430. *Steroids. Part XV.* The Tribromination of 5α-Cholestan-3-one.*

By C. W. Shoppee, Ruth E. Lack, and Janice Scott.

Monobromination of 2,2-dibromo-5α-cholestan-3-one in the presence of potassium acetate gives a mixture of unchanged material and 2,2,4ξ,5ξ-tetrabromocholestan-3-one. This tetrabromo-ketone, which is obtained under the same conditions from 2α,4α-dibromo-5α-cholestan-3-one, readily eliminates hydrogen bromide, to give 2,2,4-tribromocholest-4-en-3-one, or bromine to give 2,2-dibromocholest-4-en-3-one, which has also been prepared by monobromination of 2α-bromocholest-4-en-3-one. 2-Bromocholesta-1,4-dien-3-one has been prepared, for comparison, by elimination of hydrogen bromide from 2,4β-dibromocholest-1-en-3-one.

Monobromination of 2,2-dibromo-5α-cholestan-3-one in acetic acid in the presence of potassium acetate has been reported by Crowne *et al.*[1] to give an unstable product, m. p. 35—40°, regarded as 2,2,4β-tribromo-5α-cholestan-3-one. These workers obtained the " tribromo-ketone " by precipitation from the reaction medium with water. With 0·04N-hydrogen bromide in acetic acid at 20° it gave material from which 2α,4α-dibromo-5α-cholestan-3-one was isolated, but treatment with 0·1N-hydrogen bromide caused a marked change in specific rotation and the crude product, m. p. 61—73°, showed $\nu_{max.}$ 1706 and 1756 cm.$^{-1}$. The structure (I) proposed for the " tribromo-ketone " appeared improbable to us because of the strong interactions of axial 2β- and 4β-bromine atoms with the axial 10β-methyl group.

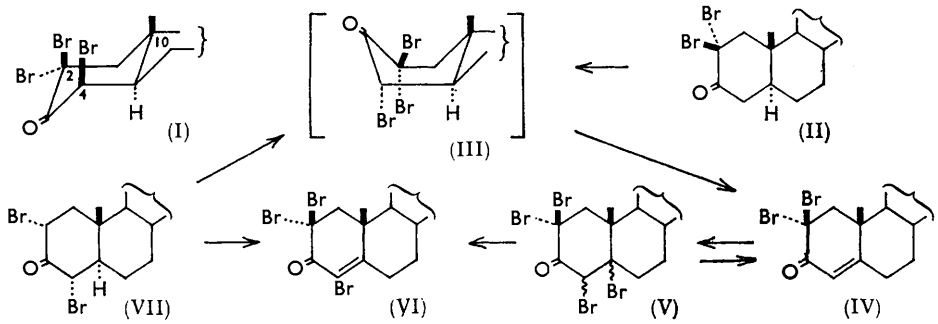
Repeating the work of Crowne *et al.*[1] we obtained a crude product, m. p. 40—45°, giving analyses for a tribromo-ketone and exhibiting an infrared band at 1735 cm.$^{-1}$ (in Nujol), but a smaller band at 1706 cm.$^{-1}$ rapidly developed in carbon tetrachloride solution. The ultraviolet absorption spectrum showed an inflection at 295 mμ, and the optical rotatory dispersion curve was very similar to that of 2,2-dibromo-5α-cholestan-3-one (II). This crude product, when chromatographed on silica gel, afforded 2,2-dibromo-5α-cholestan-3-one (II) and 2,2-dibromocholest-4-en-3-one (IV).

The " tribromo-ketone " is believed to be an approximately 1 : 1 mixture of 2,2-dibromo-5α-cholestan-3-one (II), $[\alpha]_D$ +116°, and 2,2,4ξ,5-tetrabromocholestan-3-one (V), $[\alpha]_D$ +2°, formed by addition of bromine to the unsaturated dibromo-ketone (IV), which arises by elimination of hydrogen bromide from the unstable intermediate tribromo-ketone (III). This view accounts for the analytical figures corresponding to a tribromo-ketone, and the decolorisation of the bromine solution in the preparation, although ~50% of the

* Part XIV, *J.*, 1957, 4813.

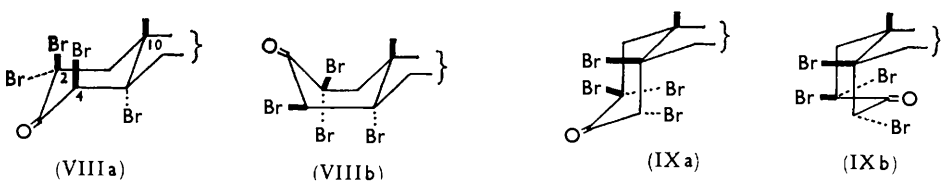
[1] Crowne, Evans, Green, and Long, *J.*, 1956, 4351.

original 2,2-dibromo-5α-cholestan-3-one (II) is recovered unchanged. The rotation, $[\alpha]_D$ +60°, reported [1] for the " tribromo-ketone " agrees with that calculated, $[\alpha]_D$ +57°, for the 1 : 1 mixture. This view has been further substantiated by carrying out the



bromination with 2 mol. of bromine; chromatography of the product on silica gel gave: (*a*) the saturated tetrabromo-ketone (V), which decomposed to yield 2,2,4-tribromocholest-4-en-3-one [2] (VI) if the solvent was not removed at low temperature in a vacuum, and on prolonged warming with acetone eliminated bromine to give 2,2-dibromocholest-4-en-3-one (IV); (*b*) unchanged ketone (II); and (*c*) 2,2-dibromocholest-4-en-3-one (IV).

The configuration of the 4- and 5-bromine atoms in the tetrabromo-ketone (V) is uncertain but we propose 2,2,4β,5α-tetrabromo-5α-cholestan-3-one in the boat conformation (VIIIb) as the most likely conformation for the product of diaxial addition [3] of bromine to the unsaturated ketone (IV); the chair conformation (VIIIa) involves strong 1,3-interactions of the axial 2β- and 4β-bromine atoms with the 10β-methyl group. The alternative diaxial addition product (IXa) is also sterically improbable, but the boat conformation (IXb) is a second possibility. The compound gives a negative Cotton effect curve and this favours structure (VIIIb) rather than (IXb) on the basis of the octant rule, but the contribution of the 5-bromine atom would affect the shape of the curve and no definite conclusion can be drawn.[4] The low figure of Δ 16 cm.$^{-1}$ for each equatorial α-bromine atom in the tetrabromo-ketone (VIIIb or IXb) may be due to steric congestion of the four bromine atoms which would twist ring A and alter the positions of the equatorial substituents.

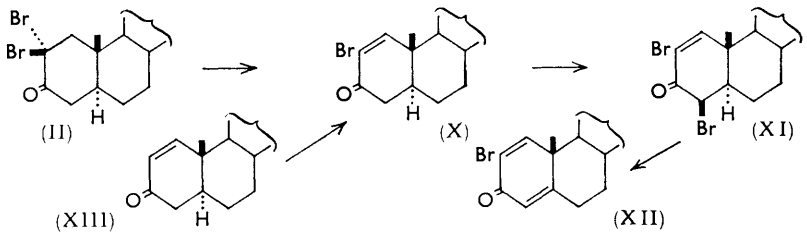


Treatment of the crude " tribromo-ketone " with 0·1N-hydrogen bromide in acetic acid gave a product, $\nu_{max.}$ 1756 and 1706 cm.$^{-1}$, from which were isolated 2,2,4-tribromocholest-4-en-3-one (VI) and 2α,4α-dibromo-5α-cholestan-3-one, the latter formed by the rearrangement of 2,2-dibromo-5α-cholestan-3-one known to occur under these conditions.[5]

Inhoffen and Becker [2b] obtained 2,2,4-tribromocholest-4-en-3-one (VI) by bromination, in the presence of hydrogen bromide, of either 2α,4α-dibromo-5α- or 2β,4β-dibromo-5β-cholestan-3-one. We find that treatment of 2α,4α-dibromo-5α-cholestan-3-one (VII) with 2

[2] (*a*) Ruzicka, Bosshard, Fischer, and Wirz, *Helv. Chim. Acta*, 1936, **19**, 1147; (*b*) Inhoffen and Becker, *Chem. Ber.*, 1952, **85**, 181.
[3] Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 370; Alt and Barton, *J.*, 1954, 4284.
[4] Djerassi, personal communication.
[5] (*a*) Wilds and Djerassi, *J. Amer. Chem. Soc.*, 1946, **68**, 2125; (*b*) Djerassi and Scholz, *ibid.*, 1947, **69**, 2406.

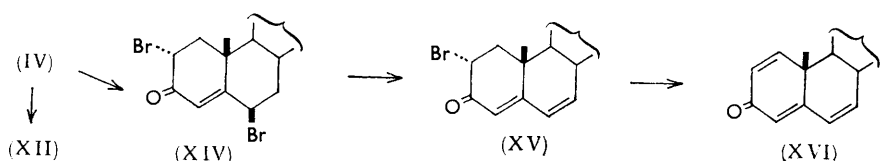
mol. of bromine in acetic acid in the presence of potassium acetate, followed by chromatography on silica gel, gives the tetrabromo-ketone (V), identical with that obtained by similar treatment of 2,2-dibromo-5α-cholestan-3-one (II), and we therefore suggest 2,2,4α-tribromo-5α-cholestan-3-one in the boat conformation (III) as the unstable intermediate in both cases.



To assist identification of the products of dehydrohalogenation of the unsaturated dibromo-ketone (IV), 2-bromocholesta-1,4-dien-3-one (XII) was prepared. Treatment of 2,2-dibromo-5α-cholestan-3-one (II) with boiling collidine under nitrogen gave 2-bromo-5α-cholest-1-en-3-one [2,6,7] (X), and the same product was obtained by the addition of bromine to 5α-cholest-1-en-3-one (XIII). The bromo-ketone (X) was converted by bromination in the presence of hydrogen bromide in acetic acid into 2,4β-dibromo-5α-cholest-1-en-3-one (XI), which on brief treatment with collidine eliminated hydrogen bromide to give 2-bromocholesta-1,4-dien-3-one (XII).

In boiling collidine or with calcium carbonate in boiling dimethylformamide [7] the unsaturated dibromo-ketone (IV) gave a mixture of dienones, together with some cholesta-1,4,6-trien-3-one (XVI) characterised by its three-banded ultraviolet absorption spectrum.[6] The dienones could not be separated chromatographically but a crystalline fraction showed spectral properties consistent with a mixture of 2-bromocholesta-1,4-dien-3-one (XII) and 2α-bromocholesta-4,6-dien-3-one (XV).

Under milder conditions (collidine at 140—145° under nitrogen) rearrangement of the axial 2β-bromine atom of ketone (IV) to the allylic 6β-position [8] occurred; the product, 2α,6β-dibromocholest-4-en-3-one (XIV) has been isolated by Inhoffen [9] and identified by



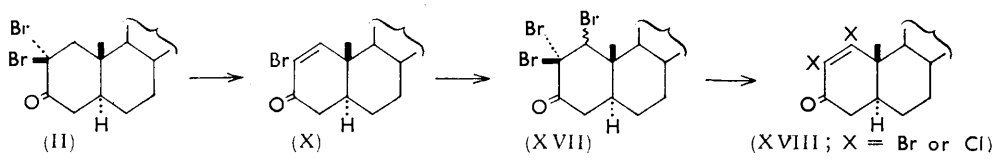
Djerassi *et al.*[10] by its ultraviolet absorption spectrum. The dibromo-ketone (IV) was unaffected by treatment with pyridine at 20° for 4 hr. Inhoffen *et al.*[2b,9] obtained a similar inseparable mixture of comparable dienones by treatment of 2,2,4-tribromocholest-4-en-3-one with collidine.

As a second possible structure for the unsaturated dibromo-ketone (IV), 1,2-dibromo-5α-cholest-1-en-3-one (XVIII; X = Br) was considered. This could be formed from the dibromo-ketone (II) by consecutive elimination of hydrogen bromide (X), addition of bromine to give the tribromo-ketone (XVII), and subsequent elimination of hydrogen bromide. This possibility appeared unlikely since the dibromo-ketone (II) was recovered

[6] Djerassi, *J. Amer. Chem. Soc.*, 1949, **71**, 1003.
[7] Green and Long, *J.*, 1961, 2532.
[8] Butenandt and Schramm, *Ber.*, 1936, **69**, 2289.
[9] Inhoffen, *Ber.*, 1936, **69**, 1134, 1702.
[10] Djerassi, Rosenkranz, Romo, Kaufmann, and Pataki, *J. Amer. Chem. Soc.*, 1950, **72**, 4534.

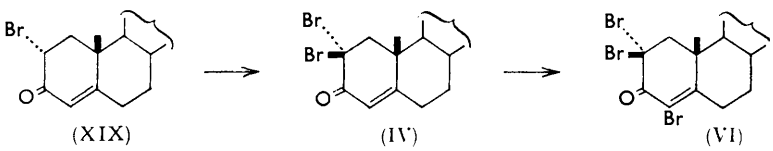
unchanged after treatment with potassium acetate in acetic acid at 80° for 2 hr.; further, the " tribromo-ketone " would be a mixture of 2,2-dibromo-5α-cholestan-3-one (II) and 1ξ,2,2-tribromo-5α-cholestan-3-one (XVII), which would not agree with the analytical figures.

An attempt was made to prepare the unsaturated dibromo-ketone (XVIII; X = Br)



by the route employed by Kirk and Petrow [11] in the synthesis of the dichloro-analogue (XVIII; X = Cl). However, the unsaturated bromo-ketone (X) was recovered unchanged when treated with bromine in dimethylformamide for 13 days at 20°.

Finally, 2,2-dibromocholest-4-en-3-one, prepared by bromination of 2α-bromocholest-4-en-3-one [6] (XIX), was found to be identical with the sample isolated after bromination of 2,2-dibromo-5α-cholestan-3-one (II).



Previous examples are known, in which bromination of 6β- [8] and 4-substituted [12] 2α-bromocholest-4-en-3-ones have given 2,2-dibromo-derivatives. The structure (IV) was established when further bromination with bromine in acetic acid in the presence of hydrogen bromide or with *N*-bromosuccinimide [13] gave 2,2,4-tribromocholest-4-en-3-one (VI); bromination of the dibromo-ketone (IV) with bromine in acetic acid in the presence of potassium acetate at 80° gave a crude product whose infrared absorption at 1745 cm.$^{-1}$ indicated the presence of the unstable tetrabromo-ketone (V) although chromatography on silica gel resulted in the isolation of 2,2,4-tribromocholest-4-en-3-one (VI) and 2,2-dibromocholest-4-en-3-one (IV), formed by the respective elimination of hydrogen bromide and bromine from the intermediate ketone (V).

Experimental

For general directions see *J.*, 1959, 630; $[\alpha]_D$ are for $CHCl_3$ solutions; ultraviolet absorption spectra were measured for EtOH solutions on a Hilger Uvispek, or a Perkin–Elmer 4000A spectrophotometer; infrared absorption spectra were determined for CCl_4 solutions in a Perkin–Elmer model 221 double-beam instrument or a Perkin–Elmer Infracord spectrophotometer. Analytical samples were dried at 20°/0·5 mm. for 2—8 hr.

Bromination of 2,2-Dibromo-5α-cholestan-3-one (II).—(*a*) 2,2-Dibromo-5α-cholestan-3-one (1 g.) in acetic acid (72 ml.) was treated with potassium acetate (3·7 g.) and bromine (441 mg., 1·5 mol.) for 30 min. at 80°. The mixture was poured into water, and the crude product, m. p. 40—45°, filtered off and dried (Found: C, 52·1; H, 6·9. Calc. for $C_{27}H_{43}Br_3O$: C, 52·0; H, 7·0%). This product was chromatographed on silica gel (80 g.). Elution with pentane gave an oil (120 mg.); then elution with ether–pentane (1 : 99) gave 2,2-dibromo-5α-cholestan-3-one (610 mg.), m. p. and mixed m. p. 157—159°. Further elution with ether–pentane (3 : 97) gave 2,2-*dibromocholest*-4-*en*-3-*one* (IV) (385 mg.), m. p. 189—191° (from ethanol), $[\alpha]_D$ +86° (*c* 0·9),

[11] Kirk and Petrow, *J.*, 1958, 1334.
[12] Shoppee, Johnston, and Lack, unpublished work.
[13] Meystre and Wettstein, *Experientia*, 1946, **2**, 408.

$\nu_{max.}$ 1706 cm.$^{-1}$, $\lambda_{max.}$ 266 mμ (log ε 4·0) (Found: C, 59·6; H, 7·7. $C_{27}H_{42}Br_2O$ requires C, 59·8; H, 7·8%).

(*b*) 2,2-Dibromo-5α-cholestan-3-one (2 g.) in acetic acid (120 ml.) was treated with potassium acetate (7·5 g.) and bromine (1·18 g., 2 mol.) for 45 min. at 80°. Water was added and the precipitated product was filtered off and chromatographed on silica gel (250 g.). Elution with pentane (7 × 200 ml.) gave 2,2,4ξ,5ξ-*tetrabromocholestan*-3-*one* (V) (300 mg.) as prisms (from pentane), m. p. 124—125°, $[\alpha]_D$ −2° (*c* 1·0), $\nu_{max.}$ 1746 cm.$^{-1}$, O.R.D. (in methanol) −1500° (350 mμ), −11,600° (300 mμ), −600° (280 mμ), −9600° (270 mμ) (Found: C, 46·2; H, 6·2. $C_{27}H_{42}Br_4O$ requires C, 46·2; H, 6·05%). Overheating of this tetrabromo-ketone (V) during crystallisation caused elimination of hydrogen bromide, to give 2,2,4-tribromocholest-4-en-3-one (VI), m. p. 179—180°, $[\alpha]_D$ −60° (*c* 1·1), $\nu_{max.}$ 1705 cm.$^{-1}$, $\lambda_{max.}$ 277 mμ (log ε 3·97) (Found: C, 52·8; H, 6·9. Calc. for $C_{27}H_{41}Br_3O$: C, 52·2; H, 6·65%). Elution with ether–pentane (1 : 19; 2 × 200 ml.) gave unchanged 2,2-dibromo-5α-cholestan-3-one (400 mg.), m. p. and mixed m. p. 160°. Further elution with the same solvent (3 × 200 ml.) gave 2,2-dibromocholest-4-en-3-one (300 mg.), m. p. and mixed m. p. 190—192°.

Treatment of 2,2,4ξ,5ξ-*Tetrabromocholestan*-3-*one* (V) *with Hydrogen Bromide.*—2,2,4ξ,5ξ-Tetrabromocholestan-3-one (100 mg.) was treated with 0·1N-hydrogen bromide in acetic acid for 12 hr. at 20°. Addition of water precipitated 2,2,4-tribromocholest-4-en-3-one (60 mg.), m. p. and mixed m. p. 179—180°.

Treatment of "Tribromo-ketone" with Hydrogen Bromide.—The crude "tribromo-ketone" [1] (200 mg.) was treated with 0·1N-hydrogen bromide in acetic acid for 12 hr. at 20°. Addition of water gave a solid, m. p. 65—80°, $\nu_{max.}$ 1756, 1706 cm.$^{-1}$, which was chromatographed on silica gel (20 g.) in pentane. Elution with ether–pentane (1 : 19; 2 × 20 ml.) gave 2,2,4-tribromocholest-4-en-3-one, m. p. and mixed m. p. 175—178°, whilst further elution with ether–pentane (1 : 10; 1 × 20 c.c.) gave 2α,4α-dibromo-5α-cholestan-3-one, m. p. and mixed m. p. 194—195°.

Bromination of 2α,4α-*Dibromo*-5α-*cholestan*-3-*one* (VII).—2α,4α-Dibromo-5α-cholestan-3-one (300 mg.) in acetic acid (18 ml.) was treated with potassium acetate (1·12 g.) and bromine (177 mg., 2 mol.) for 30 min. at 80°. Water was added and the precipitated product was chromatographed on silica gel (30 g.). Elution with pentane (8 × 30 ml.) gave 2,2,4ξ,5ξ-tetrabromocholestan-3-one (V) (150 mg.), m. p. and mixed m. p. 124—125°, with the correct infrared spectrum. Further elution with ether–pentane (1 : 19; 2 × 30 ml.) gave 2,2-dibromocholest-4-en-3-one (50 mg.), m. p. 188—190°, identical with the sample prepared as above.

2-*Bromo*-5α-*cholest*-1-*en*-3-*one* (X).—(*a*) 2,2-Dibromo-5α-cholestan-3-one [1] (m. p. 160—161°; 3·5 g.) was treated under nitrogen with collidine (12 ml.) at 180° for 30 min.; the product was extracted with ether, washed with 2N-hydrochloric acid and worked up in the usual way, forming an oil; it was purified by chromatography on aluminium oxide (90 g.) in pentane. Elution with benzene (5 × 80 ml.) gave 2-bromo-5α-cholest-1-en-3-one (2·2 g.), m. p. 108° (from acetone), $\nu_{max.}$ 1706 cm.,$^{-1}$ $\lambda_{max.}$ 256 mμ (log ε 4·0) (Found: C, 69·9; H, 9·5. Calc. for $C_{27}H_{43}BrO$: C, 69·8; H, 9·5%).

(*b*) 5α-Cholest-1-en-3-one [2b] (840 mg.) in dimethylformamide (8·5 ml.) and ether (10 ml.) was treated in the dark with bromine in acetic acid (1 : 1 mol.) at 0—30° for 16 hr. The usual working up gave an oil (800 mg.) which was chromatographed on aluminium oxide (20 g.) in pentane. Elution with benzene (6 × 20 ml.) gave 2-bromo-5α-cholest-1-en-3-one (410 mg.), m. p. and mixed m. p. 107—108°.

2,4β-*Dibromo*-5α-*cholest*-1-*en*-3-*one* (XI).—2-Bromo-5α-cholest-1-en-3-one (1·68 g.) in acetic acid (60 ml.), containing 4 drops of 4N-hydrogen bromide in acetic acid, was treated with a 7·7% w/v solution of bromine in acetic acid (7·5 ml.; 1·0 mol.) at 20° for 8 hr. The solution was poured into water, and the crude product was chromatographed on silica gel (150 g.) in pentane. Elution with ether–pentane (1 : 20; 3 × 100 ml.) gave 2,4β-*dibromo*-5α-*cholest*-1-*en*-3-*one* (1·05 g.), m. p. 125—128° (from methanol), $[\alpha]_D$ +27° (*c* 1·0), $\nu_{max.}$ 1702 cm.$^{-1}$, $\lambda_{max.}$ 262 mμ (log ε 3·83) (Found: C, 59·7; H, 7·9. $C_{27}H_{42}Br_2O$ requires C, 59·8; H, 7·8%).

2-*Bromocholesta*-1,4-*dien*-3-*one* (XII).—2,4β-Dibromo-5α-cholest-1-en-3-one (840 mg.) was treated under nitrogen with collidine (3 ml.) at 180° for 30 min. The product was isolated with ether in the usual way, forming an oil (760 mg.), which was chromatographed on aluminium oxide (25 g.) in pentane. Elution with ether–benzene (1 : 1; 12 × 25 ml.) gave 2-*bromocholesta*-1,4-*dien*-3-*one* (XII) (400 mg.), m. p. 130° (from methanol), $[\alpha]_D$ −13° (*c* 0·9), $\nu_{max.}$ 1665 cm.$^{-1}$, $\lambda_{max.}$ 255 mμ (log ε 4·2) (Found: C, 70·4; H, 9·0. $C_{27}H_{41}BrO$ requires C, 70·3; H, 9·0%).

Treatment of 2,2'-Dibromocholest-4-en-3-one (IV) *with Collidine.*—(*a*) 2,2-Dibromocholest-4-en-3-one (60 mg.) was treated with collidine (1 ml.) under nitrogen at 140—145° for 20 min. The usual working up gave a product that, crystallised from methanol, had m. p. 156°, $\lambda_{max.}$ 250 mμ and is believed to be 2α,6β-dibromocholest-4-en-3-one.

(*b*) 2,2-Dibromocholest-4-en-3-one (37 mg.) was treated with collidine (1 ml.) under nitrogen at 180° for 30 min. After the usual isolation procedure the crude product (27 mg.) was chromatographed on aluminium oxide (1 g.) in pentane. Elution with ether–pentane (1 : 10; 2 × 5 ml.) gave a mixture of monobromodienones; recrystallised from methanol, this had m. p. 121—125°, $\lambda_{max.}$ 250, 275 mμ, $\nu_{max.}$ 1665 cm.$^{-1}$ (Found: C, 70·7; H, 9·4. Calc. for $C_{27}H_{41}BrO$: C, 70·3; H, 9·0%). This is believed to be a mixture of 2-bromocholesta-1,4-dien-3-one (XII) and 2α-bromocholesta-4,6-dien-3-one.

(*c*) The dibromo-ketone (IV) (240 mg.) was treated with collidine (5 ml.) under nitrogen at 220° for 1 hr. The usual isolation procedure gave an oil (180 mg.), which was chromatographed on aluminium oxide (6 g.) in pentane. Ether–pentane (1 : 10; 7 × 5 ml.) eluted the mixture of monobromodienones (50 mg.) described in (*b*) and having m. p. and mixed m. p. 121—125°. Further elution with ether–pentane (1 : 5; 9 × 5 ml.) gave slightly impure cholesta-1,4,6-trien-3-one (XVI), m. p. 80° (from methanol), $\lambda_{max.}$ 226, 256, 300 mμ (Found: C, 84·0; H, 10·3. Calc. for $C_{27}H_{40}O$: C, 85·2; H, 10·6%).

Bromination of 2α-Bromocholest-4-en-3-one (XIX).—2α-Bromocholest-4-en-3-one (370 mg.), prepared by Djerassi's method,[6] was treated in dimethylformamide (4 ml.) and ether (6 ml.) with bromine (140 mg., 1·1 mol.) at 0° for 24 hr. The mixture was worked up in the usual way, giving a solid (448 mg.) which was chromatographed on silica gel (40 g.) in pentane. Ether–pentane (1 : 19) eluted 2,2-dibromocholest-4-en-3-one (IV) (150 mg.), m. p. and mixed m. p. 192—193°. The infrared absorption was identical with that of the sample prepared above.

Bromination of 2,2'-Dibromocholest-4-en-3-one (IV).—(*a*) The dibromo-ketone (IV) (40 mg.), in acetic acid (5 ml.) and ether (2 ml.) containing a drop of hydrogen bromide in acetic acid, was treated with bromine (12 mg., 1·0 mol.) at 20° for 18 hr. The usual isolation procedure gave 2,2,4-tribromocholest-4-en-3-one (VI) (30 mg.), m. p. and mixed m. p. 179—180°.

(*b*) The same result was obtained when the dibromo-ketone (IV) (127 mg.) was refluxed with dry *N*-bromosuccinimide (48 mg.) in dry carbon tetrachloride (15 ml.) for 1 hr.

(*c*) The dibromo-ketone (IV) (145 mg.) in acetic acid (5 ml.) containing freshly fused potassium acetate (0·4 g.) was treated with bromine (43 mg., 1·0 mol.) at 80° for 45 min. The product was precipitated by addition of water to the cooled solution; the crude product had $\nu_{max.}$ 1745 cm.$^{-1}$, indicating the presence of the tetrabromo-ketone (V), with a small peak at 1706 cm.$^{-1}$. It was chromatographed on silica gel (5 g.) in pentane. Ether–pentane (1 : 99: 3 × 5 ml.) eluted 2,2,4-tribromocholest-4-en-3-one (40 mg.), m. p. and mixed m. p. 176—179°. Further elution with ether–pentane (1 : 49) gave unchanged 2,2-dibromocholest-4-en-3-one (60 mg.), m. p. mixed m. p. 188—190°.

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