673. *The Constitution and Stereochemistry of Drimenol, a Novel Bicyclic Sesquiterpenoid.*[1]

By H. H. Appel, C. J. W. Brooks, and K. H. Overton.

The constitution and absolute stereochemistry of the sesquiterpenoid drimenol, $C_{15}H_{26}O$, obtained from the bark of *Drimys winteri* Forst. have been elucidated. The saturated drimanic and drimic acid previously obtained are shown to be identical with two known degradation products, $C_{15}H_{26}O_2$ from oleanolic acid or ambrein, and $C_{12}H_{20}O_4$ from abietic acid or onocerin. Drimenol is the first bicyclic sesquiterpenoid having the structure and absolute stereochemistry characteristic of rings A and B of the di- and tri-terpenoids. This fact has theoretical significance in the biogenesis of terpenoids.

Drimenol was isolated in 1948 from the bark of *Drimys winteri* Forst. by Appel and his collaborators [2]; it was shown to be a mono-olefinic bicyclic primary alcohol, since it consumed one mol. of peracid and on catalytic hydrogenation furnished a saturated dihydro-alcohol, drimanol, which was oxidised by Beckmann's mixture without loss of carbon to a monocarboxylic acid, drimanic acid. Oxidation of drimenol with the same reagent gave a ketone, drimone (characterised as the oxime), which could be further oxidised to a saturated dicarboxylic acid, drimic acid. A consideration of analytical values suggested for drimenol the composition $C_{16}H_{28}O$, for drimone $C_{14}H_{22}O$ and for drimic acid $C_{12}H_{20}O_4$. A continuation of these studies has now led to the elucidation of the structure and stereochemistry of drimenol.

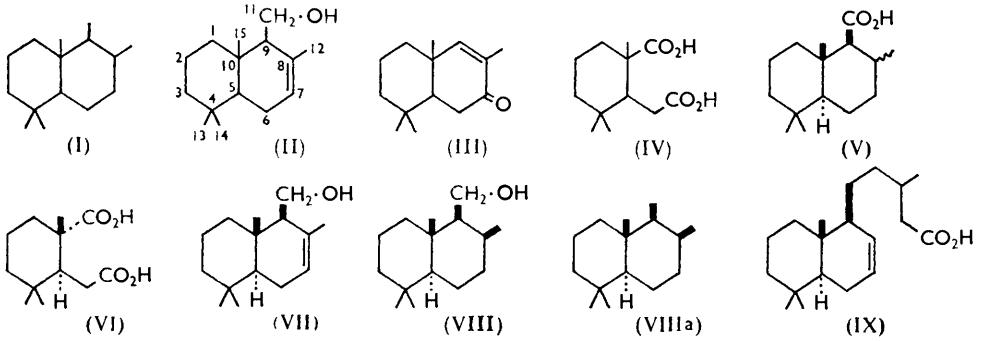
The previous data can be supplemented as follows. Drimenol further revealed its unsaturated nature in its ultraviolet ($\varepsilon_{210\,m\mu}$ 2140; $\varepsilon_{215\,m\mu}$ 950; $\varepsilon_{220\,m\mu}$ 250) and its infrared absorption ($\nu_{max.}$ 814 cm.$^{-1}$ in Nujol): these are characteristic of a triply substituted ethylenic linkage.[3,4] Moreover, drimenol gave a yellow colour with tetranitromethane, and was oxidised by monoperphthalic acid to a saturated crystalline epoxy-alcohol (see below), m. p. 96—97°, which showed no selective absorption between 210 and 300 mμ and in the infrared had (in Nujol) $\nu_{max.}$ 3400 cm.$^{-1}$ (associated OH) but no bands in the carbonyl region. Drimenol was recovered unchanged after treatment with manganese dioxide [5] in chloroform, and thus appeared not to be an allylic alcohol. Drimone was disclosed as an αβ-unsaturated ketone by its ultraviolet absorption ($\lambda_{max.}$ 235 mμ; ε 6500) whilst its infrared absorption (in CCl_4) ($\nu_{max.}$ 1670 cm.$^{-1}$) suggested that the chromophore was situated in a six-membered ring.

Our initial efforts were directed towards establishment of the carbon skeleton of drimenol. Dehydrogenation on palladised charcoal at 350° afforded as the sole identified product 1,2,5-trimethylnaphthalene, in about 30% yield. Our immediate inference was that we were dealing with a compound possessing the C_{15} carbon skeleton (I) normally found in rings A and B of the di- and tri-terpenoids. On this assumption, coupled with the evidence already presented, we were compelled to reformulate drimenol as $C_{15}H_{26}O$ and to assign to it the structure (II), particularly in order to accommodate the transformations into drimone (III) and into drimic acid (IV). This conclusion was strengthened by a comparison of the physical constants of drimanic (driman-11-oic acid *) and drimic acid

* We propose the name drimane for the saturated hydrocarbon having the structure and stereochemistry depicted in (VIIIa). The numbering follows the system proposed by Djerassi *et al.*[6]

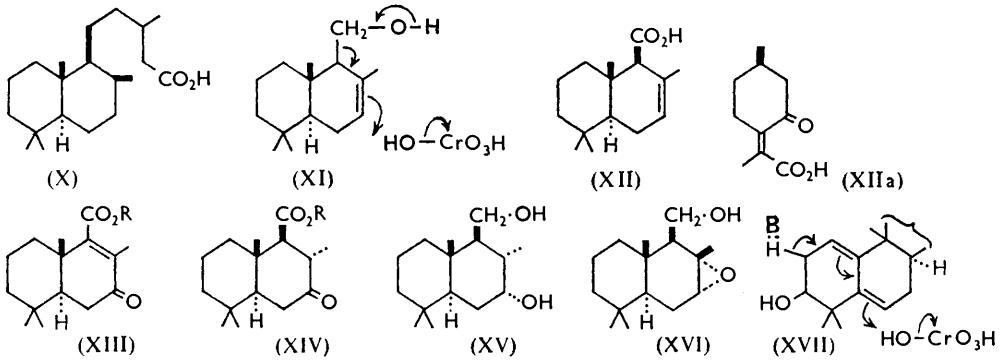
[1] Preliminary communication: Brooks and Overton, *Proc. Chem. Soc.*, 1957, 322.
[2] Appel, Gleisner, and Sahli, *Scientia (Chile)*, 1948, **15**, 31; Appel, Rotman, and Thornton, *ibid.* 1956, **23**, 19.
[3] Halsall, *Chem. and Ind.*, 1951, 867; Bladon, Henbest, and Wood, *J.*, 1952, 2737.
[4] Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 1958, p. 51.
[5] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094.
[6] Djerassi, Rittel, Nussbaum, Donovan, and Herran, *J. Amer. Chem. Soc.*, 1954, **76**, 6410.

with those recorded for the acids $C_{15}H_{26}O_2$ (V) (previously obtained from oleanolic acid and ambrein [7]) and $C_{12}H_{20}O_4$ (VI) (from onocerin and abietic acid [8]), respectively. Direct comparison subsequently confirmed these identities,* establishing the structure and absolute stereochemistry of drimenol as in (VII), if we make the reasonable assumption that no migration of the ethylenic linkage occurs during the hydrogenation of drimenol. Dr. A. Eschenmoser (Zurich) has kindly informed us that the infrared spectra of drimenol and α-bicyclofarnesol (in chloroform) are identical, thus confirming our assignment of configuration at $C_{(9)}$. We formulate drimanol as (VIII), the configuration at position 8 being tentatively assigned on the following grounds: (i) drimanol is the major product of hydrogenation, which would be expected to occur from the less hindered α-face, as in the



case [9] of cativic acid (IX); (ii) similar molecular rotation changes are associated with the hydrogenation of drimenol to drimanol (ΔM_D +73°) and of cativic acid to dihydrocativic acid (X) (ΔM_D +98°).

The genesis of " drimone " (renamed nordrimenone; systematically 11-nordrim-8-en-7-one) in the oxidation of drimenol with chromic acid or potassium dichromate in aqueous acetic acid (see p. 3322) may be considered to take place as in (XI) (arrows): a formal resemblance to the formation of oleanone from moradiol [10] is worthy of note. The proposed constitution of nordrimenone is further substantiated by its conversion into



drimic acid on ozonolysis; † the concomitant formation of acetic acid could be confirmed by its conversion into *p*-bromophenacyl acetate and by the infrared spectrum of the derived sodium acetate.

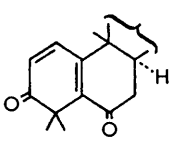
We now turn briefly to two further aspects of drimenol chemistry.

* We are grateful to Professors E. Lederer (Paris) and O. Jeger (Zurich) for authentic samples.
† This reaction provides a convenient alternative preparation of drimic acid.

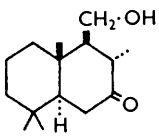
[7] Ruzicka, Gutmann, Jeger, and Lederer, *Helv. Chim. Acta*, 1948, **31**, 1746.
[8] Schaffner, Viterbo, Arigoni, and Jeger, *ibid.*, 1956, **39**, 174.
[9] Grant and Zeiss, *J. Amer. Chem. Soc.*, 1954, **76**, 5001.
[10] Barton and Brooks, *J.*, 1951, 257.

The first arose in an attempt to prepare drim-7-en-11-oic acid[7] (XII) from drimenol with chromium trioxide–pyridine [11] followed by silver oxide, in order to confirm our assignment of the ethylenic linkage in drimenol. The only crystalline compound directly isolated from the first reaction, in 12—15% yield, was a singly unsaturated, ketonic carboxylic acid, $C_{15}H_{22}O_3$, to which we assign the constitution (XIII; R = H) for the following reasons. The compound (in carbon tetrachloride) showed bands at 1685 (αβ-unsaturated cyclohexenone), 1748 (CO_2H) and 2800—2300 cm.$^{-1}$ (associated OH of CO_2H). In neutral ethanol it had $\lambda_{max.}$ 247 mμ (ε 8500) and 323 mμ (ε 42), but in 0·001N-ethanolic sodium hydroxide at room temperature it immediately showed $\lambda_{max.}$ 260 mμ (ε 11,600) whilst in 0·001N-ethanolic hydrochloric acid there was a slight hypsochromic shift [$\lambda_{max.}$ 241 mμ (ε 9400)]. There appeared to be an isosbestic point corresponding to the absorption maximum in neutral ethanol. It is relevant that the autoxidation product of menthofuran has, in ethanolic sodium hydroxide, $\lambda_{max.}$ 265 mμ (ε 8500); Woodward and Eastman [12] attribute this to the anion of (XIIa).

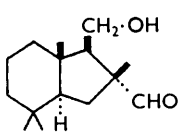
Further, in accordance with expectation (cf. the reduction of 7-keto-Diels's acid [13]), 7-oxodrim-8-en-11-oic acid (XIII; R = H) was smoothly reduced by zinc dust in acetic acid to the saturated 7-oxo-8α-driman-11-oic acid, $C_{15}H_{24}O_3$ (XIV; R = H), which had $\lambda_{max.}$ 282 mμ (ε 40) and $\nu_{max.}$ (in carbon tetrachloride), 1710 (superimposed cyclohexanone and CO_2H dimer), 1752 (CO_2H monomer), and 3525 cm.$^{-1}$ (unbonded OH of CO_2H). It was characterised as the methyl ester (XIV; R = Me) [also prepared *via* the oily methyl ester (XIII; R = Me)] which formed a 2,4-dinitrophenylhydrazone. The acid (XIV; R = H) was also prepared from drimenol α-oxide (XVI) in the following manner. Reduction of the oxide with lithium aluminium hydride afforded 8α-drimane-7α,11-diol (XV): the production of the secondary alcohol (see below) indicates the α-configuration of the oxide and permits the assignment of configuration at position 8 in the diol. Oxidation of the diol (XV) with chromic acid in acetic acid afforded the oxo-acid (XIV; R = H), thus securing the stereochemistry of this acid at positions 8 and 9, it being assumed that the equatorial position for the 8-methyl group is more stable than the axial. In agreement with this formulation, the oxo-acid (XIV; R = H) was not reconverted into the acid (XIII; R = H) by selenium dioxide in refluxing ethanol. Clearly the initial *cis*-addition product [14] of zinc reduction of the acid (XIII; R = H) is partly isomerised to (XIV; R = H) before or during working-up; a product isolated in minor quantity as the methyl ester is tentatively regarded as the 8β-epimer (see p. 3328).



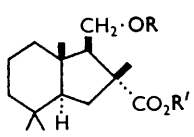
(XVIII)



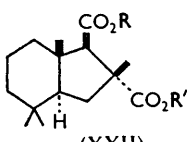
(XIX)



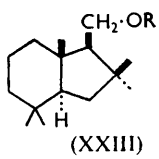
(XX)



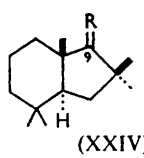
(XXI)



(XXII)



(XXIII)



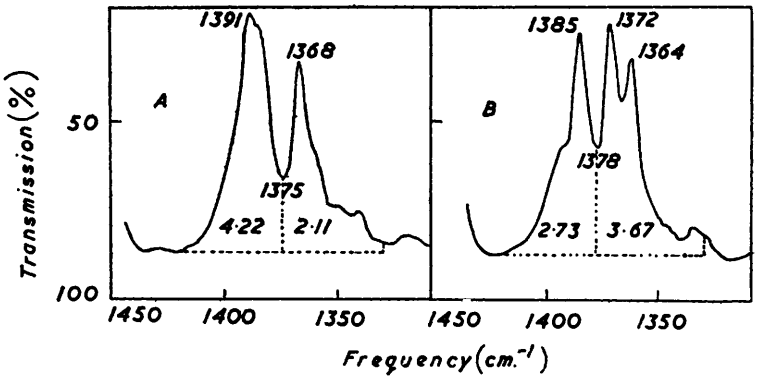
(XXIV)

The genesis of the acid (XIII; R = H) clearly bears some analogy to that of nordrimenone. A parallel example of the attack of chromium trioxide–pyridine on an ethylenic linkage is the conversion [15] of alnusadienol (XVII) into the dienedione (XVIII).

[11] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.
[12] Woodward and Eastman, *ibid.*, 1950, **72**, 399.
[13] Windaus, *Ber.*, 1908, **41**, 611.
[14] Zimmerman, *J. Amer. Chem. Soc.*, 1957, **79**, 6554, and earlier papers there cited.
[15] Beaton, Spring, Stevenson, and Stewart, *Tetrahedron*, 1958, **2**, 246.

A projected route to the compound (XIV) led to another interesting reaction. Thus, the boron trifluoride–ether complex might have been expected [16] to convert drimenol α-oxide (XVI) into the hydroxy-ketone (XIX). In fact this reagent produced an oily isomeric hydroxy-aldehyde, $C_{15}H_{26}O_2$ (characterised as the 2,4-dinitrophenylhydrazone), which on the basis of the spectroscopic data and subsequent transformations must be formulated as (XX). Thus it had infrared bands in carbon tetrachloride at 1728 and 2700 (saturated aliphatic CHO) and 3480 and 3600 cm.$^{-1}$ (OH) and an ultraviolet maximum at 280 mμ (ε ~12), whilst the 2,4-dinitrophenylhydrazone had $\lambda_{max.}$ 358 mμ (ε 25,000). Oxidation with silver oxide furnished the hydroxy-acid, $C_{15}H_{26}O_3$ (XXI; R = R′ = H) [$\nu_{max.}$ (in Nujol) 1703 (CO_2H dimer), 3220 (associated OH), and 2630 cm.$^{-1}$ (associated OH of CO_2H)], characterised as the acetate (XXI; R′ = H, R = Ac). Oxidation of the acid (XXI; R = R′ = H) with chromium trioxide in acetic acid afforded the dicarboxylic acid (XXII; R = R′ = H) [$\nu_{max.}$ (in Nujol) 1703 (CO_2H; dimer) and 3200—2600 cm.$^{-1}$ (associated OH of CO_2H)], characterised as its dimethyl ester (XXII; R = R′ = Me) [$\nu_{max.}$ (in CCl_4) 1743 cm.$^{-1}$ (ester CO)]. Similar oxidation of the oily ester (XXI; R = H, R′ = Me) gave the monomethyl ester (XXII; R = H, R′ = Me) [($\nu_{max.}$ (in Nujol)] 1730 (ester CO), 1705 (CO_2H dimer), and 3180—2650 cm.$^{-1}$ (OH of CO_2H)]. Attempts to convert the acid (XXII; R = R′ = H) into the anhydride by sublimation or by treatment with acetic anhydride were unsuccessful. Likewise the acid (XXI; R = R′ = H) showed no tendency to form a lactone. This is fully in accordance with the stereochemistry assigned to (XXII) on its mode of formation from the oxide (XVI). The rearrangement of cyclohexene epoxides is known to occur with ring contraction in sterically favourable examples.[17] The nature of the carbon skeleton of (XX) was finally secured in the following way. Wolff–Kishner reduction gave the crystalline isodrimanol (XXIII; R = H) which was not identical either with drimanol or with 8α-drimanol (which is a minor product in the hydrogenation of drimenol; see p. 3329).

Infrared spectra of (A) drimanol and (B) isodrimanol.



The structure assigned to isodrimanol is supported by a comparison of the infrared spectra of drimanol, 8α-drimanol, and isodrimanol in the region of absorption associated with the symmetrical CH deformation mode (" breathing ") of methyl groups. We are greatly indebted to Dr. G. Eglinton and Mr. J. F. Morman for the following observations and their interpretation.

Drimanol and 8α-drimanol showed very similar absorption (in carbon tetrachloride) over the region 1500—1300 cm.$^{-1}$, the main peaks being at 1469, 1460, 1445, 1391, and 1368 cm.$^{-1}$. Isodrimanol, however, showed marked differences, particularly in the methyl " breathing " region, the main peaks being at 1466, 1385, 1372, and 1364 cm.$^{-1}$ (Figure).

[16] Henbest and Wrigley, *J.*, 1957, 4596.
[17] See, *inter al.*, House and Wassen, *J. Amer. Chem. Soc.*, 1957, **79**, 1488; Naqvi, Horwitz, and Filler, *ibid.*, p. 6283.

" Breathing " vibrations of different types of methyl groups have been quoted [18,19] as occurring at the following frequencies: *gem*-dimethyl 1384 and 1364 cm.$^{-1}$; angular methyl (6,6 ring fusion) 1385 $\pm$ 9 cm.$^{-1}$ (6,5 ring fusion), 1377 $\pm$ 5 cm.$^{-1}$; ordinary methyl 1380 $\pm$ 6 cm.$^{-1}$. Thus in isodrimanol the two peaks at 1372 and 1364 cm.$^{-1}$ must represent the lower-frequency components of the CH deformations of the two differently situated *gem*-dimethyl groups: the group attached to the six-membered ring evidently gives rise to a peak slightly displaced from its position in drimanol and 8α-drimanol, presumably as a consequence of the contraction of the attached ring, whilst the second peak must be due to the new *gem*-dimethyl group arising from the contraction. The absorption due to the angular methyl group in isodrimanol is evidently contained in the peak at 1385 cm.$^{-1}$. A more detailed analysis of the bands in this region is probably unjustified in view of the considerable steric interactions between the various methyl substituents in all three alcohols.

The regions of absorption attributed to the lower component of the *gem*-dimethyl " breathing " mode were taken to range between the relevant minima of the absorption curves. For drimanol this region was 1375—1330 and for isodrimanol 1378—1330 cm.$^{-1}$. The apparent integrated absorption intensities (β) were found to be in the ratio of 1 : 1·74 in satisfactory agreement with the expected 1 : 2 relation.

The ratio of integrated absorption intensities over the region 1420—1330 cm.$^{-1}$ for drimanol and isodrimanol was almost unity though there are four methyl groups in the former and five in the latter. Evidently for this region $\beta/2$ for *gem*-dimethyl is somewhat less than β for an isolated methyl group.

Conversion of the alcohol (XXIII; R = H) by pyrolysis of its acetate (XXIII; R = Ac) [$\nu_{max.}$ (in Nujol) 1746, 1240 cm.$^{-1}$ (acetate)] into isodrim-9-ene (XXIV; R = CH_2) [$\nu_{max.}$ 880, 1645 cm.$^{-1}$ (=CH_2)] and ozonolysis afforded isonordrimanone (XXIV; R = O) which had $\nu_{max.}$ 1738 cm.$^{-1}$ (CO of cyclopentanone).

Three examples are now known of the novel class of sesquiterpenoid represented by drimenol. Of these iresin [20] and farnesiferol A [21] have the same skeletal structure as drimenol but are of the opposite absolute configuration (which is also found in the diterpenoids eperuic acid [22] and cafestol [23]). Drimenol is thus the first representative of this class possessing both the skeletal structure and absolute stereochemistry normally found in rings A and B of the di- and tri-terpenoids, and so constituting a biogenetic link between these three groups.[24] The intermediacy of drimenol gains further significance from the cyclisation of farnesylic acid *in vitro* to drimenic acid, recently clarified by Stadler, Eschenmoser, Schinz, and Stork.[25]

Experimental

Ultraviolet absorption spectra were determined with the Unicam S.P. 500 spectrophotometer and are for solutions in ethanol unless specified otherwise. Routine infrared spectra were kindly determined with the Perkin–Elmer 13 spectrophotometer by Mrs. F. Lawrie. Microanalyses were carried out by Mr. J. M. L. Cameron and his associates. The light petroleum used was of b. p. 60—80° unless stated to the contrary. Chromatographic alumina was prepared and standardised by Brockmann's procedure.[26]

[18] (*a*) Jones and Cole, *J. Amer. Chem. Soc.*, 1952, **74**, 5648; (*b*) Jones and Sandorfy, Chapter 4 in " Techniques of Organic Chemistry," Vol. IX, Interscience Publ. Inc., New York, 1956.
[19] Bottomley, Cole, and White, *J.*, 1955, 2624.
[20] Djerassi and Burstein, *J. Amer. Chem. Soc.*, 1958, **80**, 2593; Rossmann and Lipscomb, *ibid.*, p. 2592.
[21] Caglioti, Naef, Arigoni, and Jeger, *Helv. Chim. Acta*, 1958, **41**, 2278.
[22] King and Jones, *J.*, 1955, 658; Cocker and Halsall, *J.*, 1956, 262; Djerassi and Marshall, *Tetrahedron*, 1958, **1**, 247.
[23] Djerassi, Cais, and Mitscher, *J. Amer. Chem. Soc.*, 1958, **80**, 247.
[24] Ruzicka, *Experientia*, 1953, **9**, 357.
[25] Stadler, Eschenmoser, Schinz, and Stork, *Helv. Chim. Acta*, 1957, **40**, 2191.
[26] Brockmann, *Ber.*, 1941, **74**, 73.

Extraction of Drimenol.—The air-dried powdered bark was extracted exhaustively with light petroleum (b. p. 70—80°) in a Soxhlet apparatus. The light brown viscous oil (45% of the weight of bark) obtained after removal of the solvent afforded on distillation *in vacuo* a viscous yellow fraction (b. p. 120—195°/8 mm.) which crystallised. Crude drimenol (13% by weight of the extract) was obtained by filtration and washing with a little benzene. Recrystallised from light petroleum, it formed prisms, m. p. 97—98°, $[\alpha]_D$ −18° (*c* 3·55 in benzene), giving a positive reaction with tetranitromethane, $\nu_{max.}$ 3570 (free OH), 3450 (bonded OH) cm.$^{-1}$ in CS_2 (Found: C, 80·75; H, 11·7. Calc. for $C_{15}H_{26}O$: C, 81·0; H, 11·8%).

Recent experiments (H. H. Appel and R. Dohr [27]) have shown that drimenol is not an invariable constituent of the bark of Chilean *Drimys winteri* Forst. The first sample investigated happened to be particularly rich in this alcohol. Of fifteen barks obtained from different parts of the country, drimenol has been found in only four.

When a solution of drimenol (120 mg.) in chloroform (10 ml.) was shaken with manganese dioxide (1 g.) for 3 hr. there was no significant change in light absorption, and drimenol (80 mg.) was recovered.

Dehydrogenation of Drimenol.—Drimenol (1 g.) was heated with 5% palladised charcoal (1 g.) for 1 hr. at 300—350° in a stream of carbon dioxide. The hydrogen evolved amounted to 105 ml. (calc. for complete dehydrogenation, 300 ml.). Extraction of the residue with ether afforded a yellow oil (360 mg.) which appeared, from its ultraviolet absorption (principal $\lambda_{max.}$ 229 mμ, $E^{1\%}_{1cm.}$ 2780) to be substantially 1,2,5-trimethylnaphthalene. Portions were converted into the styphnate (recrystallised from ethanol–light petroleum), m. p. 126—128° (evacuated capillary) undepressed on admixture with authentic material of m. p. 127—129°, and into the 1,3,5-trinitrobenzene adduct [from ether–light petroleum (b. p. 40—60°)], m. p. 153—156° (evacuated capillary) undepressed on admixture with authentic material of the same m. p. The identity of the latter adduct with authentic material was confirmed by the infrared absorption (in Nujol). A portion of the isolated trinitrobenzene adduct was decomposed on alumina (activity I), yielding crystalline 1,2,5-trimethylnaphthalene, identified by m. p., mixed m. p., and infrared absorption (film).

Drimenol α-Oxide.—A solution of drimenol (1·22 g., 5·5 mmoles) in ether (25 ml.) was mixed with one of monoperphthalic acid in ether (25 ml.; 0·34M) and left at 5° for 67 hr. The mixture was poured into ice (100 g.), ethanol (50 ml.), sodium dithionate (3 g.), and N-sodium hydroxide (50 ml.), and the ether was removed at room temperature. The single alkaline phase so obtained was extracted with ether, and the extracts were washed with water, dried (Na_2SO_4), and evaporated. The residue crystallised from ether–light petroleum as prisms (635 mg., 49%), m. p. 96—97°. The mother-liquor gave a second crop (292 mg., 22%), m. p. 95—96°. The pure *oxide* had m. p. 96—97°, $[\alpha]_D$ +20° (*c* 1·56 in chloroform), and gave no colour with tetranitromethane (Found: C, 75·7; H, 10·65. $C_{15}H_{26}O_2$ requires C, 75·55; H, 11·0%). Drimenol α-oxide showed no selective absorption between 210 and 300 mμ.

8α-Drimane-7α,11-diol.—A solution of drimenol α-oxide (300 mg., 1·22 mmoles) in dry tetrahydrofuran (20 ml.) was added dropwise during 0·5 hr. to refluxing tetrahydrofuran (50 ml.) containing lithium aluminium hydride (600 mg.). Refluxing was continued for 21 hr. The mixture was cooled and treated successively with ethyl acetate, aqueous acetic acid, ice, and finally 2N-sulphuric acid (6 ml.) to give pH ~5. Ether-extraction afforded a solid (300 mg.), m. p. 140—146°, recrystallised from chloroform–light petroleum as prisms (146 mg., 48%), m. p. 154—155°, $[\alpha]_D$ −17° (*c* 1·15 in chloroform) (Found: C, 74·9; H, 11·6. $C_{15}H_{28}O_2$ requires C, 74·95; H, 11·75%). A second crop was purified by sublimation at 150°/1 mm., giving material (98 mg., 32%) of m. p. 150—152°.

Oxidation of Drimenol with Chromium Trioxide–Pyridine.—Drimenol (3 g.) in dry pyridine (30 ml.) was mixed with a suspension of the reagent prepared from chromium trioxide (7·5 g.) and dry pyridine (75 ml.). The mixture was left for 2·5 hr. at room temperature with occasional shaking and then poured into cold water (250 ml.). After the excess of oxidant had been destroyed by sulphur dioxide, the solution was extracted with benzene–ethyl acetate (1 : 1). The combined extracts were washed successively with water, four times with 2N-hydrochloric acid, and again with water, then dried (Na_2SO_4) and evaporated, yielding an amber gum (2·76 g.). This was chromatographed on alumina (activity V; 50 g.), giving two major fractions: (i) an intractable oil (1450 mg.), eluted at once by light petroleum (b. p. 40—60°), and (ii) a mainly crystalline fraction (680 mg.) eluted immediately after (i) by the same solvent. Fraction (i)

[27] Appel and Dohr, *Scientia (Chile)*, 1958, **25**, 137.

was rechromatographed on alumina (activity III; 40 g.) but no crystalline material could be isolated, and there was evidence of decomposition on the column. The ultraviolet absorption of various fractions from the rechromatography showed them to be crude αβ-unsaturated ketones ($\lambda_{max.}$ 235—242 mμ) but the highest intensity obtained was only $E^{1\%}_{1\,cm.}$ 170, *i.e.*, only about half that expected for a pure compound. Fractional distillation at 1 mm. afforded only partial concentration ($\lambda_{max.}$ 235 mμ, $E^{1\%}_{1\,cm.}$ ~220), and the material was converted into the 2,4-dinitrophenylhydrazone which crystallised from ether–ethanol as orange needles, m. p. 174—175°, which became orange-red in air (Found: C, 62·1; H, 6·6; N, 15·35. $C_{20}H_{26}O_4N_4$ requires C, 62·15; H, 6·8; N, 14·5%), $\lambda_{max.}$ (in chloroform) 382—383 mμ (ε 28,000), (in 99 : 1 ether–chloroform) 366—367 mμ (ε 30,000). Fraction (ii), recrystallised from ether–light petroleum, yielded prisms (360 mg.), m. p. 222—224°, $[\alpha]_D$ +47° (*c* 1·70 in chloroform) (Found: C, 72·3; H, 9·0. $C_{15}H_{22}O_3$ requires C, 71·95; H, 8·85%). In several experiments the yield of this *product* remained low. Infrared bands of the oily methyl ester in carbon tetrachloride were at 1680 (αβ-unsaturated cyclohexenone), 1730 cm.$^{-1}$ (ester CO).

Reduction of 7-*Oxodrim*-8-*en*-11-*oic Acid with Zinc and Acetic Acid.*—The unsaturated keto-acid (286 mg.) in glacial acetic acid (20 ml.) was refluxed with zinc dust (6 g.) for 10 min. The mixture was worked up in the normal way, to yield 7-*oxo*-8α-*driman*-11-*oic acid* (260 mg.) which crystallised from ether–light petroleum (b. p. 40—60°) as prisms, m. p. 202—203° (140 mg.), $[\alpha]_D$ +1° (*c* 0·76 in chloroform) (Found: C, 71·3; H, 9·55. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%). The *methyl ester*, prepared with diazomethane and recrystallised from aqueous methanol, formed prisms, m. p. 73·5—74° (Found: C, 72·05; H, 9·75. $C_{16}H_{26}O_3$ requires C, 72·15; H, 9·85%), $\nu_{max.}$ (in carbon tetrachloride) 1730 and 1710 cm.$^{-1}$. This ester was also obtained by zinc reduction of the oily methyl 7-oxodrim-8-en-11-oate. It formed a 2,4-*dinitrophenylhydrazone*, golden-yellow needles (from aqueous ethanol), m. p. 166—168° (Found: C, 59·4; H, 6·4; N, 12·55. $C_{22}H_{30}O_6N_4$ requires C, 59·2; H, 6·75; N, 12·55%), $\lambda_{max.}$ (in chloroform) 363 mμ (ε 23,500), $\nu_{max.}$ (in carbon tetrachloride) 1732 cm.$^{-1}$.

The uncrystallisable residue (150 mg.) from two preparations of 7-oxo-8α-driman-11-oic acid was methylated by diazomethane. Chromatography on alumina (activity III) gave two main ketonic fractions: (i) (52 mg.), eluted by light petroleum, identified as methyl 7-oxo-8α-driman-11-oate by conversion into the 2,4-dinitrophenylhydrazone, and (ii) (67 mg.), eluted by light petroleum–benzene (1 : 1) as an oil which yielded, after sublimation *in vacuo*, crystals, m. p. 60—61° (Found: C, 72·2; H, 9·4. Calc. for $C_{16}H_{26}O_3$: C, 72·15; H, 9·85%), $\nu_{max.}$ (in carbon tetrachloride) 1717 and 1735 cm.$^{-1}$, further characterised as a 2,4-*dinitrophenylhydrazone*, needles (from ethyl acetate–light petroleum), m. p. 197—198° (Found: C, 59·4; H, 6·5; N, 12·8. $C_{22}H_{30}O_6N_4$ requires C, 59·2; H, 6·75; N, 12·55%), $\lambda_{max.}$ (in chloroform) 370 mμ (ε 23,600), $\nu_{max.}$ (in carbon tetrachloride) 1732 cm.$^{-1}$. This second ketonic ester is tentatively regarded as methyl 7-oxo-8β-driman-11-oate. The infrared spectra of the two oxo-esters and of their dinitrophenylhydrazones are consonant with the structures proposed.

Oxidation of 8α-*Drimane*-7α,11-*diol by Chromic Acid.*—The diol (98 mg., 0·38 mmole) was dissolved directly in a 0·062N-solution of chromium trioxide (30 ml.) in 99·8% acetic acid. The oxidant was rapidly consumed, 1·85 " atoms of oxygen " being consumed within 20 min. and only a further 0·05 in the next 40 min. Worked up at this stage the solution gave as the only crystallisable product 7-oxo-8α-driman-11-oic acid (42 mg.), identical by m. p., mixed m. p., and infrared spectrum with the product described above.

Treatment of Drimenol Oxide with Boron Trifluoride.—(i) Drimenol oxide (139 mg.) in 15 ml. of dry benzene was treated with freshly distilled boron trifluoride–ether complex (0·2 ml.). After 3 min. a spot test on paper indicated the presence of a carbonyl group, and the solution was shaken with saturated aqueous sodium hydrogen carbonate and extracted with benzene. The combined extracts were washed with water and evaporated, giving an oil (130 mg.) which failed to yield crystalline material when chromatographed on alumina. Fractions eluted by benzene (92 mg.) afforded a crystalline 2,4-*dinitrophenylhydrazone*, recrystallising from aqueous ethanol as orange platelets, m. p. 171—172° (Found: C, 60·4; H, 7·45; N, 13·0. $C_{21}H_{30}O_5N_4$ requires C, 60·25; H, 7·25; N, 13·4%).

The hydroxy-aldehyde was further characterised as the *azine*, m. p. 188—189°, formed by treatment with hydrazine in refluxing aqueous ethanol and recrystallised from ether–light petroleum (Found: C, 76·75; H, 10·85; N, 6·1. $C_{30}H_{52}O_2N_2$ requires C, 76·2; H, 11·1; N, 5·95%), $\lambda_{max.}$ (in ethanol) 210 mμ (ε 19,000), $\nu_{max.}$ (Nujol mull) 1640 (C=N), 3400 and 3250 cm.$^{-1}$ (associated OH).

(ii) Drimenol oxide (300 mg.) in dry benzene (80 ml.) was treated with boron trifluoride–ether complex (0·50 ml.), and the solution was worked up as in (i) after 5 min. A solution of the crude product in ethanol (15 ml.) was added dropwise during 10 min. to a stirred suspension of silver oxide [prepared by the slow addition of 25% aqueous potassium hydroxide (8 ml.) to hot 7% aqueous silver nitrate (8 ml.) and heated on the steam-bath]. The mixture was stirred and heated under reflux for 30 min., left to cool, and filtered, and the filtrate was extracted with ether to remove non-acidic products (33 mg.). Acidification of the aqueous phase and further extraction afforded a mainly crystalline *hydroxy-acid* (240 mg.), recrystallising from ether–light petroleum as plates (163 mg., 51%), m. p. 172—173°, $[\alpha]_D$ +34° (*c* 1·15 in chloroform) (Found: C, 70·65; H, 10·5. $C_{15}H_{26}O_3$ requires C, 70·85; H, 10·3%). (In a second preparation the yield of pure product was 70%.) The corresponding *acetate*, prepared with acetic anhydride and pyridine, formed plates from ether–light petroleum and was further purified by sublimation (bath temp. 140°/1 mm.); it had m. p. 145—146°, $[\alpha]_D$ +15° (*c* 0·95 in chloroform) (Found: C, 69·1; H, 9·7. $C_{17}H_{28}O_4$ requires C, 68·9; H, 9·5%).

Oxidation of the Hydroxy-acid by Chromic Acid.—A solution of the hydroxy-acid (90 mg.; m. p. 172—173°) in acetic acid (5 ml.) was treated with chromium trioxide in acetic acid (10 ml.; 0·074N) and after 10 min. the mixture was worked up as usual to give a gummy *dicarboxylic acid* which crystallised from ether–light petroleum to yield prisms (35 mg.), m. p. 233—235°. Purification for analysis was conveniently effected by sublimation at 160°/0·1 mm. [Found: C, 67·45; H, 9·2; equiv. (potentiometric titration to first end-point) 271, (titration to second obscure end-point, pH ~11) 142. $C_{15}H_{24}O_4$ requires C, 67·15; H, 9·0%].

A similar oxidation of the oily methyl ester of the hydroxy-acid (prepared with diazomethane) yielded a *monomethyl ester* of the dicarboxylic acid, purified by sublimation (130°/0·5 mm.) and by recrystallisation from ether–light petroleum as prisms, m. p. 125—126° (Found: C, 68·05; H, 9·2. $C_{16}H_{26}O_4$ requires C, 68·05; H, 9·3%).

The dimethyl ester of the dicarboxylic acid, prepared with diazomethane and purified by recrystallisation from aqueous methanol and by sublimation (40°/0·4 mm.), had m. p. 47—48°, $[\alpha]_D$ −11° (*c* 0·63 in chloroform) (Found: C, 68·55; H, 9·35. $C_{17}H_{28}O_4$ requires C, 68·9; H, 9·5%).

Wolff–Kishner Reduction of the Crude Hydroxy-aldehyde from Boron Trifluoride Treatment of Drimenol Oxide.—The crude product, from the treatment of drimenol oxide (350 mg.) with boron trifluoride, as described above, was heated at 180° for 11 hr. with hydrazine hydrate (1 ml.), sodium ethoxide (300 mg.), and ethanol (2 ml.). The crude product (300 mg.) was chromatographed on alumina (15 g.) (activity III). The light petroleum eluates yielded plates (120 mg.) (from aqueous acetone), m. p. 80—81°, $[\alpha]_D$ +8° (*c* 0·95 in chloroform) (Found: C, 80·4; H, 12·45. $C_{15}H_{28}O$ requires C, 80·3; H, 12·6%). The *acetate*, prepared with acetic anhydride and pyridine, formed needles (from aqueous ethanol), m. p. 36°, $[\alpha]_D$ +14° (*c* 1·17 in chloroform) (Found: C, 76·9; H, 11·55. $C_{17}H_{30}O_2$ requires C, 76·75; H, 11·35%). The *toluene*-p-*sulphonate* formed needles (from aqueous acetone), m. p. 104—104·5°, $[\alpha]_D$ +16° (*c* 1·43 in chloroform), $\lambda_{max.}$ 225 mμ (ε 13,300) (Found: C, 70·0; H, 9·25. $C_{22}H_{34}O_3S$ requires C, 69·8; H, 9·05%).

Isodrimene.—Pyrolysis of isodrimanyl acetate (70 mg.) was effected by distilling it under nitrogen through a Pyrex tube (30 × 1 cm.) heated at 540°. The yellow condensate was freed from acetic acid, and the crude product (60 mg.) was chromatographed on alumina (15 g., grade V). Light petroleum (30 ml.) eluted isodrimene (32 mg.).

Ozonolysis of Isodrimene.—Isodrimene (29 mg.) in dry methylene chloride (15 ml.) was treated with ozonised oxygen at −60° until a test was negative to tetranitromethane and the solution was blue (20 min.). Decomposition of the ozonide with zinc in acetic acid followed by chromatography over activated alumina (grade III) afforded the nor-ketone.

Drimanol and 8α-Drimanol.—Drimenol (1·0 g.) was hydrogenated in "AnalaR" ethyl acetate (100 ml.) with Adams catalyst (200 mg.) at 20°/1 atm. The theoretical amount of hydrogen was absorbed in 20 min. Filtration and removal of solvent afforded *drimanol* (needles from aqueous acetone; 712 mg.), m. p. 110—111°, $[\alpha]_D$ +15° (*c* 4·27 in benzene) (Found: C, 80·4; H, 12·65. $C_{15}H_{28}O$ requires C, 80·3; H, 12·6%).

Attempts to separate 8α-drimanol from the hydrogenation product by chromatography over activated alumina (grade III) were only partly successful, 8α-drimanol being obtained pure from the head fractions in small yield.

A separation was achieved from two successive chromatograms of the mixed 3,5-dinitrobenzoates on activad tealumina (grade III), followed by fractional crystallisation from alcohol.

Obtained in this way, 8α-drimanyl 3,5-dinitrobenzoate crystallised from aqueous alcohol in needles, m. p. 103—104° (Found: C, 63·35; H, 7·55. $C_{22}H_{30}O_6N_2$ requires C, 63·15; H, 7·25%). The dinitrobenzoate was hydrolysed by heating it (13 mg.) in dioxan (0·5 ml.) and 10% methanolic potassium hydroxide (0·5 ml.) on the steam-bath for 1·5 hr. *8α-Drimanol* (7 mg.) was obtained by dilution, centrifugation, and sublimation at 10^{-3} mm., the initially colourless oil crystallising in needles, m. p. 60—62°, $[\alpha]_D$ +4° (*c* 1·16 in benzene) (Found: C, 80·0; H, 12·2. $C_{15}H_{28}O$ requires C, 80·3; H, 12·6%). *Drimanyl 3,5-dinitrobenzoate*, obtained during this separation from chloroform–ethanol in long plates, had m. p. 139—140° (Found: C, 63·05; H, 7·5; N, 6·75. $C_{22}H_{30}O_6N_2$ requires C, 63·15; H, 7·25; N, 6·7%). Hydrolysed as for 8α-drimanyl 3,5-dinitrobenzoate, it afforded drimanol, m. p. alone and mixed with material direct from the hydrogenation 110—111°.

Drimanyl α-Naphthylurethane.—Drimanol (100 mg.), α-naphthyl isocyanate (100 mg., 1·3 mol.), and light petroleum (b. p. 100—120°; 3 ml.) were kept at 120° during 45 min. Dilution with light petroleum (b. p. 100—120°; 2 ml.) and cooling afforded the *α-naphthylurethane* in needles [(from light petroleum (b. p. 100—120°)], m. p. 157—159° (Found: C, 79·6; H, 9·4. $C_{26}H_{35}O_2N$ requires C, 79·35; H, 8·95%).

Drimenyl α-Naphthylurethane.—Drimenol (100 mg.) similarly afforded its *α-naphthylurethane* in prisms [from light petroleum (b. p. 100—120°)], m. p. 110—112° (Found: C, 79·8; H, 8·55. $C_{26}H_{33}O_2N$ requires C, 79·75; H, 8·5%).

*Drimanyl Toluene-*p*-sulphonate.*—Drumanol (225 mg.) and freshly crystallised toluene-*p*-sulphonyl chloride (380 mg., 2 mol.) were kept in " AnalaR " pyridine (4 ml.) for 16 hr. at room temperature. The suspension of pyridine hydrochloride was poured into ice-cold saturated aqueous sodium carbonate. After 1 hr., ether-extraction and working-up in the usual way afforded the *drimanyl ester* (154 mg.) in needles [from light petroleum (b. p. 60—80°)], m. p. 95—97°, raised by one further crystallisation to 104—105°, $\lambda_{max.}$ 225 mμ (ε 13,000) (Found: C, 70·1; H, 9·05. $C_{22}H_{34}O_3S$ requires C, 69·8; H, 9·05%).

Driman-11-oic Acid.—To drimanol (400 mg.) in " AnalaR " acetic acid (5 ml.) was added dropwise a solution of chromic anhydride (130 mg. = 2·2 O) in 80% acetic acid (5 ml.) containing potassium hydrogen sulphate (130 mg.). After 1 hr. dilution with water, ether-extraction, etc., and removal of solvents under reduced pressure left a pale green oil which partly crystallised and had $\nu_{max.}$ (Nujol mull) 1700 (CO_2H), 3400—2390 (associated OH of CO_2H), and 1735 $cm.^{-1}$ (aldehyde).

This acid–aldehyde mixture in ethanol (15 ml.) was added dropwise and with stirring to a freshly prepared suspension of silver oxide (from 575 mg. of silver nitrate) on the steam-bath, and heated for an hour. Dilution with hot water (10 ml.), filtration, acidification, and ether-extraction, afforded a pale yellow oil from which driman-11-oic acid crystallised spontaneously as prisms (from aqueous ethanol), $[\alpha]_D$ (in chloroform) +14° (*c* 1·70), m. p. and mixed m. p. 135—136° (cf. ref. 7) (Found: C, 75·3; H, 11·1. Calc. for $C_{15}H_{26}O_2$: C, 75·6; H, 11·0%). The methyl ester formed needles (from aqueous ethanol), m. p. 49—50° (Ruzicka *et al.*[7] give m. p. 50—50·5°).

Nordrimenone.—(*a*) To drimenol (2·2 g.) in " AnalaR " acetone (15 ml.) was added dropwise and with stirring chromic anhydride (2·35 g., 3·5 O) and potassium hydrogen sulphate (2·35 g.) in 5 : 4 aqueous acetic acid (45 ml.). After 1 hr., the excess of oxidant was decomposed with methanol, most of the solvent removed at 40°, and the residue diluted with water, ether-extracted, and separated into neutral (1·89 g.) and acid (not further examined) fractions. Adsorption of the neutral fraction from benzene–light petroleum (1 : 2) on activated alumina (60 g.; grade III) and elution with the same solvent afforded nordrimenone (590 mg.) as needles. From aqueous ethanol it formed rods, m. p. 84—85°, $[\alpha]_D$ −67° (*c* 1·59 in benzene), $\lambda_{max.}$ 235 mμ (ε 6500), $\nu_{max.}$ (in chloroform) 1670 (αβ-unsaturated cyclohexanone) $cm.^{-1}$ (Found: C, 81·35; H, 10·55. Calc. for $C_{14}H_{22}O$: C, 81·50; H, 10·75%). Elution with solvent mixtures of increasing polarity gave only oils which were not further investigated.

(*b*) To drimenol (10·0 g.) in " AnalaR " acetic acid (150 ml.) was added dropwise and with stirring Beckmann's mixture (147 ml.); the rate of addition of the first 50 ml. was regulated to keep the temperature below 40°. Stirring was continued for 1 hr. more and the mixture kept at 20° for 4 days. Addition of water (500 ml.) resulted in the separation of crude nordrimenone (6—6·5 g.), which was washed with water. A further 1—1·5 g. were obtained from the mother-liquors.

Drimic Acid.—(*a*) Nordrimenone (528 mg.) in " AnalaR " acetic acid (20 ml.) was treated

dropwise and with stirring with sodium dichromate (1·56 g., 6 O) in sulphuric acid (1·1 ml.) and water (8·9 ml.). The mixture was kept for 0·5 hr. at 20°, then 0·5 hr. at 40°. Dilution with water, ether-extraction, removal of sulphuric acid by extraction with four-fifths saturated aqueous sodium chloride, extraction of the acid into 1·5N-sodium hydroxide, acidification, and re-extraction into ether afforded drimic acid (123 mg.), prisms (from acetone–light petroleum), m. p. 167—168° alone or mixed with an authentic specimen,[8] $[\alpha]_D$ −7° (*c* 4·62 in acetone) (Found: C, 63·15; H, 9·1. Calc. for $C_{12}H_{20}O_4$: C, 63·15; H, 8·85%).

(*b*) Nordrimenone (325 mg.) in dry methylene chloride was treated with ozonised oxygen at −10° until a test sample did not show $\lambda_{max.}$ 237 mμ (10 min.). Water (20 ml.) was added, and the methylene chloride removed in a stream of nitrogen while the solution was gradually warmed to 60°. The acidic product (220 mg.) recovered in the usual way was adsorbed from benzene on chromatographic silica gel (15 g.). Benzene–ether (1 : 1) eluted an oil (153 mg.) which was sublimed (3×10^{-4} mm.) and afforded drimic acid (from acetone–light petroleum), m. p. alone and mixed with material prepared by method (*a*) 166—168°.

In another experiment with 330 mg. of nordrimenone, the volatile acid formed in the ozonolysis was distilled into an equivalent amount of 0·1N-sodium hydroxide, and the solution divided into halves. One was taken to dryness and the residue exhibited $\nu_{max.}$ (KCl disc) 1585 cm.$^{-1}$ (AcO) as did an authentic specimen prepared from acetic acid.

The other half was concentrated to 5 ml., just acidified to phenolphthalein with 0·1N-hydrochloric acid and refluxed for 1 hr. with *p*-bromophenacyl bromide (225 mg.) with the addition of ethanol to produce a clear solution. Ether-extraction and adsorption of the residue on activated alumina [10 g. grade (V)] from light petroleum gave, on elution with the same solvent, first *p*-bromophenacyl bromide (8 mg.) (m. p. and mixed m. p.), followed by an oily mixture (53 mg.), and then *p*-bromophenacyl acetate (60 mg.; m. p. and mixed m. p.). Rechromatography of the oily intermediate fractions afforded a further 23 mg. of *p*-bromophenacyl acetate (total 40%).

Determination of gem-*Dimethyl Groupings in Drimanol,* 8α-*Drimanol, and Isodrimanol by Measurement of Apparent Integrated Infrared Absorption Intensities* (β).—Spectra were recorded linearly in cm.$^{-1}$ as % transmission (kindly determined by Dr. G. Eglinton, Mr. F. Gisbey, and Mr. J. F. Morman) with a Unicam S.P. 100 double-beam infrared spectrometer equipped with an S.P. 130 sodium chloride prism–1500 line per inch grating double monochromator (vacuum). The wave-number scale was calibrated [28,29] against polystyrene, methane, and water vapour and has an absolute accuracy better than ±1 cm.$^{-1}$. The spectra were determined under conditions ensuring resolution of water-vapour bands similar to that recorded by Downie *et al.*[28] (CaF_2, double pass); a spectrum of cholestanol (in carbon tetrachloride) exhibited slightly better peak separation than that in the literature [30] but was otherwise identical both in appearance and the position of peaks.

The compounds were examined as solutions in " AnalaR " carbon tetrachloride in the same pair of 2 mm. cells, over the region 1300—1500 cm.$^{-1}$ at a scanning speed of 20 cm.$^{-1}$ per min., the zero % transmission being accurately set before and after each run. 8α-Drimanol, available in very small quantity, was examined only qualitatively in a 1 cm. cell.

The apparent integrated absorpt ionintensities [31] (β), where $\beta = \frac{1}{cl}\int \ln\left(\frac{T_0}{T}\right)_\nu d\nu$ and c = molar concn., l = cell path (cm.), were determined by measurement of optical densities every

Compound *	*gem*-Me_2 alone (symmetric)		All Me groups (symmetric)		CH_2 + Total Me (antisymmetric)	
	Range	$10^{-3}\beta$	Range	$10^{-3}\beta$	Range	$10^{-3}\beta$
Drimanol	1330—1375	2·11	1375—1420	4·22	1420—1485 †	7·37
Isodrimanol	1330—1378	3·67	1378—1420	2·73	1420—1485 †	6·50

β in l. mole^{-1} cm.$^{-2}$.

* Drimanol and isodrimanol were examined as 0·0248M- and 0·0291M-solution, respectively.

† Integration was not continued beyond 1485 cm.$^{-1}$ as the lack of spectrometer energy consequent upon the rapidly increasing solvent absorption might have resulted in decreased accuracy.

[28] Downie, Magoon, Purcell, and Crawford, *J. Opt. Soc. Amer.*, 1953, **43**, 941.
[29] Plyler, Blaine, and Nowak, *J. Res. Nat. Bur. Stand.*, 1957, **58**, 195.
[30] Dobriner, Katzenellenbogen, and Jones, " Atlas of Infra Red Absorption Spectra of Steroids," Vol. I, Interscience, Publ. Inc., New York, 1953.
[31] Jones and Ramsay, *J. Amer. Chem. Soc.*, 1952, **74**, 80.

2 cm.$^{-1}$, followed by application of Simpson's rule.[32] For integration, 100% transmission was taken as that observed at 1420 cm.$^{-1}$.

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[32] Handbook of Chemistry and Physics, 39th edn., p. 318, Chemical Rubber Publ. Co.