The Aromatization of Some 3-Substituted 5α,6α-Epoxysteroids

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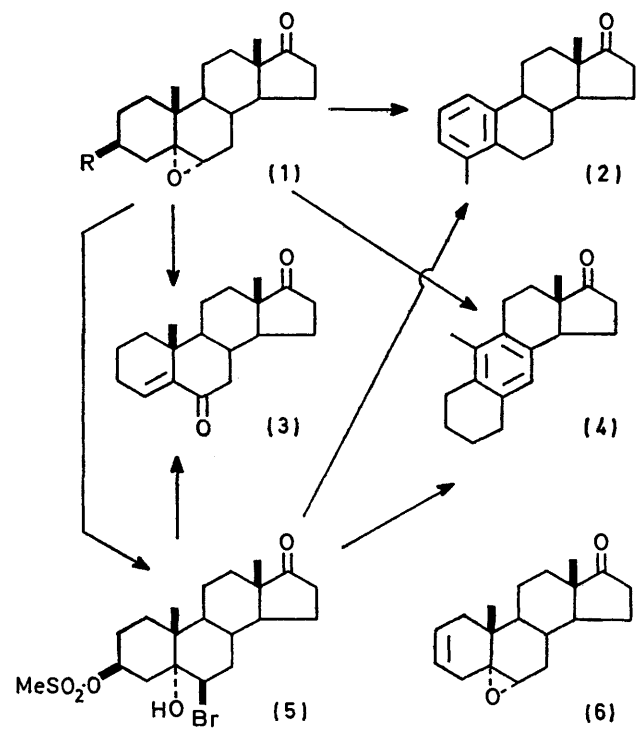
4-Methyloestra-1,3,5(10)-trien-17-one and small amounts of androst-4-ene-6,17-dione and a 17-oxoanthrasteroid are formed when 3-substituted 5α,6α-epoxyandrostan-17-ones are treated with hydrobromic acid in glacial acetic acid.

ANDROST-4-ENE-6,17-DIONE (3) and 4-methyloestra-1,3,5(10)-trien-17-one (2) were formed when the methanesulphonate of 5α,6α-epoxy-3β-hydroxyandrostan-17-one (1; R = $MeSO_2$·O) was treated with lithium bromide in dimethylformamide.[1] The formation of the aromatic product was unexpected, and in view of our interest in the aromatization of other hydroxy-epoxides [2] we have examined the reactions of some 3-substituted 5α,6α-epoxyandrostan-17-ones that lead to aromatization. Libman and Mazur have reported [3] the formation of 4-methyloestra-1,3,5(10)-trienes and anthrasteroids from 3-substituted 5,6-dibromo-steroids under similar conditions.

4-Methyloestra-1,3,5(10)-trien-17-one (2) was formed when the methanesulphonate of 5α,6α-epoxy-3β-hydroxyandrostan-17-one (1; R = $MeSO_2$·O) was treated with 48% hydrobromic acid in glacial acetic acid. It was accompanied by small amounts of androst-4-ene-6,17-dione (3) [4] and the 17-oxoanthrasteroid (4).[5] Treatment of the same methanesulphonate with 48% hydrobromic acid in chloroform at room temperature gave the methanesulphonate of 6β-bromo-3β,5α-dihydroxyandrostan-17-one (5), which in turn gave the aromatic steroids (2) and (4) with 48% hydrobromic acid in refluxing glacial acetic acid. 5α,6α-Epoxy-3α-hydroxyandrostan-17-one was prepared by treating the 3β-methanesulphonate with aqueous dimethylformamide containing lithium carbonate.[6] To ensure that no other reaction had occurred, both this and 5α,6α-epoxy-3β-hydroxyandrostan-17-one were oxidized with 8N-chromium trioxide to give the same 5α-hydroxyandrostane-3,6,17-trione.[7] Treatment of the methanesulphonates of 3α-hydroxy- and 3β-hydroxy-5α,6α-epoxyandrostan-17-one under parallel conditions with lithium bromide and lithium carbonate in dimethylformamide [1] gave the same range of products (t.l.c.), from which 4-methyloestra-1,3,5(10)-trien-17-one and androst-4-ene-6,17-dione were isolated.

The effects of variations in the nature of the 3-substituent were then examined. 4-Methyloestra-1,3,5(10)-trien-17-one (2), the 17-oxoanthrasteroid (4), and androst-4-ene-6,17-dione (3) were formed when 3β-acetoxy- (1; R = OAc), 3β-chloro- (1; R = Cl), and 3β-hydroxy- (1; R = OH) 5α,6α-epoxyandrostan-17-one were treated with 48% hydrobromic acid in refluxing glacial acetic acid. 5α,6α-Epoxyandrost-2-en-17-one (6) also gave this group of products. The formation of the aromatic steroids was accompanied by the development of a deep blue colour.



The formation of the aromatic steroids may be rationalized in terms of hydrolysis of the epoxide, and a series of elimination reactions and prototropic rearrangements to form the triene (7) and (8) which can generate the spirodiene intermediates (9) and (10) leading to either 4-methyloestra-1,3,5(10)-trien-17-one (2) or the anthrasteroid (4).

These results show that aromatization of 3-substituted 5α,6α-epoxides proceeds with a variety of C-3 leaving groups and is independent of the C-3 stereochemistry. This lends further support to the general proposal that aromatic steroids may be formed in the acid-catalysed reactions of steroids containing two double-bond equivalents and a carbonium ion source.[3,8]

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[3] J. Libman and Y. Mazur, *Chem. Comm.*, 1971, 729.
[4] L. Ruzicka, L. Grobland, and S. Raschka, *Helv. Chim. Acta*, 1940, **23**, 1518.
[5] J. Schmitt, J. J. Panouse, M. Pluchet, A. Hallot, P. J. Cornu, and P. Comoy, *Bull. Soc. chim. France*, 1965, 1934.
[6] F. C. Chang and R. T. Blickenstaff, *J. Amer. Chem. Soc.*, 1958, **80**, 2906.
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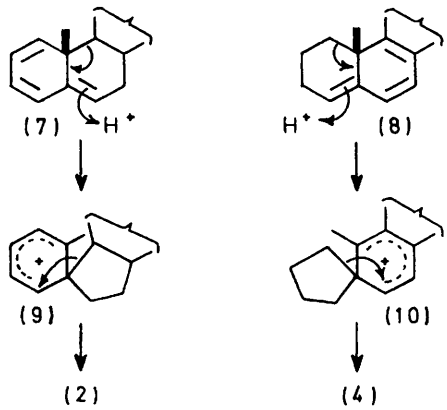
[8] J. R. Hanson and T. D. Organ, *J. Chem. Soc.* (*C*), 1971, 1313.



EXPERIMENTAL

General procedures have been described previously.[9]

5α,6α-Epoxy-3α-hydroxyandrostan-17-one.—The methanesulphonate of 5α,6α-epoxy-3β-hydroxyandrostan-17-one [1] (6·0 g) in 25% aqueous dimethylformamide (50 ml) containing lithium carbonate (6 g) was heated at 100° for 3 h. The solution was poured into water and the steroids were recovered in chloroform and chromatographed on alumina. Elution with 5% ethyl acetate–light petroleum gave 5α,6α-epoxyandrost-2-en-17-one (2·1 g), which crystallized from acetone–light petroleum as needles, m.p. 171—172° (lit.,[1] 172—174°) identified by i.r. and n.m.r. spectra. Elution with 75% ethyl acetate–light petroleum gave *5α,6α-epoxy-3α-hydroxyandrostan-17-one* (1·4 g), which crystallized from acetone–light petroleum as plates, m.p. 161—164°, $[\alpha]_D^{20}$ −16° (*c* 0·8) (Found: C, 74·9; H, 9·5. $C_{19}H_{28}O_3$ requires C, 75·0; H, 9·3%), $\nu_{max.}$ 3500 and 1735 cm^{-1}, τ 9·13 (3H, s), 8·89 (3H, s), 7·08 (1H, d, *J* 3 Hz), and 5·88 (1H, m).

The *methanesulphonate*, prepared with methanesulphonyl chloride in pyridine, crystallized from acetone–light petroleum as needles, m.p. 153—155° $[\alpha]_D^{20}$ 0° (*c* 0·5) (Found: C, 62·4; H, 7·9. $C_{20}H_{30}O_5S$ requires C, 62·8; H, 7·9%), $\nu_{max.}$ 1745 and 1175 cm^{-1}, τ 9·16 (3H, s), 8·91 (3H, s), 7·17 (1H, m), 6·95 (3H, s), and 4·84 (1H, m).

3β-Chloro-5α,6α-epoxyandrostan-17-one.— 3β-Chloroandrost-5-en-17-one [10] (2·0 g) in chloroform (50 ml) was treated with *m*-chloroperbenzoic acid (2·0 g) overnight. The solution was diluted with chloroform, washed with aqueous ferrous sulphate, aqueous sodium hydrogen carbonate, and water, and dried. Evaporation left *3β-chloro-5α,6α-epoxyandrostan-17-one* (1·5 g), which crystallized from acetone–light petroleum as needles, m.p. 175—176°, $[\alpha]_D^{20}$ −11° (*c* 0·25) (Found: C, 70·7; H, 8·2. $C_{19}H_{27}ClO_2$ requires C, 70·5; H, 8·35%), $\nu_{max.}$ 1735 cm^{-1}, τ 9·19 (3H, s), 8·89 (3H, s), 7·05 (1H, d, *J* 5 Hz), and 5·92 (1H, m). 3β-Acetoxy-5α,6α-epoxyandrostan-17-one had m.p. 219—220°, $[\alpha]_D^{20}$ −10° (*c* 0·2) (lit.,[11] m.p. 222—224°, $[\alpha]_D$ −12°). 5α,6α-Epoxy-3β-hydroxyandrostan-17-one had m.p. 226—228°, $[\alpha]_D^{20}$ −58° (*c* 0·96) (lit.,[12] m.p. 227—229°).

5α-Hydroxyandrostane-3,6,17-trione.— (i) 5α,6α-Epoxy-3α-hydroxyandrostan-17-one (100 mg) in acetone (10 ml) was treated with 8N-chromium trioxide until the reagent colour persisted. After 1 h the excess of reagent was destroyed with methanol, and the solution was concentrated and poured into water. The product was recovered in ether. 5α-Hydroxyandrostane-3,6,17-trione (65 mg) crystallized from methylene chloride–methanol as needles, m.p. 242—246° (lit.,[7] 240—244°) (Found: C, 71·9; H, 8·2. Calc. for $C_{19}H_{26}O_4$: C, 71·7; H, 8·2%), $\nu_{max.}$ 3440, 1750, 1730, and 1710 cm^{-1}, τ 9·05 (3H, s) and 8·91 (3H, s). (ii) 5α,6α-Epoxy-3β-hydroxyandrostan-17-one (100 mg) was treated in a similar manner to give 5α-hydroxyandrostane-3,6,17-trione (48 mg), identical (i.r.) with the sample obtained in (i).

Aromatization Reactions.—(i) (*cf.* ref. 1) A solution of the methanesulphonate of 5α,6α-epoxy-3α-hydroxyandrostan-17-one (600 mg) in dimethylformamide (10 ml) containing lithium bromide (600 mg) and lithium carbonate (300 mg) was heated under reflux for 3 h. The mixture was poured into dil. hydrochloric acid and the product was recovered in chloroform. The solvent was evaporated to give a residue which was chromatographed on alumina. Elution with light petroleum gave 4-methyloestra-1,3,5(10)-triene-17-one (58 mg), which crystallized from acetone–light petroleum as needles, m.p. 176—179° (lit.,[13] 180—182°), identified by its i.r. spectrum. Elution with 5% ethyl acetate–light petroleum gave androst-4-ene-6,17-dione (160 mg), which crystallized from acetone–light petroleum as needles, m.p. 190—193° (lit.,[4] 194°), identified by its i.r. spectrum

Repetition with the methanesulphonate of 5α,6α-epoxy-3β-hydroxyandrostan-17-one (*cf.* ref. 1) (500 mg) gave 4-methyloestra-1,3,5(10)-trien-17-one (50 mg) and androst-4-ene-6,17-dione (160 mg), identified by their i.r. spectra. T.l.c. of the crude products from the foregoing reactions on alumina with 20% ethyl acetate–light petroleum as the mobile phase (development with iodine vapour) revealed identical patterns of spots, R_F 0·08, 0·30, 0·38, 0·60, and 0·66.

(ii) The methanesulphonate of 5α,6α-epoxy-3β-hydroxyandrostan-17-one (1·7 g) dissolved in acetic acid (15 ml) and 48% hydrobromic acid (5 ml) was heated under reflux for 1 h. The solution was cooled and poured into aqueous sodium hydrogen carbonate. The product was recovered in ethyl acetate. The solvent was evaporated and the residue was chromatographed on alumina. Elution with light petroleum gave 4-methyloestra-1,3,5(10)-trien-17-one (670 mg), m.p. 177—179°, identified by its i.r. spectrum. Elution with 5% ethyl acetate–light petroleum gave androst-4-ene-6,17-dione (36 mg), m.p. 190°, identified by its i.r. spectrum. Preparative layer chromatography of the aromatic fractions in 20% ether–light petroleum gave the 17-oxoanthrasteroid (4) (30 mg), which crystallized from light petroleum as needles, m.p. 140—141°, $[\alpha]_D^{20}$ +138° (*c* 0·25), (lit.,[5] m.p. 138—140°, $[\alpha]_D$ +142°), $\nu_{max.}$ 1738 cm^{-1}, τ 9·04 (3H, s), 8·01 (3H, s), and 3·25 (1H, s).

(iii) 4-Methyloestra-1,3,5(10)-trien-17-one was obtained under similar conditions from the following steroids:

Steroid	mg	4-Methyloestra-1,3,5(10)-trien-17-one (mg)
3β-Acetoxy-5α,6α-epoxyandrostan-17-one	350	85
3β-Chloro-5α,6α-epoxyandrostan-17-one	500	115
5α,6α-Epoxy-3β-hydroxyandrostan-17-one	250	75
5α,6α-Epoxyandrost-2-en-17-one	210	56
6β-Bromo-5α-hydroxy-3β-methylsulphonyloxyandrostan-17-one	350	78

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[11] L. Ruzicka and A. C. Muhr, *Helv. Chim. Acta*, 1944, **27**, 503.
[12] J. Weinman and S. Weinman, *Steroids*, 1965, **3**, 683.

The anthrasteroid (4) and androst-4-ene-6,17-dione (3) were identified by t.l.c. on alumina in 20% ether–light petroleum.

Action of Hydrobromic Acid in Chloroform.—The methanesulphonate of 5α,6α-epoxy-3β-hydroxyandrostan-17-one (1·2 g) in chloroform (10 ml) was treated with 48% hydrobromic acid (2 ml) at room temperature for 6 h. The solution was poured into aqueous sodium hydrogen carbonate and the product was recovered in chloroform. Evaporation left the 6β-*bromo*-5α-*hydroxy*-3β-*methylsulphonyloxyandrostan*-17-*one* (950 mg), which crystallized from chloroform–light petroleum as needles, m.p. 169—170° (decomp.), $[\alpha]_D^{20}$ −6° (*c* 0·27) (Found: C, 54·5; H, 7·1. $C_{20}H_{31}BrSO_5$ requires C, 54·2; H, 7·0%), $\nu_{max.}$ 3520 and 1735 cm^{-1}, τ 9·10 (3H, s), 8·60 (3H, s), 6·97 (3H, s), 5·95 (1H, m), and 4·95 (1H, m).

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