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STRUCTURE OF DENDROBINE[1]

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Abstract—From degradative and spectroscopic evidence, formula XXXI is proposed as the presumable structure of dendrobine and its stereochemical structure is shown in formula XXXIV or its mirror image.

THE Chinese drug "Chin-Shih-Hu" has been used as a tonic. There has been some doubt about the plant from which the drug was originally prepared but Kimura[2] and Suzuki *et al.*[3] reported that it was probably *Dendrobium nobile* Lindl. With regard to its basic component, Suzuki *et al.*[3] reported that they isolated a new alkaloid from this drug which they called dendrobine, m.p. 134°, $[\alpha]_D$ −51·5° in 1932. They also showed that dendrobine has the molecular formula $C_{16}H_{25}O_2N$ containing a N-methyl group and no double bond, and that the oxygens are present as a γ-lactone.

Since then there have been no reports on further details of dendrobine and this prompted the authors to elucidate its structure.

This time, rather large quantities of this drug were obtained and these samples were extracted and the basic components were examined. As a result, two tertiary bases were isolated. One is dendrobine and the second is a new base, m.p. 186–188°, $[\alpha]_D^4$ −27° (*c*, 1·6, methanol) which has not previously been reported in the literature, for which the name dendramine is proposed. The water soluble base was also examined and it was concluded that the quaternary base found in this drug is the N-methyldendrobium salt.[4]

The preliminary characterization of dendrobine indicated that this alkaloid possessed the expanded molecular formula

$$C_{12}H_{19}\ (N{-}CH_3),\ \left(\rangle C{-}CH_3\right),\ (-O-CO-,\ \gamma\text{-lactone})$$

but nothing is known about its skeleton. To study this, dendrobine and dendrobinediol obtained on reduction of the base with lithium aluminum hydride were submitted to selenium dehydrogenation. Dendrobine and dendrobinediol were each heated with selenium under an N_2-atmosphere at 300 ± 10° and each reaction mixture was separated into a volatile portion, a phenolic basic portion, a non-phenolic basic portion and a neutral portion as shown in the experimental.

On careful examination of the dehydrogenation products obtained from dendrobine and from dendrobinediol, important differences were found. Thus, dendrobine gave a phenolic base as described fully later, while under the same reaction conditions dendrobinediol gave none.

As stated in the experimental section, ammonia in the volatile portion was

[1] A preliminary communication appeared in *J. Pharm. Soc. Japan* **83**, 1184 (1963).
[2] K. Kimura, *Bull. Shanghai Sci. Inst.* **6**, 1 (1936); *Ibid.* **7**, 11 (1937).
[3] H. Suzuki, I. Keimatsu and K. Ito, *J. Pharm. Soc. Japan* **52**, 1049 (1932); *Ibid.* **54**, 801 (1934).
[4] Details of isolation and characterization of these alkaloids will be presented in another journal.

characterized as ammonium picrate. The non-phenolic basic portion was not purified further, but the NMR spectrum of this portion suggested that aromatization had not occurred. The product was assumed to be a mixture of partly dehydrogenated compounds of dendrobine, and was not studied further. The UV spectrum of the neutral portion was similar to that of *p*-cymene. In its NMR spectrum[5] the signal which is due to a proton of $CHCl_3$ appeared at 2·88 τ and the fact that the up-field shift of the signal of this proton results from the aromatic nucleus has already been

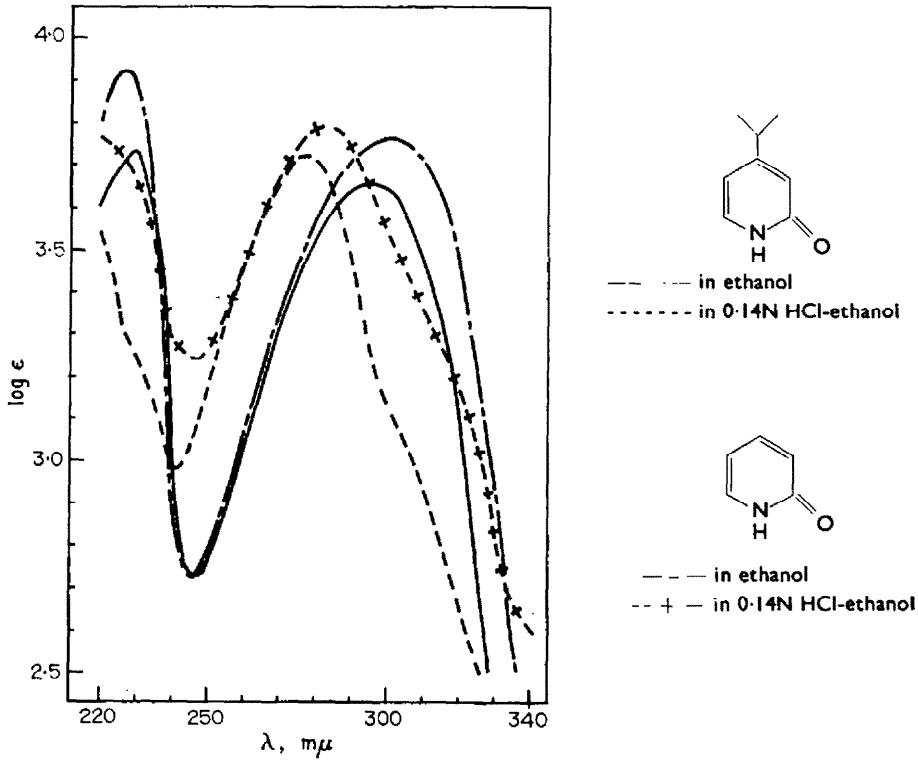


FIG. 1

noted.[6] Signals which were assignable to aromatic protons appeared at 2·59–3·12 τ and signals which suggested the presence of methyl, $-CH(CH_3)_2$ or $-CH_2-CH_3$ attached directly to the aromatic ring were also observed. Next the effect of gas chromatographic separation was studied. Although at least two peaks were recognizable, no pure compound could be isolated. From the results it was assumed that the neutral fraction consists of a mixture of alkyl benzenes.

Distillation of the phenolic basic portion gave hygroscopic crystals, m.p. 66–67° which dissolved on exposure to air. This compound gave a positive ferric chloride reaction and its IR spectrum suggested the presence of lactam carbonyl group ($\nu_{C=O}$ 1650 cm^{-1}). Because of the unsatisfactory nature for characterization the base was

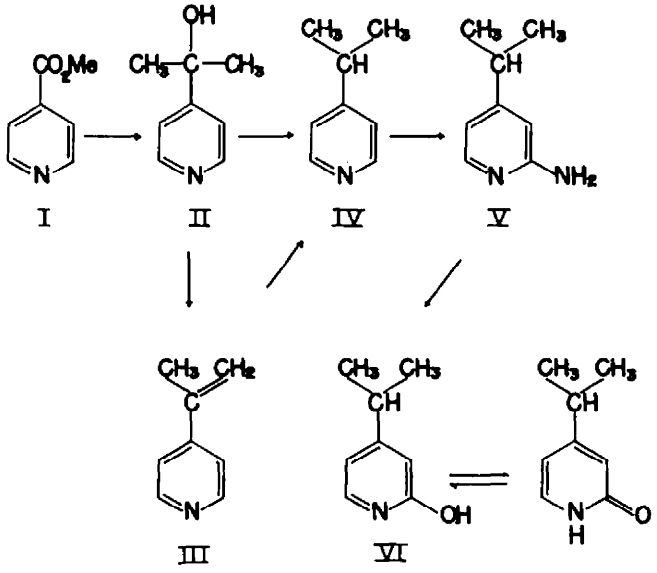
[5] Unless otherwise noted, the NMR spectra in the present paper were measured in $CDCl_3$ contaminated with a small amount of $CHCl_3$, with $SiMe_4$ as an internal standard on a Varian A-60 Spectrometer.

[6] J. A. Pople, W. G. Schneider and H. J. Bernstein, *High-Resolution Nuclear Magnetic Resonance* pp. 422. McGraw-Hill (1959).

converted to its crystalline picrate m.p. 145°, whose analytical values corresponded to a composition of $C_8H_{12}ON^+ \cdot C_6H_2N_3O_7^-$. Considerable information on the structure of this base was obtained by comparison of its UV spectrum with that of 2-pyridone. The spectrum of this base was very similar to that of 2-pyridone and especially the hypsochromic shift of the maximum found at 297 mμ with hydrochloric acid revealed characteristics of pyridones (Fig. 1). Furthermore the NMR spectrum of this base showed the following absorptions: 8·60–8·73 τ (6H) doublet (—$CH(CH_3)_2$); 7·12 τ (1H) septet (—CH); 3·84 τ (1H) quartet $|J_1| = 2·0$ c/s, $|J_2| = 7·0$ c/s; 3·60 τ (1H) broad singlet; 2·70 τ (1H) doublet $|J| = 7·0$ c/s (olefinic protons). From the foregoing data it was deduced that the phenolic base obtained from selenium dehydrogenation of dendrobine would be 4-isopropyl-2-pyridone.

This assignment of structure to the phenolic base was verified by the synthesis of 4-isopropyl-2-pyridone as shown in Chart 1. In this synthetic sequence 4-isopropyl-

CHART 1



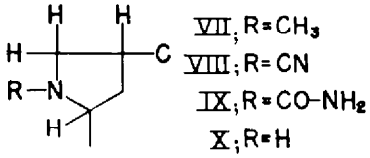
pyridine[7] was synthesized by Clemo's description. Treatment of IV with sodium amide in dry xylene[8] gave 4-isopropyl-2-aminopyridine (V) and diazotization of V followed by rapid hydrolysis afforded 4-isopropyl-2-pyridone (VI), m.p. 69–71°, which was identical in all respects with the compound obtained from dendrobine.

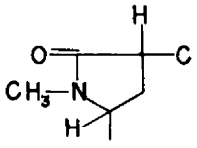
From the foregoing results, if transformation of side chain in the dendrobine molecule does not occur during the selenium dehydrogenation reaction, it can be deduced as follows: Since dehydrogenation of dendrobine gave 4-isopropyl-2-pyridone but dendrobinediol did not, it can be stated that the lactam carbonyl group of the pyridone nucleus originates from the lactone carbonyl group of dendrobine. An isopropyl group is present in the dendrobine molecule and moreover this group is substituted on the β carbon atom to the lactone carbonyl group. The nitrogen atom is separated from the lactone carbonyl group by four carbon atoms.

[7] G. R. Clemo and E. Hoggarth, *J. Chem. Soc.* 41 (1941).
[8] O. Seide, *Ber. Dtsch. Chem. Ges.* **57**, 791 (1924).

As reported by Suzuki *et al.*,[3] treatment of dendrobine (VII) with cyanogen bromide afforded a neutral substance, cyanonordendrobine (VIII),[3] $C_{16}H_{22}O_2N_2$, m.p. 194–196° whose IR spectrum showed the characteristic band of γ-lactone ($\nu_{C=O}$ 1777 cm^{-1}) and of $\rangle N-C\equiv N$ ($\nu_{C\equiv N}$ 2200 cm^{-1}). Hydrolysis of VIII with 5% sulfuric acid gave N-carbamoylnordendrobine (IX),[3] $C_{16}H_{24}O_3N_2$, m.p. 256–258° which showed in its IR spectrum the presence of γ-lactone, the lactam carbonyl group ($\nu_{C=O}$ 1758, 1660, 1607 cm^{-1}) and the amino group (ν_{N-H} 3440 and 3180 cm^{-1}). Treatment of IX with sodium nitrite in dilute hydrochloric acid afforded nordendrobine[3] (X), $C_{15}H_{23}O_2N$, m.p. 123–125°. When X was treated with formaldehyde and then hydrogenated over palladium on charcoal, dendrobine was recovered. From this experiment, it is apparent that no chemical transformation occurred during the above degradative pathways except that of a N-methyl group.

CHART 2





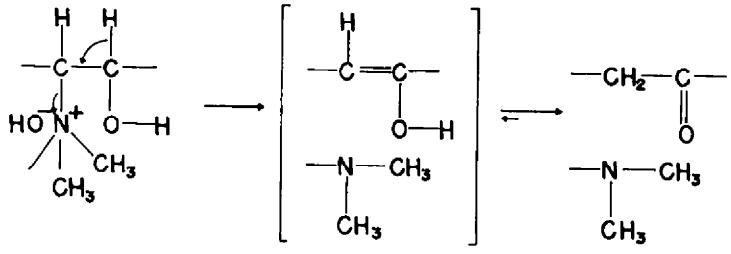
XI

On the other hand, oxidation of dendrobine with potassium permanganate–magnesium sulfate in aqueous acetone solution under carefully controlled conditions furnished a neutral substance, oxodendrobine (XI), $C_{16}H_{23}O_3N$, m.p. 212°. The IR spectrum of XI indicated the presence of γ-lactone and the lactam carbonyl group ($\nu_{C=O}$ 1779 and 1672 cm^{-1} in $CHCl_3$). Since oxodendrobine was reduced by lithium aluminium hydride to give dendrobinediol, no transformation of the ring system of dendrobine occurred in the preparation of XI.

The NMR spectra of the substance obtained above were measured and in these spectra signals which can be assigned to the protons attached to the carbon atoms adjacent to a nitrogen atom were as follows: The spectrum of VIII shows signal peaks at 6·70 τ (1H) doublet $|J| = 3{\cdot}5$ c/s $\left(\rangle N-CH\langle\right)$ and 6·12–6·87 τ (2H) septet $|J_{AB}| = 10$ c/s $\left(\rangle N-CH_AH_B-CH\langle\right)$. The spectrum of IX exhibits signal peaks at 6·20 τ (1H) doublet $|J| = 3{\cdot}5$ c/s $\left(\rangle N-CH\langle\right)$ and at 6·21–7·05 τ (2H) septet $|J_{AB}| = 9{\cdot}5$ c/s $\left(\rangle N-CH_AH_B-CH\langle\right)$. From these observations, it is proposed that structures VII, VIII, IX, X and XI represent partial structures of dendrobine, cyanonordendrobine, N-carbamoylnordendrobine, nordendrobine and oxodendrobine, respectively.

The interesting observations discussed below were from studies on Hofmann degradation on dendrobinediol. Treatment of dendrobinediol with methyl iodide gave dendrobinediol methiodide, $C_{17}H_{32}O_2NI$, m.p. 262°, which was in turn converted to its methohydroxide (XII). Hofmann degradation of XII afforded a methine base (XIII), $C_{17}H_{31}O_2N$, m.p. 90–92°. The IR spectrum of XIII showed a band at 1704 cm^{-1}

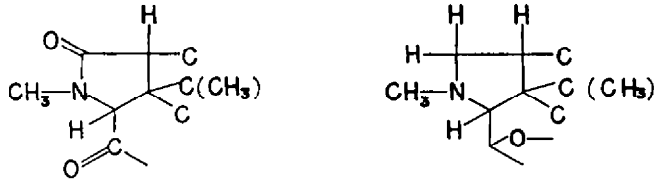
due to a carbonyl group. The NMR spectrum of this methine base exhibited signal peaks at 7·82 τ (6H) singlet (—$N(CH_3)_2$) and 7·35 → 7·65 τ (dilution shift) (OH) but no signal due to an aldehydic proton was observed. Since it is apparent that the carbonyl group created by Hofmann degradation arises from a hydroxyl group originally forming a lactone ring, it was established that the hydroxyl group forming a lactone ring is a secondary one and substituted on a carbon atom of a six or larger membered ring. This conclusion is not contradictory to that deduced from studies on the oxidation of oxodendrobinic acid methylester which will be stated later. Furthermore, from the reaction mechanism of the Hofmann degradation it could be deduced that two carbon atoms intervene between this hydroxyl group and a nitrogen atom. The carbonyl formation from a secondary hydroxyl group located in the β position to a nitrogen atom by an analogous reaction mechanism has been found in the transformation of cinchonine to cinchotoxine.[9]



XII XIII

Next the second stage Hofmann degradation was studied under various reaction conditions but a nitrogen free substance could not be obtained.

When oxodendrobine (XI) was hydrolysed with aqueous sodium hydroxide, oxodendrobinic acid, $C_{16}H_{25}O_4N$, m.p. 225° (sintered at 210°) was obtained. Oxodendrobinic acid methylester, $C_{17}H_{27}O_4N$, m.p. 197–200°, formed by the methylation of oxodendrobinic acid with diazomethane, was oxidized with CrO_3–pyridine complex to give ketoester (XIV), $C_{17}H_{25}O_4N$, m.p. 129–131°. The IR spectrum of XIV showed absorption bands due to carbonyl groups at 1733, 1704 and 1669 cm^{-1}. In the NMR spectrum a signal due to $\rangle N—CH\langle$ appeared at 6·58 τ as a singlet. Since the relative positions of the secondary hydroxyl group and the nitrogen atom have been established by the Hofmann degradation reaction, it is apparent that the ketoester contains the system —N—CH—CO—. Moreover evidence from the NMR spectra established that structure XIV represents the partial structure of the ketoester, and that structure IX represents that of dendrobine.

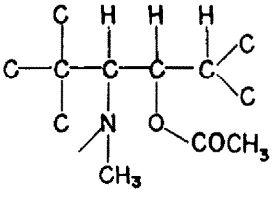


XIV XV

[9] R. B. Turner and R. B. Woodward in *The Alkaloids* (Edited by R. H. F. Manske and H. L. Holmes) Vol. 111, p. 9 (1953).

Treatment of dendrobinediol (XVIII) with acetic anhydride–sodium acetate at room temperature gave an oily substance, dendrobinediol diacetate (XIX; its methiodide, $C_{20}H_{33}O_4N{\cdot}CH_3I$, m.p. 258–260° dec). Oxidation of XIX with permanganate–magnesium sulphate in aqueous acetone solution under controlled conditions afforded oxodendrobinediol diacetate (XX) which could not be crystallized. Since on reduction of XX with lithium aluminium hydride dendrobinediol was recovered, it is apparent that no transformation of the ring system of dendrobine occurred in the preparation of XIX and XX.

Oxodendrobinediol diacetate (XX) was hydrolysed with 10% hydrochloric acid and chromatographed on alumina. Elution with benzene gave oxodendrobinediol monoacetate (XXI), $C_{18}H_{29}O_4N$, m.p. 142° in which there was evidence for the presence of a hydroxyl group (ν_{O-H} 3460 cm^{-1}) and of a carbonyl group (ν_{C-O} 1733 and 1675 cm^{-1}, these being attributable to an acetyl and a lactam group). After oxodendrobinediol monoacetate, oxodendrobinediol (XXII), $C_{16}H_{27}O_3N$, m.p. 200–201°, was eluted. The IR spectrum of XXII showed the presence of hydroxyl group (ν_{O-H} 3460 and 3425 cm^{-1} in $CHCl_3$) but no absorption band in the carbonyl region except for a lactam carbonyl band ($\nu_{C=O}$ 1670 cm^{-1} in $CHCl_3$). Compounds XX and XXI were hydrolyzed with 5% sodium hydroxide to give oxodendrobinediol (XXII), which in turn was reduced to dendrobinediol (XVIII) with lithium aluminium hydride. These experiments showed that oxodendrobinediol diacetate (XX) was partially hydrolysed under the above reaction conditions. The NMR spectrum of oxodendrobinediol monoacetate (XXI) exhibited a signal due to a proton attached to the acetyloxy group-bearing carbon atom at 4·87 τ (1H) quartet $|J_1| = 3{\cdot}5$ c/s, $|J_2| = 9{\cdot}0$ c/s. From this spectral evidence, it can be stated that the two carbon atoms situated on either side of the acetyloxy group-bearing carbon atom are each attached to one hydrogen atom, as shown below.



XXI

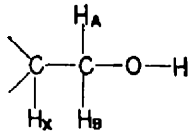
Treatment of the methine base with benzoyl chloride in benzene triethylamine solution gave an oily substance, from which dihydromethine[10] monobenzoate (XXV), $C_{24}H_{37}O_3N$, m.p. 116–118°, was obtained by sodium borohydride reduction. The IR of XXV showed the presence of a hydroxyl group (ν_{O-H} 3226 cm^{-1}) and a carbonyl group ($\nu_{C=O}$ 1709 cm^{-1}). This dihydromethine monobenzoate was obtained by an alternative route. The methine base was first reduced with sodium borohydride to give dihydromethine (XXIV), $C_{17}H_{33}O_2N$, m.p. 177–179°. Then, benzoylation of XXIV under the conditions of the former experiment, gave dihydromethine monobenzoate, which was identical in all respects with that formed by the above process. These experiments showed that one of the two hydroxyl groups was selectively

[10] In the preliminary communication, this compound was designated as hydroxymethine but the authors would like to propose this revised name here.

benzoylated under these reaction conditions, and that the benzoylated hydroxyl group was a primary one.

Treatment of dihydromethine monobenzoate (XXV) with phosphorus oxychloride in pyridine induced loss of water to give anhydrodihydromethine monobenzoate (XXVI), $C_{24}H_{35}O_2N$, m.p. 75° in good yield. The IR spectrum of XXVI indicated the presence of a trisubstituted double bond (σ_{C-H} 846 cm^{-1}). This fact was further confirmed from its NMR spectrum in which a signal due to an olefinic proton appeared at 4·58 τ, (1H) multiplet. From this chemical and spectral evidence it was concluded that one of the two carbon atoms adjacent to the hydroxyl group originally forming a lactone ring (a nitrogen atom is not attached to this carbon atom) is not a bridge-head carbon atom.

On the other hand, in the NMR spectra of dihydromethine and anhydrodihydromethine monobenzoate (XXVI), signals due to protons attached to a carbon atom bearing a primary hydroxyl group, appeared at 6·00–6·74 τ (2H) octet and 5·16–6·00 τ (2H) octet $|J_{AB}| = 10$ c/s, respectively. This spectral evidence indicated the presence of the following grouping.



XVII

The transformations described above are summarized with partial structures as in Chart 3.

Hydrolysis of nordendrobine (XXVII) with barium hydroxide solution followed by careful neutralization gave nordendrobinic acid XXVIII, $C_{15}H_{25}O_3N$, m.p. 236–240°, which showed the presence of the grouping $-COO^-$ (ν_{COO^-} 1555 cm^{-1}) in its

CHART 3

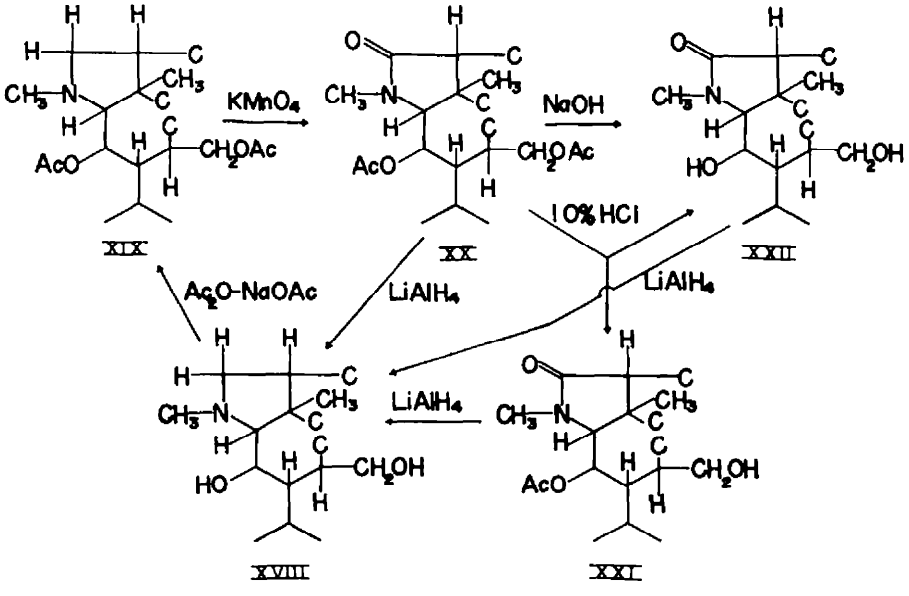
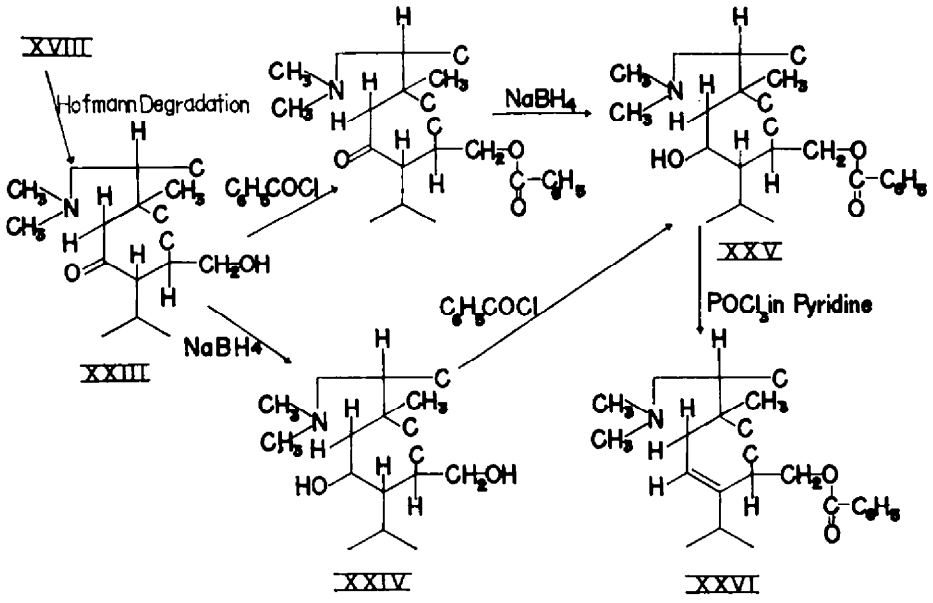
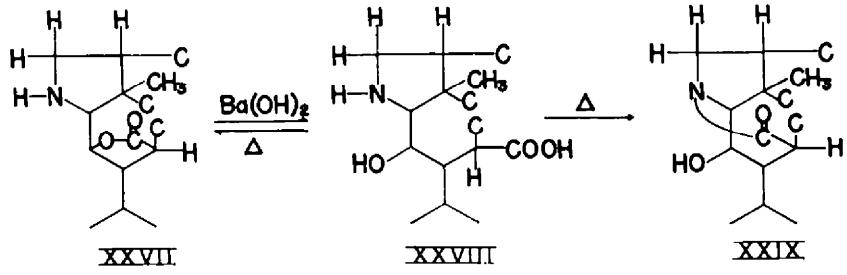


CHART 3 (*Contd.*)



IR spectrum. High vacuum distillation of XXVIII furnished an oily substance, which was separated into a basic portion and a neutral portion. Crystalline material from the basic portion, which seemed to be formed by relactonization during distillation, was identified with an authentic sample of nordendrobine. Nordendrobinic acid lactam (XXIX), $C_{15}H_{23}O_2N$, m.p. 144°, isolated from the neutral portion showed the presence of a carbonyl ($\nu_{C=O}$ 1706 cm^{-1} [11] in $CHCl_3$) and of a hydroxyl group (ν_{O-H} 3556 cm^{-1} Nujol) in its IR spectrum. These reactions could be formulated as follows.

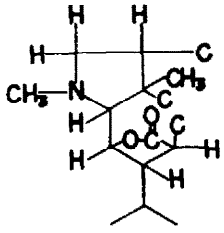


Thus, the previous observations that on selenium dehydrogenation dendrobine gave 4-isopropyl-2-pyridone but dendrobinediol did not, could be rationalized with this observation on the ready formation of an intramolecular lactam.

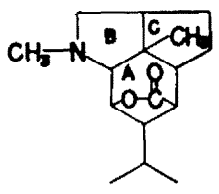
From all degradative evidence obtained so far, it could be deduced that dendrobine has the partial structure represented by formula XXX. With this partial structure the number of possible structures for dendrobine is, then, reduced to five. However, the circumstances of the three carbon atoms in the dendrobine molecule are still uncertain.

[11] The band of this lactam carbonyl group gave rather higher frequencies than those expected for six membered lactams but this anomalous observation could be explained if the nitrogen atom forming a lactam ring is situated at a bridge-head.

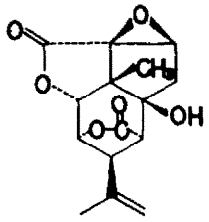
At the present stage of this work the ring bearing a lactone ring might be assumed to be a six membered one because selenium dehydrogenation of dendrobine gave a mixture of alkyl benzenes and the IR spectrum of the methine base showed a band due to a carbonyl group at 1704 cm^{-1}, which originated from the hydroxyl group forming a lactone ring. If this ring is a six membered one, the structure of dendrobine would be limited to formula XXXI.[12] Formula XXXI is closely related to the structures of naturally occurring sesquiterpenoids, picrotoxinin (XXXII)[13] and tutin. On the basis of this structural similarity, together with degradative evidence which has been described, the authors would like to propose that formula XXXI is the presumable structure of dendrobine.



XXX

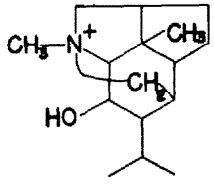


XXXI

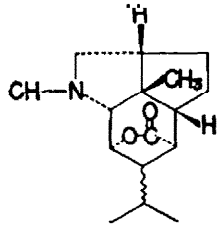


XXXII

Information on the stereochemistry of dendrobine came from the following experiments. On treatment of dendrobinediol with one equivalent of thionyl chloride at room temperature, a nitrogen atom was quaternized to produce a water soluble base which was characterized as its iodide (XXXIII), $C_{16}H_{28}ONI$, m.p. 121–122°. From the dissimilarity in properties between this quaternary ammonium iodide and dendrobinediol hydroiodide, m.p. 176°, it is apparent that this quaternary base was formed by the intramolecular attack on a carbon atom attached to a chlorine atom of an unshared electron pair on a nitrogen atom.[14] This reaction process is also supported by the ready intramolecular lactam formation of nordendrobinic acid which has been described. For this particularly ready quaternarization process, both B and C rings must be *cis* with respect to ring A and to the grouping —CH_2—OH. If the above presumable structure for dendrobine is accepted as correct, the stereochemical structure of dendrobine would be represented by formula XXXIV or its mirror image.



XXXIII



XXXIV

[12] This formula was also proposed independently by Prof. T. Okamoto and Prof. Y. Hirata at *7th. Symposium on the Chemistry of Natural Products* Japan, in Kyushu, October 17 (1963); cf. S. Yamamura and Y. Hirata, *Tetrahedron Letters* No. 2, 79 (1964).

[13] J. Holker, A. Robertson and J. Taylor, *J. Chem. Soc.* 2987 (1958).

[14] P. A. Diassi, F. L. Weisenborn, C. M. Dylion and O. P. Wintersteiner, *J. Amer. Chem. Soc.* **77**, 2028 (1955).

EXPERIMENTAL[15]

Characterization of dendrobine

The finely-cut samples of the Chinese drug were extracted with methanol and the basic components were separated into the tertiary bases and the water soluble quaternary base. The crude tertiary bases were purified chromatographically on alumina and elution of the column with benzene gave dendrobine, m.p. 134·5–136°, $[\alpha]_D^4$ −48·4 (*c*, 1·89; methanol). Repeated recrystallization from ether did not improve the m.p. Dendrobine had the following spectroscopic properties. ν_{max}^{KBr} cm^{-1}: 1767 (γ-lactone). NMR: 9·00–9·04 τ (6H) two doublets (an isopropyl group or two >CH—CH$_3$ groups), 8·67 τ (3H) singlet (>C—CH$_3$), 7·51 τ (3H) singlet (N—CH$_3$), 5·20 τ (1H) quartet (—CO—O—CH<). (Found: C, 72·85; H, 9·81; N, 5·32. $C_{16}H_{25}O_2N$ requires: C, 72·96; H, 9·57; N, 5·32%).

Dendrobinediol (XVIII)

A solution of 0·925 g dendrobine in 70 ml anhydrous ether was added to a solution of 0·8 g $LiAlH_4$ in 100 ml of ether. The mixture was stirred vigorously and refluxed on a water bath for 5 hr. Excess hydride was decomposed by the addition of ethyl acetate and NaOH aq. The precipitate was separated by decantation and washed with ether. The combined ether solutions were dried (K_2CO_3) and evaporated to leave 0·931 g (in 99% yield) dendrobinediol. Recrystallization from ether gave colorless needles, m.p. 114°; $[\alpha]_D^{\tau}$ −14·6° (*c*, 1·03; methanol). ν_{max} cm^{-1}: 3650, 3300 (in CCl_4, infinite dilution); NMR: 8·96–9·14 τ (6H) two doublets (an isopropyl group or two >CH—CH$_3$ groups), 8·88 τ (3H) singlet (>C—CH$_3$), 7·67 τ (3H) singlet (>N—CH$_3$). (Found: C, 71·58; H, 11·07; N, 5·04. $C_{16}H_{29}O_2N$ requires: C, 71·86; H, 10·93; N, 5·24%).

Selenium dehydrogenation of dendrobine

A mixture of 2·067 g dendrobine and 4·132 g powdered Se was heated in a bath (NaAc—KAc) at 200 ± 10° for 10 hr and then at 300 ± 10° for 40 hr.

(a) *Volatile portion.* The gas generated was introduced into a flask containing ethanolic picric acid. The precipitated picrate, m.p. 223–225° (dec) was shown to be ammonium picrate. (Found: C, 29·34; H, 2·52; N, 21·92. $C_6H_6O_7N_4$ requires: C, 29·28; H, 2·46; N, 22·76%).

(b) *Phenolic base.* After cooling, the residue was extracted with hot ether and evaporation of dried extracts left 1·5 g of a dark brown viscous oil which was treated with 2% HCl aq. The acidic, aqueous solutions were made basic with 5% NaOHaq and extracted with ether to remove the non-phenolic base. (c). Addition of NH_4Cl to the alkaline, aqueous solution caused the liberated phenolic, basic substance to separate which was extracted with chloroform. After drying the solution (K_2CO_3) the solvent was evaporated to leave 0·158 g the phenolic base which was sublimed at 170–180°/2 mm Hg to give colorless needles, m.p. 66–68°. Because of their hygroscopic nature they dissolved on exposure to air. This phenolic base gave a positive $FeCl_3$ reaction (reddish pink). λ_{max}^{EtOH} 229 mμ (log ε 3·73), 297 mμ (log ε 3·65); $\lambda_{max}^{EtOH+HCl}$ 273 mμ (log ε 3·72). ν_{max}^{Nujol} cm^{-1} 1650, 1621 (carbonyl group); σ_{C-H} cm^{-1} 995. For analysis, the base was converted to its picrate which was recrystallized from ethanol to give yellow needles, m.p. 144–146°. (Found: C, 46·16; H, 3·80; N, 15·28. $C_8H_{11}ON\cdot C_6H_3O_7N_3$ requires: C, 45·90; H, 3·85; N, 15·30%).

(c) *Non-phenolic base.* The ethereal extract separated from the phenolic base was evaporated to leave an oil (0·293 g) which distilled at 70–80°/2 mm Hg. The NMR spectrum of this oil showed no signal due to aromatic protons.

(d) *Neutral fraction.* The ethereal solution separated from basic components was evaporated to leave 0·888 g brown oil which was chromatographed on alumina. Elution of the column with benzene gave an oil which distilled at 130–160°/2 mm Hg. The NMR spectrum of this oil showed signals due to aromatic protons at 2·59–3·12 τ and signals due to —CH—ϕ and CH$_3$—ϕ at 6·70–7·60 τ and 7·74 τ, respectively. This oil gave two peaks at retention times of 9·75 and 13·9 min on gas chromatographic analysis.[16]

[15] All m.ps were observed on a Kofler microscope hot stage and are given as uncorrected values.

[16] Gas chromatography was carried out under the following conditions: Apparatus, Hitachi Gas Chromatography Analyzer Type KGL-2. A stainless steel column (2 m × 4 mm) was packed with Silicon DC-550. The column temp was kept at 176°. Carrier gas N_2, at a flow-rate of 33 ml/min was used.

Selenium dehydrogenation of dendrobinediol

Dendrobinediol (0·4 g) and powdered Se (1·0 g) were heated under the same conditions as in the case of dendrobine. After cooling, the residue was extracted with hot ether and the solvent was evaporated to leave 0·18 g of dark brown residue which was treated in the same way as in the separation of the dehydrogenation products of dendrobine. In this case, no phenolic, basic compound was obtained.

α,α-Dimethyl-4-pyridinemethanol (II)[7]

To the solution of CH_3MgI in ether prepared from 3·2 g dry Mg turning and 17 g CH_3I was added a solution of 5 g methyl isonicotinate in ether. The product was treated by the usual method to afford 3·6 g (60%) of a solid mass which distilled at 135–140°/3 mm Hg, m.p. 135–136·5°. ν_{max}^{Nujol} cm^{-1} 3175 (hydroxyl group); σ_{C-H}^{Nujol} cm^{-1} 837, 829. (Found: C, 70·16; H, 8·13; N, 10·04. $C_8H_{11}ON$ requires: C, 70·04; H, 8·08; N, 10·21%).

4-*Isopropenylpyridine* (III)[7]

To a solution of 0·3 g compound II in absolute ethanol was added 0·5 ml $POCl_3$ and the reaction mixture was refluxed on a water bath for 5 hr. The product was treated in the usual manner to give an oil which was distilled at 70–80° (bath temp)/3 mm Hg (0·208 g; 84%). For analysis, the base was converted to its picrate, obtained as yellow needles, m.p. 144–147° on recrystallization from methanol. (Found: C, 48·23; H, 3·54; N, 15·78. $C_8H_9N{\cdot}C_6H_3O_7N_3$ requires: C, 48·28; H, 3·49; N, 16·09%).

4-*Isopropylpyridine* (IV)[7]

(1) *From 4-isopropenylpyridine* (III). A solution of 0·75 g III in absolute ethanol was hydrogenated at atm press and room temp in the presence of 40 mg Adams catalyst. The product was treated in the usual manner to leave an oily substance which distilled at 70–180° (bath temp). To eliminate water, this distillate was warmed with a small amount of solid KOH on a water bath and redistillation gave 4 g of an oil (52%), b.p. 190°. σ_{C-H}^{sand} cm^{-1} 1385, 1368 and 819. The picrate of this base formed yellow needles from ethanol, m.p. 141°. (Found: C, 47·90; H, 3·75; N, 16·04. $C_8H_{11}N{\cdot}C_6H_3O_7N_3$ requires: C, 48·00; H, 4·03; N, 16·00%).

(2) *From α,α-dimethyl-4-pyridinemethanol* (II). A mixture of 1·2 g II, red P (0·1 g) and 1 ml conc HI was boiled over a free flame for 5 hr. After removing red P by filtration, the resulting clear filtrate was made basic with NaOH aq, extracted with $CHCl_3$, and the extract dried, leaving an oily substance. After drying (KOH), distillation gave 0·54 g of an oil. The identity of the product with that obtained in the former experiments was shown by comparison of IR spectra.

4-*Isopropyl-2-aminopyridine* (V)

To a solution of 0·4 g IV in 2 ml dry xylene was added 0·143 g sodium amide and the reaction mixture was refluxed in an oil bath for 8 hr. After cooling, 10 ml 10% HCl aq was added and the acidic, aqueous layer was separated from the organic layer. The acidic solution was made alkaline with conc. NaOH aq and extracted 4 times with $CHCl_3$. The extracts were combined, dried ($MgSO_4$) and evaporated to leave an oil. Distillation gave 96 mg of the main fraction, b.p. 150–160° (bath temp)/3 mm Hg which could not be crystallized. ν_{max}^{sand} cm^{-1} 3356, 3226 (primary amino group); σ_{max}^{sand} cm^{-1} 810. The picrate was precipitated from ethanol. Recrystallization from the same solvent gave yellow plates, m.p. 185–186°. (Found: C, 46·01; H, 4·16; N, 19·22. $C_8H_{12}N_2{\cdot}C_6H_3O_7N_3$ requires: C, 46·03; H, 4·14; N, 19·17%).

4-*Isopropyl-2-pyridone* (VI)

In a 100 ml flask fitted with a mechanical stirrer were placed 75 mg V, 0·09 ml conc. H_2SO_4 and 15 ml water. The stirrer was started and 54 mg $NaNO_2$ was added in 3 portions within 10 min. The reaction mixture was then stirred 1 hr and the organic layer separated from the acidic solution. The acidic solution was washed twice with ether, made alkaline with conc. NaOH aq and twice more with ether. Then, solid NH_4Cl was added to the alkaline solution and the phenolic base liberated extracted 5 times with $CHCl_3$. The extracts were combined, dried ($MgSO_4$) and evaporated to dryness. Distillation *in vacuo* yielded 55 mg of an oil, b.p. 150–170° (bath temp)/2 mm Hg (73%). Immediately after distillation, the distillate solidified, m.p. 69–71° but because of its hydroscopic nature the crystals

dissolved on exposure to air. ν_{max}^{Nujol} cm^{-1} 1650, 1621; σ_{C-H}^{Nujol} cm^{-1} 995. The picrate of this phenolic base formed yellow needles, m.p. 146–147° on recrystallizations from ethanol. (Found: C, 45·83; H, 3·80; N, 15·19. $C_8H_{11}ON{\cdot}C_6H_3O_7N_3$ requires: C, 45·90; H, 3·85; N, 15·30%). This picrate was proved to be identical with the picrate of the phenolic base (m.p. 144–146°) separated from the Se dehydrogenation products of dendrobine by comparison of IR spectra and mixed m.p. determinations.

Cyanonordendrobine (VIII)

To a solution of 156 mg BrCN in 10 ml ether was added a solution of 200 mg dendrobine in anhydrous ether and after standing 30 min at room temp, the reaction mixture was heated on a water bath for 30 min. The solvent was evaporated off and the resulting residue dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with 1% HCl aq to remove the basic substance. The organic layer was washed again with water, dried ($MgSO_4$), and evaporated to leave 200 mg crude product. Then, a solution of the product in benzene was chromatographed over neutral alumina and elution with benzene afforded colorless crystals. Recrystallizations from acetone gave 145 mg of needles, m.p. 194–196°. $[\alpha]_D^4$ −107° (*c*, 1·4; methanol). ν_{max}^{Nujol} cm^{-1} 1777 (γ-lactone); ν_{N-CN}^{Nujol} cm^{-1} 2200. NMR: 8·97–9·07 τ (6H) two doublets (—CH(CH$_3$)$_2$), 8·60 τ (3H) singlet >C—CH$_3$, 6·70 τ (1H) doublet $|J| = 3{\cdot}5$ c/s >N—CH<, 6·12–6·87 τ (2H) septet $|J_{AB}| = 10$ c/s >N—CH$_A$H$_B$—CH<, 5·62 τ (1H) quartet —CO—O—CH<. (Found: C, 70·31; H, 8·19; N, 10·24. $C_{16}H_{22}O_2N_2$ requires: C, 70·04; H, 8·08; N, 10·21%).

N-*Carbamoylnordendrobine* (IX)

Cyanonordendrobine (227 mg) suspended in 20 ml 5% H_2SO_4 aq was heated on a water bath for 4 hr and at the end of this period the reaction mixture was clear. To complete the reaction, heating was continued for 2 hr. After cooling, the acidic solution was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and evaporated to leave 200 mg of an oily substance which solidified upon trituration with a mixture of ether and acetone (2:1). Recrystallizations from acetone gave 160 mg colorless needles, m.p. 256–258°. ν_{max}^{Nujol} cm^{-1} 3440, 3180 (primary amino group); 1758, 1660, 1607. NMR: 8·86–9·13 τ (6H) two doublets (—CH(CH$_3$)$_2$), 8·70 τ (3H) singlet >C—CH$_3$, 6·21–7·05 τ (2H) septet $|J_{AB}| = 9{\cdot}5$ c/s >N—CH$_A$H$_B$—CH<, 6·20 τ (1H) doublet $|J| = 3{\cdot}5$ c/s >N—CH<, 5·38 τ (2H) broad singlet —CO—NH$_2$, 5·10 τ (1H) quartet —CO—O—CH<. (Found: C, 65·60; H, 8·46; N, 9·38. $C_{16}H_{24}O_3N_2$ requires: C, 65·72; H, 8·27; N, 9·58%).

Nordendrobine (X)

N-Carbamoylnordendrobine (1X; 150 mg) was dissolved in 20 ml 4% HCl aq by warming and the solution was then cooled to 2°. To the resulting clear solution was added a cold solution of 40 mg $NaNO_2$ in 2 ml water. After standing overnight at room temp, the reaction mixture was heated on a water bath for 1 hr, cooled, washed with ether, made basic with ammonia and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and evaporated to leave 130 mg of a solid mass which was crystallized from ether to afford 120 mg colorless needles, m.p. 123–125°. $[\alpha]_D^{11}$ −12·1° (*c*, 1·99; methanol). ν_{max}^{Nujol} cm^{-1} 3226 (NH group); 1770 (γ-lactone). (Found: C, 72·36; H, 9·57; N, 5·40. $C_{15}H_{23}O_2N$ requires: C, 72·25; H, 9·30; N, 5·62%).

N-*Methylation of nordendrobine*

A mixture of 50 mg nordendrobine, 0·5 ml 3% formaldehyde and 10 ml methanol was heated on a water bath for 3 hr. After cooling, a further 20 ml methanol was added and the solution was hydrogenated at atm press. and room temp in the presence of 20 mg 10% Pd—C. The reaction stopped in 3 hr and then the catalyst was removed by filtration. The filtrate was evaporated to dryness and the residue was dissolved in 10 ml 1% HCl aq, washed with ether, made basic with ammonia, and extracted with ether. The extract was dried ($MgSO_4$), and evaporated to leave a solid mass which was recrystallized from ether to give 25 mg colorless prisms, m.p. 134–136°. The product was shown to be identical with an authentic sample of dendrobine by comparison of IR spectra and mixed m.p. determination.

Oxodendrobine (XI)

Dendrobine (1·2 g) and $MgSO_4$ (1·2 g) were dissolved in a mixture of 300 ml acetone and 60 ml water. To this solution was added a solution of 1·5 g $KMnO_4$ in a mixture of 100 ml acetone and 150 ml water with stirring at 5°, and stirring was continued for a further 30 min at room temp. Excess $KMnO_4$ was destroyed by the addition of saturated solution of Na_2SO_3 in 5% H_2SO_4 and the organic solvent evaporated off under red press. The concentrated solution was extracted several times with $CHCl_3$ and the extracts were combined, dried ($MgSO_4$) and evaporated to leave 1·1 g of the crude product. The benzene solution of this product was chromatographed on neutral alumina and successive elution with benzene and ether afforded 1·0 g of a crystalline mass which was recrystallized from acetone to give colorless needles, m.p. 212°, $[\alpha]_D^{14}$ −86·2° (*c*, 2·16; $CHCl_3$). $\nu_{max}^{CHCl_3}$ cm^{-1} 1779, 1672. NMR: 8·92–9·63 τ (6H) two doublets —$CH(CH_3)_2$, 8·58 τ (3H) singlet >C—CH_3, 7·26 τ (3H) singlet —CO—N—CH_3, 6·76 τ (1H) doublet $|J| = 4·0$ c/s —N—$CH\langle$, 5·28 τ (1H) quartet —CO—O—$CH\langle$. (Found: C, 69·51; H, 8·57; N, 5·04. $C_{16}H_{23}O_3N$ requires: C, 69·28; H, 8·36; N, 5·05%).

Reduction of oxodendrobine (XI) *with* $LiAlH_4$

A solution of 50 mg oxodendrobine in 10 ml anhydrous tetrahydrofuran was added to a solution of 50 mg $LiAlH_4$ in 10 ml tetrahydrofuran and the reaction mixture was heated on a water bath for 4 hr. Decomposition of excess hydride was effected by the addition of ether saturated with water and NaOH solution. The precipitate that formed was separated by decantation and washed with ether. After evaporation of the organic solvents, the residue was dissolved in 3 ml 1% HCl. The aqueous solution was washed with ether, made basic with ammonia and extracted with ether. After drying ($MgSO_4$), the solvent was evaporated off to give 32 mg of a solid mass. Recrystallizations from ether gave 29 mg colorless needles, m.p. 114°. This product was shown to be identical with an authentic sample of dendrobinediol by comparison of IR spectra and mixed m.p. determinations.

Hofmann degradation of dendrobinediol

(1) *Dendrobinediol methiodide.* A solution of 150 mg dendrobinediol in 5 ml methanol was heated on a water bath with 2 ml CH_3I for 3 hr. The solvent and excess CH_3I were removed by evaporation, and the residue was washed thoroughly with ether. Upon trituration with acetone the residue gave crystals. Recrystallizations from a mixture of ether and acetone afforded 200 mg of colorless needles, m.p. 262°, $[\alpha]_D^{11}$ −47·6° (*c*, 1·73; methanol). (Found: C, 49·74; H, 7·92. $C_{17}H_{32}O_3NI$ requires: C, 49·87; H, 7·88%).

(2) *Dendrobinediol methohydroxide* (XII). A solution of 200 mg dendrobinediol methiodide in 5 ml methanol was shaken vigorously with freshly prepared Ag_2O for 30 min. After filtration to remove Ag salt, the solvent was evaporated off to leave 140 mg of a viscous oil.

(3) *Pyrolysis of dendrobinediol methohydroxide.* The viscous oil obtained above (140 mg) was placed in a 50 ml flask fitted with a condenser, and then heated in an oil bath at 150–160° (bath temp) under red. press. (2 mm Hg) for 15 min. The reaction product was extracted with ether and the inside of the condenser was washed with ether. The washings and extracts were combined and shaken with 1% HCl aq. The acidic solution was washed with ether, made basic with ammonia and extracted with ether. The extract was dried (K_2CO_3), concentrated to an oil which was distilled at 155° (bath temp)/5 mm Hg to afford 130 mg of a light yellow oil. The distillate in benzene was chromatographed on neutral alumina (3·0 g) and eluted successively with benzene and ether. The fraction eluted with ether gave 100 mg colorless crystals, m.p. 83–87°. Recrystallizations from a mixture of ether and n-hexane (1 : 1) furnished 90 mg of colorless prisms (XIII), m.p. 90–92°[17], $[\alpha]_D^{11}$ −4·2 (*c*, 1·98; methanol). ν_{max}^{Nujol} cm^{-1} 3401, 1704. NMR: 8·88–9·03 τ (6H) two doublets —$CH(CH_3)_2$, 8·98 τ (3H) singlet >C—CH_3, 7·82 τ (6H) singlet —$N(CH_3)_2$, 7·35 → 7·65 τ dilution shift OH. For analysis, a sample was distilled at 100° (bath temp)/0·005 mm Hg. (Found: C, 72·29; H, 11·15. $C_{17}H_{31}O_2N$ requires: C, 72·55; H, 11·10%).

[17] Results of elemental analysis showed that this sample contains water of crystallization. (Found; C, 70·42; H, 11·03. $C_{17}H_{31}O_2N \cdot \frac{1}{2}H_2O$ requires: C, 70·30; H, 11·11%).

Oxodendrobinic acid

Oxodendrobine (1 g) was dissolved in 20 ml of 5% NaOH aq by warming the mixture on a water bath until all crystals had disappeared. After 30 min, the solution was cooled and neutralized with HCl. Oxodendrobinic acid (0·85 g) which deposited, was collected by filtration. The clear filtrate was then extracted with ethyl acetate, and the extracts were combined, dried over Na_2SO_4 and evaporated to leave a further crop (0·13 g) of crystals of oxodendrobinic acid. Recrystallization from a mixture of ether and methanol afforded colorless prisms, m.p. 225° (sintered at 218°). ν_{max}^{Nujol} cm^{-1} 3484, 2780–2300 (broad), 1706, 1642. (Found: C, 65·32; H, 8·83; N, 4·69. $C_{16}H_{25}O_4N$ requires: C, 65·06; H, 8·53; N, 4·7%).

Methyl oxodendrobinate

To a solution of 980 mg oxodendrobinic acid in methanol was added excess of ethereal diazomethane. After the reaction mixture had been allowed to stand overnight, the solvent was removed by evaporation. Trituration with methanol gave crystals which were recrystallized from methanol to afford colorless prisms, m.p. 197–200°, $[\alpha]_D^4$ +22° (*c*, 2·2; $CHCl_3$). ν_{max}^{Nujol} cm^{-1} 3300, 1724, 1650. (Found: C, 65·70; H, 8·59. $C_{17}H_{27}O_4N$ requires: C, 65·99; H, 8·80%).

Ketoester (XIV)

Methyl oxodendrobinate (1·02 g) was stirred overnight with CrO_3–pyridine (15 ml) complex at room temp. The reaction mixture was then diluted with water and extracted with $CHCl_3$. The extract was dried ($MgSO_4$), evaporated to dryness and a solution of the residue in benzene was passed through a short column of alumina. The solvent was evaporated off to leave 1·01 g of ketoester, which was recrystallized from ether to give colorless prisms, m.p. 129–131°. $[\alpha]_D^4$ +58° (*c*, 1·7; $CHCl_3$). ν_{max}^{Nujol} cm^{-1} 1733, 1704, 1669. NMR: 8·94–9·23 τ (6H) two doublets —$CH(CH_3)_2$, 8·50 τ (3H) singlet $>C(CH_3)-$, 7·00 τ (3H) singlet $>N-CH_3$, 6·58 τ (1H) singlet $>N-CH<$, 6·28 τ (3H) singlet —COOMe. (Found: C, 66·19; H, 8·42. $C_{17}H_{25}O_4N$ requires: C, 66·42; H, 8·20%).

Dendrobinediol diacetate (XIX).

To a solution of 500 mg dendrobinediol in 10 ml acetic anhydride was added 400 mg powdered anhydrous sodium acetate. After standing overnight at 10°, the mixture was poured into ice-water to decompose the excess acetic anhydride. Then, the mixture was washed with ether, neutralized with $NaHCO_3$ and extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$) and evaporated on a water bath to give 610 mg viscous oil. A solution of this oil was chromatographed on neutral alumina using benzene as solvent. Successive elution with benzene and ether gave 590 mg colorless oil which resisted all attempts at crystallization. For characterization, the diacetate was converted into its methiodide. The diacetate obtained above and an excess of CH_3I in methanol were refluxed on a water bath for 6 hr giving the crystalline methiodide in quantitative yield. Recrystallization from acetone gave colorless needles, m.p. 258–260° (dec). ν_{max}^{Nujol} cm^{-1} 1733. (Found: C, 51·30; H, 7·29. $C_{20}H_{33}O_4N{\cdot}CH_3I$ requires: C, 51·11; H, 7·35%).

Oxodendrobinediol diacetate (XX).

To a solution of dendrobinediol in 40 ml acetone was added a solution of 485 mg $MgSO_4$ in 30 ml water. Then, a solution of 12 ml 3·2% $KMnO_4$ solution in 60% aq acetone was added to the mixture which was kept at 5° by moderate cooling with stirring. The temp was kept at as near 5° as possible during the addition. After the $KMnO_4$ color had disappeared (this required 30 min), a further 1 ml $KMnO_4$ solution was added keeping the solution at the same temp. After the purple color had persisted for 1 hr, the excess $KMnO_4$ was destroyed by the addition of 50 ml methanol, warming the mixture to 30–40°. The precipitated MnO_2 was removed by filtration and washed with acetone. The filtrate and washings were combined, acidified with 10% acetic acid and concentrated to 40 ml under red. press. at below 50°. The resulting aqueous solution was saturated with solid NaCl and extracted with ether. The extract was washed with 1% HCl, dried ($MgSO_4$) and evaporated to leave 530 mg viscous oil which could not be crystallized.

Reduction of oxodendrobinediol diacetate with $LiAlH_4$

To a solution of 50 mg oxodendrobinediol diacetate in 3 ml anhydrous ether was cautiously added 50 mg $LiAlH_4$. The mixture was refluxed on a water bath for 4 hr. Decomposition of excess

hydride was effected by the addition of ether saturated with water. The precipitate that formed was separated from the ether solution by decantation and washed with ether. The ethereal solution and washings were combined and extracted with 1% HCl aq. The acidic solution was made basic with ammonia, saturated with NaCl and extracted with ether. After drying ($MgSO_4$), the extract was evaporated to leave 25 mg crude crystalline mass which was recrystallized from ether to give 20 mg of colorless needles, m.p. 112–114°. The identity of the product with an authentic sample of dendrobinediol was shown by comparison of IR spectra and mixed m.p. determinations.

Oxodendrobinediol monoacetate (XXI)

To a solution of 150 mg oxodendrobinediol diacetate (XX) in 1 ml ethanol was added 10 ml 10% HCl, and the mixture was warmed on a water bath for 20 min. After cooling, the mixture was neutralized with $NaHCO_3$, extracted with $CHCl_3$, dried ($MgSO_4$) and evaporated to afford 131 mg crystalline mass. A solution of these crystals in benzene was chromatographed over neutral alumina (3 g). Successive elution with benzene and ether gave a crystalline mass which was recrystallized from benzene to afford 100 mg colorless needles, m.p. 142°, $[\alpha]_D^{11}$ +2·96 (*c*, 1·01; methanol). ν_{max}^{Nujol} cm^{-1} 3460, 1733, 1675. NMR: 8·89–9·19 τ (6H) two doublets —$CH(CH_3)_2$, 8·70 τ (3H) singlet $\rangle C(OAc)-CH_3$, 7·91 τ (3H) singlet —O—CO—CH_3, 7·16 τ (3H) singlet —CO—N—CH_3, 6·61 τ (1H) doublet $|J| = 3{\cdot}5$ c/s $\rangle CH-N\langle$, 4·87 τ (1H) quartet $|J_1| = 3{\cdot}5$ c/s, $|J_2| = 9{\cdot}0$ c/s AcO—$CH\langle$. (Found: C, 67·08; H, 9·24; N, 4·50. $C_{18}H_{29}O_4N$ requires: C, 66·84; H, 9·04; N, 4·33%).

Oxodendrobinediol (XXII)

(1) *From oxodendrobinediol diacetate.* A solution of 543 mg oxodendrobinediol diacetate in 10 ml of 5% NaOH aq was warmed on a water bath at 60° for 20 min. After cooling, the mixture was acidified with acetic acid and evaporated to dryness under red. press. at below 60°. The resulting residue was shaken vigorously with a mixture of $CHCl_3$ and water (1:1). The aqueous layer which separated was extracted with $CHCl_3$. The $CHCl_3$ extracts were combined, washed with water, dried ($MgSO_4$), and evaporated to leave 350 mg of a crystalline mass which was recrystallized from a mixture of methanol and acetone to give 158 mg colorless prisms, m.p. 200–201, $[\alpha]_D^{13}$ −3·3° (*c*, 1·03, methanol). $\nu_{max}^{CHCl_3}$ cm^{-1} 1670. (Found: C, 68·03; H, 9·52; N, 5·15. $C_{16}H_{27}O_3N$ requires: C, 68·29; H, 9·67; N, 4·98%).

(2) *From oxodendrobinediol monoacetate.* A solution of 15 mg oxodendrobine monoacetate (XXI) in 1 ml 5% NaOH aq in ethanol was warmed on a water bath at 60° for 30 min. After cooling the mixture was acidified with acetic acid and evaporated to dryness under red. press. The viscous residue was triturated with a small quantity of water and extracted with $CHCl_3$. After drying ($MgSO_4$) the solvent was evaporated off to leave 12 mg crystals. Recrystallization from a mixture of acetone and ether (2:1) gave colorless prisms, m.p. 200°. On mixture with the sample obtained from the foregoing experiments, no depression of the m.p. was observed and the IR spectra of the two compounds were identical.

Reduction of oxodendrobinediol with $LiAlH_4$

To a solution of 10 mg oxodendrobinediol in 15 ml anhydrous tetrahydrofuran was added 20 mg $LiAlH_4$. The reaction mixture was refluxed on a water bath for 3·5 hr. After standing overnight, excess hydride was decomposed by the addition of ether containing water and 3 ml of 20% NaOH solution. The precipitate that formed was washed thoroughly with ether. The ethereal solutions were combined and extracted with 1% HCl. The acidic solution was made basic with ammonia, extracted with ether, and washed with water. After drying ($MgSO_4$), the solvent was evaporated to leave 6 mg crystals. Recrystallizations from a mixture of ether and n-hexane (2:1) gave 5 mg colorless needles. The product was proved to be identical with an authentic sample of dendrobinediol by comparison of IR spectra and mixed m.p. determination.

Dihydromethine (XXIV)

To a solution of 200 mg methine base (XXIII) in 10 ml ethanol was added 100 mg $NaBH_4$, and the reaction mixture was refluxed on a water bath for 2 hrs. Then, the organic solvent was evaporated off and the residue was treated with 10 ml 5% acetic acid and 5 ml 2% HCl. The acidic solution was saturated with NaCl, made basic with ammonia and extracted thoroughly with ether. After

drying ($MgSO_4$), the extract was evaporated to leave 195 mg of crystals. For purification, the crystals were sublimed at 150° (bath temp)/0·005 mm Hg. Recrystallization from ether afforded colorless needles, m.p. 177–179, $[\alpha]_D^{11}$ −5·3 (*c*, 0·78; methanol). $\nu_{max}^{CHCl_3}$ cm^{-1} 3584. NMR: 8·90–9·00 τ (6H) two doublets —$CH(CH_3)_2$, 8·73 τ (3H) singlet >C—CH_3, 7·80 τ (6H) singlet —$N(CH_3)_2$, 6·00–6·74 τ (2H) octet >$CH—CH_2—OH$, 5·77 τ (1H) multiplet >CH—OH. (Found: C, 72·29; H, 11·63; N, 4·64. $C_{17}H_{33}O_2N$ requires: C, 72·03; H, 11·73; N, 4·94%).

Dihydromethine monobenzoate (XXV)

(1) *From the methine base.* To a solution of 100 mg of methine base (XXIV) dissolved in 3 ml dry benzene containing 4 ml triethylamine was added dropwise a solution of 500 mg benzoyl chloride in 1 ml dry benzene with stirring at 5°. After standing overnight, the reaction mixture was warmed on a water bath at 55° for 3 hrs, and then concentrated to an oily residue under red. press. at below 50°. The residue was stirred vigorously with a mixture of 5 ml 5% HCl and 10 ml ether and the aqueous layer which separated was washed with ether, made basic with ammonia with cooling, saturated with NaCl, and extracted with ether. After drying ($MgSO_4$), the extract was concentrated to leave 97 mg of light yellow oil which could not be crystallized. To a solution of 97 mg methine benzoate (oil) in 5 ml ethanol were added 50 mg $NaBH_4$ and the reaction mixture was warmed on a water bath at 55° for 2 hrs, concentrated to dryness under red. press. at below 50° and treated successively with 5% acetic acid and 5 ml 5% HCl solution. The acidic solution was washed with ether, made basic with ammonia with cooling, saturated with NaCl and extracted with ether. After drying ($MgSO_4$), the extract was evaporated to leave 90 mg crystals which were chromatographed on alumina (2·0 g) using benzene as solvent. Elution with ether gave crystals which were distilled at 180° (bath temp)/0·005 mm Hg. Recrystallization from n-hexane afforded 85 mg of colorless prisms, m.p. 116–118°, $[\alpha]_D^6$ −18·3° (*c*, 1·25; methanol). ν_{max}^{Nujol} cm^{-1} 3226, 1709, 1600, 1582. (Found: C, 74·22; H, 9·73; N, 3·60. $C_{24}H_{37}O_3N$ requires: C, 74·38; H, 9·62; N, 3·61%).

(2) *By benzoylation of dihydromethine.* To a solution of 200 mg of dihydromethine in 8 ml of benzene containing 7 ml of triethylamine was added 0·7 ml of benzoyl chloride with stirring at 5°. After standing the mixture at room temp for 1 hr the liquid was evaporated and the residue was shaken vigorously with a mixture of 10 ml 2% HCl and 20 ml ether. The aqueous, acidic solution which separated was washed once with ether, made basic with ammonia with cooling and extracted with ether. The extract was dried ($MgSO_4$) and evaporated to give 250 mg of crystals which were recrystallized from n-hexane to afford 230 mg colorless prisms, m.p. 115°. On mixture with the sample obtained from the foregoing experiments, no depression on the m.p. was observed and the IR spectra of the two compounds were quite identical.

Anhydrodihydromethine monobenzoate (XXVI)

$POCl_3$ (0·5 ml) in 3 ml dry pyridine was added dropwise to a solution of 90 mg dihydromethine in 10 ml dry pyridine with stirring, the temp being kept at about 5°. After standing overnight at room temp, the reaction mixture was warmed on a water bath at 50° for 4 hr, and evaporated to dryness at below 5° under red. press. The residue was dissolved in 50 ml of cold 1% HCl aq, washed with ether, made basic with ammonia with cooling, saturated with NaCl, and extracted with ether. After drying ($MgSO_4$), the extract was evaporated. Then, 1 ml water was added to the residue, and the mixture was evaporated on a water bath under red. press. to remove the tenaciously retained pyridine by the residue. This treatment was repeated several times. The resulting brown residue was distilled at 150° (bath temp)/0·002 mm Hg to give 81 mg of a pale yellow oil which was chromatographed on neutral alumina (1·5 g) with benzene. Elution with benzene gave a negligible amount of an oily substance which could not be crystallized. Elution with ether afforded 75 mg colorless oil which solidified gradually. Recrystallization from n-pentane gave 70 mg of anhydrodihydromethine benzoate as colorless needles, m.p. 75°, $[\alpha]_D^6$ −20·5° (*c*, 1·60; methanol). ν_{max}^{Nujol} cm^{-1} 1718. σ_{max}^{Nujol} cm^{-1} 846, 711. NMR: 8·88–9·00 τ (6H) two doublets —$CH(CH_3)_2$, 9·04 τ (3H) singlet >C—CH_3, 7·78 τ (6H) singlet —$N(CH_3)_2$, 7·09 τ (1H) multiplet >C=C—CH<, 5·16–6·00 τ (2H) octet $|J_{AB}| = 10$ c/s >$CH—CH_AH_B—O—CO—C_6H_5$, 4·58 τ (1H) multiplet olefinic proton, 1·90–2·70 τ (5H) multiplet $C_6H_5—CO—O—$ aromatic protons. (Found: C, 78·01; H, 9·82. $C_{24}H_{35}O_2N$ requires: C, 78·00; H, 9·55%).

Hofmann degradation of dihydromethine (XXIV)

(1) *Dihydromethine methiodide.* To a solution of 110 mg dihydromethine (XXIV) in 3 ml of methanol was added 1 ml CH_3I, and the mixture was refluxed on a water bath for 3 hrs. The solvent and excess CH_3I were removed by evaporation to give 160 mg of a residue which was washed thoroughly with ether. Trituration with methanol gave crystals which were recrystallized from a mixture of ether and methanol (9:1) to afford 155 mg slightly yellow needles, m.p. 262°. $[\alpha]_D^{11}$ −6·3° (*c*, 0·80; 95% ethanol). (Found: C, 50·87; H, 8·54; N, 3·49. $C_{17}H_{33}O_2N{\cdot}CH_3I$ requires: C, 50·82; H, 8·53; N, 3·29%).

(2) *Pyrolysis of dihydromethine methohydroxide.* A solution of 140 mg of dihydromethine iodide in methanol was shaken vigorously with freshly prepared Ag_2O. The precipitate was removed by filtration and washed with methanol. The methanolic solutions were combined and evaporated on a water bath under red. press. to give 93 mg of a viscous oil. Methohydroxide (93 mg) was placed in a flask and heated in an oil bath at 115°/2 mm Hg for 30 min. After cooling, the sublimated crystals were recrystallized from ether to give 80 mg colorless needles, m.p. 178° which were identical with starting material, dihydromethine.

Nordendrobinic acid (XXVIII)

A mixture of 120 mg nordendrobine, 1·0 g barium hydroxide and 15 ml 30% ethanol was refluxed on a water bath for 8 hrs. The mixture was evaporated under red. press. The residue was then dissolved in 30 ml water, neutralized to pH 7·0 with 2% H_2SO_4 aq and the resulting precipitate was removed by passing the mixture through a layer of Celite. The precipitate which separated was washed with water, and the filtrate and washings were combined and evaporated to dryness under red. press. at below 50°. Upon trituration with ethanol, the residue solidified, and recrystallization from a mixture of ether and ethanol (2:8) afforded 80 mg of nordendrobinic acid as colorless prisms, m.p. 236–240°. ν_{max}^{Nujol} cm^{-1} 3175–2326, 1555. (Found: C, 66·11; H, 9·59. $C_{16}H_{25}O_3N{\cdot}\frac{1}{2}H_2O$ requires: C, 65·90; H, 9·47%).

Nordendrobinic acid lactam (XXIX)

Nordendrobinic acid (70 mg) was sublimed at 220° (bath temp)/0·005 mm Hg. The sublimate was shaken with a mixture of water and $CHCl_3$. The $CHCl_3$ layer was separated from the aqueous solution and the latter was washed several times with $CHCl_3$. Then, the aqueous solution was evaporated to dryness on a water bath *in vacuo*, to leave 3 mg of colorless prisms, m.p. 236–240°. The IR spectra of this compound and nordendrobinic acid were identical. The $CHCl_3$ solution was extracted with 2% HCl aq, and acidic solution was made basic with ammonia and extracted with $CHCl_3$. After drying ($MgSO_4$), the solvent was evaporated off to leave 15 mg colorless needles, m.p. 122–125°, which were identified with nordendrobine. Finally, the $CHCl_3$ solution separated from the basic substance was washed with water, dried over anhydrous $MgSO_4$ and evaporated to leave 42 mg of crystals which were recrystallized from a mixture of n-hexane and ether (1:1) to afford 38 mg colorless prisms (XXIX), m.p. 144°, $[\alpha]_D^{12}$ −123° (*c*, 0·78; methanol). $\nu_{max}^{CHCl_3}$ cm^{-1} 3356, 1706. (Found: C, 71·96; H, 9·25; N, 5·37. $C_{15}H_{23}O_2N$ requires: C, 72·25; H, 9·30; N, 5·62%).

The quaternary base (XXXIII)

A mixture of dendrobinediol (0·2 g) and thionyl chloride (0·08 ml) in pyridine (8 ml) was kept overnight at room temp. After dilution with water, the mixture was evaporated to dryness *in vacuo*. The residue in water–methanol was passed through a column of Amberlite-2RA-410-OH, and the column was washed with methanol. The combined filtrate and washings were concentrated to a small volume and extracted with ether. The extract was evaporated to leave a trace of unchanged dendrobinediol. The aqueous layer was exactly neutralized with dil. HI aq and evaporated to dryness. Trituration with acetone gave crystals which were recrystallized from acetone. Colorless prisms, m.p. 122°. (Found: C, 48·43; H, 7·54. $C_{16}H_{28}NOI{\cdot}H_2O$ requires: C, 48·60; H, 7·64%). For comparison, dendrobinediol hydroiodide was made by the usual method. Needles, from a mixture of acetone and ether, m.p. 176–177°. (Found: C, 46·77; H, 8·02; N, 3·22. $C_{16}H_{29}O_2N{\cdot}HI{\cdot}H_2O$ requires: C, 46·49; H, 7·80; N, 3·39%).

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