Pergamon

0031-9422(95)00255-3

Phytochemistry, Vol. 40, No. 2, pp. 583–585, 1995

0031-9422/95 $9.50 + 0.00

HIPPOCRATEINE III, A SESQUITERPENE ALKALOID FROM *HIPPOCRATEA EXCELSA*

FERNANDO CALZADA and RACHEL MATA*†

Unidad de Investigación Médica en Farmacología de Productos Naturales, Hospital de Pediatría, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, 06725, México; †Facultad de Química, Universidad Nacional Autónoma de México, Coyoacán 04510, México D.F., México

(*Received in revised form* 21 *February* 1995)

Key Word Index—*Hippocratea excelsa*; Hippocrateaceae; root; stem barks; sesquiterpene evoninoate alkaloid; hippocrateine III; mayteine.

Abstract—A new sesquiterpene evoninoate alkaloid, hippocrateine III, was isolated together with the known compound mayteine from the root and stem barks of *Hippocratea excelsa*. The structures of both compounds were elucidated by interpretation of spectral data. The substitution pattern of the nicotinic acid moiety in hippocrateine III differs from that of emarginatine A and hippocrateines I and II.

INTRODUCTION

In a previous communication, we described the isolation and the structure determination of two novel sesquiterpene evoninoate alkaloids named hippocrateines I and II (**1**). These were isolated from the methanol extract of *Hippocratea excelsa* H.B.K. which is widely used in Mexico as a medicinal agent for the treatment of cancer and gastric ulcers [1]. The known compound, emarginatine A, was also obtained from this species [1]. In this paper, we report the isolation of two additional alkaloids from *H. excelsa*. One of these, hippocrateine III (**2**) is a new natural product and its structure was elucidated by 2D NMR techniques.

RESULTS AND DISCUSSION

Hippocrateine III (**2**), $C_{46}H_{56}N_2O_{19}$, was isolated as a gummy solid. The IR spectrum contained bands at 3400, 1740 and 1660 cm^{-1} which were indicative of hydroxyl, ester and pyridone groups, respectively. The absorption at 265 nm observed in the UV spectrum was also consistent with the presence of the pyridone moiety. The NMR properties of **2** (Table 1) clearly indicated a β-dihydroagarofuran skeleton with an evoninoate diester bridge [1–7]. The β-dihydrogarofuran moiety of **2** was almost identical to that of hippocrateine II (**1**) differing only in the C-1 substituent [1]. Comparative analysis of the NMR properties (Table 1) of both compounds clearly indicated that the benzoyl group at C-1 in **1** was replaced by an acetyl moiety in **2** (δ_C 19.46 *q*; 169.68, *s*; δ_H 1.8 *s*). On the other hand, the diester moiety of **2** contained a 3,4-substituted nicotinic acid grouping rather than a 2,3-substituted one as in the case of **1** and related alkaloids [1]. The chemical shift and the coupling pattern of the proton resonances attributable to the nicotinoyl ring of the macrocyclic diester portion in **2** [δ_H 9.0, *s*, H-2″; 8.71, *d*, J = 5.1 Hz, H-6″ and 7.38, *d*, J = 5.1 Hz, H-5″] support this structural assignment. The same type of 3,4-substituted nicotinic acid grouping is observed at the large ester ring of the related alkaloid, isowilfordine [5], whose nicotinoyl protons display the same coupling pattern and similar chemical shift to those observed for **2** (Table 1) in the present investigation. The NMR assignments (Table 1) of **2** were confirmed by DEPT, ^1H–^1H COSY and HETCOR. Mayteine was also isolated and identified by comparison of the spectral properties with those previously reported [8].

In summary, *H. excelsa* can synthesize two types of sesquiterpene alkaloids: one possessing a macrocyclic diester moiety containing a 2,3-substituted nicotinic acid grouping as in emarginatine A, mayteine and hippocrateines I and II [1]; the second class represented by hippocrateine III (**2**) possessing a 3,4-substituted nicotinic acid residue at the diester moiety.

EXPERIMENTAL

General. Mps: uncorr. ^1H and ^{13}C NMR: 300 and 75.47 MHz, respectively, on a Varian VXR-300 S spectrometer using $CDCl_3$ as the solvent and TMS as standard reference; UV: Beckman DU-7; IR: KBr, Perkin Elmer 599B spectrophotometer; CC: silica gel (70–230 mesh) Merck; TLC: precoated silica gel 60 F_{254} plates, Merck.

*Author to whom correspondence should be addressed.

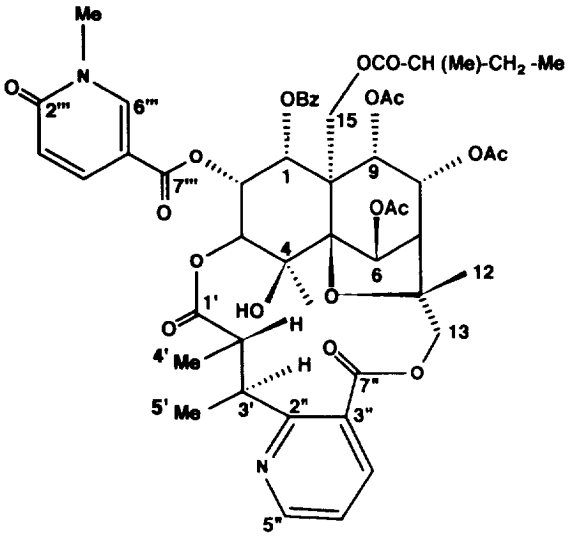
Table 1. ^1H and ^{13}C NMR spectral data of hippocrateines II (**1**) [1] and III (**2**)*

Position	**1**		**2**	
	δ_H	δ_C	δ_H	δ_C
1	6.05 *d* (4)	73.1 *d*	5.66 *d* (4)	73.2 *d*
2	5.55 *m*	69.7 *d*	5.47–5.6 *m*	69.2 *d*
3	4.87 *d* (2.3)	75.4 *d*	4.79 *d* (2.3)	75.4 *d*
4	—	70.3 *s*	—	70.1 *s*
5	—	93.8	—	93.9 *s*
6	6.94 *s*	74.0 *d*	6.93 *s*	74.0 *d*
7	2.43 *d* (4)	50.4 *d*	2.45 *d* (4)	50.6 *d*
8	5.5–5.60 *m*	68.8 *d*	5.47–5.60 *m*	68.4 *m*
9	5.47 *d* (5.70)	71.0 *d*	5.42 *d* (5.2)	70.6 *d*
10	—	52.4 *s*	—	51.8 *s*
11	—	84.4 *s*	—	84.4 *s*
12	1.75 *s*	18.5 *q*	1.62 *s*	18.5 *s*
13	4.72, 6.00 (ABq, 13)	70.0 *t*	3.76, 5.86 (ABq, 13)	70.5 *t*
14	1.58 *s*	23.0 *q*	1.55 *s*	22.9 *q*
15	4.38, 5.68 (ABq, 13)	60.5 *t*	4.24, 5.52 (ABq, 13)	60.6 *t*
2′	2.62 *q* (7)	44.9 *d*	2.75 *q* (7)	45.7 *d*
3′	4.68 *q* (7)	36.4 *d*	4.71 *q* (7)	34.0 *d*
4′	1.41 *d* (7)	9.8 *q*	1.20 *d* (7)	10.0 *q*
5′	1.23 *d* (7)	11.8 *q*	1.38 *d* (7)	11.1 *q*
2″	—	165.3 *s*	9.00 *s*	152.8 *d*
3″	—	124.9 *s*	—	124.6 *s*
4″	8.09 *dd* (1.8, 7.7)	137.8 *d*	—	156.5 *s*
5″	7.33 *m*	121.2 *d*	7.38 *d* (5.1)	121.6 *d*
6″	8.72 *dd* (1.8, 4.8)	151.7 *d*	8.71 *d* (5.1)	121.7 *d*
3‴	6.58 *d* (9.5)	119.3 *d*	6.59 *d* (9.5)	119.8 *d*
4‴	7.85 *dd* (9.5, 2.5)	139.0 *d*	7.89 *dd* (9.5, 2.5)	139.0 *d*
5‴	—	108.2 *s*	—	108.1 *s*
6‴	8.50 *d* (2.5)	144.0 *d*	8.46 *d* (2.5)	144.1 *d* (2.5)
1b	—	28.8 *s*	—	—
2b, 6b	7.74 *m*	128.5 *d*	—	—
3b, 5b	7.33 *m*	129.5 *d*	—	—
4b	7.51 *m*	133.6 *d*	—	—
N–Me	3.73 *s*	38.1 *q*	3.69 *s*	38.1 *q*
OAc-1	—	—	1.88 *s*	19.5 *q*
OAc-6	2.22 *s*	19.9 *q*	2.20 *s*	20.5 *q*
OAc-8	2.13 *s*	21.6 *d*	2.20 *s*	21.6 *q*
OAc-9	1.38 *s*	19.9 *q*	1.95 *s*	20.4 *q*
OH-4	4.62 *s*	—	4.94 *s*	—
CO-1′, CO-7″	—	173.9 *s*, 168.6 *s*	—	173.5 *s*, 169.0 *s*
CO-2‴, CO-7‴	—	163.1 *s*, 163.1 *s*	—	163.1 *s*, 162.6 *s*
CO-1, CO-6	—	169.8 *s*, 168.6 *s*	—	169.7 *s*, 169.9 *s*
CO-8, CO-9	—	164.5 *s*, 170.1 *s*	—	167.0 *s*, 170.5 *s*
CO-15	—	178.1 *s*	—	178.3 *s*
C-2 mb	2.95 *st* (7)	34.0 *d*	3.02 *st* (7)	33.5 *d*
C-3 mb	1.00–1.37 *m*	29.7 *t*	1.00–1.40 *m*	29.7 *t*
C-4 mb	1.00–1.37 *m*	19.1 *q*	1.00–1.40 *m*	19.1 *q*
C-55 mb	1.00–1.37 *m*	19.7 *q*	1.00–1.40 *m*	19.8 *q*

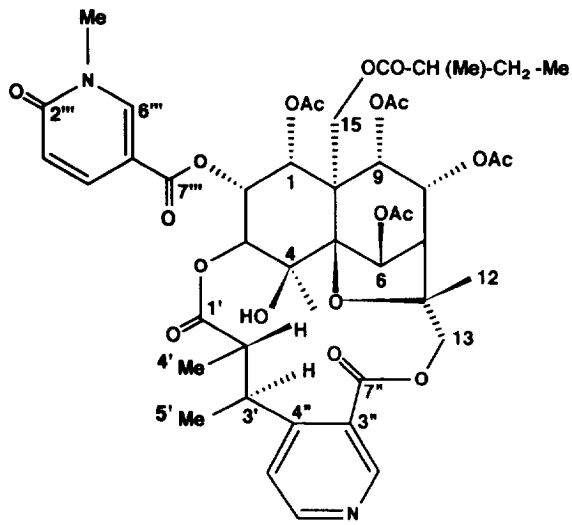
*Chemical shifts are in ppm with TMS as the internal standard. Coupling constants in Hz are given in parentheses; mb = 2-methylbutiroyl; b = benzoyl residue.

Plant material. Stem and root barks of *Hippocratea excelsa* was obtained from El Mercado de Sonora, México D.F. in October 1988. Reference samples are deposited at the National Herbarium, MEXU. Voucher: RM-188.

Isolation. Extraction and primary fraction by CC on silica gel were previously described [1]. From fractions eluted with $CHCl_3$–MeOH (97:3) a gummy residue was obtained (100 mg). This material was chromatographed by prep. TLC, using $CHCl_3$ as the developing solvent, to yield **2** and mayteine. Hippocrateine III (**2**) 30 mg (0.0010% dry wt), gum, UV λ_{max} nm: 265. IR ν_{max} cm^{-1}: 3400, 3100–3000, 1740, 1660, 1580, 1360, 1145, 1050. Anal. results: Calcd for $C_{46}H_{56}N_2O_{19}$, C, 58.66; H, 5.95;



1



2

N, 2.97%. Found: C, 58.61; H, 5.95; N, 2.99%. Mayteine, 15 mg (0.0005%), mp 171–173 (Lit. mp 172–175° [8]). IR, UV and NMR data were identical to those previously described.

Acknowledgements—This study was partially sponsored by a grant of Dirección General de Asuntos del Personal Académico (Proyecto DGAPA IN202493). The technical assistance of M. en C. Atilano Gutiérrez (NMR Laboratory, Instituto de Química, UNAM), QFB Graciela Chávez and Q. Marisela Gutiérrez (IR and UV Spectroscopy Laboratory, Facultad de Química, UNAM) is also acknowledged.

REFERENCES

1. Mata, R., Calzada, F., Díaz, E. and Toscano, R. A. (1990) *J. Nat. Prod.* **53**, 1212.
2. Kuo, Y. H., Chen, C. H., Kuo, Y. L. M., King, M. L., Wu, T. S., Chen, I. S., McPhail, D. R., A. T. and Lee, K. H. (1989) *Heterocycles* **29**, 1465.
3. Kuo, Y. H., Chen, C. H., Kuo, Y. L. M., King, M. L., Wu, T. S., Haruna, M. and Lee, K. H. (1990) *J. Nat. Prod.* **53**, 422.
4. Kuo, Y. H., Chen, C. H., King, M. L., Wu, T. S. and Lee, K. H. (1994) *Phytochemistry* **35**, 803.
5. Ya. L., Strunz, G. M. and Calhoun, L. A. (1991) *Phytochemistry* **30**, 719.
6. Baxter, R. L., Crombie, L., Simmonds, D. J., Whiting, D. A., Braenden, O. J. and Szendrie, K. (1979) *J. Chem. Soc., Perkin Trans I* 2965.
7. Baxter, R. L., Crombie, W. M. L., Crombie, L., Simmonds, D. J., Whiting, D. A. and Szendrei, K. (1979) *J. Chem. Soc., Perkin Trans I* 2982.
8. DeSousa, J. R., Pinheiro, J. A., Ribeiro, E. F., DeSousa, E. and Maia, J. G. S. (1986) *Phytochemistry* **25**, 1776.