Calciferol and its Relatives. Part 25.[1] A Chemical Degradation of 3α-Hydroxycholest-9(11)-ene to Des-*AB*-cholestane Derivatives

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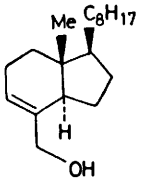
3α-Hydroxycholest-9(11)-ene was converted into 9α,11α-epoxycholesta-1,4-diene-3-one (12), which, on treatment with lithium aluminium hydride, underwent dienol–benzene cleavage of the 9,10-bond, giving the epimeric 9-hydroxy-9,10-seco-1,3,5(10)-cholestatrienes (14) and (15). These were further degraded to 8α-hydroxymethyl-des-*AB*-cholestane (19).

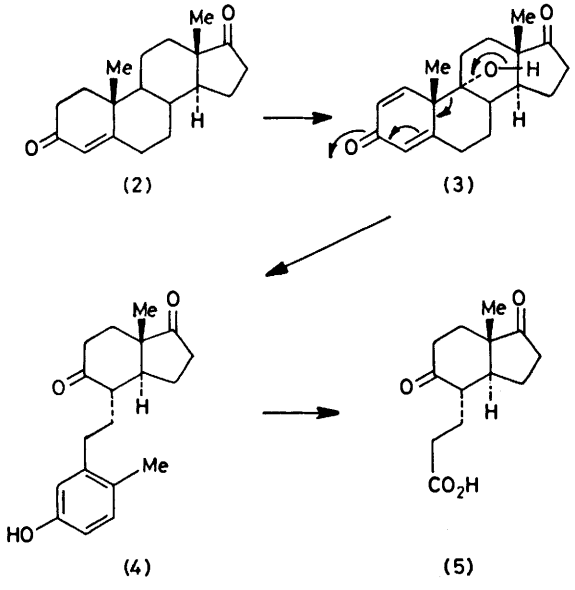
DES-*AB*-CHOLESTANE derivatives such as the allylic alcohol [2] (1) are of interest as intermediates for the synthesis of vitamin D_3 and its relatives by the *A*→*CD* route; they can be obtained either by total synthesis [3] or by degradation of an intact steroid.[2] The degradative



(1)

approach avoids many of the stereochemical problems inherent in a total synthesis, and its success depends mainly on the efficiency with which the C(9)–C(10) and C(6)–C(7) bonds can be cleaved.

Micro-organisms degrade steroids such as androst-4-



SCHEME 1

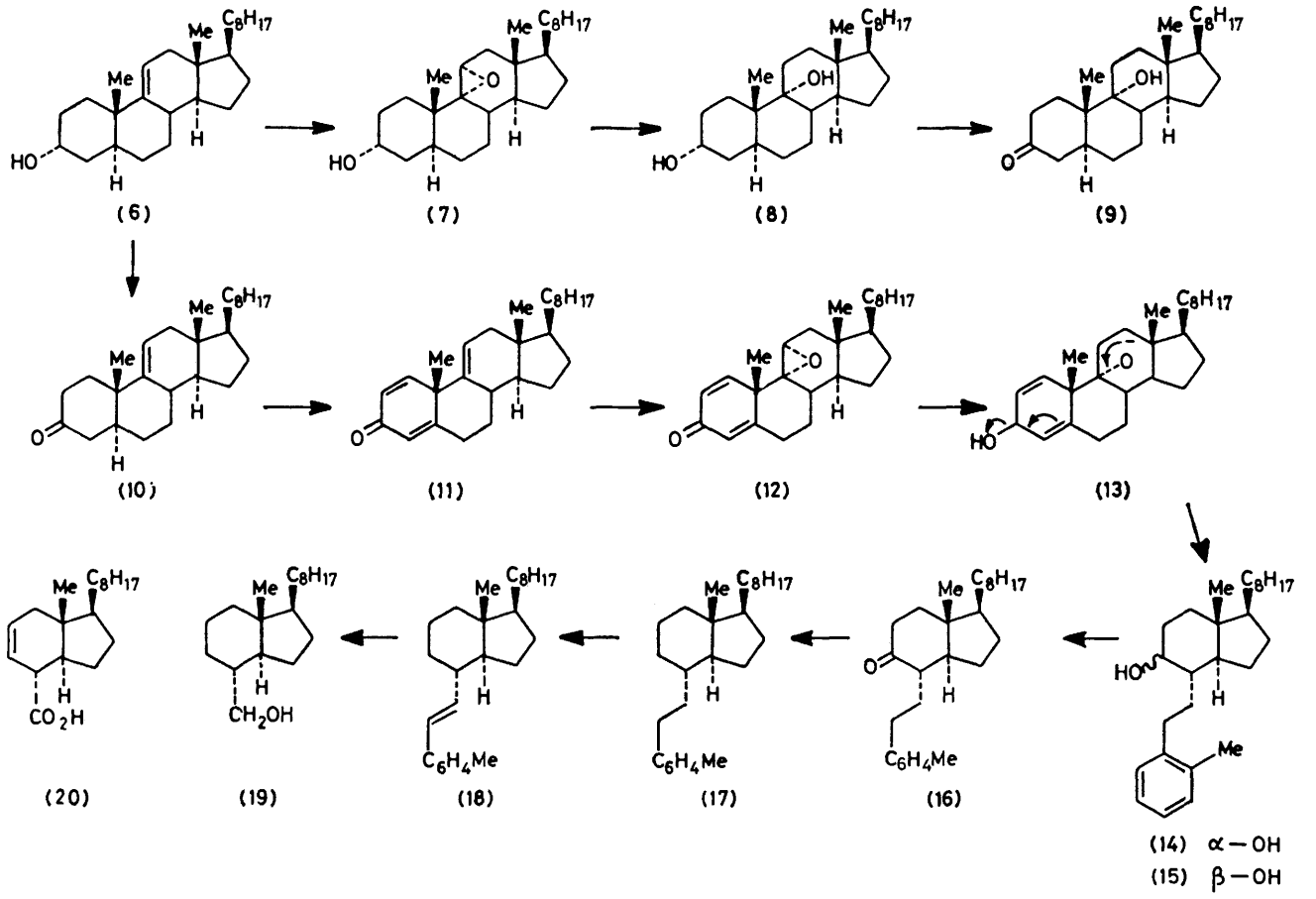
ene-3,17-dione in a well-established sequence (Scheme 1) leading [4a] to the keto-acid (5). 1,2-Dehydrogenation and 9α-hydroxylation first lead to the 9α-hydroxydienone (3), in which cleavage of the 9,10-bond is achieved by retro-aldolisation accompanied by a dienone–phenol change. The phenol (4) is then further degraded to give the keto-acid (5). Analogues of this keto-acid containing a cholestane or bile-acid side-chain at C(17) would clearly be useful intermediates for our synthetic purposes, but microbial degradation of steroids with such side-chains according to the route of Scheme 1 is not frequently observed. † In the present work we therefore attempted to achieve the results of the microbial degradation by chemical methods.

RESULTS AND DISCUSSION

3α-Hydroxycholest-9(11)-ene (6) was used as the starting material, since it offered facilities for introducing the 9α-hydroxy-group; it can be obtained from cholesterol in about 56% yield by using Breslow's [5] remote chlorination method. Reduction of the α-epoxide (7) with lithium aluminium hydride gave the 3α,9α-diol (8), which was then oxidised to give 9α-hydroxycholestan-3-one (9). We were, however, unable to convert this ketone into its 1,4-didehydro-derivative.

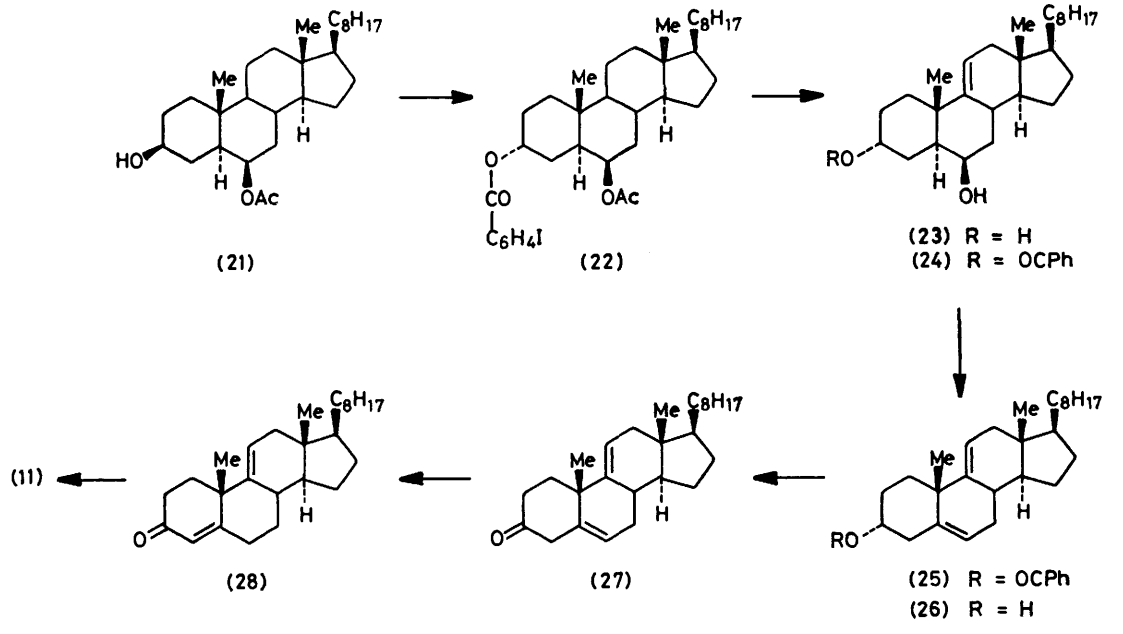
Instead, the 3-ketone (10), obtained by oxidising the 3α-ol (6), was converted by standard methods into its 2,4-dibromo-derivative, and then into the trienone (11). Treatment with *m*-chloroperbenzoic acid gave selectively the 9α,11α-epoxide (12). This was reduced with lithium aluminium hydride in order to obtain the 3,9-dihydroxy-1,4-diene, re-oxidation of which was expected to give the required hydroxydienone. However, the anion (13), which was formed as an intermediate, underwent a dienol-benzene fragmentation, which was followed by reduction of the 9-keto-group to give a mixture of the epimeric 9-hydroxy-compounds (14) and (15) in a combined yield of about 35% from the starting compound (6). Their nature as epimers was shown by their oxidation to the same 9-oxo-compound (16). This was converted into its ethylenedithioacetal, which was reduced with Raney nickel to give the *o*-tolylethyl compound (17). Its structure was shown by subjecting it to benzylic bromination, followed by dehydrobromination to the *trans*-styryl compound (18). Ozonolysis and reduction of the resulting aldehyde gave 8α-hydromethyl-des-*AB*-cholestane (19), isolated as the *p*-nitrobenzoate.

† Dr. H. L. Herzog (Schering Corporation, Bloomfield, New Jersey) has very kindly drawn our attention to the work of Hayakawa and his colleagues,[4b] who have effected such degradations of cholic acid and lithocholic acid using *Corynebacterium simplex* (*Arthrobacter simplex*).



The same compound was obtained from des-*AB*-cholest-9(11)-ene-8α-carboxylic acid [2] (20) by hydrogenation, esterification, reduction, and *p*-nitrobenzoylation of the product.

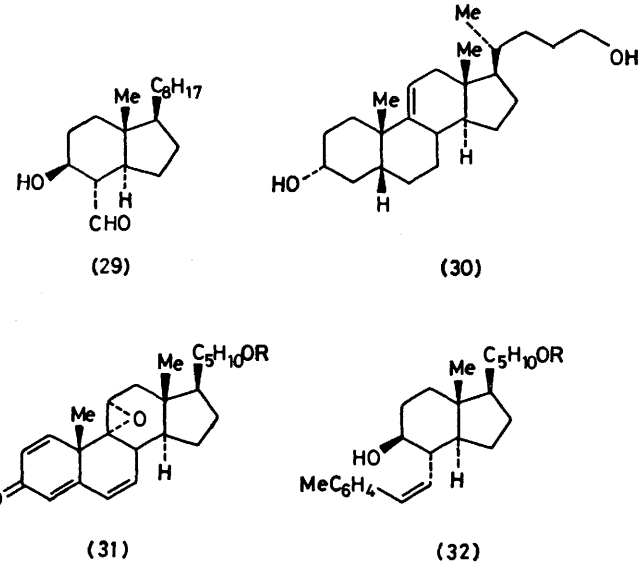
We also explored an alternative approach (Scheme 2) to the trienone (11), in which the known [6] monoacetate (21) was converted [7] into the *m*-iodobenzoate (22) and then, by Breslow's method, into the 3α,6β-dihydroxy-



SCHEME 2

9(11)-ene (23). Treatment of its 3-monobenzoate (24) with phosphoryl chloride in pyridine gave the 5,9(11)-diene (25), which was hydrolysed to the 3α-ol and then oxidised to the 3-ketone (27). Conjugation to give the 4,9(11)-dien-3-one (28) was effected by treatment with acid, and dehydrogenation with dichlorodicyanobenzoquinone [8] then gave the trienone (11). This route is longer and less efficient than that described earlier in the paper, but compounds like (27) are of interest in that they offer a possible route to 6-hydroxylated and 6-dehydro-analogues of (11) which should provide, after fragmentation, easy access to the hydroxy-aldehyde (29), and thence to the allylic alcohol (1).

Since the degradative method here described requires the preliminary introduction of a 9(11)-double bond, it may be less suitable for use with cholesterol than with, for example, deoxycholic acid, which can be converted rather easily into the 9(11)-unsaturated compound [9] (30). One can envisage a degradation of the latter through the epoxy-compound (31) to the olefin (32), from which the 25-hydroxy-derivative of the allylic alcohol (1) could be obtained. This compound would be valuable as an intermediate for the synthesis of 25-hydroxy-vitamin D derivatives.



EXPERIMENTAL

Light petroleum refers to the fraction of b.p. 60—80 °C. T.l.c. and p.l.c. were carried out using Kieselgel GF_{254}. N.m.r. data refer to solutions in deuteriochloroform, and optical rotation data to solutions in chloroform.

9α,11α-*Epoxy*-5α-*cholestan*-3α-*ol* (7).—A mixture (6.18 g) of cholest-9(11)-en-3α-ol and cholestan-3α-ol, obtained by Breslow's method,[5] was kept at room temperature for 16 h with *m*-chloroperbenzoic acid (3.5 g) in dichloromethane (50 cm³). The solvent was removed under reduced pressure and a solution of the residue in ether (100 cm³) was washed with aqueous sodium sulphite, aqueous sodium carbonate, and water, and dried and evaporated. Chromatography on silica gel (5% ethyl acetate–benzene) gave the *epoxide* (7), which formed plates (2.8 g) (from ethanol), m.p. 177—178 °C; $[\alpha]_D^{23}$ +8.1°, $\nu_{max.}$ (CCl_4) 1 115m, 1 380m, 1 465m, and 3 485m cm^{-1}; τ 6.02 (1 H, m, C*H*OH), 6.86 (1 H, d, *J* 6 Hz, CH–O–C), 8.93 (3 H, s, Me), and 9.34 (3 H, s, Me) (Found: C, 80.7; H, 11.65. $C_{27}H_{46}O_2$ requires C, 80.5; H, 11.5%).

9α-*Hydroxy*-5α-*cholestan*-3-*one* (9).—The epoxide (7) (2.25 g) and lithium aluminium hydride (1 g) were heated together under reflux under nitrogen in tetrahydrofuran (50 cm³) for 20 h. To the cooled solution 1N aqueous sodium hydroxide (5 cm³) was added, followed by magnesium sulphate. Filtration and evaporation gave 5α-*cholestane*-3α,9α-*diol* (8) (2.22 g; 98%); $\nu_{max.}$ (CCl_4) 1 375m, 1 460m, 3 300m and 3 490w cm^{-1}; τ 6.00 (1 H, br, C*H*OH) and 9.32 (3 H, s, Me) (Found: M^+, 404.336 0. $C_{27}H_{48}O_2$ requires *M*, 404.365 4).

The diol (8) (570 mg), sodium acetate (100 mg), and pyridinium chlorochromate (490 mg) were stirred together in dichloromethane (30 cm³) for 2 h. Ether (20 cm³) was added, the mixture was filtered through Celite, and the filtrate was evaporated. The residue was dissolved in ether (50 cm³) and the solution was washed with aqueous sodium hydroxide and water, and was dried and evaporated. Crystallisation of the residue from methanol gave 9α-*hydroxy*-5α-*cholestan*-3-*one* (9) as rods (520 mg; 90%), m.p. 185—187 °C; $[\alpha]_D^{32}$ +27.4°; $\nu_{max.}$ ($CHCl_3$) 1 375m, 1 465m, 1 700s and 3 510s cm^{-1}; τ 8.84 (3 H, s, Me) and 9.29 (3 H, s, Me) (Found: C, 80.35; H, 11.6. $C_{27}H_{46}O_2$ requires C, 80.5; H, 11.5%).

5α-*Cholest*-9(11)-*en*-3-*one* (10).—Oxidation of the alcohol (6) (2.87 g) with Jones reagent in acetone in the usual way gave the ketone (10) (2.77 g; 97%) which separated from methanol–ether as plates, m.p. 109—110 °C; $[\alpha]_D^{23}$ +48.8°; $\nu_{max.}$ (CCl_4) 1 370m, 1 465m, and 1 715s cm^{-1}; τ 4.65 (1 H, m, =CH–), 8.83 (3 H, s, Me), and 9.36 (3 H, s, Me) (Found: C, 84.25; H, 11.55. $C_{27}H_{44}O$ requires C, 84.3; H, 11.5%).

Cholesta-1,4,9(11)-*trien*-3-*one* (11).—The ketone (10) (200 mg) and pyridinium hydrobromide perbromide (333 mg) were stirred together at 0 °C in dry tetrahydrofuran (5 cm³) for 15 min; stirring was then continued at 20 °C for 30 min. Ether (25 cm³) was then added, and the solution was washed with 2N-hydrochloric acid, aqueous sodium carbonate, and water, and then dried and evaporated to an oil (280 mg). Crystallisation from methanol–ether gave 2α,4α-*dibromocholest*-9(11)-*en*-3-*one* as needles (150 mg), m.p. 198—201 °C (decomp.); $[\alpha]_D^{23}$ +9.1° (Found: C, 59.8; H, 7.75; Br, 29.6. $C_{27}H_{42}Br_2O$ requires C, 59.8; H, 7.8; Br, 29.5%).

When the above crude dibromide (280 mg) was heated with lithium bromide (250 mg) and lithium carbonate (500 mg) in dry dimethylformamide (5 cm³) at 135 °C under nitrogen with vigorous stirring for 2 h, dehydrobromination took place; addition of light petroleum, and washing of the solution with water, gave, after evaporation of the petroleum, a gum (220 mg), which was purified by p.l.c. to give an oil (145 mg). Crystallisation from methanol gave the *trienone* (11) as needles [127 mg; 65% from (10)], m.p. 107—110 °C; $[\alpha]_D^{23}$ −9.5°; $\lambda_{max.}$ (EtOH) 243 nm (ε 13 800); $\nu_{max.}$ (CCl_4) 905m, 1 380m, 1 470m, and 1 660s cm^{-1}; τ 2.78 (1 H, d, *J* 10 Hz, =CH), 3.72 (1 H, dd, *J* 10 and 2 Hz, =CH), 3.91 (1 H, d, *J* 2 Hz, =CH), 4.49 (1 H, m, =CH), 8.57 (3 H, s, Me), and 9.30 (3 H, s, Me) (Found: C, 85.15; H, 10.6. $C_{27}H_{40}O$ requires C, 85.2; H, 10.6%).

3α-*Hydroxycholesta*-5,9(11)-*diene* (26).—The monoacetate (21) (19 g) was subjected to reaction with triphenylphosphine (11.71 g) and *m*-iodobenzoic acid (11.1 g) in dry tetrahydrofuran (600 cm³) with diethyl azodicarboxylate (7.78 g) in

tetrahydrofuran (50 cm³); after stirring for 15 h the mixture was worked up in the usual way to give the *m*-iodobenzoate (22) as an oil (22 g), homogeneous to t.l.c.; $\nu_{max.}$ (CCl_4) 1 250s, 1 720s, and 1 735s cm^{-1}; τ 1.65—2.80 (4 H, m, Ar-H), 4.68 (1 H, br s, CHOCO), 5.06 (1 H, br s, C*H*OAc), 7.94 (3 H, s, Ac), 8.95 (3 H, s, Me), and 9.28 (3 H, s, Me). Chlorination of a portion (20.4 g) by Breslow's method,[5] and treatment of the product with hot aqueous ethanolic potassium hydroxide gave crude cholest-9(11)-ene-3α,6β-diol (23) as a solid (14.5 g); $\nu_{max.}$ (CCl_4) 1 370m, 1 470m, 3 410s, and 3 620m cm^{-1}; τ 4.65 (1 H, m, =CH), 5.82br (1 H, s, CHOH), 6.20 (1 H, s, CHOH), 8.85 (3 H, s, Me), and 9.36 (3 H, s, Me) (Found: M^+, 402.354 1. Calc. for $C_{27}H_{46}O_2$: *M*, 402.349 8). The crude diol (14 g) was treated with benzoyl chloride (4.22 g) in pyridine (100 cm³) for 16 h at 25 °C and the product was isolated in the usual way, and was purified by chromatography on silica gel (benzene). The monobenzoate (24) (11 g), $\nu_{max.}$ (CCl_4) 1 275s, 1 720s, and 3 620w cm^{-1} did not crystallise. A portion (7 g) was stirred at 0 °C in dry pyridine (50 cm³) during the addition (0.5 h) of phosphoryl chloride (3 g). Stirring was continued at 20 °C for 20 h, and the solution was then diluted with ether (200 cm³) and worked up in the usual way to give the benzoate (25) as a viscous oil (5.9 g), homogeneous to t.l.c.; $\nu_{max.}$ (CCl_4) 1 110m, 1 270s, 1 600w, and 1 720s cm^{-1}; τ 8.74 (3 H, s, Me), and 9.31 (3 H, s, Me) (Found: M^+, 488.365 98. Calc. for $C_{34}H_{48}O_2$: *M*, 488.365 41). Hydrolysis of the benzoate (5.9 g) with potassium hydroxide (4 g) in methanol (100 cm³) and benzene (20 cm³) at 20 °C for 12 h, and work-up in the usual way gave the *dienol* (26) as needles (3.2 g) (from methanol–chloroform), m.p. 131—132.5 °C; $[\alpha]_D^{23}$ −22.9°; $\nu_{max.}$ (CCl_4) 1 370m, 1 465m, and 3 580w cm^{-1}; τ 4.48 (2 H, m, =CH), 5.98 (1 H, br s, C*H*OH), 8.80 (3 H, s, Me), and 9.33 (3 H, s, Me) (Found: C, 84.1; H, 11.4. $C_{27}H_{44}O$ requires C, 84.3; H, 11.5%).

Cholesta-4,9(11)-*dien*-3-*one* (28).—Jones reagent (1.5 cm³; 2.67M) was added to a stirred solution of the dienol (26) (1.3 g) in acetone (100 cm³). After 10 min propan-2-ol (1 cm³) was added, and stirring was continued for 16 h. Solvent was then removed under reduced pressure, and the product was isolated with ether and chromatographed on silica gel (5% ethyl acetate–benzene). Crystallisation from methanol gave the *dienone* (28) as needles (760 mg), m.p. 137—138 °C; $[\alpha]_D^{23}$ −27.3°; $\lambda_{max.}$ (EtOH) 250 nm (ε 12 700); $\nu_{max.}$ (CCl_4) 1 240m, 1 465m, and 1 690s cm^{-1}; τ 3.82 (1 H, s, =CH), 4.32 (1 H, m, =CH), 8.64 (3 H, s, Me), and 9.30 (3 H, s, Me) (Found: C, 84.4; H, 10.8. $C_{27}H_{42}O$ requires C, 84.75; H, 11.1%).

The dienone (28) (760 mg) and dichlorodicyanobenzoquinone (550 mg) were heated together under reflux in benzene (20 cm³) under nitrogen for 24 h. The filtered solution was evaporated and the residue subjected to p.l.c. (5% ethyl acetate–benzene) which gave starting material (200 mg) and, as the more polar component, the trienone (11) (500 mg) which formed plates (from methanol), m.p. 108—111 °C; $[\alpha]_D^{23}$ −9.5°. Its spectral data were identical with those of material prepared from the ketone (10).

9α,11α-*Epoxycholesta*-1,4-*dien*-3-*one* (12).—This was prepared in the usual manner from the trienone (11) and *m*-chloroperbenzoic acid in dichloromethane, and purified by p.l.c.; the *epoxide* separated from light petroleum as small needles (90%), m.p. 147—148 °C; $[\alpha]_D^{23}$ +15.8°, $\lambda_{max.}$ (EtOH) 239 nm (ε 12 600); $\nu_{max.}$ (CCl_4) 1 380m, 1 465m, and 1 670s cm^{-1}; τ 3.32 (1 H, d, *J* 10 Hz, =CH), 3.76 (1 H, dd, *J* 10 and 2 Hz, =CH), 3.82 (1 H, d, *J* 2 Hz, =CH), 6.66 (1 H, d, *J* 6 Hz, CHOC), 8.49 (3 H, s, Me), and 9.25 (3 H, s, Me) (Found: C, 81.65; H, 10.1. $C_{27}H_{40}O_2$ requires C, 81.8; H, 10.2%).

Fragmentation of the Epoxydienone (12).—The epoxydienone (12) (800 mg) and lithium aluminium hydride (250 mg) were heated together under reflux in dry tetrahydrofuran (25 cm³) under nitrogen for 16 h. The cooled mixture was worked up in the usual way and the oily product was separated by p.l.c. (10% ethyl acetate–benzene) into two main components. The less polar component, 9α-*hydroxy*-9,10-*secocholesta*-1,3,5(10)-*triene* (14) formed an oil (190 mg); $\nu_{max.}$ (CCl_4) 745s, 1 460s, 1 605w, and 3 360s cm^{-1}; τ 2.86 (4 H, s, Ar-H), 5.94 (1 H, br s, C*H*OH), 7.2—7.5 (2 H, m, CH_2Ar), 7.68 (3 H, s, Ar*Me*), and 9.30 (3 H, s, Me) (Found: M^+, 384.338 52. $C_{27}H_{44}O$ requires *M*, 384.339 20). The 9β-*hydroxy-isomer* (15) formed an oil (300 mg); $\nu_{max.}$ as for the α-isomer; τ 2.87 (4 H, s, Ar-H), 6.4—6.7 (1 H, m, C*H*OH), 7.2—7.5 (2 H, m, Ar-CH_2), 7.67 (3 H, s, Ar-Me), and 9.23 (3 H, s, Me) (Found: M^+, 384.338 9).

9,10-*Seco*-1,3,5(10)-*cholestatrien*-9-*one* (16).—Oxidation of the alcohol (15) (143 mg) in dichloromethane (10 cm³) with pyridinium chlorochromate (169 mg) at room temperature for 1 h and work-up in the usual way gave the *ketone* (16) as an oil (142 mg), homogeneous to t.l.c.; $\nu_{max.}$ (film) 740m, 1 385m, 1 465m, and 1 710s cm^{-1}; τ 2.89 (4 H, s, Ar-H), 7.65 (3 H, s, Ar-Me), and 9.18 (3, H s, Me) (Found: M^+, 382.323 16. $C_{27}H_{42}O$ requires *M*, 382.323 55). The 2,4-*dinitrophenylhydrazone* formed needles (from methanol–ether), m.p. 110—112 °C; $[\alpha]_D^{23}$ −32.6° (Found: C, 70.25; H, 8.05; N, 10.0. $C_{33}H_{46}N_4O_4$ requires C, 70.4; H, 8.2; N, 10.0%).

Oxidation of the 9α-alcohol (14) yielded a ketone with properties identical to those of the material described above, and giving an identical 2,4-dinitrophenylhydrazone.

8α-*Hydroxymethyl-des*-AB-*cholestane* (19).—The ketone (16) (122 mg) was treated with ethanedithiol in hot acetic acid containing boron trifluoride–ether, and the mixture was worked up in the usual way to give the dithioacetal (140 mg), which was then desulphurised with W-2 Raney nickel in hot ethanol to give the hydrocarbon (17) (95 mg); $\nu_{max.}$ (film) 740m, 1 380m, and 1 465m cm^{-1}; τ 2.90 (4 H, m, Ar-H), 7.70 (3 H, s, Ar-Me), and 9.31 (3 H, s, Me) (Found: M^+, 368.344 01. Calc. for $C_{27}H_{44}$: *M*, 368.344 28).

The hydrocarbon (17) (60 mg) was heated under reflux in carbon tetrachloride (5 cm³) with *N*-bromosuccinimide (42 mg) and benzoyl peroxide (5 mg) for 45 min; the solution was then filtered and evaporated under reduced pressure. The residue was heated under reflux for 5 h with potassium t-butoxide [from potassium (40 mg) and t-butyl alcohol (2 cm³)] in tetrahydrofuran (3 cm³). The product, isolated in the usual way, and purified by p.l.c., was the olefin (18), an oil (41 mg); τ 2.5—3.0 (4 H, m, Ar-H), 3.48 (1 H, d, 16 Hz, =CH), 4.14 (1 H, dd, *J* 16 and 8 Hz, =CH), 7.70 (3 H, s, Ar-Me), and 9.28 (3 H, s, Me). Ozonolysis and reduction of the resulting aldehyde with lithium aluminium hydride gave the 8α-hydroxymethyl compound (19) as an oil (36 mg); $\nu_{max.}$ (film) 1 380m, 1 465m, and 3 320s cm^{-1}; τ 6.38 (1 H, dd, J_{vic} 4, J_{gem} 10 Hz, C*H*HOH), 6.62 (1 H, dd, J_{vic} 6, J_{gem} 10 Hz, CH*H*OH), and 9.32 (3 H, s, Me). The *p*-*nitrobenzoate* formed fine needles (from methanol), m.p. 69—71 °C; $[\alpha]_D^{23}$ +12.9° (Found: C, 72.55; H, 9.35; N, 3.35. $C_{26}H_{39}NO_4$ requires C, 72.7; H, 9.15; N, 3.3%).

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