

Structure of L-Stepholidine Monohydrate

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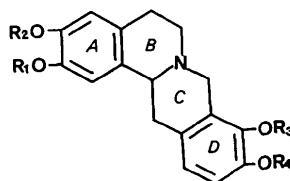
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(Received 11 March 1987; accepted 27 May 1987)

Abstract. 5,8,13,13a-Tetrahydro-3,9-dimethoxy-6H-dibenzo[a,g]quinolizine-2,10-diol monohydrate, $C_{19}H_{21}NO_4 \cdot H_2O$, $M_r = 345.45$, orthorhombic, space group $P2_12_12_1$, $a = 10.802$ (2), $b = 15.160$ (3), $c = 10.036$ (1) Å, $V = 1643.5$ (5) Å³, $Z = 4$, $D_x = 1.40$ g cm⁻³, $\lambda(\text{Cu } K\alpha) = 1.5418$ Å, $\mu = 8.45$ cm⁻¹, $F(000) = 736$, $T = 291$ K, $R = 0.037$ for 2578 observed reflections. The *trans*-fused rings B and C both have half-chair conformations. The two phenyl rings are planar and their least-squares planes are almost parallel to each other.

Introduction. The title compound is an alkaloid isolated from the roots of *Stephania intermedia* Lo., a Chinese herbal medicine. Chemical and spectroscopic studies led to the proposal of the chemical structure (I) for L-stepholidine (Cava *et al.*, 1968). This compound exerts marked physiological action, notably inhibition of dopamine receptor binding. It is also possible that the compound will be used in medicine as an antipsychotic agent. The X-ray crystallographic structural determination of the compound is of interest for the elucidation of the relationship between molecular conformation and its physiological function.



(I) $R_1 = R_4 = H$, $R_2 = R_3 = CH_3$

(II) $R_1 = R_2 = R_3 = R_4 = CH_3$

The crystal structure is compared with that of the analogous alkaloid corydalis B (II) (Wan, Qiao, Rao & Liang, 1983).

Experimental. Colourless crystal $0.3 \times 0.2 \times 0.2$ mm from a methanol/water solution. D_m was not measured. The unit-cell parameters and their standard deviations

were obtained by a least-squares best fit to the angular set of 19 reflections in the range $11 \leq 2\theta \leq 25^\circ$. The intensities of 2963 unique reflections with $(\sin\theta)/\lambda \leq 0.60$ Å⁻¹ were collected on a Huber four-circle diffractometer using Cu $K\alpha$ graphite-monochromatized radiation ($\lambda = 1.5418$ Å), index range $-12 \leq h \leq 12$, $0 \leq k \leq 18$, $0 \leq l \leq 12$. 2578 reflections with $I \geq 2.5\sigma(I)$ were used in the refinement. Standard reflection $2\bar{1}2$ checked every 50 reflections: no significant deviation was observed.

A misplaced fragment was obtained by direct methods using *SHELXS86* (Sheldrick, 1985) and translated to the correct position by means of the *TRADIR* procedure of *DIRDIF81* (Beurskens *et al.*, 1981). The remaining non-H atoms of the molecule were found with *DIRDIF81*. An O atom of the water molecule was revealed from a Fourier difference map (designated as *W*). The non-H atoms were refined anisotropically by *SHELX76* (Sheldrick, 1976) using *F*. All H atoms were located from a difference Fourier synthesis and refined with a common isotropic temperature factor ($B = 4.1$ Å²). $w = 1/(\sigma^2 + 0.0053F^2)$, $R = 0.037$, $wR = 0.044$, $S = 0.72$ for 2578 observed reflections. Final maximum shift-to-e.s.d. ratio = 0.45. Maximum and minimum heights in final difference Fourier synthesis = 0.27 and -0.31 e Å⁻³. Atomic scattering factors from *International Tables for X-ray Crystallography* (1974).

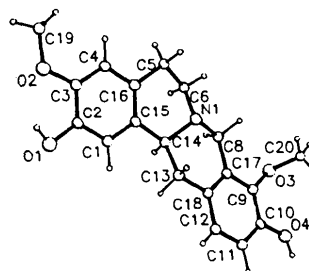


Fig. 1. View of L-stepholidine in its solid-state conformation, showing the numbering of the atoms.

At the end of the refinement, additional cycles were carried out for the two enantiomers. The *R* values in the two cases were not significantly different, but comparison of Friedel pairs indicates a preference for the configuration depicted in Fig. 1.

Table 1. Atomic coordinates ($\times 10^4$) and equivalent isotropic temperature factors (\AA^2)

$$B_{\text{eq}} = \frac{1}{3} \pi^2 \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$$

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> _{eq}
C1	8250 (2)	1237 (1)	1496 (2)	2.90 (4)
C2	8326 (2)	2149 (1)	1551 (2)	2.89 (4)
C3	9112 (2)	2591 (1)	663 (2)	2.86 (3)
C4	9843 (2)	2110 (1)	-192 (2)	2.90 (3)
C5	10648 (2)	696 (2)	-1144 (2)	3.04 (4)
C6	10204 (2)	-232 (2)	-1378 (2)	3.00 (4)
C8	9650 (2)	-1615 (1)	-401 (2)	3.00 (4)
C9	9031 (2)	-3027 (1)	688 (2)	2.66 (3)
C10	8486 (2)	-3516 (1)	1699 (2)	2.91 (3)
C11	7971 (2)	-3080 (2)	2782 (2)	3.11 (4)
C12	8037 (2)	-2163 (1)	2847 (2)	2.83 (3)
C13	8693 (2)	-678 (1)	1930 (2)	2.69 (3)
C14	8837 (2)	-257 (1)	555 (2)	2.55 (3)
C15	8980 (2)	745 (1)	612 (2)	2.57 (3)
C16	9795 (2)	1191 (1)	-222 (2)	2.68 (3)
C17	9108 (2)	-2112 (1)	750 (2)	2.60 (3)
C18	8608 (2)	-1674 (1)	1846 (2)	2.56 (3)
C19	9799 (3)	3975 (2)	-166 (3)	3.79 (5)
C20	10755 (3)	-3728 (2)	-255 (4)	4.21 (5)
N1	9914 (2)	-676 (1)	-103 (2)	2.56 (3)
O1	7606 (2)	2589 (1)	2447 (2)	4.13 (3)
O2	9072 (2)	3493 (1)	757 (2)	3.52 (3)
O3	9495 (2)	-3465 (1)	-426 (2)	3.14 (3)
O4	8451 (2)	-4411 (1)	1530 (2)	3.69 (3)
W	7911 (2)	4405 (1)	3529 (2)	3.85 (3)

Table 2. Bond distances (\AA) and angles ($^\circ$)

C2—C1	1.387 (3)	C15—C1	1.402 (3)
C3—C2	1.401 (3)	O1—C2	1.363 (3)
C4—C3	1.376 (3)	O2—C3	1.372 (3)
C16—C4	1.394 (3)	C6—C5	1.504 (3)
C16—C5	1.507 (3)	N1—C6	1.480 (3)
C17—C8	1.499 (3)	N1—C8	1.482 (3)
C10—C9	1.388 (3)	C17—C9	1.391 (3)
O3—C9	1.394 (3)	C11—C10	1.388 (3)
O4—C10	1.367 (3)	C12—C11	1.394 (3)
C18—C12	1.392 (3)	C14—C13	1.528 (3)
C18—C13	1.514 (3)	C15—C14	1.528 (3)
N1—C14	1.481 (3)	C16—C15	1.390 (3)
C18—C17	1.394 (3)	O2—C19	1.418 (3)
O3—C20	1.428 (3)		
C15—C1—C2	121.5 (2)	C3—C2—C1	119.2 (2)
O1—C2—C1	118.6 (2)	O1—C2—C3	122.2 (2)
C4—C3—C2	119.5 (2)	O2—C3—C2	114.4 (2)
O2—C3—C4	126.1 (2)	C16—C4—C3	121.4 (2)
C16—C5—C6	111.6 (2)	N1—C6—C5	110.9 (2)
N1—C8—C17	113.7 (2)	C17—C9—C10	121.7 (2)
O3—C9—C10	119.0 (2)	O3—C9—C17	119.3 (2)
C11—C10—C9	119.2 (2)	O4—C10—C9	116.8 (2)
O4—C10—C11	123.9 (2)	C12—C11—C10	119.4 (2)
C18—C12—C11	121.4 (2)	C18—C13—C14	111.9 (2)
C15—C14—C13	113.0 (2)	N1—C14—C13	107.7 (2)
N1—C14—C15	111.3 (2)	C14—C15—C1	119.7 (2)
C16—C15—C1	118.6 (2)	C16—C15—C14	121.7 (2)
C5—C16—C4	119.3 (2)	C15—C16—C4	119.8 (2)
C15—C16—C5	120.9 (2)	C9—C17—C8	119.4 (2)
C18—C17—C8	121.4 (2)	C18—C17—C9	119.2 (2)
C13—C18—C12	121.2 (2)	C17—C18—C12	119.1 (2)
C17—C18—C13	119.7 (2)	C8—N1—C6	107.6 (2)
C14—N1—C6	110.9 (2)	C14—N1—C8	110.5 (2)
C19—O2—C3	116.8 (2)	C20—O3—C9	112.3 (2)

Discussion. A view of the molecule is given in Fig. 1 (*PLUTO*; Motherwell & Clegg, 1978). The atomic parameters are given in Table 1.*

The intramolecular bond distances and angles are given in Table 2. The average is 1.513 (1) \AA for the C—C single bonds; 1.481 (2) \AA for the C—N bonds; 1.374 (2) \AA for C(arom.)—O bonds and 1.423 (2) \AA for the O—CH₃ bonds. In comparison with the crystal structure of the analogous compound corydalis B (Wan *et al.*, 1983), the corresponding bond lengths are very similar, except for the mean distance O—CH₃, which is slightly longer in corydalis B [1.444 (5) \AA]. The wide angle O(2)—C(3)—C(4) of 126.1 (2) $^\circ$ and the small angle O(2)—C(3)—C(2) of 114.4 (2) $^\circ$ result from the steric repulsion between H4(C4) and H19b(C19) (the distance H4...H19b being 2.286 \AA) and from the O1—H(O1)...O2 hydrogen bond [O1...O2 2.695 (3) \AA , O1—H(O1)...O2 115 (3) $^\circ$]. The *BC* ring fusion is *trans*, similar to that found in corydalis B. The conformations of the rings *B* and *C* are both half-chair with torsion angles -49.4 (3), 66.5 (2), -49.0 (2), 19.3 (3), -4.9 (3) and 19.6 (3) $^\circ$ for C5—C6—N1—C14—C15—C16—(*B*) and -54.2 (2), 67.3 (2), -47.8 (2), 15.9 (3),

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44096 (19 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

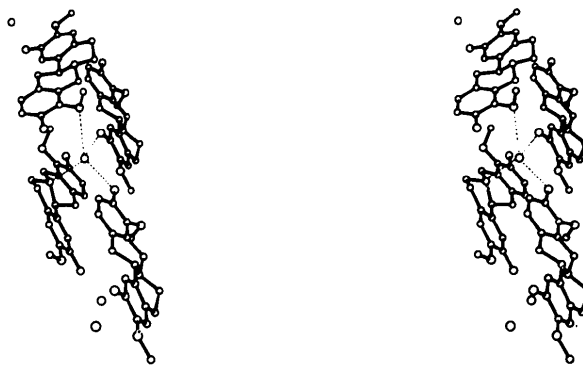


Fig. 2. Stereoscopic view showing the intermolecular packing. The broken lines indicate hydrogen bonds.

Table 3. Hydrogen bonds

Distance: $\sigma = 0.003 \text{\AA}$ for $D \cdots A$, $\sigma = 0.03 \text{\AA}$ for $H \cdots A$; angle: $\sigma = 3^\circ$.

D—H	A	D...A (\AA)	H...A (\AA)	D—H...A ($^\circ$)	Symmetry transformation of A
O1—H(O1)	O2	2.695	2.21	115	<i>x, y, z</i>
O1—H(O1)	W	2.979	2.23	146	<i>x, y, z</i>
O4—H(O4)	W	2.754	1.95	170	<i>x, y-1, z</i>
W—H(W)	N1	2.834	1.87	168	<i>2-x, y+0.5, 0.5-z</i>
W—H(W)	O3	3.144	2.43	143	<i>1.5-x, -y, z+0.5</i>

−4.5 (3) and 23.9 (3)° for C13–C14–N1–C8–C17–C18–(C).

All non-H atoms except N1, C6, C19 and C20 lie in two planes (Roberts & Sheldrick, 1975) almost parallel to each other [17(1)°]. The dihedral angle between the least-squares planes through the atoms of rings *A* and *D* is 15.1 (1)°, compared with 33° in the case of corydalis B. The C19 methoxyl group is nearly coplanar with the phenyl ring *A*, while C20 is rotated out of plane *D* by 88.8 (3)°.

The molecules are aligned in the unit cell with their long axes approximately parallel to the *b* axis. As can be seen from Fig. 2 and Table 3, the water molecule is involved in four hydrogen bonds, twice as acceptor and twice as donor. There are no hydrogen bonds between the alkaloid molecules. Hence the presence of the water molecule stabilizes the crystal.

SW, BT, JPD and MVM thank the SPPS Belgium for financial support.

Acta Cryst. (1987). **C43**, 2128–2130

Structure de l'-(Ethyanyl-1 cyclohexyloxy)-1 [(Méthoxy-2 phényl)-4 pipérazinyl-1]-3 Propanol-2-(*RS*)

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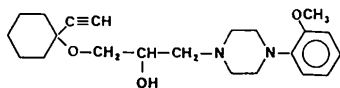
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(Reçu le 18 mars 1987, accepté le 29 mai 1987)

Abstract. C₂₂H₃₂N₂O₃, *M_r* = 372.5, monoclinic, *P*2₁/*c*, *a* = 11.11 (1), *b* = 27.28 (3), *c* = 7.49 (1) Å, β = 109.8 (1)°, *V* = 2136 Å³, *Z* = 4, *D_x* = 1.16 Mg m^{−3}, Mo *K*α, λ = 0.7107 Å, μ = 0.162 mm^{−1}, *F*(000) = 808, *T* = 298 K, *R* = 0.040, *wR* = 0.038 for 2078 independent observed reflexions. Calculated interatomic distances and angles are in the usual range. Both piperazine and cyclohexane rings exhibit a chair conformation. The molecules form zigzag lines parallel to the *b* axis held together by van der Waals forces.

Introduction. La mociprazine est un antiémétique de structure originale synthétisé par l'équipe de chimie du RL-CERM.



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Son mécanisme d'action s'explique essentiellement par une diminution de la réactivité de la zone chimio-sensible bulbaire (*trigger zone*) aussi bien à l'égard de l'apomorphine que de doses élevées de sulfate de cuivre.

Ce produit n'appartient pas à la classe des neuroleptiques compte tenu de l'absence d'effet cataleptigène chez le rat même à des doses élevées. Sur le caecum de cobaye, la molécule antagonise l'influx calcique transmembranaire.

Ce produit ne s'apparentant structuralement à aucune des familles de médicaments antiémétiques utilisés en thérapeutique, l'étude de sa structure cristalline a été entreprise dans le but de déterminer ses caractéristiques stériques et sa conformation spatiale.

Partie expérimentale. Monocristaux de forme parallélépipédique (0,35 × 0,40 × 0,05 mm) obtenus par