The Aromatization of Some 2α,3α-Epoxy-5α-hydroxy-steroids

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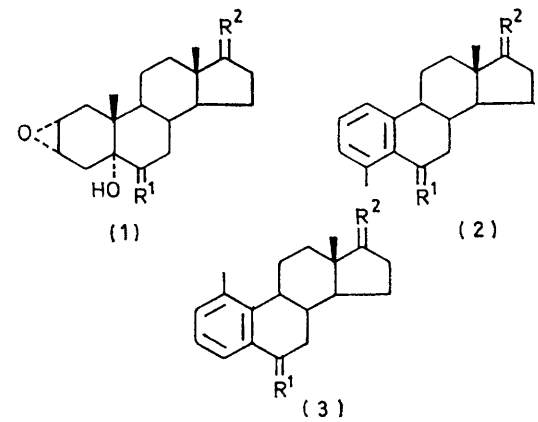
2α,3α-Epoxy-5α-hydroxyandrostan-17-one and the corresponding 17β-acetate rearrange in hydrogen bromide–glacial acetic acid to form 4-methyloestra-1,3,5(10)-trien-17-one and the corresponding 17β-acetate. The related 6,17-diones afford 1-methyloestra-1,3,5(10)-triene-6,17-dione and the corresponding 17β-acetate.

REARRANGEMENTS leading to aromatization require the juxtaposition of two double bond equivalents and a carbonium ion source. The cationic spiro-diene intermediate which is characteristic of the dienol–benzene rearrangement of steroids [1,2] may be derived from a range of compounds including 5α-hydroxy-2α,3α-epoxides. On the other hand the formation of a C-5 carbonium ion, implicit in such reactions, can also lead to products typical of Westphalen and 'backbone' rearrangements.[2] Furthermore, treatment of 2α,3α-epoxy-5α-hydroxy-steroids with hydrobromic acid can lead to 2α,5α-epoxy-3α-hydroxy-steroids.[3] Consequently, we have examined the behaviour of this system under the conditions of the dienol–benzene rearrangement.[4]

The hydroxy-epoxides were prepared in the following manner. 17β-Acetoxyandrost-2-en-5α-ol,[5] prepared by reduction of 5α,6α-epoxyandrost-2-en-17-one with lithium aluminium hydride followed by monoacetylation, was converted into its 2α,3α-epoxide (1; $R^1 = H_2$, R^2 = α-H,β-OAc) by the action of *m*-chloroperbenzoic acid. 17β-Acetoxy-3β-methylsulphonyloxyandrost-5-ene [6] was converted to its 5α,6α-epoxide with *m*-chloroperbenzoic acid. The latter epoxide was oxidized with chromium trioxide in methyl ethyl ketone [7] to the 5α-hydroxy-6-ketone. Elimination of the methanesulphonate group with collidine afforded the 2-ene, which was converted into the 2α,3α-epoxide (1; $R^1 = O$, R^2 = α-H,β-OAc) with *m*-chloroperbenzoic acid. 2α,3α-Epoxy-5α-hydroxyandrostan-17-one (1; $R^1 = H_2$, $R^2 = O$) and the corresponding 6,17-dione (1; $R^1 = R^2 = O$) were prepared by similar routes.

Treatment of 2α,3α-epoxy-5α-hydroxyandrostan-17-one and the corresponding 17β-acetate with hydrobromic acid in refluxing glacial acetic acid led to the immediate



formation of a deep blue colour and the isolation of 4-methyloestra-1,3,5(10)-trien-17-one (2; $R^1 = H_2$, $R^2 = O$) and its corresponding 17β-acetate (2; $R^1 = H_2$, R^2 = α-H,β-OAc). On the other hand, treatment of 2α,3α-epoxy-5α-hydroxyandrostane-6,17-dione and its 17β-acetate under identical conditions gave 1-methyloestra-1,3,5(10)-triene-6,17-dione (3; $R^1 = R^2 = O$) and the corresponding 17β-acetate (3; $R^1 = O$, R^2 = α-H,β-OAc) as the major isolable products.

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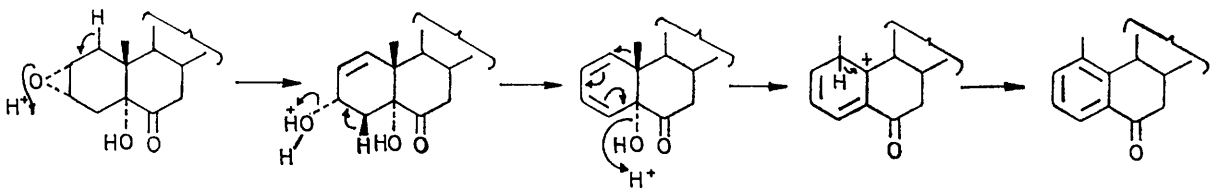
Authentic samples of both the aromatic diones (3; $R^1 = R^2 = O$) and (2; $R^1 = R^2 = O$) [1] were prepared by oxidation of 1-methyl- and 4-methyl-oestra-1,3,5(10)-trien-17-one with chromium trioxide in glacial acetic acid. They may be distinguished by their n.m.r. spectra. The 1-methyl-6-one shows signals at τ 7·60 (ArC–CH_3) and 2·06 (1H, dd, J 2 and 9 Hz, C-4 proton), whereas the 4-methyl-6-one shows resonances at τ 7·32 (ArC–CH_3) and 2·65 (3H, m).

We therefore conclude that the 2α,3α-epoxy-5α-hydroxy-steroids can undergo a spiro-diene aromatization. However the presence of a C-6 carbonyl function serves, as in the dienone–phenol rearrangement,[8] to destabilize a C-5 carbonium ion and prevents the formation of a spirocyclic intermediate. Aromatization then occurs *via* the alternative pathway of a C-10 ⟶ C-1 methyl migration, as shown in the Scheme.



SCHEME Possible mode of formation of 1-methylsteroids

EXPERIMENTAL

General details have been described previously.[9]

17β-Acetoxy-5α,6α-epoxy-3β-methylsulphonyloxyandrostane.—17β-Acetoxy-3β-methylsulphonyloxyandrost-5-ene [6] (8 g) in benzene (200 ml) was treated with *m*-chloroperbenzoic acid (9 g) at room temperature overnight. The solution was filtered, diluted with ether, washed thoroughly with aqueous iron(II) sulphate, dil. hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and dried. The solvent was evaporated off and the product crystallized from acetone to give the *5α,6α-epoxide* (5 g) as needles, m.p. 174—175°, $[\alpha]_D^{20}$ −61° (*c* 0·25) (Found: C, 61·8; H, 8·1. $C_{22}H_{34}O_6S$ requires C, 61·9; H, 8·0%), $\nu_{max.}$ 1720 cm^{-1}, τ 9·28 (3H, s, 18-H), 8·92 (3H, s, 19-H), 8·00 (3H, s, 17-OAc), 7·10 (1H, m, 6-H), 7·04 (3H, s, 3-O·SO_2Me), 5·45 (1H, t, J 9 Hz, 17-H), and 5·20 (1H, q, J 5 Hz, 3-H).

17β-Acetoxy-5α-hydroxy-3β-methylsulphonyloxyandrostan-6-one.—The foregoing epoxide (4 g) in methyl ethyl ketone (40 ml) was treated with a solution of chromium trioxide (6 g) in water (8 ml) at 40° for 20 min. The solution was cooled and diluted with water to give the *hydroxy-ketone* (2·2 g), which crystallized from aqueous acetone as needles, m.p. 178—180° (decomp.), $[\alpha]_D^{20}$ −64° (*c* 0·24) (Found: C, 59·5; H, 7·5. $C_{22}H_{34}O_7S$ requires C, 59·7; H, 7·75%), $\nu_{max.}$ 3450 and 1715 cm^{-1}, τ 9·25 (3H, s, 18-H), 9·19 (3H, s, 19-H), 7·98 (3H, s, 17-OAc), 7·00 (3H, s, 3-O·SO_2Me), 5·40 (1H, t, J 7 Hz, 17-H), and 5·04 (1H, m, 3-H).

17β-Acetoxy-5α-hydroxyandrost-2-en-6-one.—The foregoing hydroxy-ketone (1·6 g) was heated under reflux in collidine (25 ml) for 2·5 h. The solution was cooled and poured into dil. hydrochloric acid, and the product was recovered in ethyl acetate. Chromatography on alumina gave, in fractions eluted with 50% ethyl acetate–light petroleum, the *2-en-6-one* (750 mg), which crystallized from acetone–light petroleum as needles, m.p. 170—171°, $[\alpha]_D^{20}$ −38° (*c* 0·26) (Found: C, 72·5; H, 8·6. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%), $\nu_{max.}$ 3510, 1730, and 1715 cm^{-1}, τ 9·30 (3H, s, 19-H), 9·22 (3H, s, 18-H), 7·92 (3H, s, 17-OAc), 5·38 (1H, t, J 7 Hz, 17-H), and 4·38 (2H, m, 2- and 3-H).

Preparation of the 2α,3α-Epoxides.—(i) 2α,3α-Epoxy-5α-hydroxyandrostan-17-one (1; $R^1 = H_2$, $R^2 = O$), prepared by the action of *m*-chloroperbenzoic acid on 5α-hydroxyandrost-2-en-17-one,[5] crystallized from acetone–light petroleum as needles, m.p. 170—172°, $[\alpha]_D^{20}$ +82° (*c* 0·25) {lit.,[3] m.p. 173—175°, $[\alpha]_D^{20}$ +83° (*c* 1·01)} (Found: C, 75·0; H, 9·4. Calc. for $C_{19}H_{28}O_3$: C, 75·0; H, 9·3%), $\nu_{max.}$ 3500 and 1735 cm^{-1}, τ 9·16 (3H, s, 18-H), 9·07 (3H, s, 19-H), and 6·70 (2H, s, 2- and 3-H).

(ii) 17β-Acetoxy-2α,3α-epoxyandrostan-5α-ol (1; $R^1 = H_2$, R^2 = α-H,β-OAc), prepared from 17β-acetoxy-5α-hydroxyandrost-2-ene [5] by the action of *m*-chloroperbenzoic acid, crystallized from light petroleum as needles, m.p. 151—152°, $[\alpha]_D^{20}$ −10° (*c* 0·25) {lit.,[3] m.p. 151—152°, $[\alpha]_D^{22}$ +1·5° (*c* 1·01)} (Found: C, 72·5; H, 9·35. Calc. for $C_{21}H_{32}O_4$: C, 72·4; H, 9·3%), $\nu_{max.}$ 3510 and 1735 cm^{-1}, τ 9·24 (3H, s, 18-H), 9·08 (3H, s, 19-H), 8·00 (3H, s, 17-OAc), 6·70 (2H, s, 2- and 3-H), and 5·45 (1H, t, J 7 Hz, 17-H).

(iii) 5α-Hydroxyandrost-2-ene-6,17-dione [10,11] (1·1 g) was treated with *m*-chloroperbenzoic acid (1·1 g) in a mixture of benzene (25 ml) and chloroform (75 ml) at room temperature for 17 h. The solution was diluted with ether, washed thoroughly with aqueous iron(II) sulphate, dil. hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and dried. The solvent was evaporated off and the product chromatographed on alumina. Elution with 50% ethyl acetate–light petroleum gave *2α,3α-epoxy-5α-hydroxyandrostane-6,17-dione* (1; $R^1 = R^2 = O$) (550 mg), which crystallized from acetone–light petroleum as needles, m.p. 232—234°, $[\alpha]_D^{20}$ +72° (*c* 0·25) (Found: C, 71·7; H, 8·0. $C_{19}H_{26}O_4$ requires C, 71·7; H, 8·2%), $\nu_{max.}$ 3480, 1735, and 1710 cm^{-1}, τ 9·21 (3H, s, 18-H), 9·14 (3H, s, 19-H), 6·60 (2H, m, 2- and 3-H), and 6·40 (1H, s, OH).

(iv) 17β-Acetoxy-5α-hydroxyandrost-2-en-6-one (1·0 g) was treated with *m*-chloroperbenzoic acid (1·0 g) in benzene (25 ml) at room temperature for 15 h. The product was recovered as in (iii) to give *17β-acetoxy-2α,3α-epoxy-5α-hydroxyandrostan-6-one* (1; $R^1 = O$, R^2 = α-H,β-OAc), which crystallized from acetone–light petroleum as needles, m.p. 169—171°, $[\alpha]_D^{20}$ −12° (*c* 0·25) (Found: C, 69·2; H, 8·4. $C_{21}H_{30}O_5$ requires C, 69·6; H, 8·3%), $\nu_{max.}$ 3500, 1735, and 1720 cm^{-1}, τ 9·28 (3H, s) and 9·24 (3H, s, 18- and 19-H), 7·98 (3H, s, 17-OAc), 6·72 (1H, t, J 4 Hz, 2-H), 6·54 (1H, m, 3-H), 6·44 (1H, s, OH), and 5·38 (1H, t, J 7 Hz, 17-H).

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Aromatization Reactions.—(i) 2α,3α-Epoxy-5α-hydroxyandrostan-17-one (1; $R^1 = H_2$, $R^2 = O$) (130 mg) in glacial acetic acid (3 ml) and 48% hydrobromic acid (1 ml) was heated under reflux for 0·5 h. The solution was poured into aqueous sodium hydrogen carbonate and the product was recovered in ether. Chromatography on alumina gave 4-methyloestra-1,3,5(10)-trien-17-one (2; $R^1 = H_2$, $R^2 = O$) (45 mg), which crystallized from light petroleum as needles, m.p. 182—184° (lit.,[12] 184—186°), identified by i.r. spectrum.

(ii) 17β-Acetoxy-2α,3α-epoxyandrostan-5α-ol (1; $R^1 = H_2$, $R^2 = \alpha$-H,β-OAc) (620 mg) in glacial acetic acid (7 ml) and 48% hydrobromic acid (1·4 ml) was heated under reflux for 20 min. The solution was poured into aqueous sodium hydrogen carbonate and the product recovered in ether. Chromatography on alumina gave 17β-acetoxy-4-methyloestra-1,3,5(10)-triene (2; $R^1 = H_2$, $R^2 = \alpha$-H,β-OAc) (370 mg), which crystallized from light petroleum as needles, m.p. 186° (lit.,[13] 188°), identified by i.r. spectrum.

(iii) 2α,3α-Epoxy-5α-hydroxyandrostane-6,17-dione (1; $R^1 = R^2 = O$) (250 mg) in glacial acetic acid (2 ml) and 48% hydrobromic acid (0·5 ml) was heated under reflux for 15 min. The solution was poured into aqueous sodium hydrogen carbonate; the product was recovered in ethyl acetate and chromatographed on alumina to give 1-methyloestra-1,3,5(10)-triene-6,17-dione (3; $R^1 = R^2 = O$), which crystallized from light petroleum as needles, m.p. 153—154°, $[\alpha]_D^{20}$ +130° (*c* 0·25), identified by i.r. spectrum.

(iv) 17β-Acetoxy-2α,3α-epoxy-5α-hydroxyandrostan-6-one (1; $R^1 = O$, $R^2 = \alpha$-H,β-OAc) (120 mg) in glacial acetic acid (5 ml) and 48% hydrobromic acid (1 ml) was heated under reflux for 15 min. The solution was poured into aqueous sodium hydrogen carbonate. The product was recovered in ethyl acetate and chromatographed on alumina to give 17β-*acetoxy*-1-*methyloestra*-1,3,5(10)-*trien*-6-*one* (3; $R^1 = O$, $R^2 = \alpha$-H,β-OAc) (35 mg), which crystallized from acetone–light petroleum as prisms, m.p. 210°, $[\alpha]_D^{20}$ +6° (*c* 0·25) (Found: C, 76·8; H, 7·8. $C_{21}H_{26}O_3$ requires C, 77·3; H, 8·0%), $\nu_{max.}$ 1730, 1680, and 1595 cm^{-1}, τ 9·15 (3H, s, 18-H), 7·95 (3H, s, 17-OAc), 7·59 (3H, s, 1-Me), 5·23 (1H, t, *J* 7 Hz, 17-H), 2·7 (2H, m, 2- and 3-H), and 2·2 (1H, dd, *J* 8 and 3 Hz, 4-H).

1-*Methyloestra*-1,3,5(10)-*triene*-6,17-*dione*.— 1-Methyloestra-1,3,5(10)-trien-17-one [14] (350 mg) in acetic acid (7 ml) was treated with a solution of chromium trioxide (1·0 g) in water (1·5 ml) at 70° for 2 h. The excess of reagent was decomposed with methanol. The solution was diluted with water and neutralized with sodium hydrogen carbonate, and the product was recovered in ethyl acetate. Chromatography on alumina afforded 1-*methyloestra*-1,3,5(10)-*triene*-6,17-*dione* (3; $R^1 = R^2 = O$) (150 mg), which crystallized from acetone as needles, m.p. 156—158°, $[\alpha]_D^{20}$ +132° (*c* 0·9) (Found: C, 80·2; H, 7·9. $C_{19}H_{22}O_2$ requires C, 80·2; H, 7·85%), $\nu_{max.}$ 1745, 1680, and 1595 cm^{-1}, τ 9·17 (3H, s, 18-H), 7·60 (3H, s, 1-Me), 2·71 (2H, m, 2- and 3-H), and 2·06 (1H, dd, *J* 9 and 2 Hz, 4-H).

4-Methyloestra-1,3,5(10)-triene-6,17-dione [1] was prepared in a similar manner.

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