1192. *Steroids and Walden Inversion. Part LV.* 2α- and 2β-Chloro-5α-cholestane, and 3α-Chloro-5-methyl-5β-cholestane*

By C. W. Shoppee, T. E. Bellas, and Ruth Lack

5α-Cholestan-2α-ol (OH eq.) and thionyl chloride give 2α-chloro-5α-cholestane with retention of configuration; use of phosphorus pentachloride gives both 2α-chloro- and 2β-chloro-5α-cholestane. 5α-Cholestan-2β-ol (OH ax.) with thionyl chloride and with phosphorus pentachloride gives 2α-chloro-5α-cholestane with inversion.

5-Methyl-5β-cholestan-3α-ol (OH eq.) and thionyl chloride give 3α-chloro-5-methyl-5β-cholestane with retention of configuration; 5-methyl-5β-cholestan-3β-ol (OH ax.) and thionyl chloride give 3α-chloro-5-methyl-5β-cholestane with inversion.

Raney nickel desulphuration of 2α-chloro-3,3-dibenzylthio-5α-cholestane and other 3,3-dithioketals of the 5α-cholestane series gives 5α-cholest-2-ene.

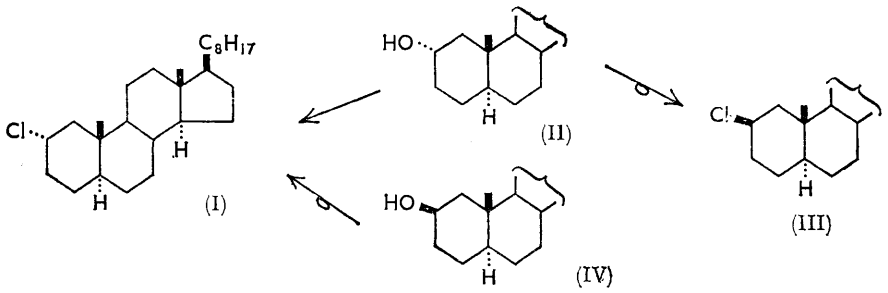
In continuation of previous studies of the stereochemical course of replacement of OH by halogen at positions 3,[1] 6,[2] and 7 [3] in the 5α-cholestane series, we now report some results at position 2.

5α-Cholestan-2α-ol [4] (II; OH eq.) by treatment with thionyl chloride in benzene at 20° gave, with retention of configuration, 2α-chloro-5α-cholestane (I; Cl eq.), $\nu_{max.}$ 757 cm.$^{-1}$,[5] accompanied by small amounts of 5α-cholest-1-ene and 5α-cholest-2-ene.[6,7] In one

* Part LIV, C. W. Shoppee, T. F. Holley, and G. P. Newsoroff, *J.*, 1965, 2349.

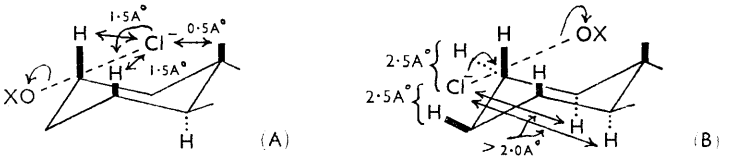
[1] C. W. Shoppee, *J.*, 1946, 1138.
[2] C. W. Shoppee and R. E. Lack, *J.*, 1960, 4864; C. W. Shoppee, M. E. H. Howden, and R. E. Lack, *ibid.*, p. 4874.
[3] R. J. W. Cremlyn and C. W. Shoppee, *J.*, 1954, 3794.
[4] A. Furst and P. A. Plattner, *Helv. Chim. Acta*, 1949, **32**, 275.
[5] D. H. R. Barton, J. E. Page, and C. W. Shoppee, *J.*, 1956, 331.
[6] H. B. Henbest, G. D. Meakins, and G. W. Wood, *J.*, 1954, 800; H. B. Henbest and R. A. L. Wilson, *J.*, 1956, 3289.
[7] R. B. Turner, W. R. Meador, and R. E. Winkler, *J. Amer. Chem. Soc.*, 1957, **79**, 4122.

experiment in which thionyl chloride was used at 20° for 5 min. without solvent, 70% of 2α-chloro-5α-cholestane was isolated accompanied by some unchanged alcohol but no olefin. 5α-Cholestan-2α-ol (II), with phosphorus pentachloride in benzene at 80°, or by trituration in chloroform at 20°, gave a chromatographically inseparable mixture of 2α-chloro-5α-cholestane (I) and 2β-chloro-5α-cholestane (III; Cl ax.), $\nu_{max.}$ 757 and 710 cm.$^{-1}$,[5] in the proportion ~2 : 1, accompanied by considerable quantities of 5α-cholest-1- and -2-ene.



5α-Cholestan-2β-ol[4] (IV; OH ax.), by reaction with thionyl chloride in benzene at 4—5°, afforded 5α-cholestan-2β-yl sulphite and 2α-chloro-5α-cholestane (I), $\nu_{max.}$ 757 cm.$^{-1}$, formed with inversion, accompanied by considerable quantities of 5α-cholest-2-ene. 5α-Cholestan-2β-ol (IV), with phosphorus pentachloride in benzene at 80°, or by trituration in chloroform at 20°, yielded 2α-chloro-5α-cholestane (I), together with considerable quantities of 5α-cholest-1- and -2-ene.

The steric course of substitution of OH by Cl in a saturated secondary alcohol using thionyl chloride and phosphorus pentachloride is believed to proceed through an ester–chloride complex, R–O–SOCl or R–O–PCl_4 (whose formation may be subject to steric retardation), which can undergo (a) simultaneous covalent exchange with rearrangement and retention of configuration (S_Ni),[8] or (b) partial heterolysis to give a close ion-pair, which may lead to substitution with retention of configuration or may collapse to an open ion-pair yielding a more or less racemised product (S_N1),[9–12] or (c) ionisation of a chlorine atom and bimolecular substitution with inversion subject to steric retardation (S_N2).[8] The four-centre covalent exchange mechanism (S_Ni) and the open ion-pair mechanism (S_N1) represent extremes, and intermediate cases can be envisaged where carbon–oxygen bond heterolysis proceeds but is incomplete when carbon–chlorine bond formation commences. It appears that chlorosulphites possess a smaller tendency than chlorophosphonates to lose a chlorine ion, so that, other things being equal, substitutions with thionyl chloride tend to proceed by the S_Ni mechanism whilst substitution with phosphorus pentachloride tends to occur by the derived S_N2 mechanism.



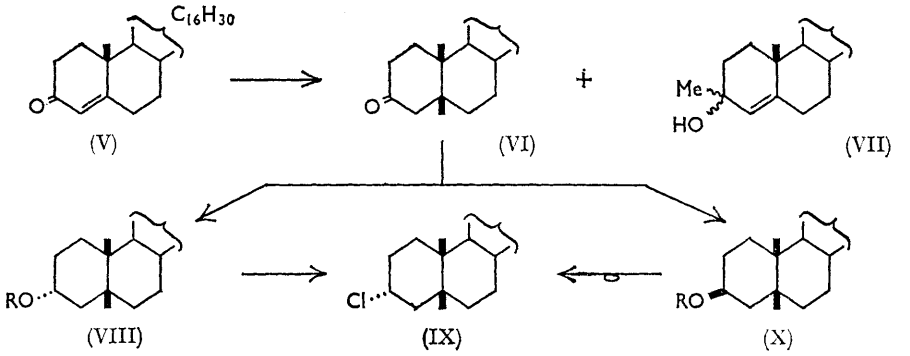
(X = SO^+ or PCl_3^+)

The geometry of the idealised S_N2 transition states for replacement by chlorine of the equatorial 2α-hydroxyl group in (II) (A) and of the axial 2β-hydroxyl group in (IV) (B) are identical. In (A), the reaction co-ordinate traversed by a chlorine anion (ionic radius,

[8] W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott, *J.*, 1937, 1252.
[9] C. E. Boozer and E. S. Lewis, *J. Amer. Chem. Soc.*, 1953, **75**, 3182.
[10] D. J. Cram, *J. Amer. Chem. Soc.*, 1953, **75**, 332.
[11] S. Winstein, P. E. Klinedinst, and G. C. Robinson, *J. Amer. Chem. Soc.*, 1961, **83**, 885; S. Winstein, P. E. Klinedinst, and E. Clippinger, *ibid.*, p. 4986.
[12] A. Streitwieser and W. D. Schaeffer, *J. Amer. Chem. Soc.*, 1957, **79**, 379.

1·81 Å) is seriously hindered by the axial 4β-hydrogen atom and the axial 10β-methyl group; the derived S_N2 process is thus relatively more difficult than the S_Ni rearrangement, so that thionyl chloride converts the 2α-ol (II) into the 2α-chloride (I) with retention by the S_Ni mechanism. In (B), the reaction co-ordinate followed by a chlorine anion is effectively unhindered, so that the derived S_N2 process is relatively easier than the S_Ni rearrangement, and thionyl chloride converts the 2β-ol (IV) into the 2α-chloride (I) with inversion by the derived S_N2 mechanism.

The greater tendency of chlorophosphonates, as compared with chlorosulphites, to ionise a chlorine atom reduces the disparity between the S_Ni and the derived S_N2 processes in (A); the 2α-ol (II) with phosphorus pentachloride thus gives in part the 2α-chloride (I) by the S_Ni mechanism and in part the 2β-chloride (III) by the derived S_N2 mechanism, or these epimers may arise (in unequal amounts) by the S_N1 mechanism. The 2β-ol (IV) with phosphorus pentachloride gives, as suggested by consideration of (B), only the 2α-chloride (I), with inversion by the relatively facile derived S_N2 mechanism.



The environment of the axial 2β-hydroxyl group in (IV), lying between secondary carbon atoms C-1 and C-3 and subject to 1,3-interaction by the axial 10β-methyl group is unique in the 5α-steroid nucleus. The same steric situation arises, however, in 5-methyl-5β-cholestan-3β-ol (X; R = H, OH ax.). It seemed therefore of interest to prepare the epimeric 3-ols (VIII and X; R = H) and to examine their reactions with thionyl chloride.

5-Methyl-5β-cholestan-3-one (VI) has been prepared [13] by addition of cyanide to cholest-4-en-3-one (V), and modification of the 5β-cyano-group. The simpler method of addition of methylmagnesium iodide to cholest-4-en-3-one (V) gives,[14,15] by 1,2-addition, the epimeric 3-methylcholest-4-en-3-ols (VII) and dehydration products thereof; catalysis of the reaction by cuprous chloride has been reported [14] to give only the same products, but a modified procedure for copper-catalysed addition has been found to increase the proportion of 1,4-addition in similar compounds.[16] Application of this method to cholest-4-en-3-one (V) afforded 10% of elimination products, shown by n.m.r. spectroscopy to be a mixture of 3-methylenecholest-4-ene (50%), 3-methylenecholesta-3,5-diene (21%), and 3-methylcholesta-2,4-diene (29%), and 6% of 5-methyl-5β-cholestan-3-one (VI), accompanied by one of the epimeric alcohols (VII), m. p. 117—119·5° (cf. ref. 14), as the major product, with a trace of the other epimeric alcohol (VII), m. p. 125—126° (cf. ref. 14). Reduction of the ketone (VI) with sodium–pentyl alcohol furnished 5-methyl-5β-cholestan-3α-ol (VIII; R = H, OH eq.); hydrogenation with Raney nickel in ethanol yielded mainly 5-methyl-5β-cholestan-3β-ol (X; R = H, OH ax.), whilst reduction with lithium aluminium hydride in boiling tetrahydrofuran gave a mixture of both 3-epimers from which the 3β-ol (X; R = H) could be isolated by column chromatography.

[13] S. Hirai, *Chem. and Pharm. Bull. (Japan)*, 1961, **9**, 854.
[14] O. C. Musgrave, *J.*, 1951, 3121.
[15] N. F. Nucherava and M. I. Ushakov, *Zhur. obshchei Khim.*, 1953, **23**, 315.
[16] A. J. Birch and M. Smith, *Proc. Chem. Soc.*, 1962, **356**.

Selected absorptions from the n.m.r. spectra of the foregoing 5β-methyl steroids are given in the Table. The results support the configurations assigned at C-3 to the epimers (VIII and X; R = H); thus, the three-proton singlet for the 5β-methyl group in (X; R = H) occurs at lower field (τ 8·91), on account of the influence of the axial 3β-hydroxyl group,[17,18] than the corresponding signal (τ 9·08) for the 5β-methyl group in (VIII; R = H), whilst the splitting patterns for the C-3 protons [19] are also consistent.

N.m.r. spectra of 5β-methyl-steroids (τ units)

	3-Me	5-Me	C-19 Me	C-18 Me	3-H	4-H
5-Methyl-5β-cholestan-3-one (VI)	—	9·08	9·12	9·32	—	7·08, 6·85
5-Methyl-5β-cholestan-3α-ol (VIII; R = H)	—	9·08	9·20	9·37	6·1 *	—
5-Methyl-5β-cholestan-3β-ol (X; R = H)	—	8·91	9·16	9·36	5·84 †	—
3-Methylcholest-4-en-3-ols (VII)	8·75, 8·77	—	8·97, 9·03	9·31, 9·32	—	4·79, 4·72

* Very broad band. † Broad band.

The n.m.r. spectrum of the ketone (VI) shows two peaks of unequal intensity at about τ 7, separated by 14 c./sec. and together equivalent to one proton. These signals are assigned to the 4α-proton, and are split by coupling with the 4β-proton. Since these protons are adjacent to the 3-carbonyl group they will be deshielded (cf. 5α-androstan-11-one in which the 12α- and 12β-protons give rise to absorption at τ 7·73)[20]; the axial 4α-proton in the ketone (VI) is also deshielded by two 1,3-axial effective alkyl groups (C-7, C-9) which shift its signal even further downfield.[21]

5-Methyl-5β-cholestan-3α-ol (VIII; R = H, OH eq.) with thionyl chloride at 20° for 5 or 15 min. gave 5-methyl-5β-cholestan-3α-yl sulphite (VIII; R = $C_{28}H_{49}$·O·SO) after recrystallisation from acetonitrile, which was homogeneous by thin-layer chromatography on silica in benzene (R_F 0·78). Treatment of the 3α-ol (VIII; R = H) with thionyl chloride in benzene for 18 hr. at 20° gave mainly 5-methyl-5β-cholestan-3α-yl sulphite accompanied by products of elimination, probably a mixture of 5-methyl-5β-cholest-2-ene and 5-methyl-5β-cholest-3-ene, and a low yield of 3α-chloro-5-methyl-5β-chloestane (IX), $\nu_{max.}$ 748 cm.$^{-1}$, with retention of configuration by the S_Ni mechanism [cf. (II) ⟶ (I)]. 5-Methyl-5β-cholestan-3β-ol (X; R = H), with thionyl chloride at 20° for 5 or 15 min., gave a homogeneous product regarded as 5-methyl-5β-cholestan-3β-yl sulphite (X; R = $C_{28}H_{49}$·O·SO) (R_F 0·87 on silica in benzene), accompanied by a trace of unsaturated material. Treatment of the 3β-ol (X; R = H) with thionyl chloride in benzene for 18 hr. at 20° gave a little 3α-chloro-5-methyl-5β-cholestane (IX) with inversion of configuration by the derived S_N2 mechanism [cf. (IV) ⟶ (I)], accompanied by unsaturated hydrocarbons, probably 5-methyl-5β-cholest-3-ene and 5-methyl-5β-cholest-2-ene (cf. refs. 22, 23) with much 5-methyl-5β-cholestan-3β-yl sulphite (X; R = $C_{28}H_{49}$·O·SO).

It is interesting to observe that where the expected S_Ni reaction with thionyl chloride suffers steric retardation, as in the case of 5α-cholestan-2β-ol and 5α-methyl-5β-cholestan-3β-ol, the main product is the sulphite, probably formed by attack of the unstable intermediate chlorosulphite ester on a second molecule of alcohol. The chlorosulphite ester group of 5-methyl-5β-cholestan-3α-ol is hindered by the 2α-, 4α-, and 9α-hydrogen atoms and likewise affords mainly the corresponding sulphite.

[17] J. N. Shoolery and M. T. Rogers, *J. Amer. Chem. Soc.*, 1958, **80**, 5121; C. Djerassi, P. A. Hart, and E. Warawa, *ibid.*, 1964, **86**, 78; C. Beard, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *ibid.*, p. 269.

[18] Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. and Pharm. Bull. (Japan)*, 1962, **10**, 338.

[19] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon, 1959, p. 116; A. Harsner and C. Heathcock, *J. Org. Chem.*, 1964, **29**, 1350.

[20] D. H. Williams, N. S. Bhacca, and C. Djerassi, *J. Amer. Chem. Soc.*, 1963, **85**, 2810.

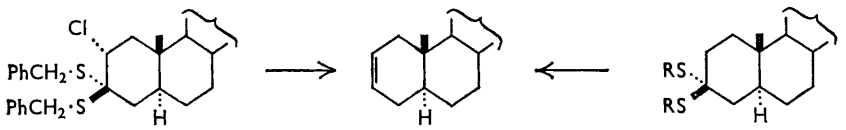
[21] E. L. Eliel, M. H. Gianni, T. H. Williams, and J. B. Stothers, *Tetrahedron Letters*, 1962, 741.

[22] D. A. H. Taylor, *Chem. and Ind.*, 1954, 250; A. Dreiding, *ibid.*, p. 1419.

[23] E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, 1955, **77**, 2505.

Since 2β-chloro-5α-cholestane (III) could not be obtained pure by substitution of the epimeric 5α-cholestan-2ξ-ols (II and IV), the preparation of the epimeric chlorides (I and III) from the 2ξ-chloro-5α-cholestan-3-ones,[24,25] by conversion into the 3,3-dibenzylthioketals and desulphuration with Raney nickel, was examined. This method has been used to prepare 6α-chloro-5α-cholestane from the corresponding 4-ketone,[2] and 6β-bromo-5α-cholestane from the corresponding 3-ketone;[2] in these cases, however, the halogen atom was not adjacent to the carbonyl group. The method has been applied to α-hydroxy- and α-acetoxy-ketones with preservation [26] and with loss of the α-substituent,[27] but not to α-chloro-ketones.[28]

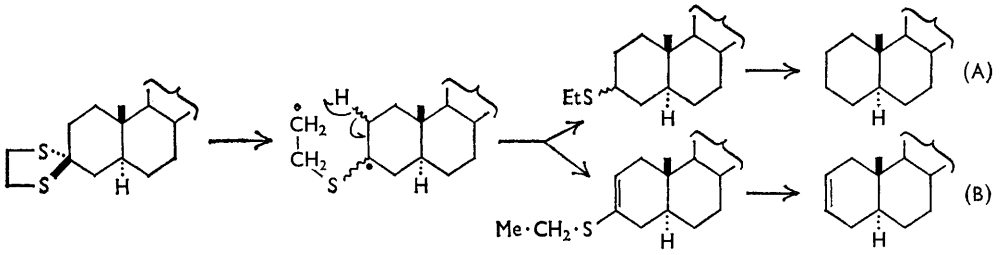
2α-Chloro-5α-cholestan-3-one [24] was converted into the 3,3-dibenzylthioketal (XI), which was desulphurised with deactivated W-1 Raney nickel in acetone; the sole product was, unexpectedly, 5α-cholest-2-ene (XII). Similarly, the 3,3-dibenzylthioketal (XIII; R = CH_2Ph), the 3,3-diethylthioketal (XIII; R = Et), and the 3,3-trimethylenedi-



(XI) (XII) (XIII)

thioketal (XIII; R–R = $[CH_2]_3$) gave 5α-cholest-2-ene (XII). In some experiments 5α-cholest-2-ene was accompanied by 5α-cholestane, and these hydrocarbons were identified by thin-layer chromatography; in four experiments with (XI) and (XIII; R = CH_2Ph, Et, and $[CH_2]_3$), respectively, traces of regenerated 5α-cholestan-3-one, $\nu_{max.}$ 1710 cm.$^{-1}$, could be identified by infrared spectroscopy.

At the time, only two cases of thioketal desulphuration to olefins had been reported; 1,3,3-tribenzylthio-5α-cholestane gave a mixture of 5α-cholest-1- and -2-ene,[29] whilst 1α,5-epidithio-5α-androstane-3α,17β-diol furnished androst-5-ene-3α,17β-diol.[30] Subsequently,

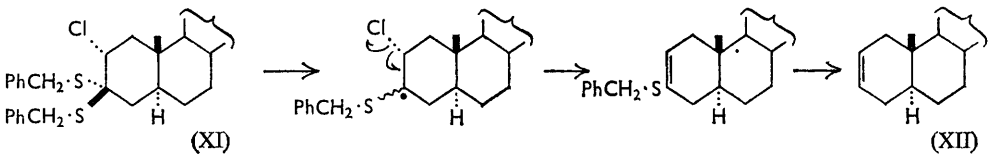


Djerassi and Williams [31] found that the 3,3-ethylenedithioketal (XIII; R–R = $[CH_2]_2$), by desulphuration with undeactivated W-2 and W-7 Raney nickel in ethanol, afforded mixtures of 5α-cholest-2-ene (XII) and 5α-cholestane, whilst W-7 catalyst, undeactivated but aged for 32 days, gave more 5α-cholest-2-ene (22%) than 5α-cholestane (17%) despite the large ratio (12 : 1) of catalyst to substrate, and deactivated W-7 catalyst, in the ratio

[24] B. Ellis and V. A. Petrow, *J.*, 1953, 3869; J. J. Beereboom, C. Djerassi, D. Ginsburg, and L. F. Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 3500.
[25] G. H. Alt and D. H. R. Barton, *J.*, 1954, 4284.
[26] M. N. Huffman, and M. H. Lott, *J. Amer. Chem. Soc.*, 1949, **71**, 719; J. C. Sheehan, R. C. Coderre, L. A. Cohen, and R. C. O'Neill, *ibid.*, 1952, **74**, 6155; J. F. Eastham, G. B. Miles, and C. A. Krauth, *ibid.*, 1959, **81**, 3114; J. Fishman, *Chem. and Ind.*, 1962, 1467.
[27] J. C. Sheehan and W. F. Erman, *J. Amer. Chem. Soc.*, 1957, **79**, 6050; S. L. Hsia, W. H. Elliott, J. T. Matschiner, E. A. Doisy, jun., S. A. Thayer, and E. A. Doisy, *J. Biol. Chem.*, 1958, **233**, 1337.
[28] L. Horner, L. Schläfer, and H. Kämmer, *Chem. Ber.*, 1959, **92**, 1700.
[29] P. A. Plattner, A. Fürst, and H. Els, *Helv. Chim. Acta*, 1932, **37**, 1399.
[30] R. C. Tweit and R. M. Dodson, *J. Amer. Chem. Soc.*, 1959, **81**, 4409.
[31] C. Djerassi and D. H. Williams, *J.*, 1963, 4046.

16 : 1 of catalyst to substrate, gave 5α-cholest-2-ene (48%) and 5α-cholestane (22%); sometimes small quantities of 3ξ-ethylthio-5α-cholestane were encountered. Fishman *et al.*[32] also reported that seven steroid ethylenedithioketals, by desulphuration with " moderately active " W-2 Raney nickel in acetone, gave good yields of olefins, accompanied by unchanged dithioketals and, in some instances, by the regenerated ketones.

The usual mechanism for nickel desulphuration of dithioketals [33] (A) has been modified by Djerassi and Williams [31] to explain the production of 5α-cholest-2-ene (B). If the concentration of hydrogen radicals is high, the intermediate diradical gives the saturated thioether, desulphurised to 5α-cholestane (A). If the concentration of hydrogen radicals is low (deactivated catalyst or small catalyst-to-substrate ratio), the intermediate diradical undergoes intramolecular hydrogen abstraction from C-2 to yield the thioenol ether, giving by desulphuration 5α-cholest-2-ene (B).



(XI) (XII)

A mechanism similar to sequence (B) can be invoked to rationalise the conversion of the 2α-chloro-3,3-dibenzylthioketal (XI) into 5α-cholest-2-ene (XII), provided that benzyl radicals are held at the reaction site on the catalyst surface (cf. ref. 31). The known preference of ring A for α-side approach to catalytic surfaces [34] would assist benzyl radicals held on the catalyst surface to cause homolysis of the adjacent 2α-chlorine atom.

Experimental

For general directions see *J.*, 1959, 345. $[\alpha]_D$ values are for chloroform solutions at 20°. Ultraviolet spectra were measured in cyclohexane in a Perkin-Elmer 4000 A spectrophotometer, whilst infrared spectra were determined in carbon disulphide in a Perkin-Elmer 221 spectrophotometer. N.m.r. spectra were measured in deuteriochloroform in a Varian A60 instrument with tetramethylsilane as internal reference. Steroid alcohols were dried azeotropically with benzene; thionyl chloride was distilled over quinoline and then fractionated from linseed oil; phosphorus pentachloride was sublimed before use. For chromatography, silica gel (Davison, 40—200 mesh), alkaline alumina (Spence type H, activity II), or neutral alumina (Woelm) were used.

5α-*Cholestan*-2β-*ol* (IV).—This was prepared from 2β,3β-epoxy-5α-cholestane, m. p. 91—92°, $[\alpha]_D$ +56° (lit.,[35] m. p. 88°, $[\alpha]_D$ +51°;[25] m. p. 89—91°, $[\alpha]_D$ +56°), by reduction with lithium aluminium hydride in ether, and had m. p. 152·5—155°, $[\alpha]_D$ +34° (lit.,[35] m. p. 153—154°, $[\alpha]_D$ +34°;[36] m. p. 154—155°, $[\alpha]_D$ +33°).

5α-*Cholestan*-2α-*ol* (II).—The 2β-ol was oxidised with the Jones reagent [37] to 5α-cholestan-2-one, m. p. 130—132°, $[\alpha]_D$ +50° (lit.,[35] m. p. 130°, $[\alpha]_D$ +51°;[36] m. p. 131°, $[\alpha]_D$ +49°), reduced by sodium–pentanol to the 2α-ol, m. p. 178—180·5°, $[\alpha]_D$ +27° (lit.,[35] m. p. 181°, $[\alpha]_D$ +26°, +28°;[36] m. p. 178—180°, $[\alpha]_D$ +36°).

2α-*Chloro- and* 2β-*Chloro*-5α-*cholestane* (I and III).—(*a*) The 2α-ol (200 mg.), dissolved in benzene, was treated with thionyl chloride (0·7 ml.) at 20° for 15 hr., and the mixture was warmed briefly at 50°, and poured into water. The product, isolated in the usual way, was dissolved in hexane and the solution filtered through a short column of neutral alumina to give, after evaporation, a colourless oil, which crystallised spontaneously. Repeated recrystallisation from acetone followed by ether–methanol gave 2α-*chloro*-5α-*cholestane* (40 g.), m. p. 134—136°, $\nu_{max.}$ 757 cm.$^{-1}$ [Found (after drying at 30°/0·3 mm. for 5 hr.): C, 79·8; H, 11·9. $C_{27}H_{47}Cl$ requires

[32] J. Fishman, M. Tomigoe, and H. Guzik, *J. Org. Chem.*, 1963, **28**, 1443.
[33] G. R. Pettit and E. E. van Tammelen, *Org. Reactions*, 1962, **12**, 356; W. Hauptmann and W. F. Walter, *Chem. Rev.*, 1962, **62**, 347.
[34] L. F. Fieser and M. Fieser, " Steroids," Reinhold, New York, 1959, p. 272.
[35] A. Fürst and P. A. Plattner, *Helv. Chim. Acta*, 1949, **32**, 279.
[36] L. Ruzicka, P. A. Plattner, and M. Furrer, *Helv. Chim. Acta*, 1944, **27**, 524.
[37] A. Bowers, T. G. Hallsall, E. R. H. Jones, and A. J. Lemin, *J.*, 1953, 2548.

C, 79·65; H, 11·6%]. The mother-liquor material, by recrystallisation from acetone, gave a mixture of 5α-cholest-1-ene and 5α-cholest-2-ene, m. p. 60—72°, $\nu_{max.}$ (CS_2) 774, 748, 728, 719, 700, and 666 cm.$^{-1}$ (lit.,[6] Δ^1: $\nu_{max.}$ 748, 718, 700; Δ^2: 774, 664 cm.$^{-1}$); the proportions of the isomers, estimated from relative peak heights, was roughly 1 : 4.

(*b*) The 2α-ol (50 mg.) was treated with thionyl chloride at 20° for 5 min.; sodium hydrogen carbonate solution was added, and the precipitated solid filtered off and dried. Thin-layer chromatography on silica in pentane revealed the presence of a chloro-compound (R_F 0·5) and unchanged 2α-ol but no olefin. Column chromatography of the solid (45 mg.) on silica (20 g.) in pentane gave, by elution with pentane, 2α-chloro-5α-cholestane (35 mg.), m. p. and mixed m. p. 134—136° (from methanol), $\nu_{max.}$ 757 cm.$^{-1}$; further elution with ether–pentane (1 : 2) gave the 2α-ol (10 mg.), m. p. and mixed m. p. 178—180°.

(*c*) The 2β-ol (200 mg.) was dissolved in benzene (10 ml.), and thionyl chloride (0·5 ml.) added to the solution at 4—5°. After 45 hr. at 4—5°, the usual working up furnished a product, which was dissolved in hexane and the solution filtered through a short column of neutral alumina. Evaporation of the filtrate gave a colourless solid (100 mg.), which was chromatographed on a long column of silica (40 g.) in pentane. Elution with pentane (5 c.c. eluates) and combination of appropriate fractions gave 5α-cholest-2-ene (48 mg.), m. p. 73—75·5° (from acetone), $\nu_{max.}$ 774, 666 cm.$^{-1}$, and 2α-chloro-5α-cholestane (47 mg.), m. p. 135—137° (from acetone), $\nu_{max.}$ 757 cm.$^{-1}$, which did not depress the m. p. of the specimen prepared by method (*a*).

(*d*) The 2β-ol (280 mg.) in benzene (7 ml.) in an ice-bath was treated with thionyl chloride (0·5 ml.), and the mixture kept at room temperature overnight. Removal of benzene by freeze-drying yielded a colourless solid (310 mg.), which by crystallisation from benzene–hexane gave *5α-cholestan-2β-yl sulphite*, m. p. 226—228° (decomp.), $\nu_{max.}$ (Nujol) 840, 830, 772, 762, 725, 678 cm.$^{-1}$ (all s) [Found (after drying at 100°/0·2 mm. overnight): C, 79·1; H, 11·7. $C_{54}H_{94}O_3S$ requires C, 78·8; H, 11·5%].

(*e*) The 2α-ol (200 mg.) and phosphorus pentachloride (250 mg.) in benzene were heated under reflux for 1 hr. The product, isolated in the usual manner, was dissolved in hexane and the solution filtered through a short column of neutral alumina. The material (100 mg.) obtained by evaporation of the filtrate was dissolved in pentane, adsorbed on a long column of silica gel (40 g.), and eluted with pentane (5 ml. fractions). Fractions 4 and 5 contained 5α-cholest-1- and -2-ene, whilst fractions 6—11 contained these olefins and chloro-steroids; fractions 12—18, which were free from hydrocarbons, were united, and recrystallised from acetone to give a chromatographically inseparable mixture of 2α-chloro-5α-cholestane, $\nu_{max.}$ 757 cm.$^{-1}$, and 2β-chloro-5α-cholestane, $\nu_{max.}$ 710 cm.$^{-1}$, m. p. 90—115° [Found (after drying at 25°/0·2 mm. for 12 hr.); C, 79·5; H, 11·6. Calc. for $C_{27}H_{47}Cl$: C, 79·65; H, 11·6%].

(*f*) The 2α-ol (50 mg.) and a few drops of chloroform were ground with phosphorus pentachloride (55 mg.) and left at 20° for 5 min. Ice was added and the product extracted with ether and isolated in the usual manner. Thin-layer chromatography on silica in pentane disclosed the presence of an olefin (R_F 0·75) and two chloro-compounds ($R_F \sim 0{\cdot}5$, two very close spots); the infrared spectrum showed two C–Cl peaks at 757 and 710 cm.$^{-1}$. Column chromatography on silica (20 g.) in pentane and elution with pentane (5 ml. fractions) with control of each fraction by thin-layer chromatography gave (i) fractions containing a mixture of 5α-cholest-1- and -2-ene, m. p. 60—72°, (ii) fractions containing olefins and chloro-steroids, (iii) fractions free from olefin, consisting of a mixture of 2α-chloro- and 2β-chloro-5α-cholestane, m. p. 90—111°, $\nu_{max.}$ 757 and 710 cm.$^{-1}$, the infrared spectrum being identical with that of the product in (*e*), estimated to contain the 2α- and 2β-epimers in the ratio 2 : 1 by the relative intensities of the principal peaks.

(*g*) The 2β-ol (217 mg.) was dissolved in benzene (10 ml.) and treated with phosphorus pentachloride (275 mg.) as in (*c*), to afford a semi-solid product from which 2α-chloro-5α-cholestane (20 mg.), m. p. and mixed m. p. 134—138°, $\nu_{max.}$ 757 cm.$^{-1}$, was isolated by repeated crystallisation from acetone.

(*h*) The 2β-ol (200 mg.) and a few drops of chloroform were ground with phosphorus pentachloride (250 mg.) and kept at 20° for 5 min. The product, isolated as in (*f*), by thin-layer chromatography on silica in pentane, contained olefin(s) (R_F 0·75) and a single chloro-compound (R_F 0·50); the infrared spectrum showed a single C–Cl peak at 756 cm.$^{-1}$. Column chromatography on silica (80 g.) in pentane and elution with pentane (5 m. fractions) gave fractions containing 5α-cholest-1- and -2-ene, m. p. 60—72°, followed by fractions containing olefin and

chloro-compound, and finally by fractions containing 2α-chloro-5α-cholestane, m. p. and mixed m. p. 134—138° (from acetone), $\nu_{max.}$ 756 cm.$^{-1}$.

5-*Methyl*-5β-*cholestan*-3-*one* (VI).—A solution of cholest-4-en-3-one (11·3 g.) and cupric acetate (550 mg.) in tetrahydrofuran (120 ml.) was added to an ethereal solution of methylmagnesium iodide [prepared from magnesium (6·6 g.) and methyl iodide (39·7 g.)]. After stirring for 4 hr. at 20°, saturated ammonium chloride solution was added and the product isolated in the usual way. Chromatography on alumina (200 g.) in hexane, and elution with hexane (3 × 100 ml.), gave a product (1·1 g.), m. p. 60—62° (from acetone), $[\alpha]_D$ +90° (*c* 1·0), $\lambda_{max.}$ 239, 275 mμ [log ε 4·2, 3·16] (Found: C, 87·9; H, 12·1. Calc. for $C_{28}H_{46}$: C, 87·9; H, 12·1%). The shape, position, and integral of the n.m.r. signals for the vinyl protons was consistent with a mixture of 50% of 3-methylenecholest-4-ene (methylene protons, τ 5·33, H-4, τ 4·15), 21% of 3-methylcholesta-3,5-diene (H-4, τ 4·28; H-6, τ 4·72), and 29% of 3-methylcholesta-2,4-diene (H-2 and H-4, centred at ~τ 4·6). This diene mixture gave only one spot by thin-layer chromatography on silica in pentane, but by refluxing (200 mg.) with ethanolic hydrochloric acid (5%; 20 ml.) furnished only 3-methylcholesta-3,5-diene (190 mg.), m. p. 78° (from methanol–acetone), $[\alpha]_D$ −115° (*c* 0·7) (lit.,[14] m. p. 79·5°, $[\alpha]_D$ −129°) (Found: C, 87·9; H, 12·1. Calc. for $C_{28}H_{46}$: C, 87·9; H, 12·1%), whose n.m.r. spectrum showed signals at τ 9·29 (singlet; C-18 Me), τ 9·09 (singlet; C-19 Me), τ 8·28 (broad; 3-methyl), τ 4·28 (H-4), and τ 4·72 (H-6). Elution with ether–hexane (1 : 10; 3 × 250 ml.) gave 5-methyl-5β-cholestan-3-one (850 mg.), m. p. 90—91·5° (from acetone–methanol) (lit.,[13] 88—89°). Elution with ether–hexane (1 : 3; 3 × 500 ml.) gave an oil (500 mg.), which furnished one epimeric 3ξ-*methylcholest*-4-*en*-3ξ-*ol* (80 mg.), m. p. 125—126°, $\nu_{max.}$ (Nujol) 1660 cm.$^{-1}$ (C=C), after three recrystallisations from methanol [Found (after drying at 20°/0·1 mm. for 15 hr.): C, 84·1; H, 12·2. $C_{28}H_{48}O$ requires C, 83·9; H, 12·1%]. Finally, elution with ether (2 × 500 ml.) gave the other epimeric 3ξ-methylcholest-4-en-3ξ-ol (7·6 g.), m. p. 117—119·5° (from methanol) (lit.,[14] m. p. 114—115·5°,[15] 112—114°).

5-*Methyl*-5β-*cholestan*-3α- *and* -3β-*ol* (VIII and X).—(*a*) 5-Methyl-5β-cholestan-3-one (VI) (350 mg.) in boiling pentanol (50 ml.) was reduced by addition of sodium (4 g.) during 1·5 hr. The usual working up gave an oil, which was chromatographed on alumina (9 g.) in hexane; elution with ether–hexane (2 : 3; 2 × 15 ml.) gave mixtures of the epimeric 3-ols, but further elution with the same eluant (4 × 15 ml.) gave 5-*methyl*-5β-*cholestan*-3α-*ol* (110 mg.), m. p. 128—130° (from acetonitrile) [Found (after drying at 20°/0·2 mm. for 15 hr.): C, 83·1; H, 12·6. $C_{28}H_{50}O$ requires C, 83·5; H, 12·5%].

(*b*) The ketone (VI) (300 mg.) was hydrogenated with freshly prepared Raney nickel (~600 mg.) overnight. The product was adsorbed on alumina (9 g.) in hexane; elution with ether–hexane (1 : 1; 5 × 15 ml.) gave 5-*methyl*-5β-*cholestan*-3β-*ol* (155 mg.), m. p. 132—134° (from acetonitrile) [Found (after drying at 20°/0·1 mm. overnight): C, 83·7; H, 12·7%].

(*c*) The ketone (VI) (200 mg.) was refluxed with lithium aluminium hydride (200 mg.) in tetrahydrofuran (20 ml.) for 30 min. The product, isolated in the usual way, was chromatographed on silica (20 g.) in pentane. Elution with ether–pentane (1 : 5) gave 5-methyl-5β-cholestan-3β-ol (70 mg.), m. p. and mixed m. p. 132—134°; further elution with the same eluant gave material (110 mg.), shown by thin-layer chromatography on silica to be a mixture of the epimeric 3-ols (VIII) and (X).

3α-*Chloro*-5-*Methyl*-5β-*cholestane* (IX).—(*a*) The 3α-ol (VIII; R = H) (250 mg.) in benzene (25 ml.) was treated with thionyl chloride (2·0 ml.), with stirring, and the mixture left at 20° overnight. The residue obtained by freeze-drying was chromatographed on a long column of silica (120 g.) in pentane. Elution with pentane (5 ml. fractions) and control of each fraction by thin-layer chromatography on silica in pentane gave: (i) fractions 10—15 (22 mg.) containing only unsaturated hydrocarbons, $\nu_{max.}$ 733, 702, 654 cm.$^{-1}$, R_F 0·74, whose n.m.r. spectrum showed a complex multiplet for the vinyl protons indicating it to be a mixture of 5-methyl-5β-cholest-2-ene and 5-methyl-5β-cholest-3-ene; (ii) fractions 16—20 (11 mg.) containing mixtures of olefins (R_F 0·74), and a chloro-steroid (R_F 0·50); (iii) fractions 21—23 (10 mg.) containing 3α-*chloro*-5-*methyl*-5β-*cholestane*, m. p. 93—95° (from acetone), $\nu_{max.}$ 748 cm.$^{-1}$ (R_F 0·50) [Found (after drying at 60°/0·5 mm. for 5 hr.): C, 80·15; H, 11·5. $C_{28}H_{49}Cl$ requires C, 79·85; H, 11·7%]. Further elution with ether–pentane (1 : 20) gave 5-*methyl*-5β-*cholestanyl*-3α-*yl sulphite* (145 mg.) as an oil, homogeneous on thin-layer chromatography on silica in benzene (R_F 0·78) and showing two characteristic peaks, $\nu_{max.}$ (film) 799w, 748s, and a set of small peaks at 880, 840, 812, and 805 cm.$^{-1}$. This crystallised from methyl cyanide,

m. p. 157—158°, $\nu_{max.}$ (Nujol) 1190 (S=O), 915, 840, 812, 805, and 775 cm.$^{-1}$ [Found (after drying at 60°/0·5 mm. for 5 hr.): C, 78·65; H, 11·8. $C_{56}H_{98}O_3S$ requires C, 79·0; H, 11·6%]. Elution with ether gave unchanged 3α-ol (VIII; R = H) (25 mg.), identified by m. p. and mixed m. p. 128—129°.

(*b*) The 3α-ol (20 mg.) was treated with thionyl chloride (0·5 ml.) at 20° for 15 min. Sodium hydrogen carbonate solution was added, and the precipitated solid was filtered off. Column chromatography of the product (24 mg.) on silica (3 g.) in pentane and elution with ether–pentane (1 : 20) gave 5-methyl-5β-cholestan-3α-yl sulphite (R_F 0·78 in benzene), identical with the sample prepared in (*a*). Further elution with ether–pentane (1 : 1) gave unaltered 3α-ol (5 mg.), m. p. and mixed m. p. 128—129°.

(*c*) The 3β-ol (X; R = H) (20 mg.) was treated with thionyl chloride (0·5 ml.) at 20° for 15 min. Column chromatography, on silica (3 g.) in pentane, of the product, isolated as in (*b*), and elution with ether–pentane (1 : 20) gave an oil (5 mg.), regarded as 5-methyl-5β-cholestan-3β-yl sulphite, which was homogeneous by thin-layer chromatography on silica in benzene (R_F 0·87) and which showed two characteristic peaks $\nu_{max.}$ (film) 774w, 752s, with a set of small absorptions at 878, 848, 820, and 805 cm.$^{-1}$.

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