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ISOLATION OF STERNBERGINE, A NEW ALKALOID FROM BULBS OF *STERNBERGIA LUTEA*

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ABSTRACT.—The bulbs of *Sternbergia lutea* were found to contain a new phenolic base, named sternbergine (**3**), as well as the previously isolated alkaloids, lycorine, tazettine, hippeastrine, galanthine, galanthamine, haemanthidine, and hippamine. Sternbergine has been shown to be 1-*O*-acetyl-isopseudolycorine. The structure proposed was confirmed by conversion of **3** to methylpseudolycorine.

Sternbergia lutea Ker-Gawl,[1] belonging to the family Amaryllidaceae (6), is a wild species indigenous to the Mediterranean area. Earlier authors reported the isolation from this plant of a variety of alkaloids (5); the main component among these, lycorine (**1**) (7), presents marked biological activities (8-10). A re-examination of acid extracts of *S. lutea* bulbs led us to isolate two more alkaloids. The first compound was recently identified as hippamine (**2**) (11), the second was a new alkaloid named sternbergine (**3**).

In this paper we report the structure of sternbergine and discuss the spectroscopic data of some pseudolycorine (**4**) (12) derivatives.

RESULTS AND DISCUSSION

The extraction was carried out as already described (13), with some minor modification in order to avoid the deacetylation of sternbergine in alkaline solutions.

Alkaloid fractionation was achieved by a combination of column and thin layer chromatography on SiO_2. This latter allowed the separation of sternbergine from hippamine.

The quantification of sternbergine by hplc enabled us to estimate the yield of sternbergine from plant material. Of the total amount of sternbergine present in the acid extracts, 58% was recovered as pure product by this procedure, in comparison with a yield of 5.4% obtained by applying the method previously described (13).

Sternbergine was a crystalline compound soluble in ordinary organic solvents and in dilute mineral acids and became red with $FeCl_3$, indicating the presence of a phenolic hydroxyl group.

The mass spectrum showed the molecular ion peak at 331 *m/z*; other significant peaks at *m/z* 314, 270, 254, and 252 and two very strong peaks at *m/z* 229 and 228. The peaks at *m/z* 228, 229, 252, and 254 were in agreement with the fragmentation scheme proposed for lycorine-type alkaloids (14, 15). The ir spectrum indicated, in particular, the presence of hydroxyl groups and a carbonyl group. The uv spectrum showed a strong absorption with a maximum at 286 nm.

The ^{1}H-nmr spectrum (Table 1) was consistent with a lycorine-type structure except for the absence of a dioxole ring. The proton shifts were assigned by considering the integration and multiplicity of the signals and by nuclear magnetic double resonance. The pattern of the signals provided further information. The signal (3H, singlet) at δ 1.91 is due to an acetyl group, which is probably attached to the C-ring; in fact, only one of the two protons bonded to aliphatic oxygenated carbons was

[1]It is not clear if *Sternbergia lutea* Ker-Gawl and *Sternbergia lutea* (L) Roem et Shult (1, 2) are the same plant or a variety of the same species (3); according to G.K. Phokas (4, 5) *Sternbergia sicula* Tin is a different species.

TABLE 1. Proton Shifts of Sternbergine (**3**[a])

H-1	5.76	dd[b]	$J_{1\text{-}2}=2.2, J_{1\text{-}11b}=2.2$ Hz
H-2	4.16	m	$J_{1\text{-}2}=2.2$ Hz; $J_{2\text{-}3}=3.3$ Hz
H-3	5.56	m	$J_{2\text{-}3}=3.3$ Hz, $J_{3\text{-}11c}=2.6$ Hz
2H-4	2.63	m	
2H-5	3.38	ddd } AX	$J_{AX}=8.8$ Hz
	2.39	br q } AX	
2H-7	4.14	d } AX	$J_{AX}=14.0$ Hz
	3.49	dd[b] } AX	$J_{AX}=14.0$ Hz, $J_{7A\text{-}11b}=2.6$ Hz
H-8	6.64	s	
H-11	6.70	s	
H-11b	2.92	ddd[b] } AB	J_{AB} 10.6 Hz, $J_{1\text{-}11b}=2.2$ Hz, $J_{7A\text{-}11b}=2.6$ Hz
H-11c	2.76	dd[b] } AB	$J_{AB}=10.6$ Hz, $J_{3\text{-}11c}=2.6$ Hz
OMe	3.80	s	
MeCO	1.91	s	
ArOH	7.35	s	

[a]Chemical shifts in δ-values (ppm) from TMS ($CDCl_3$).
[b]These multiplicities were observed in the ^{1}H-resolution enhanced spectrum.

deshielded. In addition, a singlet (3H) at δ 3.80 indicated the presence of a methoxy group attached to the aromatic ring.

The acetyl group was located on C-1 by the evidence obtained from ^{1}H-nOe difference spectra (Table 2). Results *a* and *c* allowed us to established spatial proximity between protons H-1 (δ 5.76) and H-11 (δ 6.70). Results *b* and *d* indicated that the methoxy group is located at C-10. These results suggest structure **3** for sternbergine.

TABLE 2. Nuclear Overhauser Effects Measured on **3** ($CDCl_3$)

Irradiated		Observed
6.70 (H-11)	*a*	5.76 (H-1)
	b	3.80 (OMe)
5.76 (H-1)	*c*	6.70 (H-11)
3.80 (OMe)	*d*	6.70 (H-11)

The ^{13}C-nmr data reported in Table 3 were in agreement with the proposed structure. The carbon shifts were assigned using proton noise decoupled and single frequency off-resonance decoupled spectra, attached proton test, and by single frequency selective decoupled spectra. The assignment of quaternary aromatic carbon resonances was made by comparison with the reported chemical shifts of the carbons of the corresponding ring of lycorine (16) and by measuring the residual splittings (J^3_{CH}).

Unequivocal evidence for the presence of a phenolic hydroxy group was obtained by transformation of **3** to **5** by treating with an ethanolic solution of 1-fluoro-2,4-dinitrobenzene (FDNB) according to the Sanger procedure (17). The ^{1}H-nmr of **5** was very similar to that of **3** except for the downfield shift observed for H-11 and H-8 (Δδ 0.25 and 0.33 ppm, respectively) and for the presence of a signal pattern typical of a 2,4-disubstituted benzene ring.

Further support for the structure assigned to sternbergine was obtained by treating **3** with ethanolic KOH in order to compare the deacetylated product with pseudolycorine (**4**). The deacetylated product obtained, to which structure **6** can be at-

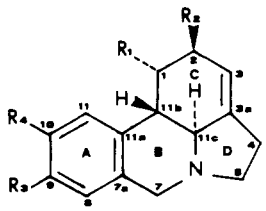
TABLE 3. ^{13}C-nmr Chemical Shift Assignments, in δ-Values (ppm) from TMS, for Sternbergine (**3**) ($CDCl_3$)

C-1	72.1	d	C-9	145.4	s[a]
C-2	69.6	d	C-10	143.6	s[a]
C-3	117.4	d	C-11	107.4	d
C-3a	144.1	s[a]	C-11a	124.9	s[a]
C-4	28.4	t	C-11b	39.0	d
C-5	56.1	t	C-11c	61.7	d
C-7	53.7	t	OCH_3	55.9	q
C-7a	128.4	s[a]	C=O	170.6	s
C-8	113.2	d	CH_3	21.0	q

[a]Assignment given by measuring the residual splitting (J^3_{CH}) and by comparison with available data for lycorine (16).

tributed, was compared with an authentic sample of pseudolycorine; different mp, $[\alpha]^{25}D$ [for **4**, lit. (18) reports mp 245° and $[\alpha]^{25}D$ −41.5°], and Rf values in two tlc systems were observed for the two products. Further, evidence that the deacetyl derivative of **3** was a structural isomer of **4** was obtained by comparing the diacetyl derivative of **3** (**7**) with the triacetyl derivative of **4** (**8**). The two derivatives (**7** and **8**) showed different Rf values in three solvent systems. Furthermore, in the ^{1}H-nmr spectrum of **7**, as compared to that of **3**, the signals of H-2 and H-8 were deshielded (Δδ 1.09 and 0.24 ppm respectively), whereas in the ^{1}H-nmr spectrum of **8** downfield shifts were observed, with reference to that of **3**, for H-2 and H-11 (Δδ 1.09 and 0.20 ppm, respectively).

Sternbergine was finally converted into methylpseudolycorine (**9**) (12, 18) by treatment of **3** with an ethereal solution of CH_2N_2. The presence of traces of KOH in the ethereal solution of CH_2N_2 was probably responsible for the deacetylation which took place on **3** during the methylation of the phenolic hydroxy group. Compound **9** exhibited similar mp, $[\alpha]^{25}D$, and uv spectrum to those reported for methylpseudolycorine from natural sources (18) and to the product obtained by performing the same procedure on **4**. The derivatives obtained by methylation of **3** and **4** showed the same Rf in three different tlc systems and similar ^{1}H-nmr spectra. The ^{1}H-nmr spectrum of **9**,

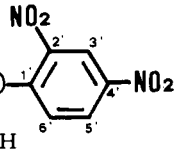


1 R_1=OH R_2=OH R_3,R_4=OCH_2O

2 R_1=OH R_2=OCH_3 R_3,R_4=OCH_2O

3 R_1=OAc R_2=OH R_3=OH R_4=OCH_3

4 R_1=OH R_2=OH R_3=OCH_3 R_4=OH



5 R_1=OAc R_2=OH R_3= R_4=OCH_3

6 R_1=OH R_2=OH R_3=OH R_4=OCH_3

7 R_1=OAc R_2=OAc R_3=OAc R_4=OCH_3

8 R_1=OAc R_2=OAc R_3=OCH_3 R_4=OAc

9 R_1=OH R_2=OH R_3=OCH_3 R_4=OCH_3

showed, as compared with that of **3**, the presence of a singlet at δ 3.85, due to the second methoxy group, the deshielding of H-8 (Δδ 0.32 ppm) and the absence of the singlet due to the acetyl group.

These results are in agreement with structure **4** for pseudolycorine, an alkaloid extracted for the first time from *Lycoris radiata* (19). This structure was proposed by Fales (18) and established by Uyeo, (cited in 12), on the basis of chemical data.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURE.—Melting points are uncorrected, optical rotations were measured on a Perkin-Elmer 141 polarimeter; ir spectra were recorded on a Perkin-Elmer 399 instrument for solutions in $CHCl_3$; uv spectra were measured on a Varian-Cary 210 spectrophotometer. ^{1}H-nmr spectra were recorded at 270 MHz on a Bruker spectrometer; ^{13}C-nmr were recorded at 50.305 MHz on a Varian XL-200 spectrometer; chemical shifts are in ppm. Mass spectra were recorded on an AEI MS-30 mass spectrometer with electron impact ionization at 70 eV. Hplc analyses were performed on a Perkin-Elmer C18/10 stainless steel column (250 × 4.6 mm i.d.) using a Perkin-Elmer series 3B liquid chromatography, equipped with a LC-75 spectrophotometric detector at 286 nm with LC autocontrol and a Perkin-Elmer 10B chromatography data station. Analytical and preparative tlc were performed on SiO_2 plates (Merck, Kieselgel 60 F_{254}, 0.25 and 2 mm respectively); the spots were visualized by exposure to I_2 vapour or uv radiation. Column chromatography was carried out on SiO_2 (Merck, Kieselgel 60, 0.063-0.2 mm).

PLANT MATERIAL.—*Sternbergia lutea* Ker-Gawl was collected near Bari and identified by Prof. O. Arrigoni, Istituto di Botanica, Università di Bari, Italy, where a voucher specimen has been deposited.

EXTRACTION AND FRACTIONATION OF ALKALOIDS.—Dried and ground bulbs (1 kg) of *S. lutea*, collected during the withering period were extracted with 1% H_2SO_4 (3 liters). The mixture was kept overnight at room temperature, then the liquid phase was squeezed out through a cloth bag. This extraction procedure was repeated twice. The combined acid extracts (7.58 liters) were decanted, centrifuged at 7520 × *g* for 30 min, and then neutralized with 4 N NaOH. The aqueous solution was extracted with EtOAc (3 × 2.5 liters), and the combined organic extracts were dried and concentrated under reduced pressure. The residue (1.198 g) containing lycorine (**1**) as the main component was fractionated by column chromatography eluting with $CHCl_3$-EtOAc-MeOH (2:2:1). Compound **3** was eluted together with hippamine (**2**); the chromatographically homogeneous fractions were combined and concentrated to give an oily residue (201.6 mg). The mixture was separated by preparative tlc using $CHCl_3$-MeOH (9:1). The upper zone afforded pure **2** (39.0 mg), whereas while the lower one furnished pure **3** as oil (27.0 mg). The central zone gave **2** mixed with **3** (91.0 mg); this was further purified by the same procedure to give 59.3 mg of **3**. The crude sternbergine (total 86.3 mg) crystallized from $CHCl_3$.

Sternbergine (1-O-acetyl-isopseudolycorine) (**3**).—White needles mp 105-112° (from $CHCl_3$) recrystallized on the hot-stage and remelted at 197-202°; $[\alpha]^{25}D$ −78.8° (=0.7, $CHCl_3$); uv λ max (CH_3CN) nm (log ε) 286 (3.51), 222 (3.90); ir ν max 3595, 3540, 1730, 1600, 1020 cm^{-1}; ^{1}H- and ^{13}C-nmr spectra are reported in Tables 1 and 3 respectively; ms *m/z* (rel. int.) 331 (M^+) (50), 314 (0.2), 270 (40), 254 (14), 252 (18), 229 (95), 228 (100), 43 (18), in hplc analysis, the retention time of a pure sample of **3** was 9.30 min when a mixture of 0.01 M ammonium carbonate-acetonitrile 8:2 at a flow rate of 2.5 ml/min was used; the minimum detectable amount was 10 ng. The true amount of **3** present in acid extracts of *S. lutea* bulbs was 14.8 mg in 100 g of dry material.

9-DNP-sternbergine (**5**).—To a solution of **3** (10.1 mg) and $NaHCO_3$ (10 mg) in H_2O (1 ml) were added 200 μl of 5% ethanolic solution of FDNB. The mixture was stirred at room temperature. After 2 h, the reaction was stopped with 6N HCl adjusting the pH to ~7. The solution was diluted with H_2O (30 ml) and extracted with $CHCl_3$ (3 × 50 ml). The combined extracts were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. Preparative tlc of the residue eluted with $CHCl_3$-MeOH (9:1) afforded pure **5** as an oil (8.2 mg, 53%): $[\alpha]^{25}D$ −21.9° (c=0.75, EtOH); uv λ max (EtOH) nm (log ε) 285 (3.79), 250 (3.70); ir ν max 1730, 1620, 1607, 1020 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 8.85 (d, *J*=2.6 Hz, H-3′), 8.28 (dd, *J*=2.6, 9.2 Hz, H-5′), 6.97 (s, H-8 or H-11), 6.95 (s, H-11 or H-8), 6.89 (d, *J*=9.2 Hz, H-6′), 5.85 (dd, *J*=2.2, 2.2 Hz, H-1), 5.61 (m, *J*=3.3, 2.6 Hz, H-3), 4.25 (m, *J*=2.2, 3.3 Hz, H-2), 4.23 (d, *J*=14.0 Hz, H-7X), 3.72 (s, 3H, OMe), 3.57 (dd, *J*=14.0, 2.6 Hz, H-7A), 3.40 (ddd, *J*=8.1 Hz, H-5X), 3.00 (ddd, *J*=10.6, 2.2, 2.6 Hz, H-11b), 2.82 (dd, *J*=10.6, 2.6 Hz, H-11c), 2.68 (m, 2H, H-4), 2.44 (br q, *J*=8.1 Hz, H-5A), 1.96 (s, 3H, MeCO); ms *m/z* (rel. int.) 497 (M^+) (33), 480 (0.8), 467 (7), 395 (12), 394 (12), 365 (8.4), 364 (7.5), 331 (15), 270 (24.2), 229 (27), 228 (100).

Deacetylation of sternbergine to **6**.—Sternbergine (27 mg) was hydrolysed under reflux in 5% ethanolic KOH for 0.5 h. After cooling, the mixture was cautiously neutralized with 12 N HCl. The NaCl was re-

moved by filtration, and the filtrate was evaporated under reduced pressure. Purification of the residue by column chromatography ($CHCl_3$-EtOAc-MeOH, 1:1:1) afforded pure **6** as a solid (19.6 mg, 83%): mp 255-258°; $[\alpha]^{25}D$ −36.8° (c=0.79, EtOH); uv λ max (EtOH) nm (log ε) 286, (3.55) 221 (3.85); ^{1}H-nmr (CD_3OD) δ 6.93 (s, H-8 or H-11), 6.62 (s, H-11 or H-8), 5.58 (m, *J*=3.3, 2.6 Hz, H-3), 4.53 (dd, *J*=2.2, 2.2 Hz, H-1), 4.19 (m, *J*=2.2, 3.3 Hz, H-2), 4.10 (d, *J*=14.0 Hz, H-7X), 3.87 (s, 3H, OMe), 3,63 (dd, *J*=14.0, 2.6 Hz, H-7A), 3.36 (ddd, *J*=8.1 Hz, H-5X), 3.01 (dd, *J*=11.0, 2.6, H-11c), 2.76 (ddd, *J*=11.0, 2.2, 2.6 Hz, H-11b), 2.69 (m, H-4A), 2.60 (m, H-4B), 2.58 (br q, *J*=8.1 Hz, H-5A); ms *m/z* (rel. int.) 289 (M^+) (38), 270 (28), 229 (94), 228 (100).

2,9-O,O′-diacetyl-sternbergine (**7**).—Acetylation of **3** (12 mg) was performed in the usual way with AC_2O (200 μl) and pyridine (200 μl). After 12 h, the reaction mixture was poured into ice cold H_2O, neutralized with 0.1 N NaOH and extracted with $CHCl_3$ (3 × 20 ml). The combined extracts were dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The pyridine was removed by evaporation of the azeotrope formed with C_6H_6. Purification of the residue by column chromatography ($CHCl_3$-*iso*-Pr, 95:5) afforded pure oily **7** (8.8 mg, 60%): $[\alpha]^{25}D$ +11.7° (c=1.2, $CHCl_3$); uv λ max (CH_3CN) nm (log ε) 280 (3.40); ir ν max 1755, 1735, 1620, 1020 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 6.88 (s, H-8 or H-11), 6.78 (s, H-11 or H-8), 5.87 (dd, *J*=2.2, 2.2 Hz, H-1), 5.53 (m, *J*=3.3, 2.6 Hz, H-3), 5.25 (m, *J*=2.2, 3.3 Hz, H-2), 4.17 (d, *J*=14.0 Hz, H-7X), 3.79 (s, 3H, OMe), 3.54 (dd, *J*=14.0, 2.6 Hz, H-7A), 3.38 (ddd, *J*=8.1 Hz, H-5X), 2.94 (ddd, *J*=10.6, 2.2, 2.6 Hz, H-11b), 2.78 (dd, *J*=10.6, 2.6 Hz, H-11c), 2.65 (m, 2H, H-4), 2.41 (br q, *J*=8.1 Hz, H-5A), 2.29 (s, 3H, MeCO), 2.09 (s, 3H, MeCO), 1.94 (s, 3H, MeCO); ms *m/z* (rel. int.) 415 (M^+) (18), 386 (0.3), 372 (2.7), 355 (11), 312 (7.6), 295 (100), 271 (11), 270 (10), 254 (22), 252 (37).

1,2,10-O,O′,O″-triacetyl-pseudolyucorine (**8**).—The compound **8** was prepared from 10 mg of **4** according to the described procedure used to obtain **7** from **3**. The reaction afforded a chromatographically homogeneous oil (10.2 mg, 76%): $[\alpha]^{25}D$ +22.2° (c=0.82, $CHCl_3$); uv λ max (CH_3CN) nm (log ε) 277 (3.4); ir ν max 1755, 1735, 1620, 1020 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 6.90 (s, H-11 or H-8), 6.69 (s, H-8 or H-11), 5.72 (dd, *J*=2.2, 2.2 Hz, H-1), 5.52 (m, *J*=3.3, 2.6 Hz, H-3), 5.25 (m, *J*=2.2, 3.3 Hz, H-2), 4.24 (d, *J*=14.0 Hz, H-7X), 3.76 (s, 3H, OMe), 3.58 (dd, *J*=14.0, 2.6 Hz, H-7A), 3.39 (ddd, *J*=8.1 Hz, H-5X), 2.90 (ddd, *J*=10.6, 2.2, 2.6 Hz, H-11b), 2.77 (dd, *J*=10.6, 2.6 Hz, H-11c), 2.65 (m, 2H, H-4), 2.41 (br q, *J*=8.1 Hz, H-5A), 2.29 (s, 3H, MeCO), 2.07 (s, 3H, MeCO), 1.92 (s, 3H, MeCO); ms *m/z* (rel. int.) 415 (M^+) (10), 372 (1.5), 355 (10), 312 (6.1), 295 (100), 271 (8.8), 270 (11.1), 254 (20), 252 (37).

Conversion of **3** *to methylpseudolycorine* (**9**).—To a solution of **3** (18 mg) in MeOH (2.5 ml) was added ethereal CH_2N_2 (5 ml). The mixture was allowed to stand at room temperature for four days and then evaporated under a stream of nitrogen. Purification of the residue by preparative tlc ($CHCl_3$-MeOH, 9:1) afforded an oil (14.4 mg, 87%), which crystallized from MeOH, mp 222-226°; $[\alpha]^{25}D$ −43.0° (c=0.4, EtOH); uv λ max (EtOH) nm (log ε) 283 (3.51) [lit. (18) mp 228-233°; $[\alpha]^{25}D$ −40°; λ max nm (log ε) 285 (3.58)]; ^{1}H-nmr (CD_3OD) δ 6.96 (s, H-8 or H-11), 6.75 (s, H-11 or H-8), 5.55 (m, *J*=3.3, 2.6 Hz, H-3), 4.53 (dd, *J*=2.2, 2.2 Hz, H-1), 4.18 (m, *J*=2.2, 3.3 Hz, H-2), 4.16 (d, *J*=14.0 Hz, H-7X), 3.85 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.55 (dd, *J*=14.0, 2.6 Hz, H-7A), 3.35 (ddd, *J*=8.8 Hz, H-5X), 2.87 (dd, *J*=10.6, 2.6 Hz, H-11c), 2.76 (ddd, *J*=10.6, 2.2, 2.6 Hz, H-11b), 2.64 (m, 2H, H-4), 2.42 (br q, *J*=8.8 Hz, H-5A); ms *m/z* (rel. int.) 303 (M^+) (58), 284 (42), 243 (96), 242 (100).

Conversion of pseudolycorine **4** to **9**.—The compound **9** was also prepared from 13.1 mg of **4** according to the procedure used for the preparation of **9** from **3**. The oil obtained (12.6 mg, 91%) crystallized from MeOH affording a solid with mp 222-228°, $[\alpha]^{25}D$ −41.0 (c=0.37, EtOH) and spectral values similar to those reported for **9** prepared from **3**.

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