

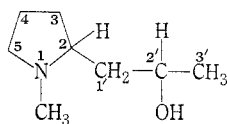
(+)-HYGROLINE, THE MAJOR ALKALOID OF *CARALLIA BRACHIATA*  
(RHIZOPHORACEAE)\*

By J. S. FITZGERALD†

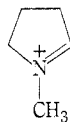
Alkaloids have been reported in only two genera of the family Rhizophoraceae, *Carallia*<sup>1</sup> and *Anisophyllea*.<sup>2</sup> *Carallia brachiata* (Lour.) Merr. belongs to the subfamily Rhizophoroidae, tribe Gynotroche, but unlike most of the Rhizophoraceae, it is not a mangrove. Widespread in east Asia, it also occurs in both New Guinea and Queensland. Alkaloids are absent from the bark but are present in the leaf, the major one being C<sub>8</sub>H<sub>17</sub>NO, m.p. 29–31°. Spectral evidence, optical activity, and direct comparison of derivatives show unequivocally that it is (+)-hygroline.

This base was first identified by Späth and Kittel<sup>3</sup> who isolated the (–) form from *Erythroxylum coca*. It was obtained from the mother liquors of a cocaine preparation after separating the corresponding ketonic base, hygrine. Synthesis and resolution were achieved by Galinovsky and Zuber,<sup>4</sup> and the configuration ascertained by Lukes *et al.*<sup>5</sup>

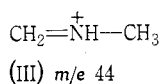
The n.m.r spectrum of the alkaloid is consistent with structure (I) although all peaks cannot be assigned with certainty on the present information. The side-chain –CH(OH)– proton gives rise to a multiplet at  $\delta$  4.0, with splittings indicative of coupling constants approximating to 6.4 c/s with the methyl group, 8.4 c/s with one of the 2'-methylene protons and 4.4 c/s with the other 2'-methylene proton. The magnitude and inequality of the latter two splittings indicate a freedom from averaging, either conformational or due to mixing of energy levels. This suggests that the molecule has one preferred conformation, presumably stabilized by intramolecular hydrogen bonding.



(I)



(II) *m/e* 84



(III) *m/e* 44

The mass spectrum is also consistent with structure (I), there being a small parent peak at *m/e* 143. The base peak, the only predominant one, at *m/e* 84, corresponds to (II), obtained by a cleavage of the C2–C1' bond. A metastable peak at *m/e* 49.5 points to the formation of this fragment from the parent ion with elimination of the neutral radical C<sub>3</sub>H<sub>7</sub>O. The next most abundant peak, about 20% of the base peak intensity at *m/e* 44, is due to (III) which is formed by a

\* Manuscript received December 11, 1964.

† Division of Organic Chemistry, CSIRO Chemical Research Laboratories, Melbourne.

<sup>1</sup> Webb, L. J., CSIRO Aust. Bull. No. 268, 1952.

<sup>2</sup> Douglas, B., and Kiang, A. K., *Malayan Pharm. J.*, 1957, **6**, 138.

<sup>3</sup> Späth, E., and Kittel, F., *Ber. dt. chem. Ges.*, 1943, **76**, 942.

<sup>4</sup> Galinovsky, F., and Zuber, H., *Mh. Chem.*, 1953, **84**, 798.

<sup>5</sup> Lukes, R., Kovar, J., Kloubek, J., and Blaha, K., *Coll. Czech. Chem. Comm.*, 1960, **25**, 483.

cleavage of the C4-C5 bond, cleavage of the N1-C2 bond, and migration of a hydrogen to the nitrogen atom.

### Experimental

Microanalyses were made by the Australian Microanalytical Service, Melbourne.

Milled leaf of *Carallia brachiata* was extracted by percolation with warm methanol and the alkaloid removed from the concentrated extract by the method described previously.<sup>6</sup> The crude base was obtained as a liquid in about 0.2% yield from the dry leaf.

Gas chromatography on a column with Silicone elastomer SE-30 as the stationary phase gave one peak, the trapped product being a solid, melting about 20°. Because of its volatility the crude base was purified by a short-path distillation in a sublimation apparatus, at 100° and 10–20 mm pressure. A subsequent distillation in an evacuated, sealed tube at 40–50° gave purer material of higher melting point, 29–31°. On a smaller scale the main base was separated from a minor one, present in about 10% of the total amount, by chromatography on cellulose, eluting with butanol-aqueous acetic acid. Paper chromatography with this solvent showed that  $R_F$  values for the major and minor bases were 0.35 and 0.75.

The n.m.r. absorption, measured in carbon tetrachloride solution at 60 Mc/s, relative to tetramethylsilane as internal standard ( $\delta$  0.00), showed: 3-proton doublet,  $\delta$  1.07,  $J$  6.4 c/s; 2-proton multiplet,  $\delta$  1.5; 5-proton multiplet,  $\delta$  1.8; 3-proton singlet (N-Me) and 1-proton multiplet,  $\delta$  2.35; 1-proton multiplets,  $\delta$  3.1 and  $\delta$  4.0; 1-proton singlet (OH),  $\delta$  4.7.

The pure alkaloid had m.p. 29–31° (lit. hygroline 33–34°,<sup>3,4</sup> 18°;<sup>5</sup>  $[\alpha]_D^{21}$  +87° (water;  $c$ , 0.90); +50° (ethanol;  $c$ , 0.77) [lit. +84° and –84° (water);<sup>4</sup> +39.3° and –31.4° (ethanol)<sup>6</sup>] (Found: C, 67.2; H, 12.0; N, 9.9; (N)-Me, 9.7; active H, 0.7; (O)-Me, nil. Calc. for  $C_8H_{17}NO$ : C, 67.1; H, 12.0; N, 9.8; (N)-Me, 10.5; one active H, 0.65%).

The infrared spectrum indicated a hydroxyl group, absorption in a broad band at 3200–3400  $cm^{-1}$ , while lack of absorption between 1500 and 2500  $cm^{-1}$  pointed to the absence of a carbonyl function.

The following derivatives have been prepared, and comparison with published data and some authentic samples confirms the identification of the alkaloid.

(+)-Hygroline methiodide, m.p. 124°; mixed with an authentic specimen of (+)-hygroline methiodide, m.p. 122–123°. Infrared spectra of the two specimens in KCl disks were identical (Found: C, 37.8; H, 7.2; N, 4.9. Calc. for  $C_8H_{20}INO$ : C, 37.9; H, 7.0; N, 4.9%).  $[\alpha]_D^{20}$  +11.0° (water;  $c$ , 2.69) (lit.<sup>5</sup> +11.2°).

(+)-Hygroline reineckate, m.p. 153°. An authentic specimen (m.p. 150–151°) of the (+)-salt on admixture gave m.p. 149–151° (Found: C, 31.2; H, 5.2; N, 21.0. Calc. for  $C_8H_{17}NO[Cr(NH)_2(SCN)]$ : C, 31.2; H, 5.0; N, 21.2%).

(+)-Acetylhygroline hydrochloride, m.p. 177° from acetone, was prepared as described by Lukes *et al.*<sup>5</sup> who did not separate and characterize it (Found: C, 53.9; H, 8.8; N, 6.4.  $C_{10}H_{19}NO_2 \cdot HCl$  requires C, 54.2; H, 9.1; N, 6.4%).

(+)-Acetylhygroline picrate had m.p. 128–129° [lit.<sup>5</sup> (+)-compound, 120–123°; (±)-compound 127–128°]. Admixture with an authentic specimen, prepared from (+)-hygroline, gave m.p. 120–123°.

### Acknowledgments

The author is indebted to Dr. T. G. Hartley and Mr. E. A. Dunstone for collecting the plant material, to Miss L. E. Banfield and Mr. D. L. Swingler of the Division of Chemical Physics, CSIRO, for running the mass spectrum, and to Dr. J. Kovar of the Czechoslovakian Academy of Science for providing specimens of hygroline derivatives.

<sup>6</sup> Fitzgerald, J. S., *Aust. J. Chem.*, 1963, **16**, 246.