Steroids and Walden Inversion. Part XIX. The Configurations of the Bromination Products of 6-Oxocholestan-3β-yl Acetate.*

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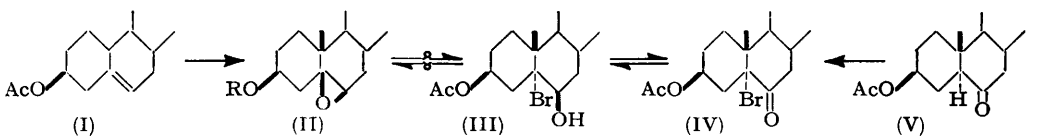
The two monobromo-derivatives of 6-oxocholestan-3β-yl acetate described by Heilbron, Jones, and Spring (*J.*, 1937, 801) are shown to be 5α- and 7α-bromo-6-oxocholestan-3β-yl acetate respectively. The 5α- and 7α-configurations now proved by chemical methods are consistent with those predicted on the basis of infra-red and ultra-violet spectroscopic evidence by Corey (*Experientia*, 1953, **9**, 329) and by Cookson (*J.*, 1954, 282) respectively.

In an examination of various routes leading to 7-dehydrocholesterol Heilbron, Jones, and Spring (*J.*, 1937, 801) studied the bromination of 6-oxocholestan-3β-yl acetate (V). Use of 1 mol. of bromine in cold acetic acid or in acetic acid–ether at 0° or 35° gave a 5-bromo-ketone, m. p. 164° (decomp.), $[\alpha]_D$ −133°, converted by treatment with pyridine into 3β-acetoxycholest-4-en-6-one, which by alkaline hydrolysis yielded cholestane-3 : 6-dione. Bromination in acetic acid–ether at 35° followed by refluxing for 2 hr. gave an isomeric bromo-ketone, m. p. 145°, $[\alpha]_D$ +40°; this was also obtained from the 5-bromo-ketone by treatment with hydrogen bromide in hot acetic acid, and was shown to be 7ξ-bromo-6-oxocholestan-3β-yl acetate by oxidation with silver nitrate in boiling pyridine to 6 : 7-dioxocholestan-3β-yl acetate.



(I) (II) (III) (IV) (V)

The brominations were shown to require the presence of hydrogen bromide and were found to be completely inhibited by excess of potassium acetate, which indicates that they are subject to kinetic as opposed to thermodynamic control.

Heilbron, Jones, and Spring implied that their 5-bromo-ketone possessed the α-configuration at $C_{(5)}$ by describing it as a cholestane derivative but their observations do not exclude its 5β-formulation as 5-bromo-6-oxocoprostan-3β-yl acetate. They also made a tentative

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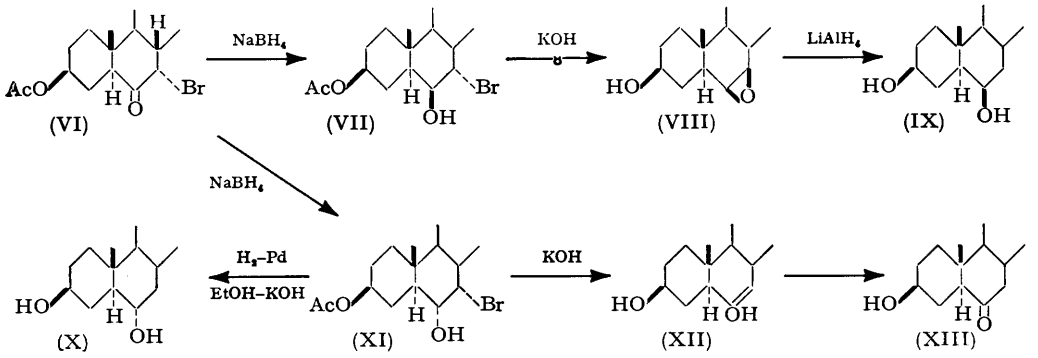
assignment * of the α-configuration at $C_{(7)}$ to their 7-bromo-ketone (cf., however, Fieser and Fieser, " Natural Products related to Phenanthrene," Reinhold Publ. Corpn., 1949, p. 268). We now show that their assignments of the α-configuration at $C_{(5)}$ and $C_{(7)}$ are in fact correct.

Cholesteryl acetate (I) by treatment with perbenzoic acid and chromatography of the product gave 5 : 6β-epoxycoprostan-3β-yl acetate (II; R = Ac), m. p. 112—113°, $[\alpha]_D$ −1° (cf. Plattner *et al.*, *Helv. Chim. Acta*, 1944, **27**, 513). Fission of the epoxide with hydrogen bromide–acetic acid at 0° gave the 5α-bromo-6β-hydroxy-compound (III), formed by *trans*-addition of hydrogen bromide with inversion of configuration at $C_{(5)}$. Oxidation with chromium trioxide–acetic acid at 15° then yielded 5α-bromo-6-oxocholestan-3β-yl acetate (IV), m. p. 166° (decomp.), $[\alpha]_D$ −131°, identical with a specimen prepared by bromination of 6-oxocholestan-3β-yl acetate (V).

Conversely, reduction of the 5α-bromo-6-ketone (IV) with sodium borohydride afforded a mixture of the 5α-bromo-6β-hydroxy-compound (III) and it 6α-epimeride, which proved difficult to separate chromatographically. The mixture was therefore treated with methanolic potassium hydroxide to give 5 : 6β-epoxycoprostan-3β-ol (II; R = H).

Reduction of 7α-bromo-6-oxocholestan-3β-yl acetate (VI) with lithium aluminium hydride gave a gelatinous product, and chromatographic separation of the epimeric 7α-bromo-3β : 6-diols proved unsatisfactory. Use of sodium borohydride, which does not attack the 3β-acetoxyl group, and chromatography on neutralised aluminium oxide furnished the 3β-acetoxy-7α-bromo-6β- (VII) and the -6α-hydroxy-compound (XI), whose structures were established as follows.



Treatment of the 7α-bromo-6β-hydroxy-compound (VII) with methanolic potassium hydroxide gave by elimination of hydrogen bromide the 6β : 7β-epoxide (VIII). The change (VII ⟶ VIII) [like the change (II ⟶ III)] is an intramolecular analogue of a bimolecular (S_N2) replacement (cf. Ingold, " Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 383, footnote 179); the β-orientation of the 6-hydroxyl group (the substituting agent) and the α-orientation of the 7-bromine atom (the entity substituted) require that the transition state be of linear type with resulting inversion of configuration at $C_{(7)}$. The epoxide (VIII), by reduction with lithium aluminium hydride, gave cholestane-3β : 6β-diol [(IX); 6β-OH(axial)] (Shoppee and Summers, *J.*, 1952, 3381) in conformity with the observations of Fürst and Plattner (Abs. Papers 12th Intern. Congr. Pure Appl. Chem., New York, 1951, p. 409; cf. Barton, *J.*, 1953, 1033, and the references summarised there), who have shown that in chemical reductions of steroid epoxides the oxygen atom invariably takes up the axial configuration.

Treatment of the 7α-bromo-6α-hydroxy-compound (XI) with methanolic potassium

* Heilbron, Jones, and Spring attributed the ready oxidation of their 7-bromo-6-ketone to the 6 : 7-diketone with silver nitrate–pyridine to " a *trans*-orientation of the halogen atom at $C_{(7)}$ relative to the hydrogen attached to $C_{(8)}$ and to the inherent reluctance [of the 7-bromo-6-ketone] to lose hydrogen bromide." The two parts of this statement are incompatible; we are, however, unable satisfactorily to explain the reluctance of the 7-bromo-6-ketone [(VI); 7α-Br(axial)/8β-H(axial); *trans*] to lose hydrogen bromide. 7α-Chlorocholestane provides another example (Cremlyn and Shoppee, *J.*, 1954, 3794).

hydroxide by *trans*-elimination of hydrogen bromide gave, *via* the enol (XII) (not isolated), 6-oxocholestan-3β-ol (XIII); further, hydrogenation of the 7α-bromo-6α-hydroxy-compound (XI) with palladium–charcoal in ethanol and mild alkaline hydrolysis yielded cholestane-3β : 6α-diol (X) (Shoppee and Summers, *loc. cit.*). These reactions establish the α-orientation of the 7-bromine atom in the bromo-ketone acetate (VI).

Recent work on the infra-red absorption spectra of cyclic α-halogeno-ketones has enabled prediction of the configuration of the halogen atom. To explain the effects of vicinal bromination on the carbonyl stretching vibration in the spectra of keto-steroids R. N. Jones *et al.* (*J. Amer. Chem. Soc.*, 1952, **74**, 2828) postulated that a coplanar arrangement of the C–Br and C=O bonds is associated with an increase of 15—20 cm.$^{-1}$ in the frequency of the carbonyl band, but that when the C–Br and C=O bonds are mutually perpendicular bromination does not change the frequency of the carbonyl band. This hypothesis has been confirmed, rationalised, and generalised by Corey (*ibid.*, 1953, **75**, 2301); he has shown that the most thermodynamically stable conformation of 2-bromo-*cyclo*hexanone is that chair form in which the bromine atom is axial (dipole–dipole interaction > steric interaction), whereas the most thermodynamically stable conformation of 2-bromo-4 : 4-dimethyl*cyclo*hexanone is that chair form in which the bromine atom is equatorial (steric interaction > dipole interaction). From data on the preferred conformations of α-bromo*cyclo*hexanones, Corey (*Experientia*, 1953, **9**, 329) has deduced the relative stabilities of the epimeric bromination products of any keto-steroid with a ketonic function in ring A, B, or C; since the more stable epimeride predominates when the bromination is thermodynamically controlled, it is possible to predict the configuration of the bromine atom in any α-bromo-ketone so formed. In the bromination of 6-oxocholestan-3β-yl acetate (V), the predicted configurations for a bromine atom at $C_{(5)}$ and $C_{(7)}$ are 5α and 7α.

Cookson (*J.*, 1954, 282) has recently shown that the effect of equatorial and axial α-halogen substitution on the ultra-violet absorption spectra of ketones enables an assignment of configuration to the halogen atom in α-halogeno-ketones to be made. The shift in the position of $\lambda_{max.}$ of a ketone produced by α-halogen substitution is a function of the angle between the C–Hal bond and the C–O bond; the change ($\Delta\lambda_e$) in position of $\lambda_{max.}$ produced by introduction of an equatorial α-halogen atom is of average value −5 mμ, whereas the corresponding change ($\Delta\lambda_a$) for axial substitution is of average value +28 mμ. In the case of 5- and 7-bromo-6-oxocholestan-3β-yl acetate, the spectroscopic properties show that both possess the bromine atom in the α(axial)-configuration.

	$\lambda_{max.}$	log ε	Δ log ε	$\Delta\lambda_a$
6-Oxocholestan-3β-yl acetate (V)	280	1·6	—	—
5α-Bromo-6-oxocholestan-3β-yl acetate (IV)	308	2·1	+0·5	+28
7α-Bromo-6-oxocholestan-3β-yl acetate (VI)	310	2·2	+0·6	+30

It is clear that the physical evidence derived from infra-red and ultra-violet spectroscopy is complementary, and provides convincing support for the chemical evidence of configuration now adduced.

Experimental

For general experimental details see *J.*, 1954, 3794; $[\alpha]_D$ are in $CHCl_3$.

5-Bromo-6β-hydroxycholestan-3β-yl Acetate.—5 : 6β-Epoxycoprostan-3β-yl acetate (340 mg.) was dissolved in acetic acid (5 c.c.), then cooled in ice-water, and a solution of hydrogen bromide in acetic acid (6 c.c. : 2%) was added. After 15 min., small needles separated and were filtered off. *5-Bromo-6β-hydroxycholestan-3β-yl acetate*, recrystallised from ether–pentane, had m. p. 177—179°, $[\alpha]_D$ −37° (*c*, 0·96) [Found (after drying at 70°/0·01 mm. for 6 hr.): C, 66·15; H, 9·2; Br, 15·5. $C_{29}H_{49}O_3Br$ requires C, 66·25; H, 9·4; Br, 15·2%].

5-Bromo-6-oxocholestan-3β-yl Acetate.—5-Bromo-6β-hydroxycholestanyl acetate (50 mg.) was dissolved in acetic acid (8 c.c.), a solution of chromium trioxide (20 mg.) in acetic acid (2 c.c.) added, and the solution left at 15° for 16 hr. Excess of chromic acid was destroyed by addition of methanol, and the solution diluted; extraction with ether and working up in the usual manner gave 5-bromo-6-oxocholestan-3β-yl acetate, m. p. 164—166° (decomp.), after recrystallisation from hexane; this gave no depression on admixture with a specimen prepared by bromination of 6-oxocholestan-3β-yl acetate according to the directions of Heilbron, Jones, and Spring (*loc. cit.*).

Reduction of 5-Bromo-6-oxocholestan-3β-yl Acetate.—A solution of sodium borohydride (55 mg.) in methanol was added to one of 5-bromo-6-oxocholestan-3β-yl acetate (520 mg.) in ether–methanol. The mixture was left at 15° for 2 hr., diluted, and extracted with ether. Working up in the usual manner afforded an oil (470 mg.), which was chromatographed on neutralised aluminium oxide (13 g.) prepared in pentane.

Elution with pentane and benzene–pentane (1 : 9) yielded material giving a positive Beilstein test, but melting over the range 140—170°. Further elution with benzene–pentane mixtures only afforded material giving a negative Beilstein test. A portion of the crude bromohydrin (70 mg.) was refluxed with potassium hydroxide (170 mg.) in methanol (10 c.c.) for 3 hr. The solution was diluted and extracted with ether. Working up in the usual way gave an oil, which was crystallised from methanol to give 5 : 6β-epoxycoprostan-3β-ol, m. p. and mixed m. p. 130°, $[\alpha]_D$ +8° (*c*, 0·96), as very thin needles.

7α-Bromo-6-oxocholestan-3β-yl Acetate.—6-Oxocholestan-3β-yl acetate (5·5 g.) in acetic acid (12·5 c.c.) and ether (65 c.c.) was treated with a solution of bromine in acetic acid (40 c.c.; 5%) at 35° during 75 min., and the mixture heated under reflux for 2 hr. Crystallisation from aqueous acetic acid gave 7α-bromo-6-oxocholestanyl acetate (3·9 g.) as lustrous plates, m. p. 145°, $[\alpha]_D$ +39° (*c*, 1·5).

Reduction of 7α-Bromo-6-oxocholestan-3β-yl Acetate.—A solution of sodium borohydride (0·1 g.) in methanol (2 c.c.) was added to 7α-bromo-6-oxocholestan-3β-yl acetate (1 g.) in ether–methanol. The mixture was set aside at 15° for 1·5 hr., diluted with water, and extracted with ether. Working up in the usual way gave an oil (980 mg.), which slowly crystallised. This was chromatographed on neutralised aluminium oxide (30 g.) prepared in pentane. Elution with pentane and benzene–pentane (1 : 9) gave material giving a negative Beilstein test, but use of benzene–pentane (1 : 6) gave *7α-bromo-6β-hydroxycholestan-3β-yl acetate* (317 mg.), m. p. 176—179°, $[\alpha]_D$ −24° (*c*, 1·18), after crystallisation from ether–pentane [Found (after drying at 70°/0·01 mm. for 6 hr.): C, 66·05; H, 9·3. $C_{29}H_{49}O_3Br$ requires C, 66·25; H, 9·4%]. Elution with benzene–pentane (2 : 3) gave *7α-bromo-6α-hydroxycholestan-3β-yl acetate* (350 mg.), double m. p. 136°/145°, $[\alpha]_D$ −9° (*c*, 1·07), after crystallisation from ether–methanol [Found (after drying at 70°/0·01 mm. for 6 hr.): C, 66·35; H, 9·2; Br, 15·4. $C_{29}H_{49}O_3Br$ requires C, 66·25; H, 9·4; Br, 15·2%].

Dehydrobromination of 7α-Bromo-6α-hydroxycholestan-3β-yl Acetate.—The bromohydrin (50 mg.) and potassium hydroxide (150 mg.) were refluxed in methanol (8 c.c.) for 3 hr. The solution, when diluted and worked up in the usual way, furnished a colourless solid (37 mg.), which by crystallisation from methanol, gave 6-oxocholestan-3β-ol (32 mg.), double m. p. 142/152°, undepressed by admixture with an authentic sample.

Hydrogenation of 7α-Bromo-6α-hydroxycholestan-3β-yl Acetate.—The bromohydrin (50 mg.), potassium hydroxide (400 mg.), and palladium–charcoal (40 mg. : 20%) in ethanol (15 c.c.) were shaken in an atmosphere of hydrogen at 25° for 4 hr. The solution was then diluted and worked up in the usual manner, to give cholestane-3β : 6α-diol, m. p. 212—215°, after crystallisation from acetone, which gave no depression on admixture with a genuine specimen.

Dehydrobromination of 7α-Bromo-6β-hydroxycholestan-3β-yl Acetate.—The bromohydrin (50 mg.) and potassium hydroxide (150 mg.) were refluxed for 3 hr. in methanol (8 c.c.). The solution was diluted and worked up in the usual way, to afford 6β : 7β-*epoxycholestan-3β-ol* (34 mg.), m. p. 156—158°, $[\alpha]_D$ −14° (*c*, 1·04), after crystallisation from aqueous acetone [Found (after drying at 60°/0·01 mm. for 6 hr.): C, 77·0; H, 11·3. $C_{27}H_{46}O_2,H_2O$ requires C, 77·1; H, 11·5%]. Acetylation with acetic anhydride–pyridine at 15° gave 6β : 7β-*epoxycholestan-3β-yl acetate*, m. p. 143°, $[\alpha]_D$ −24° (*c*, 0·9), after crystallisation from methanol [Found (after drying at 60°/0·01 mm. for 6 hr.): C, 78·1; H, 10·6. $C_{29}H_{48}O_3$ requires C, 78·3; H, 10·8%].

Reduction of 6β : 7β-Epoxycholestan-3β-ol.—6β : 7β-Epoxycholestan-3β-ol (30 mg.) in dry ether (10 c.c.) was added to a solution of lithium aluminium hydride (15 mg.) in ether (20 c.c.) at 0°. The mixture was kept for 1 hr. at 15° and the excess of reagent decomposed with ice and 2N-sulphuric acid. The solution, worked up in the usual manner, afforded cholestane-3β : 6β-diol, m. p. and mixed m. p. 190—191° after crystallisation from ethanol.

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