## 122. *Studies in the Sterol Group. Part XL. The Bromination of 7-Ketocholesteryl Acetate.*

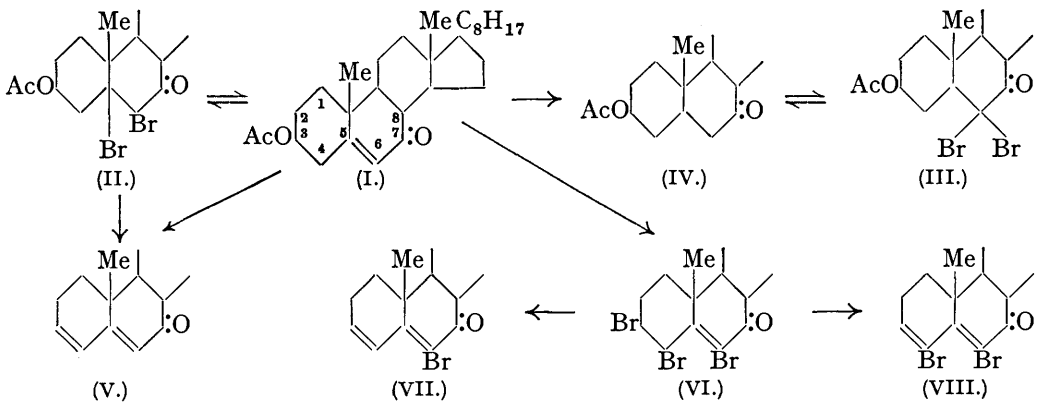
By H. Jackson and E. R. H. Jones.

**5 : 6-*Dibromo*-7-*ketocholestanyl acetate*** and **3 : 4 : 6-*tribromo*-7-*keto*-$\Delta^5$-*cholestene*** have been prepared and characterised. The effect of substituent bromine atoms upon the light absorption of steryl ketones is briefly discussed.

As a continuation of a study of the bromination of steroid ketones (Heilbron, Jones, and Spring, J., 1937, 801; Heilbron, Jackson, Jones, and Spring, J., 1938, 102; Barr, Heilbron,

Jones, and Spring, *ibid.*, p. 334; Jackson and Jones, *ibid.*, p. 1406) in attempts to obtain unsaturated compounds suitable for aromaticisation to steryl analogues of the œstrogenic hormones, we have now examined the products obtained by the bromination of 7-keto-cholesteryl acetate (7-keto-3-acetoxy-$\Delta^5$-cholestene) (I). In the presence of excess bromine, 5 : 6-*dibromo-7-ketocholestanyl acetate* (II), m. p. 146—147° (decomp.), separates after an hour from a saturated solution. Its ready reconversion into the unsaturated keto-acetate (I) with potassium iodide in acetone proves its constitution. In this behaviour and in its absorption spectrum (the ketone band being displaced to longer wave-lengths by the adjacent bromine atom), the dibromide resembles 4 : 5-dibromo-6-ketocholestanyl acetate (Jackson and Jones, *loc. cit.*), but it is considerably more stable than the latter, and attempts to prepare an unsaturated monobromide were not so successful as in the latter case. Treatment with anhydrous potassium acetate in boiling acetic acid yielded a bromo-compound which could not be obtained analytically pure, but its absorption maxima at about 2400 and 3200 A. ($E^{1\%}_{1cm.}$ 110 and 1·4 respectively) suggested that the impure unsaturated bromo-ketone had been obtained. Elimination of hydrogen bromide from 6 : 6'-dibromo-7-ketocholestanyl acetate (III) (Barr, Heilbron, Jones, and Spring, *loc. cit.*) suggested itself as a possible route to the unsaturated monobromide, but intractable gels were obtained in numerous reactions and with boiling dimethylaniline reduction occurred to yield the saturated keto-acetate (IV). Such reductions of bromo-ketones with basic reagents have been observed previously (Butenandt, Schramm, and Kudszus, *Annalen*, 1937, **531**, 192; Jackson and Jones, *loc. cit.*) and as a further example we now record the isolation of 6-ketocholestanyl acetate from the product obtained by dimethylaniline treatment of 7-bromo-6-ketocholestanyl acetate (Heilbron, Jones, and Spring, *loc. cit.*). When treated in a similar manner, the dibromide (II) yielded 7-keto-$\Delta^{3:5}$-cholestadiene (oxycholesterylene) (V), reduction being accompanied by elimination of acetic acid. This keto-diene (V) has previously been obtained in poor yield (Mauthner and Suida, *Monatsh.*, 1896, **17**, 596) by hydrolysis of 7-ketocholesteryl acetate (I) with alcoholic potassium hydroxide. We now find that this removal of acetic acid can be rapidly effected in almost quantitative yield simply by treatment of (I) with a hot acetic acid solution of hydrogen bromide. The dibromide (II) under similar conditions fails to yield any homogeneous product.

The bromination of 7-ketocholesteryl acetate (I) to products other than the dibromide (II) presented considerable difficulty and it was not until the reaction was carried out in dilute solution at 30° that a homogeneous crystalline product, an unsaturated tribromide, decomposing at about 143°, was isolated, for which we suggest the constitution 3 : 4 : 6-*tribromo-7-keto-*$\Delta^5$*-cholestene* (VI). That this tribromide is an $\alpha\beta$-unsaturated ketone was revealed by its absorption spectrum (figure), and analysis immediately indicated that removal of the acetyl group had accompanied the bromination. We have ascertained

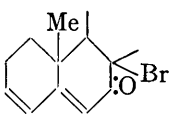



that the elimination of the acetyl group from 7-ketocholesteryl acetate (I) takes place under conditions similar to those obtaining during the preparation of the tribromide, since a good yield of 7-keto-$\Delta^{3:5}$-cholestadiene (V) was produced by the action of hydrogen

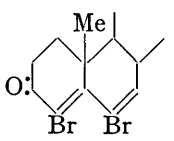
bromide in acetic acid on the unsaturated ketone at 37°. Attempts to isolate further products of the bromination reaction were ineffective, variations in the optimum experimental conditions recorded resulting in the production of the dibromide (II), the tribromide (VI) or of unresolvable mixtures, the experimental difficulties being enhanced by the ready decomposition of the tribromide in hot solvents.

Elimination of hydrogen bromide from the tribromide (VI) was smoothly effected in almost quantitative yield by treatment either with a solution of silver nitrate in pyridine (Dane, Wang, and Schulte, *Z. physiol. Chem.*, 1936, **245**, 80) or with anhydrous potassium acetate in acetic acid at 100°, to yield 4 : 6-*dibromo*-7-*keto*-$\Delta^{3:5}$-*cholestadiene* (VIII), m. p. 189—190°. A poorer yield of this diethenoid dibromide was also obtained by heating the tribromide under reflux with dimethylaniline. Further insight into the structure of these unsaturated bromides was gained when the tribromide (VI) was treated with potassium iodide in boiling acetone. The ease with which bromine is removed from the tribromide in this way provides evidence that two of the bromine atoms are situated on adjacent carbon atoms, which must be $C_3$ and $C_4$. The 6-*bromo*-7-*keto*-$\Delta^{3:5}$-*cholestadiene* (VII), m. p. 117°, so obtained is resistant to all attempts further to remove bromine. For example, it is not reduced with zinc dust in either boiling methyl alcohol or hot acetic acid, and is recovered unchanged after three hours' boiling with dimethylaniline, and attempts to reproduce the tribromide by addition of bromine were unsuccessful. The possibility of the alternative constitution, 8-bromo-7-keto-$\Delta^{3:5}$-cholestadiene (IX), for the monobromide, m. p. 117° (VII), and corresponding formulæ for the unsaturated polybromides cannot be dismissed on the available experimental evidence, but a number of factors combine to suggest that such a constitution is highly improbable. Thus, the results described here with 7-ketocholesteryl acetate are closely analogous to those obtained on bromination of $\Delta^4$-cholestenone (3-keto-$\Delta^4$-cholestene) (for summary see Butenandt, Schramm, and Kudszus, *loc. cit.*) in which no bromination in the 2-position was observed. Further, no evidence of substitution in the 8-position was revealed in a study of the bromination of 7-ketocholestanyl acetate (IV) (Barr, Heilbron, Jones, and Spring, *loc. cit.*).

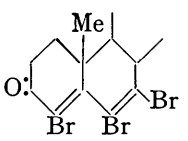
The absorption spectrum of the diethenoid monobromide (VII) is comparable (see figure) with that of 7-keto-$\Delta^{3:5}$-cholestadiene (V), and also with that of 3 : 17-diketo-$\Delta^{4:6}$-androstadiene (X) (Ruzicka and Bosshard, *Helv. Chim. Acta*, 1937, **20**, 329), being typical of a carbonyl group conjugated with a diene system where the ethylenic linkages are in different rings. Where the two linkages are situated in the same ring, as in 6-keto-3-acetoxy-$\Delta^{3:4}$-cholestadiene (Heilbron, Jackson, Jones, and Spring, *loc. cit.*), a displacement of some 300—400 A. towards longer wave-lengths is observed, a characteristic property of such systems. The dibromide (VIII) exhibits a main absorption maximum at 3030 A.; this displacement from the normal value by about 200 A. is to be attributed to the effect of the substituent bromine atoms. Similar observations have been made by Butenandt, Schramm, and Kudszus (*loc. cit.*) with 4 : 6-dibromo-3-keto-$\Delta^{4:6}$-cholestadiene (XI)



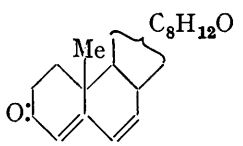
(IX.)



(XI.)



(XII.)



(X.)

[maximum (chloroform), 2970 A.; log $\varepsilon^*$ = 4·3] and to a greater extent with the tribromide (XII) [maximum (chloroform), 3130 A.; log $\varepsilon$ = 4·24], and 6-ethoxy-3-keto-$\Delta^{4:6}$-cholestadiene also shows a marked displacement to 3000 A. The displacement of the low intensity absorption band due to the carbonyl group by an α-bromine atom has frequently been observed and several examples of this phenomenon in the sterol series have been recorded (Barr, Heilbron, Jones, and Spring, *loc. cit.*). It now appears that this displace-

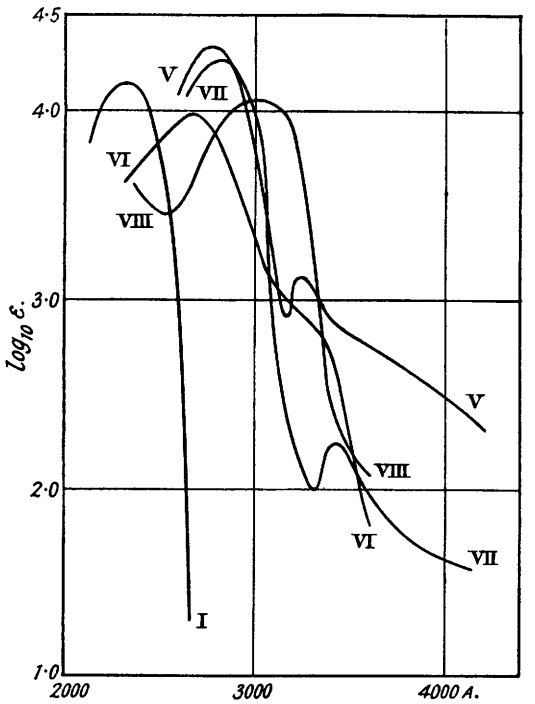
* Butenandt, Schramm, and Kudszus (*loc. cit.*) record intensity data as K (mm.$^{-1}$) for 0·02% solutions. These intensities have been converted into $\epsilon$ values by means of the relation $\epsilon$ = K × molecular weight/concentration × 2·3.

ment effect persists in the modified carbonyl band of αβ-unsaturated ketones when the bromine atoms are adjacent to the chromophoric group.

| | Supplementary maximum, A. | log ε. |
|---|---|---|
| 6-Keto-3-acetoxy-$\Delta^4$-cholestene | 3200 | 1·95 |
| 4-Bromo-6-keto-3-acetoxy-$\Delta^4$-cholestene | 3350 | 2·3 |
| 7-Keto-$\Delta^{3:5}$-cholestadiene (V) | 3250 | 3·1 |
| 6-Bromo-7-keto-$\Delta^{3:5}$-cholestadiene (VII) | 3440 | 2·2 |

## Experimental.

5 : 6-*Dibromo*-7-*ketocholestanyl Acetate* (II).—A solution of 7-ketocholesteryl acetate (4 g.) in acetic acid (25 c.c.) at 60° was treated with a cold solution of bromine in acetic acid (50 c.c.; 10%); 5 : 6-*dibromo*-7-*ketocholestanyl acetate* (3 g.) separated after an hour and was twice recrystallised from acetic acid, forming fine needles, m. p. 146—147° (decomp.) (Found : C, 57·4; H, 8·1. $C_{29}H_{46}O_3Br_2$ requires C, 57·7; H, 7·8%). *Light absorption in alcohol :* Maximum, 3140 A.; log ε = 2·2.




7-*Ketocholesteryl Acetate from the Dibromide.*—The dibromide (1 g.) was added to a mixture of potassium iodide (2 g.) and boiling acetone (50 c.c.). Iodine was liberated instantaneously and after 1 minute's boiling, the solution was diluted with water until cloudy; 7-ketocholesteryl acetate then separated in large plates, m. p. 153—154°, giving no depression when mixed with an authentic specimen.

*Treatment of* 6 : 6′-*Dibromo*-7-*ketocholestanyl Acetate* (III) *with Dimethylaniline.*—The dibromide (800 mg.) was heated under reflux with dimethylaniline (15 c.c.) for 3 hours. The cooled solution after dilution with ether was washed with dilute hydrochloric acid and water; the residue obtained from the dried ethereal solution on evaporation crystallised from methyl alcohol in plates of 7-ketocholestanyl acetate (200 mg.), m. p. 140—141°, alone and in admixture with an authentic specimen.

*Treatment of* 7-*Bromo*-6-*ketocholestanyl Acetate with Dimethylaniline.*—A solution of the bromide (500 mg.) in dimethylaniline (10 c.c.) was heated under reflux for 2 hours. Isolation of the product in the usual manner gave 6-ketocholestanyl acetate (250 mg.), m. p. 128°, undepressed on admixture with an authentic specimen (Found : C, 78·6; H, 10·5. Calc. for $C_{29}H_{48}O_3$: C, 78·3; H, 10·8%). Hydrolysis yielded 6-ketocholestanol, m. p. 139—140°, which gave the

benzoate as prisms, m. p. 170—171°, from methyl alcohol–acetone (Found : C, 80·4; H, 9·6. Calc. for $C_{34}H_{50}O_3$ : C, 80·6; H, 9·9%).

7-*Keto*-$\Delta^{3:5}$-*cholestadiene* (V).—(a) A solution of the dibromide (800 mg.) in dimethylaniline (10 c.c.) was heated under reflux for 2 hours. The residual oil, isolated as above, was taken up in ether–methyl alcohol; at 0° crystals slowly separated. Repeated crystallisation from methyl alcohol gave 7-keto-$\Delta^{3:5}$-cholestadiene, m. p. 106—107°, undepressed on admixture with authentic material. *Light absorption in alcohol* (cf. figure) : Maximum, 2800 A.; log $\varepsilon = 4{\cdot}43$.

(b) A mixture of the keto-acetate (1 g.), acetic acid (30 c.c.), and a solution of hydrogen bromide in acetic acid (2·5 c.c.; 50%) was heated under reflux for 10 minutes. 7-Keto-$\Delta^{3:5}$-cholestadiene (600 mg.), m. p. 111—112°, was isolated by dilution with water and crystallisation of the product from methyl alcohol. A similar yield of the keto-diene was obtained when the same mixture was kept at 37° for 15 hours. No depression in m. p. was observed with either specimen mixed with authentic material.

3 : 4 : 6-*Tribromo*-7-*keto*-$\Delta^{5}$-*cholestene* (VI).—To a solution of 7-ketocholesteryl acetate (2 g.) in acetic acid (35 c.c.), solutions of hydrogen bromide in acetic acid (0·2 c.c.; 50%) and bromine in acetic acid (5 c.c.; 5%) were added and the mixture was heated to 30°. When decolorisation was complete, bromine in acetic acid (43 c.c.; 5%; 3 mols. in all) was added, and the solution kept at 30° in a thermostat for 60 hours. The separated crystalline material was dissolved in the minimum volume of chloroform, and acetic acid rapidly added; 3 : 4 : 6-*tribromo*-7-*keto*-$\Delta^{5}$-*cholestene* (1 g.) then separated in fine needles, which were washed with methyl alcohol. The tribromide decomposed at about 143°, the exact temperature varying considerably with the rate of heating. A mixture with the saturated dibromide, m. p. 146—147°, decomposed at about 120° (Found : Br, 38·6, 38·7. $C_{27}H_{41}OBr_3$ requires Br, 38·6%).

4 : 6-*Dibromo*-7-*keto*-$\Delta^{3:5}$-*cholestadiene* (VIII).—(a) A mixture of the tribromide (600 mg.), freshly fused potassium acetate (1 g.), and acetic acid (25 c.c.) was heated on the steam-bath for an hour. The solid (500 mg.), m. p. 175—180°, obtained on addition of water was crystallised from aqueous acetone and then twice from dilute acetic acid, from which 4 : 6-*dibromo*-7-*keto*-$\Delta^{3:5}$-*cholestadiene* separated in hair-like needles, m. p. 189—190°. For analysis the specimen was dried in a high vacuum for 3 hours at 100° (Found : C, 60·1; H, 7·8; Br, 29·1. $C_{27}H_{40}OBr_2$ requires C, 60·0; H, 7·5; Br, 29·6%).

(b) The tribromide (100 mg.) was dissolved in a solution of silver nitrate in pyridine (5 c.c.; 10%), and the mixture set aside for 30 hours at 15°. After treatment with water and extraction with ether the ethereal solution was washed with dilute hydrochloric acid and water, dried, and evaporated. Recrystallisation of the residual solid from dilute acetic acid yielded the unsaturated dibromide (50 mg.), m. p. 189—190° both alone and in admixture with a specimen prepared by method (a).

6-*Bromo*-7-*keto*-$\Delta^{3:5}$-*cholestadiene* (VII).—The tribromide (2 g.) was added to a mixture of potassium iodide (4 g.) and acetone (80 c.c.) at the b. p., and the mixture boiled for a further minute. On cooling after careful addition of water, crystalline material was obtained, which on recrystallisation from aqueous acetone yielded 6-*bromo*-7-*keto*-$\Delta^{3:5}$-*cholestadiene* (1 g.) in long, pale yellow needles, m. p. 117°, unaltered by three further recrystallisations. The bromide gradually decomposed on keeping, but was unaffected by heating with pyridine or dimethylaniline for 3 hours (Found : C, 70·3, 70·2; H, 9·0, 9·1; Br, 17·7. $C_{27}H_{41}OBr$ requires C, 70·2; H, 9·0; Br, 17·3%).

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