Conformational Studies. Part 4.[1] Some Reactions of Spiro[cholest-4-ene-6-spirocyclopropane]-3-one

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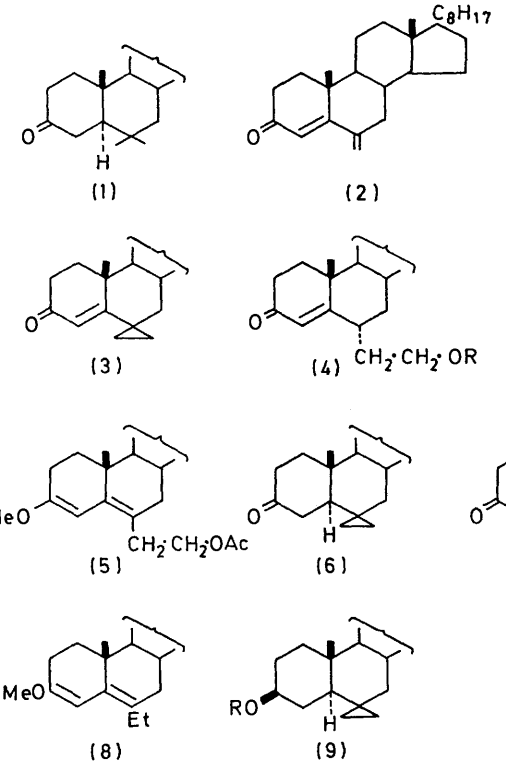
Spiro[cholest-4-ene-6-spirocyclopropane]-3-one has been prepared from 6-methylenecholest-4-en-3-one by an ylide reaction. Various reactions of this cyclopropane derivative are described.

As a result of our interest in the conformational properties of 4,4-dimethyl-3-oxo-steroids [2] we wished to investigate the chiroptical properties of the unknown isomeric 6,6-dimethyl-3-oxo-steroids (1).



6-Methylenecholest-4-en-3-one (2) was converted into spiro[cholest-4-ene-6-cyclopropane]-3-one (3) by the action of trimethylsulphonium iodide in dimethyl sulphoxide.[3] However, attempts to open the cyclopropane system symmetrically failed. Thus the action of a mixture of acetic and perchloric acids furnished an oil having the properties of a mixture of 6α- (4; R = Ac) and 6β-(2-acetoxyethyl)cholest-4-en-3-one, which readily furnished the homogeneous enol ether (5) with trimethyl orthoformate. Removal of the enolic methoxy-group gave 6α-(2-acetoxyethyl)cholest-4-en-3-one (4; R = Ac). The corresponding 6-(2-hydroxyethyl) derivative (4; R = H) was readily reconverted into (3) on treatment with pyridine–toluene-*p*-sulphonyl chloride.

Reduction of the cyclopropane (3), either catalytically, or with sodium in liquid ammonia, furnished spiro[5α-cholestane-6-spirocyclopropane]-3-one (6), the 5α-orientation of which is in accord with the positive o.r.d. curve (*a* + 24).

Treatment of the cyclopropane (6) with perchloric acid gave a mixture of 6α- and 6β-ethylcholest-4-en-3-one (7), which afforded 6-ethyl-3-methoxycholesta-3,5-diene (8) with trimethyl orthoformate.

Reduction of the cyclopropane (6) with sodium borohydride gave the 3β-ol (9; R = H), the configuration of which follows from general principles and from the chemical shift (τ 6.47) of the 3-proton. Attempts to hydrogenolyse the cyclopropane ring failed. Thus hydrogenation of the acetate (9; R = Ac) at 200 °C and 100 atm pressure with W-2-type Raney nickel resulted only in the formation of some 3β-ol (9; R = H) (contrast *e.g.* the hydrogenolysis of spiro[2.5]octane to 1,1-dimethylcyclohexane [4]).

EXPERIMENTAL

Rotations are for solutions in chloroform; i.r. data are for Nujol mulls. U.v. spectra were determined for solutions in absolute ethanol. N.m.r. spectra were determined at 60 Hz for solutions in $CDCl_3$.

Spiro[cholest-4-ene-6-cyclopropane]-3-one (3).—Sodium hydride (85%; 1.53 g) was added during 15 min to a stirred solution of trimethylsulphonium iodide (11.6 g) in dimethyl sulphoxide (100 ml) under nitrogen. A solution of 6-methylenecholest-4-en-3-one [5] (6.8 g) in tetrahydrofuran (200 ml) was added rapidly and the mixture was refluxed

[1] Part 3, M. H. Barnes and W. B. Whalley, preceding paper.
[2] J. M. Midgley, W. B. Whalley, P. A. Dodson, G. F. Katekar, and B. A. Lodge, *J.C.S. Perkin I*, 1977, 823.
[3] V. Georgian, U.S.P. 3,497,498/1970.
[4] R. W. Shortridge, R. A. Craig, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Amer. Chem. Soc.*, 1948, **70**, 946.
[5] G. M. Holder, School of Pharmacy, Ph.D. Thesis, University of London, 1966.

for 2 h, then diluted (2 : 1) with iced water. After isolation with benzene the crude product was purified by chromatography on alumina from benzene–light petroleum (b.p. 60—80 °C) (1 : 1) to yield the *cyclopropane* (3) which formed needles (5.6 g), m.p. 120° [from light petroleum (b.p. 60—80 °C)], $[\alpha]_D^{20}$ +21° (*c* 4.7) (Found: C, 85.3; H, 11.5. $C_{29}H_{46}O$ requires C, 84.8; H, 11.3%), $\nu_{max.}$ 1 660 and 1 610 cm^{-1}, τ 4.35 (H-4) and 9.59 (cyclopropane $[CH_2]_2$).

A solution of this ketone (2.0 g) in acetic acid (50 ml) containing perchloric acid (60%; 2 ml) was refluxed for 1 h. After isolation with ether a solution of the oily product (2.6 g) in tetrahydrofuran (20 ml) containing trimethyl orthoformate (2 ml) and concentrated sulphuric acid (0.1 ml) was heated on a steam-bath for 0.5 h. The cooled mixture was diluted with water (250 ml) containing pyridine (2 ml) and the product isolated with ether. Chromatography on alumina from light petroleum (b.p. 60—80 °C) gave 6-(2-*acetoxyethyl*)-3-*methoxycholesta*-3,5-*diene* (5), which formed needles (1.4 g), m.p. 75—77° (from aqueous acetone), $[\alpha]_D^{20}$ −118° (*c* 1.4) (Found: C, 79.3; H, 10.8. $C_{32}H_{52}O_3$ requires C, 79.3; H, 10.8%), $\nu_{max.}$ 1 740 and 1 242 cm^{-1} (acetate), $\lambda_{max.}$ 251 nm (ε 21 400), τ 7.99 (3 H, Ac), 6.36 (3 H, OMe), 5.88 (2 H, t, CH_2·OAc), and 4.50 (1 H, s, H-4).

A solution of this enol ether (0.2 g) in acetic acid (80%; 25 ml) was refluxed for 1.5 h to yield 6α-(2-*acetoxyethyl*)-*cholest*-4-*en*-3-*one* (4; R = Ac), which formed needles (0.15 g), m.p. 142° (from methanol), $[\alpha]_D^{19}$ +50° (*c* 1.6) (Found: C, 78.9; H, 10.3. $C_{31}H_{50}O_3$ requires C, 79.1; H, 10.7%), $\nu_{max.}$ 1 740 and 1 242 (acetate), and 1 680 and 1 615 cm^{-1} ($\alpha\beta$-unsaturated ketone), τ 7.94 (3 H, s, Ac), 5.91 (2 H, t, CH_2·OAc), and 4.21 (H-4).

Hydrolysis of 6-(2-acetoxyethyl)-3-methoxycholesta-3,5-diene occurred when a solution of this ester (1 g) in aqueous ethanol (90%; 50 ml) containing potassium hydroxide (1 g) was kept at 20 °C during 4 h, to give 6α-(2-*hydroxyethyl*)-3-*methoxycholesta*-3,5-*diene* (4; R = H), which formed needles (0.5 g), m.p. 132—134° (from aqueous methanol), $[\alpha]_D^{19}$ −102° (*c* 1.6) (Found: C, 80.9; H, 11.1. $C_{30}H_{50}O_2$ requires C, 81.4; H, 11.4%), $\nu_{max.}$ 3 380 cm^{-1} (OH), τ 6.38 (3 H, s, OMe), 6.30 (2 H, t, CH_2·OH), and 4.47 (1 H, s, H-4).

When a solution of this alcohol (0.2 g) in pyridine (2 ml) containing toluene-*p*-sulphonyl chloride (0.2 g) was kept at 18 °C during 2.5 h, and the product was isolated in the normal manner, spiro[cholest-4-ene-6-cyclopropane]-3-one (0.11 g), having the requisite m.p., mixed m.p., and i.r. and n.m.r. spectra, was obtained.

Spiro-[5α-*cholestane*-6-*cyclopropane*]-3-*one* (6).—(*a*) A solution of the cyclopropane (3) (2.0 g) in ethanol (200 ml) containing palladium–charcoal (10%; 0.2 g) was shaken in hydrogen during 4 h (uptake 115 ml). Chromatography on alumina from light petroleum (b.p. 60—80 °C) gave the *cholestan*-3-*one* (6) (1.5 g), which formed needles, m.p. 140° [from light petroleum (b.p. 60—80 °C)], $[\alpha]_D^{19}$ +22° (*c* 1.16) (Found: C, 84.0; H, 11.5. $C_{29}H_{48}O$ requires C, 84.4; H, 11.7%), $\nu_{max.}$ 1 705 cm^{-1} (C:O), τ 9.65 (cyclopropane $[CH_2]_2$).

(*b*) A solution of the cyclopropane (3) (0.5 g) in ether (100 ml) was added rapidly to a stirred solution of lithium (1 g) in liquid ammonia (150 ml). After 5 min ammonium chloride was added until the blue colour had disappeared. After evaporation of the ammonia the product was isolated with ether and purified as in (*a*) to yield the cholestan-3-one (6) (0.3 g), identical with that obtained by method (*a*). Reduction of this ketone (0.5 g) in ethanol (50 ml) at 20 °C for 1 h with sodium borohydride (0.5 g) gave *spiro*-[5α-*cholestane*-6-*cyclopropane*]-3β-*ol* (9; R = H) (0.4 g) in needles, m.p. 126° (from acetone), $[\alpha]_D^{19}$ +24° (*c* 1.13) (Found: C, 83.4; H, 11.8. $C_{29}H_{50}O$ requires C, 84.0; H, 12.2%). The *acetate* (9; R = Ac) separated from methanol in needles, m.p. 94° (Found: C, 81.2; H, 11.8. $C_{31}H_{52}O_2$ requires C, 81.5; H, 11.5%).

6-*Ethyl*-3-*methoxycholesta*-3,5-*diene* (8).—A solution of the cyclopropane (6) (0.4 g) in acetic acid (10 ml) containing perchloric acid (60%; 0.5 ml) was heated on a steam-bath for 1 h. Isolation in the usual manner furnished an oil which dissolved in tetrahydrofuran (5 ml) containing trimethyl orthoformate (0.5 ml) and concentrated sulphuric acid (0.1 ml). After 1 h at 20 °C the mixture was diluted with water (250 ml) containing pyridine (2 ml). Chromatography on alumina, and then purification from aqueous acetone gave 6-*ethyl*-3-*methoxycholesta*-3,5-*diene* (0.3 g) in needles, m.p. 84°, $[\alpha]_D^{20}$ −130° (*c* 1.18) (Found: C, 84.4; H, 11.9. $C_{30}H_{50}O$ requires C, 84.4; H, 11.8%), $\lambda_{max.}$ 249 nm (ε 17 000), τ 6.38 (3 H, s, OMe) and 4.52 (s, H-4).

A solution of the foregoing enol ether (0.5 g) in aqueous acetic acid (80%; 50 ml) was refluxed for 1 h. The resultant 6-ethylcholest-4-en-3-one was an oil, $\nu_{max.}$ 1 680 and 1 618 cm^{-1} ($\alpha\beta$-unsaturated ketone), $\lambda_{max.}$ 245 nm (ε 12 600), τ 4.18 (s, H-4). The 2,4-*dinitrophenylhydrazone* separated from ethanol in orange prisms, m.p. 215° (Found: C, 70.5; H, 8.9; N, 9.2. $C_{35}H_{52}N_4O_4$ requires C, 70.9; H, 8.8; N, 9.5%).

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