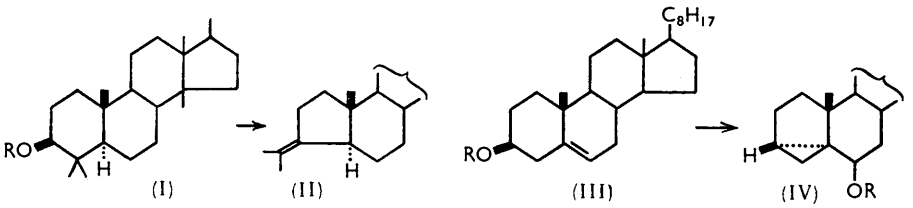
154. *The Solvolysis of* 4 : 4-*Dimethylcholest*-5-*en*-3β-*yl Toluene*-p-*sulphonate.*

By Y. M. Y. Haddad and G. H. R. Summers.

Hydrolysis of 4 : 4-dimethylcholest-5-en-3β-yl toluene-*p*-sulphonate (V; R = *p*-$C_6H_4Me{\cdot}SO_2$) in aqueous acetone in the presence of potassium acetate yields 3-*iso*propylidene-A-norcholest-5-ene as major product, with 4 : 4-dimethylcholest-5-en-3β-ol and 4 : 4-dimethyl-3 : 5-*cyclo*cholestan-6β-ol as minor products. Acetolysis of (V; R = *p*-$C_6H_4Me{\cdot}SO_2$) and lanost-8 : 24-dien-3β-yl toluene-*p*-sulphonate also gives products of Wagner rearrangement and of substitution with retention of configuration. These solvolyses are considered to involve a unimolecular mechanism.

Two reactions, which have come to be considered as diagnostic of the presence of an equatorial 3-hydroxyl group in tetra- and penta-cyclic terpenoids, and Δ^5- steroids, involve rearrangement: dehydration (brought about by phosphorus pentachloride) of 3β-hydroxyterpenoids (I) causes Wagner rearrangement, with contraction of ring A and formation of *iso*propylidene-A-nor-derivatives [1] (II), and 3β-hydroxy-Δ^5-steroids [as the toluene-*p*-



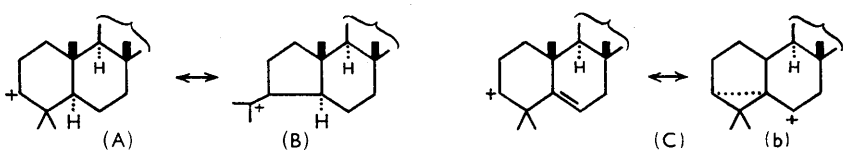
sulphonyl derivatives, R = *p*-$C_6H_4Me{\cdot}SO_2$ (III)] by solvolysis in buffered media yield 6β-substituted 3 : 5-*cyclo*steroids [2] (IV). The results contrast with the behaviour of the corresponding axial alcohols, which react principally by ionic 1 : 2-elimination without ring change.[3*] Wagner rearrangements depend upon ionisation,[5] and the alteration of the carbon skeleton by a 1 : 2-shift involves a carbonium ion. Thus the change (I ⟶ II) occurs by way of the cations (A, B), either as separate classical entities or as canonical structures of a non-classical mesomeric cation. The 3 : 5-*cyclo*steroid rearrangement is a 1 : 3-shift with stereospecific character which shows an accelerated rate (cf. cholestan-3β-yl toluene-*p*-sulphonate [6]); configurational,[7] kinetic,[8] and thermodynamic [9] studies lead to the conclusion that replacement reactions at position 3 of 3β-substituted Δ^5-steroids which lead to 1 : 3-rearrangement occur *via* a non-classical mesomeric ion (cf. C).

It was, therefore, of interest to examine structurally and kinetically the solvolysis of a system the geometry of which combined the configurational requirements of both the above rearrangements. For both rearrangements to occur concurrently, carbonium ion A

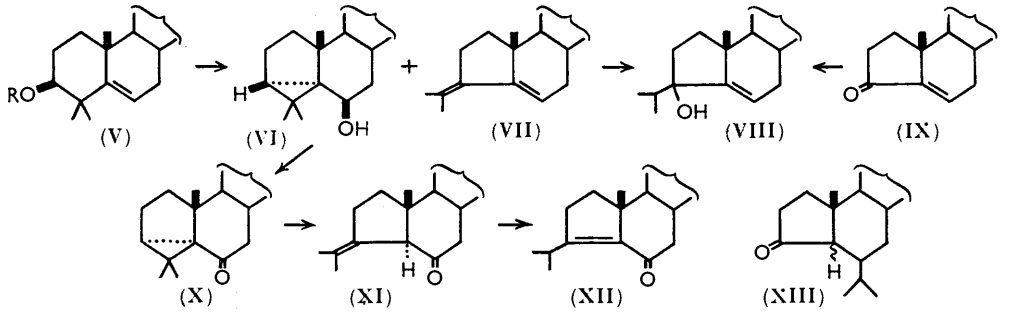
* Barton, Lewis, and McGhie [4] show that treatment of lanostan-3β-ol with phosphorus oxychloride in pyridine gives a mixture of lanost-2-ene and 3-*iso*propylidene-A-norlanostane.

[1] Dorée, McGhie, and Kurzer, *J.*, 1949, S 167; Ruzicka, Montavon, and Jeger, *Helv. Chim. Acta*, 1948, **31**, 818 (for lanosterol).
[2] Shoppee and Summers, *J.*, 1952, 3361, and references there cited.
[3] Barton, *Experientia*, 1950, **6**, 316; Evans and Shoppee, *J.*, 1953, 540.
[4] Barton, Lewis, and McGhie, *J.*, 1957, 2907.
[5] Meerwein and van Emster, *Ber.*, 1922, **55**, 2500.
[6] Nace, *J. Amer. Chem. Soc.*, 1952, **74**, 5937.
[7] Shoppee, *J.*, 1946, 1147.
[8] Winstein and Adams, *J. Amer. Chem. Soc.*, 1948, **70**, 838; Pearson, King, and Langer, *ibid.*, 1951, **73**, 414; Hafez, Halsey, and Wallis, *Science*, 1949, **110**, 475; Davies, Meecham, and Shoppee, *J.*, 1955, 679; Shoppee and Westcott, *J.*, 1955, 1891.
[9] Shoppee and Williams, *J.*, 1956, 2488; Simonetta and Winstein, *J. Amer. Chem. Soc.*, 1954, **76**, 18.

would become, in a modified form (introduction of a 5 : 6-double bond),* a canonical form of hybrid C. We now describe our structural investigations on the solvolysis of 4 : 4-dimethylcholest-5-en-3β-yl toluene-*p*-sulphonate (V; R = *p*-$C_6H_4Me{\cdot}SO_2$).



Hydrolysis of this ester (V; R = *p*-$C_6H_4Me{\cdot}SO_2$) in boiling aqueous acetone in the presence of potassium acetate for 14 hr. yielded 3β-hydroxy-4 : 4-dimethylcholest-5-ene (V; R = H) as a minor product (16%), an isomeric alcohol, m. p. 126°, $[\alpha]_D$ −25° (24%), and a hydrocarbon, m. p. 85°, $\lambda_{max.}$ 241 mμ (log ε 4·22) (60%). The hydrocarbon was also the major product of (*a*) acetolysis and (*b*) chromatography on basic aluminium oxide of the toluene-*p*-sulphonate [the minor and only other products were the acetate (V; R = Ac) and alcohol (V; R = H) respectively]. Since the amount of elimination accompanying



the 3 : 5-*cyclo*steroid rearrangement is normally small it was suspected that the hydrocarbon was 3-*iso*propylidene-A-norcholest-5-ene (VII), the product of rearrangement of the Δ^5-cation (C). Formation of 3 : 4-dimethylcholest-3 : 5-diene is excluded since the steric requirement of coplanarity of centres 3 and 4 and the 3β-ester and the 4β-methyl group is not satisfied. Structure (VII) was established by the formation of acetone on ozonolysis and by preparation of the compound from the ketone (IX) by treatment with *iso*propylmagnesium iodide. The last reaction gave also 3-*iso*propyl-A-norcholest-5-en-3α-ol (VIII) [which was dehydrated by phosphorus oxychloride in pyridine to the hydrocarbon (VII)], and a 5-membered ring ketone ($\nu_{max.}$ 1740 cm.$^{-1}$) [evidently 6-*iso*propyl-A-nor-5ξ-cholestan-3-one (XIV) formed by 1 : 4-addition of the Grignard reagent to the αβ-unsaturated ketone followed by ketonisation on hydrolysis].

The compound, m. p. 126°, we consider to be 4 : 4-dimethyl-3 : 5-*cyclo*cholestan-6β-ol (VI) from the evidence described below, its method of preparation, and the somewhat similar behaviour of the 6-hydroxyl group to that displayed by the secondary alcohol group in 6β-hydroxyoleanolic acid (sumaresinolic acid).[10] Its sensitivity to acids is shown by its conversion into the hydrocarbon (VII) by acetic acid and sulphuric or hydrochloric acid. It is notable that no 3β-substituted derivatives are produced by acid-catalysed rearrangement. Treatment with pyridine–acetic anhydride gave unchanged starting material, and sodium ethoxide at 180° (3 days) failed to yield an epimeric product.

Oxidation of the alcohol (VI) with chromium trioxide–pyridine gave a ketone in low yield, which showed carbonyl absorption at 1684 cm.$^{-1}$, consistently with conjugation

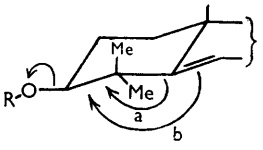
* The 5 : 6-double bond does not appreciably alter the geometry of ring A,[9] so that an equatorial bond at $C_{(3)}$ and the 4 : 5-linkage remain coplanar.

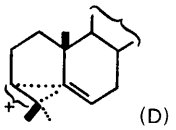
[10] Simonsen and Ross, " The Terpenes," Cambridge Univ. Press, 1957, Vol. V, p. 302.

between the *cyclo*propane and the carbonyl group and formulation of the product as 4 : 4-dimethyl-3 : 5-*cyclo*cholestan-6-one (X). The alcohol (VI) was not oxidised by aluminium *tert.*-butoxide; chromium trioxide in acetic acid gave some of the hydrocarbon (VII) and a crystalline product in small yield, which was shown by the strong absorption bands at 1733, 1684, and 1242 cm.$^{-1}$ to be a mixture of the ketone (X) and 3β-acetoxy-4 : 4-dimethylcholest-5-ene (V; R = Ac). Acid-isomerisation of the ketone (X) gave an oil, $\lambda_{max.}$ 259 mμ (log ε, 4·0), which on account of its ultraviolet absorption is thought to be 3-*iso*propyl-A-norcholest-3-en-6-one (XII) formed *via* (XI).

Position 6 in oleanane derivatives has been well established as the most hindered position in the molecule: *e.g.*, sumaresinolic acid yields the 3-monoacetate,[11] and the 6-ketone (readily formed on oxidation of the 3β-monoacetate with chromium trioxide in pyridine) resists reduction by both the Clemmensen and the Wolff–Kishner method * [11] although the modified procedure of the latter method has more recently been shown to give 33% of the deoxo-compound.[12] It seems that the lower reactivity of the alcohol (VI) than of 6β-hydroxyoleanolic acid can be tentatively related to a significant but, at present, indeterminable hindrance on the α-side of the molecule due to distortion of ring A by the 3 : 5-transannular bond (cf. the reactions of 6-keto-3 : 5-*cyclo*steroids with lithium aluminium hydride [13] and Grignard reagents [14] which give the 3 : 5-*cyclo*-6α-alcohols).

The above solvolyses agree in the main with the general pattern [4] for substitution of 3β-substituted Δ^5-steroids by weak nucleophiles.[8] Thus, in an acidic medium retention of configuration with little or no elimination occurs, whilst in a buffered medium rearrangement is the normal reaction. The significant difference is that Wagner rearrangement is predominant in both media, indicating that the easier reaction is the cleavage of the 4 : 5-bond with attack at position 3 with inversion. This is to be expected if one considers that 3β-substituted 4 : 4-dimethyl-steroids and -terpenes contain an α-substituted *neo*-pentyl system which is especially prone to rearrangement.[15] The steric conditions necessary for the formation of the above products are also suitable, the overall interaction at position 3 involving (a) α-stereoelectronic competition of the σ-electrons of the 4 : 5-bond and (b) the π-electrons of the 5 : 6 double bond. As has been previously pointed out, process (b) is known to lead to the mesomeric cation C, but for process (a) no information is





(D)

yet available, for the example cited, about the nature of the resulting cation or cations. To test whether in fact a charge produced at position 3 by heterolysis completely migrates to position 4, giving cation B, we examined the acetolysis of lanosta-8 : 24-dien-3β-yl toluene-*p*-sulphonate. Treatment with potassium acetate in acetic acid at 90° for 3 hr. gave predominantly the *iso*propylidene derivative and a little lanosta-8 : 24-dien-3β-yl acetate. There was no evidence of inversion without rearrangement, a result indicating an ionic mechanism and contrasting with the accepted behaviour of nucleophilic substitution at position 3 in saturated steroids.[16] The accompanying retention of configuration

* The 6-keto-group is not reduced by sodium borohydride.[12]

[11] Ruzicka, Jeger, Grob, and Hosli, *Helv. Chim. Acta*, 1943, **26**, 2283.
[12] Djerassi, Thomas, and Jeger, *Helv. Chim. Acta*, 1955, **38**, 1304.
[13] Ref. 2; cf. Wagner and Wallis, *J. Amer. Chem. Soc.*, 1950, **72**, 1047; Wagner, Wolff, and Wallis, *J. Org. Chem.*, 1952, **17**, 529.
[14] Summers, unpublished work.
[15] Ingold, *J.*, 1953, 2845.
[16] Shoppee, *J.*, 1946, 1138; Bridgewater and Shoppee, *J.*, 1953, 1709.

suggests the intermediate existence either of carbonium ions A and B (the latter more stable) as separate entities, or of a bridged carbonium ion D in which the charge is distributed over carbon atoms 3 and 4. A decision between these two possibilities would depend upon whether the rate of solvolysis was normal or accelerated (anchimeric assistance) as compared with, say, that for pinacolyl toluene-*p*-sulphonate. Stabilisation of the distributed positive charge by the π-orbital of the 5 : 6-double bond (b) could then lead to the 6β-3 : 5-*cyclo*-derivative by interaction of an anion at the electron-deficient centre 6. The non-classical mesomeric ion C would consequently have to be modified to a structure involving resonance between bridged ion D and canonical form C (b) (cf. the stabilisation of " phenonium " ions by resonance [9]).

Experimental

Ultraviolet absorption spectra were determined for ethanol solutions in a Unicam S.P. 500 spectrophotometer. Infrared absorption spectra were measured by use of a Grubb-Parsons GS2 double-beam grating spectrometer. Unless otherwise stated, alumina used was Spence's type H (activity II). $[\alpha]_D$ refer to chloroform solutions.

4 : 4-*Dimethylcholest*-5-*en*-3β-*yl Toluene*-p-*sulphonate*.—4 : 4-Dimethylcholest-5-en-3β-ol (5 g.) in pyridine (40 ml.) was treated with toluene-*p*-sulphonyl chloride (5 g.) and left overnight. Working up in the usual way gave an oil (7·3 g.) which on crystallisation from pentane gave 4 : 4-*dimethylcholest*-5-*en*-3β-*yl toluene*-p-*sulphonate* as needles, m. p. 92—95° (decomp.), $[\alpha]_D$ −46°, −45° (*c* 0·88, 1·4) [Found (after drying at 25°/0·02 mm. for 16 hr.): C, 76·3; H, 9·75. $C_{36}H_{56}O_3S$ requires C, 76·01; H, 9·9%].

3 : 5-cyclo-4 : 4-*Dimethylcholestan*-6β-*ol*.—A solution of 4 : 4-dimethylcholest-5-en-3β-yl toluene-*p*-sulphonate (11 g.) in acetone (240 ml.) was treated with water (60 ml.) and anhydrous potassium acetate (10 g.) and refluxed for 14 hr. The acetone was removed by evaporation under reduced pressure and the product extracted with ether. The ethereal extract was washed with water, dried (Na_2SO_4), and evaporated, giving an oil which was chromatographed on aluminium oxide (170 g.). Elution with hexane (2 × 200 ml.) gave an oil (6·23 g.) which on crystallisation from ethyl acetate gave 3-iso*propylidene*-A-*norcholest*-5-*ene*, m. p. 85°, $[\alpha]_D$ −65·7° (*c* 1·4), $\lambda_{max.}$ 241 mμ (log ε 4·22) [Found (after drying at 25°/0·02 mm. for 16 hr.): C, 87·5; H, 12·6. $C_{29}H_{48}$ requires C, 87·8; H, 12·2%]. This compound gave a positive Rosenheim test. Elution with benzene–ether (4 : 1) (7 × 200 ml.) gave a solid (2·66 g.) which on crystallisation from acetone gave 3 : 5-cyclo-4 : 4-*dimethylcholestan*-6β-*ol* as plates, m. p. 125—126°, $[\alpha]_D$ −24·7° (*c* 0·9) [Found (after drying at 40°/0·02 mm. for 18 hr.): C, 83·4; H, 12·0. $C_{29}H_{50}O$ requires C, 84·0; H, 12·15%]. Repeated elution with chloroform gave a solid (1·18 g.) which on crystallisation from acetone gave 4 : 4-dimethylcholest-5-en-3β-ol, m. p. 146—148°, $[\alpha]_D$ −61·6° (*c* 0·9).

Treatment of 4 : 4-dimethyl-3 : 5-*cyclo*cholestan-6β-ol with pyridine–acetic anhydride for 1 month failed to bring about acetylation, and starting material was recovered quantitatively.

3-iso*Propylidene*-A-*norcholest*-5-*ene*.—(*a*) 4 : 4-Dimethylcholest-5-en-3β-yl toluene-*p*-sulphonate (433 mg.) in pentane (5 ml.) was added to a column of aluminium oxide (15 g.) in pentane and left for 1 hr. Elution with pentane (3 × 30 ml.) gave an oil (240 mg.) which on crystallisation from ethyl acetate–methanol gave 3-*iso*propylidene-A-norcholest-5-ene, m. p. and mixed m. p. 80—82°. Elution with ether and chloroform gave 4 : 4-dimethylcholest-5-en-3β-ol, m. p. 147—149°.

(*b*) 4 : 4-Dimethylcholest-5-en-3β-ol (426 mg.) in hexane (50 ml.) was shaken for 0·5 hr. with phosphorus pentachloride (500 mg.). Filtration of the solution through aluminium oxide gave an oil which by repeated crystallisation from ethyl acetate gave 3-*iso*propylidene-A-norcholest-5-ene, m. p. 80—83°.

(*c*) 4 : 4-Dimethyl-3 : 5-*cyclo*cholestan-6β-ol (60 mg.) in acetic acid (5 ml.) was treated with hydrochloric (or sulphuric) acid (4 drops) and left for 0·5 hr. Working up in the usual way gave 3-*iso*propylidene-A-norcholest-5-ene, m. p. 81—82° (from ethyl acetate at 0°).

(*d*) A-Norcholest-5-en-3-one (1·1 g.; m. p. 96°) in ether (50 ml.) was added to an ether solution of *iso*propylmagnesium iodide, prepared from magnesium (1 g.) and *iso*propyl iodide (3·6 ml.), and refluxed for 2·5 hr. The solution was poured into ice and ammonium chloride solution and extracted with more ether, and the ethereal extract washed with water, dried, and evaporated, to give an oil (1·07 g.) which was chromatographed on neutral aluminium oxide

(40 g.; Woelm). Elution with pentane gave an oil (71 mg.) whose infrared spectrum was that of 3-*iso*propylidene-A-norcholest-5-ene prepared as above. Elution with hexane (8 × 200 ml.) gave 6-iso*propyl*-A-*nor*-5ξ-*cholestan*-3-*one* (760 mg.), m. p. 225—227° (from ethyl acetate), $[\alpha]_D$ +94°, +90·3° (*c* 1·4, 0·8) $\lambda_{max.}$ CCl_4 1740 cm.$^{-1}$ [Found (after drying at 40°/0·02 mm. for 18 hr.): C, 83·5; H, 11·8. $C_{29}H_{50}O$ requires C, 84·0; H, 12·15%]. Elution with ether gave a semisolid material (270 mg.) which was rechromatographed on neutral aluminium oxide (7 g.). Elution with benzene gave 6-*iso*propyl-A-nor-5ξ-cholestan-3-one, m. p. 225—228° (132 mg.); then elution with ether gave an oil (135 mg.) which was dehydrated by phosphorus oxychloride in pyridine at 0°. The oil so obtained crystallised with difficulty from ethyl acetate–methanol; the product had m. p. and mixed m. p. 78—83°.

Ozonolysis of 3-iso*Propylidene*-A-*norcholest*-5-*ene*.—3-*iso*Propylidene-A-norcholest-5-ene (1·76 g.) in carbon tetrachloride (100 ml.) was treated with excess of ozone at 0° for 2 hr. The solvent was evaporated under reduced pressure and the resulting oil boiled for 1 hr. with water (120 ml.). The aqueous mixture was distilled and the distillate treated with dinitrophenylhydrazine sulphate solution and left at 0° overnight. The orange solid was collected and crystallised from aqueous methanol, to give needles of acetone phenylhydrazone, m. p. and mixed m. p. 124—125°.

Attempted Epimerisation of 4 : 4-*Dimethyl*-3 : 5-cyclo*cholestan*-6β-*ol*.—4 : 4-Dimethyl-3 : 5-*cyclo*cholestan-6β-ol (500 mg.) was heated with sodium (1 g.) and ethanol (10 ml.) at 190° for 75 hr. After cooling, the solid was treated with water and extracted with ether. The ethereal extract was washed with water, dried, and evaporated to give an oil which readily crystallised (m. p. 117—126°). Careful chromatography on basic alumina (Woelm) failed to yield an epimeric product, and starting material (466 mg.) was recovered.

4 : 4-*Dimethyl*-3 : 5-cyclo*cholestan*-6-*one*.—4 : 4-Dimethyl-3 : 5-*cyclo*cholestan-6β-ol (3·5 g.) in pyridine (35 ml.) was treated with chromium trioxide (3·5 g.) and pyridine (35 ml.), and left overnight. The solution was diluted with ether and filtered, and the solvent evaporated under reduced pressure. The sticky solid obtained was chromatographed on aluminium oxide (90 g.). Elution with benzene–pentane (1 : 1) gave oils (310 mg.) which by repeated crystallisation from acetone–methanol gave 4 : 4-*dimethyl*-3 : 5-cyclo*cholestan*-6-*one*, m. p. 96—98°, $[\alpha]_D$ +83° (*c* 0·9), $\lambda_{max.}$ 1684 cm.$^{-1}$ in carbon tetrachloride [Found (after drying at 20°/0·02 mm. for 10 hr.): C, 84·0; H, 11·5. $C_{29}H_{48}O$ requires C, 84·4; H, 11·7%]. Elution with benzene, ether, and chloroform gave starting material (2·85 g.), m. p. 123—126°, $[\alpha]_D$ −21° (*c* 1·0).

The ketone (120 mg.) in acetic acid (10 ml.) containing 5N-sulphuric acid (2·5 ml.) was refluxed for 2 hr. Isolation of the product in the usual way gave an oil (87 mg.), $\lambda_{max.}$ 259 mμ (log ε 4·0).

Acetolysis of 4 : 4-*Dimethylcholest*-5-*en*-3β-*yl Toluene*-p-*sulphonate*.—4 : 4-Dimethylcholest-5-en-3β-yl toluene-*p*-sulphonate (890 mg.) in acetic acid (40 ml.) containing anhydrous potassium acetate (8 g.) was heated at 95° for 3 hr. The product after isolation in ether was hydrolysed with 5% methanolic potassium hydroxide (40 ml.), and the resulting oil chromatographed on aluminium oxide (24 g.). Elution with pentane (2 × 100 ml.) gave 3-*iso*propylidene-A-norcholest-5-ene (448 mg.), m. p. 79—81° (from ethyl acetate–methanol), $[\alpha]_D$ −64° (*c* 2·0). Elution with chloroform gave solid 4 : 4-dimethylcholest-5-en-3β-ol (198 mg.), needles (from acetone), m. p. 141—144°, $[\alpha]_D$ −61° (*c* 0·7).

Lanosta-8 : 24-*dien*-3β-*yl Toluene*-p-*sulphonate*.—Lanosta-8 : 24-dien-3β-ol (3·5 g.) in pyridine (30 ml.) was treated at 0° with toluene-*p*-sulphonyl chloride (3 g.) and left overnight. The product, an oil (4·7 g.), crystallised from ethyl acetate as needles, m. p. 116—122°. Recrystallisation from pentane at 0° gave *lanosta*-8 : 24-*dien*-3β-*yl toluene*-p-*sulphonate*, m. p. 119—124°, $[\alpha]_D$ +42·6° (*c* 0·9) [Found (after drying at 40°/0·02 mm. for 18 hr.): C, 76·3; H, 50·0. $C_{37}H_{56}O_3S$ requires C, 76·5; H, 9·7%].

Acetolysis of Lanosta-8 : 24-*dien*-3β-*yl Toluene*-p-*sulphonate*.—Lanosta-8 : 24-dien-3β-yl toluene-*p*-sulphonate (2·06 g.) in acetic acid (40 ml.) containing anhydrous potassium acetate (2 g.) was heated at 95° for 3 hr. The product, an oil, was hydrolysed by refluxing 5% methanolic potassium hydroxide (40 ml.) for 1 hr. The resulting solid was chromatographed on aluminium oxide (40 g.). Elution with pentane (2 × 200 ml.) gave 3-iso*propylidene*-A-*norlanosta*-8 : 24-*diene* (1·21 g.), m. p. 134—136° (from ethyl acetate), $[\alpha]_D$ +81° (*c* 0·9). Elution with ether and chloroform gave lanosterol (291 mg.), m. p. 138—139° (from ether–methanol), $[\alpha]_D$ +56°, +54° (*c* 1·1, 1·2). The infrared spectrum was identical with that of a pure specimen of lanosterol.

3-iso*Propylidene*-A-*norlanosta*-8 : 24-*diene*.—Lanosterol (995 mg.) in hexane (100 ml.) was shaken with phosphorus pentachloride (1 g.) for 0·5 hr., then added to a column of aluminium oxide (20 g.) in hexane and eluted with hexane, to give 3-*iso*propylidene-A-norlanosta-8 : 24-diene, m. p. 138—140° (from acetone), $[\alpha]_D$ +82° (*c* 0·9) [Found (after drying at 40°/0·02 mm. for 18 hr.): C, 88·2; H, 11·9. Calc. for $C_{30}H_{48}$: C, 88·2; H, 11·8%].

UNIVERSITY COLLEGE OF SWANSEA, UNIVERSITY OF WALES. [*Received, October* 15*th*, 1958.]