Aromatization of 7β,17β-Diacetoxy-4-methyleneandrost-5-ene

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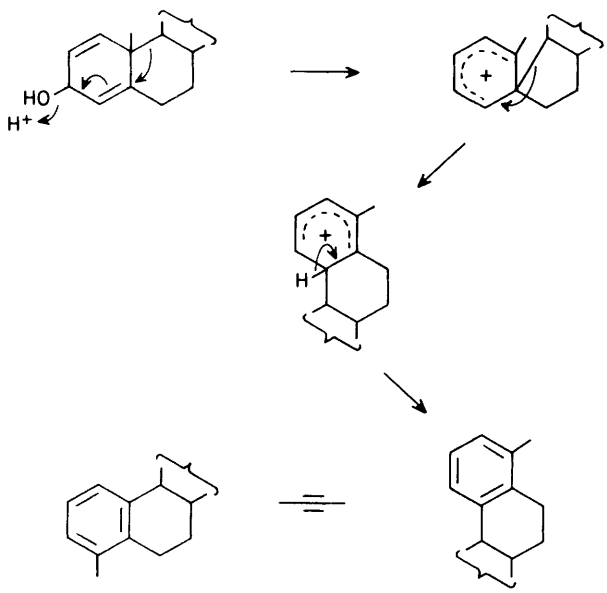
Treatment of 7β,17β-diacetoxy-4-methyleneandrost-5-ene with hydrobromic acid in glacial acetic acid affords 17β-acetoxy-1,4-dimethyloestra-1,3,5(10)-triene rather than an anthrasteroid. The incorporation of deuterium from deuterium bromide and deuterioacetic acid on the C-4 methyl group is consistent with a methyl group migration from C-10 to C-1 during the rearrangement. A minor amount of 17β-acetoxy-3,4-dimethyloestra-1,3,5(10)-triene is also formed in the rearrangement.

The rearrangement reactions of steroids containing two double bond equivalents and a carbocation source can lead to the aromatization of either rings A or B with the formation of oestratrienes or anthrasteroids.[1] Labelling studies have shown that these aromatization reactions follow a pathway involving a spiran (see the Scheme) in the majority of cases. Surprisingly, steroids such as (**1**) functionalized on ring B afford[2] predominantly oestratrienes rather than anthrasteroids on treatment with hydrobromic acid in glacial acetic acid. Steroids bearing the double bond equivalents and the carbocation source on ring A and also a 4-alkyl substituent [*e.g.* (**2**)], which would block aromatization by the spiranic pathway, still undergo aromatization but by a different route involving a methyl group migration affording in this case, 17β-acetoxy-1,4-dimethyloestra-1,3,5(10)-triene (**3**).[3] It has been the object of the present work to examine the influence of a 'blocking' C-4 substituent on the aromatization of a steroid bearing the initiating group on ring B to see if this favoured the anthrasteroid reaction or the alternative aromatization pathways of ring A.



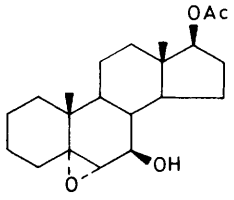
Scheme.

Treatment of dehydroisoandrosterone (**4**) with catechol chlorophosphite in pyridine followed by iodine[4] gave a high yield of 3β-iodoandrost-5-en-17-one (**5**)[5] from which the iodine was removed with zinc and acetic acid to afford androst-5-en-17-one (**6**).[6] Oxidation of the latter with t-butyl chromate gave androst-5-ene-7,17-dione (**7**).[7] Methylenation with dimethoxymethane and phosphorus oxychloride[8] gave 4-methyleneandrost-5-ene-7,17-dione (**8**) [$\lambda_{max.}$ 260 nm, log ε 4.05; δ 4.9 and 5.1 (=CH_2) and 5.9 (6-H)]. Reduction of the dione with methanolic sodium borohydride afforded a separable mixture of the 17β-alcohol (**9**), identified as its acetate, and the 7-epimeric 7,17-diols (**10**) and (**11**) in which the 7β-alcohol predominated. The stereochemistry of the 7-alcohols was assigned from the multiplicity of the 7-H resonances and the magnitude of the 7-H:8-H coupling constants [*J* 3.5 Hz in (**10**); *J* 8 Hz in (**11**)].

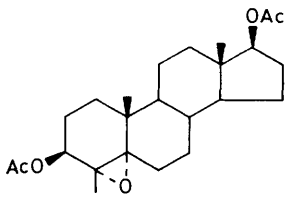
The major diol (**11**) was converted into the diacetate (**12**) with acetic anhydride in pyridine. A small amount of the 7-monoacetate (**13**) was also obtained. Treatment of the diacetate (**12**) with hydrobromic acid in glacial acetic acid for 15 min under reflux gave two aromatic steroids which were separated chromatographically. The first to be eluted was the major product. It was identified as 17β-acetoxy-1,4-dimethyloestra-1,3,5(10)-triene (**3**) from its ^{1}H n.m.r. spectrum and further characterized by hydrolysis to its crystalline 17β-alcohol.[9] A minor product, which was also obtained in previous work,[2] was 17β-acetoxy-3,4-dimethyloestra-1,3,5(10)-triene (**14**). We were unable to isolate any anthrasteroids.

Some insight into the mechanism of the dienol–benzene rearrangement has been obtained by deuteriation studies.[10] The rearrangement of 7β,17β-diacetoxy-4-methyleneandrost-5-ene (**12**) was repeated in the presence of deuterium bromide and deuterioacetic acid. The sites of the labels in (**3**) and (**14**) were established by ^{2}H n.m.r. studies. The methyl group resonances of 17β-hydroxy-1,4-dimethyloestra-1,3,5(10)-triene have been assigned previously [δ 2.31 (1-Me); δ 2.23 (4-Me)].[3] Irradiation of the C-4 methyl group led to a nuclear Overhauser enhancement (9%) of a two-proton multiplet at δ 2.62 which was therefore assigned to 6-H. Analysis of coupling constants and analogies with other aromatic steroids[11] suggested that signals at δ 1.18 and 1.85 might be assigned to 7-H. The ^{2}H n.m.r. spectra of the alcohol and the corresponding 17β-acetate showed a significant incorporation of deuterium into the C-4 methyl group, the aromatic protons, and at C-6 and C-7. However because the 6-H resonances were overlapping, it was not possible to distinguish the stereochemistry of the label at C-6. The label was approximately equally distributed between 7α-H and 7β-H. The ^{2}H n.m.r. spectrum of the 17β-acetoxy-3,4-dimethyloestra-1,3,5(10)-triene (**14**) contained resonances at $\delta_{^2H}$ 1.35 and 1.99 (7α-H and 7β-H), 2.15 and 2.28 (both 3- and 4-Me, approximately equal labelling), 2.67 (6β-H), as well as at $\delta_{^2H}$ 7.15 (ArH). There was a shoulder at δ 2.77 indicating some labelling at 6α-H.

In conclusion we have shown that despite the presence of a 'blocking' group, aromatization of ring A still takes precedence over anthrasteroid formation. The pattern of incorporation of deuterium into the 17β-acetoxy-1,4-dimethyloestra-1,3,5(10)-triene is compatible with a methyl group migration from C-10 to



(1)



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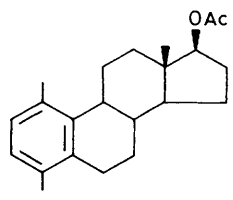

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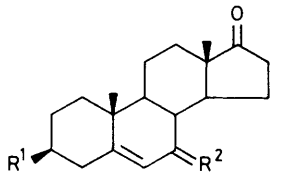
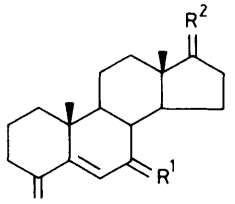
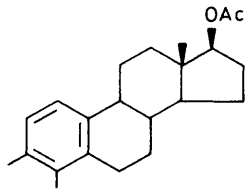


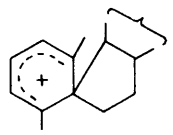
(4) R^1 = OH, R^2 = H
(5) R^1 = I, R^2 = H_2
(6) R^1 = H, R^2 = H
(7) R^1 = H, R^2 = O



(8) R^1 = R^2 = O
(9) R^1 = O, R^2 = α-H, β-OH
(10) R^1 = α-OH, β-H; R^2 = α-H, β-OH
(11) R^1 = R^2 = α-H, β-OH
(12) R^1 = R^2 = α-H, β-OAc
(13) R^1 = α-H, β-OAc; R^2 = α-H, β-OH



(14)



(15)

C-1. The presence of deuterium on both aromatic methyl groups of 17β-acetoxy-3,4-dimethyloestra-1,3,5(10)-triene (**14**) supports the intervention of the symmetrical ion (**15**) in the pathway which we proposed earlier[3] for the formation of this minor product.

Experimental

General Experimental Details.—Light petroleum refers to the fraction b.p. 60—80 °C. Silica for chromatography was Merck 9385. Extracts were dried over sodium sulphate. N.m.r. spectra (^{1}H and ^{2}H) were determined on a Bruker WH 360 spectrometer for solutions in chloroform. I.r. spectra were recorded as Nujol mulls.

4-Methyleneandrost-5-ene-7,17-dione (**8**) was prepared by the method of Annen *et al.*[8] It had m.p. 131—132 °C, $\lambda_{max.}$ 260 nm (log ε 4.05) [lit.,[8] m.p. 132 °C, $\lambda_{max.}$ 260 nm (log ε 4.05)], $\nu_{max.}$ 3 080, 1 740, 1 655, 1 625, and 1 605 cm^{-1} δ(90 MHz) 0.89 (3 H, s, 18-H_3), 1.14 (3 H, s, 19-H_3), 4.9 and 5.1 (each 1 H, m, *w*/2 4 Hz, 4-=CH_2), and 5.9 (1 H, s, 6-H).

Reduction of 4-*Methyleneandrost*-5-*ene*-7,17-*dione* (**8**).—The steroid (900 mg) in methanol (25 ml) was treated with sodium borohydride (100 mg) at 0 °C for 1 h. Acetic acid (0.5 ml) was added and the solvent was evaporated. The residue was taken up in ethyl acetate, washed consecutively with aqueous sodium hydrogen carbonate and water and the extract was dried. The solvent was evaporated and the residue chromatographed on silica. Elution with 20% ethyl acetate–light petroleum gave 17β-*hydroxy*-4-*methyleneandrost*-5-*en*-7-*one* (**9**) (350 mg) which crystallized from ethyl acetate–light petroleum as needles, m.p. 117—120 °C (Found: C, 75.6; H, 9.5. $C_{20}H_{28}O_2$·H_2O requires C, 75.4; H, 9.50%); $\nu_{max.}$ 3 250, 1 650, 1 625, 905, and 740 cm^{-1}; δ 0.78 (3 H, s, 18-H_3), 1.11 (3 H, s, 19-H_3), 3.62 (1 H, t, *J* 8.1 Hz, 17-H), 4.9 and 5.04 (each 1 H, t, *J* 2.3 Hz, 4-=CH_2), and 5.82 (1 H, s, 6-H). Elution with 40% ethyl acetate–light petroleum gave 7β,17β-*dihydroxy*-4-*methyleneandrost*-5-*ene* (**11**) (200 mg) which crystallized from ethyl acetate–light petroleum as flakes, m.p. 89—92 °C (Found: C, 77.9; H, 10.3. $C_{20}H_{30}O_2$·$\frac{1}{2}H_2O$ requires C, 77.1; H, 10.0%); $\nu_{max.}$ 3 300, 1 625, and 730 cm^{-1}; δ 0.78 (3 H, s, 18-H_3), 0.97 (3 H, s, 19-H_3), 3.65 (1 H, t, *J* 8.5 Hz, 17-H), 3.91 (1 H, dd, *J* 2.4 and 8.0 Hz, 7-H), 4.69 and 4.86 (each 1 H, t, *J* 2.3 Hz, 4-=CH_2), and 5.45 (1 H, d, *J* 2.4 Hz, 6-H). Further elution gave 7α,17β-*dihydroxy*-4-*methyleneandrost*-5-*ene* (**10**) (70 mg) which crystallized from ethyl acetate–light petroleum as needles, m.p. 142—144 °C (Found: C, 76.8; H, 10.2. $C_{20}H_{30}O_2$·$\frac{1}{2}H_2O$ requires C, 77.1; H, 10.0%); $\nu_{max.}$ 3 400, 1 620, and 740 cm^{-1}; δ 0.76 (3 H, s, 18-H), 0.91 (3 H, s, 19-H_3), 3.78 (1 H, t, *J* 8.4 Hz, 17-H), 3.97 (1 H, dd, *J* 3.5 and 5.2 Hz, 7-H), 4.75 and 4.89 (each 1 H, t, *J* 2.3 Hz, 4-=CH_2), and 5.82 (1 H, d, *J* 5.2 Hz, 6-H).

Acetylation of the Reduction Products.—The steroid (2—400 mg) was treated with acetic anhydride (2 ml) in pyridine (5 ml) at room temperature overnight. The mixture was poured into dilute hydrochloric acid and the steroids recovered in ethyl acetate. The extracts were washed with aqueous sodium hydrogen carbonate, water and dried. The solvent was evaporated and the residue crystallized or chromatographed on silica eluting with ethyl acetate–light petroleum.

(*a*) 7β,17β-*Diacetoxy*-4-*methyleneandrost*-5-*ene* (**12**). This crystallized from ethyl acetate–light petroleum as needles, m.p. 136—138 °C (Found: C, 74.4; H, 8.9;. $C_{24}H_{34}O_4$ requires C, 74.6; H, 8.9%); $\nu_{max.}$ 1 730, 1 625, 1 265, and 1 240 cm^{-1}; δ 0.82 (3 H, s, 18-H_3), 0.99 (3 H, s, 19-H_3), 2.04 (6 H, s, OAc), 4.69 (1 H, t, *J* 7 Hz, 17-H), 4.4 and 4.8 (each 1 H, t, *J* 1 Hz, 4-=CH_2), 5.12 (1 H, dd, *J* 8.4 and 2.4 Hz, 7-H), and 5.37 (1 H, d, *J* 2.4 Hz, 6-H). The 7β-monoacetate of 7β,17β-dihydroxy-4-methyleneandrost-5-ene, crystallized from ethyl acetate–light petroleum as needles, m.p. 184—186 °C, $\nu_{max.}$ 3 250, 1 735, and 1 235 cm^{-1}; δ(90 MHz) 0.78 (3 H, s, 18-H_3), 0.99 (3 H, s, 19-H_3), 2.0 (3 H, s, OAc), 3.58 (1 H, t, *J* 8.0 Hz, 17-H), 4.64 and 4.78 (each 1 H, d, *J* 2.2 Hz, 4-=CH_2), 5.08 (1 H, dd, *J* 2.4 and 8.3 Hz, 7-H), and 5.32 (1 H, d, *J* 2.4 Hz, 6-H).

(*b*) 7α,17β-*Diacetoxy*-4-*methyleneandrost*-5-*ene*. This was an oil, $\nu_{max.}$ 1 735 and 1 240 cm^{-1}; δ(90 MHz) 0.8 (3 H, s, 18-H_3), 0.93 (3 H, s, 19-H_3), 2.03 (6 H, s, OAc), 4.7 and 4.8 (3 H, m, 4-

=CH_2 and 17-H), 5.08 (1 H, t, 3 Hz, 7-H), and 5.74 (1 H, d, *J* 3 Hz, 6-H).

Reaction of 7β,17β-*Diacetoxy*-4-*methyleneandrost*-5-*ene with Hydrobromic Acid.*—The steroid (210 mg) in glacial acetic acid (5 ml) was heated with hydrobromic acid (48%; 0.5 ml) under reflux for 15 min. The reaction mixture was cooled, poured into aqueous sodium hydrogen carbonate and the product was recovered in ethyl acetate and chromatographed on silica. Elution with 3% ethyl acetate–light petroleum gave 17β-acetoxy-1,4-dimethyloestra-1,3,5(10)-triene (**3**) (170 mg) as an oil, (lit.,[3] oil), $\nu_{max.}$ 1 730, 1 235, and 805 cm^{-1}; δ 0.86 (3 H, s, 18-H_3), 2.05 (3 H, s, OAc), 2.18 (3 H, s, 4-Me), 2.31 (3 H, s, 1-Me), 4.72 (1 H, t, *J* 7.5 Hz, 17-H), 6.98 (2 H, s, 2- and 3-H). Further elution gave 17β-acetoxy-3,4-dimethyloestra-1,3,5(10)-triene (**14**) (5 mg) as needles, m.p. 175—178 °C (lit.,[12] 172—174 °C) δ 0.81 (3 H, s, 18-H_3), 2.05 (3 H, s, OAc), 2.13 (3 H, s, 4-Me), 2.26 (3 H, s, 3-Me), 4.68 (1 H, t, *J* 7.8 Hz, 17-H), and 7.0 and 7.1 (each 1 H, d, *J* 7.9 Hz, 1-H and 2-H).

Hydrolysis of 17β-*Acetoxy*-1,4-*dimethyloestra*-1,3,5(10)-*triene.*—The steroid (130 mg) in methanol (4 ml) was heated with potassium hydroxide (180 mg) under reflux for 30 min. The mixture was poured into water, acidified with dilute hydrochloric acid and the product was recovered in ethyl acetate. The solvent was evaporated and the residue was chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave 17β-hydroxy-1.4-dimethyloestra-1,3,5(10)-triene, m.p. 74 °C (lit.,[9] 74 °C). $\nu_{max.}$ 3 400 and 800 cm^{-1}; δ 0.81 (3 H, s, 18-H_3), 2.16 (3 H, s, 4-Me), 2.28 (3 H, s, 1-Me), 3.76 (1 H, t, *J* 7.5 Hz, 17-H), and 6.89 (2 H, s, 2- and 3-H).

Deuteriation Reaction.—The aromatization reaction was repeated as above with the 7β,17β-diacetate (380 mg) in [^{2}H]acetic acid (8 ml) and [^{2}H]hydrobromic acid (1 ml) to afford 17β-acetoxy-1,4-dimethyloestra-1,3,5(10)-triene (180 mg), $\delta_{^2H}$ 1.25, 1.87, 2.20, 2.69, and 6.97. Hydrolysis of the triene (40 mg) gave 17β-hydroxy-1,4-dimethyloestra-1,3,5(10)-triene (30 mg), $\delta_{^2H}$ 1.19, 1.85, 2.20, 2.65, and 7.00. 17β-Acetoxy-3,4-dimethyloestra-1,3,5(10)-triene (15 mg) had $\delta_{^2H}$ 1.35, 1.9, 2.15, 2.28, 2.67, and 7.1. The ^{1}H n.m.r. spectra showed a decrease in the 4-Me signal in (**3**) and the corresponding alcohol. The ^{1}H spectrum of (**14**) showed a decrease in both methyl signals.

Acknowledgements

We thank Dr. R. Carman for discussions, Dr. Avent for the n.m.r. spectra and the World University Service for financial support for A. T.

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Received 3rd *July* 1987; *Paper* 7/1184