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THE STRUCTURE OF MIKANOLIDE, A NEW SESQUITERPENE DILACTONE FROM MIKANIA SCANDENS (L.) WILLD.

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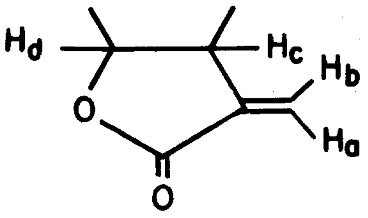
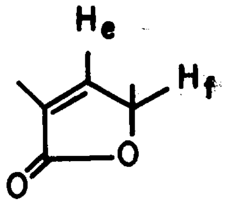
Mikania scandens (L.) Willd. (climbing hempvine, Compositae, tribe Eupatorieae Cass., subtribe Ageratinae Less.), a common plant of thickets and swamps of the Southeastern United States, elaborates an unusual polar sesquiterpene dilactone which we have called mikanolide. The evidence which establishes its structure as I is reported briefly in this communication.

Mikanolide, $C_{15}H_{14}O_6$, mw 290 (mass spectrum), mp 230-233°, $[\alpha]_D$ + 53.4° (dioxan, c 1.124), λ_{max} 206 mμ (16700), ir bands (KBr pellet) at 1767, 1752, 1666, 1630 (sh) cm^{-1}, was difficult to separate from its dihydro derivative II, mp 240-44°, $[\alpha]_D$ + 91.1° (dioxan, c 0.472), λ_{max} 217 mμ (ε 8800), ir bands (KBr) at 1760 (double intensity) and 1650 cm^{-1}, which also occurs in the plant and could be prepared by partial hydrogenation of I. Further hydrogenation of I and II led to tetrahydromikanolide (III), mp 225-8°, no uv absorption, ir bands (KBr) at 1800 and 1755 cm^{-1}.

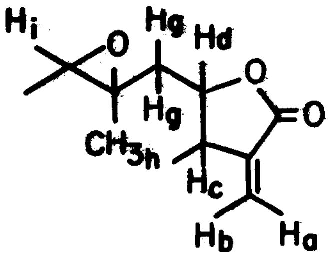
Comparison of the uv and ir spectra of I, II and III suggested the presence in I of two α,β-unsaturated lactone rings. That one of these had partial structure A present in many sesquiterpene lactones of Compositae was clear from ozonolysis (liberation of formaldehyde from I, but not from II and III) and from the nmr spectrum of I (dmso-d_6) which had the usual (1) H_a and H_b doublets at δ6.20 and δ5.92 (J = 4.5 Hz) not present in the nmr spectra of II and III, where they were replaced by a methyl doublet, and a complex multiplet (H_d) at 4.72 ppm (4.5 in II, 4.8 in III). The second chromophore was tentatively assigned to B because of a narrow doublet (J = 1.7) at 7.56 ppm (7.43 in II) which disappeared on hydrogenation and a resonance at 5.42 m (H_f, 5.28 in II) which moved upfield to 4.8 ppm in III; cf. the nmr spectra of elephantopin and its derivatives (2).



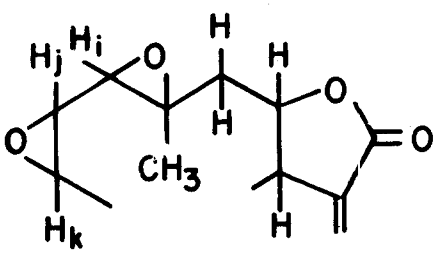
A



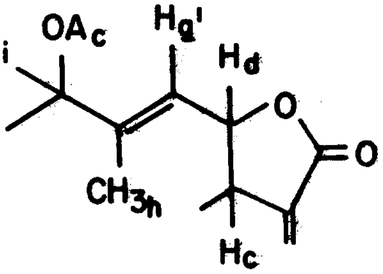
B



C



E



D

The absence of hydroxyl and ketone functions indicated spectroscopically and by chemical tests made it highly probable that the two remaining oxygen atoms were ethereal. On this basis mikanolide, because of the presence of only one quaternary methyl group (singlet at 1.01 ppm, at 0.95 ppm in II) had to possess a single carbocyclic ring.

Three additional signals at 3.96 dbr (J = 3.5, 1.1, one proton) and 3.36 m (two protons)* were tentatively assigned to hydrogen on carbon carrying ethereal oxygen. As the fourth point of attachment of the two ether bridges we postulated the carbon carrying the quaternary methyl group which, though apparently shielded in I and II by a double bond, displayed the customary chemical shift of CH_3-C-O (1.35 ppm) in III. Confirmation was the formation from I of an olefinic acetate IVa. In the nmr spectrum of IVa the quaternary methyl of I was replaced by

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*A third proton in the peak at δ3.36 could be assigned to H_c of A by comparing the nmr spectra of I, II and III and by spin decoupling.

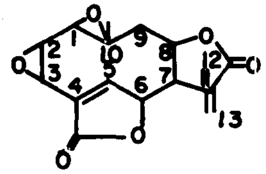
vinyl methyl at 1.72 d (J = 0.7) and an acetate methyl at 2.10 ppm, the methylene multiplet of I at 2.03 ppm (H_g of C) was replaced by a new vinyl proton ($H_{g'}$ of D, A part of AB system) at 5.32 dbr (J = 10.2, 0.7), H_d had experienced a slight downfield shift and simplification from 4.72 c to 4.82 t (B part of AB system, J = 10.2) and H_i, formerly in the 3.4 ppm cluster of I, had experienced the expected downfield shift to 5.22 d (J = 4.7). The incorporation of partial structure A into C and D as illustrated was further demonstrated by spin decoupling experiments involving H_a, H_b, H_c, H_d, H_g and $H_{g'}$, H_h and H_i which will be detailed in our full paper. Compounds Va and VIa with the expected spectral properties were similarly formed from II and III.

Hydrolysis of IVa and Va yielded IVb and Vb and was accompanied by the expected upfield shift of the H_i doublet to approximately 4.2 ppm. It was now apparent from the nmr spectra of IVa, IVb, Va and Vb and confirmed by double resonance experiments that H_i was the X component of an ABX system where H_A (in Vb, for example) was 3.35, H_B 3.82, J_{AX} 4.8, J_{AB} 4.9, J_{BX} 0 and where H_B in turn was weakly coupled to the protons in partial structure B giving rise to signals at 7.75 ppm (J = 1.5, H_e) and 5.45 ppm (J = 1.5, H_f). Hence, partial structure C could be expanded to E.

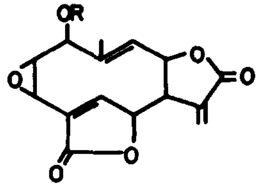
In accordance with E, manganese dioxide oxidation of IVb and Vb resulted in the α,β-unsaturated ketones VII and VIII, λ_{max} of VII 206 and 318 mμ, ε 17350 and 200, λ_{max} of VIII 206 and 318 mμ, ε 9700 and 150, λ_{max} after subtraction of the chromophores present in I and II approximately 250 (~3000) and 318 mμ (3), ir bands of VIII 1780 (saturated γ-lactone), 1747 and 1660 (conjugated γ-lactone), 1698 and 1635 cm^{-1} (relatively weak, transoid conjugated ketone), in whose nmr spectra the signals of $H_{g'}$ and H_j displayed the expected paramagnetic shifts, e.g., in VIII to 5.5 and 4.45 ppm, and the resonance of H_j had collapsed to a doublet as required by E. H_k was again weakly coupled to H_e and H_f.

Partial formulas B and E together account for all atoms of mikanolide. Two possibilities exist for the insertion of B into E: I, where H-3 (H_k) would be coupled allylically to H-5 (H_e) and homoallylically to H-6 (H_f), or I'which is biogenetically implausible and does not account for the spin coupling observed between H_k and H_e.

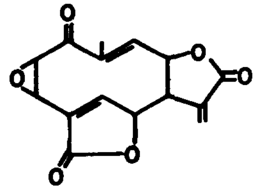
Positive chemical proof for the formulation of mikanolide as I was provided by the observation that hydrogenation of mikanolide to III was accompanied by the formation of IXb as the result of the hydrogenolytic cleavage of an allylic carbon-oxygen bond. Oxidation of IXb, which had relevant nmr signals (dmso-d_6) at 3.5 d (J = 10, H-1) and 4.3-5.0 c (three protons,



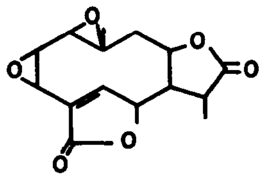
I



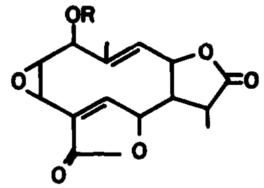
IVa,b



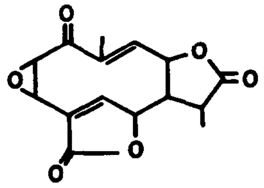
VII



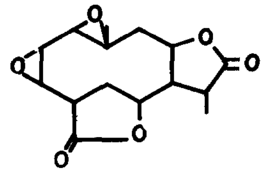
II



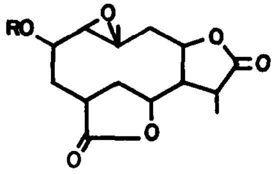
Va,b



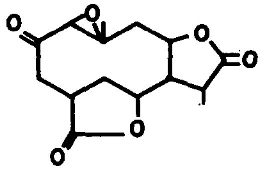
VIII



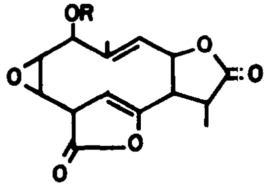
III



IXa,b

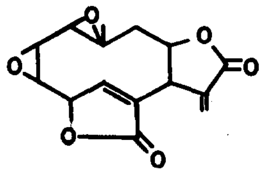


X



VIa,b

a R=Ac
b R=H



I'

H-2, H-6 and H-8--in the acetate IXa (pyridine-d_5) these occurred at 3.7 d (10, H-1), 4.65-5.1 c (H-6 and H-8) and 5.5 m (H-2)--furnished X whose H-1 resonance had shifted downfield to 4.25 ppm and had collapsed to a sharp singlet as required.

Details of these and other transformations of mikanolide, together with a description of its isolation from other Compositae species, will be given in a later, full publication. All substances referred to in the preceding paragraphs analyzed within acceptable limits.

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REFERENCES

1. W. Herz, H. Watanabe, M. Miyazaki and Y. Kishida, J. Am. Chem. Soc., 84, 2601 (1962); W. Herz, A. Romo de Vivar, J. Romo and N. Viswanathan, ibid., 85, 19 (1963).
2. S. M. Kupchan, Y. Aynehchi, M. Cassady, A. T. McPhail, G. A. Sim, H. K. Schnoes and A. L. Burlingame, ibid., 88, 3674 (1966).
3. cf. the uv absorption of similarly-constituted heliangine derivatives, H. Morimoto, Y. Sanno and H. Oshio, Tetrahedron, 22, 3173 (1966). The low intensity may be attributed to steric deformation of the chromophore.