Aromatization of Some 4,5-Epoxy-3-hydroxysteroids

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Treatment of the epimeric 17β-acetoxy-4,5-epoxyandrostan-3β-ols with hydrogen bromide in glacial acetic acid gave 17β-acetoxy-4-methyloestra-1,3,5(10)-triene by a dienol–benzene pathway. Under the same conditions 3β-hydroxy-4β,5β-epoxyandrostane-6,17-dione gave 1-methyloestra-1,3,5(10)-triene-6,17-dione, whilst 3β,17β-diacetoxy-4α,5α-epoxyandrostan-11-one gave a low yield of 17β-acetoxy-4-methyloestra-1,3,5(10)-trien-11-one, revealing that the influence of the carbonyl groups at C-6 and C-11 on this reaction is similar to that on the dienone–phenol rearrangement.

THE formation of aromatic steroids by reactions which are related to the dienol–benzene rearrangement is more general than has hitherto been realized.[1,2] We have recently shown that treatment of 5α-hydroxy-2α,3α-epoxyandrostanes with hydrogen bromide in glacial acetic acid leads to either 1- or 4-methyloestra-1,3,5(10)-trienes, depending upon the presence or absence of a C-6 carbonyl function.[3] We now report the aromatization of some 4,5-epoxy-3-hydroxy-steroids.[4]

1- and 4-Methyl-19-norcholesta-1,3,5(10)-trienes were amongst the products obtained when the 4,5-epoxy-3-*p*-tolylsulphonyloxycholestanes were heated with collidine.[5]

Testosterone was converted into a mixture of the 4α,5α-epoxy- and 4β,5β-epoxy-steroids with alkaline hydrogen peroxide.[6] The 4α,5α-epoxide was acetylated [7] and reduced with sodium borohydride to afford 17β-acetoxy-4α,5α-epoxyandrostan-3β-ol (1; $R^1 = H$, $R^2 = H_2$). The 3β,17β-diacetate (1; $R^1 = Ac$, $R^2 = H_2$) was identical with material prepared by epoxidation of 3β,17β-diacetoxyandrost-4-ene.[8] Testosterone acetate was reduced with sodium borohydride and the product was epoxidized with *m*-chloroperbenzoic acid to afford 17β-acetoxy-4β,5β-epoxyandrostan-3β-ol (2; $R^1 = H_2$, $R^2 = \alpha$-H, β-OAc).[9]

Treatment of 17β-acetoxy-4α,5α-epoxyandrostan-3β-ol (1; $R^1 = H$, $R^2 = H_2$), the corresponding 3β,17β-diacetate (1; $R^1 = Ac$, $R^2 = H_2$), and 17β-acetoxy-4β,5β-epoxyandrostan-3β-ol (2; $R^1 = H_2$, $R^2 = \alpha$-H, β-OAc) with hydrobromic acid in glacial acetic acid gave 17β-acetoxy-4-methyloestra-1,3,5(10)-triene (3; $R = H_2$) as the major aromatic steroid product, together with smaller amounts of testosterone acetate. 17β-Acetoxy-1-methyloestra-1,3,5(10)-triene was also isolated from the aromatization of compound (2; $R^1 = H_2$, $R^2 = \alpha$-H, β-OAc) in low yield.

A number of pathways may be envisaged for this reaction. One, a modification of the Westphalen rearrangement, involves a migration of the C-19 group first to C-5 and then to C-4. Another, related to the dienol–benzene rearrangement,[10] involves a spirocyclic

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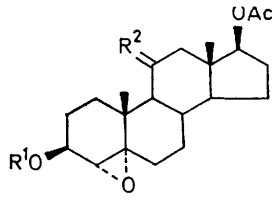
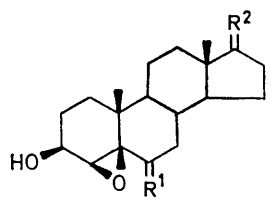
[10] For a review, see D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, London, 1968.

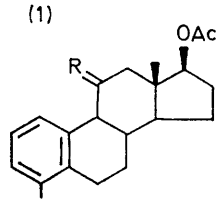
intermediate in which the 9,10-bond migrates first to C-5 and then to C-4 (*cf.* ref. 1). 17β-Acetoxy-3α-deuterio-4β,5β-epoxyandrostan-3β-ol was prepared by reduction of testosterone acetate with sodium borodeuteride



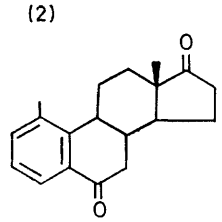
(1)



(2)



(3)



(4)

followed by epoxidation. On rearrangement this gave 1-deuterio-4-methyloestra-1,3,5(10)-trien-17β-yl acetate. This showed an n.m.r. spectrum identical with that of the aromatization product from 17β-acetoxy-3α-deuterio-3β-hydroxyandrosta-1,4-diene. In particular, multiplets at τ 3·07 (1H) and 3·19 (2H) for the undeuteriated compounds were replaced by a singlet at τ 3·19 (2H) for the deuteriated compound. Had the modified Westphalen pathway been involved, then the hydroxy-epoxide would have given a 3-deuterio-4-methyl aromatic compound with a different aromatic C–H resonance pattern.

Carbonyl groups at C-6 [11] and C-11 [12] modify the course of the dienone–phenol rearrangement. We have studied their influence on this reaction. 4β,5β-Epoxy-3β-hydroxyandrostane-6,17-dione (2; $R^1 = R^2 = O$) [13] was treated with hydrogen bromide in glacial acetic acid. The aromatic product was 1-methyloestra-1,3,5(10)-triene-6,17-dione (4). The 4-methyl isomer was not detected by t.l.c. The reaction also furnished androst-4-ene-3,6,17-trione. Thus the pathway to aromatization has been profoundly modified by a C-6 carbonyl group. As in the dienone–phenol rearrangement, the C-6 carbonyl group destabilizes an adjacent C-5 carbonium ion and thereby prevents the formation of a spirocyclic carbonium ion.

Partial reduction and acetylation of androst-4-ene-3,11,17-trione afforded 3β,17β-diacetoxyandrost-4-en-11-one,[14] which was epoxidized with *m*-chloroperbenzoic acid to give 3β,17β-diacetoxy-4α,5α-epoxyandrostan-11-one (1; R^1 = Ac, R^2 = O). This gave a low yield of 17β-acetoxy-4-methyloestra-1,3,5(10)-trien-11-one (3; R = O) on treatment with hydrogen bromide in glacial acetic acid. The alternative 1-methyl structure was excluded since the n.m.r. spectra of compounds (3; $R = H_2$) and (3; R = O) showed the Ar–C–CH_3 resonances at τ 7·79 and 7·81, unaffected by the introduction of a carbonyl group at C-11. As in the dienone–phenol rearrangement, the C-11 carbonyl group destabilizes the formation of the spirocyclic cation but completely inhibiting this pathway to aromatization.

EXPERIMENTAL

General experimental details have been described previously.[15]

17β-Acetoxy-4β,5β-epoxyandrostan-3β-ol was prepared by reduction of testosterone acetate with sodium borohydride followed by epoxidation with *m*-chloroperbenzoic acid. It crystallized from acetone–light petroleum as needles, m.p. 127—128°, $[\alpha]_D^{20}$ −17° (*c* 0·25) (lit.,[9] m.p. 128—130°, $[\alpha]_D$ −22°) (Found: C, 72·5; H, 9·4. Calc. for $C_{21}H_{32}O_4$: C, 72·4; H, 9·3%), $\nu_{max.}$ 3600 and 1720 cm^{-1}, τ 9·18 (3H, s), 8·96 (3H, s), 7·96 (3H, s), 6·87 (1H, d, *J* 5 Hz), 5·92 (1H, m), and 5·36 (1H, t, *J* 8 Hz).

17β-*Acetoxy*-4α,5α-*epoxyandrostan*-3β-*ol* (1; $R^1 = H$, $R^2 = H_2$).—17β-Acetoxy-4α,5α-epoxyandrostan-3-one [m.p. 167—168° (lit.,[7] 164—165°)] (400 mg) in methanol (10 ml) was treated with sodium borohydride (250 mg) at room temperature for 2 h. A few drops of acetic acid were added and the solution was poured into water. The product was recovered in ether and chromatographed on alumina. Elution with 30% ether–light petroleum gave 17β-*acetoxy*-4α,5α-*epoxyandrostan*-3β-*ol* (250 mg), which crystallized from light petroleum as needles, m.p. 126—127°, $[\alpha]_D^{20}$ +68° (*c* 0·25) (Found: C, 72·6; H, 9·15. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·3%), $\nu_{max.}$ 3600 and 1725 cm^{-1}, τ 9·20 (3H, s), 8·90 (3H, s), 7·90 (3H, s), 7·12 (1H, s), 6·04 (1H, m), and 5·43 (1H, t, *J* 7 Hz).

The diacetate, prepared with acetic anhydride in pyridine crystallized from light petroleum as needles, m.p. 174—175°, $[\alpha]_D^{20}$ +39° (*c* 0·24) (lit.,[8] m.p. 174°, $[\alpha]_D$ +40°) (Found: C, 70·6; H, 8·9. Calc. for $C_{23}H_{34}O_5$: C, 70·7; H, 8·8%), $\nu_{max.}$ 1735br cm^{-1}, τ 9·20 (3H, s), 8·88 (3H, s), 7·99 (6H, s), 7·15 (1H, s), 5·43 (1H, t, *J* 7 Hz), and 5·08 (1H, t, *J* 8 Hz). 3β,17β-Diacetoxyandrost-4-ene gave the same compound on treatment with *m*-chloroperbenzoic acid.[8]

3β,17β-Diacetoxyandrost-4-en-11-one crystallized from acetone–light petroleum as prisms, m.p. 173—174°, $[\alpha]_D^{20}$ +29° (*c* 0·25) (lit.,[14] 177—178°) (Found: C, 71·6; H, 8·2. Calc. for $C_{23}H_{32}O_5$: C, 71·1; H, 8·3%), $\nu_{max.}$ 1735, 1705, and 1680sh cm^{-1}, τ 9·25 (3H, s), 8·71 (3H, s), 7·98 (6H, s), 5·25 (1H, t, *J* 8 Hz), 4·84 (1H, m), and 4·75 (1H, m).

3β,17β-*Diacetoxy*-4α,5α-*epoxyandrostan*-11-*one* (1; R^1 = Ac, R^2 = O).—3β,17β-Diacetoxyandrost-4-en-11-one [14] (520 mg) in dry benzene (10 ml) was treated with *m*-chloroperbenzoic acid (800 mg) at room temperature overnight. The solution was diluted with ethyl acetate, washed thoroughly with aqueous ferrous sulphate, dil. hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried, and evaporated. The product was chromatographed on alumina. Elution with 50% ether–light petroleum gave 3β,17β-*diacetoxy*-4α,5α-*epoxyandrostan*-11-*one* (260 mg) which crystallized from acetone–light petroleum as prisms, m.p. 157—158°, $[\alpha]_D^{20}$ +56° (*c* 0·25) (Found: C, 68·8; H, 8·2. $C_{23}H_{32}O_6$ requires C, 68·3; H, 8·0%), $\nu_{max.}$ 1735 and 1705 cm^{-1}, τ 9·15 (3H, s), 8·68 (3H, s), 8·00 (3H, s), 7·95 (3H, s), 7·13 (1H, s), 5·22 (1H, m), and 5·10 (1H, t, *J* 8 Hz).

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[13] D. Baldwin and J. R. Hanson, unpublished work.
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Aromatization Reactions.—(*a*) 17β-Acetoxy-4β,5β-epoxyandrostan-3β-ol (660 mg) was dissolved in a mixture of 48% hydrobromic acid (1·2 ml) and glacial acetic acid (4·8 ml) and heated under reflux for 15 min. The solution was neutralized with sodium hydrogen carbonate and the product (450 mg) was recovered in ether and chromatographed on alumina. Elution with 5% ether–light petroleum gave 17β-bromo-4-methyloestra-1,3,5(10)-triene (40 mg), which did not crystallize. It was identified by its n.m.r. and mass spectra. Elution with 8% ether–light petroleum gave 17β-acetoxy-4-methyloestra-1,3,5(10)-triene (120 mg), m.p. 185° (lit.,[16] 188°), identified by its i.r. spectrum. Elution with 25% ether–light petroleum gave testosterone acetate (70 mg), m.p. 140—142° (lit.,[17] 139—141°), identified by its i.r. spectrum.

(*b*) Similarly 17β-acetoxy-4α,5α-epoxyandrostan-3β-ol (150 mg) gave 17β-acetoxy-4-methyloestra-1,3,5(10)-triene (60 mg) and testosterone acetate (35 mg). 3β,17β-Diacetoxy-4α,5α-epoxyandrostane (120 mg) gave 17β-acetoxy-4-methyloestra-1,3,5(10)-triene (36 mg) and testosterone acetate (10 mg).

(*c*) 3β-Hydroxy-4β,5β-epoxyandrostane-6,17-dione[13] (500 mg) was dissolved in a mixture of 48% hydrobromic acid (0·5 ml) and glacial acetic acid (2 ml) and heated under reflux for 15 min. The solution was poured into water and the product (400 mg) was recovered in chloroform and chromatographed on alumina. Elution with 40% ether–light petroleum gave 1-methyloestra-1,3,5(10)-triene-6,17-dione (50 mg), which crystallized from light petroleum as needles, m.p. 159—161°, $[\alpha]_D^{20}$ +128° (*c* 0·2) {lit.,[3] m.p. 156—158°, $[\alpha]_D^{20}$ +132° (*c* 0·8)}, identified by its i.r. and n.m.r. spectra. Elution with ether gave androst-4-ene-3,6,17-trione (110 mg), which crystallized from ethyl acetate–light petroleum as needles, m.p. 221—223°, $[\alpha]_D^{20}$ +28° (*c* 0·2) {lit.,[18] m.p. 216—217°, $[\alpha]_D^{20}$ +42° (in Me_2CO)] (Found: C, 75·95; H, 7·7. Calc. for $C_{19}H_{24}O_3$: C, 76·0; H, 8·05%), $\nu_{max.}$ 1740, 1690, 1670, and 1605 cm^{-1}, τ 9·07 (3H, s), 8·80 (3H, s), and 3·82 (1H, s). This was identified by comparison with an authentic sample prepared *via* 3β-hydroxy-5α,6α-epoxyandrostan-17-one and 5α-hydroxyandrostane-3,6,17-trione.[18]

(*d*) 3β,17β-Diacetoxy-4α,5α-epoxyandrostan-11-one (200 mg) was dissolved in a mixture of 48% hydrobromic acid (1 ml) and glacial acetic acid (4 ml) and heated under reflux for 30 min. The solution was poured into aqueous sodium hydrogen carbonate and the product was recovered in ethyl acetate and chromatographed on alumina. Elution with 10% ether–light petroleum gave 17β-*acetoxy*-4-*methyl*-*oestra*-1,3,5(10)-*trien*-11-*one* (3; R = O) (20 mg), which crystallized from light petroleum as prisms, m.p. 183—184°, $[\alpha]_D^{20}$ +114° (*c* 0·04) (Found: C, 77·5; H, 7·9. $C_{21}H_{26}O_3$ requires C, 77·3; H, 8·0%), $\nu_{max.}$ 1730, 1705, and 1600 cm^{-1}, τ 8·93 (3H, s), 7·96 (3H, s), 7·79 (3H, s), 5·30 (2H, m), and 2·80 (3H, m).

Deuteriation Experiments.—(*a*) 17β-Acetoxy-4β,5β-epoxyandrostan-3-one (250 mg) in methan[^{2}H]ol (2 ml) was treated with sodium borodeuteride (100 mg) for 1 h. The solution was acidified with a few drops of acetic [^{2}H]acid and diluted with deuterium oxide, and the product was recovered in ether to give 17β-acetoxy-4β,5β-epoxy[3α-^{2}H]-androstan-3β-ol (150 mg). The deuteriated steroid (125 mg) was dissolved in a mixture of 48% hydrobromic acid (1 ml) and glacial acetic acid (4 ml) and heated under reflux for 15 min. The product was neutralized with aqueous sodium hydrogen carbonate and recovered in ether. Chromatography on alumina afforded 17β-acetoxy-4-methyl[1-^{2}H]-oestra-1,3,5(10)-triene, m.p. 185—187°, $\nu_{max.}$ 1725 and 850 cm^{-1} (undeuteriated material 1725, 790, and 745 cm^{-1}), τ (CCl_4) 9·17 (3H, s), 8·00 (3H, s), 7·81 (3H, s), 5·41 (1H, t, *J* 8 Hz), and 3·19 (2H, s) [undeuteriated material 3·19 (2H, m) and 3·07 (1H, m)].

(*b*) 17β-Acetoxyandrosta-1,4-dien-3-one (250 mg) in methan[^{2}H]ol (2 ml) was treated with sodium borodeuteride (100 mg) for 1 h. The solution was treated with acetic [^{2}H]acid and poured into deuterium oxide and the steroid was recovered in ether. The crude product was heated under reflux in a mixture of 48% hydrobromic acid (1 ml) and glacial acetic acid (4 ml) for 15 min. The solution was neutralized with aqueous sodium hydrogen carbonate and the steroid was recovered in ether and chromatographed on alumina. Elution with 10% ether–light petroleum gave 17β-acetoxy-4-methyl[1-^{2}H]oestra-1,3,5(10)-triene (35 mg), m.p. 186—187°, i.r. and n.m.r. identical with those of the sample prepared in (*a*).

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