C17	0.7129 (4)	0.6984	0.3120 (4)	0.044 (2)
C27	0.6953 (4)	0.7286 (3)	0.3871 (4)	0.047 (2)
O27	0.7429 (3)	0.7099 (3)	0.4726 (3)	0.048 (1)
C37	0.6156 (3)	0.7209 (3)	0.3772 (4)	0.040 (1)
O37	0.5990 (2)	0.7517 (3)	0.4450 (3)	0.046 (1)
C47	0.5703 (3)	0.7419 (3)	0.2849 (4)	0.040 (2)
C57	0.5911 (3)	0.7147 (3)	0.2101 (4)	0.045 (2)
C67	0.5542 (4)	0.7396 (4)	0.1175 (5)	0.054 (2)
O67	0.5671 (2)	0.7968 (3)	0.1186 (3)	0.060 (1)
O57	0.6697 (2)	0.7194 (3)	0.2276 (3)	0.048 (1)
O47	0.4934 (2)	0.7283 (3)	0.2727 (3)	0.041 (1)
OET	0.429 (3)	0.203 (2)	0.057 (4)	0.45 (3)†
CET1O	0.370 (1)	0.183 (1)	0.075 (2)	0.115 (7)†
CET2O	0.331 (2)	0.1931 (13)	0.139 (2)	0.15 (1)†
OW61A	0.3595 (13)	0.2758 (10)	−0.0627 (12)	0.100 (8)
OW62A	0	0.4599 (3)	0	0.050 (2)
OW62B	1/2	0.1332 (8)	0	0.208 (9)
OW62C	0.4235 (6)	0.0265 (4)	0.1831 (6)	0.140 (3)
OW63	0.0446 (2)	0.3723 (3)	0.9168 (3)	0.049 (1)
OW64A	0.471 (2)	0.1826 (17)	0.152 (3)	0.22 (3)
OW65A	0.1052 (3)	0.4188 (3)	0.7975 (4)	0.077 (2)
OW66C	0.4110 (17)	0.1374 (12)	0.213 (2)	0.118 (9)†
OW21	0.0887 (3)	0.3731 (3)	0.5262 (4)	0.080 (2)
OW22	0.4411 (9)	0.1745 (7)	0.6189 (13)	0.164 (7)
OW23	0.0243 (4)	0.3948 (4)	0.3403 (6)	0.082 (2)
OW24	0.4097 (4)	0.1793 (4)	0.4666 (8)	0.119 (4)
OW26	0	0.4765 (6)	1/2	0.139 (5)
OW32	0.4870 (5)	0.0415 (6)	0.6362 (9)	0.184 (5)
OG	0.4590	0.6150	1.0380	0.19 (2)†
CG1	0.4990	0.6030	0.9820	0.34 (4)†
CG2	0.5470	0.5590	0.9550	0.17 (2)†
CG3	0.5180	0.5430	0.8520	0.15 (1)†
CG4	0.5600	0.5040	0.8050	0.27 (2)†
CG5	0.6070	0.5120	0.7380	0.31 (3)†
CG6	0.6030	0.5050	0.6360	0.37 (3)†
CG7	0.5510	0.4630	0.5780	0.32 (3)†
CG8	0.5890	0.4550	0.5080	0.29 (3)†
CG9	0.6500	0.4960	0.5140	0.20 (1)†
CG10	0.6400	0.5510	0.5160	0.51 (6)†
CG11	0.5880	0.5980	0.5210	0.28 (2)†
CG12	0.5140	0.6280	0.4710	0.26 (2)†
CX2	0.6820	0.4840	0.9430	0.16 (2)†
CX3	0.6060	0.5090	0.8960	0.23 (4)†

† U_{iso}.

Table 2. *Torsion angles of the primary hydroxy groups (°)*

	n = 1	*n* = 2	*n* = 3	*n* = 4	*n* = 5	*n* = 6	*n* = 7	Site
C4—C5—C6—O6	63	56	63	48	64	72	54	*A*
C4—C5—C6—O6	160			146	−169	−173		*B*
C4—C5—C6—O6						31		*C*
O5—C5—C6—O6	−58	−64	−60	−70	−58	−50	−67	*A*
O5—C5—C6—O6	38			26	70	66		*B*
O5—C5—C6—O6						−90		*C*

There was an absence of significant decay shown by comparison of equivalent reflections recorded near the beginning and end of data collection. Total measuring time was 8 h. The coordinates of the isomorphous 3,3-dimethylbutylamine β-CD complex (Mavridis, Hadjoudis & Tsoucaris, 1991) were used as initial coordinates for the skeleton atoms of β-CD. Subsequent $\Delta\rho$ maps revealed the primary C and O atoms as well as the atoms of the guest, water and ethanol molecules. The coordinates of the guest molecule have been optimized by fitting in the difference electron density map using the molecular graphics *O Molecular-Modelling Program* (Jones & Kjeldgaad, 1993), on a Crimson Silicon Graphics workstation; subsequently, they were kept constant during the final stages of the refinement. 12 H atoms belonging to hydroxy groups or water molecules were found from $\Delta\rho$ maps but their coordinates were not refined. The disordered O atoms were refined isotropically.

Data collection: *MADNES* (Pflugrath & Messerschmitt, 1991). Cell refinement: *MADNES*. Data reduction: *MADNES*. Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *O* (Jones & Kjeldgaad, 1993). Software used to prepare material for publication: *SHELXL*93 (Sheldrick, 1993).

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: PA1191). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

Harada, A., Li, J. & Kamachi, M. (1993). *Nature (London)*. **364**, 516–518.

Jones, T. A. & Kjeldgaad, M. (1993). *O*. Version 5.9. *Molecular-Modelling Program*. Upsala, Sweden.

Isnin, R. & Kaifer, A. E. (1991). *J. Am. Chem. Soc.* **113**, 8188–8190.

Li, G. & McGown, L. B. (1994). *Science*. **264**, 249–251.

Mavridis, I. M., Hadjoudis, E. & Tsoucaris, G. (1991). *Carbohydr. Res.* 220, 11–21.

Mentzafos, D., Mavridis, I. M., Le Bas, G. & Tsoucaris, G. (1991). *Acta Cryst.* B**47**, 746–757.

Mentzafos, D., Mavridis, I. M. & Schenk, H. (1994). *Carbohydr. Res.* **253**, 39–50.

Pflugrath, J. & Messerschmitt, A. (1991). *MADNES*. Small-molecule version. Enraf–Nonius, Delft, The Netherlands.

Sheldrick, G. M. (1993). *SHELXL*93. *Program for the Refinement of Crystal Structures*. University of Göttingen, Germany.

Wenz, G. & Keller, B. (1993). *Angew. Chem. Int. Ed. Engl.* **31**, 2, 197–199.

Acta Cryst. (1996). C**52**, 1223–1225

cis-8,10-Di-*n*-propyllobelidiol Hydrochloride Dihydrate

OBDULIO G. MIGUEL,[a] MOACIR G. PIZZOLATTI,[a] ROSENDO A. YUNES,[a] IVO VENCATO,[b] JOÃO B. CALIXTO,[c] ADAIR R. S. SANTOS,[c] ADRIANA CONTIN[d] AND EDUARDO A. MOREIRA[d]

[a]*Depto. Química, UFSC, 88040-900, Florianópolis, SC, Brazil,* [b]*Depto. Física, UFSC, 88040-900, Florianópolis, SC, Brazil,* [c]*Depto. Farmacologia, UFSC, 88040-900, Florianópolis, SC, Brazil, and* [d]*Depto. Farmácia, UFPR, 80420-170, Curitiba, PR, Brazil. E-mail: fsc1ivo@ibm.ufsc.br*

(*Received 9 May 1995; accepted 23 October 1995*)

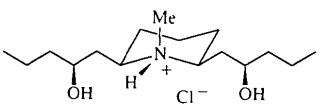
Abstract

The definitive structure and the relative configuration of the title compound, perhydro-2(*R*)-[2(*S*)-hydroxypentyl]-6(*S*)-[2(*R*)-hydroxypentyl]-*N*-methylpyridinium chloride dihydrate, $C_{16}H_{34}NO_2^+.Cl^-.2H_2O$, a new alkaloid iso-

lated from *Siphocampylus verticillatus* that exhibits a potent antinociceptive activity, has been determined.

Comment

The title compound, (I), the major alkaloid isolated from *Siphocampylus verticillatus* (*Campanulaceae*), is a compound of considerable pharmacological interest. We have demonstrated recently that it produces a dose-related antinociceptive activity in several models of nociception in mice (Santos *et al.*, 1995). Its analgesic activity, like that caused by morphine, was completely reversed by naloxone, a nonselective opioid antagonist, suggesting its possible interaction with the opioid receptor.



(I)

Piperidine alkaloids such as lobeline, lelobanonoline, lobelanine and lobelanidine have been obtained from lobelia (Manske & Holmes, 1968; Williams, Ray & Kim, 1987; Zhang, Wang & Zhou, 1990). Early studies of this species indicated the presence of an alkaloid of undetermined structure, denoted sifocampilin (Garello, 1950). The structure of (I), without the explicit definition of the relative configuration, was recently proposed (Biavatti, Brown, Contin, Leonart & Santos, 1994) on the basis of ^1H and ^{13}C NMR spectroscopy. It is important to note that solution NMR spectroscopic results using techniques such as DEPT and COSY do not give a definitive proof of the proposed structure, especially regarding the stereochemistry. It is well known that much of the biological activity of organic molecules depends on their stereochemistry. Therefore, knowledge of the stereochemistry of the substituents of (I) is of great interest since this would augment a developing understanding of its antinociceptive mechanism of action. For this reason, the X-ray structure analysis was undertaken in order to confirm the proposed structure of (I) and to determine the relative configuration of its substituents.

The structure of the alkaloid has no resemblance to that of naloxone. In fact, naloxone acts as a morphine antagonist, while the alkaloid seems to produce antinociception through a mechanism that involves, at least in part, the opioid system, because its analgesic response, like those produced by morphine, was completely reversed when animals were pretreated with naloxone.

The piperidine ring has a normal almost undistorted chair conformation. The thermal motion of the atoms C1, C2, C14 and C15 is quite high, resulting in unusual bond lengths involving these atoms. It is worthwhile to consider the possibility of slight disorder in the chains near their ends. Molecules are linked through a hydrogen-bonding network in which the water molecules and the N—HN group of the piperidine ring act as proton donors to the Cl^- ion, and both hydroxy groups, O1—HO1 and O2—HO2, act as proton donors to water molecules. The water molecules also act as proton donors towards hydroxy groups. Details of the hydrogen-bonding geometry are given in Table 3 and Fig. 2.

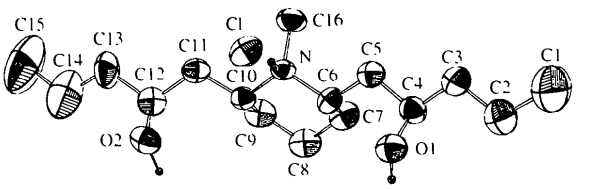


Fig. 1. Perspective view of the anion–cation pair of (I) with atomic numbering scheme. The displacement ellipsoids are drawn at the 50% probability level. The H atoms of only the NH and OH groups are shown for clarity.

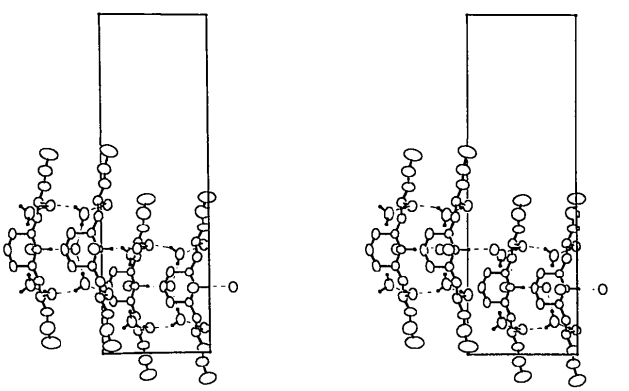


Fig. 2. Stereodrawing showing the hydrogen bonds, indicated by broken lines. The *b* axis is vertical and the *a* axis is horizontal pointing to the right.

Experimental

The compound was obtained from crude methanolic extract of the roots, stems and leaves of *Siphocampylus verticillatus* (*Campanulaceae*), by fractionation on a silica gel column with stepwise elution (AcOEt:MeOH; 10% MeOH, 20% MeOH, 30% MeOH, 50% MeOH and 100% MeOH). The alkaloid was isolated from the 50% MeOH fraction. It was not necessary to use acid extraction for this alkaloid. Purification by recrystallization from acetone–methanol gave crystals with m.p. 304–305 K suitable for X-ray diffraction.

Crystal data

$C_{16}H_{34}NO_2^+.Cl^-.2H_2O$
M_r = 343.93
Orthorhombic
Pbca
a = 8.752 (2) Å
b = 27.084 (5) Å
c = 17.973 (2) Å
V = 4260 (2) Å^3
Z = 8
D_x = 1.072 Mg m^{-3}
Mo $K\alpha$ radiation
λ = 0.7107 Å
Cell parameters from 25 reflections
θ = 9.70–13.49°
μ = 0.192 mm^{-1}
T = 295 K
Irregular
0.55 × 0.50 × 0.35 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer	R_{int} = 0.038
$\omega/2\theta$ scans	θ_{max} = 24.96°
Absorption correction: none	$h = 0 \rightarrow 10$
4237 measured reflections	$k = 0 \rightarrow 32$
2645 independent reflections	$l = 0 \rightarrow 21$
1617 observed reflections $[F > 6\sigma(F)]$	2 standard reflections frequency: 40 min intensity decay: 5.6%

Refinement

Refinement on F	$\Delta\rho_{max}$ = 0.249 e Å^{-3}
R = 0.0609	$\Delta\rho_{min}$ = −0.279 e Å^{-3}
wR = 0.0670	Extinction correction: *SHELX*76 (Sheldrick, 1976)
S = 4.45	Extinction coefficient: 10.1 (5) × 10^{-8}
1617 reflections	Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol.IV)
200 parameters	
H-atom parameters not refined	
$w = 3.1873/[\sigma^2(F) + 0.000353F^2]$	
$(\Delta/\sigma)_{max}$ = 0.16	

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$B_{eq} = (8\pi^2/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	B_{eq}
Cl	0.2483 (2)	0.30926 (5)	0.4073 (1)	4.93 (5)
Ow1	−0.1835 (4)	0.4108 (1)	0.1787 (2)	6.6 (2)
Ow2	−0.1843 (4)	0.2082 (1)	0.1817 (2)	5.9 (2)
O1	0.0116 (4)	0.4341 (1)	0.2887 (2)	4.6 (1)
O2	0.0134 (4)	0.1801 (1)	0.2910 (2)	4.9 (2)
N	−0.1017 (4)	0.3087 (2)	0.4091 (2)	3.4 (1)
C1	0.011 (1)	0.5832 (3)	0.3767 (5)	11.7 (5)
C2	−0.0260 (9)	0.5349 (3)	0.3383 (4)	7.3 (3)
C3	−0.0300 (8)	0.4912 (2)	0.3886 (3)	5.7 (3)
C4	−0.0890 (7)	0.4452 (2)	0.3505 (3)	4.3 (2)
C5	−0.0941 (6)	0.4011 (2)	0.4031 (3)	4.2 (2)
C6	−0.1520 (6)	0.3543 (2)	0.3666 (3)	3.8 (2)
C7	−0.3266 (7)	0.3536 (3)	0.3553 (3)	4.8 (3)
C8	−0.3764 (6)	0.3072 (3)	0.3144 (3)	4.9 (2)
C9	−0.3221 (7)	0.2614 (2)	0.3566 (3)	4.8 (3)
C10	−0.1480 (6)	0.2623 (2)	0.3675 (3)	3.5 (2)
C11	−0.0847 (7)	0.2168 (2)	0.4053 (3)	4.3 (2)
C12	−0.0809 (7)	0.1711 (2)	0.3556 (3)	4.7 (2)
C13	−0.0186 (9)	0.1272 (2)	0.3991 (4)	6.8 (3)
C14	−0.021 (1)	0.0810 (4)	0.3596 (6)	11.7 (5)
C15	0.016 (2)	0.0378 (4)	0.4030 (8)	16.6 (7)
C16	−0.1490 (7)	0.3091 (2)	0.4897 (3)	5.0 (2)

Table 2. *Selected geometric parameters (Å, °)*

O1—C4	1.449 (7)	C6—C7	1.542 (8)
O2—C12	1.445 (7)	C7—C8	1.520 (9)
N—C6	1.517 (7)	C8—C9	1.530 (9)
N—C10	1.517 (7)	C9—C10	1.536 (8)
N—C16	1.507 (6)	C10—C11	1.512 (8)
C1—C2	1.51 (1)	C11—C12	1.527 (9)
C2—C3	1.49 (1)	C12—C13	1.524 (9)
C3—C4	1.513 (9)	C13—C14	1.41 (1)
C4—C5	1.524 (8)	C14—C15	1.44 (2)
C5—C6	1.515 (8)		
C6—N—C10	110.4 (4)	C6—C7—C8	111.0 (5)
C6—N—C16	113.5 (4)	C7—C8—C9	110.0 (5)
C10—N—C16	114.0 (4)	C8—C9—C10	111.0 (5)
C1—C2—C3	114.5 (7)	N—C10—C9	109.9 (4)
C2—C3—C4	112.8 (6)	N—C10—C11	110.8 (4)
O1—C4—C3	108.1 (5)	C9—C10—C11	114.1 (5)
O1—C4—C5	109.3 (4)	C10—C11—C12	113.9 (5)
C3—C4—C5	112.0 (5)	O2—C12—C11	110.2 (5)
C4—C5—C6	113.4 (5)	O2—C12—C13	109.8 (5)
N—C6—C5	111.5 (4)	C11—C12—C13	109.9 (5)
N—C6—C7	110.1 (4)	C12—C13—C14	114.8 (7)
C5—C6—C7	113.5 (5)	C13—C14—C15	115.8 (9)

Table 3. *Hydrogen-bonding geometry (Å)*

D—H···A	D···A
N—HN···Cl	3.090 (4)
Ow1—H1w1···O1^i	2.804 (5)
Ow1—H2w1···Cl^i	3.210 (4)
Ow2—H1w2···O2^i	2.796 (5)
Ow2—H2w2···Cl^i	3.226 (4)
O1—HO1···Ow1	2.689 (4)
O2—HO2···Ow2	2.730 (5)

Symmetry code: (i) $x - \frac{1}{2}, y, \frac{1}{2} - z$.

H atoms were calculated at geometrical positions except those of the hydroxy and water groups, which were obtained from a difference Fourier synthesis. Calculations were performed on DEC 3000 AXP and on IBM 3090 computers.

Data collection: *CAD-4 EXPRESS* (Enraf–Nonius, 1993). Cell refinement: *MolEN* (Fair, 1990). Data reduction: *MolEN*. Program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1992). Program(s) used to refine structure: *SHELX*76 (Sheldrick, 1976). Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *MolEN*.

This work was supported by grants from PADCT, CNPq and FINEP.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: BK1156). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

Biavatti, M. W., Brown, R. T., Contin, A., Leonart, R. & Santos, C. A. M. (1994). XIII *Simpósio de Plantas Medicinais do Brasil*. 076, 20–23 September, Fortaleza, CE, Brazil.

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435–436.

Enraf–Nonius (1993). *CAD-4 EXPRESS Software*. Version 1.1. Enraf–Nonius, Delft, The Netherlands.

Fair, C. K. (1990). *MolEN. An Interative Intelligent System for Crystal Structure Analysis*. Enraf–Nonius, Delft, The Netherlands.

Garello, F. (1950). *Arch. Farm. Bioquim. Tucuman*, **5**, 5–46.

Johnson, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.

Manske, R. H. F. & Holmes, H. L. (1968). *The Alkaloids*. Vol. XI, pp. 462–469. New York: Academic Press.

Santos, A. R. S., Miguel, O. G., Pizzolatti, M. G., Yunes, R. A., Vencato, I., Contin, A., Moreira, E. A. & Calixto, J. B. (1995). *Anais da X Reunião Anual da Federação da Sociedade de Biologia Experimental*. 23–26 August, Serra Negra, SP, Brazil.

Sheldrick, G. M. (1976). *SHELX*76. *Program for Crystal Structure Determination*. University of Cambridge, England.

Williams, H. J., Ray, A. C. & Kim, H. L. (1987). *J. Agric. Food Chem.* **35**, 19–22.

Zhang, M.-Z., Wang, J.-C. & Zhou, S.-H. (1990). *Phytochemistry*, **29**, 1353–1354.