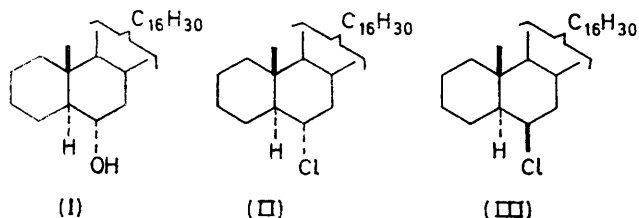


Steroids and Walden Inversion. Part LXX.¹ Re-examination of the Substitution Reactions of 5 α -Cholestan-6 α -ol

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High-pressure liquid chromatography, combined with i.r. spectroscopy and mass spectrometry, shows that treatment of 5 α -cholestan-6 α -ol with phosphorus pentachloride gives not only 6 α - but also 6 β -chloro-5 α -cholestane (5 : 1), with a little cholest-5-ene and its derivative 5,6 β -dichloro-5 α -cholestane. The formation of both the epimeric 6-chlorides was confirmed by use of g.l.c. and of a computerised g.l.c.-mass spectral system. Treatment of 5 α -cholestan-6 α -ol with thionyl chloride gives only the 6 α -chloride, with cholest-5-ene, its derivative 5-chloro-5 α -cholestane, and traces of three unidentified products.

5 α -CHOLESTAN-6 α -OL (I; OH-*eq*) has been reported² to react with phosphorus pentachloride to give, with retention of configuration, 6 α -chloro-5 α -cholestane (II; Cl-*eq*) (ca. 90%), ν_{\max} 781 and 745 cm⁻¹. The 6 α -chloride (II) was isolated by column chromatography on neutral aluminium oxide and purified by recrystallisation from acetone, but no special search was made for small amounts, formed with inversion of configuration, of the epimeric 6 β -chloro-5 α -cholestane³ (III; Cl-*ax*), ν_{\max} 696 cm⁻¹.



Since treatment of 5 α -cholestan-4 α -ol⁴ and of 5 α -cholestan-2 α -ol⁵ with phosphorus pentachloride has been found to give, respectively, 4 α -chloro-5 α -cholestane, accompanied by 4 β -chloro-5 α -cholestane, and 2 α -chloro-5 α -cholestane, accompanied by 2 β -chloro-5 α -cholestane, we have re-examined the reaction of the 6 α -ol (I) with phosphorus pentachloride (and that with thionyl chloride), using improved analytical techniques, to discover whether the 6 α -chloride (II) is accompanied by small quantities of the 6 β -chloride (III).

Product analysis was performed by high-pressure liquid chromatography (h.p.l.c.); preparative h.p.l.c. was combined with i.r. spectroscopy and mass spectrometry. Carbon-chlorine i.r. bands are fairly strong, and appear in a region in which alicyclic compounds do not absorb strongly (780–600 cm⁻¹), with an equatorial C-Cl linkage giving a peak † at a higher frequency than an axial C-Cl linkage.⁶ Appropriate fractions, so diagnosed, were subjected to analytical h.p.l.c., again combined with i.r. spectroscopy and mass spectro-

† Many equatorial chloro-steroids exhibit two bands in the region associated with the C-Cl stretching vibration, the stronger band usually appearing at a slightly higher wavenumber than the weaker band.⁶

¹ Part LXIX, C. W. Shoppee and J. Nemorin, *J.C.S. Perkin I*, 1973, 542.

² C. W. Shoppee, M. E. H. Howden, and R. E. Lack, *J. Chem. Soc.*, 1960, 4874; cf. O. Stange, *Z. physiol. Chem.*, 1933, 220, 37.

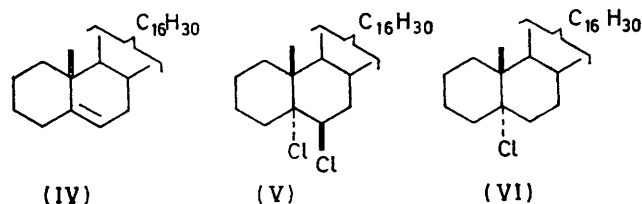
³ C. W. Shoppee and R. E. Lack, *J. Chem. Soc.*, 1960, 4864.

⁴ C. W. Shoppee, R. E. Lack, and S. C. Sharma, *J. Chem. Soc. (C)*, 1968, 2033.

⁵ C. W. Shoppee, T. E. Bellas, and R. E. Lack, *J. Chem. Soc. (C)*, 1965, 6450.

metry; the graphs produced for different fractions were matched, by using a curve resolver, to obtain the integrated areas of each peak, and so the proportions of the components, since it was not possible completely to separate the epimeric chlorides (II) and (III).

Preparative h.p.l.c. of the total product from the reaction of the 6 α -ol (I) with phosphorus pentachloride in carbon tetrachloride at 0 °C disclosed the presence of a trace of cholest-5-ene (IV), ν_{\max} 830 and 800 cm⁻¹,⁷ and of both the epimeric 6-chlorides (II) and (III) in the ratio ca. 5 : 1, as indicated by the relative intensities of the i.r. peaks at 770 and 740 for (II) and 700 cm⁻¹ for (III). 5,6 β -Dichloro-5 α -cholestane (V), ν_{\max} 655 cm⁻¹, was also present, arising from cholest-5-ene (IV) either by reaction with chlorine derived from the equilibrium $\text{PCl}_5 \rightleftharpoons \text{PCl}_3 + \text{Cl}_2$,⁸ or from sequential attack, possibly through a π -complex, of the ions PCl_4^+ and PCl_6^- derived from the autoionisation $2\text{PCl}_5 \rightleftharpoons \text{PCl}_4^+ + \text{PCl}_6^-$.⁹



Analytical h.p.l.c. of appropriate fractions, constituting 85% of the total reaction product, gave graphs showing five peaks, with the small early peaks 1 [cholest-5-ene (IV)] and 2 [unknown, possibly 5 α -cholest-6-ene¹⁰] completely separated from the later small peak 3 [5,6 β -dichloro-5 α -cholestane (V)] and the still later large, but incompletely resolved, peaks 4 [6 β -chloride (III)] and 5 [6 α -chloride (II)]. The components of peaks 1, 3, and 5 were identified by injection of authentic samples of (IV), (V), and (II), which had the same retention times (1.9, 2.1, and 2.3 min, respectively). The integrated peak areas showed that the epimeric 6-chlorides (II) and (III) were present in the ratio 81 : 19 (averaged

⁶ D. H. R. Barton, J. E. Page, and C. W. Shoppee, *J. Chem. Soc.*, 1956, 331; cf. R. M. Carman and H. C. Deeth, *Austral. J. Chem.*, 1970, 23, 1053; D. B. Cowell, A. K. Davis, D. W. Mathieson, and P. D. Nicklin, *J.C.S. Perkin I*, 1974, 1505.

⁷ P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch, and G. W. Wood, *J. Chem. Soc.*, 1957, 2402.

⁸ H. L. Goering and F. H. McCarron, *J. Amer. Chem. Soc.*, 1956, 78, 2270.

⁹ R. W. Suter, H. C. Knachel, V. P. Petro, J. H. Howatson, and S. G. Shore, *J. Amer. Chem. Soc.*, 1973, 95, 1474.

¹⁰ C. W. Shoppee, T. F. Holley, and G. P. Newsoroff, *J. Chem. Soc.*, 1965, 2349.

numbers), or roughly in the proportions 4:1, whereas the i.r. peak intensities indicated a ratio of 5 or 6:1. The averaged yields were 6 α -chloride (II) 64%, 6 β -chloride (III) 15%, cholest-5-ene (IV) 6%, and the 5,6 β -dichloride (V) 8%, based on the assumption that the refractive indices of these closely related steroids are similar; this is supported qualitatively by the observation that, in all solvent systems examined, proportionality of peak areas was maintained.

Product analysis was also attempted by gas chromatography, which gave four peaks: (i) t_R 6.3 min, very small, 5 α -cholest-6-ene (?); (ii) t_R 8.3 min, small, cholest-5-ene (IV); (iii) t_R 9.0 min, large, 6 α -chloro-5 α -cholestane (II) apparently superimposed on 6 β -chloro-5 α -cholestane (III); (iv) t_R 9.5 min, shoulder, 5,6 β -dichloro-5 α -cholestane (V). The components of peaks (ii)–(iv) were identified by injection of authentic specimens which gave t_R 8.2 (IV), 8.9 (II), and 9.7 min (V). These results were confirmed by use of a computerised g.l.c.–mass spectral technique (details to be published elsewhere).

We have also examined the reaction of the 6 α -ol (I) at 20 °C with thionyl chloride as both reagent and reaction medium. Preparative h.p.l.c. of the total product disclosed the presence of some cholest-5-ene (IV), and of the 6 α -chloride (II), unaccompanied by the 6 β -chloride (III). As expected, 5,6 β -dichloro-5 α -cholestane (V) was not formed; instead, cholest-5-ene (IV) was partly converted by addition of hydrogen chloride into 5-chloro-5 α -cholestane (VI), ν_{\max} 670 cm^{-1} ,¹¹ and some unchanged 6 α -ol (I) was also present. Analytical h.p.l.c. gave graphs showing four peaks, with the small early peaks 1 [cholest-5-ene (IV)] and 2 [unidentified, 5 α -cholest-6-ene (?)] well separated from a later small peak 3 [5-chloro-5 α -cholestane (VI)] and followed by a large peak 4 [6 α -chloro-5 α -cholestane (II)]. Injection of authentic samples of (IV), (VI), and (II) showed these to have the same retention times (1.9, 2.1, and 2.3 min, respectively); synthetic mixtures of cholest-5-ene (IV) and the 5 α -chloride (VI) and of the latter and the 6 α -chloride (II) were separated by the system. The averaged yields were 6 α -chloride (II) 80%, cholest-5-ene (IV) 11%, its hydrochloride (VI) 2%, and the unidentified component [5 α -cholest-6-ene(?)] 6%.

Product analysis by g.l.c., under the conditions given above, indicated the presence of six components: (i) t_R 6.3 min, small, 5 α -cholest-6-ene (?); (2) t_R 8.2 min, small, cholest-5-ene (IV); (iii) t_R 9.2 min, large, regarded as comprising the 6 α -chloride (II) and the isomeric 5 α -chloride (VI); (iv) t_R 11.8 min, very small, unidentified; (v) t_R 13.3 min, very small, unidentified; (vi) t_R 14.5 min, very small, unidentified. The trace components of peaks (iv)–(vi) may arise by thermal decomposition of the chlorides (II) and (VI) and isomerisation and/or polymerisation of the olefins so

* Purified with concentrated sulphuric acid and re-dried immediately before use.

¹¹ C. W. Shoppee and R. D. Lundberg, following paper.

¹² D. H. R. Barton, *Experientia*, 1955, **11**, 121 (esp. p. 129).

produced. The computerised g.l.c.–mass spectral technique indicated the presence of four major and three minor components.

The substitution reaction of the 6 α -ol (I) with phosphorus pentachloride thus follows two pathways—one yielding as the major product the 6 α -chloride (II) with retention of configuration (mechanism S_Ni), and the other giving as the minor product the 6 β -chloride (III) with inversion of configuration (mechanism S_N2). The reaction with thionyl chloride follows a single pathway furnishing the 6 α -chloride (II) with retention of configuration (S_Ni) on account of the lesser ease of ionisation of chloro-sulphites as compared with chloro-phosphonates. Small quantities of cholest-5-ene (IV) are produced by use of either phosphorus pentachloride or thionyl chloride; but whereas the formation of the 5,6 β -dichloride (V) in carbon tetrachloride (at 20 °C dielectric constant 2) requires the presence of a partially polarised chlorine molecule or a close ion-pair $\text{PCl}_4^+ \text{PCl}_6^-$, production of the 5 α -chloride (VI) in thionyl chloride (at 20 °C dielectric constant 10) involves equatorial addition of a hydrogen ion followed by axial capture of a chloride ion.¹²

EXPERIMENTAL

For general experimental directions, see *J. Chem. Soc.*, 1959, 345. M.p.s were determined with a Thomas 40 hot-stage apparatus. I.r. spectra (solutions in carbon disulphide) were measured with Beckman IR 18 and IR 33 spectrometers. ¹H N.m.r. spectra were measured with a Varian XL 100-15 instrument (solutions in deuteriochloroform with tetramethylsilane as internal reference). Preparative and analytical high-pressure liquid chromatography was carried out with a Waters 311 machine, with Porasil A [3 ft \times 1/4 in stainless steel column; flow rate of benzene–chloroform (7:3) 2 ml min^{-1}] for preparative work and neutral aluminium oxide [Woelm; 18 in \times 1/8 in column; flow rate of pentane * 1 ml min^{-1}] for analytical work. G.l.c. was performed with a Beckman GC 45 instrument (6 ft \times 1/8 in column packed with 5% SE 30; helium flow rate 37 ml min^{-1} ; isothermal at 250 °C for 2 min then linear temperature programming 250–300° during 16 min). Mass spectra were measured with a Varian-MAT 311 double-focus spectrometer.

Reaction of 5 α -Cholestan-6 α -ol (I) with Phosphorus Pentachloride.—The 6 α -ol (m.p. 131°; 1.083 g) was treated with freshly sublimed phosphorus pentachloride (1.03 g) in ethanol-free carbon tetrachloride at 0 °C for 1 h. Water (20 ml) was added, and the mixture was shaken overnight at 20 °C; the carbon tetrachloride layer was separated, dried, and completely evaporated. The crude product (1.145 g) was further dried at 20° and 1 mmHg before analysis. Preparative h.p.l.c. on Porasil A in benzene–chloroform (7:3) gave the results set out in Table 1. Further preparative h.p.l.c. of the large fraction B of Experiment 2 gave four fractions (5.5, 42, 12, and 2.5% by weight) all containing (by mass spectrometry) the chlorides (II) and (III) (M^+ 408/406) and the dichloride (V) (M^+ 444/442/440). The first and second fractions showed ν_{\max} 770, 740, and 700 [(II) and (III)], and 655 cm^{-1} (V); the third and fourth showed ν_{\max} 770 and 740 (II) and 655 cm^{-1} (V); comparison of the relative intensities ($I_{770} : I_{740} : I_{700}$) for the first and second fractions gave the

TABLE 1
Preparative h.p.l.c. of the products from the 6 α -ol (I) and phosphorus pentachloride

Fraction	Expt. 1 (% by wt.)	Expt. 2 (% by wt.)	Components	M^+ ^a	$\nu_{\max.}(\text{CS}_2)/\text{cm}^{-1}$ ^b	Relative intensities ^c ($I_{770} : I_{740} : I_{700}$)		Ratio (II) : (III) based on $I_{770} : I_{700}$	
						Expt. 1	Expt. 2	Expt. 1	Expt. 2
A	2	1	(IV)	370	830, 800				
B	50.5	62	{(II), (III) (V)}	408, 406 444, 442, 440	770, 740; 700 655	1 : 0.79 : 0.21	1 : 0.72 : 0.16	5 : 1	6 : 1
C	34.5	31	{(II), (III) ^d (V)}	408, 406 444, 442, 440	770, 740; 700 ^d 655	1 : 0.77 : 0.21	1 : 0.75 : 0 ^d	5 : 1	^d
D	12	5	{(II), (III) (I)}	408, 406 388	770, 740 3 400				

^a M^+ for (II) and (III): 408/406; for (V): 444/442/440; for (I): 388; m/e of associated peaks observed for (II) and (III): 393/391 ($M - \text{Me}$), 371 ($M - \text{Cl}$), 370 ($M - \text{HCl}$), and 355 ($M - \text{HCl} - \text{Me}$). ^b $\nu_{\max.}(\text{CS}_2)$ for (II)²: 781 and 745 cm^{-1} ; for (III)³: 696 cm^{-1} ; for (V)⁶: 652 cm^{-1} ; for (IV)⁷: 832 and 797 cm^{-1} . ^c Estimated against a reference curve for CS_2 ; $I_{770} : I_{740}$ for authentic (II): 1 : 0.74. ^d No peak seen at 700 cm^{-1} in Expt. 2.

figures 1 : 0.76 : 0.19 and 1 : 0.8 : 0.16, corresponding to ratios for the epimeric chlorides (II) and (III) of about 5 : 1 and 6 : 1, respectively.

TABLE 2

Analytical h.p.l.c. of fractions B and C of the products from the 6 α -ol (I) and phosphorus pentachloride (expt. 1)

Fraction	Integrated areas of peaks (%)					Total (%)	Ratio (II) : (III)
	1 (IV)	2 ?	3 (V)	4 (III)	5 (II)		
B	6	3	6	17	64	96	79 : 21
	6.5	3.5	9	20	54	93	73 : 27
C	6	4	8	12	68	98	85 : 15
	6	4	9	10	70	99	87 : 13

Analytical h.p.l.c. of fractions B and C of Experiment 1 constituting 85% of the reaction product, was carried out on neutral aluminium oxide in pentane with the results given in Table 2. The results for fraction B of Experiment 2 are given in Table 3.

TABLE 3

Analytical h.p.l.c. of fractions B1, B2, B3, and B4 from fraction B of the products from the 6 α -ol (I) and phosphorus pentachloride (expt. 2)

Fraction	Integrated areas of peaks (%)					Total (%)	Ratio (II) : (III)
	1 (IV)	2 ?	3 (V)	4 (III)	5 (II)		
B1	11	4	23	15	38	91	72 : 28
B2	5	4	15	33	38	95	55 : 45
B3	0	7	14	19	59	99	76 : 24
	0	6	16	20	53	95	73 : 27
B4	2	0	26	5	58	91	92 : 8
	1	0	25	5	62	93	93 : 7

oxide in pentane, or with similar results on Corasil C/18 in 80% aqueous acetone, and gave the data contained in Table 5.

TABLE 4

Preparative h.p.l.c. of the products from the 6 α -ol (I) and thionyl chloride

Fraction	% by wt.	Components	M^+ ^a	$\nu_{\max.}(\text{CS}_2)/\text{cm}^{-1}$ ^b	Relative intensities	Ratio (II) : (III)
					($I_{770} : I_{740} : I_{700}$)	from $I_{770} : I_{700}$
A	2	(IV)	370	830, 800		
B	54	{(II) (VI)}	408, 406 408, 406	770, 738 670	1 : 0.80 : 0	100 : 0
C	33	{(II) (VI)}	408, 406 408, 406	770, 740 670	1 : 0.76 : 0	100 : 0
D	11	{(II) (I)}	408, 406 388			
E	1.5	(I)	388			

^a m/e Values of associated peaks observed for (II) and (VI): 393/391 ($M - \text{Me}$), 371 ($M - \text{Cl}$), 370 ($M - \text{HCl}$), and 355 ($M - \text{HCl} - \text{Me}$). ^b $\nu_{\max.}(\text{CS}_2)$ for (II)²: 781, 745 cm^{-1} ; for (IV)⁷: 832, 797 cm^{-1} ; for (VI)¹¹: 670 cm^{-1} .

Reaction of 5 α -Cholestan-6 α -ol (I) with Thionyl Chloride.—The 6 α -ol (1.006 g) was stirred with freshly distilled thionyl chloride (3 ml) at 20 °C for 1 h. Methanol (10 ml) was added to destroy the excess of reagent; the crude product (1.35 g) was extracted with ether, and dried at 20° and 1 mmHg before analysis. Preparative h.p.l.c. on Porasil A in benzene-chloroform (7 : 3) gave the results set out in Table 4.

* The first paragraph of the Experimental section of ref. 2 says: 'Elution with hexane afforded 6 α -chloro-5 α -cholestane (490 mg), m.p. 146–148°, $[\alpha]_D + 44^\circ$ (c 1.1), $\nu_{\max.}$ 781, 745 cm^{-1} , after recrystallisation from acetone.' Reference to the Sydney University Dissertation (1957) of M. E. H. Howden shows that the 490 mg refers to material prior to crystallisation; three crystallisations from acetone gave 6 α -chloro-5 α -cholestane (150 mg) with the characteristics cited.

6 α -Chloro-5 α -cholestane (II).—The 6 α -chloride was prepared by the procedure* of Shoppee *et al.*;² m.p. 148°,

TABLE 5

Analytical h.p.l.c. of fractions B and C of the product from the 6 α -ol (I) and thionyl chloride

Fraction	Integrated areas of peaks (%)				Total (%)
	1 (IV)	2 ?	3 (VI)	4 (II)	
B	12	6	2	79	99
	9	6	2	82	99
	10	6	2	82	100
C	10	6	2	82	100
	10	7	2.5	79	98.5
	12	7	2	78	99
	12	7	2	78	99

ν_{\max} 770 and 740 cm^{-1} , δ 0.815 (3 H, s, 10-Me) and 0.65 (3 H, s, 13-Me), M^+ 408 and 406, m/e 372, 371, and 370.

5,6 β -Dichloro-5 α -cholestane (V).—A sample prepared by Shoppee and Lack³ had m.p. 119–121° (lit.,^{13,14} 121–122°), ν_{\max} 652 cm^{-1} (lit.,⁶ 652 cm^{-1}); the ¹H n.m.r. spectrum [δ 1.34 (3 H, s, 10-Me; calc.¹⁵ δ 1.36), 0.90 (3 H, s, 13-Me),

¹³ J. Mauthner and W. Suida, *Monatsh.*, 1894, **15**, 85.

¹⁴ J. Décombe and J. Rabinowitch, *Bull. Soc. chim. France*, 1939, [5] **6**, 1510.

¹⁵ R. F. Zürcher, *Helv. Chim. Acta*, 1963, **46**, 2054.

and 4.36 (6 α -H, q)] confirms the 5 α ,6 β -configuration assigned by Barton and Miller.¹⁶

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¹⁶ D. H. R. Barton and E. Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 370.
