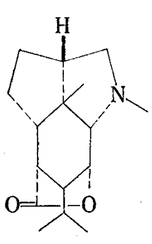
[Chem. Pharm. Bull. 14(6) 672~675 (1966)]

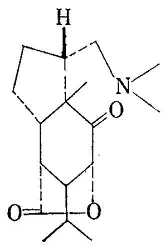
UDC 581.19 : 58.59 : 547.94

The Structure of Dendroxine[*1]
The Third Alkaloid from *Dendrobium nobile*

In the previous communication from these laboratories, it has been reported that the basic fraction of *Dendrobium nobile*[*2] consisted of four crystalline alkaloids at least,[1] among which dendrobine[2] and nobilonine[1] were fully investigated[3,4] and their structures were clarified to be I and II respectively. The present communication is concerned with the third alkaloid,[*3] for which the name of dendroxine is proposed.



I



II

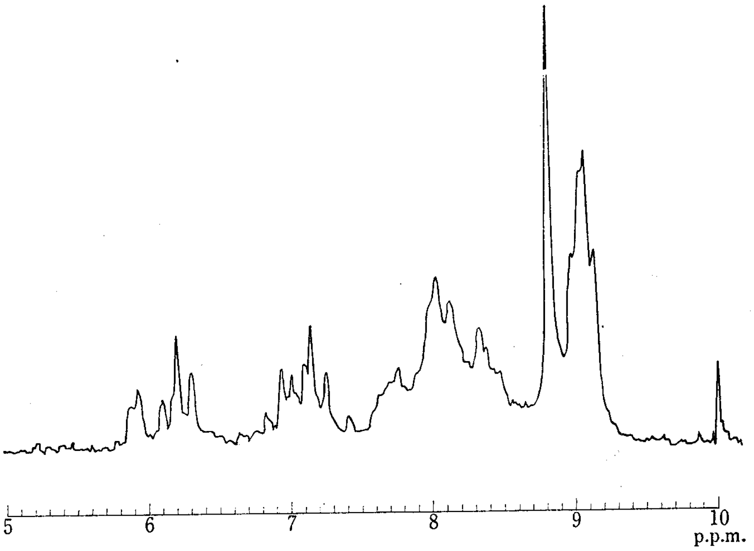


Fig. 1.

Dendroxine, m.p. 114~115°, $[\alpha]_D$ −30.1 (in EtOH), pKa′=4.5 (in 50% EtOH) possesses an empirical formula of $C_{17}H_{25}O_3N$ (*Anal.* Calcd. : C, 70.07; H, 8.65; N, 4.81. Found : C, 70.22; H, 8.67; N, 4.81. Molecular weight : 291 (mass spectrometric determination)) and the presence of γ-lactone (1778 cm^{-1}) and absence of hydroxyl group are deduced from its infrared absorption spectrum in potassium bromide.

Nuclear magnetic resonance spectrum (NMR) (Fig. 1) indicates the presence of two secondary methyl groups (9.05 τ; 6H, q, J=6 c/s), and one tertiary methyl group (8.80 τ; 3H, s) but the proton signal due to an N-methyl group can not be observed, contrary to those of dendrobine and nobilonine. The signal due to the methine proton adjacent to the lactone oxygen appears at 5.90 τ as a doublet (J=3 c/s), suggesting the partial structure (i) in dendroxine.

[*1] This paper was reported at the 85th Annual Meeting of the Pharmaceutical Society of Japan (Tokushima, Oct. 28, 1965); Abstract papers; page 315.

[*2] A species of orchid, ***Dendrobium nobile***, was presumed to be the original plant of Chinese drug Chin-Shin-Hu, whose alkaloidal constituents have been reported by Inubushi, ***et al.*** (This Bulletin, **12**, 1175 (1964)). Judging from their work, difference of the alkaloidal composition between ***Dendrobium nobile*** and Chin-Shin-Hu is obvious (cf. H. Suzuki, ***et al.*** : Yakugaku Zasshi, **54**, 821 (1934)).

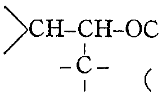
[*3] 76 mg. of pure compound is obtained from 82 kg. of fresh bulbs (stems) of ***Dendrobium nobile***.

1) T. Onaka, S. Kamata, T. Maeda, Y. Kawazoe, M. Natsume, T. Okamoto, F. Uchimaru, M. Shimizu : This Bulletin, **13**, 745 (1965).

2) ***Idem*** : ***Ibid.***, **12**, 506 (1964).

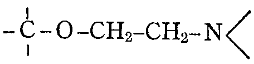
3) Y. Inubushi, ***et al.*** : Yakugaku Zasshi, **83**, 1184 (1963); Tetrahedron, **20**, 2007 (1964); Chem. & Ind. (London), **1964**, 1689.

4) Y. Hirata, ***et al.*** : Tetrahedron Letters, No. 2, 79 (1964); Nippon Kagaku Zasshi, **85**, 377 (1964).



$>CH\text{-}\underset{\underset{|}{\overset{|}{-C-}}}{CH}\text{-}OCO\text{-}$

(i)

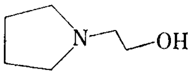


$\text{-}\overset{|}{\underset{|}{C}}\text{-}O\text{-}CH_2\text{-}CH_2\text{-}N<$

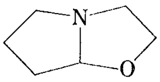
(ii)

The triplet centered at 6.20 τ (2H, J=6 c/s) is assigned to be the signal due to the methylene protons adjacent to oxygen. The shape of these signals indicates that they represent A_2 part of A_2B_2 coupling systems such as $\text{-}O\text{-}CH_2\text{-}CH_2\text{-}$. The complex multiplet at 6.8~7.3 τ (4H), attributable to the protons adjacent to nitrogen, is shown to be coupled with the triplet at 6.20 τ (double resonance experiment), so that the A_2B_2 system mentioned above can finally be formulated by the partial structure (ii).

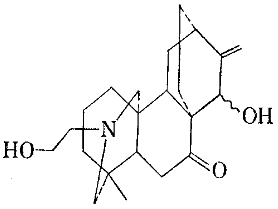
To certify these assignments, model compounds (Ⅲ and Ⅳ) are prepared⁵⁾ and a good coincidence of NMR data is observed between model compounds and dendroxine (Table I).



III



IV



XI

Table I.

	O-CH_2-CH_2-N	O-CH_2-CH_2-N	Other methylenes
Dendroxine (X)	6.20 (t, J=5.0)	6.8~7.3	
(Ⅲ)	6.47 (t, J=5.5)	7.5 (m)	8.39 (m)
(Ⅳ)	6.35 (difused)	7.0~7.5	8.20 (m)
β-Hydroxyethylnordendrobine (Ⅷ)	6.40 (t, J=5.5)	7.0~7.5	8.00 (m)
Isodendroxine (Ⅸ)	6.40 (t, J=5.5)	6.7 (m)	
Atidine (Ⅺ)⁶⁾	6.32 (t, J=6)		
Dihydroatidine⁶⁾	6.35 (t, J=6)		
Tetrahydroatidine⁶⁾	6.35 (t, J=6)		

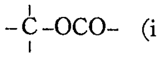
From these spectroscopic investigations the following functional groups are deduced for dendroxine: tertiary amino group without N-methyl, γ-lactone of partial structure (i) and ether oxygen of partial structure (ii).*5

When dendroxine is reduced catalytically (PtO_2/AcOH) at 40~50° an amorphous base (Ⅷ) is obtainable, showing OH or NH absorption band in its IR spectrum. The signal due to the methine proton adjacent to the lactone oxygen appears as a quartet at 5.20 τ instead of doublet at 5.90 τ of dendroxine. Its crystaline methiodide melts at 190~193°.

On the other hand, nordendrobine (Ⅶ), derived from dendrobine by Suzuki's method⁷⁾ (Chart 1), gives the same compound on treatment with ethylene oxide in methanol. This (2-hydroxyethyl)nordendrobine is also amorphous but its spectroscopic properties are in very good accord with structure (Ⅷ); IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3500 (br. OH), 1782 (γ-lactone). NMR τ_{CDCl_3}: 9.05 (6H, d, J=6 c/s, iso-C_3H_7), 8.61 (3H, s, t-CH_3), 7.36~6.76 (5H, m, methyl-

---

*5 An alternative partial structure (i′), (ii′) is also possible, which afterward is proved not to be the case.



$\text{-}\overset{|}{\underset{|}{C}}\text{-}OCO\text{-}$ (i′) $>CH\text{-}CH\text{-}O\text{-}CH_2\text{-}CH_2\text{-}N<$ (ii′)

5) N. J. Leonard: J. Am. Chem. Soc., **82**, 5148 (1960).
6) S. W. Pelletier: *Ibid.*, **87**, 799 (1965).
7) H. Suzuki, *et al.*: Yakugaku Zasshi, **54**, 801 (1934).

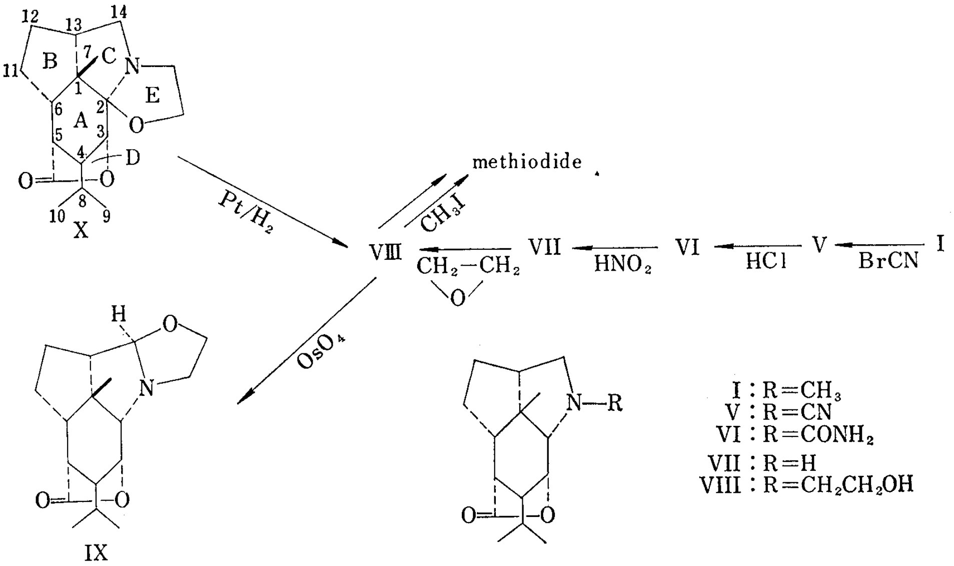


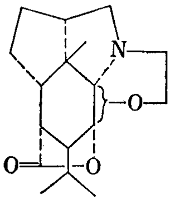
Chart 1.

enes and methines adjacent to nitrogen), 6.48 (2H, t, J=5.5 c/s, $-O-C\underline{H}_2-CH_2-N$), 5.20 $\left(1H,\ q,\ J=3\ \&\ 5\,c/s,\ -COO-\underset{\underset{|}{-CH}}{\underset{|}{C\underline{H}}}-\underset{|}{CH}-\right)$. $[\alpha]_D^{13.6}$ −56.9. pKa′ (in 50% EtOH) : 6.5.

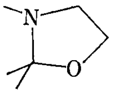
It forms a crystalline methiodide, m.p. 198~200°. *Anal.* Calcd. for $C_{18}H_{30}O_3NI$: C, 49.70; H, 6.95; N, 3.22. Found : C, 49.23; H, 6.94; N, 3.20. The presence of free hydroxyl group is confirmed by acylation with 3,5-dinitrobenzoyl cholride in pyridine. 3,5-Dinitrobenzoate; amorphous, IR $\nu_{max}^{CCl_4}$ cm^{-1} : 1785 (γ-lactone), 1740 (benzoate), 1550 and 1341 ($-NO_2$).

The identity of the product of hydrogenolysis of dendroxine and (2-hydroxyethyl)-nordendrobine is confirmed by the comparison of their IR spectra, gas and thin-layer chromatography. Optical identity is also confirmed by the comparison of $[\alpha]_D$ value.

Their crystalline methiodide is proved to be identical by means of mixed melting point determination and IR comparison. This experiment now clarifies the skeletal structure of dendroxine, and partial structure (iii) can be deduced.



(iii)



(iv)

The point of attachment of ether linkage is restricted to C_2, C_3 or C_{14} by the above reduction experiment. And, then, remarkable differense of the basicity between dendrobine and dendroxine further indicates that dendroxine is an α-carbinolamine ether (iv).

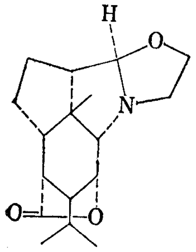
From the partial structures (i)~(iv), dendroxine is represented by the formulation of X. Mass spectroscopic evidences also agree with this structure (see succeeding communication).

Osmic acid oxidation of (2-hydroxyethyl)nordendrobine (VIII) affords a $C_{17}H_{25}O_3N$ compound, which is isomeric to dendroxine : m.p. 143~144°. *Anal.* Calcd. for $C_{17}H_{25}O_3N$: C, 70.07; H, 8.65; N, 4.81. Found : C, 70.29; H, 8.63; N, 4.85. mol. wt. (mass spec.) 291. pKa′ (in 50% EtOH) : 6.8. The compound, which is designated as isodendroxine, contains a γ-lactone (IR ν_{CO}^{KBr} : 1765 cm^{-1}) and no other carbonyl group. NMR spectrum of isodendroxine at 100 Mc. is consistent with the structure (IXa). (see Table II).

It might be interesting to point out that three dendrobium alkaloids hitherto obtained can be derived from the same original compound such as XII in orchidaceous plant. (Chart 2).

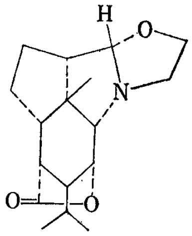
TABLE II.

Chemical shift (τ)	Intensity	Shape	J	Assignment
5.32	1H	s	0	$C_{14}\underline{H}$
5.47	1H	sym. t	4.5	$C_3\underline{H}$
6.22	2H	assym. t	6.5	$2\times C_{17}\underline{H}$
6.70	2H	m	—	$2\times C_{16}\underline{H}$
7.36	1H	d	4.5	$C_2\underline{H}$
8.54	3H	s	—	$3\times C_7\underline{H}$
9.03	6H	d	6.0	$3\times C_9\underline{H}$, $3\times C_{10}\underline{H}$



IXa

$J_{\text{calcd.}}$ =0c/s



IXb

$J_{\text{calcd.}}$ =7.8c/s

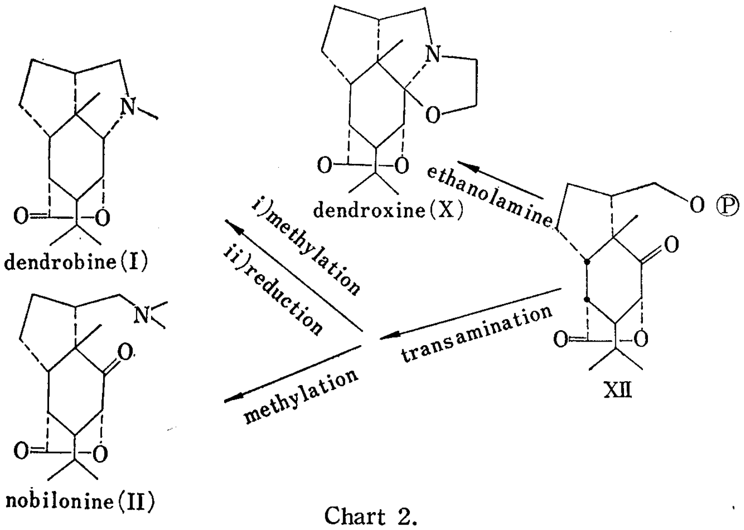


Chart 2.

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

Faculty of Pharmaceutical
Sciences, University of Tokyo,
Hongo, Tokyo

Toshihiko Okamoto (岡本敏彦)
Mitsutaka Natsume (夏目充隆)
Tadamasa Onaka (尾中忠正)

Central Research Laboratory,
Daiichi Seiyaku Co., Ltd.,
Minami-funabori-cho, Edogawa-ku, Tokyo

Fumihiko Uchimaru (内丸文彦)
Masao Shimizu (清水正夫)

Received February 28, 1966