379. *Triterpenoids. Part XII.* The Lanosterol Analogue of Provitamin D_3.*

By D. H. R. Barton and B. R. Thomas.

7-Ketolanostan-3β-yl acetate has been converted by selenium dioxide into 7-ketolanost-5-en-3β-yl acetate and thence by lithium aluminium hydride reduction followed by acid-catalysed dehydration into lanosta-5 : 7-dien-3β-ol. The stereochemistry of $C_{(7)}$ in lanostanol derivatives has been elucidated. Some miscellaneous reactions have been studied.

The solution of the constitutional and stereochemical problems posed by the lanostadienol (lanosterol) molecule, suggests that lanosterol analogues of physiologically active steroids might well prove of interest (see Barton, Proc. Ciba Conference on Adrenocortical Hormones, July, 1952). We now wish to report (for preliminary communication see Barton and Thomas, *Chem. and Ind.*, 1953, 172) the preparation of the lanosterol analogue (I; R = H) of provitamin D_3 (7-dehydrocholesterol) (II), as well as some related observations bearing on the chemistry of lanosterol.

7-Ketolanost-8-en-3β-yl acetate (III) (Birchenough and McGhie, *J.*, 1950, 1249; Cavalla and McGhie, *J.*, 1951, 744; and references there cited) was reduced by lithium in liquid ammonia (cf. Birch, *J.*, 1944, 430, and subsequent papers) to 7-ketolanostan-3β-yl acetate (IV; R = Ac), identical with the ketone obtained previously (Barton, Fawcett, and Thomas, *J.*, 1951, 3147) by the action of perbenzoic acid on lanost-7-en-3β-yl acetate (V). In the latter the configuration at $C_{(9)}$ must be the more stable α, since it is prepared under equilibrating conditions. The configuration at $C_{(8)}$ in (IV; R = Ac) must be β- because, as shown by its stability towards attempted isomerisation by alkali (see Experimental section), it represents the more stable arrangement.

Oxidation of (IV; R = Ac) by selenium dioxide in acetic acid gave 7-ketolanost-5-en-3β-yl acetate (VI) in excellent yield. Lithium aluminium hydride reduction of (VI), followed by controlled treatment with aqueous dioxan–sulphuric acid and then acetylation or benzoylation, gave, respectively, lanosta-5 : 7-dien-3β-yl acetate (I; R = Ac) or benzoate (I; R = Bz). From these operations 7-ketolanostan-3β-yl acetate (IV; R = Ac) or benzoate (IV; R = Bz) was also isolated. The latter was identical with a specimen prepared directly from the corresponding acetate. Alkaline hydrolysis of (I; R = Ac) gave lanosta-5 : 7-dien-3β-ol (I; R = H).

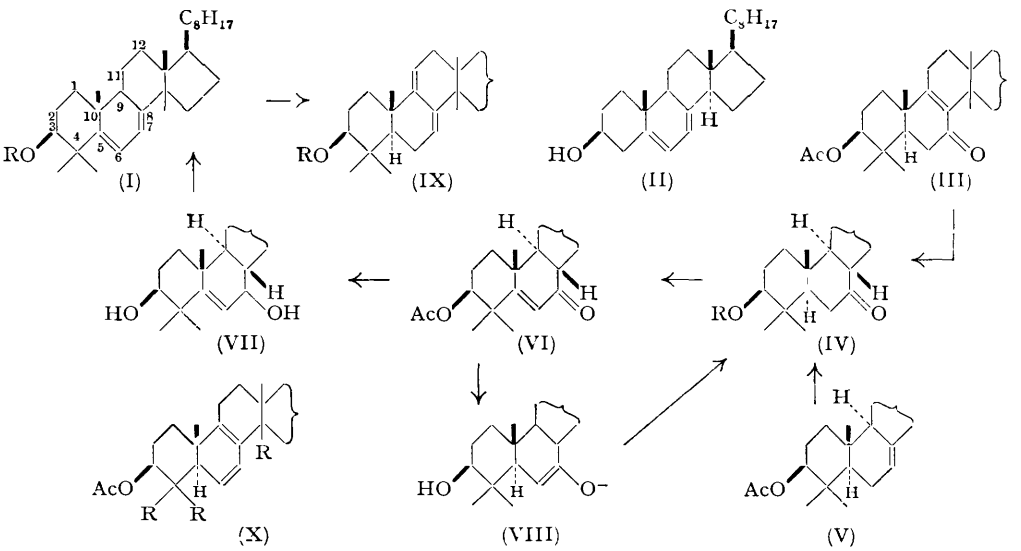
The mechanism for the re-formation of (IV) in the lithium aluminium hydride reduction was studied further. The crude reduction product showed a saturated ketone band in the infra-red at 1705 $cm.^{-1}$. Acetylation of the crude product and chromatography without acid treatment gave (IV; R = Ac). It can be concluded that (VI) is attacked by lithium aluminium hydride in two ways : (*a*) addition of hydride ion at $C_{(7)}$ produces the allylic alcohol (VII) [subsequently transformed by acid-catalysed dehydration into (I; R = H)]

* Part XI, *J.*, 1953, 1419.

and (*b*) addition of hydride ion at $C_{(5)}$ with consequent electronic displacements produces the anion (VIII) which resists further reduction.

The constitution assigned to (I) is supported by the following evidence. (i) Treatment of (I; R = Ac) with hydrogen chloride in chloroform gave lanosta-7 : 9(11)-dien-3β-yl acetate (IX; R = Ac). (ii) In the infra-red (I; R = Ac) showed bands at 1732 and 1238 cm.$^{-1}$ due to the acetate residue, and at 1640, 830 and 810 cm.$^{-1}$, due to $-CH{=}C<$. This spectrum excludes the alternative formulation (X; R = Me) which is otherwise consistent with the ultra-violet absorption spectrum and the mode of formation. Furthermore the analogous *iso*dehydrocholesterol acetate (X; R = H) (Windaus, Linsert, and Eckhardt, *Annalen*, 1938, **534**, 22) showed bands at 1735 and 1240 cm.$^{-1}$ due to the acetate residue and at 718 cm.$^{-1}$. The last band is characteristic of *cis*-CH=CH– and is entirely absent in the spectrum of (I; R = Ac). (iii) The molecular-rotation differences for (I; R = H) on acetylation and benzoylation are +131 and +351 respectively. These values are comparable with those (+110 and +178 respectively; see Barton and Cox, *J.*, 1948, 783) recorded for acylation of ergosterol, but are in contrast to the figures (+22 and +52 respectively; see Barton, *J.*, 1945, 813) for *iso*dehydrocholesterol.

The ready availability of 7-ketolanostan-3β-ol prompted us to investigate a number of derivatives. Oxidation with chromic acid gave lanostane-3 : 7-dione * (XI), also obtained by prolonged reduction of 7-ketolanost-8-en-3β-yl acetate by lithium in liquid ammonia followed by chromic acid oxidation of the product. Reduction of 7-ketolanostan-3β-yl acetate (IV; R = Ac) by lithium aluminium hydride afforded lanostane-3β : 7β-diol (XII; R = H), further characterised as the diacetate (XII; R = Ac). This diol was also obtained when 3 : 7-diketolanostane was reduced with sodium and propanol.



Hydrogenation of 3 : 7-diketolanostane in ethyl acetate solution gave 7-ketolanostan-3β-ol characterised as the acetate (IV; R = Ac). Whilst (IV; R = H) was not hydrogenated further in this medium, corresponding hydrogenation of (IV; R = Ac) in ethyl acetate–acetic acid furnished lanostane-3β : 7α-diol 3-acetate (XIII; R = Ac, R' = H) further characterised by hydrolysis to the diol (XIII; R = R' = H) and by acetylation to the diacetate (XIII; R = R' = Ac).

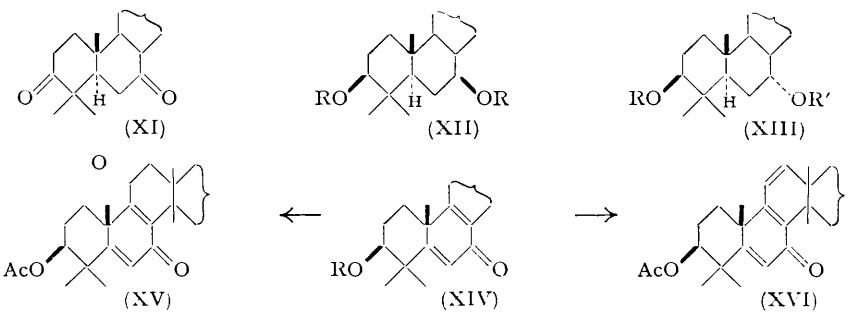
The configurations assigned at $C_{(7)}$ in these compounds are based on the following considerations. (i) The equatorial (β) character of the diol produced by sodium and propanol reduction follows from the method of preparation (Barton, *Experientia*, 1950, **6**, 316). (ii) The molecular-rotation difference on going from (XII; R = Ac) to (XIII;

* We understand that this compound has also been prepared independently by Dr. J. F. McGhie and his collaborators. We thank Dr. McGhie cordially for this information.

R = R′ = Ac) was −280. The corresponding difference in *trans*-AB saturated steroids is −351 (see Barton and Klyne, *Chem. and Ind.*, 1948, 755).

In confirmation of these configurational assignments treatment of lanostane-3β : 7α-diol 3-acetate with phosphorus oxychloride and pyridine gave, by smooth *trans*-elimination of polar 7α-OH and polar 8β-H, lanost-7-en-3β-yl acetate (V) (cf. the corresponding reaction in the cholestane series; Wintersteiner and Moore, *J. Amer. Chem. Soc.*, 1943, **65**, 1503; Fieser, Fieser, and Chakravarti, *ibid.*, 1949, **71**, 2226; Heymann and Fieser, *Helv. Chim. Acta*, 1952, **35**, 631).

As a by-product in the preparation of 7-ketolanost-8-en-3β-yl acetate we have isolated 7-ketolanosta-5 : 8-dien-3β-yl acetate (XIV; R = Ac). This was further characterised by hydrolysis to the alcohol (XIV; R = H). The constitution assigned is based on the following evidence. (*a*) The ultra-violet absorption is that of an αβ-unsaturated ketone. (*b*) The infra-red spectrum shows bands at 1738 and 1236 cm.$^{-1}$ due to the acetate residue, and at 1646 cm.$^{-1}$ indicative of a carbonyl group conjugated with two double bonds. In comparison 7-ketolanost-8-en-3β-yl acetate (III) showed bands at 1736 and 1242 cm.$^{-1}$ due to the acetate residue, and at 1662 cm.$^{-1}$ corresponding to a singly conjugated carbonyl group. (*c*) Oxidation by chromic acid afforded in good yield 7 : 11-diketolanosta-5 : 8-dien-3β-yl acetate (XV) (Voser, Montavon, Günthard, Jeger, and Ruzicka, *ibid.*, 1950, **33**, 1893). (*d*) Oxidation by selenium dioxide in acetic acid furnished 7-ketolanosta-5 : 8 : 11-trien-3β-yl acetate (XVI) (Birchenough and McGhie, *J.*, 1950, 1249). Treatment with zinc dust and acetic acid afforded an isomeric phenol, the constitution of which was not investigated further.



In Part IX of this series (*J.*, 1953, 571) we described the reduction of 7 : 11-diketolanostan-3β-yl acetate by sodium and propanol to the triequatorial lanostane-3β : 7β : 11α-triol. The corresponding reaction in the ergosterol series has now been effected. Reduction of 7 : 11-diketoergost-22-en-3β-yl acetate gave, as main product, a triol, characterised as the triacetate. The latter is formulated as 3β : 7β : 11α-triacetoxyergost-22-ene on the basis of its mode of formation (cf. Barton, *loc. cit.*; Barton and Rosenfelder, *J.*, 1951, 1048) and because its observed molecular rotation is in good agreement with that calculated from standard Tables (Barton and Klyne, *Chem. and Ind.*, 1948, 755).

In Part VII of this series (*J.*, 1952, 2339) the preparation of *inter al.*, 7 : 11 : 12-triketo-7*a*-aza-B-homolanostan-3β-yl acetate was described. Falco, Voser, Jeger, and Ruzicka recently (*Helv. Chim. Acta*, 1952, **35**, 2430) queried the m. p. (269—273°) which we recorded. Our m. p. is correct as given when taken in a Pyrex-glass capillary. In a soda-glass capillary the m. p. becomes indefinite and may be as low as 230—240°. We cannot confirm however the m. p. (208—210°) given by Falco *et al.*, which may represent therefore a different crystalline modification. The rotations recorded are in agreement.

Experimental

For general experimental directions see Part VII (*J.*, 1952, 2339). Infra-red spectra, in carbon disulphide solution, were kindly determined by Dr. J. E. Page (of Messrs. Glaxo Laboratories Ltd.) using a Perkin–Elmer double-beam instrument. $[\alpha]_D$ are in $CHCl_3$. Ultra-violet absorption spectra refer to ethanol solutions.

7-Ketolanostan-3β-ol.—7-Ketolanost-8-en-3β-yl acetate (3 g.) in sodium-dried ether (200 ml.) was added to liquid ammonia (300 ml.) during 15 min. At the same time lithium (300 mg.) was added in small pieces so as to maintain the blue colour of the solution. After a further 5 min. *tert.*-butanol in ether (20 ml.; 50%) was run in, the solution was diluted with ether, and water added. After removal of the ether *in vacuo* the product was chromatographed over alumina. Elution with 1 : 1 benzene–ether afforded 7-ketolanostan-3β-yl acetate, m. p. (from ethanol) 172°, $[\alpha]_D$ +36° (*c*, 2·4), undepressed in m. p. on admixture with an authentic specimen (Barton, Fawcett, and Thomas, *loc. cit.*). Alkaline hydrolysis of the acetate gave *7-ketolanostan-3β-ol*, m. p. (from methanol) 171—173°, $[\alpha]_D$ +28° (*c*, 1·7) (Found: C, 80·8; H, 11·75. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%), depressed in m. p. on admixture with the parent acetate, but reconverted thereinto on acetylation (m. p. and mixed m. p.).

7-Ketolanost-5-en-3β-yl Acetate.—7-Ketolanostan-3β-yl acetate (500 mg.) and selenium dioxide (500 mg.) were refluxed in " AnalaR " acetic acid (25 ml.) for 4 hr. The product was crystallised from methanol, to give *7-ketolanost-5-en-3β-yl acetate* (400 mg.), m. p. 188—189°, $[\alpha]_D$ −37° (*c*, 1·1), $\lambda_{max.}$ 238 mμ (ε = 12,500) (Found: C, 79·0; H, 10·85. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%).

Lanosta-5 : 7-dien-3β-ol.—7-Ketolanost-5-en-3β-yl acetate (400 mg.) in sodium-dried ether (20 ml.) was refluxed with lithium aluminium hydride (100 mg.) in the same solvent (20 ml.) for 2 hr. The product was dissolved in aqueous dioxan [20 ml.; 20% (v/v) of water] containing 5% (w/v) of sulphuric acid and kept at 50° for 2 hr. Preliminary experiments with spectroscopic control had shown that these were the optimum conditions. The product was acetylated and chromatographed. Elution with 1 : 1 light petroleum–benzene gave *lanosta-5 : 7-dien-3β-yl acetate* (55 mg.), m. p. (from chloroform–methanol) 134—136°, $[\alpha]_D$ −115° (*c*, 0·9), $\lambda_{max.}$ 273 mμ (ε = 11,000) (Found: C, 82·05; H, 11·1. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%). Elution with benzene afforded 7-ketolanostan-3β-yl acetate identified by m. p. and mixed m. p. This acetate was also isolated when the crude lithium aluminium hydride reduction product was acetylated and chromatographed (without sulphuric acid treatment).

In a further experiment the crude product from the acid-catalysed dehydration (180 mg.) was benzoylated and then chromatographed. Elution with 1 : 4 benzene–light petroleum gave *lanosta-5 : 7-dien-3β-yl benzoate* (60 mg.), m. p. (from chloroform–methanol) 186—187°, $[\alpha]_D$ −60° (*c*, 1·2), $\lambda_{max.}$ 230 and 273 mμ (ε = 16,000 and 14,000 respectively) (Found: C, 83·4; H, 10·15. $C_{37}H_{54}O_2$ requires C, 83·7; H, 10·25%). Elution with 1 : 1 benzene–light petroleum furnished *7-ketolanostan-3β-yl benzoate* (70 mg.), m. p. (from chloroform–methanol) 246—247°, $[\alpha]_D$ +50° (*c*, 1·1), $\lambda_{max.}$ 230 mμ (ε = 15,000) (Found: C, 81·1; H, 10·25. $C_{37}H_{56}O_3$ requires C, 80·95; H, 10·3%), identical (m. p. and mixed m. p.) with a specimen prepared directly from the corresponding acetate (see above).

Alkaline hydrolysis of lanosta-5 : 7-dien-3β-yl acetate gave the corresponding *alcohol*, m. p. (from methanol) 137—138° (after drying *in vacuo* at 80°), $[\alpha]_D$ −157° (*c*, 0·7), $\lambda_{max.}$ 274 mμ (ε = 11,500) (Found: C, 83·95; H, 11·6. $C_{30}H_{50}O$ requires C, 84·45; H, 11·8%).

Treatment of lanosta-5 : 7-dien-3β-yl acetate (5 mg.) in chloroform (5 ml.) with a stream of hydrogen chloride gas for 10 min. gave lanosta-7 : 9(11)-dien-3β-yl acetate (3 mg.), identified by m. p., mixed m. p., and absorption spectrum.

Lanostane-3 : 7-dione.—7-Ketolanost-8-en-3β-yl acetate (2·6 g.) was reduced with lithium in liquid ammonia as detailed above, except that a large excess of lithium was used and the reaction mixture was stirred for 1 hr. before addition of the *tert.*-butanol–ether solution. The reaction product in acetic acid was oxidised with chromium trioxide and then chromatographed (elution with benzene) to give *lanostane-3 : 7-dione* (850 mg.), m. p. (from methanol) 130—131°, $[\alpha]_D$ +5° (*c*, 2·4), $\lambda_{max.}$ 293 mμ (ε = 75) (Found: C, 81·0; H, 11·3. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%). This dione was also prepared by chromic acid oxidation of 7-ketolanostan-3β-ol (see above), the identity being confirmed by m. p. and mixed m. p. Lanostane-3 : 7-dione was recovered unchanged (m. p. and mixed m. p.) on refluxing with 5% methanolic potassium hydroxide solution for 30 min.

Lanostane-3 : 7-dione (35 mg.) in ethyl acetate (25 ml.) was hydrogenated over a platinum catalyst for 1 hr. The product was chromatographed over alumina. Elution with benzene afforded unchanged starting material, but elution with 1 : 1 benzene–methanol gave 7-ketolanostan-3β-ol, characterised by conversion into the acetate (180 mg.) and identified by m. p. and mixed m. p.

Lanostane-3β : 7β-diol.—7-Ketolanostan-3β-yl acetate (100 mg.) was reduced by lithium aluminium hydride and the product acetylated. Chromatography over alumina (elution with 1 : 9 ether–benzene) afforded *lanostane-3β : 7β-diol diacetate* (70 mg.), m. p. (from methanol)

185—186°, $[\alpha]_D$ +33° (*c*, 0·7) (Found: C, 76·6; H, 10·8. $C_{34}H_{58}O_4$ requires C, 76·95; H, 11·0%). Alkaline hydrolysis gave *lanostane*-3β : 7β-*diol*, m. p. (from methanol) 204—206°, $[\alpha]_D$ +37° (*c*, 2·4) (Found: C, 80·1; H, 12·15. $C_{30}H_{54}O_2$ requires C, 80·65; H, 12·2%).

Lanostane-3β : 7β-diol diacetate (70 mg.) was also obtained when lanostane-3 : 7-dione (100 mg.) was reduced with sodium and propanol, and the product acetylated. The identification was by m. p. and mixed m. p.

Lanostane-3β : 7α-*diol*.—7-Ketolanostan-3β-yl acetate (500 mg.) in 1 : 1 ethyl acetate–acetic acid (50 ml.) was hydrogenated over a platinum catalyst for 36 hr. The product was chromatographed over alumina. Elution with 99 : 1 benzene–ether afforded unchanged 7-ketolanostan-3β-yl acetate; elution with 9 : 1 benzene–ether gave *lanostane*-3β : 7α-*diol* 3-*acetate* (280 mg.), m. p. (from methanol) 205—206°, $[\alpha]_D$ +14° (*c*, 1·2), no absorption at 280 mμ (Found: C, 79·0; H, 11·8. $C_{32}H_{56}O_3$ requires C, 78·65; H, 11·55%). 7-Ketolanostan-3β-yl acetate was recovered unchanged after attempted hydrogenation (20 hr.' shaking) over platinum in ethyl acetate.

Acetylation of the monoacetate by pyridine–acetic anhydride on the steam-bath for 1 hr. gave *lanostane*-3β : 7α-*diol diacetate*, m. p. (from ethyl acetate–methanol) 167—168°, $[\alpha]_D$ −20° (*c*, 1·1) (Found: C, 76·6; H, 10·85. $C_{34}H_{58}O_4$ requires C, 76·95; H, 11·0%).

Alkaline hydrolysis of the monoacetate afforded *lanostane*-3β : 7α-*diol*, m. p. (from methanol) 163—165° after sintering at 158°, $[\alpha]_D$ +5° (*c*, 1·8) (Found: C, 78·85; H, 11·95. $C_{30}H_{54}O_2,0{\cdot}5CH_3{\cdot}OH$ requires C, 79·2; H, 12·2%).

Dehydration of Lanostane-3β : 7α-*diol* 3-*Acetate*.—The monoacetate (70 mg.) was heated on the steam-bath with dry pyridine (5 ml.) and redistilled phosphorus oxychloride (1 ml.). The product, purified by chromatography and recrystallisation from chloroform–methanol, was identified as pure lanost-7-en-3β-yl acetate (35 mg.) by m. p., mixed m. p. (for authentic specimen, see Barton, Fawcett, and Thomas, *loc. cit.*), and rotation {$[\alpha]_D$ +25° (*c*, 2·2)}.

7-*Ketolanosta*-5 : 8-*dien*-3β-*ol*.—The 7-ketolanost-8-en-3β-yl acetate used in the above experiments was purified by chromatography over alumina. The tail fractions from the chromatogram were crystallised from methanol, to give 7-*ketolanosta*-5 : 8-*dien*-3β-*yl acetate*, m. p. 186—188°, $[\alpha]_D$ −14° (*c*, 2·5), $\lambda_{max.}$ 249 mμ (ε = 13,500) (Found: C, 79·25; H, 10·9. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·45%). Alkaline hydrolysis afforded 7-*ketolanosta*-5 : 8-*dien*-3β-*ol*, m. p. (from aqueous methanol) 170° (after drying *in vacuo* at 80°), $[\alpha]_D$ −14° (*c*, 2·0) (Found: C, 81·3; H, 10·9. $C_{30}H_{48}O_2$ requires C, 81·75; H, 11·0%).

7-Ketolanosta-5 : 8-dien-3β-yl acetate (100 mg.) in "AnalaR" acetic acid (10 ml.) was oxidised with chromium trioxide (40 mg.) in a little aqueous acetic acid at 85° for 1 hr. The product was chromatographed over alumina. Elution with benzene afforded 7 : 11-diketolanosta-5 : 8-dien-3β-yl acetate (45 mg.), identified by m. p., mixed m. p., rotation {$[\alpha]_D$ +69° (*c*, 1·7)}, and absorption spectrum [$\lambda_{max.}$ 272 mμ (ε = 12,500)].

7-Ketolanosta-5 : 8-dien-3β-yl acetate (30 mg.) in "AnalaR" acetic acid (10 ml.) was refluxed with selenium dioxide (30 mg.) for 3 hr. The product was crystallised from methanol, to give 7-ketolanosta-5 : 8 : 11-trien-3β-yl acetate (15 mg.), identified by m. p., mixed m. p., rotation {$[\alpha]_D$ +66° (*c*, 1·0)}, and absorption spectrum [$\lambda_{max.}$ 258 and 326 mμ (ε = 8500 and 8500 respectively)].

7-Ketolanosta-5 : 8-dien-3β-yl acetate (100 mg.) in "AnalaR" acetic acid (10 ml.) was refluxed with zinc dust for 2 hr. The product was crystallised from methanol, to give a *phenol*, m. p. 212—214°, $[\alpha]_D$ +51° (*c*, 1·1), $\lambda_{max.}$ 287 mμ (ε = 3500), changed to $\lambda_{max.}$ 302 mμ (ε = 3500) on addition of ethanolic potassium hydroxide (Found: C, 79·9; H, 10·1. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·45%).

Reduction of 7 : 11-*Diketoergost*-22-*en*-3β-*yl Acetate* (with C. S. Barnes).—The diketone (1·0 g.) in refluxing propanol (10 ml.) was reduced by the addition of sodium until the solution was saturated. After acetylation the product was chromatographed over alumina. Elution with 1 : 1 benzene–light petroleum furnished 3β : 7β : 11α-*triacetoxyergost*-22-*ene* (350 mg.), m. p. (from chloroform–methanol) 159—161°, $[\alpha]_D$ −51° (*c*, 3·2), $[M]_D$ −279° {calculated $[M]_D$ according to the standard tables of Barton and Klyne (*loc. cit.*) −294°} (Found: C, 73·25; H, 9·8. $C_{34}H_{54}O_6$ requires C, 73·1; H, 9·75%). The compound showed no ketonic band in either the ultra-violet or the infra-red region.

Elution with benzene and benzene–ether gave mixtures which were not investigated further. Elution with ether furnished a fraction (50 mg.) which had m. p. (from chloroform–methanol) 159—161° (depressed by 30° on admixture with the 3β : 7β : 11α-triacetate), $[\alpha]_D$ −10° (*c*, 2·4) $[M]_D$ −56° (calculated for 3β : 7α : 11α-triacetoxyergost-22-ene $[M]_D$ +57°) (Found: C, 72·7; H, 9·45%). This fraction showed no ketonic band in either the ultra-violet

or the infra-red region. The fraction is almost certainly enriched in the 3β : 7α : 11α-triacetate, but there was insufficient material for further purification.

We thank the Government Grants Committee of the Royal Society, the Central Research Fund of London University, and Imperial Chemical Industries Limited, for financial assistance. We are also grateful to Messrs. Glaxo Laboratories Ltd. for gifts of chemicals, and to the International Wool Secretariat for a Post-doctorate Fellowship made available to one of us (B. R. T.).

BIRKBECK COLLEGE, LONDON, W.C.1. [*Received, February 24th,* 1953.]