560. *Steroids and Walden Inversion. Part XLIII.* The Bromination of* 3 : 5-cyclo*Steroids.*

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The reactions of 3 : 5-*cyclo*cholestane and the related 6-oxo-, 6-hydroxy-, and Δ^6-derivatives with bromine have been examined. The mechanism of the transformation of the epimeric 3 : 5-*cyclo*cholestan-6-ols into epimeric 3β : 5α : 6-tribromo-5α-cholestanes is discussed.

3 : 5-*cyclo*STEROIDS are unaffected by treatment with ozone [1] or perbenzoic acid [1,2] but readily react with hydrogen chloride, bromide, iodide,[1] or fluoride,[3] and with bromine.[1] The reactions of the epimeric 3 : 5-*cyclo*cholestan-6-ols with bromine have been used to assign configuration at $C_{(6)}$ in these alcohols and analogous compounds by Wagner, Wolff, and Wallis,[4] who thereby arrived at configurations opposite to those predicted by Dodson and Riegel,[5] assigned by Shoppee and Summers,[6] confirmed by Winstein and Kosower,[7]

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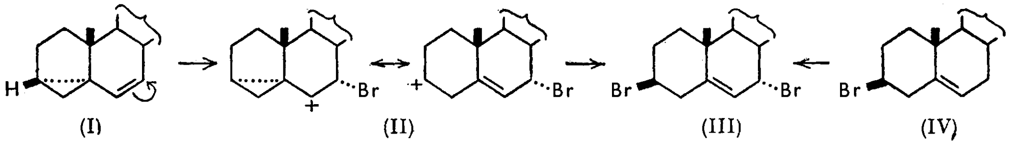
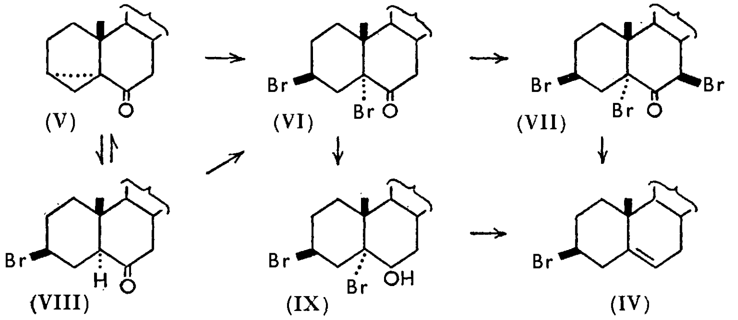
* Part XLII, *J.*, 1959, 630.

[1] Heilbron, Beynon, and Spring, *J.*, 1936, 907; 1937, 406, 1459.
[2] Wallis, Fernholz, and Gephart, *J. Amer. Chem. Soc.*, 1937, **59**, 137.
[3] Shoppee and Summers, *J.*, 1957, 4813.
[4] Wagner, Wolff, and Wallis, *J. Org. Chem.*, 1952, **17**, 529.
[5] Dodson and Riegel, *ibid.*, 1948, **13**, 424.
[6] Shoppee and Summers, *J.*, 1952, 3361.
[7] Winstein and Kosower, *J. Amer. Chem. Soc.*, 1956, **78**, 4347, 4354.

and later adopted by Smith and Wallis.[8] It seemed therefore desirable further to examine the reactions of 3 : 5-*cyclo*cholestane and some of its derivatives with bromine.



Although 3 : 5-*cyclo*cholestane undergoes electrophilic addition with hydrogen chloride,[9] bromide, and iodide,[10] to yield finally 3-methyl-A-norcholest-3-ene,[11] it does not react with bromine in ether at 15—36° (cf. ref. 10). It appears that the σ-electrons of the 3 : 5-bond require activation by an electron-attracting centre [12] or group at position 2 or 6. Thus 3 : 5-*cyclo*cholest-6-ene (I) with 1 mol. of bromine in ether at 0° readily gives 3β : 7α-dibromocholest-5-ene [13] (III), also obtained from cholesteryl bromide (IV) by treatment with *N*-bromosuccinimide.[14] We regard the reaction as an electrophilic addition initiated by α-attack at $C_{(7)}$, and proceeding by way of the mesomeric cation (II) (alternatively envisaged as a 6-carbonium bromide intimate ion-pair which collapses by internal return) to yield the more thermodynamically stable product (III).



3 : 5-*cyclo*Cholestan-6-one (V) with bromine in pentane solution at 0° slowly gives 3β : 5α-dibromocholestan-6-one (VI). This transannular addition recalls the reaction of 3 : 5-*cyclo*cholestan-6-one with the four halogen acids to furnish the 3β-halogeno-5α-cholestan-6-ones,[3,15] and is clearly due to the activating influence of the adjacent carbonyl group; electrophilic attack at position 5 yields a cation, to be represented as a carbonium ion with configuration preserved at $C_{(3)}$, or as a 3α : 5α-bromonium ion, which is attacked by a bromide ion with inversion at $C_{(3)}$. 3 : 5-*cyclo*Cholestan-6-one (V) with 2 mols. of bromine in ether at 0°, dioxan at 15°, or acetic acid at 60°, gives the dibromo-ketone (VI) accompanied by 3β : 5α : 7β-tribromocholestan-6-one (VII); bromination of the dibromo-ketone (VI) in ether at 15° or in ether–acetic acid at ~40° also yields this tribromo-ketone (VII).

The 3β-configuration of the dibromo-ketone (VI) is established by its preparation by bromination of 3β-bromo-5α-cholestan-6-one [15] (VIII), and by its reduction with sodium borohydride to the 6-epimeric dibromohydrins represented by (IX), which on treatment with zinc in acetic acid eliminate hypobromous acid [16] to give cholesteryl bromide (IV).

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[8] Smith and Wallis, *J. Org. Chem.*, 1954, **19**, 1628.
[9] Schmid and Kägi, *Helv. Chim. Acta*, 1950, **33**, 1582.
[10] Riegel, Hager, and Zenitz, *J. Amer. Chem. Soc.*, 1946, **68**, 2562; 1948, **70**, 887.
[11] Shoppee and Summers, *J.*, 1952, 2528.
[12] Kosower, *J. Amer. Chem. Soc.*, 1958, **80**, 3266.
[13] Bide, Henbest, Jones, and Peevers, *J.*, 1948, 1783.
[14] Bernstein, Sax, and Subbarow, *J. Org. Chem.*, 1948, **13**, 837.
[15] Ford and Wallis, *J. Amer. Chem. Soc.*, 1937, **59**, 1415; cf. Shoppee and Summers, *J.*, 1952, 1786.
[16] James, Rees, and Shoppee, *J.*, 1955, 1370 and references cited therein.

The polybromo-ketones (VI), (VII) were unchanged by treatment with sodium iodide in acetone, but by reduction with zinc in acetic acid gave cholestan-6-one.

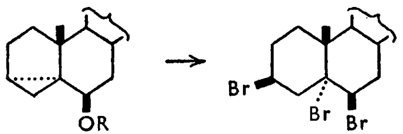
TABLE 1.

	CO : $\nu_{max.}$ (cm.$^{-1}$)	$\Delta\nu_{max.}$	$\lambda_{max.}$ (mμ)	$\Delta\lambda$	log ε	Δ log ε
5α-Cholestan-6-one	1711	—	280	—	1·6	—
3β-Bromo-5α-cholestan-6-one	1711	0	280	—	1·6	—
3β-Acetoxy-5α-cholestan-6-one [a]	1711	0	280	—	1·6	—
5α-Bromocholestan-6-one	1712	+1	308	+28	2·1	+0·5
3α : 5α-Dibromocholestan-6-one	1709	−2	308	+28	2·1	+0·5
3β : 5α-Dibromocholestan-6-one (VI)	1708	−3	309	+29	2·2	+0·6
3β-Acetoxy-5α-bromocholestan-6-one [a]	1711	0	308	+28	2·1	+0·5
3β : 5α : 7β-Tribromocholestan-6-one (VII) ...	1727	+16	306	+26	2·1	+0·5
3β-Acetoxy-5α : 7β-dibromocholestan-6-one [a,b]	1727	+16	305	+25	2·1	+0·5
3β-Acetoxy-5α : 7α-dibromocholestan-6-one [a,b]	1708	−3	340	+60	2·2	+0·6

[a] Cookson, *J.*, 1954, 282; Corey, *J. Amer. Chem. Soc.*, 1954, **76**, 175. [b] Cookson and Dandegaonker, *J.*, 1955, **352**.

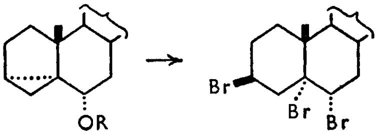
The α-configuration of the 5-bromine atom in the ketones (VI) and (VII) follows from their infrared and ultraviolet spectra, the essential features of which are recorded, with those of analogues of established configuration, in Table 1.

It will also be seen from the Table that the 7-bromine atom in the tribromo-ketone (VII) possesses the β-configuration. It is probable that bromination in acetic acid of the dibromo-ketone (VI) affords, by kinetic control, initially the 3β : 5α : 7α-tribromo-ketone, which by acid-catalysed enolisation,[17] or by reduction with hydrogen bromide and rebromination,[18] gives the 3β : 5α : 7β-tribromo-ketone (VII).



(X) (XI)

M. p. 112° [−49°],[1] [−49·6°],[4] [−51·5°].[23]



(XII) (XIII)

M. p. 160° (decomp.) [−50°] [4]

3 : 5-*cyclo*Cholestan-6β-ol (formerly "*i*-cholesterol"), its ethers, and its acetate (X; R = H, Me, Et, CH_2Ph, Ac) with bromine in anhydrous solvents at 0—15° give 3β : 5α : 6β-tribromocholestane (XI) in almost quantitative yield.[1] The alcohol and its methyl ether react thus in the presence of potassium acetate,[1] but we have observed that the bromination of the acetate is inhibited by potassium acetate. The structure of the tribromide (XI) follows from its preparation from cholesteryl bromide (IV) and bromine,[19] its 5α : 6β-configuration has been made virtually certain by Barton and Miller,[20] and is consistent with its stability to dehydrobromination by pyridine,* demonstrated by Wagner *et al.*[4] and confirmed by us.

To gain insight into the mechanism of the bromination whereby 3 : 5-*cyclo*cholestan-6β-ol and its derivatives (X; R = H, Me, Ac) give 3β : 5α : 6β-tribromocholestane (XI), we have used a deficit of bromine (<2 mols.) combined with product analysis. With bromine (1 mol.) in anhydrous 1% ethereal solution at 0°, the 3 : 5-*cyclo*-6β-alcohol (X; R = H) affords a mixture, which cannot be separated chromatographically, of cholesteryl bromide (IV) and the 3β : 5α : 6β-tribromide (XI). Similarly, 3 : 5-*cyclo*cholestan-6β-yl methyl ether (X; R = Me) with bromine (1 mol.) in pentane at 0° slowly yields cholesteryl

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* It may be noted that 4β-H and 5α-Br, although stereoelectronically suitably disposed (*trans*, diaxial), do not suffer elimination.[20]

[17] Corey, *J. Amer. Chem. Soc.*, 1954, **76**, 175.

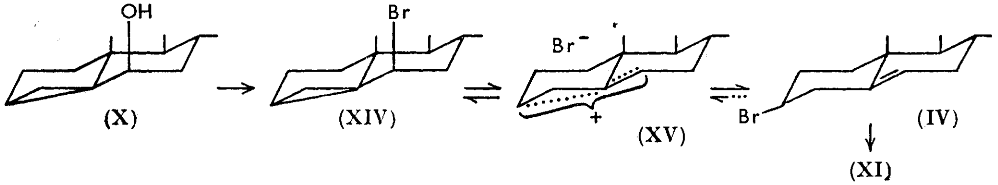
[18] Cookson and Dandegaonker, *J.*, 1955, **352**; James and Shoppee, *J.*, 1956, 1064.

[19] Kolm, *Monatsh.*, 1912, **33**, 447.

[20] Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066.

bromide and unchanged starting material; an attempt to follow the reaction kinetically failed because of the insufficient stability of solutions of bromine in pentane, whilst in carbon tetrachloride at 0° the reaction was too rapid. Finally, the 6β-acetate (X; R = Ac) with bromine (1 mol.) in pentane or carbon tetrachloride at 0° yielded a mixture of cholesteryl bromide and the 3β : 5α : 6β-tribromide.

The transformation (X ⟶ XI) thus appears to involve cholesteryl bromide as an intermediate. We suggest that 3 : 5-*cyclo*cholestan-6β-ol (X) by an S_Ni mechanism (involving attack by a partially polarised bromine molecule on the 6-oxygen atom and subsequent alkyl–oxygen fission) with retention of configuration of $C_{(6)}$ gives 3 : 5-*cyclo*cholestan-6β-yl bromide (XIV) which rearranges, or as the ion-pair (XV) collapses by internal return, under thermodynamic control to give cholesteryl bromide (IV); in the presence of available bromine this affords the 3β : 5α : 6β-tribromide (XI) by *trans*-diaxial addition. An exact analogy is provided by the elegant work of Winstein and Kosower[7]



who describe the preparation from the 3 : 5-*cyclo*cholestan-6β-ol (X) with thionyl chloride in ether at 0° of 3 : 5-*cyclo*cholestan-6β-yl chloride and its rearrangement to cholesteryl chloride. Kinetic control leads to attack on the mesomeric carbonium ion at $C_{(6)}$ with retention of configuration, whereas thermodynamic control leads to stereospecific β-attack at $C_{(3)}$; this has been shown to be true, not only for the formation and rearrangement of 3 : 5-*cyclo*cholestan-6β-yl chloride, but also for its solvolysis in the absence and in the presence of lithium acetate in 90% dioxan at 25°. It is difficult to resist the conclusion that 3 : 5-*cyclo*cholestan-6β-yl bromide would show closely similar behaviour.

Wagner, Wolff, and Wallis[4] have reported that 3 : 5-*cyclo*cholestan-6α-ol (XII) with excess of bromine (3·6 mols.) in anhydrous 1% ethereal solution at 15° gave an 18% yield of 3β : 5α : 6α-tribromocholestane (XIII). In certain runs difficulty was encountered in the isolation of this compound in pure form because of its instability, whilst chromatographic methods were unsuccessful because of decomposition on the column. The compound was debrominated with sodium iodide in acetone to cholesteryl bromide more slowly than 3β : 5α : 6β-tribromocholestane (XI), whilst with pyridine at 15° it gave an unidentified product, m. p. 141°, $[\alpha]_D$ −22°, which although not analysed was stated to arise by loss of hydrogen bromide. In order to account for the production of the epimeric tribromides (XI, XIII) Wallis and his collaborators assumed a mechanism involving S_N2 replacement of the 6-hydroxyl group by a bromine anion with inversion, followed by transannular addition of bromine, and reversed the accepted configurations at $C_{(6)}$ of the 3 : 5-*cyclo*cholestan-6-ols. This mechanism is improbable because it requires a bimolecular nucleophilic substitution by bromide anions in the presence of that uniformly electrophilic reagent, the bromine molecule. It cannot be correct because the configurations at position 6 of the 3 : 5-*cyclo*cholestanols are known with certainty.[6,7,21] Both the transformations (X ⟶ XI) and (XII ⟶ XIII) in fact involve retention of configuration at position 6, and the configurational argument based upon the structure of the tribromo-compound is invalid, even although the tribromo-compound possesses the structure (XIII).

An analogy for the production from 3 : 5-*cyclo*-6α-cholestanol (XII), in low yield and by an S_Ni mechanism, of a 6α-bromo-compound (cf. XIII) can be derived from the work of Winstein and Kosower,[7] who found that 3 : 5-*cyclo*cholestan-6α-ol (XII) with thionyl

[21] Evans and Summers, *J.*, 1957, 906; Schleyer, Trifan, and Bacskai, *J. Amer Chem. Soc.*, 1958, **80**, 6691.

chloride in ether at —78° gave mainly 3 : 5-*cyclo*cholestan-6β-yl chloride, but with indications of the formation of 10—15% of 3 : 5-*cyclo*cholestan-6α-yl chloride. Wagner *et al.*,[4] however, isolated no other product [expected on this analogy to be the very stable 3β : 5α : 6β-tribromo-compound (XI) *], and do not comment on the fate of the residual 80% of the starting material.

The debromination of 3β : 5α : 6α-tribromocholestane (XIII) by sodium iodide in acetone to cholesteryl bromide [4] (IV) is consistent with the structure assigned; the specific rotation is not. The 6-epimers (XI, XIII) have almost identical negative specific rotations, giving a molecular-rotation difference for the inversion of 6β-Br to 6α-Br of only a few units. In the absence of vicinal action the molecular rotatory contributions are $\Delta\mathrm{Br}_{6\beta}$ — 163° and $\Delta\mathrm{Br}_{6\alpha}$ + 135°,[22] giving a molecular rotation difference (6β-Br $\longrightarrow$ 6α-Br) of 300 units; similarly, for chlorine $\Delta\mathrm{Cl}_{6\beta} = -100°$ and $\Delta\mathrm{Cl}_{6\alpha} = +92°$,[22] giving a difference (6β-Cl $\longrightarrow$ 6α-Cl) of about 200°. In the presence of vicinal action $\Delta\mathrm{Br}_{6\beta}$ increases largely (Table 2); the variation in $\Delta\mathrm{Br}_{6\alpha}$ is unknown because the compound (XIII) is the only 5α : 6α-dibromo-5α-cholestane yet described.

TABLE 2. *Effect of vicinal action on the molecular-rotation contributions* $\Delta\mathrm{Hal}_{6\alpha}$ *and* $\Delta\mathrm{Hal}_{6\beta}$ *in* 5 : 6-*dihalogeno*-5α-*cholestanes.*

	3β-Substituent					
Basic structure	H	OH	OAc	OBz	Cl	Br
5α : 6α-Dibromocholestane						−304° (XIII)
5α : 6β-Dibromocholestane	−212°	−240°	−290°	−239°	−288°	−302° (XI)

Although it has not been isolated, 3β : 5 : 6α-tribromo-5β-cholestane is formed to the extent of 10% from 3β : 5 : 6β-tribromo-5α-cholestane in chloroform solution at 40°, and its specific rotation has been calculated to be +41·9°; [23] it might be expected to undergo debromination with sodium iodide in acetone to cholesteryl bromide more slowly (5β-Br/6α-Br; *eq*/*eq*) than the 3β : 5α : 6β-tribromide (XI; 5α-Br/6β-Br; *ax*/*ax*) (this is true for the 3β-chloro-analogues, and this fact was used in the preparation of 3β-chloro-5 : 6α-dibromo-5β-cholestane [23]), but its positive specific rotation appears to preclude possible identification with the Wallis tribromo-compound.

We have been unable to prepare the Wallis 3β : 5α : 6α-tribromide (XIII). 3 : 5-*cyclo*-Cholestan-6α-ol used for bromination could not be recrystallised (cf. ref. 7) but had the correct specific rotation (—79°); there seems no reason to doubt its authenticity and homogeneity, since reduction of 3 : 5-*cyclo*cholestan-6-one by lithium aluminium hydride to 3 : 5-*cyclo*cholestan-6α-ol has been shown to be almost completely stereospecific.[4,6,7] In our hands, under the conditions specified by Wagner *et al.*,[4] the sole product of bromination of 3 : 5-*cyclo*cholestan-6α-ol (XII), or its acetate or its non-crystalline methyl ether, has been 3β : 5 : 6β-tribromo-5α-cholestane (XI). Use of the basic solvent dioxan [24,15] as an alternative to ether,[29] and of *NN*-dimethylformamide, and employment of pyridine sulphate dibromide as brominating agent, afforded mixtures of cholesteryl bromide and 3β : 5 : 6β-tribromo-5α-cholestane (XI). 3 : 5-*cyclo*Cholestan-6α-ol (XII) with 1 mol. of bromine in ether at 20° gave, however, mainly cholesteryl bromide (57%), with a small quantity of 3β : 5 : 6β-tribromo-5α-cholestane (XI). Similarly, in hexane at 20° with 1·2 mols. of bromine, it gave cholesteryl bromide (69%), with only traces of the 3β : 5α : 6β-tribromide (XI). In pentane with 2·4 mols. of bromine, the product was, surprisingly, almost exclusively the 3β : 5α : 6β-tribromide (69%). It appears reasonable to conclude that the

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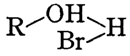
* Professor E. S. Wallis has most kindly informed us (letter of October 24th, 1958) that on occasion some of the 3β : 5α : 6β-tribromide was also isolated on reaction of the 3 : 5-*cyclo*cholestan-6α-ol with bromine.

[22] Shoppee, Howden, and Lack, unpublished work.

[23] Barton and Head, *J.*, 1956, 932.

[24] Yanovskaya, Terent'ev, and Belenkit, *Zhur. obshchei Khim.*, 1952, **22**, 1594; Dombrovskit, *ibid.*, 1954, **24**, 610.

transformation (XII ⟶ XI), like the change (X ⟶ XI), involves cholesteryl bromide as an intermediate.

These negative results were communicated in 1953 to Professor E. S. Wallis, who suggested the possible importance of traces of moisture. If adventitious traces of water were present during bromination, hydrogen bromide would be generated in a self-sustaining reaction: $Br_2 + H_2O \rightleftharpoons HOBr + HBr \xrightarrow[ROH]{} RBr + H_2O$. Esterification by hydrogen bromide of the highly reactive pseudoallylic secondary alcohol (XII) by mechanism S_N2 or S_N1 (with stereospecific 6β-attack on the 3 : 5-*cyclo*-cation under kinetic control) would lead to 3 : 5-*cyclo*cholestan-6β-yl bromide, but by mechanism S_Ni under conditions inhibiting ionisation could proceed through a configuration-preserving rearrangement of a hydrogen-bonded complex  $R\overset{OH}{\underset{Br}{\langle\rangle}}H$ to furnish 3 : 5-*cyclo*cholestan-6α-yl bromide. Even so, it is not clear how the Wallis 3β : 5α : 6α-tribromide (XIII) could arise, since all the evidence[4,6,7] indicates that 6α-substituted 3 : 5-*cyclo*steroids rearrange to 3β-substituted Δ^5-steroids, which according to the literature afford 5α : 6β-dibromides and not 5α : 6α-dibromides.

EXPERIMENTAL

For general directions see *J.*, 1959, 630. $[\alpha]_D$ refer to chloroform solutions; ultraviolet absorption spectra were measured for ethanol solutions on a Unicam S.P. 500 spectrophotometer with a corrected scale, and infrared absorption spectra were determined on a Grubb-Parsons double-beam grating instrument.

Attempted Bromination of 3 : 5-cyclo*Cholestane*.—3 : 5-*cyclo*Cholestane[6,9,27] (m. p. 77°; 300 mg.) in (*a*) ether at 20° for 24 hr., or ether–acetic acid (1 : 1) (*b*) at 0° for 2 hr. or (*c*) at 40° for 24 hr., was treated with an excess of bromine. In each case evaporation of the orange solution at 20°/10 mm. gave a nearly quantitative recovery of 3 : 5-*cyclo*cholestane, m. p. and mixed m. p. 74—76° (from acetone).

Bromination of 3 : 5-cyclo*Cholest*-6-*ene* (I).—3 : 5-*cyclo*Cholest-6-ene,[10] m. p. 73°, $[\alpha]_D$ −46° (*c* 1·0) (1 g.), in chloroform (5 c.c.) was treated with a solution of bromine (434 mg., 1 mol.) in chloroform (5 c.c.) at 0°. The colourless solution was evaporated at 20°/10 mm., and the residual oil (1·38 g.) crystallised from acetone to give 3β : 7α-dibromocholest-5-ene (III), m. p. 140—142°, which did not depress the m. p. of a specimen prepared from cholesteryl bromide and *N*-bromosuccinimide.[14]

Bromination of 3 : 5-cyclo*Cholestan*-6-*one* (V).—(*a*) 3 : 5-*cyclo*Cholestan-6-one (m. p. 97°) (1 g.) in pentane was treated with bromine (415 mg., 1 mol.) in pentane at 0° overnight. After removal of pentane at 20°/10 mm., the usual isolation procedure gave a colourless solid, which by recrystallisation from ether–methanol yielded 3β : 5-*dibromo*-5α-*cholestan*-6-*one* (VI) (690 mg.), m. p. 133—134°, $[\alpha]_D$ −121° (*c* 2·2), $\lambda_{max.}$ 309 mμ (log ε 2·2), $\nu_{max.}$ 1708 cm.$^{-1}$ [Found (after drying at 20°/0·02 mm. for 20 hr.): C, 59·1; H, 7·9; Br, 29·6. $C_{27}H_{44}OBr_2$ requires C, 59·5; H, 8·1; Br, 29·4%].

(*b*) The ketone (1 g.) in ether (15 c.c.) was treated with a 3·2% solution of bromine in ether (13 c.c., 1 mol.) at 0°. The colour was discharged immediately; the solution was kept overnight at 0°, and then worked up in the usual way to give an oil (1·38 g.), which solidified when stirred with pentane. The solid was extracted with boiling ether, and the ether-insoluble material recrystallised from dioxan, to yield 3β : 5 : 7β-*tribromo*-5α-*cholestan*-6-*one* (VII) (40 mg.), m. p. 190°, $[\alpha]_D$ −51° (*c* 2·0), $\lambda_{max.}$ 306 mμ (log ε 2·1), $\nu_{max.}$ 1727 cm.$^{-1}$ [Found (after drying at 20°/0·02 mm. for 20 hr.): C, 52·8; H, 7·0; Br, 40·5. $C_{27}H_{43}OBr_3$ requires C, 52·0; H, 6·95; Br, 38·5%]. Evaporation of the ethereal solution and recrystallisation of the resulting solid from ether–methanol gave the 3β : 5α-dibromo-ketone (VI) (281 mg.), m. p. and mixed m. p. 133—134°.

(*c*) The ketone (1 g.) in ether (15 c.c.) was similarly treated with a 3·2% solution of bromine in ether (26 c.c., 2 mol.) at 0°, to yield a product (1·60 g.) separated as above into the 3β : 5α : 7β-tribromo-ketone (VII) (370 mg.), m. p. 190°, and the 3β : 5α-dibromo-ketone (VI) (1·03 g.), m. p. 133°.

(*d*) The ketone (330 mg.) in dioxan (10 c.c.) was treated with a 2·2% solution of bromine in

[25] Chesterman, *J.*, 1935, 906.

[26] Buswell, Rodebush, and Roy, *J. Amer. Chem. Soc.*, 1938, **60**, 2528.

[27] Karrer and Schmid, *Helv. Chim. Acta*, 1949, **32**, 1371.

dioxan (10 c.c., 1·7 mol.) at 20° overnight, to yield a product separated as above into the 3β : 5α : 7β-tribromo-ketone (VII) (170 mg.), m. p. 190°, $[\alpha]_D$ −50° (*c* 1·0), and the 3β : 5α-dibromo-ketone (VI) (320 mg.), m. p. 133°, $[\alpha]_D$ −123° (*c* 1·0).

(*e*) The ketone (436 mg.) in acetic acid (10 c.c.) at 60° was treated with a 6% solution of bromine in acetic acid (5 c.c., 1·7 mol.) and boron trifluoride–ether complex (0·5 c.c.). After 15 min. at 60° and 1 hr. at 20°, the product yielded, by separation as above, the 3β : 5α : 7β-tribromo-ketone (VII) (91 mg.), m. p. 190°, and the 3β : 5α-dibromo-ketone (VI) (506 mg.), m. p. 133°.

Bromination of 3β : 5-*Dibromo*-5α-*cholestan*-6-*one* (VI).—(*a*) The 3β : 5α-dibromo-ketone (458 mg.) in ether was treated with a 3·1% solution of bromine in ether (13·4 c.c., 3 mol.) at 20° for 3 hr. to give, after separation as described above, the 3β : 5α : 7β-tribromo-ketone (VII) (80 mg.), m. p. and mixed m. p. 190° (from dioxan), and unchanged starting material, m. p. 133°.

(*b*) The 3β : 5α-dibromo-ketone (500 mg.) in 1 : 1 acetic acid–ether (5 c.c.) was treated with a 3·1% solution of bromine in acetic acid (4·6 c.c., 1 mol.) at 40° for 1 hr. and then stored overnight. The crystalline precipitate, after removal of ether at 20°/10 mm., was filtered off, washed with ether, and recrystallised from dioxan, to give the 3β : 5α : 7β-tribromo-ketone (VII) (150 mg.), m. p. and mixed m. p. 190—191°. Concentration of the filtrate and washings gave unchanged starting material (400 mg.), m. p. 133°.

Bromination of 3β-*Bromo*-5α-*cholestan*-6-*one* (VIII).—(*a*) 3β-Bromo-5α-cholestan-6-one,[15] m. p. 123°, $\lambda_{max.}$ 280 mμ (log ε 1·6), $\nu_{max.}$ 1711 cm.$^{-1}$ (200 mg.), in 2 : 1 acetic acid–ether (7 c.c.) was treated with a 15·6% solution of bromine in acetic acid (0·43 c.c., 1 mol.) at 0° overnight. Removal of ether in a vacuum produced a crystalline precipitate; filtration and recrystallisation from ether–methanol gave 3β : 5-dibromo-5α-cholestan-6-one (VI), m. p. and mixed m. p. 133—134°.

(*b*) The 3β-bromo-ketone (500 mg.) in 1 : 5 acetic acid–ether (6 c.c.) was treated with a 15·6% solution of bromine in acetic acid (1·1 c.c., 1 mol.) at 36°. The colour rapidly disappeared, and the solution was heated on a steam-bath for 0·5 hr. Evaporation at 20°/10 mm. gave crystals, which were collected and recrystallised from ether–methanol, to yield 3β : 5-dibromo-5α-cholestan-6-one, m. p. and mixed m. p. 133—134°, $[\alpha]_D$ −121° (*c* 1·0).

Reduction of 3β : 5-*Dibromo*-5α-*cholestan*-6-*one* (VI).–(*a*) The 3β : 5α-dibromo-ketone (190 mg.) was refluxed in methanol (20 c.c.) with sodium borohydride (150 mg.) for 1 hr. The usual isolation procedure furnished a mixture of the epimeric 3β : 5-dibromo-5α-cholestan-6-ols (190 mg.), which failed to crystallise and was heated with zinc dust (100 mg.) in acetic acid at 100° for 0·5 hr. The usual working up gave an oil (150 mg.), which was chromatographed on aluminium oxide (4 g.) in pentane; elution with pentane gave cholesteryl bromide (140 mg.), m. p. and mixed m. p. 96—98° (from acetone).

(*b*) The 3β : 5α-dibromo-ketone (68 mg.) in acetic acid was refluxed with zinc dust for 4 hr. The cooled solution was filtered, diluted, and extracted with pentane to yield, after working up, an oil (47 mg.) which soon crystallised and by recrystallisation from methanol yielded 5α-cholestan-6-one, m. p. and mixed m. p. 96°.

(*c*) The 3β : 5α-dibromo-ketone (214 mg.) failed to react with sodium iodide (400 mg.) in acetone (25 c.c.) at 20° during 18 hr. and was recovered unchanged (m. p. and mixed m. p. 133°).

Attempted Rearrangement of 3β : 5-*Dibromo*-5α-*cholestan*-6-*one* (VI).—The 3β : 5α-dibromo-ketone (200 mg.) in 19 : 1 acetic acid–ether (40 c.c.) was not rearranged by treatment with 48% hydrobromic acid (2 c.c.) at 20° during 18 hr. and was recovered (197 mg.) unchanged (m. p. and mixed m. p. 133°, after crystallisation from ether–methanol).

Reduction of 3β : 5 : 7β-*Tribromo*-5α-*cholestan*-6-*one* (VII).—(*a*) The 3β : 5α : 7β-tribromo-ketone (100 mg.) in acetic acid was refluxed with zinc dust for 4 hr. The product, isolated as under (*b*) above, was 5α-cholestan-6-one, m. p. and mixed m. p. 96°.

(*b*) The 3β : 5α : 7β-tribromo-ketone (317 mg.) failed to react with sodium iodide (600 mg.) in refluxing acetone during 2·5 hr., and was recovered unaltered (m. p. 188—190° after recrystallisation from dioxan).

Bromination of 3 : 5-cyclo*Cholestan*-6β-*ol and Derivatives* (X; R = H, Me, Ac).—(*a*) The alcohol, m. p. 73° (120 mg.), in ether (5 c.c.) with a 2% solution of bromine in ether (2·5 c.c., 1 mol.) at 0° overnight gave, after the usual isolation procedure, an oil, which was chromatographed on aluminium oxide (5 g.) in pentane. Elution with pentane yielded material which, after repeated recrystallisation from acetone, furnished cholesteryl bromide, m. p. and mixed m. p. 96°, whilst further elution with pentane gave material (82 mg.) which, after crystallisation from ethanol–acetone, yielded 3β : 5 : 6β-tribromo-5α-cholestane, m. p. and mixed m. p. 112°. When the alcohol (146 mg.) was treated similarly with 2·3 mol. of bromine in ether, the sole product was 3β : 5 : 6β-tribromo-5α-cholestane (230 mg.), m. p. and mixed m. p. 111—112°, which crystallised readily from ethanol–acetone. A series of brominations of the alcohol with 2·3 mols. of bromine at room temperature for 24—48 hr. in pentane, chloroform, carbon tetrachloride, or acetic acid, gave uniformly almost quantitative yields of 3β : 5 : 6β-tribromo-5α-cholestane, m. p. and mixed m. p. 112° (from ethanol–acetone).

(*b*) The methyl ether, m. p. 79° (500 mg.), in pentane with a 1·6% solution of bromine in pentane (12·5 c.c., 1 mol.) at 0° overnight gave a pale yellow solution, which by the usual working up furnished an oil. This was moistened with acetone–methanol and set aside overnight at 0°, and the resulting solid was triturated with methanol, filtered off, and recrystallised from acetone–methanol to give cholesteryl bromide, m. p. and mixed m. p. 96—97° [Found (after drying at 15°/0·03 mm. for 20 hr.): C, 72·0; H, 10·3. Calc. for $C_{27}H_{45}Br$: C, 72·2; H, 10·1%]; concentration of the methanolic filtrate gave 3 : 5-*cyclo*cholestan-6β-yl methyl ether, m. p. and mixed m. p. 78—79°. The methyl ether (500 mg.) in carbon tetrachloride, similarly treated with 1 mol. of bromine in carbon tetrachloride, gave an oil which crystallised when stirred with acetone–methanol and kept at −80° for 8 hr. The solid material was filtered off, washed with cold acetone–methanol, and recrystallised from acetone, to give crystals, m. p. 102—103°, which appeared to consist of a mixture of cholesteryl bromide and 3β : 5 : 6β-tribromo-5α-cholestane [Found (after drying at 15°/0·03 mm. for 20 hr.): C, 66·7; H, 11·1%]. The acetone–methanol filtrate and washings, on concentration, gave crystals, which were recrystallised from methanol to give the methyl ether, m. p. 75—78°. The methyl ether (1 g.) was recovered unchanged (m. p. 76—78°) after being refluxed with *N*-bromosuccinimide (1 g.) in carbon tetrachloride (20 c.c.) for 0·5 hr.

(*c*) The acetate, m. p. 73° (150 mg.), in pentane with a 4% solution of bromine in pentane (3 c.c., 2·2 mol.) after 4 days at 0°, furnished by the usual isolation procedure an oil, which was chromatographed on neutralised aluminium oxide [27] (12 g.) in pentane. Elution with pentane gave material (43 mg.) which after repeated recrystallisation from acetone gave cholesteryl bromide, m. p. and mixed m. p. 96°, whilst further elution with pentane gave material (178 mg.), which after recrystallisation from acetone–methanol gave 3β : 5 : 6β-tribromo-5α-cholestane, m. p. and mixed m. p. 111—112°, $[\alpha]_D$ −48° (*c* 0·9). A similar bromination of the acetate (200 mg.) with 2·2 mols. of bromine in carbon tetrachloride (cf. ref. 12) at 0° for 24 hr. gave on chromatography and crystallisation 3β : 5 : 6β-tribromo-5α-cholestane (227 mg.), m. p. and mixed m. p. 111—112°, and cholesteryl bromide (21 mg.), m. p. and mixed m. p. 96°. A series of brominations of the acetate with 2·8 mols. of bromine in ether at 0° for 36 hr., in chloroform at 0° for 48 hr., and in acetic acid at 25° for 20 hr., gave almost quantitative yields of 3β : 5 : 6β-tribromo-5α-cholestane, m. p. and mixed m. p. 111—112°; in acetic acid in presence of anhydrous potassium acetate bromination did not occur during 3 days at 25° and 3 : 5-*cyclo*cholestan-6β-yl acetate, m. p. and mixed m. p. 73—74° (from acetone–methanol), was recovered.

Bromination of 3 : 5-cyclo*Cholestan*-6α-*ol and its Derivatives* (XII; R = H, Ac, Me).—The alcohol was prepared from 3 : 5-*cyclo*cholestan-6-one,[6] m. p. 97°, by reduction with lithium aluminium hydride; [4,6,7] the product solidified after drying at 0·02 mm. for 48 hr., but a seed was not available and could not be procured, and despite many attempts to crystallise the product from acetone or acetonitrile [7] experiments had to be carried out on the unrecrystallised material, $[\alpha]_D$ +79° (*c* 1·3). The acetate,[4,6,7] obtained by use of acetic anhydride–pyridine at 20° for 24 hr., was an oil, $[\alpha]_D$ +98° (*c* 1·1); the *methyl ether*, prepared by refluxing the alcohol with freshly prepared silver oxide in methyl iodide for 20 hr., had b. p. 140°/0·02 mm., $[\alpha]_D$ +85° (*c* 0·8) (Found: C, 83·95; H, 12·1. $C_{28}H_{48}O$ requires C, 83·9; H, 12·1%).

(*a*) The experiments, tabulated below, were carried out simultaneously with exclusion of moisture under identical conditions of temperature (20°) and humidity. 3 : 5-*cyclo*Cholestan-6α-ol (~200 mg.) in the appropriate solvent was treated with a 1% solution of bromine in the same solvent. In each case the usual isolation procedure gave an oil; each product was therefore chromatographed on aluminium oxide (10 g.) prepared in pentane. Repeated elution with pentane eluted cholesteryl bromide and 3β : 5 : 6β-tribromo-5α-cholestane; some columns were further eluted with more powerful eluants, but only small quantities of uncrystallisable oils were obtained.

A 1 : 1 synthetic mixture of cholesteryl bromide and 3β : 5 : 6β-tribromo-5α-cholestane (100 mg.) could not completely be separated on a long column of aluminium oxide (Spence, Type H: 100 × wt. of sample). Elution with pentane gave a series of fractions: No. 1, 83°, 25 mg.; 2, 83°, 35 mg.; 3, 85°, 10 mg.; 4, 88°, 10 mg.; 5, 91°, 8 mg.; 6, 95°, 5 mg.; 7, 95° 5 mg.; 8, 95°, 2 mg. Determination of a few points on the temperature–composition diagram for mixtures of cholesteryl bromide, m. p. 98°, and 3β : 5 : 6β-tribromo-5α-cholestane, m. p. 111°, gave a simple two-branch curve with a eutectic at 79° corresponding to a content of 45% of cholesteryl bromide. From the diagram, the composition of the above eight chromatographic fractions was determined as 50, 50, 45, 39, 35, 25, 25, and 25% of cholesteryl bromide.

The following chromatographic details amplify the Table:

Bromination of 3 : 5-cyclo*cholestane*-6α-*ol*.

Exp. no.	Solvent	Alcohol (mg.)	Bromine (mol.)	Time (hr.)	Final soln.	Crude yield (mg.)	Al$_2$O$_3$ (Woelm)	Products * and yields
1	Ether	202	1	20	Colourless	251	Basic	Mono- (56%), tri-bromide (trace)
2	Ether	198	2·4	20	Colourless	331	Basic	Tribromide (63%)
3	Hexane	200	1·2	20	Colourless	325	Neutral	Mono- (69%), tri-bromide (trace)
4	Pentane	212	2·4	20	Colourless	321	Acid	Tribromide (69%)
5	Dioxan	203	2·4	24	Yellow	336	Acid	Mono- + tri-bromide
6	Chloroform	204	2·4	20	Yellow	338	Acid	Tribromide (60%)
7	Carbon tetrachloride	198	2·4	24	Orange	311	Neutral	Tribromide (50%)
8	*NN*-Dimethyl formamide	201	2·4	40	Yellow	—	Neutral	Tribromide (59%)
9	Acetic acid	200	2·4	24	Yellow	319	Basic	Tribromide (56%)
10	Chloroform	204	†	20 (in dark)	Orange	300	Acid	Mono- + tri-bromide

* Cholesteryl bromide and 3β : 5 : 6β-tribromo-5α-cholestane.

† Pyridinium sulphate dibromide.

Expt. 1. Fraction 1 (116 mg.), m. p. 98° (from acetone), undepressed by cholesteryl bromide, m. p. 96°; fraction 2 (14 mg.), m. p. 98—99° (from acetone), but some crystals had m. p. ~112°.

Expt. 2. Fraction 1 (195 mg.) [fraction 2 (2 mg.)], m. p. 112° (from ether–ethanol), undepressed by 3β : 5 : 6β-tribromo-5α-cholestane, m. p. 112°.

Expt. 3. Fractions 1 and 2 (160 mg.), m. p. 94—98° (from acetone), undepressed by authentic monobromide, m. p. 96°; some crystals from fraction 2 had m. p. ~112°, but little 3β : 5α : 6β-tribromide was present.

Expt. 4. Fraction 1 (199 mg.) and fraction 2 (15 mg.) [fraction 3 (1 mg.)], recrystallised from acetone, had m. p. 112°, undepressed by tribromide, m. p. 112°.

Expt. 5. Fractions 1 and 2 (142 mg.), fractions 3 and 4 (6 mg.), and fraction 5 (1 mg.) had m. p. <72° (from ether–ethanol). The united fractions were recrystallised from ether–ethanol; a portion did not dissolve easily, was separated, and found to be 3β : 5 : 6β-tribromo-5α-cholestane, m. p. and mixed m. p. 112°, whilst the soluble portion crystallised to give cholesteryl bromide, m. p. 89—94° (positive test with tetranitromethane in chloroform).

Expt. 6. Fractions 1, 2, and 3 (162 mg.), and fractions 4 and 5 (29 mg.) [fraction 6 (2 mg.)], all had m. p. ~110°, were united, and recrystallised from acetone, to give 3β : 5 : 6β-tribromo-5α-cholestane, m. p. and mixed m. p. 112°.

Expt. 7. Fractions 1 and 2 (156 mg.) [fractions 3 and 4 (1 mg.)] had m. p. ~110°, and from acetone–ethanol gave 3β : 5 : 6β-tribromo-5α-cholestane, m. p. and mixed m. p. 112—113°, $[\alpha]_D$ −51° (*c* 1·1).

Expt. 8. Fractions 1 and 2 (179 mg.) [fractions 3 and 4 (4 mg.)] had m. p. 108—110°, and from acetone–ethanol gave 3β : 5 : 6β-tribromo-5α-cholestane, m. p. and mixed m. p. 111—113°.

Expt. 9. Fraction 1 (173 mg.) [fraction 2 (3 mg.)] had m. p. 112—113° (from ethanol), undepressed by 3β : 5 : 6β-tribromo-5α-cholestane.

Expt. 10. Fractions 1 (155 mg.), 2 (17 mg.), and 3, 4, and 5 (together 10 mg.) were oily but crystallised from acetone to give material, m. p. 88—106°; this by recrystallisation from acetone gave impure cholesteryl bromide, m. p. 83—96° (positive test with tetranitromethane in chloroform); material from the mother-liquor, after five crystallisations from ether–ethanol, was impure 3β : 5α : 6β-tribromide, m. p. 105—111°.

3 : 5-*cyclo*Cholestan-6α-yl acetate (100 ± 4 mg.) in ether, pentane, chloroform, or carbon tetrachloride (20 c.c.) was treated with bromine (3·5 mol.) at 20° for 16—36 hr. The product, isolated in the usual way, in each case was an oil, which solidified when stirred with ethanol, and by recrystallisation gave the 3β : 5α : 6β-tribromide, m. p. and mixed m. p. 112°, in good yield. Similarly, the acetate (113 mg.) in acetic acid (25 c.c.) with a 2% solution of bromine in acetic acid (6 c.c., 3·5 mol.) at 20° for 30 hr., gave on dilution and filtration a solid (160 mg.),

which by recrystallisation from acetone–ethanol yielded the 3β : 5α : 6β-tribromide, m. p. and mixed m. p. 112—113°.

3 : 5-*cyclo*Cholestan-6α-yl methyl ether (100 mg.) in ether, pentane, chloroform, or carbon tetrachloride (20 c.c.) with bromine (3·7 mol.) at 20° for 16—30 hr. gave in each case a product, after the usual working up, which crystallised when stirred with ethanol and by recrystallisation from ethanol gave the 3β : 5α : 6β-tribromide, m. p. and mixed m. p. 112°.

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