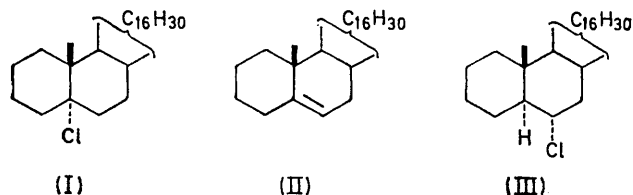


## Steroids. Part XXXVIII.<sup>1</sup> 5-Chloro-5 $\alpha$ -cholestane

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The formation of 5-chloro-5 $\alpha$ -cholestane from cholest-5-ene and hydrogen chloride in ether-ethanol at 25 °C appears to be accompanied by production of an unidentified chloro-5 $\xi$ -cholestane; 5-chloro-5 $\beta$ -cholestane could not be isolated.

5-CHLORO-5 $\alpha$ -CHOLESTANE (I) was prepared by Mauthner<sup>2-4</sup> from cholest-5-ene (II) by equatorial/axial addition<sup>5</sup> of hydrogen chloride in chloroform, or preferably in ethanol-ether (1:1). The method of reference 4 afforded the 5 $\alpha$ -chloride (I), m.p. 96–97°,  $[\alpha]_D +5^\circ$ , as the main product (ca. 55% yield), whereas in the product obtained by the procedure of references 2 and 3 a more dextrorotatory isomer predominated. This isomer, which was not obtained pure, crystallised from the mother liquor of the 5 $\alpha$ -chloride with m.p. 70–80°,  $[\alpha]_D +22^\circ$ .<sup>2-4</sup> Seng<sup>6</sup> also reported the production in ethanol-ether, of an isomer,



m.p. 91°,  $[\alpha]_D +36^\circ$ . Georg<sup>7</sup> has suggested that Mauthner's isomer is 5-chloro-5 $\beta$ -cholestane, and that Seng's isomer is 6 $\alpha$ -chloro-5 $\alpha$ -cholestane (III), formed by anti-Markovnikov addition.

In connection with other work we required a specimen of 5-chloro-5 $\alpha$ -cholestane (I). This was obtained by Mauthner's improved method;<sup>4</sup> our material had m.p. 95–97° (from ether) and  $\nu_{\max}$  670  $\text{cm}^{-1}$ , but still contained a trace of cholest-5-ene (II), as disclosed by the i.r. spectrum ( $\nu_{\max}$  800, 830, and 733  $\text{cm}^{-1}$ ).<sup>8</sup> The <sup>1</sup>H n.m.r. spectrum, however, displayed no signal below  $\delta$  2 which excludes the presence not only of a significant quantity of cholest-5-ene (II) but also of any 6 $\alpha$ -chloro-5 $\alpha$ -cholestane (III) (see Table 1, footnote §). The mother liquor did not yield crystals; the <sup>1</sup>H n.m.r. spectrum of the residual material appeared to be a superposition of the spectra of

an unidentified chloride, 5-chloro-5 $\alpha$ -cholestane (I), and 6 $\alpha$ -chloro-5 $\alpha$ -cholestane (III). In particular, there were observed only three sharp C-19 proton singlets at  $\delta$  1.065, 1.035 (I), and 0.815 (III) (Table 1), the first having about twice the intensity of the peak at  $\delta$  1.035. Since the shift of a C-19 proton singlet depends on how much the C-19 protons 'see'<sup>9</sup> of a neighbouring substituent [for (I) (5 $\alpha$ -Cl/10 $\beta$ -Me), dihedral angle  $\theta$  180°], the C-19 proton signal for the as yet unknown 5-chloro-5 $\beta$ -cholestane (5 $\beta$ -Cl/10 $\beta$ -Me;  $\theta$  60°) should appear at lower field than  $\delta$  1.035.

TABLE 1  
<sup>1</sup>H N.m.r. chemical shifts ( $\delta$  values) of methyl protons (solvent CDCl<sub>3</sub>)

Compound	19-H <sub>3</sub>	18-H <sub>3</sub>	21-H <sub>3</sub> *	26- and 27-H <sub>3</sub> †
5 $\alpha$ -Cholestane	0.80	0.66	0.93	0.87
Cholest-5-ene	1.00	0.68	0.92	0.87
(II) ‡				
5 $\alpha$ -Chloride (I)	1.035	0.66	0.91	0.87
6 $\alpha$ -Chloride (III) §	0.815	0.65	0.91	0.87
Residual material from prepn. of (I) §	{ 0.815, 1.035, 1.065 }	{ 0.65, 0.66, 0.68 }	0.91	0.87

\* Centre of 3-proton doublet. † Centre of 6-proton doublet. ‡ Multiplet for vinylic 6-H centred at  $\delta$  5.26; cf.<sup>9</sup>  $\delta$  1.025 (19-H<sub>3</sub>) and 0.734 (18-H<sub>3</sub>). § Small broad multiplet for 6 $\beta$ -H centred at  $\delta$  3.8 ( $W_{1/2}$  24 Hz).

Both 5-chloro-5 $\alpha$ -cholestane (I) and the reputed 5-chloro-5 $\beta$ -cholestane readily undergo dehydrochlorination on heating with ethanolic sodium acetate to give cholest-4-ene.<sup>2,3,7</sup> We find, however, that 6 $\alpha$ -chloro-5 $\alpha$ -cholestane (III), like Seng's 'cholest-5-ene hydrochloride,'<sup>6,7</sup> is resistant to dehydrochlorination with hot ethanolic sodium acetate and with boiling ethanolic potassium hydroxide. At the suggestion of a referee we have attempted to isolate 6 $\alpha$ -chloro-5 $\alpha$ -cholestane (III)

<sup>6</sup> R. Seng, Inaug. Diss. Göttingen, 1918, pp. 29, 30.

<sup>7</sup> A. Georg, *Archiv. Sci. (Geneva)*, 1953, **6**, 410.

<sup>8</sup> P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch, and G. W. Wood, *J. Chem. Soc.*, 1951, 2402.

<sup>9</sup> N. S. Bhacca and D. H. Williams, 'Applications of NMR Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, 1964, pp. 16, 20.

<sup>1</sup> Part XXXVII (incorrectly numbered XXXV), C. W. Shoppee, J. C. Coll, and R. E. Lack, *J. Chem. Soc. (C)*, 1970, 1893.

<sup>2</sup> J. Mauthner, *Monatsh.*, 1906, **27**, 305.

<sup>3</sup> J. Mauthner, *Monatsh.*, 1906, **27**, 421.

<sup>4</sup> J. Mauthner, *Monatsh.*, 1907, **28**, 113.

<sup>5</sup> D. H. R. Barton, *Experientia*, 1955, **11**, 121, esp. p. 129.

from the mother-liquor material of the preparation of 5-chloro-5 $\alpha$ -cholestane (I) by treatment with refluxing ethanolic anhydrous sodium acetate, destruction of resulting olefins by ozonolysis followed by oxidation with chromium trioxide-acetic acid, and removal of acidic material with 2N-potassium hydroxide. The i.r. spectrum of the neutral fraction showed a pair of strong peaks of the type normally attributable to an equatorial chloride,\*  $\nu_{\max}$  790 and 730  $\text{cm}^{-1}$  [cf. (III),<sup>10</sup>  $\nu_{\max}$  781 and 745  $\text{cm}^{-1}$ ], absorption due to a trace of an axial chloride,\*  $\nu_{\max}$  660  $\text{cm}^{-1}$  [cf. (I),  $\nu_{\max}$  670  $\text{cm}^{-1}$ ], and, surprisingly, carbonyl bands at 1720 and 1700  $\text{cm}^{-1}$ . The  $^1\text{H}$  n.m.r. spectrum showed minor peaks, perhaps C-19 proton singlets, at  $\delta$  1.273, 1.260, 1.205, and 1.134, as well as major C-19 proton singlets at  $\delta$  1.065 and 1.035, the latter corresponding to the value observed for the 5 $\alpha$ -chloride (I) (see Table 1). Clearly and unexpectedly, the tertiary 5 $\alpha$ -chloride (I) is not completely dehydrochlorinated by refluxing ethanolic sodium acetate. Analytical t.l.c. on silica in benzene, with authentic samples of the chlorides (I) ( $R_F$  0.86) and (III) ( $R_F$  0.76) and the olefin (II) ( $R_F$  0.75) for comparison, indicated a complex mixture of products (5 spots). Preparative t.l.c. on silica in benzene gave five fractions of which only two were substantial: (i)  $R_F$  0, 129 mg (25%), non-crystalline,  $[\alpha]_D -1^\circ$ , no vinyl protons; and (v)  $R_F$  0.5–0.76, 341 mg (66%), m.p. 75–76°,  $[\alpha]_D +41^\circ$ ,  $\nu_{\max}$  855 and 800  $\text{cm}^{-1}$  (no bands 800–650  $\text{cm}^{-1}$ ). Fraction (v) showed a  $^1\text{H}$  n.m.r. signal for one vinyl proton at  $\delta$  5.3 (integration ratio ca. 1:46), two C-19 proton signals at  $\delta$  1.265 and 1.015, and a single C-18 proton signal at  $\delta$  0.685, and gave a strong yellow colour with tetranitromethane-chloroform and a weakly positive Beilstein test. It appears to consist of a mixture of cholest-4-ene and cholest-5-ene (7:3) containing a compound, possibly a chloride, responsible for the C-19 singlet at  $\delta$  1.265, but no 6 $\alpha$ -chloro-5 $\alpha$ -cholestane (III); the major component, cholest-4-ene, cannot be derived directly from (III). Thus the equatorial chloride, whose presence was inferred from the i.r. maxima at 790 and 730  $\text{cm}^{-1}$  and the C-19 singlet at  $\delta$  1.065, had apparently undergone dehydrochlorination on silica in benzene, by which not only the secondary equatorial 6 $\alpha$ -chloride (III) but also the tertiary axial 5 $\alpha$ -chloride (I) is unaffected. These results were reproducible. In a second experiment, refluxing ethanolic 4N-potassium hydroxide was used instead of sodium acetate for dehydrochlorination prior to ozonolysis and oxidation; preparative t.l.c. of the neutral product on silica in benzene gave a fraction,  $R_F$  ca. 0.75, m.p. 73°,  $[\alpha]_D +49^\circ$ , showing a  $^1\text{H}$  n.m.r. signal for one vinyl proton at  $\delta$  5.3, four C-19 proton signals [ $\delta$  1.26, 1.18 (minor), 1.055 (minor), and 1.01], and one C-18 proton signal ( $\delta$  0.68), and giving a strong yellow colour with tetranitromethane-chloroform.

The primary entity produced from cholest-5-ene (II) and hydrogen chloride should be the 5-cation, which could give rise by 1,2-shifts to the related 4-, 10-, and 6-cations, and so to a complex mixture. The 5-cation is

\* Bladon *et al.*<sup>8</sup> give for cholest-4-ene  $\nu_{\max}$  680m, 700w, 810s, and 870m, and for cholest-5-ene 735w, 797s, and 832s  $\text{cm}^{-1}$ ; but olefins should have been destroyed by oxidation.

known to yield the tertiary 5 $\alpha$ -chloride (I), and could yield the tertiary 5 $\beta$ -chloride, which can undergo dehydrochlorination to cholest-4-ene and/or cholest-5-ene. Only if the as yet unknown 5 $\beta$ -chloride (Cl axial to ring A, equatorial to ring B) possesses  $^1\text{H}$  n.m.r. characteristics closely similar to those of the 5 $\alpha$ -chloride (I) ( $\delta$  1.035 and 0.66) and i.r. maxima typical of an equatorial chloride ( $\nu_{\max}$  790 and 730  $\text{cm}^{-1}$ ) do these results seem explicable; dehydrochlorination by silica is astonishing. External circumstances preclude further investigation.

#### 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 (solvent carbon disulphide) were measured with a Beckman IR 18 spectrometer.  $^1\text{H}$  N.m.r. spectra (solvent deuteriochloroform) were measured with a Varian XL 100-15 instrument, with tetramethylsilane as internal reference. G.l.c. was performed on a Varian Aerograph instrument with 5% SE 30 (stainless steel column, 24  $\times$  1/8 in; 235  $^\circ\text{C}$ ; helium flow rate 20 ml  $\text{min}^{-1}$ ).

5-Chloro-5 $\alpha$ -cholestane (I).—(a) Cholest-5-ene (m.p. 89–90.5°;  $[\alpha]_D -50^\circ$  in  $\text{CHCl}_3$ ; 950 mg) dissolved in ether (20 ml) was treated with ethanolic 40% dry hydrogen chloride (20.5 ml) at 25  $^\circ\text{C}$ .<sup>4</sup> The olefin crystallised from the stirred mixture to dissolve again within a few h; after 48 h, prisms began to separate and after a further 48 h these were filtered off (185 mg); m.p. 91–96° (softening at 89°). Recrystallisation from ether-ethanol gave 5-chloro-5 $\alpha$ -cholestane, m.p. 95–97° (lit.,<sup>4</sup> 96–97°),  $\nu_{\max}$  670  $\text{cm}^{-1}$ ; for  $^1\text{H}$  n.m.r. spectrum see Table 1; reaction with tetranitromethane in chloroform gave a weakly positive response, due to a trace of cholest-5-ene;  $\nu_{\max}$  830, 800, and 733  $\text{cm}^{-1}$  (lit.,<sup>8</sup>  $\nu_{\max}$  832, 797, and 735  $\text{cm}^{-1}$ ). The filtrate was diluted with water and extracted with hexane, and the extract was washed with 2N-sodium carbonate, dried, and evaporated, but the resultant material did not crystallise; for the  $^1\text{H}$  n.m.r. spectrum see text and Table 1; analytical g.l.c. showed the presence of some cholest-5-ene (II), much 5 $\alpha$ -chloride (I), and a small amount of another chloride ( $t_R$  5, 11, and 12 min, respectively). Column chromatography [neutral aluminium oxide (Woelm) in pentane] gave unresolved mixtures of 5-chloro-5 $\alpha$ -cholestane, cholest-5-ene, and another chloride as indicated by the i.r. and  $^1\text{H}$  n.m.r. spectra of numerous fractions.

(b) Cholest-5-ene (974 mg) was treated with dry hydrogen chloride as in (a) to yield crude 5-chloro-5 $\alpha$ -cholestane (172 mg), m.p. 95–96.5° (softening at 91°). The residual material (1.118 g), isolated by dilution with water and extraction with ether, gave a  $^1\text{H}$  n.m.r. spectrum devoid of olefinic proton signals with C-19 proton singlets at  $\delta$  1.27, 1.20, 1.16, and 1.065 (relative intensity 69) and 1.035 (relative intensity 41), and a C-18 proton singlet at  $\delta$  0.65. This material was refluxed with anhydrous sodium acetate (1 g) in ethanol (60 ml) for 1 h; neutralisation with acetic acid, dilution with water, and the usual work-up gave a yellow oil (901 mg), whose  $^1\text{H}$  n.m.r. spectrum showed an olefinic peak at  $\delta$  5.3, a broad multiplet at  $\delta$  2.3, C-19 proton singlets at  $\delta$  1.065 and 1.035 (relative intensities 87 and 41) and (new signal) 1.01, and C-18 proton singlets at  $\delta$  0.685 (new signal) and 0.65. The yellow oil was treated in chloroform at  $-5^\circ\text{C}$  with ozonised oxygen for 0.5 h; the ozonolysis product, with

<sup>10</sup> C. W. Shoppee, M. E. H. Howden, and R. E. Lack, *J. Chem. Soc.*, 1960, 4874.

TABLE 2

Fraction	$R_F$	Wt. (mg)	M.p. (°C)	$[\alpha]_D$ (°)	$\delta$				
					=CH	19-H <sub>3</sub>	18-H <sub>3</sub>	21-H <sub>3</sub> *	26- and 27-H <sub>3</sub> †
1	0	129		-1	None	1.265	0.73, 0.66	0.905 ( <i>J</i> 6.5 Hz)	0.870 ( <i>J</i> 6.5 Hz)
2	0.12	1							
3	0.32	29			None	1.26, 1.215, 1.075, 1.005	0.73, 0.71, 0.65	0.908 ( <i>J</i> 5.5 Hz)	0.868 ( <i>J</i> 6.5 Hz)
4	0.48	18			None	1.260, 1.055, 1.005	0.73, 0.71, 0.68, 0.65	0.905 ( <i>J</i> 6 Hz)	0.868 ( <i>J</i> 6.5 Hz)
5	0.51—0.76	341	75—76	+41	One, 5.3	1.265, 1.015	0.685	0.910 ( <i>J</i> 6 Hz)	0.868 ( <i>J</i> 7 Hz)

\* Centre of 3-proton doublet.

† Centre of 6-proton doublet.

efficient stirring in chloroform at 25 °C, was titrated with a chromic acid solution [chromium trioxide (134 mg), and concentrated sulphuric acid (115 ml) diluted with water to 500 ml] until a persistent yellow colour was obtained. The product was separated into acidic (64 mg) and neutral fractions (627 mg) by use of 2*N*-potassium hydroxide. The neutral fraction showed  $\nu_{\max}$  1 720, 1 700, 790s, 730s, and 660w  $\text{cm}^{-1}$ ; the <sup>1</sup>H n.m.r. spectrum disclosed a variety of minor C-19 proton singlets at  $\delta$  1.273, 1.260, 1.205, and 1.134 in addition to the major singlets at  $\delta$  1.065 and 1.035. Analytical t.l.c. on silica gel plates in benzene, after development with benzene and exposure to iodine vapour, with 5-chloro-5 $\alpha$ -cholestane (I) ( $R_F$  0.86), cholest-5-ene (II) ( $R_F$  0.74), and 6 $\alpha$ -chloro-5 $\alpha$ -cholestane (III) ( $R_F$  0.76) for comparison, gave five spots. Preparative t.l.c. on silica gel

(Merck, GF254; plates 8 × 8 in, loading 150 mg) in benzene (detection by the quenched fluorescence of the inorganic indicator) yielded five fractions (Table 2). Fraction 5 by recrystallisation from acetone afforded needles, m.p. 75—76.5°,  $[\alpha]_D +41^\circ$ , giving a strong yellow colour with tetranitromethane. Authentic 6 $\alpha$ -chloro-5 $\alpha$ -cholestane (69 mg), added in carbon disulphide solution to a similar silica gel plate, developed with benzene, and recovered (61.5 mg), gave an i.r. spectrum identical with that of the material applied to the t.l.c. plate.

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