

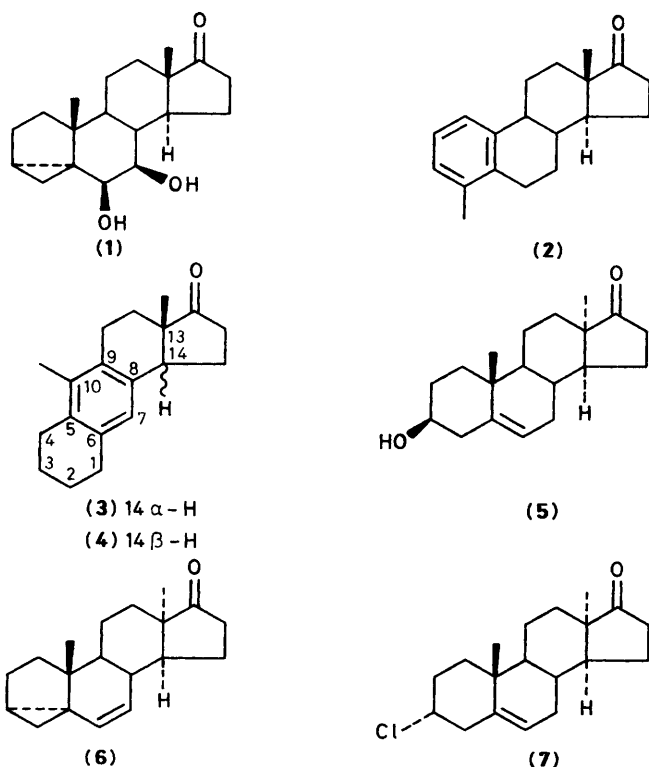
An Aromatization Reaction of a 13 α -Methyl Steroid

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Whilst treatment of 6 β ,7 β -dihydroxy-3 α ,5 α -cycloandrostan-17-one with hydrogen bromide in glacial acetic acid affords, *inter alia*, the 13 β ,14 β -*cis*-c/d-fused anthrasteroid, the corresponding 13 α -methyl epimer affords the enantiomeric 13 α ,14 α -anthrasteroid without isomerization at C-14. The stereochemistry of the anthrasteroid was established by n.O.e. measurements. Repetition using deuterium bromide led to extensive deuteration. The major aromatic steroid that was formed in each case was an estratriene.

Under acidic conditions suitably substituted polyunsaturated steroids can either undergo a dienol-benzene rearrangement of ring A to afford an estratriene [e.g. (2)] or rearrangement of ring B to form an anthrasteroid [e.g. (4)].¹ Mechanistically the reaction pathways show some similarities in that they both involve a spiran intermediate at C-5 although this differs in its structure for each pathway. However, studies in the ergosterol series have shown² that anthrasteroids which are epimeric at C-14 may be formed depending on the nature of the acid catalyst. A c/d *trans*-fused anthrasteroid is the major product obtained³ when the adduct of a steroidal 5,7-diene and 4-phenyl-4*H*-1,2,4-triazole-3,5-dione is treated with boron trifluoride-diethyl ether. It has been suggested⁴ that it is possible to distinguish between a c/d *cis*-fused anthrasteroid and a c/d *trans*-fused epimer by ¹H n.m.r. spectroscopy since in the latter the C-13 methyl (18-H₃) lies within the shielding zone of the aromatic ring and hence resonates at higher field (δ ca. 0.55 vs. δ ca. 0.95). However, the X-ray structure reported³ for a *trans*-anthrasteroid does not show C-18 particularly close to the aromatic ring. In this paper we consider the influence of the c/d ring-junction stereochemistry on the outcome of the anthrasteroid rearrangement.

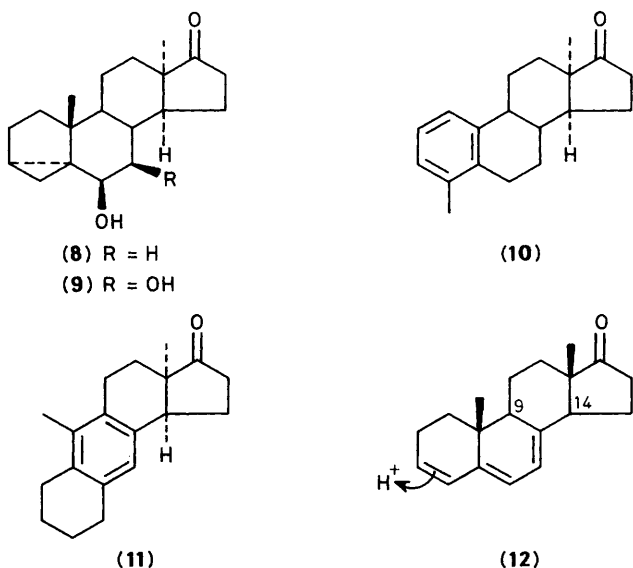


Although treatment of steroids containing double-bond equivalents on ring B with hydrogen bromide in glacial acetic acid surprisingly affords⁵ substantial amounts of 4-methylestratrienes nevertheless these are, on occasions accompanied by small amounts of less well defined anthrasteroid fractions recognizable by their single-proton resonances at δ ca. 6.8 (cf. estratrienes δ 7.0–7.2⁶). Thus when 6 β ,7 β -dihydroxy-3 α ,5 α -cycloandrostan-17-one (1)⁷ was used as a substrate, the aromatic products were 4-methylestra-1,3,5(10)-trien-17-one (2) and the anthrasteroid (4). Although the position of the 18-H₃ proton resonance in the ¹H n.m.r. spectrum of compound (4) suggested that it possessed a 14 β -H *cis* c/d geometry, definitive evidence was obtained by nuclear Overhauser enhancement (n.O.e.) ¹H n.m.r. studies. Irradiation of the 18-H₃ signal produced a 9% n.O.e. effect on a double doublet at δ 2.99 (*J* 7.2 and 10 Hz). This same signal, and a broad two-proton triplet δ 2.76 (*J* 5.5 Hz), were enhanced (13% and 12% respectively) on irradiation of the aromatic singlet, δ 6.84. The signal at δ 2.99 must therefore be assigned to 14 β -H. Only a *cis* c/d ring junction as in structure (4) can accommodate these n.O.e. results. Irradiation of the aromatic methyl, δ 2.11, produced a 21% enhancement of a four-proton multiplet at δ 2.66 which is therefore assigned to 4-H and 11-H.

When the reaction was repeated using deuterium bromide in deuterioacetic acid, the anthrasteroid (4) was extensively deuterated. Although it was not possible unambiguously to assign all the ²H and ¹³C resonances, comparison of the labelled and unlabelled species revealed the presence of deuterium on six methylenes [δ 22.93 (C-15), 23.80 (C-3), 27.31, 29.68, 30.18 (C-1, C-4, and C-11), 37.01 (C-16)] and the methine [δ 47.39 (C-14)] as well as the aromatic C-H (δ 127.47). Two aliphatic methylenes [δ 23.14 and 26.80 (C-2 and C-12)] and the two C-methyl groups [δ 14.35 and 19.86 (C-18 and C-19)] did not contain significant amounts of deuterium. The ²H n.m.r. spectrum contained signals at δ 6.87 (Ar-²H), 2.97 (13-²H), and 2.72 (1-²H) and further resonances at 2.63, 2.38, 2.31, 1.79, and 1.73. Because of the extent to which these overlapped, it was not possible to draw conclusions on the amount of deuterium at the particular centres.

A convenient method of epimerizing androstanes at C-13 involves the thermal isomerization of 17-hydroxyiminoacetates.⁸ Thus dehydroisoandrosterone (3 β -hydroxyandrost-5-en-17-one) was converted into its 13 α -methyl epimer (5). Treatment of the 3 β -alcohol with triphenylphosphine-carbon tetrachloride gave the Δ^6 -3 α ,5 α -cyclosteroid (6) together with the 3 α -chloride (7). Alternatively 13 α -dehydroisoandrosterone (5) was converted into its toluene-*p*-sulphonate and the latter was solvolysed to form the 6 β -hydroxy-3 α ,5 α -cyclosteroid (8). Dehydration of this with alumina in refluxing xylene gave the Δ^6 -3,5-cyclosteroid (6). Reaction of compound (6) with osmium tetroxide gave the 6 β ,7 β -glycol (9). The stereochemistry of

the glycol followed from the magnitude of the 6-H-7-H and 7-H-8-H coupling constants (J 3.3 and 10.0 Hz). A selective population-transfer ^1H n.m.r. experiment linked the 7-H signal to a quartet (δ 1.62, J 10.0 Hz) which was assigned to 8 β -H.



Surprisingly, treatment of the diol (9) with hydrogen bromide in glacial acetic acid gave predominantly 4-methyl-13 α -estra-1,3,5(10)-trien-17-one (10) and only a small amount of an anthrasteroid (11). This latter product possessed an identical 360 MHz ^1H n.m.r. spectrum with that of the compound obtained from the normal 13 β -methyl series. It was, however, enantiomeric with it and hence it had retained the *cis* C/D geometry.

In conclusion we have shown that the anthrasteroid which is formed under the hydrogen bromide-catalysed aromatization conditions is the C/D *cis*-isomer. A *cis*-fused hydrindanone is more stable than its *trans*-fused isomers.⁹ The isomerization at C-14 in the case of the C/D *trans*-fused steroid may be related to the very easy formation of a carbocation at this centre. If a triene such as (12) is involved in the rearrangement, protonation at C-3 may lead to either a $\Delta^{4,6,8}$ - or a $\Delta^{4,6,8(14)}$ -triene. Rearrangement *via* the latter could result in the formation of the more stable *cis* C/D ring fusion. The formation of relatively small amounts of the anthrasteroids compared with the ergostane series may be associated with the homoconjugative destabilizing effect of a C-17 carbonyl group on a C-14 carbocation involved in the aromatization. Although the deuterium labelling is compatible with the currently accepted mechanism¹ for the anthrasteroid reaction, there are a number of additional reactions that may occur with this particular substrate that make the result difficult to interpret in detail.

Experimental

General Experimental Details.—Light petroleum refers to the fraction with b.p. 60–80 °C. Silica for chromatography was Merck 9385. Extracts were dried over sodium sulphate. ^1H N.m.r. spectra were determined at 90 MHz on a Perkin-Elmer R 32 spectrometer for solutions in deuteriochloroform. The n.o.e. difference spectra, ^2H and ^{13}C spectra, were determined on a Bruker WH 360 spectrometer. I.r. spectra were recorded as Nujol mulls on a Perkin-Elmer 59 spectrophotometer. Optical rotations were determined in chloroform on a Perkin-Elmer 241 polarimeter.

Action of Hydrobromic Acid on 6 β ,7 β -Dihydroxy-3 α ,5 α -cyclo-androstan-17-one (1).—The steroid (1)⁷ (300 mg) was heated under reflux in glacial acetic acid (6 ml) with 48% hydrobromic acid (0.75 ml) for 15 min. The mixture was cooled and the solution was neutralized with sodium hydrogen carbonate. The products were recovered in ethyl acetate and chromatographed on silica. Elution with 1% ethyl acetate–light petroleum gave 1(10 \rightarrow 6)-*abeo*-14 β H-androsta-5,7,9-trien-17-one (4) (20 mg), which crystallized from acetone–light petroleum as plates, m.p. 139–145 °C; $[\alpha]_{\text{D}}^{30} +122^\circ$ (lit.,⁹ m.p. 138–140 °C; $[\alpha]_{\text{D}}^{22} +142^\circ$); ν_{max} 1 735 cm^{-1} ; δ 1.06 (3 H, s, 18-H₃), 2.11 (3 H, s, ArMe), and 6.84 (1 H, s, ArH).

Further elution gave 4-methylestra-1,3,5(10)-trien-17-one (2) (100 mg), which crystallized from acetone–light petroleum as cubes, m.p. 188–190 °C (lit.,⁹ 190–192 °C), and was identified by its n.m.r. spectrum. Repetition using 6 β ,7 β -dihydroxy-3 α ,5 α -cycloandrostan-17-one (1) (200 mg) in [^2H]acetic acid (2 ml) and [^2H]hydrobromic acid (0.5 ml) gave the [^2H]anthrasteroid (15 mg) and [^2H]-4-methylestra-1,3,5(10)-trien-17-one (60 mg). For spectral details see text.

Reaction of 3 β -Hydroxy-13 α -androst-5-en-17-one (5) with Triphenylphosphine and Carbon Tetrachloride.—A solution of 3 β -hydroxy-13 α -androst-5-en-17-one (5) (3.4 g)⁸ and triphenylphosphine (6.8 g) in a mixture of dry pyridine (4 ml) and carbon tetrachloride (75 ml) was heated under reflux for 5 h. After cooling, the solution was decanted and the brown solid was dissolved in chloroform. The combined organic phases were washed successively with dil. hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and dried. The solvent was evaporated off and the residue was chromatographed on silica. Elution with 1% ethyl acetate–light petroleum gave 3 α ,5 α -cyclo-13 α -androst-6-en-17-one (6) (1.5 g) as an oil, ν_{max} 3 020, 1 735, 1 640, and 720 cm^{-1} ; δ 0.78 (3 H, s, 18-H₃), 1.00 (3 H, s, 19-H₃), 5.26 (1 H, dd, J 2 and 10 Hz, 7-H), and 5.66 (1 H, dd, J 1 and 10 Hz, 6-H).

Further elution gave 3 α -chloro-13 α -androst-5-en-17-one (7) (900 mg), which crystallized from methanol as cubes, m.p. 167–169 °C (Found: C, 74.4; H, 8.9. C₁₉H₂₇ClO requires C, 74.4; H, 8.9%). ν_{max} 1 740, 815, 800, and 745 cm^{-1} ; δ 0.88 (3 H, s, 18-H₃), 1.02 (3 H, s, 19-H₃), 4.47 (1 H, t, J 3 Hz, 3-H), and 5.38 (1 H, d, J 4 Hz, 6-H).

6 β ,7 β -Dihydroxy-3 α ,5 α -cyclo-13 α -androstan-17-one (9).—A solution of 3 α ,5 α -cyclo-13 α -androst-6-en-17-one (6) (950 mg) in pyridine (10 ml) was treated with a solution of osmium tetroxide (1 g) in pyridine (5 ml) at room temperature for 2 h. A solution of sodium metabisulphite (2 g) in water (5 ml) was added and the solution was stirred for 1 h. The solution was diluted with water and the steroid was recovered in methylene dichloride and chromatographed on silica. Elution with 20% ethyl acetate–light petroleum gave 6 β ,7 β -dihydroxy-3 α ,5 α -cyclo-13 α -androstan-17-one (9) (900 mg), which crystallized from acetone as cubes, m.p. 165–167 °C (Found: C, 74.9; H, 9.2. C₁₉H₂₈O₃ requires C, 75.0; H, 9.3%). ν_{max} 3 500, 3 080, and 1 735 cm^{-1} ; δ 0.37 (1 H, dd, J 3 and 5 Hz), 0.55 (1 H, dd, J 5 Hz), 0.90 (3 H, s, 18-H₃), 1.02 (3 H, s, 19-H₃), 3.21 (1 H, d, J 3.3 Hz, 6-H), and 3.51 (1 H, dd, J 3.3 and 10.0 Hz, 7-H).

6 β -Hydroxy-3 α ,5 α -cyclo-13 α -androstan-17-one (8).—3 β -(*p*-Tolylsulphonyloxy)-13 α -androst-5-en-17-one, prepared from 13 α -dehydroisoandrosterone (3 β -hydroxy-13 α -androst-5-en-17-one (5) with toluene-*p*-sulphonyl chloride in pyridine, crystallized from methanol as needles, m.p. 136–138 °C (Found: C, 70.5; H, 7.9. C₂₆H₃₄O₄S requires C, 70.55; H, 7.7%). ν_{max} 1 730, 1 595, 1 185, and 1 170 cm^{-1} ; δ 0.82 (3 H, s, 18-H₃), 0.98 (3 H, s, 19-H₃), 2.41 (3 H, s, ArMe), 4.3 (1 H, m, w 20 Hz, 3-H), 5.3 (1 H, d, J 4 Hz, 6-H), and 7.3 and 7.8 (each 2 H, J 8 Hz,

ArH). The toluene-*p*-sulphonate (3.5 g) was heated in acetone (50 ml) under reflux with a solution of sodium acetate (7 g) in water (150 ml) for 1 day. The acetone was removed under reduced pressure and the steroids were recovered in ethyl acetate and chromatographed on silica. Elution with 20% ethyl acetate–light petroleum gave 6 β -hydroxy-3 α ,5 α -cyclo-13 α -androstan-17-one (**8**) (1 g), m.p. 205–208 °C (Found: C, 79.2; H, 10.0. C₁₉H₂₈O₂ requires C, 79.1; H, 9.8%); ν_{\max} . 3 500 and 1 735 cm⁻¹; δ 0.38 (1 H, dd, *J* 3 and 5 Hz), 0.45 (1 H, t, *J* 3 Hz), 0.92 (3 H, s, 18-H₃), 1.00 (3 H, s, 19-H₃), and 3.2 (1 H, t, *J* 3 Hz, 6-H).

3 α ,5 α -Cyclo-13 α -androst-6-en-17-one (**6**) (Alternative Preparation).—The above cyclosteroid (**8**) (1 g) was heated with alumina (3 g) in xylene (25 ml) under reflux for 24 h. The alumina was filtered off and thoroughly washed with methylene dichloride. The combined solvents were evaporated off and the residue was chromatographed on silica. Elution with 2% ethyl acetate–light petroleum gave 3 α ,5 α -cyclo-13 α -androst-6-en-17-one (**6**) (700 mg), identical (i.r. and n.m.r.) with the material described previously.

Action of Hydrobromic Acid on 6 β ,7 β -Dihydroxy-3 α ,5 α -cyclo-13 α -androstan-17-one (**9**).—A mixture of the steroid (**9**) (500 mg) in glacial acetic acid (10 ml) was heated under reflux with 48% hydrobromic acid (1.25 ml) for 15 min. The solution was cooled, and neutralized with aqueous sodium hydrogen carbonate. The steroids were recovered in ethyl acetate and chromatographed on silica. Elution with 2% ethyl acetate–light petroleum gave 1(10 \rightarrow 6)*abeo*-13 α -androst-5,7,9-trien-17-one (**11**) (10 mg), which crystallized from ethyl acetate–light petroleum as plates, m.p. 142–144 °C; $[\alpha]_D^{33}$ –131°; ν_{\max} . 1 735 cm⁻¹; δ 1.06 (3 H, s, 18-H₃), 2.11 (3 H, s, ArMe), and 6.84 (1 H, s, ArH) [identical with the spectrum of compound (**4**) described above].

Further elution gave 4-methyl-13 α -estra-1,3,5(10)-trien-17-one (**10**) (300 mg), which crystallized from ethyl acetate–light petroleum as cubes, m.p. 176–178 °C (Found: C, 84.85; H, 9.1. C₁₉H₂₄O requires C, 85.0; H, 9.0%); ν_{\max} . 1 730 cm⁻¹; δ 1.04 (3 H, s, 18-H₃), 2.20 (3 H, s, ArMe), 6.97 (1 H, d, *J* 7.3 Hz, 3-H), 7.05 (1 H, t, *J* 7.6 Hz, 2-H), and 7.15 (1 H, d, *J* 7.8 Hz, 1-H).

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