upper-right octant, the sign of the Cotton-effect curve would be negative.*[4] More briefly, γ-lactones having 2-carbon of (S)-series (or (R)-series)*[5] will give a positive (or negative) Cotton-effect curve. Thus, arabonolactone should show a positive Cotton-effect curve. As shown in Table I, all of the five-membered sugar-lactones examined showed signs of their ORD curves as predicted from the above generality.

The above mentioned generality on γ-lactones is deduced from the data on several lactones available in this laboratory and the writers plan to test other γ-lactones in order to know whether there is any exceptional case in the above generality. In addition, the writers also wish to survey ORD curves of six-membered sugar-lactones in an attempt to investigate whether some generality is found or not.

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Received January 17, 1964

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*[3] It is not necessary to take account of near (front) octants, because the hydroxyl groups of γ-lactone are situated in far (back) octants.

*[4] A substituent at 3- or 4-carbon seemed to make almost no contribution to the sign of an ORD curve.

*[5] After the Cahn's convention (R. S. Cahn, C. K. Ingold, V. Prelog : Experientia, 12, 81 (1956)).

[Chem. Pharm. Bull. 12 (4) 506 ~ 512]

UDC 547.94.02 : 615.32

The Structure of Dendrobine*[1]

Dendrobine was first isolated from the Chinese crude drug "Chin-Shih Hu" by Suzuki in 1932 and the composition $C_{16}H_{25}O_2N$ was given by the same author.[1] Dendrobine (I), $C_{16}H_{25}O_2N$, m.p. 135~136°, $[\alpha]_D^{28}$ −50.4 (abs. EtOH) contains one $N-CH_3$ group (NMR*[2] τ_{CDCl_3} 7.48), one five-membered ring lactone (IR : ν_{max}^{KBr} 1765 cm^{-1}, NMR τ_{CDCl_3} 5.15 ($>C\underline{H}-O-CO-$)), and the presence of three $C-CH_3$ groups were assumed in the nuclear magnetic resonance spectrum (τ_{CDCl_3} 8.59 singlet ($-\overset{|}{\underset{|}{C}}-C\underline{H}_3$), 8.94 doublet, 9.05 doublet ($2-\underset{|}{C}H-C\underline{H}_3$ or $C\underline{H}_3-\underset{|}{C}H-C\underline{H}_3$)).

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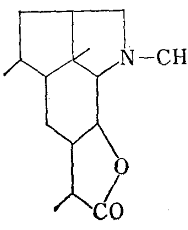
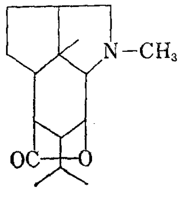
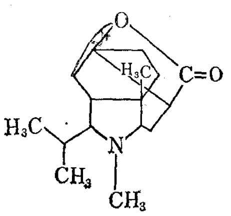
*[1] This paper was reported at the 7th Symposium on the Chemistry of Natural Products, Japan (Fukuoka, Oct. 17, 1963). Although the authors had postulated the structure (1) for dendrobine on the "Symposium Abstracts" (issued on Sep. 15, 1963, pp. 62~65), they proposed the structure (2) as the possible one at the Symposium, the proposal of which is concluded in the present communication. Y. Hirata, *et al.* reached the same conclusion as that of the present authors at the above Symposium, though they had given the other structure (3) for this alkaloid on the abstracts (pp. 66~71).



1



2

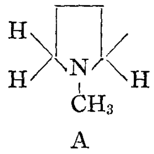


3

*[2] NMR spectra were measured by Varian DP 60 spectrometer and JNM-3-H-30 spectrometer (Japan Electron Optics Laboratory Co. Ltd.) operated at 60 Mc.

1) H. Suzuki, *et al.* : Yakugaku Zasshi, 52, 996, 1049 (1932); 54, 801 (1934).

On reacting with bromine cyanide in ether,[2] dendrobine (I) was converted into cyanonordendrobine (II), $C_{16}H_{22}O_2N_2$, m.p. 184~186°, IR ν_{max}^{KBr} cm^{-1} : 2115 (CN), 1775 (five-membered ring lactone), NMR τ_{CDCl_3} 6.08~6.83 multiplet ($-C\underline{H}_2-\overset{|}{N}-C\underline{H}-$), 5.15 quartet ($-C\underline{H}-OCO-$), which was hydrolyzed to norcarbamide (III), $C_{16}H_{24}O_3N_2$, m.p. 240°, IR ν_{max}^{KBr} cm^{-1}: 3425, 3110 (NH), 1767 (five-membered lactone), 1655, 1607 ($CONH_2$), NMR τ_{CDCl_3} 6.0~7.0 multiplet ($-C\underline{H}_2-\overset{|}{N}-C\underline{H}-$), and then to nordendrobine (IV), $C_{15}H_{22}O_2N$, m.p. 116~118°, IR ν_{max}^{KBr} cm^{-1} : 3190 (NH), 1778 (five-membered ring lactone). These reactions definitely show a sequence of the changes, $\rangle N-CH_3 \rightarrow \rangle N-CN \rightarrow \rangle N-CONH_2 \rightarrow \rangle NH$.


A

Oxidation of dendrobine (I) with chromium trioxide in pyridine affords a lactam compound (V), m.p. 205~206° (*Anal.* Calcd. for $C_{16}H_{23}O_3N$: C, 69.28; H, 8.36; N, 5.05. Found : C, 69.27; H, 8.41; N, 4.81), IR ν_{max}^{KBr} cm^{-1} : 1780 (five-membered ring lactone), 1700 (five-membered ring lactam), NMR τ_{CDCl_3} 7.18 singlet ($CO-\overset{|}{N}-C\underline{H}_3$), 6.74 doublet ($-CO-\overset{|}{N}-C\underline{H}-$), 5.25 quartet ($\rangle C\underline{H}-OCO-$)). Whereas cyanonordendrobine (II) and the norcarbamide (III) show multiple signals of $-C\underline{H}_2-N-C\underline{H}-$ group in the nuclear magnetic resonance spectra, the lactam compound (V) has only one $\underline{H}$ signal due to the group $-CO-\overset{|}{N}-C\underline{H}-$. Further the amide band at 1700 cm^{-1} in the infrared spectrum indicates a five-membered character of the nitrogen containing ring. Thus, the partial structure (A) should be given for dendrobine (I).

The lactone ring in dendrobine (I) can be hydrolyzed to corresponding hydroxy acid[2] (VI), $C_{16}H_{27}O_3N$, m.p. 230~232°, IR ν_{max}^{KBr} cm^{-1} : 3135 (OH), 1570 (COO^-), and on esterification, this gave the methyl ester (VII), $C_{17}H_{29}O_3N$, m.p. 90~93°, IR ν_{max}^{KBr} cm^{-1} : 3605 (OH), 1723 ($COOCH_3$), NMR τ_{CDCl_3} 6.17 quartet ($\underline{H}-\overset{|}{\underset{|}{C}}-OH$), 6.35 singlet ($COOC\underline{H}_3$), 7.63 singlet ($\rangle N-C\underline{H}_3$), 7.92 doublet ($\rangle N-C\underline{H}\langle$). On acetylation the ester (VII) was converted to the acetate (VIII), $C_{19}H_{31}O_4N$, m.p. 76°, NMR τ_{CDCl_3} 5.04 quartet ($\underline{H}-\overset{|}{\underset{|}{C}}-OCOCH_3$), 6.32 singlet ($COOC\underline{H}_3$), 7.84 doublet ($\rangle N-C\underline{H}\langle$), 7.95 singlet ($-OCOC\underline{H}_3$).

Oxidation of the methyl ester (VII) with chromium trioxide in pyridine gave a ketolactam compound (IX), m.p. 127~129° (*Anal.* Calcd. for $C_{17}H_{25}O_4N$: C, 66.42; H, 8.20. Found: C, 66.31; H, 8.22, IR ν_{max}^{KBr} cm^{-1} : 1745 ($COOCH_3$), 1722 (six-membered ring ketone), 1690 (five-membered ring lactam), NMR τ_{CDCl_3} 6.27 singlet ($COOC\underline{H}_3$), 6.62 singlet ($\rangle N-C\underline{H}\langle$), 7.00 singlet ($\rangle N-C\underline{H}_3$)). After hydrolysis, the ketolactam compound (IX) showed infrared absorption bands at 1720 and 1680 cm^{-1} in chloroform solution (in the presence of Et_2NH) and the band at 1722 cm^{-1} must therefore be that of the ketone group. This suggests a six-membered character of hydroxyl-containing ring of the hydroxy acid (VI). The assignment was also supported by the fact that the acetylation shift of $\underline{H}-\overset{|}{\underset{|}{C}}-OH$ (VII) → $\underline{H}-\overset{|}{\underset{|}{C}}-OCOCH_3$ (VIII) in the nuclear magnetic resonance spectra was 71 c.p.s.[3]

Dendrobine (I) was reduced with lithium aluminum hydride to the diol (X), m.p. 110~110.5° (*Anal.* Calcd. for $C_{16}H_{29}O_2N$: C, 71.86; H, 10.93; N, 5.24. Found : C, 71.54; H, 10.96; N, 5.09) and this gave a diacetate (XI) on acetylation with acetic anhydride in pyridine. The diacetate (XI) was amorphous but formed crystalline methiodide (XII), m.p. 256~257° (decomp.) (*Anal.* Calcd. for $C_{21}H_{36}O_4NI$: C, 51.11; H, 7.35. Found : C, 51.43; H, 7.28). Dendrobinediol (X) can be recovered when the acetate (XI) was reduced with lithium aluminum hydride. The diacetate (XI) showed typical ABX type signals

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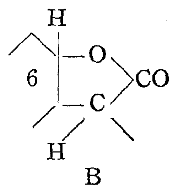
[2] The date by H. Suzuki were reexamined. cf. reference 1).

[3] T. Okamoto, Y. Kawazoe : 2nd Symposium on NMR, Nov. 21, 1962 at Tokyo. The acetylation shifts $\underline{H}-\overset{|}{\underset{|}{C}}-OH \rightarrow \underline{H}-\overset{|}{\underset{|}{C}}-OCOCH_3$ in five-membered ring are 48~56 c.p.s. and 60~78 c.p.s. in six-membered ring.



B

in the nuclear magnetic resonance spectrum at 5.6~6.2 ($CDCl_3$), $|J|_{AB}$= 10.5 c.p.s., which can be assigned to that of $-C\underline{H}_2-$ in $\rangle CH\text{-}CH_2\text{-}OCOCH_3$ group. Consequently, the presence of $\rangle CH\text{-}CO\text{-}O\text{-}$ group in dendrobine (I) was suggested. These results lead to the partial structure (B) for dendrobine (I).

Dendrobine (I) contains three $C\text{-}CH_3$ groups, one of which is tertiary ($\geqslant C\text{-}CH_3$) and the other two are probably $\rangle CH\text{-}CH_3 \times 2$ or isopropyl group from its nuclear magnetic resonance spectrum. $C\text{-}CH_3$ determination by the Kuhn-Roth method[4] gave 1.04 moles of acetic acid. Dendrobine (I) was oxidized with chromium trioxide-sulfuric acid by Karrer's method,[5] the volatile acids produced were analyzed by gas chromatography, and two acids, acetic acid (Rt. 9.1 min.) and isobutyric acid (Rt. 25.0 min.) (DC 550. H_3PO_4 on Microsorb W,[6] 20:5:100 w/w, temp. 90°, N_2 : 40 ml./min.), were detected. The acids were also identified by paper partition chromatography,[7] acetic acid, Rf 0.33, isobutyric acid, Rf 0.53 (Toyo Roshi No. 50 filter paper, 95% EtOH- conc. NH_4OH, 100:1). This identification of isobutyric acid in the oxidation products supports the presence of isopropyl group in dendrobine (I).

The following data give more information about the lactone group. On reacting with C_6H_5MgBr, dendrobine (I) was converted into diphenyldiol compound (XIII), m.p. 167~167.5° (*Anal.* Calcd. for $C_{28}H_{37}O_2N$: C, 80.15; H, 8.89. Found : C, 80.17; H, 8.96. IR ν_{max}^{KBr} cm^{-1}: 3340 (OH), 1600, 1490, 746, 704 (arom.), NMR τ_{CDCl_3} 2.0~3.0 multiplet, 10 H (arom. $\underline{H}$), 7.63 singlet ($\rangle N\text{-}C\underline{H}_3$), 9.30 doublet, 9.68 doublet ($C\underline{H}_3\text{-}\overset{|}{C}H\text{-}C\underline{H}_3$)). Treatment of XIII with acetic anhydride-pyridine at room temperature affords a monoacetate (XIV), m.p. 170~172° (*Anal.* Calcd. for $C_{30}H_{39}O_3N$: C, 78.05; H, 8.52. Found : C, 78.12: H, 8.51. IR ν_{max}^{KBr} cm^{-1} : 3510 (OH), 1745 ($OCOCH_3$), 1600, 1500, 750, 730 (arom.), NMR τ_{CDCl_3} 4.71 quartet ($\underline{H}\text{-}\overset{|}{\underset{|}{C}}\text{-}OCOCH_3$), 7.67 singlet ($\rangle N\text{-}C\underline{H}_3$), 7.96 singlet ($OCOC\underline{H}_3$), 8.71 singlet ($-\overset{|}{\underset{|}{C}}\text{-}C\underline{H}_3$), 9.31 doublet, 9.50 doublet ($C\underline{H}_3\text{-}\overset{|}{C}H\text{-}C\underline{H}_3$)). This was treated with phosphorus oxychloride-pyridine at 40~50° to give the dehydro compound (XV), amorphous, IR $\nu_{max}^{CCl_4}$ cm^{-1} : 1750 ($COCH_3$), 1600, 1490, 710 (arom.), no band corresponding to OH group was observed, NMR τ_{CDCl_3} 4.43 triplet ($\underline{H}\text{-}\overset{|}{C}\text{-}OCOCH_3$), 7.60 singlet ($>N\text{-}C\underline{H}_3$), 7.82 singlet ($-OCOC\underline{H}_3$), 8.70 singlet ($-\overset{|}{\underset{|}{C}}\text{-}C\underline{H}_3$), 9.12 doublet, 9.20 doublet ($C\underline{H}_3\text{-}\overset{|}{C}H\text{-}C\underline{H}_3$). The dehydro compound (XV) gave a crystaline methiodide (XVI), m.p. 178~180° (*Anal.* Calcd. for $C_{30}H_{37}O_2N \cdot CH_3I \cdot H_2O$: C, 61.74; H, 7.02. Found : C, 61.55; H, 6.77). These reactions may be written as shown in Chart 1. The final product (XV) has no signal of a vinylmethyl group in its nuclear magnetic resonance spectrum and, therefore C* is not a methyl group in the partial structure (C).

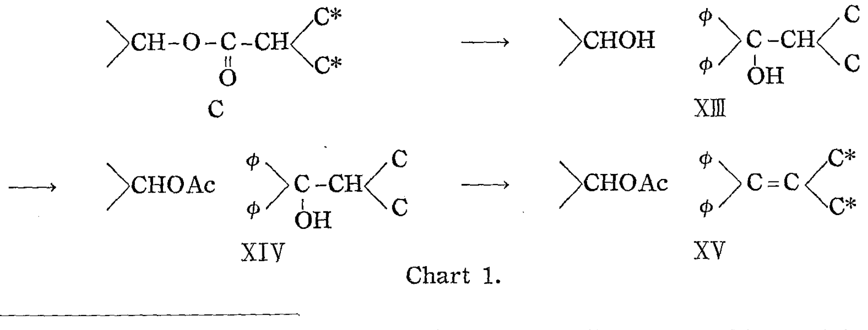


Chart 1.

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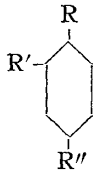
[4] E. J. Eisenbrann, S. M. McElvain, B. F. Aycock : J. Am. Chem. Soc., **76**, 607 (1954).
[5] C. F. Garbers, H. Schmidt, P. Karrer : Helv. Chim. Acta, **37**, 1336 (1954).
[6] Teflon coated support. cf. T. Onaka, T. Okamoto : This Bulletin, **10**, 757 (1962).
[7] A. G. Long, J. R. Quayle, R. J. Stedman : J. Chem. Soc., **1951**, 2197.

On selenium dehydrogenation, dendrobine (I) and dendrobinediol (X) gave alkylbenzenes as main products but neither naphthalene nor phenanthrene was isolated. The alkylbenzenes were analyzed by gas chromatography and the "chromatospectra" were obtained as shown in Fig.1. The structures of the products were assigned by comparing retention times of these with those of synthesized alkylbenzenes. These results proved the presence of a six-membered carbon ring in the skeleton of dendrobine (I) and also indicated the points of attachment of the remaining carbon chains. Thus, the partial structure (D) is given for dendrobine (I).



D

$R=CH_3$

$R', R''=$carbon chain

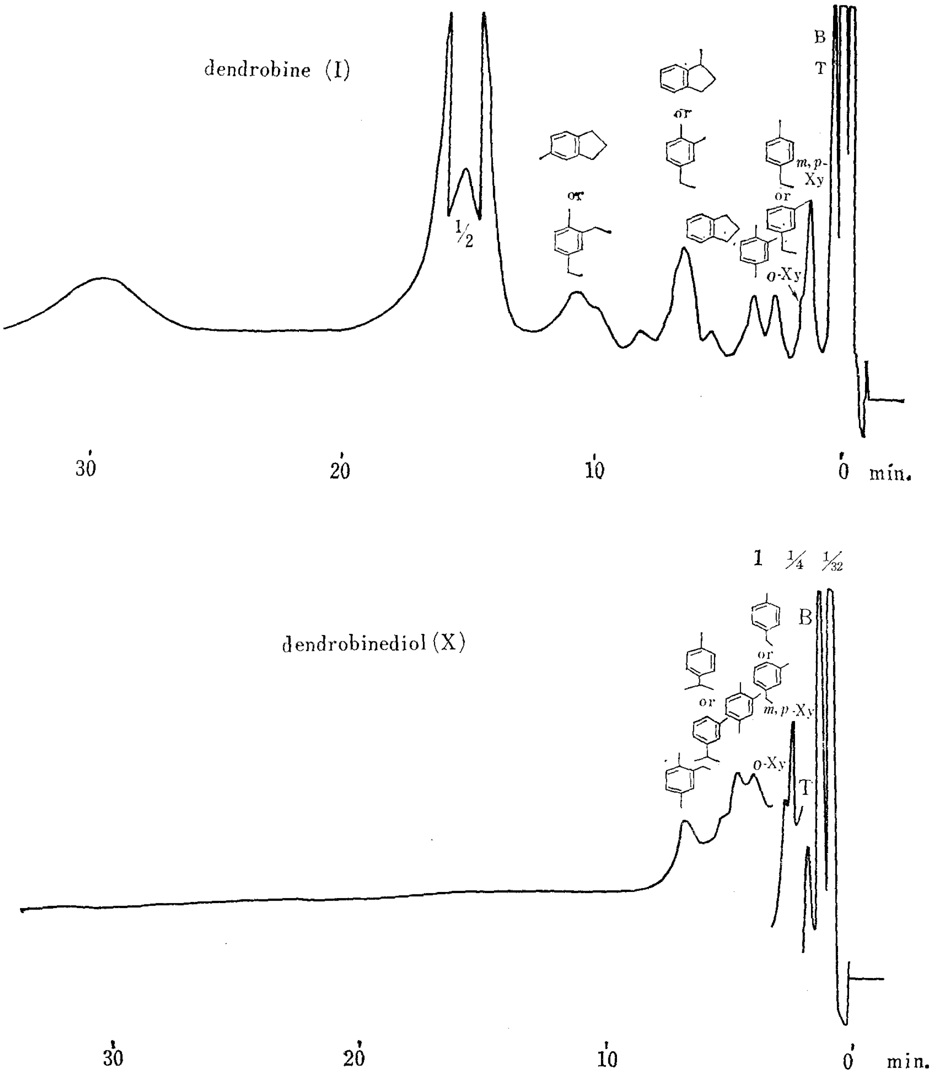
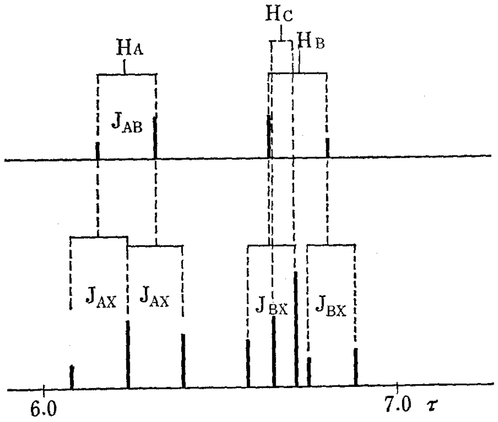


Fig. 1. Chromatospectra of the Dehydrogenation Products of Dendrobine (I) and Dendrobinediol (X)

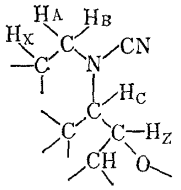
Gas chromatographic conditions
Column: Silicon DC 550 5% on Microsorb W 60~80 mesh
o.d. ¼" Cu tube 2 m. temp. 128°
Carrier gas: N_2, 1 kg./cm^2 H_2, 0.5 kg./cm^2 air, 0.5 L./min.
Detector: flame ionization detector.

More detailed information about the structure around nitrogen atom was obtained by the analysis of the nuclear magnetic resonance spectrum of cyanonordendrobine (Ⅱ). The multiple signals between 6 and 7 τ in the spectrum are assigned to those of protons of $-C\underline{H}_2-\overset{|}{N}-C\underline{H}-$ group. It was shown by the decoupling technique that the N-methine signals of $-CO-\overset{|}{N}-C\underline{H}-$, τ_{CDCl_3} 6.74, doublet in dendrobine lactam (V), are coupled with the proton signals of $\rangle C\underline{H}-OCO-$ group, τ_{CDCl_3} 5.26, quartet. Considering this fact the multiple signals of cyanonordendrobine (Ⅱ) were analyzed and these were concluded to be the signals of H_A, H_B, and H_C of ABX, CZ types as shown in Fig. 2. Further, the signals Hc are doublet and quartet in Hz and the partial structure (E) may be given. The nuclear magnetic resonance spectrum of the norcarbamide (Ⅲ) was similarly analyzed.



J_{AB}=9.5 c.p.s., J_{AX}=9.5 c.p.s., J_{BX}=7.0 c.p.s., J_{CZ}=3.5 c.p.s

Fig. 2.



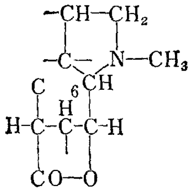
E

This partial structure (E), which has a lactone oxygen atom at β-position to the nitrogen atom is also supported by the changes of pKa′ values of dendrobine derivatives. The pKa′ values of the OH-free derivatives, which may form hydrogen bond between OH and N atom, are always larger than those of others as shown in Table I.

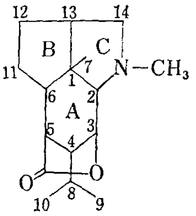
Table I.

	pKa′ (in 50% EtOH)		pKa′ (in 50% EtOH)
Dendrobine (I)	7.3	Acetyl dendrobinic acid methyl ester (Ⅷ)	6.7
Dendrobinic acid (Ⅵ)	9.15		
Dendorbinic acid methyl ester (Ⅶ)	8.7	Dendrobinediol (X)	9.0

Dendrobine (I) should have four rings in its molecule on the basis of molecular formula and the functional groups. When the partial structures A, B, C, and E, are combined, only one formula (F) is obtained. Further, considering the structures of the dehydrogenation products and the remaining isopropyl group, dendrobine (I) may be allotted the full structure (G).



F

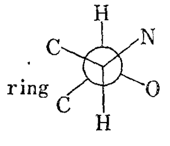


G
dendrobine

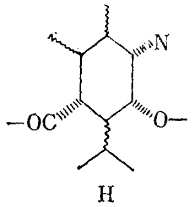
The stereochemical conformation of dendrobine (I) is analyzed as follows.

1) Five-membered ring lactone is formed at β-positions of cyclohexane ring and therefore C_3-C and C_5-CO bands must be in *cis* configuration.

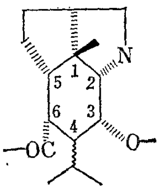
2) Formation of a hydrogen bond between N atom and OH group (in the hydroxy acid derivatives) suggests that C_2-N and C_3-O bands may be in *cis* or *trans*-di-equatrial. The latter may be excluded by the value, 4 c.p.s. of C_2HC_3H, observed in methyl dendrobinate (Ⅶ), and H remains as a possible structure.



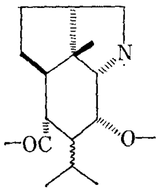
trans-di-equatrial



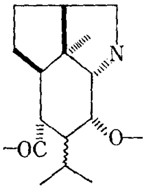
3) Possible ring fusion of the B and C ring is *cis-cis* or *cis-trans* but *trans-trans* fusion is impossible. This gives three possible formulae (I), (J), (K). Structure (J) is excluded by the value, 3 c.p.s. of $|J|_{C_5CH_6H}$ confirmed in the ketolactam compound (Ⅸ).



I



J

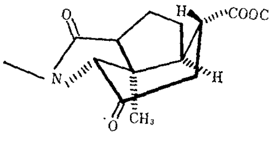


K

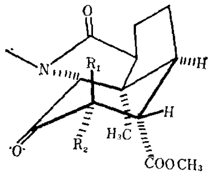
Formula	J	Bond angle	$\|J\|_{CH_5CH_6}$ Calcd.
A ring :	boat	180°	11 c.p.s.
A ring :	chair	170°	10.9

Two conformers are possible for structure (K) but these also may be excluded by the analyses of the coupling constants of $|J|_{C_6HC_5H}$, $|J|_{C_5HC_4H}$, as shown below.

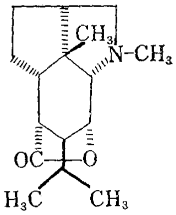
		Bond angle	$\|J\|_{Calcd.}$	$\|J\|_{Found}$
Ka	C_5H-C_6H	158°	10.0	3.0
Kb	C_5H-C_6H	80°	0.0	3.0
	C_4R_1-C_5H (R_1=H)	38°	5.0	9.0
	C_4R_2-C_5H (R_2=H)	82°	0.0	9.0



Ka



Kb



L
dendrobine

4) Configuration of the isopropyl group should be *trans* with C_3-O bond as calculated by $|J|_{C_3HC_4H}$ of dendrobine (I).

Dendrobine $\|J\|_{C_3HC_4H}$	Bond angle	$\|J\|_{Calcd.}$	$\|J\|_{Found}$
trans	35°	5.6 c.p.s.	6 c.p.s.
cis	85°	0	

As the conclusion the authors propose structure (L) for the stereochemical conformation of dendrobine.

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

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12 (4) 512 ~ 514]

UDC 547.914.02 : 582.932

Structure of (+)-Isoolivil ((+)-Cycloolivil) and Some Lignans

Previously the *trans*-(2,3)-*trans*-(3,4) configuration was determined for lyoniresinol dimethyl ether (I), resinolide (Ⅱ) and retroresinolide (Ⅲ).[1]

Above conclusion was further proved by the nuclear magnetic resonance spectra of Ⅱ,[1] Ⅲ[1] and the cyclohemiacetal (Ⅳ),[2] m.p. 173° (*Anal.* Calcd. for $C_{24}H_{30}O_8$: C, 64.56; H, 6.77. Found : C, 64.69, 64.82; H, 7.10, 7.09), minor oxidation product of I, compared with the nuclear magnetic resonance spectrum of isotaxiresinol trimethyl ether (isolariciresinol dimethyl ether) (V),[*1] m.p. 174/180~181.3° (*Anal.* Calcd. for $C_{22}H_{28}O_6 \cdot H_2O$: C, 65.01; H, 7.44. Found : C, 65.00, 64.82; H, 7.13, 7.19) as a reference compound of which *trans*-(2,3)-*trans*-(3,4) configuration was proved by Schrecker and Hartwell.[3]

The signals assigned to a hydrogen atom on the carbon atom 4 were doublets, and the *trans*-(3,4) configuration was suggested by coupling constants for compounds (Ⅱ, Ⅲ, Ⅳ and V) (Table I).

Recently two structural formulae (Ⅵ)[4] and (Ⅶ)[5] were proposed for (+)-isoolivil ((+)-cycloolivil).

The presence of a hydrogen atom on the carbon atom 3 was determined as well as *trans*-(3,4) configuration for isoolivil dimethyl ether (Ⅷ), m.p. 183.3~184° (*Anal.* Calcd. for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found : C, 65.05; H, 7.02) with the nuclear magnetic resonance spectrum of this compound compared with the data tabulated on Table I.

So the structural formula of (+)-isoolivil ((+)-cycloolivil) was determined exclusively as Ⅶ.

[*1] Obtained by methylation of isotaxiresinol, extracted from the wood of *Taxus cuspidata* Sieb. et Zucc.[6]

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5) M. Smith : *Ibid.*, **1963**, 991.
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