Steroids and Walden Inversion. Part LXIII.[1] Substitution Reactions of the 5α-Cholestan-4-ols: a Further Example of Walden Retention

By **C. W. Shoppee,* R. E. Lack,** and **S. C. Sharma,** Department of Organic Chemistry, University of Sydney, Australia

5α-Cholestan-4α-ol reacts with phosphorus pentachloride or thionyl chloride to give 4α-chloro-5α-cholestane with much elimination product, and with phosphorus pentabromide at 0° it gives 4α-bromo-5α-cholestane, in each case with retention of configuration. 5α-Cholestan-4β-ol, with phosphorus pentachloride or phosphorus pentabromide in chloroform at 20°, or with thionyl chloride, yields mainly cholest-4-ene; use of phosphorus pentachloride in benzene at 80° gives 4β,5α-dichlorocholestane.

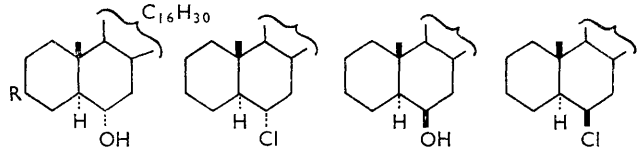
In Part XLVI [2] it was shown that 5α-cholestan-6α-ol (I; R = H) reacted with phosphorus pentachloride and with thionyl chloride to give 6α-chloro-5α-cholestane (II; R = H), $\nu_{max.}$ 745 cm.$^{-1}$, with retention of configuration; 5α-cholestan-6β-ol (III) gave only cholest-5-ene, and 6β-chloro-5α-cholestane (IV), $\nu_{max.}$ 696 cm.$^{-1}$, could only be prepared indirectly.[3]

[1] Part LXII, C. W. Shoppee and S. C. Sharma, *J. Chem. Soc.* (*C*), 1967, 245.

[2] C. W. Shoppee, M. E. H. Howden, and R. E. Lack, *J. Chem. Soc.*, 1960, 4874.

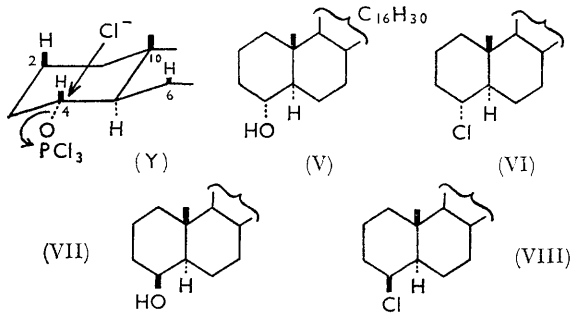
[3] C. W. Shoppee and R. E. Lack, *J. Chem. Soc.*, 1960, 4864.

In Part LIII [4] it was shown that 3β-acetoxy-, 3α-acetoxy-, and 3β-chloro-5α-cholestan-6α-ol (I; R = β-OAc, α-OAc, and β-Cl) reacted with phosphorus pentachloride to give the appropriately 3-substituted 6α-chloro-5α-cholestanes (II; R = β-OAc, α-OAc, β-Cl) with retention of configuration, a result explained in terms of steric suppression of the linear S_N2 transition state in favour of the S_Ni transition state, which is believed not to be subject to steric retardation.



(I) (II) (III) (IV)

The stereochemical environment at C-4 in 5α-cholestan-4α-ol (V) is similar to that at C-6 in 5α-cholestan-6α-ol (I; R = H). Repression of S_N2 substitution, which requires a chloride anion in the transition state (Y) to traverse a reaction co-ordinate close to the β-face of ring A hindered by the axial 2β- and 4β-hydrogen atoms and the axial 10β-methyl group, and facilitation of S_Ni substitution with retention of configuration is anticipated.



(Y) (V) (VI)

(VII) (VIII)

In 1959 R. W. Killick, in these laboratories, treated 5α-cholestan-4α-ol (V) with phosphorus pentachloride and obtained crude 4α-chloro-5α-cholestane (VI), m.p. ~86°, $\nu_{max.}$ 751 cm.$^{-1}$. A repetition of this experiment in chloroform at 0°, followed by column chromatography and removal of olefin by treatment with peracid, gave a low yield of 4α-chloro-5α-cholestane (VI), $\nu_{max.}$ 750 cm.$^{-1}$, contaminated by 4β-chloro-5α-cholestane (VIII) (*ca.* 3%) as indicated by a low intensity peak at 710 cm.$^{-1}$. Use of similar isolation techniques followed by extraction with chloroform in the reaction of the 4α-ol (V) with thionyl chloride at 0° gave cholest-4-ene and the 4α-yl chloride (VI), $\nu_{max.}$ 750 cm.$^{-1}$, with no peak at 710 cm.$^{-1}$ corresponding to (VIII), together with the 4α-yl sulphite, and a product identified tentatively as 5α-cholestan-4α-yl ethyl sulphite. These sulphites are probably formed from the intermediate 4α-yl chlorosulphite ester, either by reaction with a molecule of the 4α-ol (V) to give the normal bis-sulphite or, in the absence of an excess of 4α-ol (V), by reaction with ethanol present in the chloroform, to give the mixed sulphite. Sulphites have been found [5] as major products in the reactions of steroid alcohols with thionyl chloride where the expected S_Ni process suffers steric retardation.

5α-Cholestan-4β-ol (VII), when briefly treated with phosphorus pentachloride in chloroform at 0°, gave only cholest-4-ene and unchanged alcohol; treatment with the same reagent in benzene at 0° gave 4β-5α-dichlorocholestane, identical with a sample prepared by the addition of chlorine to cholest-4-ene. Attempts to analyse the products of this and the previous substitution reactions by v.p.c. were unsuccessful since although 4α-chloro-5α-cholestane gave a single peak, 4β,5α-dichloro-5α-cholestane decomposed to give at least three peaks under the conditions employed. Further investigation showed that pure 3β-chloro- and 6α-chloro-5α-cholestane gave single peaks whilst the axial 3α-chloro-5α-cholestane underwent considerable decomposition. The formation of vicinal dichlorides in the reaction of monohydric alcohols with phosphorus pentachloride has previously been described.[6,7] The 4β-ol (VII) reacted with thionyl chloride at 0° to give no substitution product but only olefin, the 4β-yl sulphite, and the 5α-cholestan-4β-yl ethyl sulphite.

Treatment of the 4α-ol (V) with phosphorus pentabromide at 20° gave the highly unstable 4α-yl bromide (VI with Br for Cl), $\nu_{max.}$ 678 cm.$^{-1}$, which was decomposed to cholest-4-ene either by attempted recrystallisation from acetone or by chromatography on silica gel.

The configurations assigned to the 4α-chloro- and the 4α-bromo-derivatives (VI), and to the 4α- and 4β-yl sulphites are supported by the n.m.r. spectra; relevant data are shown in the Table. Axial substituents at C-2, C-4, and C-6 have been shown [8] to deshield the C-10 methyl protons to a much greater extent than the corresponding equatorial substituents. The 10-methyl group in 4α-bromo- and 4α-chloro-5α-cholestane and the 4α-yl sulphite had the same chemical shift as the 10-methyl group in 5α-cholestane, but in the 4β-yl sulphite it was deshielded by 0·16 p.p.m. The 4α-configuration

N.m.r. spectra (τ values)

	10β-Me	4-H	W_H (c./sec.)
5α-Cholestane	9·17		
4α-Chloro-5α-cholestane	9·18	6·16	18
4α-Bromo-5α-cholestane	9·18	5·66	17
5α-Cholestan-4α-ol	9·17	6·6	22
5α-Cholestan-4β-ol	8·98	6·2	3
5α-Cholestan-4α-yl sulphite	9·17		
5α-Cholestan-4β-yl sulphite	9·01		
4β,5α-Dichlorocholestane	8·67	5·6	7

[4] C. W. Shoppee, R. E. Lack, and B. McLean, *J. Chem. Soc.*, 1964, 4996.
[5] C. W. Shoppee, T. E. Bellas, and R. E. Lack, *J. Chem. Soc.*, 1965, 6450.
[6] C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 1952, 1786.
[7] H. L. Goering and F. H. McCarron, *J. Amer. Chem. Soc.*, 1956, **78**, 2270.
[8] E. R. Malinowski, M. S. Manhas, G. H. Muller, and A. K. Bose, *Tetrahedron Letters*, 1963, 1161, and references cited therein; C. W. Shoppee, M. I. Akhtar, and R. E. Lack, *J. Chem. Soc.*, 1964, 877.

of the halides (VI) was also confirmed by the shape of the signal given by the axial 4β-proton (W_H 17—22 c./sec.).[9]

Thus as expected 5α-cholestan-4α-ol (V; OH, *eq*) undergoes substitution mainly with retention of configuration with phosphorus pentachloride, and with complete retention with thionyl chloride. The high yield of olefin and the modest yields of 4α-yl chloride suggest that the mechanism of substitution is closer to ion-pair collapse (S_Ni) than to covalent exchange (S_Ni).[10] *

EXPERIMENTAL

For general experimental directions see *J. Chem. Soc.*, 1959, 345. M.p.s were determined with a Kofler block and are corrected. Values of $[\alpha]_D$ refer to solutions in chloroform at room temperature. I.r. absorption spectra (carbon disulphide) were measured with a Perkin-Elmer 221 spectrophotometer. N.m.r. spectra were measured with Varian A60 and HA 100 instruments with deuteriochloroform as solvent and tetramethylsilane as internal reference. Column chromatography was performed on silica gel (Davison) or aluminium oxide (Spence type H, activity II). T.l.c. was performed on silica with pentane as eluant unless otherwise indicated; plates were sprayed with conc. sulphuric acid and developed at 110°; for preparative t.l.c. plates were sprayed with methanolic berberine hydrochloride and examined under u.v. light. Vapour phase chromatography (v.p.c.) was attempted in an F and M 400 instrument with 3·8% SE 30 on diatoport S (80—100 mesh) columns (1·1 m. × 3 mm. internal diam.) in helium; helium flow rate, 75 ml./min. Specimens for analysis were dried at 20°/0·2 mm. for at least 8 hr.

5α-Cholestan-4-one.—Cholest-4-ene, m.p. 82—83°, was prepared by reduction of cholest-4-en-3-one ethylene thioacetal, m.p. 106—107°, with sodium–liquid ammonia,[11] and converted by treatment with *m*-chloroperbenzoic acid into 4α,5-epoxy-5α-cholestane,[12] m.p. 100—101°; this was rearranged with boron trifluoride–diethyl ether in benzene [12,13] to 5β-cholestan-4-one, which was epimerised by sodium methoxide in methanol to 5α-cholestan-4-one, m.p. 96—98° (from acetone).

5α-Cholestan-4α-ol.—Reduction of the above ketone with sodium in pentanol under reflux gave 5α-cholestan-4α-ol,[14–16] m.p. 186—187° (from chloroform–methanol).

5α-Cholestan-4β-ol.—Reduction of the above ketone with lithium aluminium hydride in ether under reflux gave 5α-cholestan-4β-ol,[15,16] m.p. 130—132° (from methanol); the mother liquor yielded a mixture of the epimeric 4-ols, which was oxidised with sodium dichromate–sulphuric acid to regenerate the ketone.

Reaction of 5α-Cholestan-4α-ol with Phosphorus Pentachloride.—The 4α-ol (150 mg.), phosphorus pentachloride (180 mg.; freshly sublimed at 80°/2 mm.), and chloroform (0·5 ml.) were ground together. After 15 min. water was added, and the product was isolated with ether. The crude product (153 mg.) was chromatographed on a silica column (30 g.) in pentane; elution with pentane gave a non-polar product (110 mg.), and elution with benzene gave unchanged 4α-ol (34 mg.), mixed m.p. 186—187°. The non-polar product was separated by preparative t.l.c. on silica in pentane to give cholest-4-ene (60 mg.), m.p. and mixed m.p. 73—80° (from ethyl acetate–methanol), and slightly impure 4α-chloro-5α-cholestane (VI) (40 mg.), m.p. 85—89° (from acetone–methanol), $\nu_{max.}$ 750 cm.$^{-1}$ with a low intensity peak at 710 cm.$^{-1}$ (Found: C, 78·9; H, 11·55; Cl, 9·6. Calc. for $C_{27}H_{47}Cl$: C, 79·6; H, 11·6; Cl, 8·7%).

Reaction of 5α-Cholestan-4α-ol with Thionyl Chloride.—The 4α-ol (150 mg.) was treated with thionyl chloride (1·2 ml.) at 0° for 10 min. The mixture was removed from the ice-bath and set aside for 10 min. at 20°. Water was added, and the product was isolated with chloroform. Column chromatography on silica (20 g.) in pentane with pentane as eluant gave a non-polar mixture (13 mg.) of cholest-4-ene and 4α-chloro-5α-cholestane (see below); elution with benzene gave a more polar mixture (126 mg.) of three products (t.l.c.), separated by preparative t.l.c. on silica in ether–pentane (1 : 9). These were (in order of increasing polarity) (i) Bis-(*5α-cholestan-4α-yl*)*sulphite* (30 mg.), softens 196°, m.p. 213—215° (from acetone–methanol), $\nu_{max.}$ 1191 and 767 cm.$^{-1}$ (Found: C, 78·5; H, 11·4. $C_{54}H_{94}SO_3$ requires C, 78·8; H, 11·4%), (ii) *5α-cholestan-4α-yl ethyl sulphite* (22 mg.), m.p. 66—68°, $\nu_{max.}$ 1196 and 1210 cm.$^{-1}$ (Found: C, 72·4; H, 10·85; S, 6·5. $C_{29}H_{52}SO_3$ requires C, 72·5; H, 10·7; S, 6·7%), and (iii) 5α-cholestan-4α-ol (65 mg.), m.p. and mixed m.p. 182—183°. The non-polar products from a series of similar experiments were combined (100 mg.) and treated with an excess of *m*-chloroperbenzoic acid (125 mg.) in chloroform (10 ml.) at 0° for 20 hr. The usual isolation procedure gave a product (100 mg.) which was chromatographed on silica (25 g.) in pentane. Elution with pentane (10 ml.) gave unidentified oils (22 mg.); further elution (20 ml.) gave *4α-chloro-5α-cholestane*, m.p. 90—91°, $\nu_{max.}$ 750 cm.$^{-1}$ (Found: C, 79·9; H, 11·7. $C_{27}H_{47}Cl$ requires C, 79·7; H, 11·6%).

Reaction of 5α-Cholestan-4β-ol with Phosphorus Pentachloride.—(*a*) The 4β-ol (260 mg.), phosphorus pentachloride (310 mg.), and a little chloroform were mixed at 0° for 20 min. The oily product (250 mg.) isolated as usual, was chromatographed on silica (25 g.) in pentane. The column was eluted with pentane to give cholest-4-ene (220 mg.), m.p. and mixed m.p. 82—83° (from ethyl acetate–methanol), negative Beilstein test for halogen; elution with benzene gave unchanged 4β-ol (37 mg.), m.p. and mixed m.p. 131—132°.

(*b*) The 4β-ol (100 mg.) in benzene (10 ml.) was heated with phosphorus pentachloride (120 mg.) under reflux on a water bath for 1 hr. to give a crude product (95 mg.). Preparative t.l.c. gave some cholest-4-ene and 4β-5α-dichlorocholestane, m.p. and mixed m.p. (with a sample prepared by the addition of chlorine to cholest-4-ene) 122°; τ 9·35 (13-Me), 8·67 (10-Me), and 5·6 (W_H 7 c./sec., 4α-H).

4β,5α-Dichlorocholestane.—Cholest-4-ene (150 mg.) in

* However, preferential and irreversible ion-pair collapse to sulphonyl chloride (leading to steroid sulphonate esters, rather than internal return to chlorosulphite, is not observed.

[9] A. Hassner and C. Heathcock, *J. Org. Chem.*, 1964, **29**, 1352.
[10] D. J. Cram, *J. Amer. Chem. Soc.*, 1953, **75**, 332; C. E. Boozer and E. S. Lewis, *ibid.* 1953, **75**, 3182; 1954, **76**, 794; S. Winstein and C. G. Robinson, *ibid.*, 1958, **80**, 1690.
[11] R. E. Ireland, T. L. Wrigley, and W. G. Young, *J. Amer. Chem. Soc.*, 1958, **80**, 4604.
[12] C. W. Shoppee, M. E. H. Howden, R. W. Killick, and G. H. R. Summers, *J. Chem. Soc.*, 1959, 630.
[13] H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1957, 1960.
[14] R. Tschesche and A. Hagedorn, *Ber.*, 1935, **68**, 2251.
[15] D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1951, 1048.
[16] C. W. Shoppee, D. N. Jones, J. R. Lewis, and G. H. R. Summers, *J. Chem. Soc.*, 1955, 2876.

acetic acid–carbon tetrachloride (3 : 1; 12 ml.) was treated with chlorine in carbon tetrachloride (30 mg. in 2 ml.) at 20° for 1 hr. The usual isolation followed by chromatography on silica and elution with hexane gave 4β,5α-*dichlorocholestane* (90 mg.), m.p. 122° (from methanol–acetone) (Found: C, 73·4; H, 10·7. $C_{27}H_{46}Cl_2$ requires C, 73·4; H, 10·5%); τ 9·35 (13-Me), 8·67 (10-Me), and 5·6 (W_H 7 c./sec., 4α-H). V.p.c. at 235° caused decomposition of 4β,5α-dichlorocholestane to give three peaks (retention times 6·5, 7·5, and 13·5 min.). A mixed m.p. with the product of (*b*) above was 122°, but the compound depressed the m.p. of 5α,6β-dichlorocholestane (m.p. 120—123°), prepared by addition of chlorine to cholest-5-ene;[17] τ 9·3 (13-Me), 8·69 (10-Me), and 5·7 (W_H 7 c./sec., 5α-H).

Reaction of 5α-Cholestan-4β-ol with Thionyl Chloride.—The 4β-ol (200 mg.) was added to thionyl chloride (0·8 ml.) at 0°. The mixture was kept at 0° for 5 min., and at 20° for 5 min., and worked up in the usual way. The product was chromatographed on silica gel in pentane; elution with pentane gave cholest-4-ene (150 mg.), m.p. and mixed m.p. 80—81°. Further elution, with benzene, gave more polar material, shown by t.l.c. to be a mixture of three products isolated by preparative t.l.c.: (i) bis-(5α-*cholestan*-4β-*yl*) *sulphite* (15 mg.), m.p. 217—219° (from acetone–methanol), $\nu_{max.}$ 1190 and 775 cm.$^{-1}$ (Found: C, 78·7; H, 11·55), (ii) 5α-*cholestan*-4β-*yl ethyl sulphite* (10 mg.), m.p. 92—94° (from acetone–methanol), $\nu_{max.}$ 1161 and 1189 cm.$^{-1}$ (Found: C, 72·1; H, 10·4), and (iii) 5α-cholestan-4β-ol (20 mg.), m.p. and mixed m.p. 130—132°.

Reaction of 5α-Cholestan-4α-ol with Phosphorus Pentabromide.—The 4α-ol (100 mg.), phosphorus pentabromide (110 mg.), and chloroform (1 ml.) were ground together. After 10 min. at 20° ice was added and the product was extracted quickly with ether and crystallised from acetone to give crude 4α-bromo-5α-cholestane, m.p. 58—73°, $\nu_{max.}$ 680 cm.$^{-1}$ (*eq* Br) τ 9·18 (10-Me) and 5·68 (W_H 17 c./sec., 4β-H). Attempts to purify the crude product by crystallisation from acetone or by column chromatography on silica yielded only 5α-cholest-4-ene and unchanged 4α-ol (13 mg.).

Reaction of 5α-Cholestan-4β-ol with Phosphorus Pentabromide.—(*a*) The 4β-ol (220 mg.) was treated with phosphorus pentabromide (300 mg.) in chloroform (1 ml.) at 0° for 20 min. The crude product (208 mg.) was chromatographed on a silica column; elution with pentane gave a non-polar product (25 mg.), shown by n.m.r. to be slightly impure cholest-4-ene (positive Beilstein test for halogen); elution with benzene gave unchanged 4β-ol (155 mg.), m.p. and mixed m.p. 132—133° (from methanol).

(*b*) The 4β-ol (240 mg.) was treated with phosphorus pentabromide (350 mg.) in benzene (10 ml.) at 80° for 1 hr. and worked up in the usual way. Column chromatography on silica and elution with pentane gave a non-polar product (158 mg.) which gave a positive Beilstein test for halogen but consisted mainly of cholest-4-ene. Further elution with benzene gave unchanged 5α-cholestan-4β-ol (75 mg.), m.p. and mixed m.p. 132—133°.

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[17] D. H. R. Barton and E. Miller, *J. Amer. Chem. Soc.*, **1950**, **72**, 370; J. Décombe and J. Rabinowitch, *Bull. Soc. chim. France*, 1939, **6**, 1510.