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CHEMICAL STUDIES ON MEXICAN PLANTS USED IN TRADITIONAL MEDICINE, XV.[1] SESQUITERPENE EVONINOATE ALKALOIDS FROM *HIPPOCRATEA EXCELSA*

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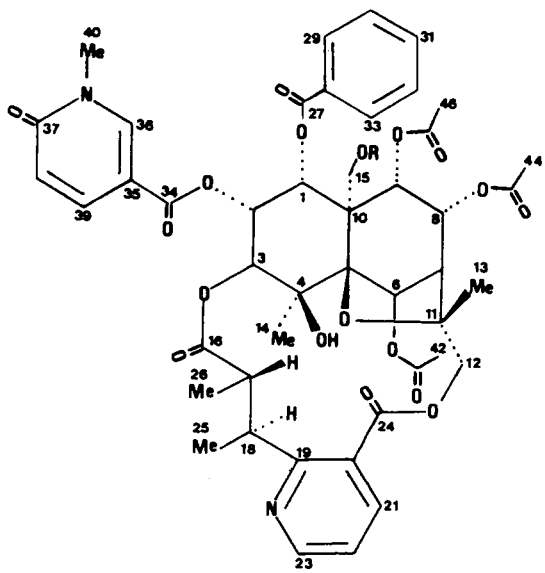
ABSTRACT.—Three sesquiterpene evoninoate alkaloids, hippocrateine I [**1**], hippocrateine II [**2**], and emarginatine A have been isolated from the root and stem barks of *Hippocratea excelsa*. Compounds **1** and **2** are new naturally occurring substances. The structure of **1** was unequivocally established by X-ray crystallographic analysis, and the structure of the second new alkaloid was deduced by spectral analysis.

In connection with our chemical studies on Mexican plants used in traditional medicine, we report the isolation of three sesquiterpene evoninoate alkaloids from the root and stem barks of *Hippocratea excelsa* H.B.K. (Hippocrateaceae). The reddish brown bark, commonly known as "cancerina," is valued for treating skin ailments and gastric ulcers and for its pesticidal properties. Previous chemical studies resulted in the isolation, in a remarkably high yield, of *trans*-polyisoprene (1) and several triterpenes (2). Defatted dried stem and root barks were extracted with MeOH. The resulting extract was partitioned between EtOAc-MeOH-H_2O (12:1:3). Si gel chromatography of



1 R=1-Ac
2 R=-C-CH(Me)CH_2Me
‖
O

[1]For Part XIV see R. Mata *et al.*, *Heterocycles*, in press (1990). Taken in part from the MS thesis of Fernando Calzada.

the organic phase followed by preparative tlc allowed the isolation of emarginatine A and compounds **1** and **2**.

Hippocrateine I [**1**] was obtained as a white crystalline solid, and the molecular formula $C_{48}H_{52}N_2O_{19}$ was indicated by fabms and cims. Both ^{1}H- and ^{13}C-nmr (Tables 1 and 2) spectra showed strong similarities to those of emarginatine A (3). Comparative analysis indicated that the acetyl group at C-1 in emarginatine A was replaced by a benzoate unit in **1**. Consistent with this proposal was the diamagnetic shift observed for the methyl group of the acetate at C-9 (δ 1.39); as previously described for several polyhydroxy agarofuran derivatives, this unusual diamagnetic effect arises when an equatorially oriented acetate on C-9 is shielded by an aromatic ester on C-1 (4–7). 2D-COSY (Figure 1), 2D-HETCOR, APT, and DEPT spectra of hippocrateine I led to the assignments of the ^{1}H- and ^{13}C-nmr data as shown in Tables 1 and 2, respectively. The 2D nmr spec-

TABLE 1. ^{1}H-nmr Spectral Data of Alkaloids **1** and **2**.[a]

Proton	Compound	
	1	**2**
H-1	5.99 (d, 4)	6.05 (d, 4)
H-2	5.57 (dd, 2.3, 4)	5.55 (m)
H-3	4.87 (d, 2.3)	4.87 (d, 2.3)
H-6	7.07 (s)	6.94 (s)
H-7	2.37 (d, 4)	2.43 (d, 4)
H-8	5.55 (dd, 5.7, 4)	5.5–5.6 (m)
H-9	5.48 (d, 5.7)	5.47 (d, 5.7)
H-12	3.72 (d, 13)	4.72 (d, 13)
H-12′	6.00 (d, 13)	6.00 (d, 13)
H-13	1.75 (s)	1.75 (s)
H-14	1.58 (s)	1.58 (s)
H-15	4.36 (d, 13)	4.38 (d, 13)
H-15′	5.71 (d, 13)	5.68 (d, 13)
H-17	2.62 (q, 7)	2.62 (q, 7)
H-18	4.69 (q, 7)	4.68 (q, 7)
H-21	8.09 (dd, 1.8, 7.7)	8.09 (dd, 1.8, 7.7)
H-22	7.28 (dd, 4.8, 7.7)	7.33 (m)
H-23	8.71 (dd, 4.8, 1.8)	8.72 (dd, 1.8, 4.8)
H-25	1.41 (d, 7)	1.41 (d, 7)
H-26	1.23 (d, 7)	1.23 (d, 7)
H-29, H-33	7.73 (m)	7.74 (m)
H-30, H-32	7.34 (m)	7.34 (m)
H-31	7.51 (m)	7.51 (m)
H-36	8.46 (d, 2.5)	8.5 (d, 2.5)
H-38	6.57 (d, 9.5)	6.58 (d, 9.5)
H-39	7.84 (dd, 9.5, 2.5)	7.85 (dd, 9.5, 2.5)
H-40	3.73 (s)	3.73 (s)
H-42	2.22 (s)	2.22 (s)
H-44	2.13 (s)	2.13 (s)
H-46	1.38 (s)	1.38 (s)
H-48	2.39 (s)	—
OH-4	4.59 (s)	4.62 (s)
H-3, H-4, H-5 mb[b]	—	1.00–1.37 (m)
H-2 mb	—	2.95 (st, 7)

[a]Recorded in $CDCl_3$. Chemical shift values are reported as δ values (ppm) from internal TMS at 500 MHz for **1** or 300 MHz for **2**; signal multiplicity and coupling constants (Hz) are shown in parentheses.

[b]mb = 2-methylbutiroyl.

TABLE 2. ^{13}C-nmr Spectral Data of Alkaloids **1** and **2**.

Carbon	Compound	
	1	**2**
C-1	73.12 (d)	73.09 (d)
C-2	69.68 (d)	69.70 (d)
C-3	75.41 (d)	75.42 (d)
C-4	70.31 (s)	70.34 (s)
C-5	93.96 (s)	93.79 (s)
C-6	73.62 (d)	73.95 (d)
C-7	50.50 (d)	50.39 (d)
C-8	68.70 (d)	68.78 (d)
C-9	71.11 (d)	71.01 (d)
C-10	52.34 (s)	52.35 (s)
C-11	84.47 (s)	84.38 (s)
C-12	60.33 (t)	60.54 (t)
C-13	18.50 (q)	18.52 (q)
C-14	23.18 (q)	23.15 (q)
C-15	69.92 (t)	69.95 (t)
C-17	44.96 (d)	44.94 (d)
C-18	36.43 (d)	36.36 (d)
C-19	165.38 (s)	165.31 (s)
C-20	124.95 (s)	124.94 (s)
C-21	137.80 (d)	137.80 (d)
C-22	121.14 (d)	121.16 (d)
C-23	151.58 (d)	151.56 (d)
C-25	9.78 (q)	9.78 (q)
C-26	11.86 (q)	11.83 (q)
C-28	128.88 (s)	128.79 (s)
C-29, C-33	128.51 (d)	128.52 (d)
C-30, C-32	129.47 (d)	129.47 (d)
C-31	133.59 (d)	133.61 (d)
C-35	108.14 (s)	108.20 (s)
C-36	144.01 (d)	144.04 (d)
C-37	162.30 (s)	162.28 (s)
C-38	119.86 (d)	119.28 (d)
C-39	138.94 (d)	139.02 (d)
C-40	38.18 (q)	38.11 (q)
C-42	21.02 (q)	20.91 (q)
C-44	21.65 (q)	21.61 (q)
C-46	19.87 (q)	19.85 (q)
C-48	21.35 (q)	—
CO	163.01 (s)	163.05 (s)
CO	164.39 (s)	164.46 (s)
CO	165.55 (s)	168.56 (s)
CO	168.55 (s)	168.61 (s)
CO	168.86 (s)	169.81 (s)
CO	169.89 (s)	170.07 (s)
CO	169.96 (s)	173.88 (s)
CO	173.89 (s)	178.14 (s)
C-2 mb[b]	—	33.99 (d)
C-3 mb	—	29.68 (t)
C-4 mb	—	19.08 (q)
C-5 mb	—	19.73 (q)

[a]Recorded in $CDCl_3$. Chemical shift values are reported as δ (ppm) values from internal TMS at 500 for **1** or 300 MHz for **2**; signal multiplicities are shown in parentheses.

[b]mb = methylbutiroyl.

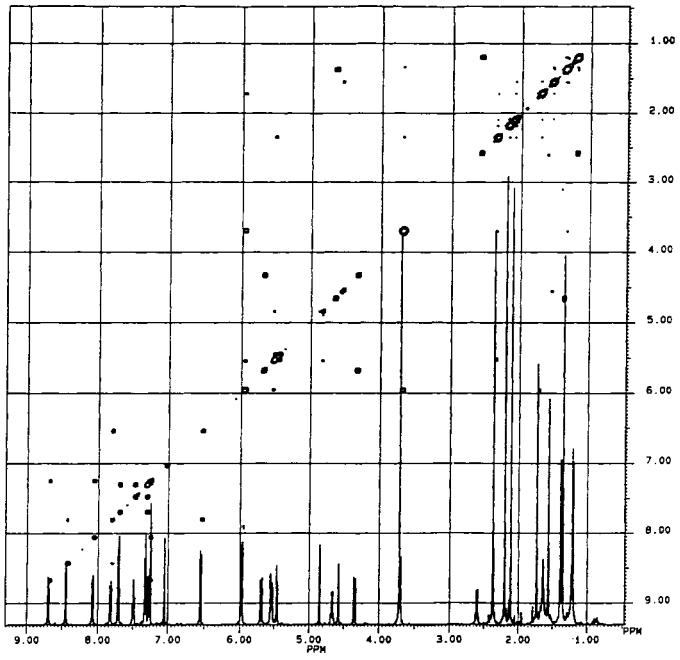


FIGURE 1. 2D proton correlation (COSY) of hippocrateine I [**1**].

trum revealed spatial interactions between H-12′ and H-13, H-13 and H-7, H-7 and H-12, and between H-26 and H-25. Proof of the alkaloid structure was made by single-crystal X-ray analysis. A computer-generated perspective drawing of hippocrateine I is given in Figure 2. As in the case of acanthothamine (8), the A and B rings adopt chair conformations. The C ring has a half-chair conformation. The absolute configuration was determined by comparison with the known absolute stereochemistry of acanthothamine (8).

Hippocrateine II [**2**] had the composition $C_{51}H_{58}N_2O_{19}$. The nmr spectra of **2** were nearly identical with those of hippocrateine I, except for the presence of the signals for a 2-methylbutyroyl unit [δ 2.95 (st, $J = 7$ Hz) and 1.00–1.37 (m) in the ^{1}H-nmr spectrum, and δ 33.99 (d), 29.68 (t), 19.73 (q), and 19.08 (q) in the ^{13}C-nmr spectrum] and the absence of the resonances for the C-15 acetate group. Thus, the acetyl group at C-15 in hippocrateine I was replaced by a 2-methylbutyroyl moiety in **2**. The properties of the third alkaloid were in good agreement with those recently described for emarginatine A (3).

Compound **1** showed slight activity in the brine shrimp lethality test (9) [$LC_{50} = 212$ μg/ml] and in the 9PS cytotoxicity test ($ED_{50} = 1.85 \times 10^{-1}$ μg/ml) but was inactive in A-549, HT-29, and MCF-7 cell culture systems ($ED_{50} > 10$ μg/ml).

Compounds **1** and **2** and emarginatine A are the only sesquiterpene evoninoate alkaloids bearing a 5-carboxy-*N*-methylpyridonyl moiety. This work constitutes the first report of the presence of alkaloids in the family Hippocrataceae. The presence of these compounds supports the relationship of this group of plants with the Celastraceae.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Uv spectra were taken on a Beckman DU-7; ir spectra were obtained in KBr on a Perkin-Elmer 599 B spectrophotometer; nmr spectra of **1** were recorded on a Bruker 500 MHz instrument at Syntex, Palo Alto; nmr spectra of **2** and emarginatine A were registered in a Varian VXR-300 S apparatus. Optical rotations were measured with a JASCO DIP 360 digital polarim-

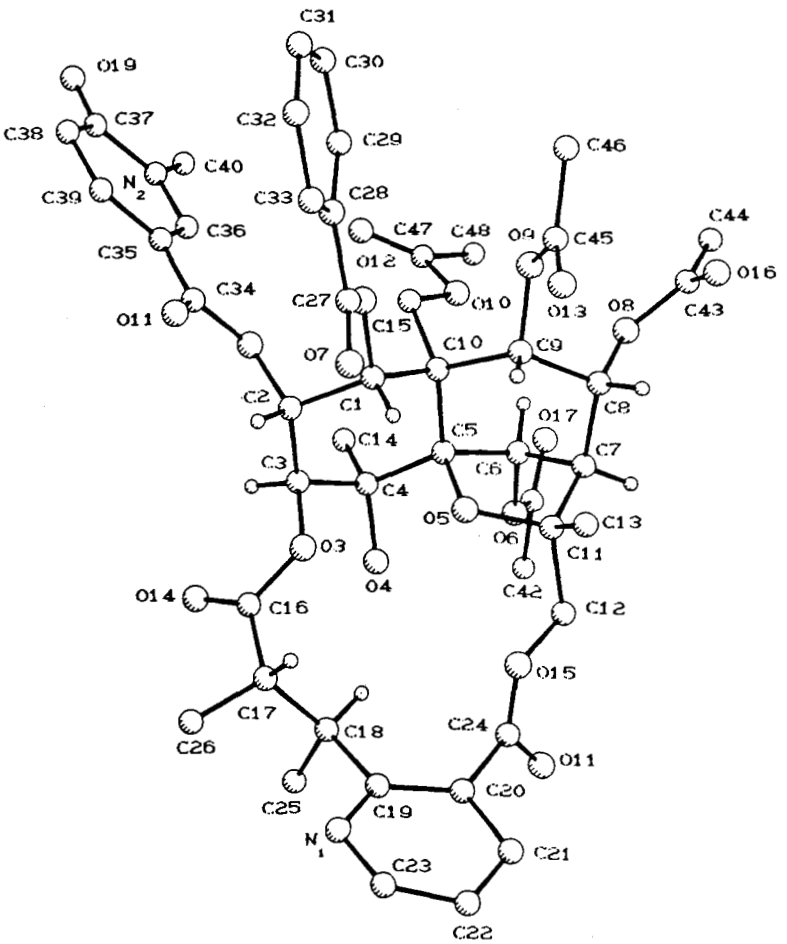


FIGURE 2. The molecular structure of compound **1**.

eter; cims and fabms were performed on a Finnigan 4000 at the School of Pharmacy and Pharmacal Sciences, Purdue University. Si gel 60 (70–230 mesh) Merck was used for cc; tlc was done on Si gel 60 GF 254 plates (Merck). X-ray data were collected on a Nicolet R 3m diffractometer with Cu-Kα radiation (Ni-filtered) using 2θ:θ scans.

PLANT MATERIAL.—Stem and root barks of *H. excelsa* were obtained from el Mercado de Sonora, México D.F. in October 1988. Reference samples have been deposited at the National Herbarium (voucher no. RM-188).

ISOLATION PROCEDURES.—The air-dried, shredded stem and root barks (3.55 kg) were extracted with hexane. The dried marc was then macerated twice with MeOH at room temperature for a two-day period. The combined MeOH extracts were evaporated to dryness to yield 280 g of a reddish residue which was partitioned between EtOAc-MeOH-H_2O (12:1:3). Evaporation of the organic solvent yielded 138.9 g of a residue. A portion (120 g) of the last residue was chromatographed on Si gel (2 kg). Elution was accomplished with a solvent gradient of increasing polarity. From fractions eluted with $CHCl_3$-MeOH (99:1) a white crystalline powder (427 mg) precipitated; this material was resolved into three components (hippocrateine I, hippocrateine II, and emarginatine A) by preparative tlc on Si gel using $CHCl_3$ as the developing solvent. Hippocrateine I [**1**]: 205 mg (0.0066% of the dry wt), mp 300° (dec); ir (KBr) 3600–3200, 2800, 1735, 1665, 1440, 1385, 1280, 1240, 1300, 1050, 710 cm^{-1}; $[\alpha]_D$ +50 (c = 0.33, $CHCl_3$); uv λ max ($CHCl_3$) 266 nm; cims *m/z* (rel. int.) $[M+1]^+$ 961 (3), 206 (8), 178 (13), 162 (8), 154 (100), 123 (75) and 110 (26); fabms (rel. int.) $[M]^+$ 960 (2), 206 (59), 178 (29), 161 (16), 154 (49), 136 (100).

Hippocrateine II [**2**].—Compound **2**, 32 mg (0.0010% of the dry wt), mp = 308°; ir (KBr) 3600–3200, 3000–2850, 1750, 1675, 1560, 1360, 1230, 1150, 1100 cm^{-1}; uv λ max ($CHCl_3$) 265 nm. *Anal.* calcd for $C_{51}H_{58}O_{19}N_2$, C 61.07, H 5.78, N 2.79; found C 60.99, H 5.59, N 2.81.

Emarginatine A.—Of this compound, 21 mg (0.0006% of the dry wt), mp = 311° [lit. (3) mp 312–313°]; ^{1}H nmr, ^{13}C nmr, uv, and ms data identical to those previously described (3).

TABLE 3. Positional Parameters and B(eq) for Hippocrateine I [**1**].

Atom	*x*	*y*	*z*	B(eq)
O-1	0.0776(4)	0.7019(3)	0.1945(3)	4.6(3)
O-2	0.0031(4)	0.5880(3)	0.2709(3)	5.0(3)
O-3	−0.0044(4)	0.4956(3)	0.1107(3)	5.1(3)
O-4	−0.1932(5)	0.5023(3)	0.1024(3)	5.5(3)
O-5	−0.0934(4)	0.6131(3)	0.0485(3)	4.8(3)
O-6	−0.3143(4)	0.6111(3)	0.0682(3)	5.7(3)
O-7	0.2049(6)	0.6740(5)	0.1265(4)	8.3(5)
O-8	−0.2299(4)	0.8135(3)	0.0865(4)	5.6(3)
O-9	−0.0484(4)	0.8139(3)	0.1406(3)	4.7(3)
O-10	−0.2188(4)	0.7314(3)	0.2241(3)	5.1(3)
O-11	0.1652(5)	0.5851(4)	0.2896(4)	7.1(4)
O-12	−0.2244(6)	0.7081(5)	0.3362(4)	7.8(4)
O-13	0.0810(5)	0.8336(4)	0.0724(4)	6.9(4)
O-14	−0.0100(7)	0.3866(4)	0.1563(4)	8.7(5)
O-15	−0.1174(5)	0.5464(5)	−0.0752(4)	8.1(4)
O-16	−0.1626(8)	0.9124(4)	0.0447(6)	10.0(6)
O-17	−0.4306(6)	0.6672(6)	0.1256(6)	9.9(6)
O-18	−0.2201(8)	0.4825(6)	−0.1296(7)	12.3(7)
O-19	−0.0046(8)	0.6399(7)	0.5825(5)	11.9(7)
O-20	0.9054(4)	0.0619(3)	0.7953(4)	7.2(4)
O-21	0.7316(6)	0.0108(5)	0.3776(6)	7.9(4)
O-22	0.2001(4)	0.4131(3)	0.2231(4)	6.3(3)
N-1	0.0775(7)	0.3641(6)	−0.1023(6)	8.8(6)
N-2	−0.0510(7)	0.6255(5)	0.4718(5)	6.8(5)
C-1	0.0159(6)	0.6524(4)	0.1599(4)	3.9(4)
C-2	0.0221(7)	0.5786(4)	0.1969(5)	4.8(4)
C-3	−0.0508(7)	0.5264(4)	0.1692(5)	4.8(4)
C-4	−0.1525(6)	0.5537(4)	0.1490(4)	4.2(4)
C-5	−0.1468(7)	0.6283(4)	0.1123(5)	4.8(4)
C-6	−0.2433(6)	0.6627(4)	0.0872(4)	4.3(4)
C-7	−0.2083(7)	0.7024(5)	0.0256(4)	4.7(4)
C-8	−0.1552(7)	0.7698(5)	0.0534(5)	5.2(4)
C-9	−0.0703(6)	0.7507(4)	0.1015(4)	4.2(4)
C-10	−0.0854(6)	0.6853(4)	0.1512(4)	4.0(4)
C-11	−0.1352(7)	0.6529(5)	−0.0095(4)	4.7(4)
C-12	−0.1890(7)	0.5976(6)	−0.0558(5)	5.7(5)
C-13	−0.0527(8)	0.6867(5)	−0.0492(5)	6.0(5)
C-14	−0.2191(7)	0.5555(5)	0.2113(5)	5.6(5)
C-15	−0.1206(6)	0.7067(4)	0.2239(5)	4.6(4)
C-16	0.0125(7)	0.4248(6)	0.1088(6)	5.8(5)
C-17	0.0520(8)	0.4003(6)	0.0418(5)	6.6(6)
C-18	−0.0333(9)	0.3916(7)	−0.0074(7)	7.4(7)
C-19	−0.002 (1)	0.4004(7)	−0.0827(7)	8.0(7)
C-20	−0.056 (1)	0.4433(9)	−0.1275(7)	8.8(8)
C-21	−0.030 (1)	0.443 (1)	−0.1990(6)	11 (1)
C-22	0.046 (1)	0.403 (1)	−0.2163(9)	12 (1)
C-23	0.103 (1)	0.368 (1)	−0.167 (1)	10 (1)
C-24	−0.140 (1)	0.4923(7)	−0.1070(6)	7.4(7)
C-25	−0.086 (1)	0.321 (1)	−0.0034(9)	12 (1)

TABLE 3. (Continued).

Atom	x	y	z	B(eq)
C-26	0.114 (1)	0.3354(8)	0.0510(7)	10.2(9)
C-27	0.1731(7)	0.7066(5)	0.1745(6)	5.7(5)
C-28	0.2292(7)	0.7563(5)	0.2181(5)	5.0(4)
C-29	0.1859(8)	0.7966(6)	0.2686(7)	7.0(6)
C-30	0.241 (1)	0.8418(7)	0.3068(7)	8.0(7)
C-31	0.342 (1)	0.8463(8)	0.2946(7)	8.2(7)
C-32	0.3841(8)	0.8086(8)	0.2427(8)	7.6(6)
C-33	0.3268(7)	0.7631(6)	0.2053(5)	6.1(5)
C-34	0.0868(8)	0.5916(5)	0.3114(5)	5.2(5)
C-35	0.0607(8)	0.6047(5)	0.3828(5)	5.6(5)
C-36	−0.0300(8)	0.6149(5)	0.4054(5)	5.6(5)
C-37	0.022 (1)	0.6288(7)	0.5206(6)	8.2(8)
C-38	0.120 (1)	0.6194(9)	0.4994(7)	8.6(8)
C-39	0.1369(9)	0.6082(7)	0.4303(6)	7.2(6)
C-40	−0.150 (1)	0.640 (1)	0.4946(7)	9.6(8)
C-41	−0.4062(8)	0.6193(6)	0.0894(7)	6.3(6)
C-42	−0.4701(9)	0.5617(8)	0.0655(8)	9.0(7)
C-43	−0.226 (1)	0.8850(6)	0.0752(7)	7.5(7)
C-44	−0.311 (1)	0.9223(7)	0.108 (1)	11 (1)
C-45	0.0285(8)	0.8525(5)	0.1188(5)	5.1(5)
C-46	0.0426(9)	0.9165(5)	0.1599(6)	6.9(6)
C-47	−0.2648(7)	0.7281(6)	0.2867(6)	5.7(5)
C-48	−0.3683(9)	0.7516(9)	0.2810(8)	9.9(8)

SINGLE CRYSTAL X-RAY ANALYSIS OF HIPPOCRATEINE I [**1**].[2]—Crystal data: $C_{48}H_{52}N_2O_{19}\cdot 3H_2O$, MW = 1014.99, orthorhombic, space group $P2_12_12_1$, $a = 13.735\ (2)$, $b = 18.716\ (2)$, $c = 19.541\ (2)$ Å, $V = 5023$ Å^3, $Z = 4$, $D_c = 1.34$ g/cm^3, Cu radiation, $\lambda = 1.54178$ Å, μ (CuKα) = 8.6 cm^{-1}, $F(\theta\theta\theta) = 2144$. Of the 3574 independent reflections measured ($2\theta < 110°$), 2557 had $I > 3\sigma$ (I). The data were corrected for Lorentz and polarization factors; no absorption correction was applied. The structure was solved using a 36° atom fragment from acanthothamine (8) as input to program PATSEE (10). Its located position input to SHELXS 86 (11) gave the position of all non-hydrogen atoms and was refined anisotropically. The position of the hydrogen atoms were idealized, C-H = 0.96. Hydrogen atoms attached to heteroatoms could not be located and were not included except for a water molecule; assigned isotropic thermal parameters 1.2 times B(eq) of parent atoms were used for hydrogens. Refinement was by full matrix least-squares to $R = 0.064$, $R_w = 0.083$ [$W^{-1} = \sigma^2(F) + 0.09\,F^2$]. The maximum and minimum residual electron densities in the final ΔF map were 0.91 and −0.22 eÅ, respectively. All computations were done on a DEC vaxstation II using the TEXSAN (11) system. Final atomic coordinates are listed in Table 3.

BIOASSAYS.—Compound **1** was evaluated for lethality to brine shrimp larvae as previously described (9). Cytotoxicity tests were performed at the Purdue Cell Culture Laboratory, Purdue Cancer Center: 9KB (human nasopharyngeal carcinoma), 9PS (murine lynphocytic leukemia), A-549 (human lung carcinoma), and HT-29 (human colon adenocarcinoma).

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[2]Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

Uv, ir, and optical rotations analyses were provided by the Laboratorio de Espectroscopía, Facultad de Química, UNAM; the assistance of the staff is acknowledged. We also thank Quim. Federíco de Río and M. en C. Josefina Espiñeira, Instituto de Química, UNAM for nmr determinations. F. Calzada acknowledges fellowship support from CONACyT.

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