Carbon-13 and Proton Magnetic Resonance Study of the Structure and Conformation of a New Germacranolide Sesquiterpene Dilactone

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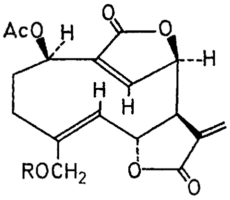
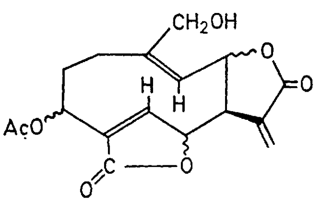
Summary The structure of melampodin B, a new sesquiterpene dilactone isolated from *Melampodium leucanthum*, has been elucidated on the basis of physical properties, predominantly ^{13}C and ^{1}H n.m.r. data.

In our biochemical systematic study of the three white-rayed species of the genus *Melampodium* (Compositae) we isolated a number of new sesquiterpene lactones. Several populations of *M. leucanthum* from west Texas provided a new substance, which we named melampodin B. Melampodin B (**1a**) $C_{17}H_{18}O_7$,†‡ m.p. 222—226° (decomp.), showed strong u.v. end absorption; $\nu_{max.}$ (Nujol) 3420 (OH), 1780 (γ-lactone), 1730 ($\alpha\beta$-unsat. ester), and 1655 cm^{-1} (double bonds). Treatment of (**1a**) with acetic anhydride–pyridine gave the acetate (**1b**) $C_{19}H_{20}O_8$,† m.p. 198—201° (decomp.), $\lambda_{max.}$ (MeOH) 206 nm (ϵ 30,000); c.d. (*c* 7·1 × 10^{-4} in MeOH) $[\theta]_{216} - 29 \times 10^3$, $[\theta]_{233} + 45 \times 10^3$; ν_{max} (Nujol) 1788, 1770, 1732, 1660, and 1240 cm^{-1}. The absence of an OH absorption from the i.r. spectrum of (**1b**) showed that (**1a**) contained only one hydroxy-group.

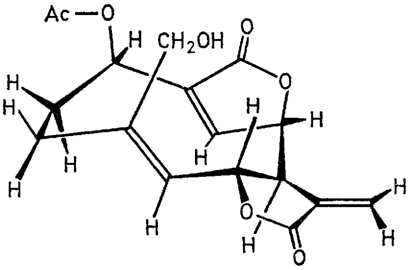
The structure of melampodin B was mainly deduced on the basis of correlations of 25·2 MHz ^{13}C and 300 MHz ^{1}H n.m.r. spectral information obtained for solutions in [$^{2}H_5$]-pyridine. The ^{13}C n.m.r. data obtained under proton noise decoupled and single frequency off centre decoupled conditions and ^{13}C chemical shift considerations indicate that the compound contains 17 carbon atoms and possesses the following skeletal systems: three of each of $-C(=O)-O$, $>C=$, and $C-CH-O$, two each of $HC=$ and $C-CH_2-C$, and one each of $H_2C=$, $C-CH_2-O$, $C-CH-C$, and $-CH_3$.





(2)

(1a); R = H
(1b); R = Ac



(1c)

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† Satisfactory elemental analysis was obtained.

‡ Several empirical formulae were in agreement with the elemental analyses for melampodin B. The others were excluded by the finding of 17 carbon signals in the ^{13}C n.m.r. spectrum.

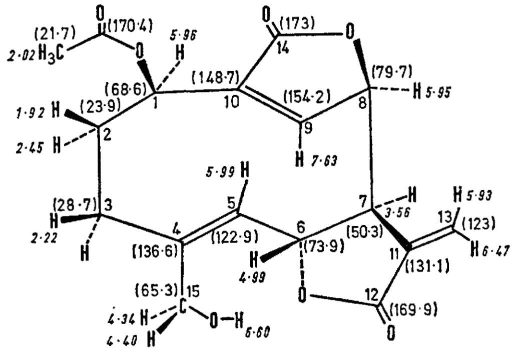

FIGURE. N.m.r. spectral parameters (^{13}C in parentheses; ^{1}H in italics). δ Values for solutions in [$^{2}H_5$]pyridine.

The ^{1}H n.m.r. data not only support the above contention but also lead to the final structure elucidation. The 300 MHz n.m.r. spectrum exhibits doublets at δ 6·47 and 5·93 and a broad 1H multiplet at δ 3·56 characteristic of αβ-unsaturated sesquiterpene γ-lactones. The presence of one methyl singlet typical of an acetate system, and the lack of any other resonances for methyl or aldehyde protons suggests that the C-4 and C-10 methyl functions in the sesquiterpene skeleton must be oxidised to alcohol and/or carboxylic acid functions. Since acetylation of (**1a**) causes a significant downfield shift of the proton absorptions at δ 4·34 and 4·40, the OH group must be attached to a methylene group, at either C-14 or C-15, the remaining carbon atom being present as a carboxylic acid derivative, possibly a lactonic carbonyl group. The above structural information strongly suggest that melampodin B is a germacranolide-type sesquiterpene dilactone which contains one primary alcohol and one acetate function. Strong irradiation of the multiplets at δ 1·92 (1H) and 2·45 (1H) results in the collapse of the two triplets at δ 2·22 (2H) and 5·96 (1H) into two singlets, indicating that (*a*) the low-field signal at δ 5·96 corresponds to the proton at C-1 [H-1 has a geminal attachment to a strongly electron-withdrawing group such as an acetate and does not have any proton(s) in vicinal position at C-10 but is allylically coupled to H-9 (δ 7·63)]; (*b*) the high-field triplet at δ 2·22 is assigned to the two C-3 methylene hydrogen atoms which also have no vicinal proton at C-4; and (*c*) the two multiplets at δ 1·92 and 2·45 represent the two chemically nonequivalent protons at C-2. The results of double-resonance experiments performed on the signals at δ 3·56, 4·99, and 7·63 suggest that the complex multiplet at δ 3·56 corresponds to H-7, since it shows spin–spin interactions with the two exocyclic methylene protons at C-13 (δ 5·93 and 6·47), H-8 (δ 5·95), and H-6 (δ4·99) (see Figure). The resonances of protons at C-8 and C-6 show further spin–spin interactions of 1·5 and 10 Hz with H-9 and H-5, respectively. The proton spin–spin interactions ($J_{5,6}$ 10, $J_{6,7}$ 10, $J_{7,8}$ 2·5, and $J_{8,9}$ 1·5 Hz) suggest that the torsion angles between the respective protons are *ca.* 180, 180, 80, and 80°, respectively. These spectral assignments are in full agreement with a skeletal arrangement as shown in structure (**1a**). However, melampodin-B could also exist in another structural arrangement (**2**). This structure was excluded on the basis of the following arguments: from biogenetic considerations and the co-occurance of melampodin,[1,2] a compound with known absolute configuration,[3,4] it was assumed that H-7 is α to the plane of the medium-sized ring. Inspection of stereomodels for the different isomeric possibilities of structure (**2**) revealed that in the least strained conformations none of the configurational arrangements around carbon atoms 6, 7, and 8 are in agreement with the experimentally obtained proton spin–spin interactions in melampodin B. On the contrary, the torsion angles between the protons at carbon atoms 5—9 in a stereomodel of (**1a**) tally with the indicated structure. The acetoxy-function at C-1 in (**1a**) is assigned a β-orientation on the basis of the torsion angles between H-1 and H-2α and H-2β. The observed *J* values ($J_{1,2\alpha} = J_{1,2\beta} =$ 5·5 Hz) can only be explained if the C(1)–H bond bisects the angle between the two C(2)–H bonds with *ca.* 45° torsion angles between H-1 and H-2α and H-2β. Models clearly show that the only possible configuration which satisfies the experimental data must have an α-proton at C-1. Therefore we suggest the configurational structure (**1a**) for melampodin B and (**1c**) for its major conformation.

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