144. X-Ray Crystallographic and MO Studies on the Conformation of Corynoline and the Related Compounds

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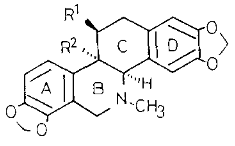
The crystal structure of (±)-corynoline (**1**) has been determined by X-ray diffraction methods. The rings B and C form the half-chair and the twist-half-chair conformations, respectively. The B/C ring conjunction exists in an *anti-cis* conformation, with a N···H–O intramolecular H-bond. Conformational energy calculation by the CNDO/2 method show that the conformations of **1**, (+)-chelidonine (**2**), and their acetates, observed in crystal structures, are all in the one of total energy minimum.

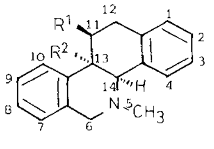
Introduction. – The biologically important compounds (±)-corynoline (**1**) and (+)-chelidonine (**2**) belong to the hydrobenzo[*c*]phenanthridine alkaloids class [1]. Alkaloid **2** was first isolated from *Chelidonium majus* (Papaveraceae) in 1839 [2], and **1** from *Corydalis incisa* (Papaveraceae) in 1962 [3], and extensive chemical and spectroscopic studies led to the corresponding structures [4] [5].

Previous investigations on the conformations of hydrobenzo[*c*]phenanthridine alkaloids have dealt extensively with the axial/equatorial orientation of C(11)–O group and with the half-chair/half-boat form of rings B and C in solution, using IR and NMR spectroscopic methods [6].

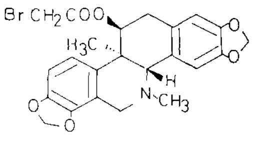
While the *cis*-fused B/C moiety of these alkaloids has a flexibility so that it can exist in two conformers, *anti-cis* and *syn-cis* [7], little attention has been paid to this aspect. Generally, the *syn-cis* conformer is regarded to have higher energy than the *anti-cis* conformer. When the X-ray structure determination of (+)-chelidonine-*p*-bromobenzoate (**3**) was carried out in 1979 [7], however, **3** was found to be the *syn-cis* conformer.



1 $R^1 = OH$, $R^2 = CH_3$ ((±)-Corynoline)
2 $R^1 = OH$, $R^2 = H$ ((+)-Chelidonine)
3 $R^1 = OCOC_6H_4(p\text{-}Br)$,
$R^2 = H$ ((+)-Chelidonine-(*p*-bromobenzoate))
4 $R^1 = OCOCH_3$, $R^2 = CH_3$ ((±)-Corylonine-acetate)
5 $R^1 = OCOCH_3$, $R^2 = H$ ((+)-Chelidonine-acetate)



6 $R^1 = OH$, $R^2 = CH_3$
7 $R^1 = OH$, $R^2 = H$
8 $R^1 = OCOCH_3$, $R^2 = CH_3$
9 $R^1 = OCOCH_3$, $R^2 = H$



10 ((+)-14-Epicorynoline-bromoacetate)

The aim of the present study is firstly to determine the molecular structure of **1** by X-ray analysis in order to obtain the typical model compound in *anti-cis* conformation, and secondly to estimate the total-energy values for *syn-cis* and *anti-cis* conformers of **1**, **2**, (±)-corynoline-acetate (**4**), and (+)-chelidonine-acetate (**5**).

Experimental. – *Crystal Structure Determination and Refinement.* (±)-Corynoline (**1**) was isolated from *Corydalis incisa* in the usual way. Transparent prismatic crystals of **1** were grown from AcOEt/MeOH/H_2O, m.p. 216–217°. Single crystal (*ca.* 0.2 × 0.2 × 0.2 mm) was used for X-ray studies. Preliminary photographs showed the crystal to be triclinic with space group $P1$ or $P\bar{1}$. The distribution of the normalized E coefficients indicated $P\bar{1}$. Crystallographic data are shown in *Table 1*.

Table 1. *Crystal Data of (±)-Corynoline* (**1**)

Formula	$C_{21}H_{21}NO_5$	Cell Constants	a [Å]	12.369(2)	V [Å^3]	865.6
Mol.wt.	367.401		b [Å]	9.960(1)	Z	2
M.p. [°]	216–217		c [Å]	7.490(1)	d_x [g · cm^{-3}]	1.409(1)
Crystal system	Triclinic		α [°]	101.89(1)	d_m [g · cm^{-3}]	1.398(1)
Space group	$P\bar{1}$		β	101.74(1)	F(000)	194
			γ	78.29(1)	Radiation	CuK_α
					λ [Å]	1.5405

The density was measured by flotation in KI soln. Three-dimensional intensity data were collected using the *Rigaku-Denki* automatic four-circle diffractometer using graphite-monochromated CuK_α radiation at r.t. The observed intensities of 2966 independent reflexions with $\sin\theta/\lambda \leqslant 0.60$ Å^{-1} by the ω-2θ scan technique were corrected for *Lorentz* and polarization factors, but not for absorption. Standard reflections, measured for every 50 reflections of the data set, showed no deterioration in intensity during the run. The scan speed was 1°/min and the background was taken for 5 s.

The structure was solved by direct methods with the MULTAN program and refined by full-matrix least-squares analysis with isotropic thermal parameters. From a difference map, the positions of all 21 H-atoms were clearly shown. The final least-squares refinement was computed with anisotropic temp. factors for non-H-atoms and with isotropic temp. factors for H-atoms. The final R value is 0.068. The structure refinements were carried out using the UNICS program with atomic scattering factors from *International Tables for X-Ray Crystallography*.

Conformational Energy Calculation. The method utilized in the computation was the molecular-orbital CNDO/2 procedure. Compounds **1**, **2**, **4**, **5**, and **6**–**9** were investigated for *syn*- and *anti*-type conformers. The atomic parameters of these conformers were based on the torsion angles obtained by the X-ray analyses of **1**, **3**, and **10** [8]. The bond lengths and angles of the common C-skeleton about two conformers were taken from the present **1**, because the discrepancy R value was the lowest for **1**, compared to other compounds.

All numerical calculations were carried out on an *ACOS-900* computer of the Computation Center of Osaka University.

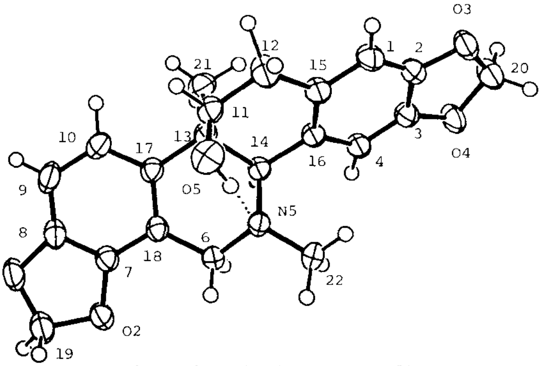


Fig. 1. *The molecular structure of* **1**

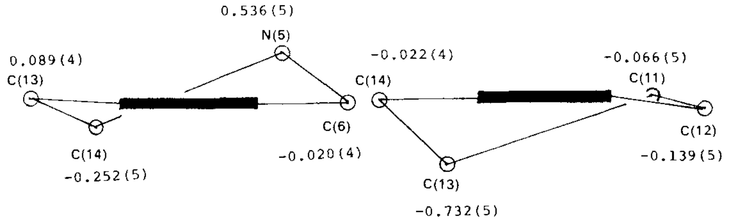
Table 2. *Bond Lengths and Angles* (standard deviations in parentheses)

Bond lengths [Å]			
N(5)–C(6)	1.469(3)	C(11)–C(13)	1.549(4)
N(5)–C(14)	1.488(3)	C(11)–O(5)	1.417(3)
N(5)–C(22)	1.462(4)	C(13)–C(14)	1.551(3)
C(11)–C(12)	1.522(4)	C(13)–C(21)	1.529(4)
Bond angles [°]			
C(6)–N(5)–C(14)	108.2(2)	C(11)–C(12)–C(15)	115.6(3)
C(6)–N(5)–C(22)	107.7(2)	C(11)–C(13)–C(14)	109.3(2)
C(14)–N(5)–C(22)	114.9(2)	C(11)–C(13)–C(21)	109.6(2)
N(5)–C(6)–C(18)	111.0(2)	C(14)–C(13)–C(17)	111.1(2)
C(12)–C(11)–C(13)	112.0(2)	N(5)–C(14)–C(13)	108.5(2)
C(12)–C(11)–O(5)	111.8(2)	C(13)–C(14)–C(16)	111.0(2)
C(13)–C(11)–O(5)	112.2(2)	N(5)–C(14)–C(16)	112.9(2)

Results and Discussion. – *Molecular Structure of (±)-Corynoline* (**1**). The (±)-corynoline (**1**) molecule projected on the ring-A plane is presented in *Fig. 1*, along with the atomic numbering. Bond lengths and angles for non-H-atoms with their standard deviations are given in *Table 2*. Coordinates and thermal parameters of non-H-atoms with their standard deviations are given in *Table 3*. The coordinates and thermal parameters for H-atoms are shown in *Table 4*.

Table 4. *H-Atom Coordinates and Isotropic Temperature Factors.* Standard deviations in parentheses.

Atom	*x*	*y*	*z*	*B*	Atom	*x*	*y*	*z*	*B*
H(1)	0.538(3)	0.550(4)	0.217(5)	3.3(8)	H(12)	0.466(2)	0.834(2)	0.240(3)	0.3(5)
H(2)	0.355(3)	0.179(4)	−0.099(6)	5.0(9)	H(13)	0.528(3)	0.781(3)	0.444(5)	3.0(7)
H(3)	0.411(3)	0.125(4)	0.095(5)	4.0(8)	H(14)	0.141(2)	0.784(2)	0.375(3)	0.4(5)
H(4)	0.165(3)	0.540(3)	0.289(4)	2.1(6)	H(15)	0.288(3)	0.587(3)	0.653(5)	3.0(7)
H(5)	0.060(2)	0.862(3)	0.642(4)	1.7(6)	H(16)	0.157(3)	0.625(4)	0.639(5)	3.2(7)
H(6)	0.147(2)	0.901(3)	0.842(4)	1.1(5)	H(17)	0.239(3)	0.678(3)	0.849(4)	2.2(6)
H(7)	0.067(3)	1.309(4)	1.120(5)	5.0(9)	H(18)	0.252(3)	0.838(3)	0.116(5)	3.1(7)
H(8)	−0.071(3)	1.361(4)	0.999(5)	4.0(7)	H(19)	0.243(3)	1.004(4)	0.175(5)	3.7(8)
H(9)	0.138(3)	1.385(4)	0.561(5)	3.3(8)	H(20)	0.141(3)	0.940(3)	0.163(5)	2.9(7)
H(10)	0.225(3)	1.192(3)	0.379(4)	2.5(7)	H(21)	0.375(3)	0.870(4)	0.700(5)	3.4(8)
H(11)	0.401(2)	0.999(3)	0.452(4)	1.8(6)					



(a) Ring B (b) Ring C

Fig. 2. *Schematic projection of rings B and C.* Deviations of atoms from the least-squares planes of aromatic ring. The thick bar stands for the aromatic ring, indicating ring A in (*a*) and ring D in (*b*). Deviations in Å, with e.s.d.'s in parentheses.

Table 3. *Atomic Coordinates and Anisotropic Thermal Parameters of Non-H-Atoms.* Estimated standard deviations in parentheses. The anisotropic temperature factors are expressed in the following form: $\exp[-(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + B_{12}hk + B_{13}hl + B_{23}kl)]$.

Atom	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
C(1)	0.4670(2)	0.5427(3)	0.2341(4)	0.0045(2)	0.0091(3)	0.0229(6)	−0.0020(4)	0.0086(5)	0.0026(7)
C(2)	0.4208(2)	0.4255(3)	0.1742(4)	0.0054(2)	0.0077(3)	0.0186(6)	−0.0006(4)	0.0080(5)	0.0026(6)
C(3)	0.3132(2)	0.4213(3)	0.1971(4)	0.0055(2)	0.0070(3)	0.0172(5)	−0.0036(4)	0.0059(5)	0.0003(6)
C(4)	0.2486(2)	0.5355(2)	0.2823(4)	0.0047(2)	0.0070(3)	0.0184(5)	−0.0031(3)	0.0062(5)	0.0011(6)
C(6)	0.1405(2)	0.8941(2)	0.7083(3)	0.0057(2)	0.0061(2)	0.0149(5)	−0.0019(3)	0.0066(5)	0.0019(5)
C(7)	0.0946(2)	1.1537(2)	0.7676(3)	0.0046(2)	0.0069(3)	0.0165(5)	−0.0030(3)	0.0044(5)	0.0008(6)
C(8)	0.0934(2)	1.2836(3)	0.7330(4)	0.0052(2)	0.0060(3)	0.0235(6)	−0.0021(3)	0.0061(5)	0.0003(6)
C(9)	0.1413(3)	1.3015(3)	0.5936(5)	0.0083(2)	0.0060(3)	0.0295(8)	−0.0031(4)	0.0097(7)	0.0067(7)
C(10)	0.1923(2)	1.1820(3)	0.4888(4)	0.0069(2)	0.0076(3)	0.0224(6)	−0.0039(4)	0.0082(6)	0.0070(7)
C(11)	0.3836(2)	0.9182(3)	0.4780(4)	0.0047(2)	0.0073(3)	0.0200(6)	−0.0047(3)	0.0049(5)	0.0023(6)
C(12)	0.4527(2)	0.7940(3)	0.3736(5)	0.0045(2)	0.0090(3)	0.0316(8)	−0.0053(4)	0.0088(6)	−0.0016(8)
C(13)	0.2563(2)	0.9214(2)	0.4118(3)	0.0045(2)	0.0063(2)	0.0160(5)	−0.0042(3)	0.0042(4)	0.0016(6)
C(14)	0.2241(2)	0.7857(2)	0.4411(3)	0.0037(2)	0.0063(2)	0.0148(5)	−0.0029(3)	0.0033(4)	0.0016(5)
C(15)	0.4038(2)	0.6617(3)	0.3237(4)	0.0044(2)	0.0078(3)	0.0193(6)	−0.0035(3)	0.0054(5)	0.0015(6)
C(16)	0.2955(2)	0.6582(2)	0.3488(3)	0.0042(2)	0.0068(3)	0.0155(5)	−0.0028(3)	0.0042(4)	0.0016(6)
C(17)	0.1938(2)	1.0498(2)	0.5226(3)	0.0045(2)	0.0065(2)	0.0152(5)	−0.0032(3)	0.0029(4)	0.0030(6)
C(18)	0.1431(2)	1.0333(2)	0.6660(3)	0.0042(2)	0.0062(2)	0.0144(5)	−0.0028(3)	0.0021(4)	0.0014(5)
C(19)	0.0138(3)	1.3095(3)	0.9849(4)	0.0073(2)	0.0074(3)	0.0236(7)	−0.0021(4)	0.0078(6)	−0.0016(7)
C(20)	0.3803(3)	0.2142(3)	0.0407(5)	0.0067(2)	0.0085(3)	0.0262(7)	−0.0021(4)	0.0097(6)	−0.0038(7)
C(21)	0.2273(2)	0.9287(3)	0.2053(4)	0.0074(2)	0.0099(3)	0.0159(5)	−0.0061(4)	0.0054(5)	0.0040(7)
C(22)	0.2270(3)	0.6583(3)	0.6952(4)	0.0092(3)	0.0060(3)	0.0222(6)	−0.0007(4)	0.0107(7)	0.0068(7)
N(5)	0.2329(2)	0.7900(2)	0.6432(3)	0.0050(1)	0.0056(2)	0.0153(4)	−0.0017(3)	0.0045(4)	0.0033(5)
O(1)	0.0384(2)	1.3830(2)	0.8569(3)	0.0081(2)	0.0061(2)	0.0308(5)	−0.0007(3)	0.0144(5)	−0.0021(5)
O(2)	0.0398(2)	1.1637(2)	0.9151(3)	0.0070(1)	0.0073(2)	0.0216(4)	−0.0022(3)	0.0116(4)	−0.0009(5)
O(3)	0.4651(2)	0.2993(2)	0.0797(3)	0.0075(2)	0.0069(2)	0.0314(6)	−0.0005(3)	0.0162(5)	−0.0008(5)
O(4)	0.2862(2)	0.2916(2)	0.1232(3)	0.0074(2)	0.0066(2)	0.0297(5)	−0.0043(3)	0.0149(5)	−0.0050(5)
O(5)	0.4139(2)	0.9254(2)	0.6722(3)	0.0054(1)	0.0117(2)	0.0206(4)	−0.0065(3)	−0.0014(4)	0.0049(5)

All bond lengths and angles are normal and in the range found in the crystal structures of hydrobenzo[*c*]phenanthridine-type alkaloids and related protoberberine-type alkaloids [9]. The dihedral angle between the mean planes of rings A and D is 46.79°.

Ring B is in a half-chair conformation, and ring C is in a twist-half-chair conformation *(Fig. 2)*. A relaxation of 1,3-diaxial interaction between the bonds C(14)–N(5) and C(11)–O(5) seems to be the reason for its twist-half-chair conformation of the ring C.

The torsion angle between the aromatic rings A and D in the *Newman* projection (C(13)–C(14)) is 173.6°. This value shows that the conformation of B/C-ring moiety forms an *'anti-cis'*-type conformation *(Fig. 3)*.

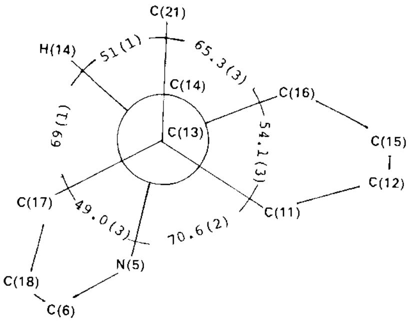


Fig. 3. *Torsion angles* [°] *with standard deviations about the bond C(13)–C(14)*

(±)-Corynoline (**1**) contains an axial OH-group at C(11) and an equatorial *N*-CH_3 group. An intramolecular H-bond is formed between the OH group and the N-atom. The N(5)···O(5) distance is 2.79 Å. This result agrees with that found for **1** on the basis of IR- and NMR-spectroscopic data [6].

Conformational Energy Values. – *Table 5* shows the total-energy values of *anti-cis* and *syn-cis* conformers for **1**, **2**, **4**, **5**, and **6**–**9** by CNDO/2 calculations. The differences between the total energies for the two conformers of all compounds are 20–30 kcal/mol. In fact, the crystallographic and spectroscopic results show that **2**, **1** and its **4** are in *anti-cis* conformation, and only (+)-chelidonine-acetate (**5**) takes *syn-cis* conformation in solution and the solid state.

Table 5. *CNDO/2 Conformational Energy Values*

Compound	Total energy [kcal/mol]		Δ |*anti-syn*|	Preferred conformation	Ref.
	anti	*syn*			
1	–169149.69	–169120.70	28.99	*anti*	This work
2	–163761.21	–163730.71	30.50	*anti*	[6]
4	–190625.81	–190598.77	27.04	*anti*	[6] [11]
5	–185186.38	–185207.77	21.40	*syn*	[6] [7]
6	–113716.79	–113688.49	28.30	*anti*	
7	–135185.13	–135159.65	25.48	*anti*	
8	–108329.69	–108301.70	27.99	*anti*	
9	–129749.15	–129772.80	23.66	*syn*	

Compounds **1** and **2** are slightly more stable than their acetates, possibly because of the intramolecular H-bond in **1** and **2**. According to *Lippincott-Schroeder*'s equation [10], it would correspond to the energy of 7 kcal/mol. The H-bond may also be partly responsible for the predominance of the *anti-cis* conformer for **1** and **2**. But the fact that (±)-corynoline-acetate (**4**) also takes *anti-cis*-conformation shows that other factors must also be involved.

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