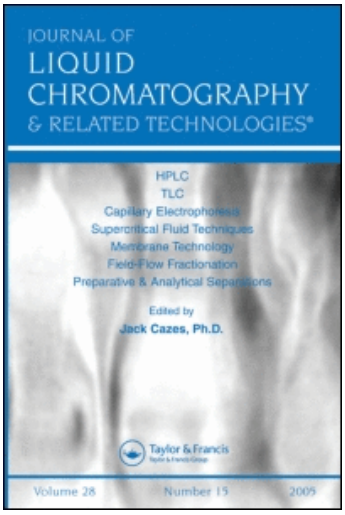

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Ibogaine and Noribogaine: Structural Analysis and Stability Studies. Use of LC-MS to Determine Alkaloid Contents of the Root Bark of *Tabernanthe Iboga*

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Abstract: The aim of this study was: i) to carry out a structural analysis of ibogaine and noribogaine, ii) to identify products formed under light exposure (daylight or 254 nm, 20°C) of the two drugs in methanolic solutions, and iii) to examine the alkaloid contents of a specimen of root bark of the *Tabernanthe iboga* shrub using liquid chromatography-electrospray mass spectrometry. After daylight exposure, two oxidation products were detected: ibochine and iboluteine from ibogaine, and

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desmethoxyibochine and desmethoxyiboluteine from noribogaine. After exposure to 254 nm of the ibogaine solution, another compound that could possibly be the analogous lactam of iboluteine was detected. From the liquid chromatography electrospray-mass spectrometry analysis of the root barks of a specimen of the *Tabernanthe iboga* shrub, seven alkaloids were detected: ibochine (m/z 325), ibogaline (m/z 341), iboluteine (m/z 327), ibogaine (m/z 311), ibogamine (m/z 281) and voacangine (m/z 369). The last compound characterized by the protonated species $(M + H)^+$ at m/z 309 has not been identified. In all samples, ibogaine was the principal alkaloid observed; its concentration ranged from 1.8 to 5.93 mg/g. For the other indole alkaloids, the peak areas of ibogaline, ibogamine and voacangine represent 11.9, 21.5, and 30.5% of that of ibogaine, respectively.

Keywords: Ibogaine, Noribogaine, NMR, IR, LC-MS, Stability studies, Alkaloids of *Tabernanthe iboga*

INTRODUCTION

Ibogaine (12-methoxyibogamine, (6R,6aS,7S,9R)-7-ethyl-2-methoxy-6,6a,7,8,9,10,12,13-octahydro-5*H*-6,9-methanopyrido[1′,2′:1,2]azepino[4,5-*b*]indole) is a naturally occurring psychoactive indole alkaloid, which is found in a variety of African shrubs of the Tabernanthe genus.[1] The root of the *Tabernanthe iboga* plant is the most frequently cited source of ibogaine.[2] Chemically, ibogaine is classified as a tryptamine, being a rigid analog of melatonin.[3] Ibogaine was first extracted from the *Tabernanthe iboga* root in 1901 by Dybowsky and Landrin.[4] It can also be synthesized from nicotinamide by way of 13 or 14 step processes.[5]

Ibogaine has previously been reported to have CNS stimulant, anxiogenic, and hallucinogenic properties.[4,6,7] Recent studies, reported the efficacy of this drug in the treatment of drug addictions.[8] In the body, ibogaine undergoes desmethylation to its principal metabolite, noribogaine, or 12-hydroxyibogamine ((6R,6aS,7S,9R)-7-ethyl-6,6a,7,8,9,10,12,13-octahydro-5H-6,9-methanopyrido[1′,2′:1,2]azepino[4,5-b]indol-2-ol). Noribogaine is formed by the action of cytochrome P450 enzymes in the liver.[1] Ibogaine was cleared rapidly from the blood, while noribogaine concentrations remained high. Thus, the purported efficacy of ibogaine following single dose administrations for the treatment of drug dependence may be due in part to the formation of noribogaine.[9,10] Ibogaine is a restricted substance (possession is illegal) in some countries, including the US, Switzerland, Denmark, Sweden, and Belgium.

The ibogaine structure was established in 1957 through chemical studies[11] and X-ray crystallographic investigations have fixed the configuration of the ethyl group.[12] Moreover, ^{13}C nuclear magnetic resonance (NMR) data[13] were reported compared with several iboga of similar structures. Surprisingly, no data are available in the literature for noribogaine.

Ibogaine is heat and light sensitive and can spontaneously oxidize in solution, giving iboluteine and ibochine.[7,11]

The aim of this study was i) to carry out a structural analysis of both ibogaine and noribogaine, ii) to identify products formed under light exposure of these two drugs in solution (methanol-purified water, 20:80, v/v), and iii) to examine the alkaloid contents of a specimen of root bark of the *Tabernanthe iboga* shrub using liquid chromatography-electrospray mass spectrometry.

EXPERIMENTAL

Instrumentation and Chromatographic Conditions

Nuclear Magnetic Resonance (NMR) Spectroscopy

1D and 2D NMR spectra were obtained at 305K on a Brucker 400 Avance spectrometer (Bruker BioSpin, Wissembourg, France), with a reverse ^{1}H probe (TBI $^{1}H/^{13}C$-BB Z-GRD). Samples dissolved in methanol-d4 were prepared in the dark. Chemical shifts (δ) are quoted in ppm relative to the residual hydrogen (3.50 ppm) or carbon (49.30 ppm) resonance of methanol-D4. Relaxation delay was set to 1s in all 2D NMR experiments. The heteronuclear multiple bond correlation (HMBC) spectra were recorded using the pulse sequence proposed by Bax and Summers involving low pass J-filters (140 Hz) and a delay for the long range coupling of 70 ms.

Fourier Transform-Infrared (FTIR) Spectroscopy

FTIR-Attenuate Total Reflection spectra were recorded on a Perkin Elmer Spectrum One (Courtaboeuf, France) with powder samples. Absorption bands (ν) are given in cm^{-1}.

Liquid Chromatography-Electrospray Mass Spectrometry (LC-ESI-MS)

The LC-MS analysis was performed using an Agilent 1100 quadrupole mass spectrometer (Agilent Technologies, Les Ulis, France) equipped with an electrospray interface and a data acquisition station (HPChem software, version 08.04). The mass spectrometer was coupled to a Hewlett Packard LC system equipped with a quaternary pumping unit, a diode-array UV detector, and an autosampler with a loading valve fitted with a 100 μL sample loop (Interchim, Montluçon, France), and set at 4°C.

LC-MS conditions for the quantitation of ibogaine and noribogaine in human matrices have been previously published.[14] Briefly, separation of the analytes was performed at room temperature (20°C) on a Zorbax eclipse

XDB C8 column (150 × 4.6 mm I.D.) packed with particles of 5 μm (Agilent Technologies, Palo Alto, CA). A C_{18} Symmetry column (20 × 3.9 mm I.D., 5 μm particles) obtained from Waters (Paris, France) was used as the guard column. A 20 min mobile phase gradient was used. Mobile phase A was 0.02% (v/v) trimethylamine in acetonitrile and mobile phase B consisted of 2 mM formate buffer (pH 3). The gradient started from 15% of phase A and then went up to 35% in 5 min. It increased to 50% in 6.2 min, then to 80% in 3.8 min. The column was then washed for 1 min with 80% of phase A, brought back to the initial conditions over 1 min, and re-equilibrated for 3 min. The flow rate started at 1 mL/min, then decreased to 0.5 mL/min from 1 to 5 min, and remained unchanged for 6.2 min. It increased directly to 1 mL/min in the next 4.8 min and then remained stable. The injection volume was 20 μL.

The mass spectrometer was calibrated in the positive ion mode (ESI +) using a mixture of NaI and CsI. The MS system was operated with a capillary voltage of 4.0 kV and a cone voltage of 135 V. The drying gas temperature and flow were maintained at 350°C and 10 L/min, respectively, and the nebulizer pressure was set at 13 psi.

Reagents

Ibogaine hydrochloride (molecular weight, 346.9) and trifluoroacetic acid (TFA) were purchased from Sigma (St. Louis, MO, USA). Noribogaine base (molecular weight, 296.4) was kindly supplied by Reform Italia (Endine, Italy). Ibogaine and noribogaine were stored, protected from light, at normal room temperature (20°C). HPLC grade acetonitrile, methanol, and methanol-D4 were obtained from Carlo Erba (Val de Reuil, France). The formate buffer solution (pH 3) consisted of ammonium formate (126 mg/L) in purified water. Ultrapure water was used (Milli-Q device, Millipore Corporation, Bedford, MA).

The drug stock solution of ibogaine hydrochloride was prepared in purified water at a concentration of 89.5 mg/L (expressed as free form equivalent). The noribogaine stock solution was prepared in methanol at concentrations of 100 mg/L. Stock solutions were stored at 4°C; under these storage conditions, ibogaine and noribogaine were stable for at least 6 months.[15]

Stability Studies

In a previous paper,[15] we have shown that, at 20°C with daylight exposure, ibogaine and noribogaine at concentrations of 22.4 and 25 μg/L, respectively showed a rapid decrease in drug concentrations. The corresponding half-lives were 81.5 min for ibogaine and 11 min for noribogaine.

Thus, to identify products formed under light exposure (20°C), duplicate test solutions of ibogaine (1800 μg/L) and noribogaine (2000 μg/L) were prepared, from stock solutions, in polypropylene tubes by dilution in a mixture of methanol-water (20:80, v/v) and exposed to daylight for a 1 day period or to 254 nm for 16 h under a UV light. Before analysis using LC-MS conditions described above, each flask was manually shaken, then 2 to 5 fold diluted with a mixture of 1 mL/L TFA in water and acetonitrile (85:15, v/v). A 20 μL aliquot of each sample was injected onto the LC system and analyzed using diode-array and MS (scan mode) detection in sequence, to identify peaks present on the chromatogram and to verify that each observed peak elutes free from potential interferences. In a second step, the same samples were injected into the LC-MS system using different cone voltages, from 135 to 350 V, to obtain daughter ions used for identification. Degradation products were identified on the basis of its spectral data and comparison of literature.[11,16–18]

Plant Material and Extraction of Alkaloids

A specimen of the root bark of *Tabernanthe iboga* shrub collected in June 2006 in Gabon was analyzed to examine the alkaloid contents. This specimen included roots of small, medium, and big sizes. The bark was collected from each sample and then powdered. Powdered barks (500 mg) were gently stirred overnight in methanol. The methanolic extracts were suspended in 5% hydrochloric acid, extracted with dichloromethane, and then the pH of the aqueous acidic fractions was adjusted to 9 with ammonia. After extraction with dichloromethane, the organic phases were evaporated to dryness under a stream of nitrogen at 40°C. The dried residues were reconstituted in 1 mL of mobile phase. A 20 μL aliquot was injected into the system.

All the alkaloids were identified compared with literature data and, for some of them, by reference to authentic samples.

RESULTS

Structural Analysis

Assignment of the 1D NMR spectra of ibogaine and noribogaine was achieved in methanol using 2D homo- and hetero-nuclear correlation spectroscopies (Table 1). The HMBC experiment provided easy determination of all quaternary carbon atoms, differentiation of the three methyl groups bearing nitrogen atoms, and confirmation of the 12 substituted indole pattern. The 2D NMR spectra recorded on noribogaine are shown in Figure 1. They were quite similar to those obtained with ibogaine.

The IR spectra of ibogaine and noribogaine are presented in Figure 2.

Table 1. NMR chemical shift assignment

A ^{13}C NMR spectra			B RMN ^{1}H spectra	
(100.13 MHz, δppm): MeOH-d4 at 303K Calibration at 49.3 ppm			(400.13 MHz, δppm): MeOH-d4 at 303K, calibration at 3.50 ppm	
Noribogaine	Ibogaine		Noribogaine	Ibogaine
151.93	155.74	C11	7.29 (d, J = 8.6 Hz, 1H, H14)	7.36 (d, J = 8.7 Hz, 1H, H14)
140.88	140.7	C17	7.01 (d, J = 2.3 Hz, 1H, H11)	7.14 (d, J = 2.4 Hz, 1H, H11)
131.66	132.19	C15	6.85 (dd, J = 8.6 Hz, J = 2.3 Hz, 1H, H13)	6.94 (dd, J = 8.7, J = 2.4 Hz, 1H, H13)
130.51	130.21	C10	–	4.00 (s, 3H, OCH_3)
112.67	112.90	C13	3.88 (dt, J = 4.2 Hz, J = 13.4 Hz, 1H, H7)	3.88 (dt, J = 4.2, J = 13.5 Hz, 1H, H7)
112.40	112.82	C14	3.85–3.72 (m, 2H, H5, H7′)	3.80–3.70 (m, 3H, H5, H7′)
107.03	107.66	C9	3.67–3.58 (m, 2H, H19)	3.65–3.52 (m, 3H, H18, H19)
103.17	101.36	C11	3.54 (ddd, J = 12.0 Hz, J = 4.6 Hz, J = 1.8 Hz, 1H, H18)	–
61.83	61.91	C5	3.44 (ddd, J = 11.4 Hz, J = 4.3 Hz, J = 17.8 Hz, 1H, H8′)	3.48–3.30 (m, 2H, H8)
57.72	57.82	C7	3.32 (dt, J = 17.8 Hz, J = 4.0 Hz, 1H, H8)	–
–	56.67	OCH_3	2.57–2.44 (m, 1H, H1)	2.55–2.42 (m, 1H, H1)
52.34	52.31	C19	2.42–2.28 (m, 2H, H2, H3′)	2.37–2.25 (m, 2H, H2, H3′)
40.69	40.65	C4	2.27–2.14 (m, 1H, H4)	2.24–2.1 (m, 1H, H4)
36.90	36.72	C18	2.00–1.77 (m, 3H, H20, H1′)	1.95–1.80 (m, 3H, H20, H1′)
32.90	32.87	C1	1.63–1.54 (m, 1H, H3)	1.64–1.52 (m, 1H, H3)
30.54	30.41	C3	1.23 (t, J = 7.3 Hz, 3H, H21)	1.22 (t, J = 7.3 Hz, H3, H21)
27.64	27.63	C20		
25.71	25.57	C2		
19.83	19.70	C8		
12.17	12.20	C21		

From the full scan spectra (Figure 3A, B), ibogaine and noribogaine were characterized by the protonated molecules $(M + H)^+$ at m/z 311.1 and m/z 297.1, respectively. Fragment ions were observed at m/z 122.2 and m/z 174 for ibogaine, and m/z 122.2 and m/z 160 for noribogaine. In accordance with the paper of Taylor,[11] a fragmentation pattern is presented in Figure 4. The compound present in the ibogaine hydrochloride raw material detected in a previous paper[15] was identified as ibogamine. This compound was characterized by LC-MS and its structure confirmed by ^{1}H NMR. Ibogamine was characterized by the protonated molecule at m/z 281.1 (Figure 3C); fragment ions were obtained at m/z 122.1 and m/z 144.1 (Figure 4).

Under the chromatographic conditions described above, noribogaine (retention time $t_r = 6.74$ min), ibogaine ($t_r = 10.2$ min), and ibogamine ($t_r = 10.8$ min) exhibited well separated, narrow and symmetrical peaks.

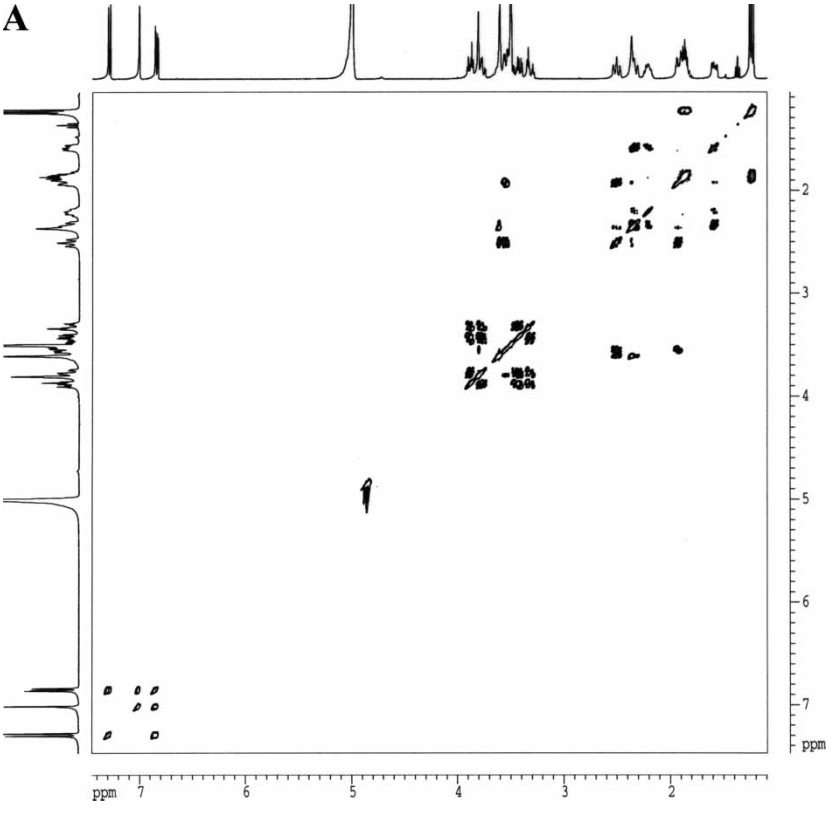

Figure 1. NMR spectra of noribogaine. (A) correlation spectroscopy ^{1}H-^{1}H (COSY45), (B) heteronuclear multiple quanta correlation (HMQC), (C) heteronuclear multiple bond correlation (HMBC).

(*continued*)

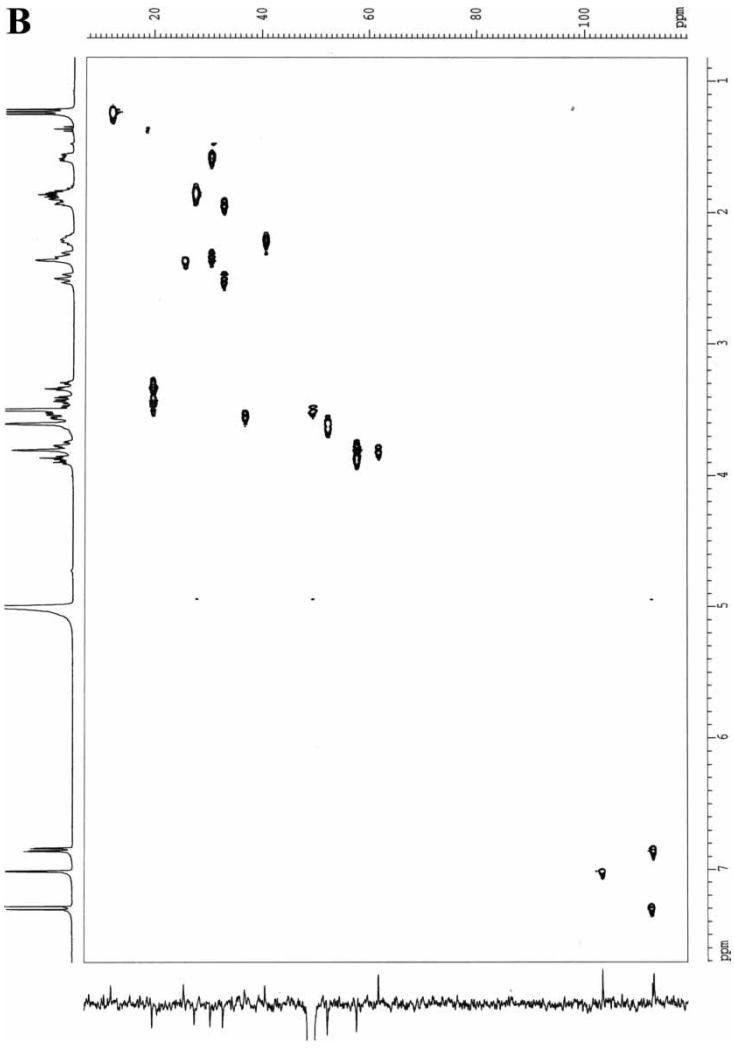

Figure 1. Continued.

Stability Results

After daylight exposure of ibogaine solutions, two products with retention times different from that of ibogaine and ibogamine were detected on the full scan spectra. The first compound at 6.4 min was assumed to be ibochine. This compound was characterized by the protonated molecule $(M + H)^+$ at m/z 325. Fragment ions were observed at m/z 203 and m/z 122.1. The second compound at 9.6 min could correspond to iboluteine ($[M + H]^+$ at m/z 327). Fragment ions were obtained at m/z 122.1 and

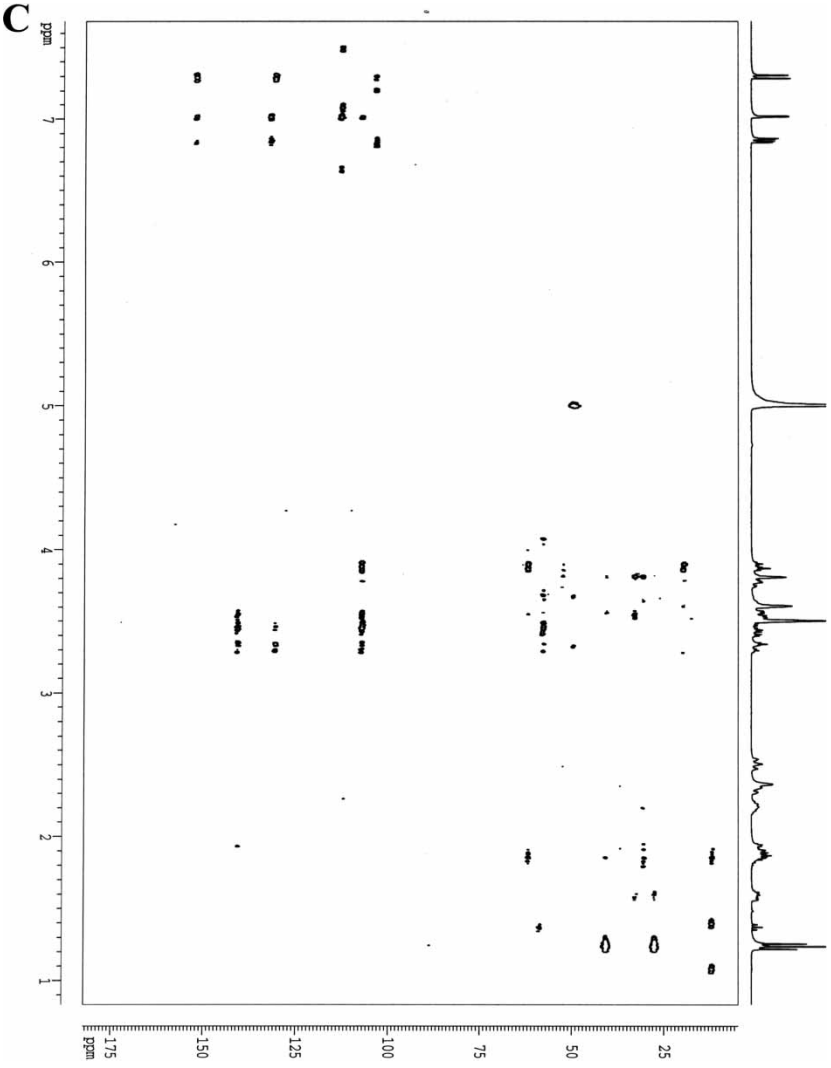

Figure 1. Continued.

m/z 150.1 characteristics of the iboluteine moiety.[16] Moreover, the UV spectrum found for this compound was in accordance with the paper of Goutarel et al.[17] A representative chromatogram is presented in Figure 5A. After exposure to 254 nm, another compound with a retention time of 5.7 min was detected. This compound was characterized by the protonated molecule $(M + H)^+$ at 341; a fragment ion was obtained at m/z 122.1. This product could possibly be attributed to the analogous lactam of iboluteine.

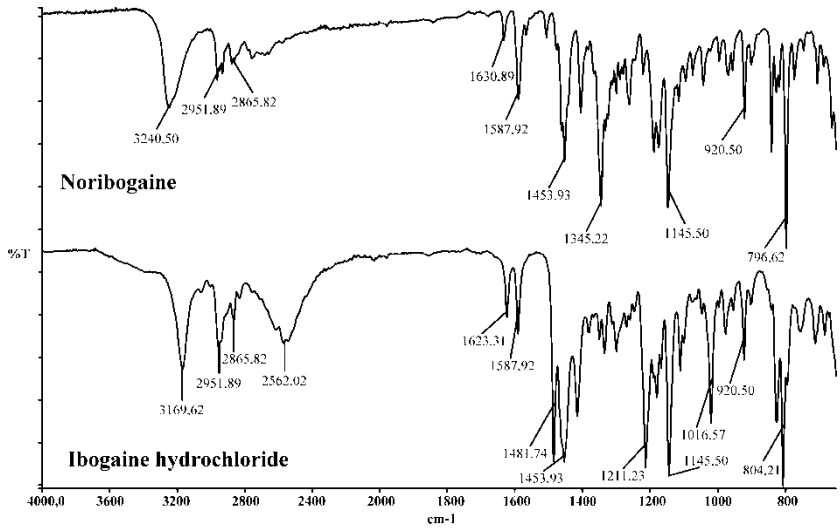

Figure 2. The IR spectra of ibogaine and noribogaine.

After daylight exposure of noribogaine solutions, two products were detected on the full scan spectra (Figure 5B). The first compound with a retention time of 5.3 min could be desmethoxyibochine. This compound was characterized by the protonated molecule $(M + H)^+$ at m/z 311; fragment ion was observed at m/z 122.1. The second compound, with a retention time of 6.0 min, was assumed to be desmethoxyiboluteine $(M + H^+$ at m/z 313). As observed for iboluteine, fragment ions were obtained at m/z 122.1 and m/z 150.1 characteristics of the iboluteine moiety. After exposure to 254 nm, no other compounds were detected.

Structure of the oxidation products are presented in Figure 6.

Alkaloid Contents from a Specimen of *Tabernanthe Iboga* Shrub

In the three root samples analyzed (small, medium, and big), LC-MS analysis of the dichloromethane extracts indicated the presence of at least 7 alkaloids with molecular weight ranging from 280 to 368. Analysis of the fragmentation pattern of the alkaloids in LC-MS, compared with literature data, and, for some of them, standards co-injection, suggested the presence of ibochine (retention time: 6.4 min; protonated species $(M + H)^+$ at m/z 325; fragment ions at m/z 203 and m/z 122.1), ibogaline (retention time: 8.9 min; protonated species $(M + H)^+$ at m/z 341; fragment ions at m/z 122.1 and m/z 204.1.), iboluteine (retention time: 9.6 min; protonated species $(M + H)^+$ at m/z 327; fragment ions at m/z 122.1 and m/z 150.1), ibogaine (retention time: 10.2 min; protonated species $(M + H)^+$ at m/z 311; fragment ions at m/z

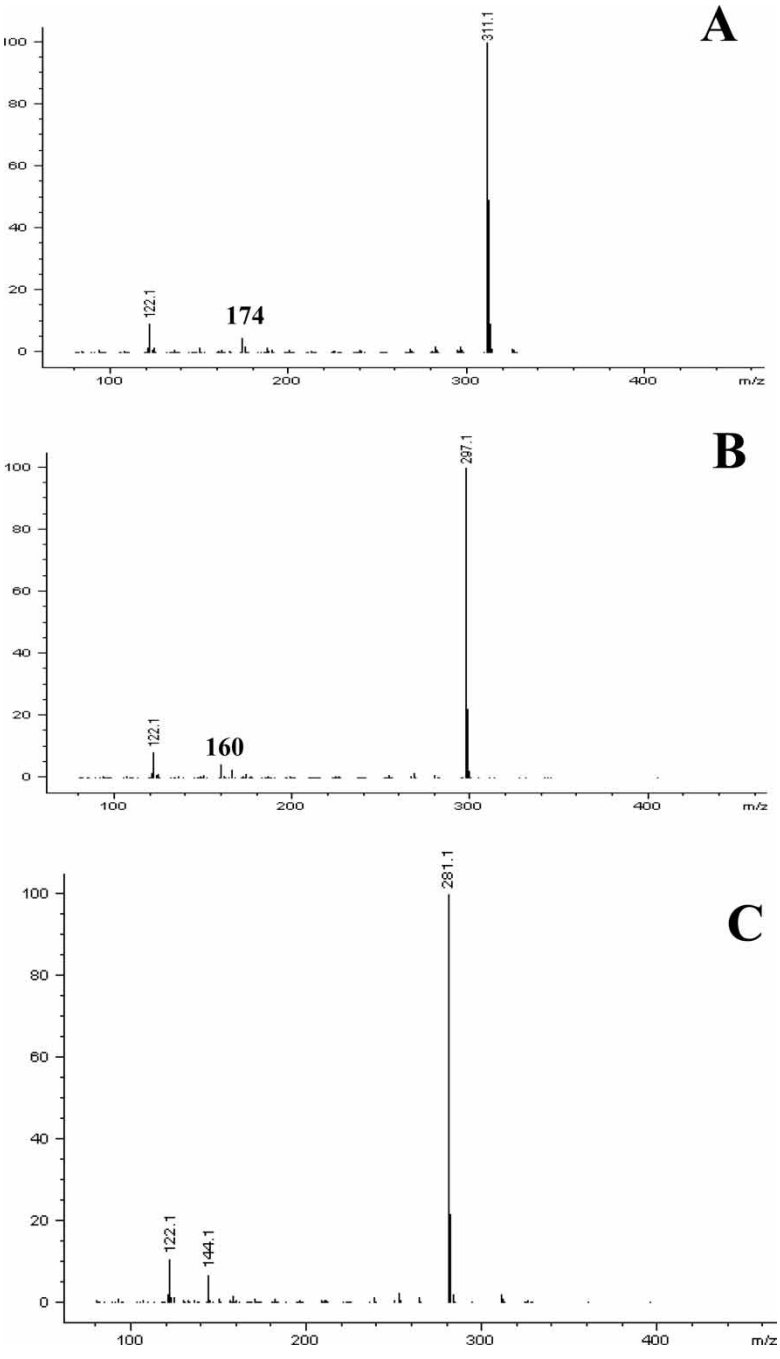

Figure 3. Mass spectra (scan mode) of (A) ibogaine and (B) noribogaine and (C) ibogamine.

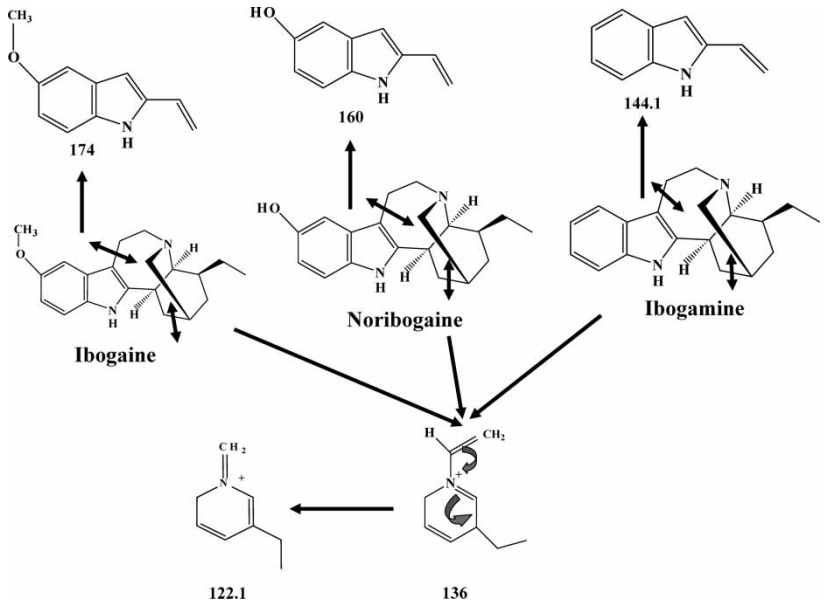

Figure 4. Fragmentation pattern of ibogaine, noribogaine and ibogamine (from Taylor[11]).

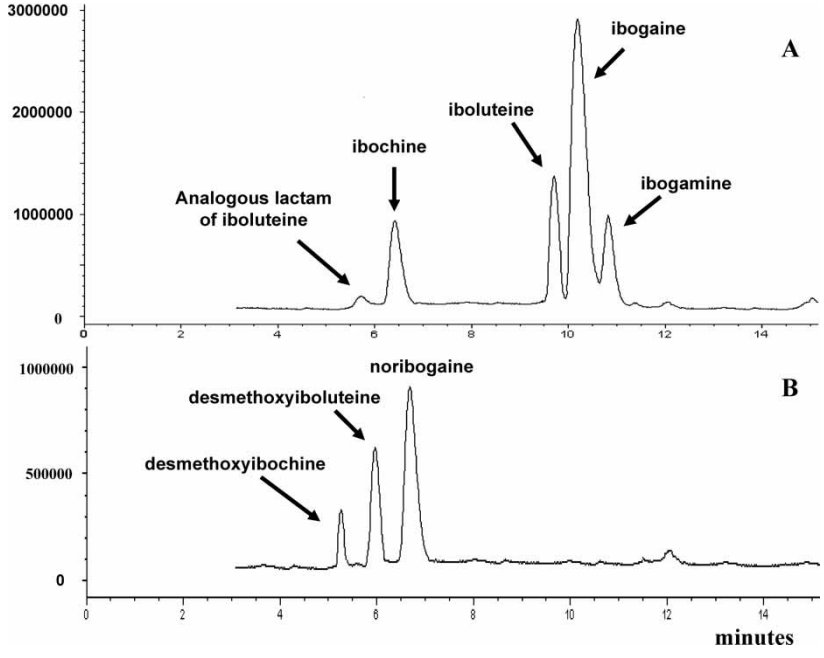

Figure 5. Representative chromatograms of degradation products formed from A) ibogaine and B) noribogaine/. For LC-MS conditions see instrumentation section.

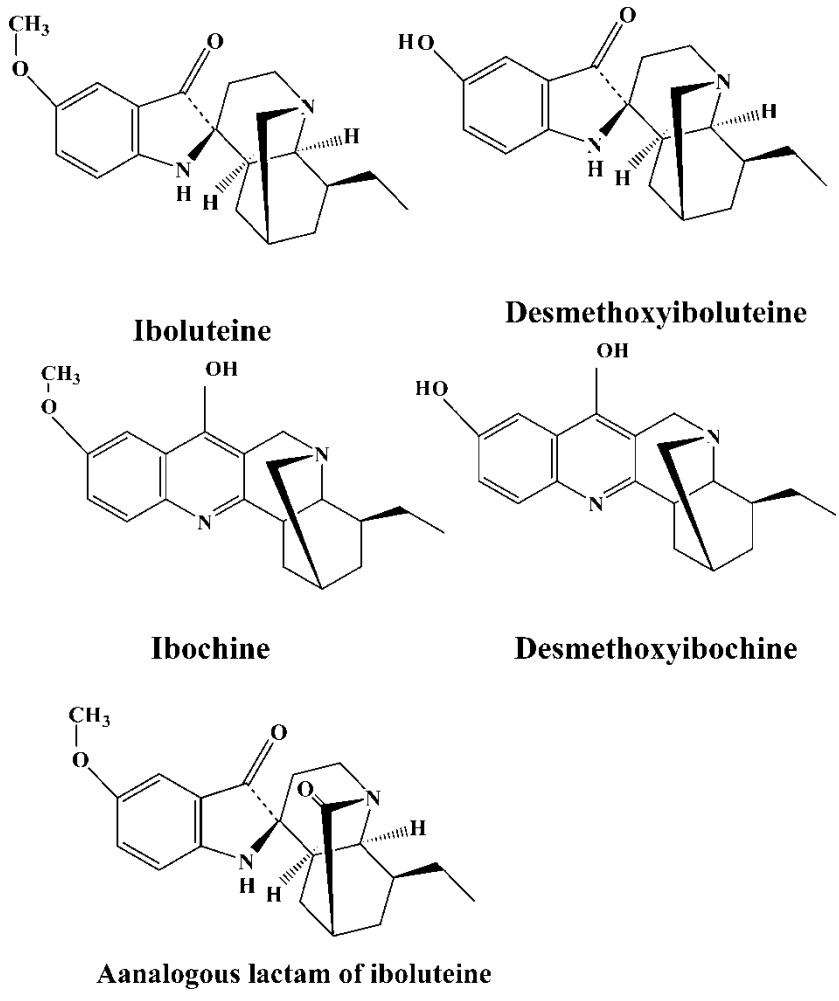

Figure 6. Chemical structure of oxidation products.

122.1 and m/z 174), ibogamine (retention time: 10.8 min; protonated species $(M + H)^+$ at m/z 281; fragment ions at m/z 122.1 and m/z 144.1) and voacangine (retention time: 11.0 min, protonated species $(M + H)^+$ at m/z 369; fragment ions at m/z 122.1 and m/z 136). An unknown compound was detected at retention time 9.7 min; it was characterized by the protonated species $(M + H)^+$ at m/z 309, fragment ion was observed at m/z 122.1. Figure 7 shows a typical chromatogram (full scan) obtained from a dichloromethane extract. In all samples, ibogaine was the principal alkaloid observed; concentrations were 5.93, 2.1, and 1.8 mg/g in small, medium, and big roots, respectively. In the three root samples analyzed, the

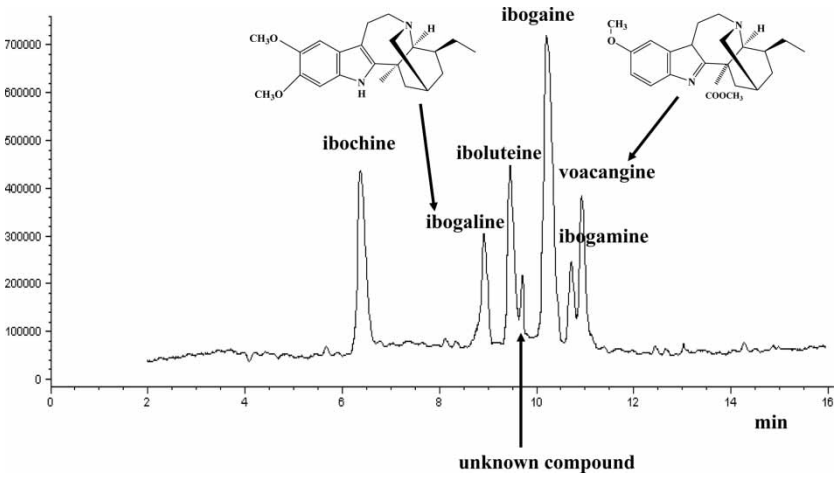

Figure 7. Chromatogram (scan mode) obtained from a dichloromethane extract (big root). For LC-MS conditions see instrumentation section.

mean percentages of ibogaline, ibogamine, and voacangine appear to be 11.9% (11.8-12), 21.5% (20-23) and 30.5% (23-38), respectively, judging by the peak area corresponding to the different compounds using the following equation:

$$\left[\frac{\text{Peak area of ibogaline, ibogamine or voacangine}}{\text{peak area of ibogaine}}\right] \times 100$$

Concerning the two oxidation products, ibochine and iboluteine, the peak areas represent 6.6% (3.5–9.2) and 6.8% (6.6–7.0) of that of ibogaine, respectively.

DISCUSSION AND CONCLUSION

In the present paper, a structural analysis of both ibogaine and noribogaine was performed; moreover, a LC-ESI-MS method was used to identify degradation products formed from these two compounds under light exposure (daylight and 254 nm, 20°C). As previously reported by Popik and Skolnick[7] and Taylor,[11] ibogaine is light sensitive and is spontaneously oxidized in solution, giving ibochine and iboluteine. These two compounds were identified from their mass spectra. In the present paper, we reported for the first time, degradation products of noribogaine. As ibogaine, noribogaine suffers facile oxidation in solution giving desmethylated oxidation products of ibochine and iboluteine. In the present work, retention times and mass spectra of iboluteine and desmethoxyiboluteine were similar to

those found after the analysis of tissues and fluids of a man following poisoning, which involved the root bark of the *Tabernanthe Iboga* Shrub.[19] At 254 nm, an additional compound was detected that could possibly be attributed to the analogous lactam of iboluteine. Unfortunately, we were unable to positively confirm these structures; attempts to obtain standards of these substances proved unsuccessful.

The LC-MS method described in this paper was used to analyse alkaloid contents from a specimen of the *Tabernanthe iboga* shrub collected in June 2006 in Gabon. Seven alkaloids were detected. Analysis of the fragmentation pattern of the alkaloids in LC-MS, compared with literature data and, for some of them, standards co-injection, suggested the presence of ibogaline, ibogaine, ibogamine, and voacangine, and of two oxidation products of ibogaine, iboluteine, and ibochine. According to Taylor,[11] many of the iboga alkaloids easily undergo autoxidation. Therefore, the isolation of iboluteine and ibochine from the root shrub cannot, by itself, be taken as proof of its natural occurrence. The last alkaloid detected is characterized by the protonated species $(M + H)^+$ at m/z 309; unfortunately, this compound has not been identified. In all samples, ibogaine was the principal alkaloid observed; its concentration ranged from 1.8 to 5.93 mg/g. These concentrations were similar to those reported by Jenks.[20] Surprisingly, the higher concentrations of ibogaine were found in the rootlets. For the other indole alkaloids, the peak areas of ibogaline, ibogamine, and voacangine represent 11.9, 21.5, and 30.5% of that of ibogaine, respectively.

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