The Structure of Leonotin, a Novel Furanoid Diterpene

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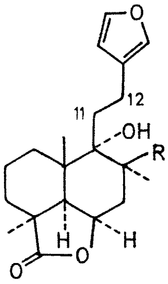
Summary The structure of leonotin has been determined as 8β-hydroxymarrubiin.

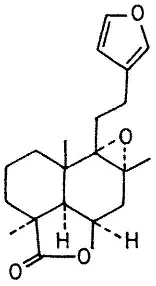
INVESTIGATION of chemical constituents of *Leonotis nepetaefolia* R. Br. (Labiatae)† has led to isolation of several novel diterpenoids. We report the structural elucidation of leonotin (I), a labdane type[1] and one of the two most abundant diterpenoid constituents of *L. nepetaefolia*.

Leonotin (I), m.p. 175°, $[\alpha]_D$ + 62·7° (*c* 0·86, EtOH), i.r. ($CHCl_3$) 3700, 3600, 1745, and 875 cm.$^{-1}$, has the composition $C_{20}H_{28}O_5$ from elemental analysis and mass-spectral parent peak at *m/e* 348·1944. The base peak (*m/e* 81·0340) in the mass spectrum of (I) corresponds to cleavage between C-11 and C-12.[2] The n.m.r. spectrum [$(CD_3)_2SO$–$CDCl_3$] of (I) has several features in common with that of marrubiin (II),[3] including signals [δ 6·25 (1H, s), 7·17 (1H, s), and 7·27 (1H, t, *J* 1 Hz)] characteristic of a 3-substituted furan, a doublet of triplets (δ 4·71, *J* 6 and 8 Hz) ascribed to the C-6 proton, and singlets (δ 1·20 and 1·00) corresponding to C-18 and C-20 methyl groups. The three-proton doublet at δ 1·07 in marrubiin is absent in leonotin, and is replaced by a singlet at δ 1·26 for the C-17 methyl group. In addition, two one-proton singlets at δ 3·30 and 4·07 which are absent in D_2O, suggest the presence of two hydroxy-groups in leonotin.

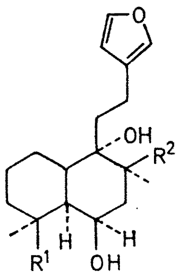
Dehydration of (I) with phosphorus oxychloride in pyridine led to an epoxide (III), m.p. 118—119°, $[\alpha]_D$ +60·0° (*c* 1·05 $CHCl_3$), i.r. ($CHCl_3$) 1760 and 870 cm.$^{-1}$ (no OH), mass-spectral parent peak *m/e* 330, in 65% yield. The downfield shift (δ 1·26) of the C-17 methyl group again confirmed its attachment to carbon bearing an oxygen function. Although (III) was resistant to chromous chloride or sodium borohydride, reduction with lithium aluminium hydride in refluxing tetrahydrofuran gave marrubenol (IV), identical by comparison of m.p., optical rotation, and i.r. and mass spectra with authentic marrubenol[4] prepared by reduction of marrubiin.‡ This result,



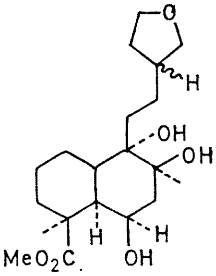
(I) R = OH
(II) R = H



(III)



(IV) R^1=CH_2OH, R^2=H
(V) R^1=CO_2H, R^2=OH
(VI) R^1=CO_2Me, R^2=OH



(VII)

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† We are grateful to Mr. M. Hasmathullah, Trinidad, West Indies, for collection of leaves of this plant and to Dr. K. Jewers, Tropical Products Institute, London, for identification of a botanical specimen.

‡ We are indebted to Professor D. M. S. Wheeler, University of Nebraska and to Dr. D. E. A. Rivett, Rhodes University, Grahamstown, South Africa, for samples of marrubiin.

taken with the requirement for *trans*-diaxial opening, establishes the configuration of the epoxide in (III) as α and strongly suggests that the C-8 hydroxy-group in leonotin has the β-configuration. The direction of reductive opening of the epoxide to give exclusively a 9 α-ol is presumably the result of steric control and has close analogy in the recently reported correlation of solidagenone with marrubiin.[5]

Vigorous hydrolysis of (I) produced leonotic acid (V), m.p. 102—103°, $[\alpha]_D + 24{\cdot}7°$ (*c* 2·1, $CHCl_3$, M^+ 366, i.r. ($CHCl_3$) 3400, 2600 (broad), 1725, and 890 cm.$^{-1}$, which was esterified with diazomethane to give (VI), m.p. 126—127°, $[\alpha]_D + 9{\cdot}3°$ (*c* 1·5, $CHCl_3$), M^+ 380, i.r. ($CHCl_3$) 3350, 1705, and 870 cm.$^{-1}$. Attempts to establish the configuration at C-8 through formation of an acetonide or cyclic carbonate of the tetrahydro-derivative (VII) of (VI) were unsuccessful. However, the pronounced downfield shift (103 Hz) of the C-20 methyl group in tetrahydroleonotin and in leonotin itself when n.m.r. spectra were measured in pyridine solution gave evidence of a strong anisotropic effect. Solvent shifts of this type have been shown to provide reliable evidence for a 1,3-diaxial relationship between hydroxy- and methyl groups.[6] The structure and stereochemistry of leonotin is therefore defined as (I).§

We are grateful to Eli Lilly and Company for financial support in the form of an unrestricted research grant.

(*Received, September 17th*, 1969; *Com.* 1407.)

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§ Dr. D. E. A. Rivett informs us that leonotin has been isolated from *Leonotis leonotis* in his laboratory. He concurs with our structural assignment.

[1] R. McCrindle and K. H. Overton, *Adv. Org. Chem.*, 1965, **5**, 47.
[2] C. R. Enzell and R. Ryhage, *Arkiv Kemi*, 1965, **23**, 367.
[3] D. M. S. Wheeler, M. M. Wheeler, M. Fétizon, and W. H. Castine, *Tetrahedron*, 1967, **23**, 3909.
[4] W. Cocker, B. E. Cross, S. R. Duff, J. T. Edward, and T. F. Holley, *J. Chem. Soc.*, 1953, 2540.
[5] T. Anthonsen, P. H. McCabe, R. McCrindle, and R. D. H. Murray, *Tetrahedron*, 1969, **25**, 2233.
[6] P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Amer. Chem. Soc.*, 1968, **90**, 5480.