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STRUCTURES OF NOBILINE AND DENDROBINE

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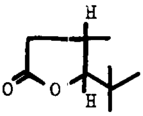
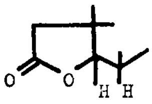
An alkaloid, dendrobine (m.p. 135 - 136°, $C_{16}H_{25}O_2N$), was first isolated in 1932 from *dendrobium nobile* by Suzuki et al.,[1] who reported only the presence of a γ-lactone and a tertiary N-methyl group in dendrobine. We have isolated two kinds of alkaloid from *dendrobium nobile*, one of which is the same as that reported by Suzuki et al. The other is a new alkaloid, nobiline, m.p. 87 - 88° (Found: C, 69.71; H, 9.30; N, 4.74. $C_{17}H_{27}O_3N$ requires: C, 69.59; H, 9.28; N, 4.77%). In this communication we wish to report the structures of nobiline and dendrobine.[2]

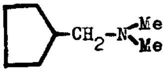
Nobiline has a molecular formula, $C_{17}H_{27}O_3N$; mol. wt. 293 (mass spec.); ORD ϕ^{P}_{320} +10.4 × 10^2 (in MeOH); pKa' 8.50 (in water); ν^{KBr}_{max} 2850 - 2700 (NMe), 1785 (γ-lactone) and 1706 cm^{-1} (saturated six-membered ring ketone); NMR signals at 9.06 (methyl doublet J = 6 c.p.s.), 9.03 (methyl doublet J = 6 c.p.s.), 8.66 (methyl singlet), 7.90 (N-dimethyl singlet) and 5.52 τ(1H doublet J = 5 c.p.s.) (in $CDCl_3$); C-Me (Kuhn-Roth oxidation) 1.41 mol. (for nobiline hydrochloride);[3] mass spec. peaks at m/e 293 (4.6), 250 (2.0), 206 (1.9), 97 (2.1), 91 (2.8), 84 (5.7) and 58 (base peak). The remarkable NMR peak at 5.52 τ(1H doublet J = 5 c.p.s.) and IR spectrum (ν^{KBr}_{max} 1785 cm^{-1}) indicate the presence of the partial structure (I) or (II).



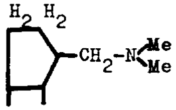
(I)



(II)



(III)

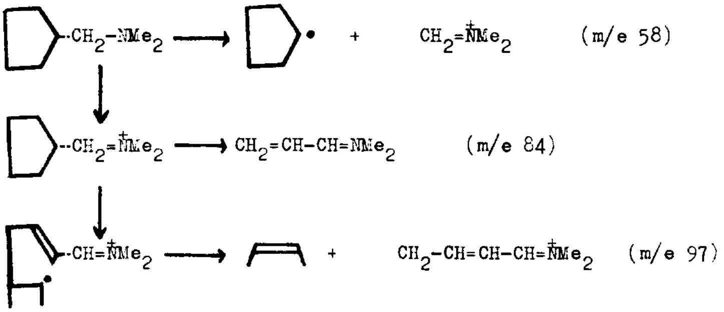


(IV)

The NMR signals at 9.06 and 9.03 τ(two methyl doublets J = 6 c.p.s.) and the peak at m/e 250 suggest that nobiline has an isopropyl group.[4]

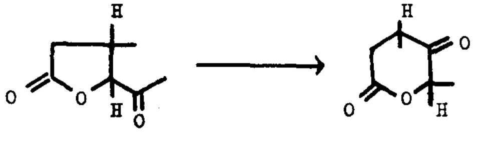
Treatment of nobiline with methyl iodide in methanol gave a methiodide of nobiline, m.p. 275 - 276°, $C_{18}H_{30}O_3NI$, ν_{max}^{KBr} 1772 and 1715 cm^{-1}. Hofmann degradation of the methiodide gave trimethyl amine and deaminonobiline, m.p. 179 - 183°, $C_{15}H_{20}O_3$, ν_{max}^{KBr} 1740 and 1725 cm^{-1}. The maximum at 1740 cm^{-1} indicates that the original γ-lactone has been changed to a δ-lactone during the Hofmann degradation,[5] as discussed later. Ozonolysis of deaminonobiline in CH_2Cl_2 gave formaldehyde, which was identified as 2,4-dinitrophenyl hydrazone and a diketone, m.p. 119 - 122°, $C_{14}H_{18}O_4$; ν_{max}^{KBr} 1745, 1740 (saturated five-membered ring ketone and δ-lactone) and 1723 cm^{-1} (saturated six-membered ring ketone); any strong UV absorption maximum could not be observed in both MeOH and 1N-KOH - MeOH. The above facts indicate the presence of the partial structure (III), which can be extended to the partial structure (IV) on the basis of the mass spectrum of nobiline (m/e 58, 84 and 97), as shown in Scheme A.[6]

Scheme A



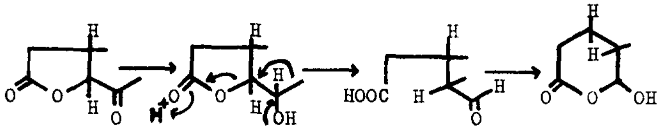
Treatment of nobiline with hydrochloric acid gave nobiline hydrochloride, m.p. 206 - 208°, $C_{17}H_{28}O_3NCl$, ν_{max}^{KBr} 2700 - 2500 br., 1775 and 1703 cm^{-1}, which was reconverted to the original nobiline by concd. ammonia. On the other hand, treatment of nobiline with alc. 2N-KOH at room temperature followed by acidification with hydrochloric acid gave an isonobiline hydrochloride (V), m.p. 183 - 185°, $C_{17}H_{28}O_3NCl$, ν_{max}^{KBr} 2700 - 2500 br., 1740 and 1668 cm^{-1}. The IR spectrum of V as well as deaminonobiline shows that a γ-lactone is changed to a δ-lactone,[5] as shown in Scheme B. The above fact indicates the presence of the partial structure (VI) in nobiline. This is supported by the following reactions: i) reduction of nobiline with lithium aluminum hydride in tetrahydrofuran gave an amorphous triol [ν_{max}^{film} 3600 and 3300 br. cm^{-1} (no absorption band in the carbonyl region)]. This compound consumed about one mole of lead tetraacetate in the solution of acetic acid. ii) reduction of nobiline with sodium borohydride in tetrahydrofuran gave an amorphous hydroxynobiline (VII), ν_{max}^{film} 1770 and 3400 br. cm^{-1}, which was treated with hydrochloric acid under the same condition as that of nobiline to give hydroxyisonobiline (VIII), m.p. 217 - 219°, $C_{17}H_{30}O_3NCl$, ν_{max}^{KBr} 1737 and 3400 br. cm^{-1}, as shown in Scheme C.

Scheme B



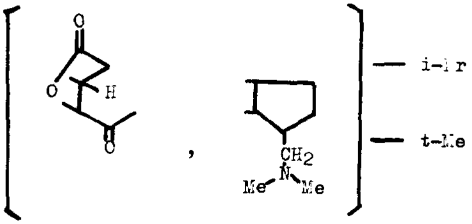
(VI) (V)

Scheme C

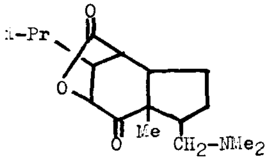


(VII) (VIII)

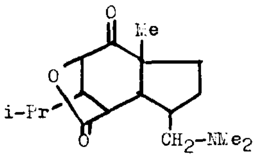
Nobiline has the following partial structures, as shown below.



Therefore, nobiline should have a structure either IX or X, since it has only two rings except for the γ-lactone.[7] Treatment of nobiline with 40% KOH under a drastic condition followed by acidification with hydrochloric acid gave a hydroxy acid (XI), dec. 310°, $C_{16}H_{28}O_3NCl$,



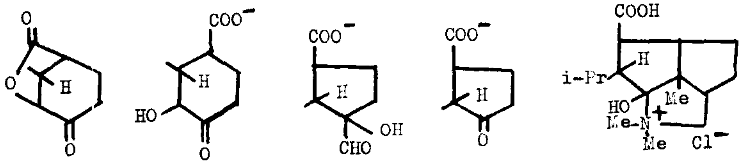
(IX)



(X)

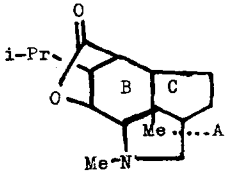
ν_{max}^{KBr} 3400 br. (-OH) and 1716 cm^{-1} (-COOH), pKa' 3.65 (in water), as shown in Scheme D. The easy formation of XI shows that the structure (IX) should be favored rather than X.

Scheme D

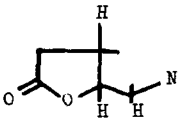


(XI)

Dendrobine is expected to have the same skeleton as that of nobiline from the comparison of their physical data, but we have not succeeded in the direct conversion of the latter to the former. If this is actually the case, the structure (XII) will be given for dendrobine. In fact, the structure (XII) satisfied all physical data and chemical reactions of dendrobine and its derivatives: dendrobine has a molecular formula, $C_{16}H_{25}O_2N$; mol. wt. 263 (mass spec.); pKa' 7.80 (in water); C-Me (Kuhn-Roth oxidation) 1.05 ± 0.1 mol.;[3] ν_{max}^{KBr} 2850 (NMe) and 1758 cm^{-1} (γ-lactone); NMR signals at 9.02 (dimethyl doublet J = 6 c.p.s.), 8.53 (methyl singlet), 7.48 (N-methyl singlet), 7.30 (1H doublet J = 3 c.p.s.), 7.5 - 7.1 (1H superimposed to other peaks), 6.80 (1H triplet J = 8.5 c.p.s.) and 5.16 τ(1H quartet J = 3 and 5 c.p.s.) (in $CDCl_3$); mass spec. peaks at m/e 263 (50), 235 (10), 220 (81) 210 (metastable peak), 184 (metastable peak), 178 (14), 136 (18), 109 (17), 108 (17), 96 (base peak) and 58 (43). The NMR signal at 9.02 τ and the strong peak at m/e 220 indicate the presence of isopropyl group in dendrobine.[8] The remarkable peaks at 5.16 (ABX-type, J_{AX} = 3, J_{BX} = 5 c.p.s.) and 7.30 τ(CH-N doublet J = 3 c.p.s.), and IR spectrum (ν_{max}^{KBr} 1758 cm^{-1}) indicate the presence of the partial structure (XIII) in dendrobine.[9] The A and B rings and the position of a tertiary methyl group are confirmed by the mass spectrum and chemical reactions of dendrobine: i) the strongest peak at m/e 96 is probably due to a fragment ion (XIV). ii) saponification of dendrobine with alc. 2N-KOH followed by oxidation with chromium trioxide-pyridine and esterification with diazomethane gave an oxodendrobinic acid methyl ester, m.p. 127 - 129°,



(XII)



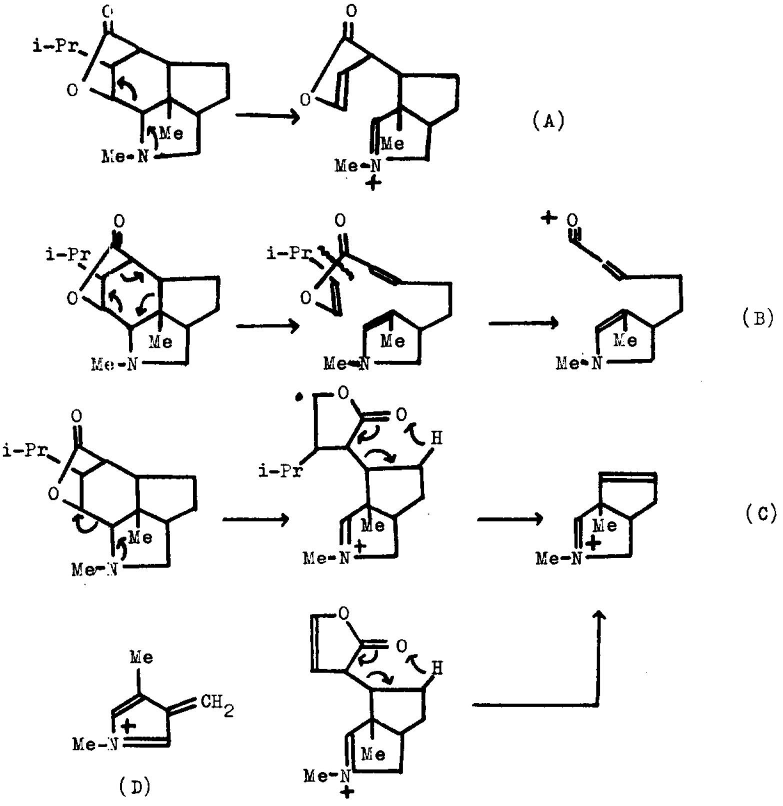
(XIII)

(XIV)

$C_{17}H_{25}O_4N$; ν_{max}^{KBr} 1737 (-COOMe), 1706 (saturated six-membered ring ketone) and 1670 cm^{-1} (γ-lactam); ORD ϕ_{320}^{P} $+3.6 \times 10^3$ (in MeOH); mass spec. peaks at m/e 307 (3.6), 279 (56), 254 (metastable peak), 236 (base peak), 200 (metastable peak), 123 (59), 110 (18) and 58 (78).

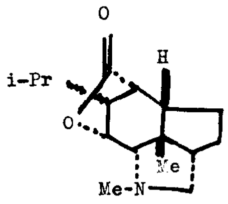
We have no chemical evidence about the C ring, but the main mass spec. peaks of dendrobine (m/e 220, 178, 136, 108 and 96) support the structure (XII), as shown in Scheme E.[10]

Scheme E

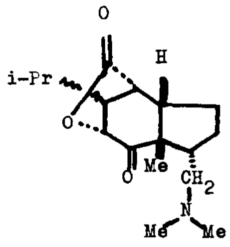


A: m/e 220; B: m/e 178; C: m/e 136; D: m/e 108.

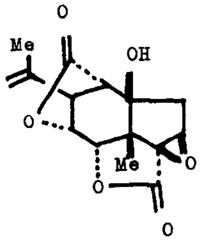
Reduction of dendrobine with lithium aluminum hydride gave a diol, m.p. 113 - 114°, $C_{16}H_{29}O_2N$; mol. wt. 267 (mass spec.), pKa' 9.12 (in water). Acetylation of the diol with acetic anhydride-pyridine gave an amorphous diacetate, ν_{max}^{film} 1740 and 1225 cm^{-1}, pKa' 7.52 (in water), which was converted to the original diol by alc. 2N-KOH. The diol (9.12) is more basic than that of dendrobine (7.80) and of the diacetate (7.52). This fact indicates that the vicinal hydroxyl and amino groups should be cis to each other.[11] Treatment of the diol with acetic anhydride-pyridine (2 : 1) under a drastic condition[12] gave a monoacetoxy acetate salt, m.p. 169 - 170°, $C_{20}H_{33}O_4N$; ν_{max}^{KBr} 1740 (-OAc) and 1577 cm^{-1} (AcO^-); NMR signals at 3.87 (dimethyl doublet J = 5.8 c.p.s.), 3.54 (methyl singlet), 1.4 - 0.8 (8H multiplet)[13] and -0.32 p.p.m. (1H multiplet) (H_2O as internal ref. in D_2O). From the result of the above acetylation experiment the relative configuration (XV) can be given for dendrobine. Therefore, nobiline will have a relative configuration (XVI). This is also supported by the easy rearrengement of nobiline to hydroxy acid (XI). The striking feature of the above results is that the structure of these alkaloids has close similarity to that of picrotoxinin (XVII).[14] There seems to be a certain biogenetic relationship of these natural products, and further studies in this field are awaited.



(XV)



(XVI)



(XVII)

The authors are indebted to Takemura Teisho and Hitachi Co., Ltd. for measurement of the mass spectra. We wish to thank Takeda Pharmaceutical Co., Ltd. for supporting our research.

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1 Suzuki, Keimatu and Ito, *Nippon Yakugaku Zasshi (Japan)* 52, 996 (1932); *ibid.*, 1049 (1932); *ibid.*, 54, 801 (1934).

2 This work was already reported at 7th symposium on Natural Product, Kyusyu, 1963.

3 Kuhn-Roth oxidation suggests that nobiline has one tertiary methyl group and one isopropyl group rather than one tertiary and two secondary methyl groups.

4 The peak at m/e 250 is attributable to the removal of isopropyl or acetyl group from molecular ion.

5 Treatment of the methiodide with silver hydroxide gave a zwitter ion, ν_{max}^{film} 1580 cm^{-1} ($-COO^{-}$), and then recyclization of the carboxyl group is expected to give the δ-lactone, because of the steric strain or conformational change.

6 These degradation mechanisms are compared with those of model compounds, such as pregnane amine and conamine; W. Vetter, P. Longevialle, M. F. Kuuong-Huu-Laine, Q. Khuong-Huu and R. Goutarel, *Bull. Soc. chim. France* 1324 (1963).

7 The position of a tertiary methyl group would be suggested by the comparison of nobiline with dendrobine, as discussed later, and by the bromination experiment. Bromination of nobiline with only bromine, with bromine in acetic acid and in chloroform all gave only nobiline hydrobromide, m.p. 215 - 217°, $C_{17}H_{28}O_3NBr$, ν_{max}^{KBr} 2700 - 2500 br., 1773 and 1703 cm^{-1}, indicating that the carbonyl group could not be enolized.

8 That the peak at m/e 220 is attributable to the removal of the isopropyl group is supported by the appearance of a metastable peak at m/e 184 br., and its very strong intensity suggests the

presence of iso-Pr-C-N or iso-Pr-C-C-C-N.

9 The vicinal protons in the system (O-CH-CH-N) were confirmed by a decoupling technique; T. Okamoto, M. Natume, Y. Kawazoe, T. Onaka, S. Kamata, T. Maeda, M. Shimizu and H. Uchimaru, Abstr. of Papers, 7th symposium on Natural Product p. 62, Kyusyu (1963).

10 Fragment ions of even mass number are expected to contain a nitrogen atom in the mass spectrum of alkaloid which has only one nitrogen atom.

11 D. E. Ayer, G. Büchi, P. Reynolds-Warnhoff and D. W. White, J. Am. Chem. Soc. **80**, 6146 (1958).

12 The diol in acetic acid-pyridine (2 : 1) was heated for 2 hrs. on a water bath, and then an excess of reagent was removed under red. press.

13 NMR signals at 1.4 - 0.8 p.p.m. are attributable to eight protons on three carbon atoms attached to the nitrogen atom.

14 H. Conroy, J. Am. Chem. Soc. **79**, 5550 (1957).