Ring-contraction of 5β,6β-Epoxyandrostane-4,17-dione

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Stereospecific methods for the preparation of 5α,6α- and 5β,6β-epoxyandrostane-4,17-dione are described. A Favorskii-type ring contraction of the 5β,6β-epoxide affords a rapid route to A-nor-steroids.

THE anionic rearrangement of βγ-epoxy-ketones to γ-hydroxy-αβ-unsaturated ketones is well documented in the steroid series.[1] However the anionic ring-contraction of αβ-epoxy-ketones, exemplified in the monoterpene series by the conversion of piperitone oxide (1) into the piperitolenic acids (2),[2] has not been described despite considerable interest in the ring contraction of steroids.[3] There are many examples of transannular bond formation in steroids between C-3 and C-5 (*e.g. i*-steroids [4]); hence the C-3 anion of a 5,6-epoxyandrostan-4-one formed a suitable substrate in the context of a Favorskii type rearrangement.

The epoxy-ketones were prepared as follows. Stereospecific epoxidation of the diol (3) [5] was achieved using t-butyl hydroperoxide and vanadyl acetylacetonate [6] to afford 5β,6β-epoxy-3β,4β-dihydroxyandrostan-17-one (4). The less-hindered 3β-hydroxy group was selectively acylated with toluene-*p*-sulphonyl chloride in pyridine to afford the 3β-monotoluene-*p*-sulphonate (5). The H-3 n.m.r. signal showed the appropriate downfield shift (Δδ 1.48 p.p.m.). Treatment of the monotoluene-*p*-sulphonate (5) with sodium hydride in dry tetrahydrofuran gave the 5β,6β-epoxyandrostane-4,17-dione (6). Acetylation of the diol (3) removed the directing effect of the 4β-hydroxy group. Epoxidation of the diacetate (7) with *m*-chloroperbenzoic acid afforded the 5α,6α-epoxide. Careful hydrolysis, selective acylation with toluene-*p*-sulphonyl chloride, and reaction with sodium hydride in dry tetrahydrofuran afforded the 5α,6α-epoxy-ketone (8).

An alternative method of preparation of the 5β,6β-epoxide involved the base-catalysed epoxidation of androst-5-ene-4,17-dione. The determining feature of the stereochemistry of these base-catalysed epoxidations is the requirement for the hydroperoxide, allylic to the enolate anion of the transition state, to possess an axial configuration for maximum orbital overlap. In this case this leads to the 5β,6β-epoxy-4-ketone.

When a solution of the 5β,6β-epoxy-4,17-dione (6) was heated under reflux in t-butyl alcohol containing potassium t-butoxide, the carboxylic acid (9) was obtained in good yield. On the other hand, the 5α,6α-epoxy-4,17-dione (8) was unchanged under these conditions. The structure and stereochemistry of the acid (9) rest on the following evidence. The ^1H and ^{13}C n.m.r. spectra of the methyl ester (10) revealed the presence of a trisubstituted double bond [δ_H 5.51 (m, H-6); δ_C 145.7 (s, C-5), and 118.7 p.p.m. (d, C-6)] and a deshielded methine carbon [δ_H 3.61 (t, J 8 Hz, H-3); δ_C 46.2 p.p.m. (d, C-3)]. When the ester (10) was treated with sodium methoxide, the double bond moved into conjugation to afford the $\Delta^{3(5)}$αβ-unsaturated ester, $\lambda_{max.}$ 232 nm. Correlation with the androstane series was obtained as follows. The reduction of 3β-*p*-tolylsulphonyloxycholest-5-en-4β-ol with lithium aluminium hydride has been shown [7] to lead to cholest-4-ene, cholest-5-en-4β-ol, and 3-hydroxymethyl-A-norcholest-5-ene. Similar treatment of 4β-acetoxy-3β-*p*-tolylsulphonyloxyandrost-5-en-17-one (11) gave 17β-hydroxy-3β-hydroxymethyl-A-norandrost-5-ene (12). The A-nor-steroid was isolated by oxidation with chromium trioxide to afford the carboxylic acid (9) which was then readily separated from a ketonic neutral fraction. Examination (n.m.r.) of the neutral fraction from this oxidation revealed the presence of androst-5-ene-4,17-dione and androst-4-en-17-one which were not separated.

There are a number of features of mechanistic interest. First, the ring contraction with potassium t-butoxide in t-butyl alcohol affords a βγ-unsaturated acid rather than a lactone or a t-butyl ester. A plausible mechanism is given in the Scheme. A variant involving the breakdown of the alcohol corresponding to the intermediate (13), through the attack of a hydroxide ion, cannot be completely excluded. A second feature is the lack of reactivity of the 5α,6α-epoxide. In this epoxy-ketone ring A can adopt a chair conformation. Abstraction of the axial 3α-proton affords a carbanion on the same face of the molecule as the 5α,6α-epoxide precluding rear-side attack. Not only is a boat conformation of ring A required to produce the β-oriented axial carbanion necessary for rear-side attack of the epoxide but also molecular models suggest that the cyclopropyl intermediate corresponding to (13) is considerably more difficult to generate than its epimer.

The stereochemical requirements for attack by the carbanion derived from a methylene ketone, on the rear-side of an epoxide adjacent to the ketone, are met by a

[1] C. Djerassi, E. Batres, M. Velasco, and G. Rosenkranz, *J. Amer. Chem. Soc.*, 1952, **74**, 1712; J. P. Ruelas, J. Iriarte, F. Kincl, and C. Djerassi, *J. Org. Chem.*, 1958, **23**, 1744; F. Sondheimer, S. Burstein, and R. Mechoulam, *J. Amer. Chem. Soc.*, 1960, **82**, 3209; D. H. R. Barton and Y. Houminer, *J.C.S. Perkin I*, 1972, 919.

[2] W. Treibs, *Ber.*, 1931, **64B**, 2545; R. H. Reitsema and V. J. Varnis, *J. Amer. Chem. Soc.*, 1956, **78**, 3792; H. O. House and W. F. Gilmore, *ibid.*, 1961, **83**, 2972.

[3] R. M. Scribner in 'Organic Reactions in Steroid Chemistry,' vol. 2., ed. J. Fried and J. A. Edwards, Van Nostrand–Reinhold, New York, 1972.

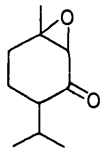
[4] For a review see D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, p. 236.

[5] B. Ellis, V. Petrow, and D. N. Stannay, B.P. 1.134,071/1968.

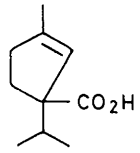
[6] K. B. Sharpless and R. C. Michaelson, *J. Amer. Chem. Soc.*, 1973, **95**, 6136.

[7] R. H. Starky and W. H. Reusch, *J. Org. Chem.*, 1969, **34**, 3522.

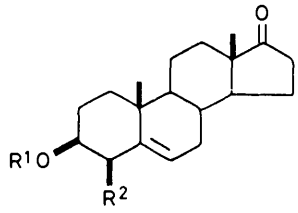
4β,5β-epoxy-6-ketone (15). In this case the axial 7α-carbanion might displace the 5β-epoxide with the generation of a 4β-hydroxy-5,7-cyclo-6-ketone, which



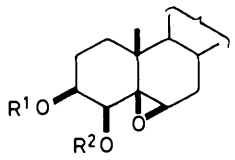
(1)



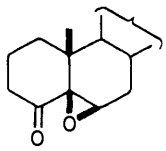
(2)



(3) R^1 = H, R^2 = OH
(7) R^1 = Ac, R^2 = OAc
(11) R^1 = Ts, R^2 = OAc
(14) R^1 = Ts, R^2 = OH



(4) R^1 = R^2 = H
(5) R^1 = Ts, R^2 = H



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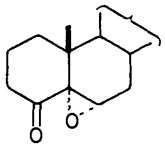

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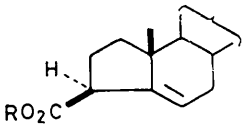
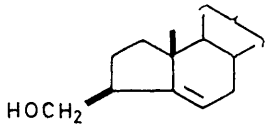
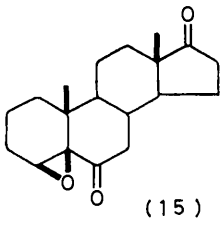


(9) R = H
(10) R = Me



(12) (17β-OH)



(15)

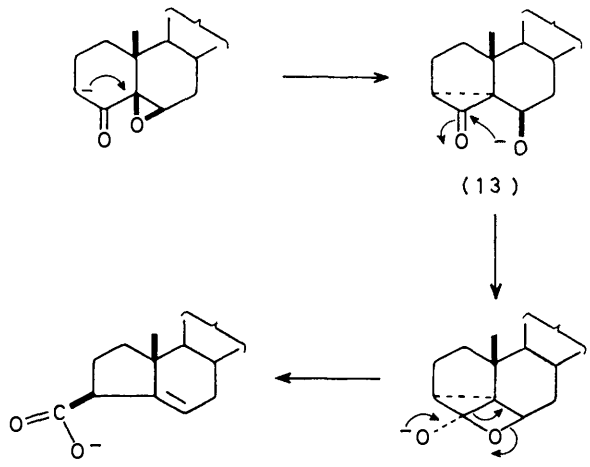
might in turn rearrange to a B-nor-carboxylic acid. The substrate, 4β,5β-epoxyandrostane-6,17-dione, was prepared by the base-catalysed epoxidation of the corresponding androst-4-en-6-one.[8] However this epoxide did not react with potassium t-butoxide in t-butyl alcohol. The difference in reactivity between the 5β,6β-epoxyandrostan-4-one and the 4β,5β-epoxyandrostan-6-one may reflect the difference in ease of formation of the intermediate cyclo-steroid. A comparable difference is revealed by the lack of cyclo-steroid formation in the solvolysis of pseudo-cholesterol derivatives.[9]

Since the 3,4-dihydroxy-5-enes are readily prepared and epoxidised, this ring contraction affords a useful route to A-nor-steroids.

EXPERIMENTAL

General experimental details have been described previously.[10]

5β,6β-*Epoxy*-3β,4β-*dihydroxyandrostan*-17-*one* (4).—3β,4β-Dihydroxyandrost-5-en-17-one (3) (10 g) [5] in dry benzene (200 ml) was treated with t-butyl hydroperoxide (3 ml) and vanadyl acetylacetonate (100 mg) under reflux for 15 min. The solution was cooled and poured through a plug of alumina. The products were then eluted with ethyl



(13)

SCHEME

acetate. Fraction (i) was discarded; fraction (ii) contained compounds (3) and (4) (t.l.c.) and was concentrated, *in vacuo*, to afford a crystalline residue. The reaction sequence was repeated twice to afford pure 5β,6β-*epoxy*-3β,4β-*dihydroxyandrostan*-17-*one* (8 g) as needles, m.p. 183—185° (from ethyl acetate), $[\alpha]_D^{20}$ +56° (*c* 0.2) (Found: C, 70.8; H, 8.6. $C_{19}H_{28}O_4$ requires C, 71.2; H, 8.75%), $\nu_{max.}$ 3 595, 3 470, and 1 730 cm^{-1}, δ 0.82 (3 H, s, 18-H_3), 1.16 (3 H, s, 19-H_3), 3.22 (1 H, d, *J* 2 Hz, 6-H), 3.36 (1 H, d, *J* 3 Hz, 4-H), and 3.58 (1 H, m, 3-H). The 3β-*monotoluene*-p-*sulphonate* (5) prepared from (4) and toluene-*p*-sulphonyl chloride in pyridine at −5 °C overnight, crystallized from ethyl acetate as needles, m.p. 161—164°, $[\alpha]_D^{20}$ +12° (Found: C, 66.2; H, 7.0. $C_{26}H_{34}O_6S$ requires C, 65.8; H, 7.2%), $\nu_{max.}$ 3 510 and 1 740 cm^{-1}, δ 0.80 (3 H, s, 18-H_3), 1.17 (3 H, s, 19-H_3), 2.3 (3 H, s, Ar-CH_3), 3.08 (1 H, d, *J* 2 Hz, 6-H), 3.66 (1 H, d, *J* 3 Hz, 4-H), 4.46 (1 H, m, 3-H), and 7.10 and 7.61 (each 2 H, d, *J* 8 Hz, ArH).

5β,6β-*Epoxyandrostane*-4,17-*dione* (6)—(i) The toluene-*p*-sulphonate (5) (2 g) in dry tetrahydrofuran (100 ml) was

[8] L. Ruzicka, C. Grob, and S. Raschka, *Helv. Chim. Acta*, 1940, **23**, 1518.

[9] C. W. Shoppee, G. H. R. Summers, and R. J. W. Williams, *J. Chem. Soc.*, 1956, 1893.

[10] J. R. Hanson and T. D. Organ, *J. Chem. Soc.* (*C*), 1970, 513.

treated with sodium hydride (80% oil dispersion) (5 g) under reflux for 3 h. Immediately the starting material had been consumed (t.l.c.), the reaction was quenched with glacial acetic acid. The solvent was removed and the steroid was recovered in ethyl acetate to give 5β,6β-*epoxyandrostane*-4,17-*dione* (6) (1.2 g) as needles, m.p. 168—170° (from ether), $[\alpha]_D$ +97° (*c* 0.2) (Found: C, 75.1; H, 8.4. $C_{19}H_{26}O_3$ requires C, 75.5; H, 8.7%), $\nu_{max.}$ 1 735 and 1 700 cm^{-1}, δ 0.87 (3 H, s, 18-H_3), 1.04 (3 H, s, 19-H_3), and 3.20 (1 H, d, *J* 2 Hz, 6-H).

(ii) Androst-5-ene-4,17-dione (540 mg) in methanol (50 ml) and benzene (2 ml) was treated with 30% hydrogen peroxide (3 ml) followed by 4N-sodium hydroxide (3 ml). The solution was left at room temperature for 15 h. The solvent was evaporated off and the residual liquid poured into water. The steroid was recovered in ether and chromatographed on silica [ethyl acetate–light petroleum (1 : 1)] to give the epoxide (6) (350 mg).

3β,4β-*Diacetoxy*-5α,6α-*epoxyandrostan*-17-*one*.— 3β,4β-Diacetoxyandrost-5-en-17-one [5] (10 g) in chloroform (100 ml) was treated with *m*-chloroperbenzoic acid (10 g) at room temperature for 3 h. The solution was washed with aqueous sodium hydrogensulphite containing a trace of sodium iodide as indicator, aqueous sodium hydrogencarbonate, and water, and dried. Evaporation gave a gum which was carefully crystallized from ether to afford the α-*epoxide* as cubes, m.p. 215—217°, $[\alpha]_D^{20}$ −32° (*c* 0.2) (Found: C, 68.6; H, 8.0. $C_{23}H_{32}O_6$ requires C, 68.3; H, 8.0%), $\nu_{max.}$ 1 730 cm^{-1}, δ 0.83 (3 H, s, 18-H_3), 1.23 (3 H, s, 19-H_3), 2.00 and 2.16 (each 3 H, s, OAc), 3.23 (1 H, d, *J* 3.5 Hz, 6-H), 4.53 (1 H, d, *J* 4 Hz, 4-H), and 5.00 (1 H, m, 3-H). P.l.c. of the mother liquors gave more α-epoxide together with a small amount of the β-isomer.

Hydrolysis of the 3β,4β-*Diacetate*.—The above epoxide (5 g) in methanol (50 ml) was treated with a solution of sodium hydroxide (5 g) in water (15 ml) for 2 h at room temperature (t.l.c. control). The solution was neutralized with acetic acid and concentrated, and the product filtered off to afford 5α,6α-*epoxy*-3β,4β-*dihydroxyandrostan*-17-*one* (3.5 g) as plates, m.p. 237—239° (from ether), $[\alpha]_D^{20}$ −8° (*c* 0.2) (Found: C, 71.2; H, 8.7. $C_{19}H_{28}O_4$ requires C, 71.2; H, 8.7%), $\nu_{max.}$ 3 400 and 1 750 cm^{-1}, δ(C_5D_5N) 0.76 (3 H, s, 18-H_3), 1.53 (3 H, s, 19-H_3), 3.13 (1 H, d, *J* 3 Hz, 6-H), 3.66 (1 H, d, *J* 4 Hz, 4-H), and 4.21 (1 H, m, 3-H), δ($CDCl_3$) 0.86, 1.26, 3.06, 3.23, and 3.83. The 3β-*monotoluene*-p-*sulphonate* was prepared using toluene-*p*-sulphonyl chloride in pyridine. It crystallized from ether as needles, m.p. 163—167°, $[\alpha]_D^{20}$ +41° (*c* 0.3) (Found: C, 65.7; H, 7.5. $C_{26}H_{34}O_6S$ requires C, 65.8; H, 7.2%), δ 0.8 (3 H, s, 18-H_3), 1.23 (3 H, s, 19-H_3), 2.43 (3 H, s, $ArCH_3$), 3.03 (1 H, d, *J* 4 Hz, 6-H), 3.33 (1 H, d, *J* 4 Hz, 4-H), 4.57 (1 H, m, 3-H), and 7.10 and 7.61 (each 2 H, d, *J* 8 Hz, ArH).

5α,6α-*Epoxyandrostane*-4,17-*dione*.—The above toluene-*p*-sulphonate (1 g) in dry tetrahydrofuran (50 ml) was treated with sodium hydride (2 g) under reflux for 1 h. As soon as the starting material had been consumed (t.l.c.) the reaction was quenched by cautious addition of glacial acetic acid. The solvents were evaporated off and the product was recovered in ethyl acetate and purified by p.l.c. to afford 5α,6α-*epoxyandrostane*-4,17-*dione* (450 mg) as needles, m.p. 193—195° (from ether), $[\alpha]_D^{20}$ +8° (*c* 0.2) (Found: C, 75.1; H, 8.5. $C_{19}H_{26}O_3$ requires C, 75.5; H, 8.7%), $\nu_{max.}$ 1 730br cm^{-1}, δ 0.82 (3 H, s, 18-H_3), 1.00 (3 H, s, 19-H_3), and 4.04 (1 H, d, *J* 4 Hz, 6-H).

Ring-contraction Reaction.—5β,6β-Epoxyandrostane-4,17-dione (1 g) in dry t-butyl alcohol (50 ml) containing potassium t-butoxide (1 g) was heated under reflux for 3 h. The reaction was quenched with glacial acetic acid. The solvent was removed *in vacuo* and the steroid was recovered in ethyl acetate. 3β-*Carboxy*-A-*norandrost*-5-*en*-17-*one* (9) (600 mg) crystallized from ether as needles, m.p. 227—228°, $[\alpha]_D^{20}$ +86° (*c* 0.2) (Found: C, 75.7; H, 8.7. $C_{19}H_{26}O_3$ requires C, 75.5; H, 8.7%), $\nu_{max.}$ 3 170, 1 730, 1 690, and 1 670 cm^{-1}, δ 0.9 (3 H, s, 18-H_3), 1.0 (3 H, s, 19-H_3), 3.38 (1 H, t, *J* 8 Hz, 3-H), and 5.62 (1 H, d, *J* 1 Hz, 6-H). The *methyl ester* (10), prepared with diazomethane, crystallized from ether as needles, m.p. 121—122°, $[\alpha]_D^{20}$ +94° (Found: C, 75.8; H, 8.9. $C_{20}H_{28}O_3$ requires C, 75.9; H, 8.9%), $\nu_{max.}$ 1 740 cm^{-1}, δ 0.83 (3 H, s, 18-H_3), 0.90 (3 H, s, 19-H_3), 3.61 (1 H, t, *J* 8 Hz, 3-H), 3.3 (3 H, s, OMe), and 5.51 (1 H, m, 6-H).

3-*Methoxycarbonyl*-A-*norandrost*-3-*en*-17-*one*. 3-Methoxycarbonyl-A-norandrost-5-en-17-one (100 mg) in dry methanol (10 ml) was treated with sodium methoxide (100 mg) for 2 days at room temperature. The reaction was quenched with acetic acid and the solvent was evaporated off. The steroid was recovered in ethyl acetate to afford 3-*methoxycarbonyl*-A-*norandrost*-3-*en*-17-*one* (90 mg) as needles, m.p. 92—94° (from light petroleum), $[\alpha]_D^{20}$ +140° (*c* 0.2) (Found: C, 75.3; H, 8.6. $C_{20}H_{28}O_3$ requires C, 75.9; H, 8.9%), $\nu_{max.}$ 1 750, 1 710, and 1 640 cm^{-1}, $\lambda_{max.}$ 232 nm (ε 12 000), δ 0.90 (3 H, s, 18-H_3), 1.03 (3 H, s, 19-H_3), and 3.7 (3 H, s, OMe).

Reduction of 4β-*Acetoxy*-3β-p-*tolylsulphonyloxyandrost*-5-*en*-17-*one*.—The toluene-*p*-sulphonate (11) (10 g) [5] in dry ether (500 ml) was treated with lithium aluminium hydride (10 g) for 1 h under reflux. The mixture was poured into dilute hydrochloric acid and the steroids were extracted with ethyl acetate. The solvent was evaporated off to afford a gum which was dissolved in acetone (100 ml) and treated with 8N-chromium trioxide solution (20 ml) for 0.5 h at room temperature. The oxidant was destroyed with aqueous sodium sulphite, the acetone was evaporated off, and the steroids were recovered in ethyl acetate. The extract was separated into acidic and neutral fractions with aqueous sodium hydrogen carbonate. The acid fraction afforded 3β-carboxy-A-norandrost-5-en-17-one (2.5 g) as needles, m.p. 227—228° (from ether), identical (mixed m.p., i.r., and n.m.r.) with the sample described above. The neutral fraction comprised an inseparable mixture of androst-5-ene-4,17-dione and androst-4-en-17-one.

4β,5β-*Epoxyandrostane*-6,17-*dione*.— Androst-4-ene-6,17-dione [8] (0.5 g) in methanol (30 ml) was treated with sodium hydroxide (0.3 g) in water (1 ml) and hydrogen peroxide (3 ml) at room temperature for 1.5 h. Acetic acid was added and the solution was concentrated, poured into water, and extracted with ethyl acetate. Evaporation gave 4β,5β-*epoxyandrostane*-6,17-*dione* (15) (0.4 g) as plates, m.p. 167—169° (from ethyl acetate), $[\alpha]_D^{20}$ +53° (*c* 0.2) (Found: C, 75.4; H, 8.8. $C_{19}H_{26}O_3$ requires C, 75.5; H, 8.7%), $\nu_{max.}$ 1 730 and 1 710 cm^{-1}, δ 0.93 (3 H, s, 18-H_3), 1.03 (3 H, s, 19-H_3), and 3.07 (1 H, t, *J* 2 Hz, 4-H).

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