67. *Studies in the Sterol Group. Part XXXV. The Bromination of 7-Ketocholestanyl Acetate.*

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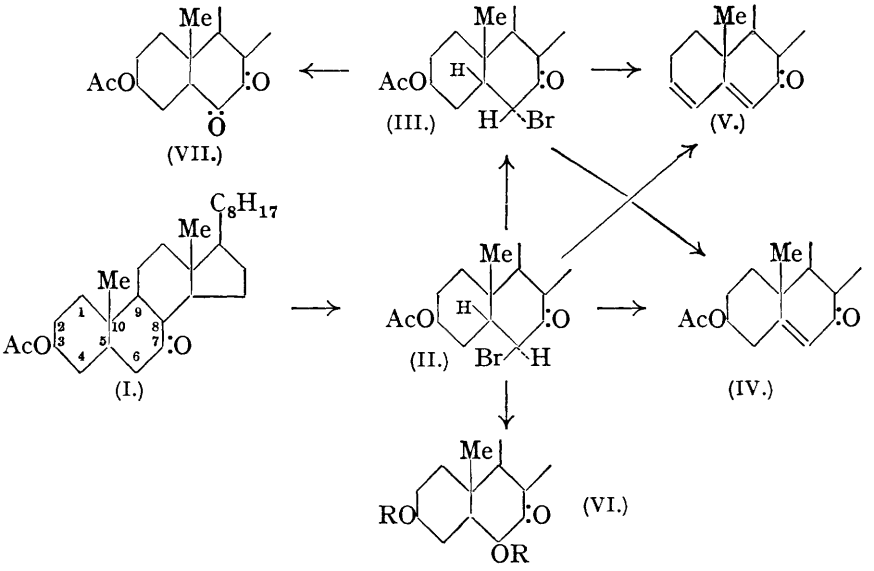
In continuation of our study of the bromination of steroid ketones, which has as its ultimate object the preparation of heavily unsaturated derivatives, an investigation of 7-ketocholestanyl acetate has been undertaken. Two monobromides were obtained with one mole of bromine and shown to be stereoisomeric 6-bromo-7-ketocholestanyl acetates.

In contradistinction to 6-ketocholestanyl acetate (Heilbron, Jones, and Spring, J., 1937, 801; Heilbron, Jackson, Jones, and Spring, this vol., p. 102) the isomeric 7-ketocholestanyl acetate (I) is not brominated in acetic acid at room temperature. In chloroform at room temperature with one mole of bromine, however, α-6-*bromo*-7-*ketocholestanyl acetate* (II), m. p. 173—175°, is obtained, the constitution of which is established by its facile conversion into 7-keto-3-acetoxy-Δ^5-cholestene (IV) and 7-keto-$\Delta^{3:5}$-cholestadiene (V) on treatment with pyridine. Hydrolysis of the monobromide with methyl-alcoholic potassium hydroxide gives 3 : 6-dihydroxy-7-ketocholestane (VI, R = H), characterised as a disecondary alcohol by its *dibenzoate* (VI, R = COPh), m. p. 184—186°. Both from the mother-liquor of the monobromide, m. p. 173—175°, and also by the action of hydrogen bromide on the α-monobromide the isomeric β-6-*bromo*-7-*ketocholestanyl acetate* (III), m. p. 142—143°, is obtained, which with pyridine likewise gives (IV) and (V), the elimination of hydrogen bromide, however, being effected in this case only with difficulty. The difference in orientation of the halogen atom in the two new monobromides is clearly illustrated by their reactions with silver nitrate and pyridine. Whereas the α-isomer readily gives the unsaturated ketone (IV), the β-bromide gives 6 : 7-diketocholestanyl acetate (VII), a behaviour reminiscent of the stable 7-bromo-6-ketocholestanyl acetate (Heilbron, Jones, and Spring, *loc. cit.*), and which we again attribute to an inherent difficulty of removal of hydrogen halide, with consequent tendency to hydrolysis and oxidation. These results would appear to indicate that in the α-isomer the hydrogen attached to C_5 and the C_6 bromine atom are *cis*-oriented and that in the β-bromide the *trans*-orientation obtains.

Treatment of 7-ketocholestanyl acetate with two moles of bromine or of either of the monobromides with one mole of bromine in the presence of hydrogen bromide, gives a

dibromide, m. p. 176—177°. The formation of this compound from 7-ketocholestanyl acetate must proceed *via* the α-6-monobromide, followed by isomerisation to the β-isomeride. This is shown by the fact that, when one mole of bromine and one mole of hydrogen bromide are used, the velocity of bromination of the α-monobromide is markedly less than in the case of its stereoisomer. The dibromide does not react with *o*-phenylenediamine in alcohol and only unworkable gels are obtained by the action of pyridine, pyridine and silver nitrate, methyl-alcoholic potassium hydroxide and potassium acetate in alcohol.



An observation of some interest is revealed by a consideration of the ultra-violet absorption spectra of the mono- and di-bromo-substitution products of 6- and 7-ketocholestanyl acetates :—

	Maximum, A.	Log ε.
7-Ketocholestanyl acetate	2870	1·6
α-6-Bromo-7-ketocholestanyl acetate	3130	2·2
β-6-Bromo-7-ketocholestanyl acetate	2820	1·6
Dibromo-7-ketocholestanyl acetate	3040	2·2
6-Ketocholestanyl acetate	2800	1·6
5-Bromo-6-ketocholestanyl acetate	3080	2·1
7-Bromo-6-ketocholestanyl acetate	3100	2·2
5 : 7-Dibromo-6-ketocholestanyl acetate	3400	2·2
5′ : 7-Dibromo-6-ketocholestanyl acetate	3050	2·1

A marked displacement of the absorption band due to the carbonyl group by the introduction of a bromine atom in the α-position is only observed when the halogen atom has a particular steric arrangement. Thus in the case of 7-ketocholestanyl acetate the band at 2870 A. is displaced to 3130 A. in α-6-bromo-7-ketocholestanyl acetate, but no such effect is observed in the case of the β-isomer. This phenomenon becomes especially clear from a consideration of the isomeric dibromides of 6-ketocholestanyl acetate (Heilbron, Jackson, Jones, and Spring, *loc. cit.*). In the case of 5 : 7-dibromo-6-ketocholestanyl acetate, the observed single displacements (approximately 300 A.) of the 5- and 7-monobromides are additive in effect; on the other hand, the 5′ : 7-isomer exhibits only a single displacement due to the effect of the C_7 halogen atom, the bromine at $C_{5'}$ being without optical influence.

Experimental.

7-Ketocholestanyl Acetate (cf. Windaus and Kirchner, *Ber.*, 1920, **53**, 614).—A suspension of 7-keto-3-acetoxy-Δ^5-cholestene (10 g.) in acetic acid (120 c.c.) was shaken with palladium–norit and hydrogen until absorption of gas was complete. The solution was filtered and diluted

with water, and the solid crystallised from ether–methyl alcohol, from which 7-ketocholestanyl acetate (9·8 g.) separated in lustrous plates, m. p. 142—143°.

Reduction of 7-Ketocholestanol to Cholestanol.—The observation that both 6- and 7-ketocholestanes give the same dicarboxylic acid on oxidation (Windaus, *Ber.*, 1920, **53**, 496) indicates that rings A and B in the two ketones have the same relative configuration. It is conceivable, however, that during such an oxidation inversion of C_5 may have occurred. We have now shown that 7-ketocholestanyl acetate is a derivative of cholestane and not of coprostane, since reduction by the Wolff–Kishner method, *via* the semicarbazone, gives cholestanol. A solution of 7-ketocholestanol (Windaus and Kirchner, *loc. cit.*) (3·2 g.) in hot alcohol (50 c.c.) was treated with alcoholic semicarbazide acetate, and the mixture set aside at room temperature for 60 hours. The crude semicarbazone obtained by addition of water was crystallised once from alcohol and, after drying, the solid (2·8 g.) was heated at 190° in a sealed tube for 7 hours with sodium ethoxide in alcohol (25 c.c.; 20%). The reaction mixture was treated with water, and the product isolated with ether. Trituration of the residual gum with acetone gave a solid (1·2 g.), two crystallisations of which from alcohol yielded cholestanol (0·6 g.), m. p. 141°, not depressed on admixture with an authentic specimen.

α-6-*Bromo*-7-*ketocholestanyl Acetate* (II).—7-Ketocholestanyl acetate (5 g.) in chloroform (30 c.c.) was treated at 20° with a freshly prepared solution of bromine in chloroform (13 c.c.; 15%). The mixture was stirred throughout the addition, which extended over 5 minutes, the chloroform removed under reduced pressure, and the residual solid triturated with acetone and filtered. After one crystallisation from the same solvent α-6-*bromo*-7-*ketocholestanyl acetate* (2·8 g.) separated in thick plates, m. p. 173—175°, $[\alpha]_D^{19°}$ + 35° (l = 1, c = 1·0 in chloroform) (Found: C, 66·8; H, 9·1. $C_{29}H_{47}O_3Br$ requires C, 66·5; H, 9·1%).

β-6-*Bromo*-7-*ketocholestanyl Acetate* (III).—(a) The first acetone mother-liquor of α-6-bromo-7-ketocholestanyl acetate was evaporated and the solid obtained was repeatedly crystallised from dilute acetic acid to give β-6-*bromo*-7-*ketocholestanyl acetate* (1 g.) in leaflets, m. p. 142—143°, $[\alpha]_D^{19°}$ − 8·8° (l = 1, c = 1·0 in chloroform) (Found: C, 66·5; H, 9·0%).

(b) α-6-Bromo-7-ketocholestanyl acetate (0·5 g.) in acetic acid (50 c.c.) was treated with a solution of hydrogen bromide in acetic acid (5 c.c.; 50%), and the mixture heated on the steam-bath for 15 minutes, the colour of the solution passing through red to a deep brown. The oil precipitated with water was isolated by ether extraction and taken up in hot aqueous acetic acid; β-6-bromo-7-ketocholestanyl acetate separated in leaflets, m. p. 142—143°, not depressed by the specimen prepared by method (a).

Treatment of α- and β-6-Bromo-7-ketocholestanyl Acetates with Pyridine.—A solution of α-6-bromo-7-ketocholestanyl acetate (1·0 g.) in anhydrous pyridine (10 c.c.) was heated under reflux for 6 hours. The cold solution was diluted with water and the product, isolated with ether, was crystallised from methyl alcohol, yielding 7-keto-3-acetoxy-Δ^5-cholestene, m. p. 155—156° either alone or in admixture with an authentic specimen. From the mother-liquor, 7-keto-$\Delta^{3:5}$-cholestadiene was isolated, m. p. 110—112°, giving no depression with an authentic specimen and exhibiting the typical light absorption in alcohol (maximum, 2800 A.). In the case of β-6-bromo-7-ketocholestanyl acetate a satisfactory elimination of hydrogen bromide was only effected if the treatment with pyridine was continued for at least 8 hours. After this time 7-keto-3-acetoxy-Δ^5-cholestene and 7-keto-$\Delta^{3:5}$-cholestadiene were isolated and identified as described above.

7-*Keto*-3 : 6-*dibenzoyloxycholestane.*—α-6-Bromo-7-ketocholestanyl acetate (0·9 g.) was heated under reflux with methyl-alcoholic potassium hydroxide (30 c.c.; 10%) for 2 hours. Addition of water to the reaction mixture gave a gum, which was isolated by means of ether and solidified on boiling with methyl alcohol. The keto-diol separated from methyl alcohol in leaflets, softening at 140°, m. p. 148—150°. When it was kept at room temperature for 18 hours with benzoyl chloride and pyridine, 7-*keto*-3 : 6 *dibenzoyloxycholestane* was obtained; this crystallised from acetone–methyl alcohol in small prisms, softening at 182°, m. p. 184—186° (Found: C, 78·4; H, 8·7. $C_{41}H_{54}O_5$ requires C, 78·5; H, 8·7%).

Treatment of α- and β-6-Bromo-7-ketocholestanyl Acetates with Silver Nitrate and Pyridine.—A solution of either α- or β-6-bromo-7-ketocholestanyl acetate (1·0 g.) and silver nitrate (2·0 g.) in anhydrous pyridine (20 c.c.) was heated under reflux for 5 hours. Ether was added to the cold solution, which was then washed with dilute sulphuric acid and water. In the case of the α-isomer the product obtained after removal of the ether readily crystallised from methyl alcohol, yielding 7-keto-3-acetoxy-Δ^5-cholestene, m. p. 156—157° both alone and in admixture with an authentic specimen. In the case of the β-isomer removal of the ether gave a gum, which solidified after trituration with methyl alcohol, repeated crystallisation from the same solvent

yielding 6 : 7-diketocholestanyl acetate (100 mg.) in needles, m. p. 156—157°, showing no depression when mixed with an authentic specimen, and giving the characteristic quinoxaline derivative, m. p. 184—186°.

Dibromo-7-ketocholestanyl Acetate.—(a) A freshly prepared solution of bromine in chloroform (13 c.c.; 15%; 2·0 mols.) was added at 20° to a solution of 7-ketocholestanyl acetate (2·5 g.) in chloroform (25 c.c.) during 40 minutes. After being set aside at room temperature for 48 hours, the reaction mixture was washed with aqueous sodium bicarbonate and dried, the chloroform removed under diminished pressure, and the residue crystallised. *Dibromo-7-ketocholestanyl acetate* (1·6 g.) separated from acetone or light petroleum (b. p. 40—60°) in plates, m. p. 176—177°, $[\alpha]_D^{19°}$ + 38·1° (l = 1, c = 2·9 in chloroform) (Found: C, 57·7; H, 7·5. $C_{29}H_{46}O_3Br_2$ requires C, 57·8; H, 7·7%).

(b) A solution of α-6-bromo-7-ketocholestanyl acetate (2·0 g.) in acetic acid (350 c.c.) and ether (100 c.c.) was treated with a solution of bromine in acetic acid (13 c.c.; 5%; 1 mol.) and a solution of hydrogen bromide in acetic acid (5 c.c.; 50%; 8 mols.). After the mixture had been set aside at room temperature for 48 hours, dibromo-7-ketocholestanyl acetate separated, and a further quantity was obtained by dilution with water and extraction with ether (total yield, 0·75 g.); m. p. 176—177°, not depressed by a specimen prepared by method (a).

(c) A solution of β-6-bromo-7-ketocholestanyl acetate (1 g.) in acetic acid (40 c.c.) was treated with a solution of bromine in acetic acid (6·5 c.c.; 5%; 1·0 mol.) and a solution of hydrogen bromide in acetic acid (0·3 c.c.; 50%; 1 mol.), the mixture then being set aside at room temperature for 48 hours. Dibromo-7-ketocholestanyl acetate separated and after crystallisation from acetone (0·8 g.) had m. p. 176—177° both alone and in admixture with an authentic specimen.

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