Gymnomitrol and Related Sesquiterpenoids from the Liverwort *Gymnomitrion obtusum* (Lindb) Pears (Hepaticae). A Novel Tricyclic Skeleton [1]

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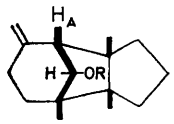
Gymnomitrol, a novel tricyclic sesquiterpenoid from the liverwort *Gymnomitrion obtusum* (Lindb) Pears, is shown to be (1*S*,2*S*,6*S*,7*R*,11*S*)-1,2,6-trimethyl-8-methylenetricyclo[5.3.1.$0^{2,6}$]undecan-11-ol (1) by chemical and spectroscopic methods. Seven compounds containing the same skeleton were also obtained from the extract. The bridge 11-hydroxy-group of isogymnomitrol (18) is epimerised on treatment with acid. Treatment of 1,2,6-trimethyl-5-oxo-8,8-oxymethylenetricyclo[5.3.1.$0^{2,6}$]undecan-11-yl acetate (24) with sodium borohydride gives 5,8-epoxy-8-hydroxymethyl-1,2,6-trimethyltricyclo[5.3.1.$0^{2,6}$]undecan-11-yl acetate (25).

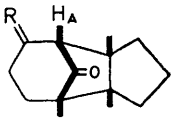
In a continuation of our studies [2,3] of the terpenoid constituents of the Hepaticae we investigated the liverwort *Gymnomitrion obtusum* (Lindb) Pears which proved to be a rich source of sesquiterpenoids with a novel tricyclic carbon skeleton. Eight new compounds were isolated from the extract, the major component being the alcohol, gymnomitrol, whose structure was established as (1) in the following manner.

Gymnomitrol, $C_{15}H_{24}O$, has hydroxy and exomethylene absorption in the i.r. ($\nu_{max.}$ 3625, 1640, and 890 cm^{-1}) and is therefore tricarbocyclic. The n.m.r. spectrum shows δ 0·93, 1·07, and 1·21 (3 × CMe), 3·70 (s, C*H*OH), 4·63 and 4·65 (both s, $:CH_2$). Another diagnostic signal is a singlet at δ 2·32. Its chemical shift suggests that it is an allylic proton and double irradiation experiments indicated that it is coupled to the carbinol proton with a very small coupling constant. The changes of chemical shift and multiplicity of this proton, labelled H_A in (1), as the functional groups were modified provided valuable information in the structural elucidation.

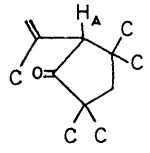
Acetylation of gymnomitrol (1) gave the corresponding acetate (2), which also occurs naturally. Acetylation



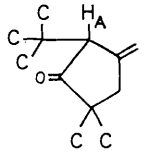
(1) R = H
(2 R = Ac



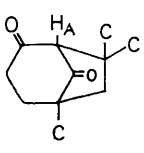
(3) R = CH_2
(5) R = O



(4a)



(4b)



(6)

was slow at room temperature and a reasonable rate of conversion was only achieved by heating, in accord with the hindered nature of the hydroxy-group. Saponification or reduction with lithium aluminium hydride of the acetate (2) regenerated gymnomitrol (1).

Oxidation of gymnomitrol afforded the ketone, gymnomitrone (3) ($\nu_{max.}$ 1745 cm^{-1}). Hence the hydroxy-group of gymnomitrol is in a five-membered ring. H_A in (3) is deshielded (δ 2·63) and the signal is sharper, confirming the loss of coupling to the original carbinol proton. On this evidence the part structures (4a) and (4b) can be drawn. The lack of coupling of H_A and of the carbinol proton in (1) requires substitution on the adjacent positions as shown. Reduction of gymnomitrone gave back only the original alcohol (1).

Ozonolysis of gymnomitrone (3) yielded the oily nor-diketone (5) ($\nu_{max.}$ 1748 and 1710 cm^{-1}). The introduction of the second carbonyl group further deshielded H_A (δ 3·00). It appears, therefore, that the nor-diketone (5) is a β-diketone with one α-proton (H_A). However (5) showed no sign of enolisation in the u.v., even on addition of alkali, thus suggesting that the two carbonyl groups form part of a bridged bicyclic system. From the i.r. data we favoured a bicyclo[3.2.1]octane, as in part structure (6), and later evidence substantiated this choice. The stereochemistry of the hydroxy-group in gymnomitrol as in (1) also follows from this since the torsion angle between the carbinol proton and H_A is close to 90°, resulting in a low coupling constant. In the epimeric alcohol (7) a coupling constant of *ca.* 4 Hz would be expected (see below).

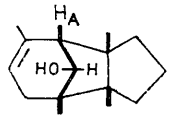
Evidence for the six-membered ring of the bicyclic system was obtained in several ways. First, ozonolysis of gymnomitrol acetate (2) gave the oily nor-ketoacetate (8) ($\nu_{max.}$ 1749 and 1718 cm^{-1}) whose ethylene acetal has a base peak in the mass spectrum at *m/e* 99, corresponding to the fragment (9). Reduction of the nor-ketoacetate with sodium borohydride resulted in the formation of only one alcohol (10), the *endo*-isomer. The multiplicity of the resonance due to the new carbinol proton of (10) is consistent with the presence of three neighbouring protons. H_A is not visible in the normal spectrum but on addition of $Eu(dpm)_3$ it moves downfield as a doublet (*J* 3 Hz). Decoupling experiments confirmed the assignment. This evidence puts beyond doubt the allylic and bridgehead nature of H_A in gymnomitrol. An additional feature of the shifted spectrum of (10) is the relatively small magnitude of the induced

[1] Preliminary communication, J. D. Connolly, A. E. Harding, and I. M. S. Thornton, *J.C.S. Chem. Comm.*, 1972, 1320.

[2] J. D. Connolly and I. M. S. Thornton, *Phytochemistry*, 1973, **12**, 631.

[3] J. D. Connolly and I. M. S. Thornton, *J.C.S. Perkin I*, 1973, 736.

shifts of the methyl resonances. In the $Eu(dpm)_3$ shifted spectrum of the isomeric hydroxy-acetate (11),



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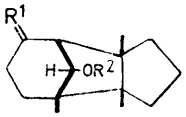
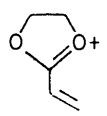
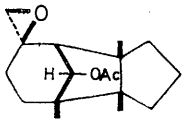


(8) R^1=O, R^2=Ac
(10) R^1=H, α-OH, R^2=Ac
(11) R^1=H, α-OAc, R^2=H



(9)



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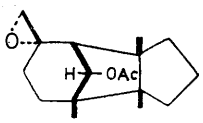

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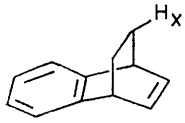
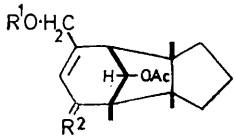


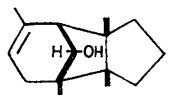
(14)

much larger relative shifts of the methyls are observed. The significance of these results will be discussed below. The isomeric hydroxy-acetate was obtained by sodium borohydride reduction of the nor-diketone (5), followed by selective acetylation.

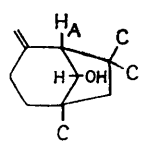
The second approach made use of another naturally occurring compound, epoxygymnomitrol acetate (12). This was readily prepared from gymnomitrol acetate by reaction with *m*-chloroperbenzoic acid. The major product of this reaction is identical with the natural epoxide (12) and arises from *exo*-attack of the peracid, as anticipated. A small amount of the α-epoxide (13) was also formed. This has the C*H*OAc resonance at δ 4·87br (s) whereas in the β-epoxide (12) the corresponding resonance is at δ 5·26. This deshielding in the β-isomer is presumably due to the proximity of the epoxy-oxygen to the bridge proton. A similar effect has been reported [4] for H_X in the *endo*- and *exo*-epoxides of 1,4-dihydro-1,4-ethanonaphthalene (14). The above observations support the previous assignment of stereochemistry of the hydroxy-group in gymnomitrol (1). Both epoxides (12) and (13) rearranged in acid to the allylic primary alcohol (15) [δ 4·00br (2H, s, CH_2OH) and 5·44br (s, vinyl proton)], which was also isolated from the extract of the liverwort. The corresponding diacetate (16) was oxidised by sodium chromate to the enone (17) [$\nu_{max.}$ 1751, 1680, and 1645 cm^{-1}; $\lambda_{max.}$ 240 nm (ε 10,000)]. The n.m.r. spectrum of the enone has no signals between δ 1·7 and 3·0, apart from H_A at 2·45, indicating the fully substituted nature



(15) R^1= H, R^2= H_2
(16) R^1= Ac, R^2= H_2
(17) R^1= Ac, R^2= O



(18)

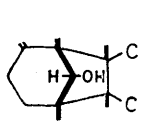


(19)

of the position α to the carbonyl group. In addition, a methyl resonance in the diacetate (16) is deshielded on formation of the enone.

Third, the same information was available from gymnomitrol itself. On treatment with either dry hydrogen chloride gas in chloroform or dilute sulphuric acid in methanol, gymnomitrol was converted into isogymnomitrol (18). This transformation was also achieved by attempted hydrogenation of gymnomitrol over 10% Pd–C. The n.m.r. spectrum of isogymnomitrol clearly shows the presence of a vinylic methyl group at δ 1·62 and a vinyl proton at 5·05. Irradiation at the vinylic methyl frequency leaves the vinyl proton as a clean triplet ($J_{obs.}$ 3 Hz) and simultaneously reveals the allylic methylene group as a double AB system. This confirms the fully substituted nature of the next carbon atom in the sequence. The part structure (19) can now be constructed for gymnomitrol and three methyl groups, three methylene groups, and one additional ring remain to be allocated.

The $Eu(dpm)_3$ shifted spectrum of gymnomitrol provided the necessary information for a total solution of the structural problem. Relative to a carbinol proton shift of 4·4 p.p.m., the H_A signal moves downfield by 2·5 p.p.m. and all three methyl signals by *ca.* 2 p.p.m. The fact that all three methyl groups show the same downfield shift suggests that they are nearly equidistant from the oxygen function and close to it. These requirements are uniquely met by placing the methyl



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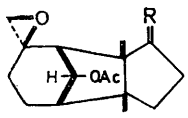
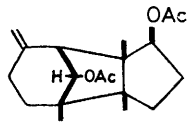


(21) R=H, β-OAc
(23) R=H, β-OH
(24) R=O



(22)

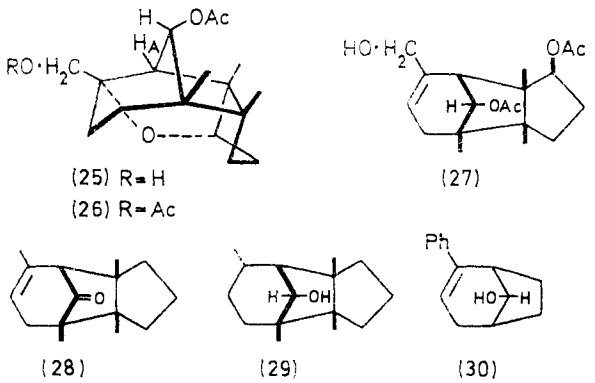
groups as shown in part structure (20). The possibility of a *gem*-dimethyl group is excluded. This structure accounts satisfactorily for the hindered nature of the hydroxy-group in gymnomitrol and the $Eu(dpm)_3$ results obtained for the isomeric hydroxy-acetates (10) and (11). Having arrived at the part structure (20) we had no alternative but to complete the structure of gymnomitrol by adding a second five-membered ring. Thus gymnomitrol has the constitution (1) with a new tricyclic skeleton. Confirmatory evidence for the second five-membered ring was obtained in the following way.

Two of the minor components of the extract, the epoxy-diacetate (21), and the exomethylene-diacetate (22), are oxygenated in the third ring. The exomethylene-diacetate (22) was converted into (21) by treatment with *m*-chloroperbenzoic acid. Selective hydrolysis of the ' new ' acetoxy-group in (21) afforded the hydroxy-acetate (23) [δ 4·58 (q, $J_{obs.}$ 11 and 6 Hz, C*H*OH) and 5·23 (s, C*H*OAc)]. The selectivity of the hydrolysis is possible because of the hindered nature of the bridge acetoxy-group. Collins oxidation of (23) yielded the

[4] K. Tori, K. Kitahonoki, Y. Takano, H. Tanida, and T. Tsuji, *Tetrahedron Letters*, 1964, 559.

acetoxy-cyclopentanone (24) ($\nu_{max.}$ 1735, 1745sh, and 1755sh cm^{-1}). The third ring is therefore five-membered. The assignment of the position and the configuration of the hydroxy-group in the hydroxy-acetate (23) rests on $Eu(dpm)_3$ shift evidence (see Experimental section). One of the epoxide protons suffers an upfield shift.

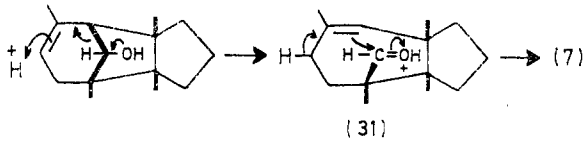
Confirmation of the position and stereochemistry of the hydroxy-group in (23) was expected to come from the preparation of the epimeric alcohol by sodium borohydride reduction of the cyclopentanone (24). It was anticipated that reduction would occur from the *exo*-face. In the event, even in the presence of a large excess of borohydride, reaction was slow and the product was not the epimeric alcohol. The n.m.r. spectrum of the product shows loss of the epoxide, and the presence of a primary hydroxy-group [δ 3·41br (2H, s)] unsplit by neighbouring protons and a new >CH–O– proton [δ 4·08 (t, $J_{obs.}$ 3 Hz)]. This compound readily formed an acetate [δ 3·86 and 4·06 (ABq, J 11 Hz)] with no hydroxy-absorption in the i.r. These data suggest that the reduction product is the ether (25) [acetate



(26)]. It presumably arises by intramolecular opening of the epoxide by the newly formed *endo*-hydroxy-group. The formation of the ether (25) provides valuable confirmatory evidence for the constitution and relative stereochemistry of the epoxy-diacetate (21) and indeed for gymnomitrol itself. Treatment of the epoxy-diacetate (21) with dilute acid afforded the hydroxy-diacetate (27), identical with another of the minor products from the extract.

Another interesting reaction is the isomerisation of gymnomitrol (1) under the influence of hydrogen chloride in chloroform. A second isomeric product was formed in addition to isogymnomitrol (18) (see above). Its n.m.r. spectrum shows δ 5·47br (s, :CH·), 1·67 (t, J 2 Hz, :CMe), 3·86 (d, J 4·2 Hz, C*H*OH), and 1·94 (d, J 4·2 Hz, H_A). Double irradiation clearly established the relationship between H_A and the carbinol proton and indicated that this compound is the epimeric alcohol (7). The magnitude of the coupling constant is in agreement with the new torsion angle between H_A and the carbinol proton. Oxidation of the alcohol (7) with Jones reagent yielded isogymnomitrone (28) ($\nu_{max.}$ 1746 cm^{-1}), identical with the ketone prepared by oxidation of isogymnomitrol (18) or acidic isomerisation of gymnomitrone (3).

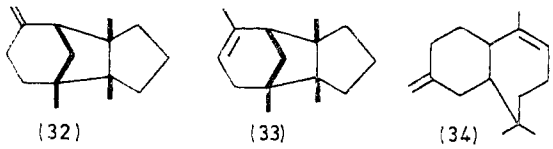
The double bond is a necessary feature for this epimerisation since dihydrogymnomitrol (29), the sole product of hydrogenation of gymnomitrol over platinum, is stable to the reaction conditions. A plausible mechanism for this epimerisation is depicted in Scheme 1.



SCHEME 1

The intermediate protonated aldehyde (31) can, in principle, cyclise to give both epimeric alcohols (18) and (7). The latter, however, is appreciably more stable thermodynamically since it lacks the severe steric interactions between the hydroxy-group and the tertiary methyl groups which destabilise gymnomitrol (1) and isogymnomitrol (18). It is not surprising that an equilibration strongly favours (7). This type of epimerisation was previously observed [5] by Buchanan and McLay during their investigations of the bicyclo-[3.2.1]octane derivative (30).

The least polar compound to be isolated from the extract was the parent hydrocarbon gymnomitrene (32) [δ 0·83, 0·89, and 1·02 (3 × CMe), and 4·58br (s, :CH_2)]. Acidic isomerisation of (32) afforded isogymnomitrene (33) [δ 0·86, 0·91, and 1·01 (3 × CMe), 1·67 (t, J 2 Hz, :CMe), and 5·17br (s, :CH)]. These two hydrocarbons are identical with β- and α-barbatene respectively which Andersen, Huneck, and their colleagues isolated [6] from several liverworts of the genus *Barbilophozia*. Further investigations by these workers



have shown [7] that these hydrocarbons occur widely in the Hepaticae. Gymnomitrene co-occurs [8,9] with bazzanene (34) in *Bazzania trilobata*.

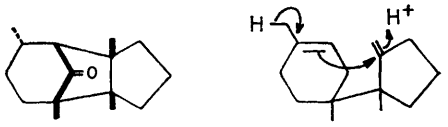
We endeavoured to correlate gymnomitrol (1) directly with gymnomitrene (32), but this was more difficult than anticipated. Gymnomitrol failed to react with toluene-*p*-sulphonyl chloride, presumably because of the hindered nature of the hydroxy-group. The epimeric alcohol (7) readily formed a tosylate, but reduction with lithium aluminium hydride gave only the original alcohol (7). The complete dominance of S–O cleavage

[5] G. L. Buchanan and G. W. McLay, unpublished results.
[6] N. H. Andersen, C. R. Costin, C. M. Kramer, Y. Ohta, and S. Huneck, *Phytochemistry*, 1973, **12**, 2709.
[7] N. H. Andersen and S. Huneck, personal communication.
[8] N. H. Andersen and S. Huneck, *Phytochemistry*, 1973, **12**, 1818.
[9] P. Stafford, B.Sc. Thesis, Glasgow, 1973.

can also be explained by the steric hindrance of the methyl groups.

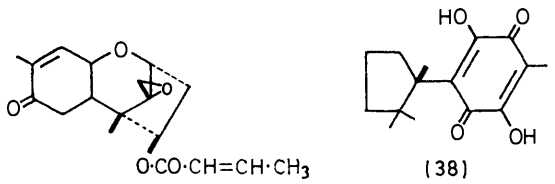
Wolff–Kishner reduction of gymnomitrone (3) under a variety of conditions failed to give any hydrocarbon product. Success was eventually achieved by Clemmensen reduction of (3) which gave isogymnomitrene (33). An unidentified isomeric hydrocarbon was also formed (see Experimental section).

The absolute configuration of gymnomitrol and its congeners was readily elucidated by use of circular dichroism (c.d.). Both the nor-ketoacetate (8) and dihydrogymnomitrone (35) exhibit negative Cotton effects ($\Delta\varepsilon$ −1·5) in agreement with predictions from the

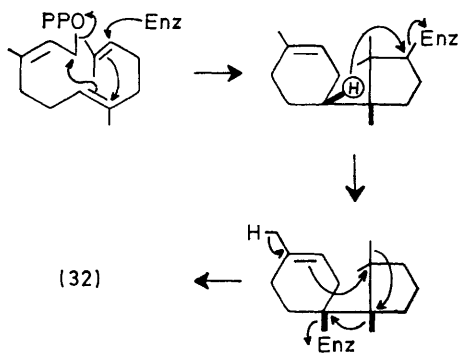


(35) (36)

octant diagrams. The absolute configuration was placed beyond doubt by the c.d. of isogymnomitrone (28) which shows a large negative Cotton effect ($\Delta\varepsilon$ −3) at 298 nm. The geometry of the chromophore in (28) is very close to that described in the classic paper by Moscowitz *et al.*[10] on the inherently dissymmetric $\beta\gamma$-unsaturated carbonyl chromophore. The large negative curve recorded for isogymnomitrone suggests an absolute stereochemistry which is in complete accord



(37) (38)



SCHEME 2

with that deduced from the c.d. curves of (8) and (35). The c.d. curve of gymnmitrone (3) itself is bisignate and of low amplitude and is difficult to interpret.

A plausible biogenetic derivation of the new gymnomitrene skeleton is from γ-bisabolene *via* the trichodiene intermediate (36). This biogenesis is closely related to those of the trichothecane antibiotics and cuparene sesquiterpenoids which have recently been the subject of intensive study by several groups.[11-16] Their results clearly demonstrate that γ-bisabolene is not a biosynthetic intermediate in the formation of trichothecin (37) and helicobasidin (38). In view of this the biosynthesis of the gymnomitrene skeleton might be better considered to derive from an enzyme-bound farnesyl pyrophosphate which, on concerted cyclisation, leads to a trichodiene-type intermediate and thence to gymnomitrene (Scheme 2).

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. N.m.r. spectra were recorded on a Varian HA-100 or T-60 spectrometer using tetramethylsilane as internal reference in deuteriochloroform. U.v. spectra were measured for ethanolic solution using a Unicam SP 800 spectrometer, and i.r. solution spectra on a Unicam SP 100 double beam spectrometer or on a Perkin-Elmer 225 instrument using carbon tetrachloride as solvent, unless otherwise stated. Routine mass spectra were determined on an A.E.I.-G.E.C. MS 12 mass spectrometer, high resolution spectra being obtained on an A.E.I. MS902s instrument. Optical rotations were measured in chloroform solution. C.d. spectra were recorded by Professor W. Klyne and Dr. P. M. Scopes, Westfield College, London.

Light petroleum refers to the fraction of b.p. 40—60°.

Extraction.—Powdered *G. obtusum* (100 g) was extracted with hot chloroform in a Soxhlet apparatus and the crude extract (22 g) chromatographed over basic alumina (grade H) using ether and gradually increasing concentrations of ethyl acetate in ether. The column was finally washed with ethyl acetate and methanol.

Preparative t.l.c. (p.l.c.) of the early hydrocarbon fraction over $AgNO_3$–silica gave *gymnomitrene* (1,2,6-*trimethyl*-8-*methylenetricyclo*[5.3.1.$0^{2,6}$]*undecane*) (32) (60 mg), which distilled as an oil at 60° and 0·01 mmHg, $[\alpha]_D$ −26° (*c* 4·97), $\nu_{max.}$ 3070, 1641, and 890 cm^{-1}, δ 0·83, 0·89, and 1·02 (3 × CMe), 4·58br (2H, s, :CH_2) (Found: C, 88·25; H, 12·05. $C_{15}H_{24}$ requires C, 88·15; H, 11·85%).

The main component of the extract was gymnomitrol (1,2,6-trimethyl-8-methylenetricyclo[5.3.1.$0^{2,6}$]undecan-11-ol) (1) (800 mg) which was purified by p.l.c. and sublimed at 50° and 0·01 mmHg, m.p. 114—116°, $[\alpha]_D$ +7° (*c* 2·28), $\nu_{max.}$ 3628sh (free OH), 3070, 1641, and 888 cm^{-1}, δ 0·97, 1·07, and 1·21 (3 × CMe), 2·32 (s, H_A), 3·70 (s, C*H*OH), and 4·63 and 4·65 (s, :CH_2) (Found: C, 81·5; H, 10·95. $C_{15}H_{24}O$ requires C, 81·75; H, 11·0%).

Gymnomitrol acetate (2) (300 mg) was also isolated from the extract and sublimed at 75° and 0·01 mmHg, m.p. 64—65°, $[\alpha]_D$ +19° (*c* 4·25), $\nu_{max.}$ 3070, 1740, 1641, and 891 cm^{-1}, δ 0·85, 1·04, and 1·12 (3 × CMe), 2·03 (AcO), 2·37 (s, H_A), 4·68 (s, C*H*OAc), and 4·71 and 4·76 (:CH_2) (Found: C, 77·9; H, 10·05. $C_{17}H_{26}O_2$ requires C, 77·8; H, 9·9%).

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From the intermediate fractions of the extract 1,2,6-*trimethyl*-8,8-*oxymethylenetricyclo*[5.3.1.$0^{2,6}$]*undecane*-5,11-*diyl diacetate* (21) (250 mg) was separated by t.l.c. and recrystallised from cold petroleum as needles, m.p. 155—156°, $[\alpha]_D$ −60° (*c* 0·58), $\nu_{max.}$ 1730 cm^{-1}, δ 0·92, 1·07, and 1·15 (3 × CMe), 2·03 and 2·05 (2 × AcO), 1·36 (s, H_A), 2·76 (2H, s, oxiran-H), 5·28 (s, C*H*OAc), and 5·55 and 5·65 (q, *J* 11 and 6 Hz, C*H*OAc) (Found: C, 67·65; H, 8·3. $C_{19}H_{28}O_5$ requires C, 67·85; H, 8·4%). A minor component of these fractions was 1,2,6-*trimethyl*-8-*methylenetricyclo*[5.3.1.$0^{2,6}$]*undecane*-5,11-*diyl diacetate* (22), (80 mg) which distilled 110° and 0·01 mmHg as an oil, $[\alpha]_D$ +14° (*c* 2·84), $\nu_{max.}$ 3075, 1739, 1645, and 897 cm^{-1}, δ 0·87, 1·08, and 1·12 (3 × CMe), 1·99 and 2·06 (2 × AcO), 2·44 (s, H_A), 4·82 (partially obscured s, C*H*OAc), 5·03 and 5·13 (q, *J* 11 and 6 Hz, C*H*OAc), and 4·82 and 4·78 (:CH_2) (Found: C, 71·4; H, 9·05. $C_{19}H_{28}O_4$ requires C, 71·2; H, 8·81%). 1,2,6-*Trimethyl*-8,8-*oxymethylenetricyclo*-[5.3.1.$0^{2,6}$]*undecan*-11-*yl acetate* (12) (60 mg) was separated by p.l.c. and sublimed at 110° and 0·01 mmHg, m.p. 149—150°, $[\alpha]_D$ −27° (*c* 2·25), $\nu_{max.}$ 1749 cm^{-1}, δ 0·92, 1·09, and 1·16 (3 × CMe), 2·04 (AcO), 2·65 (2H, s, oxiran-H), and 5·26 (s, C*H*OAc) (Found: C, 73·4; H, 9·6. $C_{17}H_{26}O_3$ requires C, 73·35; H, 9·4%).

The more polar fractions of the extract yielded 8-*hydroxymethyl*-1,2,6-*trimethyltricyclo*[5.3.1.$0^{2,6}$]*undec*-8-*en*-11-*yl acetate* (15) (60 mg) which, after p.l.c., was distilled at 100° and 0·005 mmHg as an oil, $[\alpha]_D$ +52° (*c* 4·85), $\nu_{max.}$ 3615 (free OH, increases on dilution), 3500 (very br, bonded OH, disappears on dilution), and 1749 and 1735 cm^{-1} (AcO absorption, no change on dilution), δ 0·94, 1·05, and 1·14 (3 × CMe), 2·07 (AcO), 4·00br (2H, s, $W_{\frac{1}{2}}$ 6·5 Hz, CH_2OH), 5·02 (s, C*H*OAc), 5·44br (s, $W_{\frac{1}{2}}$ 7 Hz, :CH·) (Found: C, 73·15; H, 9·45. $C_{17}H_{26}O_3$ requires C, 73·4; H, 9·4%). The major product from the polar fractions 8-*hydroxymethyl*-1,2,6-*trimethyltricyclo*[5.3.1.$0^{2,6}$]*undec*-8-*ene*-5,11-*diyl diacetate* (27) (200 mg), which distilled at 160° and 0·05 mmHg as an oil, $[\alpha]_D$ +35° (*c* 0·85), $\nu_{max.}$ 3620br (free OH) and 3550 (very br, bonded OH) 1735 cm^{-1}, δ 0·94 and 1·10 (6H) (3 × CMe), 2·03 and 2·09 (2 × AcO), 2·17 (s, H_A), 4·03br (2H, s, $W_{\frac{1}{2}}$ 7 Hz, CH_2OH), 5·07 (s, C*H*OAc), 4·09 and 5·21 (q, *J* 11 and 6 Hz, C*H*OAc), and 5·56br (s, $W_{\frac{1}{2}}$ 7 Hz, :CH·) (Found: C, 67·75; H, 8·35. $C_{19}H_{25}O_5$ requires C, 67·85; H, 8·4%).

Oxidation of Gymnomitrol (1).—Gymnomitrol (1) (50 mg) in dry acetone (5 ml) was treated with a slight excess of 6N-Jones reagent at room temperature for 5 min. Normal work-up and p.l.c. gave *gymnomitrone* (1,2,6-*trimethyl*-8-*methylenetricyclo*[5.3.1.$0^{2,6}$]*undecan*-11-*one*) (3) (46 mg) which sublimed at 85° and 0·01 mmHg, m.p. 84—85°, $\nu_{max.}$ 3080, 1745 (cyclopentanone), 1639, and 892 cm^{-1}, δ 0·82, 0·91, and 0·92 (3 × CMe), 2·63 (s, H_A), and 4·74 and 4·77 (:CH_2) (Found: C, 82·65; H, 10·05. $C_{15}H_{22}O$ requires C, 82·5; H, 10·15%). Sodium borohydride reduction of the ketone (3) gave exclusively gymnomitrol (1).

Ozonolysis of Gymnomitrone (3).—The ketone (3) (40 mg) in ethyl acetate (5 ml) was cooled to −70° and ozone was passed through the solution for 15 min. The resultant blue solution was kept at −70° for 1 h after which the solvent was removed at room temperature by blowing with nitrogen. Aqueous methanol was added and the mixture was stirred overnight at room temperature. Normal extraction procedure followed by p.l.c. and sublimation at 95° and 0·01 mmHg furnished 1,2,6-*trimethyltricyclo*[5.3.1.$0^{2,6}$]*undecane*-8,11-*dione* (5) (35 mg) as an amorphous solid, $\nu_{max.}$ 1749 (cyclopentanone) and 1710 (cyclohexanone), δ 0·91, 1·02, and 1·09 (3 × CMe), and 3·00 (s, H_A), (Found: C, 76·55; H, 9·25. $C_{14}H_{20}O_2$ requires C, 76·3; H, 9·15%).

11-*Hydroxy*-1,2,6-*trimethyltricyclo*[5.3.1.$0^{2,6}$]*undecan*-8-*yl Acetate* (11).—The nor-diketone (5) (30 mg) in methanol (10 ml) was treated with an excess of sodium borohydride for 0·5 h at room temperature. Normal work-up yielded a product which was acetylated in pyridine (2 ml) and acetic anhydride (2 ml) at 20° overnight. Purification and sublimation at 120° and 0·01 mmHg gave the *nor-hydroxy-acetate* (11), m.p. 108—109°, $\nu_{max.}$ 3625 (sh, free OH, increases on dilution), 3500 (very br, bonded OH, decreases on dilution), and 1739 and 1729 cm^{-1} (double carbonyl absorption, no change on dilution), δ 0·94, 1·10, and 1·12 (3 × CMe), 2·02 (AcO), 5·69 (s, C*H*OH), and 5·0 (m, C*H*OAc) (Found: C, 72·1; H, 9·95. $C_{16}H_{26}O_3$ requires C, 72·15; H, 9·85%).

Acetylation of Gymnomitrol (1).—Gymnomitrol (50 mg) in pyridine (2 ml) and acetic anhydride (2 ml) was heated on a steam-bath for 4 h. Normal work-up followed by p.l.c. yielded gymnomitrol acetate (2) (46 mg) identical with the naturally occurring acetate.

Ozonolysis of Gymnomitrol Acetate (2).—The acetate (2) (40 mg) was ozonised under the same conditions as described for the ketone (3) to give 1,2,6-*trimethyl*-8-*oxotricyclo*-[5.3.1.$0^{2,6}$]*undecan*-11-*yl acetate* (8) (34 mg) which distilled at 110° and 0·02 mmHg as an oil, $\nu_{max.}$ 1749 (acetate) and 1718 cm^{-1} (cyclohexanone), δ 0·96, 1·06, and 1·16 (3 × CMe), 2·04 (AcO), 2·45 (s, H_A), and 5·04 (s, C*H*OAc) (Found: C, 72·75; H, 9·05. $C_{16}H_{24}O_3$ requires C, 72·7; H, 9·15%).

Sodium borohydride reduction of the nor-ketoacetate (8) afforded 8-*hydroxy*-1,2,6-*trimethyltricyclo*[5.3.1.$0^{2,6}$]*undecan*-11-*yl acetate* (10) which sublimed at 120° and 0·02 mmHg, m.p. 135—136°, $\nu_{max.}$ 3610 (free OH), 3500 (very br, bonded OH), 1740 (shoulder), and 1725 cm^{-1} (sh, acetate), δ 0·83, 1·05, and 1·12 (3 × CMe), 2·03 (AcO), 4·13 (m, C*H*OH), and 4·59 (s, C*H*OAc) (Found: C, 72·25; H, 10·1. $C_{16}H_{26}O_3$ requires C, 72·15; H, 9·85%).

Treatment of Gymnomitrol (1) *with Acid*.—Dry HCl gas was bubbled for 1 h through a solution of gymnomitrol (1) (50 mg) in AnalaR chloroform (15 ml). The mixture was washed with water, and the chloroform layer was dried and evaporated under reduced pressure. P.l.c. afforded two products. The minor product, *isogymnomitrol* (1,2,6,8-*tetramethyltricyclo*[5.3.1.$0^{2,6}$]*undec*-8-*en*-11-*ol*) (18) (18 mg) was sublimed at 80° and 0·04 mmHg as needles, m.p. 82—84°, $\nu_{max.}$ 3625 (sh, free OH) and 1669 cm^{-1}, δ 0·92, 0·99, and 1·15 (3 × CMe), 1·47 (s, disappears on addition of D_2O, OH), 1·62 (:CMe), 1·76 (s, H_A), 3·97 (s, C*H*OH), and 5·05br (s, $W_{\frac{1}{2}}$ 9 Hz, :CH) (Found: C, 81·75; H, 11·1. $C_{15}H_{24}O$ requires C, 81·75; H, 11·0%).

The major product was the *epimeric alcohol* (7) (29 mg), sublimed at 80° and 0·01 mmHg as oily crystals, m.p. 57—59°, $\nu_{max.}$ 3630 (sh, free OH) and 3570 cm^{-1} (sh, bonded OH), δ 0·86, 0·88, and 1·04 (3 × CMe), 1·67 (t, *J* 2 Hz, :CMe), 1·94 (d, *J* 4·2 Hz, H_A), 3·86 (d, *J* 4·2 Hz, C*H*OH), and 5·47br (s, $W_{\frac{1}{2}}$ 8 Hz, :CH) (Found: C, 81·7; H, 11·15. $C_{15}H_{24}O$ requires C, 81·75; H, 11·0%).

Gymnomitrol (1) (10 ml) was stirred for 3 h in methanol (10 ml) and 3M-H_2SO_4 (3 ml) to give isogymnomitrol (18) (7 mg) and the epimeric alcohol (7) (2 mg). Treatment of isogymnomitrol (18) with HCl gas in chloroform gave the epimeric alcohol (7) as the major product with a small amount of recovered starting material.

1,2,6,8-*Tetramethyltricyclo*[5.3.1.$0^{2,6}$]*undec*-8-*en*-11-*one*

(28).—Jones oxidation of isogymnomitrol (18) (20 mg) gave *isogymnomitrone* (28) (17 mg) which distilled at 100° 0·01 mmHg as an oil, $\nu_{max.}$ 1746 cm^{-1} (cyclopentanone), δ 0·80 and 0·94 (6H) (3 × CMe), 1·69 (t, *J* 2 Hz, :CMe), 2·02 (s, H_A), and 5·32br (s, $W_{\frac{1}{2}}$ 7 Hz, :CH) (Found: C, 82·8; H, 10·4. $C_{15}H_{22}O$ requires C, 82·5; H, 10·15%). This ketone (28) can also be prepared by Jones oxidation of the epimeric alcohol (7) or by acidic isomerisation of gymnomitrone (3).

Hydrogenation of Gymnomitrol (1).—Hydrogenation of gymnomitrol (1) (20 mg) at atmospheric pressure for 1·5 h over Adams catalyst in ethyl acetate gave *dihydrogymnomitrol* (1,2,6,8-*tetramethyltricyclo*[5.3.1.0^{2,6}]*undecan*-11-*ol*) (29) (18 mg), which sublimed at 80° and 0·02 mmHg, m.p. 72—73°, $\nu_{max.}$ 3625 (sh, free OH) and 3470 cm^{-1} (very br, bonded OH), δ 0·91, 1·09, and 1·21 (3 × CMe), 1·10 (d, *J* 7 Hz, CH*Me*), and 3·68 (s, C*H*OH) (Found: C, 81·2; H, 11·9. $C_{15}H_{26}O$ requires C, 81·0; H, 11·8%).

Use of palladium–charcoal as catalyst in the hydrogenation gave only isogymnomitrol (18). Only starting material was recovered on treatment of dihydrogymnomitrol (29) with HCl gas in chloroform.

1,2,6,8-*Tetramethyltricyclo*[5.3.1.0^{2,6}]*undecan*-11-*one* (35).—Dihydrogymnomitrol (29) (15 mg) was oxidised in the usual manner with Jones reagent to give *dihydrogymnomitrone* (35) (13 mg) which distilled at 90° and 0·01 mmHg as an oil, $\nu_{max.}$ 1740 cm^{-1}, δ 0·78, 0·86, and 0·92 (3 × CMe), 1·14 (d, *J* 7 Hz, CH*Me*) (Found: C, 81·9; H, 11·05. $C_{15}H_{24}O$ requires C, 81·85; H, 11·0%).

Epoxidation of Gymnomitrol Acetate (2).—The acetate (2) (100 mg) in AnalaR chloroform (10 ml) was stirred at room temperature for 1 h with *m*-chloroperbenzoic acid (110 mg). After filtration through a short column of basic alumina, evaporation of the solvent and p.l.c. yielded two products. The more polar product (76 mg) was sublimed at 110° and 0·01 mmHg, to give the β-epoxyacetate (12) identical with that found in the extract. The less polar product (19 mg) was distilled at 110° and 0·01 mmHg to give the *α-epoxyacetate* (13), as an oil, $[\alpha]_D$ +107° (*c* 0·42), $\nu_{max.}$ 1745 and 1731 cm^{-1} (double acetate absorption), δ 0·92, 1·08, and 1·11 (3 × CMe), 1·41 (s, H_A), 2·61 (2H, s, oxiran H), and 4·87 (s, C*H*OAc) (Found: C, 73·5; H, 9·6. $C_{17}H_{26}O_3$ requires C, 73·35; H, 9·4%).

The Hydroxyacetate (15).—The epoxyacetate (12) (30 mg) in aqueous methanol (10 ml) was treated with dilute sulphuric acid (1 ml) and stirred at room temperature for 2 h. Work-up gave the hydroxyacetate (15) (28 mg) identical with the naturally occurring material. The derived *diacetate* (8-*acetoxymethyl*-1,2,6-*trimethyltricyclo*-[5.3.1.0^{2,6}]*undec*-8-*en*-11-*yl acetate*) (16) distilled at 115° and 0·01 mmHg as an oil, $\nu_{max.}$ 1745 cm^{-1}, δ 0·92, 1·04, and 1·13 (3 × CMe), 2·06 (6H, 2 × AcO), 4·4br (2H, s, $W_{\frac{1}{2}}$ 4·5 Hz, :C·CH_2OAc), 5·01 (s, C*H*OAc), and 5·49br (s, $W_{\frac{1}{2}}$ 7 Hz, :CH) (Found: C, 71·3; H, 8·85. $C_{19}H_{28}O_4$ requires C, 71·2; H, 8·8%).

Allylic Oxidation of the Diacetate (16).—The diacetate (16) (12 mg) in acetic acid (1·3 ml) and acetic anhydride (0·7 ml) was stirred at 30° overnight with anhydrous sodium chromate (10 mg). After cooling and addition of water the crude product was extracted with chloroform. Purification by p.l.c. yielded 8-*acetoxymethyl*-1,2,6-*trimethyl*-10-*oxotricyclo*[5.3.1.0^{2,6}]*undec*-8-*en*-11-*yl acetate* (17) (8 mg) which (distilled at 120° and 0·015 mmHg as an oil, $\lambda_{max.}$ 240 nm (ε 10,000), $\nu_{max.}$ 1751 (acetate), 1680 (enone), and 1645 cm^{-1}, δ 1·08, 1·12, and 1·25 (3 × CMe), 2·08 and 2·13 (2 × AcO), 2·45 (s, H_A), 4·77 (2H, d, *J* 2 Hz, :C·CH_2OAc), 4·85 (s, C*H*OAc), and 6·06br (s, $W_{\frac{1}{2}}$ 4 Hz, :CH) (Found: C, 68·45; H, 8·05. $C_{19}H_{28}O_5$ requires C, 68·25; H, 7·85%).

Interconversion of the Epoxydiacetate (21) *and the Hydroxydiacetate* (27).—The epoxydiacetate (21) (10 mg) was treated with dilute sulphuric acid (1 ml) in methanol (5 ml) for 1 h at room temperature. The product obtained was identical with the naturally occurring hydroxydiacetate (27).

Hydrolysis of the Epoxydiacetate (21).—To the epoxydiacetate (21) (50 mg) in methanol (5 ml) and water (3 ml), potassium carbonate (100 mg) was added and the mixture was refluxed for 1 h. After cooling, normal extraction and purification procedures gave 5-*hydroxy*-1,2,6-*trimethyl*-8,8-*oxymethylenetricyclo*[5.3.1.0^{2,6}]*undecan*-11-*yl acetate* (23) (38 mg) which sublimed at 140° and 0·005 mmHg as needles, m.p. 122—123°, $\nu_{max.}$ 3625 (free OH, increases on dilution), 3490 (very br, disappears on dilution), and 1749 and 1735 (double acetate absorption, no change on dilution), δ 0·91, 1·08, and 1·11 (3 × CMe), 2·06 (AcO), 2·77 and 2·68 (ABq, J_{AB} 4 Hz, 2 × oxiran H), 4·53 and 4·63 [q (after D_2O exchange), *J* 11 and 6 Hz, C*H*OH], and 5·23 (s, C*H*OAc) (Found: C, 69·25; H, 9·0. $C_{17}H_{26}O_4$ requires C, 69·35; H, 8·9%). The following downfield shifts (p.p.m.) were observed with a 0·5 molar ratio of Eu(dpm)$_3$: CMe's 2·7, 1·5, 0·7; H_A 2·0; C*H*OH 6·0; C*H*OAc 1·0; one oxiran H 0·6. The other oxiran H moved upfield by 0·13 p.p.m.

1,2,6-*Trimethyl*-5-*oxo*-8,8-*oxymethylenetricyclo*[5.3.1.0^{2,6}]-*undecan*-11-*yl Acetate* (24).—Chromium trioxide (60 mg) was added to a stirred solution of pyridine (95 mg) in acid-free methylene chloride (1·5 ml). The flask was stoppered with a drying tube and the deep burgundy coloured solution was stirred for 15 min at room temperature. A solution of the alcohol (23) (30 mg) in a small volume of methylene chloride was then added in one portion. A black tar separated immediately and after stirring for an additional 15 min at 20°, the solution was decanted from the residue. The latter was washed twice with methylene chloride and the combined methylene chloride solutions were washed with saturated sodium hydrogen carbonate solution, water, and then dried. After evaporation of the solvent, p.l.c. furnished the *epoxy-ketoacetate* (24) (29 mg) which sublimed at 140° and 0·01 mmHg as plates, m.p. 161—162°, $\nu_{max.}$ 1735, with shoulders at 1745 and 1755 cm^{-1}, δ 0·96, 1·25, and 1·26 (3 × CMe), 2·06 (AcO), 2·65 and 2·83 (ABq, J_{AB} 4 Hz, 2 × oxiran H), and 5·25 (s, C*H*OAc) (Found: C, 70·0; H, 8·35. $C_{17}H_{26}O_4$ requires C, 69·85; H, 8·25%).

Sodium Borohydride Reduction of the Epoxy-ketoacetate (24).—The epoxy-ketoacetate (24) (20 mg) in methanol (5 ml) was stirred at 20°, and sodium borohydride was added over 4 h. Normal work-up followed by p.l.c. gave starting material (24) (5 mg) and 5,8-*epoxy*-8-*hydroxymethyl*-1,2,6-*trimethyltricyclo*[5.3.1.0^{2,6}]*undecan*-11-*yl acetate* (25) (11 mg), $\nu_{max.}$ 3590, 3460, and 1739 cm^{-1} (acetate), δ 0·92, 1·06, and 1·16 (3 × CMe), 1·61 (s, disappears with D_2O, OH), 2·03 (AcO), 3·41 [2H, s (after D_2O exchange), $W_{\frac{1}{2}}$ 3 Hz, CH_2OH], 4·08 (t, *J* 3 Hz, CH—O), and 5·04 (s, C*H*OAc).

The *derived acetate* (26) distilled at 130° and 0·01 mmHg as an oil, $\nu_{max.}$ 1744 cm^{-1}, δ 0·92, 1·07, and 1·15 (3 × CMe), 2·05 and 2·08 (2 × AcO), 3·86 and 4·06 (ABq, J_{AB} 11 Hz, CH_2OAc), 4·03 (partially obscured t, *J* 3 Hz, CH—O), and 5·08 (s, C*H*OAc) (Found: C, 67·95; H, 8·55. $C_{19}H_{28}O_5$ requires C, 67·85; H, 8·4%).

Isogymnomitrene (33).—Gymnomitrene (32) (10 mg)

was treated with dry HCl gas in chloroform, as described previously. Subsequent p.l.c. gave *isogymnomitrene* (1,2,6,8-*tetramethyltricyclo*[5.3.1.$0^{2,6}$]*undec*-8-*ene*) (33) which distilled at 60° and 0·01 mmHg as an oil, $\nu_{max.}$ 3070 and 1620, δ 0·96, 0·91, and 1·01 (3 × CMe), 1·67 (t, *J* 2 Hz, :CMe), and 5·17br ($W_{\frac{1}{2}}$ 8 Hz, :CH), (Found: M^+, 204·1879. $C_{15}H_{24}$ requires *M*, 204·1878).

Clemmensen Reduction of Gymnomitrone (3).—Amalgamated zinc dust was prepared by shaking zinc powder (300 mg), mercury(II) chloride (20 mg), conc. HCl (0·015 ml), and water (2 ml) for 5 min at room temperature. The aqueous solution was decanted off and the amalgamated zinc covered with conc. HCl (2·5 ml) and water (3 ml). Gymnomitrone (3) (100 mg) in ethanol (2 ml) was added and reflux started immediately. After 4 h reflux and extraction with ether, two hydrocarbon products were obtained. These were separable by g.l.c. (2·5% SE-30 capillary column, linear temperature programme 100—220° at 2° per min) or by p.l.c. using silica impregnated with 30% silver nitrate. The less polar hydrocarbon (38 mg) was identified as isogymnomitrene (33). The slightly more polar hydrocarbon (41 mg) has δ 0·82, 0·99, and 1·10 (3 × CMe), 1·64 (:CMe), and 5·01br (d, *J* 2·5 Hz, :CH), (Found: M^+, 204·187218. Calc. for $C_{15}H_{24}$: *M*, 204·187790).

Attempted Interconversion of the Epimeric Alcohol (7) *with Isogymnomitrene* (33).—The alcohol (7) (20 mg) in dry pyridine (2 ml) was treated with a slight excess of toluene-*p*-sulphonyl chloride at room temperature overnight to give the corresponding tosylate (18 mg). Reduction of the tosylate with an excess of lithium aluminium hydride in dry ether (5 ml) under reflux for 3 h gave only unchanged tosylate. When the reaction was repeated using dry tetrahydrofuran as solvent under reflux for 4 h the alcohol (7) was the only detectable product.

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