Steroids and Walden Inversion. Part LXII.[1] The Chlorination of 5α-Cholestan-1-one

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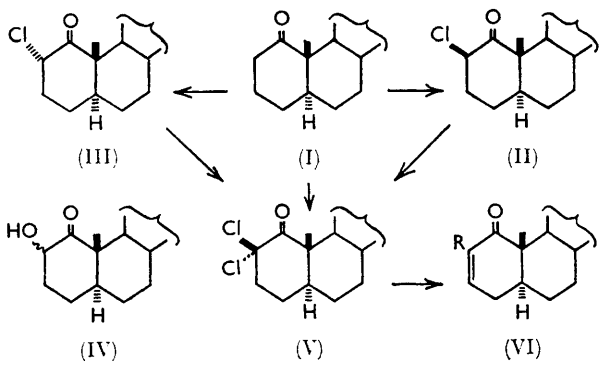
Monochlorination of 5α-cholestan-1-one is slow and yields 28% of the axial 2β-chloro-ketone and 32% of the equatorial 2α-chloro-ketone under conditions in which the 2β-chloro-ketone undergoes inversion to the extent of 49%; the values, 28 and 32%, take account of this transformation caused by acid-catalysed enolisation. Monochlorination of the axial 2β-chloro-ketone to give the 2,2-dichloro-ketone is virtually quantitative at 20° after 30 hours, whereas the equatorial 2α-chloro-ketone under the same conditions yields only 12% of the 2,2-dichloro-ketone after 96 hours. The more significant u.v., i.r., o.r.d., and n.m.r. characteristics of the above chloro-ketones and some related compounds are recorded.

THE generalisation of Corey [2] on the stereochemistry of bromination of cyclohexanones and keto-steroids, if extended to chlorination, suggests (*a*) that the product of kinetic control should be the axial chloro-ketone because orbital overlap in the transition state is more favourable to this molecular geometry, (*b*) that, in the absence of steric interaction between the axial chlorine atom and other substituents, the product of kinetic control should also be the thermodynamically favoured product, and (*c*) that, in the presence of such steric interaction, the axial chloro-ketone should be converted into the equatorial chloro-ketone under conditions of thermodynamic control (by acid-catalysed enolisation).

Recently we reported [1] that chlorination of 5α-cholestan-2-one at 20° rapidly gave 19% of the equatorial 3β-chloro-5α-cholestan-2-one under conditions in which inversion of the axial 3α-chloro-5α-cholestan-2-one did not occur. This result recalls the work of Nakano, Hasegawa, and Djerassi,[3] who found that bromination of 5α-cholestan-2-one at 20° rapidly afforded not less than ~44% of the equatorial 3β-bromo-5α-cholestan-2-one.

It seemed desirable to parallel previous studies [4,5] of the bromination of 5α-cholestan-1-one (I) with an investigation of its chlorination. Sigg and Tamm [4] found that bromination of (I) in acetic acid containing hydrogen bromide at 22° was extremely slow, and gave after 16 hr. ~3% of the axial 2β-bromo-ketone [cf. (II)] (which could not always be isolated), 42% of the equatorial 2α-bromo-ketone [cf. (III)], and 18% of the 2,2-dibromo-ketone [cf. (V)]. Shoppee *et al.*,[5] working under the same conditions, obtained at 20° after 16 hr. 39% of the 2α-bromo-ketone, and 19% of the 2,2-dibromo-ketone, but were unable to isolate the 2β-bromo-ketone.



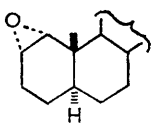
Monochlorination of 5α-cholestan-1-one (I) in acetic acid containing a trace of hydrochloric acid proceeded very slowly at 20°; after 24 hr., there were isolated 11% of the 2β-chloro-ketone (II), 43% of the 2α-chloro-ketone (III), 6% of the 2,2-dichloro-ketone (V), and 31%

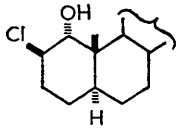
[1] Part LXI, C. W. Shoppee and S. C. Sharna, *J. Chem. Soc.* (*C*), 1967, 2385.
[2] E. J. Corey, *J. Amer. Chem. Soc.*, 1953, **75**, 2301; 1954, **76**, 175.
[3] T. Nakano, M. Hasegawa, and C. Djerassi, *Chem. and Pharm. Bull.* (*Japan*), 1963, **11**, 465.
[4] H. P. Sigg and C. Tamm, *Helv. Chim. Acta*, 1960, **43**, 1402.
[5] C. W. Shoppee, S. K. Roy, and B. S. Goodrich, *J. Chem. Soc.*, 1961, 1583

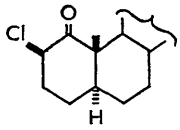
of unchanged 5α-cholestan-1-one. Since the axial 2β-chloro-ketone (II) under these conditions during 24 hr. undergoes inversion to give 49% of the equatorial 2α-chloro-ketone (III), the 11% of the 2β-chloro-ketone isolated in the above chlorination represents the residue of 22% 2β-chloro-ketone produced, whilst the 43% of 2α-chloro-ketone isolated corresponds to the original formation of 32% of this compound. It is shown in the sequel that monochlorination of the 2β-chloro-ketone (II) is rapid compared with that of the 2α-chloro-ketone (III), so that the 6% of 2,2-dichloro-ketone (V) isolated in the above chlorination may be regarded as representing 6% of initially formed 2β-chloro-ketone; thus the amount of axial 2β-chloro-ketone (II) originally formed is ~28%, compared with ~32% of the epimeric 2α-chloro-ketone (III) produced by direct equatorial attack.[6,7]

Kinetically controlled monochlorination of 5α-cholestan-1-one (I) in acetic acid–carbon tetrachloride in the presence of one equivalent of sodium acetate [6] for 24 hr. gave only 0·1% of the 2β-chloro-ketone (II) (estimated by g.l.c.).

Fission of 1α,2α-epoxy-5α-cholestane [8] (VII) with hydrochloric acid in chloroform at 20° furnished the crystalline 2β-chloro-1α-hydrin (VIII), which by oxidation with sodium dichromate in 10% acetic acid [9] at 15° gave 85% of the 2β-chloro-ketone (II) (retention time at 240°, 17·5 min.) and 15% of the 2α-chloro-ketone (III) (retention time at 240°, 21·5 min.). It seems probable that, even under the very mild conditions employed for oxidation, acid-catalysed enolisation of the 2β-chloro-ketone occurs leading to inversion to give the 2α-chloro-ketone.


(VII)


(VIII)


(II)

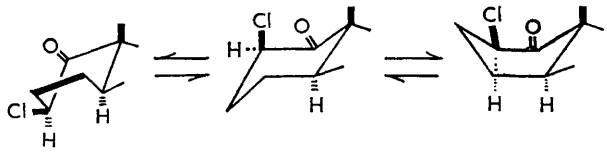
Alkaline hydrolysis of the 2α-chloro-ketone (III) yielded both 2α-hydroxy- [4] and 2β-hydroxy-5α-cholestan-1-one [4] [as (IV)]; the i.r. spectrum of the 2α-hydroxy-ketone (IVα) disclosed hydrogen-bonding of the equatorial 2α-hydroxylic hydrogen atom, which did not occur with the axial 2β-hydroxy-ketone (IVβ) [dihedral angle of C(2)–O and C=O bonds: (IVα) ~10°, (IVβ) ~110°; 2ξ–OH/O=C separation: (IVα) 2·2 Å, (IVβ) 3·2 Å (from Dreiding models)]. Dehydrochlorination of the epimeric 2-chloro-ketones (II) and (III) furnished rapidly by use of lithium iodide–lithium carbonate–dimethylformamide, or slowly by use of *s*-collidine, 5α-cholest-2-en-1-one [4,5,10] (VI; R = H).

Monochlorination of the 2β-chloro-ketone (II) in acetic acid–chloroform in the presence of a trace of hydrochloric acid at 20° for 12 hr. gave ~66% of the 2,2-dichloro-ketone (V); after 30 hr. the yield of 2,2-chloro-ketone isolated was 95%, and t.l.c. showed the reaction to be quantitative. On the contrary, monochlorination of the 2α-chloro-ketone (III) under the same conditions afforded after 96 hr. only 12% of the 2,2-dichloro-ketone (V). Direct formation of the 2,2-dichloro-ketone by equatorial attack [(II) ⟶ (V)] is thus much more easy than the expected production of the 2,2-dichloro-ketone by axial attack [(III) ⟶ (V)]; this is to be attributed to the relative difficulty of the axial reaction co-ordinate arising from the steric requirements of the axial 10β-methyl group. Dehydrochlorination of the 2,2-dichloro-ketone (V) with lithium iodide–lithium carbonate in dimethylformamide furnished 2-chloro-5α-cholest-2-en-1-one (VI: R = Cl), $\lambda_{max.}$ 243 mμ, log ε 3·85, whose positive o.r.d. curve showed the multiple Cotton effects characteristic of αβ-unsaturated ketones.

Dichlorination of 5α-cholestan-1-one (I) in acetic acid containing a trace of hydrogen chloride at 20° during 4 days gave 42% of the 2α-chloro-ketone (III) accompanied by 49% of the 2,2-dichloro-ketone (V).

The u.v., i.r., and o.r.d. characteristics of the chloro-ketones (II), (III), (V), and (VI: R = Cl), and of the epimeric hydroxy-ketones [as (IV)] are collected in Table 1. They are consistent with the formulae assigned.

The spectral properties of the 2β-chloro-ketone (II) are unusual; in the u.v. Δλ is about one quarter of the usual value, whilst in the i.r. two carbonyl stretching frequencies Δν − 3 and Δν + 19, with integrated intensities of 4 : 1, appear; in the solid phase using a 'Nujol' mull only the peak at 1709 cm.$^{-1}$ is visible. In view of the large 1,3-diaxial steric interaction between a 2β-chlorine atom and a 10β-methyl group,[11] some conversion to a boat conformation [(IIa), (IIb)] may possibly occur in solution at the expense of a moderately increased repulsion between the $\overset{+}{C}$–$\overset{-}{O}$ and $\overset{\delta+}{C}$–$\overset{\delta-}{Cl}$ dipoles.


(IIa) (II) (IIb)

The dihedral angle between these dipoles is ~10° in (IIa) and ~40° in (IIb) with the 2β-chlorine atom essentially equatorial in both cases; it is known [12] that a boat-

[6] R. Villotti, H. J. Ringold, and C. Djerassi, *J. Amer. Chem. Soc.*, 1960, **82**, 5693.
[7] C. Djerassi, N. Finch, R. C. Cookson, and C. W. Bird, *J. Amer. Chem. Soc.*, 1960, **82**, 5488; R. Mauli, H. J. Ringold, and C. Djerassi, *ibid.*, p. 5494.
[8] H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1956, 3289.
[9] J. F. Biellmann and G. Ourisson, *Bull. Soc. chim. France*, 1960, 348.
[10] P. Striebel and C. Tamm, *Helv. Chim. Acta*, 1954, **37**, 1094.
[11] C. W. Shoppee, T. E. Bellas, R. E. Lack, and S. Sternhell, *J. Chem. Soc.*, 1965, 2483.
[12] D. H. R. Barton, D. A. Lewis, and J. F. McGhie, *J. Chem. Soc.*, 1957, 2907; C. Djerassi, N. Finch, and R. Mauli, *J. Amer. Chem. Soc.*, 1959, **81**, 4997; R. Mauli, H. J. Ringold, and C. Djerassi, *ibid.*, 1960, **82**, 5494.

TABLE 1

Light absorption properties of derivatives of 5α-cholestan-1-one

Compound	$\lambda_{max.}$ (mμ) in dioxan	Δλ (mμ)	$\nu_{max.}$ (cm.$^{-1}$) in CS_2	Δν (cm.$^{-1}$)	Substituent configuration
(I) 5α-Cholestan-1-one	296		1712		
(II) 2β-Chloro-1-one	301	+5	1709, 1731 ‖	−3, +19	*ax.*
(III) 2α-Chloro-1-one	289	−7	1732	+20	*eq.*
(V) 2,2-Dichloro-1-one	307	+11	1732	+20	*ax., eq.*
(VI) 2-Chloro-2-en-1-one	243 *	−53	1702 †	−10	
(IVα) 2α-Hydroxy-1-one ¶	277	−19	1706, 3467 ‡	−6	*eq.*
(IVβ) 2β-Hydroxy-1-one ¶	300	+4	1717, 3595 §	+5	*ax.*

* Log ε 3·85. † In 'Nujol' 1694 cm.$^{-1}$. ‡ Hydrogen bonding: 2α-OH/O=C separation 2·2 Å. § No hydrogen bonding; 2β-OH/O=C separation 3·2 Å. ‖ In 'Nujol' 1709 cm.$^{-1}$ only. ¶ Sigg and Tamm [4] report for (IVα) $\lambda_{max.}$ 279 mμ, $\nu_{max.}$ (CH_2Cl_2) 1698 cm.$^{-1}$, and for (IVβ) $\lambda_{max.}$ 302 mμ, $\nu_{max.}$ (CH_2Cl_2) 1707 cm.$^{-1}$.

Compound	Cotton curve in dioxan, sign and molar amplitude, 10^{-2} -	Molar dispersion contribution of substituent, Δ*a*	Position of 1st trough (or peak), λ* (mμ)	Δλ* (mμ)	Halogen configuration
(I)	+1		338		
(II)	−113 (−110 †)	−112 (2β)	342 (334 †)	+4	*ax.*
(III)	+5	+4 (2α)	294	−44	*eq.*
(V)	−93	−98 (2β), +10 (2α)	340	+2	*ax., eq.*

† Shoulder. Δλ* represents the difference (mμ) between the first trough (peak) of the derivative and the parent ketone.

TABLE 2

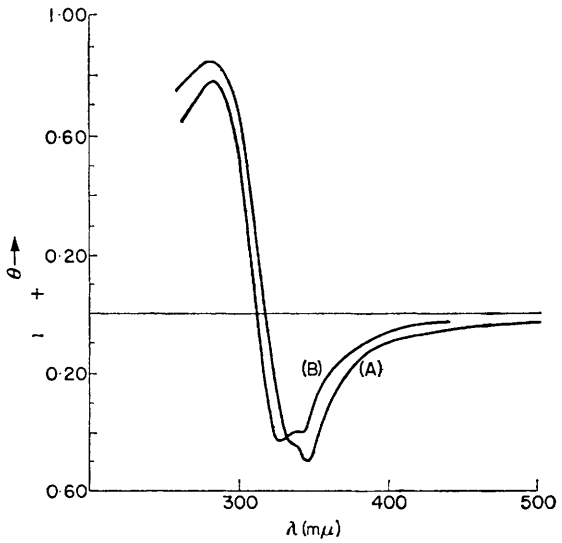
Nuclear magnetic resonance data on halogeno-derivatives of 5α-cholestan-1-one

Compound	Chemical shift (τ) Me-19	1-H	2-H	3-H	Proton config(s)
(I) 5α-Cholestan-1-one	8·93				
(II) 2β-Chloro-1-one	8·72		5·52,* $J_{2\alpha,3\alpha} + J_{2\alpha,3\beta} = 5·4$ c./sec.		2α-*eq.*
(III) 2α-Chloro-1-one	8·85		5·04,† $J_{2\beta,3\alpha} + J_{2\beta,3\beta} = 18·2$ c./sec.		2β-*ax.*
2α-Bromo-1-one	8·83		4·94,‡ $J_{2\beta,3\alpha} + J_{2\beta,3\beta} = 18$ c./sec.		2β-*ax.*
(V) 2,2-Dichloro-1-one	8·65				
(VI) 2-Chloro-2-en-1-one	8·95			3·29,* $J_{3,4\alpha} + J_{3,4\beta} = 4$ c./sec.	
(VIII) 1α-Hydroxy-2β-chloro-5α-cholestane §	8·92	4·25,† $W_H = 5$ c./sec.	3·88,† $W_H = 7$ c./sec.		1β-*eq.*, 2α-*eq.*

* Triplet. † Multiplet. ‡ Doublet of doublets. § Singlet at τ 8·52, exchangeable with D_2O, for 1α-OH.

equatorial α-bromine atom increases the stretching frequency of a carbonyl group, and a similar effect would be expected for a boat-equatorial α-chlorine atom.

The signs of the Cotton curves confirm the configurations assigned to the three chloro-ketones (II), (III), and (V), on the assumption that in dioxan solution ring A has the chair conformation (only slightly deformed by the trigonal 1-carbon atom); an axial 2β-chlorine atom makes the predicted negative contribution [13] to the molecular dispersion, whereas an equatorial 2α-chlorine atom makes an effectively zero contribution. The Cotton curve for the 2β-chloro-ketone (II) in the polar solvent acetonitrile is similar to that in dioxan, but the shoulder (324 mμ) observed on the trough (342 mμ) in dioxan is reversed in acetonitrile and now occurs at 340 mμ on the trough (327 mμ). Since conformational change, (II) ⟶ (IIa) or (II) ⟶ (IIb), should be dependent on the polarity of the solvent [14] with a polar solvent favouring the equatorial conformer (IIa) or (IIb), this observation lends some support to the suggested presence in solution of these boat conformations (Figure).



2β-Chloro-5α-cholestan-1-one (II): Cotton curves (A) in dioxan, (B) in acetonitrile, at 28°

[13] W. Moffitt, A. Moscowitz, R. B. Woodward, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, 1961, **83**, 4013.
[14] J. Allinger and N. L. Allinger, *Tetrahedron*, 1958, **2**, 64.

Whilst the signs and amplitudes of the Cotton curves in dioxan are normal, the positions of the extrema are anomalous as shown by the values of $\Delta\lambda$*; the curves are all displaced towards the region of shorter wavelength. The Cotton curve for the 2α-chloro-ketone (III) closely resembles that of 5α-chlolestan-1-one [15] (I) in form but the first peak suffers an unexplained hypsochromic displacement of some 40 mμ.

A selection of n.m.r. spectral signals for halogeno-derivatives of 5α-cholestan-1-one is given in Table 2. It has been shown [11] that the n.m.r. signals of α-protons in α-halogeno-cyclohexanones permit assignment of configuration to the α-proton; it will be seen that the proton configurations assigned on the basis of the magnitude of coupling constants or of width at half-height confirm those assigned above for the α-halogen atoms.

We confirm the finding of Djerassi *et al.*[3] that 5α-cholestan-1-one does not yield an enol acetate.

EXPERIMENTAL

For general experimental directions see reference 16. M. p.s were determined on a Kofler block and are corrected. The $[\alpha]_D$ values refer to chloroform solutions at room temperature. U.v. (in dioxan) and i.r. absorption spectra (in carbon disulphide) were measured with Perkin-Elmer 4000 A and 221 spectrophotometers. O.r.d. curves were measured in dioxan at 22°, using a Jasco model ORD/UV-5 recorder. N.m.r. spectra were measured on a Varian A 60 instrument with deuteriochloroform as solvent and tetramethylsilane as internal reference. Chromatography was on silica gel (Davison) or aluminium oxide (Spence type H, activity II). T.l.c. was on silica gel in hexane, unless otherwise indicated, and plates were sprayed with concentrated sulphuric acid and developed at 110°; for preparative t.l.c. plates were sprayed with a methanolic solution of berberine hydrochloride and examined in u.v. light. G.l.c. was performed in an F and M 400 instrument using a 1·1 m. × 3 mm. column of 3·8% SE 30 on Diatoport S (80—100 mesh), and a helium flow rate of 75 ml./min. Retention time for 5α-cholestane, 6 min. Specimens for analysis were dried at 20°/0·2 mm. for at least 8 hr.

5α-Cholestan-1-one.— 5α-Cholest-2-en-1-one,[8,10] m. p. 62—63°, by hydrogenation with platinum–acetic acid gave a mixture of the required ketone and 5α-cholestan-1β-ol (~2 : 1), which was separated by chromatography on silica in hexane and elution with benzene–hexane (1 : 9). Oxidation of the 1β-ol, m. p. 100°, with sodium dichromate dihydrate in benzene–acetic acid, gave more 5α-cholestan-1-one, m. p. 86°.

Monochlorination of 5α-Cholestan-1-one.—(*a*) The ketone (386 mg.) in acetic acid (50 ml.), containing a few drops of a 50% solution of hydrochloric acid in acetic acid, was treated with a solution of chlorine (78 mg., 1·1 mol.) in chloroform at 20° for 24 hr. T.l.c. showed four spots, later identified as (I), (II), (III), and (V). The product (400 mg.), isolated in the usual way, was chromatographed on silica (40 g.) in hexane. Elution with benzene–hexane (1 : 99 to 1 : 19) yielded successively 2,2-*dichloro-5α-cholestan-1-one* (V) (23 mg.), m. p. 163—166° (from acetone–methanol), $\lambda_{max.}$ 307 mμ, $\nu_{max.}$ 1732 cm.$^{-1}$, o.r.d. in dioxan: ϕ − 3840° (trough, 340 mμ), +8414° (peak, 285 mμ) (Found: C, 71·05; H, 9·9. $C_{27}H_{44}Cl_2O$ requires C, 71·2; H, 9·7%), and 2β-*chloro-5α-cholestan-1-one* (II) (48 mg.), m. p. 118—119° (from acetone–methanol), $\lambda_{max.}$ 301 mμ, $\nu_{max.}$ (in Nujol) 1709 cm.$^{-1}$, (in CS_2) 1709 and 1731 cm.$^{-1}$, o.r.d. in dioxan: ϕ − 4087° (trough, 343 mμ), −3797° (shoulder, 337 mμ), +7182° (peak, 282 mμ) [another determination gave ϕ − 4790° (trough, 342 mμ), −4435° (shoulder, 334 mμ), +7628° (peak, 280 mμ)], o.r.d. in acetonitrile: ϕ − 4402° (shoulder, 340 mμ), −4647° (trough, 327 mμ), +7142° (peak, 286 mμ (Found: C, 77·4; H, 11·0. $C_{27}H_{45}ClO$ requires C, 77·0; H, 10·8%). Further elution gave a mixture of 2α-chloro-5α-cholestan-1-one and unchanged ketone, which by preparative t.l.c. on silica in benzene furnished 2α-*chloro-5α-cholestan-1-one* (III) (180 mg.), m. p. 130—131° (from acetone–methanol), $\lambda_{max.}$ 289 mμ, $\nu_{max.}$ 1732 cm.$^{-1}$, o.r.d. in dioxan: ϕ + 3442° (peak, 294 mμ), −2895° (trough, 271 mμ) (Found: C, 76·95; H, 10·8%). and 5α-cholestan-1-one (120 mg.), m. p. and mixed m. p. 85—86° (from acetone–methanol).

(*b*) To the ketone (100 mg.), in carbon tetrachloride–acetic acid (1 : 4; 5 ml.), was added dropwise chlorine (20 mg., 1·1 mol.) and anhydrous sodium acetate (23 mg., 1·1 mol.) in the same solvent (5 ml.) during 15 min. at 20°. After 2 hr. t.l.c. showed only unchanged ketone; after 24 hr., the product, isolated in the usual way and subjected to g.l.c. at 242° on an SE 30 column, was shown to consist of unchanged ketone (retention time, 9·5 min.) and ~0·1% 2β-chloro-5α-cholestan-1-one (II) (retention time, 16 min.); crystallisation from acetone–methanol gave 5α-cholestan-1-one, m. p. and mixed m. p. 85—86°.

Interconversion of the Epimeric 2-Chloro-ketones (II) *and* (III).—(*a*) The 2β-chloro-ketone (II) (20 mg.) in acetic acid (5 ml.) was treated with a few drops of a 50% solution of 10N-hydrochloric acid in acetic acid, and kept at 20° for 24 hr. The product was found by t.l.c. to be a mixture of the 2β-chloro-ketone (II) and the 2α-chloro-ketone (III) in the ratio of ~1 : 1; g.l.c. disclosed the presence of the 2β-chloro-ketone (II) (51%; retention time at 242°, 16 min.) and the 2α-chloro-ketone (III) (49%; retention time at 242°, 19·5 min.). The epimers were separated by preparative t.l.c. on silica in benzene, and identified by mixed m. p.

(*b*) The 2β-chloro-ketone (II) (20 mg.) in acetic acid (5 ml.) was treated with a few drops of 70% perchloric acid at 20° for 2 hr. T.l.c. showed only one spot corresponding to the starting material; isolation of the product in the usual manner gave the 2β-chloro-ketone, m. p. and mixed m. p. 116—118° (from acetone–methanol).

(*c*) The 2β-chloro-ketone (II) (20 mg.) in acetic acid (5 ml.) was heated with a few drops of 70% perchloric acid at 95—96° for 1·5 hr. T.l.c. of the crude product revealed >50% inversion to the 2α-chloro-ketone (III).

(*d*) The 2α-chloro-ketone (III) (20 mg.) in acetic acid–chloroform (3 : 1; 10 ml.) was heated with a few drops of 70% perchloric acid at 90—92° for 1 hr. The product was shown by t.l.c. to be starting material, and crystallisation from acetone–methanol gave the 2α-chloro-ketone, m. p. and mixed m. p. 129—131°.

Partial Synthesis of 2β-Chloro-5α-cholestan-1-one (II).—5α-Cholest-1-ene [8] (100 mg.) in chloroform (2 ml.) at 0° was treated with *m*-chloroperbenzoic acid (150 mg.) in chloroform (2 ml.). After 24 hr. at 0°, the product was isolated in the usual way and chromatographed on silica (10 g.) in

[15] C. Djerassi, W. Closson, and A. E. Lippman, *J. Amer. Chem. Soc.*, 1956, **78**, 3163.
[16] C. W. Shoppee and J. C. P. Sly, *J. Chem. Soc.*, 1959, 345.

hexane. Elution with ether–hexane (1 : 49) gave 1α,2α-epoxy-5α-cholestane (VII) (52 mg.), m. p. 83—85° (from methanol); recrystallisation from acetone raised the m. p. to 86—88° (lit.,[8] m. p. 86—88°).

The 1α,2α-epoxide (VII) (31 mg.) in chloroform (1 ml.) was shaken with 5N-hydrochloric acid (0·5 ml.) at 20° for 8 min. Dilution with water and extraction with ether furnished an oil (30 mg.), which crystallised from ether–methanol to give 1α-*hydroxy*-2β-*chloro*-5α-*cholestane* (VIII), m. p. 106—108° (Found: C, 77·0; H, 11·1. $C_{27}H_{47}ClO$ requires C, 76·65; H, 11·2%).

The chlorohydrin (VIII) (16 mg.) in acetic acid (7 ml.) was oxidised with sodium dichromate dihydrate (482 mg.) in 10% acetic acid at 15° (cf. reference 9) during 14 hr. The usual isolation procedure gave a crystalline solid, shown by g.l.c. at 240° to consist of 2β-chloro-5α-cholestan-1-one (II) (85%; retention time, 17·5 min.) and 2α-chloro-5α-cholestan-1-one (III) (15%; retention time, 21·5 min.).

2α- *and* 2β-*Hydroxy*-5α-*cholestan*-1-*one* (*as* IV).—The 2α-chloro-ketone (III) (100 mg.) in ethanol (7·5 ml.) was refluxed under nitrogen with 2N-potassium hydroxide (1·2 ml.) for 2·5 hr. The product, isolated in the usual way, was an oil (95 mg.), which showed four spots by t.l.c. on silica in benzene. Column chromatography on silica (10 g.) in benzene and elution with benzene gave two fractions (11, 12 mg., unidentified), then 2α-hydroxy-5α-cholestan-1-one (IVα) (36 mg.), m. p. 105—107° (from ether–methanol), $\lambda_{max.}$ 277 mμ, $\nu_{max.}$ 3467 and 1706 cm.$^{-1}$ (lit.,[4] m. p. 104—106°), followed by 2β-hydroxy-5α-cholestan-1-one (IVβ) (20 mg.), m. p. 140—142°, $\lambda_{max.}$ 300 mμ, $\nu_{max.}$ 3595 and 1717 cm.$^{-1}$ (lit.,[4] m. p. 139—142°).

5α-*Cholest*-2-*en*-1-*one* (VI; R = H).—(*a*) The 2β-chloro-ketone (II) (20 mg.) was refluxed with lithium iodide (40 mg.) and lithium carbonate (50 mg.) in dimethylformamide (1 ml.) under nitrogen for 12 min. The isolated reaction product (14 mg.) was homogeneous by t.l.c. on silica in benzene and by g.l.c. at 245° (retention time, 8·5 min.); passage of an ether–hexane solution through a short column of alumina gave 5α-cholest-2-en-1-one, m. p. 61—62° (from methanol), $\lambda_{max.}$ (EtOH) 224 mμ (log ε 3·65), $\nu_{max.}$ 1684 cm.$^{-1}$ [lit.,[10] double m. p. 58 and 69°, $\lambda_{max.}$ (EtOH) 222 mμ (log ε 3·90), $\nu_{max.}$ 1692 cm.$^{-1}$; [8] m. p. 56—57°, $\lambda_{max.}$ (EtOH) 224 mμ (log ε 3·9)].

(*b*) The 2α-chloro-ketone (III) (42 mg.) was dehydrochlorinated with lithium iodide (80 mg.) and lithium carbonate (100 mg.) in dimethylformamide (1 ml.) under nitrogen for 20 min. The product was homogeneous by t.l.c., and, purified as under (*a*), yielded 5α-cholest-2-en-1-one (27 mg.), m. p. and mixed m. p. 61—62° (from methanol).

(*c*) The 2α-chloro-ketone (III) (55 mg.) was refluxed with *s*-collidine (1 ml.) under nitrogen for 4 hr. The product, isolated in the usual way, showed two spots on t.l.c. corresponding to the starting material and the unsaturated ketone (VI; R = H); preparative t.l.c. on silica in benzene afforded the 2α-chloro-ketone (III) (32 mg.), m. p. and mixed m. p. 128—130° (from acetone–methanol), and 5α-cholest-2-en-1-one (12 mg.), m. p. and mixed m. p. 59—61° (from methanol).

Dichlorination of 5α-*Cholestan*-1-*one*.—The ketone (250 mg.) in acetic acid (25 ml.), containing two drops of a 50% solution of 10N-hydrochloric acid in acetic acid, was treated with chlorine (98 mg., 2·1 mol.) in chloroform–acetic acid (1 : 3) at 20° for 4 days. The product, isolated in the usual way, contained by t.l.c. only two compounds, which were separated by preparative t.l.c. on silica in benzene and identified as the 2α-chloro-ketone (III) (115 mg.), m. p. and mixed m. p. 129—130° (from acetone–methanol), and the 2,2-dichloro-ketone (V) (145 mg.), m. p. and mixed m. p. 163—166° (from acetone–methanol).

Monochlorination of 2β-*Chloro*-5α-*cholestan*-1-*one* (II).—The 2β-chloro-ketone (42 mg.) in acetic acid–chloroform (3 : 1; 10 ml.) was treated with chlorine (8 mg., 1·1 mol.) in chloroform–acetic acid (1 : 3; 2 ml.) at 20°. After 12 hr., t.l.c. disclosed ~66% conversion to the 2,2-dichloro-ketone (V); after 30 hr. this was the sole reaction product. Isolated in the usual way, 2,2-dichloro-5α-cholestan-1-one (V) (43 mg.) had m. p. and mixed m. p. 164—166° (from acetone–methanol).

Monochlorination of 2α-*Chloro*-5α-*cholestan*-1-*one* (III).—(*a*) The 2α-chloro-ketone (100 mg.) in acetic acid (15 ml.), containing a few drops of a 50% solution of 2N-hydrochloric acid in acetic acid, was treated with chlorine (20 mg., 1·2 mol.) in chloroform–acetic acid (1 : 3; 5 ml.) at 20° for 4 days. The product, isolated in the usual way, gave, by column chromatography on silica (15 g.) in hexane and elution with ether–hexane (1 : 250), 2,2-dichloro-5α-cholestan-1-one (V) (13 mg.), m. p. and mixed m. p. 163—165° (from acetone–methanol). Further elution with ether–hexane mixtures afforded unchanged 2α-chloro-ketone (78 mg.), m. p. and mixed m. p. 130—131° (from acetone–methanol).

(*b*) The 2α-chloro-ketone (65 mg.), in acetic acid (8 ml.) containing anhydrous sodium acetate (320 mg.), and chlorine (14 mg., 1·25 mol.) in acetic acid were heated in a sealed tube at 95—100° for 45 min. The product, isolated in the usual manner, was separated by preparative t.l.c. on silica in benzene into 2,2-dichloro-5α-cholestan-1-one (V) (2 mg.) and unchanged 2α-chloro-ketone (56 mg.), which was identified by m. p. and mixed m. p.

2-*Chloro*-5α-*Cholest*-2-*en*-1-*one* (VI; R = Cl).—The 2,2-dichloro-ketone (V) (75 mg.) was refluxed with lithium iodide (150 mg.) and lithium carbonate (175 mg.) in dimethylformamide (2 ml.) under nitrogen for 15 min. The product (69 mg.), isolated in the usual way, was chromatographed on silica (6 g.) in hexane. Elution with benzene gave the crude unsaturated chloro-ketone (48 mg.), which was purified by preparative t.l.c. on silica in benzene to give 2-*chloro*-5α-*cholest*-2-*en*-1-*one* (VI; R = Cl), m. p. 128—130°, $\lambda_{max.}$ 243 mμ (log ε 3·85), $\nu_{max.}$ 1702 cm.$^{-1}$; o.r.d. in dioxan: ϕ + 1318° (peak, 394 mμ), +1236° (trough, 384 mμ), +1404° (peak, 375 mμ), +1236° (trough, 226 mμ), and +2864° (peak, 330 mμ), +2752° (trough, 298 mμ, curve incomplete); g.l.c. retention time at 245°; 16 min. (Found: C, 77·2; H, 10·2. $C_{27}H_{43}ClO$ requires C, 77·4; H, 10·35%). Further elution with benzene gave a mixture (12 mg.) of (VI; R = Cl) and an unidentified compound (retention time at 245°, 8·25 min.) in the ratio of 3 : 2 as estimated by g.l.c.

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