Formation of Oestratrienes from 5,6-Epoxyandrostan-7-ols

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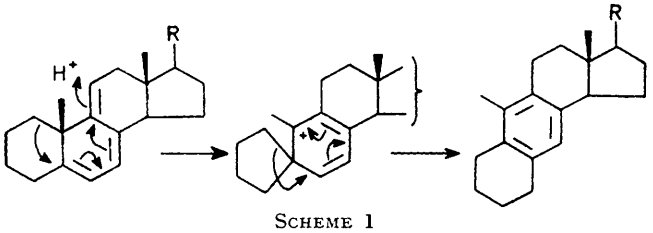
The preparation of the four isomeric 17β-acetoxy-5,6-epoxyandrostan-7-ols is described. On treatment with hydrobromic acid in glacial acetic acid, they yield 17β-acetoxy-4-methyloestra-1.3.5(10)-triene rather than an anthrasteroid. The formation of 17β-acetoxy-1.4-dimethyloestra-1.3.5(10)-triene from 17β-acetoxy-5β.6β-epoxy-3α-methylandrostan-7β-ol indicates that the reaction involves a skeletal rearrangement rather than a methyl group migration.

TREATMENT of steroidal 5,7,9(11)-trienes and 5,7,9(11),14-tetraenes with acid leads to the formation of anthrasteroids (Scheme 1).[1] This reaction has a formal similarity to the steroidal dienol–benzene rearrangement leading to oestratrienes.[2] Since a number of steroidal ring A hydroxy-epoxides [3] rearrange on treatment with hydrobromic acid in glacial acetic acid to afford oestratrienes, we have examined their ring B counterparts under these conditions for the formation of aromatic steroids.[4,5]



SCHEME 1

The four isomeric 17β-acetoxy-5,6-epoxyandrostan-7-ols were prepared in the manner illustrated (Scheme 2). 17β-Acetoxyandrost-5-ene (1) [6] was oxidized with t-butyl chromate [7] to give 17β-acetoxyandrost-5-en-7-one (2).[8] This ketone was reduced with lithium tri-t-butoxyaluminium hydride to afford 17β-acetoxyandrost-5-en-7β-ol (4) as the major product and the 7α-epimer (5) as the minor product. This is in contrast to the hydride reduction of saturated steroidal 7-ketones [9] or Δ^4-7-ketones [10] in which there is a preponderance of the α-isomer. The stereochemistry assigned received support by correlation with the saturated series. Thus catalytic reduction of 17β-acetoxyandrost-5-en-7β-ol (4) gave 17β-acetoxyandrostan-7β-ol, which formed the major product of reduction of 17β-acetoxyandrostan-7-one with lithium tri-t-butoxyaluminium hydride [11] and the minor product when sodium borohydride was the reducing agent. On the other hand, catalytic reduction of the 7α-epimer (5) gave 17β-acetoxyandrostan-7α-ol, which was the major product of reduction of 17β-acetoxyandrostan-7-one by both the acid-catalysed hydrogenation and treatment with sodium borohydride. These stereochemical assignments are also in accord with the chemical shift of the C-6 olefinic protons and with the magnitude of the 6-H,7-H coupling constants.[12] 17β-Acetoxyandrost-5-en-7α-ol (5) was more readily prepared by photo-oxygenation of 17β-acetoxyandrost-5-ene followed by reduction of the 7α-hydroperoxide with sodium iodide.[13]

Epoxidation of 17β-acetoxyandrost-5-en-7α-ol (5) with *m*-chloroperbenzoic acid gave 17β-acetoxy-5α,6α-epoxyandrostan-7α-ol (7), whereas epoxidation of the 7β-ol (4) gave a mixture of the 5α,6α- (10) and 5β,6β-epoxides (3). Greater stereoselectivity was obtained in the latter case by using vanadyl acetonylacetonate and t-butyl hydroperoxide,[14] which afforded entirely the 5β,6β-epoxide. Oxidation of 17β-acetoxy-5α,6α-epoxyandrostan-7α-ol (7) with chromium trioxide in pyridine gave 17β-acetoxy-5α,6α-epoxyandrostan-7-one (8), which was also obtained by epoxidation of 17β-acetoxyandrost-5-en-7-one (2) with *m*-chloroperbenzoic acid. This unsaturated ketone was not readily epoxidized with alkaline hydrogen peroxide. Reduction of 17β-acetoxy-5α,6α-epoxyandro-

[1] W. R. Nes and E. Mosettig, *J. Amer. Chem. Soc.*, 1954, **76**, 3182; 3186; W. R. Nes, *ibid.*, 1956, **78**, 193; W. R. Nes, R. B. Kostic, and E. Mosettig, *ibid.*, 1956, **78**, 436; W. R. Nes, J. A. Steele, and E. Mosettig, *ibid.*, 1958, **80**, 5233.

[2] E. Caspi, D. M. Piatak, and P. K. Grover, *J. Chem. Soc.* (*C*), 1966, 1034.

[3] J. R. Hanson and H. J. Shapter, *J.C.S. Perkin I*, 1972, 1445; D. Baldwin and J. R. Hanson, *ibid.*, p. 1889.

[4] J. Libman and Y. Mazur, *Chem. Comm.*, 1971, 730.

[5] Preliminary communication, D. Baldwin and J. R. Hanson, *J.C.S. Chem. Comm.*, 1974, 211.

[6] A. Crastes de Paulet and J. Bascoul, *Bull. Soc. chim. France*, 1966, 939.

[7] K. Heusler and A. Wettstein, *Helv. Chim. Acta*, 1952, **35**, 284.

[8] J. Siemann, W. Pohnert, and S. Schwarz, *Experientia*, 1964, **20**, 249.

[9] W. G. Dauben, E. J. Blanz, J. Jiu, and R. Micheli, *J. Amer. Chem. Soc.*, 1956, **78**, 3752.

[10] G. J. Kent and E. Wallis, *J. Org. Chem.*, 1959, **24**, 1235.

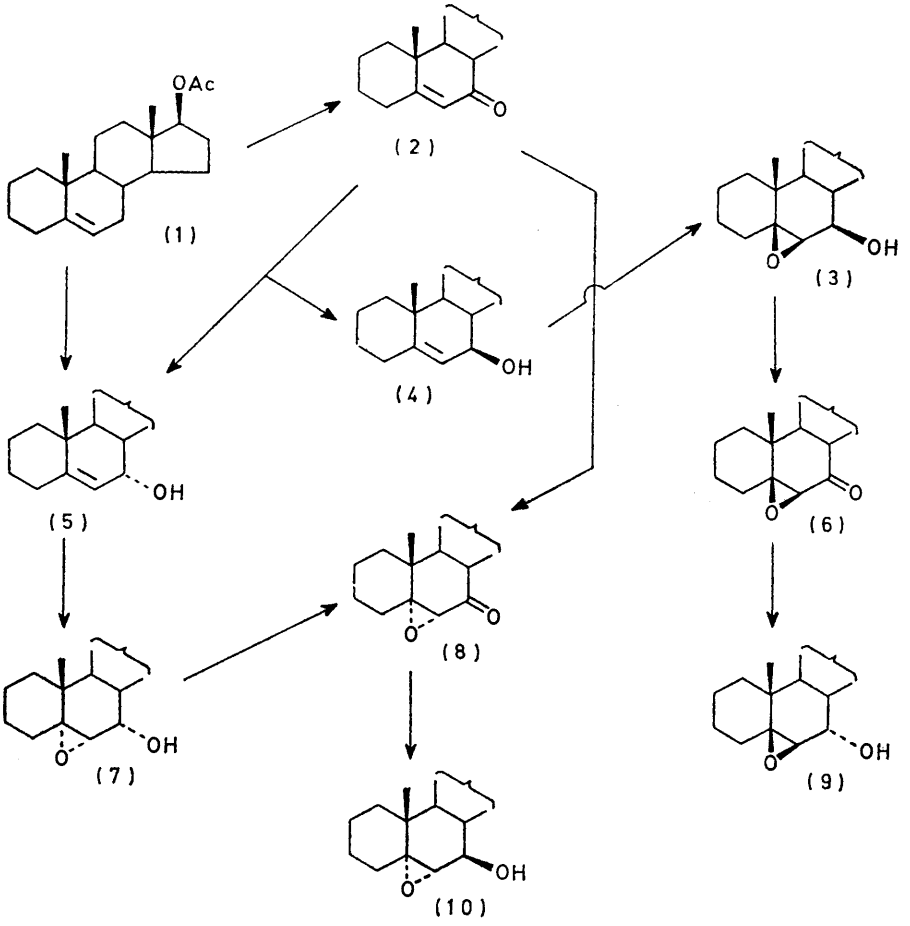
[11] J. Fajkos, *Coll. Czech. Chem. Comm.*, 1959, **24**, 2284.

[12] C. W. Shoppee and B. C. Newman, *J. Chem. Soc.* (*C*), 1968, 981.

[13] P. Morand and A. Van Tongerloo, *Steroids*, 1973, **21**, 47.

[14] K. B. Sharpless and R. C. Michaelson, *J. Amer. Chem. Soc.*, 1973, **95**, 6136.

stan-7-one (8) with sodium borohydride gave 17β-acetoxy-5α,6α-epoxyandrostan-7β-ol (10), the diacetate of which was identical with the product of epoxidation of 7β,17β-diacetoxyandrost-5-ene. Epoxidation of 7α,17β-diacetoxyandrost-5-ene with *m*-chloroperbenzoic acid gave a mixture of the 5α,6α- and 5β,6β-epoxides. The final member of the series was prepared by oxidation of 17β-acetoxy-5β,6β-epoxyandrostan-7β-ol to the corresponding ketone (6) with chromium trioxide followed by reduction with sodium borohydride to give the 7α-alcohol (9).



SCHEME 2

The stereochemistry assigned to the epoxides followed from their method of preparation. In the absence of directing effects, electrophilic epoxidation of the double bond takes place predominantly from the α-face of the molecule. However a 7β-hydroxy-group can direct [15] epoxidation to the β-face. The stereochemistry assigned to the epoxy-ketones was in accord with application of the 'reversed octant rule' [16] to their c.d. curves. 17β-Acetoxy-5α,6α-epoxyandrostan-7-one (8) showed a positive Cotton effect ($\Delta\varepsilon_{315}$ +4.08) whereas the 5β,6β-epoxide (6) had a negative effect ($\Delta\varepsilon_{296}$ −1.23).

N.m.r. spectra of the 17β-acetoxy-5,6-epoxyandrostan-7-ols

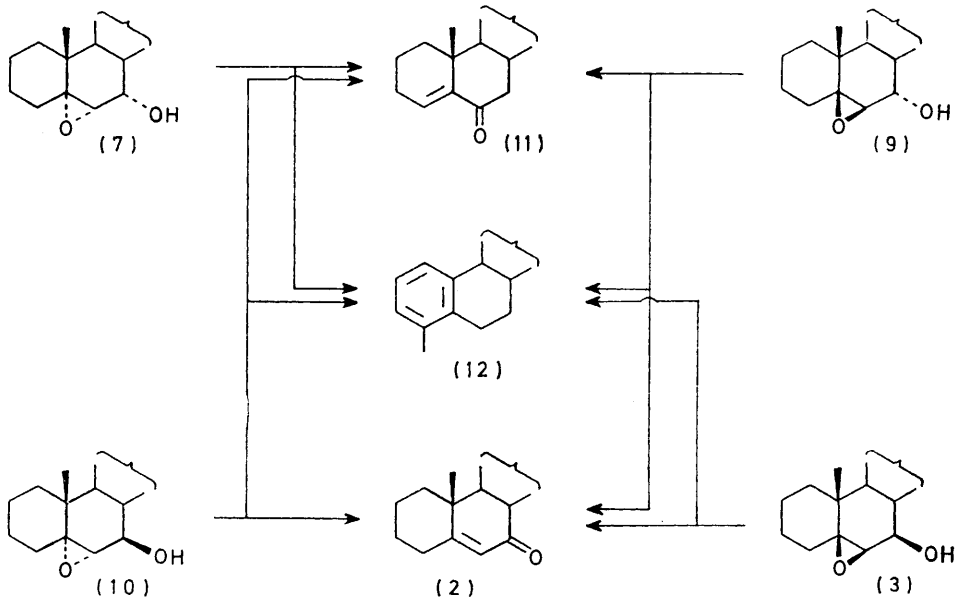
	6-H		7-H		10-CH_3	
	τ	*J*/Hz	τ	*J*/Hz	obs. τ	calc. τ
5α,6α-Epoxy-7α-ol Acetate	6.79 (d)	5	6.15br (m)		8.96	8.97
	6.73 (d)	5	5.4br (m)			
5α,6α-Epoxy-7β-ol Acetate	7.17 (s)		6.3 (m)		8.91	8.93
	7.29 (s)		5.24 (d)	7		
5β,6β-Epoxy-7α-ol Acetate	6.96 (d)	3.5	5.96 (t)	3.5	9.01	9.04
	6.95 (d)	3.5	4.80 (q)	2.5 and 3.5		
5β,6β-Epoxy-7β-ol Acetate	6.93 (d)	2	6.52 (q)	2 and 8	9.01	9.01
	6.90 (d)	1	5.11 (q)	1 and 9		

Additional support for the stereochemistry assigned to the alcohols followed from the magnitude of the 6-H,7-H and 7-H,8-H coupling constants (see Table). In the

[15] H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1957, 1958.
[16] C. Djerassi, W. Klyne, T. Norin, G. Ohloff, and E. Klein, *Tetrahedron*, 1965, **21**, 163.

case of 17β-acetoxy-5α,6α-epoxyandrostan-7α-ol (7), $J_{6,7}$ corresponds to a torsion angle of *ca.* 45° whereas in the case of the 7β-epimer (10) the angle is *ca.* 90°. The coupling constants for 17β-acetoxy-5β,6β-epoxyandrostan-7α-ol (9) correspond to torsion angles of *ca.* 55° between C(6)–H and C(7)–H and between C(7)–H and C(8)–H, whereas those for the 7β-epimer (3) correspond to torsion angles of *ca.* 70° between the C(6)–H and C(7)–H and *ca.* 160° between the C(7)–H and C(8)–H.

of both a 3α-methyl group and a 7β-hydroxy-group directed the epoxidation exclusively to the β-face of the molecule. Treatment of 17β-acetoxy-5β,6β-epoxy-3α-methylandrostan-7β-ol with hydrobromic acid in glacial acetic acid gave 17β-acetoxy-1,4-dimethyloestra-1,3,5(10)-triene (characterized as the crystalline 17β-alcohol) in which the methyl groups have retained their 1,4-relationship. Thus the reaction involved a skeletal rearrangement. The aromatic products in this case



SCHEME 3

When each epoxy-alcohol was treated with hydrobromic acid in glacial acetic acid (Scheme 3), the major isolable aromatic product was 17β-acetoxy-4-methyloestratriene (12),[17] obtained together with small amounts (*ca.* 5% by t.l.c.) of the corresponding 17-bromo-steroid; *i.e.* a ring A aromatic steroid was formed rather than an anthrasteroid. 17β-Acetoxy-5α,6α-epoxyandrostan-7α-ol (7) also gave 17β-acetoxyandrost-4-en-6-one (11), and 17β-acetoxy-5β,6β-epoxyandrostan-7β-ol (3) gave 17β-acetoxyandrost-5-en-7-one (2). Both unsaturated ketones (2) and (11) were obtained from the 5α,6α-epoxy-7β-alcohol (10) and the 5β,6β-epoxy-7α-alcohol (9).

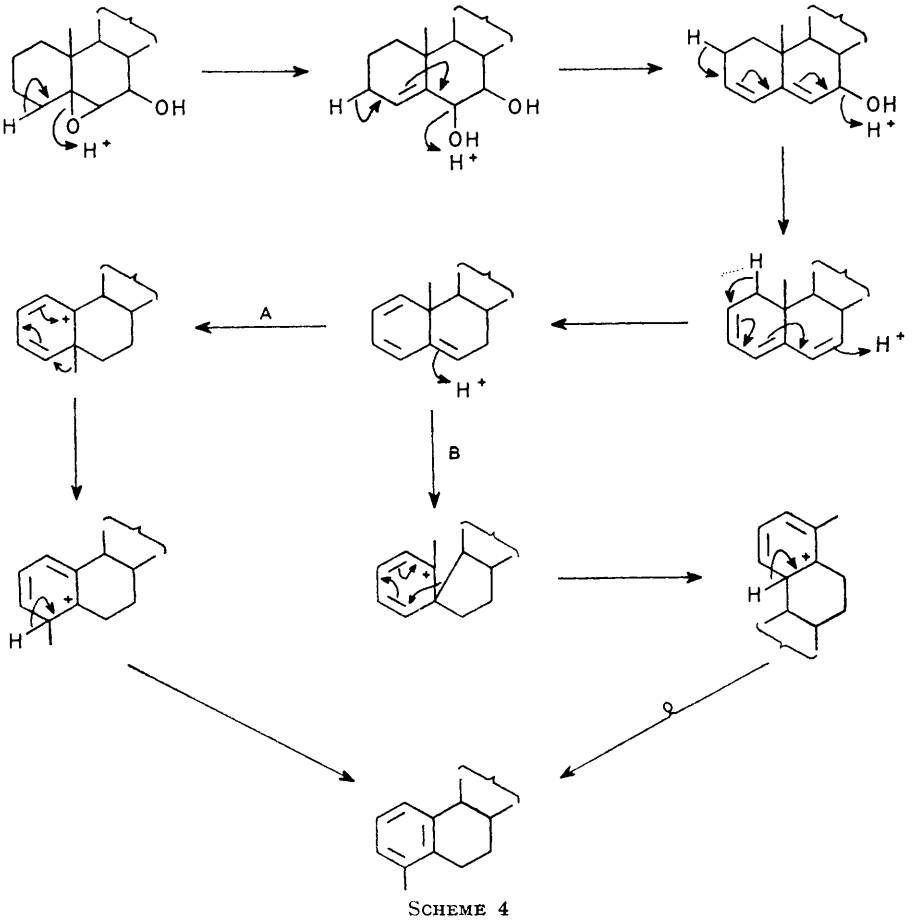
The formation of the aromatic steroid may take the form of a methyl group migration (path A) or a skeletal rearrangement (path B). These pathways (Scheme 4) were distinguished by examining the aromatization of 17β-acetoxy-5β,6β-epoxy-3α-methylandrostan-7β-ol. Path A would lead to a 3,4-dimethyloestratriene whereas path B would give a 1,4-dimethyloestratriene. The substrate was prepared by conjugate addition of methylmagnesium iodide in the presence of copper(II) acetate [18] to 17β-acetoxyandrosta-3,5-dien-7-one. 17β-Acetoxy-3α-methylandrost-5-en-7-one was reduced with sodium borohydride and the resultant 7β-alcohol was epoxidized with *m*-chloroperbenzoic acid. In this case the presence included a small amount of an anthrasteroid. The site of methylation on ring A was not established. Although C-2 is the most likely site, the methyl group could be at C-3, depending upon which bond migrates in the post-spiran stage. The ketonic product which was also obtained was identified as 17β-acetoxy-3α-methylandrost-5-en-7-one.

The formation of oestratrienes in this reaction was unexpected. A 5β-epoxide is suitably oriented to induce migration of the 1,10-bond to C-5 to afford a spiran which might lead to an anthrasteroid. Furthermore 5,6-dibromo-steroids have been reported [4] to give anthrasteroids. A possible explanation for the formation of ring A products lies in the different stereochemical interactions in the transitions states. In the spirodiene carbocation leading to the aromatization of ring B (see Scheme 1) as C-10 changes from sp^3 to sp^2 hybridization, interactions are introduced between the C-10 methyl group and C-11 and subsequently the new C-1. On the other hand in each of the double-bond isomerizations transferring the unsaturation to ring A and in the spirodiene carbocation ion leading to aromatization of ring A (see Scheme 4), there is a release of steric interactions, for example between C-1 and C-11. The formation of the unsaturated ketones can be rationalized

[17] J. Schmitt, J. J. Panouse, P. J. Cornu, A. Hallot, H. Pluchet, and P. Comoy, *Bull. Soc. chim. France*, 1965, 1934.

[18] K. Yasuda and H. Mori, *Chem. and Pharm. Bull.* (*Japan*), 1967, **15**, 179.

in the following terms. Cleavage of the 5,6-epoxide can lead to the generation of a 4-en-6-ol. In the case of 17β-acetoxy-5α,6α-epoxyandrostan-7α-ol, the 7α-hydroxy-group then has a diaxial relation with the allylic 6β-hydrogen atom. Elimination leads to an enol of 17β-acetoxyandrost-4-en-6-one. On the other hand with 17β-acetoxy-5β,6β-epoxyandrostan-7β-ol, the 6β-hydroxy-group has a diaxial relation with the 7α-hydrogen atom. Elimination in this case leads to an enol of 17β-acetoxyandrost-5-en-7-one. With the other epoxides there is less to distinguish between the paths leading to these unsaturated ketones.



SCHEME 4

EXPERIMENTAL

General experimental details have been described previously.[19]

Reduction of 17β-Acetoxyandrost-5-en-7-one.—17β-Acetoxyandrost-5-en-7-one [8] (2.0 g) in tetrahydrofuran (40 ml) was treated with lithium tri-t-butoxyaluminium hydride (2.5 g) at room temperature for 40 h. The excess of reagent was destroyed with water and the mixture was poured into dilute hydrochloric acid. The steroids were recovered in ether and chromatographed on alumina. Elution with 2% ethyl acetate–light petroleum gave 17β-*acetoxyandrost-5-en-7β-ol* (700 mg), which crystallized from light petroleum as needles, m.p. 119—121°, $[\alpha]_D^{20}$ −43° (*c* 0.2) (Found: C, 76.1; H, 9.8. $C_{21}H_{32}O_3$ requires C, 75.9; H, 9.7%), $\nu_{max.}$ 3 580 and 1 730 cm^{-1}, τ 9.21 (3 H, s, 18-H), 8.97 (3 H, s, 19-H), 7.98 (3 H, s, 17-OAc), 6.16 (1 H, m, 7-H), 5.38 (1 H, q, *J* 8 and 10 Hz, 17-H), and 4.8 (1 H, t, *J* 2 Hz, 6-H). Elution with 4% ethyl acetate–light petroleum gave 17β-*acetoxyandrost-5-en-7α-ol* (200 mg), which crystallized from light petroleum as needles, m.p. 134—135°, $[\alpha]_D^{20}$ −150° (*c* 0.2) (Found: C, 76.2; H, 9.9. $C_{21}H_{32}O_3$ requires C, 75.9; H, 9.7%), $\nu_{max.}$ 3 550, 3 500, and 1 725 cm^{-1}, τ 9.19 (3 H, s, 18-H), 9.01 (3 H, s, 19-H), 7.96 (3 H, s, 17-OAc), 6.16 (1 H, m, 7-H), 5.33 (1 H, q, *J* 8 and 10 Hz, 17-H), and 4.47 (1 H, q, *J* 2 and 6 Hz, 6-H).

7β,17β-*Diacetoxyandrost-5-ene*, prepared with acetic anhydride in pyridine, crystallized as needles from light petroleum, m.p. 110—112°, $[\alpha]_D^{20}$ +42° (*c* 0.2) (Found: C, 73.6; H, 9.1. $C_{23}H_{34}O_4$ requires C, 73.8; H, 9.15%), $\nu_{max.}$ 1 730 cm^{-1}, τ 9.19 (3 H, s, 18-H), 8.94 (3 H, s, 19-H), 7.97 (6 H, s, 7- and 17-OAc), 5.4 (1 H, m, 17-H), and 4.90 (2 H, m, 6- and 7-H).

7α,17β-*Diacetoxyandrost-5-ene*, prepared with acetic anhydride in pyridine, crystallized from aqueous methanol as needles, m.p. 110—111°, $[\alpha]_D^{20}$ −268° (*c* 0.2) (Found: C, 74.0; H, 8.9. $C_{23}H_{34}O_4$ requires C, 73.8; H, 9.15%), $\nu_{max.}$ 1 730 cm^{-1}, τ 9.21 (3 H, s, 18-H), 9.01 (3 H, s, 19-H), 7.96 (6 H, s, 7- and 17-OAc), 5.35 (1 H, q, *J* 8 and 10 Hz, 17-H), 5.02 (1 H, m, 7-H), and 4.52 (1 H, q, *J* 2 and 6 Hz, 6-H).

Reduction of 17β-Acetoxyandrost-5-en-7α- and -7β-ols.—The 7α-alcohol (332 mg) in ethyl acetate (40 ml) was shaken

[19] J. R. Hanson and T. D. Organ, *J. Chem. Soc.* (*C*), 1970, 513.

under hydrogen in the presence of 5% palladium–barium carbonate (100 mg) until uptake ceased (3 h). The catalyst was filtered off and the solution evaporated to give 17β-*acetoxyandrostan-7α-ol* (200 mg), which crystallized from light petroleum as plates, m.p. 163—165°, $[\alpha]_D^{20}$ −17° (*c* 0.2) (Found: C, 75.3; H, 10.2. $C_{21}H_{34}O_3$ requires C, 75.4; H, 10.25%), $\nu_{max.}$ 3 550 and 1 725 cm^{-1}, τ 9.23 (6 H, s, 18- and 19-H), 7.98 (3 H, s, 17-OAc), 6.18 (1 H, m, 7-H), and 5.38 (1 H, m, 17-H).

Hydrogenation of 17β-acetoxyandrost-5-en-7β-ol as above afforded 17β-*acetoxyandrostan-7β-ol*, which crystallized from light petroleum as needles, m.p. 122—123°, $[\alpha]_D^{20}$ +26° (*c* 0.2) (Found: C, 75.7; H, 10.1. $C_{21}H_{34}O_3$ requires C, 75.4; H, 10.25%), $\nu_{max.}$ 3 580 and 1 730 cm^{-1}, τ 9.20 (6 H, s, 18- and 19-H), 7.98 (3 H, s, 17-OAc), 6.64 (1 H, m, 7-H), and 5.43 (1 H, q, *J* 8 and 10 Hz, 17-H).

17β-*Acetoxy-5α-androstan-7-one*.— 17β-Acetoxyandrosta-3,5-dien-7-one (1.0 g) in ethyl acetate (50 ml) was shaken under hydrogen in the presence of 5% palladium–charcoal (100 mg) until uptake ceased (4 h). The solution was filtered and evaporated to afford 17β-acetoxy-5α-androstan-7-one, which crystallized as needles, m.p. 131—133°, $[\alpha]_D^{20}$ −65° (*c* 0.2) (lit.,[20] m.p. 128—129°, $[\alpha]_D$ −60°), $\nu_{max.}$ 1 735 and 1 705 cm^{-1}, τ 9.19 (3 H, s, 18-H), 8.92 (3 H, s, 19-H), 7.95 (3 H, s, 17-OAc), and 5.35 (1 H, q, *J* 8 and 10 Hz, 17-H).

Reduction of 17β-*Acetoxy-5α-androstan-7-one*.—(i) The ketone (250 mg) in tetrahydrofuran (20 ml) was treated with lithium tri-t-butoxyaluminium hydride (250 mg) at room temperature for 1 h. The excess of reagent was destroyed with water and the mixture poured into dilute hydrochloric acid. The product was recovered in ether. 17β-Acetoxyandrostan-7β-ol (50 mg), m.p. 122—123°, crystallized from light petroleum and was identified by its i.r. spectrum. The n.m.r. spectrum of the mother liquor showed it to be a mixture of the 7α- and 7β-alcohols (1 : 3).

(ii) The ketone (1 g) was dissolved in methanol (40 ml) and treated with sodium borohydride (250 mg) for 1 h at 0 °C. Acetic acid (1 ml) was added. The solution was poured into water and the steroid filtered off. 17β-Acetoxyandrostan-7α-ol (500 mg) crystallized from light petroleum as plates, m.p. 163—165°, and was identified by its i.r. spectrum. The n.m.r. spectrum of the residue showed it to be a mixture of the 7α- and 7β-alcohols (3 : 1).

(iii) The ketone (1 g) in acetic acid (15 ml) containing perchloric acid (0.1 ml) was shaken in hydrogen in the presence of platinum oxide (25 mg) until uptake ceased (3 h). The solution was filtered and poured into water and the steroid recovered in ether. 17β-Acetoxyandrostan-7α-ol (700 mg) crystallized from light petroleum as needles, m.p. 163—165°.

Photo-oxygenation of 17β-*Acetoxyandrost-5-ene*.—The steroid (7.5 g) in pyridine (100 ml) containing haematoporphyrin (30 mg) was irradiated with four 6 in Phillips TL4W fluorescent tubes while oxygen was bubbled through the solution for 7 days. The solution was poured into dilute hydrochloric acid and the steroid was recovered in ethyl acetate and chromatographed on alumina. Elution with 10% ethyl acetate–light petroleum afforded starting material (2.0 g). Elution with 20% ethyl acetate–light petroleum gave 17β-*acetoxy-7α-hydroperoxyandrost-5-ene* (4.0 g), which crystallized from methanol as needles, m.p. 158—160°, $[\alpha]_D^{20}$ +36° (*c* 0.2) (Found: C, 72.4; H, 9.5. $C_{21}H_{32}O_4$ requires C, 72.4; H, 9.3%), $\nu_{max.}$ 3 450 and 1 715 cm^{-1}, τ 9.16 (3 H, s, 18-H), 8.84 (3 H, s, 19-H), 7.94 (3 H, s, 17-OAc), 5.67 (1 H, q, *J* 2 and 4 Hz, 7-H), 5.4 (1 H, q, *J* 8 and 10 Hz, 17-H), and 4.27 (1 H, d, *J* 4 Hz, 6-H). The hydroperoxide (3.5 g) in ether (75 ml) and ethanol (375 ml) containing acetic acid (1 ml) was stirred overnight with sodium iodide (21.5 g). The solvents were removed *in vacuo* and the residue was dissolved in ether. The extract was washed with sodium thiosulphate solution and water, dried, and evaporated and the residue was chromatographed on alumina. Elution with 20% ethyl acetate–light petroleum gave 17β-acetoxyandrost-5-en-7α-ol (2.0 g), identical with the material described above.

Epoxidation Reactions.—(i) 17β-Acetoxyandrost-5-en-7α-ol (500 mg) in chloroform (50 ml) was treated with *m*-chloroperbenzoic acid (650 mg) and left at room temperature overnight. The solution was diluted with chloroform, washed thoroughly with aqueous iron(II) sulphate, dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried, and evaporated to give 17β-*acetoxy-5α,6α-epoxyandrostan-7α-ol* (250 mg), which crystallized from aqueous methanol as needles, m.p. 135—137°, $[\alpha]_D^{20}$ −106° (*c* 0.2) (Found: C, 72.6; H, 9.1. $C_{21}H_{32}O_4$ requires C, 72.4; H, 9.3%), $\nu_{max.}$ 3 560 and 1 735 cm^{-1}, τ 9.27 (3 H, s, 18-H), 8.96 (3 H, s, 19-H), 7.98 (3 H, s, 17-OAc), 6.79 (1 H, d, *J* 4.5 Hz, 6-H), 6.15 (1 H, m, 7-H), and 5.38 (1 H, q, *J* 8 and 10 Hz, 17-H). The 7α,17β-*diacetate*, prepared with acetic anhydride in pyridine, crystallized from aqueous methanol as needles, m.p. 124—125°, $[\alpha]_D^{20}$ −173° (*c* 0.2) (Found: C, 70.5; H, 8.7. $C_{23}H_{34}O_5$ requires C, 70.7; H, 8.8%), $\nu_{max.}$ 1 740 cm^{-1}, τ 9.29 (3 H, s, 18-H), 8.95 (3 H, s, 19-H), 7.98 and 7.90 (each 3 H, s, 7- and 17-OAc), 6.73 (1 H, d, *J* 5 Hz, 6-H), 5.4 (1 H, m, 17-H), and 4.98 (1 H, t, *J* 5 Hz, 7-H).

Under similar conditions 17β-acetoxyandrost-5-en-7β-ol gave a mixture of 5α,6α- and 5β,6β-epoxides (3 : 4 by n.m.r.).

(ii) t-Butyl hydroperoxide (260 mg) was added to a solution of 17β-acetoxyandrost-5-en-7β-ol and vanadyl acetonylacetonate (10 mg) in refluxing benzene (100 ml). The solution was heated under reflux for 30 min, diluted with ethyl acetate, washed thoroughly with aqueous iron(II) sulphate, dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried, and evaporated to give 17β-*acetoxy-5β,6β-epoxyandrostan-7β-ol* (400 mg), which crystallized from light petroleum as needles, m.p. 132—134°, $[\alpha]_D^{20}$ +20° (*c* 0.2) (Found: C, 72.2; H, 9.2. $C_{21}H_{32}O_4$ requires C, 72.4; H, 9.3%), $\nu_{max.}$ 3 420 and 1 715 cm^{-1} τ 9.24 (3 H, s, 18-H), 9.01 (3 H, s, 19-H), 7.98 (3 H, s, 17-OAc), 6.93 (1 H, d, *J* 2 Hz, 6-H), 6.52 (1 H, q, *J* 2 and 8 Hz, 7-H), and 5.44 (1 H, t, *J* 8 Hz, 17-H).

The 7β,17β-*diacetate*, prepared with acetic anhydride in pyridine, crystallized from light petroleum as needles, m.p. 144—145°, $[\alpha]_D^{20}$ +57° (*c* 0.2) (Found: C, 70.6; H, 8.5. $C_{23}H_{34}O_5$ requires C, 70.7; H, 8.8%), $\nu_{max.}$ 1 730 cm^{-1}, τ 9.21 (3 H, s, 18-H), 8.97 (3 H, s, 19-H), 7.97 (3 H, s) and 7.92 (3 H, s) (7- and 17-OAc), 6.90 (1 H, s, 6-H), 5.44 (1 H, m, 17-H), and 5.11 (1 H, q, *J* 1 and 9 Hz, 7-H).

(iii) Treatment of 17β-acetoxyandrost-5-en-7-one with *m*-chloroperbenzoic acid as above gave 17β-*acetoxy-5α,6α-epoxyandrostan-7-one*, which crystallized from light petroleum as needles, m.p. 117—118°, $[\alpha]_D^{20}$ +60° (*c* 0.2) (Found: C, 73.0; H, 9.0. $C_{21}H_{30}O_4$ requires C, 72.8; H, 8.7%), $\nu_{max.}$ 1 730 and 1 705 cm^{-1}, τ 9.19 (3 H, s, 18-H), 8.95 (3 H, s, 19-H), 7.95 (3 H, s, 17-OAc), 6.99 (1 H, s, 6-H), and 5.4 (1 H, q, *J* 8 and 10 Hz, 17-H).

[20] J. A. Saboz, T. Iizuka, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, 1968, **51**, 1362.

(iv) Treatment of 7α,17β-diacetoxyandrost-5-ene with *m*-chloroperbenzoic acid as above gave 7α,17β-diacetoxy-5α,6α-epoxyandrostane and 7α,17β-diacetoxy-5β,6β-epoxyandrostane (1 : 1), which were separated by preparative layer chromatography.

(v) Treatment of 7β,17β-diacetoxyandrost-5-ene with *m*-chloroperbenzoic acid as above gave 7β,17β-diacetoxy-5α,6α-epoxyandrostane, which crystallized from light petroleum as needles, m.p. 109—110°.

Oxidation of 17β-*Acetoxy*-5α,6α-*epoxyandrostan*-7α-*ol*.—The steroid (100 mg) in pyridine (2 ml) was added to a stirred solution of chromium trioxide (100 mg) in pyridine (2 ml) and the solution was then stirred at room temperature overnight, diluted with ether, washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and dried. Evaporation afforded 17β-acetoxy-5α,6α-epoxyandrostan-7-one (50 mg), which crystallized from light petroleum as needles, m.p. 117—118°.

Under similar conditions 17β-acetoxy-5β,6β-epoxyandrostan-7β-ol gave 17β-*acetoxy*-5β,6β-*epoxyandrostan*-7-*one*, which crystallized from light petroleum as needles, m.p. 149—150°, $[\alpha]_D^{20}$ −100° (*c* 0.2) (Found: C, 73.0; H, 8.8. $C_{21}H_{30}O_4$ requires C, 72.8; H, 8.7%), $\nu_{max.}$ 1 735 and 1 715 cm^{-1}, τ 9.22 (3 H, s, 18-H), 8.81 (3 H, s, 19-H), 7.97 (3 H, s, 17-OAc), 6.88 (1 H, s, 6-H), and 5.38 (1 H, q, *J* 8 and 10 Hz, 17-H).

Reduction of 17β-*Acetoxy*-5α,6α-*epoxyandrostan*-7-*one*.—The steroid (200 mg) in methanol (10 ml) was treated with sodium borohydride (80 mg) at room temperature for 1 h. A few drops of acetic acid were added and the solution was poured into water. The steroid was recovered in ether and purified by preparative layer chromatography to give 17β-*acetoxy*-5α,6α-*epoxyandrostan*-7β-*ol* (100 mg), which crystallized from light petroleum as needles, m.p. 167—169°, $[\alpha]_D^{20}$ −75° (*c* 0.2) (Found: C, 72.2; H, 9.4. $C_{21}H_{32}O_4$ requires C, 72.4; H, 9.35%), $\nu_{max.}$ 3 480 and 1 715 cm^{-1}, τ 9.24 (3 H, s, 18-H), 8.91 (3 H, s, 19-H), 7.97 (3 H, s, 17-OAc), 7.17 (1 H, s, 6-H), 6.3 (1 H, m, 7-H), and 5.4 (1 H, q, *J* 8 and 10 Hz, 17-H). The 7β,17β-*diacetate*, prepared with acetic anhydride in pyridine, crystallized from light petroleum as needles, m.p. 109—110°, $[\alpha]_D^{20}$ +1° (*c* 0.2) (Found: C, 70.8; H, 8.5. $C_{23}H_{34}O_5$ requires C, 70.7; H, 8.8%), $\nu_{max.}$ 1 730 cm^{-1}, τ 9.26 (3 H, s, 18-H), 8.90 (3 H, s, 19-H), 7.99 (3 H, s) and 7.95 (3H, s) (7- and 17-OAc), 7.29 (1 H, s, 6-H), 5.46 (1 H, q *J* 8 and 10 Hz, 17-H), and 5.24 (1 H, d, *J* 7 Hz, 7-H).

Under similar conditions reduction of 17β-acetoxy-5β,6β-epoxyandrostan-7-one gave 17β-*acetoxy*-5β,6β-*epoxyandrostan*-7α-*ol*, which crystallized from light petroleum as needles, m.p. 166—167°, $[\alpha]_D^{20}$ −52° (*c* 0.2) (Found: C, 72.1; H, 9.2. $C_{21}H_{32}O_4$ requires C, 72.4; H, 9.3%), $\nu_{max.}$ 3 480 and 1 720 cm^{-1}, τ 9.24 (3 H, s, 18-H), 9.01 (3 H, s, 19-H), 7.98 (3 H, s, 17-OAc), 6.96 (1 H, d, *J* 3.5 Hz, 6-H), 5.96 (1 H, m, 7-H), and 5.39 (1 H, q, *J* 8 and 10 Hz, 17-H). The 7α,17β-*diacetate*, prepared with acetic anhydride in pyridine, crystallized from light petroleum as needles, m.p. 146—147°, $[\alpha]_D^{20}$ −70° (*c* 0.2) (Found: C, 70.8; H, 8.8. $C_{23}H_{34}O_5$ requires C, 70.7; H, 8.8%), $\nu_{max.}$ 1 730 cm^{-1}, τ 9.24 (3 H, s, 18-H), 8.99 (3 H, s, 19-H), 7.98 (3 H, s) and 7.90 (3 H, s) (7- and 17-OAc), 6.95 (1 H, d, *J* 3.5 Hz, 6-H), 5.4 (1 H, m, 17-H), and 4.80 (1 H, q, *J* 2.5 and 3.5 Hz, 7-H).

17β-*Acetoxy*-5β,6β-*epoxy*-3α-*methylandrostan*-7β-*ol*.—17β-Acetoxy-3α-methylandrost-5-en-7-one [18] was reduced with sodium borohydride as above to afford 17β-*acetoxy*-3α-*methylandrost*-5-*en*-7β-*ol*, which crystallized from light petroleum as needles, m.p. 148—150°, $[\alpha]_D^{20}$ −30° (*c* 0.2) (Found: C, 76.0; H, 9.9. $C_{22}H_{34}O_3$ requires C, 76.3; H, 9.9%), $\nu_{max.}$ 3 560, 1 725, and 1 675w cm^{-1}, τ 9.21 (3 H, s, 18-H), 9.18 (3 H, d, *J* 8 Hz, 3-CH_3), 8.97 (3 H, s, 19-H), 7.98 (3 H, s, 17-OAc), 6.15 (1 H, m, 7-H), 5.4 (1 H, q, *J* 8 and 10 Hz, 17-H), and 4.81 (1 H, t, *J* 2 Hz, 6-H). Epoxidation of the alcohol with *m*-chloroperbenzoic acid as described above gave 17β-*acetoxy*-5β,6β-*epoxy*-3α-*methylandrostan*-7β-*ol*, which crystallized from light petroleum as needles, m.p. 129—130°, $[\alpha]_D^{20}$ −4° (*c* 0.2) (Found: C, 72.9; H, 9.45. $C_{22}H_{34}O_4$ requires C, 72.9; H, 9.45%), $\nu_{max.}$ 3 550 and 1 720 cm^{-1}, τ 9.25 (3 H, s, 18-H), 9.17 (3 H, d, *J* 7.5 Hz, 3-CH_3), 9.03 (3 H, s, 19-H), 8.00 (3 H, s, 17-OAc), 6.97 (1 H, d, *J* 1.5 Hz, 6-H), 6.48 (1 H, q, *J* 1.5 and 7.5 Hz), and 5.4 (1 H, q, *J* 8 and 10 Hz, 17-H).

Aromatization Reactions.—17β-Acetoxy-5α,6α-epoxyandrostan-7α-ol (500 mg) in 48% hydrobromic acid (1 ml) and glacial acetic acid (4 ml) was heated under reflux for 15 min. The solution was neutralized with aqueous sodium hydrogen carbonate and the product (400 mg) was recovered in ether and chromatographed on alumina. Elution with 6% ether–light petroleum gave 17-bromo-4-methyloestra-1,3,5(10)-triene (20 mg) as a yellow oil which was identified by its mass spectrum (*m/e* 334 and 332). Elution with 10% ether–light petroleum gave 17β-acetoxy-4-methyloestra-1,3,5(10)-triene (200 mg), which crystallized from light petroleum as needles, m.p. 184—185° (lit.,[17] 188°), identified by its i.r. spectrum. Elution with 50% ether–light petroleum gave 17β-acetoxyandrost-4-en-6-one (20 mg), which crystallized from methanol as needles, m.p. 160—161° (lit.,[21] 159—164°), identified by its i.r. spectrum.

Under similar conditions 17β-acetoxy-5β,6β-epoxyandrostan-7β-ol (120 mg) gave 17-bromo-4-methyloestra-1,3,5(10)-triene (5 mg), 17β-acetoxy-4-methyloestra-1,3,5(10)-triene (25 mg), and 17β-acetoxyandrost-5-en-7-one (5 mg). 17β-Acetoxy-5β,6β-epoxyandrostan-7α-ol (250 mg) gave 17β-acetoxy-4-methyloestra-1,3,5(10)-triene (50 mg), 17β-acetoxyandrost-5-en-7-one (5 mg), and 17β-acetoxyandrost-4-en-6-one (10 mg). 17β-Acetoxy-5α,6α-epoxyandrostan-7β-ol (120 mg) gave 17β-acetoxy-4-methyloestra-1,3,5(10)-triene (30 mg), 17β-acetoxyandrost-5-en-7-one (5 mg), and 17β-acetoxyandrost-4-en-6-one (5 mg).

17β-Acetoxy-5β,6β-epoxy-3α-methylandrostan-7β-ol (1.0 g) in glacial acetic acid (8 ml) and 48% hydrobromic acid (2 ml) was heated under reflux for 15 min. The solution was poured into aqueous sodium hydrogen carbonate and the product was recovered in ether. The extract was washed with water, dried, and evaporated. The residue (900 mg) was heated under reflux for 30 min in methanol (15 ml) containing potassium hydroxide (600 mg). The solution was poured into water (200 ml), which was then acidified with dilute hydrochloric acid. The product was recovered in ethyl acetate and chromatographed on alumina. Elution with 7% ethyl acetate–light petroleum gave an anthrasteroid fraction (100 mg), τ 9.05 (3 H, s, 18-H), 8.85 (3 H, d, *J* 12 Hz, ring A CH_3), 7.96 (3 H, s, 19-H), 6.24 (1 H, m, 17-H), and 3.46 (1 H, s, 7-H), as an oil. Elution with 10% ethyl acetate–light petroleum gave 1,4-dimethyloestra-1,3,5(10)-trien-17β-ol (150 mg), which crystallized from acetone–light petroleum as needles, m.p. 76°, $[\alpha]_D^{20}$ +119° (*c* 0.2) {lit.,[22] m.p. 74°, $[\alpha]_D$ +153° (in EtOH)} (Found: C, 84.2; H, 9.8. Calc. for $C_{20}H_{28}O$: C, 84.4; H,

[21] C. H. Robinson, O. Gnoj, and F. E. Carlon, *Tetrahedron*, 1965, **21**, 2509.

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

9.9%), $\nu_{max.}$ 3 350 cm^{-1}, τ 9.15 (3 H, s, 18-H), 7.78 (3 H, s, 4-CH_3), 7.65 (3 H, s, 1-CH_3), 6.22 (1 H, m, 17-H), and 3.09 (2 H, s, 2- and 3-H). Elution with 17% ethyl acetate–light petroleum gave 17β-hydroxy-3α-methylandrost-5-en-7-one (30 mg), which crystallized from aqueous methanol as needles, m.p. 156—157°, $\nu_{max.}$ 3 300, 1 670, and 1 630 cm^{-1}. The acetate, prepared with acetic anhydride in pyridine, was identical (i.r. and t.l.c.) with the material described above.

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