224. *The Synthesis of Lanosterol (Lanostadienol).*

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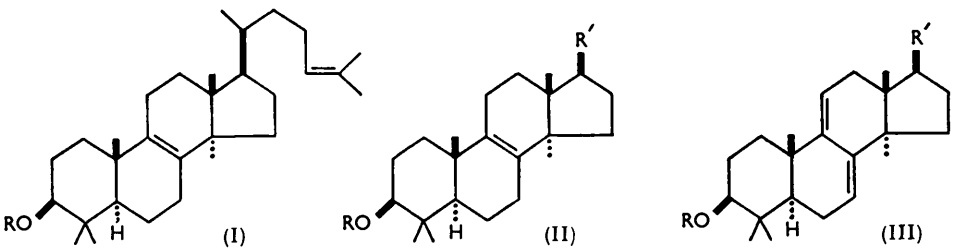
Cholesterol has been converted in a series of steps (*a*) into 14-methylcholestanol, identical with material obtained earlier from lanostenol, and (*b*) into lanostenol. By further processes the latter has been transformed into lanosterol (lanosta-8 : 24-dienol) and agnosterol [lanosta-7 : 9(11) : 24-trienol]. These changes, coupled with the already known conversion of lanostenol into γ-lanosterol [lanosta-7 : 9(11)-dienol], represent total syntheses of all four wool-fat triterpenoids.

THE triterpenoid fraction of wool fat consists of four alcohols : lanosterol (lanosta-8 : 24-dienol) (I; R = H) and lanostenol (II; R = H, R′ = C_8H_{17}) which are present in major amount, and agnosterol [lanosta-7 : 9(11) : 24-trienol] (III; R = H, R′ = C_8H_{15}) and γ-lanosterol [lanosta-7 : 9(11)-dienol] (III; R = H, R′ = C_8H_{17}) which are present in minor amount.[1] The constitutions of these compounds have been established by degradation [2] and by *X*-ray crystallography.[3] The relative stereochemistry was also established in the latter investigations as well as by chemical [4] and biochemical [5] considerations. The absolute stereochemistry, already proposed from molecular-rotation arguments,[6] was also supported by these biochemical considerations. We now report (for preliminary communications see ref. 7) the conversion of cholesterol into all four wool-fat triterpenoids. This work not only provides an unambiguous confirmation for



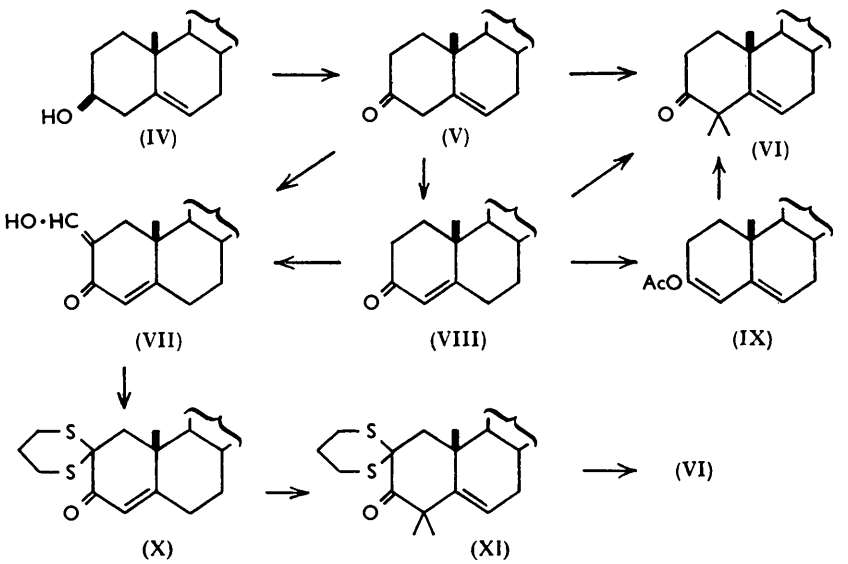
all the conclusions summarised in the references cited above but, having regard to the total syntheses of cholesterol already effected,[8] also constitutes a total synthesis of all four wool-fat triterpenoids.[9]

We consider first the introduction of the *gem.*-dimethyl grouping into ring A of cholesterol (IV). Cholesterol can be readily converted through cholest-5-en-3-one (V) and cholest-4-en-3-one (VIII) (for rapid and convenient procedures for the preparation of

[1] For summary, see Elsevier's " Encyclopaedia of Organic Chemistry," Vol. 14 and supplement.
[2] Voser, Mijovic, Heusser, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 2414, and many earlier papers; Cavalla, McGhie, and Pradhan, *J.*, 1951, 3142, and earlier papers; Barnes, Barton, Cole, Fawcett, and Thomas, *J.*, 1953, 571, and earlier papers.
[3] Curtis, Fridrichsons, and Mathieson, *Nature*, 1952, **170**, 321; Fridrichsons and Mathieson, *J.*, 1953, 2159.
[4] Barnes, Barton, Fawcett, and Thomas, *J.*, 1953, 576.
[5] Kyburz, Riniker, Schenk, Heusser, and Jeger, *Helv. Chim. Acta*, 1953, **36**, 1891; Woodward and Bloch, *J. Amer. Chem. Soc.*, 1953, **75**, 2023.
[6] Klyne, *J.*, 1952, 2916.
[7] Woodward, Patchett, Barton, Ives, and Kelly, *J. Amer. Chem. Soc.*, 1954, **76**, 2852; Barton, Ives, Kelly, Woodward, and Patchett, *Chem. and Ind.*, 1954, 605.
[8] Woodward, Sondheimer, and Taub, *J. Amer. Chem. Soc.*, 1951, **73**, 3548; Woodward, Sondheimer, Taub, Heusler, and McLamore, *ibid.*, 1952, **74**, 4223; Cardwell, Cornforth, Duff, Holtermann, and Robinson, *J.*, 1953, 361.
[9] Cf. Halsall and Thomas, *J.*, 1956, 2431.

these ketones see ref. 10) into the enol acetate [11] (IX). Treatment of the acetate with potassium amide and methyl iodide in liquid ammonia [12] afforded, albeit in poor yield, 4 : 4-dimethylcholestenone (VI). An alternative methylation procedure using potassium *tert.*-butoxide and methyl iodide (see below) gave a much superior yield of the desired ketone (VI).

The methods of synthesis of (VI) indicated above do not, within the limits of microanalysis, define its constitution unambiguously. A proof of constitution was achieved by the following stepwise synthesis. Cholest-4-en-3-one (VIII) was converted into its hydroxymethylene derivative [13] (VII), and the latter treated with the ditoluene-*p*-sulphonate of propane-1 : 3-dithiol in the presence of potassium acetate, a procedure developed by one of us (R. B. W.) in collaboration with Dr. Irwin Pachter, to give the dithioketal (X). Methylation of this compound with potassium *tert.*-butoxide and methyl iodide furnished (XI), the constitution of which is defined by the absence of an αβ-unsaturated ketone band in the ultraviolet spectrum. Removal of the dithioketal protecting grouping with Raney nickel gave 4 : 4-dimethylcholestenone (VI) of defined constitution.

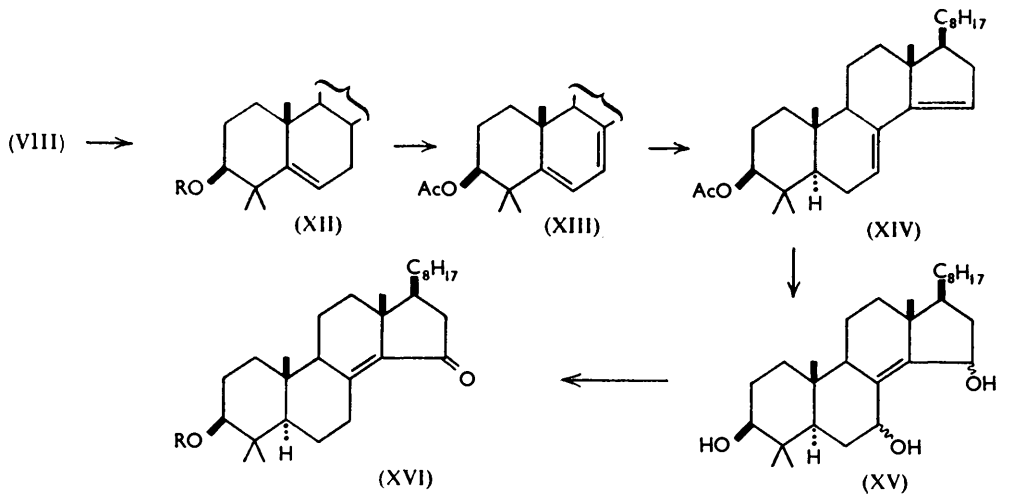


The most convenient synthesis of the ketone (VI) was finally realised in direct methylation of the precursors (V) or (VIII) by potassium *tert.*-butoxide and methyl iodide under carefully defined conditions. The yield from either ketone was in excess of 60%.

In order to effect methylation at $C_{(14)}$ along the lines developed above for methylation at $C_{(4)}$, it was conceived that the 15-oxo-$\Delta^{8(14)}$-system would constitute a suitable intermediate, especially as a convenient route to such compounds had been reported.[14] The desired 3β-hydroxy-4 : 4-dimethylcholest-8(14)-en-15-one (XVI; R = H) was obtained in the following way. Reduction of 4 : 4-dimethylcholestenone (VI) with lithium aluminium hydride gave 4 : 4-dimethylcholesterol (XII; R = H), characterised as its acetate (XII; R = Ac). Treatment of the latter with *N*-bromosuccinimide in carbon tetrachloride solution and then with collidine [15] afforded 7-dehydro-4 : 4-dimethylcholesteryl

[10] Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 5421.
[11] Westphal, *Ber.*, 1937, **70**, 2128.
[12] Cf. Birch, Quartey, and Smith, *J.*, 1952, 1768, and references there cited.
[13] Burr, Holton, and Webb, *J. Amer. Chem. Soc.*, 1950, **72**, 4903.
[14] Barnes, Barton, and Laws, *Chem. and Ind.*, 1953, 616; Barton and Laws, *J.*, 1954, 52.
[15] Cf. Bide, Henbest, Jones, Peevers, and Wilkinson, *J.*, 1948, 1783; Buisman, Stevens, and Vliet, *Rec. Trav. chim.*, 1947, **66**, 83; Redel and Gauthier, *Bull. Soc. chim. France*, 1948, 607; Antonucci, Bernstein, Littell, Sax, and Williams, *J. Org. Chem.*, 1952, **17**, 1341.

acetate (XIII). The constitution of the latter acetate was established by its ultraviolet absorption spectrum [$\lambda_{max.}$ 273 and 282 mμ (ε = 11,200 and 11,000 respectively)], its strong negative rotation ([α]$_D$ − 107°), and its mode of preparation. Treatment of this acetate with hydrogen chloride in chloroform at −40° and then with anhydrous ammonia in methanol at −60° furnished 4 : 4-dimethylcholesta-7 : 14-dienyl acetate (XIV), the constitution of which is established by analogy [16] and by its further reactions (see below). Reaction of this with perphthalic acid, followed by saponification, gave a triol which, from analogy,[14] is formulated as 4 : 4-dimethylcholest-8(14)-ene-3β : 7ξ : 15ξ-triol (XV). This triol was very insoluble in chloroform, which fact greatly facilitated its purification. Its dehydration with ethanolic hydrochloric acid gave the desired 3β-hydroxy-4 : 4-dimethylcholest-8(14)-en-15-one (XVI; R = H), characterised as the derived benzoate.



Whilst these experiments were in hand parallel studies on the methylation of the 15-oxo-$\Delta^{8(14)}$-system in known compounds were being prosecuted. Although treatment of 15-oxoergosta-8(14) : 22-dien-3β-yl acetate (XVII; R = Ac, R′ = C_9H_{17}) with only a slight excess of potassium *tert.*-butoxide and methyl iodide (conditions for preparing 4 : 4-dimethylcholestenone : see above) gave unchanged starting material, methylation by means of a very large excess of the *tert.*-butoxide (approx. 50 mols.) and methyl iodide (approx. 70 mols.) afforded 3β-methoxy-14-methylergosta-7 : 22-dien-15-one (XVIII; R = Me, R′ = C_9H_{17}) in moderate yield. This compound showed infrared maxima (in CCl_4 solution) at 1738 (*cyclo*pentanone), 1104 (C–O–C of methyl ether), 962 (*trans*-CH=CH– in side chain) and 1410 cm.$^{-1}$ (CH_2·CO in five-membered ring) in agreement with the assigned constitution. By chromatography of the reaction product 14-methyl-15-oxoergosta-7 : 22-dien-3β-yl acetate (XVIII; R = Ac, R′ = C_9H_{17}), characterised by hydrolysis to the corresponding alcohol (XVIII; R = H, R′ = C_9H_{17}), could also be isolated. The acetate was, however, the minor product of the reaction. The 15-oxo-grouping in these compounds was sterically hindered and could not be removed by Wolff–Kishner reduction under ordinary conditions. Thus attempted reduction of the ether (XVIII; R = Me, R′ = C_9H_{17}) gave only the corresponding alcohol (XIX; R = Me, R′ = C_9H_{17}, R″ = H) which was characterised as the acetate (XIX; R = Me, R′ = C_9H_{17}, R″ = Ac). The configuration of the hydroxyl group is regarded as probably α on the basis of conformational (see ref. 14) and molecular-rotation (see ref. 17) considerations. However, application of the modified Wolff–Kishner reduction conditions

[16] Cf. Barton and Brooks, *J.*, 1951, 277.
[17] Klyne and Stokes, *J.*, 1954, 1979.

of Barton, Ives, and Thomas,[18] which are specially suited for the reduction of hindered ketones, afforded without difficulty 3β-methoxy-14-methylergosta-7 : 22-diene (XX; R = Me, R′ = C_9H_{17}), characterised by hydrogenation over palladised calcium carbonate to 3β-methoxy-14-methylergost-7-ene (XX; R = Me, R′ = C_9H_{19}). The assignment of the nuclear ethylenic linkage to the 7(8)- rather than 8(9)-position in these and related compounds (see below) was based originally on molecular-rotation considerations. The assignment is, however, rigidly established by further transformations outlined in the sequel.

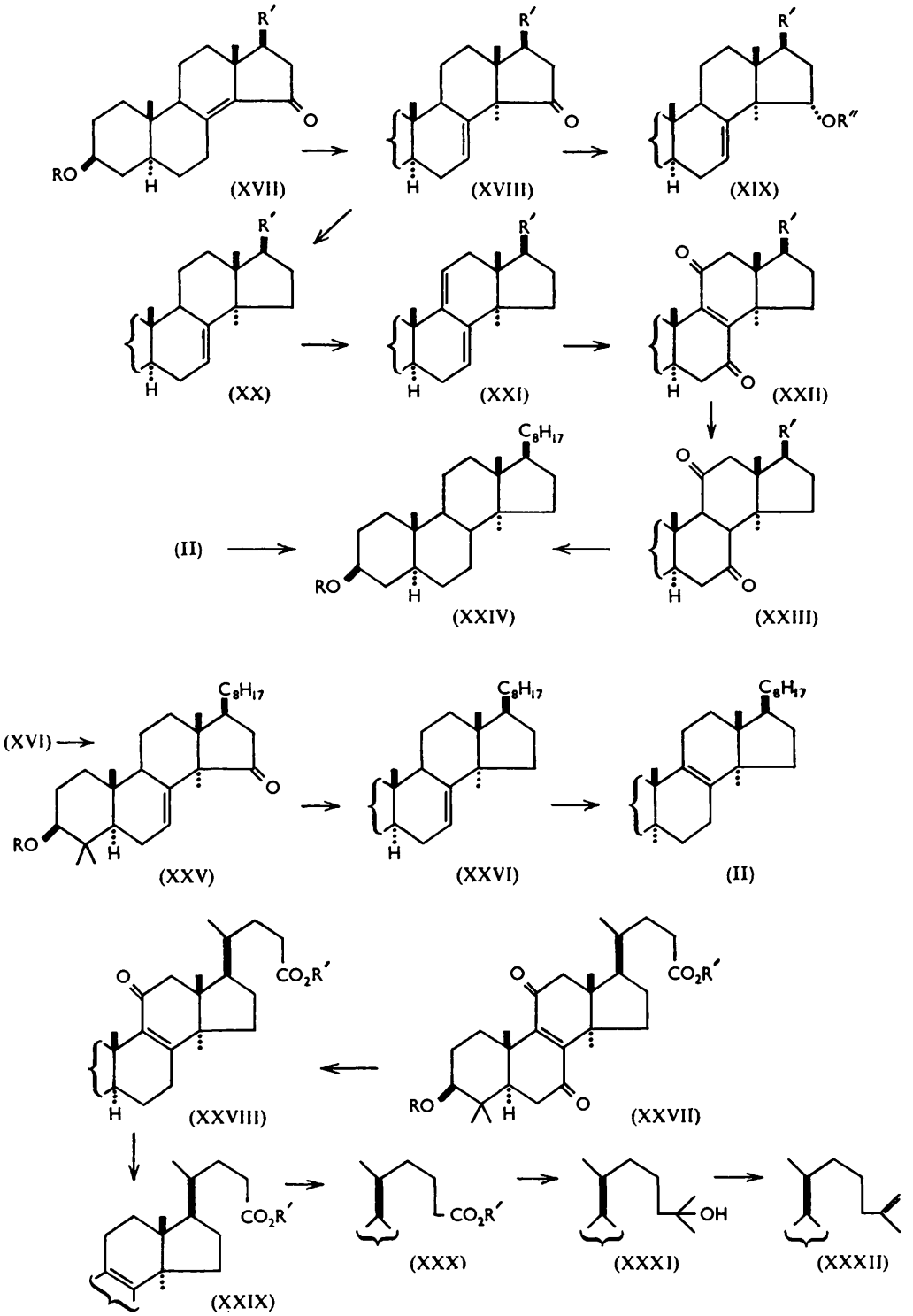
Under analogous conditions 15-oxocholest-8(14)-en-3β-yl acetate (XVII; R = Ac, R′ = C_8H_{17}) was converted into 3β-methoxy-14-methylcholest-7-en-15-one (XVIII; R = Me, R′ = C_8H_{17}) and thence into 3β-methoxy-14-methylcholest-7-ene.

Although the desired methylation at $C_{(14)}$ had been effected in the above-mentioned compounds, the concomitant methylation at $C_{(3)}$ precluded any direct comparison with lanostenol derivatives. In order to protect the 3-hydroxyl group, methylation of the appropriate benzoates was investigated. Methylation of 15-oxoergosta-8(14) : 22-dien-3β-yl benzoate (XVII; R = Bz, R′ = C_9H_{17}), prepared essentially according to the method of Barton and Laws,[14] gave 14-methyl-15-oxoergosta-7 : 22-dien-3β-yl benzoate (XVIII; R = Bz, R′ = C_9H_{17}) which was smoothly reduced by the modified Wolff–Kishner method to 14-methylergosta-7 : 22-dien-3β-ol (XX; R = H, R′ = C_9H_{17}). The way was now clear for direct inter-relation of cholesterol and lanostenol through the known 14-methylcholestanol.[19] To this end 15-oxocholest-8(14)-en-3β-yl benzoate (XVII; R = Bz, R′ = C_8H_{17}) was methylated to give 14-methyl-15-oxocholest-7-en-3β-yl benzoate, reduction of which afforded, after rebenzoylation, 14-methylcholest-7-en-3β-yl benzoate (XX; R = Bz, R′ = C_8H_{17}). In a second reduction the crude product was acetylated to give the corresponding acetate (XX; R = Ac, R′ = C_8H_{17}). Oxidation of 14-methylcholest-7-en-3β-yl benzoate (XX; R = Bz, R′ = C_8H_{17}) with selenium dioxide afforded the derived 7 : 9(11)-diene (XXI; R = Bz, R′ = C_8H_{17}) which, without isolation, was oxidised further with chromium trioxide to furnish 14-methyl-7 : 11-dioxocholest-8-en-3β-yl benzoate (XXII; R = Bz, R′ = C_8H_{17}). Treatment of this compound with zinc dust and acetic acid gave 14-methyl-7 : 11-dioxocholestan-3β-yl benzoate (XXIII; R = Bz, R′ = C_8H_{17}), further reduced by the modified Wolff–Kishner method [18] to give, after rebenzoylation, 14-methylcholestan-3β-yl benzoate (XXIV; R = Bz), identical with a specimen prepared by benzoylation of the known 14-methylcholestanol obtained by degradation of lanostenol.[19] The identity was confirmed by comparison of the appropriate alcohols (XXIV; R = H) and acetates (XXIV; R = Ac).

With these preliminaries completed we return to the direct route from cholesterol to lanostenol. Methylation of 4 : 4-dimethyl-15-oxocholest-8(14)-en-3β-yl benzoate (XVI; R = Bz) (see above) gave the expected 4 : 4 : 14-trimethyl-15-oxocholest-7-en-3β-yl benzoate (XXV; R = Bz), which was reduced by the modified Wolff–Kishner method [18] to lanost-7-enol (XXVI; R = H).[20] The identity was established by a detailed comparison of the alcohols and of the derived acetates. Lanost-7-enol, in which the position of the ethylenic linkage has been rigidly established,[21] was then converted into its benzoate which, on treatment with hydrogen chloride in chloroform, gave, on careful chromatography, some lanostenyl benzoate (II; R = Bz). The identity of the latter was established by direct comparison and also by hydrolysis to lanostenol (II; R = H) and conversion of this into its acetate (II; R = Ac). The oxidation of lanostenol to γ-lanosterol (dihydroagnosterol) (III; R = H, R′ = C_8H_{17}) has been reported on many previous occasions.[1]

With the successful completion of the synthesis of the two wool-fat triterpenoids with saturated side chains, attention was directed to the conversion of lanostenol (II; R = H, R′ = C_8H_{17}) into lanosterol (II; R = H) and agnosterol (III; R = H, R′ = C_8H_{15}).

[18] Barton, Ives, and Thomas, *J.*, 1955, 2056.
[19] *Idem*, *J.*, 1954, 903.
[20] Marker, Wittle, and Mixon, *J. Amer. Chem. Soc.*, 1937, **59**, 1368.
[21] Cavalla, McGhie, and Pradhan, *J.*, 1951, 3142; Barton, Fawcett, and Thomas, *J.*, 1951, 3147.


R′
RO
O
H
(XVII)
(XVIII)
OR″
(XIX)
(XX)
(XXI)
(XXII)
(II)
C_8H_{17}
(XXIV)
(XXIII)
(XVI)
(XXV)
(XXVI)
(II)
CO_2R'
(XXVIII)
(XXVII)
(XXIX)
(XXX)
OH
(XXXI)
(XXXII)

Vigorous oxidation of lanosteryl acetate with chromic acid gave, although in poor yield, the known 7 : 11-dioxotrisnorlanostenoloic acid acetate (XXVII; R = Ac, R′ = H), giving on hydrolysis the alcohol (XXVII; R = R′ = H) and by methylation the acetate methyl ester (XXVII; R = Ac, R′ = Me). The compounds of this series are more conveniently available by chromic acid oxidation of suitable derivatives of technical " lanosterol " (see ref. 22). Wolff–Kishner reduction of methyl 7 : 11-dioxotrisnorlanostenoloate acetate (XXVII; R = Ac, R′ = Me) under Huang-Minlon conditions [23] furnished, after remethylation and reacetylation, methyl 11-oxotrisnorlanost-8-enoloate acetate (XXVIII; R = Ac, R′ = Me). Further Wolff–Kishner reduction of the latter under the modified conditions of Barton, Ives, and Thomas [18] afforded, after remethylation and reacetylation, methyl trisnorlanost-8-enoloate acetate (XXIX; R = Ac, R′ = Me). The two stage Wolff–Kishner reduction is essential since the application of the vigorous conditions of Barton, Ives, and Thomas [18] to 7 : 11-dioxolanostenyl acetate directly afforded only the *saturated* lanostanol. The position of the ethylenic linkage in the ester (XXIX; R = Ac, R′ = Me) was established by the fact that technical " lanosteryl acetate " could be ozonised at −60° in chloroform to afford, after further oxidation at room temperature with potassium permanganate, an acid fraction which on methylation furnished a methyl trisnorlanost-8-enoloate acetate of defined constitution and identical with that obtained by the Wolff–Kishner reduction technique outlined above. The ozonolysis procedure is, in fact, the more convenient preparative technique.

Of the various possible methods for building up again the lanosterol side chain the scheme summarised in the sequel seemed the most promising. Methyl trisnorlanost-8-en-oloate acetate was hydrolysed and then reacetylated to give trisnorlanost-8-enoloic acid acetate (XXIX; R = Ac, R′ = H). This was converted into the acid chloride by Wilds and Schunk's method [24] and this then subjected to Arndt–Eistert homologation in methanol solution, to give methyl bisnorlanost-8-enoloate acetate (XXX; R = Ac, R′ = Me). Reaction of the latter with an excess of the methyl Grignard reagent furnished, after reacetylation, 3β-acetoxylanost-8-en-25-ol (XXXI; R = Ac). Dehydration of this by heating it with fuller's earth in xylene afforded a crystalline mixture shown by its infrared band at 885 cm.$^{-1}$ to be rich in the *iso*propenyl compound (XXXII; R = Ac). With the limited amount of material available it was not possible to define acidic conditions which would isomerise the *iso*propenyl group to the desired *iso*propylidene form without at the same time tending to equilibrate the nuclear ethylenic linkage between positions 7(8) and 8(9). The difficulty was overcome in the following way.

Methyl 11-oxotrisnorlanost-8-enoloate acetate (XXVIII; R = Ac, R′ = Me) was homologated to methyl 11-oxobisnorlanost-8-enoloate acetate (XXXIII; R = Ac, R′ = Me) exactly as in the scheme outlined above. Reaction with excess of the methyl Grignard reagent followed by reacetylation then afforded 3β-acetoxy-11-oxolanost-8-en-25-ol (XXXIV; R = Ac). Treatment of this alcohol with dioxan–sulphuric acid at room temperature gave 11-oxolanosta-8 : 24-dienyl acetate (XXXV; R = Ac), and thence the alcohol (XXXV; R = H). Wolff–Kishner reduction of the acetate (XXXV; R = Ac) under the modified conditions [18] afforded, after reacetylation, lanosteryl acetate (I; R = Ac), identical with an authentic specimen kindly supplied by Dr. J. F. McGhie (Chelsea Polytechnic).

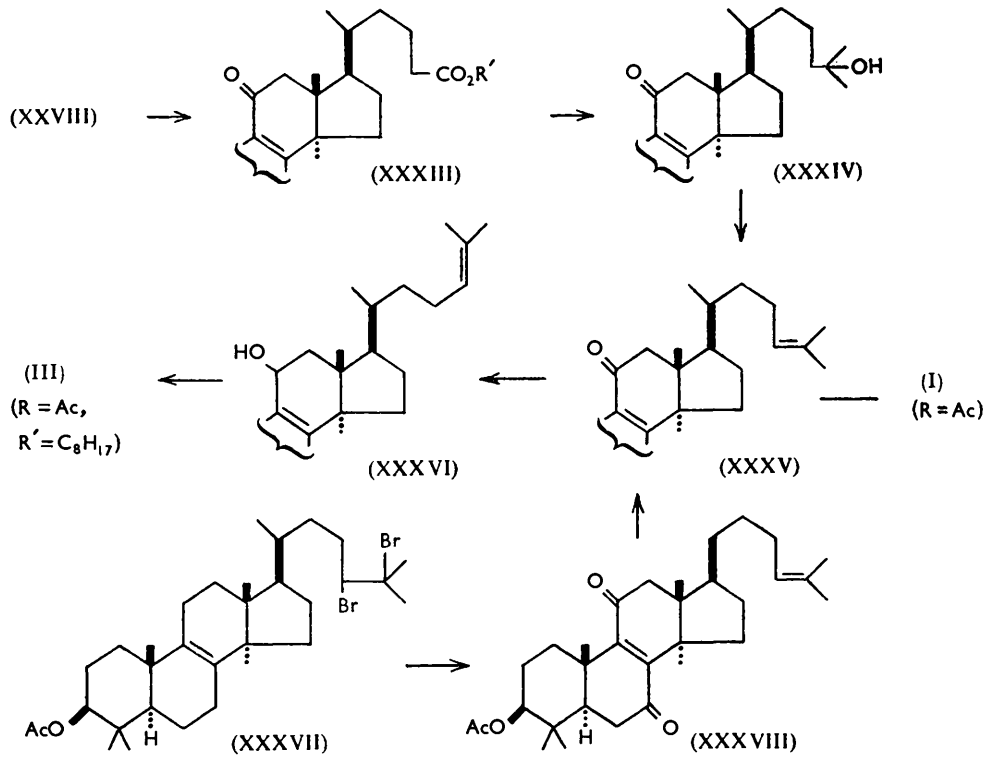
11-Oxolanosta-8 : 24-dien-3β-yl acetate was conveniently obtained from technical " lanosterol acetate " through the dibromide (XXXVII) * by chromic acid oxidation to

* We thank Dr. J. F. McGhie for his kindness in informing us of a convenient procedure for the preparation of this dibromide.[25] It is our understanding that Dr. McGhie and his colleagues have also obtained the diketone (XXXVIII) by a similar route to that described here.

[22] McGhie, Pradhan, Cavalla, and Knight, *Chem. and Ind.*, 1951, 1165; Voser, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 497.
[23] Huang-Minlon, *J. Amer. Chem. Soc.*, 1949, **71**, 3301.
[24] Wilds and Shunk, *J. Amer. Chem. Soc.*, 1950, **72**, 2388.
[25] Lewis and McGhie, *Chem. and Ind.*, 1956, 550.

the corresponding 7 : 11-diketone, which with sodium iodide gave the diketone (XXXVIII). Selective Wolff–Kishner reduction, followed by reacetylation, then afforded the desired 11-oxolanosta-8 : 24-dien-3β-yl acetate (XXXV; R = Ac).

The synthesis of the fourth wool-fat triterpenoid, agnosterol, was also secured by using this oxo-acetate. Reduction with lithium aluminium hydride furnished lanosta-8 : 24-



diene-3β : 11β-diol (XXXVI), converted when heated with acetic anhydride and a trace of toluene-*p*-sulphonic acid into the required agnosteryl acetate (III; R = Ac, R' = C_8H_{15}). A prior conversion of lanosterol into agnosterol does not appear to be recorded in the literature.

[*Added, January 12th,* 1957.—Dr. J. F. McGhie (Chelsea Polytechnic) has kindly informed us that, in collaboration with Dr. D. A. Lewis, he has also effected independently the conversion of lanosterol into agnosterol.]

Experimental

Rotations were determined in $CHCl_3$ solution, and ultraviolet absorption spectra in EtOH. Infrared spectra were determined either at Harvard or through the courtesy of Messrs. Glaxo Laboratories Ltd. Operations involving potassium *tert.*-butoxide were carried out under dry oxygen-free nitrogen.

4 : 4-*Dimethylcholest-5-en-3-one.*—(a) *From 3-acetoxycholesta-3 : 5-diene.* Potassium (1·54 g.) in liquid ammonia (500 ml.) was treated with a trace of ferric nitrate. When the blue colour had been discharged 3-acetoxycholesta-3 : 5-diene [11] (4·8 g.) in dry ether (40 ml.) was added. After 6 hours' stirring methyl iodide (4·0 ml.) was added. Two further additions of methyl iodide (17 ml. in all) were made during 45 min. The crude product in 95% ethanol (50 ml.) and concentrated hydrochloric acid (0·5 ml.) was refluxed for 20 min., then chromatographed over alumina (115 g.; Merck), to give mainly cholest-4-en-3-one with some 4 : 4-*dimethylcholest-5-en-3-one* (200 mg.), m. p. (from ethanol) 176—177°, $[\alpha]_D$ +1° (*c* 2·19) (Found : C, 84·15; H, 11·9. $C_{29}H_{48}O$ requires C, 84·4; H, 11·7%).

The enol-acetate is more efficiently methylated by the following procedure. The enol-acetate (24·2 g., 0·0567 mole) in dry *tert.*-butyl alcohol (450 ml.) was treated with potassium (0·17 mole) in the same solvent (130 ml.). Then methyl iodide (21·2 ml.) in dry *tert.*-butyl alcohol (30 ml.) was at once admitted under nitrogen. After 10 min. the solution was refluxed for 1 hr. Filtration of the product over alumina in 2 : 1 light petroleum–benzene and crystallisation from chloroform–95% ethanol gave 4 : 4-dimethylcholest-5-en-3-one (13·9 g.).

(b) *From* 2 : 2-*trimethylenedithiocholest-4-en-3-one*. 2-Hydroxymethylenecholest-4-en-3-one[13] (1·5 g.) and propane-1 : 3-dithiol ditoluene-*p*-sulphonate (1·9 g.; kindly supplied by Dr. Irwin Pachter) in warm absolute ethanol (26 ml.) were treated with anhydrous potassium acetate (2·53 g.) in absolute ethanol (7 ml.) under reflux for 7 hr. Filtration of the product in benzene over alumina, and crystallisation from acetone, gave the *dithioketal*, m. p. 161—165° (1·18 g.). Further purification in the same way afforded a product, m. p. 179—180° (Found: C, 73·75; H, 9·95. $C_{30}H_{48}OS_2$ requires C, 73·7; H, 9·9%). The dithioketal (800 mg.), suspended in dry *tert.*-butyl alcohol (40 ml.), was treated with potassium (350 mg.) in *tert.*-butyl alcohol (5 ml.) under nitrogen with stirring. Methyl iodide (0·82 ml.) in dry butyl alcohol (10 ml.) was added. After 3 min. the temperature was raised from 40° to the b. p. and the mixture refluxed for 1 hr. Chromatography of the product over alumina (26 g.; Merck) gave 2 : 2-*trimethylenedithio*-4 : 4-*dimethylcholest*-3-*one* (280 mg.). Recrystallised from acetone this had m. p. 178—179° (Found: C, 73·3; H, 9·9. $C_{32}H_{52}OS_2,Me_2CO$ requires C, 73·1; H, 10·15%). The dithioketal (103 mg.) in 95% ethanol (65 ml.) was refluxed for 6 hr. with Raney nickel (5 ml. of settled suspension; deactivated by refluxing for 3 hr. each with ethyl acetate and with acetone). Crystallisation of the product from 95% ethanol afforded 4 : 4-dimethylcholest-5-en-3-one (63 mg.) identical in m. p., mixed m. p., and infrared spectrum with material obtained as described under (a).

(c) *From cholest-4-en-3-one*. The ketone (9·58 g.) in dry *tert.*-butyl alcohol (160 ml.) at 40° was treated with a solution of potassium (2·92 g.) in the same solvent (60 ml.). At once methyl iodide (9·3 ml.) in dry *tert.*-butyl alcohol (10 ml.) was added and the mixture refluxed for 1 hr. Crystallisation of the product from chloroform–95% ethanol furnished 4 : 4-dimethylcholest-5-en-3-one (6·4 g.).

(d) *From cholest-5-en-3-one*. The ketone (79·6 g.) in dry *tert.*-butyl alcohol (1400 ml.) at 40° was treated with potassium (24·3 g.) in the same solvent (475 ml.). At once methyl iodide (77·5 ml.) was added and the mixture refluxed for 1 hr. Crystallisation of the product as above gave 4 : 4-dimethylcholest-5-en-3-one (53·8 g.).

4 : 4-*Dimethylcholesterol*.—4 : 4-Dimethylcholest-5-en-3-one (33·0 g.) in dry ether (2·6 l.) was added to lithium aluminium hydride (6·06 g.) in the same solvent (575 ml.) with vigorous stirring during 45 min. (gentle reflux). Crystallisation of the product from ether–methanol gave 4 : 4-*dimethylcholesterol* (25 g.), m. p. 144—146°. Recrystallised for analysis this compound had m. p. 150—151°, $[\alpha]_D$ −64° (*c* 1·16) (Found: C, 83·6; H, 11·85. $C_{29}H_{50}O$ requires C, 84·0; H, 12·15%). Acetylation with pyridine–acetic anhydride on the steam-bath for 35 min. gave the derived *acetate*, m. p. (from chloroform–methanol) 136—137°, $[\alpha]_D$ −48° (*c* 2·15) (Found: C, 81·2; H, 11·35. $C_{31}H_{52}O_2$ requires C, 81·5; H, 11·5%).

7-*Dehydro*-4 : 4-*dimethylcholesteryl Acetate*.—4 : 4-Dimethylcholesteryl acetate (10·0 g.) in carbon tetrachloride (150 ml.) was treated with finely powdered *N*-bromosuccinimide (4·68 g.; added in one portion) with good stirring. A previously heated oil-bath held at 90—95° was raised up so that the carbon tetrachloride solution was totally immersed. At the same time illumination from a GE sun-lamp was directed into the reaction mixture. After 7½ min. a yellow-green colour developed and the reaction became exothermic. After a further 45 sec. the lamp was turned off and the hot oil-bath quickly replaced by a pan of ice and water. The time required for the exothermic reaction to begin is variable, but it is important that the start be recognised and the reaction stopped within a minute of its commencement.

With the ice-bath in position stirring was continued for a further 5 min. and the cold solution then filtered into redistilled collidine (20 ml.). The carbon tetrachloride was removed *in vacuo*, more collidine (5 ml.) added, and the reaction mixture heated on the steam-bath for 1½ hr. Dilution with light petroleum (b. p. 60—80°) precipitated collidine hydrobromide (4·21 g., 95%). Repeated filtration of the resulting yellow-brown solution through Hy-Flo removed most of the colour. After washing of the filtrate with 5% hydrochloric acid, and 5% aqueous sodium carbonate, and drying ($MgSO_4$), removal of the solvent *in vacuo* and crystallisation from ether–methanol gave 7-*dehydro*-4 : 4-*dimethylcholesteryl acetate* (6·7 g., 67·5%). Recrystallised for

analysis from chloroform–methanol this had m. p. 151—152°, $[\alpha]_D$ −107° (*c* 1·27), $\lambda_{max.}$ 273 and 282 mμ (ε 11,200 and 11,000 respectively) (Found: C, 81·85; H, 11·0. $C_{31}H_{50}O_2$ requires C, 81·9; H, 11·1%).

4 : 4-*Dimethylcholesta*-7 : 14-*dien*-3β-*yl Acetate*.—7-Dehydro-4 : 4-dimethylcholesteryl acetate (3·0 g.) in chloroform (105 ml.) was treated with hydrogen chloride gas at −39° for 2 hr. The temperature was reduced to −60° and the hydrogen chloride neutralised by the addition of anhydrous ammonia in methanol at the same temperature. Crystallisation of the product from chloroform–methanol gave 4 : 4-*dimethylcholesta*-7 : 14-*dien*-3β-*yl acetate* (2·2 g.), m. p. 113—118°, $[\alpha]_D$ −136° (*c* 1·65). Recrystallisation changed the constants to m. p. 123—125°, $[\alpha]_D$ −132° (*c* 1·54), $\lambda_{max.}$ 244 mμ (ε 11,000) (Found: C, 82·2; H, 11·05. $C_{31}H_{50}O_2$ requires C, 81·9; H, 11·1%).

4 : 4-*Dimethylcholest*-8(14)-*ene*-3β : 7ξ : 15ξ-*triol*.—The mixture rich in 4 : 4-dimethylcholesta-7 : 14-dien-3β-yl acetate (see above) (3·0 g.) in anhydrous ether (150 ml.) was treated with monoperphthalic acid (1·372 g.) in the same solvent (24 ml.) at room temperature for 45 hr. The product (2·78 g.) in 95% ethanol (450 ml.) with potassium hydroxide (13 g.) was refluxed for 3 hr. and the ethanol removed *in vacuo*. After it had been washed with water, digestion of the product with chloroform (25 ml.) gave 4 : 4-*dimethylcholest*-8(14)-*ene*-3β-7ξ : 15ξ-*triol* (1·51 g.). Recrystallised from methanol this had m. p. 240—241° (Found: C, 77·75; H, 11·1. $C_{29}H_{50}O_3$ requires C, 77·95; H, 11·3%).

3β-*Hydroxy*-4 : 4-*dimethylcholest*-8(14)-*en*-15-*one*.—4 : 4-Dimethylcholest-8(14)-ene-3β : 7ξ : 15ξ-triol (1·51 g.), suspended in 95% ethanol (100 ml.) containing concentrated hydrochloric acid (5 ml.), was heated under reflux for 3 hr. Crystallisation of the product from aqueous ethanol gave 3β-*hydroxy*-4 : 4-*dimethylcholest*-8(14)-*en*-15-*one* (0·39 g.), m. p. 156—160°. Crystallisation from methanol afforded an analytical specimen of m. p. 161—162°, $[\alpha]_D$ +135° (*c* 1·44), $\lambda_{max.}$ 261 mμ (ε 14,700) (Found: C, 81·0; H, 11·1. $C_{29}H_{48}O_2$ requires C, 81·25; H, 11·3%). Treatment with pyridine–benzoyl chloride furnished the derived *benzoate*, m. p. (from 95% ethanol) 154—155°, $[\alpha]_D$ +137° (*c* 1·56), $\lambda_{max.}$ 232 and 260 mμ (ε 17,000 and 16,600 respectively) (Found: C, 80·85; H, 9·9. $C_{36}H_{52}O_3$ requires C, 81·15; H, 9·85%).

3β-*Hydroxy*-14-*methylergosta*-7 : 22-*dien*-15-*one and its Derivatives*.—To potassium (4·0 g.) in anhydrous *tert.*-butyl alcohol (70 ml.) there was added 15-oxoergosta-8(14) : 22-dien-3β-yl acetate [14] (500 mg.) in methyl iodide (10 ml.) in one portion. The solution was stirred at room temperature until neutral and the product reacetylated with pyridine–acetic anhydride on the steam-bath for 1 hr. Chromatography over alumina and elution with 1 : 1 light petroleum (b. p. 40—60°)–benzene gave 3β-*methoxy*-14-*methylergosta*-7 : 22-*dien*-15-*one*, m. p. (from methanol) 124—126°, $[\alpha]_D$ +31° (*c* 0·97) (Found: C, 81·85; H, 10·85. $C_{30}H_{48}O_2$ requires C, 81·75; H, 11·0%). Further elution with benzene afforded 14-*methyl*-15-*oxoergosta*-7 : 22-*dien*-3β-*yl acetate*, m. p. (from aqueous methanol) 150—152°, $[\alpha]_D$ +31° (*c* 1·31) (Found: C, 79·65; H, 10·15. $C_{31}H_{48}O_3$ requires C, 79·4; H, 10·3%). Alkaline hydrolysis furnished 3β-*hydroxy*-14-*methylergosta*-7 : 22-*dien*-15-*one*, m. p. (from aqueous methanol) 161—162°, $[\alpha]_D$ +34° (*c* 0·94) (Found: C, 81·2; H, 10·85. $C_{29}H_{46}O_2$ requires C, 81·65; H, 10·85%).

3β-*Methoxy*-14-*methylergosta*-7 : 22-*diene and its Derivatives*.—3β-Methoxy-14-methylergosta-7 : 22-dien-15-one (100 mg.) was heated in a sealed tube for 14 hr. at 180° with sodium (200 mg.) in absolute ethanol (2 ml.) and anhydrous hydrazine (0·5 ml.). Chromatography of the product over alumina and elution with ether gave 3β-*methoxy*-14-*methylergosta*-7 : 22-*dien*-15(?α)-*ol*, m. p. (from methanol) 109—110° (Found: C, 81·2; H, 11·35. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·35%). Acetylation with pyridine–acetic anhydride on the steam-bath for 1 hr. afforded the *acetate*, m. p. (from chloroform–methanol) 129—130°, $[\alpha]_D$ +14° (*c* 1·06) (Found: C, 79·45; H, 10·3. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%).

In contrast, Wolff–Kishner reduction of 3β-methoxy-14-methylergosta-7 : 22-dien-15-one by the procedure of Barton, Ives, and Thomas [18] for the preparation of lanostanol gave 3β-*methoxy*-14-*methylergosta*-7 : 22-*diene* (70%), m. p. (from methanol) 99—100°, $[\alpha]_D$ −24° (*c* 1·50) (Found: C, 84·1; H, 11·55. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%).

3β-Methoxy-14-methylergosta-7 : 22-diene (400 mg.) was hydrogenated in ethyl acetate solution in presence of palladised calcium carbonate. Crystallisation of the product from chloroform–methanol afforded 3β-*methoxy*-14-*methylergost*-7-*ene*, m. p. 88—89°, $[\alpha]_D$ −5° (*c* 1·54) (Found: C, 84·3; H, 11·8. $C_{30}H_{52}O$ requires C, 84·05; H, 12·2%).

3β-*Methoxy*-14-*methylcholest*-7-*en*-15-*one*.—To potassium (2·5 g.) in *tert.*-butyl alcohol (50 ml.) there was added 15-oxocholest-8(14)-en-3β-yl acetate (800 mg.) in methyl iodide (8 ml.)

in one portion. The solution was stirred until neutral. Chromatography of the product over alumina and elution with benzene afforded 3β-*methoxy*-14-*methylcholest*-7-*en*-15-*one* (400 mg.), m. p. (from aqueous methanol) 86—87°, $[\alpha]_D$ +56° (*c* 0·92) (Found : C, 81·6; H, 11·2. $C_{29}H_{46}O_2$ requires C, 81·65; H, 10·85%). Wolff–Kishner reduction of this ketone as for the preparation of lanostanol [18] furnished 3β-*methoxy*-14-*methylcholest*-7-*ene* (80%), m. p. (from methanol) 66°, $[\alpha]_D$ +5° (*c* 1·66) (Found : C, 83·5; H, 12·0. $C_{29}H_{50}O$ requires C, 84·0; H, 12·15%).

14-*Methylergosta*-7 : 22-*dien*-3β-*ol and its Derivatives*.—Ergosta-7 : 14 : 22-trien-3β-yl benzoate (ergosterol B_3 benzoate) [16] (18·0 g.) was converted into 15-*oxoergosta*-8(14) : 22-*dien*-3β-*yl benzoate* (12·0 g.), m. p. (from ether–methanol) 175°, $[\alpha]_D$ +75° (*c* 1·50), $\lambda_{max.}$ 230 and 259 mμ (ε 21,100 and 16,800 respectively) (Found : C, 81·45; H, 9·45. $C_{35}H_{48}O_3$ requires C, 81·35; H, 9·35%), essentially by the method used by Barton and Laws [14] for the corresponding acetate but without separation into acid and neutral moieties.

To potassium (6·7 g.) in dry *tert.*-butyl alcohol (400 ml.) there was added 15-oxoergosta-8(14) : 22-dien-3β-yl benzoate (3·3 g.) in methyl iodide (35 ml.). The solution was stirred at room temperature until neutral (about 15 min.). Chromatography of the product over alumina (100 g.) and elution with mixtures of light petroleum (b. p. 40—60°) and benzene gave 14-*methyl*-15-*oxoergosta*-7 : 22-*dien*-3β-*yl benzoate* (1·2 g.), m. p. (from chloroform–methanol) 158—159°, $[\alpha]_D$ +36° (*c* 1·60), $\lambda_{max.}$ 229 mμ (ε 15,600) (Found : C, 81·05; H, 9·1. $C_{36}H_{50}O_3$ requires C, 81·45; H, 9·5%).

14-Methyl-15-oxoergosta-7 : 22-dien-3β-yl benzoate (500 mg.) was reduced by the Wolff–Kishner procedure as detailed by Barton, Ives, and Thomas [18] for the preparation of lanostanol. Crystallisation of the product from methanol gave 14-*methylergosta*-7 : 22-*dien*-3β-*ol* (300 mg., crude), m. p. 149—150°, $[\alpha]_D$ −15° (*c* 1·30) (Found : C, 84·1; H, 11·55. $C_{29}H_{48}O$ requires C, 84·4; H, 11·7%).

14-*Methylcholest*-7-*en*-3β-*yl Benzoate and its Derivatives*.—7-Dehydrocholesteryl benzoate (Messrs. Glaxo Laboratories Ltd.) (20 g.) was treated with hydrogen chloride gas as for the preparation of ergosta-7 : 14 : 22-trien-3β-yl benzoate.[16] The crude mixture of benzoates resulting after crystallisation from chloroform–methanol, was enriched in cholesta-7 : 14-dien-3β-yl benzoate {$[\alpha]_D$ −100° (*c* 1·67); (10 g.)}. This mixture was treated with perphthalic acid and the whole product further processed essentially according to the method of Barton and Laws.[14] The crude product (10 g.) was chromatographed over alumina. Elution with benzene gave 15-*oxocholest*-8(14)-*en*-3β-*yl benzoate* (3·8 g., pure), m. p. (from chloroform–methanol) 156°, $[\alpha]_D$ +103° (*c* 2·04), $\lambda_{max.}$ 230 and 258 mμ (ε 15,900 and 15,700 respectively) (Found : C, 80·7; H, 9·55. $C_{34}H_{48}O_3$ requires C, 80·9; H, 9·6%).

To potassium (5·0 g.) in dry *tert.*-butyl alcohol (250 ml.) there was added 15-oxocholest-8(14)-en-3β-yl benzoate (3·0 g.) in methyl iodide (30 ml.) in one portion. The solution was stirred until neutral. Chromatography of the product over alumina and elution with 1 : 1 light petroleum (b. p. 40—60°)–benzene afforded 14-*methyl*-15-*oxocholest*-7-*en*-3β-*yl benzoate* (670 mg.), m. p. (from chloroform–methanol) 145—147°, $[\alpha]_D$ +51° (*c* 0·50) (Found : C, 81·2; H, 9·75. $C_{35}H_{50}O_3$ requires C, 81·05; H, 9·7%).

14-Methyl-15-oxocholest-7-en-3β-yl benzoate (1·25 g.) was reduced by the Wolff–Kishner method as developed for the preparation of lanostanol.[18] The crude product was benzoylated with benzoyl chloride–pyridine and chromatographed over alumina. Elution with benzene afforded 14-*methylcholest*-7-*en*-3β-*yl benzoate* (750 mg.), m. p. (from chloroform–methanol) 174—176°, $[\alpha]_D$ +9° (*c* 1·20) (Found : C, 82·95; H, 10·4. $C_{35}H_{52}O_2$ requires C, 83·3; H, 10·4%). In a second experiment the crude alcohol was acetylated with pyridine–acetic anhydride to the *acetate*, m. p. (from chloroform–methanol) 95—96°, $[\alpha]_D$ +4° (*c* 1·19) (Found : C, 81·4; H, 11·15. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%).

14-*Methyl*-7 : 11-*dioxocholest*-8-*en*-3β-*yl Benzoate*.—14-Methylcholest-7-en-3β-yl benzoate (735 mg.) in glacial acetic acid (20 ml.) was refluxed with selenium dioxide (750 mg.) for 3 hr. The product, after filtration in benzene through a short column of alumina, was dissolved in glacial acetic acid (20 ml.) with addition of chromium trioxide (650 mg.) and heated at 90° for 2 hr. Chromatography of the neutral product over alumina and elution with benzene furnished 14-*methyl*-7 : 11-*dioxocholest*-8-*en*-3β-*yl benzoate* (280 mg.), m. p. (from chloroform–methanol) 180° (long needles), $[\alpha]_D$ +95° (*c* 1·44), $\lambda_{max.}$ 230 and 272 mμ (ε 16,600 and 9300 respectively) (Found : C, 78·75; H, 9·05. $C_{35}H_{48}O_4$ requires C, 78·9; H, 9·1%).

14-*Methyl*-7 : 11-*dioxocholestan*-3β-*yl Benzoate*.—14-Methyl-7 : 11-dioxocholest-8-en-3β-yl benzoate (220 mg.) in glacial acetic acid (15 ml.) was refluxed with zinc dust (250 mg.) for 1 hr.

Crystallisation of the product from chloroform–methanol gave 14-*methyl*-7 : 11-*dioxocholestan*-3β-*yl benzoate*, m. p. 168°, $[\alpha]_D$ +52° (*c* 1·50) (Found : C, 78·35; H, 9·75. $C_{35}H_{50}O_4$ requires C, 78·6; H, 9·4%).

Conversion of 14-*Methyl*-7 : 11-*dioxocholestan*-3β-*yl Benzoate into* 14-*Methylcholestan*-3β-*ol and its Derivatives.*—The diketone (420 mg.) was reduced by the modified Wolff–Kishner method as applied for the preparation of lanostanol.[18] Rebenzoylation of the product and crystallisation from chloroform–methanol gave 14-*methylcholestan*-3β-*yl benzoate* (280 mg.), m. p. 167—168°, $[\alpha]_D$ +32° (*c* 1·86), undepressed in m. p. on admixture with an authentic specimen of comparable physical constants prepared by benzoylation of the 14-methylcholestanol from lanostenol [19] (Found : C, 82·9; H, 10·8. $C_{35}H_{54}O_2$ requires C, 82·95; H, 10·75%). The identity was further checked by hydrolysis to 14-methylcholestanol {m. p., mixed m. p., and $[\alpha]_D$ +39° (*c* 1·28)} and by acetylation of the latter to 14-methylcholestanyl acetate (m. p. and mixed m. p.).

4 : 4 : 14-*Trimethyl*-15-*oxocholest*-7-*en*-3β-*yl Benzoate.*—To potassium (1·4 g.) in dry *tert.*-butyl alcohol (40 ml.) there was added 4 : 4-dimethyl-15-oxocholest-8(14)-en-3β-yl benzoate (see above) (326 mg.) in methyl iodide (5·25 ml.). The solution was stirred until neutral. The product, crystallised from chloroform–methanol, afforded 4 : 4 : 14-*trimethyl*-15-*oxocholest*-7-*en*-3β-*yl benzoate* (225 mg.), m. p. 212—213°, $[\alpha]_D$ +84° (*c* 1·42), $\lambda_{max.}$ 229, 273, and 281 mμ (ε 15,200, 1000, and 800 respectively) (Found : C, 80·95; H, 9·8. $C_{37}H_{54}O_3$ requires C, 81·25; H, 9·95%).

The 15-oxo-benzoate (see above) (100 mg.) was added to diethylene glycol (10 ml.) containing dissolved sodium (200 mg.) at 175°. Anhydrous hydrazine, prepared by refluxing 95% hydrazine for 7 hr. under nitrogen with an equal weight of sodium hydroxide pellets, was distilled in until the mixture refluxed at 175°. The refluxing was continued for 12 hr., then excess of hydrazine was distilled off until the temperature reached 210°, which temperature was then held for 24 hr. All operations were carried out under nitrogen in an all-glass apparatus protected against moisture. Crystallisation of the product from ether–methanol gave lanost-7-enol (52 mg.), identified by m. p., rotation {$[\alpha]_D$ +10° (*c* 1·45)}, and analysis (Found : C, 83·9; H, 12·15. Calc. for $C_{30}H_{52}O$: C, 84·05; H, 12·25%). The identity was confirmed by conversion into the acetate {m. p., mixed m. p., $[\alpha]_D$ +27° (*c* 1·27), infrared spectrum, and analysis (Found : C, 81·65; H, 11·55. Calc. for $C_{32}H_{54}O_2$: C, 81·45; H, 11·7%)}.

Lanost-7-enyl Benzoate and its Equilibrium with Lanost-8-enyl Benzoate.—Lanost-7-enol (prepared *via* the acetate according to Marker, Wittle, and Mixon [20]) was converted into the *benzoate* with pyridine–benzoyl chloride. Recrystallised from chloroform–methanol, this had m. p. 207—208°, $[\alpha]_D$ +51° (*c* 1·09) (Found : C, 83·3; H, 10·5. $C_{37}H_{56}O_2$ requires C, 83·4; H, 10·4%).

Lanost-7-enyl benzoate (1·0 g.) in dry chloroform (50 ml.) was treated with hydrogen chloride gas at room temperature for 2 hr. The product was carefully chromatographed over alumina. The first fraction (228 mg.), eluted with 4 : 1 light petroleum (b. p. 40—60°)–benzene, had m. p. (from chloroform–methanol) 193—195°, $[\alpha]_D$ +71° (*c* 1·80), undepressed in m. p. on admixture with an authentic specimen of m. p. 194—195° and $[\alpha]_D$ +71°. The identity was confirmed by hydrolysis to lanostenol {m. p., mixed m. p., and $[\alpha]_D$ +59° (*c* 1·35)} and by acetylation of the latter to lanostenyl acetate {m. p., mixed m. p. and $[\alpha]_D$ +60° (*c* 1·76)}.

Oxidation of Lanostenyl Acetate to 7 : 11-*Dioxotrisnorlanostenoloic Acid Acetate.*—7 : 11-Dioxolanostenyl acetate, prepared by oxidation of lanostenyl acetate [26] (28 g.) in glacial acetic acid (700 ml.) and acetic anhydride (28 ml.), was treated with chromium trioxide (60 g.) in water (70 ml.), acetic acid (280 ml.), and concentrated sulphuric acid (14 ml.), added slowly at room temperature, and the solution was stirred overnight. Dilution with water and extraction with benzene (washed well with water) gave a product (14 g.) which, on chromatography over alumina and elution with 4 : 1 methanol–acetic acid, gave 7 : 11-dioxotrisnorlanostenoloic acid acetate (4·6 g.), identified by m. p. (192—194°, from chloroform–light petroleum), mixed m. p., and rotation {$[\alpha]_D$ +96° (*c* 1·27)}. The identity was confirmed by alkaline hydrolysis to 7 : 11-dioxotrisnorlanostenoloic acid, identified by m. p. (202—204° from aqueous methanol), mixed m. p., and rotation {$[\alpha]_D$ +103° (*c* 1·19)}. The authentic specimens of acetate and alcohol [27] had m. p. 193—194°, $[\alpha]_D$ +96° (*c* 1·37), and m. p. 202—204°, $[\alpha]_D$ +103° (*c* 1·78), respectively. The identity was further confirmed by conversion of the acetate into the acetate methyl ester, identified by m. p. (140—142° from methanol), mixed m. p., and rotation {$[\alpha]_D$ +94° (*c* 2·06)}. The authentic acetate methyl ester [27] had m. p. 140—142°, $[\alpha]_D$ +94° (*c* 1·32).

[26] Ruzicka, Rey, and Muhr, *Helv. Chim. Acta*, 1944, **27**, 472.
[27] Voser, Jeger, and Ruzicka, *ibid.*, 1952, **35**, 497.

Methyl 11-Oxotrisnorlanost-8-enoloate Acetate.—Methyl 7 : 11-dioxotrisnorlanostenoloate acetate (see above) (5 g.) was heated with 60% hydrazine hydrate (5 ml.) in diethylene glycol (200 ml.) for 1 hr. at 200° under reflux. The solution was cooled and sodium (5 g.), dissolved in diethylene glycol (80 ml.), added; refluxing was continued for a further 6 hr. Methylation (diazomethane), acetylation (pyridine–acetic anhydride on the steam-bath for 1 hr.), and chromatography over alumina gave *methyl 11-oxotrisnorlanost-8-enoloate acetate* (2·1 g.), m. p. (from methanol) 145—149°, $[\alpha]_D$ +129° (*c* 1·64), $\lambda_{max.}$ 256 mμ (ε 7600) (Found: C, 74·1; H, 9·4. $C_{30}H_{46}O_5$ requires C, 74·05; H, 9·55%).

Methyl Trisnorlanost-8-enoloate Acetate.—(a) *From methyl 11-oxotrisnorlanost-8-enoloate acetate.* The ketone (see above) (2·1 g.) was added to a solution of sodium (1·0 g.) in diethylene glycol (50 ml.) at 180° and freshly prepared anhydrous hydrazine was distilled in until the solution refluxed freely. The refluxing was continued at 180° for 24 hr. and then the temperature was raised to 210° by distilling off hydrazine. The refluxing period at 210° was prolonged for a further 24 hr. The product, when methylated (diazomethane), acetylated (pyridine–acetic anhydride on the steam-bath for 1 hr.), and chromatographed, gave *methyl trisnorlanost-8-enoloate acetate* (700 mg.), m. p. (from chloroform–methanol) 174—176°, $[\alpha]_D$ +58° (*c* 1·65) (Found: C, 76·2; H, 10·35. $C_{30}H_{48}O_4$ requires C, 76·2; H, 10·25%). The application of the vigorous Wolff–Kishner reduction conditions to an 8-unsaturated 7 : 11-dioxo-compound directly, such as 7 : 11-dioxolanostenyl acetate, gave only the fully saturated compound (lanostanol) in approximately the same yield as starting with the saturated diketone (7 : 11-dioxolanostanyl acetate).

(b) *From "lanosteryl acetate."* "Lanosteryl acetate" (6·0 g.) (from acetylation of technical "lanosterol"), suspended in chloroform (250 ml.), was ozonised at −60° until the solution was clear. Zinc dust (1·0 g.) and acetic acid (20 ml.) were added and the solution was allowed to warm to room temperature with stirring. The crude product in "AnalaR" acetone (500 ml.) was treated with potassium permanganate (500 mg.) in water (20 ml.) and left at room temperature for 1½ hr. The excess of permanganate was destroyed with sulphur dioxide, and the solution diluted with water and extracted with benzene. The crude product was chromatographed over alumina. Elution with 4 : 1 methanol–acetic acid gave an acid fraction which on methylation (diazomethane) and filtration in benzene through alumina afforded methyl trisnorlanost-8-enoloate acetate (1·25 g.), m. p. 174—176°, $[\alpha]_D$ +58° (*c* 1·20), undepressed in m. p. on admixture with material prepared as under (*a*) above. The ozonolysis route is the more convenient procedure for the preparation of this compound.

Methyl Bisnorlanost-8-enoloate Acetate.—Methyl trisnorlanost-8-enoloate acetate (1·3 g.) was hydrolysed with 5% methanolic potassium hydroxide, and the resulting alcohol-acid reacetylated (pyridine–acetic anhydride on the steam-bath for 1 hr.). The acetate acid thus formed was left overnight in sodium-dried benzene (5 ml.) with oxalyl chloride [24] (1 ml.) at 0°. The benzene and excess of oxalyl chloride were removed *in vacuo* and the residual acid chloride in dry ether (100 ml.) was added slowly with good stirring to an excess of diazomethane in the same solvent. The solution was left at room temperature for 90 min. and the ether then removed *in vacuo* at the same temperature. The crude diazo-ketone in dry methanol (75 ml.) was treated with silver oxide (100 mg.) (see ref. 28) at 50° for 1 hr. and then refluxed for 15 min. The solvent was removed *in vacuo* and the product chromatographed over alumina in benzene, to give *methyl bisnorlanost-8-enoloate acetate* (750 mg.), m. p. (from chloroform–methanol) 133—134°, $[\alpha]_D$ +64° (*c* 1·75) (Found: C, 76·75; H, 10·25. $C_{31}H_{50}O_4$ requires C, 76·5; H, 10·35%).

3β-*Acetoxylanost-8-en-25-ol.*—Methyl iodide (7·5 g.) in dry ether (20 ml.) was added slowly to magnesium turnings (1·5 g.) under dry ether (80 ml.) and the mixture stirred and refluxed for 1 hr. Methyl bisnorlanost-8-enoloate acetate (see above) (1·0 g.) in dry ether (50 ml.) was added and the solution refluxed overnight. The crude product, after re-acetylation with pyridine–acetic anhydride on the steam-bath for 1 hr., was chromatographed over alumina. Elution with benzene gave 3β-*acetoxylanost-8-en-25-ol* (400 mg.), m. p. (from methanol) 167—169°, $[\alpha]_D$ +71° (*c*, 1·15) (Found: C, 78·95; H, 11·1. $C_{33}H_{54}O_3$ requires C, 78·95; H, 11·2%). The crystalline alcohol (220 mg.) in xylene (20 ml.) was refluxed for 4 hr. with activated fuller's earth (210 mg.). After filtration over alumina in 1 : 1 light petroleum (b. p. 40—60°)–benzene the product had m. p. (from chloroform–methanol) 145—155° and was clearly a mixture. It

[28] "Syntheses using Diazomethane," Newer Methods of Preparative Organic Chemistry, Interscience Publ., New York, 1948.

was depressed in m. p. on admixture with either the starting material or lanosterol acetate and showed a strong methylene band at 885 cm.$^{-1}$.

Methyl 11-Oxobisnorlanost-8-enoloate Acetate and Related Products.—Methyl 11-oxotrisnorlanost-8-enoloate acetate (see above) was converted *via* the corresponding acetate acid by Arndt–Eistert homologation into *methyl 11-oxobisnorlanost-8-enoloate acetate*, as described above for the 11-deoxo-analogue. Recrystallised from methanol, the 11-oxo-ester had m. p. 150—153°, $[\alpha]_D$ +127° (*c* 1·22) (Found: C, 74·45; H, 9·6. $C_{31}H_{48}O_5$ requires C, 74·35; H, 9·65%). It was treated with methylmagnesium iodide and further processed as described above, except that it was advantageous to carry out the reacetylation at room temperature overnight. Crystallisation of the chromatographed product from aqueous methanol afforded 3β-*acetoxy*-11-*oxolanost*-8-*en*-25-*ol*, m. p. 192—195°, $[\alpha]_D$ +133° (*c* 1·48) (Found: C, 76·9; H, 10·55. $C_{32}H_{52}O_4$ requires C, 76·75; H, 10·45%). This alcohol (200 mg.) in dioxan (42·5 ml.) and concentrated sulphuric acid (2·5 ml.) was left at room temperature overnight. The product was reacetylated for 1 hr. on the steam-bath with pyridine (2 ml.) and acetic anhydride (1 ml.). Chromatography over alumina in benzene and crystallisation from chloroform–methanol gave 11-oxolanosta-8 : 24-dienyl acetate (see below), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +125° (*c* 1·03)}. The identity was checked by hydrolysis to the corresponding alcohol (m. p. and mixed m. p.).

7 : 11-*Dioxolanosta*-8 : 24-*dienyl Acetate*.—Lanosterol acetate dibromide (main isomer, prepared according to directions kindly supplied by Dr. J. F. McGhie [25]) (9·0 g.), suspended in acetic acid (450 ml.), was treated at room temperature with chromium trioxide (10·0 g.) in the minimum of water. Concentrated sulphuric acid (4·5 ml.) was added cautiously and the solution stirred overnight at the same temperature. The solution was diluted with water and extracted with ether, and the ethereal layer washed with water. After removal of the ether *in vacuo* the crude product was filtered through alumina in 1 : 1 benzene–ether to remove acidic impurities. The eluted material in acetone (200 ml.) was refluxed for 4 hr. with sodium iodide (25 g.) in the same solvent (200 ml.). Dilution with water, extraction with benzene, washing with sodium thiosulphate solution (to remove iodine), and removal of the benzene *in vacuo* gave a crude product which, on crystallisation from methanol, afforded 7 : 11-*dioxolanosta*-8 : 24-*dien*-3β-*yl acetate* (2·1 g.), m. p. 143—144°, $[\alpha]_D$ +81° (*c* 1·13), $\lambda_{max.}$ 272 mμ (ε 9100) (Found: C, 76·9; H, 9·65. $C_{32}H_{48}O_4$ requires C, 77·35; H, 9·75%).

11-*Oxolanosta*-8 : 24-*dien*-3β-*yl Acetate*.—7 : 11-Dioxolanosta-8 : 24-dien-3β-yl acetate (see above) (2·0 g.) in diethylene glycol (100 ml.) and 60% hydrazine hydrate (2·5 ml.) were refluxed for 1 hr. Sodium (2·5 g.) in diethylene glycol (40 ml.) was added and the solution refluxed for a further 6 hr. The crude product was reacetylated with pyridine–acetic anhydride on the steam-bath and chromatographed over alumina to furnish 11-*oxolanosta*-8 : 24-*dien*-3β-*yl acetate* (850 mg.), m. p. (from aqueous methanol) 112—113°, $[\alpha]_D$ +125° (*c* 1·06) (Found: C, 79·65; H, 10·3. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·45%). Alkaline hydrolysis in the usual way gave 11-*oxolanosta*-8 : 24-*dien*-3β-*ol*, m. p. (from aqueous methanol) 135—136°, $[\alpha]_D$ +98° (*c* 0·57) (Found: C, 81·85; H, 11·15. $C_{30}H_{48}O_2$ requires C, 81·75; H, 11·0%).

11-Oxolanosta-8 : 24-dien-3β-yl acetate (450 mg.) was added to a solution of sodium (1·0 g.) in diethylene glycol (50 ml.). The solution was heated to 180° and anhydrous hydrazine (see above) distilled in until the solution refluxed at this temperature. The refluxing was continued overnight, the temperature raised to 210° by distilling out some of the hydrazine, and refluxing continued at this temperature for 24 hr. The crude product was reacetylated with pyridine–acetic anhydride on the steam-bath and then chromatographed over alumina in benzene solution. Crystallisation from chloroform–methanol gave lanosteryl (lanosta-8 : 24-dienyl) acetate, identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +58° (*c* 1·87)}.

Conversion of 11-*Oxolanosta*-8 : 24-*dien*-3β-*yl Acetate into Agnosteryl Acetate*.—The 11-oxo-acetate (1·0 g.) in sodium-dried ether (150 ml.) was refluxed with lithium aluminium hydride (750 mg.) for 4 hr. Crystallisation of the product from chloroform–methanol gave *lanosta*-8 : 24-*diene*-3β : 11β-*diol* (750 mg.), m. p. 153—155°, $[\alpha]_D$ +58° (*c* 1·19) (Found: C, 82·2; H, 11·6. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%). The diol (800 mg.) was refluxed in acetic anhydride (50 ml.) with toluene-*p*-sulphonic acid (10 mg.) for 1 hr. Filtration of the product in benzene through alumina afforded agnosteryl acetate [lanosta-7 : 9(11) : 24-trien-3β-yl acetate] (600 mg.), m. p. (from chloroform–methanol) 180—181°, $[\alpha]_D$ +90° (*c* 1·59), $\lambda_{max.}$ 236, 243, 252 mμ (ε 14,700, 17,400, and 11,400 respectively). The m. p., rotation, and absorption

intensity are all slightly higher [25] than the recorded constants.[29] However, the value of ε at $\lambda_{max.}$ 243 mμ corresponds almost exactly with that recorded for lanosta-7 : 9(11)-dien-3β-yl acetate.[30]

We are indebted to Messrs. Glaxo Laboratories Ltd. for a generous supply of pure 7-dehydrocholesterol. One of us (D. A. J. I.) thanks the International Wool Secretariat for a Pre-doctorate Fellowship. This work was carried out by another of us (A. A. P.) during the tenure of an Ethyl Corporation Pre-doctoral Fellowship. We also acknowledge the receipt of a Beaverbrook Scholarship (R. B. K.).

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[*Received, September 24th,* 1956.]

[29] Ruzicka, Denss, and Jeger, *Helv. Chim. Acta*, 1946, **29**, 204.
[30] Barton, Fawcett, and Thomas, *J.*, 1951, 3147.