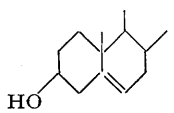
330. *Steroids. Part II.*† *The Preparation of* epi*Cholesteryl Chloride and Bromide.*

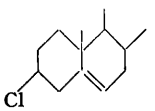
By C. W. Shoppee and G. H. R. Summers.

The preparation of *epi*cholesteryl chloride and *epi*cholesteryl bromide from the corresponding 3α-halogenocholestan-6β-ols is described.

It has been shown (Shoppee, *J.*, 1946, 1147) that the conversion of cholesterol (I) into cholesteryl chloride (II) (or bromide) occurs with preservation of configuration at $C_{(3)}$. It seemed possible that conditions might be found for the analogous conversion of *epi*cholesterol (III) into *epi*cholesteryl chloride (IV) (or bromide). Despite numerous experiments (to be described subsequently in another connexion) such conditions have not been found, but we have been able to prepare *epi*cholesteryl chloride (IV*a*) and *epi*cholesteryl bromide by a suitable modification of the route, described in the preceding paper, leading to the cholesteryl halides (as II).



(I)



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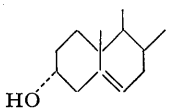

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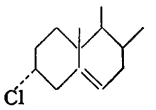


(IV*a*)

3β-Hydroxycholestan-6-one (V) was converted by treatment with phosphorus pentachloride into 3α-chlorocholestan-6-one (VI*a*) (Windaus and Stein, *Ber.*, 1904, **37**, 3699; Windaus and von Staden, *ibid.*, 1921, **54**, 1059). The configuration at $C_{(3)}$ of (VI*a*) has been proved (Shoppee, *J.*, 1948, 1032), and by reduction with lithium aluminium hydride at 0—20° this compound furnished 3α-chlorocholestan-6β-ol (VII*a*), unaccompanied by any detectable quantity of the 6α-epimeride and reconverted into the 3α-chloro-ketone by chromium trioxide. Dehydration of the 3α-chloro-alcohol (VII*a*) with phosphorus oxychloride and pyridine at 20° readily gave *epi*cholesteryl chloride (IV*a*).

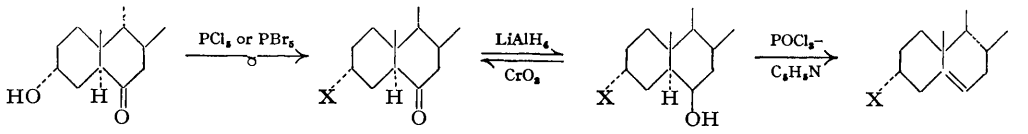
Similarly, by use of phosphorus pentabromide there was obtained 3α-bromocholestan-6-one (VI*b*), reduced to 3α-bromocholestan-6β-ol (VII*b*), which was dehydrated to yield *epi*cholesteryl bromide (IV*b*).

The hydroxy-ketone (V) has been converted into *epi*cholesteryl chloride by two other routes. Reduction with lithium aluminium hydride gives cholestane-3β : 6β-diol (VIII)

* Aluminium oxide (Spence, type H) was warmed for 1 hour on a steam-bath with 5% nitric acid, filtered off, and washed until the filtrate was free from NO_3^-. The material was then extracted twice with boiling methanol for 1 hour, and reactivated at 250°/10 mm. for 1 hour.

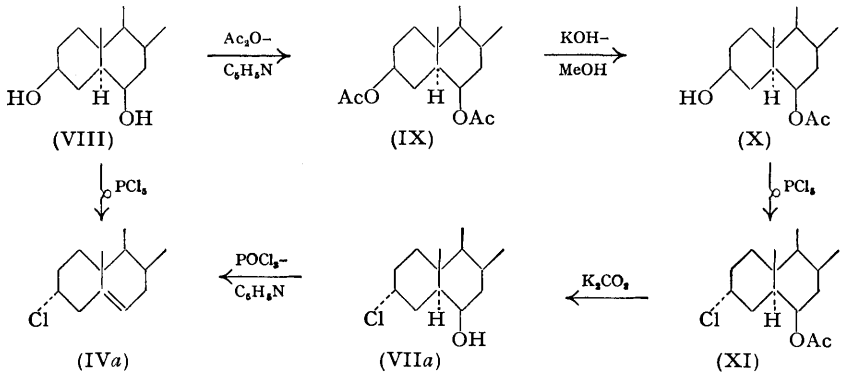
† Part I, preceding paper.

(Marker and Krueger, *J. Amer. Chem Soc.*, 1940, **62**, 79; Plattner and Lang, *Helv. Chim. Acta*, 1944, **27**, 1872) as the main product, accompanied by some cholestane-3β : 6α-diol (Windaus, *Ber.*, 1917, **50**, 133; Barton and Rosenfelder, *J.*, 1951, 2381). The 3β : 6β-diol



(V) (VI*a*; X = Cl) (VI*b*; X = Br) (VII*a*; X = Cl) (VII*b*; X = Br) (IV*a*; X = Cl), m. p. 107°, $[\alpha]_D$ −3° (IV*b*; X = Br), m. p. 105°, $[\alpha]_D$ −5°

(VIII), when treated with phosphorus pentachloride, undergoes substitution with inversion of configuration at $C_{(3)}$, and subsequent dehydration gives *epi*cholesteryl chloride (IV*a*) accompanied by some cholesta-3 : 5-diene. Alternatively, the 3β : 6β-diol (VIII) may be converted into the 3β : 6β-diacetoxy-compound (IX), which by partial hydrolysis affords the 6β-acetoxycholestan-3β-ol (Plattner and Lang, *loc. cit.*); this, on treatment with phosphorus pentachloride, undergoes replacement with inversion of configuration at $C_{(3)}$, to yield 3α-chloro-6β-acetoxycholestane (XI), which is hydrolysed by potassium carbonate at 20° to 3α-chlorocholestan-6β-ol (VII*a*); this in turn is dehydrated by phosphorus oxychloride and pyridine to *epi*cholesteryl chloride (IV*a*).



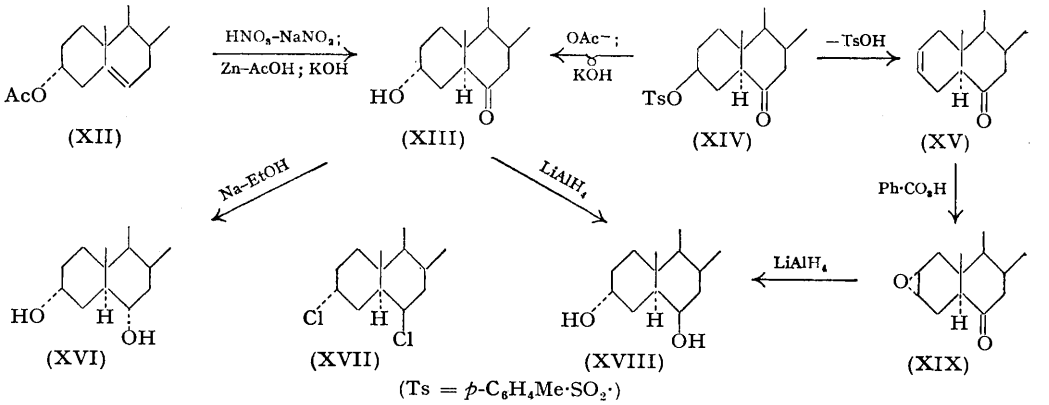
(VIII) (IX) (X) (IV*a*) (VII*a*) (XI)

Both *epi*cholesteryl chloride and bromide are stable crystalline substances; in the Rosenheim test, which depends on the formation of a diene system, both give an immediate pale pink colour which rapidly deepens to red. Whereas cholesteryl chloride and bromide by hydrogenation furnish good yields of 3β-chloro- and 3β-bromo-cholestane respectively, *epi*cholesteryl chloride gives only a little 3α-chlorocholestane accompanied by much cholestane. Other reactions of the *epi*cholesteryl halides will be described later.

The conversion of cholestane-3β : 6β-diol (VIII) into *epi*cholesteryl chloride (IV*a*) by treatment with phosphorus pentachloride may be contrasted with the behaviour of cholestane-3β : 6α-diol with the same reagent to furnish 3α : 6β-dichlorocholestane (Windaus, *Ber.*, 1917, **50**, 133) and compared with its conversion as the 3β : 6β-dimethanesulphonate into cholesteryl acetate by treatment with silver acetate in acetic acid (Reich and Lardon, *Helv. Chim. Acta*, 1946, **29**, 671). In the first-named reaction, substitution (S_N2) with inversion of configuration at $C_{(3)}$ precedes ionic 5 : 6-elimination (*E*2). In the last-named transformation, the ionic 5 : 6-elimination reaction precedes the substitution reaction (S_N1) at $C_{(3)}$, which, by intervention of the π-electrons so provided, proceeds with preservation of configuration.

It seemed of interest to examine the reactions of cholestane-3α : 6α-diol (XVI) and -3α : 6β-diol (XVIII) with phosphorus pentachloride. These diols were obtained from 3α-hydroxycholestan-6-one (XIII), which was prepared (*a*) from *epi*cholesteryl acetate (XII) by successive nitration, reduction, and hydrolysis, and (*b*) from 3β-toluene-*p*-

sulphonyloxycholestan-6-one (XIV) by acetolysis and subsequent hydrolysis [cholest-2-en-6-one (XV) was also formed]. Reduction of the 3α-hydroxy-ketone (XIII) with sodium and ethanol gave cholestane-3α : 6α-diol (XVI), whilst use of lithium aluminium hydride furnished cholestane-3α : 6β-diol (XVIII). Both these diols by oxidation with



(Ts = *p*-$C_6H_4Me{\cdot}SO_2{\cdot}$)

chromium trioxide gave cholestane-3 : 6-dione; the structure of the 3α : 6β-diol was also confirmed by an alternative preparation. It has been shown (Plattner and Fürst, *Helv. Chim. Acta*, 1949, **32**, 275) that cholest-2-ene and perbenzoic acid yield a single 2α : 3α-epoxide; cholest-2-en-6-one (XV) similarly affords a single substance, which we formulate by analogy as 2α : 3α-epoxycholestan-6-one (XIX), reduced by lithium aluminium hydride to cholestane-3α : 6β-diol (XVIII).

Treatment of the 3α : 6β-diol (XVIII) with phosphorus pentachloride resulted in a double dehydration reaction, whereby both polar hydroxyl groups were eliminated to give cholesta-3 : 5-diene. Windaus (*Ber.*, 1917, **50**, 133) has reported that the doubly epimeric cholestane-3β : 6α-diol, in which both hydroxyl groups are equatorial, with phosphorus pentachloride furnishes by substitution a dichlorocholestane, m. p. 128°, which we regard as 3α : 6β-dichlorocholestane (XVII). Treatment of the 3α : 6α-diol (XVI) (3, polar; 6, equatorial) with phosphorus pentachloride gave a product containing halogen and eluted by pentane from a column of aluminium oxide; we have been unable to crystallise this but it may contain 6β-chlorocholest-2-ene.

Experimental

For general experimental directions see preceding paper. Microanalyses are by Drs. Weiler and Strauss, Oxford.

3α-Chlorocholestan-6-one (VI*a*).—Freshly sublimed phosphorus pentachloride (8 g.) was added in small portions during 1·5 hours to a solution of 3β-hydroxycholestan-6-one (4 g.) in pure dry chloroform (200 c.c.) at 0°, containing a suspension of calcium carbonate (5 g.). After being shaken at 20° overnight, the mixture was poured into water and extracted with ether, and the extract washed with water, 2N-sodium carbonate, and water, dried, and evaporated. 3α-Chlorocholestan-6-one (4·1 g.) was obtained as needles (from acetone), m. p. 181°.

3α-Chlorocholestan-6β-ol (VII*a*).—3α-Chlorocholestan-6-one (VI*a*) (2 g. in 200 c.c. of dry ether) was added dropwise during 0·25 hour to an ice-cold solution of lithium aluminium hydride (1·2 g.) in ether (300 c.c.). The solution was poured into ice-water, and the ethereal solution washed with 2N-sulphuric acid, sodium hydrogen carbonate solution, and water. After drying, removal of the ether yielded 3α-chlorocholestan-6β-ol as an oil (1·94 g.) which crystallised from methanol in long needles, double m. p. 96° and 108°, $[\alpha]_D$ +13° ±2° (*c*, 4·35) (Found, after drying at 60—70°/0·05 mm. for 1 hour: C, 76·9; H, 11·3. $C_{27}H_{47}OCl$ requires C, 76·6; H, 11·1%), which gave no colour with tetranitromethane in chloroform. 3α-Chlorocholestan-6β-ol (76 mg.) was treated in acetic acid (3 c.c.) with a 2% solution of chromium trioxide in acetic acid (2 c.c.), and the mixture left at 20° overnight. Excess of chromium trioxide was destroyed with methanol and, after dilution with water, the product was extracted with ether. The ethereal extract, after the usual washing and drying, by evaporation yielded a

solid (43 mg.), which crystallised from methanol in needles, m. p. 178—180°, undepressed by admixture with an authentic specimen of 3α-chlorocholestan-6-one (VI*a*).

epi*Cholesteryl Chloride* (IV*a*).—Phosphorus oxychloride (0·6 c.c.) was added, with ice-cooling, to a solution of 3α-chlorocholestan-6β-ol (500 mg.) in dry pyridine (5 c.c.) and left at 20° overnight. The mixture was poured into ice-water, and the product extracted with ether. The ethereal extract after the usual purification and drying yielded an oil (467 mg.) which was further purified by filtration of a pentane solution through a column of aluminium oxide. The colourless oil readily crystallised, and recrystallised from acetone as needles, m. p. 105—107° $[\alpha]_D$ −3°±2° (*c*, 1·930) (Found, after drying at 20°/0·1 mm. for 20 hours: C, 79·6; H, 11·4. $C_{27}H_{45}Cl$ requires C, 79·5; H, 11·2%).

3α-*Bromocholestan*-6-*one* (VI*b*).—3β-Hydroxycholestan-6-one (m. p. 142°; 1·5 g.) and freshly sublimed phosphorus pentabromide (2 g.) were rubbed together in a mortar for 0·25 hour. The mixture was warmed at 40° with water for 0·5 hour, then cooled, and the product extracted with ether and purified by the usual procedure. Removal of the ether gave 3α-bromocholestan-6-one (640 mg.) which separated from methanol–ether as needles, m. p. 173°, $[\alpha]_D$ +10°±1° (*c*, 1·00) (Found, after drying at 20°/0·1 mm. for 20 hours: C, 69·8; H, 9·55. $C_{27}H_{45}OBr$ requires C, 69·8; H, 9·55%).

epi*Cholesteryl Bromide* (IV*b*).—3α-Bromocholestan-6-one (103 mg.) in ether (10 c.c.) was shaken with lithium aluminium hydride (211 mg.) in ether (50 c.c.) at 0° for 10 minutes. The solution was poured into ice-water, and the ethereal solution separated and purified in the usual way. Evaporation of the ether gave an oil, 3α-bromocholestan-6β-ol (VII*b*), which failed to crystallise. Oxidation of this product with a 2% solution of chromium trioxide in acetic acid yielded 3α-bromocholestan-6-one. 3α-Bromocholestan-6β-ol (44 mg.) in dry pyridine (1 c.c.) at 0° was treated with phosphorus oxychloride (3 drops) and left at 20° overnight; the usual method of isolation of the reaction product gave an oil, which after filtration of a pentane solution through a column of neutral * aluminium oxide gave epi*cholesteryl bromide*, m. p. 103—105°, $[\alpha]_D$ −5°±2° (*c*, 1·234), as needles from acetone (Found, after drying at 15°/0·01 mm. for 20 hours: C, 71·8; H, 10·2. $C_{27}H_{45}Br$ requires C, 72·1; H, 10·1%). The compound gave a positive Beilstein test.

Cholestane-3β : 6β-*diol* (VIII).—3β-Hydroxycholestan-6-one (2·1 g.) in ether (200 c.c.) was added during 20 minutes to a solution of lithium aluminium hydride (2 g.; commercial material) in dry ether (300 c.c.) at room temperature; gentle refluxing was continued for 1 hour. The mixture was cooled in ice, and ice-cold 2N-sulphuric acid added carefully, followed by a large volume of water. The ethereal solution was washed to neutrality in the usual way, dried, and evaporated, yielding a solid which crystallised from acetone–dioxan as prismatic needles, m. p. 185—190°. Recrystallisation from acetone gave cholestane-3β : 6β-diol (1·82 g.) as needles, m. p. 196°. The mother-liquors yielded a residue, which by crystallisation from ethanol formed crystals, m. p. 214—216°, which did not depress the m. p. of authentic cholestane-3β : 6α-diol.

6β-*Acetoxycholestan*-3β-*ol* (X).—Cholestane-3β : 6β-diol diacetate (IX) (2·5 g.) was refluxed for 1·5 hours with potassium hydroxide (6·25 g.) in methanol (1500 c.c.). The solution was acidified with concentrated hydrochloric acid, the excess of acid neutralised with ammonia, and the methanol removed under reduced pressure. The neutral oily residue was dried by repeated evaporation with dry benzene and chromatographed on aluminium oxide (100 g.). 6β-Acetoxycholestan-3β-ol was isolated by elution with pentane–benzene mixtures (4 : 1 to 1 : 1) in 75% yield and crystallised from methanol in needles, double m. p. 80° and 128° (Plattner and Lang, *Helv. Chim. Acta*, 1944, **27**, 1872, give m. p. 124—125°). Elution with chloroform gave cholestane-3β : 6β-diol.

3α-*Chlorocholestan*-6β-*yl Acetate* (XI).—Phosphorus pentachloride (freshly sublimed; 1·4 g.) was added in small portions during 1 hour at 0° to a solution of 6β-acetoxycholestan-3β-ol (500 mg.) in dry chloroform (20 c.c.) containing a suspension of dry calcium carbonate (1 g.). The solution was shaken for 1·5 hours and the temperature allowed to rise to 20°. The reaction mixture was digested with water and shaken for a further hour. The chloroform layer was worked up in the usual manner and evaporated, to give 3α-*chlorocholestan*-6β-*yl acetate* as an oil (356 mg.) which solidified and was recrystallised from methanol as needles, m. p. 127—129°, $[\alpha]_D$ −16°±2° (*c*, 0·442) (Found, after drying at 25°/0·01 mm. for 5 hours: C, 74·4; H, 10·7. $C_{29}H_{49}O_2Cl$ requires C, 74·9; H, 10·6%). The compound gave a positive Beilstein test. 3α-Chlorocholestan-6β-yl acetate (200 mg.) on treatment with an aqueous methanolic solution of potassium carbonate (20 c.c.; 5% solution) at room temperature for 48 hours gave 3α-chlorocholestan-6β-ol.

* See footnote, p. 1790.

epi*Cholesteryl Chloride* (IV*a*).—Cholestane-3β : 6β-diol (3 g.) in dry chloroform (250 c.c.) was treated with phosphorus pentachloride (5 g.) at 0° during 1·5 hours. The solution was digested with water and vigorously shaken for 1·5 hours. The chloroform layer yielded a neutral oil (2·7 g.) which was chromatographed on neutral aluminium oxide (90 g.), and the column was eluted with pentane. The first eluates contained cholesta-3 : 5-diene, m. p. 79°, undepressed on admixture with a genuine specimen; later pentane eluates yielded *epi*cholesteryl chloride (1·97 g.) identical with the material obtained by the dehydration of 3α-chlorocholestan-6β-ol described above.

3α-*Hydroxycholestan-6-one* (XIII).—(*a*) 3α-Hydroxycholestan-6-one was prepared from 3β-toluene-*p*-sulphonyloxycholestan-6-one (XIV) by the method of Dodson and Riegel (*J. Org. Chem.*, 1948, **13**, 424). The toluene-*p*-sulphonate (14·6 g.), after acetolysis and hydrolysis of the product, yielded a dark red oil; this was chromatographed on a column of aluminium oxide (1250 g.) prepared in pentane. Pentane or pentane–benzene (1 : 1) eluted nothing; benzene (8 × 400 c.c.) eluted cholest-2-en-6-one (4·7 g.) (XV), m. p. 102—104° (from acetone); after ether–benzene (1 : 1; 8 × 400 c.c.) had removed a little oil, ether eluted first (7 × 400 c.c.) 3α-hydroxycholestan-6-one (XIII) (2·3 g.), m. p. 156—160° (from aqueous ethanol), and then (6 × 400 c.c.) 3β-hydroxycholestan-6-one (V), m. p. 140—142°. An ethanolic solution of the mother liquors from (XIII) was treated with a solution of digitonin in warm 96% ethanol; a white precipitate was formed which was allowed to settle out overnight. The precipitate was filtered off and decomposed with warm pyridine, to give in the usual manner 3β-hydroxycholestan-6-one, whilst from the filtrate there was obtained 3α-hydroxycholestan-6-one.

(*b*) *epi*Cholesteryl acetate (XII) (m. p. 85°; 618 mg.) was stirred at 20° for 1 hour with concentrated nitric acid (15 c.c.; *d* 1·42), to which potassium nitrite (265 mg.) was added. The thick creamy suspension was filtered on a sintered-glass crucible and was washed thoroughly with water, and dried in a vacuum for 3 days. The compound was not crystallised but was reduced directly with zinc dust and acetic acid for 1½ hours. The resulting solution was diluted with water and extracted with benzene. The extract after purification gave on evaporation an oil, which solidified when rubbed with methanol. This product after hydrolysis with 5% alcoholic potassium hydroxide yielded a solid (215 mg.), which was chromatographed on aluminium oxide (5 g.) and eluted with ether. Crystallisation from aqueous ethanol gave plates, m. p. 156—159°, undepressed by admixture with 3α-hydroxycholestan-6-one.

Cholestane-3α : 6α-*diol* (XVI).—3α-Hydroxycholestan-6-one (700 mg.) in ethanol (50 c.c.) was heated under reflux with sodium (5·5 g.) for 0·5 hour; excess of sodium was destroyed by the addition of ethanol. The reaction mixture was poured into water and extracted with ether. The ethereal extract after purification yielded *cholestane*-3α : 6α-*diol* as a white solid (653 mg.) which crystallised from ethanol–acetone as needles, which melted at 211° with the formation of small droplets; these gradually crystallised into needles and finally melted at 219—220°, and had $[\alpha]_D$ +43°±3° (*c*, 0·67 in dioxan) (Found, after drying at 20°/0·01 mm. for 12 hours and at 100°/0·01 mm. for 1 hour: C, 79·8; H, 11·8. $C_{27}H_{48}O_2$ requires C, 80·1; H, 11·9%). The acetyl derivative could not be obtained crystalline. The diol by oxidation with chromium trioxide–acetic acid gave cholestane-3 : 6-dione, needles (from acetone), m. p. 171—173°, undepressed on admixture with an authentic specimen.

Cholestane-3α : 6β-*diol* (XVIII).—3α-Hydroxycholestan-6-one (1·3 g.) in dry ether (100 c.c.) was added to a solution of lithium aluminium hydride (0·54 g.) in ether (150 c.c.) at 20°. After 0·5 hour the mixture was poured into ice-water, and the ethereal solution separated and purified by the usual procedure. Removal of the ether gave a yellowish-white solid, which separated from all solvents as a gel and could not be obtained crystalline. On oxidation with chromium trioxide–acetic acid, cholestane-3 : 6-dione, m. p. 171—173°, was formed. Acetylation with acetic anhydride–pyridine at 20° gave an oil, which after filtration of a pentane solution through a column of aluminium oxide gave *cholestane*-3α : 6β-*diol diacetate* which, crystallised from acetone after cooling to −10° for several days, had m. p. 87—89°, $[\alpha]_D$ −17°±3° (*c*, 5·06) (Found, after drying at 20°/0·01 mm. for 12 hours: C, 76·3; H, 10·55. $C_{31}H_{52}O_4$ requires C, 76·2; H, 10·7%).

Cholesta-3 : 5-*diene*.—Cholestane-3α : 6β-diol (200 mg.) in dry pyridine (3 c.c.) was treated at 0° with phosphorus oxychloride (0·4 c.c.), and the mixture left at 20° for 12 hours. The product obtained by working up in the usual way was a neutral oil (140 mg.) which crystallised from acetone as needles, m. p. 78—80°, undepressed by admixture with authentic cholesta-3 : 5-diene.

2α : 3α-*Epoxycholestan-6-one* (XIX).—Cholest-2-en-6-one (XV) (1·53 g.) in chloroform (10 c.c.) was treated with a chloroform solution of perbenzoic acid (14·4 c.c.; 1·1 mols. of per-

benzoic acid), and kept at −10° for 15 hours. The solution was washed successively with potassium iodide solution, 0·01N-thiosulphate, sodium hydrogen carbonate solution, and water. Removal of the chloroform gave a colourless oil (1·47 g.), which by crystallisation from acetone gave 2α : 3α-*epoxycholestan*-6-*one* as plates, m. p. 141—142°, $[\alpha]_D$ −14°±2° (*c*, 3·32) (Found, after drying at 20°/0·01 mm. for 2 hours : C, 81·3; H, 11·2. $C_{27}H_{44}O_2$ requires C, 80·9; H, 11·1%).

2α : 3α-Epoxycholestan-6-one (1·43 g.) in ether (200 c.c.) was reduced at 20° with lithium aluminium hydride (1·2 g. in 500 c.c. of ether) in the usual way. The product was isolated as a gel, which was acetylated with acetic anhydride–pyridine at 20° overnight. The product (1·46 g.), isolated in the usual manner, was chromatographed on a column of aluminium oxide (30 g.) prepared in pentane, and gave cholestane-3α : 6β-diol diacetate, m. p. 87—89° (1·34 g.), by elution with pentane (6 × 100 c.c.).

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