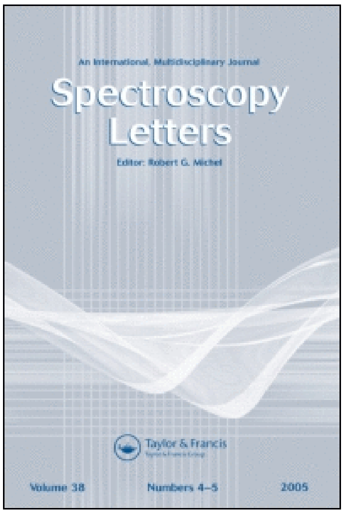

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Fasciculide-A, a New Sesquiterpene Lactone from Vernonia Fasciculata Michx

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FASCICULIDE- A, A NEW SESQUITERPENE LACTONE FROM VERNONIA FASCICULATA MICHX.

KEY WORDS:Vernonia fasciculata Michx, Fasciculide- A, Sesquiterpene lactone, Structure, IR, UV, MS, NMR(^{1}H, ^{13}C).

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ABSTRACT

A new sesquiterpene lactone, fasciculide-A, was isolated from the chloroform extract of the leaves of *Vernonia fasciculata* Michx. The structure of fasciculide-A,1, is deduced by interpretation of the spectroscopic data.

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INTRODUCTION

In the course of studies on biologically active components from Vernonia fasciculata Michx[1,2,3], a new germacranolide, which was named fasciculide- A, 1, was isolated and its structure has been established.

RESULTS AND DISCUSSION

Fasciculide- A, 1, $C_{23}H_{30}O_9$, obtained from the chloroform extract of the leaves has the following properties: mp 61- 63^o, $[\alpha]^{20}_{224}$ -33. 78 and CD^{238} + 59. Its IR spectrum shows the presence of a hydroxyl group (s) (3550 cm^{-1}), an α,β - unsaturated ester (1750 and 1650cm^{-1}), a conjugated γ - lactone (1767 and 1640 cm^{-1}), an acetate moiety (1720 and1240 cm^{-1}) and a gem- dimethyl group (1375 cm^{-1}). The presence of a α- methylene-γ- lactone group was also verified by the infrared absorption at 960 cm^{-1}. The UV spectrum of 1, supports the presence of an unsaturated lactone group, λ_{max} 212 nm (ξ17,000). Another weaker absorption at 285 nm (ξ3,200) implied the presence of an acetate carbonyl group in fasciculide- A.

Initial classification of the compound as a sesquiterpene was based on ^1H NMR and ^{13}C NMR studies. A 100 MHz ^1H NMR spectrum of fasciculide- A has four tertiary methyl singlets atδ 1. 24, 1.57, 1. 84 and 1. 94. The singlets atδ 1.84 and 1.94 are assigned to methyls on a double- bonded carbon, and the singlet at δ 1.57 is typical of methyl group on a carbon bearing an epoxide ring or an acetate group[4].The remaining methyl singlet at δ 1.24 is assigned to a tertiary methyl on a carbon bearing a hydroxyl group. A singlet at δ 2. 07 (3H)indicates an acetate group, while complex multiplets between δ 2. 29- 2.74 for five protons appear to be methylene and methine protons. Disappearance of signals at δ 3.87 and 4. 12 when the sample is shaken with deuterium oxide confirms their assignments as hydroxy protons. The tertiary nature of both hydroxyl groups is suggested by their resistance to acetylation under various experimental conditions. The spectrum also has a two- proton signal at δ 4.90 which could be attributed to the presence of a CH_2OCOCH_3 group attached to a double bonded carbon in agreement with the chemical shift of known CH_2OCOCH_3 groups attached to double bonded carbons[5]. Other signals include a broad singlet at 5. 89 for two vinylic protons and two multiplets (1H each) at δ 5.20 and 5. 35 for protons on carbons carrying oxygen. In addition, the ^1H NMR spectrum of fasciculide- A exhibits the typical two doublets at δ 5.66 and 6.23 for an exocyclic methylene group conjugated with a lactone[6].

Further support of the assignment made by proton NMR spectra comes from a ^{13}C NMR spectrum of fasciculide- A. Its interpretation is given in Table 1. In the proton decoupled ^{13}C NMR spectrum of fasciculide- A, there are 23 lines. Assignments for the types of carbons (Table 1) are based on their chemical shifts and multiplicities in gated decoupled carbon magnetic resonance spectra. Particular emphasis was given to the characteristic chemical shifts of aliphatic carbons bearing oxygens, multibonded carbon atoms[7,8] and vinyl carbons. The vinyl carbon signals are divided into two categories: those bearing a vinyl protons and those which have no directly bonded protons. The assignments of these resonances were made utilizing gated decoupled techniques, alkyl

TABLE 1

^{13}C NMR Chemical Shift Data of Fasciculide- A in $CDCl_3$.[a]

Carbon atom	Chemical Shift	Carbon atom	Chemical Shift
C- 1	77.96 (s)	C-13	126.70 (t)
C-2	139.00 (d)[b]	C-14	25. 30 (q)[f]
C-3	126. 10(d)[b]	C-15	18. 01 (q)[f]
C-4	77.96 (s)	C-1'	165. 60(s)[e]
C-5	31. 91 (t)[c]	C-2'	135. 10 (s)
C-6	65. 90 (d)[d]	C-3'	165.10(s)
C-7	29.00 (d)	C-4'	11. 89 (q)[g]
C-8	65. 50 (d)[d]	C-5'	14. 56 (q)[g]
C-9	37. 90 (t)[c]	C-6'	55.45 (t)
C-10	81.80 (s)	$\overset{*}{C}OCH_3$	169.58 (s)
C-11	166.10 (s)[e]	$\overset{*}{C}H_3CO$	20. 63 (q)
C-12	108. 12 (s)		

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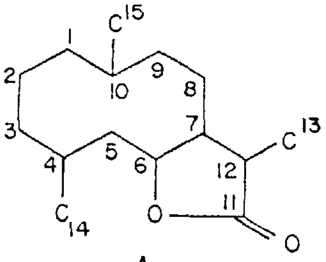
a. The chemical shifts (δ) are reported in parts per million with respect to tetramethyl silane. Signal multiplicity is denoted by s,d, t, q respectively.

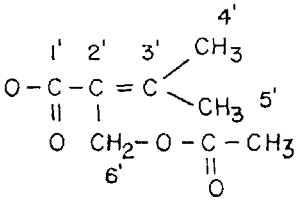
b,c, d,.........................g may be interchanged.

substituent effects, and the recognized[9] deshielding of aβ - carbon in α ,β- unsaturated carbonyl systems. The IR, UV, and ^{1}H and ^{13}C NMR spectra reveal fasciculide- A has an exocyclic methylene group conjugated with a lactone group, an acetate group and an α,β- unsaturated ester function. Moreover, the presence of a CH_2OCOCH_3 group on a double bonded carbon at 55.45 ppm and existence of three carbon-carbon double bonds in fasciculide- A (Table 1) can be inferred from the ^{13}C NMR spectrum of 1, One double bond is associated with the exocyclic methylene group, and the chemical shifts from ^1H and ^{13}C NMR spectra of the CH_2OCOCH_3 moiety implied attachment to a double bonded carbon[4]. If the CH_2OCOCH_3 group is assigned to either C- 14 or C- 15 in the sesquiterpene skelton, the number of methyl groups would be reduced from five to four. This number of methyl moieties would be inconsistent with the ^1H and ^{13}C NMR spectral data. The placement of $-CH_2OCOCH_3$ group on the ester portion of the molecule appears to be most consistent with the isoprene rule[10] and the chemical shifts of methyl groups. Consequently, the fragments A and B, can be proposed.

The ester portion B is further strengthened by the presence of dimethyl groups on an acrylic acid esters as evidenced by the ^1H and ^{13}C NMR spectra of fasciculide- A and by the absence of α- proton signal in its proton NMR spectrum[11].



A



B

Hydrogenation of fasciculide- A afforded a hexahydro derivative. The proton NMR spectrum of the hydrogenated derivative displayed two signals at δ 1. 25 (broad, 12 H) and 0. 90 (poorly resolved doublet, 6 H,) substantiating hydrogenation of all the double bonds. In addition, the acetate moiety was lost during the hydrogenation since a new secondary methyl signal appeared and the signal for CH_2OCOCH_3 at 4.9 disappeared in the proton NMR spectrum of the hydrogenated derivative. Such a loss suggests the existance of an allylic acetate function. Furthermore, an IR spectrum of hydrogenated fasciculide- A indicates no conjugation for the lactone and the absence of an acetate carbonyl frequency. Additional support for the loss of this group came from the mass spectrum of hydrogenated derivative, which shows an expected fragment at m/e 396 (M- HOAC). Therefore, the double bond which activated the hydrogenalysis of acetate must be associated with the conjugated lactone[5] or the carbonyl and is consistent with the assigment of CH_2OCOCH_3 on the ester side chain (B).

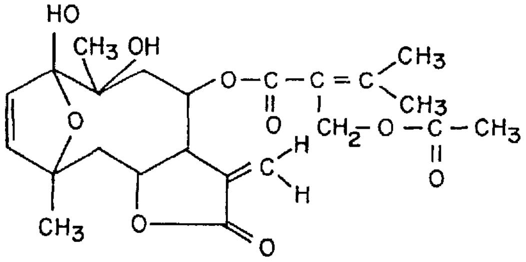
The detection of molecular ions in the mass spectra of both fasciculide- A and hydrogenated derivative could not be achieved, but the absence of the molecular ion in the mass spectra of sesquiterpene lactones especially with tertiary hydroxyl group (s) is not uncommon[12]. Supporting evidence for the molecular ion of fasciculide-A at m/e 450 was obtained from the mass spectrum of hydrogenated derivative which showed an intense peak at m/e 396(M- HOAC). Other peaks at m/e 43, 69, 83, 85, and 99 are typical of tiglic, angelic, and dimethyl acrylic acid esters.

Since eight out of nine oxygens in the $C_{23}H_{30}O_9$ molecular formula and their neighbors have been assigned to lactone, the acetate, the ester and two hydroxyl groups, the last oxygen must form an ethereal ring because spectroscopic data indicate it is neither hydroxyl nor carbonyl oxygen.The double bond equivalence of 9, calculated for $C_{23}H_{30}O_9$ which included carbon- carbon double bonds, rings and carbonyls, is in full agreement with its ^{13}C NMR spectrum.

Therefore, eliminating other possible structures on the basis of isoprene rule[10], structure 1, is assigned to this new sesquiterpene lactone, fasciculide- A.

EXPERIMENTAL

The mps were taken on a Fisher- Johns apparatus and are uncorrected. UV spectra were recorded in ethanol on a Cary Model- 14 and IR spectra as KBr pellets or melt on Beckman Models IR-8 and IR-12. NMR spectra were recorded on Varian A- 60 and JOEL-100 in $CDCl_3$ with tetramethyl silane as internal reference. The mass spectra were obtained with a



1

Perkin- Elmer- Hitachi Model RMU- 6E double focussing instrument, Merck Silica gel HF-254 was used for TLC.

The powdered, dry leaves of *Vernonia fasciculata* Michx (5.4 kg), collected near Sandwitch, Illinois, in summers of 1970- 1972, were extracted with chloroform (5 l). The solvent was removed in vacuo and the gummy residue was exhaustively extracted with 50% hot ethanol. The aqueous alcohlic extracts after filteration were concentrated in vacuo and cooled overnight. The precipitated material (A, 130.5 g) was collected. When A was redissolved in chloroform, B (0.5 g) was obtained as insoluble material and was removed by filteration. Evaporation of the filtrate to dryness yielded a solid material C (130 g). The initial filtrate secured after removal of fraction A was cooled for several days to yield a yellow solid. Recrystallization of this solid from 95% ethanol and water gave 8 g of a yellow solid (F_1 which proved to contain fasciculide- A).

Isolation of fasciculide- A. The final separation and purification of this compound was achieved by preparative silica gel TLC (multiple dips, 0.5 mm, benzene: methanol; 96:4). Fasciculide- A, was obtained (chloroform-methanol) as a colorless solid (104.6 mg). It has mp 61-63^{o}, $[\alpha]^{20}_{224}$ - 33.78^{0}, CD^{238} + 59, IR ν_{max} (KBr) 3350, 1767, 1750, 1720, 1650, 1640, 1240 cm^{-1}; λ_{max} 212 nm (ϵ17,000), 285 (3, 200);δ1.24 (3 H, s, HO- C- $\underline{CH_3}$) , 1.57 (3H, s, C-O-C-$\underline{CH_3}$), 1.84 (3H, s, C=C-$\underline{CH_3}$), 1.94 (3 H, s, C=C-$\underline{CH_3}$), 2.07 (3H, s,-O-CO-CH_3), 2.29- 2.74 (5H, m, CH_2, CH-), 3.87 (1H, s, OH), 4.12 (1H, s, OH), 4.90- 4. 94 (2H, br,s, CH_2O-), 5.20 (1H,m, -H-C-O),5.35 (1H, m, H-C-O) 5.66 (1 H, d, =C-H), 5.89 (2H, br, H-C=C-H), 6.23 (1H,d, =C-H), ^{13}C NMR Table 1, and m/e 404 (M -46), 392 (M-58), 362 (M-88), 338 (M-112), 278 [M-172 (side chain)],219 (172 + 2 CH_3 + OH), 191 (172 +18 +OH),188 ($C_6H_{12}O_5$), 163 ($C_6H_{11}O_5$), 99 ($C_5H_7O_2$), 83 (base peak), 69 (C_3H_6O), 43 (C_2H_3O).

Hydrogenation of fasciculide- A. Hydrogenation of fasciculide- A was carried out in a Brown's hydrogenator[13]. Fasciculide- A (17mg) was dissolved in absolute ethanol (10 ml) containing platinum oxide (4mg), and the apparatus was flushed with hydrogen.Hydrogen was formed by a standard sodium borohydride solution added to a hydrogen generator containing 50% acetic acid.The reaction was done over 3 hrs. Evaporation Of the solvent yielded a mixture (15.2 mg) of compounds. The major compound was isolated by preparative silica gel TLC (0.75 mm, ethyl acetate: benzene, 1:1); IR ν_{max} (melt), 3500, 3000, 2950, 1725, 1450, 1375, 1260, 1190, 1025, 970, 925, 800, 750 cm^{-1}; NMR ($CDCl_3$) δ o.88 (br, s), 1.25 (s). 2. 31 (m), 2.92 (m), 3.62 (m), 3.93 (m) ; m/e 396, 380, 292, 280, 263, 256, 223, 205, 186, 149.

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