

135. The Solid and Solution Conformations of (\pm)-Corycavine

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The crystal structure of corycavine, a protopine-type alkaloid, has been determined by X-ray analysis. A conformational feature observed is the existence of a strong electrostatic interaction between the N- and C-atom at a distance of 2.618 Å. Such an interaction stabilizes the 10-membered ring conformation of the structure. Analyses of NMR spectra indicate that corycavine has the same conformation in solution as in the crystal state.

Introduction. – Corycavine isolated from *Corydalis cava (tuberosa)* [1] and *C. incisa* [2], Papaveraceae, is a protopine-type alkaloid whose structure has been elucidated by chemical methods [3].

While protopine-type alkaloids are the key intermediates on the biosynthetic pathway of the biologically important benzo[*c*]phenanthridine-type alkaloids [4] [5], little attention has been paid to the spatial structure. In spite of the presence of an asymmetric C-atom at position 13, corycavine shows no optical rotations. Therefore, it has been deduced that corycavine is racemic [1].

We have determined the solid-state structure of corycavine by X-ray diffraction. In addition, a detailed NMR-study on the solution conformation of corycavine was carried out.

Experimental. – *Crystal Structure Determination and Refinement.* Corycavine was isolated from *Corydalis incisa* in the usual way. The transparent prismatic crystals were crystallized from MeOH. A single crystal (dimensions being $0.4 \times 0.4 \times 0.5$ mm³) was used for the X-ray crystal analysis. Cell parameters were obtained from a least-squares fit of the setting angles of 45 reflections ($30^\circ < 2\theta < 60^\circ$) measured on a Rigaku AFC-5 diffractometer with graphite-monochromated Cu-K α radiation ($\lambda = 1.5405$ Å). Crystal data are: C₂₁H₂₁NO₅, Mol.wt. = 367.40, monoclinic, space group *P*2₁/*a*, *a* = 12.306(4), *b* = 12.184(3), *c* = 12.355(4) Å, $\beta = 106.53(2)^\circ$, *U* = 1776(1) Å³, *D_m* = 1.373(2) (floatation in H₂O-sat. aq. KI mixture), *D_x* = 1.374 g · cm⁻³, *Z* = 4, $\mu(\text{Cu-K}\alpha) = 7.68$ cm⁻¹, *F*(000) = 776.

X-Ray diffraction intensities within $2\theta = 130^\circ$ were measured at 293 K by the same diffractometer employing the θ - 2θ scan technique with a scan speed of 3° min⁻¹; the scan width was $(1.0 + 0.15 \tan\theta)^\circ$ (in θ) with 3-s backgrounds measured at the two extremes of the scan peak. The intensities of 4 standard reflections measured every 100 reflections remained constant to within $\pm 1\%$ of their mean values. The measured intensities were then subjected to Lorentz and polarization corrections; absorption correction was also applied based on the intensity variation of a (*0k0*) reflection for the ϕ scan at $\chi = 90^\circ$. A total of 3037 independent reflections was used for structure determination and refinement.

The structure was solved by direct methods with the program MULTAN [6], and then refined by the full-matrix least-squares method with isotropic thermal parameters, and then by the block-diagonal least-squares method with anisotropic ones. The H-atomic positions were located from a subsequent difference Fourier map. The function minimized was $\Sigma w(|F_o| - |F_c|)^2$. The weighting scheme used for the last refinement was as follows:

$w = 1.43032$ for $F_o = 0.0$ and $w = 1.0/[\sigma(F_o)^2 - 3.32235|F_o| + 0.14889|F_o|]^2$ for $F_o > 0.0$, where $\sigma(F_o)^2$ is the standard deviation based on counting statistics. Discrepancy indexes R and R_w were 0.064 and 0.052, respectively; S ($= [w(|F_o| - |F_c|)^2 / (M - N)]^{1/2}$, where M = no. of observed reflections and N = no. of variables) was 1.98. None of the positional parameters shifted more than one fifth of its standard deviation, and maximum electron density in the final *Fourier* synthesis was $0.34 \text{ e} \cdot \text{\AA}^{-3}$.

For all crystallographic computations, the UNICS programs [7] were used, and atomic scattering factors were from *International Tables for X-Ray Crystallography* [8]. All numerical calculations were carried out on an *ACOS-900* computer of the Computation Center of Osaka University.

¹H-NMR Spectroscopy. The ¹H-NMR spectra were obtained at 200 MHz on a *Varian XL-200* instrument. Solns. (0.14M) in CDCl₃ were measured at 24°. The chemical shifts are in ppm (δ) relative to internal TMS.

Results and Discussion. – *Molecular Structure of Corycavine.* The corycavine molecule projected on the ring-A plane is presented in *Fig. 1*, along with the atomic numbering. The X-ray results confirmed the structure derived from spectral and chemical data.

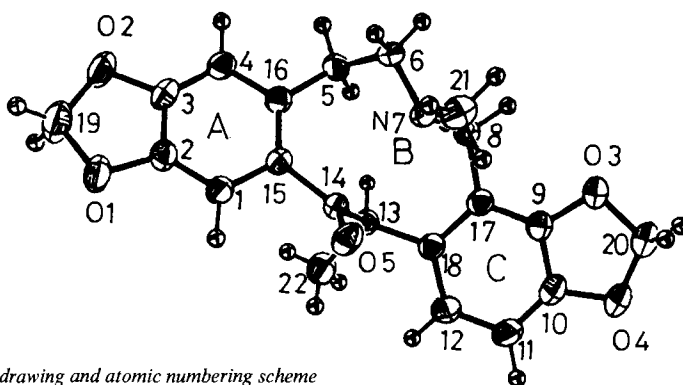


Fig. 1. ORTEP drawing and atomic numbering scheme

Coordinates and thermal parameters of non-H-atoms, with their standard deviations, are given in *Table 1*.

Bond lengths and angles for non-H-atoms with their standard deviations are given in *Table 2*. All values lie in the normal region allowed for related compounds such as protopine [9], cryptopine [10], canadine [11], capaurine [12], and capaurimine-*p*-bromobenzoate [13].

As indicated in *Fig. 1*, the molecule of corycavine takes a relatively extended conformation, not bending into a V-shape or twisted shape. The dihedral angle between the aromatic rings A and C is 35.88° .

The 10-membered ring B has been normally regarded as taking a relatively flexible conformation. In this crystal, however, it is kept rigid by the intramolecular interaction between the ternary N(7)-atom and the carbonyl C(14)-atom in the middle of ring B. The distance between N(7) and C(14) is 2.618 \AA . This contact is short, compared with the normal *van der Waals* distance of 3.2 \AA , it reflects the strong electrostatic force between the two functional atoms.

The packing diagram of the crystal viewed along the *b*-axis, is shown in *Fig. 2*. The corycavine molecules related by diad symmetry are piled up along the *b*-axis, forming infinite layers. These layers are stabilized by *van der Waals* contacts with neighboring layers extended in the *a*- and *c*-directions, no H-bond was observed.

Table 1. Atomic Coordinates and Isotropic Thermal Parameters of Non-H-Atoms (e.s.d.'s in parentheses)

Atom	x	y	z	B_{eq}
O(1)	0.4168(1)	0.3865(1)	1.3208(1)	4.58(6)
O(2)	0.5850(1)	0.3649(1)	1.2748(1)	4.64(6)
O(3)	-0.0424(1)	0.3228(1)	0.4849(1)	4.47(6)
O(4)	-0.2117(1)	0.4108(1)	0.4740(1)	4.65(6)
O(5)	0.09877(9)	0.3455(1)	0.94488(9)	3.59(5)
C(1)	0.2944(1)	0.3861(1)	1.1244(1)	2.98(7)
C(2)	0.3958(1)	0.3814(1)	1.2054(1)	3.14(7)
C(3)	0.4958(1)	0.3687(1)	1.1774(1)	3.24(7)
C(4)	0.4989(1)	0.3604(1)	1.0691(1)	3.20(7)
C(5)	0.4054(1)	0.3604(1)	0.8629(1)	3.19(7)
C(6)	0.3410(1)	0.2642(1)	0.7951(1)	3.25(7)
N(7)	0.2181(1)	0.2827(1)	0.7649(1)	2.72(5)
C(8)	0.1784(1)	0.3543(1)	0.6662(1)	2.95(7)
C(9)	-0.0294(1)	0.3909(1)	0.5769(1)	3.09(7)
C(10)	-0.1309(1)	0.4433(1)	0.5704(1)	3.37(7)
C(11)	-0.1418(1)	0.5152(2)	0.6506(2)	3.65(7)
C(12)	-0.0455(1)	0.5322(1)	0.7413(1)	3.44(7)
C(13)	0.1590(1)	0.4951(1)	0.8508(1)	2.76(6)
C(14)	0.1782(1)	0.3959(1)	0.9297(1)	2.72(6)
C(15)	0.2946(1)	0.3818(1)	1.0103(1)	2.59(6)
C(16)	0.3967(1)	0.3693(1)	0.9818(1)	2.74(6)
C(17)	0.0670(1)	0.4080(1)	0.6634(1)	2.77(6)
C(18)	0.0568(1)	0.4796(1)	0.7496(1)	2.78(6)
C(19)	0.5378(2)	0.3883(2)	1.3646(2)	5.5(1)
C(20)	-0.1598(2)	0.3269(2)	0.4245(2)	4.38(8)
C(21)	0.1545(2)	0.1807(2)	0.7473(2)	3.96(8)
C(22)	0.1510(2)	0.5946(2)	0.9244(2)	4.20(8)

Table 2. Bond Lengths and Angles (standard deviations in parentheses)

Bond lengths [Å]			Bond angles [°]				
C(5)–C(6)	1.525(3)	C(13)–C(14)	1.528(2)	C(6)–C(5)–C(16)	114.9(1)	C(14)–C(13)–C(18)	111.7(1)
C(5)–C(16)	1.507(2)	C(13)–C(18)	1.512(2)	C(5)–C(6)–N(7)	111.0(1)	C(14)–C(13)–C(22)	105.7(1)
C(6)–N(7)	1.465(2)	C(13)–C(22)	1.535(3)	C(6)–N(7)–C(8)	112.2(1)	C(18)–C(13)–C(22)	114.2(1)
N(7)–C(8)	1.468(2)	C(14)–C(15)	1.504(2)	C(6)–N(7)–C(21)	112.3(1)	C(13)–C(14)–C(15)	117.3(1)
N(7)–C(21)	1.452(2)	C(14)–O(5)	1.213(2)	C(8)–N(7)–C(21)	110.3(1)	C(13)–C(14)–O(5)	120.9(1)
C(8)–C(17)	1.510(2)			N(7)–C(8)–C(17)	111.3(1)	C(15)–C(14)–O(5)	119.8(1)

Conformational analyses of protopine-type alkaloids in solution are generally not so easy because of the flexibility of the 10-membered ring in the structure. Therefore, it appears important to make clear the correlation between the crystal and solution structures. A $^1\text{H-NMR}$ spectrum of corycavine was obtained in CDCl_3 . Proton connectivities were established by decoupling and NOE techniques. The chemical shifts and coupling constants are shown in Table 3. The dihedral angles calculated according to *Abraham's* equation [14] (66° for $J(5a,6a)$, 163° for $J(5a,6b)$, 63° for $J(5b,6a)$, and 70° for $J(5b,6b)$) agree with the values (69° , 174° , 46° , and 70° , respectively) observed in the crystal structure. Therefore, it is deduced that the spectral data in solution reflect the conformational features of the crystal structure.

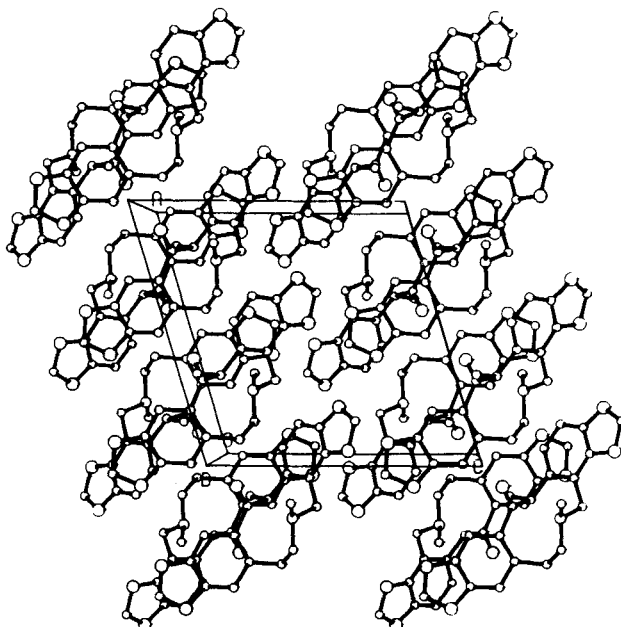
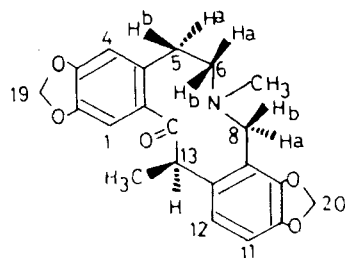


Fig. 2. Crystal packing diagram of corycavine


 Table 3. Chemical Shifts [ppm] and Coupling Constants in the $^1\text{H-NMR}$ Spectrum of Corycavine

Chemical shifts (δ)		Coupling constants [Hz]
H-C(1)	7.02 (<i>s</i>)	* $J(5a,5b) = 15$
H-C(4)	6.67 (<i>s</i>)	* $J(6a,6b) = 13$
H _a -C(5)	3.45 (<i>ddd</i> *)	* $J(5a,6a) = 2$
H _b -C(5)	2.56 (<i>ddd</i> *)	* $J(5a,6b) = 13$
H _a -C(6)	2.89 (<i>ddd</i> *)	* $J(5b,6a) = 2.5$
H _b -C(6)	2.30 (<i>td</i> *)	* $J(5b,6b) = 1.5$
N-CH ₃	1.83 (<i>s</i>)	
H _a -C(8)	3.85 (<i>d</i>)	$J = 14$
H _b -C(8)	3.50 (<i>d</i>)	
H-C(11)	6.81 (<i>d</i>)	$J = 8.5$
H-C(12)	6.87 (<i>d</i>)	
H-C(13)	4.26 (<i>q</i>)	
C-CH ₃	1.36 (<i>d</i>)	$J = 7.3$
2 H-C(19)	5.96 (<i>s</i>)	
2 H-C(20)	5.98, 6.01 (<i>d</i>)	$J = 1.0$

In addition, further evidence for the similarity between solution and solid conformations has been provided by the NOE measurements. Enhancements between the protons $H_a-C(5)$ and $H-C(13)$ (9.1%), $H_b-C(5)$ and $H_a-C(8)$ (16.0%), and $H_a-C(8)$ and $H-C(13)$ (6.5%) were observed. This finding implies that the corycavine adopts a conformation with the three protons ($H_a-C(5)$, $H_a-C(8)$, and $H-C(13)$) lying inside of the 10-membered ring. The conformation observed in the crystal structure accounts well for these NOE results: the inter-proton distances between $H_a-C(5)$ and $H-C(13)$, $H_a-C(5)$ and $H_a-C(8)$, and $H_a-C(8)$ and $H-C(13)$ are 2.06 Å, 2.22 Å, and 2.20 Å, respectively. It may be concluded from these 1H -NMR data that the conformation observed in the crystal structure is also in the most stable forms in aprotic solution.

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