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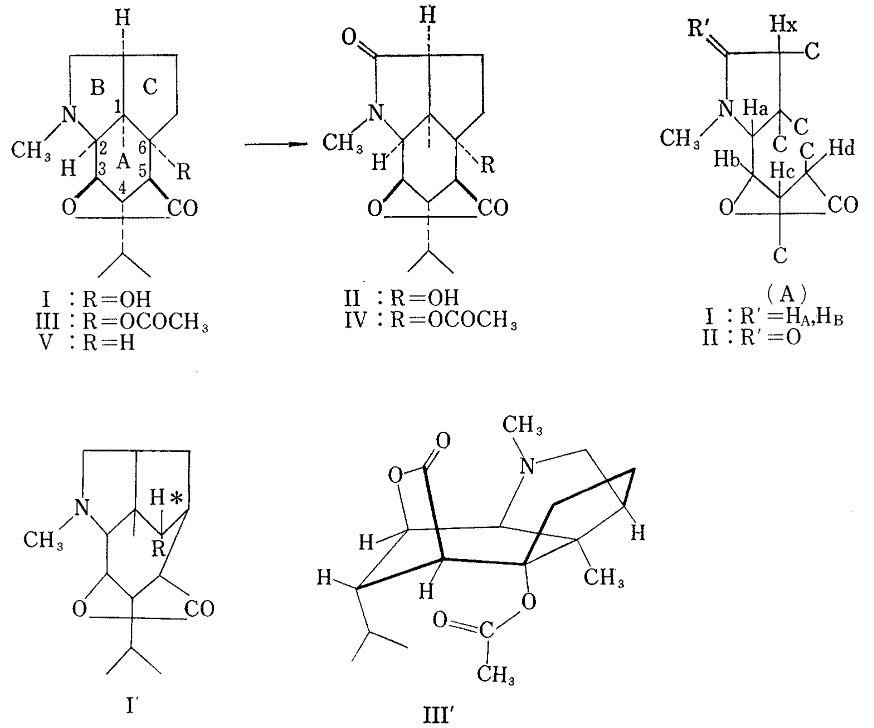
The Structure of Dendramine

Dendramine, a minor alkaloid of *Dendrobium nobile* LINDL (金石斛), was first isolated by Inubushi, *et al.*[1] and characterised as m.p. 186~188°, $[\alpha]_D$ $-27°$ ($CHCl_3$), with the formula $C_{16}H_{25}O_3N$. It contains a hydroxyl (3125 cm^{-1}) and a γ-lactone (1779 cm^{-1}) groupings as suggested by its IR (Nujol) spectrum, together with N-methyl (7.56 τ, 3H, s), $-\overset{|}{\underset{|}{C}}-CH_3$ (8.63 τ, 3H, s) and two secondary C-methyl grouping (8.90~9.10 τ, 6H, t, J=6 c.p.s.) which could probably consist an isopropyl function. In this preliminary communication we present its structure by the formulation (I).

Modified permanganate oxidation[2] of dendramine yielded a lactam, oxodendramine (II), m.p. 291°, $C_{16}H_{23}O_4N$, IR (Nujol) : 3472 (OH), 1745 (γ-lactone) and 1684 cm^{-1} (γ-lactam), IR ($CHCl_3$) : 3571 sharp and 3400 broad (OH), 1783 and 1773 shoulder (γ-lactone), and 1672 cm^{-1} (γ-lactam). Its IR spectrum showed that the compound is γ-lactam. The NMR (nuclear magnetic resonance) (see Fig. 1 and 2) and NMDR[*1] examinations of dendramine and oxodendramine revealed the partial structures (A) for these compounds. Dendramine exhibited the complicated peaks corresponding to four hydrogens between 6.8~7.5 τ along with the N-methyl (7.56 τ, s) and-$C\underline{H}_b$-O-CO- (5.21 τ, 1H, diffused q. J=3 and 5 c.p.s.) signals, those must be attributable to H_A, H_B, H_a, and H_d. The doublet at 7.47 τ (1H, J=3 c.p.s.) was assigned to H_a and confirmed being coupled with H_b by NMDR. The oxidation of dendramine to oxodendramine not only removes two protons (H_A, H_B) from that region but reduces N-methyl and H_a signals to 7.16 τ and 6.79 τ (d. J=3 c.p.s.),



I : R=OH
III : R=OCOCH₃
V : R=H

II : R=OH
IV : R=OCOCH₃

(A)
I : R'=HA,HB
II : R'=O

I'

III'

Chart 1.

[*1] NMDR experiments were carried by the magnetic field swept method using Varian A-60 spectrometer and the results were confirmed by the frequency swept method using Hitachi H-60 spectrometer.

[1] Y. Inubushi, H. Ishii, B. Yasui, T. Konita, T. Harayama : This Bulletin, **12**, 1175 (1964).

[2] O. Achmatowicz, Jr., Y. Tsuda, L. Marion : Canad. J. Chem., **43**, 2336 (1965).

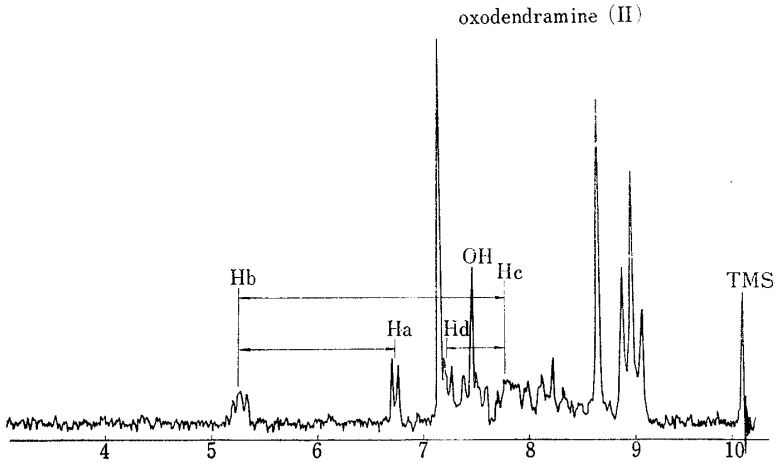


Fig. 1.

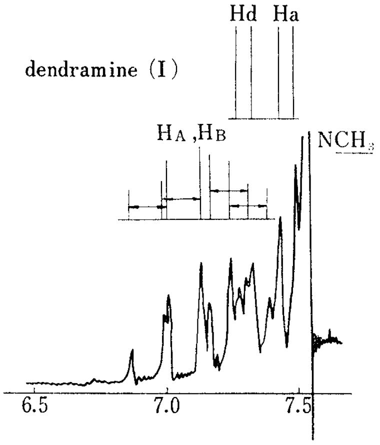


Fig. 2.

respectively, thus remaining a doublet signal (H_d) at 7.22 τ (1H, J=4 c.p.s.) which corresponds to the doublet at 7.30 τ (J=3.3 c.p.s.) in dendramine. Hence the methylene protons (H_A, H_B) in dendramine was analyzed as an AB octet of ABX component as illustrated in the Fig. 2, which provides the evidence that there is present one proton (H_X) adjacent to the methylene ($CH_A \cdot H_B$) group. Further NMDR experiments on oxodendramine established the sequence of H_a, H_b, H_c, and H_d as that in A (Fig. 1). H_d was shown to be coupled with the about 32 c.p.s. higher field multiplet proton (H_c) which being further coupled with the lowest hydrogen H_b (diffused q. J=3 and 5 c.p.s.), and H_b is again coupled with H_a.

Dendramine was recovered unchanged by acetylation with acetic anhydride and pyridine but gave acetyldendramine (Ⅲ), m.p. 156～158°, $C_{18}H_{27}O_4N$, (M^+ 321), on heating with acetic anhydride and *p*-toluenesulfonic acid; IR ($CHCl_3$) : 1780 (γ-lactone), 1732 cm^{-1} (OAc) and no OH absorption, NMR : 9.04, 9.06 (two d. of 3H, J=6 c.p.s. $-CH(C\underline{H}_3)_2$), 8.64 (3H, s, $-\overset{|}{\underset{|}{C}}-CH_3$), 7.98 (3H, s, $COCH_3$), 7.53 (3H, s, $N-CH_3$), 7.42 (1H, d, J=3.5 c.p.s., H_d), and 5.22 τ (1H, diffused q. J=3 and 4 c.p.s., H_b). Oxodendramine gave similarly acetyloxodendramine (Ⅳ), m.p. 195～197°, $C_{18}H_{25}O_5N$, (M^+ 335); IR (Nujol) : 1783 (γ-lactone), 1731 (OAc), and 1689 cm^{-1} (γ-lactam), NMR : 9.01 (6H, t, J=5.5 c.p.s., $-CH(C\underline{H}_3)_2$), 8.57 (3H, s, $-\overset{|}{\underset{|}{C}}-CH_3$), 7.94 (3H, s, $COCH_3$), 7.14 (3H, s, $CO-N-C\underline{H}_3$), 6.64 (1H, d, J=3 c.p.s., H_a), 6.32 (1H, d, J=4 c.p.s., H_d), and 5.20 τ (1H, diffused q, J=3 and 4.5 c.p.s., H_b). All attempts of chromic acid oxidation of oxodendramine were unsuccesful and the starting material was recovered unchanged. This result suggests that the hydroxyl group of dendramine is tertiary. The marked low field shifts of H_d in the acetates (0.93 p.p.m. in Ⅰ→Ⅲ, and 0.90 p.p.m. in Ⅱ→Ⅳ, respectively), however, led us to be sometimes aware of the possibility such as Ⅰ′ for the structure of dendramine, in which the above mentioned proton (H_d) could be assigned to H*. Since chemical shifts of these signals are too high for $-C\underline{H}-OAc$ unless some strong shielding effect to be accounted, which is, however, highly unacceptable from any stereochemical arrangement of Ⅰ′, and since the sequence of $H_a \sim H_d$ was determined as A by NMDR, such a low field shift of H_d is conceivable by a suitable conformation of acetoxyl carbonyl such as Ⅲ′. The possibility of Ⅰ′ was also discarded by the reasons described below.

Accepting the partial structure A for dendramine the presence and the position of $-CH(CH_3)_2$, $-\overset{|}{\underset{|}{C}}-CH_3$, and OH functions were elucidated from its mass spectrum.[3] The

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[3] Details of the fragmentations of the various dendrobium alkaloids and their derivatives will be published elsewhere (cf. Y. Tsuda, E. Katarao, Y. Inubushi : "Symposium on Mass Spectroscopy for Structural Problems," November 27, 1965, Tokyo).

mass spectrum of dendramine showed a great similarity with that of dendrobine (V) suggesting that they have the same structure except hydroxyl substitution for the former (Table I). The fragments a~d confirmed the presence of isopropyl group at C_4, and the fragments g~i indicated that the hydroxyl group is at C_6. The base peak j defines the position of the tertiary methyl group at C_1. The evidences therefore could be summarized in the structure (I).

Table I.

	M^+	a	b	c	d			g	h	i'	i	j	k
(I)	279 (27)	251 (4)	236 (31)	222 (7)	208 (3)	193 (12)		152 (23)	122 (4)	109 (28)	108 (22)	96 (100)	81 (7)
(V)	263 (32)	235 (9)	220 (93)	206 (11)	192 (11)	178 (16)	164 (6)	136 (16)	122 (4)	109 (19)	108 (22)	96 (100)	81 (10)

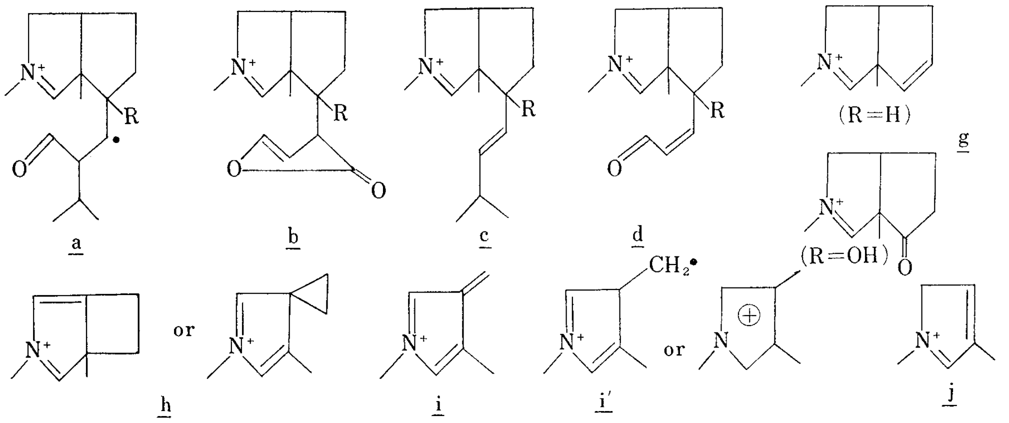

Chart 2.

The final decision of the structure (I) was obtained from the dealdolization of dendramine to VI. Dendramine was heated with 10% ethanolic sodium hydroxide under reflux for 30 min. and the amphoteric product was heated with acetic anhydride at 100° for 30 min. The latter procedure changes the dendraminic acid, the simple hydrolysis product, into a neutral rearranged lactam such as VII.[4] The basic product (VI), m.p. 152~154°, $C_{16}H_{25}O_3N$, (M^+ 279), thus isolated, had γ-lactone (1774 cm^{-1}) and an additional carbonyl absorption (1732 cm^{-1}) in IR ($CHCl_3$) spectrum, but dit not contain any acetyl function being indicated by NMR spectrum; NMR: 9.07 (6H, d, J=6 c.p.s., $-CH(C\underline{H}_3)_2$), 8.73 (3H, s, $-\overset{|}{\underset{|}{C}}-CH_3$), 7.64 (3H, s, $-\overset{|}{N}-CH_3$), and 5.38 (1H, broad, $-\overset{|}{C}\underline{H}-O-CO-$). Hence the carbonyl absorption at 1732 cm^{-1} in VI must be owing to the formation of a (five membered ring) ketone. The confirmation of the structure (VI) for this product was again available from its mass spectrum which exhibited an extreme strong base peak at m/e 152 as expected. The second intense peak at m/e 108 (32%) was derived from m/e 152 by a probable fragmentation shown below since the presence of a metastable peak at m/e 77 confirmed the frangmentation m/e 152→m/e 108.

The similarities of the NMR spectra of dendramine and dendrobine, and oxodendramine and oxodendrobine suggest the identical stereochemistries for both the alkaloids. The suggestion therefore led us to the stereostructure (I) which was now confirmed by the following evidences. Dendramine has the comparable basicity (pKa'~7.1) with that

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4) Y. Inubushi, Y. Tsuda, E. Katarao: This Bulletin, **13**, 1482 (1965).

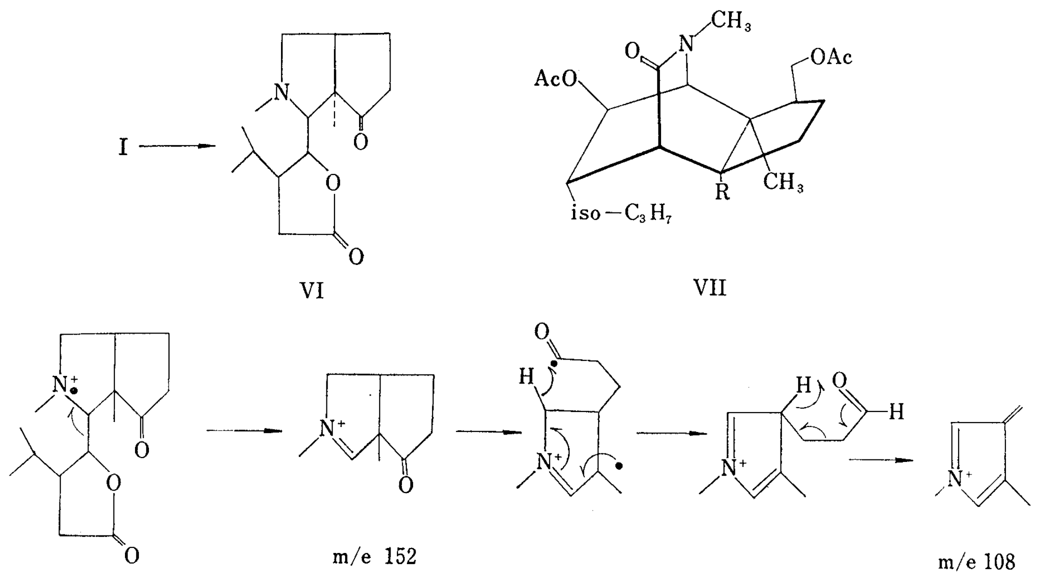

Chart 3.

of dendrobine (pKa′∼7.5); the fact which rules out the possibility of hydrogen bonding between the hydroxyl group and the basic nitrogen. On the other hand, the great increase of pKa by about 1.4 unit in the lithium aluminum hydride reduction product (pKa′∼8.4), amorphous, indicates that the B, C ring and the lactone grouping are arranged to be *cis* as that of dendrobine, for which pKa′ increases 1.4 unit by the same reduction.⁵⁾ This conclusion was supported by the observation that hydrolysis and the following acetolysis of dendramine produces a lactam analog (VII) (IR ($CHCl_3$): 1730 and 1666 cm^{-1}) as a by-product.

The isopropyl group is assigned to be *trans* to the lactone grouping from the evidence that $J_{H_c-H_d}$ in dendramine derivatives are always about 4 c.p.s. The Dreiding model for I gave the dihedral angle $\theta_{H_c-H_d}$ about 40°, for which the calculated magnitude⁶⁾ of J is ca. 5.0 c.p.s. The structure epimeric at C_4 should have J∼0 c.p.s. since the dihedral angle between H_c and H_d is about 80°.

We are obliged to Drs. T. Shingu and T. Ibuka, Kyoto University, for measurements of NMR, NMDR, and mass spectra.

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5) T. Onaka, *et al.*: This Bulletin, **12**, 506 (1964); S. Yamamura, Y. Hirata: Tetrahedron Letters, No. 2, 79 (1964); cf., Y. Inubushi, E. Katarao, Y. Tsuda, B. Yasui: Chem. & Ind. (London), **1964**, 1689.

6) H. Conroy: "Advances in Organic Chemistry, Method and Results," p. 308 (1960), New York Interscience Publishers.