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A NOVEL SESQUITERPENE LACTONE FROM VERNONIA ERINACEA

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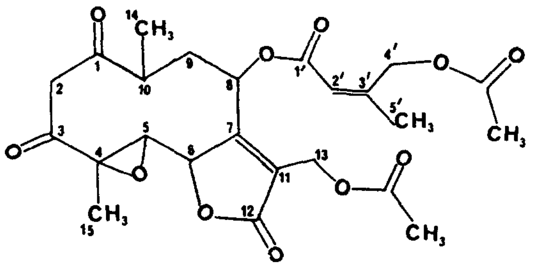
Summary: A new glaucolide containing a non-enolisable β-diketone on the ten membered ring was isolated. Acid catalysed cyclisation and dehydration yielded the hirsutinolide (furan-type germacranolide) structure. Degradative hydrogenation yielded a series of compounds which aided structure determination.

The Compositae family, and, in particular, the large genus Vernonia are rich in sesquiterpene lactones.[1] These molecules show interesting biological activity[2] and their diverse structures are useful taxonomic markers.[3] Many of these lactones are highly functionalised and, as this work demonstrates, may undergo alteration during the processes of extraction and purification.

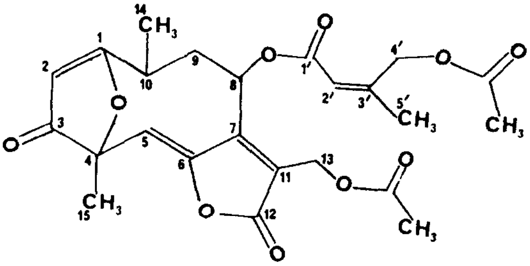
Vernonia erinacea (Wild)[4] was extracted with chloroform and after solvent evaporation the residue was partitioned between hexane and 5% aqueous methanol. Repeated flash column chromatography (SiO_2) of the polar extract yielded two lactones (as detected by i.r.). The first compound, ($C_{24}H_{28}O_{11}$) crystallised from chloroform-diethyl ether, m.p. 105-106 C, $[\alpha]_D^{18}$ -357.2° (c 0.18, $CHCl_3$). Structure (1) was assigned to it on the basis of its i.r., u.v., and n.m.r. spectra. The presence of an unsaturated γ-lactone followed from an i.r. peak at 1770 cm^{-1} (shoulder 1775 cm^{-1}, Fermi resonance) and a u.v. maximum at 218 nm (ε 17,409). Ester and ketone



(1)

functionalities were indicated by absorption peaks (i.r.) at 1745 cm^{-1} and 1705 cm^{-1} respectively. The side chain proton n.m.r. signals occur at δ5.74 (sextet, H-2'), δ5.13 (d, J = 2 Hz, CH_2-4') and δ1.95 (d, J = 2 Hz, CH_3-5'). For comparison purposes, we synthesised a mixture of Z- and E- methyl 4-acetoxy-3-methyl-2-butenoates. The Z- CH_2 signals occurred at δ5.15 while the E- CH_2 signals were found at δ4.56, thus confirming the Z- configuration in the lactone. The allylic protons on C-13 in this lactone are not equivalent and occur as doublets (J = 12.5 Hz) at δ 4.81 and δ 4.80. The protons at positions 5 and 6 are trans (J = 9.2 Hz) appearing as clean doublets at δ 2.79 and δ 4.99. No homoallylic coupling was observed to the H-13 protons. The H-8 proton is deshielded and appears at δ 4.9 coupled to the two H-9 protons (J = 12.4 and 3.1 Hz). The ester side chain deshields one of these H-9 protons (δ 2.58, m) with the second one appearing as a double double doublet (δ 2.21, $J_{9,9}$ = 10.6 Hz, $J_{10,9}$ = 1.2 Hz, $J_{9,8}$ = 12.4). The protons on C-14 are coupled to H-10 and, by virtual coupling, to at least one of the methylene C-9 protons. The C-2 carbon appears at δ_C 55.5,[5] and off-resonance decoupling shows that it is substituted by two protons, (δ 3.59, d, and δ 3.89, d, J = 16.3 Hz). This methylene group is adjacent to two ketones, δ_C 206.5 and δ_C 197.0, but no evidence for enolisation is observed.

The second lactone failed to crystallise. Spectroscopic examination clearly indicated a close relationship to the first lactone, with the ester side chain being identical in both and the C-13 acetoxy substitution still intact. The absence of the geminal protons on C-2 and also the doublets from H-5 and H-6 in (1) coupled with the appearance of two olefinic protons at δ 5.91, and 5.47, both s, led to structure (2). The i.r. spectrum has an absorption at 1595 cm^{-1} of intensity comparable to that of a ketone. This is quite characteristic of a β-alkoxy α-β ,unsaturated ketone. Further evidence for this hirsutinolide system comes from ^{13}C n.m.r. where the β-effect of

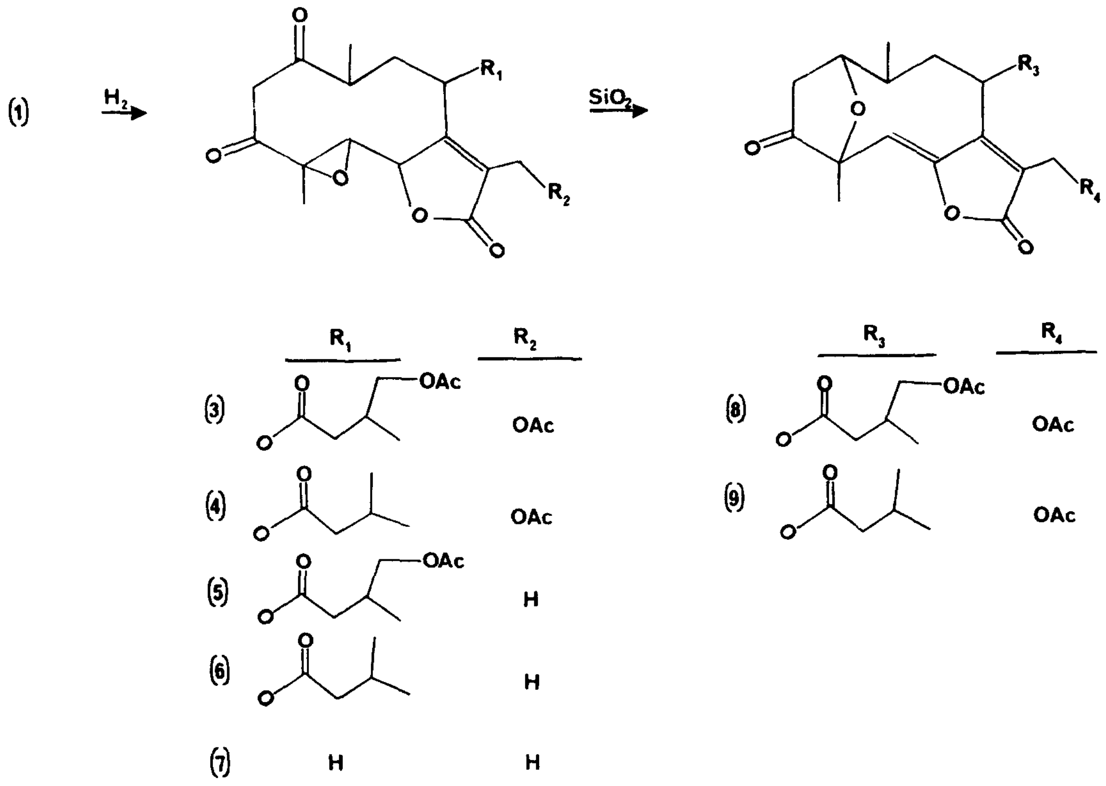


(2)

the carbonyl group plus the effect of the alkoxy group shifts the olefinic carbon signal to δ_C 195.0. The olefinic proton, H-2, appears at δ 5.47 as a broad singlet while H-5 is a sharp singlet at δ 5.91. The increased congugation to the lactone ring is observed in the u.v. where λmax (EtOH) 290nm (ε 8640). The proton, H-8, appears at δ 6.25 experiencing a downfield shift of 1.4 p.p.m. from lactone (1). Dreiding models of structure (2), irrespective of the stereochemistry at C-8, has the ether oxygen approaching very close to H-8 and thus van der Waals interaction is very significant.

A chemical transformation of glaucolide (1) to hirsutinolide (2) could be effected on preparative silica (SiO_2). ^{1}H n.m.r. examination of the crude plant extract before chromatography showed no features of the spectrum of structure (2) but those of (1) were very evident. Thus hirsutinolide (2) is not naturally occurring. The literature indicates that a number of hirsutinolides, including structure (2), have been isolated after silica purification of plant extracts.[6] It seems quite probable that these are artefacts and not natural products as claimed.

Hydrogenation of (1) in ethyl acetate over 10% palladium on carbon yielded, after flash column purification, a series of new lactones [(3)-(9)].



These structures were arrived at by comparing the ^{1}H and ^{13}C n.m.r. spectra of the purified materials with those of structures (1) and (2). The hirsutinolides were formed during the column purification. These structures assisted in confirming those of (1) and (2).

The glaucolide (1) has five chiral centres whereas the hirsutinolide (2) has only three. The latter has two possible conformations of the nine membered ring either of which would suit the observed deshielding of H-8 and the H-9/H-8 coupling constants. Structure (1) is more flexible and assignment of the relative configurations even more difficult. The literature on similar molecules has some inconsistencies in stereochemical assignments[7] and thus the spectroscopic data to date available for (1) are insufficient to postulate the relative stereochemistries

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(b) W.E. Tully, 'Sesquiterpene lactones from Vernonia and the synthesis of α-methylene γ-lactones', Ph.D. thesis, Trinity College Dublin, 1984, p22-36.

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3. T.J. Mabry, Z.Abdel-Baset, W.G. Padolina and S.B. Jones, Jr. Biochemical Systematics and Ecology, 1975, 2, 185.

4. Plant specimens were collected in Zambia. Identification by C.H.S. Kabuye, The Herbarium, Nairobi, Kenya. Voucher specimen deposited in Botany Department, Trinity College, Dublin.

5. ^{13}C n.m.r. (20.4 MHz) δ_C values C-1 and C-3(206.5 or 197.0), C-2(55.5), C-4(unobserved), C-5(62.4), C-6(80.2), C-7 and C-1$'$(162.0 or 164.0), C-8(66.4), C-9(36.5), C-10(43.1), C-11(129.0), C-12(170.5), C-13(55.5), C-14(18.9), C-15(15.0), C-2$'$(116.3), C-3$'$(157), C-4$'$(63.5), C-5$'$(21.5), $OCO\underline{C}H_3$(20.6) and (20.5).

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7. F. Bohlmann, C. Zdero, R.M. King and H. Robinson, Phytochemistry, 1982, 21, 695.

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