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ABSOLUTE CONFIGURATIONS AND THE C-RING CONFORMATIONS OF LYCORINE AND RELATED COMPOUNDS EVIDENCED BY NMR AND CD SPECTROSCOPIES

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STEREOCHEMICAL structure of lycorine, which is a main basic component of Lycoris radiata Herb. (HIGANBANA), was elucidated by Takeda and Kotera on the basis of chemical evidences on dihydrolycorine (1,2), while Nakagawa and Uyeo proposed the absolute configurations of lycorine and dihydrolycorine by the application of Mills's rule to some lycorine derivatives, as shown as the formulae Ia and IIa, respectively (3). However, there is no conclusive evidence for supporting their *trans*-B/C ring juncture, and furthermore, the applicability of Mills's rule to alkaloids such as lycorine derivatives has not generally been proved. Therefore, we report here confirmatory evidences for the absolute configurations of Ia, IIa, caranine (Ib)(2,4), and zephyranthine (IIb)(5) and their conformations of ring C by examination of nuclear magnetic resonance (NMR) and circular dichroism (CD) spectra of their derivatives.*[1]

In general, it is not simple to assign signals of protons on carbon atoms contiguous to the nitrogen atom in NMR spectra of quinolizidine and indolizine derivatives, as demonstrated by several workers (6). Therefore, we firstly examined the spectra of the D-ring *seco*-derivatives (IIIa-IIId) derived from IIa and α-dihydrocaranine (1,4), next

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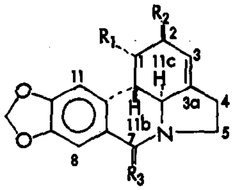
*[1] The new compounds described in this communication gave satisfactory analyses and bear clear stereochemical relations to the structures of Ia and IIa.

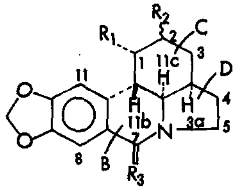


(Ia) $R_1=R_2=OH$, $R_3=H_2$
(Lycorine)

(Ib) $R_1=OH$, $R_2=H$, $R_3=H_2$
(Caranine)

(Ic) $R_1=R_2=OAc$, $R_3=H_2$

(Id) $R_1=R_2=OAc$, $R_3=>O$



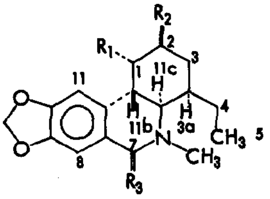
(IIa) $R_1=OH$, $R_2=\beta\text{-}OH$, $R_3=H_2$
(Dihydrolycorine)

(IIb) $R_1=OH$, $R_2=\alpha\text{-}OH$, $R_3=H_2$
(Zephyranthine)

(IIc) $R_1=OAc$, $R_2=\beta\text{-}OAc$, $R_3=H_2$

(IId) $R_1=OAc$, $R_2=\beta\text{-}OAc$, $R_3=>O$

(IIe) $R_1=OAc$, $R_2=\alpha\text{-}OAc$, $R_3=>O$

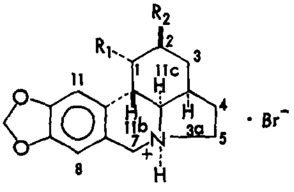


(IIIa) $R_1=OAc$, $R_2=H$, $R_3=H_2$

(IIIb) $R_1=OAc$, $R_2=H$, $R_3=>O$

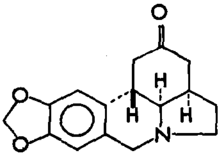
(IIIc) $R_1=R_2=OAc$, $R_3=H_2$

(IIId) $R_1=R_2=OAc$, $R_3=>O$



(IVa) $R_1=R_2=OH$

(IVb) $R_1=R_2=OAc$



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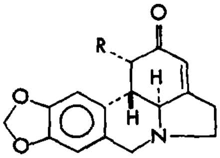
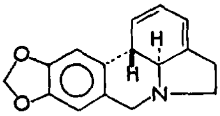


(VIa) R=H

(VIb) R=OAc



(VII)

investigated the spectra of derivatives (IIc–IIe) of IIa and IIb, and finally proceeded to the examination of the spectra of derivatives (Ic and Id) of Ia. The NMR spectral data obtained are listed in TABLE I, and examples of the spectra are shown in FIGS. 1–4.*2

As shown in FIGS. 1 and 2, the spectra of IIIc and its lactam IIId show not well-resolved triplets for the C-1 proton signals at τ 4.49 and 4.35 ($W_{1/2}$=~7 c.p.s.), and quartets for the C-2 proton signals at τ 5.07 and 5.02 (J=2.7 c.p.s.), respectively, which disappear in the spectra of IIIa and its lactam IIIb. These facts indicate that the C-1 and C-2 acetoxyl groups in IIIc and IIId, and the C-1 acetoxyl group and the C-11b hydrogen in IIIa–IIId have all <u>trans</u>-diaxial configurations on the chair C-ring, on the basis of the well-known Karplus correlation (7). In the spectrum of IIId (FIG. 2), an AB-type quartet further split into a doublet at τ 6.11 (J=13.0 and 3.7 c.p.s.) and a quartet at τ 6.52 (J=13.0, 2.7, and 0.8 c.p.s.). On double irradiation at the C-1 proton resonance frequency, the C-2 proton signal is reduced to a triplet, and the C-11 proton signal at τ 3.36 and the signal at τ 6.52 become sharper. Furthermore, double irradiation of the C-11 proton makes the signal at τ 6.52 into a clear quartet and the C-1 proton signal into somewhat sharper triplet. These findings demonstrate that the signals at τ 6.11 and 6.52 arise from the C-11c and C-11b protons, respectively, and that the presence of a long-range spin coupling between the C-11 and C-1 protons, besides the benzylic coupling (8) between the C-11 and C-11b protons is evidently recognized. Similarly, the assignments of signals in the spectra of IIIa, IIIb, and IIIc were performed by the proton spin-decoupling experiments. The C-7 proton signals in

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*2 All the NMR spectra were taken with a Varian HA-100 spectrometer operating at 100 Mc.p.s. field by using about 5% deuteriochloroform solutions containing about 1% tetramethylsilane (TMS) as an internal reference, unless otherwise noted. Proton spin-decoupling experiments were performed by using a Hewlett-Packard 200 ABR oscillator in the frequency sweep and TMS locked mode operation. Chemical shifts are expressed in τ-unit and coupling constants (J, apparent absolute value) and half-height signal width ($W_{1/2}$) in c.p.s.

TABLE I. NMR Spectral Data on Lycorine and Its Related Compounds in Deuteriochloroform[a]

Com-pounds	Chemical Shift (τ) and Apparent Coupling Constants J (c.p.s., in parentheses)									
	H_1	H_2	H_3	$H_{7\alpha}H_{7\beta}$	H_8	H_{11}	H_{11b}	H_{11c}	H_{12}	OAc
(Ic)	4.29(t) $W_{1/2}$=4	4.76(m) $W_{1/2}$=7	4.50(m) $W_{1/2}$=7	{5.87(d) {6.51(d-m) (14.5)	3.46(s)	3.28(s)	~6.16[b]	b	4.12(s)	{7.96(s) {8.09(s)
(Id)	4.26(m) $W_{1/2}$=5	4.71(m) $W_{1/2}$=6	4.38(m) $W_{1/2}$=6		2.46(s)	3.33(d) (1.2)	6.97(d-q) (12.5, 2.3, 1.2)	5.77(d-m) (12.5)	4.01(s)	{7.92(s) {7.98(s)
(IIc)	4.35(q) (3.0, 2.0)	5.10(d-q) (10.0, 5.5, 2.0)		{6.00(d) {6.28(d-m) (14.5)	3.46(s)	3.37(s)	~6.94[b]	b	4.13(s)	{8.08(s) {7.94(s)
(IId)	4.39(t) (3.2)	4.97(d-q) (7.8, 4.8, 3.2)			2.54(s)	3.49(d) (1.0)	6.79(d-q) (13.0, 3.2, 1.0)	6.07(d-d) (13.0, 9.2)	4.02(s)	{7.92(s) {8.00(s)
(IIe)	4.14(t) $W_{1/2}$=5	4.94(d-q) (11.2, 6.5, 2.5)			2.60(s)	3.48(d) (1.0)	7.09(d-q) (12.7, 2.2)	6.12(d-d) (12.7, 8.3)	4.02(m)	{7.94(s) {7.99(s)
(IVa)	5.39(q) $W_{1/2}$=7	5.88(q) $W_{1/2}$=8		{5.97(d) {5.39(d) (14.8)	2.66(s)	2.49(s)	6.82(d-m) (12.2)	b	3.57(s)	
(IVb)	4.27(q) (3.5, 2.0) $W_{1/2}$=7	4.80(q) (3.5) $W_{1/2}$=10		{5.30(d) {5.83(d) (14.5)	3.41(s)	3.04(s)	6.56(d-q) (12.0, 2.0, 1.0)	6.17(d-d) (12.0, 7.0)	4.01(m)	{7.82(s) {7.88(s)

TABLE I (continued)

Compounds	Chemical Shift (τ) and Apparent Coupling Constants J (c.p.s., in parentheses)									
	H_1	H_2	$H_{7\alpha}H_{7\beta}$	H_8	H_{11}	H_{11b}	H_{11c}	H_{12}	NCH_3	OAc
(IIIa)	4.38(q) $W_{1/2}$=7		6.27(d) 6.67(d-m) (14.7)	3.58(s)	3.34(s)	7.08(d-m) (11.0)	7.56(d-d) (11.0, 4.0)	4.16(s)	7.71(s)	8.16(s)
(IIIb)	4.27(q) $W_{1/2}$=7			2.40(s)	3.41(d) (1.0)	6.95(d-q) (13.5, 2.7, 1.0)	6.15(d-d) (13.5, 4.0)	4.04(m)	6.96(s)	8.05(s)
(IIIc)	4.49(t) $W_{1/2}$=7	5.07(q) (2.7)	6.27(d) 6.68(d-m) (15.0)	3.56(s)	3.31(s)	6.67(d-m) (11.0)	7.54(d-d) (11.0, 3.7)	4.15(s)	7.72(s)	7.94(s) 8.15(s)
(IIId)	4.35(t) $W_{1/2}$=7	5.02(q) (2.7) $W_{1/2}$=9		2.37(s)	3.36(d) (0.8)	6.52(d-q) (13.0, 2.7, 0.8)	6.11(d-d) (13.0, 3.7)	4.04(m)	6.97(s)	7.94(s) 8.03(s)

[a] Peak multiplicities are represented by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). For example, d-q represents a doublet of quartets. $W_{1/2}$ is half-height band width (c.p.s.).

[b] Obscured by other signals.

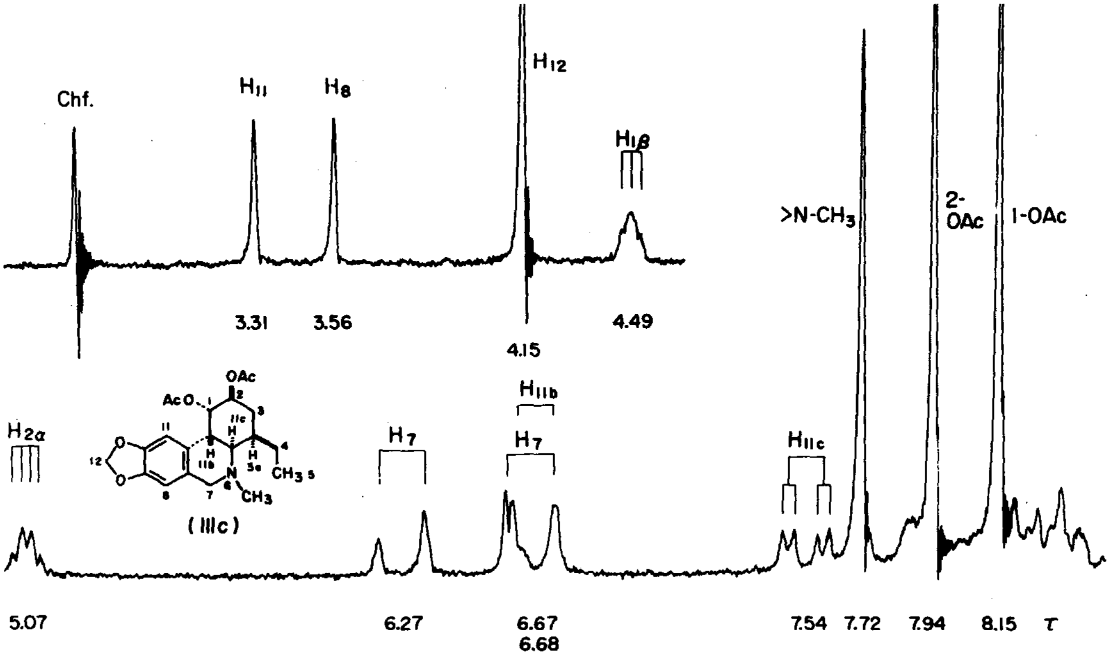

FIG. 1 NMR Spectrum of IIIc in $CDCl_3$ at 100 Mc.p.s.

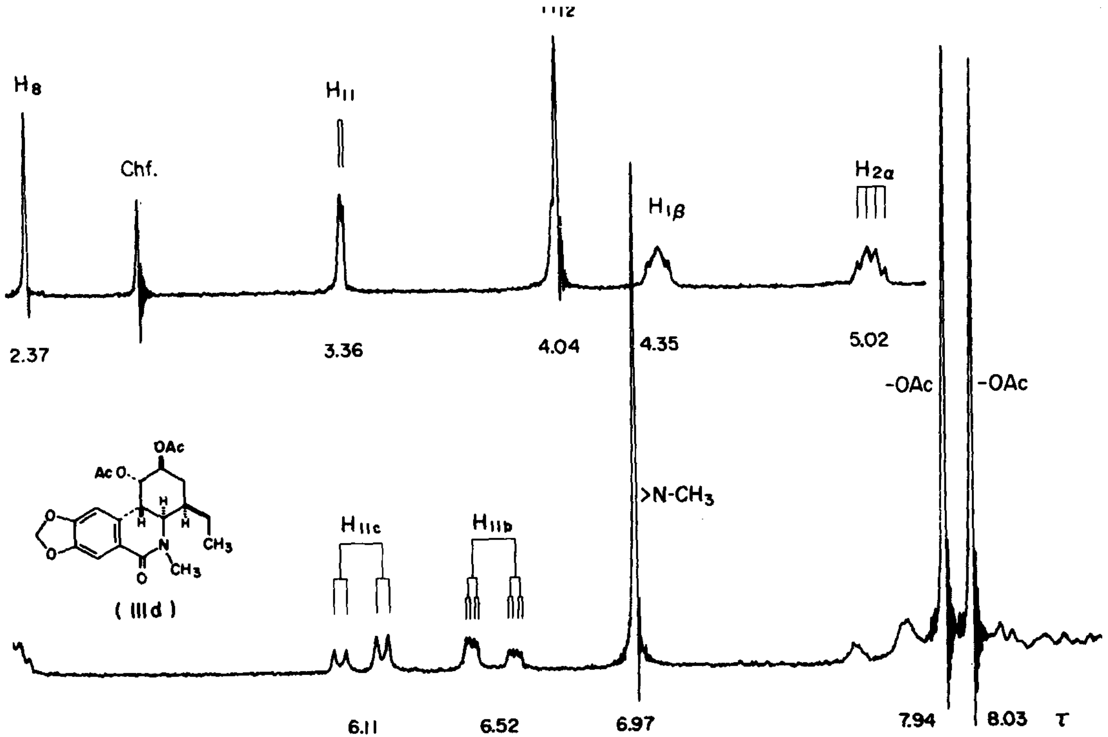

FIG. 2 NMR Spectrum of IIId in $CDCl_3$ at 100 Mc.p.s.

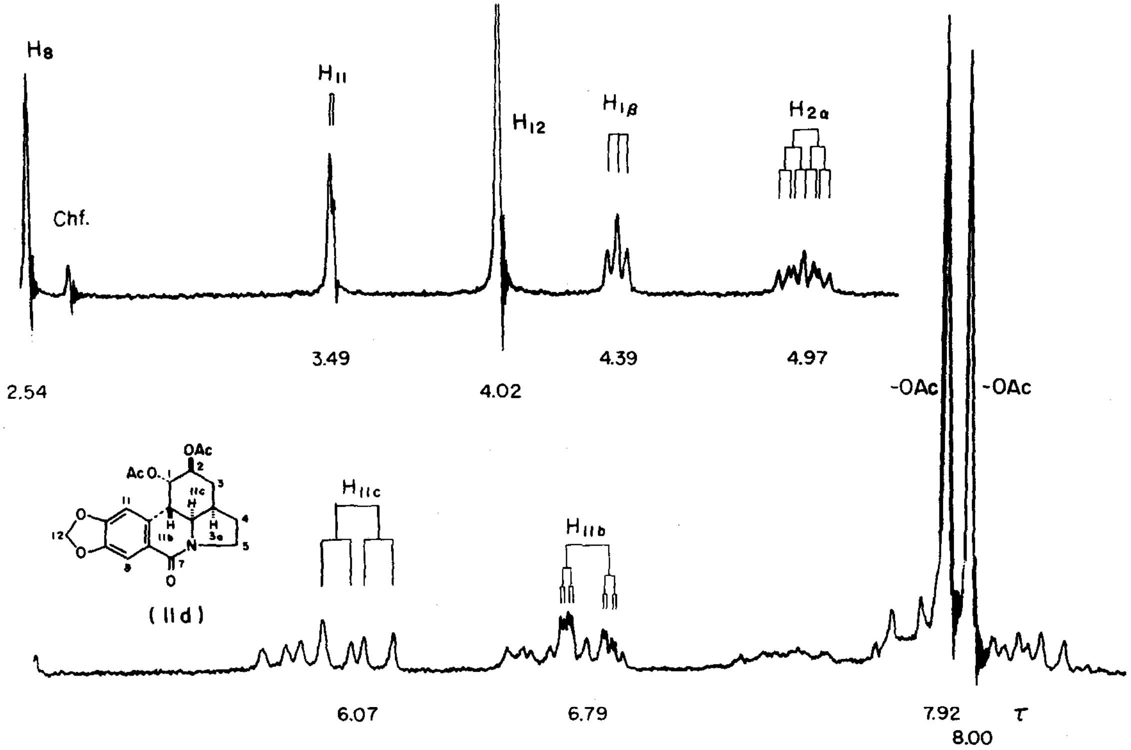

FIG. 3 NMR Spectrum of Diacetyldihydrolycorine Lactam (IId) in $CDCl_3$ at 100 Mc.p.s.

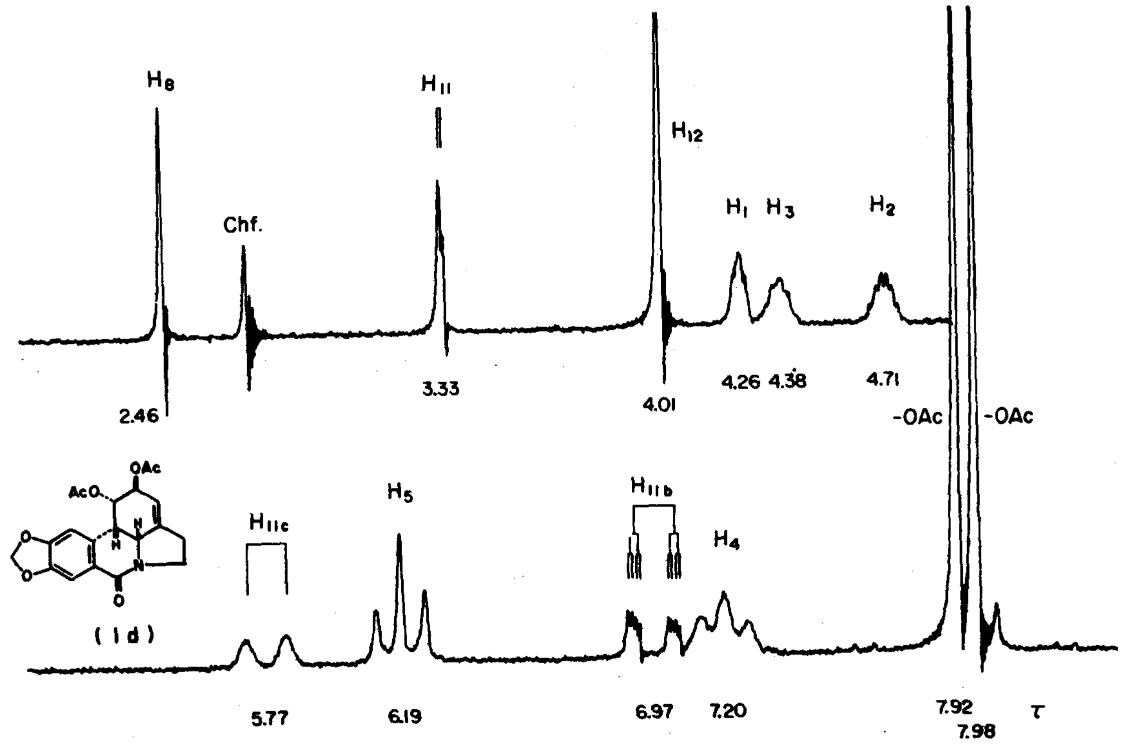

FIG. 4 NMR Spectrum of Diacetyllycorine Lactam (Id) in $CDCl_3$ at 100 Mc.p.s.

IIIc appear at τ 6.27 and 6.68 as an AB-type quartet. The long-range homobenzylic coupling (8) between one of the C-7 and C-11b protons together with the benzylic coupling between the C-7 and C-8 protons was also observed. As a result, from the large coupling constants between C-11b and C-11c protons and the small coupling constants between C-11c and C-3a protons, it was confirmed that the compounds IIIa-IIId have *trans*-B/C ring juncture, and that the ethyl group attached to C-3a has an axial configuration (7). Another evidence for the 1,3-diaxial relations among the C-2 acetoxyl group, the C-11b hydrogen, and the ethyl group can be obtained from the fact that the signals of the C-11b proton and the methylene protons in the ethyl group in IIIc and IIId are shifted downfield due to the C-2 acetoxyl group when compared with those in IIIa and IIIb.

The spectrum of IId shows a more complicated pattern because of the appearance of the signals arising from the C-5 protons at relatively lower fields, but decoupling experiments confirmed the assignments shown in FIG. 3. Here also, we recognized *trans*-B/C and *cis*-C/D ring junctures from the coupling constants of the C-11b and C-11c proton signals and the presence of the long-range couplings between the C-11 and C-11b protons and between the C-11 and C-1 protons. In particular, a doublet of quartets signal at τ 4.97 (J=7.8, 4.8, and 3.2 c.p.s.) corresponding to the C-2 proton gives an evidence for the conformation of ring C, which is evidently of a twisted form (7). However, in the spectrum of IIc, we cannot definitely assign the C-11c proton signal which is shifted upfield because of the benzene ring-current effect and obscured by other signals. The C-ring in IIc is also indicated to have a twisted conformation by the octet C-2 proton signal (TABLE I). On the other hand, the spectrum of IIe, in which the C-2 acetoxyl group was chemically confirmed to have *cis*-relation to the C-1 acetoxyl group, shows an octet at τ 4.94 (J=11.2, 6.5, and 2.5 c.p.s.) for the C-2 proton and indicates that in this molecule ring C is of a slightly distorted chair. The spectra of hydrobromides of IIa and IIc (IVa and IVb, respectively) in deuterium oxide solutions containing DSS as an internal reference show two quartets with small coupling constants (TABLE I) for the C-1 and C-2 protons. These facts imply that the C-rings of IVa and IVb take slightly distorted chair confomations. This conformational change of the C-ring might result from conversion of free bases or lactams into quarternary salts in which the ring strain might be reduced.

Finally, spin-decoupling experiments in Id (FIG. 4) provide a complete evidence for the *trans*-B/C juncture. However, we could not clearly find the C-11b and C-11c proton signals in the lower field region in the spectrum of Ic, in which these protons can be much shielded by the double bond and benzene ring, as suggested by examination of CENCO-Petersen models.

The ORD and CD curves of the ketone V show a conspicuous negative Cotton effect (a=-77, $[\theta]_{291}$=-6520 in methanol).[*3] Applying the octant rule (9) to the formula V and its mirror image, we interprete this fact as an evidence that the absolute configuration should be V and not its mirror image, irrespective of the C-ring conformations. An additional support for this evidence was obtained from the coincidence in the ORD curves of the conjugated ketone VIa ($[\phi]_{371}$=+2330 (peak), $[\phi]_{335}$=+5770) and B-nor-cholest-4-en-3-one ($[\phi]_{375}$=+5260 (peak)(10)). Furthermore, introduction of an acetoxyl group into the C-1 of VIa results in a large bathochromic shift of the CD maximum ($[\phi]_{360}$=+2070 for VIb), which must be attributed to an axial character of the acetoxyl group. This fact is in accordance with the NMR results. Therefore, these results confirm the absolute configurations of lycorine, dihydrolycorine, caranine, and zephyranthine as expressed in formulae Ia, IIa, Ib, and IIb, respectively. Incidentally, the CD

[*3] The ORD and CD curves were recorded on an automatic recording spectropolarimeter ORD/UV-5 of Nihon-Bunko.

curve of VII shows two negative maxima ($[\theta]_{295}$=-13900 and $[\theta]_{254}$=-17400, in methanol). If the diene rule (11) is applicable for the prediction of the sign of Cotton effect of such a system, a positive Cotton effect would be expected from the stereochemistry. The discrepancy between the predicted and observed signs can be explained by homoconjugation of the diene chromophore with the nitrogen atom and the phenyl chromophore. Such possibility is testified by the fact that the hydrochloride of VII exhibits a positive Cotton effect ($[\theta]_{270}$=+27400).

The present conclusions about the absolute configuration and the conformation of ring C of IVa have further been confirmed by X-ray analysis of a crystal of IVa (12).

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