# 908. *A New Leaf-gum Constituent: Labdane-8α,15-diol.*

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and R. A. Raphael

A diterpene diol isolated from the leaf-gum of *Aeonium lindleyi* (Crassulaceae) is shown to be labdane-8α,15-diol. Infrared measurements demonstrate the existence of intramolecular hydrogen bonding for this and related compounds in dilute solution in carbon tetrachloride.

In the course of an extensive study of the hydrocarbon constituents of the leaf waxes of the sub-family Sempervivoideae (Crassulaceae) [1] we examined the gummy exudate which coats the leaves of the species *Aeonium lindleyi* (W. and B.).

The gum could be removed with chloroform or ethanol. Chromatography of the neutral portion gave substantial quantities of a pure substance, $C_{20}H_{38}O_2$, m. p. 83—84°, whose fully saturated nature followed from its failure to undergo catalytic hydrogenation and from the absence of absorption in the ultraviolet region. The infrared spectrum (Table and Figure) indicated a *gem*-dimethyl grouping (doublet at 1380 and 1370 cm.$^{-1}$) and two hydroxyl groups: this evidence established the bicyclic nature of the molecule

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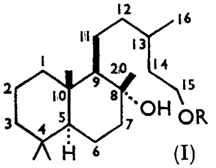
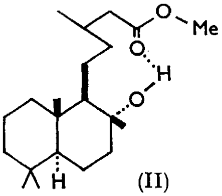
[1] Eglinton, Gonzalez, Hamilton, and Raphael, *Nature*, 1962, **193**, 739; *Phytochem.*, 1962, **1**, 89.

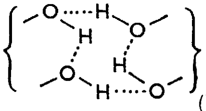
which was confirmed and extended by the nuclear magnetic resonance (interpreted by Dr. A. Melera) that required the hydroxyls to be in groupings $R{\cdot}CH_2{\cdot}CH_2{\cdot}OH$ and $Me{\cdot}CR^1R^2{\cdot}OH$. Mild acetylation converted the diol into a monoacetate which was dehydrated by phosphorus oxychloride in pyridine to the expected vinylidene derivative [$\gamma$(CH) for $R^1R^2C{=}CH_2$ at 890 cm.$^{-1}$].



(I)



(II)



(III)

We inferred tentatively that the leaf-gum constituent might be a saturated diol of the labdane series; it was then found that labdane-8α,15-diol (I; R = H) which had been obtained[2] by reduction of methyl labdanolate with lithium aluminium hydride possessed properties closely resembling those of our diol. The identity was established by direct comparison, and our diol was characterised by conversion into the known[2] labdane-8α,15,20-triol.

Labdane-8α,15-diol appears to be the first natural saturated diterpene diol to be isolated, though closely related unsaturated diols such as sclareol are well known. Labdanolic acid and the diol (I) bear an obvious biogenetic relationship and it is probable that diols of the latter type are present in the neutral fraction of gum labdanum. Infrared examination has shown that such diols are probable constituents of the leaf gums of other *Aeonium* species of the section Goochia (*e.g.*, *Ae. spathulatum* and *Ae. goochiae*).

The region, 3000—3700 cm.$^{-1}$, where most hydroxyl stretching frequencies occur, is now amenable to precise study by using commercially available, high-resolution, grating infrared spectrometers.[3] Measurements are conveniently carried out at high dilution (0·01—0·001M) in cells of long path length (0·5—5 cm.). It is frequently assumed that intermolecular hydrogen bonding is absent at such low concentrations, except in special cases such as the carboxylic acids[4] where rather stable dimeric species are known. In this and other work,[5] however, we have encountered several types of compound where intermolecular association, presumably dimeric, is unusually persistent.

We have examined several compounds of the labdane type and find (see Table and Figure) that intramolecular hydrogen bonding involving " closure " of a ten-membered ring occurs to a detectable extent in very dilute solutions in carbon tetrachloride. Such a structure is sterically unexceptionable and models indicate many possible favourable conformations of such a " ring " involving minimal bond oppositions and transannular interactions; one of these (II) is shown for methyl labdanolate. Similar measurements show the presence of an analogous intramolecularly hydrogen-bonded structure in the solution of labdane-8α,15-diol monoacetate (I; R = Ac). The hydroxyl absorption pattern for each compound is concentration-independent up to the highest concentration tested (0·01M). It does not seem feasible to assign the absorption near 3550 cm.$^{-1}$ unambiguously either to $-OH \cdots O{=}C{-}O$ or to $OH \cdots O{-}C{=}O$.[6,7] The carbonyl absorption band is a little wider than normal [cf. 15-acetoxylabd-8(20)-ene (Table), and methyl stearate, $\nu_{max.}$ (in $CCl_4$) 1743 cm.$^{-1}$, $\Delta\nu_{\frac{1}{2}}^{a}$ 16 cm.$^{-1}$, $\varepsilon_a$ ~500], presumably as a result of this partial bonding. There is evidence in the incompletely resolved absorption near 3610 cm.$^{-1}$ of

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[2] Cocker and Halsall, *J.*, 1956, 4262; 1957, 4401.

[3] Eglinton, *Spectrovision*, 1960, **9**, 1.

[4] Brooks, Eglinton, and Morman, *J.*, 1961, 106.

[5] Unpublished results.

[6] Bigley, Rogers, and Barltrop, *J.*, 1960, 4613; Barltrop, " Progress in Organic Chemistry," 1961, Vol. V, p. 96, ed. Cook and Carruthers, Butterworths Scientific Publns., London.

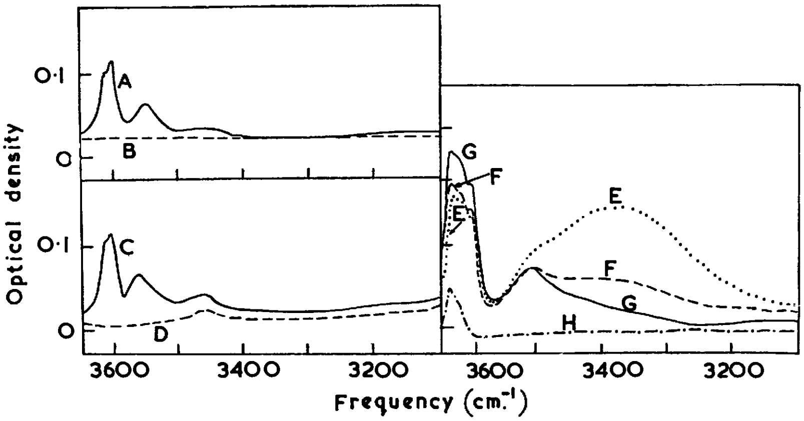
[7] West, Korst, and Johnston, *J. Org. Chem.*, 1960, **25**, 1976.

Stretching absorptions of hydroxyl and carbonyl groups ($CCl_4$ solutions).

| | | HO stretching absorption | | | | C=O stretching absorption | | | |
|---|---|---|---|---|---|---|---|---|---|
| Compound and molarity | Cell (cm.) | $\nu$ (cm.$^{-1}$) | $\Delta\nu_{\frac{1}{2}}^{a}$ (cm.$^{-1}$) | $\varepsilon_a$ | Assignment | Cell (cm.) | $\nu$ (cm.$^{-1}$) | $\Delta\nu_{\frac{1}{2}}^{a}$ (cm.$^{-1}$) | $\varepsilon_a$ |
| Me labdanolate * | | | | | | | | | |
| 0·00152 | 2 | 3613sh<br>3605 | 36 | 30 | free | 0·5 | 1741 | 18 | 480 |
| | | 3550 | 47 | 15 | intra, OH ··· O | | | | |
| Labdane-8α,15-diol monoacetate (I; R = Ac) * | | | | | | | | | |
| 0·0023 | 2 | 3612sh<br>3605 | 30 | 20 | free | 0·5 | 1742 | 17 | 470 |
| | | 3563 | 56 | 10 | intra, OH ··· O | | | | |
| 15-Acetoxylabd-8(20)-ene * | | | | | | | | | |
| 0·00154 | | | | | | 0·5 | 1743 | 15 | 690 |
| Labdane-8α,15-diol (I; R = H) | | | | | | | | | |
| 0·00078 | 5 | 3636<br>3607sh | 48 | 65 | free | | | | |
| | | 3515 | 90 | 15 | intra, OH ··· OH | | | | |
| 0·0078 | 0·5 | 3637<br>3605sh | 52 | 50 | free | | | | |
| | | 3500sh | — | 30 | intra, OH ··· OH | | | | |
| | | 3370 | 270 | 42 | inter, OH ··· OH | | | | |
| Heptane-1,7-diol | | | | | | | | | |
| Saturated solution | 5 | 3637 † | 25 | — | free | | | | |

The hydroxyl absorptions for methyl labdanolate and labdanediol monoacetate were concentration-independent up to 0·01M. " Frequency " values are accurate to ±1 cm.$^{-1}$ for sharply defined peaks. $\varepsilon_a$ values are quoted to the nearest 5 units.

* These compounds have a weak ($\varepsilon_a$ ~5) concentration-independent band at *ca.* 3460 cm.$^{-1}$ which is ascribed to the $\nu$(C=O) first overtone. † Unsymmetrical band.



Hydroxyl absorptions for carbon tetrachloride solutions of (A) methyl labdanolate (0·00152M in 2 cm.), (C) labd-8α,15-diol monoacetate (I; R = Ac) (0·0023M in 2 cm.), (D) 15-acetoxylabd-8(20)-ene (0·00154M in 2 cm.), (E), (F), and (G) labdane-8α,15-diol (I; R = H) (0·0078M in 0·5 cm., 0·002M in 2 cm., and 0·00078M in 5 cm., respectively), and (H) heptane-1,7-diol (saturated solution in 5 cm.). Curve (B) is a solvent–solvent background (2 cm. cells).

more than one conformation of the non-bonded hydroxyl grouping [cf. t-butyl alcohol, $\nu_{max.}$ (in $CCl_4$) 3617 cm.$^{-1}$, $\Delta\nu_{\frac{1}{2}}^{a}$ 17, $\varepsilon_a$ ~60].

Labdane-8α,15-diol (I; R = H) is interesting in that even at the relatively low concentration of 0·0078M there is a prominent, concentration-dependent, broad absorption band at 3370 cm.$^{-1}$, which, in view of other studies,[5] could be ascribed to $\nu$(OH) of a fully bonded dimeric species involving an eight-membered ring of four hydrogen atoms bonded by ordinary and by hydrogen bonds as depicted in (III). Progressive dilution to 0·00078M reveals a second band at 3515 cm.$^{-1}$ which almost certainly represents an intra-hydrogen-bonded –OH • • • OH monomeric structure. The bulk of the attached alicyclic ring system undoubtedly facilitates both the inter- and the intra-molecular hydrogen bonding by restricting the number of available conformations; thus heptane-1,7-diol shows no absorption band in this region other than that due to free hydroxyl. The asymmetry of such free hydroxyl bonds has been discussed in conformational terms by Oki and Iwamura.[8]

The above results emphasise the importance of carrying out such hydrogen-bonding studies under precisely controlled and calibrated conditions with a range of dilutions, if misleading conclusions are to be avoided. Methyl labdanolate is a case in point; Bigley, Rogers, and Barltrop [6] have reported that this compound does not show intramolecular hydrogen bonding in carbon disulphide solution, and they therefore allocate a configuration at C-13 in methyl labdanolate on the basis that the molecular-rotation difference method will be valid in the absence of such bonding. In view of our results this assignment, and those for related compounds such as methyl eperuate and methyl cativate, are again open to question.*

## EXPERIMENTAL

Rotations refer to solutions in chloroform. M. p.s were determined on a Kofler block and are uncorrected. Nuclear magnetic resonance measurements were made in carbon tetrachloride on Varian A60 instruments, and infrared spectra were recorded on Perkin-Elmer 137 (thin films) and Unicam S.P. 130 (solutions and potassium halide discs) spectrophotometers. Light petroleum refers to the fraction of b. p. 40—60°; the alumina used for chromatography had activity III (Brockmann). Microanalyses were performed by Mr. J. M. L. Cameron, B.Sc., and his associates.

*Isolation of Labdane-*8α,15-*diol* (I).—The intact, fleshy leaves (10 kg.) of *Aeonium lindleyi* (W. and B.) were either set aside in ethanol (5 l.) for several days or briefly treated with several volumes of cold solvent. Filtration and evaporation of the extracts afforded a brown gum which was dissolved in ether and freed from acidic material by washing it with N-sodium hydroxide, followed by water. The ethereal solution was dried and evaporated and the residual gum (8·7 g.) chromatographed over alumina (200 g.). Elution with ether–methanol (3 : 2; 300 ml.) gave a pale yellow gum (7·8 g.), which separated from light petroleum as colourless prisms (5·6 g.) containing petroleum of crystallisation. The yield depended on the season and on occasion reached 20% of the dry-leaf weight, These crystals lost their solvent of crystallisation in 24 hr at 0·1 mm., affording pure labdane-8α-15-diol (I) as an amorphous white powder, m p. 83—84°, $[\alpha]_D^{20}$ −10° (*c* 1·7) (Found: C, 77·0; H, 12·2. Calc. for $C_{20}H_{38}O_2$: C, 77·35; H, 12·35%). The mass-spectrometric molecular weight was 310 (theor., 310). Significant infrared absorption bands occurred at 3460, 3380, 1388, 1375, and 1080 cm.$^{-1}$ (KCl disc). The diol had no appreciable ultraviolet absorption (in hexane) and did not take up hydrogen when shaken in ethyl acetate over 10% palladium–charcoal. It was identical with a genuine sample kindly supplied by Dr. T. G. Halsall. The nuclear magnetic resonance spectrum disclosed the presence of five methyl groups (τ 8·84 for $Me{\cdot}CR^1R^2{\cdot}OH$, and 9·03, 9·12, and 9·2), sixteen skeletal hydrogens (principal peaks at τ 8·27, 8·38, 8·45, 8·65), two hydroxyl protons (τ 7·94), and the two α-hydrogens of a grouping $R{\cdot}CH_2{\cdot}CH_2{\cdot}OH$ (τ 6·21, 6·32, and 6·42).

Gas–liquid chromatography [4 ft. column of 1% silicone elastomer (SE 30) on Embacel (80—100 mesh) at 220° and 30 ml. of argon per min.] of the crude semisolid diol showed a small peak [$r_t$ = 18 min.; possibly due to a stereoisomer of (I)] in addition to the main peak [due to (I); $r_t$ = 12 min.].

15-*Acetoxylabd*-8(20)-*ene*.—The diol (I; R = H) was converted into the monoacetate (I; R = Ac) by Cocker and Halsall's procedure.[2] The properties of the acetate were in close accord with those described by these authors.

A solution of the monoacetate (I; R = Ac) (0·52 g.) in dry pyridine (20 ml.) containing

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* Dr. Barltrop informs us that he is re-investigating his previous hydrogen-bonding results with a view to establishing the stereochemistry of sclareol and manool at C-13.

[8] Oki and Iwamura, *Bull. Chem. Soc. Japan*, 1959, **32**, 950.

phosphorus oxychloride (0·9 g.) was heated under reflux for 45 min. After chromatography in benzene over alumina, 15-*acetoxylabd*-8(20)-*ene* (0·44 g.) was obtained as a colourless syrup, $[\alpha]_D^{20}$ +44° (*c* 0·98) (Found: C, 78·65; H, 11·6. $C_{22}H_{38}O_2$ requires C 79·0; H, 11·45%), $\nu_{max.}$ (film) at 3090, 1738, 1645, 1240, and 890 cm.$^{-1}$.

Hydrogenation (10% palladium–charcoal; ethyl acetate) afforded 15-*acetoxylabdane* as a colourless syrup, $[\alpha]_D$ +38° (*c* 0·84) (Found: C, 78·6; H, 11·5. $C_{22}H_{40}O_2$ requires C, 78·5; H, 12·0%), $\nu_{max.}$ (film) 1745, 1035 cm.$^{-1}$.

*Labdane*-8α,15,20-*triol.*—This compound was obtained through labd-8(20)-en-15-ol by the recorded method.[2] Crystallisation from light petroleum–benzene gave pure labdane-8α,15,20-triol (120 mg.), m. p. 126—127° $[\alpha]_D$ −21° (*c* 0·86) (Found: C, 73·4; H, 11·5. Calc. for $C_{20}H_{38}O_3$: C, 73·55; H, 11·75%). Cocker and Halsall[2] report m. p. 124—125·5°, $[\alpha]_D$ −17° (*c* 1·01).

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