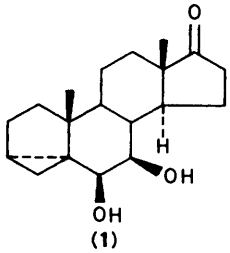
An Aromatization Reaction of a 13α-Methyl Steroid

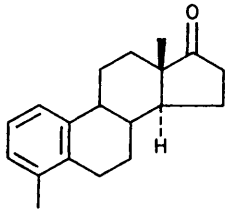
James R. Hanson* and Almaz Truneh
School of Molecular Sciences, University of Sussex, Brighton, Sussex, BN1 9QJ

Whilst treatment of 6β,7β-dihydroxy-3α,5α-cycloandrostan-17-one with hydrogen bromide in glacial acetic acid affords, *inter alia*, the 13β,14β-*cis*-C/D-fused anthrasteroid, the corresponding 13α-methyl epimer affords the enantiomeric 13α,14α-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 deuteriation. The major aromatic steroid that was formed in each case was an estratriene.

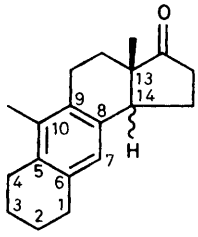
Under acidic conditions suitably substituted polyunsaturated steroids can either undergo a dienol–benzene rearrangement of ring A to afford an estratriene [*e.g.* (**2**)] or rearrangement of ring B to form an anthrasteroid [*e.g.* (**4**)].[1] Mechanistically the reaction pathways show some similarities 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 shown[2] 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 obtained[3] 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 suggested[4] that it is possible to distinguish between a C/D *cis*-fused anthrasteroid and a C/D *trans*-fused epimer by ^{1}H n.m.r. spectroscopy since in the latter the C-13 methyl (18-H_3) 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 reported[3] 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.



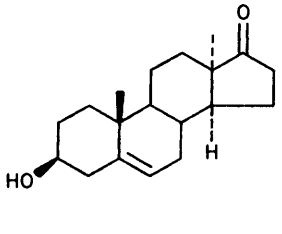
(1)



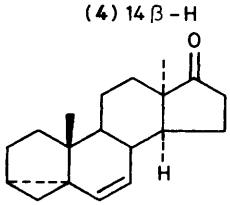
(2)



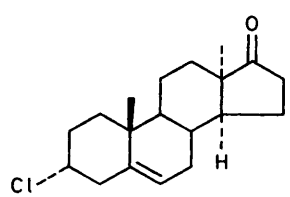
(3) 14α-H
(4) 14β-H



(5)



(6)



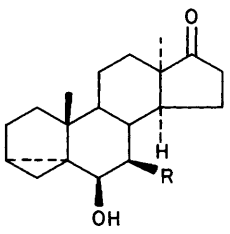
(7)

Although treatment of steroids containing double-bond equivalents on ring B with hydrogen bromide in glacial acetic acid surprisingly affords[5] 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—7.2[6]). Thus when 6β,7β-dihydroxy-3α,5α-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-H_3 proton resonance in the ^{1}H n.m.r. spectrum of compound (**4**) suggested that it possessed a 14β-H *cis* C/D geometry, definitive evidence was obtained by nuclear Overhauser enhancement (n.O.e.) ^{1}H n.m.r. studies. Irradiation of the 18-H_3 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 14β-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.

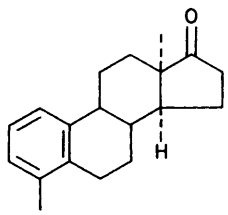
When the reaction was repeated using deuterium bromide in deuterioacetic acid, the anthrasteroid (**4**) was extensively deuteriated. Although it was not possible unambiguously to assign all the ^{2}H and ^{13}C resonances, comparison of the labelled and unlabelled species revealed the presence of deuterium 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 ^{2}H n.m.r. spectrum contained signals at δ 6.87 (Ar-^{2}H), 2.97 (13-^{2}H), and 2.72 (1-^{2}H) 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-hydroxyimino-acetates.[8] Thus dehydroisoandrosterone (3β-hydroxyandrost-5-en-17-one) was converted into its 13α-methyl epimer (**5**). Treatment of the 3β-alcohol with triphenylphosphine–carbon tetrachloride gave the Δ^6-3α,5α-cyclosteroid (**6**) together with the 3α-chloride (**7**). Alternatively 13α-dehydroisoandrosterone (**5**) was converted into its toluene-*p*-sulphonate and the latter was solvolysed to form the 6β-hydroxy-3α,5α-cyclosteroid (**8**). Dehydration of this with alumina in refluxing xylene gave the Δ^6-3,5-cyclosteroid (**6**). Reaction of compound (**6**) with osmium tetraoxide gave the 6β,7β-glycol (**9**). The stereochemistry of

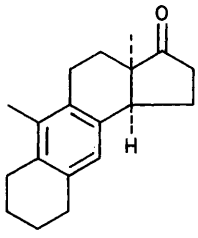
the glycol followed from the magnitude of the 6-H–7-H and 7-H–8-H coupling constants (*J* 3.3 and 10.0 Hz). A selective population-transfer ^{1}H n.m.r. experiment linked the 7-H signal to a quartet (δ 1.62, *J* 10.0 Hz) which was assigned to 8β-H.



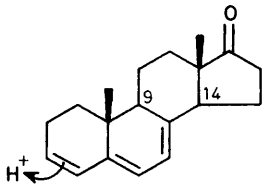
(**8**) R = H
(**9**) R = OH



(**10**)



(**11**)



(**12**)

Surprisingly, treatment of the diol (**9**) with hydrogen bromide in glacial acetic acid gave predominantly 4-methyl-13α-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 ^{1}H n.m.r. spectrum with that of the compound obtained from the normal 13β-methyl series. It was, however, enantiometric 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 mechanism[1] 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. ^{1}H 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, ^{2}H 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 6β,7β-*Dihydroxy*-3α,5α-*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 → 6)-*abeo*-14βH-androsta-5,7,9-trien-17-one (**4**) (20 mg), which crystallized from acetone–light petroleum as plates, m.p. 139—145 °C; $[\alpha]_D^{30}$ +122° (lit.,[9] m.p. 138—140 °C; $[\alpha]_D^{22}$ + 142°); $\nu_{max.}$ 1 735 cm^{-1}; δ 1.06 (3 H, s, 18-H$_3$), 2.11 (3 H, s, Ar*Me*), 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 6β,7β-dihydroxy-3α,5α-cycloandrostan-17-one (**1**) (200 mg) in [^{2}H]acetic acid (2 ml) and [^{2}H]hydrobromic acid (0.5 ml) gave the [^{2}H]anthrasteroid (15 mg) and [^{2}H]-4-methylestra-1,3,5(10)-trien-17-one (60 mg). For spectral details see text.

Reaction of 3β-*Hydroxy*-13α-*androst*-5-*en*-17-*one* (**5**) *with Triphenylphosphine and Carbon Tetrachloride.*—A solution of 3β-hydroxy-13α-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 3α,5α-cyclo-13α-androst-6-en-17(one (**6**) (1.5 g) as an oil, $\nu_{max.}$ 3 020, 1 735, 1 640, and 720 cm^{-1}; δ 0.78 (3 H, s, 18-H$_3$), 1.00 (3 H, s, 19-H$_3$), 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 3α-*chloro*-13α-*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. $C_{19}H_{27}ClO$) requires C, 74.4; H, 8.9%); $\nu_{max.}$ 1 740, 815, 800, and 745 cm^{-1}; δ 0.88 (3 H, s, 18-H$_3$), 1.02 (3 H, s, 19-H$_3$), 4.47 (1 H, t, *J* 3 Hz, 3-H), and 5.38 (1 H, d, *J* 4 Hz, 6-H).

6β,7β-*Dihydroxy*-3α,5α-*cyclo*-13α-*androstan*-17-*one* (**9**).—A solution of 3α,5α-cyclo-13α-androst-6-en-17-one (**6**) (950 mg) in pyridine (10 ml) was treated with a solution of osmium tetraoxide (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 6β,7β-*dihydroxy*-3α,5α-*cyclo*-13α-*androstan*-17-*one* (**9**) (900 mg), which crystallized from acetone as cubes, m.p. 165—167 °C (Found: C, 74.9; H, 9.2. $C_{19}H_{28}O_3$ requires C, 75.0; H, 9.3%); $\nu_{max.}$ 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-H$_3$), 1.02 (3 H, s, 19-H$_3$), 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).

6β-*Hydroxy*-3α,5α-*cyclo*-13α-*androstan*-17-*one* (**8**).—3β-(p-*Tolylsulphonyloxy*)-13α-*androst*-5-*en*-17-*one*, prepared from 13α-dehydroisoandrosterone (3β-hydroxy-13α-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. $C_{26}H_{34}O_4S$ requires C, 70.55; H, 7.7%); $\nu_{max.}$ 1 730, 1 595, 1 185, and 1 170 cm^{-1}; δ 0.82 (3 H, s, 18-H$_3$), 0.98 (3 H, s, 19-H$_3$), 2.41 (3 H, s, Ar*Me*), 4.3 (1 H, m, $w_{\frac{1}{2}}$ 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 6β-*hydroxy*-3α,5α-*cyclo*-13α-*androstan*-17-*one* (**8**) (1 g), m.p. 205—208 °C (Found: C, 79.2; H, 10.0. $C_{19}H_{28}O_2$ requires C, 79.1; H, 9.8%); $\nu_{max.}$ 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-H_3), 1.00 (3 H, s, 19-H_3), and 3.2 (1 H, t, *J* 3 Hz, 6-H).

3α,5α-*Cyclo*-13α-*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 3α,5α-cyclo-13α-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 6β,7β-*Dihydroxy*-3α,5α-*cyclo*-13α-*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 → 6)*abeo*-13α-androsta-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°; $\nu_{max.}$ 1 735 cm^{-1}; δ 1.06 (3 H, s, 18-H_3), 2.11 (3 H, s, Ar*Me*), and 6.84 (1 H, s, ArH) [identical with the spectrum of compound (**4**) described above].

Further elution gave 4-*methyl*-13α-*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. $C_{19}H_{24}O$ requires C, 85.0; H, 9.0%); $\nu_{max.}$ 1 730 cm^{-1}; δ 1.04 (3 H, s, 18-H_3), 2.20 (3 H, s, Ar*Me*), 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).

Acknowledgements

A. T. thanks the World University Service for financial support. We thank Dr. R. Carman (University of Queensland) for helpful discussions.

References

1 D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, London, 1968, pp. 354—355.
2 K. Tsuda, R. Hayatsu, J. A. Steele, O. Tanaka, and E. Mosettig, *J. Am. Chem. Soc.*, 1963, **85**, 1126.
3 N. Bosworth, A. Enke, J. M. Midgeley, C. J. Moore, W. B. Whalley, G. Ferguson, and W. C. Marsh, *J. Chem. Soc., Perkin Trans. 1*, 1977, 805.
4 J. A. Steele, L. A. Cohen, and E. Mosettig, *J. Am. Chem. Soc.*, 1963, **85**, 1134.
5 *e.g.* D. Baldwin and J. R. Hanson, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1941.
6 J. R. Hanson, P. B. Reese, and I. H. Sadler, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2938.
7 J. R. Hanson and A. Truneh, *J. Chem. Soc., Perkin Trans. 1*, 1988, preceding paper.
8 R. B. Boar, F. K. Jetuah, J. F. McGhie, M. S. Robinson, and D. H. R. Barton, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2163; J. P. L. Botts, *Recl. Trav. Chim. Pays-Bas*, 1958, **77**, 1010.
9 N. L. Allinger, *J. Org. Chem.*, 1956, **21**, 915.

Received 23*rd September* 1987; *Paper* 7/1703