Acid-catalysed Ring Contraction of Steroidal 4β,5β-Epoxy-1-en-3-ones

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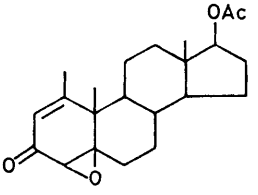
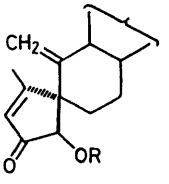
The reaction of 17β-acetoxy-4β,5β-epoxy-1-methylandrost-1-en-3-one with formic acid gives rise to a rearrangement, which, involving C(1)–C(10) bond migration, leads to the spirans (2) and (4). The 4β,5β-diol (6), derived from the alternative epoxide cleavage at C-4, is also obtained.

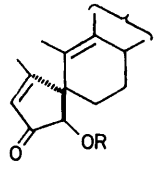
WE have previously[1] reported that treatment of steroidal 1α,2α-epoxy-4-en-3-ones with acidic reagents leads to A-nor compounds in good yields. As part of a study to determine whether the reaction is sensitive to changes in the position of the functional groups in ring A, we have examined the rearrangement of 17β-acetoxy-4β,5β-epoxy-1-methylandrost-1-en-3-one (1) with formic acid to see if it is possible to obtain ring A-contracted compounds.



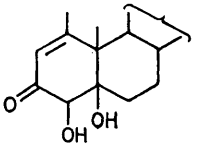
(1)



(2) R = CHO
(3) R = H



(4) R = CHO
(5) R = H



(6)

It has been reported[2] that the acid-catalysed reaction of 4,5-epoxycholest-2-en-1-ones leads to products of *trans*-diaxial epoxide ring opening only. As we describe below, from the unsaturated epoxide (1) we have instead obtained two isomeric A-nor-C_5-spiro compounds (2) and (4), derived from a C(1)–C(10) bond migration.

A-Nor-C_5-spirans have also been obtained from the boron trifluoride-catalysed rearrangement of 5,6-epoxy-3-oxocholestanes[3a] and the effect of changes in substituents at C-3,[3b] C-19,[3c] and C-17[3d] on 5,6-epoxyandrostanes has been widely investigated.

The unsaturated epoxide (1) was prepared by oxidation of 17β-acetoxy-1-methylandrosta-1,4-dien-3-one[4,†] either with alkaline hydrogen peroxide or with monoperphthalic acid, affording only the 4β,5β-epoxide (1) in 80 and 50% yield, respectively. Stereoselective 4β,5β-attack seems to be intrinsic to the rings A and B quasi-*cis*-conformation of the 1,4-dien-3-one system.[5]

Treatment of the epoxide (1) with formic acid at room temperature gave a mixture, which, after separation, afforded three products. To two of them, (2) in 28% yield, and (4) in 19% yield, the A-nor-C_5-spiran structure was assigned on the basis of spectroscopic data. The ^1H n.m.r. spectrum of the spiro compound (2) showed no 10-methyl signal and the presence of methylene protons at δ 5.16 and 5.40, while in the ^1H n.m.r. spectrum of spiro compound (4) the 10-methyl signal appeared at δ 1.65. The i.r. spectra of both spirans (2) and (4) clearly showed the presence of a cyclopentenone system ($\nu_{max.}$ 1 720 cm^{-1}). The mass spectra and elemental analysis of the two spirans were also in accord with the structures assigned. The third product was identified by chemical correlation with the 4β,5β-diol obtained by *cis*-hydroxylation of 17β-acetoxy-1-methylandrosta-1,4-dien-3-one with osmium tetraoxide.[6]

Although it is well known[7] that an endocyclic olefin is distinctly less stable than the corresponding exocyclic methylene derivative, only in the Westphalen rearrangement of a 9β-cholestan-5α-ol[8] has a $\Delta^{9(10)}$-C_5-spiran (in 70% yield) been isolated together with the 10-methylene-C_5-spiran (in 17% yield).

We have demonstrated acid-catalysed isomerisation of the two spiro compounds (2) and (4) by conversion of the spiran (4) into the exocyclic derivative (2), in 66% yield, in formic acid for 68 h. The composition of the mixture was determined from the integrated intensities of the characteristic formyl ^1H n.m.r. signal.

From our work on acid-catalysed ring contraction of 1α,2α-epoxy-Δ^4-3-oxo steroids,[1] we can say that the ring-A-flattened conformation makes bond migration easier. In the case of the rearrangement of the Δ^1-unsaturated 4β,5β-epoxide (1), ring contraction, which involves ring opening and migration of the C(1)–C(10) linkage, is probably synchronous with β-epoxide opening and proceeds through a concerted mechanism leading to the spiro compounds (2) and (3) and (4) and (5).

The diol (6) could be derived from the alternative ring opening of the epoxide (1) at C-4[9,‡] and from the subsequent acid-catalysed epimerisation of the 4α-hydroxy group to give the more stable 4β,5β-dihydroxy derivative (6).

EXPERIMENTAL

M.p.s were measured with a Kofler hot-stage apparatus. Optical rotations were taken at 20 °C with a Schmidt–

† The dienone is preferably obtained from the Δ^1-3-oxo compound by treatment with thallium triacetate in acetic acid, using a method found in our laboratories.[4b]

‡ The formate anion is a polarizable nuclephilic reagent and attacks the less hindered C-4 assisted by neighbouring orbital overlap with the carbonyl group at C-3.

Haensch polarimeter for solutions in chloroform in a 1 dm cell. I.r. spectra were recorded on a Perkin-Elmer 521 grating spectrophotometer. U.v. spectra were determined with a Beckman D.U.-2 spectrophotometer for solutions in ethanol. ^{1}H N.m.r. spectra were measured for solutions in deuteriochloroform (tetramethylsilane as internal standard) with a JEOL C-60 HL or Varian EM-390 spectrometer. 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*-4β,5β-*epoxy*-1-*methylandrost*-1-*en*-3-*one* (1).—(*a*) 17β-Acetoxy-1-methylandrosta-1,4-dien-3-one [4] (1.02 g) in methanol (32 ml) was treated at 12 °C with 30% hydrogen peroxide (1.3 ml) and 0.4% methanolic sodium hydroxide (5 ml) with stirring and kept at 5 °C overnight. Dilution with water (320 ml) gave a precipitate, which was filtered, dissolved in benzene, dried, and evaporated gave a residue which was purified on silica [p.l.c.; benzene–ether (7 : 3) as eluant] to give the β-*epoxide* (1) (850 mg), m.p. 168—169° (from di-isopropyl ether), $[\alpha]_D$ +174° (*c* 1.0), $\nu_{max.}$ (KBr) 1 730, 1 670, and 1 610 cm^{-1}, δ 0.81 (3 H, s, 13-Me), 1.35 (3 H, s, 10-Me), 1.95 (3 H, d, *J* 3 Hz, 1-Me), 2.01 (3 H, s, 17β-OAc), 3.20 (1 H, d, *J* 3 Hz, 4α-H), 4.55 (1 H, m, 17α-H), and 5.82br (1 H, s, 2-H) (Found: C, 73.7; H, 8.45. $C_{22}H_{30}O_4$ requires C, 73.7; H, 8.45%).

(*b*) An ethereal solution of 17β-acetoxy-1-methylandrosta-1,4-dien-3-one (170 mg) and an excess of monoperphthalic acid solution (4 ml; 40 g l^{-1}) was set aside at room temperature for 48 h. The excess of acid was removed by washing the solution with 2N-sodium hydroxide and water; drying and evaporation gave, after purification, the β-epoxide (1) (87 mg), m.p. 168—169° (from di-isopropyl ether), $[\alpha]_D$ +174° (*c* 1.0), $\nu_{max.}$ 1 730, 1 670, and 1 610 cm^{-1}.

Reaction of Epoxide (1) *with Formic Acid at Room Temperature.*—The epoxide (1) (240 mg) was treated with formic acid (24 ml) at room temperature for 120 h. The solution was poured into ice; the mixture was stirred for 20 min and extracted with ether. The combined extracts were washed with sodium hydrogencarbonate solution and water, dried (Na_2SO_4), and evaporated. P.l.c. of the crude residue (250 mg) [methylene chloride–ether (95 : 5) as eluant, three runs] gave 4-*formyloxy*-1-*methyl*-10-*methylene*-1(10) ⟶ 5-abeo-*androst*-1-*en*-3-*one* (2) (28%), an oil, $\nu_{max.}$ ($CHCl_3$) 1 720, 1 670, and 1 580 cm^{-1}, δ 0.70 (3 H, s, 13-Me), 2.01 (3 H, s, 17β-OAc), 2.16 (3 H, d, *J* 1.5 Hz, 1-Me), 4.57br (1 H, s, 17α-H), 5.16—5.40br (2 H, CH_2=C), 5.78 (1 H, apparent s, 2-H), 6.0br (1 H, s, 4α-H), and 8.1 (1 H, s, OCHO) (Found: C, 71.35; H, 8.0. $C_{23}H_{30}O_5$ requires C, 71.5; H, 7.8%), the $\Delta^{9(10)}$-*isomer* (4) (19%), m.p. 214—216° (from ethyl acetate–n-hexane), $[\alpha]_D$ −33° (*c* 0.6), $\nu_{max.}$ ($CHCl_3$) 1 720, 1 670, and 1 620 cm^{-1}, δ 0.82 (3 H, s, 13-Me), 1.65 (3 H, s, 10-Me), 2.0 (3 H, d, *J* 1.5 Hz, 1-Me), 2.03 (3 H, s, 17β-OAc), 4.56br (1 H, s, 17α-H), 5.64br (1 H, s, 2- or 4-H), 5.75br (1 H, s, 2- or 4-H), and 8.24 (1 H, s, OCHO) (Found: C, 68.25; H, 8.05. $C_{23}H_{30}O_5$,H_2O requires C, 68.3; H, 7.95%), and a third impure product (46%), which was characterised when the reaction mixture, in a further preparation, was chromatographed on deactivated alumina. In a second reaction, the β-*epoxide* (1) (650 mg) was treated with formic acid (65 ml). The usual work-up gave a residue (670 mg), which was chromatographed on deactivated alumina (33 g). Elution with benzene–methylene chloride (1 : 1) gave the *spiran* (3) (20%), m.p. 120—122° (from n-hexane), $[\alpha]_D$ +46.4° (*c* 0.69), $\lambda_{max.}$ 280 nm (log ε 4.37), $\nu_{max.}$ (KBr) 3 450, 3 410, 1 730, 1 710, 1 675, 1 650, and 1 585 cm^{-1}, δ 0.83 (3 H, s, 13-Me), 2.04 (3 H, s, 17β-OAc), 2.09 (3 H, d, *J* 1.5 Hz, 1-Me), 3.56 (1 H, d, *J* 3 Hz, 4β-OH), 4.05 (1 H, d, *J* 3 Hz, 4α-H), 4.6br (1 H, s, 17α-H), 5.56—5.71 (2 H, CH_2=C), and 5.99br (1 H, s, 2-H) (Found: C, 73.65; H, 8.35%; M^+, 358. $C_{22}H_{30}O_4$ requires C, 73.7; H, 8.45%; M^+, 358.45); elution with methylene chloride–benzene (7 : 3) gave a product, which, further purified by p.l.c. [methylene chloride–ether (9 : 1) as eluant, six runs], furnished the *spiran* (5) (9%), m.p. 175—176° (from n-hexane), $[\alpha]_D$ +46° (*c* 1.0), $\nu_{max.}$ ($CHCl_3$) 3 460, 1 715, 1 655, and 1 615 cm^{-1}, δ 0.84 (3 H, s, 13-Me), 1.63 (3 H, s, 10-Me), 2.0 (3 H, d, *J* 1.5 Hz, 1-Me), 2.03 (3 H, s, 17β-OAc), 3.69br (1 H, s, 4β-OH), 4.28 (1 H, s, 4α-H), 4.58br (1 H, s, 17α-H), and 5.79 (1 H, apparent d, *J* 2 Hz, 2-H), *m/e* 376 and 358 (Found: C, 69.95; H, 8.7. $C_{22}H_{30}O_4$,H_2O requires C, 70.2; H, 8.55%). Elution with ether–ethyl acetate (7 : 3) gave a product which was subjected to further p.l.c. in methylene chloride–ether (9 : 1) as eluant (two runs) to give 17β-*acetoxy*-4β,5β-*dihydroxy*-1-*methylandrost*-1-*en*-3-*one* (6) (12%), m.p. 228—230° (from ethyl acetate–n-hexane), $[\alpha]_D$ +40° (*c* 1.0), $\nu_{max.}$ (KBr) 3 540, 3 470, 1 725, 1 655, and 1 610 cm^{-1}, δ 0.81 (3 H, s, 13-Me), 1.27 (3 H, s, 10-Me), 2.02 (3 H, s, 17β-OAc), 2.03 (3 H, d, *J* 1.5 Hz, 1-Me), 3.72 (1 H, s, 4β-OH), 4.56br (1 H, s, 17α-H), 4.65 (1 H, s, 4α-H), and 6.02 (1 H, s, 2-H) (Found: C, 70.2; H, 8.55. $C_{22}H_{32}O_5$ requires C, 70.2; H, 8.55%).

Hydroxylation of 17β-*Acetoxy*-1-*methylandrosta*-1,4-*dien*-3-*one.*—A solution of the dienon (0.15 mmol) in dry pyridine (0.5 ml) was treated with osmium tetraoxide (0.15 mmol) in dry ether solution and was allowed to stand in a dark place at room temperature for three days. The precipitated osmate was treated with sodium metabisulphite (0.5 mmol) and water (0.8 ml) overnight. The solution was diluted with methylene chloride and washed with 2N-HCl and water. The organic layer, dried and evaporated, gave the 4β,5β-diol,[6] identical with the dihydroxy derivative (6), m.p. 228—230° (from ethyl acetate–n-hexane), $[\alpha]_D$ +41° (*c* 1.0).

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