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Studies on the Constituents of *Bocconia cordata*. II.[1] Bocconine

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Bocconine, one of the nematocidal alkaloids from *Bocconia cordata*, has been investigated by means of the nuclear magnetic resonance spectroscopy and the nuclear Overhauser effect measurements to establish the structure.

In 1965, one of us reported the isolation of the three nematocidal alkaloids from *Bocconia cordata*.[1] Two of them were identified to be sanguinarine and chelerythrine. The third was the unknown to be named bocconine. Bocconine was shown to contain benzo[*c*]phenanthridine skelton with two methylenedioxy, one methoxyl, and N-CH_3 group. This paper is concerned with the elucidation of the structure of bocconine by the nuclear magnetic resonance (NMR) spectroscopy using a 100 Mc instrument and the application of the nuclear Overhauser effect (NOE).

As shown in Chart 1, sanguinarine and chelerythrine are the typical benzo[*c*]phenanthridine derivatives which are able to mutually transform between I-, II-, and III-form. I was reduced with sodium borohydride to yield the dihydro-compound (IV)[3] and oxidized with potassium ferricyanide to yield the oxy-compound (V).[3] Bocconine also exhibited the same chemical behaviors as mentioned above. When bocconine chloride (VI) was treated with ammonia, followed by the extraction with ethyl acetate, it was converted to a syrupy material which on treatment with alcohol gave ethoxybocconine (VII), mp 224—226°, $C_{22}H_{21}O_6N$.[1] VI was reduced with sodium borohydride to yield dihydrobocconine (VIII), mp 206—207°, $C_{21}H_{17}O_5N$ and oxidized with potassium ferricyanide to yield oxybocconine (IX), mp 295—296°, $C_{21}H_{15}O_6N$.

The NMR signals of ethoxy-, dihydro-, and oxy-compound of these alkaloids are shown in Table I—III. All protons in III and IV can be easily assigned to the signals in the spectra. Thus, the valuable deductions will be drawn from the correlations of these spectra with that of the series of bocconine.

As shown in Table I and II, the signals for C_1-H, C_4-H, C_{12}-H, and $CH_2\langle^{O-}_{O-}$ of D ring are still remained nearly unchanged regardless of the replacement of one hydrogen at C_6 by ethoxyl group (IV→III). This observation is qualitatively similar to that reported by MacLean, *et al.*[4] and easily expected from that C_6 is too far from these protons to affect magnetically. The spectra of the series of bocconine also show the four unchangeable signals in the same region as that of the series of sanguinarine and chelerythrine. Accordingly, the signals at 2.89 (s), 2.27 (s), 2.53 (d), and 4.00 (s) τ are able to be assigned to C_1-H, C_4-H, C_{12}-H, and $CH_2\langle^{O-}_{O-}$ of D ring, respectively. The spectrum of dihydrobocconine shows the two doublets, 2.53 (d, J=9) and 1.65 τ (d, J=9 cps), in the aromatic region. Since the doublet at 2.53 τ was assigned to C_{12}-H, the other at 1.65 τ must be attributed to C_{11}-H.

1) Part I: M. Onda, K. Takiguchi, M. Hirakura, H. Fukushima, M. Akagawa, and F. Naoi, *Nippon Nogeikagaku Kaishi*, **39**, 168 (1965).
2) Location: *a*) *Minato-ku, Tokyo*; *b*) *Akishima-shi, Tokyo*.
3) C. Tani and N. Takao, *Yakugaku Zasshi*, **82**, 755 (1962).
4) D.B. MacLean, D.E.F. Gracey, and J.K. Saunders, *Can. J. Chem.*, **47**, 1951 (1969).

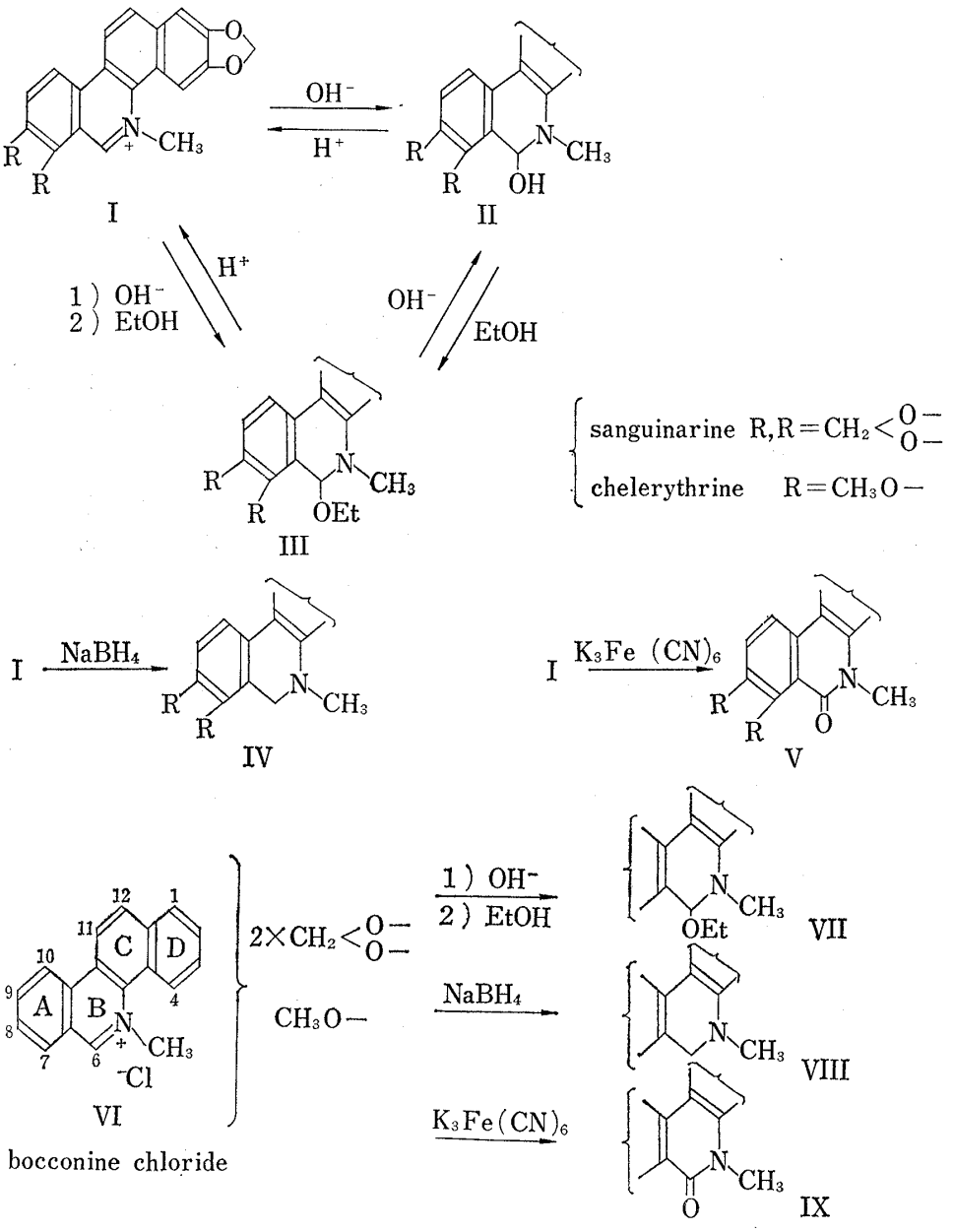


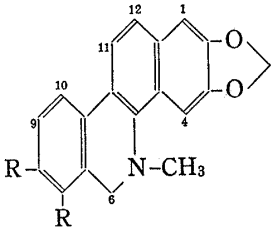
Chart 1

Now, the fact that C_{11}-H in ethoxy- and dihydrobocconine move more downfield by 0.67 ppm than that in III and IV suggests the existence of a substituent at C_{10} to paramagnetically affect it. These considerations suggest the four possible structures for dihydrobocconine. (X—XIII)

Peri-proton for carbonyl group in α-tetralones was found to be more deshielded by *ca.* 1.0 ppm than that in tetralins.[5] A similar situation pertained to isoquinoline alkaloids[6] (XIV and XV) was also known. The difference between the singnals for H_A in dihydro- and oxybocconine is only 0.35 ppm (Table I and III). Since this figure rather corresponds to that of *meta*- or *para*-proton for carbonyl group, H_A in the series of bocconine can not be C_7–H. The above deductions can reasonably preclude XI and XIII from the four possible structures.

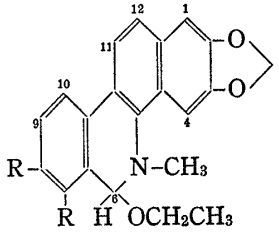
5) R.C. Cambie, F. Carlisle, C.J.Le Quesne, and T.D.R. Manning, *J. Chem. Soc.*, **1969**, 1234.
6) K. Kotera, Y. Hamada, K. Tori, A. Aono, and K. Kuriyama, *Tetrahedron Letters*, **1966**, 2009.

Table I. Nuclear Magnetic Resonance Signals of IV and Dihydrobocconine



R,R	N–CH_3	–OCH_3	$CH_2\langle^{O-}_{O-}$	$C_6\langle^{H}_{H}$	C_1-H	C_4-H	C_9-H	C_{10}-H	C_{11}-H	C_{12}-H
$CH_2\langle^{O-}_{O-}$	7.46(s)		4.01(s)	5.86(s)	2.90(s)	2.28(s)	3.17(d) $J=8$	2.70(d) $J=8$	2.31(d) $J=9$	2.54(d) $J=9$
CH_3O–	7.44(s)	6.16 (C_8) 6.12 (C_7)	3.99(s)	5.72(s)	2.90(s)	2.29(s)	3.08(d) $J=8$	2.50(d) $J=8$	2.31(d) $J=8$	2.53(d) $J=8$
Dihydro-bocconine	7.46(s)	6.19	4.04(s) (A ring) 4.00(s) (D ring)	5.93(s)	2.89(s)	2.28(s)	H_A 3.41(s)		1.65(d) $J=9$	2.53(d) $J=9$

Table II. Nuclear Magnetic Resonance Signals of III and Ethoxybocconine

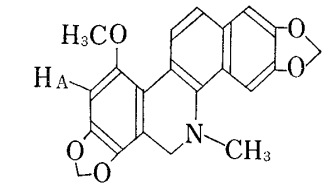


R,R	CH_3CH_2–	CH_3CH_2O–	N–CH_3	–OCH_3	C_6–H
$CH_2\langle^{O-}_{O-}$	8.98(t) $J=7$	6.28(m)	7.32(s)		4.54(s)
CH_3O–	8.96(t) $J=7$	6.28(m)	7.31(s)	6.15(s) (C_8) 6.08(s) (C_7)	4.31(s)
Ethoxy-bocconine	8.98(t)	6.28(m)	7.33(s)	6.17(s)	4.60(s)

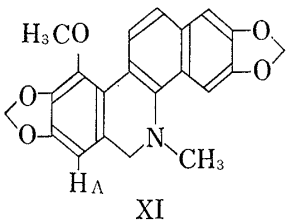
$CH_2\langle^{O-}_{O-}$	C_1-H	C_4-H	C_9-H	C_{10}-H	C_{11}-H	C_{12}-H
4.01(s) (D ring) {3.99(d) {3.93(d) $J=2$ (A ring)	2.87(s)	2.28(s)	3.08(d) $J=8$	2.57(d) $J=8$	2.21(d) $J=9$	2.52(d) $J=9$
4.00(s)	2.87(s)	2.29(s)	2.99(d) $J=8$	2.37(d) $J=8$	2.21(d) $J=8$	2.52(d) $J=8$
4.00(s) (D ring) {4.01(d) {3.96(d) $J=2$ (A ring)	2.89(s)	2.29(s)	H_A 3.33(s)		1.53(d) $J=9$	2.53(d) $J=9$

Table III. Nuclear Magnetic Resonance Signals of Oxychelerythrine and Oxybocconine

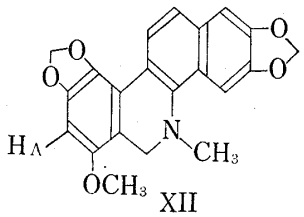
	$N-CH_3$	$-OCH_3$	$CH_2<^{O-}_{O-}$	C_1–H	C_4–H	C_9–H	C_{10}–H	C_{11}–H	C_{12}–H
Oxychelerythrine (V: R=CH_3O)	6.16(s)	6.06(s) (C_8) 5.94(s) (C_7)	3.98(s)	2.94(s)	2.56(s)	2.60(d) J=8	2.12(d) J=8	2.12(d) J=8	2.60(d) J=8
Oxybocconine	6.18(s)	6.03(s)	3.97(s) (D ring) 3.81(s) (A ring)	2.90(s)	2.54(s)		H_A 3.06(s)	1.00(d) J=9	2.53(d) J=9



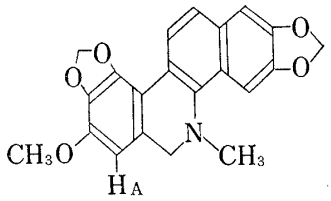
X



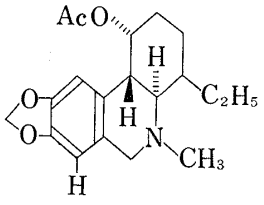
XI



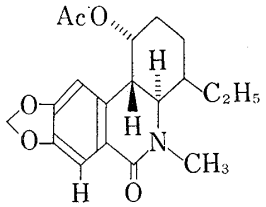
XII



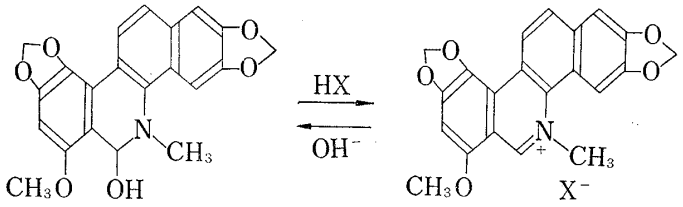
XIII



3.58 τ XIV



2.40 τ XV



XVI

Chart 2

On the other hand, methoxyl group in 5- and 7-methoxy-α-tetralones is more deshielded by *ca.* 0.10 ppm than that in the corresponding tetralins.[4] As seen in Table I and III, C_8–OCH_3 in the series of chelerythrine, which is closely related to the methoxyl group in the above compounds, similarly moves downfield by 0.10 ppm. However, C_7–OCH_3 moves further more downfield (0.18 ppm) due to the magnetic anisotropy and/or the dipole contribution of the carbonyl group. That methoxyl group in the series of bocconine moves downfield in the same order (0.16 ppm) as C_7–OCH_3 in the series of chelerythrine suggests the structure (XII) for dihydrobocconine.

Thus, NOE measurements were carried out to confirm the foregoing considerations. When dihydrobocconine was irradiated at 6.19 τ (the signal attributed to methoxyl group) an increase in area of 47% was observed for only one signal at 3.41 τ corresponding to H_A (Fig. 1 and 2) and no effects were found on any other signal in the aromatic region. If methoxyl group is at C_{10}, NOE should be observed between methoxyl group and C_{11}-H (1.65 d τ).

This fact precludes X and XI. That irradiation at 5.93 τ (the signal attributed to $C_6\langle^{H}_{H}$) did not affect H_A (3.41 τ) also precludes XI and XIII. NOE measurements also supports the structure (XII) for dihydrobocconine, and naturally, the structure for bocconine should be XVI.

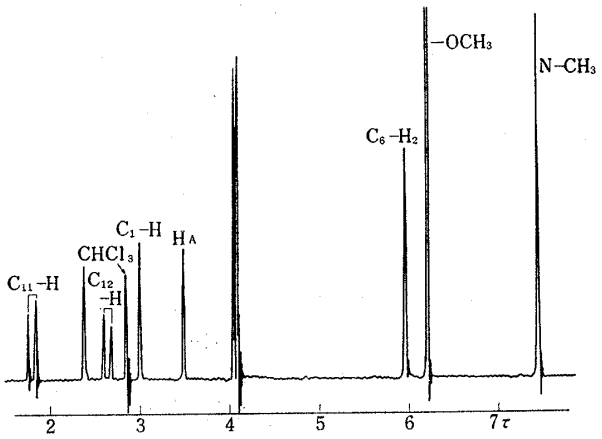


Fig. 1. NMR Spectrum of Dihydrobocconine in $CDCl_3$ (100 Mc)

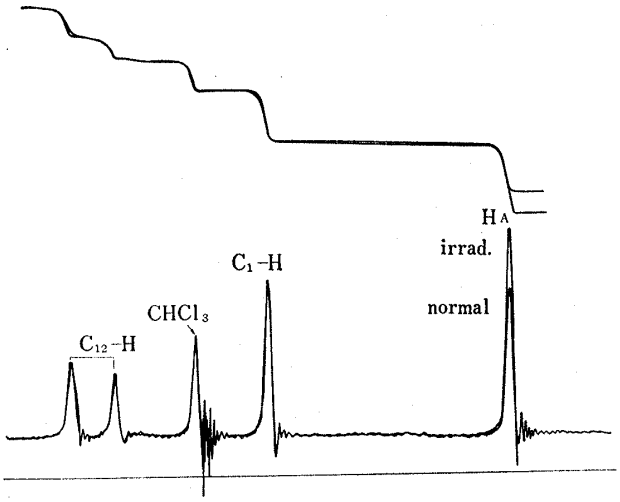


Fig. 2. The NOE's Result of Dihydrobocconine

Experimental

Melting points were determined on a micro hot-stage and were uncorrected. Nuclear magnetic resonance spectra were measured in $CDCl_3$ with a Varian HA-100. Chemical shifts were given in τ values, using tetramethylsilane as internal reference and coupling constants (J) in cps. The following abbreviations were used to describe the signals—s, singlet; d, doublet; t, triplet; m, multiplet. For nuclear Overhauser effect measurements, a 6 w/v% solution of the sample in $CDCl_3$ was degassed. Degassing was carefully done by repeated freezing, and melting under high vacuum. A JEOL's JNM-4H-100 NMR spectrometer (100 Mc) in the frequency sweep mode was used to determine the spectra. Each peak was integrated repeatedly with no irradiated power and optimum irradiated power.

Dihydrobocconine——To a solution of ethoxybocconine[1] (190 mg) in benzene (10 ml) was added conc. HCl (0.5 ml). Bocconine chloride (180 mg) immediately precipitated in a deep red crystal. After filtration and washing with acetone, the chloride was used without purification. $NaBH_4$ (90 mg) was added to a solution of the chloride (180 mg) in MeOH (10 ml) and the solution was refluxed for 1 hr. After evaporation of MeOH, the residue was extracted with benzene, followed by washing with H_2O and drying over Na_2SO_4. The residue was recrystallized from MeOH to yield colorless needles (137 mg), mp 206—207°. *Anal.* Calcd. for $C_{21}H_{17}O_5N$: C, 69.41; H, 4.71; N, 3.85. Found: C, 69.52; H, 4.67; N, 3.70.

Oxybocconine——To a hot solution (90°) of bocconine chloride (470 mg) in H_2O (100 ml) was added a hot solution (80°) of $K_3Fe(CN)_6$ (2.4 g) and KOH (1.2 g) in H_2O (50 ml) with stirring. Stirring was continued for 3 hr at 90°. After cooling, the precipitate was collected, followed by treatment with 1% HCl to remove the unreacted chloride. The solid was dissolved in $CHCl_3$ and the solution was washed with H_2O and dried over Na_2SO_4. The residue (389 mg) was recrystallized from $CHCl_3$–acetone to yield light yellow needles (318 mg), mp 295—296°. *Anal.* Calcd. for $C_{21}H_{15}O_6N$: C, 66.84; H, 4.01; N, 3.71. Found: C, 66.63; H, 4.07; N, 3.66.

Acknowledgement The authors are grateful to Tanabe Seiyaku Co., Ltd. for the supply of the alkaloids.