484. *Steroids and Walden Inversion. Part XXXIII.* The Configurations of the Coprostanyl Halides.*

By C. W. Shoppee, R. J. Bridgwater, D. N. Jones, and G. H. R. Summers.

3α-Chlorocoprostane has been prepared by an unambiguous synthesis. Coprostane-3β : 6β-diol (as the 6-monoacetate) with phosphorus pentachloride gave 3α-chlorocoprostan-6β-ol (after treatment with lithium aluminium hydride), which was (*a*) oxidised to 3α-chlorocoprostan-6-one and isomerised by mineral acid to the known 3α-chlorocholestan-6-one, (*b*) reduced as the toluene-*p*-sulphonate with lithium aluminium hydride to 3α-chlorocoprostane, identical with the material of Bridgwater and Shoppee.[1] The configuration of 3β-chlorocoprostane follows by exclusion, and the configurations of the epimeric 3-bromocoprostanes by analogy.

Associated studies have led to the preparation of 3β-chlorocoprostan-6-one, isomerised by acid to the known 3β-chlorocholestan-6-one, and of 3β-chloro-5 : 6α-epoxycholestane, the 3β-chlorocholestane-5 : 6-diols, and various related compounds.

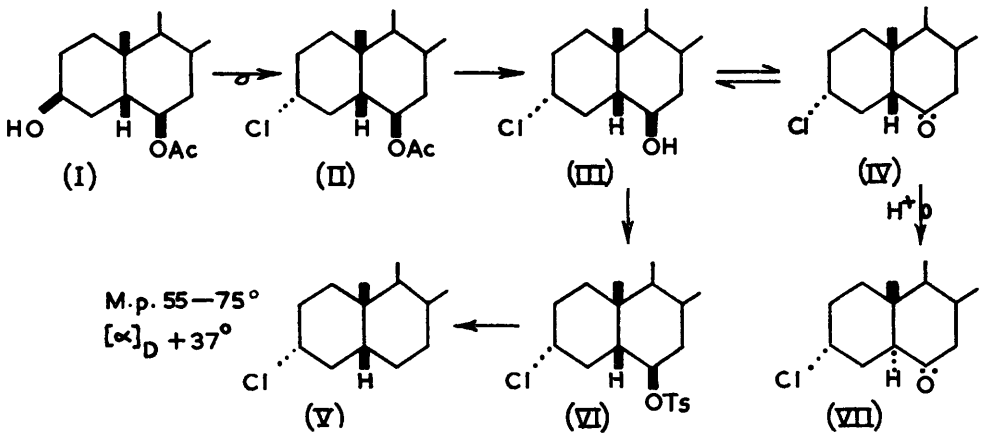
In Part XI, Bridgwater and Shoppee [1] described the preparation of the epimeric coprostan-3-yl chlorides and bromides. The chlorides were assigned configurations on the basis of the acetolysis at 130° of the 3β-epimeride, m. p. 123°, $[\alpha]_D$ +23°, to *epi*coprostanyl acetate and of the 3α-epimeride, double m. p. 55° and 75°, $[\alpha]_D$ +31°, to coprostanyl acetate. The production of only a single epimeric acetate in each case indicated the occurrence of a bimolecular acetolysis (S_N2) proceeding with inversion of configuration, but an attempt to prove that the acetolysis of coprostan-3β-yl bromide, m. p. 113°, $[\alpha]_D$ +18°, was kinetically of the first order with respect to both the bromide and the acetate ion encountered experimental difficulties and was inconclusive. The following experiments were therefore initiated in an attempt to prepare one or other epimeride independently. Since their commencement evidence has been presented which supports the published configurations of these halides, first, hydrogenation of 3α-chloro- and 3α-bromo-cholest-5-ene to 3α-chloro- and 3α-bromo-coprostane [2] and, secondly, analysis [3] of the infrared spectra of 3-halogeno-steroids.

Configuration at $C_{(3)}$, $C_{(5)}$, and $C_{(6)}$ in coprostane-3β : 6β-diol is established; [4] since this diol is a saturated compound, its 6-monoacetate (I), would be expected, on treatment with phosphorus pentachloride, to undergo inversion [5] at $C_{(3)}$, yielding 6β-acetoxy-3α-chlorocoprostane (II), converted by lithium aluminium hydride into 3α-chlorocoprostan-6β-ol (III). That the inversion occurs and that the chloro-alcohol obtained has the structure (III) and specifically α-configuration at $C_{(3)}$, are proved as follows. Oxidation of the alcohol (III) with chromium trioxide gives 3α-chlorocoprostan-6-one (IV), which showed an infrared absorption band at 1705 cm.$^{-1}$ (6-membered ring ketone of the A/B-*cis*-series [6]), could be reconverted into the chloro-alcohol (III) by lithium aluminium hydride, and like other *cis*-α-decalones undergoes keto-enol prototropy with inversion at $C_{(5)}$ on treatment with mineral acid, giving the thermodynamically more stable *trans*-α-decalone analogue, 3α-chlorocholestan-6-one (VII),[7,8] in which the α-configuration of the 3-chlorine atom is established.[9] Conversion of 3α-chlorocoprostan-6β-ol (III) into the toluene-*p*-sulphonate (VI), followed by reduction with lithium aluminium hydride and repeated chromatography

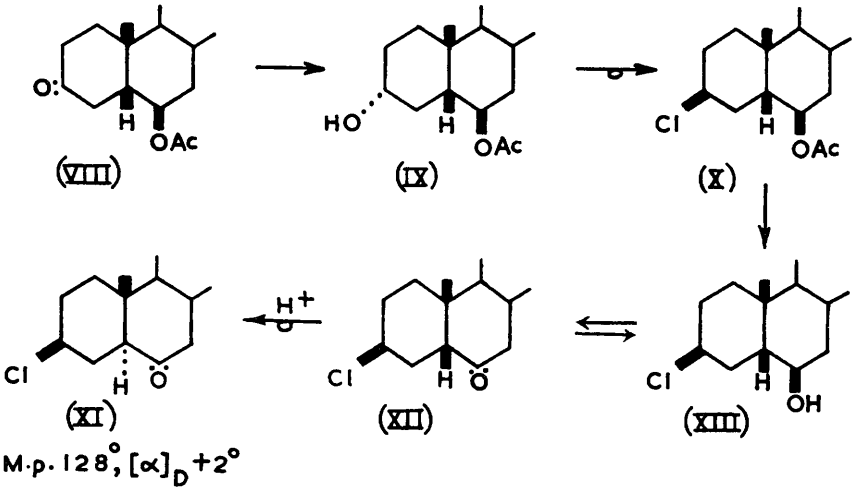
* Part XXXII, preceding paper.

[1] Bridgwater and Shoppee, *J.*, 1953, 1709.
[2] Lewis and Shoppee, *J.*, 1955, 1365.
[3] Barton, Page, and Shoppee, *J.*, 1956, 331.
[4] Prelog and Tagmann, *Helv. Chim. Acta*, 1944, **27**, 1880.
[5] Shoppee, *J.*, 1946, 1138.
[6] Jones, Humphries, and Dobriner, *J. Amer. Chem. Soc.*, 1950, **72**, 956.
[7] Shoppee and Summers, *J.*, 1952, 1790.
[8] Jones, Lewis, Shoppee, and Summers, *J.*, 1955, 2876.
[9] Shoppee, *J.*, 1948, 1032.

of the product, furnishes 3α-chlorocoprostane (V), m. p. 70—71°, $[\alpha]_D$ +36°, identical with the specimen prepared by Bridgwater and Shoppee.[1]



By an analogous procedure, 6β-acetoxy-3β-chlorocoprostane has been synthesised from coprostane-3β : 6β-diol. Reduction of 6β-acetoxycoprostan-3-one (VIII) by sodium borohydride or hydrogen–platinum in ether gave 3α-hydroxycoprostan-6β-yl acetate (IX), which with phosphorus pentachloride yielded 6β-acetoxy-3β-chlorocoprostane (X). Treatment with lithium aluminium hydride yielded 3β-chlorocoprostan-6β-ol (XIII)



which with chromium trioxide in acetic acid gave 3β-chlorocoprostan-6-one (XII); this showed an infrared absorption band at 1708 cm.$^{-1}$ (6-membered-ring ketone of the A/B-*cis*-series), and was isomerised by mineral acid to 3β-chlorocholestan-6-one[10] (XI). The foregoing conversions (I ⟶ III ⟶ V) and (I ⟶ VIII ⟶ XI) provide formal structural proofs of the configurations originally assigned to the epimeric coprostanyl halides by Bridgwater and Shoppee.[1]

Another synthetic approach to the coprostanyl halides, employed with partial success, has been the reduction of derivatives of 3β-chlorocholest-4-ene. This involved a prior study of the oxidation of cholesteryl chloride.

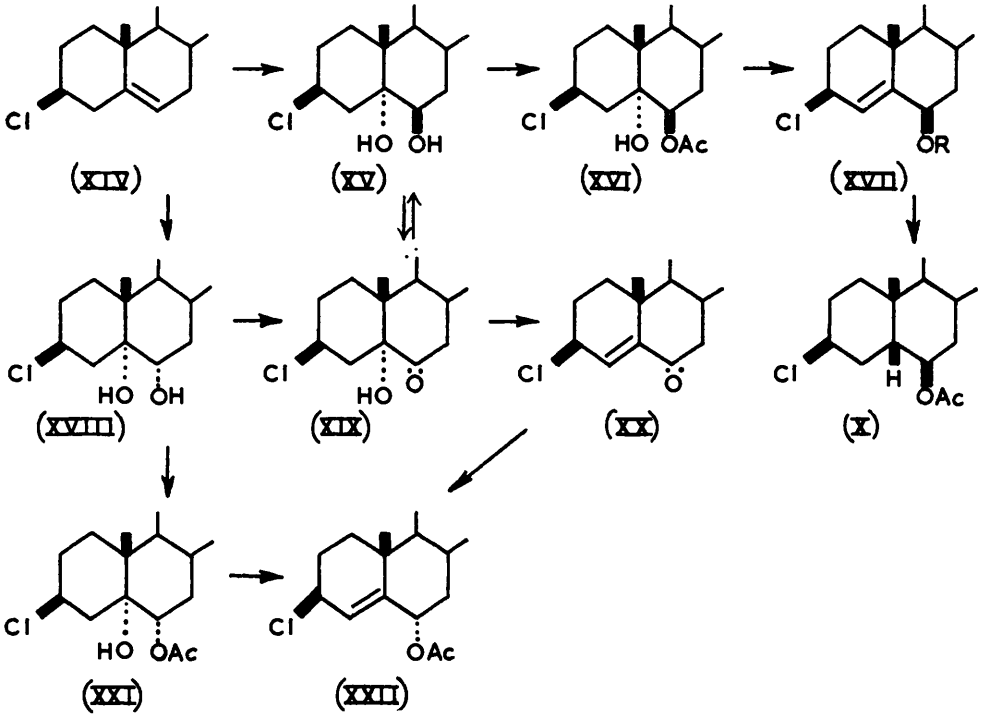
Cholesteryl chloride (XIV) with peracetic acid gave 3β-chlorocholestane-5 : 6β-diol (XV)

[10] Dodson and Riegel, *J. Org. Chem.*, 1948, **13**, 424.

which on further oxidation with chromium trioxide–acetic acid yielded 3β-chloro-5-hydroxycholestan-6-one (XIX), smoothly dehydrated by thionyl chloride–pyridine at 0—15° to 3β-chlorocholest-4-en-6-one (XX), $\lambda_{max.}$ 239 mμ (log ε 4·2). Dehydration of the 6β-monoacetate (XVI) with thionyl chloride–pyridine at 0° gave 3β-chlorocholest-4-en-6β-yl acetate (XVII; R = Ac), which with lithium aluminium hydride at 0° yielded 3β-chlorocholest-4-en-6β-ol (XVII; R = H).

Cholesteryl chloride (XIV) with osmium tetroxide gave 3β-chlorocholestane-5 : 6α-diol (XVIII), which by dehydration as the 6α-monoacetate (XXI) with thionyl chloride–pyridine furnished 3β-chlorocholest-4-en-6α-yl acetate (XXII), also obtained by reduction of the αβ-unsaturated ketone (XX) with lithium aluminium hydride followed by acetylation.

3β-Chlorocholest-4-en-6β-yl acetate (XVII; R = Ac) and 3β-chlorocholest-4-en-6-one (XX) are allylic chlorides, and attempts were made to discover conditions leading to hydrogenation of the double bond without hydrogenolysis of the chlorine atom. In the ketone (XX), the 6-carbonyl group was expected by conjugation with the π-electrons of the

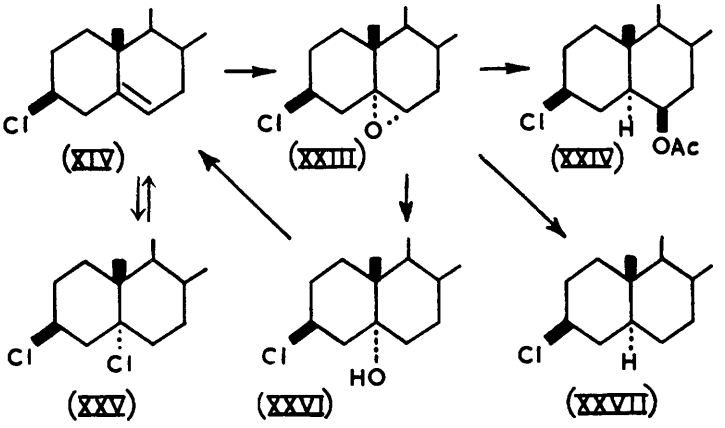


4 : 5-double bond to reduce the reactivity of the 3β-chlorine atom, and so to produce a situation analogous to that prevailing in 3β-chlorocholest-5-en-7-one where acetolysis leads to inversion at $C_{(3)}$.[11] Hydrogenation of 3β-chlorocholest-4-en-6-one (XX) with palladium in neutral media under various conditions yielded, however, complex ketonic products deficient in chlorine (*e.g.*, 2% of chlorine instead of ~8%), indicating concomitant hydrogenolysis. Reduction of the crude hydrogenation products by the Clemmensen method gave cholestane as the only identifiable product, and condensation with toluene-ω-thiol gave oils which gave a negative Beilstein test, thus indicating the unsuitability of the thioketal method for the reduction of reactive halogeno-ketones. Finally, however, catalytic hydrogenation of the acetate (XVII; R = Ac) with a special platinum catalyst

[11] Marker, Kamm, Fleming, Popkin, and Wittle, *J. Amer. Chem. Soc.*, 1937, **59**, 619; Shoppee, *J.*, 1946, 1147.

in ethanol followed by careful chromatography of the product gave, in small yield, 6β-acetoxy-3β-chlorocoprostane (X), identical with the specimen described above.

Finally, attempts were made to synthesise 3β-chlorocholest-4-ene. Cholest-5-ene, by addition of hydrogen chloride, gives 5-chlorocholestane converted by treatment with quinoline into cholest-4-ene,[12] whereas 5-chlorocholestan-3β-ol (cholesterol hydrochloride) on treatment with potassium acetate yields cholest-4-en-3β-ol.[13] Treatment of cholesteryl chloride in ether–ethanol with dry hydrogen chloride gave 3β : 5-dichlorocholestane (XXV), which was dehydrohalogenated by ethanolic potassium acetate to cholesteryl chloride as



the only identifiable product. Treatment of cholesteryl chloride (XIV) with perbenzoic acid gave the 5α : 6α-epoxide (XXIII), hydrogenated with platinum–acetic acid to a mixture of 3β-chlorocholestan-5-ol (62%) (XXVI), 6β-acetoxy-3β-chlorocholestan-5-ol (32%) (XXIV) (formed by acetolysis), and 3β-chlorocholestane (6%) (XXVII) (formed by hydrogenolysis). Treatment of the 5α : 6α-epoxide (XXIII) with lithium aluminium hydride gave the alcohol (XXVI) in quantitative yield, whence dehydration with thionyl chloride–pyridine at −6° afforded cholesteryl chloride (XIV) unaccompanied by 3β-chlorocholest-4-ene.

Chlorination of cholest-4-en-3β-ol with phosphorus pentachloride in carbon tetrachloride proceeds readily, to yield 3ξ-chlorocholest-4-ene. The structure and reactions of this allylic chloride will be reported later but it is relevant that hydrogenation yields only coprostane.

Experimental

For general experimental directions, see *J.*, 1956, 1649. $[\alpha]_D$ are in $CHCl_3$ unless otherwise stated. Ultraviolet absorption spectra were determined in EtOH on a Unicam SP 500 spectrometer with corrected scale, and infrared absorption spectra in CS_2 on a Perkin-Elmer double-beam instrument.

6β-*Acetoxy*-3α-*chlorocoprostane*.—3β-Hydroxycoprostan-6β-yl acetate (3·96 g.) in carbon tetrachloride (250 c.c.) containing dry calcium carbonate (20 g.) in suspension was treated with phosphorus pentachloride (11·86 g.; freshly sublimed) added during 0·5 hr. at room temperature with stirring. The mixture was stirred for a further 6 hr., left for 10 hr., poured into sodium carbonate solution containing ice, and extracted with ether. The crystalline product was purified by chromatography on aluminium oxide (100 g.). Elution with pentane (15 × 250 c.c.) gave material, m. p. 108—119°, which after four recrystallisations from acetone gave 6β-*acetoxy*-3α-*chlorocoprostane*, m. p. 116—118°, $[\alpha]_D$ +6·4° (*c* 0·92) (2·7 g.) [Found (after drying at 50°/0·01 mm. for 3 hr.) : C, 74·6; H, 10·5. $C_{29}H_{49}O_2Cl$ requires C, 74·9; H, 10·6%]. Elution with ether–benzene (1 : 1) gave unchanged starting material, m. p. and mixed m. p. 142—144°.

[12] Mauthner, *Monatsh.*, 1907, **28**, 1113.
[13] Windaus, *Annalen*, 1927, **453**, 101.

3α-*Chlorocoprostan*-6β-*ol*.—6β-Acetoxy-3α-chlorocoprostane (2·5 g.) on treatment with lithium aluminium hydride in boiling ether followed by the usual isolation procedure gave a mobile oil, converted by acetic anhydride–pyridine at 20° into 6β-acetoxy-3α-chlorocoprostane, m. p. and mixed m. p. 116—118°.

3α-*Chlorocoprostan*-6-*one*.—The above oily alcohol (200 mg.) was treated in acetic acid (15 c.c.) with a 2% solution of chromium trioxide in acetic acid (4 c.c.) at 20° for 18 hr. After being worked up in the usual way, the product (171 mg.) crystallised rapidly, and recrystallisation from acetone gave rods, m. p. 85—92°; further recrystallisation from ether–methanol gave 3α-*chlorocoprostan*-6-*one*, m. p. 85—92°, $[\alpha]_D$ −63° (*c* 0·8) [Found (after drying at 20°/0·01 mm. for 20 hr.): C, 77·2; H, 10·7. $C_{27}H_{45}OCl$ requires C, 77·0; H, 10·8%].

3α-Chlorocoprostan-6-one (30 mg.) was refluxed in ethanol (10 c.c.) and concentrated hydrochloric acid (3 drops) for 0·25 hr. Evaporation of the solvent gave a solid which crystallised from ether as needles, m. p. 170—181°. Recrystallisation and sublimation of the product at 150°/0·01 mm. yielded needles, m. p. 181—183° alone or mixed with 3α-chlorocholestan-6-one.

Treatment of 3α-chlorocoprostan-6-one with lithium aluminium hydride in boiling ether followed by acetylation of the product with acetic anhydride–pyridine at 15° gave 6β-acetoxy-3α-chlorocoprostane.

3α-*Chlorocoprostane*.—3α-Chlorocoprostan-6β-ol (526 mg.) in dry pyridine (20 c.c.) was treated with toluene-*p*-sulphonyl chloride (530 mg.) at 40° for 72 hr. Isolation in the usual way gave an oil (704 mg.) which gave a positive test for sulphur. The toluene-*p*-sulphonate was refluxed with lithium aluminium hydride (300 mg.) in dry ether for 24 hr. Working up in the usual manner gave a colourless oil (450 mg.) which was chromatographed on neutral aluminium oxide (15 g.). Elution with pentane gave a colourless oil (206 mg.) which gave a positive Beilstein test. Rechromatography on neutral alumina of high activity furnished in the later pentane eluates an oil which crystallised from acetone–methanol as plates, m. p. 62—70°. Three further recrystallisations from acetone–methanol furnished 3α-chlorocoprostane as plates, m. p. and mixed m. p. 70—71°, $[\alpha]_D$ +36·3° (*c* 1·05). Redetermination of the constants of the specimen prepared by Dr. R. J. Bridgwater gave m. p. 74—75°, $[\alpha]_D$ +37° (*c* 1·03).

3α-*Hydroxycoprostan*-6β-*yl Acetate*.—(*a*) 6β-Acetoxycoprostan-3-one (4 g.) was dissolved in moist ether–methanol, and sodium borohydride (600 mg.) added. The mixture was left at 20° for 6 hr., poured into water, and worked up in the usual manner, to give crystals, m. p. 139—141°. Crystallisation from acetone gave 6β-*acetoxycoprostan*-3α-*ol* as plates, m. p. 140—142°, $[\alpha]_D$ +9° (*c* 0·95) [Found (after drying at 55°/0·01 mm. for 6 hr.): C, 78·0; H, 11·3. $C_{29}H_{50}O_3$ requires C, 78·1; H, 11·3%].

(*b*) 6β-Acetoxycoprostan-3-one (1 g.) in ether was hydrogenated in the presence of platinic oxide (100 mg.). Uptake of hydrogen ceased after 3 hr. and crystallisation of the product from acetone gave a solid, m. p. 120—130°, which was chromatographed on aluminium oxide (30 g.). Elution with benzene gave unchanged starting material (200 mg.), and elution with ether–benzene (1 : 9) gave a solid (620 mg.) which on crystallisation from methanol gave 3α-hydroxycoprostan-6β-yl acetate, m. p. 140—141°, $[\alpha]_D$ +13° (*c* 2·82). Further elution with ether–benzene (1 : 9) gave a molecular compound, m. p. 136—138°, of 3α- and 3β-hydroxycoprostan-6β-yl acetate.

3α-Hydroxycoprostan-6β-yl acetate with boiling acetic anhydride gave an oil which from methanol yielded 3α : 6β-diacetoxycoprostane, m. p. 100—104°, $[\alpha]_D$ +12° (*c* 1·1) [Found (after drying at 55°/0·01 mm. for 6 hr.): C, 76·1; H, 10·5. $C_{31}H_{52}O_4$ requires C, 76·1; H, 10·8%].

6β-*Acetoxy*-3β-*chlorocoprostane*.—3α-Hydroxycoprostan-6β-yl acetate (1·4 g.) in carbon tetrachloride (90 c.c.) was stirred vigorously with powdered calcium carbonate (7 g.) and freshly prepared phosphorus pentachloride (3·56 g.) for 11 hr. at 20°. The product, isolated in the usual way, was a colourless oil which was purified by chromatography on acid-washed aluminium oxide (40 g.). Elution with benzene–pentane (1 : 4) gave a colourless oil which crystallised from methanol, to give 6β-*acetoxy*-3β-*chlorocoprostane*, m. p. 67—69°, $[\alpha]_D$ +12° (*c* 2·08) [Found (after drying at 20°/0·01 mm. for 6 hr.): C, 74·4; H, 10·7. $C_{29}H_{49}O_2Cl$ requires C, 74·9; H, 10·6%].

3β-*Chlorocoprostan*-6β-*ol*.—6β-Acetoxy-3β-chlorocoprostane (500 mg.) was treated with lithium aluminium hydride (150 mg.) in ether at 20° for 1 hr. The oily product was chromatographed on neutral aluminium oxide (15 g.). Elution with ether–benzene (1 : 9) and crystallisation from methanol gave 3β-*chlorocoprostan*-6β-*ol*, m. p. 116—118°, $[\alpha]_D$ +21° (*c* 1·09) [Found (after drying at 70°/0·05 mm. for 4 hr.): C, 76·8; H, 11·4; Cl, 8·7. $C_{27}H_{47}OCl$ requires C, 76·7; H, 11·2; Cl, 8·4%].

3β-*Chlorocoprostan*-6-*one*.—3β-Chlorocoprostan-6β-ol (70 mg.) was dissolved in acetic acid (5 c.c.), and a 2% solution of chromium trioxide in acetic acid (1·2 c.c.) added. After 14 hr. at

20°, the product (62 mg.), worked up in the usual way, crystallised from acetone, to give 3β-*chlorocoprostan-6-one* as needles, m. p. 148—150°, $[\alpha]_D$ −30° (*c* 0·99) [Found (after drying at 60°/0·05 mm. for 2 hr.) : C, 76·8; H, 10·8. $C_{27}H_{45}OCl$ requires C, 77·0; H, 10·8%].

3β-Chlorocoprostan-6-one (22 mg.) was refluxed with 0·3N-methanolic hydrogen chloride (15 c.c.) for 0·5 hr. The product on crystallisation from acetone gave 3β-chlorocholestan-6-one, m. p. and mixed m. p. 129—131°, $[\alpha]_D$ +2° (*c* 0·55).

Treatment of 3β-chlorocoprostan-6-one with lithium aluminium hydride in boiling ether gave only 3β-chlorocoprostan-6β-ol, m. p. 117°.

3β-*Chlorocholestane*-5 : 6β-*diol*.—Cholesteryl chloride (28 g.) in hot acetic acid (600 c.c.) was treated with hydrogen peroxide (120 c.c.; 30%) and kept at 95° for 0·5 hr. After removal of the solvent in a vacuum the oily product was extracted with ether and purified in the usual way, to give an oil (29 g.) which was chromatographed on aluminium oxide (600 g.). Elution with benzene–pentane (3 : 7) gave cholesteryl chloride (3·36 g.), ether–benzene (1 : 9) gave an oil (9·1 g.), and ether gave crystals (15 g.) which on crystallisation from ether–pentane gave 3β-*chlorocholestane*-5 : 6β-*diol* as needles, m. p. 126° (after drying), $[\alpha]_D$ −6·6° (*c* 1·5) [Found (after drying at 80°/0·06 mm. for 5 hr.) : C, 74·0; H, 10·6. $C_{27}H_{47}O_2Cl$ requires C, 73·85; H, 10·8%]. Acetylation with boiling acetic anhydride gave a solid which on crystallisation from acetone gave 3β-*chloro*-5-*hydroxycholestan*-6β-*yl acetate* as plates, m. p. 150—151°, $[\alpha]_D$ −21° (*c* 1·0) [Found (after drying at 70°/0·04 mm. for 5 hr.) : C, 72·6; H, 10·3. $C_{29}H_{49}O_3Cl$ requires C, 72·4; H, 10·3%].

3β-*Chloro*-5-*hydroxycholestan*-6-*one*.—3β-Chlorocholestane-5 : 6β-diol (130 mg.) in acetic acid (0·5 c.c.) was treated with a 2% solution of chromium trioxide in acetic acid (2 c.c.) at 20° for 2 hr. Working up in the usual manner gave a solid (120 mg.) which on crystallisation from aqueous acetic acid gave 3β-*chloro*-5-*hydroxycholestan*-6-*one*, m. p. 182—183°, $[\alpha]_D$ −38° (*c* 1·52) [Found (after drying at 100°/0·001 mm. for 3 hr.) : C, 74·1; H, 10·2. $C_{27}H_{45}O_2Cl$ requires C, 74·2; H, 10·4%].

3β-Chlorocholestane-5 : 6β-diol (220 mg.), dissolved in ether (4 c.c.), methanol (1 c.c.), and water (1 c.c.), was treated with *N*-bromosuccinimide (120 mg.); after 40 min. ether was added, and the solution washed with water, sodium metabisulphite solution, and water, dried, and evaporated. The solid residue (210 mg.), on recrystallisation from acetone, gave 5-hydroxy-3β-chlorocholestan-6-one, m. p. 182°.

Treatment of the ketone with lithium aluminium hydride in ether gave 3β-chlorocholestane-5 : 6β-diol, m. p. 124°.

3β-*Chlorocholest*-4-*en*-6-*one*.—3β-Chloro-5-hydroxycholestan-6-one (100 mg.) was treated in pyridine (5 c.c.) with thionyl chloride (0·75 c.c.) at 0°; the mixture was kept at 20° for 1 hr., poured into water, and worked up in the usual way, to give an oil which was dissolved in pentane and filtered through neutral aluminium oxide. The oil (64 mg.) recovered, when crystallised from ether–methanol, gave 3β-*chlorocholest*-4-*en*-6-*one* as needles, m. p. 164—165°, $[\alpha]_D$ +84·6° (*c* 0·98), $\lambda_{max.}$ 239 mμ (log ε 4·2) [Found (after drying at 100°/0·001 mm. for 3 hr.) : C, 77·2; H, 10·2. $C_{27}H_{43}OCl$ requires C, 77·4; H, 10·3%].

3β-*Chlorocholest*-4-*en*-6β-*yl Acetate*.—3β-Chloro-5-hydroxycholestan-6β-yl acetate (815 mg.) was treated in pyridine (10 c.c.) with thionyl chloride (2 c.c.) at 0°; the mixture was kept at 20° for 1 hr. Working up in the usual way gave an oil (614 mg.) which on crystallisation from acetone gave 3β-*chlorocholest*-4-*en*-6β-*yl acetate* as plates, m. p. 97—98°, $[\alpha]_D$ +3·4° (*c* 1·6) [Found (after drying at 80°/0·001 mm. for 2 hr.) : C, 75·3; H, 10·2. $C_{29}H_{47}O_2Cl$ requires C, 75·2; H, 10·2%].

Treating the acetate with lithium aluminium hydride in ether at 0° for 15 min. gave an oil which on crystallisation from light petroleum (b. p. 40—60°) gave 3β-*chlorocholest*-4-*en*-6β-*ol* as needles, m. p. 124—126° [Found (after drying at 60°/0·01 mm. for 3 hr.) : C, 76·8; H, 10·4. $C_{27}H_{45}OCl$ requires C, 77·0; H, 10·8%].

3β-*Chlorocholestane*-5 : 6α-*diol*.—Cholesteryl chloride (300 mg.) in ether (15 c.c.) containing pyridine (0·5 c.c.) was treated with osmium tetroxide (250 mg.) for 72 hr. at 25°. After removal of the solvent, the complex was decomposed by a refluxing aqueous-methanolic solution of sodium sulphite for 2·5 hr.; an ethereal solution of the product was shaken with 3N-sodium hydroxide and mannitol. The ether layer on evaporation gave a white solid (245 mg.) which gave 5 : 6α-*dihydroxy*-3β-*chlorocholestane* as plates (from acetone), m. p. 142—144°, $[\alpha]_D$ +24·6° (*c* 1·2) [Found (after drying at 60°/0·01 mm. for 3 hr.) : C, 73·5; H, 10·6. $C_{27}H_{47}O_2Cl$ requires C, 73·85; H, 10·8%].

With acetic anhydride–pyridine at 15° for 16 hr. this gave 3β-*chloro*-5-*hydroxycholestan*-6α-*yl acetate* which crystallised from acetone as rods, m. p. 160—162°, $[\alpha]_D$ +44·1° (*c* 1·1) [Found

(after drying at 60°/0·01 mm. for 3 hr.): C, 72·0; H, 10·3. $C_{29}H_{49}O_3Cl$ requires C, 72·4; H, 10·3%].

Oxidation of the 5 : 6α-diol at room temperature with a 2% solution of chromium trioxide in acetic acid gave 3β-chloro-5-hydroxycholestan-6-one, m. p. 181°, identical with the above specimen.

3β-*Chlorocholest-4-en-6α-yl Acetate.*—(*a*) 3β-Chloro-5-hydroxycholestan-6α-yl acetate (100 mg.) in pyridine (5 c.c.) was treated with thionyl chloride (1 c.c.) at 0°, and left for 1 hr. The deep red solution was worked up in the usual way, to give an oil (95 mg.), which by crystallisation from ether–methanol gave 3β-*chlorocholest-4-en-6α-yl acetate* as needles, m. p. 95—98° [Found (after drying at 60°/0·01 mm. for 3 hr.): C, 75·3; H, 10·1. $C_{29}H_{47}O_2Cl$ requires C, 75·2; H, 10·2%].

(*b*) 3β-Chlorocholest-4-en-6-one (500 mg.) was treated with lithium aluminium hydride in ether at 0° for 0·5 hr. Working up in the usual way gave an oil which from methanol–acetone very slowly gave 3β-chlorocholest-4-en-6α-ol as rosettes, m. p. 111—113°, $[\alpha]_D$ +68° (*c* 1·25) [Found (after drying at 60°/0·01 mm. for 3 hr.): C, 77·1; H, 10·45. $C_{27}H_{45}OCl$ requires C, 77·0; H, 10·8%]. Acetic anhydride–pyridine at 15° gave the acetate, m. p. 96°, undepressed by the above specimen, but depressed to 78° on admixture with 3β-chlorocholest-4-en-6β-yl acetate.

Reduction of 3β-*Chlorocholest-4-en-6-one.*—3β-Chlorocholest-4-en-6-one (300 mg.) in ether (20 c.c.) was hydrogenated in the presence of palladium (135 mg.). After a lapse of 30 min., the hydrogen uptake was rapid, being complete (theoretical) in less than 20 min. The product was worked up in the usual way and recrystallised from aqueous acetone, to give plates (180 mg.), m. p. 100—110°. The mother-liquors gave a substance (20 mg.), m. p. 95—105°. The two fractions were combined and, recrystallised from aqueous acetone, gave plates, m. p. 105—108° (127 mg.) (Found: C, 82·6; H, 11·4; Cl, 2·0. Calc. for $C_{27}H_{45}OCl$: C, 77·0; H, 10·8; Cl, 8·4%). The mother-liquors were combined and chromatographed on aluminium oxide. Elution with benzene–pentane (1 : 9) gave a solid which from aqueous acetone gave plates (25 mg.), m. p. 100—104°.

[*With* F. C. Johnson.] *Reduction of* 6β-*Acetoxy*-3β-*chlorocholest-4-ene.*—The platinic oxide catalyst was prepared according to *Org. Synth.*, Coll. Vol. I, 1st edn., p. 463, with the exception that the fusion was conducted at 600° (Méker burner); this gave a less active product.

6β-Acetoxy-3β-chlorocholest-4-ene (50 mg.) was added to pre-reduced platinic oxide (20 mg.) in ethanol (5 c.c.). Hydrogenation was complete in 20 min., and the product, isolated in the usual way as an oil, was chromatographed on aluminium oxide (1·5 g.). Elution with pentane gave an oil which on crystallisation from acetone–methanol yielded 6β-acetoxy-3β-chlorocoprostane, m. p. 65—68°, $[\alpha]_D$ +18° (*c* 0·5), undepressed on admixture with the specimen described above and giving an identical infrared spectrum.

3β : 5-*Dichlorocholestane.*—Cholesteryl chloride (1·5 g.) was dissolved in ether (20 c.c.), and absolute ethanol (20 c.c.) added. Dry hydrogen chloride was passed through the solution for 2 hr., a solid separating. After 10 days, the solid was filtered off and crystallised from benzene–ethanol (1 : 9), to give needles, m. p. 104—107°. Two further recrystallisations yielded 3β : 5-dichlorocholestane, m. p. 115—116°, $[\alpha]_D$ +9·8° (*c* 0·7).

3β : 5-Dichlorocholestane (0·5 g.) was refluxed with anhydrous potassium acetate (2·5 g.) in ethanol (50 c.c.) for 5 hr. Dilution of the solution with water gave a solid (289 mg.) which had m. p. 85—87°, $[\alpha]_D$ −24° (*c* 2·0), and by crystallisation from acetone gave cholesteryl chloride. The mother-liquors on extraction with ether gave an oil (90 mg.) which was purified by chromatography on aluminium oxide but failed to crystallise.

3β-*Chloro*-5 : 6α-*epoxycholestane.*—Cholesteryl chloride (11 g.) in chloroform (100 c.c.) was treated with a solution of perbenzoic acid (1·1 mol.) in chloroform and left at −8° for 20 hr. The mixture was then washed with ice-cold sodium hydrogen carbonate solution, water, and sodium thiosulphate solution and on evaporation yielded a solid (11·15 g.). Repeated crystallisation from acetone gave the *epoxide* (8·1 g.) as needles, m. p. 89·5—90·5°, $[\alpha]_D$ −35·6° (*c* 1·2) [Found (after drying at 70°/0·04 mm. for 5 hr.): C, 76·9; H, 10·5. $C_{27}H_{45}OCl$ requires C, 77·0; H, 10·8%].

3β-*Chlorocholestan-5-ol.*—(*a*) 3β-Chloro-5 : 6α-epoxycholestane (7·03 g.) in ether (40 c.c.) and acetic acid (360 c.c.) was hydrogenated in the presence of platinic oxide (0·8 g.). The resulting oil was chromatographed on aluminium oxide (210 g.). Elution with pentane (2 × 700 c.c.) gave 3β-chlorocholestane (0·45 g.), m. p. and mixed m. p. 109—112°; elution with benzene–pentane (1 : 1) gave a solid (4·4 g.) which by crystallisation from aqueous acetone gave 3β-*chlorocholestan-5-ol* as plates, m. p. 107·5—8·5°, $[\alpha]_D$ +24·5° (*c* 1·6) [Found (after drying at

90°/0·01 mm. for 5 hr.) : C, 76·9, 76·45; H, 10·9, 11·0; Cl, 8·6. $C_{27}H_{47}OCl$ requires C, 76·6; H, 10·7; Cl, 8·4%]. Elution with ether–benzene mixtures gave an oil (2·6 g.) which by crystallisation from methanol gave 3β-chloro-5-hydroxycholestan-6β-yl acetate as plates, m. p. 151·5—152·5°, $[\alpha]_D$ −15·5° (*c* 1·01).

(*b*) 3β-Chloro-5 : 6α-epoxycholestane (100 mg.) was treated with lithium aluminium hydride in boiling ether for 0·5 hr. Isolation of the product in the usual way gave 3β-chlorocholestan-5-ol, m. p. 110° undepressed on admixture with the above specimen.

Cholesteryl Chloride.—3β-Chlorocholestan-5-ol (52 mg.) in pyridine (1·5 c.c.) was treated with thionyl chloride (0·2 c.c.) at −6° for 10 min. Working up in the usual way gave an oil which after filtration of a pentane solution through aluminium oxide gave crystals, m. p. 94—95°, undepressed on admixture with cholesteryl chloride.

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UNIVERSITY COLLEGE, SWANSEA,
UNIVERSITY OF WALES.

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