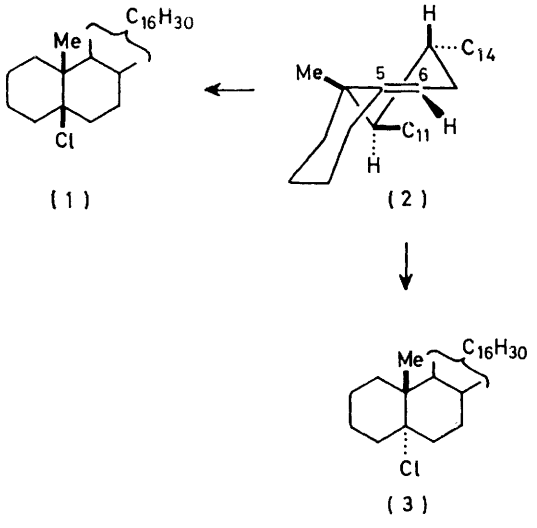
# Steroids. Part 39.[1] 5-Chloro-5β-cholestane

By **Charles W. Shoppee,* Reinhold J. Hart,** and **Merlin E. H. Howden,** School of Chemistry, Macquarie University, North Ryde, Sydney, 2113, Australia

The isolation and properties of 5-chloro-5β-cholestane are described.

In 1906, Mauthner[2,3] isolated what was reputedly[4] impure 5-chloro-5β-cholestane (1), m.p. 70—80 °C, $[\alpha]_D$ +22°, from the product of the addition of hydrogen chloride in chloroform to cholest-5-ene (2), together with 5-chloro-5α-cholestane (3), m.p. 96—97 °C, $[\alpha]_D$ +5° [lit.,[1] m.p. 95—97 °C, $\nu_{max.}$ ($CS_2$) 670 $cm^{-1}$]. Seng[5] reported the isolation, from the product of the addition of hydrogen chloride in ether–ethanol[6] to cholest-5-ene, of a chlorocholestane, m.p. 91 °C, $[\alpha]_D$ +36°, resistant to dehydrochlorination with hot ethanolic sodium acetate, suggested by Georg[4] to be 6α-chloro-5α-cholestane [lit.,[7] m.p. 149 °C, $[\alpha]_D$ +46°, $\nu_{max.}$ 781 and 745 $cm^{-1}$], but Barton and Schaeppi[8] were unable to confirm the formation of a stable secondary chloride under Seng's conditions.




In 1957, Howden[9] attempted unsuccessfully to repeat Mauthner's early work[2,3] and isolate the reputed 5β-chloride (1). Shoppee and Lundberg,[1] using Mauthner's improved method[6] for the preparation of the 5α-chloride (3), examined the non-crystalline material from the mother-liquor, and found that the $^1H$ n.m.r. spectrum appeared to be a superposition of the spectra of an unidentified chloride (1?), the 5α-chloride (3), and 6α-chloro-5α-cholestane (19-$H_3$ at δ 1.065, 1.035, and 0.815, respectively), but were unable to isolate (1) or the 6α-chloride. We now report the isolation of the 5β-chloride (1), in which the C–Cl bond is axial to ring A and equatorial to ring B.

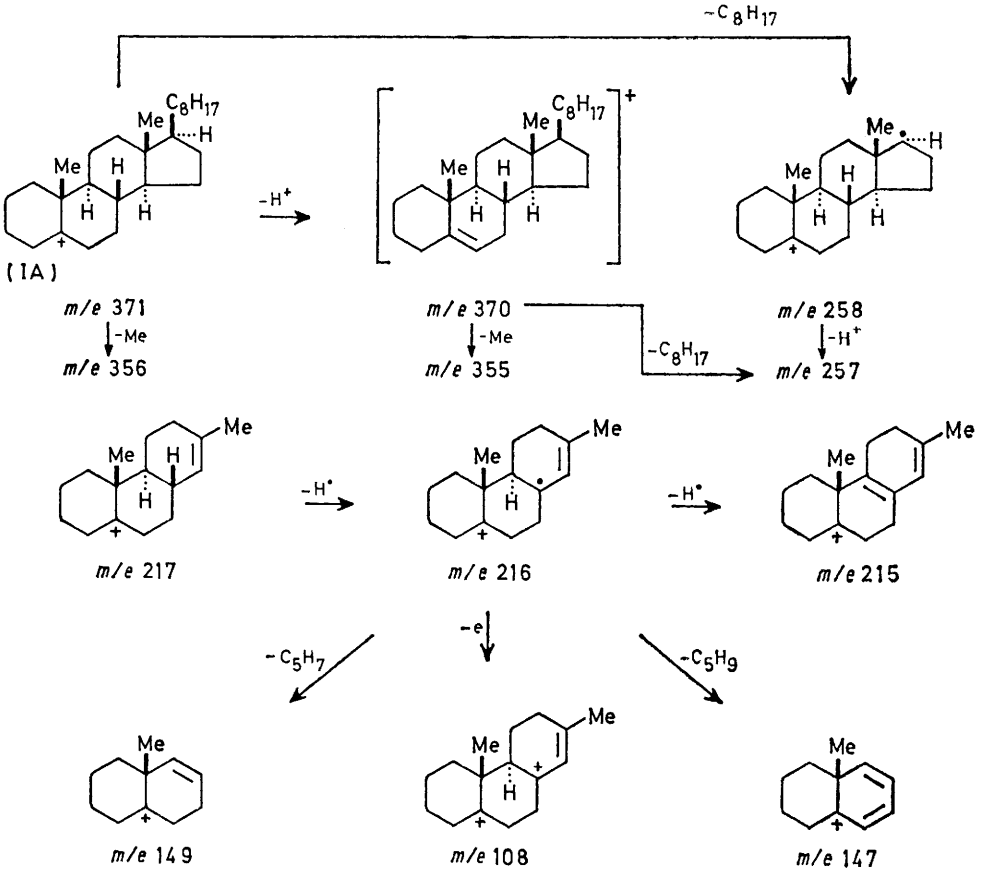
## RESULTS AND DISCUSSION

Cholest-5-ene (2) and dry hydrogen chloride in chloroform at 20 °C gave a mixture containing the 5β-chloride (1) and the 5α-chloride (3). After removal of the crystalline 5α-chloride, crystallisation of the residue from ether–ethanol at 0—20 °C gave a fraction, m.p. 66—70 °C, $[\alpha]_D$ +14°, and at −20—0 °C a fraction, m.p. 67—85 °C, $[\alpha]_D$ +22°; both fractions were saturated to tetranitromethane–chloroform and gave only two spots by t.l.c. on silica in various solvent systems. The mother-liquor material, expected to contain a higher proportion of the more soluble 5β-chloride, by t.l.c. on silica treated with dimethylchlorosilane, furnished a better separation of the two components; an enriched 5β-chloride fraction (higher $R_F$) by further t.l.c. on Kieselgel H (Merck) gave crude 5β-chloride (1), m.p. 62—64 °C, $[\alpha]_D$ +32°. It was found, however, that crystalline fractions, rich in 5β-chloride, saturated to tetranitromethane–chloroform and showing no vinyl proton signal in their $^1H$ n.m.r. spectra, lost hydrogen chloride unless kept below 0 °C. We therefore abandoned chromatography and reverted to fractional crystallisation from ether–ethanol at −20 °C. This procedure ultimately furnished a polymorph of the 5β-chloride (1) (28% yield), m.p. 72—75 °C, $[\alpha]_D^{20}$ +37°, as small clusters of iridescent plates, and another polymorph of (1) (1—30% yield depending on conditions), m.p. 94—95 °C, $[\alpha]_D^{20}$ +34°, as large shining prisms. The physical properties of these two polymorphs are effectively identical (the i.r. spectra are superposable) and are set out in Table 1.

The field-desorption (f.d.) mass spectra of both polymorphs showed the molecular ion $M^+$ at *m/e* 408, 406. These parent peaks were not seen in the electron-impact (e.i.) mass spectra of the two polymorphs, but the fragmentation patterns corresponded closely. The different thermal stabilities of the two polymorphs to dehydrochlorination, mentioned incidentally above, were confirmed by observations made in taking their f.d. mass spectra; the polymorph of m.p. 75 °C, lost hydrogen chloride in the mass spectrometer ($M^+$ $H^{35}Cl$, 36%; $H^{37}Cl$, 38%) almost without heating the emitter wire (heating current 2 mA), whereas the polymorph of m.p. 95 °C only lost hydrogen chloride when the emitter heating current was *ca.* 18—20 mA. Since polymorphs possess different internal crystal structures, we attribute these differing thermal stabilities to different crystal-

lattice energies. The product of dehydrochlorination of both polymorphs was a mixture of cholest-4-ene and cholest-5-ene (which have the same $R_f$ on both glass and metal columns packed with 3% OV 17 on Gaschrom Q), m.p. 73—75 °C, $[\alpha]_D$ +49°, containing 80% of cholest-4-ene and 20% of cholest-5-ene (2),[1,10] showing a peak for one vinyl proton in the $^1$H n.m.r. spectrum.

The $^1$H n.m.r. spectra of the two polymorphs are superposable and exhibit a sharp three-proton singlet at δ 1.055 (see Table 1) for the C-19 protons. The proton-noise-decoupled $^{13}$C n.m.r. spectrum of the polymorph of m.p. 95 °C exhibits 27 peaks (for assignment see Table 2) in agreement with the molecular formula $C_{27}H_{47}Cl$. The peak for the quaternary carbon atom C-5, bearing the electronegative chlorine atom,[11] occurs as a sharp singlet at δ 83.7, with singlets for C-18 and C-19 at δ 12.0 and 19.5, respectively. In the single-frequency off-resonance decoupled (SFORD) $^{13}$C spectrum, the C-5 signal remains a sharp singlet at δ 83.7, whilst the signals for C-18 and C-19, being angular methyl groups, become quartets. These observations prove the structure (1) for this polymorph.




The proton-noise-decoupled $^{13}$C n.m.r. spectrum of the polymorph of m.p. 75 °C (see Table 2) likewise exhibits a sharp singlet for the quaternary carbon atom C-5, bearing the chlorine atom, at δ 83.5 and singlets for C-18 and C-19 at δ 11.9 and 19.5, respectively. In the SFORD $^{13}$C spectrum, the C-5 signal remains a sharp singlet at δ 83.5, whilst the signals for C-18 and C-19 become quartets. These observations prove the structure (1) for this polymorph.

For comparison, we have examined the $^{13}$C spectra of 5-chloro-5α-cholestane (3), prepared by one of us (R. J. H.) at the University of Sydney (see Table 2). The proton-

TABLE 1

Properties of the two polymorphs of 5-chloro-5β-cholestane (1)

| | | | | $^1$H n.m.r. spectrum [δ($CD_2Cl_2$), −30 °C] | | | |
|---|---|---|---|---|---|---|---|
| M.p. (°C) | $[\alpha]_D$(°) | $\nu_{max}$ ($CS_2$) ($cm^{-1}$) | $M^+$ | 19-$H_3$ [a] | 18-$H_3$ [a] | 21-$H_3$ [b] | 26- and 27-$H_3$ [c] |
| 72—75 | +37 | 734, 639 | 408, 406 | 1.056 | 0.647 | 0.892 | 0.830 |
| 94—95 | +34 | 734, 639 | 408, 406 | 1.055 | 0.650 | 0.892 | 0.830 |

[a] Singlet. [b] Centre of three-proton doublet. [c] Centre of six-proton multiplet.

noise-decoupled $^{13}C$ n.m.r. spectrum disclosed a sharp singlet for the quaternary carbon C-5, bearing the chlorine atom, at δ 86.4 and singlets for C-18 and C-19 at δ 12.3 and 16.1, respectively. In the SFORD $^{13}C$ spectrum, the C-5 signal remains a sharp singlet at δ 86.4, whilst the signals for C-18 and C-19 become quartets.

We also report an unusual, but not unique, occurrence. Initially, the 5α-chloride (3) crystallised first from ether–ethanol solutions of the reaction product; later, after the 5β-chloride (1) had been isolated, the polymorph of m.p. 95 °C, crystallised first from the solutions; $^1H$ n.m.r. monitoring confirmed this, and showed that fraction 6 contained a 1 : 1 mixture of the isomeric chlorides (1) and (3). We suggest that the Macquarie

TABLE 2

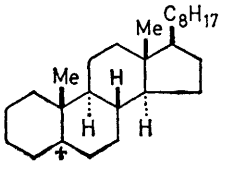
Comparative $^{13}C$ n.m.r. data for the polymorphs of 5-chloro-5β-cholestane and for 5-chloro-5α-cholestane in $CDCl_3$ (δ relative to $SiMe_4$)

| | 5-Chloro-5β-cholestane (1) | | 5-Chloro-5α-cholestane (3) |
|---|---|---|---|
| Carbon | m.p. 75 °C (spectrum at +8 °C) | m.p. 95 °C (spectrum at +27 °C) | (spectrum at +30 °C) |
| 1 | 34.4 | 34.5 | 32.0 |
| 2 | 21.8 | 21.9 | 20.7 |
| 3 | 22.3 | 22.3 | 26.9 |
| 4 | 31.6 | 31.7 | 36.7 |
| 5 | 83.5 | 83.7 | 86.4 |
| 6 | 39.5 | 39.5 | 36.7 |
| 7 | 29.4 | 29.5 | 28.4 |
| 8 | 34.6 | 34.8 | 34.8 |
| 9 | 43.4 | 43.6 | 46.8 |
| 10 | 41.7 | 41.9 | 41.1 |
| 11 | 20.0 | 20.1 | 21.2 |
| 12 | 39.9 | 40.1 | 40.0 |
| 13 | 42.3 | 42.4 | 42.7 |
| 14 | 56.4 | 56.6 | 56.2 |
| 15 | 23.8 | 23.8 | 24.0 |
| 16 | 28.3 | 28.3 | 28.0 |
| 17 | 56.1 | 56.2 | 56.2 |
| 18 | 11.9 | 12.0 | 12.3 |
| 19 | 19.5 | 19.5 | 16.1 |
| 20 | 35.8 | 35.8 | 35.9 |
| 21 | 18.6 | 18.7 | 18.7 |
| 22 | 36.1 | 36.2 | 36.3 |
| 23 | 24.2 | 24.2 | 24.0 |
| 24 | 39.2 | 39.3 | 39.6 |
| 25 | 28.1 | 28.0 | 28.2 |
| 26 | 22.6 | 22.6 | 22.7 |
| 27 | 22.9 | 22.8 | 22.9 |

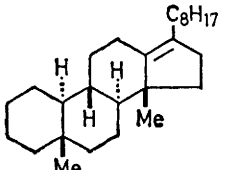
University laboratory became contaminated with traces of the 5β-chloride (1), which then inoculated solutions; for this reason a pure specimen of the 5α-chloride (3) was made in the Sydney University laboratories.

In 1957 one of us (M. E. H. H.) examined the addition to cholest-5-ene (2) of dry hydrogen bromide, in the absence of oxygen and light, at 20 °C. The product was 5-bromo-5β-cholestane, m.p. 81—83 °C, $[\alpha]_D^{20}$ +33°, the 5β-configuration being assigned on the basis of the positive specific rotation and of comparative molecular rotation differences.

Addition of hydrogen chloride to cholest-5-ene (2) occurs in two steps: (*i*) formation of the 5-carbocation (4), (*ii*) co-ordination of a chlorine anion.[12] To investigate the properties of the 5-carbocation (4), we generated it from cholest-5-ene by use of 73% perchloric acid in ether–ethanol at 20 °C; the perchlorate anion may well afford an ion pair $[R^+][ClO_4]^-$, but should not add to give a covalent compound $R{-}ClO_4$. The non-crystalline reaction product by g.l.c. gave a main peak (70%, $R_t$ 4.3 min), which appears to contain a back-bone rearrangement product, *e.g.* (5). This formulation is consistent with the $^1H$ n.m.r. spectrum (δ 0.86, s, 5β-Me; 0.89, s, 14β-Me) (*cf.*[13] δ 0.83, 0.88), which contained no vinyl proton signal. The proton-noise-decoupled $^{13}C$ n.m.r. spectrum showed singlets at δ 23.6 (C-19, now attached to C-5?) and δ 12.0 (C-18, now attached to C-14?), but significant signals for the anticipated olefinic quaternary carbon atoms C-13 and C-17 could not be seen. In the SFORD $^{13}C$ n.m.r., spectrum, the signals at δ 23.6 and 12.0, attributed to migrated angular methyl carbon atoms, became ill defined multiplets. The e.i. mass spectrum showed a molecular ion $M^+$ at *m/e* 370 (with small satellites at *m/e* 366, 367, 368, 369, 371, 372), with a group of small peaks centred round *m/e* 385 (383, 384, 386, 387) ($M^+$ + Me?), and a



(4)



(5)

group of small peaks at *m/e* 399 ($M^+$ + Et?) (400, 401, 402, 403); the latter may be derived by capture of an ethyl group, present in the original reaction mixture *i.e.* $EtOH + HClO_4 \rightleftharpoons [Et]^+[ClO_4]^- + H_2O$. Combined g.l.c.–m.s. produced a fragmention pattern similar to those of the polymorphs of (1), but showing some differences (see Experimental section).

## EXPERIMENTAL

M.p.s were taken on a Gallenkamp apparatus with a corrected thermometer; values of $[\alpha]_D$ were determined in $CHCl_3$ using a Perkin-Elmer photoelectric polarimeter (model 241). I.r. spectra were obtained with a Perkin-Elmer spectrometer (model 580) in $CS_2$ or using KBr discs. $^1H$ N.m.r. spectra were taken in $CD_2Cl_2$ at −30 °C using a Varian XL100 instrument, whilst $^{13}C$ n.m.r. spectra were taken in $CDCl_3$ using a Varian CFT machine at +8 °C [(1), m.p. 75° C], at +27 °C [(1), m.p. 95 °C], and at +30 °C (3); $SiMe_4$ was the internal standard in all spectra. Mass spectra were obtained in the field-desorption mode using a Varian 311A instrument equipped with a combined electron-impact/field-ionisation/field-desorption source; tungsten wire (diameter 10 μm) field-ion emitters activated in benzonitrile vapour were used (anode potential 3 kV, cathode −5 kV, source temperature 75 °C); mass spectra were also obtained by electron impact with an AEI MS12 instrument. G.l.c. was performed on a Becker gas chromatograph (model 407) using stainless steel columns (6 ft × 1/16 in) packed with OV17 on Chromosorb (oven temperature 230 °C; $N_2$ flow rate, 30 $cm^3$ $min^{-1}$).

*5-Chloro-5β-cholestane* (1).—(*a*) Cholest-5-ene {3 g, m.p. 90—91 °C, $[\alpha]_D$ −56.7° in $CHCl_3$, $\nu_{max.}$(KBr) 828 and 796 $cm^{-1}$, $^1H$ n.m.r. δ 1.000 (s, 19-$H_3$), 0.68 (s, 18-$H_3$), 0.912 (d, 21-

$H_3$), and 0.83 (m, 26- and 27-$H_3$), prepared by the reduction of cholesteryl chloride with Na–liquid $NH_3$ [14]}, was dissolved in freshly dried and redistilled $CHCl_3$ (50 ml), and the solution saturated with dry hydrogen chloride and allowed to stand in a closed flask at 20 °C for 4 days. Rotatory evaporation of the solvent and concomitant removal of excess of hydrogen chloride at 20 °C gave a yellow oil which was dissolved in ether (10 ml) at 0 °C, and ethanol (100 ml) at 0 °C was added until some oily material was precipitant and amorphous crystals commenced to form. The supernatant solution was decanted and kept at −20 °C overnight; the crystals which separated were twice recrystallised by the same procedure to give *5-chloro-5β-cholestane* (1) (0.57 g), m.p. 72—75 °C, $[\alpha]_D^{20}$ +37° (*c* 0.80); $\nu_{max.}$ (KBr) 734, 639, and 507 $cm^{-1}$; *m/e* 408, 406 ($M^+$), saturated to $C(NO_2)_4$ in $CHCl_3$; for $^1H$ and $^{13}C$ n.m.r. spectra, see Tables 1 and 2 (Found: C, 80.3; H, 11.9. $C_{27}H_{47}Cl$ requires C, 79.7; H, 11.7%). The mother-liquor on standing at −20 °C for 1 week deposited *5-chloro-5β-cholestane* (1) (35 mg), m.p. 94—95 °C, $[\alpha]_D$ +34° (*c* 0.44); $\nu_{max.}$ (KBr) 736, 639, and 506 $cm^{-1}$; *m/e* 408, 406 ($M^+$), saturated to $C(NO_2)_4$ in $CHCl_3$; for $^1H$ and $^{13}C$ n.m.r. spectra, see Tables 1 and 2 (Found: C, 79.9; H, 11.9. $C_{27}H_{47}Cl$ requires C, 79.7; H, 11.7%).

(*b*) A larger quantity of the polymorph of m.p. 95 °C of (1) could be isolated by modifying the crystallisation procedure. The oily product derived from cholest-5-ene (2 g) and hydrogen chloride was dissolved in $CHCl_3$ and the solution filtered into ethanol cooled with solid $CO_2$; this solution on standing overnight at −20 °C afforded crystals (1.76 g) of m.p. 74—85 °C. Repeating this procedure twice yielded 5-chloro-5β-cholestane (1) (*ca.* 600 mg) as needles, m.p. 93—94 °C, $[\alpha]_D^{20}$ +33° (*c* 0.64); $\nu_{max.}$ ($CS_2$) 739 and 640 $cm^{-1}$; $\nu_{max.}$ (KBr) 736, 640, and 510 $cm^{-1}$.

*Dehydrochlorination of the Epimeric Chlorides* (1) *and* (3).—The original mixture from the addition of cholest-5-ene (2) and hydrogen chloride [1 g; shown by $^1H$ n.m.r. to contain *ca.* equal quantities of the epimeric chlorides (1) and (3)] was refluxed with anhydrous potassium acetate (2 g) in ethanol for 12 h. The product, isolated in the usual way and twice recrystallised from $CHCl_3$–ethanol, had m.p. 74—75 °C, $[\alpha]_D^{20}$ +49°; $\nu_{max.}$ (KBr) 859, 807, and 793 $cm^{-1}$, and consisted of cholest-4-ene (80%), $[\alpha]_D$ +76°, and cholest-5-ene (20%), $[\alpha]_D$ −56°.

*5-Chloro-5α-cholestane* (3).—(a) *At the University of Sydney.* Cholest-5-ene (1.05 g, m.p. 90—91 °C, $[\alpha]_D^{20}$ −56.7°) was dissolved in ether (20 ml) and treated with a saturated solution of dry hydrogen chloride in ethanol (20 ml) at 20 °C for 4 days. A lower oily layer was withdrawn with a pipette and the supernatant solution on standing formed large prisms during 10 days. These by recrystallisation from ether–ethanol gave 5-choloro-5α-cholestane, m.p. 94 °C, $[\alpha]_D^{20}$ +6°; $\nu_{max.}$ (KBr) 630, 588, and 572 $cm^{-1}$; δ 1.034 (s, 19-$H_3$), 0.651 (s, 18-$H_3$), 0.90 (d, 21-$H_3$), and 0.83 (d, 26- and 27-$H_3$) {lit.,[1] m.p. 95—97 °C, $[\alpha]_D$ +5°; $\nu_{max.}$ ($CS_2$) 670 $cm^{-1}$; δ 1.035, 0.66, 0.91, and 0.87; lit.,[6] m.p. 96—97 °C, $[\alpha]_D$ +5°}, saturated to $C(NO_2)_4$ in $CHCl_3$; for the $^{13}C$ n.m.r. spectrum see Table 2. The mother-liquor was rich in 5-chloro-5β-cholestane (1) according to the $^1H$ n.m.r. spectrum.

(b) *At Macquarie University.* Cholest-5-ene (1 g) dissolved in peroxide-free freshly distilled dioxan (70 ml), in a ' one-pot ' operation designed to avoid inoculation by crystallites of 5-chloro-5β-cholestane (1) at any stage, was saturated (*ca.* 3 h) with dry hydrogen chloride at 20 °C. After 3 days, rotatory evaporation at 20 °C yielded a product, which was dissolved in ether (5 ml) and divided into two equal portions: (*i*) after removal of ether, the material was dissolved in dioxan (5 ml), the solution allowed to stand overnight at −20 °C, then at room temperature for 0.5 h, the crystals filtered off, dried *in vacuo*, and recrystallised similarly from dioxan to give 5-chloro-5α-cholestane (3), m.p. 91 °C, $[\alpha]_D^{20}$ +4.5° (*c* 0.42), $^1H$ n.m.r. spectra as in (a); (*ii*) after removal of ether, the material was dissolved in acetone (8 ml), the solution kept at −20 °C overnight, and the crystals filtered off and recrystallised similarly from acetone to give (3), m.p. 85—87 °C, $[\alpha]_D^{20}$ +7° (*c* 1.3), shown by the $^1H$ n.m.r. spectrum to contain a small amount of 5-chloro-5β-cholestane (1).

*Acid-catalysed Rearrangement of Cholest-5-ene* (2).—Cholest-5-ene (500 mg), dissolved in $CHCl_3$ (12.5 ml) and ethanol (12.5 ml), was treated with AnalaR perchloric acid (25 ml, 71—73%) at 20 °C for 72 h. The lower $CHCl_3$ layer was withdrawn, and the supernatant layer extracted twice with $CHCl_3$ (25 ml); the combined $CHCl_3$ solutions were washed with water (5 × 20 ml) until neutral, dried with potassium carbonate, and evaporated. The resulting viscous yellow oil (5?) (350 mg), {$[\alpha]_D^{20}$ +28° (*c* 1.0); $\nu_{max.}$ (KBr) 952, 832, and 759 $cm^{-1}$} failed to crystallise, but gave one main peak by g.l.c. with $R_t$ 4.3 min ($R_t$ for cholest-5-ene 7.5 min); for the $^1H$ and $^{13}C$ n.m.r. spectra see text; combined g.l.c.–m.s.: *m/e* 370 (8%), 356 (8%), 355 (18%), 288 (4%), 259 (6%), 258 (24%), 257 (100%), 256 (56%), 255 (4%), 207 (4%), 163 (4%), 161 (5%), 149 (6%), and 147 (5%).

*5-Bromo-5β-cholestane* [as (1) *with* Br *for* Cl].—Nitrogen was passed through a solution of cholest-5-ene (1 g) in $CHCl_3$ (30 ml) at 20 °C for 1 h; dry hydrogen bromide and nitrogen were passed through the solution in the dark at 20 °C for 2 h. Dilution with ether (200 ml) and the usual work-up gave an oil (1.17 g) which crystallised from acetone in leaflets and small amorphous clumps. The latter were removed by hand-picking but could not be crystallised satisfactorily from acetone; the leaflets were recrystallised from acetone to yield *5-bromo-5β-cholestane*, m.p. 81—83 °C, $[\alpha]_D^{20}$ +33° (*c* 1.3) [Found (after drying at 20 °C at 0.9 mmHg for 24 h): C, 71.7; H, 10.3. $C_{27}H_{47}Br$ requires C, 71.8; H, 10.5%].

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