945. *Steroids and Walden Inversion. Part XLV.* 6β-Chloro- and 6β-Bromo-5α-cholestane.*

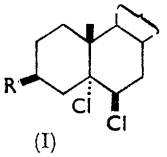
By C. W. Shoppee and Ruth Lack.

6β-Chloro-5α-cholestane chloride has been obtained from 6α-bromo-5α-cholestane by exchange with tetrabutylammonium chloride in dioxan at 100°; several unsuccessful indirect approaches are described.

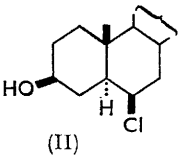
6β-Bromo-5α-cholestane has been prepared by reversed (anti-Markovnikov) addition of hydrogen bromide to cholesteryl acetate, and subsequent elimination of the 3β-acetoxyl group. The detailed mechanism of this and related radical additions of hydrogen bromide is discussed.

Having failed to find conditions permitting conversion of the epimeric 5α-cholestan-6-ols into the 6β-halogeno-5α-cholestanes (see following paper), we were compelled to examine indirect methods of preparation.

Décombe and Rabinovitch,[1] although unable to reduce 5α,6β-dichlorocholestane [2] (I; R = H) with hydrogen and platinum black in ether (as we have confirmed), claimed to have accomplished partial hydrogenation of cholesterol dichloride (5α,6β-dichlorocholestan-3β-ol) [2,3,4] (I; R = OH) with the same catalyst in aqueous ether to 6β-chloro-5α-cholestan-3β-ol (II), which they also obtained, accompanied by 5α-cholestan-3β-ol, by similar partial reduction of 5α,6β-dichlorocholestan-3-one [2] (III).



(I)



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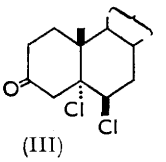


(III)

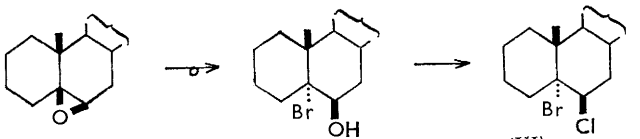
Despite numerous attempts under a variety of conditions, we have been unable to repeat the work of Décombe and Rabinovitch; attempts made at Imperial College, London, through the kindness of Professor D. H. R. Barton, F.R.S., were also unsuccessful. We therefore explored the partial reduction of a mixed 5α,6β-dihalide.

Cholest-5-ene was found to add iodine monochloride readily in acetic acid; Markovnikov orientation being assumed, the extremely unstable product was 5α-chloro-6β-iodocholestane, which by immediate hydrogenation with palladium or platinum in anhydrous neutral media gave 5α-chlorocholestane accompanied by variable amounts of cholest-5-ene, formed by elimination of iodide monochloride. 5β,6β-Epoxycholestane [5,6,7]

* Part XLIV, preceding paper.

[1] Décombe and Rabinovitch, *Bull. Soc. chim. France*, 1939, **6**, 1510.
[2] Barton and Miller, *J. Amer. Chem. Soc.*, 1952, **72**, 370, 1066.
[3] Berg and Wallis, *J. Biol. Chem.*, 1946, **162**, 683.
[4] Décombe and Rabinovitch, *Compt. rend.*, 1947, **225**, 583.
[5] Ruzicka, Fürter, and Thomann, *Helv. Chim. Acta*, 1933, **11**, 332.
[6] Henbest and Wrigley, *J.*, 1957, 4596; Hallsworth and Henbest, *ibid.*, p. 4604.
[7] Shoppee, Jenkins, and Summers, *J.*, 1958, 1657.

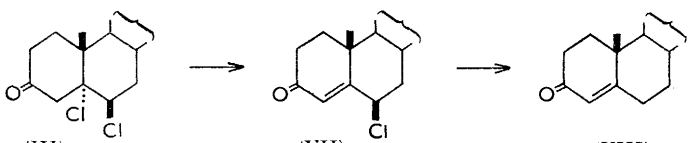
(IV), by fission with hydrogen bromide, gave 5α-bromocholestane-6β-ol (V), converted by thionyl chloride, *via* an intermediate 5α,6α-bromonium ion [8] and so with retention of configuration at $C_{(6)}$, into 5α-bromo-6β-chlorocholestane (VI). The 5α-bromo-6β-chloride (VI) was unchanged by treatment with hydrogen and palladium or platinum in anhydrous dioxan, anhydrous ether, or ether containing a trace of perchloric acid; with platinum and hydrogen in aqueous ether the sole product was 5α-cholestane. The compound (VI) was unaffected by lithium aluminium hydride in ether at 35°. An attempt to prepare



(IV) (V) (VI)

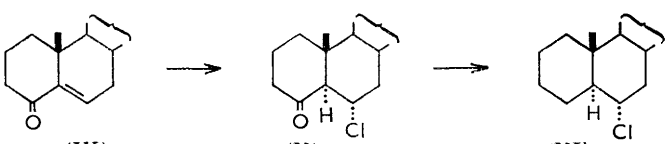
from the 5β-6β-epoxide (IV) the 5α-iodo-6β-alcohol (cf. V) and to convert this into the 5α-iodo-6β-chloride (cf. VI) was unsuccessful and furnished only cholest-5-ene.

We next attempted to raise the reactivity toward removal of the 5α-halogen atom in a 5α,6β-dihalide by provision of an activating group. 5α,6β-Dichlorocholestan-3-one [2] (III) was converted by dehydrochlorination with potassium acetate in ethanol into 6β-chlorocholest-4-en-3-one [2] (VII). This was subjected to hydrogenation with a deactivated platinum catalyst in ethyl acetate in the hope that conjugation with the 3-carbonyl of the π-electrons of the 4,5-double bond might diminish the reactivity of the allylic 6β-chlorine atom; [9] however, the sole isolable hydrogenation product was cholest-4-en-3-one (VIII).



(III) (VII) (VIII)

Despite the *cis*-axial-equatorial addition of deuterium chloride to cholest-5-ene,[10] we investigated the addition of hydrogen chloride to cholest-5-en-4-one [11,12] (IX). Here, *cis*-axial-equatorial addition again occurred, presumably by 5α-protonation of the 5,6-double bond and intermediate formation of a 6-carbonium ion, to give 6α-chloro-5α-cholestan-4-one (X), whose structure was proved by conversion into the dibenzyl thioketal



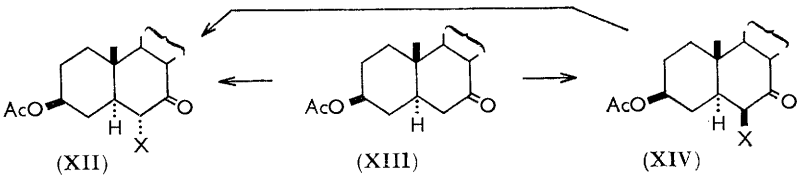
(IX) (X) (XI)

and desulphurisation with deactivated Raney nickel [13,14] in ethanol to 6α-chloro-5α-cholestane (XI), m. p. 149°, $[\alpha]_D$ +46°, $\nu_{max.}$ 781 and 745 cm.$^{-1}$ in CS_2 (see following paper).

3β-Acetoxy-5α-cholestan-7-one (XIII), although unattacked by bromine in acetic acid

[8] Barton, Miller, and Young, *J.*, 1951, 2598; cf. Ziegler and Shabica, *J. Amer. Chem. Soc.*, 1952, **74**, 4891.
[9] Shoppee, Bridgewater, Jones, and Summers, *J.*, 1956, 2492.
[10] Barton, Campos-Neves, and Cookson, *J.*, 1956, 3500.
[11] Butenandt and Ruhenstroth-Bauer, *Ber.*, 1944, **77**, 397.
[12] Jones, Lewis, Shoppee, and Summers, *J.*, 1955, 2876.
[13] Spero, McIntosh, jun., and Levin, *J. Amer. Chem. Soc.*, 1948, **70**, 1907.
[14] Rosenkranz, Kaufmann, and Romo, *J. Amer. Chem. Soc.*, 1949, **71**, 3689.

at 35°, underwent bromination [15] in chloroform at 20° to afford epimeric monobromo-derivatives, which were shown [16] to be the 6β- (XIV; X = Br) and the 6α-bromo-ketone (XII; X = Br); consistently, the axial 6β-bromo-ketone produced under kinetic control is converted by hydrogen bromide into the equatorial 6α-bromo-ketone.[17] Using the acetoxy-ketone (XIII) as a model we examined its chlorination.

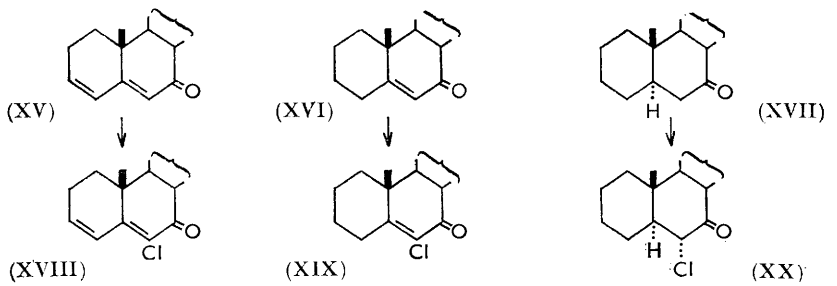


(XII) (XIII) (XIV)

Chlorination of 3β-acetoxy-5α-cholestan-7-one (XIII) in acetic acid at 20° gave a single chloro-ketone, identified by its spectra as 3β-acetoxy-6α-chloro-5α-cholestan-7-one [17] (XII; X = Cl); it did not give a 2,4-dinitrophenylhydrazone (cf. ref. 16) and failed to furnish a dibenzyl thioketal. Since the chloro-ketone (XII) may arise from the first-formed 6β-chloro-epimer (XIV; X = Cl) by acid-catalysed enolisation,[17] we examined base-catalysed chlorination,[18] but 3β-acetoxy-5α-cholestan-7-one (XIII) was recovered unchanged from acetic acid at 90° containing anhydrous potassium acetate and a large excess of chlorine.

We next investigated the monochlorination of the 7-ketones (XV, XVI, XVII). Cholesta-3,5-dien-7-one [19] (XV) in glacial acetic acid, treated with 1·05 mol. of chlorine in acetic acid at 20°, gave 6-chlorocholesta-3,5-dien-7-one (XVIII). The bathochromic displacement, $\Delta\lambda_{max.}$ +15 mμ, for the chloro-ketone (XVIII) is comparable with that (14·5 mμ) observed for 4-chlorocholesta-4,6-dien-3-one.

Cholest-5-en-7-one [20] (XVI) similarly gave 6-chlorocholest-5-en-7-one. Chlorination of 5α-cholestan-7-one [20–23] (XVII) in acetic acid at 20° gave a single chloro-ketone which was identified by its spectra as 6α-chloro-5α-cholestan-7-one (XX). The chloro-ketone did not give a 2,4-dinitrophenylhydrazone (cf. ref. 16) or a dibenzyl thioketal. In an attempt to avoid acid-catalysed enolisation and inversion at $C_{(6)}$ leading to the production of (XX), the base-catalysed chlorination of the ketone (XVII) in acetic acid at 90° was



(XV) (XVI) (XVII)

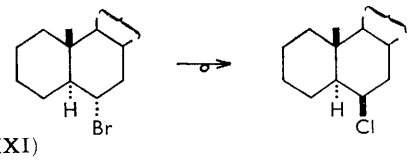
(XVIII) (XIX) (XX)

examined; despite use of a large excess of chlorine, the ketone was recovered unchanged.

Finally 6β-chloro-5α-cholestane was prepared by the exchange reaction: [24] $RBr + Cl^- \rightleftharpoons RCl + Br^-$. 6α-Bromo-5α-cholestane (XXI), m. p. 141°, $[\alpha]_D$ +50°, $\nu_{max.}$

[15] Barr, Heilbron, Jones, and Spring, *J.*, 1938, 334.
[16] James and Shoppee, *J.*, 1956, 1064.
[17] Corey, *J. Amer. Chem. Soc.*, 1954, **76**, 175.
[18] Cf. Crowne, Evans, Green, and Long, *J.*, 1956, 4354.
[19] Stavely and Bergmann, *J. Org. Chem.*, 1937, **1**, 567.
[20] Windaus, *Ber.*, 1920, **53**, 488; Windaus and Kirchner, *ibid.*, p. 614.
[21] Heilbron, Shaw, and Spring, *Rec. Trav. chim.*, 1938, **57**, 529.
[22] Dauben, Dickel, Jeger, and Prelog, *Helv. Chim. Acta*, 1953, **36**, 325.
[23] Cremlyn and Shoppee, *J.*, 1954, 3515.
[24] Bateman, Hughes, and Ingold, *J.*, 1940, 1017; Hughes, Juliusberger, Masterman, Scott, Topley, and Weiss, *J.*, 1935, 1525; 1936, 1173; Cowdrey, Hughes, Nevell, and Wilson, *J.*, 1938, 209.

710 cm.$^{-1}$ (see following paper), on treatment with tetrabutyl- or tetraethyl-ammonium chloride in anhydrous dioxan at 100° gave after 3 hr. a mixture separable by fractional crystallisation into unchanged 6α-bromo- and 6β-chloro-5α-cholestane (XXII), m. p. 94°, $[\alpha]_D$ −2°, $\nu_{max.}$ 696 cm.$^{-1}$ (axial C–Cl stretching frequency).



(XXI) (XXII)

For the preparation of 6β-bromo-5α-cholestane the partial reduction of 5α,6β-dibromocholestane [25-27] (cf. I; R = H) was examined. The compound was unchanged by hydrogen and palladium in ether–methanol, and was partially converted *via* cholest-5-ene into 5α-cholestane with platinum in ethyl acetate (cf. ref. 1); surprisingly, 5α,6β-dibromocholestane was isomerised by lithium aluminium hydride in ether at 35° in 1·5 hr. to the more thermodynamically stable 5β,6α-dibromocholestane.[28] A successful and radically different procedure was worked out as follows.

Cholesterol (XXIV; R = H) with hydrogen bromide in chloroform at 20°, or in carbon tetrachloride–ether in the presence of ferric chloride at 20°, gives 5α-bromocholestan-3β-ol [29] (XXIII; R = H). Cholesteryl acetate (XXIV; R = Ac) similarly yields 3β-acetoxy-5α-bromocholestane (XXIII; R = Ac),[30] m. p. 127—131°, $[\alpha]_D$ +3°, $\nu_{max.}$ 665 cm.$^{-1}$ (axial bromine), but in the presence of oxygen and the complete absence of moisture affords 3β-acetoxy-6β-bromo-5α-cholestane * (XXV; R = Ac), m. p. 140°, $[\alpha]_D$ −30°, $\nu_{max.}$ 660 cm.$^{-1}$ (axial bromine).

By hydrolysis with 1% methanolic hydrogen bromide at 20°, the acetate (XXV; R = Ac) gives 6β-bromo-5α-cholestan-3β-ol (XXV; R = H) [$\nu_{max.}$ 665 cm.$^{-1}$ (axial bromine)], oxidised by chromium trioxide in acetic acid at 20° to 6β-bromo-5α-cholestan-3-one (XXVIII) [$\nu_{max.}$ 670 cm.$^{-1}$ (axial bromine)]. This ketone furnishes the crystalline dibenzyl thioketal (XXVII), which is smoothly desulphurised by deactivated Raney nickel [13,14] in ethanol at 70° to 6β-bromo-5α-cholestane (XXVI), m. p. 125°, $[\alpha]_D$ −15°, $\nu_{max.}$ 660 cm.$^{-1}$ (axial bromine), giving a large m. p. depression with 6α-bromo-5α-cholestane, m. p. 142°, $[\alpha]_D$ +50°, $\nu_{max.}$ 710 cm.$^{-1}$ (see following paper).

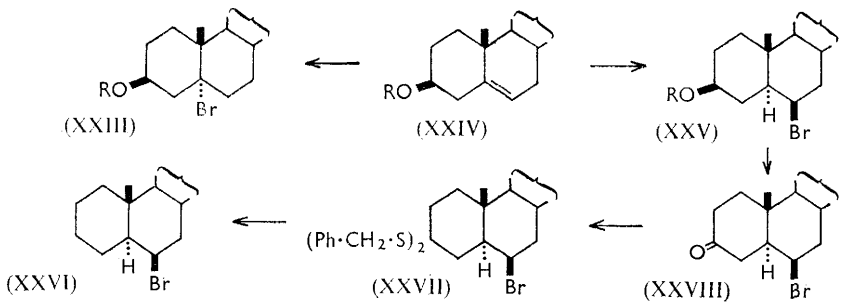
The reversal of the normal (Markovnikov) orientation of the addition of hydrogen bromide to cholesteryl acetate (XXIV ⟶ XXIII) in the presence of oxygen suggests that the bromine atom, as opposed to the bromine cation, is the active agent in the reaction (XXIV ⟶ XXV). The stereochemical outcome in that reaction is *trans*-diaxial addition, and it appears that not only carbonium ions [10] and carbanions,[31,32] but also carbon radicals, unite with the appropriate species (X^-, H^+, or H) to furnish the more stable configuration.

The established structure and configuration of the bromide (XXVI), taken together with the fixed conformation of steroid ring B, permit certain conclusions concerning the detailed mechanism of the reaction (XXIV ⟶ XXV), which may possess general validity for radical additions to cyclohexene systems: (*a*) the initiating bromine atom

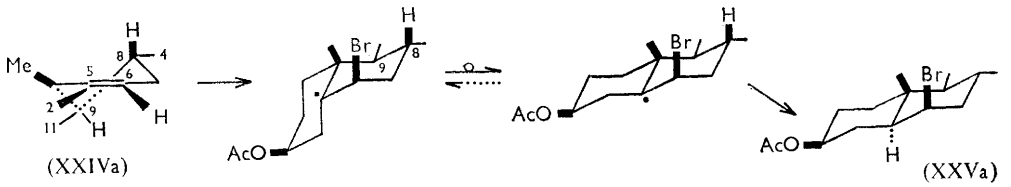
* Curiously, we were unable to effect radical addition of hydrogen bromide to cholest-5-ene under corresponding conditions.

[25] Mauthner and Suida, *Monatsh.*, 1894, **15**, 85; Mauthner, *ibid.*, 1906, **27**, 421.
[26] Grob and Winstein, *Helv. Chim. Acta*, 1952, **35**, 782.
[27] Kwart and Weisfeld, *J. Amer. Chem. Soc.*, 1956, **78**, 635.
[28] Barton and Head, *J.*, 1956, 932.
[29] Urushibara and Mori, *J. Chem. Soc. Japan*, 1943, **64**, 1285; cf. *Chem. Abs.*, 1947, **41**, 3807.
[30] Kon, *J. Chem. Soc. Japan*, 1943, **64**, 405; cf. *Chem. Abs.*, 1950, **44**, 7336.
[31] Barton and Robinson, *J.*, 1954, 3045.
[32] Roberts and Shoppee, *J.*, 1954, 3418.

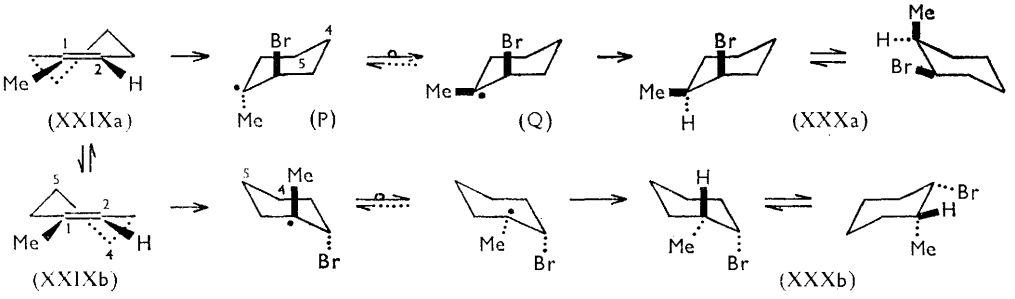
traverses preferentially that reaction co-ordinate which produces an axial bromine substituent; (*b*) the intermediate carbon radical acquires a thermodynamically preferred pyramidal configuration, provided that any configurational inversion is fast compared



with the final radical transfer. Thus the apparently stereospecific reaction (XXIV ⟶ XXV) could be written as (XXIVa) ⟶ (XXVa).



Consistently, the anti-Markovnikov addition of hydrogen bromide in the presence of benzoyl peroxide to the conformationally flexible 1-methylcyclohexene (XXIXa, b) (and to 1-chloro- and 1-bromo-cyclohexene) affords 100% of the *trans*-diaxial product (±)-*cis*-2-bromo-1-methylcyclohexane (XXXa, b).[33]

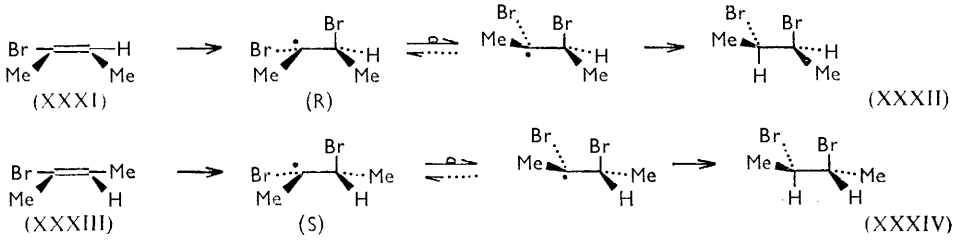


Brand and Stevens [34] regard (Q) as the conformation initially produced in the radical addition of nitrogen dioxide to 1-methylcyclohexene, which furnishes 100% of the *trans*-diaxial adduct; they attribute, in our view correctly, this exclusive *trans*-addition to steric compression, especially 1,3-diaxial repulsions, so that the life of (P) is short in comparison with that of (Q).

[33] Goering, Abell, and Aycock, *J. Amer. Chem. Soc.*, 1952, **74**, 3588; Goering and Sims, *ibid.*, 1955, **77**, 3465.

[34] Brand and Stevens, *J.*, 1958, 629.

The photocatalysed anti-Markovnikov addition of hydrogen bromide at −70° to *cis*- and *trans*-2-bromobut-2-ene reported by Goering and Larsen [35] is not completely stereospecific; the *cis*-isomer (XXXI) gives 92% of *meso*-2,3-dibromobutane (XXXII) with 5% of the racemic variety (XXXIV), whilst the *trans*-isomer (XXXIII) gives 83% of racemic



2,3-dibromobutane (XXXIV) with 8% of the *meso*-form (XXXII). These results can be interpreted in respect of the major products as reflecting the increase in thermodynamic stability resulting from inversion of configuration at $C_{(2)}$ with elimination of the eclipsed and gauche (skew) interactions in conformations (R) and (S), and in respect of the minor products by the assumption that the rate of the final radical transfer is comparable with that of the inversion, so that hydrogen transfer to the conformations (R) and (S) gives (by *cis*-addition) the racemate (XXXIV) and the *meso*-form (XXXII), respectively.*

It may be noted that radical addition of thiolacetic acid [36] to, *inter alia*, 1-methylcyclohexene gives mixtures of *trans*- and *cis*-products in proportions which vary with the conditions; we are investigating the corresponding reaction for the conformationally unambiguous cholest-5-ene system.

Experimental

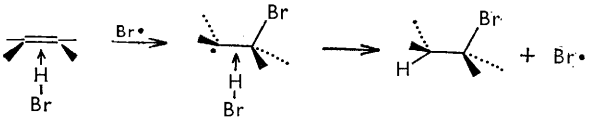
$[\alpha]_D$ relate to ~1% $CHCl_3$ solutions; ultraviolet absorption spectra were measured for EtOH solutions on a Uvispek spectrophotometer; infrared absorption spectra were determined, on a Perkin–Elmer Model 21 instrument for CS_2 solutions. Compounds submitted for analysis were generally dried in a high vacuum for 2—3 hr. at ~20°.

Unsuccessful Hydrogenations.—Only starting material was recovered after the following attempted hydrogenations at room temperature:

5α,6β-Dichlorocholestane [1] (200 mg.) with pre-reduced Adams catalyst (40 mg.) and ethyl acetate (60 ml.).

5α,6β-Dichlorocholestan-3β-ol: [1,2] (*a*) 200 mg., with pre-reduced Adams catalyst (500 mg.) and ether (50 ml.)–water (10 ml.); (*b*) 500 mg., with pre-reduced Adams catalyst (500 mg.), acetic acid (100 ml.), and perchloric acid (2 drops); (*c*) 500 mg., with pre-reduced Adams catalyst (500 mg.), ethyl acetate (50 ml.), acetic acid (20 ml.), and perchloric acid (2 drops); (*d*) 67·6 mg., with Willstätter–Waldschmidt-Leitz's platinum black (102 mg.) in ether (6 ml.) and water (3 ml.); (*e*) an experiment with the alcohol (69 mg.) and similar platinum black

* Dr. H. Goering, in a personal discussion at the University of Wisconsin, pointed out that telomerisation is not observed in radical additions of hydrogen bromide to olefins, and suggested that the species undergoing addition may be, not the olefin, but a hydrogen bromide π-complex, which after attack by Br· leads immediately to a *trans*-addition product.



[35] Goering and Larsen, *J. Amer. Chem. Soc.*, 1957, **79**, 2653.
[36] Bordwell and Hewett, *J. Amer. Chem. Soc.*, 1957, **79**, 3493.

(200 mg.) in dibutyl ether (6 ml.) and water (3 ml.) gave a mixture whence only cholestanol, double m. p. 118°/139°, was isolated. We are indebted to Mr. A. Stössl, of Imperial College of Science and Technology, London, for experiments (*d*) and (*e*).

Addition of Iodine Monochloride to Cholest-5-ene.—Iodine monochloride (0·75 g.) in acetic acid (10 ml.) was added to cholest-5-ene (1 g.) in dry ether (10 ml.) at 20°. The mixture was poured immediately into an excess of sodium hydrogen carbonate solution; extraction with ether, followed by washing with sodium hydrogen sulphite solution, gave 5α-*chloro*-6β-*iodocholestane*, crystallising as white plates from acetone, m. p. 95°, $[\alpha]_D$ −30°, $\nu_{max.}$ 650 cm.$^{-1}$. The sample darkened slightly whilst awaiting analysis and decomposed rapidly when kept (Found: C, 61·7; H, 8·9. $C_{27}H_{46}ClI$ requires C, 60·8; H, 8·7%).

Hydrogenation of 5α-*Chloro*-6β-*iodocholestane.*—(*a*) 5α-Chloro-6β-iodocholestane (200 mg.) was shaken with pre-reduced Adams catalyst (50 mg.) in ethyl acetate (40 ml.) under hydrogen for 1 hr. The usual working-up gave a product, crystallising from acetone and having m. p. 75—77°, $[\alpha]_D$ −13° (Found: C, 78·7; H, 11·1. Calc. for $C_{27}H_{47}Cl$: C, 79·65; H, 11·6%), which was probably impure 5α-chlorocholestane.

(*b*) 5α-Chloro-6β-iodocholestane (200 mg.) was shaken with pre-reduced Adams catalyst (50 mg.) in ether (40 ml.) and hydrogen for 1 hr. The usual working-up gave a product (unsaturated to tetranitromethane; probably a mixture of 5α-chlorocholestane and cholest-5-ene), m. p. 72—75°, $[\alpha]_D$ −30° (Found: C, 81·4; H, 11·7. Calc. for $C_{27}H_{47}Cl$: C, 79·65; H, 11·6%).

(*c*) The mixed halide (200 mg.) was shaken with pre-reduced Adams catalyst (50 mg.) and sodium hydrogen carbonate (1 g.) in ether (50 ml.) under hydrogen for 2 hr. The solution than gave mainly unchanged 5α-chloro-6β-iodocholestane (160 mg.), m. p. 90—95° (Found: C, 62·0; H, 8·7. Calc. for $C_{27}H_{46}ClI$: C, 60·8; H, 8·7%).

(*d*) 5α-Chloro-6β-iodocholestane (1·3 g.) was shaken with pre-reduced Adams catalyst (200 mg.) and sodium hydrogen carbonate (1 g.) in ethyl acetate (70 ml.) and hydrogen for 8 hr. (60 ml. absorbed). The usual working-up gave cholest-5-ene (970 mg.), m. p. 88°, $[\alpha]_D$ −56° (Found: C, 87·1; H, 12·5. Calc. for $C_{27}H_{46}$: C, 87·6; H, 12·4%).

5β,6β-*Epoxycholestane.*—(*a*) Cholest-5-ene (m. p. 90°; 5 g.) in benzene (150 ml.) was treated with a benzene solution of perbenzoic acid (1·2 mol.) at 0° for 3 days. No separation of the α- and β-isomers was obtained by chromatography, but recrystallisation from ethanol gave 5α,6α-epoxycholestane (3·5 g.), m. p. 80°, and repeated recrystallisation of the residue from the mother-liquors from ethanol gave 5β,6β-epoxycholestane [5-7] (200 mg.), m. p. 56°, $[\alpha]_D$ −9°.

(*b*) 6-Nitrocholest-5-ene [20] was converted into 5α-cholestan-6-one by reduction with zinc dust. This ketone (3·22 g.) in ether (85 ml.) and acetic acid (25 ml.) with bromine in acetic acid (16 ml. of 2·8% v/v solution; 1·05 mol.) yielded 5α-bromocholestan-6-one, m. p. 101—102°, $[\alpha]_D$ −139° (lit.,[6,7] m. p. 101°, $[\alpha]_D$ −146°). Reduction of this bromo-ketone (2·83 g.) in dry ether (100 ml.) with lithium aluminium hydride (62 mg.) at 35° for 10 min., followed by working-up in the usual manner, gave an oil which was chromatographed on aluminium oxide (90 g.) in pentane. Elution with pentane (3 × 25 ml.) gave 5β,6β-epoxycholestane (400 mg.), m. p. 55—57°, $[\alpha]_D$ −9°, after crystallisation from acetone.

(*c*) Treatment of 5α-cholestan-5α,6β-diol [12] (3 g.) in chloroform (60 ml.) with acetyl chloride (24 ml.) in the presence of dimethylaniline (30 ml.) under reflux for 16 hr., followed by the usual isolation procedure, gave the diacetate as an oil (even after chromatography). This oil was heated with sodium hydroxide (3·75 g.) in ethanol (150 ml.) at 80° for 2·5 hr.; the product, was chromatographed on aluminium oxide (90 g.) in pentane. Elution with pentane (10 × 25 ml.) gave 5β,6β-epoxycholestane (2·2 g.), m. p. 78°, $[\alpha]_D$ −1° (lit.,[6] m. p. 80—81°, $[\alpha]_D$ +8°). A personal communication from Professor H. B. Henbest reports a repetition of the above experiment to give a product, m. p. 79—80°, $[\alpha]_D$ +1°.

5α-*Bromo*-6β-*chlorocholestane.*—5β,6β-Epoxycholestane (m. p. 78°, $[\alpha]_D$ −1°; 500 mg.) was dissolved in acetic acid (50 ml.) containing hydrogen bromide (105 mg.). The specific rotation determined immediately thereafter was $[\alpha]_D$ −26°, which was unchanged after 10 min. The solution was poured into aqueous sodium hydrogen carbonate. The usual isolation procedure gave 5α-bromocholestan-6β-ol as an oil. Treatment of this oil with thionyl chloride (5 ml.) for 12 hr. at 20°, followed by isolation in the usual manner and chromatography on aluminium oxide (15 g.) and elution with pentane (4 × 25 ml.), gave 5α-*bromo*-6β-*chlorocholestane* (470 mg.), which recrystallised from ethanol as plates, m. p. 111°, $[\alpha]_D$ −46° (Found: C, 66·4; H, 9·5. $C_{27}H_{46}BrCl$ requires C, 66·7; H, 9·5%).

This product was recovered unchanged after attempted hydrogenation with pre-reduced Adams catalyst in ethyl acetate, ether, dioxan, or acetic acid containing perchloric acid. When it (100 mg.) was shaken in hydrogen with pre-reduced Adams catalyst (100 mg.) in ether (40 ml.) and water (10 ml.) for 2 hr., the aqueous layer contained halide ion, and evaporation gave an oil, which crystallised from methanol to give 5α-cholestane, m. p. 75—80° (Found: C, 87·0; H, 12·7. Calc. for $C_{27}H_{48}$: C, 87·1; H, 12·9%). 5α-Bromo-6β-chlorocholestane (200 mg.) in ether (20 ml.) was unchanged when treated with lithium aluminium hydride (140 mg.) at 35° for 1 hr.

Attempted Preparation of 6β-*Chloro*-5α-*iodocholestane*.—5β,6β-Epoxycholestane (m. p. 78°, $[\alpha]_D$ −1°; 100 mg.) was treated with hydrogen iodide (20 mg.) in acetic acid (10 ml.) for 5 min. The solution was poured into aqueous sodium hydrogen carbonate and the usual isolation procedure gave an oil (70 mg.) which, treated with thionyl chloride (1 c.c.) for 2 hr., gave cholest-5-ene, m. p. 87—88°, $[\alpha]_D$ −53°.

5α,6β-*Dichlorocholestan*-3-*one*.—5α,6β-Dichlorocholestan-3β-ol [1,2] (11 g.) in acetic acid (200 ml.) and ether (50 ml.) was heated for 1 hr. at 50° with chromium trioxide (2·5 g.) in water (5 ml.). The product recrystallised from acetone to give 5α,6β-dichlorocholestan-3-one [1,2] (6·4 g.) as needles, m. p. 114—116°.

6β-*Chlorocholest*-4-*en*-3-*one*.—5α,6β-Dichlorocholestan-3-one (5·8 g.) in ethanol (250 ml.) was treated with freshly fused potassium acetate (6 g.) at 80° for 1 hr. Dilution with water, extraction with ether, and crystallisation from ethyl acetate–methanol, gave 6β-chlorocholest-4-en-3-one as needles, m. p. 127—128°, $\lambda_{max.}$ 241 mμ (log ε 4·17) [lit.,[2] m. p. 129°, $\lambda_{max.}$ 241 (log ε 4·18)].

Partial Hydrogenation of 6β-*Chlorocholest*-4-*en*-3-*one*.—6β-Chlorocholest-4-en-3-one (1·4 g.) was shaken in hydrogen with pre-reduced Adams catalyst (100 mg.) in acetic acid (55 ml.) for 30 min. (69 ml., 1 mol., absorbed). The catalyst was removed and the solution, concentrated in a vacuum, poured into water, and extracted with ether to give a colourless oil (1·2 g.). This was chromatographed on neutralised aluminium oxide (30 g.); elution with pentane gave cholest-4-en-3-one (814 mg.), m. p. 78—80°, giving a red 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 228°.

6α-*Chloro*-5α-*cholestan*-4-*one*.—Cholest-5-en-4-one [12] (500 mg.) in dry chloroform (10 ml.) was treated with a stream of dry hydrogen chloride for 2 hr. Extraction with ether and isolation in the usual way gave 6α-*chloro*-5α-*cholestan*-4-*one* (400 mg.) as prisms (from acetone), m. p. 88—89°, $\nu_{max.}$ 770, 777s, $[\alpha]_D$ +1° (Found: C, 77·5; H, 10·5. $C_{27}H_{45}ClO$ requires C, 77·05; H, 10·7%). This ketone (1·0 g.) was dissolved in toluene-ω-thiol (2 ml.) and cooled to 0°; then a suspension of 72% aqueous perchloric acid (2 drops) in the thiol (3 ml.) was added. The mixture was shaken for 2 min., and after a further 10 min. water was added and the product isolated with ether in the usual way. This gave an oil (1·2 g.), which was chromatographed on aluminium oxide (30 g.) in hexane. Elution with benzene–hexane (1 : 5; 4 × 25 ml.) gave the dibenzyl mercaptal (480 mg.), m. p. 57—58°.

6α-*Chloro*-5α-*cholestane*.—The above mercaptal (480 mg.) in ethanol (50 ml.) was heated with deactivated Raney nickel [13,14] (4 g.) at 70° for 4 hr. After filtration and concentration to 10 ml. in a vacuum, the product (310 mg.) separated at 0°. Recrystallisation from acetone gave 6α-chloro-5α-cholestane, m. p. 148—149°, $[\alpha]_D$ +43° (Found: C, 79·6; H, 11·5. Calc. for $C_{27}H_{47}Cl$: C, 79·65; H, 11·6%), which did not depress the melting point of an authentic sample.[37]

Chlorination of 3β-*Acetoxy*-5α-*cholestan*-7-*one*.—(a) *Acid-catalysed*. A solution of the ketone [15,20] (2·5 g.; m. p. 142°, ν_{max} 1737, 1236 (OAc), and 1713 cm.$^{-1}$ (CO) in acetic acid (50 ml.) was treated with a freshly prepared solution of chlorine (1·6 g., 4 mol.) in acetic acid (30 ml.) at 20° for 1 hr. Water (50 ml.) was added, and the precipitated solid was filtered off, to give a crude product, m. p. 118—145°. Repeated crystallisation from acetone gave 3β-acetoxy-5α-cholestan-7-one (520 mg.), m. p. 142° (Found: C, 78·1; H, 10·6. Calc. for $C_{29}H_{48}O_3$: C, 78·4; H, 10·8%). Evaporation of the acetone mother-liquors gave a solid (1·8 g.), which was chromatographed on neutralised aluminium oxide [38] (50 g.) in pentane. Elution with benzene–pentane (3 : 2; 2 × 50 ml.) gave a solid, m. p. 90—105° (270 mg.), which was not identified (Found: C, 77·7; H, 10·3%), but elution with benzene (6 × 50 ml.) and ether–benzene (1 : 10; 6 × 50 ml.) afforded 3β-acetoxy-6α-chloro-5α-cholestan-7-one (1·3 g.), crystallising as needles

[37] Shoppee, Howden, and Lack, following paper.
[38] Reichstein and Shoppee, *Discuss. Faraday Soc.*, 1949, **7**, 205.

(from acetone), m. p. 165°, $[\alpha]_D$ 0°, $\lambda_{max.}$ 280 mμ, $\nu_{max.}$ 1738, 1234 (OAc), 1735 cm.$^{-1}$ (CO adjacent to one equatorial Cl atom). This ketone did not give a dibenzyl mercaptal when treated as above, or a 2,4-dinitrophenylhydrazone.

(b) *Base-catalysed.* The ketone (500 mg.) in acetic acid (60 ml.) at 90° was added to anhydrous potassium acetate (2·25 g.) in acetic acid (15 ml.) at 90° and treated immediately with chlorine (300 mg.) in acetic acid (10 ml.) at 90° for 0·5 hr. On dilution with water and isolation in the usual manner, unchanged material (410 mg.; m. p. and mixed m. p. 142°) was obtained.

Chlorination of Cholesta-3,5-dien-7-one. This ketone [19] (2 g.) in acetic acid (15 ml.) was treated with chlorine (380 mg.) in acetic acid (10 ml.) at 20° for 1 hr. The usual isolation procedure gave a pale yellow oil, which was chromatographed on neutralised aluminium oxide [38] (60 g.) in pentane. Elution with benzene–pentane (1 : 10, 7 × 20 ml.) gave *6-chlorocholesta-3,5-dien-7-one* (385 mg.); recrystallised from acetone, this had m. p. 137—138°, $\lambda_{max.}$ 294 mμ (log ε 4·3), $\nu_{max.}$ 1689 cm.$^{-1}$ (Found: C, 77·6; H, 10·1. $C_{27}H_{41}ClO$ requires C, 77·8; H, 9·9%). Further elution with benzene–pentane (1 : 1; 2 × 50 ml.) and with benzene (2 × 50 ml.) gave unchanged cholesta-3,5-dien-7-one (1·0 g.), m. p. and mixed m. p. 112—114°.

Cholest-5-en-7-one.—Cholesta-3,5-dien-7-one (4·8 g.) in acetic acid (50 ml.) was shaken with 20% palladium–charcoal (500 mg.) in hydrogen for 3 hr. until the theoretical quantity of hydrogen was absorbed (280 ml.). The usual isolation gave cholest-5-en-7-one,[20] m. p. 110—111°, $\lambda_{max.}$ 238 mμ (log ε 4·08), $\nu_{max.}$ 1677 cm.$^{-1}$, giving a yellow 2,4-dinitrophenylhydrazone, m. p. 195°.

Chlorination of Cholest-5-en-7-one.—Cholest-5-en-7-one (2 g.) in acetic acid (15 ml.) was treated with chlorine (380 mg.) in acetic acid (10 ml.) at 20° for 1 hr. Isolation in the usual manner gave an oil, which was chromatographed on neutralised aluminium oxide [38] (60 g.) in pentane. Elution with pentane (5 × 20 ml.) and with benzene–pentane (1 : 10, 5 × 25 ml.) gave unchanged material (800 mg.), m. p. and mixed m. p. 110—111°. Further elution with benzene–pentane (1 : 10, 3 × 25 ml.) gave *6-chlorocholest-5-en-7-one* (380 mg.), needles (from acetone–methanol), m. p. 145°, $\lambda_{max.}$ 253 mμ (log ε 4·02), $\nu_{max.}$ 1693 cm.$^{-1}$ (Found: C, 77·1; H, 10·6. $C_{27}H_{43}ClO$ requires C, 77·4; H, 10·3%).

Chlorination of 5α-Cholestan-7-one.—(*a*) This ketone [20–23] [1 g.; m. p. 117°; λ_{max} 288 mμ (log ε 1·6); ν_{max} 1709 cm.$^{-1}$] in ether (30 ml.) was treated with chlorine (240 mg., 1·3 mol.) in acetic acid (20 ml.) at 20° for 3 hr. After the addition of water (30 ml.), the white solid was filtered off and recrystallised from acetone, giving *6α-chloro-5α-cholestan-7-one* (950 mg.), m. p. 137°, $\lambda_{max.}$ 286 mμ (log ε 1·6), $\nu_{max.}$ 1731 cm.$^{-1}$ (Found: C, 76·85; H, 10·9. $C_{27}H_{45}ClO$ requires C, 77·0; H, 10·7%), which gave neither a dibenzyl mercaptan nor a 2,4-dinitrophenylhydrazone.

(*b*) 5α-Cholestan-7-one (200 mg.), in acetic acid (20 ml.) at 90°, was added to anhydrous potassium acetate (750 mg.) in acetic acid (5 ml.) at 90°, and was immediately treated with chlorine (150 mg., 4 mols.) in acetic acid (10 ml.) at 90° for 1 hr. On cooling in ice, unchanged material separated (m. p. 115°, $\lambda_{max.}$ 288 mμ, $\nu_{max.}$ 1709 cm.$^{-1}$). Addition of water to the mother-liquor, followed by the usual isolation, gave more of it (110 mg.), m. p. 115°.

6β-Chloro-5α-cholestane.—(*a*) 6α-Bromo-5α-cholestane [37] (200 mg.), m. p. 141°, $[\alpha]_D$ +50°, $\nu_{max.}$ 710 cm.$^{-1}$, was treated with tetrabutylammonium chloride [39] (500 mg.) in dry dioxan (10 ml.) at 100° for 1 hr., then cooled to 0°. Water (10 ml.) was added and the precipitate was filtered off; recrystallisation from acetone gave 6α-bromo-5α-cholestane (100 mg.), m. p. 142°, $[\alpha]_D$ +45°. Extraction of the acetone mother-liquors and the original filtrate with ether, followed by evaporation, gave a further yield of the 6α-bromide (50 mg.), m. p. 141°. Repeated recrystallisation from methanol of the residue from the mother-liquor gave *6β-chloro-5α-cholestane* (6·5 mg.), m. p. 91—92°, $[\alpha]_D$ +2° (Found, on <2 mg.: C, 80·5; H, 13·2. $C_{27}H_{47}Cl$ requires C, 79·65; H, 11·6%).

(*b*) 6α-Bromo-5α-cholestane (200 mg.) was treated with tetrabutylammonium chloride (500 mg.) in dry dioxan (10 ml.) at 100° for 24 hr. The usual isolation procedure gave a product, m. p. 80—120°. Repeated recrystallisation from acetone gave 6α-bromo-5α-cholestane (70 mg.), m. p. 140°; material from the mother-liquor, on repeated recrystallisation from methanol, gave a product (30 mg.), m. p. 80—81°, $[\alpha]_D$ −20°, with, however, $\nu_{max.}$ 696 cm.$^{-1}$ (Found: C, 84·5; H, 12·2%). This product gave a yellow colour with tetranitromethane and was a mixture of 6β-chloro-5α-cholestane with much cholest-5-ene.

(*c*) 6α-Bromo-5α-cholestane (200 mg.) was treated with tetraethylammonium chloride

[39] Hughes, Ingold, Mok, Patai, and Pocker, *J.*, 1957, 1228.

(1 g.) in dry dioxan at 100° for 3 hr. The usual isolation procedure gave a solid, whence repeated recrystallisation from acetone afforded unchanged bromide [37] (82 mg.), m. p. 140—142°, $\nu_{max.}$ 710 cm.$^{-1}$; evaporation of the mother-liquors followed by repeated recrystallisation from methanol gave 6β-chloro-5α-cholestane (20 mg.), m. p. 94°, $[\alpha]_D$ −2°, $\nu_{max.}$ 696 cm.$^{-1}$ (Found: C, 79·9; H, 11·8%).

Attempted Partial Hydrogenation of 5α,6β-*Dibromocholestane.*—No hydrogenation occurred with 5% palladium–charcoal in ether–methanol. With Adams catalyst in ethyl acetate, 5α-cholestane was obtained.

Treatment of 5α,6β-*Dibromocholestane with Lithium Aluminium Hydride.*—5α,6β-Dibromocholestane (200 mg.) in dry ether (20 ml.) was treated with lithium aluminium hydride (14 mg.) for 0·25 hr. at 0°. The usual working-up procedure gave unchanged 5α,6β-dibromocholestane, m. p. 108° (180 mg.). Repetition of the experiment for 1·5 hr. at 35° gave 5β,6α-dibromocholestane [25–28] (160 mg.), m. p. 140—141°, $[\alpha]_D$ +31° (Found: C, 61·3; H, 8·6. Calc. for $C_{27}H_{46}Br_2$: C, 61·1; H, 8·7%).

Addition of Hydrogen Bromide to Cholesteryl Acetate.—(a) *In absence of oxygen.* Cholesteryl acetate (m. p. 115°; 2 g.) in chloroform (50 ml.) was treated with a stream of hydrogen bromide under nitrogen at 20° for 1 hr. The usual isolation procedure gave a good yield of 3β-acetoxy-5α-bromocholestane which crystallised from acetone in (i) plates, m. p. 126—127°, $[\alpha]_D$ +3° (lit.,[30] m. p. 127°, $[\alpha]_D$ +3·5°), and (ii) long prisms, m. p. 131°, $[\alpha]_D$ +3°, exhibiting identical infrared absorption spectra, $\nu_{max.}$ (in CS_2) 665 cm.$^{-1}$, and (in Nujol) 580, 610w, 672 cm.$^{-1}$, and giving the same analytical figures [Found: (i) C, 68·7; H, 9·7; (ii) C, 68·3; H, 9·8. Calc. for $C_{29}H_{49}BrO_2$: C, 68·35; H, 9·7%].

(b) *In presence of oxygen.* Cholesteryl acetate (2 g.; dried by azeotropic distillation with benzene) in dry carbon tetrachloride (40 ml.) was treated simultaneously with streams of dry oxygen and dry hydrogen bromide at 20° for 1 hr. After addition of ether, solvents were completely removed at 20° in a vacuum; the product crystallised from acetone, to give 3β-acetoxy-6β-bromo-5α-cholestane, m. p. 140°, $[\alpha]_D$ −30° (lit.,[30] m. p. 141°, $[\alpha]_D$ −29°), $\nu_{max.}$ (in CS_2) 660 cm.$^{-1}$, and (in Nujol) 533, 607w, 658 cm.$^{-1}$ (Found: C, 68·6; H, 9·7%).

6β-*Bromo*-5α-*cholestan*-3β-*ol.*—3β-Acetoxy-6β-bromo-5α-cholestane (1 g.) in ether (30 ml.) was hydrolysed with a 1% solution of hydrogen bromide in methanol (30 ml.) at 20° for 16 hr. Solvent was removed in a vacuum at 20°; isolation in the usual way gave 6β-*bromo*-5α-*cholestan*-3β-*ol* (900 mg.), m. p. 107—108°, raised by recrystallisation from acetone to 112°, $[\alpha]_D$ −8·5°, $\nu_{max.}$ (in CS_2) 665 cm.$^{-1}$, and (in Nujol) 534, 606w, 660 cm.$^{-1}$ (Found: C, 69·5; H, 10·3. $C_{27}H_{47}BrO$ requires C, 69·35; H, 10·1%).

6β-*Bromo*-5α-*cholestan*-3-*one.*—6β-Bromo-5α-cholestan-3β-ol (1 g.) in ether–acetic acid (1 : 2; 15 ml.) was treated with a 2% solution of chromium trioxide in acetic acid (11 ml.) at 20° for 18 hr. After removal of acetic acid at 30° in a vacuum, the usual isolation procedure gave 6β-*bromo*-5α-*cholestan*-3-*one* (910 mg.), m. p. 155—157°, $[\alpha]_D$ −6·5°, $\nu_{max.}$ (in CS_2) 670 cm.$^{-1}$, and (in Nujol) 530, 600w, 680 cm.$^{-1}$, after recrystallisation from acetone (Found: C, 69·3; H, 9·7. $C_{27}H_{45}BrO$ requires C, 69·6; H, 9·7%). The ketone (0·5 g.) gave, on treatment as outlined above, a *dibenzyl mercaptal* (400 mg.), m. p. 149° (from acetone–methanol) (Found: C, 70·9; H, 8·5. $C_{41}H_{59}BrS_2$ requires C, 70·8; H, 8·5%).

This mercaptal (500 mg.) was heated with deactivated Raney nickel [13,14] (4 g.) in ethanol (50 ml.) at 70° for 4 hr. After filtration and concentration of the filtrate to 10 ml. in a vacuum, the product (350 mg.) separated on cooling to 0°. Recrystallisation from acetone gave 6β-*bromo*-5α-*cholestane*, m. p. 125°, $[\alpha]_D$ −16°, $\nu_{max.}$ (in CS_2) 660 cm.$^{-1}$ and (in Nujol) 536, 608w, 663 cm.$^{-1}$ (Found: C, 71·6; H, 10·2. $C_{27}H_{47}Br$ requires C, 71·8; H, 10·5%).

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