Steroids. Part X. The Preparation of Unsaturated Steroids.*

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A general method for introduction of unsaturation into the steroid nucleus is described. It involves the reaction sequence: –CO·CHR– ⟶ –CO·CRBr– ⟶ –CH(OR')·CRBr– ⟶ –CH:CR–, and is exemplified by introduction of unsaturation at the 6 : 7-position.

It is shown by reference to the literature and to the present example, 7α-bromo-6β- and -6α-hydroxycholestan-3β-yl acetate, that pairs of *trans*- and *cis*-1 : 2-bromohydrins on treatment with zinc in ethanol furnish the same olefin in good yield and at apparently approximately similar rates. It is suggested that these reactions involve the conjugate base derived from either bromohydrin by the irreversible extraction of a bromonium ion by an atom of zinc in the rate-controlling stage.

Steroids with carbonyl groups at the various nuclear positions are relatively accessible substances, and readily afford α-bromo-ketones, which have been shown (Shoppee and Summers, *J.*, 1952, 1786, 1790) to furnish *vic*-halogenohydrins on reduction with lithium aluminium hydride or sodium borohydride. Since the reaction of *vic*-halogenohydrins and their derivatives with zinc to yield olefins has been shown to be general (Straus and Rohrbacher, *Ber.*, 1921, **54**, 40; Boord *et al.*, *J. Amer. Chem. Soc.*, 1930, **52**, 3396; 1931, **53**, 1505; 1932, **54**, 751; 1933, **55**, 3293), the sequence, –CO·CHR– ⟶ –CO·CRBr– ⟶ –CH(OR')·CRBr– ⟶ –CH:CR–, should permit introduction of unsaturation at any position (other than Δ^8 and $\Delta^{8(14)}$) in the steroid nucleus.

We now report such introduction of unsaturation at the 6 : 7-position (cf. Garmaise and Shoppee, *J.*, 1953, 245). Since this work was commenced in 1951, the above reaction sequence has been used to give steroids unsaturated at the 2 : 3-position (Fieser and Dominguez, *J. Amer. Chem. Soc.*, 1953, **75**, 1704; Corey, *ibid.*, p. 4832; Fieser and Huang, *ibid.*, p. 4837), the 3 : 4-position (Fieser and Ettorre, *ibid.*, p. 1700; Fieser and Dominguez, and Fieser and Huang, *locc. cit.*), the 5 : 6-position (Mori, *J. Chem. Soc. Japan*, 1949, **70**, 303; Ueno, *J. Pharm. Soc. Japan*, 1952, **72**, 1622), the 9 : 11-position (Fried and Szabo,

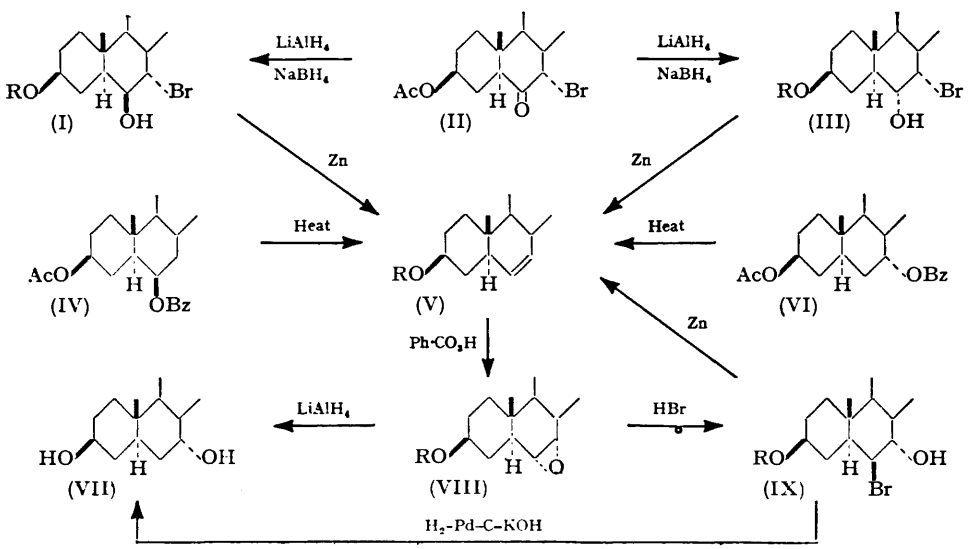
* Part IX, preceding paper.

J. Amer. Chem. Soc., 1953, **75**, 2273), and the 11 : 12-position (Cornforth, Osbond, and Phillipps, *J.*, 1954, **907**; Elks, Phillipps, Taylor, and Wyman, *ibid.*, p. 1739).

7α-Bromo-6-oxocholestan-3β-yl acetate (II) by reduction with lithium aluminium hydride affords a mixture of epimeric 7α-bromocholestane-3β : 6-diols (I, III; R = H), converted by zinc and acetic acid in high yield into cholest-6-en-3β-ol (V; R = H). By use of sodium borohydride the 7α-bromo-ketone acetate (II) gives 7α-bromo-6β-hydroxycholestan-3β-yl acetate (I; R = Ac) and the 6α-epimer (III; R = Ac); *both* epimers on treatment with activated zinc in ethanol give cholest-6-en-3β-yl acetate (V; R = Ac), also obtained by acetylation of the alcohol (V; R = H), and hydrolysed thereto by treatment with lithium aluminium hydride. The alcohol was characterised by preparation of the benzoate and 3 : 5-dinitrobenzoate; the presence of a hydroxyl group in the alcohol and of an acetoxyl group in its acetate, and the presence of a *cis*-disecondary double bond, were confirmed by infra-red absorption spectroscopy. The acetate was shown by direct comparison to be identical with the materials obtained by Barton and Resenfelder (*J.*, 1949, 2459) and by Wintersteiner and Moore (*J. Amer. Chem. Soc.*, 1950, **72**, 1923) by pyrolysis of 6β-benzoyloxycholestan-3β-yl acetate (IV) and of 7α-benzoyloxycholestan-3β-yl acetate (VI) respectively. The physical constants of our samples of the alcohol, its acetate and benzoate, and those of Barton and Rosenfelder's and of Wintersteiner and Moore's samples are as follows :

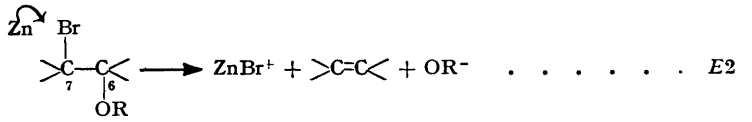
	Cholest-6-en-3β-ol		Acetate		Benzoate	
	m. p.	$[\alpha]_D$	m. p.	$[\alpha]_D$	m. p.	$[\alpha]_D$
This work	124—126°	−88°	108°	−93°	132—133°	−85°
Barton and Rosenfelder ...	114—115	−92	103—105	−89	123—124	−75
Wintersteiner and Moore	129—131	−81	104—106	−88	128—129	−74

Cholest-6-en-3β-yl acetate (V) and perbenzoic acid give 6α : 7α-epoxycholestan-3β-yl acetate (VIII), converted by lithium aluminium hydride into cholestane-3β : 7α-diol (VII) (Wintersteiner and Moore, *J. Amer. Chem. Soc.*, 1943, **65**, 1503; Buser, *Helv. Chim. Acta*, 1947, **30**, 1379; Fieser, Fieser, and Chakravarti, *J. Amer. Chem. Soc.*, 1949, **71**, 2226). By

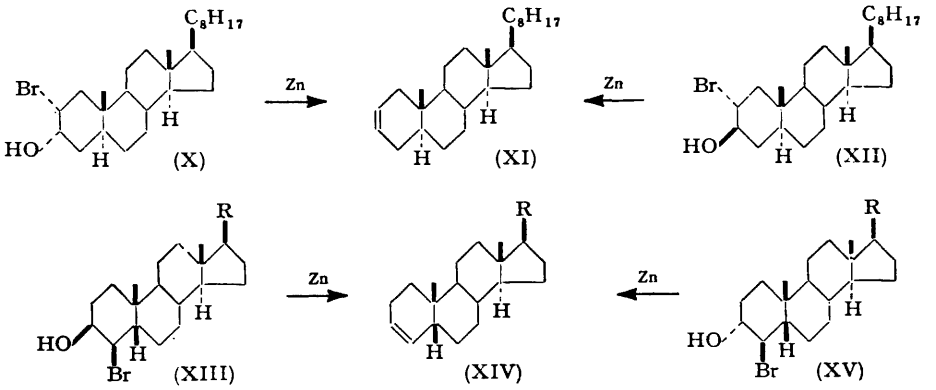


treatment with hydrogen bromide–acetic acid the 6α : 7α-epoxide (VIII) gives the 6β-bromo-7α-ol 3-acetate [IX; 6β-Br(axial)/7α-OH(axial) : *trans*] converted by zinc into cholest-6-en-3β-yl acetate (V), and hydrogenated by palladium to give cholestane-3β : 7α-diol (VII). The 6β-bromo-7α-ol 3-acetate (IX), by treatment with methanolic potassium hydroxide, regenerated (after acetylation) the 6α : 7α-epoxide (VIII).

Two mechanisms for ionic elimination reactions are in current use. In the present context the bimolecular mechanism involving synchronous processes may be written :

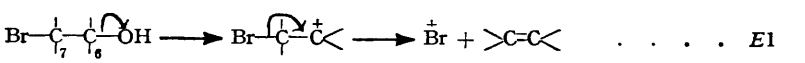


The geometrical condition for relatively ready bimolecular elimination is that the four reaction centres are coplanar and *trans*-orientated (Hughes, Ingold, *et al.*, *J.*, 1948, 2117; cf. Young, Pressman, and Coryell, *J. Amer. Chem. Soc.*, 1939, **61**, 1640; Winstein, Pressman, and Young, *ibid.*, p. 1645), which is satisfied by the bromohydrin [I; 6β-OH(axial)/7α-Br(axial) : *trans*]. A non-planar *cis*-orientation of the groups to be eliminated as in the bromohydrin [III; 6α-OH(equatorial)/7α-Br(axial) : *cis*] should energetically discourage, although not necessarily exclude,* the synchronous mechanism *E*2. Yet both bromohydrins readily furnish cholest-6-en-3β-ol (V; R = H). Other examples have been reported; thus Fieser and Dominguez (*loc. cit.*), using a mixture (m. p. 104°, $[\alpha]_D$ +25°) of 2α-bromocholestan-3α-ol, m. p. 117°, $[\alpha]_D$ +33° [X; 2α-Br(equatorial)/3α-OH(axial) : *cis*], and 3β-ol, m. p. 113°, $[\alpha]_D$ +12° [XII; 2α-Br(equatorial)/3β-OH(equatorial) : *trans*] (cf. Corey, *J. Amer. Chem. Soc.*, 1953, **75**, 4832; Fieser and Huang, *loc. cit.*), obtained pure cholest-2-ene (XI) in good yield by brief treatment with zinc–acetic acid.



Similarly, the bile acid derivatives [XIII; R = $C_4H_8{\cdot}CO_2Me$: 3β-OH (axial)/4β-Br(equatorial) : *cis*] and [XV; R = $C_4H_8{\cdot}CO_2Me$: 3α-OH (equatorial)/4β-Br(equatorial) : *trans*] have been shown by Fieser and Ettorre (*loc. cit.*) both to afford the pure chol-3-enic ester (XIV) in good yield on treatment with zinc–acetic acid; whilst the mixture (m. p. 138—139°, $[\alpha]_D$ +58·5°) of 3β-[XIII; R = OAc : 3β-OH(axial)/4β-Br(equatorial) : *cis*] and 3α-hydroxy-4β-bromotestan-17β-yl acetate [XV; R = OAc : 3α-OH(equatorial)/4β-Br(equatorial) : *trans*] used by Fieser and Dominguez (*loc. cit.*; cf. Fieser and Huang, *loc. cit.*) likewise gave pure test-3-en-17β-yl acetate (XIV; R = OAc) in good yield on similar treatment.

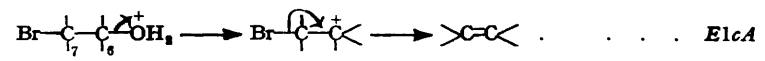
In the alternative unimolecular mechanism, which may here be written :



a rate-controlling heterolysis leads to a carbonium ion, which if sufficiently long-lived, will become planar, so that elimination of the bromine atom should be independent of the

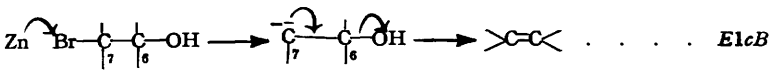
* Cristol and Hause (*J. Amer. Chem. Soc.*, 1952, **74**, 2193) have shown that *trans*-11 : 12-dichloro-9 : 10-dihydro-9 : 10-ethanoanthracene on treatment with potassium hydroxide undergoes *cis*-dehydrohalogenation some ten times faster than the *cis*-11 : 12-dichloro-isomeride undergoes *trans*-dehalogenation; this is entirely due to the entropy of activation, which favours *cis*-elimination by a factor of 2000, since the *trans*-dehydrohalogenation requires an energy of activation lower by 4 kcal.

original geometry. If, however, elimination of the bromine atom occurs before the hydroxyl group has receded far enough to leave a planar ion, then *trans*-geometry will be preferred and coplanarity desirable. Such a mechanism seems improbable because the essential reagent appears to be the zinc since, as we have observed, the solvent can be changed without affecting the ease of elimination from both the *cis*- and the *trans*-bromohydrins (cf. Fieser and Ettorre, *loc. cit.*). This change of solvent from acetic acid to ethanol also appears to exclude a variant in which the rate-determining heterolysis involves the conjugate acid of the bromohydrin



E1cA

We suggest that another variant (cf. Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell & Sons, London, 1953, 423), in which the rate-controlling step involves the irreversible extraction of a bromonium ion by an atom of zinc (cf. Ingold and Shoppee, *J.*, 1928, 371), may be operative :



E1cB

The same intermediate carbanion might well be obtained from both bromohydrins, that carbanion derived directly from (I) (in which the lone pair destined to form the double bond can enter the octet of $C_{(6)}$ on the side opposite to that from which the hydroxyl anion departs) being also rapidly produced from (III) by inversion * at $C_{(7)}$ (cf. Roberts, Shoppee, and Stephenson, *J.*, 1954, 2705; Roberts and Shoppee, *ibid.*, p. 3418).

We find that the *trans*- (I) and the *cis*-bromohydrin acetate (III) are unchanged by zinc in ethanol at 50° for 45 hr. : after 3 hr. at ~78°, the *trans*-isomeride was completely converted into cholest-6-en-3β-yl acetate (V; R = Ac), whereas some of the *cis*-isomeride could be recovered; this suggests a small qualitative difference in the rates of dehydroxybromination, since after 6 hr. at ~78° both isomerides were completely converted into the olefin (V; R = Ac). The heterogeneous character of the reaction in the presence of zinc dust has prevented a kinetic investigation; we are seeking some suitable bivalent cation for use in place of zinc, which may be capable of extracting a bromonium ion in an appropiate medium furnishing a homogeneous system, and so permitting kinetic measurements.

It seems probable that dehalogenation of *vic*-dihalides by zinc in ethanol may also occur by the mechanism *E1cB*; for although product specificity has been observed by Young, Jasaitis, and Levanas (*J. Amer. Chem. Soc.*, 1937, **59**, 403), Cristol and Hause (*loc. cit.*) have found that *cis*- and *trans*-11 : 12-dichloro-9 : 10-dihydro-9 : 10-ethanoanthracene on treatment with zinc in ethanol yield the same olefin.

[*Added February 18th*, 1955.]—An example of elimination from *cis*- and *trans*-2 : 3-dimethanesulphonates of the sapogenin series has just been reported by Wendler and Slates (*Chem. and Ind.*, 1955, 167); both 2α[equatorial] : 3α[axial]- (A) and 2α[equatorial] : 3β[equatorial]-dimethanesulphonyloxy-5α : 22*a*-spirostan-12-one (B), by treatment with sodium iodide in acetone at 100°, give 5α : 22*a*-spirost-2-en-12-one. These reactions appear to involve mechanism *E1cB*, wherein the initial stage is the extraction of a methanesulphonyloxy-group as the cation by an iodide anion. The fact that both 2β[ax] : 3β[eq]- (C) and 2β[axial] : 3α[axial]-dimethanesulphonyloxy-5α : 22*a*-spirostan-12-one (D) are essentially unaffected by treatment with sodium iodide in acetone at 100° suggests that the *mutual* orientation of the groups eliminated is not a factor in the reaction. It seems probable that steric retardation at $C_{(2)}$ and $C_{(3)}$ may be the controlling factor, since the order of increasing steric hindrance is *trans*-2α : 3β[equatorial : equatorial] (A) < *cis*-2α : 3α[equatorial : axial] † (B) < *cis*-2β : 3β[axial : equatorial] ‡ (C) < *trans*-2β : 3α-[axial : axial] (D). Another example of a *cis*-elimination has been described by Djerassi

* An analogous inversion was envisaged by Cristol and Hause (*loc. cit.*).
† 1 : 2-Interactions with 1α-H and 5α-H.
‡ 1 : 2-Interactions with 4β-H and 10β-Me.

and Fishman (*Chem. and Ind.*, 1954, 1320) in which *cis*-2ξ : 3ξ-dimethanesulphonyloxy-22*a*-spirostan by treatment with sodium iodide in acetone furnishes 22*a*-spirost-2-ene.

Experimental

For general experimental directions see *J.*, 1954, 4224; $[\alpha]_D$ are in $CHCl_3$, and infra-red absorption spectra were determined in CS_2 on a Perkin-Elmer double-beam spectrometer.

Reduction of 7α-Bromo-6-oxocholestan-3β-yl Acetate.—(a) *With lithium aluminium hydride.* The 7α-bromo-ketone (m. p. 145°; 1 g.), dissolved in ether, was added to a solution of lithium aluminium hydride (200 mg.) in ether at 20°; after 0·25 hr. at 36° excess of the reagent was destroyed by addition of ice, and the neutral product isolated in the usual way. The resultant oil soon solidified, but recrystallisation from ether–pentane or acetone–pentane tended to give gels whilst the crystalline material melted over a large range. A specimen consisting of a mixture of 7α-bromocholestane-3β : 6β- and 3β : 6α-diol had m. p. 178—182° after softening, $[\alpha]_D$ −14° (*c*, 3·4) [Found (after drying at 60°/0·05 mm. for 3 hr.) : C, 67·6; H, 10·0. Calc. for $C_{27}H_{47}O_2Br$: C, 67·2; H, 9·8%]. Chromatographic separation of the diols was unsuccessful.

(b) *With sodium borohydride.* Reduction of the 7α-bromo-ketone and chromatography of the product gave the 7α-bromo-6β-ol acetate (I; R = Ac), m. p. 178°, $[\alpha]_D$ −24°, and the 6α-epimer acetate (III; R = Ac), double m. p. 136°/145°, $[\alpha]_D$ −9° (cf. James and Shoppee, *J.*, 1954, 4224).

Cholest-6-en-3β-ol.—(a) *From the mixed diols.* The diol mixture (660 mg.) was heated under reflux with zinc dust in acetic acid for 1 hr.; after cooling, water was added and the product extracted with ether, washed to neutrality, dried, and evaporated. The solid product (520 mg.) by recrystallisation from acetone–methanol gave cholest-6-en-3β-ol (V; R = H), m. p. 124—126°, $[\alpha]_D$ −88° ± 2° (*c*, 1·19) [Found (after drying at 65°/0·05 mm. for 3 hr.) : C, 80·3; H, 11·8. Calc. for $C_{27}H_{46}O,H_2O$: C, 80·1; H, 11·95%], giving a yellow colour with tetranitromethane–chloroform and a violet colour with acetic anhydride–sulphuric acid. The infra-red absorption spectrum of a Nujol mull showed bands at 3530—3200 and 1058 cm.$^{-1}$ (hydroxyl) and 1640, 770, 739, and 702 cm.$^{-1}$ [*cis*-CH=CH, consistent with a 6 : 7-double bond (cf. Henbest, Meakins, and Wood, *J.*, 1954, 800)]. Acetylation (acetic anhydride–pyridine at 100°) and recrystallisation of the product from methanol gave cholest-6-en-3β-yl acetate (V; R = Ac), m. p. 112—114°, $[\alpha]_D$ −93° ± 2° (*c*, 2·30) [Found (after drying at 20°/0·01 mm. for 18 hr.) : C, 81·4; H, 11·5. Calc. for $C_{29}H_{48}O_2$: C, 81·2; H, 11·3%], giving a violet colour in the Liebermann–Burchard test, and showing bands in the infra-red when examined in 2% carbon disulphide solution at 1734 and 1238 cm.$^{-1}$ (acetate) and 1634, 770, 739, and 702 cm.$^{-1}$ (*cis*-CH=CH : Δ^6). The benzoate (benzoyl chloride–pyridine at 20° for 18 hr.) had m. p. 132—133°, $[\alpha]_D$ −89°, −85° (*c*, 1·92, 1·0) [Found (after drying at 20°/0·01 mm. for 20 hr.) : C, 82·7; H, 10·2. Calc. for $C_{34}H_{50}O_2$: C, 83·2; H, 10·3%], after recrystallisation from methanol. The 3 : 5-*dinitrobenzoate* (3 : 5-dinitrobenzoyl chloride–benzene–pyridine at 20° for 18 hr.) had m. p. 188—190°, $[\alpha]_D$ −77° ± 2° (*c*, 1·27) [Found (after drying at 20°/0·01 mm. for 20 hr.) : C, 69·8; H, 8·2. $C_{34}H_{48}O_6N_2$ requires C, 70·2; H, 8·3%].

(b) *From 7α-bromo-6β-hydroxycholestan-3β-yl acetate* (I; R = Ac). The 7α-bromo-6β-hydroxy-acetate (45 mg.) was refluxed with activated zinc (400 mg.) (Fieser and Johnson, *J. Amer. Chem. Soc.*, 1940, **62**, 576) in ethanol for 6 hr. The product (31 mg.), isolated in the usual way, by crystallisation from acetone gave cholest-6-en-3β-yl acetate (V; R = Ac), m. p. and mixed m. p. 112—114°. Hydrolysis of the acetate with 5% methanolic potassium hydroxide gave cholest-6-en-3β-ol, m. p. 124—126°, after recrystallisation from acetone–methanol.

(*c*) *From the 6α-analogue* (III; R = Ac). The 6α-compound acetate (45 mg.) on similar treatment with activated zinc in hot ethanol for 6 hr. gave cholest-6-en-3β-yl acetate (33 mg.), m. p. and mixed m. p. 112—114° after recrystallisation from acetone. The acetate (100 mg.), by treatment with lithium aluminium hydride (50 mg.) in ether at 20° for 18 hr. and subsequent working up, gave cholest-6-en-3β-ol, m. p. 122—124°, after recrystallisation from acetone–methanol.

6α : 7α-*Epoxycholestan-3β-yl Acetate.*—Cholest-6-en-3β-yl acetate (735 mg.) was treated with monoperphthalic acid (50 mg./c.c. : 2 mols.) in ethereal solution at 15° for 5 days (consumption : 1 mol. of peracid). Excess of peracid was destroyed with potassium iodide solution, and the ethereal solution washed with 0·1N-sodium thiosulphate. Working up in the usual manner yielded a crystalline solid (720 mg.). Recrystallisation from methanol gave 6α : 7α-*epoxycholestan-3β-yl acetate* (590 mg.) as needles, m. p. 179—180°, $[\alpha]_D$ −23° (*c*, 1·05) [Found (after drying at 60°/0·01 mm. for 2 hr.) : C, 78·2; H, 11·0. $C_{29}H_{46}O_3$ requires C, 78·3; H, 10·9%].

Reduction of 6α : 7α-*Epoxycholestan*-3β-*yl Acetate*.—6α : 7α-Epoxycholestan-3β-yl acetate (70 mg.) in dry ether (25 c.c.) was added to a solution of lithium aluminium hydride (40 mg.) in ether (20 c.c.). The solution was refluxed for ½ hr. and excess of the reagent decomposed with ice and 2N-sulphuric acid. Working up in the usual manner afforded cholestane-3β : 7α-diol, m. p. 151—152°, $[\alpha]_D$ +10° (*c*, 1·15), after crystallisation from methanol. Acetylation with acetic anhydride–pyridine at 15° gave the diacetate, m. p. 137—138°, $[\alpha]_D$ −16° (*c*, 1·12).

6β-*Bromo*-7α-*hydroxycholestan*-3β-*yl Acetate*.—6α : 7α-Epoxycholestan-3β-yl acetate (300 mg.) was dissolved in acetic acid (12 c.c.) cooled in ice water, and a 5% solution of hydrogen bromide in acetic acid (5 c.c.) added; after ½ hr. fine needles began to separate. Extraction with ether and the usual working up yielded 6β-*bromo*-7α-*hydroxycholestan*-3β-*yl acetate* (360 mg.), m. p. 149—150°, $[\alpha]_D$ −46·5° (*c*, 0·81), after crystallisation from ether–pentane [Found (after drying at 60°/0·01 mm. for 2 hr.) : C, 66·2; H, 9·5; Br, 15·2. $C_{29}H_{49}O_3Br$ requires C, 66·25; H, 9·4; Br, 15·2%].

Hydrogenation of 6β-*Bromo*-7α-*hydroxycholestan*-3β-*yl Acetate*.—6β-Bromo-7α-hydroxycholestan-3β-yl acetate (75 mg.), potassium hydroxide (600 mg.), and 20% palladium–charcoal (50 mg.) in ethanol (25 c.c.) were shaken in hydrogen at 25° for 6 hr. The solution, by dilution and working up, gave cholestane-3β : 7α-diol, m. p. 152°, undepressed by admixture with the specimen obtained by lithium aluminium hydride reduction of 6α : 7α-epoxycholestan-3β-yl acetate.

Cholest-6-*en*-3β-*yl Acetate from the* 6β-*Bromo*-7α-*alcohol* (IX; R = Ac).—6β-Bromo-7α-hydroxycholestan-3β-yl acetate (45 mg.) was refluxed with activated zinc (450 mg.) in ethanol (12 c.c.) for 3 hr. The product (38 mg.), isolated in the usual way, on crystallisation from acetone gave cholest-6-en-3β-yl acetate, m. p. and mixed m. p. 112—113°.

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