Steroids and Walden Inversion. Part XII. The Epimeric 3-Cholesterylacetic and 3-Cholestanylacetic Acids.*

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The epimeric 3-cholesterylacetic acids have been prepared and the configuration of 3α-cholesterylacetic acid has been established by partial synthesis from 6-oxo- and 6β-hydroxy-3β-cholestanyl toluene-*p*-sulphonate by condensation with diethyl sodiomalonate.

3β-Cholesterylacetic acid has been degraded by the Wieland–Barbier procedure to cholest-5-ene-3β-carboxylic acid and has been regenerated from this acid by the Arndt–Eistert reaction.

By catalytic hydrogenation 3β-cholesterylacetic acid gives 3β-cholestanylacetic acid, but 3α-cholesterylacetic acid gives 3α-coprostanylacetic acid. 3α-Cholestanylacetic acid has been prepared by an unambiguous partial synthesis from 3β-cholestanyl toluene-*p*-sulphonate and diethyl sodiomalonate, which establishes its configuration, and, by exclusion, that of 3β-cholestanylacetic acid.

Wieland–Barbier degradation of 3β-cholestanylacetic acid gives cholestane-3β-carboxylic acid, and 3α-cholestanylacetic acid similarly affords cholestane-3α-carboxylic acid.

By condensation of cholesteryl toluene-*p*-sulphonate with diethyl sodiomalonate in xylene Kaiser and Svarz (*J. Amer. Chem. Soc.*, 1945, **67**, 1309) obtained a mixture of malonic esters, converted by alkaline hydrolysis into a mixture of malonic acids. They isolated an " acid A," m. p. 206° (decomp.), $[\alpha]_D$ −22·5°, characterised by a dimethyl ester, double m. p. 88°/106°, $[\alpha]_D$ −28°, reacting with 1 mol. of perbenzoic acid; they regarded this as a 3-cholesterylmalonic acid. Decarboxylation of " acid A " at the m. p. failed to yield any crystalline material, but " crude acid A," m. p. *ca.* 180°, gave a ~10% yield of a 3-cholesterylacetic acid, m. p. 213°, characterised by a methyl ester, m. p. 108°. They also isolated an impure amorphous " acid B," $[\alpha]_D$ +39·5°, giving an oily methyl ester reacting with only 0·31 mol. of perbenzoic acid, which by decarboxylation at 140° furnished <5% of the 3-cholesterylacetic acid, m. p. 213°. On account of the positive value of the specific rotation and the absence of a double bond, they regarded the main component of " acid B " as 3 : 5-*cyclo*cholestan-6β-ylmalonic acid, which they subsequently isolated, m. p. 174° (decomp.), $[\alpha]_D$ +65°, characterised as the dimethyl ester, m. p. 71°, $[\alpha]_D$ +58° (*ibid.*, 1947, **69**, 847), and decarboxylated to 3 : 5-*cyclo*cholestan-6β-ylacetic acid, m. p. 112°, $[\alpha]_D$ +32° (*ibid.*, 1949, **71**, 517).

Recently, a product fortuitously but correctly (see below) described as 3β-cholesterylmalonic acid {m. p. 203°, $[\alpha]_D$ −30·5° (methyl ester, m. p. 84—89°)} was obtained by Ralls (*ibid.*, 1953, **75**, 2123); cholesta-3 : 5-dien-7-one by addition of diethyl sodiomalonate gave diethyl 7-oxo-3β-cholesterylmalonate, from which the 7-oxygen function was removed by the thiol–Raney nickel procedure; there seems little doubt that this preparation is identical with the " acid A " of Kaiser and Svarz.

Similarly, a product incorrectly described as 3β-cholesterylacetic acid (m. p. 210—220°; methyl ester, m. p. 106—108°) has been obtained by Tsuda and Hayatsu (*J. Pharm. Soc. Japan*, 1952, **72**, 1303); cholesteryl toluene-*p*-sulphonate by treatment with hot

* Part XI, *J.*, 1953, 1709.

γ-picoline gave a 3-cholesteryl-4′-pyridylmethane (also prepared by condensation of 4-pyridylmethyl-lithium and cholesteryl bromide), which as the methiodide was oxidised with potassium ferricyanide to the pyridone, further oxidised by chromium trioxide to a 3-cholesterylacetic acid, which was shown by direct comparison, as the methyl ester, to be identical with the decarboxylation product of Kaiser and Svarz's " crude acid A."

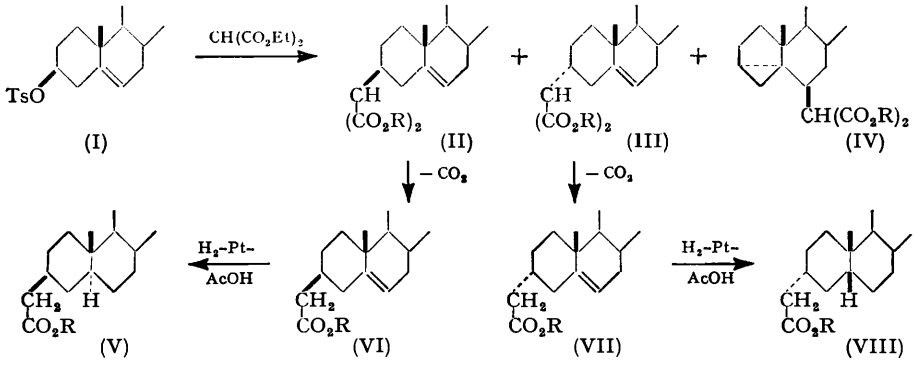
Baker and Petersen (*J. Amer. Chem. Soc.*, 1951, **73**, 4080) extended the $C_{(3)}$-side chain of the cholest-5-ene-3-carboxylic acid (Marker's acid), obtained from cholesteryl chloride by treatment with magnesium and carbon dioxide (Marker, Oakwood, and Crookes, *ibid.*, 1936, **58**, 481), by the reaction sequence:

$$-CO_2H \xrightarrow{LiAlH_4} -CH_2\cdot OH \xrightarrow{TsCl\text{-}Py} -CH_2\cdot OTs \xrightarrow{NaI} -CH_2I \xrightarrow{Mg\text{-}CO_2} -CH_2\cdot CO_2H$$

(Ts = *p*-$C_6H_4Me\cdot SO_2$; Py = C_5H_5N),

which preserves the original configuration at $C_{(3)}$, and obtained another 3-cholesterylacetic acid, m. p. 175°, $[\alpha]_D$ −31°, giving a methyl ester, m. p. 79°, $[\alpha]_D$ −32°. They attributed the 3β-configuration to the acid, m. p. 213°, of Kaiser and Svarz, and assigned the 3α-configuration to their isomeric acid, m. p. 175°, and so by implication to Marker's acid; they supported these configurational assignments by reference to Squire's work (*ibid.*, 1951, **73**, 5768), which appeared " clearly to demonstrate that opposite configurations are obtained by carbonating [3β-]cholestanyl or cholesteryl Grignard reagents." As will be shown later (Part XIII, in the press), this " demonstration " is devoid of experimental foundation.

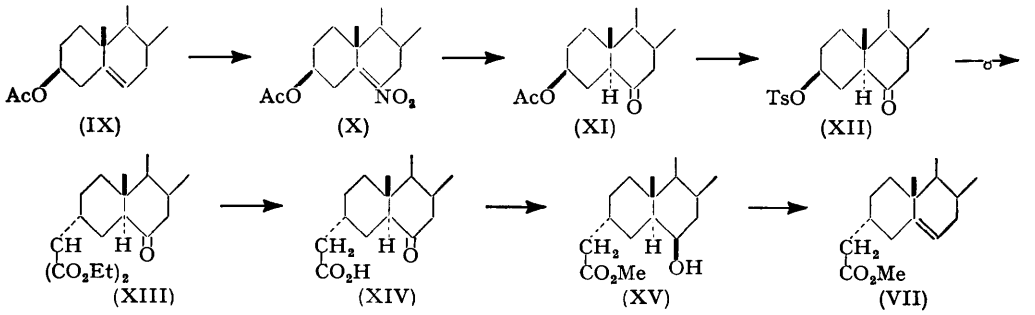
We have repeated Kaiser and Svarz's work; we find that these workers isolated a minor reaction product (" acid A ") but failed to obtain the major unrearranged product. Condensation of cholesteryl toluene-*p*-sulphonate (I) with diethyl sodiomalonate and alkaline hydrolysis of the reaction product gives a mixture containing much 3β-cholesterylmalonic acid (" acid A ") (II; R = H) and a little 3α-cholesterylmalonic acid (III; R = H). Repeated fractional crystallisation gave a product, m. p. 205° (decomp.), $[\alpha]_D$ −31°, consisting essentially of the 3β-malonic acid (II; R = H), although still slightly contaminated with the epimeric 3α-acid (III; R = H), and giving by decarboxylation at 205°/0·5 mm. an 80% yield of 3β-cholesterylacetic acid (VI; R = H), isolated chromatographically as the methyl ester, identical with Baker and Petersen's acid, and converted by catalytic hydrogenation into 3β-cholestanylacetic acid (V; R = H). The small proportion of 3α-cholesterylmalonic acid (III; R = H) also underwent decarboxylation, to yield 3α-cholesterylacetic acid (VII; R = H), isolated by repeated fractional crystallisation as the methyl ester and identical with Kaiser and Svarz's acid. Catalytic hydrogenation of 3α-cholesterylacetic acid (VII; R = H) gave an acid which we regard as 3α-coprostanylacetic acid (VIII), the formation of which appears to furnish a further example of the influence of a 3α-substituent on the stereochemical course of hydrogenation of an appropriately located double bond (Lewis and Shoppee, *Chem. and Ind.*, 1953, 897).



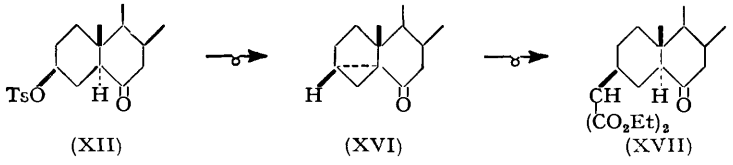
3α-Cholesterylacetic acid is much less soluble than the 3β-epimeride in acetone, and is readily separated from mixtures with it by fractional crystallisation from acetone. It is because of this marked difference that Kaiser and Svarz isolated only some 10% of the

minor reaction product, 3α-cholesterylacetic acid (VII), after decarboxylation of their " crude acid A."

The configuration of 3α-cholesterylacetic acid (VII; R = H) follows from the following partial syntheses. Cholesteryl acetate (IX) by nitration yielded 6-nitrocholesteryl acetate (X), transformed by treatment with zinc–acetic acid into 6-oxocholestan-3β-yl acetate (XI); this which was converted by alkaline hydrolysis and re-esterification into 6-oxocholestan-3β-yl toluene-*p*-sulphonate (XII). Toluene-*p*-sulphonates of saturated steroids are known to undergo alkyl–oxygen fission, Ts-O—¦R, so that substitution takes place with inversion of configuration (Plattner and Fürst, *Helv. Chim. Acta*, 1943, **26**, 2266; Prelog and Szpilfogel, *ibid.*, 1944, **27**, 390; Plattner *et al.*, *ibid.*, 1948, **31**, 1457, footnote 1; Nace, *J. Amer. Chem. Soc.*, 1952, **74**, 5937; Elks and Shoppee, *J.*, 1953, 241); condensation of the toluene-*p*-sulphonate (XII) with diethyl sodiomalonate gave diethyl 6-oxocholestan-3α-ylmalonate (XIII), converted by alkaline hydrolysis into the related malonic acid, which was decarboxylated at 170°/0·5 mm. to 6-oxocholestan-3α-ylacetic acid (XIV). This acid was esterified with diazomethane, and the keto-ester was reduced with sodium borohydride * to methyl 6β-hydroxycholestan-3α-ylacetate (XV), which by ionic dehydration with phosphorus oxychloride and pyridine [6β-OH(polar) : 5α-H(polar) : *trans*] was smoothly converted into methyl 3α-cholesterylacetate (VII; R = Me).



The neutral fraction isolated from the reaction of 6-oxocholestan-3β-yl toluene-*p*-sulphonate (XII) with the diethyl malonate anion $^-CHR_2$ consisted mainly of 3 : 5-*cyclo*cholestan-6-one (XVI) accompanied by a little of a ketonic substance, m. p. 185°, which we have not yet identified. Since 3 : 5-*cyclo*cholestan-6-one (XVI) is readily formed by elimination (*E*2) from 6-oxocholestan-3β-yl toluene-*p*-sulphonate (XII), by treatment with anions ^-OR (cf. Shoppee and Summers, *J.*, 1952, 3361), an alternative pathway in which the 3 : 5-*cyclo*-ketone simulates the properties of an αβ-unsaturated ketone (cf. Linstead *et al.*, *J.*, 1952, 3610; 1953, 1799) and undergoes a Michael reaction with *trans*-addition to the bridge bond could be written :

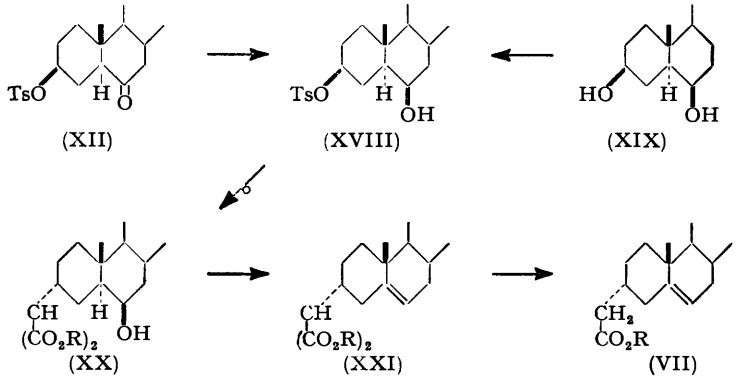


Such a process, involving two successive inversions, would lead to diethyl 6-oxocholestan-3β-ylmalonate (XVII). We find, however, that 3 : 5-*cyclo*cholestan-6-one does not react with diethyl sodiomalonate under the conditions used for the substitution reaction with 6-oxocholestan-3β-yl toluene-*p*-sulphonate.

Our conclusion that the condensation of 6-oxocholestan-3β-yl toluene-*p*-sulphonate with diethyl sodiomalonate is a substitution reaction [S_N2] taking place with inversion (XII → XIII) has been confirmed as follows. Reduction of 6-oxocholestan-3β-yl

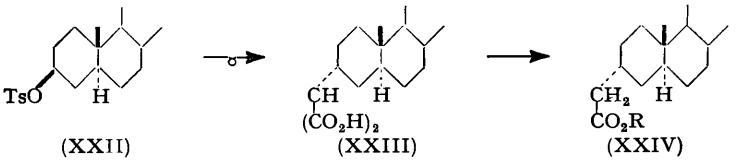
* Use of lithium aluminium hydride furnished the same 2-(6β-hydroxycholestan-3α-yl)ethanol, characterised as the diacetate, as was obtained by reduction of the 6β-hydroxy-ester (XV) with lithium aluminium hydride.

toluene-*p*-sulphonate (XII) with sodium borohydride occurs with preservation of the toluene-*p*-sulphonyloxy-group, to yield 6β-hydroxycholestan-3β-yl toluene-*p*-sulphonate (XVIII), identical with a specimen previously prepared from cholestane-3β : 6β-diol (XIX) by treatment with 1 mol. of toluene-*p*-sulphonyl chloride in pyridine (Shoppee and Summers, unpublished work; cf. Reich and Lardon, *Helv. Chim. Acta*, 1946, **29**, 761). Condensation with diethyl sodiomalonate gave, after alkaline hydrolysis, 6β-hydroxycholestane-3α-ylmalonic acid (XX; R = H), dehydrated as the dimethyl ester to dimethyl 3α-cholesterylmalonate (XXI; R = Me). Alkaline hydrolysis furnished 3α-cholesterylmalonic acid (XXI; R = H), which by decarboxylation afforded 3α-cholesterylacetic acid (VII; R = H).



(XII) (XVIII) (XIX) (XX) (XXI) (VII)

Finally, we have obtained 3α-cholestanylacetic acid (XXIV; R = H) by the following unambiguous partial synthesis. 3β-Cholestanyl toluene-*p*-sulphonate (XXII) by condensation with diethyl sodiomalonate gave, after alkaline hydrolysis, 3α-cholestanylmalonic acid (XXIII), and thence 3α-cholestanylacetic acid (XXIV; R = H) (characterised as the crystalline methyl ester) which was different from 3β-cholestanylacetic acid (V; R = H) and from 3α-coprostanylacetic acid (VIII).



(XXII) (XXIII) (XXIV)

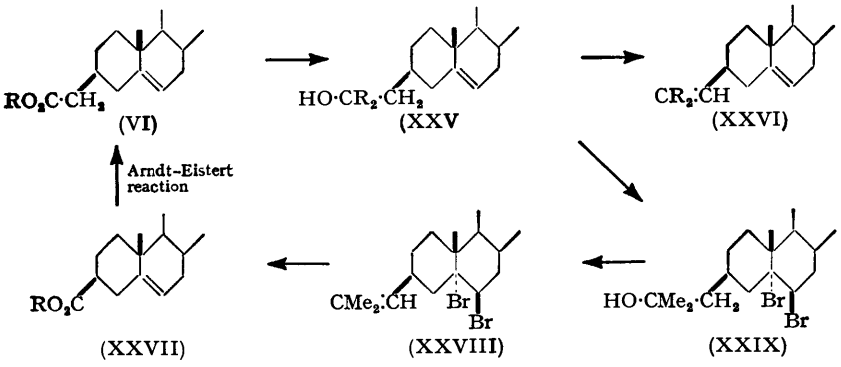
The foregoing partial syntheses establish the configurations of 3α-cholesterylacetic acid (VII; R = H) and 3α-cholestanylacetic acid (XXIV; R = H), and by exclusion those of 3β-cholesterylacetic acid (VI; R = H) and 3β-cholestanylacetic acid (V; R = H). The optical rotatory powers of these acids, their methyl esters, and the related primary alcohols are in agreement with these structures, since 3β-substituted cholestane compounds are invariably less dextrorotatory than the epimeric 3α-substituted derivatives (cf. Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, 3rd edn., 1949, p. 215) (see Table). The optical rotatory differences, although small, are definite, and our data are condensed from several determinations.

	$[M]_D$ of cholesteryl derivatives			$[M]_D$ of cholestanyl derivatives		
3-Substituent	3α	3β	Δ[3β − 3α]	3α	3β	Δ[3β − 3α]
$CH_2 \cdot CO_2H$	−120°	−133°, −133° *	−13°	+121°	+99°	−22°
$CH_2 \cdot CO_2Me$	−128	−141, −141 *	−13	+109	+86	−23
$CH_2 \cdot CH_2 \cdot OH$	−118	−128	−10	+105	+76	−29

* Baker and Petersen's values (*loc. cit.*).

3β-Cholesterylacetic acid has been degraded by a modification of the Wieland–Barbier method. Methyl 3β-cholesterylacetate (VI; R = Me), on treatment with phenylmagnesium bromide, gave the alcohol (XXV; R = Ph), dehydrated by refluxing acetic anhydride to the olefin (XXVI; R = Ph); this resisted oxidation by chromium trioxide

in acetic acid at 5—10°, and only after the modified method involving ozonolysis (see below) had been studied was it found that oxidation at 25° for 16 hr. yielded some 10% of cholest-5-ene-3β-carboxylic acid (XXVII; R = H). Methyl 3β-cholesterylacetate (VI; R = Me) was therefore transformed by treatment with methylmagnesium iodide into the alcohol (XXV; R = Me), dehydrated by thionyl chloride and pyridine to (XXVI; R = Me); the alcohol was converted into the 5α : 6β-dibromide (XXIX), which was dehydrated with thionyl chloride and pyridine to the 5 : 6-dibromo*iso*butene (XXVIII); ozonolysis, hydrolysis, oxidation, and debromination with zinc in aqueous acetic acid gave cholest-5-ene-3β-carboxylic acid (XXVII; R = H) (Marker's acid), isolated as the methyl ester.



We have also converted cholest-5-ene-3β-carboxylic acid (XXVII; R = H) (Marker's acid) into 3β-cholesterylacetic acid (VI; R = H) by the Arndt–Eistert reaction. This confirms the configurational identity, first established by Baker and Petersen and now shown to involve β-orientation, of the acids (VI and XXVII; R = H).

Methyl 3β-cholestanylacetate (V; R = Me) and methylmagnesium iodide or phenylmagnesium bromide similarly gave the appropriate alcohols and olefins; the latter, by ozonolysis and oxidation, yielded cholestane-3β-carboxylic acid, previously obtained by Marker *et al.* (*loc. cit.*) from cholest-5-ene-3β-carboxylic acid (XXVII; R = H) by hydrogenation. Also, 3α-cholestanylacetic acid has been degraded by the Wieland–Barbier procedure: the methyl ester and phenylmagnesium bromide gave the expected tertiary alcohol and thence the olefin, which was oxidised by chromium trioxide in acetic acid at 40° to cholestane-3α-carboxylic acid. This acid has unusual properties: it is soluble in pentane, and it cannot be extracted from ethereal solution with potassium hydroxide because its potassium salt is soluble in ether.

In conclusion, we refer briefly to the production, in the reaction of cholesteryl toluene-*p*-sulphonate (I) and diethyl sodiomalonate, of diethyl 3α-cholesterylmalonate (III). It has been shown that replacement reactions such as hydrolysis, acetolysis, etc., of cholesteryl chloride and toluene-*p*-sulphonate, and, more generally, of 3β-substituted Δ^5-steroids, proceed with retention of configuration at $C_{(3)}$ or with rearrangement to 6β-substituted 3 : 5-*cyclo*-steroids (Shoppee, *J.*, 1946, 1147; Winstein and Adams, *J. Amer. Chem. Soc.*, 1948, **70**, 838; Shoppee and Summers, *J.*, 1952, 3361). This was interpreted in terms of a unimolecular mechanism [S_N1] leading to a carbonium ion in which configuration was maintained at $C_{(3)}$ by intervention of the π-electrons of the 5 : 6-double bond. It now appears that, under suitable conditions and with appropriate nucleophiles, the unimolecular substitution [S_N1] leading to retention [(II)] or rearrangement [(IV)] may be accompanied by a bimolecular substitution [S_N2] leading to inversion [(III)]. We are investigating this new aspect.

Experimental

For general details see *J.*, 1953, 243. Neutralised aluminium oxide was used where stated (for preparation, see *J.*, 1953, 543). $[\alpha]_D$ are in $CHCl_3$ except where noted; ultra-violet absorption spectra were determined in EtOH on a Unicam SP. 500 spectrophotometer, with a corrected scale.

Cholest-5-en-3β-ylmalonic Acid.—This was prepared by Kaiser and Svarz's method (*J. Amer. Chem. Soc.*, 1945, **67**, 1309); we obtained identical results by the use of refluxing toluene, instead of xylene at 105°. To a solution of diethyl sodiomalonate, prepared by refluxing toluene (100 c.c.). sodium (3·45 g.) and diethyl malonate (27 c.c.) until all the sodium had dissolved, was added a solution of cholesteryl toluene-*p*-sulphonate (40 g.) (Wallis, Fernholz, and Gephart, *ibid.*, 1937, **59**, 137) in toluene (100 c.c.). Refluxing was continued for 16 hr., the solution was cooled, the precipitated sodium toluene-*p*-sulphonate was filtered off, washed with toluene, and the combined toluene extracts were evaporated under reduced pressure. The oil obtained was dissolved in ether and washed with water, and the solution was dried and evaporated. Attempts to separate the mixture of esters by chromatography were unsuccessful. Therefore the oil was refluxed with 5% methanolic potassium hydroxide (150 c.c.) for 16 hr. The precipitated potassium salt was dissolved in water (500 c.c.), and any non-acidic material removed in ether. After acidification with ice-cold 2N-sulphuric acid, the precipitated acid was extracted with ether, and the ethereal solution washed to neutrality, dried, evaporated to a small volume, and diluted with pentane. After 24 hr. at 0°, the precipitated crude cholest-5-en-3β-ylmalonic acid was filtered off (7 g., 8 g.), m. p. 160—170° (decomp.), $[\alpha]_D$ −28·5° (*c*, 1·6 in EtOH). Four recrystallisations from ether–pentane gave cholest-5-en-3β-ylmalonic acid, m. p. 205°, $[\alpha]_D$ −31° (*c*, 1·7 in EtOH). The dimethyl ester, prepared by using diazomethane in ether, crystallised from ether–methanol as colourless needles, m. p. 88—89°, to a turbid liquid clearing at 105°, $[\alpha]_D$ −29·5° (*c*, 1·7).

Cholest-5-en-3α- and -3β-ylacetic Acid.—These were prepared by heating the slightly impure cholest-5-en-3β-ylmalonic acid (m. p. 205°; 5 g.) at 205°/0·5 mm. until effervescence commenced. The temperature was then lowered to 170°, and after 30 min. the product was cooled, esterified with diazomethane, and crystallised from ether–methanol. This furnished material (860 mg.), m. p. 68—92°, which by recrystallisation from acetone gave methyl cholest-5-en-3α-ylacetate (250 mg.), m. p. 105—108°, $[\alpha]_D$ −29° (*c*, 1·8). Hydrolysis of the ester (100 mg.) by refluxing it for 2 hr. with 5% methanolic potassium hydroxide (15 c.c.) gave, after acidification, ether extraction, and crystallisation from acetone cholest-5-en-3α-ylacetic acid as needles, m. p. 205—210°, $[\alpha]_D$ −28° (*c*, 2·2). This is the " cholesteryl acetic acid " of Kaiser and Svarz (*J. Amer. Chem. Soc.*, 1945, **67**, 1309). The m. p. (70—74°) of the residual material (3·62 g.) (~80% overall yield from cholest-5-en-3β-ylmalonic acid) was not raised appreciably by recrystallisation, but a portion (700 mg.) was purified by chromatography on aluminium oxide (20 g.) in pentane. After elution with pentane–benzene (1 : 19 and 1 : 9; 70 c.c.) use of pentane–benzene (1 : 9; 70 c.c.) gave a solid (293 mg.) which, crystallised from ether–methanol, had m. p. 70—74°. Further elution with pentane–benzene (1 : 9; 3 × 70 c.c.) gave material (341 mg.), which by crystallisation from ether–methanol gave *methyl cholest-5-en-3β-ylacetate* as plates, m. p. 76—78°, $[\alpha]_D$ −32° (*c*, 1·6) (Found, after drying at 15°/0·02 mm. for 14 hr.: C, 81·3; H, 11·3. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%). Further elution with the same eluant gave material melting over the range 63—70°. The ester (100 mg.) by hydrolysis for 2 hr. with 5% methanolic potassium hydroxide (15 c.c.), followed by acidification and extraction with ether, drying, evaporation, and recrystallisation from a concentrated acetone solution, gave *cholest-5-en-3β-ylacetic acid* as needles, m. p. 165—167°, $[\alpha]_D$ −31° (*c*, 1·4) (Found, after drying at 15°/0·02 mm. for 14 hr.: C, 80·9; H, 11·4. $C_{29}H_{48}O_2$ requires C, 81·3; H, 11·3%). The material (800 mg.) from the mother-liquor of the first recrystallisation of crude cholest-5-en-3β-ylmalonic acid, m. p. 160—170° (decomp.), was decarboxylated at 170°/0·5 mm. for 15 min. Crystallisation from acetone gave cholest-5-en-3α-ylacetic acid, m. p. 205—210°, identical with that obtained as above. The ratio of epimers present in the crude cholesterylmalonic acid of Kaiser and Svarz (*loc. cit.*) is therefore about 9 : 1, the β-epimer predominating.

2-(*Cholest-5-en-3β-yl*)*ethanol.*—To a solution of finely powdered lithium aluminium hydride (150 mg.) in ether (10 c.c.) was added a solution of methyl cholest-5-en-3β-ylacetate (150 mg.) in ether (10 c.c.). After 1 hour's refluxing excess of hydride was destroyed by ice and 2N-sulphuric acid. Extraction with ether, washing, drying, and evaporation gave an oil, which by crystallisation from ether–methanol gave 2-(*cholest-5-en-3β-yl*)*ethanol* (110 mg.) as colourless needles, m. p. 124—126°, $[\alpha]_D$ −31° (*c*, 3·2) (Found, after drying at 100°/0·01 mm. for 4 hr.: C, 83·3; H, 12·0. $C_{29}H_{50}O$ requires C, 84·0; H, 12·2%).

2-(*Cholest-5-en-3α-yl*)*ethanol.*—This was prepared as above from methyl 3α-cholesteryl-acetate (100 mg.) and lithium aluminium hydride (100 mg.) in ether (20 c.c.). Crystallisation from ether–methanol gave 2-(*cholest-5-en-3α-yl*)*ethanol* as colourless needles, m. p. 154—155°, $[\alpha]_D$ −28° (*c*, 1·8) (Found, after drying at 100°/0·01 mm. for 4 hr.: C, 83·6; H, 12·2%).

2-(*Cholest-5-en-3β-yl*)-1 : 1-*diphenylethanol.*—Methyl cholest-5-en-3β-ylacetate (300 mg.),

dried by azeotropic distillation with benzene and dissolved in ether (10 c.c.), was added to a solution of phenylmagnesium bromide prepared from ether (5 c.c.), bromobenzene (1·6 c.c.) and magnesium (330 mg.). After refluxing for 2 hr. the solution was cooled and poured into ice-cold saturated ammonium chloride solution, and the product extracted in ether, washed with 2N-sulphuric acid, water, and 2N-potassium hydroxide to neutrality, dried, and evaporated. Chromatography on aluminium oxide (10 g.) prepared in pentane, and elution with pentane (4 × 60 c.c.), gave a solid (containing bromobenzene) which crystallised from ether–methanol as plates, m. p. 65°, $\lambda_{max.}$ 213 (log ε 4·6) and 248 mμ (log ε 4·7), identified as diphenyl. Further elution with benzene–pentane (1 : 7, 5 × 60 c.c.) gave 2-(*cholest-5-en-3β-yl*)-1 : 1-*diphenylethanol* as needles (from ether–methanol) (330 mg., 90%), m. p. 149—150°, $[\alpha]_D$ −23°, (*c*, 1·0), $\lambda_{max.}$ 210 mμ (log ε 4·2) (Found, after drying at 100°/0·01 mm. for 4 hr.: C, 86·7; H, 10·3. $C_{41}H_{58}O$ requires C, 86·9; H, 10·3%).

2-(*Cholest-5-en-3β-yl*)-1 : 1-*diphenylethylene*.—To a solution of the foregoing ethanol (500 mg.) in pyridine (10 c.c.) was added thionyl chloride (1·5 c.c.) with ice-cooling. After 1 hr. excess of thionyl chloride was destroyed by ice, the product extracted with ether, and the ethereal solution washed with 2N-hydrochloric acid and with water. The *ethylene* crystallised from ether–methanol as needles, m. p. 183—184°, $[\alpha]_D$ 0° (*c*, 1·0), $\lambda_{max.}$ 210 (log ε 4·3) and 253 mμ (log ε 4·2) (Found, after drying at 90°/0·03 mm. for 3 hr.: C, 89·3; H, 10·4. $C_{41}H_{56}$ requires C, 89·7; H, 10·3%).

Cholest-5-ene-3β-carboxylic Acid.—Attempts to oxidise 2-(cholest-5-en-3β-yl)-1 : 1-diphenylethylene by chromium trioxide–acetic acid at 5° (winter) failed to give the required acid; after the discovery that ozonolysis of 2-(cholest-5-en-3β-yl)-1 : 1-dimethylethylene as its 5α : 6β-dibromide gave (after debromination) cholest-5-ene-3β-carboxylic acid, it was found that chromium trioxide–acetic acid was effective to some extent at 15—20° (summer). (Cholest-5-en-3β-yl)-1 : 1-diphenylethylene (160 mg.) was oxidised in dioxan (30 c.c.) with chromium trioxide (270 mg.) in acetic acid (20 c.c.). After 16 hr. excess of trioxide was destroyed by methanol, and solvents were removed under reduced pressure. Addition of 2N-sulphuric acid and extraction with ether gave a sticky solid, which when triturated with pentane gave an insoluble acidic residue (10 mg.); this was cholest-5-ene-3β-carboxylic acid, m. p. 218—220°, giving no m. p. depression with the acid obtained by treatment of cholesterylmagnesium bromide with carbon dioxide. The pentane-soluble portion, crystallised from ether–methanol, had m. p. 183° and gave no m. p. depression with the starting material.

2-(*Cholest-5-en-3β-yl*)-1 : 1-*dimethylethanol*.—Methyl cholest-5-en-3β-ylacetate (1·33 g.) in benzene (20 c.c.) was added to a solution of methylmagnesium iodide, prepared from methyl iodide (4·5 c.c.), magnesium (1·7 g.), and ether (40 c.c.), the mixture refluxed for 2 hr., and poured into cold saturated ammonium chloride solution (200 c.c.). Extraction with ether followed by washing with 2N-sulphuric acid, water, and dilute sodium thiosulphate solution, and drying, gave 2-(*cholest-5-en-3β-yl*)-1 : 1-*dimethylethanol* as colourless prisms (from ether–methanol), m. p. 158—160°, $[\alpha]_D$ −26° (*c*, 1·8) (Found, after drying at 70°/0·01 mm. for 5 hr.: C, 83·7, 84·0; H, 12·2, 12·3. $C_{31}H_{54}O$ requires C, 84·1; H, 12·3%).

2-(*Cholest-5-en-3β-yl*)-1 : 1-*dimethylethylene*.—To a solution of 2-(cholest-5-en-3β-yl)-1 : 1-dimethylethanol (387 mg.) in pyridine (4 c.c.) was added thionyl chloride (0·5 c.c.) with cooling. After 20 min. the solvents were removed under reduced pressure, water was added, and the residue extracted with ether. By the usual procedure the ethylene was obtained as a brown oil (310 mg.). An attempt to oxidise the hydrocarbon (100 mg.) in ether (6 c.c.) with a 2% solution of chromium trioxide in acetic acid (3 c.c.) at 5° for 16 hr. gave no acidic material, and the neutral portion (89 mg.) was an oil.

2-(5α : 6β-*Dibromocholestan-3β-yl*)-1 : 1-*dimethylethanol*.—This was prepared by adding bromine (300 mg.) in ether (12 c.c.) to a solution of 2-(cholest-5-en-3β-yl)-1 : 1-dimethylethanol (680 mg.) in ether (20 c.c.). After 1·5 hr. at 5°, the solvent was removed under reduced pressure. Crystallisation from ether–methanol gave 2-(5α : 6β-dibromocholestan-3β-yl)-1 : 1-dimethylethanol as needles, m. p. 59—62°, decomposing over a period of hours at room temperature. The dibromo-compound was therefore not usually isolated.

2-(5α : 6β-*Dibromocholestan-3β-yl*)-1 : 1-*dimethylethylene*.—Dehydration of the dibromocholestanylethanol (prepared from 680 mg. of the alcohol) in pyridine (5 c.c.) was carried out at 0° with thionyl chloride (2 c.c.). After 15 min. the temperature was allowed to rise to 15° for a further 15 min. and the excess of thionyl chloride was then decomposed. After extraction with ether followed by the usual washing and drying, solvent was removed under reduced pressure, to yield 2-(5α : 6β-dibromocholestan-3β-yl)-1 : 1-dimethylethylene as a brown oil.

Methyl Cholest-5-ene-3β-carboxylate.—The 5α : 6β-dibromo-hydrocarbon obtained in the

previous reaction was dissolved in ethyl acetate (100 c.c.), cooled in solid carbon dioxide–acetone, and a current of ozonised oxygen was passed in for 0·5 hr. After a further 0·5 hr. at −70°, solvent was removed under reduced pressure, the oil was dissolved in acetic acid (90 c.c.), and water (10 c.c.) and zinc dust (2·5 g.) were added. The mixture was refluxed for 0·5 hr. and, after removal of the solvents under reduced pressure, the residue was extracted with ether, and the ether extracts were washed with 2N-sulphuric acid. Extraction of the acidic material with two portions of N-potassium hydroxide, acidification, and ether-extraction gave a solid acid (162 mg.). This was esterified with diazomethane and chromatographed on a column of neutralised aluminium oxide (5 g.) prepared in pentane. Elution with benzene–pentane (3 : 7; 4 × 15 c.c.) gave a solid (90 mg.), which crystallised from ether–methanol to yield methyl cholest-5-ene-3β-carboxylate as colourless needles, m. p. 99—100°, giving no depression on admixture with a sample prepared by treatment of cholesterylmagnesium bromide with carbon dioxide. Further elution with benzene (15 c.c.) and ether (15 c.c.) gave only oils.

Methyl 3β-Cholestanylacetate.—Methyl cholest-5-en-3β-ylacetate (1·5 g.), in acetic acid (250 c.c.), was shaken in hydrogen with platinum oxide (200 mg.) for 20 min. (theoretical absorption in 10 min.). After removal of the solvent and catalyst, crystallisation from ether–methanol gave methyl 3β-cholestanylacetate, m. p. 78—82°, $[\alpha]_D$ +16° (*c*, 3·6). 3β-Cholestanylacetic acid, prepared from the ester by methanolic N-potassium hydroxide, crystallised from acetone as colourless needles, m. p. 170—172°, $[\alpha]_D$ +18° (*c*, 2·3). Both the acid and its ester so prepared gave a faint yellow colour with tetranitromethane–chloroform. The unsaturated impurities were removed by dissolving crude methyl 3β-cholestanylacetate (675 mg.) in benzene (10 c.c.) and adding a mixture of formic acid (98%; 5 c.c.) and hydrogen peroxide (100-vol.; 4 c.c.). The mixture was warmed to 40° and shaken occasionally; after 3 hr., ether was added and the solution washed to neutrality. Drying and evaporation gave a solid which after filtration in pentane through aluminium oxide gave *methyl 3β-cholestanylacetate* (669 mg.), which crystallised from ether–methanol as plates, m. p. 85°, $[\alpha]_D$ +20° (*c*, 1·7), giving no colour with tetranitromethane (Found, after drying at 15°/0·03 mm. for 18 hr.: C, 81·0; H, 11·8. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%). Treatment of the mother-liquors from the first crystallisation of the ester gave a further quantity (250 mg.) of pure methyl 3β-cholestanylacetate.

3β-Cholestanylacetic Acid.—3β-Cholestanylacetic acid was prepared by refluxing methyl 3β-cholestanyl acetate (100 mg.) in methanolic N-potassium hydroxide (15 c.c.) for 2 hr. Acidification and ether-extraction gave *3β-cholestanylacetic acid* as needles (from acetone), m. p. 177°, $[\alpha]_D$ +23° (*c*, 1·1) (Found, after drying at 100°/0·01 mm. for 4 hr.: C, 80·7; H, 11·6. $C_{29}H_{50}O_2$ requires C, 80·9; H, 11·7%).

2-(3β-Cholestanyl)ethanol.—This was prepared by adding a solution of lithium aluminium hydride (150 mg.) in ether (15 c.c.) to a solution of methyl 3β-cholestanyl acetate (104 mg.) in ether (10 c.c.). After 1 hour's refluxing, excess of lithium aluminium hydride was decomposed with cold 2N-sulphuric acid, and the product extracted with ether. Drying and evaporation gave *2-(3β-cholestanyl)ethanol*, which crystallised as needles, m. p. 119—121°, $[\alpha]_D$ +18° (*c*, 2·7), from ether–methanol (Found, after drying at 15°/0·03 mm. for 18 hr.: C, 83·4; H, 12·5. $C_{29}H_{52}O$ requires C, 83·6; H, 12·6%). Alternatively, 2-(cholest-5-en-3β-yl)ethanol (25 mg.; m. p. 124—126°) was shaken in acetic acid (20 c.c.) in hydrogen with platinum oxide (15 mg.) for 1 hr. After removal of the catalyst and solvent, 2-(3β-cholestanyl)ethanol was obtained as needles (from ether–methanol), m. p. 118—120°, giving no depression by admixture with the previous preparation.

2-(3β-Cholestanyl)-1 : 1-dimethylethanol.—A solution of methyl 3β-cholestanylacetate (500 mg.; dried by azeotropic distillation with benzene), dissolved in benzene (5 c.c.), was added to methylmagnesium iodide, prepared from methyl iodide (1·5 c.c.), magnesium (560 mg.), and ether (12 c.c.). After 2 hours' refluxing, the solution was cooled and poured into cold saturated ammonium chloride solution (100 c.c.). Extraction with ether, followed by washing and drying, yielded *2-(3β-cholestanyl)-1 : 1-dimethylethanol*, which crystallised from ether–methanol as needles, double m. p. 110°/128°, $[\alpha]_D$ +23° (*c*, 1·4) (Found, after drying at 15°/0·02 mm. for 12 hr.: C, 83·4; H, 12·7. $C_{31}H_{56}O$ requires C, 83·7; H, 12·7%).

2-(3β-Cholestanyl)-1 : 1-dimethylethylene.—2-(3β-Cholestanyl)-1 : 1-dimethylethanol (460 mg.) in benzene (8 c.c.) and pyridine (0·5 c.c.) was treated with thionyl chloride (0·5 c.c.), and the mixture was kept at 15° for 0·5 hr. Excess of thionyl chloride was destroyed by ice, and the product extracted with ether. The ethereal extract gave, after washing, drying, and evaporation, a brown oil (406 mg.) which, after filtration through a column of aluminium oxide (15 g.) prepared in pentane, afforded a colourless solid (360 mg.), which crystallised from

ether–methanol to give 2-(3β-cholestanyl)-1 : 1-dimethylethylene as prisms, m. p. 96—98°, $[\alpha]_D$ +21° (*c*, 1·5) (Found, after drying at 15°/0·02 mm. for 12 hr.: C, 86·2; H, 12·8. $C_{31}H_{54}$ requires C, 87·2; H, 12·8%). An attempt was made to oxidise this hydrocarbon by using chromium trioxide in acetic acid; to the hydrocarbon (160 mg.) in ether (6 c.c.) was added a 2% solution of chromium trioxide in acetic acid (4 c.c.), and the mixture was kept overnight at 5°. No acidic material was produced; the neutral product (150 mg.), crystallised from ether–methanol, had m. p. 90—92° and gave no depression on admixture with starting material.

Cholestane-3β-carboxylic Acid.—A solution of 2-(cholestan-3β-yl)-1 : 1-dimethylethylene (170 mg.) in ether (3 c.c.) and acetic acid (40 c.c.) was treated with ozonised oxygen for 0·5 hr. at 20°. Water (4 c.c.) was then added and the mixture refluxed for 0·5 hr.; after removal of the solvents under reduced pressure, the oily residue was dissolved in ether (5 c.c.), and a 2% solution of chromium trioxide in acetic acid (3 c.c.) added. The mixture was set aside at 15° for 16 hr. and methanol added before removal of the solvents under reduced pressure. After acidification with 2N-sulphuric acid, the product was extracted with ether and the ethereal extract shaken with 3 portions of N-potassium hydroxide. This alkaline extract was acidified and extracted with ether; drying and evaporation of the solvent gave cholestane-3β-carboxylic acid (36 mg.), which crystallised from ether–pentane as needles, m. p. 204—207°. A mixed m. p. with cholestane-3β-carboxylic acid (prepared by the catalytic hydrogenation of methyl cholest-5-ene-3β-carboxylate and subsequent alkaline hydrolysis) showed no depression.

2-(3β-*Cholestanyl*)-1 : 1-*diphenylethanol.*—Methyl 3β-cholestanylacetate (500 mg.) dried by azeotropic distillation with benzene, was dissolved in ether (10 c.c.) and added to a solution of phenylmagnesium bromide, prepared from bromobenzene (2·3 c.c.), ether (10 c.c.), and magnesium (0·53 g.). After standing for 4 hr. at 15° the mixture was poured into a cold saturated ammonium chloride solution (100 c.c.). Extraction with ether, followed by washing of the extract with 2N-sulphuric acid and N-potassium hydroxide, drying, and evaporation, gave a solid which even after several crystallisations appeared to melt over a wide temperature range. The material at 160°/0·02 mm. gave a sublimate (24 mg.), m. p. 50—58° (? diphenyl), whilst the residue, after crystallisation from ether–methanol, gave 2-(3β-*cholestanyl*)-1 : 1-*diphenylethanol* as needles, double m. p. 94°/157°, $[\alpha]_D$ +13·5 (*c*, 1·4) (Found, after drying at 15°/0·02 mm. for 12 hr.: C, 85·35; H, 10·2. $C_{41}H_{60}O$ requires C, 86·5; H, 10·6%). The poor analytical result probably arises through retention of some methanol of crystallisation.

2-(3β-*Cholestanyl*)-1 : 1-*diphenylethylene.*—2-(3β-Cholestanyl)-1 : 1-diphenylethanol (230 mg.) was refluxed with acetic anhydride (10 c.c.) for 15 min. Removal of the reagent under reduced pressure gave 2-(3β-*cholestanyl*)-1 : 1-*diphenylethylene* as needles (185 mg.) (from ether–methanol), m. p. 173°, $[\alpha]_D$ +4° (*c*, 2·8) (Found, after drying at 15°/0·02 mm. for 12 hr.: C, 89·2; H, 10·4. $C_{41}H_{58}$ requires C, 89·4; H, 10·6%).

Cholestane-3β-carboxylic Acid.—A solution of 2-(3β-cholestanyl)-1 : 1-diphenylethylene (136 mg.) in ethyl acetate (50 c.c.) was treated with ozonised oxygen at −70° for 15 min. After 20 min. at room temperature, the solvent was removed under reduced pressure. The resulting oil was dissolved in acetic acid (30 c.c.), and water (1 c.c.) was added. After 1 hr. at 100° the solvents were removed in a vacuum, the oily product was dissolved in ether (5 c.c.), and a 2% solution of chromium trioxide in acetic acid (1·5 c.c.) was added; after 12 hr., methanol was added and solvents were again removed. The residue was treated with 2N-sulphuric acid and extracted with ether. Shaking the ethereal extract with N-potassium hydroxide gave after acidification and ether-extraction cholestane-3β-carboxylic acid (30 mg.), m. p. 210°, identical with the acid prepared from 2-(3β-cholestanyl)-1 : 1-dimethylethylene. This was esterified with diazomethane and chromatographed on neutralised aluminium oxide (3 g.) prepared in pentane. Elution with benzene–pentane (1 : 19; 2 × 3 c.c.) yielded oil (2·5 mg.) but use of benzene–pentane (3 : 7, 1 × 3 c.c.; and 2 : 3, 1 × 3 c.c.) yielded an oil (23 mg.), which crystallised from ether–methanol in needles, m. p. 64—69°, identical with methyl cholestane-3β-carboxylate prepared by hydrogenation of methyl cholest-5-ene-3β-carboxylate.

Methyl Cholest-5-en-3β-ylacetate.—Cholest-5-ene-3β-carboxylic acid (250 mg.; dried by azeotropic distillation with benzene) was dissolved in pyridine (2 c.c.) and benzene (25 c.c.); thionyl chloride (0·5 c.c.) was then added and the solution was kept at 0° for 30 min. The solution was then warmed at 40° for 10 min. and the solvents were removed under reduced pressure. A further quantity of benzene (5 c.c.) was then added and the mixture again evaporated completely in a vacuum. The acid chloride, dissolved in benzene (10 c.c.), was then filtered into an excess of dry ethereal diazomethane. After 1 hr. at 15° the solution was evaporated to dryness and the residual solid warmed with methanol (40 c.c.) and freshly prepared

silver oxide (150 mg.). After 10 min. at 50° the solution was refluxed and small quantities of silver oxide (totalling 150 mg.) were added periodically during 40 min. After removal of silver oxide and methanol, the oil was chromatographed on a column of neutralised aluminium oxide prepared in pentane. Elution with benzene–pentane (1 : 9; 1 × 20 c.c.) gave a trace of oil whilst use of benzene–pentane (3 : 17; 1 × 20 c.c.) gave a solid (25 mg.), m. p. 66—71°. Further elution with benzene–pentane (3 : 17; 4 × 20 c.c.) gave a solid (49 mg.), which, crystallised from ether–methanol, yielded methyl cholest-5-en-3β-ylacetate, m. p. 76—78°. No depression of m. p. was observed by admixture with methyl cholest-5-en-3β-ylacetate prepared by decarboxylation of cholest-5-en-3β-ylmalonic acid.

6-*Oxocholestan*-3β-*yl Toluene*-p-*sulphonate*.—6-Nitrocholesteryl acetate, m. p. 100—103°, was prepared by the procedure of Shoppee and Summers (*J.*, 1952, 3361), and converted by treatment with zinc–acetic acid into 3β-acetoxycholestan-6-one, m. p. 129°, hydrolysed by hot methanolic N-potassium hydroxide to 3β-hydroxycholestan-6-one, double m. p. 142°/149°. The hydroxy-ketone (25 g.; dried at 20°/0·01 mm.) was dissolved in pyridine (125 c.c.) and treated with purified toluene-*p*-sulphonyl chloride (25 g.); after standing for 16 hr. at 25°, most of the pyridine was removed under reduced pressure. The product was extracted with chloroform, and, after being washed in the usual manner, was isolated and recrystallised from acetone, to give 6-oxocholestan-3β-yl toluene-*p*-sulphonate as cubic prisms, m. p. 180° (decomp.) (cf. Dodson and Riegel, *J. Org. Chem.*, 1948, **13**, 424, who record 169—179°).

6-*Oxocholestan*-3α-*ylmalonic Acid*.—A solution of diethyl sodiomalonate was prepared by refluxing sodium (2·13 g.), toluene (125 c.c.), and diethyl malonate (23 c.c.), and a solution of 6-oxocholestan-3β-yl toluene-*p*-sulphonate (23 g.) in toluene (130 c.c.) was added and refluxing continued for 72 hr. The precipitated sodium toluene-*p*-sulphonate was filtered off and washed with toluene, and the combined toluene extracts were evaporated to dryness under reduced pressure. The residual oil was dissolved in ether, washed with water, dried, and evaporated. Hydrolysis was carried out with boiling methanolic N-potassium hydroxide (125 c.c.) for 16 hr. The precipitated potassium salt was filtered off and shaken with water and ether, to remove any non-acidic impurities; the aqueous layer, after acidification and extraction of the precipitated acid with ether, gave 6-*oxocholestan*-3α-*ylmalonic acid* (8·2 g.), which crystallised from ether–pentane as the dihydrate, m. p. 179° (decomp.), $[\alpha]_D$ −30° (*c*, 1·6) (Found, after drying at 70°/0·01 mm. for 5 hr.: C, 68·6; H, 9·9. $C_{30}H_{48}O_5,2H_2O$ requires C, 68·7; H, 10·0%). The *dimethyl ester*, prepared with diazomethane, crystallised from ether–methanol as needles, m. p. 129—131°, $[\alpha]_D$ −31° (*c*, 1·6) (Found, after drying at 70°/0·01 mm. for 5 hr.: C, 74·3; H, 10·3. $C_{32}H_{52}O_5$ requires C, 74·4; H, 10·1%). The methanolic potassium hydroxide solution obtained after filtration of the potassium salt gave only a trace of oily acid when diluted with water and extracted with ether. The neutral ethereal extracts were combined, washed, dried, and evaporated, and the residue was warmed with methanol. The methanol-soluble portion crystallised as plates, m. p. 90—94°, identified as 3 : 5-*cyclo*cholestan-6-one (8 g.), the normal 3 : 5-elimination product obtained by the action of potassium hydroxide on 3β-toluene-*p*-sulphonyloxycholestan-6-one. The methanol-insoluble portion, after several crystallisations from dioxan, gave an unidentified *substance* as needles (2 g.), m. p. 186°, $[\alpha]_D$ +3·5° (*c*, 1·2); the infra-red spectrum shows a maximum at 1710 cm.$^{-1}$, characteristic of an unconjugated carbonyl group in a six-membered ring, whilst a faint colouration with tetranitromethane may be due to the presence of a double bond (Found, after drying at 70°/0·01 mm. for 5 hr.: C, 77·5; H, 10·7. $C_{27}H_{42}O_3$ requires C, 78·2; H, 10·2%). The structure of this compound is being investigated.

Treatment of 3 : 5-cyclo*Cholestan*-6-*one with Diethyl Sodiomalonate*.—3 : 5-*cyclo*Cholestan-6-one (2 g.) in toluene (10 c.c.) was added to a solution of diethyl sodiomalonate [from diethyl malonate (2·8 c.c.) and sodium (0·26 g.) in toluene (20 c.c.)], and the whole was refluxed for 72 hr. The solvent was removed in a vacuum, and the product heated with methanolic 2N-potassium hydroxide (50 c.c.) for 3 hr. After saturation with carbon dioxide, removal of methanol in a vacuum, and addition of water, the product was extracted with ether and separated into acidic and neutral fractions. The former gave no insoluble acidic material by acidification of the aqueous alkaline solution; the latter gave 3 : 5-*cyclo*cholestan-6-one (85%), m. p. 90—94° after crystallisation from methanol, identical with the starting material.

6-*Oxocholestan*-3α-*ylacetic Acid*.—6-Oxocholestan-3α-ylmalonic acid was decarboxylated at 160—170°/0·5 mm. (1 hr.). The product was crystallised from ether–pentane, to give 6-*oxocholestan*-3α-*ylacetic acid* as needles (7·8 g.), m. p. 171—173°, $[\alpha]_D$ −28° (*c*, 1·5) (Found, after drying at 70°/0·01 mm. for 5 hr.: C, 78·3; H, 10·8. $C_{29}H_{48}O_3$ requires C, 78·3; H, 10·9%). The acid (5·8 g.) with an excess of ethereal diazomethane gave *methyl* 6-*oxocholestan*-3α-*ylacetate* as needles (5·3 g.) (from acetone), m. p. 116°, $[\alpha]_D$ −28° (*c*, 1·3) [Found, (*a*) after sub-

limation at 120°/0·05 mm., (*b*) after drying at 70°/0·01 mm. for 5 hr. : C, 78·9, 78·0; H, 10·8, 10·8. $C_{30}H_{50}O_3$ requires C, 78·6; H, 11·0%].

Methyl 6β-Hydroxycholestan-3α-ylacetate.—The keto-ester was dissolved in methanol (25 c.c.) and ether (5 c.c.), a solution of sodium borohydride (85 mg) in water (2 c.c.) and methanol (15 c.c.) was added, and the mixture was kept at 15° for 30 min. Excess of sodium borohydride was destroyed by the addition of a little 2N-sulphuric acid, and the product extracted with ether. The ethereal extract was washed, dried, and completely evaporated in a high vacuum, but methyl 6β-hydroxycholestan-3α-ylacetate failed to crystallise and was extremely soluble in the usual solvents. Chromatography of the product (995 mg.) on neutralised aluminium oxide gave only oils.

2-(6β-*Hydroxycholestan-3α-yl)ethanol.*—(*a*) A suspension of finely powdered lithium aluminium hydride (1 g.) in ether (50 c.c.) was added to a solution of methyl 6-oxocholestan-3α-ylacetate (1 g.) in ether (100 c.c.). The mixture was kept at 15° for 15 min. and then refluxed for 30 min. Excess of hydride was decomposed by adding ice and 2N-sulphuric acid, and the product extracted with ether. The ether extract was washed, dried, and evaporated, to yield 2-(6β-*hydroxycholestan-3α-yl)ethanol*, which crystallised from ether–pentane as plates (470 mg.), m. p. 155—157°, $[\alpha]_D$ +23° (*c*, 1·2) (Found, after sublimation at 150°/0·05 mm. : C, 80·1; H, 11·9. $C_{29}H_{52}O_2$ requires C, 80·5; H, 12·1%). The *diacetate* was prepared from the diol (110 mg.) with pyridine (2 c.c.) and acetic anhydride (0·5 c.c.) at 15° for 15 hr., and crystallised from ether–methanol as prisms, m. p. 98—101°, $[\alpha]_D$ +11° (*c*, 1·9) (Found, after sublimation at 100°/0·01 mm. : C, 76·5; H, 11·0. $C_{33}H_{56}O_4$ requires C, 76·7; H, 10·9%).

(*b*) Methyl 6β-hydroxycholestan-3α-ylacetate (64 mg.) in ether (10 c.c.) was refluxed for 10 min. with a solution of lithium aluminium hydride (100 mg.) in ether (5 c.c.). The product was extracted as in (*a*) above. Crystallisation from ether–pentane gave 2-(6β-hydroxycholestan-3α-yl)ethanol, identical with that obtained as in (*a*).

6β-*Hydroxycholestan-3α-ylacetic Acid.*—The methyl hydroxy-ester (217 mg.) was hydrolysed for 1 hr. with boiling methanolic 0·5N-potassium hydroxide (20 c.c.). Dilution with water, followed by acidification and the usual ether-extraction, gave 6β-*hydroxycholestan-3α-ylacetic acid*, which crystallised from ether–pentane as needles (188 mg.), m. p. 168—171°, $[\alpha]_D$ +31° (*c*, 1·5) (Found, after drying at 90°/0·03 mm. for 3 hr. : C, 77·6; H, 11·3. $C_{29}H_{50}O_3$ requires C, 78·0; H, 11·3%).

6β-*Acetoxycholestan-3α-ylacetic Acid.*—The hydroxy-acid (403 mg.) with pyridine (4 c.c.) and acetic anhydride (4 c.c.) at 15° for 16 hr. gave 6β-*acetoxycholestan-3α-ylacetic acid* as an amorphous solid which could not be crystallised, $[\alpha]_D$ +8° (*c*, 0·8) (Found, after drying at 10°/0·01 mm. for 12 hr. : C, 76·2; H, 10·7. $C_{31}H_{52}O_4$ requires C, 76·2; H, 10·7%).

Methyl Cholest-5-en-3α-ylacetate.—Methyl 6β-hydroxycholestan-3α-ylacetate (156 mg.), dissolved in pyridine (2·5 c.c.), was treated with phosphorus oxychloride (0·3 c.c.). After 1 hr. at 15° the solution was diluted with water, and the product extracted with ether. The ethereal solution was washed, dried, and evaporated, and the product was chromatographed on aluminium oxide (6 g.) prepared in pentane. Elution with benzene–pentane (1 : 1; 1 × 10 c.c.) gave a sticky solid but further elution with benzene–pentane (1 : 1; 4 × 10 c.c.) gave a solid (64 mg.) which, crystallised twice from acetone, yielded methyl cholest-5-en-3α-ylacetate, m. p. 104—108°, giving a yellow colour with tetranitromethane in chloroform; no depression of m. p. was observed on admixture with a specimen of methyl cholest-5-en-3α-ylacetate isolated from the decarboxylation of crude cholest-5-en-3β-ylmalonic acid.

3α-*Coprostanylacetic Acid.*—Methyl cholest-5-en-3α-ylacetate (52 mg.), dissolved in acetic acid (6 c.c.) and ethyl acetate (4 c.c.) containing a trace of perchloric acid, was shaken in hydrogen with platinum oxide (170 mg.) for 3 hr. Removal of solvents and catalyst furnished an oil, which after hydrolysis with hot 2N-methanolic potassium hydroxide for 2 hr. gave an acid. This was isolated in the usual manner and recrystallised from acetone and then from ether–pentane, to yield 3α-*coprostanylacetic acid* (16 mg.), m. p. 150—152°, $[\alpha]_D$ +33° (*c*, 0·9) (Found, after sublimation at 160°/0·01 mm. : C, 80·9; H, 11·7. $C_{29}H_{50}O_2$ requires C, 80·9; H, 11·7%).

6β-*Hydroxycholestan-3β-yl Toluene-*p*-sulphonate.*—6-Oxocholestan-3β-yl toluene-*p*-sulphonate (10·3 g.) in dioxan (150 c.c.) was treated with a solution of sodium borohydride (785 mg., 1·2 mol.) in water (1 c.c.) and methanol (100 c.c.). After 1·5 hr. at 30° gas evolution had ceased; dilution with an equal volume of water furnished a solid which, after filtration, washing with water, and drying, was recrystallised from ether–pentane to give 6β-hydroxycholestan-3β-yl toluene-*p*-sulphonate, double m. p. 140°/160° (decomp.), $[\alpha]_D$ −9° (*c*, 1·9) (8·83 g., 85%) (cf. Reich and Lardon, *Helv. Chim. Acta*, 1946, **29**, 671, who give double m. p. 139°/150°). The compound was

identical with a sample previously prepared by Dr. G. H. R. Summers from cholestane-3β : 6β-diol by treatment with toluene-*p*-sulphonyl chloride (1 mol.) in pyridine at 15°.

6β-*Hydroxycholestan*-3α-*ylmalonic Acid.*—(*a*) To a solution of diethyl sodiomalonate prepared from sodium (0·86 g.) and diethyl malonate (6·8 c.c.) in toluene (50 c.c.), was added a solution of 6β-hydroxycholestan-3β-yl toluene-*p*-sulphonate (7·5 g.) in toluene (50 c.c.). After 72 hours' refluxing the precipitated sodium toluene-*p*-sulphonate was filtered off and washed with toluene, the combined toluene extracts were evaporated to dryness in a vacuum, and the residue was refluxed for 3 hr. with methanolic 2N-potassium hydroxide. Dilution with water, ether-extraction of non-acidic material, acidification of the aqueous layer, ether-extraction, and the usual working up, gave 6β-*hydroxycholestan*-3α-*ylmalonic acid*, m. p. 168—170° (decomp.), $[\alpha]_D$ +9° (*c*, 1·6), obtained as a microcrystalline powder from ether–pentane (Found, after drying at 40°/0·02 mm. for 12 hr.: C, 69·8; H, 10·1. $C_{30}H_{50}O_5,1\frac{1}{2}H_2O$ requires C, 69·6; H, 10·3%). The *dimethyl ester*, although crystalline, $[\alpha]_D$ +7° (*c*, 1·4), was soluble in all the usual solvents and could not satisfactorily be recrystallised. A sample sublimed at 180°/0·02 mm. had m.p. 108—113° (Found: C, 74·1; H, 10·6. $C_{32}H_{54}O_5$ requires C, 74·1; H, 10·6%).

(*b*) Dimethyl 6-oxocholestan-3α-ylmalonate (1·27 g.) was suspended in methanol (50 c.c.), and a solution of sodium borohydride (103 mg.) in water (2 c.c.) and methanol (10 c.c.) added. The solid dissolved and after 30 min. potassium hydroxide (3 g.) was added, and the mixture refluxed for 30 min. Acidification and ether-extraction gave, after the usual working up, 6β-hydroxycholestan-3α-ylmalonic acid, m. p. 168—170° (decomp.), giving no depression of m. p. with material prepared by method (*a*).

Dimethyl Cholest-5-*en*-3α-*ylmalonate.*—Dimethyl 6β-hydroxycholestan-3α-ylmalonate (1 g.) in pyridine (10 c.c.) was treated with phosphorus oxychloride (1 c.c.) at 0°. After 5 hr. at 15°, the mixture was poured into ice-water, and the product extracted with ether. The extract was worked up, to give an oil (750 mg.), of which a portion (390 mg.) was chromatographed on neutralised aluminium oxide (12 g.) prepared in benzene–pentane (1 : 1). Elution with benzene–pentane (1 : 1; 2 × 40 c.c.) gave an oil (29 mg.), whilst use of benzene–pentane (7 : 3; 40 c.c.) yielded partly crystalline material (32 mg.); further elution with benzene–pentane (7 : 3, 40 c.c.; 4 : 1, 3 × 40 c.c.) afforded a solid (140 mg.), which recrystallised from methanol to give *dimethyl cholest*-5-*en*-3α-*ylmalonate*, m. p. 118°, $[\alpha]_D$ −49° (*c*, 1·4) (Found, after sublimation at 160°/0·02 mm.: C, 76·9; H, 10·6. $C_{32}H_{52}O_4$ requires C, 76·8; H, 10·5%). Further elution with benzene, ether, and methanol gave oils.

Cholest-5-*en*-3α-*ylmalonic Acid.*—The above dimethyl ester (50 mg.) was refluxed with methanolic 2N-potassium hydroxide (10 c.c.) for 2 hr. After removal of part of the methanol in a vacuum, dilution with water, and extraction of any neutral material with ether, acidification of the alkaline solution gave a solid acid. Crystallisation from ether–pentane gave *cholest*-5-*en*-3α-*ylmalonic acid* (25 mg.), m. p. 190° (decomp.), $[\alpha]_D$ −36° (*c*, 1·10 in EtOH) (Found, after drying at 40°/0·02 mm. for 12 hr.: C, 74·3; H, 10·1. $C_{38}H_{48}O_4,\frac{1}{2}H_2O$ requires C, 74·8; H, 10·3%).

Cholest-5-*en*-3α-*ylacetic Acid.*—Decarboxylation of cholest-5-en-3α-ylmalonic acid at 200°/0·01 mm., followed by sublimation of the product at 200—210°/0·01 mm., gave cholest-5-en-3α-ylacetic acid as needles (from acetone), m. p. 205—208°, mixed m. p. 205—208° with specimens obtained by other methods (see above).

3α-*Cholestanylmalonic Acid.*—To a solution of diethyl sodiomalonate, prepared from sodium (3·45 g.) and diethyl malonate (27 c.c.) in toluene (150 c.c.), was added 3β-cholestanyl toluene-*p*-sulphonate (28 g.) in toluene (200 c.c.). After 72 hours' refluxing the mixture was cooled, sodium toluene-*p*-sulphonate was filtered off, the filtrate evaporated in a vacuum, and the residual oil hydrolysed with potassium hydroxide (20 g.) in methanol (150 c.c.) and *iso*propanol (200 c.c.). After 3 hr. the suspension was cooled, and the precipitated potassium salt was collected and converted into the free acid; recrystallisation from ether–pentane gave 3α-*cholestanylmalonic acid*, m. p. 193° (decomp.), $[\alpha]_D$ +30° (*c*, 1·6 in EtOH) (12·5 g.) (Found, after drying at 40°/0·02 mm. for 12 hr.: C, 76·0; H, 10·7. $C_{30}H_{50}O_4$ requires C, 75·9; H, 10·6%). The *dimethyl ester*, prepared by ethereal diazomethane and recrystallised from ether–methanol, had m. p. 147°, $[\alpha]_D$ +20° (*c*, 1·80) (Found, after sublimation at 160°/0·01 mm.: C, 76·3; H, 10·7. $C_{32}H_{54}O_4$ requires C, 76·4; H, 10·8%).

3α-*Cholestanylacetic Acid.*—3α-Cholestanylmalonic acid (11·5 g.) was decarboxylated at 215°/760 mm. for 15 min.; the product on crystallisation from ether–acetone gave 3α-*cholestanylacetic acid*, m. p. 210°, $[\alpha]_D$ +24·5° (*c*, 1·91) (Found, after sublimation at 200°/0·01 mm.: C, 80·4; H, 11·5. $C_{29}H_{50}O_2$ requires C, 80·9; H, 11·7%). The *methyl ester*, prepared by ethereal diazomethane and crystallised from ether–methanol, had m. p. 118°, $[\alpha]_D$ +28° (*c*, 1·51)

(Found, after sublimation at 160°/0·01 mm.: C, 80·8; H, 11·6. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%).

2-(3α-*Cholestanyl*)*ethanol*.—Methyl 3α-cholestanylacetate (100 mg.) was refluxed with lithium aluminium hydride (100 mg.) in ether (20 c.c.) for 15 min. Excess of the reagent was destroyed by addition of water, and the product isolated in the usual way. Crystallisation from methanol gave 2-(3α-*cholestanyl*)*ethanol* (92 mg.), m. p. 111°, $[\alpha]_D$ +25° (*c*, 1·3) (Found, after sublimation at 160°/0·01 mm.: C, 83·8; H, 12·3. $C_{29}H_{52}O$ requires C, 83·6; H, 12·6%).

2-(3α-*Cholestanyl*)-1 : 1-*diphenylethanol*.—Methyl 3α-cholestanylacetate (9 g.; dried by azeotropic distillation with benzene), dissolved in benzene (75 c.c.), was treated with a solution of phenylmagnesium bromide [prepared from bromobenzene (46 c.c.) and magnesium (10·5 g.) in ether (150 c.c.)]; after 2 hours' refluxing the mixture was poured into ice-water and worked up in the usual way. The resultant oil was chromatographed on aluminium oxide (250 g.) prepared in pentane. Elution with pentane gave an oil consisting mainly of bromobenzene and diphenyl, whilst elution with benzene–pentane (1 : 1; 2 × 1 l.) gave 2-(3α-cholestanyl)-1 : 1-diphenylethanol as an oil (9·7 g.).

2-(3α-*Cholestanyl*)-1 : 1-*diphenylethylene*.—The above oil (9·7 g.), dissolved in pyridine (45 c.c.), was treated with thionyl chloride (10 c.c.) at 0° for 5 min. and then at 15° for 15 min. Dilution with ice-water, ether-extraction, and the usual working up gave an oil, which was dissolved in pentane and filtered through a column of aluminium oxide. Evaporation of the filtrate gave 2-(3α-*cholestanyl*)-1 : 1-*diphenylethylene* as plates (5·9 g.), m. p. 92°, $[\alpha]_D$ +64° (*c*, 0·91), from ethanol (Found, after sublimation at 160°/0·01 mm.: C, 89·4; H, 10·5. $C_{41}H_{58}$ requires C, 89·4; H, 10·6%).

Cholestane-3α-*carboxylic Acid*.—2-(3α-Cholestanyl)-1 : 1-diphenylethylene (2·3 g.), dissolved in purified chloroform (20 c.c.) and acetic acid (150 c.c.), was oxidised with a solution of chromium trioxide (2 g.) in 90% acetic acid at 15° for 2 hr. Excess of chromium trioxide was destroyed by addition of methanol, and solvents were removed in a vacuum. After addition of water and a little 2N-sulphuric acid, extraction with ether gave an ethereal solution from which no acid was extracted by 2N-potassium hydroxide. Evaporation of the dry ethereal solution gave an opaque solid, which afforded a precipitate when triturated with pentane. Collection of this potassium salt, acidification of its aqueous solution, and extraction with ether gave *cholestane*-3α-*carboxylic acid* (760 mg.), m. p. 163°, $[\alpha]_D$ +24° (*c*, 1·71), after crystallisation from 90% acetone (Found, after sublimation at 160°/0·01 mm.: C, 80·8; H, 11·4. $C_{24}H_{48}O_2$ requires C, 80·7; H, 11·6%). The *methyl ester*, prepared by ethereal diazomethane, formed prisms, m. p. 92°, $[\alpha]_D$ +27° (*c*, 3·1) (Found, after sublimation at 160°/0·01 mm.: C, 81·0; H, 11·7. $C_{30}H_{50}O_2$ requires C, 81·0; H, 11·7%).

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