Two New Indole Alkaloids from *Tabernaemontana hystrix* STEUD. (Apocynaceae)

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Two new monoterpene indole alkaloids named ibogamine-7,8-dione (**1**) and 12-methoxyvoachalotine (**2**), and eight known ones, coronaridine (**3**), coronaridine hydroxyindolenine (**4**), 5-oxocoronaridine (**5**), 3-oxocoronaridine hydroxyindolenine (**6**), 3-oxocoronaridine (**7**), vobasine (**8**), ibogamine (**9**), and olivacine (**10**), were isolated from a CH_2Cl_2 extract of the root bark from *Tabernaemontana hystrix*. The structures of the compounds were elucidated on the basis of spectroscopic data analyses, mainly ^{1}H- and ^{13}C-NMR, including 2D experiments (^{1}H,^{1}H-COSY, HMBC, and HMQC).

Introduction. – In our continuing research on the isolation and identification of alkaloids of the Apocynaceae family from the Atlantic Rainforest as a part of the Natural Product Chemistry Group of the Universidade Estadual do Norte Fluminense Darcy Ribeiro [1–6], a CH_2Cl_2 extract of the root bark from *Tabernaemontana hystrix* STEUD. (Apocynaceae) was obtained. *T. hystrix*, commonly known as 'espeta' in the Atlantic Rainforest in the north of the Rio de Janeiro State, grows as bushes of 2–4 m height and is generally considered poisonous. *Tabernaemontana* is a large genus that is both chemically complex and interesting in distribution [7].

The genus *Tabernaemontana* includes about 110 species widespread in the pantropical regions, and their species are rich in alkaloids [7–10]. This genus appears as a very rich source of an impressive number of indole alkaloids, revealing a considerable variety of carbon skeletons and novel biological activities [11].

We have previously reported the structures of several indole and *bis*-indole alkaloids possessing novel carbon skeletons isolated from the Brazilian species of the *Tabernaemontana* [3–6]. This article reports the structural characterization of additional two new indole alkaloids, named as ibogamine-7,8-dione (**1**) and 12-methoxyvoachalotine (**2**), from the root bark CH_2Cl_2 extract of this species together with eight known ones, coronaridine (**3**), coronaridine hydroxyindolenine (**4**), 5-oxocoronaridine (**5**), 3-oxocoronaridine hydroxyindolenine (**6**), 3-oxocoronaridine (**7**), vobasine (**8**), ibogamine (**9**), and olivacine (**10**). The structures were characterized by spectral data, involving mainly ^{1}H- and ^{13}C-NMR spectra, including comparison with literature values disposable mainly for the known compounds.

Results and Discussion. – Elaboration of the root bark CH_2Cl_2 extract of *T. hystrix* by classical chromatographic methods resulted in the isolation of ten monoterpene

indole alkaloids (**1**–**10**), whose structures are shown in the *Figure*. The known indole alkaloids, coronaridine (**3**) [12][13], coronaridine hydroxyindolenine (**4**) [14][15], 5-oxocoronaridine (**5**) [13][16], 3-oxocoronaridine hydroxyindolenine (**6**) [17], 3-oxocoronaridine (**7**) [13][18], vobasine (**8**) [6][14][19–21], ibogamine (**9**) [13][14][19][22], and olivacine (**10**) [13][14] were identified on the basis of ^{1}H- and ^{13}C-NMR spectral data, especially 2D-NMR and mass spectral data and comparison with values described in the cited literature.

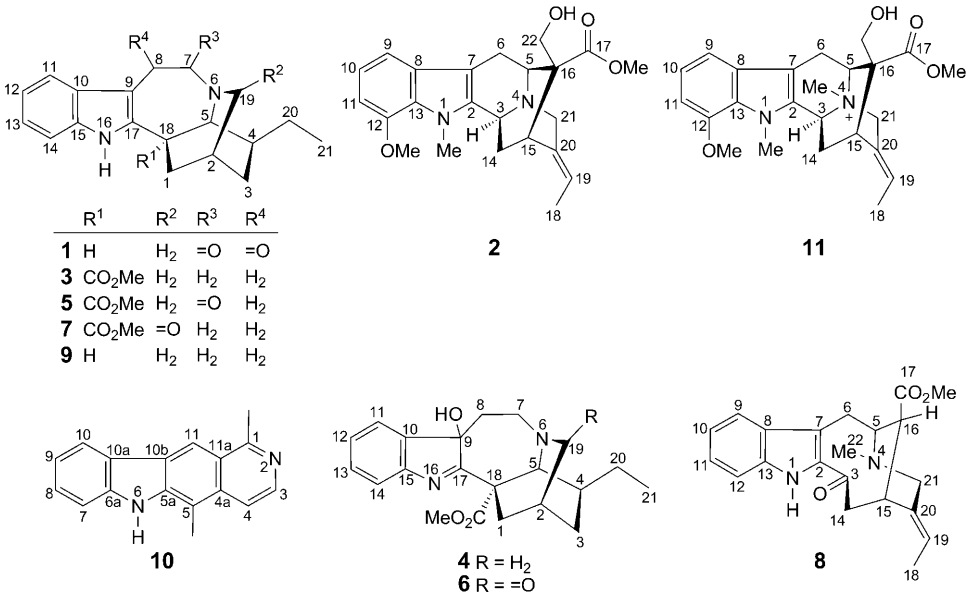


Figure. *Alkaloids isolated from* Tabernaemontana hystrix

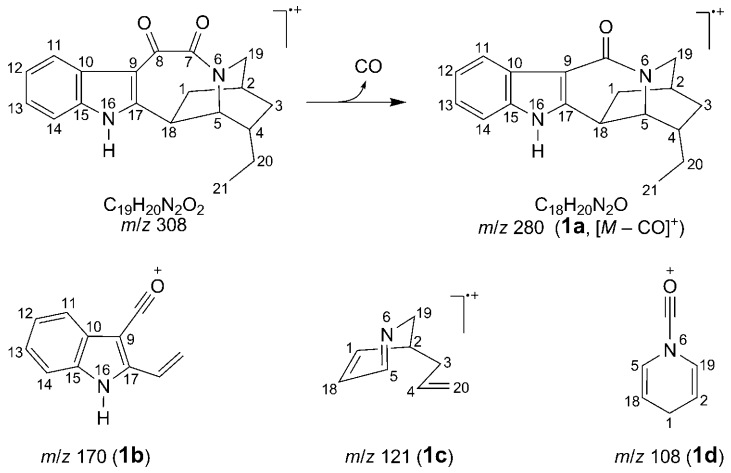
Alkaloid **1** was isolated as a yellow oil, with $[\alpha]_D^{23} = +30$ ($c = 0.02$, $CHCl_3$). The IR spectrum showed bands at $\tilde{\nu}_{max}$ 3217 (N–H stretching), 3100–2890 (C–H stretching), 1636 and 1612 (stretching of the two CO groups), in addition to other bands at $\tilde{\nu}_{max}$ 1600 and 1490 (C=C stretching of the benzene ring), and 750 cm^{-1} (C–H bending of benzene ring) [23].

Comparative analysis of the {^{1}H}- and APT-^{13}C-NMR spectra (*Table 1*) revealed signals corresponding to 19 C-atoms, allowing to recognize the presence of signals corresponding to six nonhydrogenated C-atoms (all sp^2 (four attributed to the indole system and the two CO groups at δ(C) 184.73 and 169.82)), eight CH groups (four sp^3 (including one linked to an N-atom at δ(C) 55.36) and four sp^2 (all aromatic)), four sp^3 CH_2 groups (including one linked to an N-atom at δ(C) 49.65) and one Me group (δ(C) 11.93).

The EI-MS spectrum of **1** showed a molecular-ion peak (M^+) at m/z 308, which, together with the ^{13}C-NMR spectrum enabled us to propose the molecular formula $C_{19}H_{20}N_2O_2$, revealing ten degrees of unsaturation (six corresponding to the indole moiety, two to CO groups, and two additional rings), consistent with an ibogamine

skeleton [13][14][19][21][22]. The main peaks observed in the mass spectrum were attributed to fragments summarized in *Scheme 1*.

Scheme 1. *Fragments Proposed to Justify the Main Peaks Observed in the EI-MS of* **1**



The ^{1}H,^{1}H-COSY spectrum of **1** was used to establish homonuclear H-atom interactions (geminal and vicinal), and HMQC and HMBC experiments to recognize heteronuclear correlations through interactions between C- and H-atoms *via* direct ($^1J(H \rightarrow C)$) and long-range couplings, involving two ($^2J(H \rightarrow C)$) and three ($^3J(H \rightarrow C)$) bonds (*Table 1*). These data suggested similarity of **1** and ibogamine (**9**) (*vide infra*). The principal difference between these two alkaloids lies in the presence of two CO groups in **1**, replacing two CH_2 groups in **9**. The presence of the indole nucleus was clearly indicated by chemical shifts of the ^{1}H- and ^{13}C-NMR signals (*Table 1*).

Typically, the ^{13}C-NMR of **1** revealed two signals corresponding to CO groups at δ(C) 169.82 C(7) and 184.73 C(8). The location of these groups was determined by analysis of the HMBC spectrum, which revealed cross-peaks corresponding to heteronuclear spin-spin couplings *via* three ($^3J(H \rightarrow C)$) bonds of the CO group at C(7) (δ(C) 169.82, O=C–N, lactam function) with both H-atoms of CH_2(19) (δ(H) 3.89 and 3.29–3.25) and with H–C(5) (δ(H) 4.04) linked to N(6). The complete analysis of the HMBC spectrum confirmed the presence of a skeleton as that of the indole alkaloid ibogamine and allowed complete ^{1}H- and ^{13}C-NMR chemical shift assignments (*Table 1*).

The peaks at *m/z* 280 (**1a**, $[M - CO]^+$), 170, and 108 (attributed to fragments **1b** and **1d**, resp.; *Scheme 1*) revealed by mass spectrum were also used to confirm the presence of an ibogamine alkaloid skeleton sustaining CO groups at positions C(7) and C(8).

Thus, the new ibogane indole alkaloid isolated from *T. hystrix* was characterized as ibogamine-7,8-dione (**1**).

The alkaloid **2** was obtained as an amorphous powder, with a m.p. 255–260° and $[\alpha]_D^{23} = -3.5$ ($c = 0.02$, $CHCl_3$). The IR spectrum showed bands at ν_{max} 3300 (O–H stretching), 2995 (N–Me stretching), 1738 (stretching of the ester CO group), and 1618, 1572, and 731 cm^{-1} (benzene ring) [23].

Table 1. *^{13}C- and ^{1}H-NMR Data*[a]) *of Alkaloid* **1** *and Comparison with Data of Alkaloid* **9**. Measured in $CDCl_3$; δ in ppm, J in Hz.

	1				**9**
	δ(C)	δ(H)	HMBC (H → C), ^{2}J	HMBC (H → C), ^{3}J	δ(C)
CH_2(1)	31.07	2.39 (br. *t*, *J* = 11.0), 1.71 (*dd*, *J* = 11.0, 6.7)	C(18)	C(17), C(19)	34.19
H–C(2)	28.64	2.19 (br. *s*)			26.52
CH_2(3)	29.76	1.99–1.96 (*m*), 1.50–1.45 (*m*)	C(4)	C(1), C(5)	32.13
H–C(4)	38.79	1.98–1.93 (*m*)			41.97
H–C(5)	55.36	4.04 (*d*, *J* = 2.2)	C(4)	C(3), C(7), C(17), C(19)	57.55
C(7) or CH_2(7)	169.82	–			49.93
C(8) or CH_2(8)	184.73	–			20.65
C(9)	110.66	–			109.22
C(10)	126.46	–			129.73
H–C(11)	121.04	8.19–8.15 (*m*)		C(13), C(15)	117.89
H–C(12)	122.79	7.25–7.20 (*m*)		C(10), C(14)	119.08
H–C(13)	123.84	7.25–7.20 (*m*)		C(11), C(15)	120.92
H–C(14)	111.99	7.52–7.45 (*m*)	C(15)	C(10), C(12)	110.06
C(15)	135.87	–			134.65
H–N(16)	–	10.85 (*s*)	C(15), C(17)	C(9), C(10)	–
C(17)	155.20	–			141.83
H–C(18)	37.68	3.37–3.30 (*m*)	C(17)	C(4), C(9)	41.49
CH_2(19)	49.65	3.89 (br. *d*, *J* = 9.9), 3.29–3.25 (*m*)		C(3), C(5), C(7)	54.15
CH_2(20)	28.31	1.63–1.57 (*m*), 1.53–1.47 (*m*)	C(4), C(21)	C(3), C(5)	27.83
Me(21)	11.93	0.95 (*t*, *J* = 7.3)	C(20)	C(4)	11.90

[a]) Assignments determined by a combination of 1D- and 2D- (^{1}H,^{1}H-COSY, HMQC, and HMBC) NMR experiments.

Comparative analysis of the {^{1}H}- and APT-^{13}C-NMR spectra (*Table 2*) revealed signals corresponding to 23 C-atoms, allowing to recognize the presence of signals corresponding to eight nonhydrogenated C-atoms (seven sp^2 (five attributed to indole system (C(2), C(7), C(8), C(12), and C(13), including one linked to an O-atom with a signal at δ(C) 149.29, attributed to C(12)), one ester CO group at δ(C) 174.21 and one C=C bond at δ(C) 128.22) and one sp^3 (C(16), α to the COOMe group)), seven CH groups (three sp^3 (including two linked to an N-atom at δ(C) 59.42 and 65.87) and four sp^2 (three aromatic and one allylic)), four sp^3-CH_2 groups (including one linked to an O-atom at δ(C) 63.91, and one carbinolic at δ(C) 65.80), and four Me groups (including two MeO groups at δ(C) 56.03 and 53.24; one MeN group at δ(C) 33.14 and one allylic Me group at δ(C) 12.79).

The EI-MS spectrum of **2** showed the molecular-ion peak M^+ at m/z 396, which, together with the ^{13}C-NMR spectrum, enabled us to confirm the molecular formula $C_{23}H_{28}N_2O_4$, which is consistent with the structure of alkaloids containing the nucleus of

Table 2. *^{13}C- and ^{1}H-NMR Data of Alkaloid* **2** ($CDCl_3$)[a]), *and Comparison with Data of Alkaloid* **11** ((D$_4$)methanol). δ in ppm, J in Hz.

	2				**11**
	δ(C)	δ(H)	HMBC (H → C), ^2J	HMBC (H → C), ^3J	δ(C)
C(2)	133.25	–			126.4
H–C(3)	59.42	5.05 (*d*, *J* = 10.0)	C(2)	C(5)	56.6
H–C(5)	65.87	4.99 (*d*, *J* = 6.2)		C(3), C(7), C(17)	64.2
CH_2(6)	20.13	3.79 (*d*, *J* = 18.3), 3.29 (*dd*, *J* = 18.3, 6.7)	C(7)	C(2), C(8), C(16)	19.2
C(7)	103.25	–			100.9
C(8)	129.02	–			127.1
H–C(9)	112.61	7.10 (*d*, *J* = 7.8)		C(7), C(13)	111.3
H–C(10)	121.85	7.01 (*t*, *J* = 7.8)		C(8), C(12)	119.3
H–C(11)	105.26	6.75 (*d*, *J* = 7.8)	C(12)	C(9), C(13)	103.7
C(12)	149.29	–			147.9
C(13)	128.59	–			126.4
CH_2(14)	29.34	2.50 (*d*, *J* = 13.7)		C(16)	28.0
H–C(15)	31.09	3.36 (br. *s*)			29.5
C(16)	56.56	–			55.7
C(17)	174.21	–			172.7
Me(18)	12.79	1.68 (*d*, *J* = 7.0)	C(19)	C(20)	12.3
H–C(19)	120.96	5.49 (*q*, *J* = 7.0)		C(15), C(21)	120.4
C(20)	128.22	–			132.4
CH_2(21)	65.80	4.41–4.40 (*m*), 3.61–3.59 (*m*)	C(20)	C(3)	64.2
CH_2(22)	63.91	3.71 (*d*, *J* = 10.8); 3.59 (*d*, *J* = 10.8)		C(5), C(17)	62.2
MeN(1)	33.14	3.95 (*s*)		C(2), C(13)	33.1
*Me*O–C(12)	56.03	3.93 (*s*)		C(12)	–
*Me*O–C(17)	53.24	3.75 (*s*)		C(17)	55.4

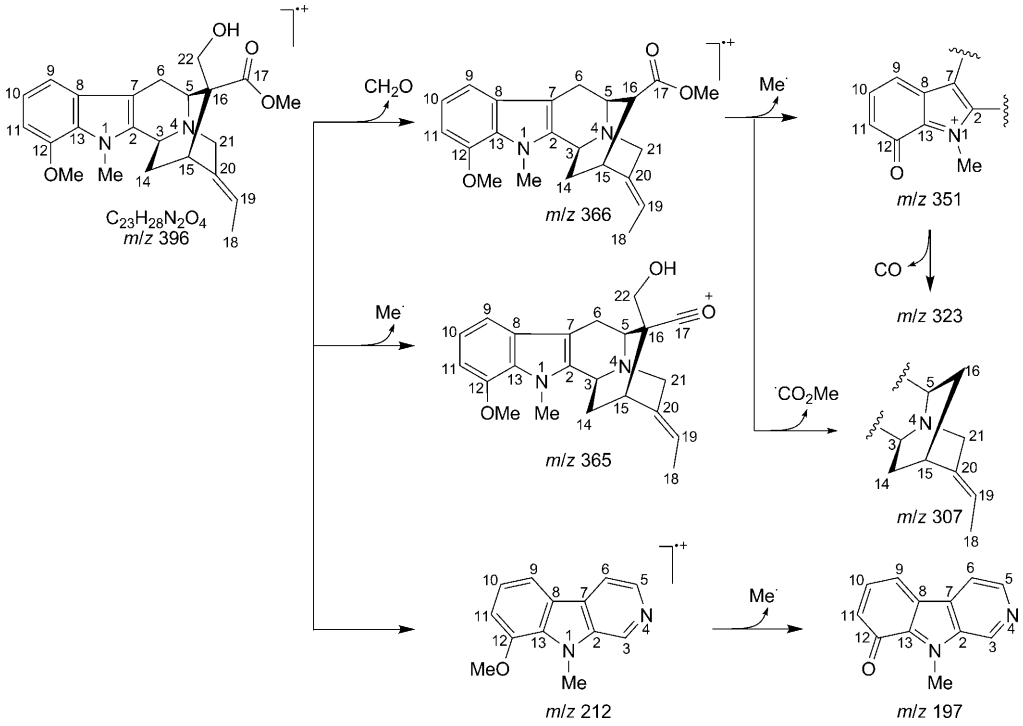
[a]) Assignments determined by a combination of 1D- and 2D- (^{1}H,^{1}H-COSY, HMQC, and HMBC) NMR experiments.

sarpagan [5][13][14][19][21][22] as basic structure (eleven degrees of unsaturation, thereof six corresponding to the indole unit, one CO group, one C=C bond, and three additional rings). The principal peaks revealed by the mass spectrum are consistent with the fragments summarized in *Scheme 2*.

The ^{1}H,^{1}H-COSY, HMQC, and HMBC experiments established geminal and vicinal H-atom interactions as well as direct (^1J(H → C)) and two- and three-bond correlations between H- and C-atoms in the structure postulated (*Table 2*). These data revealed that the structure of **2** is closely related to N_b-methyl-12-methoxyvoachalotine (**11**), isolated from *Peschiera campestris* and *P. fuchsiaefolia* [24][25], differing by the absence of the Me group linked to the aliphatic N_b. The presence of the indole nucleus was clearly indicated by the ^{1}H- and ^{13}C-NMR aromatic signals (*Table 2*).

Typically, the ^{1}H-NMR revealed three *singlet* signals corresponding to Me groups at δ(H) 3.95, 3.93, and 3.75. Through analysis of the HMBC spectrum, these signals were assigned by corresponding cross-peaks, due to heteronuclear spin-spin coupling *via*

Scheme 2. *Fragments Proposed to Justify the Main Peaks Observed in the EI-MS of* **2**



three ($^3J(H \rightarrow C)$) bonds, to a COOMe function, a MeO group linked to C(12), and one Me group linked to the indole N-atom, respectively: C(17) (δ(C) 174.21) with MeO–C(17) (δ(H) 3.75), H–C(5) (δ(H) 4.99), and CH_2(22) (δ(H) 3.71 and 3.59), C(12) (δ(C) 149.29) with MeO–C(12) (δ(H) 3.93) and H–C(10) (δ(H) 7.01), and MeN (δ(H) 3.95) with C(2) (δ(C) 133.25) and C(13) (δ(C) 128.59).

The complete analysis of the HMBC spectrum, in combination with additional NMR spectral data, also allowed to confirm the presence of an identical basic skeleton as that of the indole alkaloid N_b-methyl-12-methoxyvoachalotine (**11**) [24][25] and the total ^{1}H- and ^{13}C-NMR chemical shift assignments, as summarized in *Table 2*.

The relative configuration at C(16), shown in **2**, was clearly indicated by the chemical shift of the signal at δ(H) 3.75 corresponding to the H-atoms of the MeO–C(17) (COOMe group). In its 16-epimer, this signal appears at δ(H) *ca.* 2.50 [5].

Thus, the new indole alkaloid isolated from *T. hystrix* was characterized as 12-methoxyvoachalotine (**2**).

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Experimental Part

General. Chromatographic purifications were carried out over silica gel *60* (SiO_2; 70–230 mesh). TLC: silica gel *60* F_{254}. M.p.: *Microquímica MQRPF*; uncorrected. Optical rotations: *Perkin-Elmer 343* digital polarimeter. FT-IR Spectra: *FT-IR-8300 Shimadzu* spectrometer, as KBr disks. ^{1}H- and ^{13}C-NMR spectra: *Bruker DRX-500* spectrometer, equipped with inverse probes and field gradient, operating at 500 (^{1}H) and 125 (^{13}C) MHz; $CDCl_3$ was used as solvent and TMS as internal reference; chemical shifts are given in the δ scale [ppm], and coupling constants J in Hz; one dimensional (1D) ^{1}H- and ^{13}C-NMR spectra were acquired under standard conditions by using a direct detection 5 mm ^{1}H/^{13}C dual probe; standard pulse sequences were used for 2D spectra by using a multinuclear inverse detection 5-mm probe with field gradient. EI-MS (low resolution): *Shimadzu QP5050A* mass spectrometer.

Plant Material. The root bark of *Tabernaemontana hystrix* STEUD. was collected in March 2002 at Varre e Sai City, Rio de Janeiro State, Brazil, and identified by Dr. *A. J. M. Leeuwenberg* of the Agricultural University of Wageningen, The Netherlands. A voucher specimen (WAG) was deposited with the Agricultural University of Wageningen herbarium, Netherlands.

Extraction and Isolation. Dried and powdered root bark (920 g) from *T. hystrix* was extracted with CH_2Cl_2 at r.t., furnishing, after solvent evaporation, 18.0 g of crude CH_2Cl_2 extract. The CH_2Cl_2 extract was chromatographed over a SiO_2 column with a gradient of MeOH/CH_2Cl_2, to afford ten fractions. *Fr. 4* (860 mg) was rechromatographed with a gradient of MeOH/CH_2Cl_2 furnishing 12 fractions. *Fr. 4.5* (504.7 mg) was rechromatographed over a SiO_2 column with a gradient of AcOEt/hexane yielding alkaloid **3** (210.0 mg). *Fr. 5* (2.25 g) was chromatographed over a SiO_2 column with a gradient of MeOH/CH_2Cl_2 supplying ten fractions. *Fr. 5.5* (80.8 mg) was submitted on a prep. TLC with AcOEt/hexane (7:3 (*v*/*v*)), yielding **4** (37.9 mg). *Frs. 5.8* (15.9 mg) and *5.9* (32.4 mg) were submitted on a prep. TLC with CH_2Cl_2/MeOH (98:2 (*v*/*v*)) yielding **5** (15.9 mg) and a mixture (11.7 mg) of **6** and **7**, resp. *Fr. 7* (0.71 g) was chromatographed over a SiO_2 column with a gradient of MeOH/CH_2Cl_2 yielding alkaloid **8** (35.9 mg). *Fr. 8* (5.9 g) was chromatographed over a SiO_2 column with a gradient of MeOH/CH_2Cl_2 supplying six fractions. *Fr. 8.2* (1.63 g) was chromatographed over a SiO_2 column with a gradient of MeOH/CH_2Cl_2 yielding alkaloid **1** (9.8 mg). *Fr. 8.3* (1.91 g) was chromatographed over a neutral alumina column with a gradient of MeOH/CH_2Cl_2 yielding **9** (204.4 mg) and **10** (9.7 mg). *Fr. 10* (1.54 g) was chromatographed over a SiO_2 column with a gradient of MeOH/CH_2Cl_2, supplying four fractions. *Fr. 10.4* (661.7 mg) was crystallized from CH_2Cl_2 to yield alkaloid **2** (150 mg).

Ibogamine-7,8-dione (**1**). Yellow oil. $[\alpha]_D^{23} = +30$ ($c = 0.02$, $CHCl_3$). IR (KBr): 3217 (N–H), 3100–2890 (C–H), 1636, 1612 (C=O), 1600, 1490 (C=C), 1219, 1177, 750 (benzene ring). ^{1}H- (500 MHz, $CDCl_3$) and ^{13}C-NMR (125 MHz, $CDCl_3$): *Table 1*. EI-MS: *Scheme 1*.

12-Methoxyvoachalotine (= *Methyl (15α,19*E*)-16-(Hydroxymethyl)-12-methoxy-1-methylsarpagan-17-oate*; **2**). Amorphous powder. M.p. 255–260°. $[\alpha]_D^{23} = -3.5$ ($c = 0.02$, $CHCl_3$). IR (KBr): 3300 (O–H), 2995 (N–Me), 1738 (C=O), 1618, 1572, 731 (benzene ring). ^{1}H- (500 MHz, $CDCl_3$) and ^{13}C-NMR (125 MHz, $CDCl_3$): *Table 2*. EI-MS: *Scheme 2*.

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