Acid-catalysed Ring Contraction of Steroidal 1α,2α-Epoxy-4-en-3-ones

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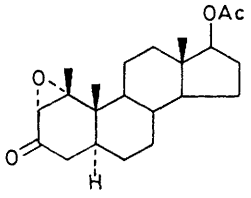
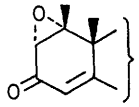
The reaction of 17β-acetoxy-1α,2α-epoxy-1β-methylandrost-4-en-3-one with formic acid at 100 °C gives 17β-acetoxy-1β-methyl-A-norandrost-3-en-2-one (5) in high yields. The same reaction at room temperature leads to both the 1α,2β-dihydroxy-compound (6) and the A-nor-derivative (5). Chemical correlations allow the configuration at C-1 to be assigned.

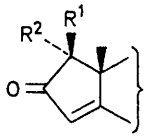
MUCH work on the behaviour of saturated steroidal epoxides with acidic reagents has been reported: such



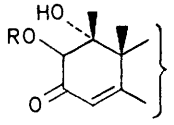
(1)



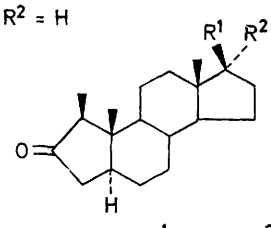
(2)



(3) R^1 = Me, R^2 = CHO
(4) R^1 = CHO, R^2 = Me
(5) R^1 = Me, R^2 = H



(6) R = H
(7) R = CHO



(8) R^1 = OH, R^2 = H
(9) R^1R^2 = O

reactions have been shown in some cases [1] to give A-nor-derivatives. We describe here the reaction of 17β-acetoxy-1α,2α-epoxy-1β-methylandrost-4-en-3-one (2) with formic acid.

The unsaturated epoxide (2) was prepared by dehydrogenation of 17β-acetoxy-1α,2α-epoxy-1β-methyl-5α-androstan-3-one (1) [1d] with selenium dioxide. Treatment of the epoxide (2) with formic acid at 100 °C gave the A-nor-compound (5),† in 80% yield, identified on the basis of ^{1}H n.m.r., i.r., and u.v. spectra. The 1β-methyl configuration has been confirmed by conversion into 1β-methyl-A-nor-5α-androstane-2,17-dione (9),[1d] by reduction with lithium in liquid ammonia to give the ketol (8), followed by oxidation with Jones reagent.

By contrast, treatment of the unsaturated epoxide (2) with formic acid at room temperature gave the A-norandrost-3-en-2-one (5), in 15% yield, and the 1α,2β-dihydroxy-compound (6),‡ in 55% yield, identified on the basis of spectroscopic data. Further treatment of compound (6) with formic acid at 100 °C gave the A-nor-unsaturated derivative (5), in 95% yield.

We were unable to isolate any aldehydic intermediates [(3) or (4)] of the type reported [1d] as being produced from saturated steroidal epoxides; the ethylenic double bond conjugated with the ketonic carbonyl group presumably facilitates deformylation.

To our knowledge this is the first example of an acid-catalysed ring contraction of an unsaturated ring A

† The procedures usually followed to obtain steroidal A-nor-3-en-2-ones are described in ref. 1*b*, vol. I, p. 346 and ref. 1*c*, vol. II, p. 410.

‡ We were unable to isolate the 2β-formate (7), presumably because it was hydrolysed during purification.

[1] (*a*) D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, ch. 8; (*b*) 'Terpenoids and Steroids,' Chem. Soc. Specialist Periodical Report, 1971, vol. I, p. 365; (*c*) 'Organic Reactions in Steroid Chemistry,' ed. J. Fried and J. A. Edwards, Van Nostrand-Reinhold, New York, 1971; (*d*) V. Tortorella, L. Toscano, C. Vetuschi, and A. Romeo, *J. Chem. Soc.* (*C*), 1971, 2422.

steroidal epoxide,* although photochemical ring contraction of steroidal 1α,2α-epoxy-4-en-3-ones, leading to A-nor-Δ^3-2-oxo-derivatives, has been described.[2] However, Hirschmann *et al.*[3] have reported that the benzilic acid rearrangement of steroidal diosphenols provides an efficient synthesis of ring-A-contracted steroids, at the same time providing evidence for the migration of the 4,5-double bond into ring B.

The above results demonstrate that it is the dihydroxy-derivative (6) which undergoes the ring contraction. There is no evidence that the A-nor-unsaturated compound (5) comes directly from the epoxide ring opening, by-passing the intermediate (6). The presence of the 2β-oxygen function in compound (6) probably leads to an intermediate which is held in a conformation affording some relief of steric interactions between the angular C-10 methyl group and the 2β-oxygen group; the conformer so obtained has bonds opportunely placed for migration.

EXPERIMENTAL

M.p.s were determined with a Büchi oil-bath apparatus. I.r. spectra were recorded for KBr discs with a Perkin-Elmer 521 spectrometer. U.v. spectra were determined with a Beckman DU-2 spectrophotometer for solutions in ethanol. Optical rotations were taken for solutions in chloroform at room temperature with a Schmidt-Haensch polarimeter (1 dm cell). ^{1}H N.m.r. spectra (solvent $CDCl_3$) were determined at 60 MHz with a Varian A-60 spectrometer (Me_4Si as internal standard). Preparative layer chromatography (p.l.c.) was carried out with Merck HF_{254} silica gel (layers 0.5 mm thick). Alumina used for column chromatography was Woelm neutral (Brockman grade III).

17β-*Acetoxy*-1α,2α-*epoxy*-1β-*methylandrost*-4-*en*-3-*one* (2).—Dehydrogenation of 17β-acetoxy-1α,2α-epoxy-1β-methyl-5α-androstan-3-one[1d] (1) (2.4 g) was carried out with selenium dioxide (675 mg) in t-butyl alcohol (135 ml) and acetic acid (1.5 ml),[4] and gave the 4-*en*-3-*one* (2) (40%), m.p. 162—163° (from di-isopropyl ether), $[\alpha]_D$ +170° (*c* 1.0), $\nu_{max.}$ 1 722, 1 670, and 1 628 cm^{-1}, δ 0.85 (3 H, s, 13-Me), 1.35 (3 H, s, 10-Me), 1.56 (3 H, s, 1β-Me), and 2.04 (3 H, s, 17β-OAc) (Found: C, 73.65; H, 8.55. $C_{22}H_{30}O_4$ requires C, 73.7; H, 8.45%).

17β-*Acetoxy*-1β-*methyl*-A-*norandrost*-3-*en*-2-*one* (5).—The unsaturated epoxide (2) (1.29 g) in formic acid (129 ml) was kept at 100 °C for 2 h. After cooling, the solution was poured into ice; the mixture was stirred for 20 min and extracted with ether. The combined extracts were washed with sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and evaporated. The residue (1.3 g) was chromatographed on deactivated alumina (65 g). Elution with benzene–hexane (8 : 2) and benzene gave a pure product (685 mg) and 435 mg of the same substance which had to be further purified on silica [p.l.c.; benzene–ether (9 : 1) as eluant] (yield 260 mg; total 945 mg). The *product* (5) had m.p. 139—140° (from hexane), $[\alpha]_D$ −45° (*c* 1.0), $\lambda_{max.}$ 233 nm (log ε 4.21), $\nu_{max.}$ 3 060, 1 740, 1 695, and 1 620 cm^{-1}, δ 0.85 (3 H, s, 13-Me), 1.05 (3 H, s, 10-Me), 1.11 (3 H, d, *J* 8 Hz, 1β-Me), and 2.04 (3 H, s, 17β-OAc) (Found: C, 76.2; H, 9.15. $C_{21}H_{30}O_3$ requires C, 76.3; H, 9.15%).

17β-*Hydroxy*-1β-*methyl*-A-*nor*-5α-*androstan*-2-*one* (8).—A solution of 17β-acetoxy-1β-methyl-A-norandrost-3-en-2-one (5) (345 mg) in dry tetrahydrofuran–ether (1 : 1; 34 ml) was added dropwise to a stirred solution of lithium (250 mg) in liquid ammonia (70 ml) over 10 min. After 30 min, ammonium chloride (4.5 g) was added and the ammonia was allowed to evaporate. The residue was dissolved in methylene chloride; the solution was washed with water, dried (Na_2SO_4), and evaporated to leave the ketol (8) (305 mg), which was used without further purification.

1β-*Methyl*-A-*nor*-5α-*androstane*-2,17-*dione* (9).—A solution of the 17β-hydroxy-derivative (8) (150 mg) in acetone (20 ml; distilled over $KMnO_4$) was treated dropwise with Jones reagent (0.5 ml). Extraction with ether gave the dione (9) (160 mg), m.p. 139—141° (from hexane), $[\alpha]_D$ +225° (*c* 1.0), $\nu_{max.}$ 1 740 and 1 730 cm^{-1}, δ 0.87 (3 H, s, 13-Me), 0.74 (3 H, s, 10-Me), and 1.08 (3 H, d, *J* 7 Hz, 1β-Me), identical with an authentic sample.[1d]

Reaction of 17β-*Acetoxy*-1α,2α-*epoxy*-1β-*methylandrost*-4-*en*-3-*one* (2) *with Formic Acid at Room Temperature*.—The epoxide (2) (200 mg) was treated with formic acid (20 ml) at room temperature for 48 h. The usual work up gave a residue (205 mg), which was chromatographed on deactivated alumina (10 g). Elution with methylene chloride–benzene (7 : 3) furnished the A-nor-ketone (5) (34 mg, 19%); elution with methylene chloride–ether (7 : 3) and ether–ethyl acetate (7 : 3) gave 17β-*acetoxy*-1α,2β-*dihydroxy*-1β-*methylandrost*-4-*en*-3-*one* (6) (118 mg, 55%), m.p. 208—212° (from ethyl acetate), $[\alpha]_D$ +103° (*c* 1.0), $\nu_{max.}$ 3 420, 3 360, 1 740, 1 680, and 1 610 cm^{-1}, δ 0.86 (3 H, s, 13-Me), 1.09 (3 H, s, 10-Me), 1.44 (3 H, s, 1β-Me), and 2.03 (3 H, s, 17β-OAc) (Found: C, 70.2; H, 8.55. $C_{22}H_{32}O_5$ requires C, 70.2; H, 8.55%). The dihydroxy-derivative (6) (36 mg), further treated with formic acid (3.6 ml) at 100 °C for 2 h, yielded the A-nor-unsaturated compound (5) (95%), m.p. 137—138° (from hexane), $\lambda_{max.}$ 232 nm (log ε 4.36).

[6/452 *Received*, 5*th March*, 1976]

* Acid-catalysed ring contraction of monoepoxides derived from cyclohexadienones leading to cyclopentenone derivatives has been reported (H. Hart, I. Huang, and P. Lavrik, *J. Org. Chem.*, 1974, **39**, 999; H. Hart and E. M. Shih, *ibid.*, 1975, **40**, 1128).

[2] J. Pfister, C. Lehmann, and H. Wehrli, *Helv. Chim. Acta*, 1968, **51**, 1505.
[3] R. Hirschmann, G. A. Bailey, R. Walker, and J. M. Chemerda, *J. Amer. Chem. Soc.*, 1959, **81**, 2822.
[4] C. H. Meystre, H. Frey, W. Voser, and A. Wettstein, *Helv. Chim. Acta*, 1956, **39**, 734.