ACTA CHEMICA SCANDINAVICA 25 (1971) 717–720

Studies on Orchidaceae Alkaloids

XXI.* 6-Hydroxynobiline, a New Alkaloid from *Dendrobium hildebrandii* Rolfe

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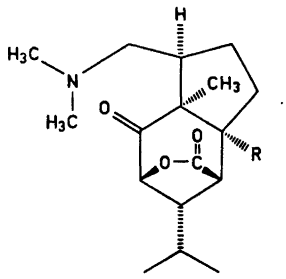
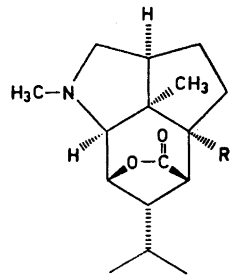
Nobiline, dendramine, and a new alkaloid, 6-hydroxynobiline (I), have been isolated from *Dendrobium hildebrandii* Rolfe. The constitution and absolute configuration of I are assigned on the basis of spectroscopic properties and the transformation of I into dendramine.

Alkaloids of the dendrobine type have been found in *Dendrobium nobile* Lindl.,[2] *D. linawianum* Rchb. f.,[3] and *D. findlayanum* Par. *et Rchb. f.*[4] In the present communication the occurrence of nobiline (II), dendramine (III), and a new alkaloid, 6-hydroxynobiline (I), in *D. hildebrandii* Rolfe is reported.



I R = OH, 6-hydroxynobiline
II R = H, nobiline



III R = OH, dendramine
IV R = H, dendrobine

Comparison of the spectroscopic properties of nobiline (II), $C_{17}H_{27}NO_3$, and compound I, $C_{17}H_{27}NO_4$, shows that the alkaloids are closely related. The additional oxygen in I together with an absorption at 3620 cm^{-1} ($CHCl_3$)

* No. XX of this series, see Ref. 1.

in its IR spectrum suggest that I is a hydroxylated nobiline. The NMR spectrum of I shows *inter alia* a doublet at τ 7.13, assigned to H-5, and indicating that the hydroxyl group is situated at C-6. The transformation of I into dendramine (III) proved that the hydroxyl group was situated in the 6-position, and hence I is 6-hydroxynobiline.

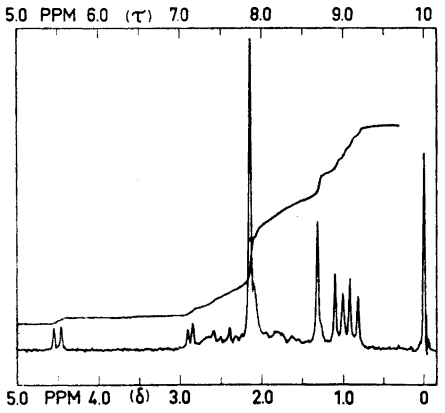


Fig. 1. NMR spectrum of 6-hydroxynobiline (I) in $CDCl_3$.

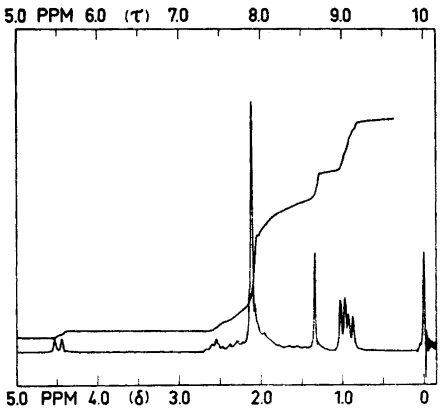
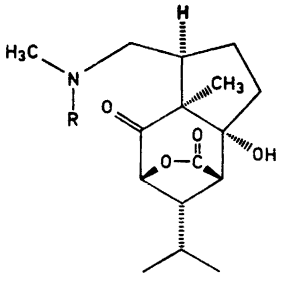
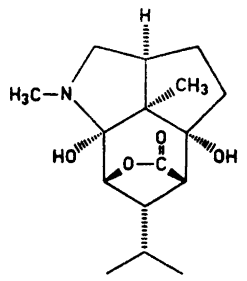


Fig. 2. NMR spectrum of nobiline (II) in $CDCl_3$.

Onaka *et al.*[5] have reported the transformation of nobiline (II) into dendrobine (IV) by catalytic hydrogenation (Adams catalyst, 65 atm., 200°, 1.5 h) of cyanonornobiline. As this procedure, in our hands, gave a poor yield of dendrobine (IV) another cyclization process was investigated. Treatment of I with cyanogen bromide in tetrahydrofuran yielded cyano-6-hydroxynornobiline (V). On reacting V with hydrogen peroxide in methanol in the presence of sodium hydrogen carbonate, the carbamoyl derivative VI was formed. Attempts to hydrolyse V with sulfuric acid in the same way as reported for cyanonordendrobine [6] were unsuccessful. Treatment of VI with an equimolar amount of sodium nitrite in dilute hydrochloric acid afforded *N*-nitroso-6-



V R = -C≡N
VI R = -CONH2
VII R = -N=O



VIII 2,6-dihydroxydendrobine

hydroxynornobiline (VII), and a base, presumably 2,6-dihydroxydendrobine (VIII), which was not further investigated. When a large excess of sodium nitrite was used, VII was formed as the major product. Catalytic hydrogenation of either VII or VIII in acetic acid (Adams catalyst, 1 atm., 25°, 4 h) generated dendramine (III) in a quantitative yield, indistinguishable from an authentic sample.

The absolute configuration of dendrobine (IV) has been established by ORD measurements on two dendrobine derivatives.[7] Spectroscopic studies have shown dendramine (III)[8,9] to have the same relative configuration as dendrobine (IV). From the similarity of their CD curves (Fig. 3) it is obvious that they have the same absolute configuration. Therefore, the transformation of I into dendramine (III) establishes the absolute configuration of I.

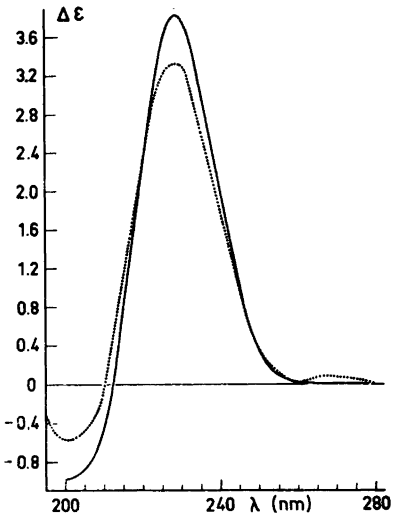


Fig. 3. CD curves of dendramine (III) (- - - -), and dendrobine (IV) (———) in methanol.

EXPERIMENTAL

All melting points are corrected. Mass spectra were recorded on an LKB 9000 spectrometer (ionization energy 70 eV). IR spectra were recorded on a Perkin-Elmer 257 instrument and the NMR spectra in deuterochloroform on a Varian A60-A spectrometer, with TMS as internal reference.

Isolation of alkaloids. Fresh plants of *Dendrobium hildebrandii* Rolfe (21 kg) were extracted in essentially the same way as described for *D. findlayanum* Par. *et* Rchb. f.,[4] to give the crude alkaloid extract. The bases were chromatographed on neutral alumina, using chloroform as eluent. The first fraction contained nobiline (II) and dendramine (III), and the second fraction pure 6-hydroxynobiline (I, 0.3 g). Nobiline (II) and dendramine (III) were separated by chromatography on silica gel. Elution with methanol gave dendramine (III, 0.1 g), m.p. 184 – 185.5°, $[\alpha]_D^{23}$ – 25° (*c* 0.1, chloroform), and nobiline (II, 0.3 g), m.p. 86.5 – 88°, $[\alpha]_D^{23}$ + 21° (*c* 0.48, chloroform), further identified by their MS, IR and NMR spectra.

Characterization of 6-hydroxynobiline (I). Crystallization of I from benzene gave needles, m.p. 158 – 159.5°; $[\alpha]_D^{23}$ + 62° (*c* 0.58, chloroform). (Found: C 66.0; H 8.82; N 4.57; O 20.7. Calc. for $C_{17}H_{27}NO_4$: C 66.0; H 8.80; N 4.53; O 20.7.) IR spectrum: σ_{max} (KBr) 3600 – 2600 (polymer OH); 1828 (m), 1808 (s), 1793 (s) (γ-lactone); 1710 (s) (6-membered

ring ketone) cm^{-1}; σ_{max} ($CHCl_3$) 3620 (m) (monomer OH); 1805 (s), 1790(s), 1783(s) (γ-lactone); 1717(s) (6-membered ring ketone) cm^{-1}. NMR spectrum: τ 5.49 (d, 1 H, $J = 5.5$ cps), τ 7.13 (d, 1 H, $J = 3.5$ cps), τ 7.85 (s, 6 H), τ 8.68 (s, 3 H), τ 8.95 (d, 3 H, $J = 6$ cps), τ 9.13 (d, 3 H, $J = 6$ cps). Pertinent mass spectral peaks *m/e* (rel. intensity): M^+ 309 (1), 84 (2), 58 (100).

Cyano-6-hydroxynornobiline (*V*). A solution of I (200 mg) and cyanogen bromide (100 mg) in tetrahydrofuran (15 ml) was refluxed for 6 h. The solution was evaporated to dryness and the residue dissolved in chloroform. The chloroform solution was washed with hydrochloric acid, dried ($MgSO_4$) and evaporated to dryness. The residue was recrystallized from acetone-ether (2:1) at $-20°$ giving V (160 mg), m.p. 203 – 204°; $[\alpha]_D^{23}$ +69° (*c* 0.28, chloroform). (Found: C 64.1; H 7.35; N 8.66; O 20.1. Calc. for $C_{17}H_{24}N_2O_4$: C 63.7; H 7.55; N 8.75; O 20.0.) IR spectrum: σ_{max} (KBr) 2205 (s) (–C≡N); 1827(m), 1809(s), 1793(s) (γ-lactone); 1702(s) (6-membered ring ketone) cm^{-1}.

N-*Carbamoyl-6-hydroxynornobiline* (*VI*). Hydrogen peroxide (45 %. 0.2 ml) and sodium hydrogen carbonate (40 mg) were added to a solution of V (144 mg) in methanol (15 ml), and the mixture was stirred for 42 h at room temperature. The reaction mixture was concentrated, diluted with water (15 ml), and extracted with chloroform (3 × 15 ml). Evaporation of the chloroform gave VI (127 mg). Crystallization from acetone-ether (1:5) yielded the pure substance, m.p. 185 – 186°; $[\alpha]_D^{24}$ +17° (*c* 0.44, chloroform). (Found: N 8.32; O 23.7. Calc. for $C_{17}H_{26}N_3O_5$: N 8.28; O 23.6.) IR spectrum: σ_{max} (KBr) 1824(m), 1808(s), 1793(s) (γ-lactone); 1713(s) (6-membered ring ketone); 1650(s), 1590(s) (>N–CO–NH_2) cm^{-1}.

N-*Nitroso-6-hydroxynornobiline* (*VII*). VI (98 mg) was dissolved in aqueous hydrochloric acid (4 %, 20 ml) by warming, and the solution was cooled to 0°. To the clear solution sodium nitrite (100 mg) in water (2 ml) was added. After standing for 20 h at room temperature, the reaction mixture was refluxed for 45 min, cooled and extracted with chloroform (3 × 15 ml). The extract was dried ($MgSO_4$) and evaporated, leaving crude VII (55 mg) which was crystallized from ether. Recrystallization from benzene yielded the pure substance, m.p. 173 – 175°; $[\alpha]_D^{24}$ +32° (*c* 0.34, chloroform). (Found: C 59.5; H 7.36; N 8.67; O 24.6. Calc. for $C_{16}H_{24}N_2O_5$: C 59.2; H 7.46; N 8.64; O 24.7.) IR spectrum: σ_{max} (KBr) 1808(s), 1790(s) (γ-lactone); 1714(s) (6-membered ring ketone) cm^{-1}.

Hydrogenation of VII. A solution of VII (4 mg) in acetic acid (4 ml) was hydrogenated over Adams catalyst at room temperature and under atmospheric pressure. After 4 h the catalyst was filtered off, the solution concentrated, made alkaline and extracted with chloroform. The chloroform solution was evaporated to dryness, leaving a crystalline residue, m.p. 182 – 184°, $[\alpha]_D^{23}$ –22° (*c* 0.3, chloroform), which was indistinguishable from dendramine (III) by TLC, GLC, IR and MS.

Acknowledgements. We are indebted to Dr. Björn Lüning for his interest in this work, to Prof. Bengt Lindberg for valuable discussions, and to Dr. Ragnar Ryhage for determining the mass spectra. We thank Dr. Rolf Lindskog for measuring the CD spectra. A fellowship from *Stiftelsen Bengt Lundqvists Minne* to one of us (K. L.) is gratefully acknowledged. This work was supported by the *Swedish Natural Science Research Council*.

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Received June 30, 1970.