Tetrahedron Letters,Vol.28,No.31,pp 3543-3546,1987 0040-4039/87 $3.00 + .0
Printed in Great Britain Pergamon Journals Ltd.

THE STRUCTURE OF 1-CINNAMOYLMELIANOLONE, A NEW INSECTICIDAL TETRANORTRITERPENOID, FROM MELIA AZEDARACH L. (MELIACEAE)

S. Mark Lee*, James A. Klocke, and Manuel F. Balandrin
NPI, University of Utah Research Park
417 Wakara Way, Salt Lake City, Utah 84108, U.S.A.

Summary: 1-Cinnamoylmelianolone (1), a new insecticidal tetranortriterpenoid, was isolated from methanolic extracts of the fruit of Melia azedarach L. The structure of 1 is proposed on the basis of spectral data.

Melia azedarach L. (Meliaceae), the Chinaberry or Persian lilac tree, has long been recognized as an insecticidal and medicinal plant$^{1)}$. One of the constituents isolated from M. azedarach fruit is azadirachtin (2)$^{2)}$, a highly potent limonoid insect antifeedant and ecdysis inhibitor$^{3)}$. Using insect bioassay-guided$^{4)}$ fractionation techniques$^{5)}$, we have isolated a new tetranortriterpenoid structurally related to azadirachtin, with equipotent insecticidal activity, from methanolic extracts of the fruit of M. azedarach. Herein we report the preliminary proposed structure of this new insecticide, designated as 1-cinnamoylmelianolone (1).

1 exhibited the following spectral data: IR (KBr): 3700-3200, 2930, 1710, 1670, 1640 and 760 cm^{-1}; UV (CH_3OH): λ_{max} 279 and 217 nm (ϵ : 14500 and 7750); ^{1}H-NMR: Table 1; ^{13}C-NMR: Table 2; FAB-MS: m/z 621 $(M-H_2O+H)^+$, 603 $(M-2H_2O+H)^+$, 585 $(M-3H_2O+H)^+$ and 131 $(C_9H_7O)^+$; FAB-MS salt (NaCl) dosing$^{6)}$ (glycerol:methanol (1:1) matrix): m/z 661 $(M+Na)^+$, corresponding to molecular weight 638 (molecular formula, $C_{35}H_{42}O_{11}$). ^{13}C-NMR (DEPT spectra$^{7)}$) and ^{1}H-NMR (D_2O exchange) data indicate that 1 contains 4 CH_3, 4 CH_2, 18 CH, 9 carbons not bonded to hydrogen, and 4 protons due to OH groups. Furthermore, NMR spectral data suggest that the structure of 1 is similar to that of azadirachtin (2)$^{8)}$ except for the following.

i). In the NMR spectra of 1, the carbon signal corresponding to the C-11 hemiketal carbon (δ 104.10) in 2 and proton resonances due to the 11-OH (δ 5.05) in 2 and the 11-H (δ 4.47) in 3-tigloylazadirachtol$^{9)}$ are absent. Instead, a carbonyl carbon signal appears at δ 208.99, while the 9-H signal remains a singlet at δ 3.53 in 1. These data suggest the presence of a carbonyl group in 1 at C-11 (δ 208.99, s).

ii). In the NMR spectra of 1, both the ^{1}H- and ^{13}C-NMR signals corresponding to the C-12 and C-29 methoxycarbonyl groups of 2 are missing.

Instead, the ^{1}H-NMR spectrum of **1** exhibits two additional singlet methyl resonances at δ 1.21 (29-CH_3) and δ 1.78 (12-CH_3). Corresponding carbon signals for the C-12 (δ 21.42, q) and C-29 (δ 20.36, q) methyl groups in **1** were found on the basis of two-dimensional (2D) heteronuclear (^{13}C-^{1}H) correlation spectroscopy$^{10)}$. The assignment of these methyl groups to the positions indicated was based solely on limonoid biogenetic considerations and not on spectral analysis. NMR spectral experiments are currently being conducted for unequivocal assignment of the methyl groups.

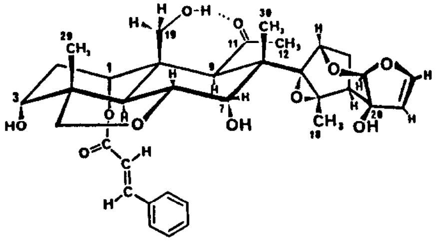
iii). ^{1}H-NMR data (D_2O exchange experiments) indicated the presence of four hydroxyl groups in **1**, and its FAB-MS spectrum showed three consecutive losses of H_2O (18 amu) from the quasi-molecular ion. Two D_2O-exchangeable singlet hydroxyl proton signals of **1** were readily assignable as 7-OH (δ3.31) and 20-OH (δ 2.93) on the basis of spectral comparison with **2**. The absence of an acetyl group signal at C-3 (δ 1.95, s in **2**) and a significant upfield shift of the 3-H_{eq} signal (δ 3.87 (ddd, $^3J_{3,OH}$ = 7.2, $^3J_{3,2\alpha}$ = $^3J_{3,2\beta}$ = 2.5) in **1** vs. 5.50 in **2**), which upon D_2O exchange collapsed to an apparent triplet (dd, $^3J_{3,2\alpha}$ = $^3J_{3,2\beta}$ = 2.5), indicated the presence of an axial hydroxyl group at C-3 in **1**. Further collapsing of two doublets of doublets corresponding to 19-Ha (δ 3.53, $^2J_{19a,b}$ = 17.5, $^3J_{19a,OH}$ = 4.0) and 19-Hb (δ 4.15, $^2J_{19b,a}$ = 17.5, $^3J_{19b,OH}$ = 5.6) to two AB doublets ($^2J_{19a,b}$ = 17.5) was observed in the presence of D_2O. A sharp splitting pattern observed for the hydroxyl proton at C-19 (δ 3.11, dd, $^3J_{19\text{-}OH,a}$ = 4.0, $^3J_{19\text{-}OH,b}$ = 5.6) might be due to its intramolecular H-bonding with the neighboring C-11 carbonyl group, consequently forming a pseudo-seven-membered ring system. This might explain the larger C-19 methylene geminal coupling constant ($^2J_{19a,b}$ = 17.5) observed in the ^{1}H-NMR spectrum of **1** compared to the corresponding coupling constant seen in the five-membered ring system of **2** ($^2J_{19a,b}$ = 9.6).

The presence of hydroxyl groups at C-3 and C-19 in **1** was further confirmed via acetylation with acetic anhydride in pyridine. Acetylation at 3-OH gave the monoacetate (FAB-MS: m/z 663 $(M-H_2O+H)^+$; ^{1}H-NMR ($CDCl_3$)δ 1.89 (s, 3H, CH_3CO-) and 4.97 (dd, 1H, $^3J_{3,2\alpha}$ = $^3J_{3,2\beta}$ = 2.9, 3-H_{eq})). Acetylation at both 3-OH and 19-OH gave the diacetate (FAB-MS: m/z 705 $(M-H_2O+H)^+$; ^{1}H-NMR ($CDCl_3$)δ 1.89 (s, 3H, 3-CH_3CO-), 2.13 (s, 3H, 19-CH_3CO-), 4.35 (d, 1H, $^2J_{19a,b}$ = 16.1, 19-Ha), 4.48 (d, 1H, $^2J_{19b,a}$ = 16.1, 19-Hb) and 4.97 (dd, 1H, $^3J_{3,2\alpha}$ = $^3J_{3,2\beta}$ = 2.9, 3-H_{eq})).

iv). The presence of a cinnamoyl moiety in **1** was evident because of its characteristic proton and carbon NMR signals (Tables 1 and 2), FAB-MS data (m/z 131 $(C_9H_7O)^+$), and UV (CH_3OH) (λ_{max} at 279 nm (ϵ : 14500)) data. The absence of ^{1}H- and ^{13}C-NMR signals corresponding to a tigloyl group indicated that the cinnamoyl moiety replaced the tigloyl group of 2 at C-1 in 1.

The complete spectral data of 1 and its derivatives, and their respective insecticidal activities, will be published in detail elsewhere.

Acknowledgement. This work was supported by a grant awarded by the U.S. National Science Foundation (PCM-8314500).



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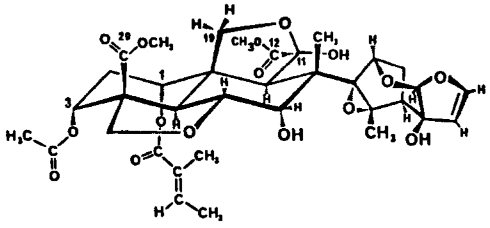

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Table 1. ^{1}H-NMR data of 1-cinnamoylmelianolone (1) (200 MHz, $CDCl_3$) and azadirachtin (2)[8,9] (δ in ppm; J in Hz).

	1	2
1-H	4.63 (dd, J2.7, 2.7)	4.75 (dd, J2.9, 3.1)
2-Hα	2.28 (br m)	2.34 (ddd, J16.7, 2.9, 2.7)
2-Hβ	2.28 (br m)	2.13 (ddd, J16.7, 3.1, 2.9)
3-H	3.87 (ddd, J7.2, 2.5, 2.5)	5.50 (dd, J2.7, 2.9)
5-H	2.76 (d, J12.4)	3.35 (d, J12.5)
6-H	4.21 (dd, J12.4, 3.1)	4.60 (dd, J12.5, 2.7)
7-H	4.55 (d, J3.1)	4.75 (d, J2.7)
9-H	3.53 (s)	3.34 (s)
12-CH_3	1.78 (s)*	--
15-H	4.53 (d, J3.5)	4.67 (d, J3.4)
16-Ha	1.65 (m)[a]	1.73 (ddd, J13.0, 3.4, 5.1)
16-Hb	1.26 (d, J13.3)[b]	1.31 (d, J13.0)
17-H	2.30 (br d)[c]	2.38 (d, J5.1)
18-CH_3	2.08 (s)*	2.01 (s)
19-Ha	3.53 (dd, J17.5, 4.0)	3.63 (d, J9.6)
19-Hb	4.15 (dd, J17.5, 5.6)	4.15 (d, J9.6)
21-H	5.69 (s)	5.65 (s)
22-H	5.03 (d, J2.9)	5.05 (d, J2.9)
23-H	6.43 (d, J2.9)	6.46 (d, J2.9)
28-Hα,β	4.16 (d, J7.6) 3.71 (d, J7.6)	4.08 (d, J9.0) 3.76 (d, J9.0)
29-CH_3	1.21 (s)**	--
30-CH_3	1.15 (s)**	1.74 (s)
3-OH	1.97 (d, J7.2)	--
7-OH	3.31 (s)	3.02 (br s)
11-OH	--	5.05 (s)
19-OH	3.11 (dd, 5.6, 4.0)	--
20-OH	2.93 (s)	2.92 (br s)
CH_3CO-	--	1.95 (s)
CO_2CH_3	-- --	3.76 (s) 3.68 (s)
Cinnamoyl/ Tigloyl		
2'-H	6.44 (d, J16.0)	--
3'-H	7.80 (d, J16.0)	6.93 (qq, J7.0, 1.5)
4'-CH_3	--	1.78 (dq, J7.0, 1.1)
5',9'-H	7.51 (m)	1.85 (dq, J1.5, 1.1)
6',7',8'-H	7.39 (m)	--

[a] In $(CD_3)_2CO$, this signal is at 1.46 (ddd, J 12.6, 5.5, 3.7).

[b] In $(CD_3)_2CO$, this signal is at 1.12 (d, J12.6).

[c] In $(CD_3)_2CO$, this signal is at 2.24 (d, J5.5).

*, ** Assignments could be reversed.

Table 2. ^{13}C-NMR data of 1-cinnamoylmelianolone (1) (50.32 MHz, $CDCl_3$) and azadirachtin (2)[8] (δ in ppm).

	1	2
C-1	74.42d	70.51d
C-2	29.72t	29.37t
C-3	70.32d	66.99d
C-4	40.95s	52.52s
C-5	36.82d	37.06d
C-6	73.29d	73.79d
C-7	74.62d	74.37d
C-8	44.24s	45.41s
C-9	47.36d	44.69d
C-10	48.58s	50.19s
C-11	208.99s	104.10s
C-12	21.42q*	171.70s
C-13	67.18s	68.53s
C-14	69.47s	69.69s
C-15	76.07d	76.43d
C-16	25.06t	25.06t
C-17	48.00d	48.67d
C-18	18.23q*	18.49q
C-19	70.04t	69.07t
C-20	83.55s	83.55s
C-21	108.66d	108.70d
C-22	107.71d	107.30d
C-23	146.99d	147.00d
C-28	78.14t	72.99t
C-29	20.36q**	173.20s
C-30	17.07q**	21.33q
CO_2CH_3	-- --	53.52q 52.72q
CH_3CO-	-- --	169.50s 20.88q
Cinnamoyl/ Tigloyl		
C-1'	165.70s	166.10s
C-2'	116.71d	128.60s
C-3'	146.61d	137.50d
C-4'	133.74s	14.29q
C-5',9'	128.25d	11.94q
C-6',8'	129.06d	--
C-7'	130.95d	--

*, ** Assignments could be reversed.

(Received in USA 23 January 1987)