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Studies on Orchidaceae Alkaloids

XXVIII.* The Absolute Configuration of the Dendrobine Alkaloids

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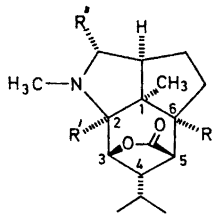
The absolute configuration of the dendrobine alkaloids has been established by comparing the circular dichroism curve of dihydroketopicrotoxinic acid (XXII), derived from picrotoxinin (XIV), with that of δ-nobilonine (XXV), derived from nobilonine (VII).

Thirteen alkaloids (eight bases and five quaternary compounds) of the dendrobine type have hitherto been reported to occur in various *Dendrobium* species (Scheme 1). Of these, 2-hydroxydendrobine (II),[3] dendrine (IV),[2,4] dendroxine (V),[2] and nobilonine (VII)[2] have been correlated chemically with dendrobine (I). Circular dichroism measurements on dendramine (III, 6-hydroxydendrobine),[5] 6-hydroxydendroxine (VI),[7] 6-hydroxynobilonine (VIII)[7] and their non-hydroxylated counterparts[5,7] have shown that they possess the same absolute configuration. The five quaternary compounds have been transformed into or synthesised from their corresponding bases, and thus possess the same absolute configuration as dendrobine (I).

Two concordant investigations of the absolute configuration of dendrobine (I) have been reported.[8,9] In these, the lactone rule[8] and the octant rule[8,9] were applied to dendrobine (I) and some of its derivatives. The opposite absolute configuration of that deduced for dendrobine (I) has, however, been reported for nobilonine methiodide.[10] The latter result was based on an X-ray investigation.

In this communication we report a determination of the absolute configuration of the dendrobine alkaloids, based on a comparison of the circular dichroism curve of dihydroketopicrotoxinic acid (XXII), derived from picrotoxinin (XIV), with that of δ-nobilonine (XXV), derived from nobilonine (VII). The absolute configuration of picrotoxinin (XIV) has previously been established by an X-ray diffraction investigation of α-bromopicrotoxinin (XVII).[11,12]

* For number XXVII of this series, see Ref. 1.

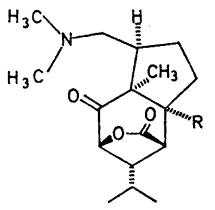


I: R = R' = R'' = H, dendrobine[2]

II: R = R'' = H, R' = OH, 2-hydroxydendrobine[3]

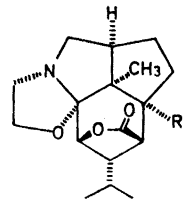
III: R' = R'' = H, R = OH, dendramine[2]

IV: R = R' = H, R'' = CH_2COOCH_3, dendrine[2,4]



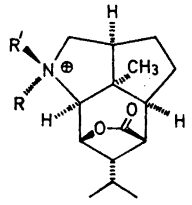
VII: R = H, nobilonine[2]

VIII: R = OH, 6-hydroxynobilonine[5]



V: R = H, dendroxine[2]

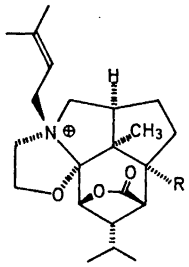
VI: R = OH, 6-hydroxydendroxine[2]



IX: R = R' = CH_3, *N*-methyldendrobine[2,6]

X: R = CH_3, R' = CH_2-CH=C$(CH_3)_2$, *N*-isopentenyldendrobine[6]

XI: R = O^-, R' = CH_3, dendrobine *N*-oxide[6]

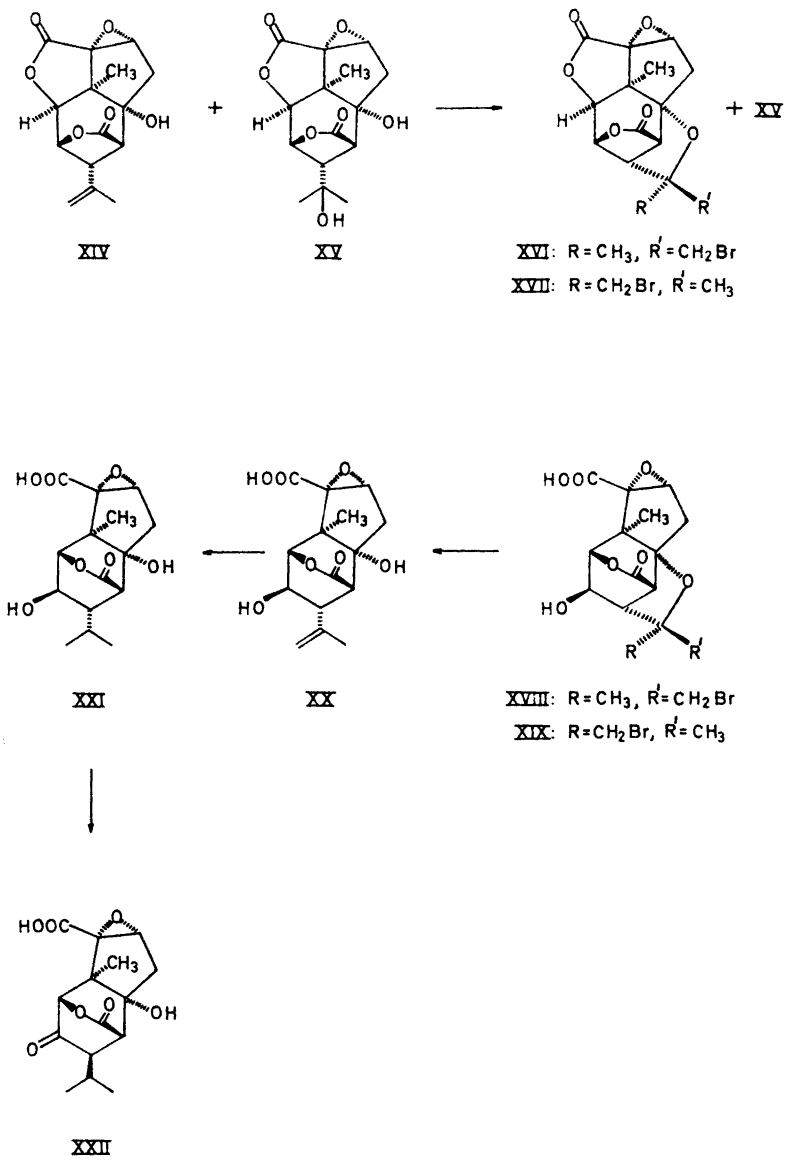


XII: R = H, *N*-isopentenyldendroxine[6,7]

XIII: R = OH, *N*-isopentenyl-6-hydroxydendroxine[6,7]

Scheme 1.

Dihydroketopicrotoxinic acid (XXII) was synthesised from picrotoxinin (XIV) as depicted in Scheme 2. Picrotoxin, which is a molecular compound comprising picrotoxinin (XIV) and picrotin (XV) in the ratio 1:1, was treated with bromine in water. The resulting mixture of α- and β-bromopicrotoxinin (XVI and XVII)[13] was hydrolysed with aqueous sodium hydroxide (2 M, 100°) to α- and β-bromopicrotoxinic acid (XVIII and XIX).[14] Debromination



Scheme 2.

of XVIII and XIX with zinc and ammonium chloride afforded α-picrotoxinic acid (XX).[14] Hydrogenation of XX using Adams catalyst (1 atm., 25°) yielded α-dihydropicrotoxinic acid (XXI),[14] which was oxidised with Jones reagent[15] to dihydroketopicrotoxinic acid (XXII). The circular dichroism curve of

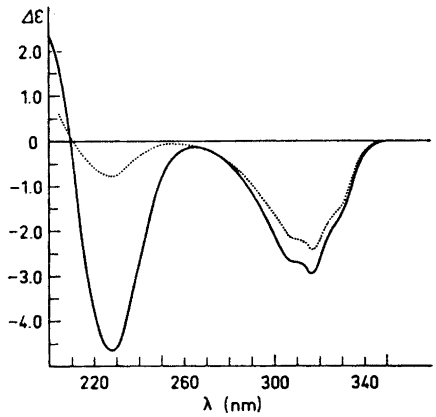


Fig. 1. CD curves of dihydroketopicrotoxinic acid (XXII) (——), and δ-nobilonine (XXV) (·····) in methanol.

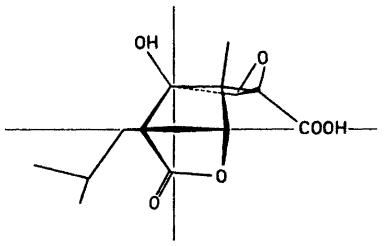
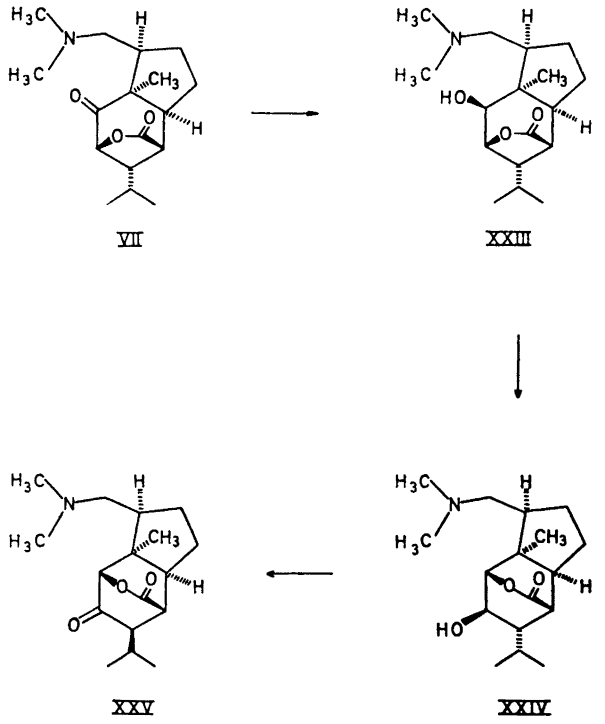


Fig. 2. Octant projection of dihydroketopicrotoxinic acid (XXII).

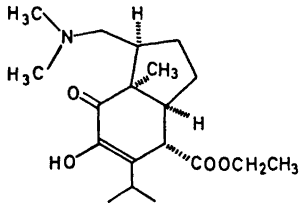
XXII is shown in Fig. 1, and its octant projection in Fig. 2. The *negative* Cotton effect at 317 nm implies that an epimerisation has occurred at C-4 during the oxidation, giving the more stable isomer.



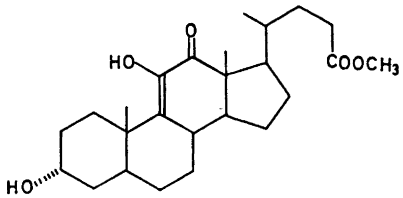
Scheme 3.

δ-Nobilonine (XXV) was synthesised from nobilonine (VII) as depicted in Scheme 3. Reduction of nobilonine (VII) with sodium borohydride in tetrahydrofuran gave crystalline dihydronobilonine (XXIII), previously obtained as an amorphous solid.[16,17] Isomerisation of XXIII in aqueous hydrochloric acid to dihydro-δ-nobilonine (XXIV), followed by oxidation with Jones reagent [15] gave δ-nobilonine (XXV). The circular dichroism curve of XXV is shown in Fig. 1. The *negative* Cotton effect at 317 nm implies, as in the case of dihydroketopicrotoxinic acid (XXII), that an epimerisation has occurred at C-4 during the oxidation. It follows from the similarity of the circular dichroism curves of XXII and XXV that these compounds have the same absolute configuration, and hence that the dendrobine alkaloids possess the absolute configuration depicted in Scheme 1. This assignment is in accordance with that of Inubushi [8] and Huang.[9]

Another route to δ-nobilonine (XXV) was first investigated. Yamamura and Hirata have reported the preparation of isonobilonine hydrochloride [16,17] by treatment of nobilonine (VII) with ethanolic potassium hydroxide (2 M) at room temperature, followed by acidification with hydrochloric acid. The substance obtained, assumed to be the hydrochloride of XXV, melted at 183 – 185° and exhibited infrared bands (KBr) *inter alia* at 1740 and 1668 cm^{-1}. When performing the above reaction, we obtained a base for which we propose the structure XXVI. The hydrochloride of XXVI melted with decomposition at 226 – 232°.



XXVI



XXVII

The molecular formula of XXVI, $C_{19}H_{31}NO_4$, was established by mass spectrometry of the base and elemental analysis of its hydrochloride. Its infrared spectrum ($CHCl_3$) shows bands *inter alia* at 1740 cm^{-1} (ester), 1675 and 1642 cm^{-1} (α,β-unsaturated ketone). The proposed structure for XXVI is strongly supported by its ultraviolet spectrum, which shows a maximum at 278 nm (ε 5800) in ethanol, displaced to 322 nm (ε 3500) in alkaline ethanol. The steroid XXVII,[18] which has the same chromophore as XXVI, exhibits an ultraviolet maximum at 280 nm (ε 5200) in ethanol. Information concerning the configuration at C-5 was gained from the NMR spectrum of XXVI. The C-5 hydrogen appears as a doublet (τ 6.62) with a coupling constant of 2.0 Hz, which is consistent with a dihedral angle of approximately 60° or 110° between H-5 and H-6. In the most stable conformation of the *endo* epimer (XXVI) the dihedral angle H-5, H-6 is close to 60°. The corresponding value for the *exo* epimer should be ~150°.

EXPERIMENTAL

All melting points are corrected. Mass spectra were measured on an LKB 9000 spectrometer (ionization energy 70 eV), the optical rotations on a Perkin-Elmer 141 polarimeter, and the circular dichroism spectra on a Cary 60 spectropolarimeter. The IR spectra were recorded on a Perkin-Elmer 257 instrument, the UV spectra on a Beckman DK2 instrument, and the NMR spectra on a Varian A-60A spectrometer.

Dihydroketopicrotoxinic acid (XXII). α-Dihydropicrotoxinic acid [14] (XXI, 500 mg) was dissolved in acetone (45 ml) and an excess of Jones reagent [15] was added. After stirring the solution at room temperature for 45 min, sodium hydrogen sulphite was added to destroy the excess of chromic acid. The reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was recrystallised from water giving XXII (380 mg), m.p. 170 – 180° (dec.), $[\alpha]_D^{23}$ −80° (*c* 0.45, methanol). (Found: C 56.4; H 6.20; O 37.5. Calc. for $C_{15}H_{18}O_7 \cdot \frac{1}{2}H_2O$: C 56.4; H 6.00; O 37.6.) IR spectrum: σ_{max} (KBr) 3520(s), 3280(s), 1748(s), 1723(s) cm^{-1}. UV spectrum, nm (ε): λ_{max} (methanol) 309 (26), 207 (1100). NMR spectrum (pyridine-d_5) τ: −1.10 (s, broad, 2 H), 4.18 (s, 1 H), 5.81 (s, broad, 1 H), 6.65 (d, 1 H, $J = 1.5$ Hz), 6.94 (q, 1 H, $J_1 = 6.5$ Hz, $J_2 = 1.5$ Hz), 7.2 – 7.4 (m, 2 H), 7.5 – 8.1 (m, 1 H), 8.48 (s, 3 H), 8.91 (d, 3 H, $J = 5$ Hz) 9.01 (d, 3 H, $J = 5$ Hz).

Dihydronobilonine (XXIII). Sodium borohydride (400 mg) was added to a solution of nobilonine (VII, 200 mg) in tetrahydrofuran (50 ml). The mixture was refluxed for 7 h, cooled, acidified with hydrochloric acid (1 M) and diluted with water to 130 ml. After 10 min, the solution was neutralised with sodium hydrogen carbonate and extracted with ether (6 × 40 ml). The combined ether solutions were evaporated to dryness, and the residue was chromatographed on silica gel (1.3 × 10 cm) using methanol as eluent. The second fraction consisted of chromatographically pure dihydronobilonine (XXIII, 60 mg), which after crystallisation from hexane afforded needles, m.p. 77 – 79°, (lit.[16,17] amorphous solid), $[\alpha]_D^{23}$ +3.1° (*c* 3.0, methanol). (Found: C 69.0; H 9.85. Calc. for $C_{17}H_{29}NO_3$: C 69.1; H 9.89.) IR spectrum: σ_{max} ($CHCl_3$) 1765(s) cm^{-1}. NMR spectrum ($CDCl_3$) τ: 5.37 (H-3, q, $J_1 = 5.4$ Hz, $J_2 = 1.4$ Hz), 6.26 (H-2, d, $J = 1.4$ Hz).

Dihydro-δ-nobilonine (XXIV). A solution of dihydronobilonine (XXIII, 53 mg) in aqueous hydrochloric acid (4 M, 4 ml) was heated at 90° for 6 h. The solution was cooled, diluted with water to 15 ml, neutralised with sodium hydrogen carbonate and extracted with ether (5 × 7 ml). The combined ether solutions were dried (Na_2SO_4) and evaporated to dryness. The residue (31 mg) was chromatographed on neutral alumina (1.4 × 8 cm) using chloroform as eluent. The first fraction contained a small amount of unreacted dihydronobilonine (XXIII). The second fraction consisted of dihydro-δ-nobilonine (XXIV, 25 mg), which was crystallised from ether at −20° giving needles, m.p. 134 – 135.5°, $[\alpha]_D^{23}$ −22° (*c* 1.1, methanol). (Found: C 69.0; H 9.92. Calc. for $C_{17}H_{29}NO_3$: C 69.1; H 9.89.) IR spectrum: σ_{max} ($CHCl_3$) 1750(s) cm^{-1}. NMR spectrum ($CDCl_3$) τ: 5.32 (H-2, d, $J = 1.2$ Hz), 6.03 (H-3, q, $J_1 = 1.2$ Hz, $J_2 = 2.8$ Hz). The hydrochloride of dihydro-δ-nobilonine was obtained as needles from ethanol, m.p. 255 – 265° (dec.). Yamamura and Hirata reported [16,17] m.p. 217 – 219° for the hydrate. (Found: C 61.4; H 9.15. Calc. for $C_{17}H_{30}ClNO_3$: C 61.5; H 9.11.) IR spectrum: σ_{max} (KBr) 1740(s) cm^{-1}.

δ-Nobilonine (XXV). Dihydro-δ-nobilonine (XXIV, 21 mg) was dissolved in acetone (2 ml) and an excess of Jones reagent [15] was added. After stirring the solution at room temperature for 1 h, sodium hydrogen sulphite was added. The reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in water, and the solution was made alkaline with sodium hydrogen carbonate and extracted with ether. The ether solution was evaporated to dryness giving XXV (9 mg), which did not crystallise, $[\alpha]_D^{23}$ −76° (*c* 0.45, methanol). IR spectrum: σ_{max} ($CHCl_3$) 1768(s), 1740(s) cm^{-1}. NMR spectrum ($CDCl_3$) τ: 5.35 (H-2, s). The hydrochloride was crystallised from ethanol, m.p. 210 – 225° (dec.). (Found: C 61.9; H 8.69. Calc. for $C_{17}H_{28}ClNO_3$: C 61.9; H 8.56.)

Treatment of nobilonine (VII) with ethanolic potassium hydroxide. Nobilonine (VII 100 mg) was dissolved in potassium hydroxide in ethanol (2 M, 16 ml) and the solution was left for 24 h. The resulting yellow solution was acidified with hydrochloric acid (2 M). After 10 min the reaction mixture was made alkaline with sodium hydrogen carbonate and extracted with ether. The extract was dried and filtered through a column of alumina using ether as eluent. Evaporation of the eluate to dryness gave XXVI (50

mg), which did not crystallise, $[\alpha]_D^{23}$ $-121°$ (*c* 0.90, chloroform). IR spectrum: σ_{max} ($CHCl_3$) 3420(m), 1740(s), 1675(m), 1642(s) cm^{-1}. UV spectrum, nm (ε): λ_{max} (ethanol) 278 (5800); λ_{max} (alkaline ethanol) 322 (3500). NMR spectrum, ($CDCl_3$) τ: 6.62 (H-5, d, $J = 2.0$ Hz). The *hydrochloride* was crystallised from ethanol, m.p. 226 – 232° (dec.). (Found: C 61.1; H 8.75; N 3.88; O 17.2. Calc. for $C_{19}H_{32}ClNO_4$: C 61.0; H 8.63; N 3.75; O 17.1.)

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