440. *Studies in the Steroid Group. Part LXXI.* The Preparation and Reactions of 9α-Methylergostane Derivatives.*

By E. R. H. Jones, G. D. Meakins, and J. S. Stephenson.

Treatment of 3β-acetoxy-9α- and -9β-Δ^7-11-ketones of the ergostane series in methyl iodide with potassium *tert.*-butoxide in *tert.*-butyl alcohol gives high yields of compounds containing a 9α-methyl group. During this process the 3-methyl ethers are formed to an appreciable extent.

Some properties of the 9α-methyl-steroids are described. The presence of this additional substituent has a profound effect on the reactions of adjacent unsaturated centres and 11-oxygen functions.

Interest in steroids possessing additional methyl groups at various nuclear positions has developed recently from several points of view. The original impetus for such studies was the recognition of tetracyclic triterpenes as 4 : 4 : 14-trimethyl-steroids. Degradation of lanosterol derivatives gave 14-methyl-steroids,[1,2,3] which were subsequently synthesised from steroidal materials,[4] and later cholesterol was converted into lanost-8-enol.[5] A second focus of attention is the effect of nuclear methyl groups on physiological activity: thus 2- and 6-alkyl compounds [6,7] are more potent, for example, in the glycogen deposition

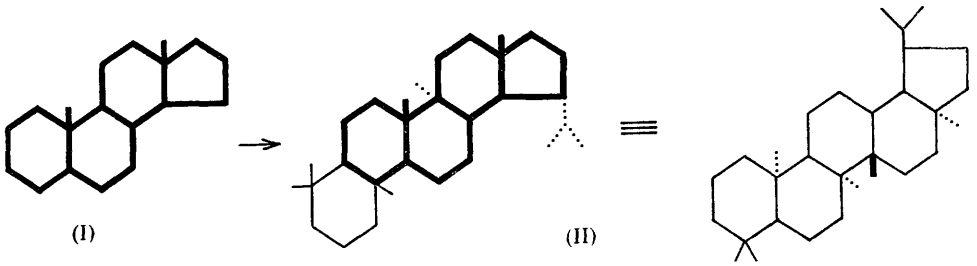
* Part LXX, *J.*, 1955, 3420.

[1] Voser, White, Heusser, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 830.
[2] Voser, Heusser, Jeger, and Ruzicka, *ibid.*, 1953, **36**, 299.
[3] Barton, Ives, and Thomas, *J.*, 1954, 903.
[4] Barton, Ives, Kelly, Woodward, and Patchett, *Chem. and Ind.*, 1954, 605.
[5] *Idem*, *J.*, 1957, 1131.
[6] Hogg, Lincoln, Jackson, and Schneider, *J. Amer. Chem. Soc.*, 1955, **77**, 6401; Ringold and Rosenkrantz, *J. Org. Chem.*, 1956, **21**, 1335.
[7] Spero, Thompson, Magerlein, Hanze, Murray, Sebek, and Hogg, *J. Amer. Chem. Soc.*, 1956, **78**, 6213; Ringold, Batres, and Rosenkrantz, *J. Org. Chem.*, 1957, **22**, 99.

test, than the parent hormones. Various 4-monomethyl- [8] and 4 : 4-dimethyl-steroids [9] have also been described, and the 3-methyl compounds have been used as a basis for stereochemical studies.[10]

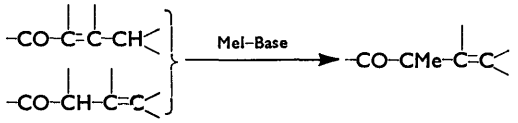
The present work is concerned with the preparation and properties of 9-methyl-steroids. Introduction of a 9-methyl group is a critical stage in a scheme for converting a steroid into the enantiomer of a pentacyclic triterpene [cf. (I) ⟶ (II)], a project of some interest in that the fundamental structures of the β-amyrin–lupeol group, although well substantiated, have not yet been finally confirmed by partial or total synthesis. The possible effects of a 9-methyl group on the biological activity of steroid hormones are also of interest, especially as other 9α-substituents [11] (notably fluorine) cause marked variations in hormone activity.

A more immediate consequence of 9-methylation is that it produces a system with methyl groups at the neighbouring positions 9 and 10, which might be expected to modify the characteristic properties normally associated with various steroidal functional groups, particularly the almost universal rule of rear approach of certain reagents.



(I) (II)

The best possibility of obtaining 9-methylation appeared to be through alkylation of an αβ- or a βγ-unsaturated 11-ketone:

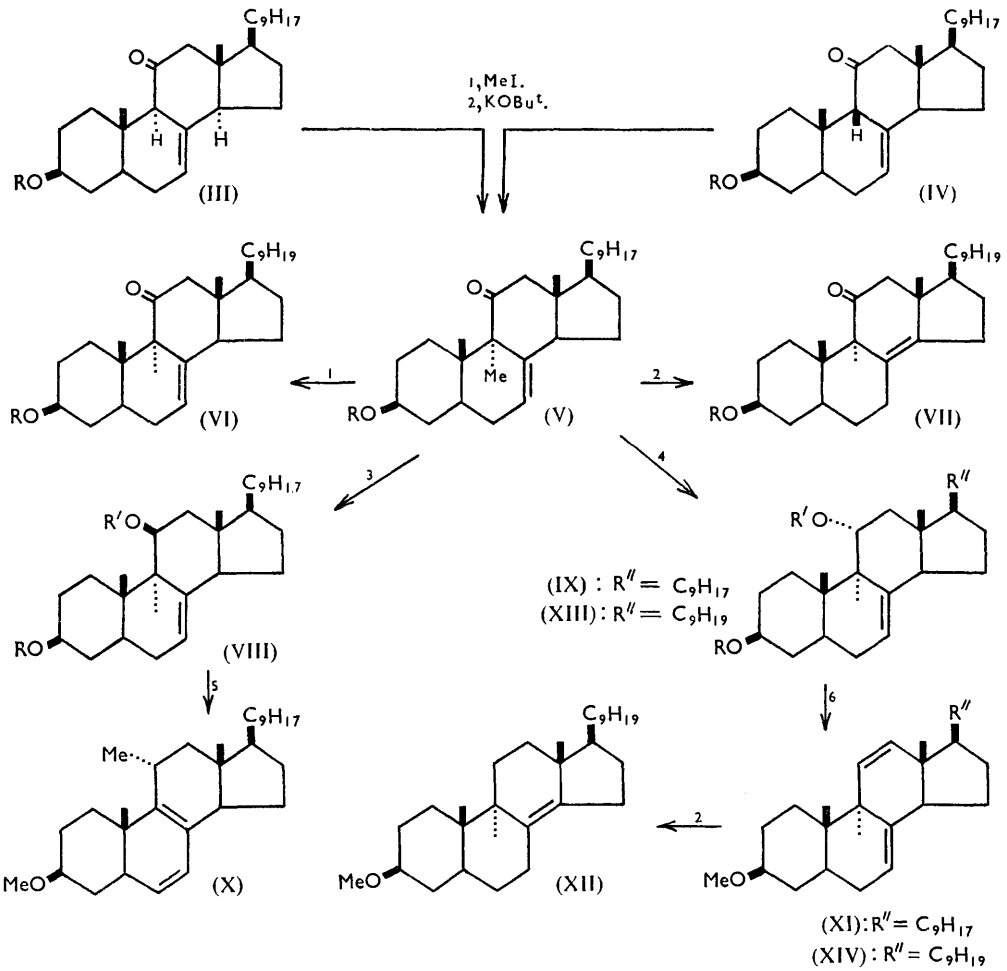


Methylation of the conjugated ketone 3β-acetoxyergost-8-en-11-one [12] was first attempted, but the results were obscured by a base-induced isomerisation of the steroid ketone. Detailed investigation (to be published later) indicated that the Δ^7-11-ketones [(III) and (IV); R = Ac] [12] were more promising starting materials since, with double activation at $C_{(9)}$, they produce anions more readily than the αβ-unsaturated isomer. In order to take advantage of this factor and to prevent the derived anion from isomerising (to the Δ^8-11-keto-system) it was desirable that the anion, when once formed, should be methylated very rapidly. This was achieved by reversing the usual sequence, *i.e.*, by adding the base (potassium *tert.*-butoxide in *tert.*-butyl alcohol) to a solution of the Δ^7-11-ketone [(III) and (IV); R = Ac] in methyl iodide. After saponification of the products two 9α-methyl-Δ^7-11-ketones were isolated: the 3β-hydroxy-compound (V; R = H) in 50% yield, and the 3β-methoxy-derivative (V; R = Me) in ~17% yield.

The structures proposed for compounds based on formula (V) are supported by the following evidence. Studies of the C–H bending region of the infrared spectrum (notably bands near 1380 cm.$^{-1}$) showed that derivatives of (V) have a higher methyl group content

[8] Beton, Halsall, Jones, and Phillips, *J.*, 1957, 145; Meakins and Rodig, *J.*, 1956, 4679; Hartman, Tomasewski, and Dreiding, *J. Amer. Chem. Soc.*, 1956, **78**, 5662.
[9] Cooley, Ellis, and Petrow, *J.*, 1955, 2998; Adams, Patel, Petrow, Stuart-Webb, and Sturgeon, *J.*, 1956, 4490.
[10] Barton, Campos-Neves, and Cookson, *J.*, 1956, 3500.
[11] Fried and Sabo, *J. Amer. Chem. Soc.*, 1957, **79**, 1130; Spero, Thompson, Lincoln, Schneider, and Hogg, *ibid.*, p. 1515.
[12] Part LXII, *J.*, 1953, 2921.

than related steroidal reference compounds. Spectroscopic examination of compounds (V; R = Ac and Me) disclosed the presence of side-chain (Δ^{22}) unsaturation and a tri-substituted double bond which, from the mode of genesis of these compounds, must be placed at position 7 : 8. The stability of these Δ^7-11-ketones under alkaline conditions



Reagents: 1, H_2–Pt–EtOAc. 2, H_2–Pt–AcOH. 3, $LiAlH_4$. 4, Li–NH_3–EtOH. 5, $POCl_3$–C_5H_5N. 6, Pyrolysis of benzoates.

which cause isomerisation of the 9-hydrogen ketones (III) and (IV) is thus strong presumptive evidence for methylation at position 9. The α-orientation of the 9-substituent is based on rotational data {compare, for example, the $[M]_D$ values of the Δ^7-11-ketones: (III; R = Ac) with 9αH, +114°; (V; R = Ac) with 9αMe, +146°; (IV; R = Ac) with 9βH, −820°}. A more powerful demonstration of this feature is provided by the rotatory dispersion curves of the acetate (V; R = Ac) and its derivatives kindly determined for us by Professor C. Djerassi.

In investigation of the chemistry of the 9α-methyl-steroids attention has been concentrated on the 7 : 8-double bond and the 11-keto-group. We had in mind the eventual removal of either or both of these features and expected to discern effects due to the 9α-methyl group. In many cases it was more convenient to work with the 3-methyl ethers

in order to avoid complications due to hydrolysis, elimination, etc., of the 3-hydroxy- or -acyloxy-group.

Hydrogenation of the acetate (V; R = Ac) with platinum in ethyl acetate affected only the $\Delta^{22:23}$-bond to give compound (VI; R = Ac), while reduction in acetic acid using a large proportion of catalyst caused simultaneous migration of the nuclear double bond, producing an isomeric dihydro-compound (VII; R = Ac). In the 9α-methyl series the $\Delta^7 \longrightarrow \Delta^{8(14)}$ isomerisation under acidic hydrogenation conditions requires a high ratio (approximately equal weights) of catalyst to substrate: the ease of conversion may also depend on the nature of the 3-substituent. Thus reduction of the alcohols (V; R = H) and (IX; R = Me, R′ = H) with normal catalyst proportions did not bring about migration, whereas from the ether (XI) a $\Delta^{8(14)}$-compound was formed when a large proportion of catalyst was used. [The positions of nuclear unsaturation in these compounds and others described in this work follow from their spectroscopic characteristics. A useful general distinction between 11-ketones with 7 : 8- and 8 : 14-double bonds is that only the former give appreciable C=C stretching bands (near 1665 cm.$^{-1}$). The ultraviolet end-absorption data for Δ^7- and $\Delta^{8(14)}$-compounds are collected in the Experimental part.]

Attempts to induce migration of nuclear double bonds in 9-methyl-steroids by acid were unsuccessful. Thus, for instance, the Δ^7- (V; R = Bz) and the $\Delta^{8(14)}$ (VII; R = Me) compounds were unchanged after treatment with hydrogen chloride in chloroform. Similar observations with 3β-methoxy-9α-methylergost-8(14)-ene (XII) show that the 11-oxygen function is not responsible for these results, which differ from normal steroid behaviour.

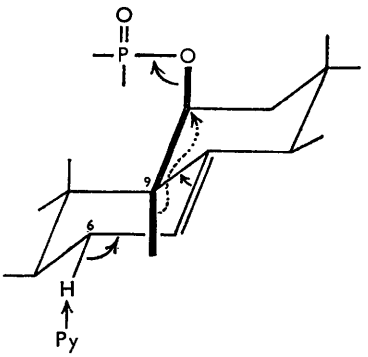
Reduction of the 11-keto-group of the ether (V; R = Me) with lithium–ammonia–ethanol and with lithium aluminium hydride gave high yields of different products which, from their methods of preparation, are formulated as the (equatorial) 11α- and (axial) 11β-epimers (IX and VIII respectively; R = Me, R′ = H). It was expected that the hydroxyl group in the latter alcohol would be very resistant to esterification.[13] However, treatment with acetic anhydride–pyridine at 20° afforded the corresponding acetate (VIII; R = Me, R′ = Ac) in 20% yield. Although acetylation of the 11β-hydroxyl group in the related 9α-hydrogen compound (ergosta-7 : 22-diene-3β : 11β-diol [13]) was not studied in detail, it appears that the 9α-methyl compound is the more reactive in this respect. Recent work with normal steroids [14] shows that an 8 : 9- or 8 : 14-double bond facilitates esterification of 11β-hydroxyl groups. The reactivity of the hydroxyl group in the Δ^8-compounds appears to be very similar to that found in the 9α-methyl-Δ^7-system.

Participation of the 9-methyl group was first met in dehydration studies with the epimeric 11-alcohols. With pyridine and phosphorus oxychloride at room temperature the 11β-alcohol (VIII; R = Me, R′ = H) gave an alkali-soluble phosphorus ester, but at 115° a dehydrated product was obtained. This contained a conjugated system ($\lambda_{max.}$ 2750 Å, ε 6150, shoulder at 2800 Å), showing that removal of the 11-hydroxyl group is accompanied by some skeletal change. Formulation (X) accommodates the similarity of the ultraviolet absorption to that of *iso*dehydrocholesterol [15] ($\lambda_{max.}$ 2710 and 2780 Å, ε 3800) and is supported by the occurrence in the infrared spectrum of a band (720 cm.$^{-1}$) corresponding to a disubstituted *cis*-double bond.[16] After the formation of a phosphorus ester from the alcohol (VIII; R = Me, R′ = H) and subsequent ionisation of this group, the 9α-methyl group is ideally placed for migration along the α-face of the molecule [see the planar arrangement of Me, $C_{(9)}$, $C_{(11)}$, and O indicated by heavy lines in the diagram (*A*)]. The rearrangement is completed by double-bond migration to supply the electron-deficiency at $C_{(9)}$, and concomitant loss of a proton (shown arbitrarily as 6α) from $C_{(6)}$.

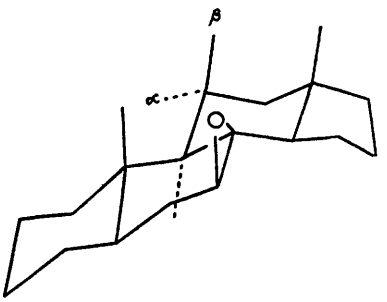
[13] Part LXV, *J.*, 1954, 731; Part LXX, *J.*, 1955, 3420.
[14] Wendler, Graber, Snoddy, and Bollinger, *J. Amer. Chem. Soc.*, 1957, **79**, 4476.
[15] Barton and Cox, *J.*, 1949, 218.
[16] Part LXVII, *J.*, 1954, 800.

The occurrence of this mode of dehydration rather than the simple alternative involving *trans*(diaxial)-elimination between 11β-OH and 12α-H is a good illustration of the well-known difficulty of forming 11 : 12-double bonds by ionic eliminations.[13]

Dehydration of the 11α-alcohol (IX; R = Me, R′ = H) with phosphorus oxychloride was much more difficult and gave small amounts of trienes (X) and (XI). The unconjugated 7 : 11 : 22-triene-ether (XI) was much better prepared by pyrolysis of the 11α-benzoate (IX; R = Me, R′ = Bz), in which there should be no rearrangement *via* ionic intermediates. The infrared spectrum of this triene-ether indicated the presence of a disubstituted (Δ^{11})-bond, so the original methylation did not occur at $C_{(12)}$ as well as at $C_{(9)}$. The related unconjugated 7 : 11-diene-ether (XIV) was prepared from the 11α-alcohol (IX;



(*A*)



(*B*)

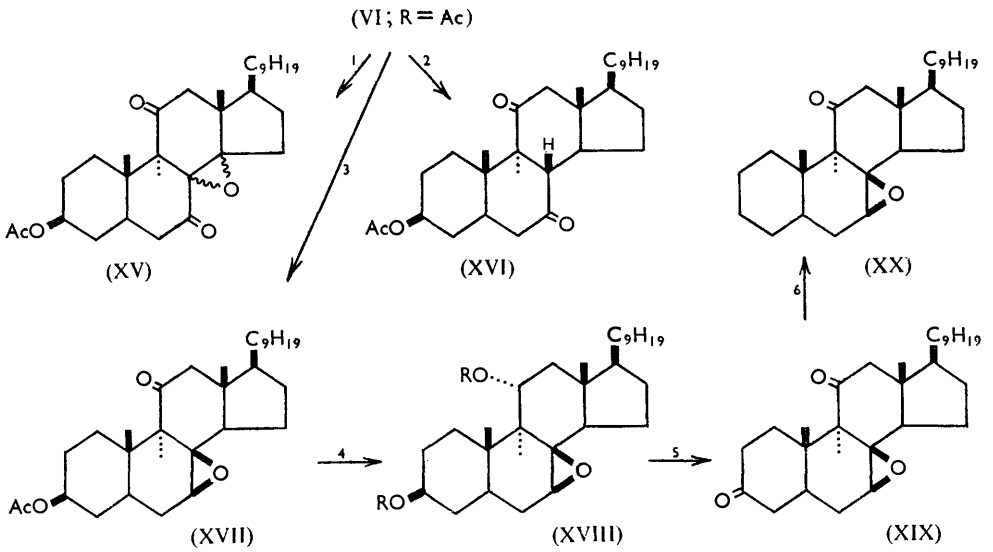
R = Me, R′ = H) by reduction of the side-chain [to give the ether (XIII; R = Me, R′ = H)], benzoylation (to XIII; R = Me, R′ = Bz), and pyrolysis. Hydrogenation of the triene-ether (XI) gave 3β-methoxy-9α-methylergost-8(14)-ene (XII), providing a method of removing the original 11-oxygen function. The double-bond migration from the 7 : 8- to the 8 : 14-position accompanying this process could presumably have been prevented by using less catalyst in the hydrogenation stage.

Oxidation of the 7 : 8-double bond was studied with the Δ^7-11-ketone (VI; R = Ac). Only the main oxidation products and their derivatives are considered here (minor, unidentified, substances are recorded in the Experimental part). The chief features of the structures assigned to these compounds are well supported by analytical and spectroscopic data: the stereochemical aspects are discussed in later paragraphs.

Oxidation of the Δ^7-11-ketone (VI; R = Ac) with chromic anhydride in acetic acid yielded three neutral products, one of which (20% yield) was almost certainly the 7 : 11-dioxo-8 : 14-oxide (XV). With hydrogen peroxide in acetic acid at 100° the ketone (VI; R = Ac) gave a small amount of the 7 : 11-diketone (XVI), and at room temperature a low yield of the 7 : 8-epoxide (XVII). The epoxide was produced quantitatively by treatment with perbenzoic acid in benzene. Refluxing the epoxide (XVII) with lithium aluminium hydride in tetrahydrofuran for 6 hours failed to open the oxide ring; the product, a diol-oxide (XVIII; R = H), was remarkable in forming a diacetate (XVIII; R = Ac) on acetylation at room temperature. Chromic acid oxidation of the diol-oxide (XVIII; R = H) afforded the corresponding dioxo-oxide (XIX), from which Wolff–Kishner reduction removed the unhindered 3-keto-group to give the 11-oxo-7 : 8-epoxide (XX).

Stereochemical uncertainty arises at $C_{(8)}$ in the 7 : 11-diketone (XVI). However, the conditions under which the compound is formed should ensure stereomutation to the more stable configuration, and an 8β(H)-structure, which allows an all-chair conformation, is to be expected.

The configuration of the epoxy-group in compound (XVII) and its derivatives is more difficult to predict. Previous oxidations of 7 : 8-double bonds in normal steroids with per-acid [17,18] are considered to give α-epoxides in accordance with the general tendency for rear approach of reagents to the steroid molecule. Application of this concept to the oxidation of the compound (VI; R = Ac) is clearly vitiated by the extra (9α-)methyl group; indeed its presence could be construed as providing *prima facie* evidence for β-attack by per-acid. A better argument can be based on the unusually ready acetylation of the 11-hydroxyl group in the derived diol oxide (XVIII; R = H). Models indicate that with an α-7 : 8-epoxide, which would have ring B in a semi-boat form, access to either



Reagents: 1, CrO_3–AcOH. 2, H_2O_2–AcOH at 100°. 3, BzO_2H–C_6H_6 or H_2O_2–AcOH at 20°. 4, $LiAlH_4$. 5, CrO_3. 6, Wolff–Kishner.

11α- or 11β-hydroxyl groups would be severely impeded. This view is supported by the behaviour of 8α-ergostane derivatives where both 11-hydroxyl groups are unreactive.[19] A β-7 : 8-oxide system can adopt an all-chair form (see Figure *B*) in which, although the 11β-hydroxyl group is again subject to severe hindrance, the corresponding 11α(equatorial)-group is relatively free. For this reason the diol oxide (XVIII; R = H) is provisionally formulated as a 3β : 11α-dihydroxy-7β : 8β-epoxide. The β-epoxide configuration will, of course, also apply to (XVII), (XIX), and (XX).

The 7 : 8-double bond of compound (VI; R = Ac) did not react with osmium tetroxide even under conditions in which other unreactive bonds were attacked.[20] This is in accordance with the greater steric requirements of osmium tetroxide than of perbenzoic acid, and with the hindrance by methyl groups on both faces of the 9α-methyl-steroid molecule.

Experimental

M. p.s were determined on a Kofler block and are corrected. Rotations were determined for $CHCl_3$ solutions at room temperature. Peter Spence alumina (grades O and H) was used for chromatography: deactivated alumina was prepared by treating grade H material with 5% (by volume) of 10% aqueous acetic acid. Light petroleum refers to the fraction with b. p.

[17] Alt and Barton, *J.*, 1954, 1356.
[18] Grigor, Laird, Maclean, Newbold, and Spring, *J.*, 1954, 2333; Grigor, Newbold, and Spring, *J.*, 1955, 1170.
[19] Bream, Eaton, and Henbest, *J.*, 1957, 1974.
[20] Castells and Meakins, *Chem. and Ind.*, 1956, 248.

60—80°. Ultraviolet spectra were determined for EtOH solutions with a Unicam spectrometer. Infrared spectra were recorded on a Perkin-Elmer model 21 double-beam instrument, carbon disulphide solutions being used unless stated otherwise.

Methylation of 3β-*Acetoxy*-9β-*ergosta*-7 : 22-*dien*-11-*one* (IV; R = Ac).—A M-solution of potassium *tert.*-butoxide in *tert.*-butyl alcohol (215 c.c.) was added quickly to a stirred solution of the ketone [12] (3 g.) in methyl iodide (70 c.c.) at 20°. After 20 min. the mixture was poured into water, and the material isolated by ether-extraction was refluxed with 10% ethanolic potassium hydroxide (150 c.c.) for 4 hr. under nitrogen. Standard manipulation gave a mixture (2·7 g.) which was adsorbed from light petroleum–benzene (10 : 1) on deactivated alumina (200 g.). Light petroleum–benzene (4 : 1; 3 l.) eluted material (513 mg.) which crystallised from methanol to give 3β-*methoxy*-9α-*methylergosta*-7 : 22-*dien*-11-*one* (V; R = Me) (400 mg.), m. p. 130—132·5°, $[\alpha]_D$ +47° (*c* 1·1) (Found: C, 82·05; H, 10·9. $C_{30}H_{48}O_2$ requires C, 81·8; H, 11·0%). Light absorption: $\nu_{max.}$ 3014 sh, 1705, 1668, 973, 825, and 795 cm.$^{-1}$. Elution with benzene–ether (10·1; 1 l.) yielded 3β-*hydroxy*-9α-*methylergosta*-7 : 22-*dien*-11-*one* (V; R = H) (1·4 g.), m. p. 160—163°. After recrystallisation the alcohol was obtained as needles, m. p. 161—164°, or as plates, m. p. 165—169°, $[\alpha]_D$ +51° (*c* 1·0) (Found: C, 81·45; H, 10·8. $C_{29}H_{46}O_2$ requires C, 81·6; H, 10·9%). Light absorption: $\nu_{max.}$ 3617, 3014 sh, 1703, 1665, 972, 820, and 795 cm.$^{-1}$.

3β-*Acetoxy*-9α-*methylergosta*-7 : 22-*dien*-11-*one* (prepared by treatment with acetic anhydride–pyridine at 20° and crystallised from ethanol) had m. p. 133·5—134·5°, $[\alpha]_D$ +31° (*c* 0·85) (Found: C, 79·2; H, 10·2. $C_{31}H_{48}O_3$ requires C, 79·4; H, 10·3%). Light absorption: $\nu_{max.}$ 3017 sh, 1735, 1705, 1662, 1246, 1028, 972, 825, and 800 cm.$^{-1}$. The 3β-*benzoate*, obtained by the action of benzoyl chloride–pyridine at 20°, crystallised from ethanol as needles, m. p. 207—212°, $[\alpha]_D$ +35° (*c* 0·98) (Found: C, 81·45; H, 9·6. $C_{36}H_{50}O_3$ requires C, 81·45; H, 9·6%). Oxidation of the 3β-alcohol in acetone with 8N-chromic acid yielded 9α-*methylergosta*-7 : 22-*diene*-3 : 11-*dione*, needles (from methanol), m. p. 156—158°, $[\alpha]_D$ +63° (*c* 0·9) (Found: C, 81·8; H, 10·5. $C_{29}H_{44}O_2$ requires C, 82·0; H, 10·4%). Light absorption: $\nu_{max.}$ 3014 sh, 1720, 1710, 1667, 972, and 825 cm.$^{-1}$.

Methylation of 3β-*Acetoxyergosta*-7 : 22-*diene*-11-*one* (III; R = Ac).—A M-solution of potassium *tert.*-butoxide in *tert.*-butyl alcohol (86 c.c.) was added to the ketone [12] (500 mg.) in methyl iodide (28 c.c.) at 20°. Subsequent treatment similar to that of the preceding experiment and chromatographic separation of the products gave 3β-methoxy-9α-methylergosta-7 : 22-dien-11-one (90 mg.), m. p. 128—130°, $[\alpha]_D$ +46° (*c* 1·1), and 3β-hydroxy-9α-methylergosta-7 : 22-dien-11-one (250 mg.), m. p. 161—163°, $[\alpha]_D$ +48° (*c* 0·9).

3β-*Acetoxy*-9α-*methylergost*-7-*en*-11-*one* (VI; R = Ac).—A solution of 3β-acetoxy-9α-methylergosta-7 : 22-dien-11-one (1 g.) in ethyl acetate (50 c.c.) was shaken in hydrogen with Adams catalyst (500 mg.) until hydrogenation ceased (uptake 1 mol.). The residue obtained after removal of catalyst and solvent crystallised from methanol, to give the *keto-acetate* as needles (0·82 g.), m. p. 125·5—127·5°, $[\alpha]_D$ +43° (*c* 0·85) (Found: C, 79·05; H, 10·8. $C_{31}H_{50}O_3$ requires C, 79·1; H, 10·7%). Light absorption: $\nu_{max.}$ 3014 sh, 1735, 1705, 1667, 1241, 1027, 825, and 800 cm.$^{-1}$

3β-*Hydroxy*-9α-*methylergost*-7-*en*-11-*one* (VI; R = H).—A solution of the corresponding 7 : 22-dienol (102 mg.) in ethyl acetate (4 c.c.) was hydrogenated in the presence of prereduced Adams catalyst (50 mg.) for 1 hr. More catalyst (100 mg.) was added and the shaking was continued for a further hour. The *keto-alcohol*, isolated in the usual way, crystallised from methanol as needles (90 mg.), m. p. 168—170°, $[\alpha]_D$ +53° (*c* 0·98) (Found: C, 81·1; H, 11·25. $C_{29}H_{48}O_2$ requires C, 81·25; H, 11·3%). Light absorption: $\nu_{max.}$ 3595, 3022 sh, 1701, 1663, 1037, 810, and 794 cm.$^{-1}$.

3β-*Acetoxy*-9α-*methylergost*-8(14)-*en*-11-*one* (VII; R = Ac).—A solution of 3β-acetoxy-9α-methylergosta-7 : 22-dien-11-one (100 mg.) in acetic acid (8 c.c.) was shaken in hydrogen with Adams catalyst (100 mg.) for 7 hr. Standard manipulation gave the *keto-acetate*, needles (from methanol), m. p. 136—137·5°, $[\alpha]_D$ +104° (*c* 0·95) (Found: C, 79·0; H, 10·75. $C_{31}H_{50}O_3$ requires C, 79·1; H, 10·7%). Light absorption: $\nu_{max.}$ 1730, 1705, 1241, and 1028 cm.$^{-1}$.

Isomerisation of the 7 : 8-double bond appears to depend on the ratio of catalyst to substrate and possibly on the nature of the 3-substituent. Thus hydrogenation of 3β-hydroxy-9α-methylergosta-7 : 22-dien-11-one (2 g.) in acetic acid (50 c.c.) in the presence of Adams catalyst (0·5 g.) for 6 hr. yielded 3β-hydroxy-9α-methylergost-7-en-11-one (1·2 g.), m. p. 168—170°.

3β-*Hydroxy*-9α-*methylergost*-8(14)-*en*-11-*one* (VII; R = H).—Hydrolysis of the foregoing

acetate (1·07 g.) with 10% ethanolic potassium hydroxide gave the *keto-alcohol* (0·9 g.) which crystallised from aqueous methanol as plates, double m. p. 65—70° and 106—109°, $[\alpha]_D$ +130° (*c* 0·85) (Found: C, 81·05; H, 11·25. $C_{29}H_{48}O_2$ requires C, 81·25; H, 11·3%). Light absorption: $\nu_{max.}$ 3570, 1705, and 1040 cm.$^{-1}$. The 3 : 5-dinitrobenzoate (not analysed) of the alcohol had m. p. 182·5°, $[\alpha]_D$ +71° (*c* 1·1). Treatment of the alcohol with benzoyl chloride–pyridine at 20° gave the *benzoate* which crystallised from methanol, double m. p. 127—129° and 136—138°, $[\alpha]_D$ +92° (*c* 0·95) (Found: C, 80·75; H, 9·95. $C_{36}H_{52}O_3$ requires C, 81·15; H, 9·8%).

Attempted Isomerisation of Δ^7- *and* $\Delta^{8(14)}$-9α-*Methyl Compounds under Acidic Conditions.*—(*a*) A stream of dry hydrogen chloride was passed for 2 hr. through a solution of 3β-benzoyloxy-9α-methylergosta-7 : 22-dien-11-one (V; R = Bz) (500 mg.) in chloroform (20 c.c.) at −30°. The solution was diluted with ether, stirred with sodium hydrogen carbonate for 30 min., and poured into water. The material isolated from the ether layer crystallised from ethanol to give material (400 mg.), $[\alpha]_D$ +38° (*c* 1·0), m. p. 208—212° undepressed on admixture with starting material

3β-Benzoyloxy-9α-methylergost-8(14)-en-11-one (VII; R = Bz) and 3β-methoxy-9α-methylergost-8(14)-ene (XII) were also unchanged by treatment under these conditions.

(*b*) Hydrogen chloride was passed for 2 hr. through a solution of 3β-acetoxy-9α-methylergost-7-en-11-one (VI; R = Ac) (100 mg.) in acetic acid (40 c.c.) at 20°, and the mixture was kept for 3 days. Removal of solvent under reduced pressure and crystallisation of the residue from methanol afforded starting material (90 mg.), m. p. 125—127°.

(*c*) A solution of 3β-methoxy-9α-methylergost-8(14)-ene (XII) (0·5 g.) in a mixture of chloroform (5 c.c.), acetic acid (10 c.c.), and 10N-hydrochloric acid (2 c.c.) was boiled for 2 hr. Spectroscopic examination of the fractions obtained by chromatography of the product showed the absence of Δ^{14}-compounds: none of the fractions crystallised.

3β-*Methoxy*-9α-*methylergosta*-7 : 22-*dien*-11β-*ol* (VIII; R = Me, R′ = H).—A stirred solution of 3β-methoxy-9α-methylergosta-7 : 22-dien-11-one (1·2 g.) in dry ether (100 c.c.) was refluxed with lithium aluminium hydride (0·4 g.) for 1 hr. After the addition of ethyl acetate and then dilute sulphuric acid the product was isolated with ether. Crystallisation from methanol gave the *alcohol* (0·91 g.) as plates, m. p. 137—139°, $[\alpha]_D$ −54° (*c* 1·0) (Found: C, 81·4; H, 11·55. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%). Light absorption: $\nu_{max.}$ 3642, 1657, 1102, 972, 818, and 798 cm.$^{-1}$.

Acetylation of 3β-*Methoxy*-9α-*methylergosta*-7 : 22-*dien*-11β-*ol* (VIII; R = Me, R′ = H).—A solution of the alcohol (300 mg.) in acetic anhydride–pyridine (1 : 1; 40 c.c.) was kept at 20° for 15 hr. Dilution with water, extraction with ether, and removal of solvents *in vacuo* yielded material (280 mg.) which was adsorbed from light petroleum (5 c.c.) on deactivated alumina (100 g.). The fraction (60 mg.) eluted with light petroleum–benzene (2 : 1; 150 c.c.) crystallised from methanol, to give 11β-*acetoxy*-3β-*methoxy*-9α-*methylergosta*-7 : 22-*diene*, m. p. 123—125°, $[\alpha]_D$ −27° (*c* 0·8) (Found: C, 79·2; H, 10·7. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%). Light absorption: $\nu_{max.}$ 1728, 1683, 1239, 1100, 1019, and 980 cm.$^{-1}$. Further elution with the same solvent mixture (300 c.c.) gave starting material (180 mg.), m. p. 136·5—137·5° after crystallisation from methanol.

Dehydration of 3β-*Methoxy*-9α-*methylergosta*-7 : 22-*dien*-11β-*ol* (VIII; R = Me, R′ = H).—A solution of the alcohol (100 mg.) in pyridine (30 c.c.) was boiled with phosphorus oxychloride (3 c.c.) for 2 hr. under nitrogen, and then poured on ice. The material isolated by ether-extraction was chromatographed on alumina (10 g.; Grade 0). The fraction (68 mg.) eluted with light petroleum (250 c.c.) crystallised from acetone–methanol to give a product considered to be 3β-*methoxy*-11α-*methylergosta*-6 : 8 : 22-*triene* (X), m. p. 76—78°, $[\alpha]_D$ −21° (*c* 0·5) (Found: C, 84·55; H, 11·4. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%). Light absorption: $\lambda_{max.}$ 2750 Å (ε 6150), 2800 Å sh; $\nu_{max.}$ 3020 sh, 1102, 973, and 720 cm.$^{-1}$.

3β-*Methoxy*-9α-*methylergosta*-7 : 22-*dien*-11α-*ol* (IX; R = Me, R′ = H).—Lithium (0·6 g.) was added to a stirred solution of 3β-methoxy-9α-methylergosta-7 : 22-dien-11-one (1·53 g.) in ether (60 c.c.) and liquid ammonia (60 c.c.). After 30 min. absolute ethanol was added slowly until the blue colour disappeared. The ammonia was allowed to evaporate and water was added. Isolation with ether and crystallisation from methanol gave the *alcohol* (1·2 g.), m. p. 113—120°, which on recrystallisation had m. p. 125—126°, $[\alpha]_D$ −33° (*c* 1·0) (Found: C, 81·5; H, 11·3. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%). Light absorption: $\nu_{max.}$ 3636, 3006 sh, 1100, 972, 818, and 794 cm.$^{-1}$.

Treatment of this product (747 mg.) in pyridine (50 c.c.) with benzoyl chloride (5 c.c.) at

100° for 12 hr. gave 11α-*benzoyloxy*-3β-*methoxy*-9α-*methylergosta*-7 : 22-*diene* (670 mg.), m. p. 197—203° (from methanol), $[\alpha]_D$ −63° (*c* 1·1) (Found: C, 81·0; H, 10·0. $C_{37}H_{54}O_3$ requires C, 81·3; H, 9·95%).

3β-*Methoxy*-9α-*methylergost*-7-*en*-11α-*ol* (XIII; R = Me, R′ = H).—A solution of 3β-methoxy-9α-methylergosta-7 : 22-dien-11α-ol (3 g.) in acetic acid (400 c.c.) was shaken in hydrogen with Adams catalyst (0·5 g.) for 15 hr. The solution was filtered and diluted with water, and the product was collected. Two crystallisations from methanol gave the *alcohol* (2·21 g.), m. p. 156—157°, $[\alpha]_D$ −22° (*c* 0·9) (Found: C, 80·8; H, 11·6. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%). Light absorption: $\nu_{max.}$ 3616, 3027 sh, 1095, 995, 813, and 790 cm.$^{-1}$.

The 11α-alcohol (1·84 g.) in pyridine (50 c.c.) was treated with benzoyl chloride (10 c.c.) and kept at 50° for 2 hr. and then at 20° for 12 hr. Standard manipulation followed by crystallisation from ethyl acetate gave the 11α-*benzoyloxy-compound* (1·98 g.), m. p. 198—202°, $[\alpha]_D$ −6° (*c* 1·1) (Found: C, 80·9; H, 10·4. $C_{37}H_{56}O_3$ requires C, 81·0; H, 10·3%).

Pyrolysis of 11α-*Benzoates*.—(*a*) A Pyrex-glass tube (½″ internal diameter) containing 11α-benzoyloxy-3β-methoxy-9α-methylergosta-7 : 22-diene (117 mg.) was evacuated and flushed out with nitrogen several times, and then heated at 300°/20 mm. for 1 hr. The mixture was treated with ethanol, in which part of it (largely benzoic acid) dissolved. After the addition of excess of 0·01N-aqueous sodium hydroxide the mixture was titrated with 0·01N-hydrochloric acid. (The figures showed that the elimination had proceeded to the extent of 90%.) Dilution with water and extraction with ether was followed by chromatography of the product on alumina (15 g.; Grade 0). Light petroleum–benzene (50 : 1; 400 c.c.) eluted 3β-*methoxy*-9α-*methylergosta*-7 : 11 : 22-*triene* (XI) (64 mg.), m. p. 138—139° (needles from methanol), $[\alpha]_D$ −27° (*c* 0·95) (Found: C, 84·75; H, 11·6. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%). Light absorption: $\nu_{max.}$ 3007 sh, 1102, 973, and 745 cm.$^{-1}$.

(*b*) Pyrolysis of 11α-benzoyloxy-3β-methoxy-9α-methylergost-7-ene by the same method gave 3β-*methoxy*-9α-*methylergosta*-7 : 11-*diene* (XIV), m. p. 125—126° (from methanol), $[\alpha]_D$ −11° (*c* 1·05) (Found: C, 84·6; H, 11·6. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%). Light absorption: $\nu_{max.}$ 3007 sh, 1100, 797, and 744 cm.$^{-1}$.

3β-*Methoxy*-9α-*methylergost*-8(14)-*ene* (XII).—3β-Methoxy-9α-methylergosta-7 : 11 : 22-triene (250 mg.) in acetic acid (50 c.c.) was shaken in hydrogen with Adams catalyst (246 mg.) for 15 hr. The product isolated in the usual way was adsorbed from light petroleum on alumina (35 g.; Grade 0). Light petroleum–benzene (33 : 1) eluted material (240 mg.) which on crystallisation from acetone–methanol gave the *tetrahydro-compound* as needles, m. p. 53·5—55·5°, $[\alpha]_D$ +25° (*c* 0·83) (Found: C, 84·0; H, 12·2. $C_{30}H_{52}O$ requires C, 84·0; H, 12·2%). Light absorption: ε_{2100} 9700, ε_{2200} 3000; $\nu_{max.}$ 1102 cm.$^{-1}$.

Oxidation of 3β-*Acetoxy*-9α-*methylergost*-7-*en*-11-*one* (VI; R = Ac).—(a) *With chromium trioxide in acetic acid.* Chromium trioxide (450 mg.) was added to a solution of the Δ^7-11-ketone (600 mg.) in acetic acid (20 c.c.), and the mixture was stirred at 60° for 4 hr. Dilution with water and extraction with ether gave a gum (550 mg.) which was adsorbed from light petroleum–benzene (2 : 1, 30 c.c.) on alumina (100 g.; Grade 0). Elution with benzene–ether (19 : 1, 600 c.c.) afforded a *compound* (100 mg.) of unknown structure which, crystallised from methanol, had m. p. 183—185°, $[\alpha]_D$ +46° (*c* 0·71) (Found: C, 76·2, 76·6; H, 10·0, 10·2%). Light absorption: $\lambda_{max.}$ 2320 Å (ε 8700); $\nu_{max.}$ 1735, 1709, 1678, 1625, 1239, 1036, and 900 cm.$^{-1}$. Benzene–ether (9 : 1; 600 c.c.) afforded a second compound (120 mg.) which was almost certainly 3β-*acetoxy*-8ξ : 14ξ-*epoxy*-9α-*methylergostane*-7 : 11-*dione* (XV), m. p. 184—186° (from methanol), $[\alpha]_D$ +34° (*c* 0·75) (Found: C, 74·4; H, 9·7. $C_{31}H_{48}O_5$ requires C, 74·4; H, 9·7%). Light absorption: $\nu_{max.}$ 1735, 1725, 1702, 1239, 1028, and 901 cm.$^{-1}$; no selective absorption in the ultraviolet. Benzene–ether (4 : 1; 500 c.c.) eluted a third substance (55 mg.) (of unknown structure), m. p. 165—169° (from methanol), $[\alpha]_D$ +152° (*c* 0·75). Light absorption: $\lambda_{max.}$ 2490 Å (ε 8500); $\nu_{max.}$ 1735, 1715, 1651, 1239, 1026, 977, and 903 cm.$^{-1}$.

(b) *With hydrogen peroxide–acetic acid at* 20°. Aqueous hydrogen peroxide (0·3 c.c. of 100-vol. reagent) was added to a solution of the Δ^7-11-ketone (80 mg.) in acetic acid (4 c.c.). After 15 hr. at 20° water was added and the product was collected by filtration, dried, and adsorbed from light petroleum (3 c.c.) on deactivated alumina (10 g.). Elution with light petroleum–benzene (2 : 1; 50 c.c.) gave starting material (62 mg.). Benzene (20 c.c.) eluted a fraction (10 mg.) which proved to be 3β-acetoxy-7β : 8β-epoxy-9α-methylergostan-11-one, m. p. and mixed m. p. with an authentic specimen (described below), 135—137°.

(c) *With hydrogen peroxide–acetic acid at* 100°. A mixture of aqueous hydrogen peroxide

(0·6 c.c. of 100-vol. reagent) and acetic acid (0·6 c.c.) was added during 15 min. to a solution of the Δ^7-11-ketone (150 mg.) in acetic acid (6 c.c.) at 100°. After 2 hr. at 100° more hydrogen peroxide (0·6 c.c.; 100-vol.) was added and the heating was continued for a further 2 hr. The product, isolated by dilution with water and extraction with ether, was adsorbed from light petroleum–benzene (3 : 2; 7 c.c.) on deactivated alumina (20 g.). Elution with light petroleum–benzene (1 : 1; 100 c.c.) gave material (8 mg.), m. p. 178—180° (from methanol). From its infrared spectrum ($\nu_{max.}$ 1740, 1723, 1709, 1239, and 1026 cm.$^{-1}$) and lack of selective ultraviolet absorption, this compound is assumed to be 3β-acetoxy-9α-methylergostane-7 : 11-dione (XVI). The later fractions, eluted with more polar solvents, did not crystallise.

(d) *With perbenzoic acid.* Perbenzoic acid (20 c.c. of an 0·25M-solution in benzene) was added to the Δ^7-11-ketone (2 g.) in benzene (40 c.c.), and the mixture was left in the dark at 20° for 15 hr. After the removal of acidic material with dilute alkali the benzene solution was washed with water, dried, filtered, and evaporated *in vacuo*. Crystallisation of the residue from methanol gave 3β-*acetoxy*-7β : 8β-*epoxy*-9α-*methylergostan*-11-*one* (XVII) (1·94 g.), m. p. 134—136°. The pure product obtained by a further crystallisation from methanol had m. p. 138—139·5°, $[\alpha]_D$ −15° (*c* 1·0) (Found: C, 76·25; H, 10·3. $C_{31}H_{50}O_4$ requires C, 76·5; H, 10·4%). Light absorption: $\nu_{max.}$ 1730, 1690, 1245, and 1030 cm.$^{-1}$.

7β : 8β-*Epoxy*-9α-*methylergostane*-3β : 11α-*diol* (XVIII; R = H).—The foregoing epoxy-ketone (1 g.) in ether (100 c.c.) was refluxed with lithium aluminium hydride (1 g.) for 1 hr. The excess of reagent was decomposed with ethyl acetate, water was added, and the mixture was stirred for 30 min. (The use of mineral acid at this stage was avoided in order to exclude the possibility of acid-catalysed opening of the oxide ring.) Ether-extraction gave a product which was adsorbed from benzene (30 c.c.) on deactivated alumina (100 g.). Benzene–ether (4 : 1; 800 c.c.) eluted the *diol* (745 mg.; laths from methanol), m. p. 196—197°. Recrystallisation gave material, m. p. 200—207°, $[\alpha]_D$ −7° (*c* 1·0) (Found: C, 78·0; H, 11·5. $C_{29}H_{50}O_3$ requires C, 78·0; H, 11·3%). Light absorption: $\nu_{max.}$ (in Nujol) 1031, 976, and 922 cm.$^{-1}$. Repetition of this experiment with tetrahydrofuran as solvent and a reflux time of 6·5 hr. gave the same result.

3β : 11α-*Diacetoxy*-7β : 8β-*epoxy*-9α-*methylergostane* (XVIII; R = Ac).—A solution of the above diol (480 mg.) in pyridine (20 c.c.) and acetic anhydride (15 c.c.) was kept at 20° for 15 hr. and then poured slowly into ice-water. The material isolated with ether was adsorbed from light petroleum (20 c.c.) on deactivated alumina (50 g.). Elution with light petroleum–benzene (1 : 1; 30 c.c.) and crystallisation from methanol gave a product (440 mg.), m. p. 165—167°. Recrystallisation afforded the *diacetate* as needles, m. p. 165·5—167·5°, $[\alpha]_D$ −6° (*c* 1·1) (Found: C, 74·5; H, 10·5. $C_{33}H_{54}O_5$ requires C, 74·7; H, 10·3%). Light absorption: $\nu_{max.}$ no OH band, 1740, 1239, 1026, 977, 922, and 888 cm.$^{-1}$. The compound gave no colour with tetranitromethane.

7β : 8β-*Epoxy*-9α-*methylergostane*-3 : 11-*dione* (XIX).—8N-Chromic acid was added dropwise to a solution of the preceding diol (595 mg.) in acetone (100 c.c.) until the supernatant liquid remained yellow. The mixture was poured into water and extracted with ether. The material (571 mg.) so obtained was adsorbed from light petroleum (15 c.c.) on deactivated alumina (100 g.). Light petroleum–benzene (2 : 3; 900 c.c.) eluted a fraction (473 mg.) which crystallised from methanol to give the *dione*, m. p. 121—122·5°, $[\alpha]_D$ +7° (*c* 0·97) (Found: C, 78·8; H, 10·6. $C_{29}H_{46}O_3$ requires C, 78·7; H, 10·5%). Light absorption: $\nu_{max.}$ 1723, 1697, 969, and 919 cm.$^{-1}$.

7β : 8β-*Epoxy*-9α-*methylergostan*-11-*one* (XX).—A solution of the above epoxy-3 : 11-diketone (300 mg.) and 90% hydrazine hydrate (5 c.c.) in diethylene glycol (125 c.c.) was heated at 100° for 30 min., and then refluxed gently for 1 hr. Potassium hydroxide (1 g.) was added and the mixture was distilled slowly until the temperature of the solution reached 220°. The mixture was refluxed for 4 hr., cooled, and poured into dilute hydrochloric acid, and the whole was extracted with ether. The ether solution was washed with water, dried, and evaporated, and the residue (279 mg.) was chromatographed on alumina (50 g.; Grade 0). Light petroleum (250 c.c.) eluted a gum (30 mg.; $\nu_{max.}$ 1705 cm.$^{-1}$). Light petroleum–benzene (9 : 1; 800 c.c.) eluted a fraction (238 mg.) which crystallised from methanol, to give the *keto-oxide*, m. p. 88—90°, $[\alpha]_D$ −26° (*c* 1·1) (Found: C, 81·1; H, 11·3. $C_{29}H_{48}O_2$ requires C, 81·25; H, 11·3%). Light absorption: $\nu_{max.}$ 1694, 969, and 823 cm.$^{-1}$.

Ultraviolet End-absorption of Δ^7- *and* $\Delta^{8(14)}$-*Compounds.*—The data for some of the substances

described in this section are collected in the Table. The figures confirm the expectation [21] that compounds containing tetrasubstituted 8 : 14-bonds absorb much more intensely in the 2050—2200 Å region than those with trisubstituted 7 : 8-double bonds.

Δ^{7}-*Compounds*

Substituents			Double bonds	ε_{2100}	ε_{2150}	ε_{2200}
3β	9α	11	—	—	—	—
AcO	Me	=O	7	2900	1300	800
AcO	Me	=O	7 : 22	2200	1000	250
MeO	Me	HO-α	7	2000	600	100
MeO	Me	—	7 : 11 : 22	3600	300	10

$\Delta^{8(14)}$-*Compounds*

Substituents			Double bonds	ε_{2100}	ε_{2150}	ε_{2200}
AcO	H	=O	8(14)	9350	6580	2870
AcO	H	HO-β	8(14)	10,000	8700	—
AcO	H	=O	8(14) : 22	11,800	8000	3580
AcO	Me	=O	8(14)	6600	3200	2000
MeO	H	—	8(14)	10,000	5000	2600
MeO	Me	—	8(14)	9700	6000	3000

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[21] Bladon, Henbest, and Wood, *J.*, 1952, 2737.