219. *Steroids and Walden Inversion. Part XXIX.* The Configurations of the Bromination Products of 7-Oxocholestan-3β-yl Acetate.*

By D. R. James and C. W. Shoppee.

Configurations have been assigned by chemical methods to the epimeric 6-bromo-derivatives of 7-oxocholestan-3β-yl acetate described by Barr, Heilbron, Jones, and Spring;[1] these are consistent with those predicted by Corey[2] and those derived[3] from infrared and ultraviolet spectroscopic evidence.

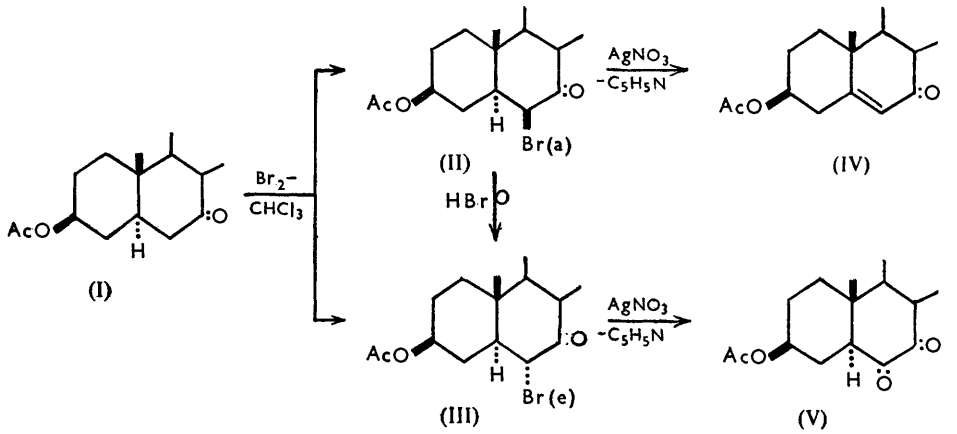
Barr, Heilbron, E. R. H. Jones, and Spring[1] found that 7-oxocholestan-3β-yl acetate (I) is not brominated in acetic acid at 35°, but in chloroform at 20° yields two monobromo-derivatives, m. p. 175—176°, $[\alpha]_D$ +35°, and m. p. 142°, $[\alpha]_D$ −9°, the former being convertible into the latter by treatment with hydrogen bromide in acetic acid at 100° for 15 min. The compounds were shown to be epimeric 6-bromo-ketones by their conversion with boiling pyridine (6—8 hr.) into 7-oxocholest-5-en-3β-yl acetate (IV). The 5-bromo-ketone, m. p. 175°, has also been obtained by Tsuda and Hayatsu[4] from (I) by bromination with *N*-bromosuccinimide in carbon tetrachloride at 77° in presence of benzoyl peroxide. On the basis of the dehydrobromination of the bromo-ketone, m. p. 175°, with silver nitrate in boiling pyridine to 7-oxocholest-5-en-3β-yl acetate (IV), and of the transformation of the bromo-ketone, m. p. 142°, by the same reagent into 6 : 7-dioxocholestan-3β-yl acetate (V), Barr, Heilbron, Jones, and Spring[1] assigned the α-configuration to the bromine atom of the epimeride of m. p. 175°, and the β-configuration to the bromine atom of the epimeride of m. p. 142°, erroneously attributing the reluctance of the latter to undergo dehydrobromination to a *trans*-orientation of the atoms involved. These assignments of configuration have been reversed by Fieser and Fieser,[5] and we now prove this reversal to be justified.

Conversion of cholest-6-en-3β-yl acetate (VI) by monoperphthalic acid into the 6α : 7α-epoxide (VII) and cleavage of this with hydrogen bromide in acetic acid has been shown by James, Rees, and Shoppee[6] to furnish 6β-bromo-7α-hydroxycholestan-3β-yl acetate [VIII (6β-Br/7α-OH : diaxial)], from which the 6α : 7α-epoxide (VII) may be regenerated by treatment with potassium hydroxide and subsequent acetylation. Oxidation of

* Part XXVIII, preceding paper.

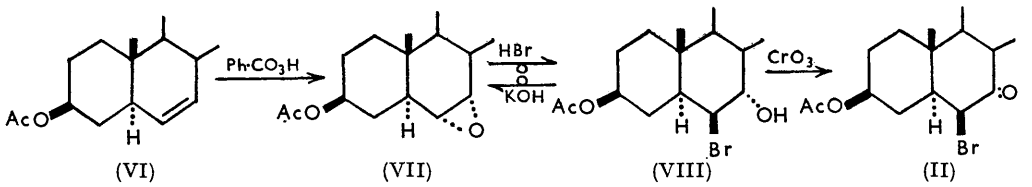
[1] Barr, Heilbron, E. R. H. Jones, and Spring, *J.*, 1938, 334.
[2] Corey, *J. Amer. Chem. Soc.*, 1954, **76**, 175.
[3] Cookson, *J.*, 1954, 282.
[4] Tsuda and Hayatsu, *J. Amer. Chem. Soc.*, 1955, **77**, 665.
[5] Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold, New York, 1949, p. 268.
[6] James, Rees, and Shoppee, *J.*, 1955, 1370.

6β-bromo-7α-hydroxycholestan-3β-yl acetate (VIII) with chromium trioxide in acetic acid at 15° gives 6β-bromo-7-oxocholestan-3β-yl acetate (II), m. p. 175—176°, $[\alpha]_D$ +31°,



(II); M. p. 175°, $[\alpha]_D$ +35°. (III); M. p. 142°, $[\alpha]_D$ −9°.

exhibiting an infrared spectrum identical with that of a specimen prepared by bromination of 7-oxocholestan-3β-yl acetate (I). It follows that the epimeride, m. p. 142°, $[\alpha]_D$ −9°, is by exclusion 6α-bromo-7-oxocholestan-3β-yl acetate (III).



Corey [2] has developed methods for predicting the configuration of the bromine atom in α-bromoketo-steroids whose stereochemistry is subject to either thermodynamic or kinetic control. In the case of 7-oxocholestan-3β-yl acetate (I), the predicted configuration of the bromination product under kinetic control is the 6β-bromo-ketone (II), whilst that of the product of thermodynamic control is the 6α-bromo-ketone (III).

R. N. Jones *et al.*[7] have shown that the coplanar arrangement of an equatorial C–Br bond and an adjacent C=O bond leads to an increase (Δ) of 15—20 cm.$^{-1}$ in the frequency of the infrared carbonyl band; but that the mutually perpendicular arrangement of an axial C–Br bond and an adjacent C=O bond has little effect. The infrared absorption spectra of the ketone (I) and the epimeric 6-bromo-ketones (II and III) were determined by Dr. Page, using specimens prepared by Professor D. H. R. Barton and Dr. C. H. Robinson, some years ago, and we are most grateful to Dr. Page and Professor Barton for permission to record the following annexed figures which support the configurations assigned above.

	CO : $\nu_{max.}$ (cm.$^{-1}$) (in CS_2)	Δ	Configuration of $C_{(6)}$–Br bond
7-Oxocholestan-3β-yl acetate (I)	1713	—	—
6β-Bromo-7-oxocholestan-3β-yl acetate (II)	1714	1	Axial
6α-Bromo-7-oxocholestan-3β-yl acetate (III)	1734	21	Equatorial

Cookson [3] has shown that the shift of the wavelength of the ultraviolet absorption maximum of a ketone produced by α-halogen substitution is a function of the angle between the C–Hal and the C=O bond. The change in the position and intensity ($\Delta\lambda$, $\Delta \log \varepsilon$) of $\lambda_{max.}$ produced by introduction of an axial α-bromine atom is pronounced ($\Delta\lambda_a$ *ca.* +28 mμ, $\Delta \log \varepsilon$ *ca.* +0·6), whilst that produced by introduction of an equatorial α-bromine atom is

[7] R. N. Jones, Ramsay, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2828.

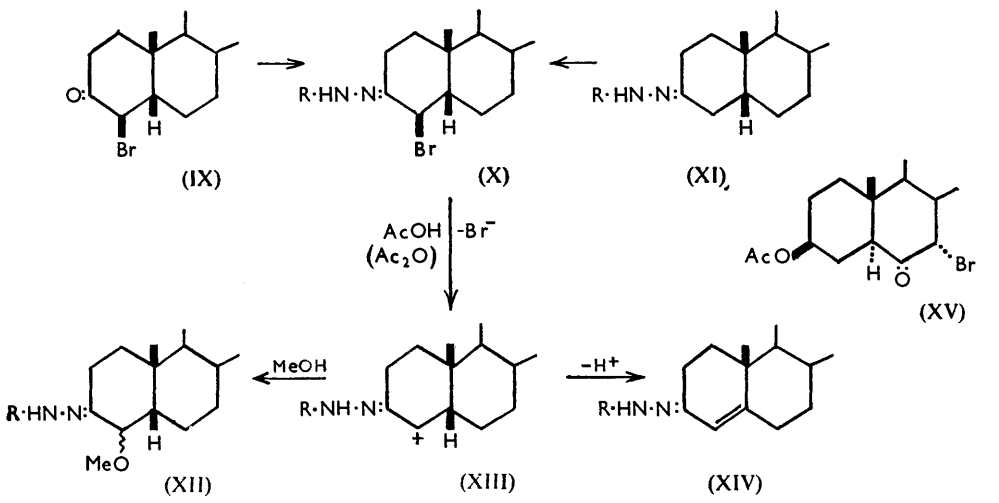
small ($\Delta\lambda_e$ *ca.* −5 mμ, Δ log ε *ca.* 0—+0·3). The annexed figures derived from the measurements recorded by Barr *et al.*[1] confirm the configurations assigned above.

	$\lambda_{max.}$	log ε	Δ log ε	$\Delta\lambda_a$	$\Delta\lambda_e$
7-Oxocholestan-3β-yl acetate (I)	287	1·6	—	—	—
6β-Bromo-7-oxocholestan-3β-yl acetate (II)	313	2·2	+0·6	+26	—
6α-Bromo-7-oxocholestan-3β-yl acetate (III)	282	1·6	0	—	−5

Cookson and Dandegaonker [8] have criticised the mechanism of acid-catalysed enolisation assumed by Corey [2] for the epimerisation of steroid α-bromo-ketones, and have shown that in certain cases hydrogen bromide is a specific catalyst and that epimerisation involves reduction of the α-bromo-ketone by hydrogen bromide followed by rebromination. The conversion (II ⟶ III) fails in the presence of perchloric acid, but proceeds in the presence of hydrogen bromide, and may therefore take place by reduction and rebromination.

It was discovered by Mattox and Kendall [9] that steroid α-bromo-ketones are dehydrobrominated by dinitrophenylhydrazine, and Djerassi [10] has shown that 4β-bromo-3-ketones of the 5β-series (IX) and 2α-bromo-3-ketones of the 5α-series are converted by dinitrophenylhydrazine in hot acetic acid in 3—5 min. into Δ^4-3-hydrazones (XIV) and Δ^1-3-hydrazones respectively in ~90% yield. The essential intermediate is the 4β-bromo-3-hydrazone (X) which can also be obtained from the 3-oxohydrazone (XI) by bromination in chloroform, and the mechanism proposed by Mattox and Kendall [11] involves a mesomeric cation represented by (XIII), which may unite with an external anion, *e.g.*, in methanol to give the 4ξ-methoxy-3-hydrazone (XII), or expel a proton to yield the Δ^4-3-hydrazone (XIV).

4α-Bromo-3-ketones of the 5α-series are not readily accessible, and therefore do not seem to have been examined, although ready conversion into Δ^4-3-hydrazones (XIV) would be expected since the configurational difference at $C_{(4)}$ must disappear in a mesomeric cation of type (XIII). It seemed therefore of interest to examine the action of dinitro-



phenylhydrazine on the 6-bromo-7-ketones (II and III). Unexpectedly, both 6-bromo-7-ketones were recovered unchanged after treatment with dinitrophenylhydrazine in hot acetic acid or in ethanol–sulphuric acid. The rate-determining step in hydrazone formation is nucleophilic attack at the carbonyl-carbon atom, and normally this proceeds without difficulty at $C_{(7)}$ since cholestan-7-one readily affords a dinitrophenylhydrazone; [12]

[8] Cookson and Dandegaonker, *J.*, 1955, 352.
[9] Mattox and Kendall, *J. Amer. Chem. Soc.*, 1948, **70**, 882.
[10] Djerassi, *ibid.*, 1949, **71**, 1003.
[11] Mattox and Kendall, *ibid.*, 1950, **72**, 2290; cf. McGuckin and Kendall, *ibid.*, 1952, **74**, 5811.
[12] Cremlyn and Shoppee, *J.*, 1954, 3575.

similarly, although cholestan-6-one readily forms a dinitrophenylhydrazone,[13] 7α-bromo-6-oxocholestan-3β-yl acetate (XV) fails to do so. Differences in the reactivities of α-bromo-2 : 4-dinitrophenylhydrazones have been encountered by Ramirez and Kirby.[14]

Experimental

For general experimental directions see preceding paper. $[\alpha]_D$ are in $CHCl_3$, and infrared absorption spectra were determined in CS_2 in a Perkin-Elmer double-beam instrument.

7-Oxocholestan-3β-yl Acetate.—7-Oxocholest-5-en-3β-yl acetate, m. p. 156—158°, obtained from cholesteryl acetate by oxidation with chromium trioxide in acetic acid at 55°, was hydrogenated with 20% palladium–charcoal in acetic acid;[15] the resulting solution was filtered, diluted, and extracted with pentane. Working up gave 7-oxocholestan-3β-yl acetate, m. p. 141—142°, after recrystallisation from ether–methanol; the infrared absorption spectrum in 1% carbon disulphide solution showed bands at 1737 and 1236 cm.$^{-1}$ (OAc) and 1713 cm.$^{-1}$ (CO).

Bromination of 7-Oxocholestan-3β-yl Acetate.—A freshly prepared solution of bromine (0·84 g.) in chloroform (15 c.c.) was added to a solution of 7-oxocholestan-3β-yl acetate (2·2 g.) in chloroform (15 c.c.) at 20°, during 15 min. Chloroform was removed under reduced pressure and the residual solid recrystallised from acetone, to give 6β-bromo-7-oxocholestan-3β-yl acetate (550 mg.), m. p. 175—176°, $[\alpha]_D$ +37° (*c*, 1·12), which in 1% carbon disulphide solution showed bands at 1738 and 1234 cm.$^{-1}$ (OAc) and 1714 cm.$^{-1}$ (CO, adjacent to axial Br).

The acetone mother-liquor was evaporated and the residual solid (1·5 g.) chromatographed in pentane on aluminium oxide (50 g.). Elution with pentane and benzene–pentane (1 : 9; 3 × 150 c.c.) gave material which could not be crystallised, but elution with benzene–pentane (1 : 2; 2 × 150 c.c.) afforded 6α-bromo-7-oxocholestan-3β-yl acetate (350 mg.), m. p. 141—142°, $[\alpha]_D$ −10·5° (*c*, 1·41), after crystallisation from aqueous acetic acid. The infrared spectrum in 1% carbon disulphide solution showed bands at 1738 and 1234 cm.$^{-1}$ (OAc) and 1734 cm.$^{-1}$ (CO, adjacent to equatorial Br).

Oxidation of 6β-Bromo-7α-hydroxycholestan-3β-yl Acetate.—6β-Bromo-7α-hydroxycholestan-3β-yl acetate (50 mg.) was dissolved in acetic acid (10 c.c.), a solution of chromium trioxide in acetic acid (1 c.c.; 2%) added, and the solution left at 15° for 16 hr. Excess of chromic acid was destroyed by methanol, and the solution diluted; extraction with ether and working up in the usual manner gave 6β-bromo-7-oxocholestan-3β-yl acetate, m. p. 175—176°, $[\alpha]_D$ +31° (*c*, 0·66), after recrystallisation from acetone; this gave no depression on admixture with a specimen prepared by bromination of 7-oxocholestan-3β-yl acetate according to the directions of Barr *et al.*[1] The infrared absorption in 1% carbon disulphide solution showed bands at 1738 and 1234 cm.$^{-1}$ (OAc) and 1714 cm.$^{-1}$ (CO, adjacent to axial Br), and was identical with that of a genuine specimen.

Treatment with Dinitrophenylhydrazine.—(*a*) The 6β-bromo-7-ketone (II) (72 mg.) was dissolved in acetic acid (5 c.c.; saturated with nitrogen) in an atmosphere of nitrogen. Dinitrophenylhydrazine (30 mg., 1·1 mols.) was added and the solution heated at ~120° for 5 min. On cooling, no precipitate was formed, but needles of the starting material separated gradually; dilution and filtration gave unchanged 6β-bromo-7-ketone, m. p. 174—176°, mixed m. p. 175°. In a second experiment, the 6β-bromo-7-ketone, similarly dissolved in ethanol, was heated to boiling with a solution of 2 : 4-dinitrophenylhydrazine in a few drops of concentrated sulphuric acid and ethanol; no hydrazone separated on cooling.

(*b*) The 6α-bromo-7-ketone (III) (70 mg.), dissolved in acetic acid (4 c.c.), was treated with 2 : 4-dinitrophenylhydrazine (30 mg., 1·1 mols.) at 120° for 5 min. as under (*a*). No precipitate was formed on cooling, and dilution and filtration yielded the unchanged 6α-bromo-7-ketone, m. p. 140°, mixed m. p. 140—142°.

(*c*) The 7α-bromo-6-ketone (XV) (112 mg.) was heated with 2 : 4-dinitrophenylhydrazine (47 mg., 1·1 mols.) in acetic acid (5 c.c.) at 100° for 5 min. as under (*a*). No precipitate was formed, and after 16 hr. only a little of the unchanged 7α-bromo-6-ketone, m. p. and mixed m. p. 144—145°, had separated.

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[13] Jenkins, Shoppee, and Summers, to be published.
[14] Ramirez and Kirby, *J. Amer. Chem. Soc.*, 1952, **74**, 4331; 1953, **75**, 6026.
[15] Windaus and Kirchner, *Ber.*, 1920, **53**, 614.