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CONFORMATIONAL ANALYSIS OF CORYNOLINE AND ITS RELATED COMPOUNDS*

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The structures of corynoline(I) and base V(V), which are main alkaloids isolated from Corydalis incisa Pers. (Papaveraceae), were proposed by Takao on the basis of the chemical evidences1),2). We also have independently elucidated the latter structure in full accordance with the proposed structure(V)3). The conformational analysis of these alkaloids, however, has not been investigated. Recently, Seoane demonstrated that the structures of chelidonine(III) and its O-acetate(IV), being of the same benzo(c)phenanthridine type skeleton as corynoline, have the cis B/C boat-chair and boat-boat conformations, respectively4).

In this communication, we wish to report our result of the reexamination on the conformations of III and IV, and also to discuss the conformations of I, its O-acetate(II) and V. The cis B/C ring juncture in I and III is effectively characterized by the infra-red absorption bands at 3000-3100 cm^{-1} for both alkaloids associated with the hydrogen bond between C-12 hydroxyl group and the nitrogen atom1),4),5), and by the conversion of I to V having an oxide bridge between C-5 and C-121),3). From the examination by the Dreiding model, the cis B/C half boat-half chair conformation reported4) for III can not explain the hydrogen bond observed in the infra-red spectra since the orientation of C-12 hydroxyl group is far from the lone pair electrons of the nitrogen atom and there is a steric hindrance between C-5 methylene and C-12 hydroxyl groups. On the contrary, the cis B/C half chair-half chair conformations of I and III are

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suitable to form the hydrogen bond. Thus, the infra-red and steric evidences strongly indicate that both I and III exist in the cis B/C half chair-half chair conformation. This conformation is consistent with the nuclear magnetic resonance (NMR) spectral data** listed in TABLE I. Apparently from the Newman projections for C_5-C_{4a} axis illustrated by FIGS. I-A and I-B, the anisotoropy of the benzene ring may lead to that the C-5 methylene protons ($H_{5\alpha}$ and $H_{5\beta}$) in the half boat ring B (FIG. I-A) are nonequivalent leading to an AB type quartet, whereas in the half chair conformation (FIG. I-B) they are almost equivalent. Unexpectedly, the C-5 methylene proton signals of I and III are observed as an AB type quartet. This contradictory fact is explained by taking

TABLE I

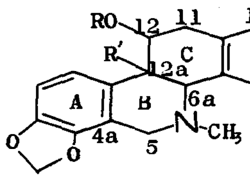
NMR Spectral Data of Corynoline and Its Related Compounds[a]

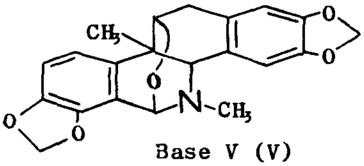
Chemical Shifts(δ) and Apparent Coupling Constants J (c.p.s., in parentheses)

	I	II	III	IV	V
$H_{5\alpha}$, $H_{5\beta}$	3.46(d) 4.05(d) (16.3)	3.56(d) 3.89(d) (15.5)	3.37(d) 4.15(d) (16.0)	3.34(d) 3.84(d) (17.5)	5.29(s,1H)
H_{6a}	3.32(s)	3.53(s)	3.57(d) (3.5)	4.12(d) (5.5)	3.03(s)
$H_{11\alpha}$, $H_{11\beta}$	3.12(d) (3.0)	2.90(d) (8.0)	3.15(bs)[b] $W_{\frac{1}{2}}$=6	2.90(d) (3.0) 2.75(bs) $W_{\frac{1}{2}}$=4	2.86(d) (2.5) 3.02(d) (4.0)
H_{12}	3.94(m)	5.22(t) (8.0)	4.26(m)	5.33(d-q) (9.5,7.2, 3.5)	3.65(q) (2.5,4.0)
H_{12a}	——	——	2.97(q) (3.5,2.5)	3.60[c]	——
N-Me	2.20(s)	2.47(s)	2.27(s)	2.54(s)	2.15(s)
C_{12a}-Me	1.13(s)	1.27(s)	——	——	1.28(s)
OH	7.65	——	7.65	——	——
OAc	——	1.84(s)	——	2.15(s)	——

[a] Peak multiplicities are represented by s(singlet), d(doublet), t(triplet), q(quartet), m(multiplet) and d-q(double-quartet).
[b] bs(broad singlet) with half-height signal width($W_{\frac{1}{2}}$) in c.p.s..
[c] Obscured by other signals.

** All NMR spectra were taken on Varian A-60 spectrometer in deuterio chloroform with tetramethylsilane as an internal standard at room temperature. Proton spin decoupling experiments were performed by using a Varian V-6058 spin decoupler in the frequency sweep. Chemical shifts are expressed in δ-unit and coupling constants (J, apparent absolute value) in c.p.s..

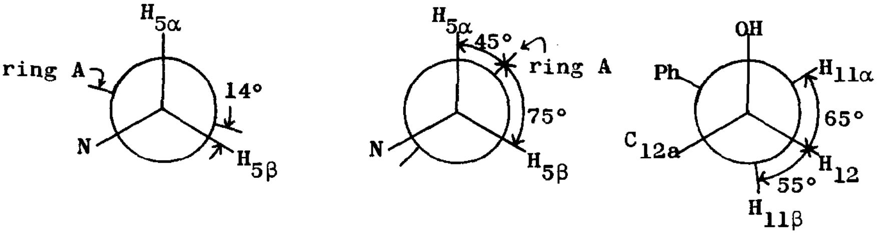




Base V (V)

		R'	R
(I)	Corynoline	CH_3	H
(II)	Corynoline O-acetate	CH_3	Ac
(III)	Chelidonine	H	H
(IV)	Chelidonine O-acetate	H	Ac

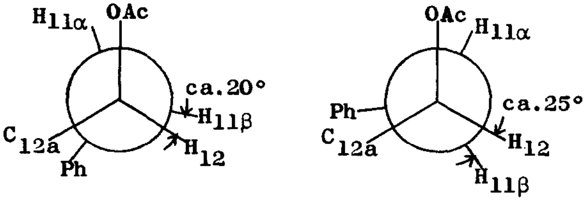
FIG. I



half boat
ring B
A

half chair
ring B
B

half chair
ring C (I,III)
C



twist half boat
ring C (II)
D

twist half chair
ring C (IV)
E

account of the anisotoropy of the nitrogen atom$^{6),7)}$ adjacent to the benzylic protons***.

The NMR spectrum of I shows a multiplet for H_{12} proton at δ 3.94 and a doublet for $H_{11\alpha}$ and $H_{11\beta}$ at δ 3.12 (J=3.0 c.p.s.). The low field proton signal for H_{12} of III at δ 4.26 is a multiplet. These evidences are readily reconciled with the half chair ring C of I and III, in which the angles between H_{12} and C-11 methylene protons ($H_{11\alpha}$ and $H_{11\beta}$) are around 60° as shown by FIG. I-C being consistent with the small coupling constants$^{8)}$.

For their O-acetate, II and IV, the similar steric hindrances are also found between C-5 methylene and C-12 acetoxyl groups when their ring B are in the half boat conformation. This suggests that their ring B are in the half chair conformation in agreement with the NMR evidences for their C-5 methylene protons (TABLE I) discussed above. In the NMR spectrum of IV, H_{12} proton appears at δ 5.33 as a double-quartet ($J_{12,11\alpha}$=7.2, $J_{12,11\beta}$=9.5 and $J_{12,12a}$=3.5 c.p.s.). In comparison with the J values of III, $J_{12,11\alpha}$ and $J_{12,11\beta}$ are increased (ca. 3.0 ⟶ 9.5 and 7.2 c.p.s.), and $J_{12,12a}$ is slightly increased (2.5 ⟶ 3.5 c.p.s.). These evidences imply that the half chair ring C of III is distorted to the twist half chair form by acetylation of the hydroxyl group, since the increment of $J_{12,11\alpha}$ and $J_{12,11\beta}$ reflects the change of dihedral angles between H_{12} and $H_{11\alpha}$(or $H_{11\beta}$)(FIG. I-E).

On the other hand, the acetyl proton signal of II appears at higher field, δ 1.34, than other usual acetyl proton signal. This fact rationalizes that II has the <u>cis</u> B/C half chair-twist half boat conformation in which the acetyl group is above the plane of benzene ring, whereas the <u>cis</u> B/C half chair twist half chair form do not explain the high field shift of the acetyl signal. The H_{12}, $H_{11\alpha}$ and $H_{11\beta}$ proton signals are analyzed as an ABX system, and $J_{12,11\alpha}$ and $J_{12,11\beta}$ are nearly equal to 8.0 c.p.s.. This coupling constant is consistent with the dihedral angles between H_{12} and C-11 methylene protons

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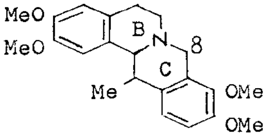
*** d-Corydaline having the <u>trans</u> B/C half chair half chair conformation(9) shows the similar anisotropic effect. Its C-8 methylene proton signals were confirmed to appear at δ 4.25 as an AB type quartet (J=16.0 c.p.s.) by the proton spin decoupling experiments(3).



in the twist half boat conformation (FIG. I-D).

These conformational changes of ring C by acetylation of I and III may result from the introduction of the bulky acetyl group into the molecule. The conformational difference between II and IV in ring C may be attributable to the repulsive interaction between the angular C_{12a} methyl group and C_{12} proton.

In this study, the following conformations are suggested; the cis B/C half chair-half chair form for I and III, the cis B/C half chair-twist half boat form for II and the cis B/C half chair-twist half chair form for IV. Finally, base V(V) has a rigid structure, and the only possible conformation for it is the cis B/C half boat-twist half chair form.

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References

1) N. Takao, Chem. Pharm. Bull. (Tokyo), **11**, 1306, 1312 (1963).
2) Private communication from Dr. N. Takao.
3) Unpublished results.
4) E. Seoane, Anales Fisica Quim., **61-B**, 755 (1965).
5) H. W. Bersch, Arch. Pharm., **291**, 491 (1958).
6) H. P. Hamlow, S. Okuda and N. Nakagawa, Tetrahedron Letters, **1964**, 2553.
7) F. Bohlmann, Tetrahedron Letters, **1965**, 176.
8) M. Karplus, J. Amer. Chem. Soc., **85**, 2870 (1963); also refer to N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry", Chapter 6, Holden-Day, Inc., San Francisco (1964).
9) P. W. Jeffs, Experientia, **21**, 690 (1965).