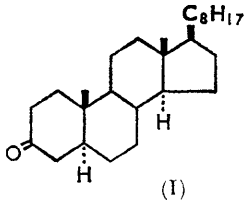
959. *Steroids. Part XXIII.* The Polyhalogenation of 5α-Cholestan-3-one.*

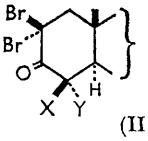
By C. W. Shoppee, P. J. Havlicek, and Ruth E. Lack.

The compound previously described as 2,2,4ξ,5ξ-tetrabromocholestan-3-one is shown to be 2,2,4,4-tetrabromo-5α-cholestan-3-one. Various 2,2,4α-trihalogeno-5α-cholestan-3-ones have been prepared. The conformation of ring A in these polyhalogeno-ketones is discussed in the light of their spectroscopic properties.

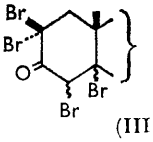
In Part XV [1] we reported an investigation of the reputed tribromination [2] of 5α-cholestan-3-one (I); we found that base-catalysed monobromination of 2,2-dibromo-5α-cholestan-3-one (II; X = Y = H) gives a mixture of unchanged starting material and a tetrabromo-ketone, regarded as 2,2,4ξ,5ξ-tetrabromocholestan-3-one (III). The nuclear magnetic resonance (n.m.r.) spectrum of the tetrabromo-ketone now shows that there is no proton attached to C-4, and that the true structure is 2,2,4,4-tetrabromo-5α-cholestan-3-one (II; X = Y = Br).



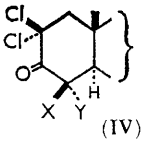
(I)



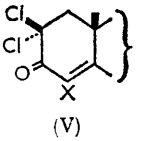
(II)



(III)



(IV)



(V)

The acid-catalysed decomposition [1] of the tetrabromo-ketone (II; X = Y = Br) to hydrogen bromide and 2,2,4-tribromocholest-4-en-3-one may occur by protonation of the carbonyl group to give a 3α,5-cyclo-5α-cholestan-3β-ol, which undergoes pinacolic rearrangement with loss of the 4β-bromine atom.[3] The subsequent hydrogen bromide-catalysed

* Part XXII, *J.*, 1964, 3619.

[1] Shoppee, Lack, and Scott, *J.*, 1962, 2233.
[2] Crowne, Evans, Green, and Long, *J.*, 1956, 4351.
[3] Birch, Graves, and Siddall, *J.*, 1963, 4234; cf. Parham, Soeder, and Dodson, *J. Amer. Chem. Soc.*, 1962, **84**, 1755.

debromination in acetone [4] of 2,2,4-tribromocholest-4-en-3-one was stated [1] to give 2,2-dibromocholest-4-en-3-one. The n.m.r. spectrum of this product reveals the absence of a vinyl proton at C-4 and the presence of an axial proton of C-2, attached to the same carbon as one bromine atom and coupled to the equatorial and axial protons at C-1, giving a signal at τ 5·08 (J = 5·5, 13·5 c./sec.). The supposed 2,2-dibromocholest-4-en-3-one is thus 2α,4-dibromocholest-4-en-3-one and is also obtained from 2α-bromocholest-4-en-3-one by monobromination in dimethylformamide–ether at 0° for 24 hr.[1]

We have now obtained 2,2,4α-tribromo-5α-cholestan-3-one (II; X = H, Y = Br) from the 2,2-dibromo-ketone (II; X = Y = H) by monobromination in acetic acid–chloroform at 25° for 3 days. The 2,2,4α-tribromo-ketone, m. p. 118°, shows an increased carbonyl stretching frequency in the infrared spectrum, corresponding to the presence of two equatorial bromine atoms. The signal for the axial 4β-proton is split by interaction with the single axial 5α-proton, and appears in the n.m.r. spectrum as a doublet (J = 12·5 c./sec.).

Ellis and Petrow,[5] by bromination of 2,2-dichloro-5α-cholestan-3-one (IV; X = Y = H) in acetic acid–chloroform at 20° for 3 days, prepared a compound, which they regarded as 4-bromo-2,2-dichloro-5α-cholestan-3-one (IV; X = Br, Y = H). Kirk and Petrow,[6] by chlorination of compound (IV; X = Y = H) later obtained a trichloro-ketone, to which they assigned the structure 2,2,4β-trichloro-5α-cholestan-3-one (IV; X = Cl, Y = H) by analogy with the preferred formulation by Crowne *et al.*[2] of the reputed 2,2,4β-tribromo-5α-cholestan-3-one.

As in the case of the reputed 2,2,4β-tribromo-ketone, the structures (IV; X = Br, Cl; Y = H) appeared improbable to us on account of the powerful repulsions of the axial 4β-halogen atom, the axial 2β-chlorine atom, and the axial 10β-methyl group in the chair conformation; we have therefore reinvestigated the chlorination and bromination of 2,2-dichloro-5α-cholestan-3-one (IV; X = Y = H). Acid-catalysed monochlorination [6] gives 2,2,4α-trichloro-5α-cholestan-3-one (IV; X = H, Y = Cl). This exhibits spectral properties indicating two equatorial chlorine atoms and one axial chlorine atom, whilst the n.m.r. spectrum discloses the presence of the axial 4β-proton, the signal for which, on account of splitting by the single axial 5α-proton, appears as a doublet (J = 12·5 c./sec.). Similarly, acid-catalysed monobromination of 2,2-dichloro-5α-cholestan-3-one,[5] gives 4α-bromo-2,2-dichloro-5α-cholestan-3-one (IV; X = H, Y = Br), with spectral characteristics indicating two equatorial halogen atoms and one axial chlorine atom and whose n.m.r. spectrum again discloses the presence of the axial 4β-proton, which appears as a doublet (J = 12·5 c./sec.). Dehydrobromination with *s*-collidine at 80° under nitrogen gives 2,2-dichlorocholest-4-en-3-one (V; X = H), $\lambda_{max.}$ 255 mμ (log ε 3·68), $\nu_{max.}$ 1718 cm.$^{-1}$. The bromination product also contains, in addition to (IV; X = H, Y = Br), 4-bromo-2,2-dichlorocholest-4-en-3-one (V; X = Br), $\lambda_{max.}$ 268 mμ (log ε 4·4), $\nu_{max.}$ 1715 cm.$^{-1}$, and 4-bromo-2-chlorocholesta-1,4-dien-3-one, possibly containing some of its rearrangement product, 4-bromo-2α-chlorocholesta-4,6-dien-3-one.

Base-catalysed dibromination of 2,2-dichloro-5α-cholestan-3-one (IV; X = Y = H) at 80° furnished 4,4-dibromo-2,2-dichloro-5α-cholestan-3-one (IV; X = Y = Br) with spectral properties indicating two axial and two equatorial halogen atoms; the n.m.r. spectrum shows that there are no protons on the carbon atoms bearing the halogen atoms. By treatment with hydrogen bromide in acetic acid at 25°, the tetrahalogeno-ketone (IV; X = Y = Br) undergoes dehydrobromination to yield the Δ^4-3-ketone (V; X = Br).

The optical properties of the various polyhalogeno-5α-cholestan-3-ones are collected in the Table. Attention has previously been directed [7] to the anomalous ultraviolet spectral shifts, Δλ, given by the *gem*-dihalogeno-ketones (II, IV; X = Y = H); this anomaly does

[4] Green and Long, *J.*, 1961, 2532.
[5] Ellis and Petrow, *J.*, 1953, 3859.
[6] Kirk and Petrow, *J.*, 1958, 1334.
[7] Cookson, *J.*, 1954, 282.

not apply to 3,3-dibromo-5α-cholestan-2-[8] and -4-one,[9] in which the axial halogen atoms are α-orientated and so not subject to serious steric repulsions in the chair conformation. The 2,2,4α-trihalogeno-ketones also show anomalous shifts in the ultraviolet region; the

Optical properties of halogeno-5α-cholestan-3-ones.

Compound	$\lambda_{infl.}$ [a] (mμ)	log ε	Δλ [b] (mμ)	$\nu_{max.}$ [c] (cm.$^{-1}$)	Δν [b] (cm.$^{-1}$)	Cotton effect sign and molar amplitude 10^{-2} [a]	Posn. of 1st trough (or peak) λ (mμ)	Δλ [d] (mμ)
(I)	286	1·35	—	1714	—	+54*	307·5*	—
(II; X = Y = H) [e]	294	2·1	+8	1735	+21	+186 [f]	330	40
(II; X = H, Y = Br) ...	284	1·61	−2	1751	+37	+110 [g]	323	>27
(II; X = Y = Br)	328	2·1	+42	1746	+32	negative curve [g]	320	—
(IV; X = Y = H) [h]	294	2·05	+8	1744	+30	+146 [f]	325 [f]	50
(IV; X = H, Y = Cl) ...	292	1·86	+6	1753	+39	+134	314	52
(IV; X = H, Y = Br)...	284	2·2	−2	1758	+44	+125 [g]	320	>50
(IV; X = Y = Br)	324	2·25	+38	1753	+39	negative curve [g]	350	—

[a] In cyclohexane. [b] Relative to compound (I). [c] In carbon tetrachloride. [d] Separation of first and second extrema. [e] Warnhoff (*J. Org. Chem.*, 1963, **28**, 887) gives $\lambda_{max.}$ (EtOH–$CHCl_3$; 4 : 1) 300 mμ, $\nu_{max.}$ (CS_2) 1737 cm.$^{-1}$. [f] Djerassi, Osiecki, Riniker, and Riniker, *J. Amer. Chem. Soc.*, 1958, **80**, 1216. [g] Incomplete. [h] Warnhoff (*loc. cit.*) gives $\lambda_{max.}$ (EtOH) 295 mμ, $\nu_{max.}$ (CS_2) 1745 cm.$^{-1}$.

* Revised value: Djerassi and Klyne, *J.*, 1963, 2390.

positive Cotton effect curves are consistent with the existence of ring A in the chair conformation (probably somewhat distorted by 2β-halogen–10β-methyl repulsions). The negative Cotton effect curves given by the tetrahalogeno-ketones do not furnish information about the geometry of ring A because some of the substituents may enter the front octants.[10]

Experimental

The general experimental directions were as described earlier.[11] M. p.s were determined on a Kofler hot-stage apparatus and are corrected. Ultraviolet spectra were determined for cyclohexane solutions, unless otherwise stated, on a Perkin-Elmer 4000A spectrophotometer. Infrared spectra were measured for CCl_4 solutions by use of a Perkin-Elmer 221 spectrophotometer. Chromatography was on silica gel (Davison 40—200 mesh).

2,2,4α-*Trichloro*-5α-*cholestan*-3-*one* (IV; X = H, Y = Cl).—This compound, described by Kirk and Petrow [6] as the 2,2,4β-isomer, was prepared as described by these authors and had m. p. 115—117° (lit.,[6] 116—117°), $\nu_{max.}$ 1753 cm.$^{-1}$, after elution from silica gel with hexane containing 0·6% ether, and recrystallisation from hexane.

2,2,4α-*Tribromo*-5α-*cholestan*-3-*one* (II; X = H, Y = Br).—2,2-Dibromo-5α-cholestan-3-one [2] (250 mg.), in chloroform (2 ml.) and acetic acid (2 ml.), was treated with bromine in acetic acid (2·5 ml. of a 1% v/v solution, 1·1 mol.) at 25° for 3 days. The mixture was diluted with water and the product extracted with ether and chromatographed on silica gel (30 g.). Elution with hexane containing 0·6% ether gave the *tribromo-compound* (160 mg.), m. p. 116—118° (from ether–hexane) (Found: C, 52·05; H, 7·05. $C_{27}H_{43}Br_3O$ requires C, 52·1; H, 6·95%).

4α-*Bromo*-2,2-*dichloro*-5α-*cholestan*-3-*one* (IV; X = H, Y = Br).—Bromination of 2,2-dichloro-5α-cholestan-3-one (1·16 g.) as described by Ellis and Petrow [5] and chromatography of the product on silica gel (120 g.) in hexane gave (i) the 4α-bromo-2,2-dichloro-ketone (630 mg.), m. p. 108—110, eluted with hexane–0·6% ether, described by Ellis and Petrow [5] as the 4-bromo-2,2-dichloro-compound and by Kirk and Petrow [6] as the 4β-bromo-2,2-dichloro-isomer (lit.,[5] m. p. 109—110°, $[\alpha]_D$ +61·5°) (Found: C, 60·5; H, 8·25. Calc. for $C_{27}H_{43}BrCl_2O$: C, 60·7; H, 8·1%), (ii) starting material (100 mg.), m. p. 150—154°, eluted with the same solvent, (iii) 4-bromo-2,2-dichlorocholest-4-en-3-one (V; X = Br) (240 mg.), m. p. 171—173° (from methanol), $\lambda_{max.}$ 268 mμ (log ε 4·39), $\nu_{max.}$ 1715 cm.$^{-1}$ (Found: C, 60·7; H, 7·4. $C_{27}H_{41}BrCl_2O$

[8] Shoppee and Bellas, *J.*, 1963, 3366.
[9] Shoppee and Lack, *J.*, 1961, 3271.
[10] Djerassi and Klyne, *J.*, 1963, 2390, esp. 2393.
[11] Shoppee and Sly, *J.*, 1959, 345.

requires C, 60·9; H, 7·75%) eluted with hexane—1·1% ether, and (iv) a mixture, inseparable by crystallisation, of 4-bromo-2-chlorocholesta-1,4-dien-3-one and 4-bromo-2α-chlorocholesta-4,6-dien-3-one, m. p. 179—182° (from acetone–methanol), $\lambda_{max.}$ 256, 296 mμ, $\nu_{max.}$ 1710, 1680 cm.$^{-1}$ (Found: C, 65·7; H, 8·3. Calc. for $C_{27}H_{40}BrClO$: C, 65·4; H, 8·3%) eluted with hexane–1·2% ether.

Dehydrohalogenation of 4α-*Bromo*-2,2-*dichloro*-5α-*cholestan*-3-*one*.—(*a*) The bromodichloro-ketone (315 mg.) was refluxed with a solution of potassium iodide (1 g.) in methyl ethyl ketone (15 ml.) under nitrogen for 7 hr. The cooled mixture was shaken with sodium thiosulphate solution, the product (285 mg.) extracted with ether, and chromatographed on silica gel (30 g.) in hexane. Elution with hexane–0·6% ether gave starting material (80 mg.), m. p. and mixed m. p., 108—110° (from methanol). Elution with hexane–4% ether furnished 2α-chloro-5α-cholestan-3-one (30 mg.), m. p. and mixed m. p., 184—189° (from acetone–methanol), $\nu_{max.}$ 1738 cm.$^{-1}$, and 2α-chlorocholest-4-en-3-one (130 mg.), m. p. 98—100° (lit.,[5] 97—98°, $[\alpha]_D$ +87°), $\lambda_{max.}$ 235 mμ (log ε 3·31), $\nu_{max.}$ 1692 cm.$^{-1}$ (Found: C, 77·5; H, 10·4. Calc. for $C_{27}H_{43}ClO$: C, 77·4; H, 10·35%).

(*b*) The bromodichloro-ketone (100 mg.) was heated with *s*-collidine (2 ml.; B.D.H.) at 80° for 1 hr. under nitrogen. The product, isolated in the usual way, was chromatographed on silica gel (10 g.) in hexane. Elution with hexane–1·3% ether gave a product regarded as 2,2-dichlorocholest-4-en-3-one (V; X = H) (25 mg.), m. p. 173—176°, $\lambda_{max.}$ 256 mμ, log ε 3·99, $\nu_{max.}$ 1718 cm.$^{-1}$, for which a satisfactory analysis could not be obtained (Found: C, 69·5; H, 9·35%).

4,4-*Dibromo*-2,2-*dichloro*-5α-*cholestan*-3-*one* (IV; X = Y = Br).—2,2-Dichloro-5α-cholestan-3-one (400 mg.) was dissolved in acetic acid (20 ml.) and heated to 80°; anhydrous potassium acetate (1·4 g.) dissolved in acetic acid at 80° was added, followed immediately by a solution of bromine in acetic acid (8·8 ml. of a 1% v/v solution, 2·0 mol.). Heating at 80° was continued until the colour was discharged (1 hr.). The mixture was cooled rapidly and poured on to ice. The product was filtered off, dried briefly in a vacuum desiccator, and chromatographed on silica gel (50 g.) in hexane. Elution with hexane gave the *tetrahalogeno-compound*, m. p. 94—96° (from hexane) (Found: C, 53·0; H, 7·4. $C_{27}H_{42}Br_2Cl_2O$ requires C, 54·45; H, 6·75%).

Dehydrobromination of 4,4-*Dibromo*-2,2-*dichloro*-5α-*cholestan*-3-*one*.—The dibromodichloro-ketone (200 mg.) was dissolved in acetic acid (25 ml.) containing hydrogen bromide, set aside overnight at 20°, and poured into ice–water. The product was filtered off, dried, and chromatographed on silica gel (25 g.). Elution with hexane–1·2% ether gave 4-bromo-2,2-dichlorocholest-4-en-3-one, m. p. and mixed m. p. 173—175° (from acetone–methanol).

Optical Rotatory Dispersions (*in Methanol*).—2,2,4α-Tribromo-5α-cholestan-3-one (II; X = H, Y = Br): $[\phi]$ +8900° (323 mμ, peak), −2100° (295 mμ, lowest wavelength measured); 2,2,4α-trichloro-5α-cholestan-3-one (IV; X = H, Y = Cl); $[\phi]$ +6400° (314 mμ, peak) −7030° (262 mμ, trough); 4α-bromo-2,2-dichloro-5α-cholestan-3-one (IV; X = H, Y = Br): $[\phi]$ +5790° (320 mμ peak), −6530°, (270 mμ, lowest wavelength measured).

One of us (P. J. H.) acknowledges support during 1963 from the Monsanto Research Grant to the Department of Organic Chemistry. We thank Professors G. Badger, W. Klyne, and C. Djerassi for the optical rotatory dispersion curves for compounds (II; X = H, Y = Br), (IV; X = H, Y = Cl), and (IV; X = H, Y = Br), respectively. We are grateful to a Referee for directing our attention to work described in refs. 3 and 4.

Department of Organic Chemistry,
The University of Sydney, Australia. [*Received, February 20th*, 1964.]