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ALKALOIDS FROM *BOOPHANE FLAVA*

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Key Word Index—*Boophane flava*; Amaryllidaceae; bulbs; alkaloids; 5,6-dihydrobicolorine; lycorine; hamayne; 3-*O*-acetylhamayne; crinamine; crinine; epivittatine; buphanisine; epibuphanisine; undulatine; augustine; buflavine; 8-*O*-demethylbuflavine; montabuphine.

Abstract—Fourteen alkaloids have been isolated from bulbs of *Boophane flava*. The alkaloids, buflavine, 8-*O*-demethylbuflavine and montabuphine are reported here for the first time. The structure and stereochemistry of these new alkaloids were established by physical and spectroscopic methods. ^{1}H and ^{13}C NMR spectra of epivittatine and epibuphanisine were completely assigned by means of 2-D NMR techniques.

INTRODUCTION

Boophane flava is an endemic Amaryllidaceae species from southern Africa, growing in the winter rainfall area. The present paper deals with the isolation and structural elucidation of fourteen alkaloids from the bulbs of this unhitherto studied plant species. Three of them, lycorine, augustine and crinamine, were found to be the principal cytotoxic and antimalarial constituents of the bulbs of *Crinum amabile* and, among the 5,10b-ethanophenanthridines, augustine appeared to be the most active alkaloid [1]. Montabuphine (**3**) is the first natural β-5,11-methanomorphanthridine alkaloid obtained from this plant family; furthermore, buflavine (**4**) and 8-*O*-demethylbuflavine (**5**) are representative of the odd natural amaryllidaceous alkaloids with an eight-membered *N*-heterocyclic ring, which only had been previously reported from *Galanthus nivalis* [2].

RESULTS AND DISCUSSION

Epivittatine (**1**), $C_{16}H_{17}NO_3$, had been previously reported from bulbs of *Nerine bowdenii* [3] and *Crinum erubescens* [4], epibuphanisine (**2**), $C_{17}H_{19}NO_3$, from bulbs of *Ammocharis coranica* [5]. The literature lacks information on the spectroscopical data of both alkaloids, with the exception of the ^{1}H NMR spectrum of **1** [6], which was incomplete. Their EI mass spectra showed the typical crinine-type fragmentation pattern of compounds with no bridge substituent and having a double bond in the 1,2-position [7]. The mass spectrum of **1** was very similar to that of vittatine and (−)-siculine [8, 9] and the mass spectrum of **2**, with $[M]^+$ at *m/z* 285 and base peak at *m/z* 215, was very similar to that of (+)-buphanisine [9]. The ^{1}H NMR spectra of **1** and **2** (Table 1) exhibited methylenedioxy doublets and aromatic proton singlets like vittatine and (+)-buphanisine. In agreement with the (−)-siculine data [9], the C-3 substituent groups were pseudoequatorial and had a *cis*-relationship with the 5-10b-ethano bridges, because the coupling constant between H-2 and H-3 was small (1 Hz), the coupling constant between H-3 and H-4α was large (*ca* 11 Hz) and an allylic coupling of *ca* 2 Hz between the vinylic H-1 and the allylic H-3 was observed. The methoxyl group of compound **2** at the 3-pseudoequatorial position (δ3.39) induced a shielding effect on H-3 and a deshielding effect on H-2 and H-4β, with respect to the compound **1** data. The ^{1}H, ^{1}H-couplings were confirmed by 2-D COSY experiments. The absolute configurations of these alkaloids were determined from CD-curves, which were qualitatively similar to those of the α-5,10b-ethanophenanthridine alkaloids [10] and were in agreement with published data [11]. The ^{13}C NMR spectra of **1** and **2** (Table 2), confirmed by HMQC [12] and HMBC [13] techniques, were consistent with the proposed structures and, relative to the crinine and buphanisine data [14], only small differences were observed.

The mass spectrum of the new natural alkaloid montabuphine (**3**), $C_{17}H_{19}NO_4$, showed a typical montanine-type fragmentation pattern [15] with the $[M]^+$ at *m/z* 301 as the most intense peak and a $[M-15]^+$ ion at *m/z* 286 due to the loss of the *O*-methyl group. The relatively low abundance of the *m/z* 270 ion, compared to alkaloids like montanine with a methoxyl group at the C-2 position, suggested the presence of a methoxyl substituent at C-3 [15]. An abundant peak at *m/z* 243, originating from retro-Diels Alder fragmentation, to-

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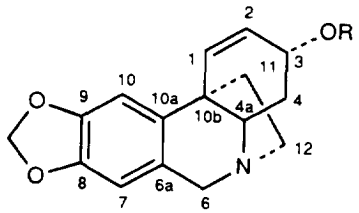

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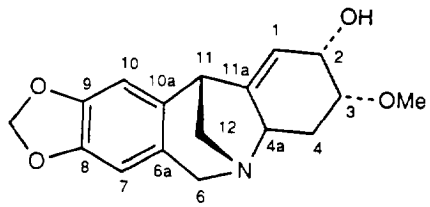
2: R= Me



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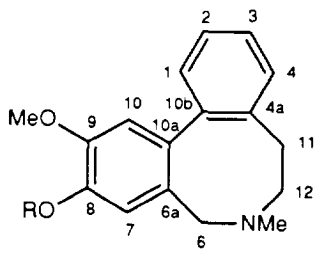

4: R= Me
5: R= H

gether with peaks at *m/z* 223, 214, 199 and 185, were also present. The molecular ellipticity of **3** showed a CD-curve which was qualitatively the reverse of the known 5,11-methanomorphanthridine alkaloids with an α-configuration for the methano-bridge [10, 16]. This fact led us to propose that the 5-11-methano bridge has the β-configuration. The ^{1}H NMR spectra allowed the identification of two *para*-positioned aryl protons, as well as two methylenedioxy protons with a geminal coupling of *ca* 1.5 Hz. The two H-6 protons were clearly differentiated as an AB-system with geminal coupling of 16.5 Hz. The assignment of these two protons was confirmed by ROESY [17] experiments. The cyclohexane ring D bore an axial 3-OMe (δ3.39) and a pseudoequatorial 2-OH group and existed in the C_4 half-chair conformation. The *cis*-configuration of these vicinal substituents was confirmed by the $J_{2,3}$ value of 5 Hz, the small coupling constant (J = 1.5 Hz) between H-3 and H-4*ax*, together with the NOE contour correlation between H-2 and H-4*ax* [16, 18]. On the other hand, H-1 showed a transoid allylic coupling (J = 2 Hz) with H-4a; the signal at

Table 1. ^{1}H NMR data for compounds **1** and **2** (J given in Hz in parentheses)

H	1*	2†
1	6.43 *dd* (2.2, 10.2)	6.36 *dd* (2.1, 10.3)
2	5.63 *dd* (1.0, 10.2)	5.82 *dd* (1.0, 10.3)
3	4.19 *m*	3.96 *m*
4α	1.45 *ddd* (10.5, 12.5, 13.0)	1.57 *ddd* (11.0, 13.0, 13.0)
4β	1.88 *brd* (12.5)	2.46 *brd* (13.0)
4a	3.16 *dd* (3.0, 13.0)	3.34 *dd* (3.5, 13.0)
6α	3.73 *d* (16.5)	3.88 *d* (16.5)
6β	4.26 *d* (16.5)	4.52 *d* (16.5)
7	6.59 *s*	6.49 *s*
10	6.96 *s*	6.79 *s*
11 *endo*	2.02 *ddd* (5.0, 9.0, 12.0)	2.22 *ddd* (5.0, 9.0, 12.5)
11 *exo*	1.97 *ddd* (6.0, 10.0, 12.0)	2.16 *ddd* (6.0, 10.5, 12.5)
12 *endo*	2.86 *ddd* (6.0, 9.0, 13.0)	3.00 *ddd* (6.0, 9.0, 13.0)
12 *exo*	3.32 *ddd* (5.0, 10.0, 13.0)	3.61 *ddd* (5.0, 10.5, 13.0)
–O–CH_2–O–	5.91 *d*-5.92 *d* (1.5)	5.89 *d*-5.90 *d* (1.5)
3-OMe	—	3.39 *s*

*Measured in DMSO-d_6.
†Measured in $CDCl_3$.

Table 2. ^{13}C NMR chemical shift assignments of compounds **1** and **2**

C	1*	2†
1	127.4 *d*	127.9 *d*
2	132.8 *d*	129.5 *d*
3	65.8 *d*	75.7 *d*
4a	66.2 *d*	66.7 *d*
6	61.0 *t*	61.2 *t*
6a	125.6 *s*	123.4 *s*
7	106.9 *d*	107.0 *d*
8	145.2 *s*	146.3 *s*
9	145.7 *s*	146.7 *s*
10	103.1 *d*	103.0 *d*
10a	138.3 *s*	137.3 *s*
10b	44.1 *s*	44.8 *s*
11	44.5 *t*	43.9 *t*
12	52.4 *t*	52.8 *t*
–OCH_2O–	100.5 *t*	101.1 *t*
3-OMe	—	56.2 *q*

*Measured in DMSO-d_6.
†Measured in $CDCl_3$.

δ1.58 was assigned to the H-4*ax* proton by ROESY experiments and because of the *trans*-diaxial H-4*ax*, H-4a relationship (J = 13 Hz). In addition, the H-4*ax* and H-4*eq* protons showed a geminal coupling constant of 13 Hz. The H-12 protons were observed as a doublet at δ3.07 and a double doublet at δ3.11; the low field signal was assigned to H-12*eq* because of its coplanarity with the nitrogen lone pair and the coupling constant with

H-11 ($J = 2$ Hz). The coupling between H-11 and H-12*ax* ($J < 1$ Hz) was in accordance with a dihedral angle of *ca* 90° and, together with the NOE effect between H-6β and H-12*ax*, ratified the assignment of the H-12 protons. Additional long-range coupling of H-11 with H-1 (allylic) and H-10 (*peri*) and H-12*eq* with H-6α (W-mechanism), respectively, caused line-broadening of H-11, H-12*eq*, H-10 and H-6α. The ^{13}C NMR spectrum played an important role in distinguishing the montanine type from the other ring systems found in Amaryllidaceae alkaloids, because the singlet at δ150.8, due to the olefinic carbon C-11a, is only observed in this type of alkaloids [16]. The ^{13}C assignments were confirmed by means of HMQC and HMBC correlations and, with the exception of the small changes mainly in the shift range of $\delta > 90$, were similar to those of pancracine and montanine [16, 19]. Methoxylation at the C-3 position was confirmed because of the downfield shift of the C-3 resonance (δ77) compared with the chemical shift (*ca* δ70) when this position was hydroxylated.

The alkaloid **4**, $C_{18}H_{21}NO_2$, and its 8-*O*-demethyl derivative **5**, $C_{17}H_{19}NO_2$, were isolated as amorphous solids for the first time from a natural source. Their EI mass spectra displayed a similar fragmentation pattern, with significant $[M]^+$ at *m/z* 283 and 269, for **4** and **5**, respectively. The base peaks at *m/z* $[M-43]^+$ were in agreement with the loss of a C_2H_5N fragment. Important fragment ions at *m/z* $[M-15]^+$, $[M-58]^+$, $[M-86]^+$, 165, 153 and 152 were obtained for both structures. Their ^{1}H NMR spectra (Table 3) were very close and only the absence of a methoxyl group signal in **5** was noteworthy. Both alkaloids have two aromatic rings. The ring A showed two aromatic protons *para*-oriented, which was consistent with their multiplicity. The ring C was consistent with an *ortho*-disubstituted aromatic ring. Additionally, three or two singlets, corresponding to the methoxyl group(s) and the *N*-methyl group were observed. The ascription of the methoxyl group in the ring A of compound **5** was carried out by a ROESY experiment. Thus, while H-10 showed a NOE contour correlation with H-1 and the methoxyl group, spatial proximity between H-7 and H-6 pseudoequatorial as well as with the *N*-methyl group were established, confirming the assignation of the hydroxyl group at C-8. The H-6 pseudoequatorial and the H-12*exo* were assigned a lower fields due to their *cis*-relation with the nitrogen lone pair [20]. Finally, both compounds showed small coupling constants between H-11 *endo* and H-12 *exo* and between H-11 *exo* and H-12 *endo* ($J < 1$ Hz), which were in accordance with dihedral angles of *ca* 90°. The ^{13}C NMR spectra of **4** and **5** (Table 4) showed six carbon singlets for the aromatic rings which were assigned, taking into account the correlations observed in HMBC experiments. The carbon singlets C-9 and C-8 were assigned at lower fields than is usual for Amaryllidaceae alkaloids, C-9 being more deshielded because of its three-bond correlation with the methoxyl protons and the methine proton H-7. Compound **5** showed only one methoxyl group which had correlation with C-9, confirming the assignment of the hydroxyl substituent at the C-8 position. The quaternary carbons of the C-ring, C-10b and C-4a, were ascribed by means of their correlations with the methine protons H-2, H-4 and the methylene proton H-11 or with H-3, H-1 and H-12, respectively. As far as C-10a is concerned, it was clearly differentiated from C-6a because of its three-bond connectivities to H-6, H-7 and H-1. The rest of the signals were unambiguously assigned by HMBC and HMQC correlations.

Table 3. ^{1}H NMR data for compounds **4** and **5** (J given in Hz in parentheses)

H	4	5
1	7.30 *dd* (2.0, 8.0)	7.26 *dd* (2.0, 8.0)
2	7.32 *ddd* (2.0, 8.0, 8.0)	7.29 *ddd* (2.0, 8.0, 8.0)
3	7.36 *ddd* (2.0, 8.0, 8.0)	7.34 *ddd* (2.0, 8.0, 8.0)
4	7.25 *dd* (2.0, 8.0)	7.23 *dd* (2.0, 8.0)
6 *pseudoeq.*	3.78 *d* (13.5)	3.86 *d* (13.5)
6 *pseudoax.*	3.31 *d* (13.5)	3.39 *d* (13.5)
7	7.01 *s*	7.07 *s*
10	6.81 *s*	6.78 *s*
11 *endo*	2.61 *m*	2.63 *m*
11 *exo*	2.79 *dd* (7.5, 14.5)	2.78 *dd* (7.5, 14.5)
12 *endo*	2.75 *dd* (12.0, 12.5)	2.93 *dd* (12.0, 12.5)
12 *exo*	3.39 *dd* (7.5, 12.5)	3.38 *dd* (7.5, 12.5)
8-OMe	3.96 *s*	—
9-OMe	3.89 *s*	3.88 *s*
N-Me	2.61 *s*	2.63 *s*

Table 4. ^{13}C NMR chemical shift assignments of compounds **4** and **5**

C	4	5
1	129.1 *d*	129.2 *d*
2	126.3 *d*	126.2 *d*
3	128.1 *d*	127.9 *d*
4	129.5 *d*	129.4 *d*
4a	139.9 *s*	140.0 *s*
6	58.0 *t*	57.4 *t*
6a	128.3 *s*	128.3 *s*
7	113.9 *d*	118.0 *d*
8	148.2 *s*	145.4 *s*
9	148.5 *s*	146.5 *s*
10	112.2 *d*	111.8 *d*
10a	133.2 *s*	132.6 *s*
10b	140.8 *s*	140.8 *s*
11	32.0 *t*	31.4 *t*
12	58.4 *t*	58.1 *t*
8-OMe	55.9 *q*	—
9-OMe	55.9 *q*	55.9 *q*
N-Me	45.3 *q*	44.4 *q*

EXPERIMENTAL

General. Mps uncorr. IR measured in KBr discs or $CHCl_3$. EIMS at 70 eV. ^{1}H, ^{13}C NMR, DEPT, ^{1}H COSY, HMQC, HMBC and ROESY spectra were recorded using a Varian VXR 500, using the solvent

specified and TMS as int. standard. Chemical shifts are reported in δ(ppm) values and coupling constants (J) in Hz. Silica gel SDS Chromagel 60 A CC (230–400 mesh) was used for flash CC and Sephadex LH-20 Pharmacia for gel filtration. Silica gel 60 F_{254} (Merck) was used for TLC. Spots on chromatograms were detected under UV light (254 nm) and by Dragendorff's reagent.

Plant material. Bulbs of *B. flava* W.J. Barker ex Snijman were collected in December 1991 in the Karoo National Gardens, Worcester, South Africa. A voucher specimen has been deposited in the Compton Herbarium (Terry 1126), National Botanical Gardens, Kirstenbosch, Cape Town, South Africa.

Extraction and isolation of alkaloids. Bulbs (913 g) were crushed and macerated with EtOH for 48 hr. The extract was evapd under red. pres. and acidified to pH 4. After removing neutral material with Et_2O, the acidic soln was extracted with $CHCl_3$ to provide fr. A (490 mg). Basifying the soln to pH 8–9 and extracting with $CHCl_3$ gave fr. C (750 mg). Finally, $CHCl_3$–MeOH extraction of the basic soln gave fr. D (970 mg). Fr A, C and D were combined and chromatographed by flash CC on silica gel eluting with CH_2Cl_2–MeOH (19:1); 5 frs were collected. Fr. I was chromatographed by prep. TLC using Me_2CO as solvent; after final purification on Sephadex LH-20, 5,6-dihydrobicolorine (4 mg) was isolated. Lycorine crystallized directly from fr. II; recrystallization with MeOH afforded 29 mg. The rest of fr. II was again chromatographed by prep. TLC, eluting twice with MeOH and Me_2CO as solvents; after purification on Sephadex LH-20, 3-*O*-acetylhamayne (22 mg) was isolated. Finally, after purification by similar processing to that for fr. II, fr. III afforded **4** (68 mg), **5** (41 mg), crinamine (156 mg), undulatine (7 mg) and augustine (5 mg), fr. IV, **3** (36 mg), buphanisine (58 mg) and **2** (11 mg), and, fr. V, hamayne (34 mg), crinine (23 mg) and **1** (10 mg).

Epivittatine (**1**). Found: C, 70.80; H, 6.40; N, 5.10 Calc. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16%. Mp 208–210°. $[\alpha]_D^{22}$ + 102° (EtOH; *c* 0.25). CD $[\Theta]_{249}$ − 2580, $[\Theta]_{289}$ + 5150. IR ν_{max} cm^{-1}: 3200–3100 (–OH), 2980, 1495, 1045, 945 (–OCH_2O–). EIMS 70 eV, *m/z* (rel. int.): 271 $[M]^+$ (100), 254 (12), 228 (24), 216 (18), 199 (68), 187 (60), 173 (18), 115 (10). ^1H NMR (500 MHz, DMSO-d_6), see Table 1. ^{13}C NMR (50 MHz, DMSO-d_6), see Table 2.

Epibuphanisine (**2**). Found: C, 71.63; H, 6.76; N, 4.85 Calc. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91%. Mp 123–125°. $[\alpha]_D^{22}$ + 129° (EtOH; *c* 0.224). CD $[\Theta]_{249}$ − 3200, $[\Theta]_{282}$ + 5730. IR ν_{max} cm^{-1}: 2930, 1515, 1480, 1035, 940 (–OCH_2O–). EIMS 70 eV, *m/z* (rel. int.): 285 $[M]^+$ (80), 270 (31), 254 (38), 230 $[M - C_3H_5N]^+$ (19), 215 $[M - C_3H_5N - Me]^+$ (100), 201 (29), 185 (29), 172 (24), 167 (24), 157 (40), 149 (41), 129 (35), 128 (35), 115 (54). ^1H NMR (500 MHz, $CDCl_3$), see Table 1. ^{13}C NMR (50 MHz, $CDCl_3$), see Table 2.

Montabuphine (**3**). Found: C, 67.55; H, 6.30; N, 4.63. $C_{17}H_{19}NO_4$ requires: C, 67.77; H, 6.31; N, 4.65%. Mp 162–164°. $[\alpha]_D^{22}$ + 157° (EtOH; *c* 0.106). CD $[\Theta]_{291}$ + 3180 $[\Theta]_{252}$ + 21922, $[\Theta]_{241}$ − 2940, $[\Theta]_{239}$ + 3066. IR ν_{max} cm^{-1}: 2400–3100 (–OH), 2925, 1683, 1481, 1234, 1091, 1037, 935 (–OCH_2O–), 768. EIMS 70 eV, *m/z* (rel. int.): 301 $[M]^+$ (100), 300 (35), 286 (27), 270 (26), 243 $[C_{14}H_{13}NO_3]^+$ (47), 242 (27), 241 (29), 226 (20), 223 (29), 215 (20), 214 (41), 212 (21), 199 (44), 185 $[C_{12}H_9O_2]^+$ (62), 141 (24), 129 (22), 128 (34), 127 (24), 115 (44). ^1H NMR (500 MHz, $CDCl_3$): δ1.58 (1H, *ddd*, J = 1.5, 13.0, 13.0 Hz, H-4*ax*), 2.70 (1H, *ddd*, J = 4.5, 4.5, 13.0 Hz, H-4*eq*), 3.07 (1H, *d*, J = 11.0 Hz, H-12*ax*), 3.11 (1H, *dd*, J = 2.0, 11.0 Hz, H-12*eq*), 3.30 (1H, *d*, J = 2.0 Hz, H-11), 3.39 (3H, *s*, 3-OMe), 3.54 (1H, *brd*, J = 13.0 Hz, H-4a), 3.70 (1H, *ddd*, J = 1.5, 4.5, 5.0 Hz, H-3), 3.87 (1H, *d*, J = 16.5 Hz, H-6β), 4.18 (1H, *ddd*, J = 2.5, 3.5, 5.0 Hz, H-2), 4.38 (1H, *d*, J = 16.5 Hz, H-6α), 5.53 (1H, *dd*, J = 2.0, 2.5 Hz, H-1), 5.86–5.88 (2H, 2*d*, J = 1.5 Hz, OCH_2O), 6.46 (1H, *s*, H-7), 6.54 (1H, *s*, H-10). ^{13}C NMR (50 MHz, $CDCl_3$): δ31.6 (*t*, C-4), 44.8 (*d*, C-11), 55.1 (*t*, C-12), 57.4 (*q*, 3-OMe), 58.7 (*d*, C-4a), 60.0 (*t*, C-6), 67.8 (*d*, C-2), 77.0 (*d*, C-3), 100.8 (*t*, OCH_2O), 106.7 (*d*, C-7), 107.6 (*d*, C-10), 117.6 (*d*, C-1), 122.6 (*s*, C-6a), 130.9 (*s*, C-10a), 146.3 (*s*, C-9), 146.9 (*s*, C-8), 150.8 (*s*, C-11a).

Buflavine (**4**). Found: C, 75.99; H, 7.38; N, 4.90. $C_{18}H_{21}NO_2$ requires: C, 76.33; H, 7.42; N, 4.95%. Mp 106–108°. IR ν_{max} cm^{-1}: 3400, 2932, 1601, 1518, 1465, 1252, 1144, 1024, 860, 751. EIMS 70 eV, *m/z* (rel. int.): 283 $[M]^+$ (94), 282 (21), 268 (59), 241 (24), 240 (100), 226 (19) 225 (81), 197 (49), 195 (16), 182 (20), 181 (15), 179 (58), 178 (20), 167 (21), 166 (19), 165 (49), 154 (20), 153 (35), 152 (35), 115 (14). ^1H NMR (500 MHz, $CDCl_3$), see Table 3. ^{13}C NMR (50 MHz, $CDCl_3$), see Table 4.

8-*O-demethylbuflavine* (**5**). Found: C, 75.62; H, 7.10; N, 5.14. $C_{17}H_{19}NO_2$ requires: C, 75.84; H, 7.06; N, 5.20%. Mp 112–114°. IR ν_{max} cm^{-1}: 3320, 2925, 1739, 1511, 1447 1235, 1035, 874, 756. EIMS 70 eV, *m/z* (rel. int.): 269 $[M]^+$ (83), 268 (46), 254 (43), 240 (11), 227 (20), 226 (100), 225 (31), 211 (88), 195 (30), 194 (27), 183 (45), 181 (20), 166 (36), 165 (85), 155 (21), 153 (35), 152 (36), 141 (23), 115 (35). ^1H NMR (500 MHz, $CDCl_3$), see Table 3. ^{13}C NMR (50 MHz, $CDCl_3$), see Table 4.

5,6-*Dihydrobicolorine* [21], *lycorine* [1, 22], *hamayne* [23], 3-*O-acetylhamayne* [23], *crinamine* [24, 25, 26], *crinine* [14], *buphanisine* [14], *undulatine* [14], *and augustine* [1, 27]. These were identified by a comparison of their chromatographic and spectroscopic properties (TLC, IR, CD, MS, ^1H and ^{13}C NMR) with those of authentic samples obtained from other plant sources.

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