c* 0·3) (Found: C, 76·2; H, 10·3. $C_{23}H_{36}O_3$ requires C, 76·6; H, 10·1%), $\nu_{max.}$ 3440 and 1705 cm^{-1}, τ 9·18 (3H, s, 18-H), 9·08, 9·00, and 8·90 (each 3H, s, 2α-, 2β-Me and 19-H_3), 6·15 (1H, m, 3-H), 5·40 (1H, t, *J* 8 Hz, 17-H), and 4·8 (1H, s, 4-H).

The 3β,17β-*diacetate*, prepared with acetic anhydride in pyridine, crystallized from acetone as plates, m.p. 159—161°, $[\alpha]_D^{20}$ −48° (*c* 0·2) (Found: C, 74·8; H, 9·4. $C_{25}H_{38}O_4$ requires C, 74·6; H, 9·45%), $\nu_{max.}$ 1735 cm^{-1}, τ 9·21 (3H, s, 18-H_3), 9·10, 9·04, and 8·90 (each 3H, s, 2α-, 2β-Me, and 19-H_3), 7·98 and 7·94 (each 3H, s, 3- and 17-OAc), 5·42 (1H, t, *J* 8 Hz, 17-H), and 4·96 and 4·94 (each 1H, s, 3- and 4-H).

3β,17β-*Diacetoxy*-4α,5α-*epoxy*-2,2-*dimethylandrostane* (8).—The foregoing olefin (535 mg) in benzene (15 ml) was treated with *m*-chloroperbenzoic acid (605 mg) at room temperature overnight. The solution was diluted with ethyl acetate, washed thoroughly with iron(II) sulphate, dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and dried. The solvent was evaporated off to give 3β,17β-*diacetoxy*-4α,5α-*epoxy*-2,2-*dimethylandrostane* (8) (410 mg) which crystallized from acetone–light petroleum as plates, m.p. 177—179° (Found: C, 71·8; H, 9·0. $C_{25}H_{38}O_5$ requires C, 71·7; H, 9·15%), $\nu_{max.}$ 1735 cm^{-1}, τ 9·2 (3H, s, 18-H_3), 9·17, 8·82, and 8·76 (each 3H, s, 2α-, 2β-Me, and 19-H_3), 7·99 and 7·92 (each 3H, s, 3- and 17-OAc), 7·15 (1H, d, *J* 2 Hz, 4-H), 5·40 (1H, t, *J* 8 Hz, 17-H), and 5·07 (1H, d, *J* 2 Hz, 3-H).

Reaction of 3β,17β-*Diacetoxy*-4α,5α-*epoxy*-2,2-*dimethylandrostane with Hydrobromic Acid in Acetic Acid*.—The epoxide (400 mg) in glacial acetic acid (5 ml) and 48% hydrobromic acid (0·8 ml) was heated under reflux for 25 min. The solution was poured into aqueous sodium hydrogen carbonate and the product was recovered in ether. Chromatography on alumina afforded, in the fractions eluted with 5% ether–light petroleum, 17β-*acetoxy*-2,3,9-*trimethyloestra*-1,3,5(10)-*triene* (10) (5 mg) which crystallized from light petroleum as needles, m.p. 151—153° (Found: C, 81·6; H, 9·2%; *m/e* 340. $C_{23}H_{32}O_2$ requires C, 81·6; H, 9·5%; *M*, 340), $\nu_{max.}$ 1735, 1240, and 860 cm^{-1}, τ 9·2 (3H, s, 18-H_3), 9·05 (3H, s, 9-Me), 8·04 (3H, s, 17-OAc), 7·90 and 7·80 (each 3H, s, 2- and 3-Me), 5·38 (1H, t, *J* 8 Hz, 17-H), and 3·32 and 3·16 (each 1H, s, 1- and 4-H).

The fractions eluted with 20% ether–light petroleum afforded 17β-*acetoxy*-2,2-*dimethylandrost*-5-*en*-4-*one* (9) (25 mg) which crystallized from acetone–light petroleum as plates, m.p. 189—191°, $[\alpha]_D^{20}$ −98° (*c* 0·2) (Found: C, 76·7; H, 9·2. $C_{23}H_{34}O_3$ requires C, 77·05; H, 9·6%), $\nu_{max.}$ 1730, 1690, 1625, and 1245 cm^{-1}, τ 9·20 (3H, s, 18-H_3), 9·08, 8·96, and 8·93 (each 3H, s, 2α-, 2β-Me, and 19-H_3), 7·98 (3H, s, 17-OAc), 5·38 (1H, t, *J* 8 Hz, 17-H), and 3·41 (1H, m, 6-H), $\lambda_{max.}$ 246 nm (ε 7000).

The fractions eluted with 30% ether–light petroleum afforded 17β-acetoxy-2,2-dimethylandrost-4-en-3-one (7) (11 mg) identified by its i.r. and n.m.r. spectra.

17β-*Acetoxy*-4-*methylandrost*-4-*en*-3β-*ol*.— 17β-Acetoxy-4-methylandrost-4-en-3-one [9] (4·5 g) in methanol (200 ml) was treated with sodium borohydride (1 g) at 0°. The solution was left to stand for 1 h, acidified with glacial acetic acid, and poured into water. The product was filtered off and dried to give 17β-*acetoxy*-4-*methylandrost*-4-*en*-3β-*ol* which crystallized from ethyl acetate as prisms, m.p. 157—159°, $[\alpha]_D^{20}$ +53° (*c* 0·3) (Found: C, 76·3; H, 10·0. $C_{22}H_{34}O_3$ requires C, 76·3; H, 9·9%), $\nu_{max.}$ 3580, 3270, 1735, and 1250 cm^{-1}, τ 9·18 (3H, s, 18-H$_3$), 8·95 (3H, s, 19-H$_3$), 8·28 (3H, s, 4-Me), 7·95 (3H, s, 17-OAc), 5·98 (1H, m, 3-H), and 5·40 (1H, t, *J* 7·5 Hz, 17-H).

The *diacetate*, prepared with acetic anhydride in pyridine, crystallized from acetone–light petroleum as needles, m.p. 141—143°, $[\alpha]_D^{20}$ +30° (*c* 0·3) (Found: C, 74·3; H, 9·5. $C_{24}H_{36}O_4$ requires C, 74·2; H, 9·3%), $\nu_{max.}$ 1725 and 1235 cm^{-1}, τ 9·18 (3H, s, 18-H$_3$), 8·92 (3H, s, 19-H$_3$), 8·42 (3H, s, 4-Me), 7·96 (3H, s, 17-OAc), 7·93 (3H, s, 3-OAc), 5·41 (1H, t, *J* 7·5 Hz, 17-H), and 4·59 (1H, d, *J* 6 Hz, 3-H).

3β,17β-*Diacetoxy*-4α,5α-*epoxy*-4β-*methylandrostane* (11).— 3β,17β-Diacetoxy-4-methylandrost-4-ene (1·95 g) in benzene (50 ml) was treated with *m*-chloroperbenzoic acid (2·5 g) at room temperature overnight. The solution was diluted with ethyl acetate, washed thoroughly with aqueous iron(II) sulphate, dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and dried. The solvent was evaporated to give 3β,17β-*diacetoxy*-4α,5α-*epoxy*-4β-*methylandrostane* (11) (1·7 g) which crystallized from acetone–light petroleum as needles, m.p. 179—181°, $[\alpha]_D^{20}$ +42° (*c* 0·3) (Found: C, 71·5; H, 9·0. $C_{24}H_{36}O_5$ requires C, 71·25; H, 9·0%), $\nu_{max.}$ 1735 and 1240 cm^{-1}, τ 9·17 (3H, s, 18-H$_3$), 8·88 (3H, s, 19-H$_3$), 8·74 (3H, s, 4-Me), 7·95 (3H, s, 17-OAc), 7·91 (3H, s, 3-OAc), 5·39 (1H, t, *J* 7·5 Hz, 17-H), and 5·02 (1H, t, *J* 7·5 Hz, 3-H).

17β-*Acetoxy*-4β,5β-*epoxy*-4α-*methylandrostan*-3β-*ol*.— 17β-Acetoxy-4-methylandrost-4-en-3β-ol (1·3 g) in benzene (25 ml) was treated with *m*-chloroperbenzoic acid (1·6 g) at room temperature overnight. The solution was diluted with ethyl acetate, washed with aqueous iron(II) sulphate, dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and dried. The solvent was evaporated off to give 17β-*acetoxy*-4β,5β-*epoxy*-4α-*methylandrostan*-3β-*ol* (1·03 g) which crystallized from acetone–light petroleum as needles, m.p. 111—113°, $[\alpha]_D^{20}$ +18° (*c* 0·3) (Found: C, 72·5; H, 9·6. $C_{22}H_{34}O_4$ requires C, 72·9; H, 9·45%), $\nu_{max.}$ 3540, 1720, and 1230 cm^{-1}, τ 9·19 (3H, s, 18-H$_3$), 8·98 (3H, s, 19-H$_3$), 8·55 (3H, s, 4-Me), 7·96 (3H, s, 17-OAc), 6·21 (1H, t, *J* 3 Hz, 3-H), and 5·40 (1H, t, *J* 8 Hz, 17-H).

Treatment of the crude product with acetic anhydride in pyridine followed by chromatography on alumina gave, in the fractions eluted with 5% ethyl acetate–light petroleum, 3β,17β-*diacetoxy*-4β,5β-*epoxy*-4α-*methylandrostane* (12) (600 mg) which crystallized from acetone–light petroleum as needles, m.p. 95—97°, $[\alpha]_D^{20}$ +12° (*c* 0·23) (Found: C, 71·2; H, 8·9. $C_{24}H_{36}O_5$ requires C, 71·25; H, 9·0%), $\nu_{max.}$ 1730 and 1235 cm^{-1}, τ 9·18 (3H, s, 18-H$_3$), 8·94 (3H, s, 19-H$_3$), 8·66 (3H, s, 4-Me), 7·95 (3H, s, 17-OAc), 7·87 (3H, s, 3-OAc), 5·38 (1H, t, *J* 8 Hz, 17-H), and 4·90 (1H, t, *J* 3·5 Hz, 3-H). Elution with 10% ethyl acetate–light petroleum gave 3β,17β-diacetoxy-4α,5α-epoxy-4β-methylandrostane (54 mg), identified by its i.r. and n.m.r. spectrum.

Reaction of the 3β,17β-*Diacetoxy*-4,5-*epoxy*-4-*methylandrostanes with Hydrobromic Acid in Acetic Acid*.—(i) 3β,17β-Diacetoxy-4α,5α-epoxy-4β-methylandrostane (800 mg) in glacial acetic acid (8 ml) and 48% hydrobromic acid (1·6 ml) was heated under reflux for 25 min. The solution was poured into aqueous sodium hydrogen carbonate and the product was recovered in ether. Chromatography on alumina afforded, in the fractions eluted with 2·5% ethyl acetate–light petroleum, 17β-acetoxy-1,4-dimethyloestra-1,3,5(10)-triene (13) (250 mg) as an oil, $[\alpha]_D^{20}$ +111° (*c* 0·3) (lit.,[10] +110°), $\nu_{max.}$ 1730, 1235, and 805 cm^{-1}, τ 9·15 (3H, s, 18-H$_3$), 7·96 (3H, s, 17-OAc), 7·82 (3H, s, 4-Me), 7·69 (3H, s, 1-Me), 5·28 (1H, t, *J* 7·5 Hz, 17-H), and 3·12 (2H, s, 2- and 3-H). These fractions also gave 17β-acetoxy-3,4-dimethyloestra-1,3,5(10)-triene (14) (10 mg) which crystallized from light petroleum as needles, m.p. 168—170° (lit.,[11] 172—174°) identified by its i.r. and n.m.r. spectra, $\nu_{max.}$ 1735, 1240, and 840 cm^{-1}, τ 9·20 (3H, s, 18-H$_3$), 7·96 (3H, s, 17-OAc), 7·88 (3H, s, 4-Me), 7·73 (3H, s, 3-Me), 5·30 (1H, t, *J* 8 Hz, 17-H), and 2·95 (2H, AB, dd, *J* 7 Hz, 1- and 2-H).

The fractions eluted with 7·5% ethyl acetate–light petroleum gave 17β-acetoxy-4-methylandrost-4-en-3-one (118 mg) identified by its i.r. and n.m.r. spectra.

(ii) 3β,17β-Diacetoxy-4β,5β-epoxy-4α-methylandrostane (550 mg) in glacial acetic acid (6 ml) and 48% hydrobromic acid (1·1 ml) was heated under reflux for 25 min. The solution was poured into aqueous sodium hydrogen carbonate and the product recovered in ether. Chromatography on alumina afforded, in the fractions eluted with 2·5% ethyl acetate–light petroleum, 17β-acetoxy-1,4-dimethyloestra-1,3,5(10)-triene (13) (196 mg) as an oil, identified by its i.r. and n.m.r. spectra. Elution with 5% ethyl acetate–light petroleum afforded 17β-acetoxy-4-methylandrost-4-en-3-one (70 mg) identified by its i.r. and n.m.r. spectra.

(iii) 3β,17β-Diacetoxy-3α-deuterio-4α,5α-epoxy-4β-methylandrostane (*m/e* 405) was prepared as above. The deuterio-steroid (310 mg) in glacial acetic acid (5 ml) and 48% hydrobromic acid (1 ml) was heated under reflux for 4 min. The solution was poured into aqueous sodium hydrogen carbonate and the product recovered in chloroform and chromatographed on alumina. Elution with light petroleum gave deuterio-17β-acetoxy-1,4-dimethyloestra-1,3,5(10)-triene (60 mg) as an oil identical (n.m.r. in CCl_4) with the sample described above except that the resonance at τ 3·12 (s) integrated for 1·1H.

1,4-*Dimethyloestra*-1,3,5(10)-*trien*-17β-*ol*.— 17β-Acetoxy-1,4-dimethyloestra-1,3,5(10)-triene (110 mg) in methanol (4 ml) containing potassium hydroxide (180 mg) was heated under reflux for 30 min. The solution was poured into water, acidified, and the product recovered in ethyl acetate. Chromatography on alumina gave, in the fractions eluted with 10% ethyl acetate–light petroleum, 1,4-dimethyloestra-1,3,5(10)-trien-17β-ol which crystallized from acetone–light petroleum as needles, m.p. 76°, $[\alpha]_D^{20}$ +121° (*c* 0·3) (lit.,[10] m.p. 74°, $[\alpha]_D^{20}$ +153°) (Found: C, 84·2; H, 9·75. Calc. for $C_{20}H_{28}O$: C, 84·45; H, 9·9%), $\nu_{max.}$ 3350 and 806 cm^{-1}, τ 9·15 (3H, s, 18-H$_3$), 7·78 (3H, s, 4-Me), 7·65 (3H, s, 1-Me), 6·22 (1H, m, 17-H), and 3·09 (2H, s, 2- and 3-H). The sample was identical (i.r. and n.m.r.) with one prepared from 17β-acetoxyandrosta-1,4-dien-3-one and methylmagnesium iodide.

17β-*Acetoxy*-1,4-*dimethyloestra*-1,3,5(10)-*trien*-6-*one*.—17β-Acetoxy-1,4-dimethyloestra-1,3,5(10)-triene (400 mg) in acetic acid (10 ml) was treated with chromium trioxide (200 mg) in water (1·5 ml) at 70° for 3 h. Methanol was added and the solution was diluted with water, neutralized

with aqueous sodium hydrogen carbonate, and the steroid recovered in ethyl acetate. Chromatography on alumina gave, in the fractions eluted with 2·5% ethyl acetate–light petroleum, unchanged starting material followed by 17β-*acetoxy*-1,4-*dimethyloestra*-1,3,5(10)-*trien*-6-*one* (31 mg) which crystallized from acetone–light petroleum as needles, m.p. 187—188°, $[\alpha]_D^{20}$ +32° (*c* 0·2) (Found: C, 77·3; H, 8·4. $C_{22}H_{28}O_3$ requires C, 77·6; H, 8·3%), $\nu_{max.}$ 1725, 1680, 1565, 1240, and 830 cm^{-1}, τ 9·12 (3H, s, 18-H_3), 8·02 (3H, s, 17-OAc), 7·67 (3H, s, 1-Me), 7·49 (3H, s, 4-Me), 5·32 (1H, t, *J* 8 Hz, 17-H), and 3·02 (2H, AB dd, *J* 8 Hz, 2- and 3-H).

1-*Methyl*-4-[$^2H_3$]*methyloestra*-1,3,5(10)-*trien*-17β-*ol*.—This was prepared by the procedure described above. 17β-Acetoxy-4-[$^2H_3$]methylandrost-4-en-3-one had m.p. 158—160°, *m/e* 347. 17β-Acetoxy-4-[$^2H_3$]methylandrost-4-en-3β-ol had m.p. 157—159°, *m/e* 349, n.m.r.; no resonance at τ 8·28 for 4-Me. 3β,17β-Diacetoxy-4-[$^2H_3$]methylandrost-4-ene had m.p. 138—140°, *m/e* 391, n.m.r.; no resonance at τ 8·42 for 4-Me. 3β,17β-Diacetoxy-4α,5α-epoxy-4β-[$^2H_3$]-methylandrostane had m.p. 182°, *m/e* 407, n.m.r.; no resonance at τ 8·74 for 4-Me. 1-Methyl-4-[$^2H_3$]methyloestra-1,3,5(10)-trien-17β-yl acetate was isolated as an oil and hydrolysed to 1-methyl-4-[$^2H_3$]methyloestra-1,3,5(10)-trien-17β-ol, m.p. 78—80°, $[\alpha]_D^{20}$ +177°, $\nu_{max.}$ 3350, 2190w, 2050w, and 796 cm^{-1}, τ 9·16 (3H, s, 18-H_3), 7·65 (3H, s, 1-Me), 6·20 (1H, m, 17-H), and 3·08 (2H, s, 2- and 3-H), *m/e* 287.

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