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STRUCTURE OF DENDRINE

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STUDIES on the basic components of the Chinese drug "Chin-Shih-Hu" (Dendrobium nobile LINDL.) have resulted in the isolation of four crystalline alkaloids; dendrobine1), its metho-salt2), nobiline3) (=nobilonine4)) and dendramine2). Among these the structures2),3),4) of the first three have been established.

In this communication the authors wish to report the structure elucidation of dendrine which was first isolated as a minor alkaloid from this drug.

Dendrine (I), mp.* 191-192° has a molecular formula $C_{19}H_{29}NO_4$*; mol. weight 335 (mass spect.*); pKa' 5.2: $[\alpha]_D^{11}=-114°$ (c,0.85, $CHCl_3$); IR, $\nu_{max}^{CHCl_3}$ 1767 (γ-lactone) and 1727cm^{-1} (ester carbonyl group); NMR*, 8.90-9.15 (6H, doublet, isopropyl), 8.64 (3H, singlet, $\geqslant C-CH_3$), 7.54 (3H, singlet, $>N-CH_3$), 7.15 (1H, doublet, $J=2.8$ c.p.s., $>N-\overset{|}{\underset{|}{C}}-H$), 6.35 (3H, singlet, $-O-CH_3$), 5.11 τ (1H, quartet, $J_1=5.0$ c.p.s., $J_2=2.8$ c.p.s. $-O-\overset{|}{\underset{|}{C}}-H$).

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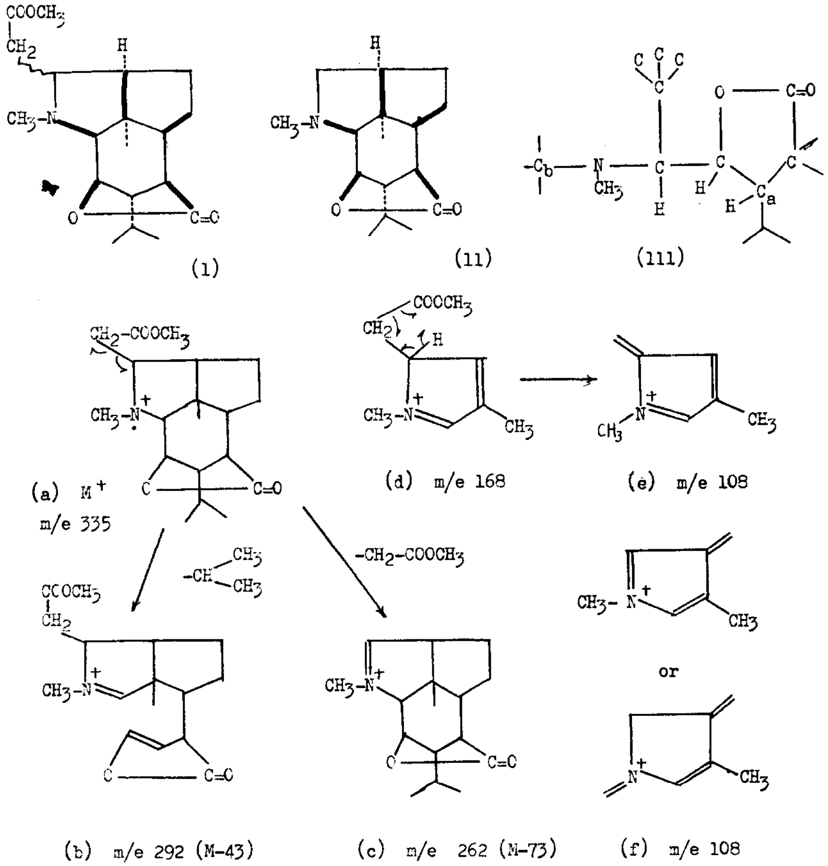
* All melting points were observed on a Kofler type microscopic hot stage and are uncorrected. All compounds given by formula in this communication gave correct elementary analysis. All PKa' values were measured in 50% EtOH. All NMR spectra were taken on Varian A-60 machine in $CDCl_3$ with $SiMe_4$ as an internal standard. Mass spectrum was measured with a Hitachi mass spectrometer model RMU 6C equipped with a heated inlet system: Ion accel. voltage m/e 600; Chamber voltage 80 V.; Total emission 80μA; Target current 55μA.

From the parallelism of IR and NMR spectra of dendrine and those of dendrobine it would be anticipated that dendrine has the same skeleton as that of dendrobine (II), and the NMR signals at 7.15 (1H, doublet) and 5.11τ(1H, quartet) suggest the partial structure of the right side from a nitrogen atom in formula (III). However, an increment of $C_3H_4O_2$ in the molecular formula as compared with that of dendrobine ($C_{16}H_{25}NO_2$) is noteworthy.

The mass spectrum of dendrine showed prominent peaks at m/e 335 (M^+, 4), 320 (4), 292 (13), 263 (18), 262 (base peak), 168 (7), 108 (15). The appearance of the peak at m/e 292 (M-43, b in Chart I) corresponding to the peak at m/e 220 (M-43)[3] in dendrobine suggests the presence of an isopropyl group at C_a in formula (III). Information on the circumstance of C_b in formula (III) came from further inspection of the mass spectrum. The base ion peak appeared at m/e 262 (m-73, c) is presumably due to loss of $C_3H_5O_2$ unit from the molecular ion. The presence of a metastable ion at m/e 205 seems to substantiate such a fragmentation. This fact, coupled with evidences from IR and NMR spectra, indicates that $C_3H_5O_2$ unit would be the carbomethoxymethylene group, and the strongest intensity[5] of the peak at m/e 262 would suggest that this group is substituted on C_b in formula (III). The assumption on the position of this group was also supported by another finding, thus dendrine has a pKa' of 5.2 compared with 7.5 for dendrobine and the acidic strength of the former is nearly the same order as that of acetonyldendrobine (VI, pKa' 5.6, vide infra). An ion at m/e 108 (e) may conceivably arise from the ion m/e 168 (d) by the bond fission cited in Chart I. Existence of a metastable ion at m/e 69.5 seems to substantiate such a fragmentation process. However, it has been reported by Hirata et al.[3] that an ion at m/e 108 (f) appeared in the mass spectrum of dendrobine. Therefore, the peak at m/e 108 seems to be an overlapped peak, each arising from at least two different fragmentations.

On the basis of these spectral evidences, the structure of dendrine could

Chart 1



be represented by formula (1).

An attempt was then made by means of chemical correlation of dendrine with dendrobine to establish firmly the structure of dendrine. For this purpose an alcohol (1V) was chosen as a relay substance.

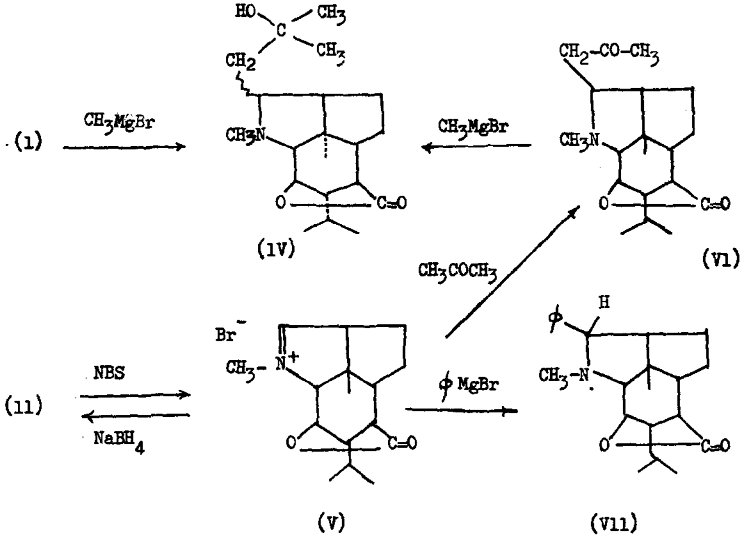
Oxidation of dendrobine (11) with N-bromosuccinimide afforded the immonium salt (V) (hygroscopic), mp. 238-241° (decomp.), $C_{16}H_{24}NO_2Br\cdot 1/2H_2O$; IR_{max}^{KBr} 1781 (γ-lactone), 1673cm^{-1} ($>C=N^{+}<$); NMR 8.68-9.11 (6H, two doublets, isopropyl), 8.33 (3H, singlet, $\geqslant C-CH_3$), 6.00 (3H, broad singlet, $\geqslant N^{+}-CH_3$), 5.11 (1H, doublet, J =3.5 c.p.s., $\geqslant N^{+}-\overset{|}{\underset{|}{C}}-H$), 4.77 (1H, triplet, J =3.5 c.p.s., $O-\overset{|}{\underset{|}{C}}-H$), 0.67 τ (1H., multiplet, $>N^{+}=C\langle_{H}$). Reduction of the immonium salt with sodium borohydride regenerated dendrobine as expected. Chromatography of (V) on neutral alumina with acetone gave acetonyldendrobine (VI), $C_{19}H_{29}NO_3$, mp. 88-90°; IR_{max}^{KBr} 1780 (γ-lactone), 1718cm^{-1} ($C=O$); NMR 8.90-9.17 (6H, doublet, isopropyl), 8.64 (3H, singlet, $\geqslant C-CH_3$), 7.85 (3H, singlet, $-CO-CH_3$), 7.54 (3H, singlet, $>N-CH_3$), 7.17 (1H, doublet, J =3.0 c.p.s., $>N-\overset{|}{\underset{|}{C}}-H$), 5.11 (1H, quartet J_1 =5.0 c.p.s.; J_2 =3.0 c.p.s., $-O-\overset{|}{\underset{|}{C}}-H$). This reaction sequence was demonstrated by analogous reaction of the immonium salt with phenylmagnesium bromide, providing phenyldendrobine (VII), mp. 128-129°, $C_{22}H_{29}NO_2$, IR_{max}^{Nujol} 1767 (γ-lactone), 747, 701cm^{-1} (aromatic ring). In the NMR spectrum of (VII) the signal at 6.58-6.86 τ (1H, doublet, J =11.0 c.p.s.) was suggestive to the position of the phenyl group attached to the dendrobine nucleus.

Treatment of methylmagnesium iodide with acetonyldendrobine afforded an alcohol (IV), mp. 78-81°, $C_{20}H_{33}NO_3\cdot 1/2H_2O$[**]; IR_{max}^{KBr} 3450 (OH), 1775cm^{-1} (γ-lactone); $[\alpha]_D^{11}$=-140° (c,0.80,MeOH): NMR, 9.04 (6H, doublet, J =6.0 c.p.s., isopropyl), 8.75 (6H, singlet, two methyl groups), 8.60 (3H, singlet, $\geqslant C-CH_3$), 7.55 (3H, singlet, $>N-CH_3$), 7.15 (1H, doublet, J =2.8 c.p.s., $>N-\overset{|}{\underset{|}{C}}-H$), 5.11 τ (1H, quartet, J_1 =5.0 c.p.s., J_2 =2.8 c.p.s., $-O-\overset{|}{\underset{|}{C}}-H$).

On the other hand the alcohol obtained by Grignard reaction of dendrine with methylmagnesium iodide was proved to be identical in all respects with that derived from dendrobine (thinlayer chromat., mixed mp., $[\alpha]_D$, IR, NMR).

[**] A distilled sample (oil) gave the following analytical data : $C_{20}H_{33}NO_3$ requires : C, 71.60; H, 9.92; Found : C, 71.15; H, 10.20.

Consequently, dendrine is represented by stereostructure (I) with only the configuration of the carbomethoxymethylene group to be settled.



There still remains a question that dendrine might be an artifact arising from dendrobine during the extraction procedure. However, the failure of direct introduction of the carbomethoxymethylene group to the immonium salt (V) would eliminate this possibility. The assumption that the immonium salt or its equivalent might be an intermediate of biosynthetic route of dendrine from dendrobine would be yet probable.

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