360. *Studies in the Sterol Group. Part XLVII. A New Route to 7-Dehydrocholesterol (Provitamin D_3) and its Derivatives.**

By A. E. Bide, H. B. Henbest, E. R. H. Jones, R. W. Peevers, and P. A. Wilkinson.

The methods hitherto available for converting sterols into their 7-dehydro-derivatives are reviewed. Bromination of cholesteryl acetate (III) with *N*-bromosuccinimide gives 7-bromocholesteryl acetate (VII; R = OAc) which on treatment with diethylaniline followed by hydrolysis gives a mixture of 7-dehydrocholesterol (VIII; R = OH) and cholesta-4 : 6-dien-3(β)-ol (IX; R = OH). The overall yield of the dehydro-sterol, based on cholesterol, is about 30%. Cholesteryl benzoate, chloride, and bromide similarly yield 7-bromo-derivatives which are converted into 7-dehydro-compounds on dehydrobromination.

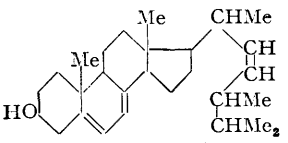
As a result of animal nutrition experiments (*inter al.*, Waddel, *J. Biol. Chem.*, 1934, **105**, 711), particularly with rats and chickens kept on a vitamin-D-deficient diet, it gradually became apparent that the vitamin D of fish-liver oils was not identical with the vitamin D_2 (calciferol) (II), obtained by irradiating ergosterol (I). In 1935, Windaus, Lettré, and Schenck (*Annalen*, **520**, 98) described the preparation from cholesteryl acetate (III), by the route indicated below, of the so-called 7-dehydrocholesterol (IV) which on irradiation gave a highly antirachitic product (vitamin D_3) (V) (Windaus, Schenck, and von Werder, *Z. physiol. Chem.*, 1936, **241**, 100). Shortly afterwards Brockmann (*Z. physiol. Chem.*, 1936, **241**, 104; 1937, **245**. 96) isolated vitamin D from tunny- and halibut-liver oils and found that this substance was identical with the vitamin D_3 (V) derived by irradiating Windaus's 7-dehydrocholesterol (IV).

The classical method developed by the Göttingen workers for the preparation of 7-dehydrocholesterol, only however in about 4% yield based on cholesterol, has since been used for the synthesis of several related 7-dehydro-steroids (*inter al.*, Linsert, *Z. physiol. Chem.*, 1936, **241**, 125; Wunderlich, *ibid.*, p. 116; Haslewood, *Biochem. J.*, 1939, **33**, 454; Butenandt, Hausmann, and Paland, *Ber.*, 1938, **71**, 1316; Ruigh, *J. Amer. Chem. Soc.*, 1942, **64**, 1900; Bergmann, Lyon, and McLean, *J. Org. Chem.*, 1944, **9**, 290), but the yields have not been appreciably improved, although a number of valuable and interesting minor modifications have been made. Thus Haslewood (*J.*, 1938, 224) observed that treatment of a dibenzoate such as that of (III*a*) with boiling dimethylaniline gave an improved yield of the monobenzoate of the dehydro-steroid, and Wintersteiner and Ruigh (*J. Amer. Chem. Soc.*, 1942, **64**, 1177) used the same procedure

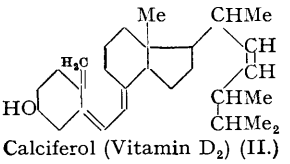
* Cf. *Nature*, 1946, **158**, 169; B.P. 574,432 and other patents pending.

with the 7-monobenzoate; this latter method is probably the best hitherto available of converting Δ^5-steroids into their $\Delta^{5:7}$-dehydro-derivatives.

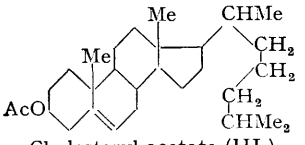
A number of direct dehydrogenation methods of preparing 7-dehydrocholesterol have been described but the yields do not appear to be very satisfactory. Thus Milas and Heggie (*J. Amer. Chem. Soc.*, 1938, **60**, 984; cf. Sah, *Rec. Trav. chim.*, 1940, **59**, 454; Mazza and Migliardi, *Chem. Abs.*, 1943, **37**, 3762) treated cholesteryl acetate with a variety of reagents including benzoquinone and chloranil, and obtained up to 8% conversions into the dehydro-acetate, estimated spectrographically.



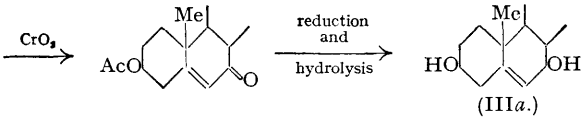
Ergosterol (I.)



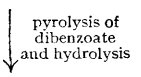
Calciferol (Vitamin D_2) (II.)

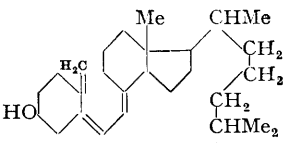


Cholesteryl acetate (III.)

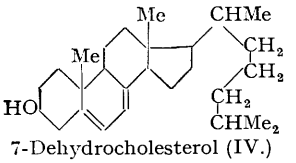


(III*a*.)





Vitamin D_3 (V.)



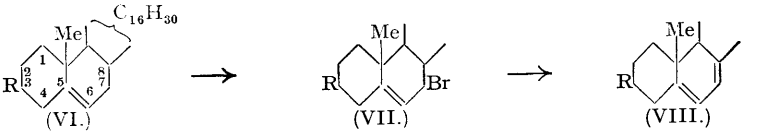
7-Dehydrocholesterol (IV.)

It seemed possible that by employing *N*-bromosuccinimide (Ziegler, *Annalen*, 1942, **551**, 80) 4- and/or 7-bromo-compounds could be obtained from cholesteryl esters and that on subsequent removal of hydrogen bromide the 7-bromo-compounds would yield 7-dehydrocholesteryl esters. Cholesteryl acetate (VI; R = OAc) was found to react at widely varying rates with *N*-bromosuccinimide suspended in various media. By working under carefully controlled conditions with light petroleum, it was eventually possible to isolate a crystalline monobromo-compound (m. p. 109°; $[\alpha]_D^{20°}$ − 245°) in 30—42% yield. A further considerable quantity of this bromo-compound remained in the mother liquors (as shown by the reaction with piperidine, forthcoming publication), but it could not be separated from the other substances present. Although there is little doubt that polybromination of cholesteryl acetate does occur when excess of *N*-bromosuccinimide is employed, attempts further to brominate the monobromo-compound with this reagent were unsuccessful, and no pure dibromo-compound could be isolated.

Of the various possible structures for this bromo-compound the epimeric 4-bromo- and 7-bromo-cholesteryl acetates were the first to be considered, although structures such as 5-bromo-Δ^6- and 6-bromo-Δ^4-cholestenyl acetates, arising from anionotropic rearrangements of primary bromination products, were not overlooked. On the basis of a considerable amount of evidence, presented in this and the three following papers, the crystalline bromo-compound is formulated as " β "-*7-bromocholesteryl acetate* (VII; R = OAc).* The main arguments may be summarised as follows. Dehydrobromination followed by hydrolysis (see below) gives 7-dehydrocholesterol, 7-substituted cholesterol derivatives are obtained in substitution reactions (see Part XLIX, this vol., p. 1792), and conversely, halogenation of 7-hydroxycholesterol derivatives gives halogeno-compounds of the same series (see Part XLVIII, following paper). This

* It is now generally accepted practice in the steroid series to denote stereochemical configuration in relation to the angular methyl group at C_{10} by the suffixes (*α*) and (*β*). Thus " 3(*β*)-hydroxy " implies that the 3-hydroxyl group is on the same side of the plane of the steroid molecule as the C_{10} methyl group, and further it is arbitrarily assumed that, with the steroid formula written in the conventional manner, the hydroxyl and methyl groups project *above* the plane of the paper (represented by a full-line bond). For a full account of these conventions see Shoppee, *Ann. Reports*, 1946, **43**, 200. For 7-substituted sterol derivatives (as distinct from the bile-acid series), configuration relative to the C_{10} methyl group has yet to be established with certainty and hence the use of the conventional method of

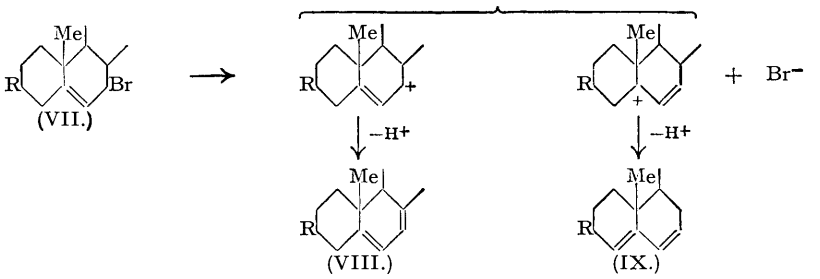
bromination reaction is superficially analogous to the chromic acid oxidation of cholesteryl acetate which leads to the 7-keto-derivative (Windaus, Lettré, and Schenck, *loc. cit.*) in contrast to oxidation with selenium dioxide which involves substitution in the 4-position (Rosenheim and Starling, *J.*, 1937, 377; Petrow, Rosenheim, and Starling, *J.*, 1938, 677; Paige, *J.*, 1943, 437).



Cholesteryl benzoate (VI; R = OBz), cholesteryl chloride, and cholesteryl bromide have also been brominated in the same manner, but with these the reactions proceeded too slowly in the lower-boiling solvents, and light petroleum (b. p. 80—100°) or carbon tetrachloride was employed. By analogy with the cholesteryl acetate product, and on dehydrobromination and other evidence, the crystalline bromo-compounds obtained are formulated as "β"-7-*bromocholesteryl benzoate* (VII; R=OBz), "β"-7-*bromocholesteryl chloride* (VII; R=Cl), and "β"-7-*bromocholestery bromide* (VII; R = Br) respectively. The yields of these products were somewhat higher than those obtained when working with the acetate, and this is attributed to their rather greater stability and crystallising tendencies, resulting in easier isolation from the crude reaction products.

Extensive studies have been made of the dehydrobromination of the bromo-acetate (VII; R = OAc), followed by hydrolysis, to 7-dehydrocholesterol (provitamin D_3) (VIII; R = OH). The proportion of the latter compound in reaction products can readily be ascertained spectrographically, since it exhibits a characteristic triplet band with maxima at 2700, 2810, and 2920 A. The bromo-compound reacts with primary and secondary amines to give amino-steroids (forthcoming publication), but with tertiary amines at moderate temperatures the bromo-steroid undergoes a smooth dehydrobromination reaction. The proportion of 7-dehydrocholesterol in the final product varies considerably, however, with the nature of the tertiary amine employed. Diethylaniline was found to give a 40—50% yield of dehydrosterol, estimated spectrographically, and this was confirmed by isolation of the 7-dehydrocholesterol as its sparingly soluble 3 : 5-dinitrobenzoate (Windaus, Lettré, and Schenck, *loc. cit.*) which was subsequently hydrolysed by the method of Huber, Ewing, and Kriger (*J. Amer. Chem. Soc.*, 1945, **67**, 609).

The nature of the remainder of the dehydrobromination product was of interest. It was observed that in the crude hydrolysed product the characteristic light-absorption band of the 7-dehydrocholesterol was invariably accompanied by a high-intensity maximum at 2400 A. The material responsible for this absorption could not readily be isolated from the product obtained by treatment with diethylaniline, but other bases gave products with rather more intense maxima in the 2400 A. region, and, from an experiment using 2 : 6-lutidine, cholesta-4 : 6-dien-3(β)-ol (IX; R = OH) was isolated in about 65% yield. This substance had been described previously by Petrow (*J.*, 1940, 66) and Spring and Swain (*J.*, 1941, 320), and these authors noted its high-intensity absorption at 2390 A. The simultaneous formation of these two dehydrosterols by dehydrobromination of the 7-bromo-compound is clearly in accordance with the ionisation (E_1) mechanism of elimination reactions (Hughes and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 657; Hughes, *J.*, 1946, 968), *viz.* :



representing stereochemical configuration (*e.g.*, 7(β)-bromo-, etc.) is unjustifiable. For this reason it has been decided to use the above notation, *e.g.*, "β"-7-bromo- (cf. Petrow and Starling, *J.*, 1946, 749), which is not intended to have any absolute significance, but does serve to relate 7-substituted sterols to the epimeric and trivially named α- and β-7-hydroxycholesterols described some years ago (Windaus, Lettré, and Schenck, *loc. cit.*; Barr, Heilbron, Parry, and Spring, *J.*, 1936, 1437) before the present system became generally adopted. The stereochemistry of the 7-substituted sterols is discussed more fully in Parts XLVIII and XLIX (following papers).

The preponderance of the $\Delta^{4:6}$-isomer (IX; R = OH) under most conditions is doubtless related to the relatively greater stability of systems containing conjugated double bonds distributed between two rings. Although a large number of tertiary bases have been examined as dehydrobrominating agents no correlation between the relative proportions of the alcohols (VIII) and (IX) and base strengths has been discerned, and it seems certain that other factors, especially of a steric nature, are involved.

Dehydrobromination of the bromo-benzoate (VII; R = OBz) with diethylaniline gave a product containing the benzoates (VIII and IX; R = OBz) in the ratio of about 1 : 4, and when using 2 : 6-lutidine it was possible to isolate some of the cholesta-4 : 6-dienyl benzoate (IX; R = OBz) by crystallisation. Treatment of 7-bromocholesteryl chloride and the corresponding bromide with diethylaniline yielded *7-dehydrocholesteryl chloride* (VIII; R = Cl) and *7-dehydrocholesteryl bromide* (VIII; R = Br), with light-absorption properties very similar to those of 7-dehydrocholesterol. These materials could be separated from some contaminant (probably a cholestatriene) only with considerable loss.

After the researches described in this and the following three papers had been finished and the writing of the papers almost completed, our attention was directed to a publication by Buisman, Stevens, and Vliet (*Rec. Trav. chim.*, 1947, **66**, 83) entitled "A New Synthesis of 7-Dehydrocholesterol". These authors decided to publish these "preliminary results" in view of the appearance of our earlier note (*Nature, loc. cit.*). In principle the synthesis is identical with the new route described in our preliminary account and in more detail above. However, since our study appears to have been more comprehensive and brought to a greater degree of completion it was decided not to alter our papers in any way but to discuss the common features here and also at the end of Part XLIX (*loc. cit.*).

The bromination procedure of Buisman *et al.* involves the use of carbon tetrachloride, as originally recommended by Ziegler, and the Dutch workers have found it advantageous to employ ultra-violet irradiation to accelerate the reaction (cf. Meystre *et al.*, *Helv. Chim. Acta*, 1945, **28**, 1252). It seems probable that the somewhat impure nature of the bromination product from cholesteryl benzoate and their failure to obtain a crystalline product by the bromination of cholesteryl acetate may be attributable to these variations in experimental conditions.

The Dutch workers have also found tertiary amines to be most suitable as dehydrobrominating agents, but in our experience *s*-collidine does not yield such satisfactory results as diethylaniline. They appreciated the presence of another sterol (absorbing below 2500 A.) accompanying 7-dehydrocholesterol in the dehydrobromination product, and suggested that it might be cholesta-4 : 6-dien-3(β)-ol; in this paper this has been proved conclusively.

Experimental.

In this and the following three papers, rotations were measured in chloroform solutions (l = 1 dcm.), and light-absorption data were determined on alcoholic solutions except where otherwise mentioned.

"β"-*7-Bromocholesteryl Acetate* (VII; R = OAc).—Finely powdered *N*-bromosuccinimide (28 g.; 1·2 mols.) was added to a solution of cholesteryl acetate (56 g.) in light petroleum (250 c.c.; b. p. 60—80°), and the mixture was refluxed on the steam-bath with vigorous mechanical stirring. The reaction began slightly exothermically with the development of a yellow colour which deepened during the reaction, and with some batches of material, the succinimide formed as a voluminous crystalline deposit. The correct reaction time was ascertained by filtering the cooled reaction mixture, washing the succinimide with light petroleum (b. p. 60—80°), and weighing the dried material. When the time of reaction was such that the weight of succinimide corresponded to complete bromine uptake, this reaction time was used in subsequent preparations using these particular batches of materials.

The filtered petroleum solution was evaporated under reduced pressure (water-pump) to remove most of the solvent. The residue was dissolved in acetone (25 c.c.) and again evaporated under reduced pressure to remove the residual petroleum. The orange-brown gum ($[\alpha]_D^{20°}$ *ca.* − 110°) was dissolved in acetone (50 c.c.), and the solution was cooled to 0°, seeded, and left overnight at 0°. The resulting semi-solid mass was then crushed to a slurry of fine crystals and shaken periodically during 6 hours. After cooling to −20°, the bromo-compound was filtered off rapidly through a pre-cooled funnel, washed with cold (− 20°) acetone, thoroughly pressed on the filter, and then dried in a vacuum desiccator. At this stage the product was colourless, and the yield varied from 25 to 35 g. with $[\alpha]_D^{20°}$ − 220° to − 235°. This material was recrystallised by dissolving it in about 250 c.c. of light petroleum (b. p. 40—60°) by slight warming, cooling to 0° to start crystallisation, and finally cooling to − 40°. The bromo-compound was filtered off rapidly and washed with the minimum quantity of cold (— 40°) light petroleum (b. p. 40—60°). The "β"-*7-bromocholesteryl acetate* (20—28 g., *i.e.*, 30—42%) so obtained formed a microcrystalline powder, m. p. 109—110°; $[\alpha]_D^{20°}$ − 245° (*c*, 1·28). Slow crystallisation from dilute solutions in the same solvent gave the bromo-compound in poor yield as long needles, with the same physical constants (Found: C, 68·3; H, 9·4; Br, 15·3, 16·0. $C_{29}H_{47}O_2Br$ requires C, 68·6; H, 9·3; Br, 15·7%). The bromo-compound decomposes slowly at room temperature, an odour of acetic acid soon becoming apparent. It is stable for many weeks at 0°.

"*β*"-7-*Bromocholesteryl Benzoate* (VII; R = OBz).—A mixture of cholesteryl benzoate (15 g.), finely powdered *N*-bromosuccinimide (7·5 g.; 1·38 mols), and light petroleum (b. p. 80—100°) (150 c.c.) was heated to boiling with vigorous stirring; reaction soon started with the development of a yellow colour. The mixture was refluxed with stirring for 5 minutes, cooled to 40°, and filtered, the succinimide being washed with light petroleum, dried, and weighed (4·0 g.). The solvent was removed under reduced pressure, the orange gum so obtained was dissolved in acetone (100 c.c.), and after crystallisation had been initiated the mixture was kept at room temperature for 1 hour with intermittent shaking. Recrystallisation of the resulting solid from acetone–ethyl acetate (1 : 1) gave slightly impure bromobenzoate (5·8 g.), m. p. 136—140°. This material was dissolved in warm benzene (7·5 c.c.); addition of acetone (20 c.c.) and cooling to 0° gave "*β*"-7-*bromocholesteryl benzoate* (3·7 g.), m. p. 140°; $[\alpha]_D^{18°}$ — 172° (*c*, 1·01) (Found: C, 72·0; H, 8·5. $C_{34}H_{49}O_2Br$ requires C, 71·7; H, 8·7%).

"*β*"-7-*Bromocholesteryl Chloride* (VII; R = Cl).—A solution of cholesteryl chloride (50 g.) in petroleum (200 c.c.; b. p. 80—100°) was refluxed with finely powdered *N*-bromosuccinimide (25 g.; 1·14 mols.) with vigorous stirring for 20 minutes; it was then cooled and filtered, giving succinimide (13·3 g.; 95%). The filtrate was evaporated under reduced pressure, and the residue dissolved in acetone (200 c.c.). The bromo-compound (32·3 g., m. p. 139°) soon started to crystallise; it was recrystallised by dissolving it in warm benzene (50 c.c.) and adding acetone (50 c.c.); "*β*"-7-*bromocholesteryl chloride* (26·7 g.) was obtained as granular prisms, m. p. 142°; $[\alpha]_D^{20°}$ — 242° (*c*, 1·09) (Found: C, 67·0; H, 9·05. $C_{27}H_{44}ClBr$ requires C, 67·0; H, 9·2%).

Improved Preparation of Cholesteryl Bromide.—A solution of cholesterol (50 g.) in chloroform (100 c.c.) and diethylaniline (20 c.c.) was rapidly stirred and cooled (ice) while a solution of thionyl bromide (12 c.c.; 1·2 mols.) in chloroform (38 c.c.) was added during 20 minutes, the internal temperature being kept at 15—20°. After being stirred for an hour at 20° the solution was poured slowly with stirring into alcohol (500 c.c.), and the precipitation was completed by keeping at 0° overnight. The solid (41 g.; m. p. 94—96°, softens at *ca.* 84°) was filtered off and recrystallised from acetone (300 c.c.), giving fairly pure cholesteryl bromide (34 g.) as plates, m. p. 97—99°. (If this crystallisation mixture is allowed to stand too long or cooled below room temperature there is a tendency for an impurity to crystallise out as needles, m. p. 82—84°, after the plates of cholesteryl bromide have separated.) Further crystallisation of the product yielded pure cholesteryl bromide (26·5 g.), m. p. 100—102°, $[\alpha]_D^{20°}$ — 21·6° (Kolm, *Monatsh.*, 1912, **33**, 447, gives m. p. 98°, $[\alpha]_D^{19°}$ — 19·1°; Marker *et al.*, *J. Amer. Chem. Soc.*, 1936, **58**, 338, give m. p. 96°; Heilbron *et al.*, *J.*, 1936, 907, give $[\alpha]_D$ — 20·8°).

"*β*"-7-*Bromocholesteryl Bromide* (VII; R = Br).—A solution of cholesteryl bromide (40 g.) in redistilled carbon tetrachloride (180 c.c.) was refluxed with finely powdered *N*-bromosuccinimide (16 g.; 1·0 mol.) with vigorous stirring for 25 minutes. On cooling and filtering, 9·02 g. of succinimide were obtained, and the filtrate was evaporated under reduced pressure. The residue was dissolved in acetone (125 c.c.) and cooled to 0° overnight. The crystalline product (34·3 g.; m. p. 140—142°), after several recrystallisations from light petroleum (b. p. 60—80°), gave "*β*"-7-*bromocholesteryl bromide* (14 g.) as needles, m. p. 145° (decomp.); $[\alpha]_D^{20°}$ — 205° (Found: C, 61·5; H, 8·35; Br, 30·55. $C_{27}H_{44}Br_2$ requires C, 61·35; H, 8·4; Br, 30·25%).

Dehydrobromination of "β"-7-Bromocholesteryl Acetate.—(a) *With diethylaniline.* (i) A mixture of "*β*"-7-bromocholesteryl acetate (6 g.) and diethylaniline (10 c.c., once distilled from sodium) was heated on the steam-bath for 3 hours; diethylaniline hydrobromide began to crystallise out after 10 minutes. The cooled mixture was treated with light petroleum (100 c.c.; b. p. 40—60°), allowed to stand for 30 minutes, and then filtered, giving 2·45 g. of diethylaniline hydrobromide (theoretical, 2·72 g.). The petroleum solution was washed with hydrochloric acid (10%) until the excess of diethylaniline had been removed; during this washing some white amorphous material separated. After being washed with sodium hydrogen carbonate solution, the petroleum solution was filtered and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a gum (5 g.) that readily solidified. Absorption-spectrum assay indicated the presence of approximately 40% of 7-dehydrocholesteryl acetate and about 45% of cholesta-4 : 6-dienyl acetate.

The dehydrobrominated product (5 g.) was hydrolysed by refluxing it with potassium hydroxide (1 g.) in methanol for 30 minutes. The steroid (4·6 g., 45% 7-dehydrocholesterol *) was crystallised from methanol to give a crystalline product (2·8 g.), containing *ca.* 55% of 7-dehydrocholesterol.* This (2·6 g.) was treated with 3 : 5-dinitrobenzoyl chloride (2 g.) in dry pyridine (40 c.c.) at room temperature for 3 days. Ice and water were added, and the solid product was filtered off, washed with sodium hydrogen carbonate solution, and then treated with acetone (30 c.c.) at room temperature for 3 hours. The insoluble yellow solid was crystallised from chloroform–acetone to give 7-dehydrocholesteryl 3 : 5-dinitrobenzoate (1·24 g.) as yellow needles, m. p. 206°, undepressed on admixture with an authentic specimen; $[\alpha]_D^{20°}$ — 43° (*c*, 0·76). Light absorption: Maxima, 2820 and 2970 A.; ϵ = 12,500 and 6500 respectively {Windaus, Lettré, and Schenck, *Annalen*, 1935, **520**, 98, give m. p. 207°, $[\alpha]_D^{20°}$ — 45·7° (*c*, 1·64)}.

(ii) "*β*"-7-Bromocholesteryl acetate (3 g.) was dehydrobrominated with diethylaniline (5 c.c.) as described above. The crude sterol (2·5 g.) obtained by alkaline hydrolysis, and containing approximately 40% of dehydrocholesterol,* was allowed to stand at room temperature for 48 hours with 3 : 5-dinitrobenzoyl chloride (3 g.) and pyridine (15 c.c.). The ester obtained by dilution with ice and water was washed successively with sodium hydrogen carbonate solution, methanol, and acetone until the washings were colourless. The product was dissolved in hot chloroform (20 c.c.) and filtered; acetone (5 c.c.) was added, and the solution cooled (finally to 0°) to give the crystalline 3 : 5-dinitrobenzoate (1·21 g.) with the same physical constants as the material from the above preparation. The overall yield of 7-dehydrocholesterol isolated as the 3 : 5-dinitrobenzoate was 35%, agreeing well with the estimated content of 40% in the crude material.

(b) *With 2 : 6-lutidine.* A mixture of "*β*"-7-bromocholesteryl acetate (3 g.) and 2 : 6-lutidine (5 c.c.) was heated at 100° for 1 hour, the hydrobromide starting to separate after a few minutes. The mixture was diluted with light petroleum (b. p. 40—60°), and the steroid acetate, which would not

* 7-Dehydrocholesterol content computed from light-absorption data.

crystallise, isolated in the usual way. It was refluxed with a solution of potassium hydroxide (0·3 g.) in methanol (50 c.c.) for 30 minutes. Water (5 c.c.) was added, and the solution cooled to 0° to give a sterol mixture (1·8 g.), m. p. 85—90°, which was recrystallised from methanol to give cholesta-4 : 6-dien-3(β)-ol (1·5 g.), m. p. 120°, unchanged on further crystallisation (Petrow, *J.*, 1940, 66, gives m. p. 126—127°; Spring and Swain, *J.*, 1941, 320, give m. p. 119—120°).

The cholesta-4 : 6-dienol (m. p. 120°; 0·6 g.) was dissolved in a mixture of acetic anhydride (2·5 c.c.) and dry pyridine (5 c.c.) and kept overnight at room temperature. The product, isolated with ether, solidified on standing at 0°, and two recrystallisations from methanol–acetone (1 : 1) gave cholesta-4 : 6-dienyl acetate (0·25 g.), m. p. 77°, $[\alpha]_D^{20°}$ − 63° (*c*, 0·54). Light absorption: Maximum, 2400 A.; ε = 26,000 (Petrow, *loc. cit.*, gives m. p. 78—79°, $[\alpha]_D^{20°}$ − 71·6°. Light absorption: Maximum, 2390 A.; ε = 26,000. Spring and Swain, *loc. cit.*, give m. p. 77—78°, $[\alpha]_D$ − 67°. Light absorption: Maximum, 2390 A.; ε = 22,000).

Dehydrobromination of "β"-7-Bromocholesteryl Benzoate.—(a) *With diethylaniline.* The benzoate (1 g.) and redistilled diethylaniline (2·5 c.c.) were heated on the steam-bath for 4 hours. Dilution with 50 c.c. of light petroleum (b. p. 40—60°) precipitated diethylaniline hydrobromide (0·36 g., 89% theoretical). After the excess of diethylaniline had been removed by washing with dilute hydrochloric acid, the solvent was removed under reduced pressure, leaving a residue which readily solidified. This product had light absorption corresponding to about 30% of 7-dehydrocholesteryl benzoate. Recrystallisation from acetone did not alter the composition of the above mixture appreciably.

(b) *With 2 : 6-lutidine.* A mixture of the benzoate (0·5 g.) and 2 : 6-lutidine (2 c.c.) was heated on the steam-bath for 2 hours, after which the steroid was isolated with ether. (Some material insoluble in both the ether and the aqueous layer was removed by filtration.) Two recrystallisations from acetone–methanol (2 : 1) gave a poor yield of cholesta-4 : 6-dienyl benzoate (72 mg.) as plates, m. p. 126°; $[\alpha]_D^{16°}$ − 92° (*c*, 2·05). Light absorption: Maximum, 2370 A.; ε = 34,500.

7-Dehydrocholesteryl Chloride (VIII; R = Cl).—A mixture of powdered "β"-7-bromocholesteryl chloride (12 g.) and diethylaniline (25 c.c.) was heated on the steam-bath for 6 hours. Cooling, followed by the addition of light petroleum (100 c.c.; b. p. 40—60°), gave 5·3 g. of diethylaniline salts. Isolation of the steroid in the usual way gave a product which had light absorption corresponding to about 40% 7-dehydrocholesteryl chloride. Trituration of the product with cold acetone gave a powdery solid, containing very little cholestatriene, which after three crystallisations from acetone gave *7-dehydrocholesteryl chloride* (1·15 g.) in long needles, m. p. 132°; $[\alpha]_D^{16°}$ − 100° (*c*, 1·12) (Found: C, 80·4; H, 10·7. $C_{27}H_{43}Cl$ requires C, 80·45; H, 10·75%). Light absorption in chloroform: Maxima, 2770, 2840 and 2960 A.; ε = 11,000, 12,000 and 7,500 respectively.

7-Dehydrocholesteryl Bromide (VIII; R = Br).—A solution of "β"-7-bromocholesteryl bromide (34 g.) in diethylaniline (75 c.c.) was heated at 95° for 3 hours. Cooling, followed by the addition of light petroleum (250 c.c.; b. p. 60—80°), gave diethylaniline hydrobromide (15·5 g.). Isolation of the steroid in the usual way gave, after crystallisation from acetone, a product (10·4 g.), m. p. 136—140°, which had light absorption in *cyclo*hexane corresponding to a 7-dehydrocholesteryl bromide content of about 80%. However, it was not readily separated from an impurity by crystallisation, and two recrystallisations from ethyl acetate (100 c.c.) were required in order to obtain pure *7-dehydrocholesteryl bromide* (2·9 g.) as needles, m. p. 147—148°, $[\alpha]_D^{20°}$ − 86° (*c*, 4·2) (Found: C, 72·75; H, 9·6; Br, 17·65. $C_{27}H_{43}Br$ requires C, 72·45; H, 9·7; Br, 17·85%). Light absorption in *cyclo*hexane: Maxima, 2750, 2850, and 2970 A.; ε = 13,000, 13,500 and 9,000 respectively.

The authors thank the Directors of Glaxo Laboratories Ltd. for permission to publish the results contained in this and the following paper. Two of them (E. R. H. J. and H. B. H.) wish to acknowledge generous gifts of materials from Glaxo Laboratories Ltd., and also a maintenance grant (H. B. H.) from the Department of Scientific and Industrial Research.

Imperial College of Science and Technology, London, S.W.7.
Glaxo Laboratories Ltd., Greenford, Middlesex. [*Received, December 16th*, 1947.]