Unsaturated Steroids. Part 6.[1] A Route to Cholesta-5,7-diene-1α,3β-diol; Preparation of Steroidal 4,6,8(14)-Trienes

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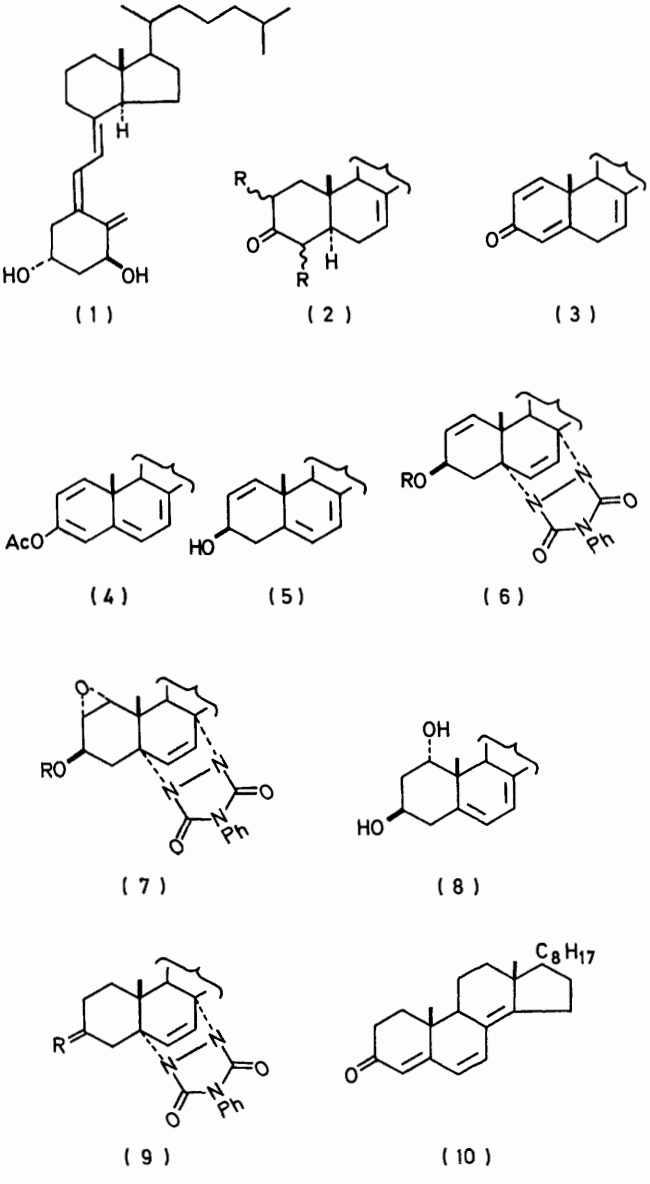
Bromination of 5α-cholest-7-en-3-one to give the corresponding 2ξ.4ξ-dibromo-derivative followed by dehydrobromination gives cholesta-1,4,7-trien-3-one (3). The corresponding cholesta-1,3,5,7-tetraen-3-yl acetate (4) was converted by the method of Kaneko *et al.* into the adduct of cholesta-1,5,7-trien-3β-ol with 4-phenyl-1,2,4-triazoline-3,5-dione. The corresponding dimethyl-t-butylsilyl ether was transformed into the 1α,2α,-epoxide, which was readily converted into cholesta-5,7-diene-1α,3β-diol (8). Treatment of the adduct from a steroidal 5,7-dien-3-one and 4-phenyl-1,2,4-triazoline-3,5-dione with boron trifluoride–ether yields the corresponding 4,6,8(14)-trien-3-one (10).

THE biological significance [2] of the 1α-hydroxy-derivative (1) of cholecalciferol has led to much activity in this area of synthetic chemistry. We now report a route to cholesta-5,7-diene-1α,3β-diol, and hence to 1α-hydroxycholecalciferol, from 5α-cholest-7-en-3β-ol.[3]

Oxidation of 5α-cholest-7-en-3β-ol with 4N-Jones reagent gave 5α-cholest-7-en-3-one (2; R = H) which on bromination (tri-*N*-methylanilinium perbromide) afforded 2ξ,4ξ-dibromo-5α-cholest-7-en-3-one (2; R = Br). This with lithium carbonate–dimethylformamide–lithium bromide furnished (in high yield) cholesta-1,4,7-trien-3-one (3), which on treatment with isopropenyl acetate–toluene-*p*-sulphonic acid in benzene gave cholesta-1,3,5,7-tetraen-3-yl acetate (4). The acetate was not normally purified but was reduced immediately with calcium borohydride (*cf.* ref. 4) to cholesta-1,5,7-trien-3β-ol (5),[2] which was converted into the adduct (6; R = H) with 4-phenyl-1,2,4-triazoline-3,5-dione (*cf.* ref. 4). Although epoxidation of (6; R = H) with *m*-chloroperbenzoic acid (*cf.* ref. 4) gave a mixture of the corresponding 1α,2α- and 1β,2β-epoxides, the dimethyl-t-butylsilyl ether [5] (6; R = Bu^tMe_2Si) furnished, as anticipated, exclusively and essentially quantitatively the 1α,2α-epoxide (7; R = Bu^tMe_2Si), from which the silyl group was removed (acetic acid–tetrahydrofuran at 40 °C) to form the epoxy-alcohol (7; R = H). Reduction of (7; R = H) with lithium aluminium hydride gave cholesta-5,7-diene-1α,3β-diol (8) (*cf.* refs. 4 and 6). Since the diol (8) has been converted [6] into 1α-hydroxycholecalciferol, our work completes a synthesis of this material.

During this work the adduct (9; R = H,OH) was converted into the ketone (9; R = O), which, in view of earlier observations,[7] was treated with boron trifluoride–ether, to generate, in high yield, cholesta-4,6,8(14)-trien-3-one (10). Ergosterol likewise furnished ergosta-4,6,8(14),22-tetraen-3-one.[8] The method appears to be



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of potential utility for the preparation of steroidal 4,6,8(14)-trienes (*cf.* ref. 9).

EXPERIMENTAL

Unless stated otherwise i.r. spectra and optical rotations were determined for solutions in chloroform; n.m.r. spectra were determined for solutions in deuteriochloroform and u.v. spectra for solutions in ethanol.

5α-Cholest-7-en-3-one.—A solution of 5α-cholest-7-en-3β-ol [3] (10 g) in acetone (500 ml) was treated (dropwise) with an excess of 4N-Jones reagent during 0.5 h. Isolated in the normal manner, the 5α-cholest-7-en-3-one (7.7 g) was purified from ether–methanol containing pyridine (5 drops) to furnish needles, m.p. 144—146°, $[\alpha]_D^{20}$ +26° (*c* 3.94) (lit.,[10] m.p. 146—148°, $[\alpha]_D$ +25°, for material prepared by an alternative method).

Cholesta-1,4,7-trien-3-one.—A solution of 5α-cholest-7-en-3-one (1 g) in tetrahydrofuran (20 ml) containing tri-*N*-methylanilinium perbromide (2 g) was stirred during 15 min at 0 °C, and at room temperature for a further 15 min. The mixture was poured into water and the product isolated with ether to yield 2ξ,4ξ-dibromocholest-7-en-3-one (1 g), which was normally utilised directly for the next reaction. Purification from ether–methanol gave the *dibromide* in needles (1 g), m.p. 192—195° (decomp.), $[\alpha]_D^{20}$ −18.3° (*c* 0.89), $\nu_{max.}$ 1 752 cm^{-1} (C=O) (Found: C, 59.7; H, 7.9; Br, 29.5. $C_{27}H_{42}Br_2O$ requires C, 59.8; H, 7.8; Br, 29.8%).

A solution of the unpurified dibromide (6 g) in dimethylformamide (30 ml) containing lithium carbonate (10 g) and lithium bromide (5 g) was stirred vigorously at 130 °C, during 40 min, while a stream of nitrogen was passed through the mixture. Purification of the product from ether and then methanol gave *cholesta-1,4,7-trien-3-one* [5.0 g from 5α-cholest-7-en-3-one (10 g)] in pale yellow needles, m.p. 130—132° (Found: C, 85.4; H, 10.7. $C_{27}H_{40}O$ requires C, 85.2; H, 10.6%), $[\alpha]_D^{20}$ −17.6° (*c* 2.84), $\nu_{max.}$ 1 650, 1 622, and 1 604 cm^{-1}, $\lambda_{max.}$ 241 nm (ε 14 300), τ 2.92 (1 H, d, $J_{1,2}$ 10 Hz, H-1), 3.18 (1 H, dd, $J_{1,2}$ 10, $J_{2,4}$ 1.5 Hz, H-2), 3.88 (1 H, d, $J_{2,4}$ 1.5 Hz, H-4), 4.75br (1 H, s, H-7), 7.00 (2 H, m, H_2-6; from double resonance experiments, $J_{6\alpha,6\beta}$ 18.5 Hz), and 9.38 (3 H, s, H_3-18).

Purification of accumulated residues from this preparation gave small quantities of *5α-cholesta-1,7-dien-3-one*, which formed pale yellow needles, m.p. 108—109° (from ether–methanol) (Found: C, 84.8; H, 10.9. $C_{27}H_{42}O$ requires C, 84.8; H, 11.1%), $[\alpha]_D^{19}$ −16° (*c* 1.11), $\nu_{max.}$ 1 675 cm^{-1} (αβ-unsaturated C:O), $\lambda_{max.}$ 228 nm (ε 7 350), τ 2.98 (1 H, d, $J_{1,2}$ 10 Hz, H-1), 4.10 (1 H, d, $J_{1,2}$ 10 Hz, H-2), 4.72br (1 H, s, H-7), and 9.42 (3 H, s, H_3-18) (*cf.* ref. 11).

Cholesta-1,5,7-trien-3β-ol.—A solution of cholesta-1,4,7-trien-3-one (0.38 g) in benzene (12 ml) containing isopropenyl acetate (3 ml) and toluene-*p*-sulphonic acid (0.15 g) was refluxed during 2 h to yield *cholesta-1,3,5,7-tetraen-3-yl acetate* (0.3 g), which formed pale yellow needles, m.p. 122—124° (from ether–methanol containing a trace of pyridine) (Found: C, 82.4; H, 9.8. $C_{29}H_{42}O_2$ requires C, 82.4; H, 10.0%), $[\alpha]_D^{20}$ −508° (*c* 1.5), $\nu_{max.}$ 1 755, 1 640, and 1 575 cm^{-1}, $\lambda_{max.}$ 252 (ε 93 800) and 360 nm (73 200), τ 4.06br (4 H, s), 4.32 (1 H, d), 7.83 (3 H, s, OAc), and 9.35 (3 H, s, H_3-18). A solution of the unpurified acetate (0.5 g) in ether (50 ml) was added dropwise at 0 °C to a stirred solution of calcium borohydride in ethanol–methanol [from calcium chloride (1.5 g) in methanol (35 ml) and sodium borohydride (0.75 g) in ethanol (40 ml)]. After 2 h the excess of reagent was destroyed with acetone and the majority of the solvent removed *in vacuo*. After addition of sufficient acetic acid to dissolve the resultant precipitate, the product was extracted with ether to yield, after chromatography on alumina from ether–light petroleum (b.p. 60—80 °C), cholesta-1,5,7-trien-3β-ol in needles (0.3 g), m.p. 125—127° (from ether–light petroleum) (lit.,[4] m.p. 127—129°, for a specimen prepared by an alternative method).

Cholesta-1,5,7-trien-3β-yl acetate separated from methanol in needles, m.p. 124—126° (Found: C, 82.1; H, 10.5. $C_{29}H_{44}O_2$ requires C, 82.0; H, 10.4%), $[\alpha]_D^{19}$ −69.5° (*c* 1.0), $\nu_{max.}$ 1 726 cm^{-1} (acetate), $\lambda_{max.}$ 262 (ε 8 700), 269 (11 600), 280 (11 600), and 290 nm (6 250), τ 4.16 (1 H, d, $J_{6,7}$ 10 Hz), 4.45 (1 H, d, $J_{6,7}$ 10 Hz), 4.38 (1 H, s), 4.60 (1 H, s), 4.64 (1 H, dd, *J* 10 and 6 Hz, H-3), 7.96 (3 H, s, OAc), and 9.37 (3 H, s, H_3-18).

The adduct of cholesta-1,5,7-trien-3β-ol [from cholesta-1,4,7-trien-3-one (0.5 g)] and 4-phenyl-1,2,4-triazoline-3,5-dione formed needles (0.5 g), m.p. 169—170° (decomp.), $[\alpha]_D^{19}$ −36° (*c* 1.9) (lit.,[4] m.p. 175—182°). The *benzoate* of this adduct separated from ether–methanol in plates, m.p. 137—139° (Found: C, 76.0; H, 8.0; N, 6.3. $C_{42}H_{51}N_3O_4$ requires C, 76.2; H, 7.8; N, 6.4%), $[\alpha]_D^{19}$ +42° (*c* 1.2). The p-*nitrobenzoate* separated from ether–methanol in pale yellow rhombs, m.p. 188° (decomp.) (Found: C, 71.7; H, 7.1; N, 8.5. $C_{42}H_{50}N_4O_6$ requires C, 71.4; H, 7.1; N, 7.9%), $[\alpha]_D^{19}$ +22° (*c* 1.68).

Cholesta-5,7-diene-1α,3β-diol.—The adduct (6; R = H) (0.9 g) dissolved in dimethylformamide (2 ml) was treated with imidazole (0.4 g) and dimethyl-t-butylsilyl chloride (0.4 g) at 35 °C during 18 h. The product was isolated by extraction with ether to yield the *silyl ether* (6; R = $SiMe_2Bu^t$) (0.8 g) as wax-like plates, m.p. 163—165° (from benzene) (Found: C, 73.6; H, 9.2; N, 6.2. $C_{41}H_{61}N_3O_3Si$ requires C, 73.3; H, 9.1; N, 6.3%), $[\alpha]_D^{20}$ 0° (*c* 1.27), τ 9.28 (9 H, s, Bu^t) and 9.98 (6 H, s, $SiMe_2$). A solution of this ether (0.8 g) in chloroform (25 ml) was stirred at room temperature with *m*-chloroperbenzoic acid (0.5 g) during 24 h. More peroxy-acid (0.3 g) was added and the mixture stirred for another 24 h. The *epoxide* was isolated with chloroform and separated from ether–methanol in needles, m.p. 154—157° (Found: C, 71.4; H, 9.0; N, 6.0. $C_{41}H_{61}N_3O_4Si$ requires C, 71.6; H, 8.9; N, 6.1%). The unpurified epoxide (0.84 g) was dissolved in tetrahydrofuran (12 ml), acetic acid (12 ml), and water (6 ml) and the mixture maintained at 40 °C during 4 days. Purified by chromatography on silica from light petroleum (b.p. 40—60 °C)–ether (3 : 7), the adduct 1α,2α-epoxide (0.4 g) separated from methanol in prisms, m.p. 193—195° (lit.,[4] m.p. 152—154°; but no elemental analysis recorded, and no molecular ion in the mass spectrum) (Found: C, 73.3; H, 8.4; N, 7.3%; M^+, 601. Calc. for $C_{35}H_{47}N_3O_4$: C, 73.3; H, 8.3; N, 7.3%; *M*, 601).

A solution of this 1α,2α-epoxide (0.22 g) in tetrahydrofuran (40 ml) containing lithium aluminium hydride (0.25 g) was refluxed during 2 h to yield cholesta-5,7-diene-1α,3β-

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diol (0.1 g) in small needles, m.p. 156—159° (from methanol), $[\alpha]_D^{19}$ −39° (*c* 1.0) (lit.,[4] m.p. 155—158°, $[\alpha]_D^{19}$ −45°; but no elemental analysis recorded) (Found: C, 80.5; H, 11.1. Calc. for $C_{27}H_{44}O_2$: C, 80.9; H, 11.1%).

Cholesta-4,6,8(14)-*trien*-3-*one* (10).—The adduct (3 g) from cholesta-5,7-dien-3β-ol and 4-phenyl-1,2,4-triazoline-3,5-dione dissolved in acetone (600 ml) was oxidised with an excess of 4N-Jones reagent to yield the corresponding *ketone* (2.8 g) in pale yellow prisms, m.p. 159—161° (decomp.) (from methanol), $[\alpha]_D^{20}$ −54° (*c* 1.63) (Found: C, 75.0; H, 8.6; N, 7.8. $C_{35}H_{47}N_3O_3$ requires C, 75.4; H, 8.5; N, 7.5%).

A solution of this adduct (1 g) in benzene (25 ml) was treated with boron trifluoride–ether (2 ml) during 15 min. After isolation in the usual manner, the product was purified by preparative t.l.c. [hexane–ethyl acetate (19 : 1)] to yield *cholesta*-4,6,8(14)-*trien*-3-*one* (0.5 g) in prisms, m.p. 61—63° (from hexane), $[\alpha]_D^{20}$ +647° (*c* 1.23) (Found: C, 85.0; H, 10.4. $C_{27}H_{40}O$ requires C, 85.2; H, 10.6%), τ 3.38 (1 H, d, $J_{6,7}$ 10 Hz, H-7), 3.96 (1 H, d, $J_{6,7}$ 10 Hz, H-6), and 4.26 (1 H, s, H-4).

Similarly, the adduct of ergosterol and 4-phenyl-1,2,4-triazoline-3,5-dione was oxidised to the *ketone*, which formed needles, m.p. 166—169° (decomp.) (from methanol), $[\alpha]_D^{23}$ −120° (*c* 1.13) (Found: C, 75.9; H, 8.0; N, 7.6. $C_{36}H_{47}N_3O_3$ requires C, 75.9; H, 8.3; N, 7.4%).

Treatment of this ketone (0.4 g) dissolved in benzene (16 ml) with boron trifluoride–ether (0.8 ml) during 15 min gave ergosta-4,6,8(14),22-tetraen-3-one (0.2 g) in pale yellow plates, m.p. 113—115° (from methanol), $[\alpha]_D^{22}$ +606° (*c* 1.0) (Found: C, 85.7; H, 10.3%; M^+, 392. Calc. for $C_{28}H_{40}O$: C, 85.7; H, 10.3%; *M*, 392), $\lambda_{max.}$ 348 nm (ε 25 300) {lit.,[8] m.p. 114—115°, $[\alpha]_D$ +590° (in $CHCl_3$), $\lambda_{max.}$ 348 nm (ε 26 500)}.

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