# 329. *Steroids. Part I. A New Preparation of the Cholesteryl Halides.*

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A new route leading to cholesteryl chloride, bromide, and iodide is described.

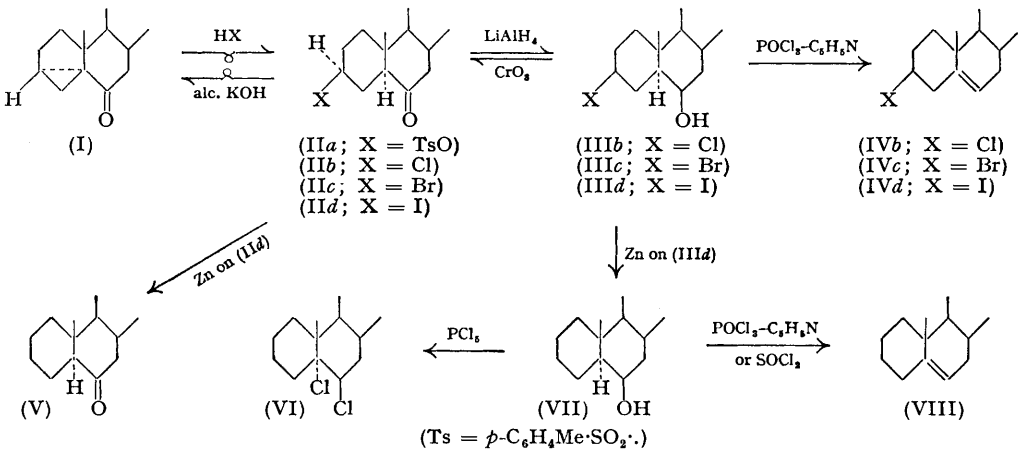
Two methods are available for the preparation of cholesteryl halides from cholesterol. One of these is the direct replacement of the 3β-hydroxyl group by phosphorus pentachloride (Mauthner, *Monatsh.*, 1894, **15**, 87), by thionyl chloride (Diels, Abderhalden, and Blumberg, *Ber.*, 1904, **37**, 3092; 1911, **44**, 287; Daughensbaugh and Allison, *J. Amer. Chem. Soc.*, 1929, **51**, 3665), or by hydrogen chloride (this paper), leading to cholesteryl chloride, or by use of phosphorus tribromide (Kolm, *Monatsh.*, 1912, **33**, 447; Lieb, Winkelmann, and Köppl, *Annalen*, 1934, **509**, 214) or thionyl bromide (Bide, Henbest, Jones, and Wilkinson, *J.*, 1948, 1787), leading to cholesteryl bromide. The other method involves the conversion of cholesterol into 6β-hydroxy-, 6β-methoxy-, or 6β-acetoxy-3 : 5-*cyclo*cholestane [formerly termed *i*-cholesterol, *i*-cholesteryl methyl ether and acetate] (Shoppee and Summers, to be published) or into 3 : 5-*cyclo*cholest-6-ene [formerly termed *i*-cholestadiene] (Riegel, Hager, and Zenitz, *J. Amer. Chem. Soc.*, 1946, **68**, 2562), which by treatment with hydrogen chloride, hydrogen bromide, or hydrogen iodide in acetic acid at 20° readily rearrange to furnish cholesteryl chloride, bromide, or iodide (Beynon, Heilbron, and Spring, *J.*, 1936, 907; 1937, 1459; Wallis and Ford, *J. Amer. Chem. Soc.*, 1937, **59**, 1415).

In connection with other investigations, the hitherto unknown *epi*cholesteryl chloride was required. Direct replacement by chlorine of the 3α-hydroxyl group of *epi*cholesterol proving unsatisfactory, and the 3 : 5-*cyclo*steroid rearrangement appearing to be β-stereospecific and so inapplicable, we have devised a new route to cholesteryl chloride, bromide, and iodide, and have applied it to the preparation of *epi*cholesteryl chloride and bromide (see following paper).

The starting material chosen was 3 : 5-*cyclo*cholestan-6-one [formerly called "cholesten-6-one" and *i*-cholestanone] (I) (Windaus and Dalmer, *Ber.*, 1919, **52**, 162; Windaus and von Staden, *ibid.*, 1921, **54**, 1059; Ford, Chakravorty, and Wallis, *J. Amer. Chem. Soc.*, 1938, **60**, 413; Heilbron, Hodges, and Spring, *J.*, 1938, 759), which was prepared by treatment of the toluene-*p*-sulphonate of 3β-hydroxycholestan-6-one (II*a*) with alcoholic potassium hydroxide (Dodson and Riegel, *J. Org. Chem.*, 1948, **13**, 424).

The ketone (I) is quantitatively converted by hydrogen chloride in acetic acid at 20° into 3β-chlorocholestan-6-one (II*b*) (Ford, Chakravorty, and Wallis, *loc. cit.*); this change involves inversion of configuration at $C_{(3)}$, and we find that by use respectively of hydrogen bromide and hydrogen iodide under appropriate conditions there are produced similarly 3β-bromo- (II*c*), and 3β-iodo-cholestan-6-one (II*d*). The 3β-iodo-ketone (II*d*) is reduced by zinc to cholestan-6-one (V) ["heterocholestanone"] (Windaus and Dalmer, *loc. cit.*; Windaus, *Ber.*, 1920, **53**, 488). The 3β-halogeno-ketones (II*b*—*d*) by reduction with lithium aluminium hydride at low temperature (0—20°) afford respectively 3β-chloro- (III*b*), 3β-bromo- (III*c*) and 3β-iodo-cholestan-6β-ol (III*d*), which are unaccompanied by appreciable amounts of the 6α-epimerides and are reconverted into the appropriate 3β-halogeno-ketones (II) by oxidation with chromium trioxide. The 3β-chloro-alcohol (III*b*) by reduction with sodium and amyl alcohol, or better the 3β-iodo-alcohol (III*d*) by reduction with zinc, gives cholestan-6β-ol, m. p. 82° (VII) [acetate, m. p. 75°; benzoate, m. p. 79°]. Plattner, Petrzilka, and Lang (*Helv. Chim. Acta*, 1944, **27**, 513) by reduction of 5α : 6α-epoxycholestane isolated cholestan-5α-ol but could not obtain the accompanying cholestan-6-ol (which should be the β-epimeride); the acetate, m. p. 75°, of a cholestan-6-ol has previously been described by Reich and Lardon (*ibid.*, 1946, **29**, 671) without assignment of configuration at $C_{(6)}$. The compound described in Elsevier's "Encyclopædia" (Vol. XIV, p. 66) as cholestan-6β-ol is in fact cholestan-6α-ol, m. p. 130° [acetate, m. p. 95°; benzoate, m. p. 103°], obtained from cholestan-6-one by reduction with sodium and ethanol (Tschesche, *Ber.*, 1932, **65**, 1842); cholestan-6α-ol. m. p. 127—129°, although described as cholestan-6β-ol,

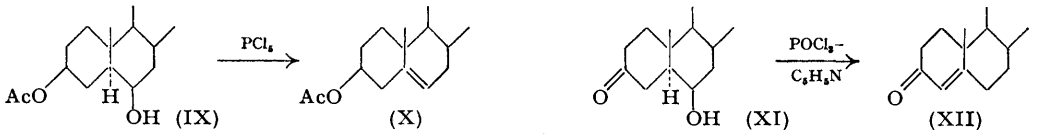
was also the substance used by Karrer, Asmis, Sareen, and Schwyzer (*Helv. Chim. Acta*, 1951, **34**, 1022) and was characterised as the toluene-*p*-sulphonate, m. p. 108·5—110° (which we have also prepared) (private communication from Prof. Karrer).




It will be seen not only that in the 3β-halogeno-alcohols (III*b*—*d*) the 5α-hydrogen atom and the 6β-hydroxyl group possess the *trans*-arrangement, but also that both atom and group are united to carbon atoms of ring B by bonds belonging to the set of six lying in a plane perpendicular to the general plane of ring B and termed polar (Beckett, Pitzer, and Spitzer, *J. Amer. Chem. Soc.*, 1947, **69**, 2488; cf. Hassell and Viervoll, *Acta Chem. Scand.*, 1947, **1**, 149). Thus the four centres 5α-H, $C_{(5)}$, $C_{(6)}$, and 6β-O(H) are coplanar and comply with the conditions for minimisation of the activation energy of a synchronous ionic elimination reaction ($E_2$) (Dhar, Hughes, Ingold, Mandour, Maw, and Woolf, *J.*, 1948, 2093; cf. Barton, *Experientia*, 1950, **6**, 316; Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 370, 1066; Barton and Rosenfelder, *J.*, 1951, 1048; Barton, Miller, and Young, *ibid.*, p. 2598). Dehydration of the 3β-halogeno-alcohols (III*b*—*d*) proceeds readily with phosphorus oxychloride and pyridine at 20° to give respectively cholesteryl chloride (IV*b*), cholesteryl bromide (IV*c*), and cholesteryl iodide (IV*d*).

It is of interest that, whilst treatment of cholestan-6α-ol with thionyl chloride leads to substitution with retention of configuration and formation of 6α-chlorocholestane, m. p. 151°, $[\alpha]_D$ +51° (Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 371), the epimeric cholestan-6β-ol (VII) with thionyl chloride undergoes dehydration with formation of cholest-5-ene (VIII). Employment of phosphorus pentachloride in the case of cholestan-6α-ol leads to substitution with inversion, to give 6β-chlorocholestane, m. p. 147°, $[\alpha]_D$ −45° (Stange, *Z. physiol. Chem.*, 1933, **220**, 34), but in the case of cholestan-6β-ol this reagent furnishes 5α : 6β-dichlorocholestane (VI), m. p. 119°, $[\alpha]_D$ −29° (cf. Mauthner, *Monatsh.*, 1906, **27**, 421; Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 370). We believe that this compound arises by facile dehydration of cholestan-6β-ol (VII) to cholest-5-ene (VIII) and subsequent *trans*-addition of a molecule of chlorine derived from phosphorus pentachloride by the reaction $PCl_5 \rightleftharpoons PCl_3 + Cl_2$. An analogous equilibrium involving phosphorus trichloride and bromine has been shown to exist in carbon tetrachloride solution at 20° (C. C. Price, unpublished observation): $PCl_3Br_2 \rightleftharpoons PCl_3 + Br_2$. We are greatly obliged to Professor Price, of Notre Dame University, Indiana, for this information which appears to afford a satisfactory explanation for the above conversion of a monohydric alcohol into a dichloride. A further example appears to be the conversion of cholesterol, by grinding it with phosphorus pentachloride, into cholesteryl chloride, whereas in the presence of benzene cholesteryl chloride dichloride is formed (Pirrone, *Gazzetta*, 1932, **62**, 63). On the other hand it may be noted that the 3-acetate (IX) of cholestane-3β : 6β-diol with phosphorus pentachloride in benzene gave cholesteryl acetate (X) and not cholesteryl acetate dichloride (Barton and Rosenfelder, *J.*, 1949, 2459). Treatment of 6β-

hydroxycholestan-3-one (XI) with phosphorus oxychloride and pyridine probably yields cholest-5-en-3-one as the initial reaction product although the material isolated under our conditions was cholest-4-en-3-one (XII).




(IX) (X) (XI) (XII)

## Experimental

M. p.s were determined thermo-electrically on a Kofler block (limit of error ±2°). Solvents for chromatographic operations were rigorously purified and dried and, unless stated otherwise, aluminium oxide (Spence type H, activity ~II) was used. For drying of ethereal extracts, brief treatment with anhydrous sodium sulphate was used. [α] are recorded for chloroform solutions.

3 : 5-cyclo*Cholestan*-6-*one* (I).—3β-Hydroxycholestan-6-one (m. p. 142—143°; 15 g.) was dried by repeated evaporation with dry benzene under reduced pressure, and finally by heating it at 100°/0·1 mm. for 0·5 hour. The ketone in dry pyridine (10 c.c.) was treated with toluene-*p*-sulphonyl chloride (12·3 g.), and the deep red solution kept at 25° for 15 hours. The pyridine was largely removed under reduced pressure at 40° and the residue poured into ice-cold 2N-hydrochloric acid and set aside for 0·5 hour. The product was extracted with chloroform–ether, and the extract washed to neutrality with water, 2N-sodium hydrogen carbonate, and water. Evaporation yielded a thick crust of 3β-toluene-*p*-sulphonyloxycholestan-6-one (II*a*), which was recrystallised from acetone, to give needles, m. p. 186° (decomp.), $[\alpha]_D$ −5° ± 1° (*c*, 1·133) (Riegel and Dodson, *J. Org. Chem.*, 1948, **13**, 424, give m. p. 169—179°, $[\alpha]_D$ −5·5° ± 0·7°); the yield after repeated crystallisation was 16·7 g. This material was converted by the method of Dodson and Riegel (*loc. cit.*) into 3 : 5-*cyclo*cholestan-6-one, which was finally purified by filtration of a pentane solution through a column of aluminium oxide and had m. p. 96—97°.

3β-*Chlorocholestan*-6β-*ol* (III*b*).—3β-Chlorocholestan-6-one (II*b*) (m. p. 129—130°; 1·47 g. in 100 c.c. of dry ether) was added dropwise during 0·25 hour to an ice-cold solution of lithium aluminium hydride (0·5 g.) in ether (150 c.c.). The solution was poured into ice-water, and the ethereal layer washed with 2N-sulphuric acid, sodium hydrogen carbonate solution, and water. After drying, removal of the ether yielded 3β-*chlorocholestan*-6β-*ol* as an oil (1·34 g.) which crystallised from pentane in needles, m. p. 96°, $[\alpha]_D$ +14·5° ± 2° (*c*, 4·10) (Found, after drying at 20°/0·01 mm. for 20 hours: C, 76·6; H, 11·0. $C_{27}H_{47}OCl$ requires C, 76·6; H, 11·1%). It gave no colour with tetranitromethane in chloroform. 3β-Chlorocholestan-6β-ol (250 mg.) in acetic acid (5 c.c.) was treated with a 2% solution of chromium trioxide in acetic acid (2 c.c.), and the mixture left at 20° for 12 hours. Excess of chromium trioxide was destroyed with methanol, and, after dilution with water, the product was extracted with ether. The ethereal extract was washed with water, 2N-sodium carbonate, and water, then dried, and evaporated to yield an oil (237 mg.) which crystallised from methanol in needles, m. p. 127—128°, undepressed by admixture with an authentic specimen of 3β-chlorocholestan-6-one which had $[\alpha]_D$ −1° ± 1·5° (*c* = 1·17).

*Cholesteryl Chloride* (IV*b*).—(*a*) Phosphorus oxychloride (0·5 c.c.) was added with ice-cooling to a solution of 3β-chlorocholestan-6β-ol (108 mg.) in dry pyridine (6 c.c.) and left at 20° overnight. The reaction mixture was poured into ice-water, and the product extracted with ether. The ethereal extract after the usual purification and drying yielded an oil (79 mg.) which was further purified by filtration of a pentane solution through a column of aluminium oxide. The colourless oil readily crystallised (exhibiting anisotropic transformation colours) and separated from acetone–methanol as plates, m. p. 94—96°, undepressed on admixture with an authentic specimen.

(*b*) Cholesterol (2·2 g.) (m. p. 148°; commercial material purified by successive bromination, crystallisation of cholesterol dibromide from ether–ethanol, and debromination with sodium iodide) in absolute methanol (200 c.c.) was heated under reflux for 7 hours with concentrated hydrochloric acid (20 c.c.). The yellow solution was reduced to half its volume in a vacuum, poured into water, and extracted with ether, and the extract dried and evaporated to give a crystalline solid. This was chromatographed on aluminium oxide (70 g.), and the chromatogram eluted with pentane and pentane–benzene (19 : 1) until no further material was obtained.

The oil (76 mg.) so obtained crystallised from ether–methanol as needles, m. p. 95—96° undepressed on admixture with a genuine specimen of cholesteryl chloride.

3β-*Bromocholestan*-6β-*ol* (III*c*).—3β-Bromocholestan-6-one (m. p. 123—125°; 550 mg.), prepared by treatment of an acetic acid solution of 3 : 5-*cyclo*cholestan-6-one with 48% hydrobromic acid, was treated in dry ether (50 c.c.) with a solution of lithium aluminium hydride (220 mg.) in ether (100 c.c.). The mixture was cooled in an ice-bath and after 0·25 hour was worked up as described for 3β-chlorocholestan-6β-ol. 3β-*Bromocholestan*-6β-*ol* was isolated as an oil (550 mg.) which crystallised from methanol as prisms, m. p. 95°, $[\alpha]_D$ +14° ± 2° (*c*, 3·97) (Found,* after drying at 20°/0·01 mm. for 16 hours: C, 70·95; H, 10·7. $C_{27}H_{47}OBr$ requires C, 69·35; H, 10·1%). The substance gave a positive Beilstein test but no colour with tetranitromethane.

3β-*Bromocholestan*-6-*one* (II*c*).—3β-Bromocholestan-6β-ol (70 mg.) in acetic acid (3 c.c.) was warmed to 50° for 5 minutes with a 2% solution of chromium trioxide in acetic acid (3 c.c.) and the whole then poured into water; the product was extracted with ether, and the extract purified in the usual way. 3β-Bromocholestan-6-one was obtained as needles (from acetic acid), m. p. 123° undepressed on admixture with an authentic specimen, which had $[\alpha]_D$ +3° ± 1° (*c*, 4·29).

*Cholesteryl Bromide* (IV*c*).—3β-Bromocholestan-6β-ol (III*d*) (200 mg.) in pyridine (6 c.c.) with phosphorus oxychloride (2 c.c.) and subsequent treatment as for (III*c*) yielded 3β-bromocholest-5-ene, m. p. 96—98°, in quantitative yield.

3β-*Iodocholestan*-6-*one* (II*d*).—3 : 5-*cyclo*Cholestan-6-one (1·7 g.) was dissolved in pure acetic acid (25 c.c.) and treated with 54% hydriodic acid (5 c.c.). The turbid solution was made clear by the addition of ether; almost immediately needles formed on the surface of the solution and after storage overnight a thick cluster of very long needles had formed at the bottom of the flask. The supernatant liquid was decanted, the needles were washed with acetic acid, and the washings combined with the main solution. This was diluted with water and the product extracted with ether–benzene. The extract was worked up in the usual way and a red-violet oil was obtained which solidified on being moistened with acetic acid. 3β-*Iodocholestan*-6-*one* crystallised from acetic acid in needles, m. p. 137—138°, $[\alpha]_D$ +8° ± 2° (*c*, 4·13) (total yield 1·72 g.) (Found, after drying at 20°/0·05 mm. for 16 hours: C, 63·5; H, 8·75. $C_{27}H_{45}OI$ requires C, 63·3; H, 8·8%). The compound gave a positive Beilstein test.

3β-*Iodocholestan*-6β-*ol* (III*d*).—3β-Iodocholestan-6-one (1·45 g.) in ether (120 c.c.) was shaken with a solution of lithium aluminium hydride (0·5 g.) at 0° for 10 minutes. The solution was poured into ice-water, and the ethereal layer separated and washed with 4N-sulphuric acid, and then water to neutrality. Evaporation of the solvent afforded a colourless oil (1·5 g.), which crystallised on cooling. Recrystallisation from ethanol or methanol–acetone gave 3β-*iodocholestan*-6β-*ol* as needles, m. p. 109—110°, $[\alpha]_D$ +15° ±3° (*c*, 4·79) (Found, after drying at 20°/0·05 mm. for 8 hours: C, 63·0; H, 9·2. $C_{27}H_{47}OI$ requires C, 62·9; H, 9·2%). The substance was saturated to tetranitromethane. 3β-Iodocholestan-6β-ol (20 mg.) was dissolved in acetic acid (1 c.c.), treated with a 2% solution of chromium trioxide in acetic acid (1 c.c.), and warmed at 40° for 10 minutes. The solid neutral product, isolated in the usual way, consisted of 3β-iodocholestan-6-one, m. p. 137°.

*Cholesteryl Iodide* (IV*d*).—3β-Iodocholestan-6β-ol (100 mg.) in pyridine (4 c.c.) was treated with phosphorus oxychloride (1 c.c.) and left overnight at room temperature. Working up as described above gave an oil which solidified in rosettes and crystallised from ethanol in long plates (84 mg.), m. p. 105—106°, undepressed on admixture with authentic 3β-iodocholest-5-ene.

*Cholestan*-6-*one* (V).—3β-Iodocholestan-6-one (25 mg.) in glacial acetic acid (5 c.c.) was heated under reflux for 0·25 hour with zinc dust (70 mg.). The acetic acid was removed under reduced pressure, the crystalline residue extracted with ether, and the extract filtered from the zinc dust; working up in the usual way gave a colourless oil, which crystallised from methanol in plates (16 mg.), m. p. 97—98°, undepressed on admixture with genuine cholestan-6-one.

*Cholestan*-6β-*ol* (VII).—Reduction of 3β-iodocholestan-6β-ol with zinc dust in a similar manner gave cholestan-6β-ol, m. p. 81°, in quantitative yield.

*Cholest*-5-*ene* (VIII).—Cholestan-6β-ol (50 mg.) in pyridine (1 c.c.) was treated with phosphorus oxychloride (3 drops) at 0° and left overnight at 20°. The product, isolated in the usual way, was identical with cholest-5-ene, m. p. 89°, prepared by reduction of cholesteryl chloride with sodium–amyl alcohol. Thionyl chloride in pyridine at 20° gave the same product.

5α : 6β-*Dichlorocholestane* (VI).—Cholestan-6β-ol (74 mg.) was ground with phosphorus pentachloride (200 mg.) and benzene (1 c.c.) for 10 minutes. The mixture became a brilliant purple.

* We are unable to record a good analysis for this substance, a second set of figures being C, 71·2; H, 10·2%.

After the whole had been warmed with water 5α : 6β-*dichlorocholestane* was isolated as an oil which crystallised from methanol as leaflets, m. p. 114—116°, $[\alpha]_D$ −29° ± 2° (*c*, 1·830) (Found, after drying at 80°/0·01 mm. for 2 hours: C, 73·6; H, 10·3. $C_{27}H_{46}Cl_2$ requires C, 73·5; H, 10·5%). The compound gave a positive Beilstein test and was saturated to tetranitromethane.

*Cholest-4-en-3-one.*—6β-Hydroxycholestan-3-one (m. p. 184°; 176 mg.) in pyridine (4 c.c.) was treated at 0° with phosphorus oxychloride (1 c.c.), and the mixture left at 20° overnight. An oily product was isolated which solidified on being rubbed with methanol. Chromatography on neutral alumina * gave, by elution with pentane, cholest-4-en-3-one, m. p. 79—81° (146 mg.).

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