Phytochemistry, 1980, Vol. 19, pp. 313–315. © Pergamon Press Ltd. Printed in England. 0031-9422/80/0201-0313 $02.00/0

CANTHINONES FROM *SIMABA CUSPIDATA**

A. M. GIESBRECHT*, H. E. GOTTLIEB†, O. R. GOTTLIEB‡, M. O. F. GOULART §, R. A. DE LIMA§ and A. E. G. SANT'ANA§

* Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, Brazil; † The Weizmann Institute of Science, Rehovot, Israel; ‡ Instituto de Química, Universidade de São Paulo, São Paulo, Brazil; § Departamento de Química, Universidade Federal de Alagoas, Maceió, Brazil

(*Received* 17 May 1979)

Key Word Index—*Simaba cuspidata;* Simaroubaceae; canthinone alkaloids; 8-methoxycanthin-6-one; 3-methoxycanthin-2,6-dione.

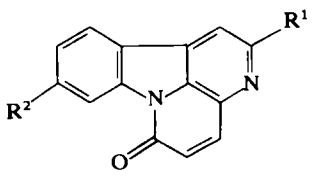
Abstract—Two new alkaloids, 8-methoxycanthin-6-one and 3-methoxycanthin-2,6-dione, were isolated from the EtOH extract of the bark of *Simaba cuspidata* Spruce ex Engl. Elucidation of the structure of the latter compound included ^{13}C NMR spectral comparison with 2-methoxypyridine-*N*-oxide and *N*-methoxy-2-pyridone.

INTRODUCTION

Simaba cuspidata Spruce ex Engl., var. *typica* Cronquist, an arborescent shrub or small tree, is common in the Rio Negro forest of Amazonas, Brazil [1]. Its bark gave an EtOH extract from which a yellow and a red alkaloid, characterized respectively as 8-methoxycanthin-6-one (**1a**) and 3-methoxycanthin-2,6-dione (**2a**), were isolated.

RESULTS

The yellow alkaloid ($C_{15}H_{10}O_2N_2$, mp 175–176°) shows in the IR spectrum a band at 1670 cm^{-1} in agreement with the presence of a lactam. The MS exhibits a M^+ (*m/e* 250) compatible with a methoxycanthinone and a fragmentation pattern similar to that of other canthinones [2–4]. The UV spectrum is also compatible with a canthinone structure [2–5]: addition of acid, but not of base, causes a bathochromic shift of the maxima. The reduction product of the yellow alkaloid with Zn/HCl has a UV reminiscent of β-carboline derivatives [6]. The ^1H NMR spectrum at 100 MHz permits a detailed analysis indicating the absence of substitution on rings C and D and the presence of a methoxy group. This must be located at C-8, since the signal at δ8.13, attributed to H-7 by virtue of its low field location, shows no *ortho*-coupling (Table 1). Structure **1a** is therefore proposed.



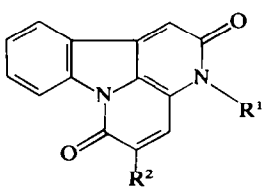
1a $R^1 = H$, $R^2 = OMe$
1b $R^1 = R^2 = H$
1c $R^1 = OMe$, $R^2 = H$

The red alkaloid (mp > 320°, strong green fluorescence in solution) shows in the IR spectrum an intense band at 1640 cm^{-1}, indicating again at least one lactam carbonyl group. There is no evidence of OH groups. The high-resolution MS and elemental analysis signify a molecular formula of $C_{15}H_{10}O_3N_2$ with one more oxygen atom than **1a**. Otherwise, the MS is similar to that of **1a**, except for the facile loss of 31 amu, probably a OMe group, from the M^+.

The UV spectrum is again in agreement with a canthinone structure. This time, however, the spectrum is not altered by the addition of either acid or base, indicating the absence of a phenolic function and the lack of basicity of *both* nitrogen atoms. Again, the UV spectrum of the Zn/HCl reduction product indicates a β-carboline.

The ^1H NMR spectrum at 270 MHz, including the irradiation of each signal in turn, unambiguously establishes a sequence of 4 protons in ring A and of 2 protons in ring D (Table 1). Both the OMe group and the additional oxygen must therefore be located at ring C. This ring must also contain the only remaining proton, represented by a singlet at δ7.27. This relatively high field position excludes one possible structure, 1-methoxycanthin-6-one-3-oxide (**5a**), since in the unsubstituted *N*-oxide, i.e. in canthin-6-one-3-oxide (**5b**), H-1 and H-2 appear at δ7.78 and 8.32, respectively [4].

Thus only two structures need to be considered: 2-methoxycanthin-6-one-3-oxide (**5c**) and 3-methoxycanthin-2,6-dione (**2a**). To enable the differentiation



2a $R^1 = OMe$, $R^2 = H$
2b $R^1 = H$, $R^2 = OMe$

* Part I in the proposed series 'The Chemistry of Brazilian Simaroubaceae'.

Table 1. NMR data of canthinones **1a** and **2a***

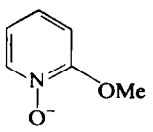
Position	**1a** ^{1}H (100 MHz)	**2a** ^{1}H (270 MHz)	**2a** ^{13}C (22.6 MHz)†
1	7.76; *d*, *J* = 5	7.27; *s*	115.1
2	8.72; *d*, *J* = 5		
4	7.96; *d*, *J* = 10	7.74; *d*, *J* = 10	132.4
5	6.90; *d*, *J* = 10	6.93; *d*, *J* = 10	128.5
7	8.13; *d*, *J* = 2	8.60; *d*, *J* = 8	118.0
8		7.68; *t*, *J* = 8	126.0‡
9	7.01; *dd*, *J* = 7; 2	7.49; *t*, *J* = 8	126.6‡
10	7.85; *d*, *J* = 7	7.95; *d*, *J* = 8	123.8
OMe	3.96; *s*	4.20; *s*	64.8

* Chemical shifts in ppm from internal TMS for $CDCl_3$ solutions; coupling constants in Hz.

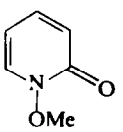
† Non-protonated carbon signals cannot be clearly identified due to low signal to noise ratio.

‡ Signals may be interchanged.

of these possibilities, the ^{13}C NMR spectrum of the natural product was obtained (Table 1). The methine carbon signals could be in part assigned by correlating residual couplings in the single-frequency off-resonance decoupled (sford) spectrum with the known ^{1}H chemical shifts and by chemical shift considerations. A striking feature in the spectrum is the low field absorption of the OMe carbon (δ64.8), as compared with other MeO-aryl functions, e.g. 2-methoxypyridine (δ53.1) [7]. Since both *N*-oxide formation and the substitution of the OMe group on nitrogen could conceivably cause deshielding of the carbon in question, 2-methoxypyridine-*N*-oxide (**3**) and its thermal rearrangement product, *N*-methoxy-2-pyridone (**4**) [8–10] were run as models (Table 2). While the



3



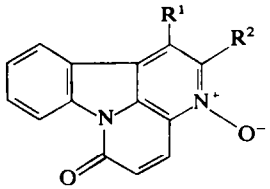
4

chemical shift of the OMe group in the former compound is 'normal' (δ57.3), in the latter its signal appears at δ64.5, almost the same as in the natural product. The red substance is, therefore, 3-methoxycanthin-2,6-dione (**2a**). This structure explains the high intensity of the carbonyl band in the IR, the lack of basicity and the loss of OMe in the MS by fragmentation of the weak N—O bond.

DISCUSSION

Simaba indica Baill. has been excluded from the genus and named *Samandera indica* (Baill.) Gaertn. [1]. Interestingly, however, it contains **2b** (indacanthinone) [11], an isomer of **2a** and the only additional known canthin-2,6-dione.

The co-occurrence of canthin-6-one (**1b**), indacanthinone (**2b**) [11] and canthin-6-one-3-oxide (**5b**)



5a R^1 = OMe, R^2 = H
5b R^1 = R^2 = H
5c R^2 = OMe, R^1 = H

[2, 4] in the bark of Simaroubaceae species suggests the ease of bio-oxidation of both positions, C-2 and N-3, to be similar. It can thus be proposed, albeit only tentatively, that in *Simaba cuspidata* **1b** was not detected due to rapid turnover into **1c** whose *N*-oxide

Table 2. NMR data of model compounds **3** and **4***

	3 ^{1}H†	**3** ^{13}C‡	**4** ^{1}H†	**4** ^{13}C‡, §
2		158.3		158.6
3	7.13; *dd*, *J* = 8; 1.5	108.5	6.66; *ddd*; *J* = 9; 1.5; 0.5	122.9
4	7.39; *ddd*; *J* = 8; 7; 1.5	128.2	7.34; *ddd*; *J* = 9; 6.5; 2	138.9
5	7.03; *ddd*; *J* = 7; 6.5; 1.5	117.8	6.18; *ddd*; *J* = 7; 6.5; 1.5	105.4
6	8.21; *dd*; *J* = 6.5; 1.5	139.1	7.59; *ddd*; *J* = 7; 2; 0.5	135.5
OMe	4.13; *s*	57.3	4.08; *s*	64.7

* Chemical shifts in ppm from internal TMS for $CDCl_3$ solutions; coupling constants in Hz.

† 270 MHz.

‡ 22.6 MHz.

§ Assigned by correlating ^{13}C to ^{1}H signals using the residual couplings in the sford spectrum.

would then rearrange to **2a**. Such a rearrangement is a well known reaction [8–10] and one cannot, from present evidence, be certain that **2a** exists as such in the plant or if it is formed during the extraction or isolation procedures, thus adding one more question to several others [12] concerning the origin and role of *N*-oxides in plants.

EXPERIMENTAL

Isolation of constituents. A specimen of *S. cuspidata* from the vicinity of Manaus, was identified by Dr. W. A. Rodrigues, INPA, Manaus, Amazonas. Air-dried, powdered trunk bark (1 kg) was extracted with EtOH. The solvent was evapd over Si gel and the residue extracted successively with petrol, $CHCl_3$ and MeOH. The $CHCl_3$-residue (10 g) was chromatographed on acid-washed Al_2O_3 (300 g, activity I). Elution with C_6H_6–$CHCl_3$ 6:4 and 1:1 afforded fractions which after repeated crystallizations from the indicated solvents gave respectively **1a** (40 mg, EtOH) and **2a** (80 mg, HOAc).

8-*Methoxycanthin*-6-*one* (**1a**), yellow, mp 175–176° (EtOH) (Found: C, 72.26; H, 4.31; N, 10.60. $C_{15}H_{10}O_2N_2$ requires: C, 71.99; H, 4.03; N, 11.19%). ν_{max}^{KBr} cm^{-1}: 1670, 1640, 1606, 1500. λ_{max}^{MeOH} nm: 225 infl., 264 infl., 272, 307, 355 (log ε 5.25, 5.34, 5.53, 4.94, 5.15). $\lambda_{max}^{MeOH+HCl}$ nm: 278, 313 sh., 320, 380 (log ε 5.40, 5.02, 5.08, 5.27). ^1H NMR: Table 1. MS (*m/e*): 251 (49%) $M^+ + 1$, 250 (100) M^+, 249 (50), 235 (22), 222 (37), 221 (52), 220 (32), 208 (10), 207 (65), 193 (15), 192 (27), 179 (54), 153 (20), 152 (12), 127 (14), 126 (22).

3-*Methoxycanthin*-2,6-dione (**2a**), red, mp > 330° (HOAc), S absent (Found: M, 266.0612; $C_{15}H_{10}O_3N_2$ requires: 266.0689). ν_{max}^{KBr} cm^{-1}: 1640, 1603, 1500. λ_{max}^{MeOH} nm: 226, 247, 253 sh., 290, 302, 325, 400 sh., 422, 446 (log ε 4.16, 4.13, 3.04, 3.63, 3.65, 3.43, 3.59, 3.85, 3.90). ^1H and ^{13}C NMR: Table 1. MS (*m/e*): 267 (25), $M^+ + 1$, 266 (100) M^+, 236 (77), 235 (81), 208 (51), 207 (77), 180 (10), 179 (43), 153 (41), 152 (39), 128 (18), 127 (10), 101 (30).

Acknowledgements—The authors are indebted to Conselho Nacional de Desenvolvimento Científico e Tecnológico and to Fundação de Amparo à Pesquisa do Estado de São Paulo for financial support and to Dr. P. M. Baker, NPPN, Universidade Federal do Rio de Janeiro, for the HRMS.

REFERENCES

1. Cronquist, A. (1944) *Lloydia* **7,** 81.
2. Cordell, G. A., Ogura, M. and Farnsworth, N. R. (1978) *Lloydia* **41,** 166.
3. Lassak, E. V., Polonsky, J. and Jacquemin, H. (1977) *Phytochemistry* **16,** 1126.
4. Ohmoto, T., Tanaka, R. and Tamotsu, N. (1976) *Chem. Pharm. Bull.* **24,** 1532.
5. Scheuer, P. J. and Pattabhiraman, T. R. (1965) *Lloydia* **28,** 95.
6. Kump, C., Seibl, J. and Schmid, H. (1963) *Helv. Chim. Acta* **46,** 499.
7. Retcofsky, H. L. and Friedel, R. A. (1968) *J. Phys. Chem.* **72,** 2619.
8. Gardner, J. N. and Katritzky, A. R. (1957) *J. Chem. Soc.* 4375.
9. Dinan, F. J. and Tieckelmann, H. (1964) *J. Org. Chem.* **29,** 1650.
10. Schöllkopf, U. and Hoppe, I. (1972) *Annalen* **765,** 153.
11. Seshadri, T. R., Iyer, V. S. and Rangaswami, S. (1972) *Curr. Sci.* **41,** 140.
12. Phillipson, J. D. and Handa, S. S. (1978) *Lloydia* **41,** 385.