Steroids and Walden Inversion. Part XIII. The Epimeric Cholest-5-ene-3-carboxylic Acids and the Epimeric Cholestane-3-carboxylic Acids.*

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Cholest-5-ene-3β-carboxylic acid (Marker's acid) has been obtained from cholesteryl and *epi*cholesteryl bromide by successive reaction with potassium cyanide and hydrolysis. Cholest-5-ene-3α-carboxylic acid has been prepared by epimerisation of Marker's acid, and by Wieland–Barbier degradation of 3α-cholesterylacetic acid. Cholest-5-ene-3β-carboxylic acid has been converted into cholesteryl cyanide.

Grignard carboxylation of the epimeric cholestanyl bromides gives one and the same cholestane-3β-carboxylic acid, identical with the product obtained by hydrogenation of Marker's acid. Reaction of either of the epimeric cholestanyl bromides with potassium cyanide affords an equilibrium mixture of cholestanyl and *epi*cholestanyl cyanide; the epimeric cholestane-3-carboxylic acids have been transformed into their respective nitriles, which undergo epimerisation to an equilibrium mixture. The cholestane-3-carboxylic acids and methyl esters undergo similar epimerisation.

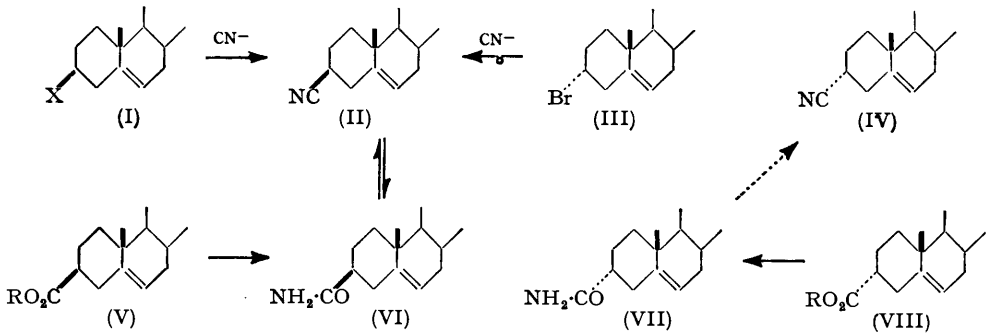
The configuration of Marker's acid as cholest-5-ene-3β-carboxylic acid follows from that established for 3β-cholesterylacetic acid (Shoppee and Stephenson, Part XII*), and has now been confirmed by degradation of the related methyl ketone (as 5α : 6β-dibromide) with perbenzoic acid to cholesteryl acetate.

Treatment of cholesteryl chloride (I; X = Cl) with magnesium and carbon dioxide was reported by Marker, Oakwood, and Crookes (*J. Amer. Chem. Soc.*, 1936, **58**, 481) to yield a product regarded as a "*dl*-mixture" of cholest-5-ene-3-carboxylic acids. In 1948 we concluded after careful fractional crystallisation and rigorous chromatography of the methyl ester of the acidic reaction product, that a single acid (Marker's acid), m. p. 220°, $[\alpha]_D$ −10° (methyl ester, m. p. 103°, $[\alpha]_D$ −11°), was formed; this conclusion was also reached in the simultaneous and independent work of Baker and Squire (*ibid.*, 1948, **70**, 4134). Subsequently, following the preparation of the 3-epimeride of Marker's acid and observation of its unusual properties (see below), we repeated our work and confirmed our previous conclusion. It is now shown that Marker's acid is cholest-5-ene-3β-carboxylic acid (V; R = H).

Cholest-5-ene-3β-carboxylic acid (V; R = H) has also been prepared from cholesteryl chloride by treatment with lithium, sodium, or potassium followed by carboxylation with carbon dioxide or diethyl carbonate (B.P. 516,030). Tsuda and Hayatsu (*J. Pharm. Soc. Japan*, 1952, **72**, 1303) claim to have obtained both the epimeric cholest-5-ene-3-carboxylic acids; 3β-cholesterylpyridinium toluene-*p*-sulphonate by pyrolysis at 250—260° gave 4-(3β-cholesteryl)pyridine, which by conversion into the methiodide and oxidation of the quaternary ammonium hydroxide with chromium trioxide–acetic acid at 20—40° gave an acidic product, m. p. 222—225°. Esterification with methanol–sulphuric acid gave 18% of methyl cholest-5-ene-3β-carboxylate, m. p. 100—102° (incorrectly described as the 3α-epimeride). The residual material, by alkaline hydrolysis, gave an acid, m. p. 222—225°, giving 31% of an ethyl ester, m. p. 87—90°, regarded as ethyl cholest-5-ene-3α-carboxylate (although described as the 3β-epimeride) because it gave a small m. p. depression with genuine ethyl cholest-5-ene-3β-carboxylate, m. p. 82—83° (Marker, Oakwood, and Crookes, *loc. cit.*). We have now obtained Marker's acid from cholesteryl bromide (I; X = Br) by successive treatment with potassium cyanide and hydrolysis, and have also prepared its 3-epimeride, cholest-5-ene-3α-carboxylic acid (VIII; R = H), m. p. 155°, $[\alpha]_D$ −40° (methyl ester, m. p. 114°, $[\alpha]_D$ −40°), by Wieland–Barbier degradation of 3α-cholesteryl-acetic acid (Shoppee and Stephenson, *loc. cit.*), and by epimerisation of Marker's acid with a solution from sodium and diethylene glycol.

* Part XII, *J.*, 1954, 2230.

Relatively few examples of the conversion of secondary alkyl halides into cyanides occur in the literature because replacement is accompanied by preferential dehydrohalogenation; thus, whereas *n*-amyl chloride and sodium cyanide give 95% of *n*-amyl cyanide, *sec.*-amyl chloride gives only 30% of *sec.*-amyl cyanide, and *tert.*-amyl chloride furnishes only olefin(s) (Hass and Marshall, *Ind. Eng. Chem.*, 1931, **23**, 352). *cyclo*Pentyl bromide, however, gives 27% of *cyclo*pentyl cyanide (Rogers and Roberts, *J. Amer. Chem. Soc.*, 1946, **68**, 843). An unsuccessful attempt to convert cholesteryl toluene-*p*-sulphonate by treatment with potassium cyanide in xylene at 140°, and cholesteryl bromide by fusion with cuprous cyanide at 130°, into cholesteryl cyanide was reported by Baker and Squire (*ibid.*, 1948, **70**, 1487), whilst we independently and unsuccessfully attempted to convert cholesteryl toluene-*p*-sulphonate and cholesteryl bromide into the cyanide by prolonged treatment with silver cyanide in boiling benzene. Recently, ethylene glycol, a more polar medium, has been used as a solvent for sodium cyanide whereby *iso*propyl bromide afforded 39% of *iso*propyl cyanide (Lewis and Susi, *ibid.*, 1952, **74**, 840); by use of potassium cyanide in diethylene glycol at 235° cholesteryl bromide (I; X = Br) yields the cyanide (II) with retention of configuration, as well as cholesta-3 : 5-diene and unidentified products. The configuration of cholesteryl cyanide (II) is proved by its preparation from cholest-5-ene-3β-carboxylic acid (V; R = H) by conversion into the amide (VI) (cf. Baker and Squire, *ibid.*, 1948, **70**, 4134) and dehydration of this with phosphorus oxychloride in toluene at 100°. We regard the reaction (I ⟶ II) as proceeding by a unimolecular substitution (S_N1) involving the cholest-5-en-3β-yl cation (sp^3-hybridisation with a vacant *p* orbital), whose stability is enhanced and whose configuration is preserved by interaction with the π-electrons of the 5 : 6-double bond.



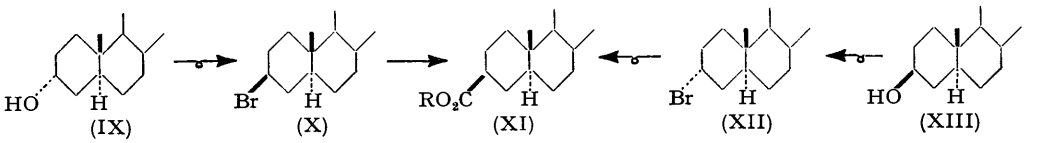
Similar reaction of *epi*cholesteryl bromide (III) gave some cholesteryl cyanide (II) accompanied by much cholesta-3 : 5-diene. We regard the production of cholesteryl cyanide as occurring by direct displacement with inversion of configuration (S_N2); the first unambiguous example of substitution with inversion at $C_{(3)}$ in a Δ^5-steroid has recently been recorded by Shoppee and Stephenson, *loc. cit.*). Much of the *epi*cholesteryl bromide undergoes unimolecular heterolysis to furnish the cholest-5-en-3α-yl cation, whose molecular geometry prevents stabilisation by interaction with the π-electrons of the 5 : 6-double bond; consequently, the cation must acquire stability by rearrangement (Evans and Shoppee, *J.*, 1953, 543) or expulsion of a proton to give cholesta-3 : 5-diene. These results recall those of King and Bigelow (*J. Amer. Chem. Soc.*, 1952, **74**, 6238) who, by treatment of *epi*cholesteryl toluene-*p*-sulphonate with pyridine or piperidine at 100°, obtained cholesterylpyridinium toluene-*p*-sulphonate (8%) or cholesterylpiperidine (10%) by substitution with inversion (S_N2), accompanied by much cholesta-3 : 5-diene (73—75%). We have attempted to prepare *epi*cholesteryl cyanide (IV) from cholest-5-ene-3α-carboxylic acid (VIII; R = H), but the crude amide (VII) proved unexpectedly resistant to dehydration; this will be reinvestigated when larger quantities of material become available.

Cholest-5-ene-3β-carboxylic acid (V; R = H) on treatment with a solution from sodium and diethylene glycol at 235° is epimerised to yield about 5% of cholest-5-ene-3α-carboxylic acid (VIII; R = H), characterised as the methyl ester, and also obtained by Wieland–Barbier degradation of 3α-cholesterylacetic acid. The epimeric acids and esters (V, VIII)

differ in their m. p., optical rotation, and solubilities [(VIII; R = H) is readily soluble in pentane]. We have obtained the ethyl ester (VIII; R = Et) crystalline, m. p. 56—58°; this figure and the m. p. 155° of the pure acid suggest that the acidic material, m. p. 222—225°, and the ethyl ester, m. p. 87—90°, described by Tsuda and Hayatsu (*loc. cit.*) cannot have contained an appreciable proportion of 3α-acid or -ester respectively.

We have also investigated the Grignard carboxylation of the epimeric 3-bromocholestanes; these compounds were carefully purified and were completely free from unsaturated material. 3β-Bromocholestane (X) was prepared from *epi*cholestanol (IX) (Ruzicka, Wirz, and Meyer, *Helv. Chim. Acta*, 1935, **18**, 998), or more conveniently from cholesteryl bromide by hydrogenation with platinum–acetic acid in the presence of perchloric acid; by treatment with magnesium and carbon dioxide it gave uniquely cholestane-3β-carboxylic acid (XI; R = H), identical with the product obtained by catalytic hydrogenation of cholest-5-ene-3β-carboxylic acid (V; R = H) (Marker, Oakwood, and Crookes, *loc. cit.*). In a similar way, cholestanol (XIII) yielded 3α-bromocholestane (XII), which by treatment with magnesium and carbon dioxide gave uniquely the *same* cholestane-3β-carboxylic acid (XI; R = H). The conversion (X) → (XI) thus involves complete overall retention, whilst (XII) → (XI) at some stage involves complete inversion.

During 1948—1951 we attempted unsuccessfully to prepare the acid (XI; R = H) and its 3α-epimeride from the epimeric 3-chlorocholestanes by treatment with magnesium and carbon dioxide; in 1951, however, Squire (*J. Amer. Chem. Soc.*, 1951, **73**, 2586) reported the preparation of cholestanylmagnesium chloride. In a letter dated July 9th, 1951, Dr. E. N. Squire



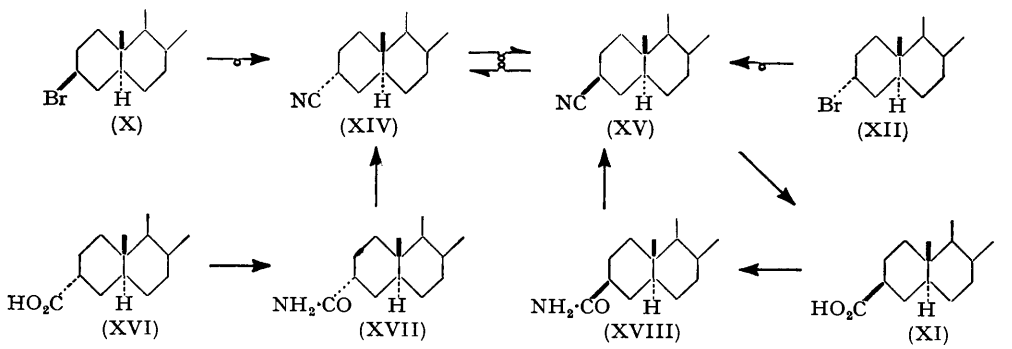
R = H; m. p. 210° ($[\alpha]_D$ +28°)
R = Me; m. p. 52°/69° ($[\alpha]_D$ +27°)

informed the senior author that he had carried out the preparation from 3β-chlorocholestane by treatment with magnesium and carbon dioxide of " cholestane-3β-carboxylic acid," m. p. 206—207°, $[\alpha]_D$ +29°, yielding " methyl cholestane-3β-carboxylate," m. p. 66—67·5°, $[\alpha]_D$ +17°. By hydrogenation of Marker's acid and its methyl ester respectively, Dr. Squire prepared " cholestane-3α-carboxylic acid," m. p. 209—211°, $[\alpha]_D$ +41°, and " methyl cholestane-3α-carboxylate," m. p. 73°, $[\alpha]_D$ +30°; he regarded these pairs of acids and esters as epimeric and assigned configurations on the basis of their optical rotatory powers. Dr. Squire was good enough to send us samples of his four products, which we examined. Whilst his " α-acid " and " α-ester " were saturated compounds, his " β-acid " and " β-ester " contained unsaturated material since they gave yellow colours with tetranitromethane–chloroform; his " α-acid " and " β-acid " gave no m. p. depression, and his " β-ester " melted, not at 66—67·5°, but over a range of 8° (58—66°) either alone or admixed with his " α-ester." Finally, his " α-ester " gave no m. p. depression when mixed with methyl cholestane-3β-carboxylate (XI; R = Me) obtained from pure 3α- or 3β-bromocholestane. We informed Dr. Squire of these facts (letter of July 17th, 1951, acknowledged by letter dated July 23rd, 1951), suggesting that his " β-acid " and " β-ester " are impure * specimens of his " α-acid " and " α-ester "; his subsequent paper (*J. Amer. Chem. Soc.*, 1951, **73**, 5768) makes no reference to these facts and describes his " β-acid " and " β-ester " as homogeneous individuals. It is clear that his configurational assignments are without justification. Analogy suggests that the 17-oxoandrostane-3-carboxylic acid described by Marker *et al.* (*ibid.*, 1936, **58**, 1948) as a mixture of *cis*- and *trans*-stereoiso-

* The probable impurities are cholest-5-ene-3β-carboxylic acid [Marker's acid] (V; R = H) and its methyl ester. 3β-Chlorocholestane, prepared by catalytic hydrogenation of cholesteryl chloride, invariably contains unreduced cholesteryl chloride (cf. Squire, *J. Amer. Chem. Soc.*, 1953, **75**, 493) which must be removed by oxidation with chromium trioxide (Shoppee, *J.*, 1946, 1147) or, better, with perbenzoic acid; this precaution was not taken by Squire. 3β-Chlorocholestane is so considerably more unreactive than cholesteryl chloride toward magnesium that the proportion of unsaturated material in the acid product resulting from carboxylation would be markedly increased.

merides is a single 3β-carboxylic acid, whilst the 17β-hydroxyandrostane-3-carboxylic acid prepared by Baker and Squire (*ibid.*, 1949, **71**, 1383), and the stigmast-5-ene- and stigmastane-3-carboxylic acids described by Squire (*ibid.*, 1953, **75**, 493) are also single 3β-carboxylic acids.

We have also examined the reaction of the epimeric 3-bromocholestanes with potassium cyanide. 3β-Bromocholestane (X) with potassium cyanide in diethylene glycol at 235° gave a 21% yield of a mixture (~2 : 1) of 3β- (XV) and 3α-cyanocholestane (XIV), accompanied by cholest-2-ene. We regard the primary product as 3α-cyanocholestane [XIV; 3α-CN(axial)], formed by bimolecular replacement (S_N2) with inversion, which undergoes partial epimerisation to the more thermodynamically stable 3β-cyanocholestane [XV; 3β-CN(equatorial)] under the conditions of the reaction; some small proportion of 3β-cyanocholestane may arise directly, together with an approximately equal proportion of 3α-cyanocholestane, by the unimolecular mechanism (S_N1), which is probably responsible for the production, following loss of a proton ($E1$), of cholest-2-ene. Similar reaction of 3α-bromocholestane (XII) gave a 5% yield of a mixture (~2 : 1) of 3β-cyanocholestane (XV) [formed by bimolecular substitution with inversion (S_N2)] and 3α-cyanocholestane (XIV) (formed by equilibration), accompanied by much cholest-2-ene [probably formed mainly, but not exclusively, by ionic *trans*-elimination ($E2$)], and unidentified products. The above interpretation is supported by the preparation (i) of 3α-cyanocholestane (XIV), m. p. 168°, $[\alpha]_D$ +21°, from cholestane-3α-carboxylic acid (XVI) (Shoppee and Stephenson, *loc. cit.*) by conversion into the amide (XVII) and dehydration with phosphorus oxychloride, and (ii) of 3β-cyanocholestane (XV), m. p. 152°, $[\alpha]_D$ +28°, from cholestane-3β-carboxylic acid (XI) by similar conversion into the amide (XVIII) and dehydration. Either cyanide by treatment with a trace of potassium cyanide in diethylene glycol at 235° furnished an equilibrium mixture, m. p. 124—127°, $[\alpha]_D$ +26°, +27°, containing approximately 33% of (XIV) and 67% of (XV). Hydrolysis of 3β-cyanocholestane (XV) with potassium hydroxide in diethylene glycol at 235° gave cholestane-3β-carboxylic acid (XI).

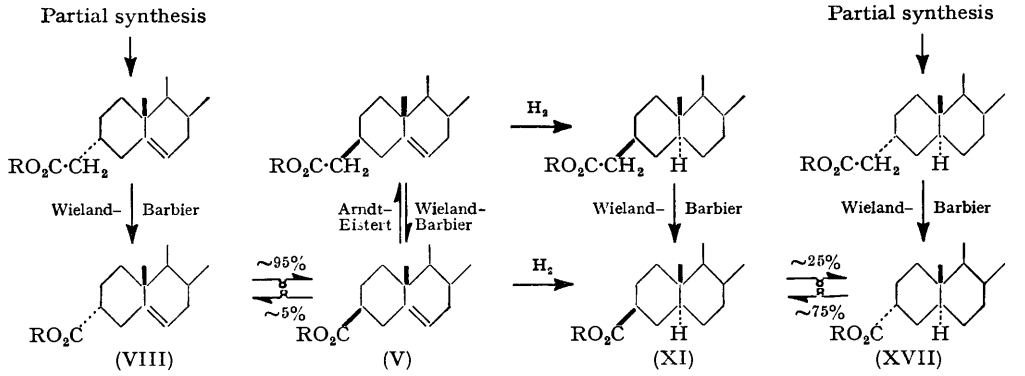


The configurations assigned above to the epimeric cholest-5-ene-3- and cholestane-3-carboxylic acids are established by their relation to the epimeric 3-cholesteryl- and 3-cholestanyl-acetic acids, whose configurations were proved by unambiguous partial syntheses (Shoppee and Stephenson, *loc. cit.*). These relations are summarised in the annexed diagram.

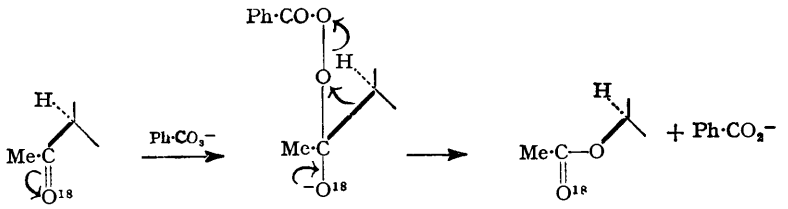
The thermodynamic stabilities of the epimeric pairs (V, VIII) and (XI, XVII) are also consistent. Thus the unsaturated acid (VIII; R = H) and its methyl ester [3α-CO_2R(axial)] * undergo substantially complete epimerisation (~95% conversion) to [V; 3β-CO_2R(equatorial)*]. Likewise, the saturated acid and its methyl ester [XVII: 3α-CO_2R(axial)] undergo similar but less complete epimerisation to [(XI);

* As pointed out previously (Evans and Shoppee, *J.*, 1953, 540; cf. King and Bigelow, *J. Amer. Chem. Soc.*, 1952, **74**, 6241) ring A in cholest-5-ene is a strained chair-form; three contiguous carbon atoms [$C_{(4)}$, $C_{(5)}$, $C_{(10)}$] are coplanar, and conversion into a boat form is impossible, but substituents deviate only slightly from normal equatorial and axial conformations as in *cyclo*hexane. Ring B has the "half-chair" conformation as in *cyclo*hexene with four contiguous coplanar carbon atoms [$C_{(5)}$ $C_{(6)}$, $C_{(7)}$, $C_{(10)}$] (cf. Barton, Cookson. Klyne, and Shoppee, *Chem. and Ind.*, 1954, 21).

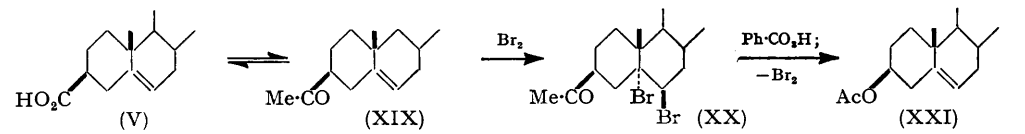
3β-CO_2R(equatorial)] by treatment with a solution from sodium and diethylene glycol or with sodium methoxide.



The foregoing configurational proofs involve the partial synthesis of an appropriately orientated steroid-3-acetic acid and its degradation to a steroid-3-carboxylic acid. We have therefore correlated cholest-5-ene-3β-carboxylic acid (V; R = H) with cholesterol, whose configuration is established (Shoppee, *J.*, 1948, 1032), by oxidation with perbenzoic acid. The conversion of steroid 20-ketones into 17-acetoxy-steroids by oxidation with persulphuric acid or by Caro's acid was first achieved by Marker *et al.* (*J. Amer. Chem. Soc.*, 1940, **62**, 525, 650, 2543, 2621, 3003) and it was later observed that perbenzoic acid was also effective (Burckhardt and Reichstein, *Helv. Chim. Acta*, 1942, **25**, 1434; Sarett, *J. Amer. Chem. Soc.*, 1947, **69**, 2899; Wieland and Miescher, *Helv. Chim. Acta*, 1949, **32**, 1768, 1922). The stereochemical course of these peroxidations was studied by Turner (*J. Amer. Chem. Soc.*, 1950, **72**, 878) and by Gallagher and Kritchevsky (*ibid.*, p. 882), who proved that configuration is preserved. The mechanism has been elucidated by Doering *et al.* (*ibid.*, 1950, **72**, 5515; 1953, **75**, 5595) and by Bunton, Lewis, and Llewellyn (*Chem. and Ind.*, 1954, 191) using isotopic oxygen, and shown to involve the pinacolic change :



The migrating steroid nucleus never leaves the system; thus it has been shown by Mislow and Brenner (*J. Amer. Chem. Soc.*, 1953, **75**, 2318) that optically active 3-phenylbutan-2-one is converted by treatment with perbenzoic acid into optically active 1-phenylethyl acetate with retention of configuration ($Ph\cdot\overset{*}{C}HMe\cdot CO\cdot CH_3 \longrightarrow Ph\cdot\overset{*}{C}HMe\cdot OAc$), which is consistent with the preservation of configuration quoted above and observed in other pinacolic migrations (Kenyon *et al.*, *J.*, 1939, 916; 1946, 25; Lane and Wallis, *J. Amer. Chem. Soc.*, 1941, **63**, 1674). The acid (V) was converted into the ketone (XIX) by successive



treatment with thionyl chloride and dimethylcadmium as described by Baker and Squire (*J. Amer. Chem. Soc.*, 1948, **70**, 1487), who proved that these compounds correspond in regard to configuration at $C_{(3)}$ by regenerating the acid from the ketone by King's method

(*ibid.*, 1944, **66**, 894, 1612). The ketone (XIX) was converted by treatment with bromine into the 5α : 6β-dibromide (XX), which by prolonged treatment with perbenzoic acid in chloroform at 0° and debromination with potassium iodide–acetone gave cholesteryl acetate (XXI). Marker's acid is therefore cholest-5-ene-3β-carboxylic acid.*

We have examined the Grignard carboxylation of *epi*cholesteryl bromide, but we defer discussion of this reaction and of the stereochemical course of the Grignard carboxylations of cholesteryl bromide and the epimeric cholestanyl bromides. We wish here, however, to draw attention to the anomalous optical rotatory power of cholest-5-ene-3β-carboxylic acid. The molecular rotations of the epimeric cholest-5-ene- and cholestane-carboxylic acids and cholesteryl- and cholestanyl-acetic acids and their methyl esters are given in the Table.

	Cholest-5-ene-carboxylic acids			Cholestane-carboxylic acids		
	3α	3β	$\Delta_{3\beta-3\alpha}$	3α	3β	$\Delta_{3\beta-3\alpha}$
Acid	−165°	−41°	+124°	+100°	+121°	+21°
Methyl ester	−171	−53	+118	+116	+128	+12
	Cholesterylacetic acids			Cholestanylacetic acids		
	3α	3β	$\Delta_{3\beta-3\alpha}$	3α	3β	$\Delta_{3\beta-3\alpha}$
Acid	−120°	−133°	−13°	+121°	+99°	−22°
Methyl ester	−128	−141	−13	+109	+86	−23

It will be seen that the carboxylic acids and esters break the rule that the difference $\Delta[M_D]_{\beta-\alpha}$ is a negative quantity for 3-substituted cholest-5-enes and cholestanes; the Δ value is especially large for the unsaturated cholest-5-ene-3-carboxylic acids and esters.

Experimental

Cholesteryl Bromide.—Cholesteryl bromide was prepared by a slight modification of the method of Bide, Henbest, Jones, Peevers, and Wilkinson (*J.*, 1948, 1786). Cholesterol (50 g.) was dissolved in chloroform (100 c.c.) and dimethylaniline (20 c.c.). The mixture was stirred under conditions to exclude moisture, and a solution of thionyl bromide (12 c.c.) in chloroform (40 c.c.) was added with ice-cooling during 15 min. Stirring was then continued at 20° for a further 0·5 hr. and the mixture poured into 95% ethanol (500 c.c.). After cooling for 1 hr. in cold water, the crystalline product was removed and the mother-liquors were diluted with water (150 c.c.) to give a further quantity of crystalline material. The crystalline product, recrystallised from acetone (300 c.c.), gave cholesteryl bromide (48 g., 85%) as plates, m. p. 97—98° (the previous workers reported a yield of 34 g., 60%, but their m. p. of 100—102° could not be observed even after repeated crystallisation from acetone).

3β-*Cholestanyl Bromide.*—Cholesteryl bromide (10 g.) in ether (100 c.c.) and acetic acid (20 c.c.) was shaken in hydrogen with platinum oxide (800 mg.) for 18 hr. The catalyst was filtered off and the acetic acid removed from the ether layer by alkaline washing. Drying and removal of solvent furnished 3β-cholestanyl bromide still containing some unsaturated material. The product was therefore dissolved in carbon tetrachloride (100 c.c.) and acetic anhydride (10 c.c.), sulphuric acid (1·4 c.c.) was added slowly, the mixture shaken for 15 min., and water added. After being washed to neutrality with sodium chloride solution and 2N-sodium carbonate, the solution was dried and evaporated. The product was passed through a column of aluminium oxide (100 g.) in pentane, the filtrate evaporated, and the residue crystallised from acetone, to furnish 3β-cholestanyl bromide, m. p. 114—115°, giving no colour with tetranitromethane–chloroform.

3α-*Cholestanyl Bromide.*—Cholestanol (18 g.) was dissolved in refluxing benzene (100 c.c.), and phosphorus tribromide (9 c.c.) added dropwise during 1 hr. After 1·5 hr., the solvents were removed in a vacuum and the residue poured into water. Extraction with ether, removal of a trace of insoluble material, washing, drying, and removal of solvent, furnished a product which was filtered in pentane through a column of aluminium oxide (100 g.). The crude 3α-cholestanyl bromide was dissolved in chloroform (100 c.c.), and a solution of perbenzoic acid (30 c.c.; 0·0266 g./c.c.) added. After 24 hr., the excess of perbenzoic acid was destroyed and the product worked up in the usual manner to furnish a product, which was chromatographed in pentane on aluminium oxide (100 g.). Pentane (1·1 l.) eluted 3α-cholestanyl bromide (7·9 g.), m. p. 103° (from acetone), giving no colour with tetranitromethane–chloroform.

* Since this paper was written, a similar conclusion has been reached by Corey and Sneen (*J. Amer. Chem. Soc.*, 1953, **75**, 6234) by a similar conversion of the acid (XI; R = H) into cholestanol.

Cholest-5-ene-3β-carboxylic Acid.—Cholesteryl bromide (100 g.), dissolved in ether (1 l.), was added during 3 hr. to a solution of methylmagnesium iodide, prepared from methyl iodide (40 c.c.), in ether (400 c.c.), and magnesium (36 g.). A further addition of methyl iodide (10 c.c.) was made after 12 hr. of a total reflux period of 40 hr. The mixture was then cooled and an excess of solid carbon dioxide added; after 1 hr., the complex was hydrolysed by addition of ice-cold 2N-sulphuric acid. The aqueous layer was removed and after being washed with water and dilute sodium thiosulphate solution the ethereal layer was filtered to remove the suspension of " bicholesteryl " and cholest-5-ene-3β-carboxylic acid (yield, 36·5 g.). After being dried, the ethereal filtrate was evaporated and the residue extracted with pentane to leave the insoluble cholest-5-ene-3β-carboxylic acid. The pentane-soluble material was dissolved in pentane and extracted with N-potassium hydroxide. Acidification and ether-extraction of the aqueous washings furnished a pentane-insoluble residue (700 mg.), m. p. 218—220°, identical with the main product. No trace of the pentane-soluble epimeric 3α-acid could be found. Most of the " bicholesteryl " was removed from the first crystalline fraction by warming with ether (1000 c.c.) removing the insoluble " bicholesteryl," and evaporating the filtrate to dryness. The total yield of acid was 48 g. All three fractions crystallised from ether–pentane as needles, m. p. 218—220°, $[\alpha]_D$ −10° (*c*, 1·0).

Methyl Cholest-5-ene-3β-carboxylate.—Crude cholest-5-ene-3β-carboxylic acid was esterified with ethereal diazomethane; the product was dissolved in acetone–methanol and filtered to remove " bicholesteryl." Fractional crystallisation from methanol gave methyl cholest-5-ene-3β-carboxylate as long needles, five consecutive fractions melting between 99° and 101°. A sample of the crude ester (1 g.) was chromatographed on a column of aluminium oxide (30 g.) prepared in pentane; elution with pentane (100 c.c.) gave five fractions, which after crystallisation from methanol had identical m. p. 100—101°, and gave no depression on admixture. Further elution of the column did not yield any material. Subsequently, the crude acid (25 g.) was dissolved in methanol (3 l.), and concentrated sulphuric acid (25 c.c.) was slowly added. After refluxing for 8 hr., the mixture was decanted from the contaminating " bicholesteryl," and the solution was concentrated. Cooling gave methyl cholest-5-ene-3β-carboxylate as long needles, which, recrystallised from methanol had m. p. 101°, $[\alpha]_D$ −11° (*c*, 1·4) (23 g.).

Cholestane-3β-carboxylic Acid.—(*a*) Cholest-5-ene-3β-carboxylic acid (200 mg.) in ether (10 c.c.) and acetic acid (10 c.c.) was shaken in hydrogen with platinum oxide (50 mg.). Hydrogenation was completed within 10 min. Removal of solvent and catalyst gave cholestane-3β-carboxylic acid, recrystallised from ether–pentane as needles, m. p. 206—208°, $[\alpha]_D$ +29° (*c*, 1·1). The methyl ester, prepared by using ethereal diazomethane and crystallised from methanol, had a double m. p. 54—56°/69°, $[\alpha]_D$ +27°.

(*b*) 3β-Cholestanyl bromide (5 g.) was added during 6 hr. to a solution of methylmagnesium iodide prepared from magnesium (1 g.), methyl iodide (0·3 c.c.), and ether (60 c.c.). Further methyl iodide (0·6 c.c.) was added with the 3β-cholestanyl bromide, and a further portion (0·6 c.c.) after 12 hr. After 20 hours' refluxing, solid carbon dioxide was added and after being kept for 1·5 hr. the complex was decomposed by ice-cold 2N-sulphuric acid. The ethereal solution was washed, the insoluble " bicholestanyl " removed, the solution dried and evaporated, and the product extracted with pentane to leave cholestane-3β-carboxylic acid as a solid which was esterified with diazomethane and chromatographed on a column of aluminium oxide (50 g.) prepared in pentane. Pentane (5 × 50 c.c.) eluted " bicholestanyl " (56 mg.), m. p. 298°, after separation of a little cholestane, m. p. and mixed m. p. 75—77°, by treatment with hot ethyl acetate–methanol; further elution with pentane (5 × 50 c.c.) and benzene–pentane (1 : 9; 4 × 50 c.c.) furnished a solid (total, 0·82 g.) which recrystallised from methanol; all the individual fractions melted at 68°, some exhibiting a double m. p. 52—54°/68°. No depression of m. p. was observed with methyl cholestane-3β-carboxylate obtained by the previous method.

(*c*) 3α-Cholestanyl bromide (5 g.) in ether (70 c.c.) was added during 5 hr. to a solution of methylmagnesium iodide prepared from magnesium (1·2 g.), methyl iodide (1·5 c.c.), and ether (50 c.c.). A further quantity of methyl iodide (0·6 c.c.) was added during the reflux period of 28 hr. Solid carbon dioxide was added and then, after 16 hr., the complex was decomposed with 2N-sulphuric acid, the product was extracted with ether, the suspended " bicholestanyl " was removed, and the ether extracts were washed, dried, and evaporated. The residue was extracted with pentane, and the pentane-insoluble material esterified with diazomethane, dissolved in acetone–methanol, and filtered to remove insoluble " bicholestanyl," m. p. ~298°. Fractional crystallisation from acetone–methanol afforded three crops of crystals: (1) needles, m. p. 69°; (2) plates, m. p. 68—70°; (3) plates, double m. p. 56°/68—70°, $[\alpha]_D$ +26° (*c*, 0·61), all consisting of methyl cholestane-3β-carboxylate. The mother-liquor material was chromato-

graphed on a column of aluminium oxide (6 g.) prepared in pentane. Benzene–pentane (1 : 4) eluted all the material, which crystallised from methanol, to give methyl cholestane-3β-carboxylate as needles, m. p. 69°.

(*d*) Cholestane-3α-carboxylic acid (Shoppee and Stephenson, *loc. cit.*) (27 mg.) was refluxed in diethylene glycol (4 c.c.) with potassium hydroxide (80 mg.) for 1 hr., the mixture cooled and poured into cold 2N-sulphuric acid, and the precipitate filtered off, washed, and dried. The product was dissolved in ether and decanted from a trace of amorphous material. Fractional crystallisation from ether–pentane furnished crystals (10 mg.), m. p. 203—207°, showing no depression when admixed with cholestane-3β-carboxylic acid. A further crop of crystals (10 mg.) melted over the range 160—195°.

(*e*) Methyl cholestane-3α-carboxylate (20 mg.) was heated at 180° for 3 hr. with N-sodium methoxide in methanol (4 c.c.). The usual working up afforded cholestane-3β-carboxylic acid which, crystallised from ether–pentane, had m. p. and mixed m. p. 206—208°. Methyl cholestane-3β-carboxylate (m. p. 54—56°; 16 mg.) was refluxed for 2 hr. with dry N-sodium methoxide (6 c.c.); the product consisted only of neutral material, and by recrystallisation from methanol gave unchanged starting material, m. p. and mixed m. p. 54—56°.

"*Bicholestan-3β-yl.*"—Formed from either of the cholestanyl bromides, this had m. p. and mixed m. p. 297—298°, $[\alpha]_D$ +42°, +38° [*c*, 0·09, 0·06, determined in a 4-dm. tube; Squire (*J. Amer. Chem. Soc.*, 1951, **73**, 2586) gives decomp. at 265—270°, m. p. >300°, $[\alpha]_D$ 0°]. The highest m. p. we observed was 305°.

2-(*Cholest-5-en-3α-yl*)-1 : 1-*diphenylethanol.*—To a solution of phenylmagnesium bromide, prepared from magnesium (1·05 g.), bromobenzene (4·6 c.c.), and ether (15 c.c.), was added a solution of methyl cholest-5-en-3α-ylacetate (1·15 g.) in ether (20 c.c.). After 3 hr. at 15°, the solution was poured into ice-cold ammonium chloride solution; the product was extracted with ether, washed, dried, and evaporated. The residual oil on being heated at 100°/0·03 mm. for 10 min., gave a sublimate (600 mg.), identified as diphenyl. The residue (1·3 g.) did not crystallise.

2-(*Cholest-5-en-3α-yl*)-1 : 1-*diphenylethylene.*—2-(Cholest-5-en-3α-yl)-1 : 1-diphenylethanol (1·3 g.), dissolved in benzene (50 c.c.) containing pyridine (4 c.c.), was treated with thionyl chloride (2 c.c.) at 0°. After 20 min., excess of thionyl chloride was destroyed by adding water, the product extracted with ether, and the solution, washed, dried, and evaporated. The residual oil was freed from coloured impurities by filtration in pentane through a column of aluminium oxide to furnish 2-(cholest-5-en-3α-yl)-1 : 1-diphenylethylene (870 mg.) as an oil which failed to crystallise.

Cholest-5-ene-3α-carboxylic Acid.—(*a*) Cholest-5-ene-3β-carboxylic acid (10·5 g.) was added to a solution from sodium (5 g.) in diethylene glycol (400 c.c.), the mixture refluxed for 3 hr., cooled, poured into water, acidified, and filtered, and the precipitate washed and dried. The powdered product was shaken with pentane (100 c.c.) and filtered; the pentane-soluble portion was crystallised from acetone (20 c.c.) to remove a quantity (~50 mg.) of cholest-5-ene-3β-carboxylic acid. The acetone solution was evaporated to dryness and the residue crystallised from 90% acetic acid, to yield cholest-5-ene-3α-carboxylic acid (420 mg.), m. p. 155°, $[\alpha]_D$ −40° (*c*, 1·2) [Found (after sublimation at 180°/0·01 mm.): C, 79·8; H, 10·9. Calc. for $C_{28}H_{46}O_2$: C, 81·1; H, 11·2%]. Although the acid gave poor analyses the *methyl ester*, prepared by ethereal diazomethane and crystallised from ether–methanol, had m. p. 112—114°, $[\alpha]_D$ −40° (*c*, 1·2) and was pure [Found (after sublimation at 140°/0·01 mm.): C, 81·3; H, 11·4. $C_{29}H_{48}O_2$ requires C, 81·2; H, 11·3%]. The ethyl ester, prepared by diazoethane, had m. p. 56—59° (from methanol); 9 g. of cholest-5-en-3β-yl-carboxylic acid were recovered.

(*b*) 2-(Cholest-5-en-3α-yl)-1 : 1-diphenylethylene (870 mg.) was dissolved in dioxan (50 c.c.) and acetic acid (100 c.c.). A solution of chromium trioxide (1 g.) in water (2 c.c.) was added and the solution kept at 25° for 14 hr. Excess of chromium trioxide was destroyed by adding methanol, the solvents were removed in a vacuum, 2N-sulphuric acid was added, and the product extracted with ether. Extraction of the ether layer with N-potassium hydroxide furnished, after acidification and ether-extraction, a solid soluble in pentane and acetone. Esterification with ethereal diazomethane furnished a sticky solid (150 mg.), chromatographed on a column of neutralised aluminium oxide (9 g.) prepared in pentane. Elution with benzene–pentane (2 : 3; 2 × 15 c.c.) furnished a solid (26 mg.), which crystallised from methanol as plates, m. p. 112°, and gave no depression on admixture with methyl cholest-5-ene-3α-carboxylate prepared by the previous method. Further elution gave only oils.

Cholest-5-ene-3β-carboxyamide.—Cholest-5-ene-3β-carboxylic acid (1·0 g.) was refluxed for 2 hr. in benzene (12 c.c.) with thionyl chloride (1 c.c.). The solvents were then removed under

reduced pressure, the acid chloride was dissolved in ether (15 c.c.), and a current of dry ammonia gas bubbled through for 15 min. Dilution with ether, washing, drying, and removal of solvent gave, after crystallisation from ether–pentane, cholest-5-ene-3β-carboxyamide, m. p. 227—229° (Baker and Squire, *J. Amer. Chem. Soc.*, 1948, **70**, 4134, give m. p. 227—228°, $[\alpha]_D$ −26°).

Cholestane-3β-carboxyamide.—Cholestane-3β-carboxylic acid (350 mg.) was refluxed in benzene (5 c.c.) with thionyl chloride (0·5 c.c.) for 2 hr.; removal of solvent, and treatment of the acid chloride dissolved in ether (5 c.c.) with dry ammonia, gave after further dilution with ether and the usual washing, drying, and removal of solvent, *cholestane-3β-carboxyamide* which, crystallised from ether–pentane, had m. p. 210—212°, $[\alpha]_D$ +26° (*c*, 1·0) (yield 310 mg.) [Found (after sublimation at 210/0·02 mm.): C, 80·6, H, 11·7. $C_{28}H_{49}ON$ requires C, 80·9; H, 11·9%].

Cholestane-3α-carboxyamide.—Cholestane-3α-carboxylic acid (300 mg.) was refluxed in benzene (5 c.c.) with thionyl chloride (0·5 c.c.) for 1·15 hr. After removal of solvents under reduced pressure, the acid chloride, dissolved in dry ether (5 c.c.), was treated with ammonia for 15 min., the product diluted with ether, washed, and dried, and the solvent removed, to furnish *cholestane-3α-carboxyamide* which, crystallised from ether–pentane, had m. p. 160—162°, $[\alpha]_D$ +22° (*c*, 0·8) (yield 250 mg.) [Found (after sublimation at 170°/0·02 mm.): C, 81·0; H, 12·1; N, 3·8. $C_{28}H_{49}ON$ requires C, 80·9; H, 11·9; N, 3·4%]. The mixture of this amide with the acid (m. p. 163°) from which it was derived melted at 170° and then resolidified to melt again at 206—210°.

Cholest-5-en-3β-yl Cyanide.—(*a*) Cholesteryl bromide (2 g.) was added to a solution of potassium cyanide (2 g.) in diethylene glycol (20 c.c.), and the mixture refluxed for 30 min. at 235°; some hydrogen cyanide was evolved. The mixture was cooled, diluted with water, and extracted with ether to yield, after the usual working up, an oil which was chromatographed on a column of aluminium oxide (50 g.) prepared in pentane. Elution with pentane (3 × 200 c.c.) furnished a solid (856 mg.) which, crystallised from acetone, had m. p. 70—73°, and gave an immediate red Rosenheim colour and no depression of m. p. on admixture with cholesta-3 : 5-diene. Further elution with pentane–benzene (3 : 7, 200 c.c.; 2 : 1, 200 c.c.) gave a solid (400 mg.) which crystallised from ether–methanol, to give *cholest-5-en-3β-yl cyanide* (75 mg.) as plates, m. p. 179—180°, $[\alpha]_D$ −16·5° (*c*, 1·7) [Found (after sublimation at 180°/0·02 mm.): C, 84·8; H, 11·5; N, 3·4. $C_{28}H_{45}N$ requires C, 85·0; H, 11·5; N, 3·5%]. Elution with benzene and then with ether gave only oils.

(*b*) *epi*Cholesteryl bromide (1 g.) with a solution of potassium cyanide (1 g.) in diethylene glycol (15 c.c.) was raised to 235° during 10 min.; refluxing was then continued for a further 15 min., the solution cooled, diluted with water, and extracted with ether, and the extract washed, dried, and evaporated. The product was chromatographed on aluminium oxide (25 g.). Pentane (2 × 75 c.c.) eluted a solid (586 mg.) which, crystallised from acetone, had m. p. 70—73° and consisted essentially of cholesta-3 : 5-diene. Elution with benzene (1 × 75 c.c.) furnished a sticky solid, which crystallised from ether–ethanol as plates (17·5 mg.), m. p. 150—175°. A further elution with benzene (1 × 75 c.c.) gave a solid which crystallised from ether–methanol to furnish cholest-5-en-3β-yl cyanide (3·5 mg.), m. p. and mixed m. p. with material obtained from cholesteryl bromide, 179—181°. Further elution with benzene and ether gave only oils.

The material, m. p. 150—175°, was rechromatographed on aluminium oxide (1·5 g.). Elution with pentane–benzene (17 : 3; 4 c.c.) gave a solid (8·2 mg.), which crystallised from ether–ethanol as plates, m. p. 135—160°. Further elution with pentane–benzene (3 : 1, 4 c.c.) furnished material (11·0 mg.), which crystallised from ether–ethanol as plates, m. p. 170—176°, mixed m. p. with cholest-5-en-3β-yl cyanide, 172—178°.

(*c*) Cholest-5-ene-3β-carboxyamide (140 mg.) was dissolved in toluene (5 c.c.) and treated with phosphorus oxychloride (0·5 c.c.) at 100° for 30 min. The solvents were removed under reduced pressure, the product was dissolved in ether, and the solution washed, dried, and evaporated. Crystallisation from ether–methanol furnished cholest-5-en-3β-yl cyanide, m. p. 178—180°, giving no depression of melting point with specimens prepared by methods (*a*) and (*b*).

3α-Cholestanyl Cyanide.—Cholestane-3α-carboxyamide (150 mg.) was treated as in (*c*) above, giving *3α-cholestanyl cyanide*, plates, m. p. 168°, $[\alpha]_D$ +21° (*c*, 0·8) [Found (after sublimation at 180°/0·02 mm.): C, 84·8; H, 12·1. $C_{28}H_{47}N$ requires C, 84·6; H, 11·9; N, 3·5%].

3β-Cholestanyl Cyanide.—Cholestane-3β-carboxyamide (120 mg.), similarly treated, gave *3β-cholestanyl cyanide*, m. p. 152°, $[\alpha]_D$ +27·5° (*c*, 1·5) [Found (after sublimation at 170°/0·02 mm.): C, 84·6; H, 11·9; N, 3·8%].

3α-Cholestanyl Cyanide (Equilibrium Mixture).—(*a*) 3α-Cholestanyl bromide (1 g.) was refluxed with potassium cyanide (1 g.) in diethylene glycol (15 c.c.) for 30 min.; the solution was cooled, diluted, and extracted with ether, and the ethereal extract washed, dried, and evaporated. Chromatography of the product on a column of aluminium oxide (25 g.) prepared in pentane

gave a solid (490 mg.) when pentane (2 × 75 c.c.) was used as eluant. Crystallisation from acetone gave needles, m. p. 66—67°, giving no depression on admixture with cholest-2-ene. Elution with benzene (3 × 75 c.c.) gave a solid (49 mg., 5%), which crystallised from methanol as needles, m. p. 124—126°, $[\alpha]_D$ +26·5° (*c*, 1·7), and consisted of a mixture of cholestan-3β- and 3α-yl cyanides [Found (after sublimation at 170°/0·02 mm.): C, 84·7; H, 12·2; N, 3·4%]. Further elution with benzene and ether gave only oils.

(*b*) 3β-Cholestanyl bromide (8·3 g.) was refluxed with potassium cyanide (10 g.) in diethylene glycol for 45 min. Working up in the usual way gave an oil which was introduced on to a column of aluminium oxide (220 g.), prepared in pentane. Elution with pentane furnished a solid, m. p. 66°, which crystallised from acetone as needles, m. p. 66—68°, identical with the cholest-2-ene isolated in the previous experiment. Elution with pentane–benzene (7 : 3, 2 × 800 c.c.; 3 : 2, 2 × 800 c.c.; 1 : 1, 800 c.c.) furnished a solid (total, 1·55 g., 21%), which crystallised from ether–ethanol to give 3αβ-cholestanyl cyanide, m. p. 125°, identical with that obtained in the previous preparation. Traces of crystalline material could, however, be observed in the melt until 150°, and this inhomogeneity was apparent in all fractions obtained by fractional crystallisation of the product from ether–ethanol. Further elution with ether gave only oils.

(*c*) 3α-Cholestanyl cyanide (12 mg.; m. p. 168°) was refluxed with potassium cyanide (15 mg.) in diethylene glycol (1·5 c.c.) for 1 hr. Dilution with water, followed by extraction of the product with ether, gave, after the usual working up, 3αβ-cholestanyl cyanide, which crystallised from ether–methanol to give a product of m. p. and mixed m. p. 124—126° with material prepared by methods (*a*) and (*b*).

(*d*) 3β-Cholestanyl cyanide (33 mg.; m. p. 152°) was refluxed in diethylene glycol with potassium cyanide (60 mg.) for 45 min. The usual working up gave a product which, crystallised from ether–methanol, had m. p. 126—128°, giving no depression of m. p. by admixture with cholestan-3αβ-yl cyanide prepared by methods (*a*), (*b*), and (*c*).

Synthetic mixtures of cholestan-3α- and -3β-yl cyanide gave the following melting points: 75% 3β-cholestanyl cyanide + 25% 3α-cyanide 128—147°; 50% 3β-cholestanyl cyanide + 50% 3α-cyanide 126°; 25% 3β-cholestanyl cyanide + 75% 3α-cyanide 160—168°. The equilibrium mixture described as 3αβ-cholestanyl cyanide therefore contains approx. 60% of the 3β-epimeride.

Cholestane-3β-carboxylic Acid.—Attempts to hydrolyse 3αβ-cholestanyl cyanide by refluxing methanolic potassium hydroxide or methanolic sulphuric acid furnished only starting material.

3αβ-Cholestanyl cyanide (150 mg.) was refluxed in diethylene glycol (12 c.c.) with potassium hydroxide (250 mg.) for 30 min. The usual working up gave a product which crystallised from ether–pentane as fine needles, m. p. 204—206°, showing no depression of m. p. by admixture with authentic cholestane-3β-carboxylic acid, m. p. 209—210°. A specimen of the methyl ester melted at 69°, both alone and by admixture with methyl cholestane-3β-carboxylate.

Cholest-5-ene-3β-carboxylic Acid.—Cholest-5-en-3β-yl cyanide (70 mg.) was refluxed in diethylene glycol (5 c.c.) with a solution of potassium hydroxide (80 mg.) in water (0·2 c.c.) for 1 hr., then diluted with water, acidified, and extracted with ether. The product, obtained by the usual working up, gave by trituration with pentane a crystalline solid (50 mg.), m. p. 217—222°, giving no depression by admixture with authentic cholest-5-ene-3β-carboxylic acid.

3β-*Acetylcholest-5-ene.*—A solution of methylmagnesium iodide, prepared from magnesium (2·75 g.), methyl iodide (4·4 c.c.), and ether (50 c.c.), was added slowly at 0° to a well-stirred suspension of cadmium chloride (11·7 g.) in ether (50 c.c.) in an atmosphere of nitrogen. The mixture was then refluxed for 30 min.

Cholest-5-ene-3β-carboxylic acid (12·9 g.) was refluxed in benzene (100 c.c.) with thionyl chloride (10 c.c.) for 3 hr. and kept at 15° for a further 12 hr.; the solvents were removed under reduced pressure. The acid chloride was added in ether (100 c.c.) to the dimethylcadmium in an atmosphere of nitrogen and refluxed with stirring for 1 hr.; 2N-hydrochloric acid was added, and the product isolated in the usual way. Filtration of a pentane solution through a column of aluminium oxide yielded, after removal of solvent and crystallisation from ether–methanol, 3β-acetylcholest-5-ene (9 g.), m. p. 103—104°, $[\alpha]_D$ −16·5° (*c*, 1·7) (Baker and Squire, *J. Amer. Chem. Soc.*, 1948, **70**, 1487, report m. p. 103—105°, $[\alpha]_D$ −11° (*c*, 3·4)].

3β-*Acetyl-5α*: 6β-*dibromocholestane.*—To a solution of 3β-acetylcholest-5-ene (1 g.) in chloroform (0·5 c.c.) and acetic acid (5 c.c.) was added a solution of bromine (0·42 g., 1·1 mol.) in acetic acid (3 c.c.). After 10 min., the solution was diluted with methanol, to yield the *dibromide*, which crystallised from ether–methanol as plates, m. p. 101°, $[\alpha]_D$ −55° (*c*, 1·8) (710 mg.) [Found (after drying at 20°/0·02 mm.): C, 61·0; H, 8·5; Br, 28·1. $C_{29}H_{48}OBr_2$ requires C, 60·8; H, 8·5; Br, 27·9%].

Cholesteryl Acetate.—3β-Acetyl-5α : 6β-dibromocholestane (100 mg.) was kept in a solution of perbenzoic acid (4 mol.) in chloroform (2 c.c.) for 4 weeks at 0°; the excess of perbenzoic acid was then destroyed, and the product worked up in the usual manner to yield an oil, which was debrominated by shaking with potassium iodide (300 mg.) in acetone (10 c.c.) for 10 min. at 15°. Dilution with water, extraction with ether, and washing with sodium thiosulphate solution, followed by drying and removal of solvent, gave an oil (61 mg.), which was introduced on to a column of aluminium oxide (2 g.) prepared in pentane. Pentane as eluant (3 × 6 c.c.) gave a solid (25 mg.), which after two crystallisations from acetone–methanol had m. p. 112°, and gave no depression by admixture with an authentic specimen of cholesteryl acetate, m. p. 113°. Elution with benzene–pentane combinations gave only oils.

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