[Chem. Pharm. Bull. 14(6) 676~680 (1966)]

UDC 581.19 : 582.59 : 547.94.02

The Structure of Dendramine(6-Oxydendrobine) and 6-Oxydendroxine*1 The Fourth and Fifth Alkaloid from *Dendrobium nobile**2

In the preceding paper[1] from these laboratories, the structure (II) has been proposed for dendroxine, the third alkaloid from *Dendrobium nobile*. The present communication is concerned with the structural investigation of the fourth and the fifth alkaloids from *Dendrobium nobile*.

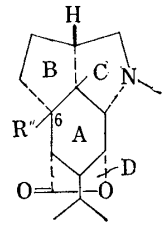
The fourth alkaloid, m.p. 178~180°, $[\alpha]_D$ −18.6 (EtOH) possesses an empirical formula of $C_{16}H_{25}O_3N$ (*Anal.* Calcd.: C, 68.78; H, 9.02; N, 5.01. Found: C, 68.98; H, 9.25; N, 4.92. mol. wt. 279 (mass spec.)) and the presence of γ-lactone (1779 cm^{-1}) and hydroxyl group (3100~3300 cm^{-1}; br.) is deduced from its infrared absorption spectrum in potassium bromide. The same $C_{16}H_{25}O_3N$ compound was isolated independently from Chinese crude drug Chin-Shin-Hu by Inubushi, *et al.*[2] and designated as dendramine.

Although the direct comparison of both alkaloids has not been examined, their identity is obvious by the comparison of their physical and spectroscopic properties.

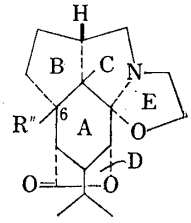
Nuclear magnetic resonance (NMR) spectrum of this alkaloid is nearly superimposible to that of dendrobine though some little differences of chemical shift are observed (Table I).

Table I.

	>CH-CH(>CH)-CH-O-CO-	>N-CH$_3$	-C(CH$_3$)-	iso-C$_3$H$_7$
Dendrobine	5.20 (q, J=3 & 6)	7.51	8.67	9.00~9.04 (d×2, J=6)
Dendramine	5.21 (q, J=3 & 4)	7.56	8.67	8.90~9.10 (d×2, J=6)



I : R″=H
III : R″=OH



II : R″=H
IV : R″=OH

The only difference observed is the presence of the singlet (one proton equivalent) at 8.02 τ, which disappears by addition of a trace of acetic acid and, therefore, is attributable to a hydroxyl proton. Then dendramine might be a hydroxylated dendrobine, when the resemblance of NMR and IR data is taken into account. The additional hydroxyl group is tertiary because of the absence of hydrogen adjacent to hydroxyl group in the NMR spectrum. As the NMR data (Table I) further eliminate the possiblity of presence of the additional hydroxyl group at C_2, C_3, C_4, or C_8, so this hydroxyl group is to be located to a remaining tertiary carbon atom, to be more precise C_5, C_6 or C_{13}.

The structure of dendramine is, then, further investigated by means of mass spectroscopy. Fig. 1 shows the mass spectra of dendrobine (I), dendroxine (II) and dendramine (III). The mass spectrum of dendrobine was briefly discussed by Hirata, *et al.*[3] during their structural studies on this alkaloid. Now that the structure of

*1 This paper was reported at the 85th Annual Meeting of the Pharmaceutical Society of Japan. (Tokushima, Oct. 28, 1965 : Abstract of papers; page 315) and also at the first Symposium on Mass Spectroscopy for Structural Problems of Organic Compounds. (Tokyo, Nov. 27, 1965 : Abstract of papers; page 34).

*2 高貴石斛 (kōkisekkoku)

1) T. Okamoto, *et al.* : This Bulletin, **14**, 672 (1966).
2) Y. Inubushi, *et al.* : *Ibid.*, **12**, 1175 (1964).
3) S. Yamamura, Y. Hirata : Tetrahedron Letters, No. 2, 79 (1964); Nippon Kagaku Zasshi, **85**, 377 (1964).

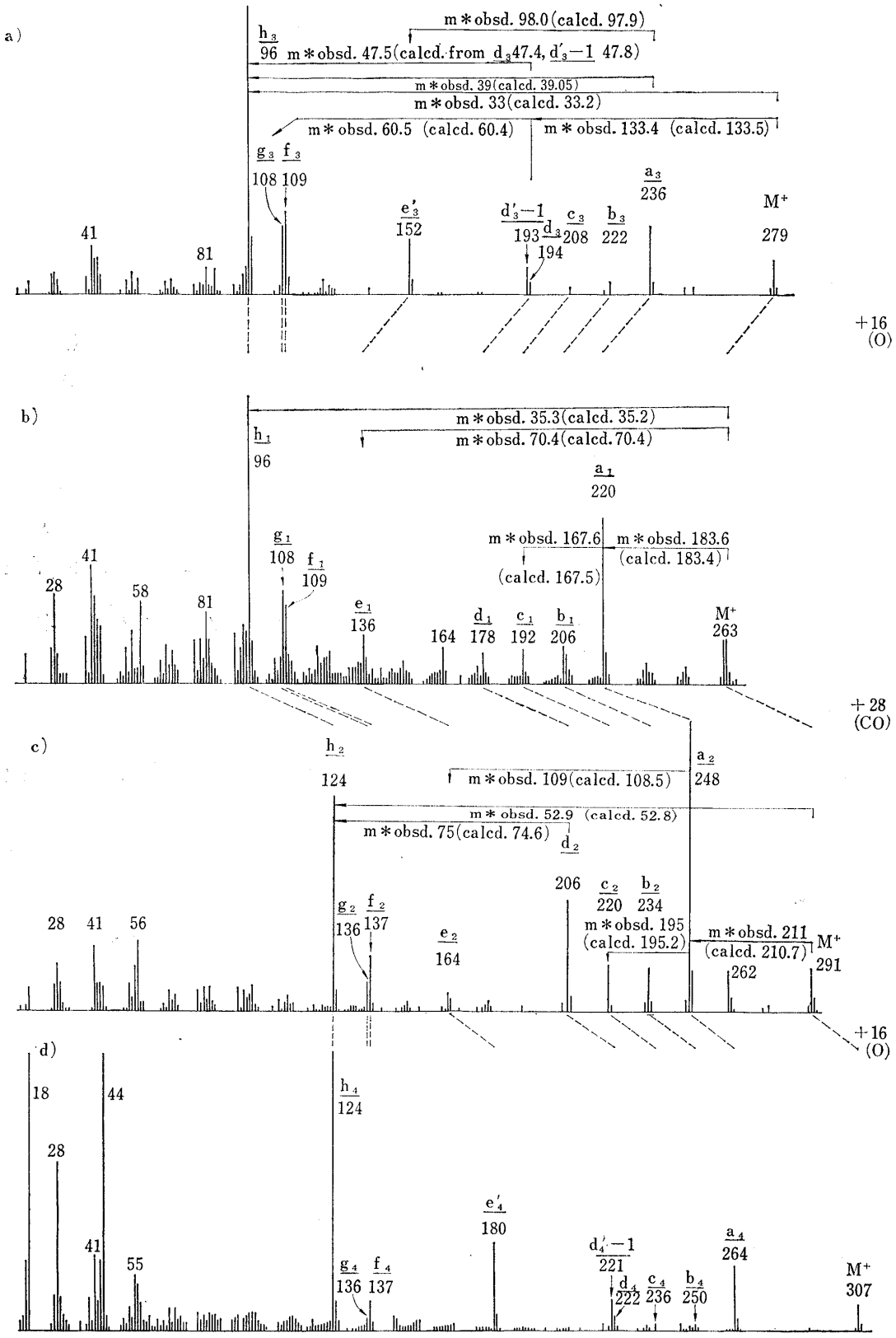


Fig. 1.

a) Dendramine (Ⅲ) (6-Oxydendrobine)
b) Dendrobine (Ⅰ)
c) Dendroxine (Ⅱ)
d) 6-Oxydendroxine (Ⅳ)

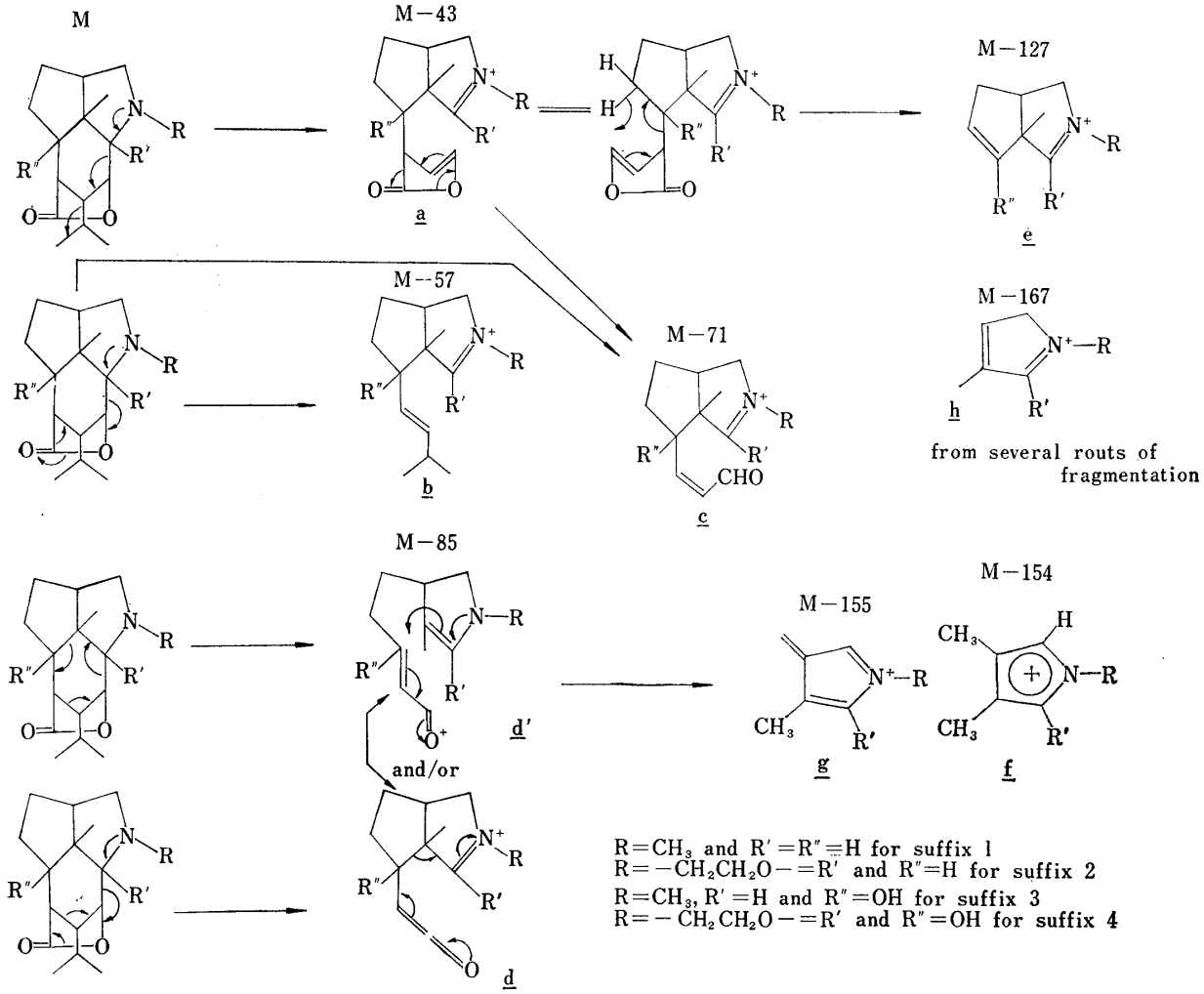


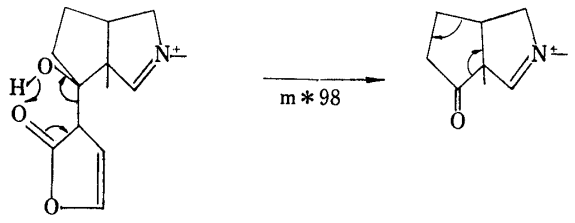
Chart 1.

dendrobine[4~6] and dendroxine[1] has been perfectly proved, mass spectra of these alkaloids can be accurately interpreted with little difficulty. Dendroxine (Ⅱ) exhibits a fragmentation behavior which is completely analogous to that of dendrobine (I) except for the appropriate 28 mass unit increment due to the oxazolidine ring E. The close similarity in behavior of dendrobine (I) and dendroxine (Ⅱ) upon electron impact demonstrates that all of the common characteristic fragments (a, b, c, d, e, f, g and h) contain C, E ring of these alkaloids. The structural assignment of fragment ions and the fragmentation processes are summerized in Chart 1. The metastable ions at apropriate position, which is shown in Fig. 1, prove some of above fragmentation processes.

Now, in the mass spectrum of dendramine (Ⅲ), the lower mass range down from m/e 109 is identical with that of dendrobine (I), whereas the higher mass range is shifted by 16 mass unit because of an additional oxygen. Thus the structure of the ions at m/e 96, 108 and 109 is identical to that of dendrobine (h_1, g_1, and f_1, respectively), while the ions at 279, 236, 222, 208, 194 and 152 retain an additional hydroxyl oxygen in them. It is deduced from these facts that C ring of dedramine is identical to that

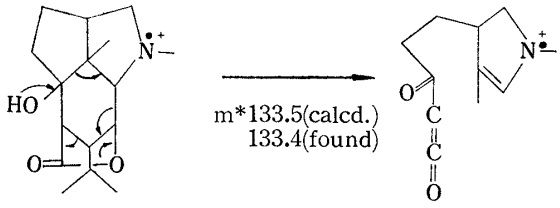
4) T. Onaka, S. Kamata, T. Maeda, Y. Kawazoe, M. Natsume, T. Okamoto, F. Uchimaru, M. Shimizu: This Bulletin, **12**, 506 (1964); *Ibid.*, **13**, 745 (1965).
5) H. Matsuda, Y. Tomiie, I. Nitta: The 18th Annual Meeting of Chemical Society of Japan. (Osaka, Apr. 2, 1965; Abstract of Papers; page 215).
6) Y. Inubushi, *et al.*: Yakugaku Zasshi, **83**, 1184 (1963); Tetrahedron, **20**, 2007 (1964).

of dendrobine (I) and does not bear the additional hydroxyl group in it. The lowest mass ion which bears the additional oxygen appears at m/e 152 as a rather intense peak. It corresponds to the fragment e whose fragmentation from a has been proved by metastable ion in the spectrum of dendroxine (II) (see Fig. 1), and may be represented by the structure e'_3 (Chart 2).



a_3 e'_3

Chart 2.

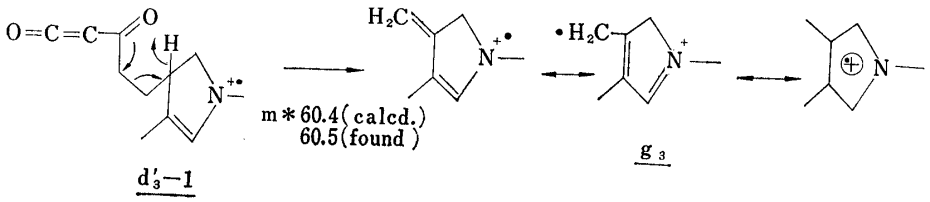


M^+ d'_3-1

Chart 3.

Therefore, the additional oxygen of dendramine must be located at ring B, and the structure III is readily assigned for dendramine, when the tertiary nature of additional hydroxyl group is taken into account. The m/e 193 peak of dendramine (III) does not correspond to the ion d (M–85), but loss of one mass unit is observed. The recognition of a metastable ion at m/e 133.4 demonstrates that the d'–1 ion above mentioned is formed, at least in part, directly from molecular ion ($m^*_{calcd.}=133.5$) (Chart 3).

The further decomposition of the d'–1 ion proceeds by transfer of the C–13 hydrogen atom in a six-membered transition state to yield the fragment ion g, that is proved by the presence of metastable ion at m/e 60.5 (Chart 4).



d'_3-1 g_3

Chart 4.

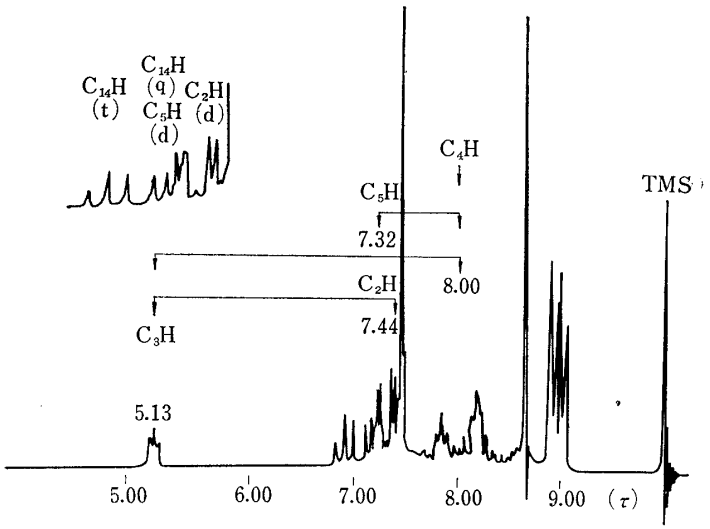


Fig. 2.

This formulation of fragments also rationalizes the structure (III) of dendramine. Other fragmentation processes are analogous to dendrobine and summarized in Chart 1.

Further NMR study at 100 Mc. provides an additional proof for the structure of dendramine. There are rather complex signals at 6.9~7.5 τ in the NMR spectrum of dendramine (III) (Fig. 2), which will be interpreted as the combination of a triplet, a quartet and two doublets by analogy of cyanonordendrobine.[4] The double resonance technique proves

that the quartet at 5.13 τ is coupled with the doublet at 7.44 τ (J=3.4 c/s) and also with the multiplet at 8.00 τ. The doublet at 7.32 τ (J=3.8 c/s) collapses to a singlet by irradiation of 8.00 τ. From these experimental results the following four important conclusion are deduced :

i) doublet at 7.44 τ is N-$C_2\underline{H}$- and coupled with $C_3\underline{H}$-OCO- at 5.13.
ii) $C_3\underline{H}$ is also coupled with $C_4\underline{H}$ which appears at 8.00 τ as a mutiplet.
iii) the doublet at 7.32 τ is coupled with $C_4\underline{H}$ at 8.00 τ, which, therefore, represents a methine proton at C_5(>C_4H-$C_5\underline{H}$-COO-).
iv) doublet nature of C_5 methine proton indicates that there is no proton at C_6.

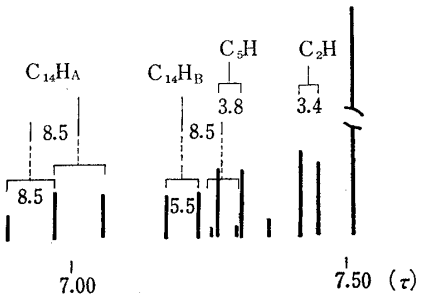


Fig. 3.

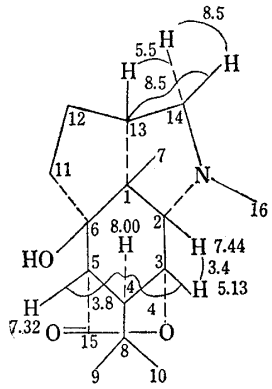


Fig. 4.

The results of the analysis are summarized in Fig. 3 and 4, which indicate the presence of a proton at C_{13} and absence of proton at C_6. 6-Oxydendrobine (Ⅲ) is, then, finally proposed for the structure of dendramine.

The fifth alkaloid from *Dendrobium nobile* is amorphous and possesses an empirical formula of $C_{17}H_{25}O_4N$ (*Anal.* Calcd. : C, 66.42; H, 8.20; N, 4.56. Found : C, 66.06; H, 8.25; N, 4.38. mol. wt. : 307 (mass spec.)). The presence of γ-lactone (ν_{CO} 1782 cm^{-1}) and hydroxyl group is deduced from its infrared absorption spectrum in carbon tetrachloride. Its NMR spectrum is virtually superimposible to that of dendroxine (Ⅱ) as is in the case of dendrobine (Ⅰ) and dendramine (Ⅲ).

In its mass spectrum (Fig. 1) the fifth alkaloid (Ⅳ) again exhibits a fragmentation behavior identical to that of dendramine (Ⅲ) except for the appropriate 28 mass unit increment due to an oxazolidine ring, which has already been observed in the case of dendrobine (Ⅰ) and dendroxine (Ⅱ) (*vide supra*). This close similarity of mass spectrum with that of dendramine (Ⅲ) together with the same similarity of NMR spectrum with that of dendroxine (Ⅱ) clarifies that the fifth alkaloid from *Dendrobium nobile* must be 6-oxydendroxine (Ⅳ).

The authors are grateful to Dr. J. Shinoda and Dr. T. Ishiguro for their kind encouragements.

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Received February 28, 1966