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Lindcarpine, an Alkaloid from *Lindera pipericarpa* Boerl (Lauraceae) ¹

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Lindcarpine, an alkaloid isolated from the roots of Lindera pipericarpa, has been characterised as 2,11-dihydroxy-1,10-dimethoxynoraporphine.

THE leaves and bark of Lindera pipericarpa were reported to contain a small amount of an alkaloid, laurotetanine (I).² We had previously characterised two β,β-triketones, linderone and methyl-linderone, which were isolated from the ether extract of the roots of this plant,³ and which have recently been synthesised.⁴ We now wish to report the characterisation of a new phenolic alkaloid, lindcarpine, isolated from the methanol extract of the roots.

Lindcarpine (II), C₁₈H₁₉O₄N, isolated from the methanol extract of the root, crystallises from ethyl acetate in colourless needles, $[\alpha]_{p}^{22} + 166^{\circ}$ (in EtOH), m. p. 195° (decomp.); analyses show it has two methoxyl groups and no N-methyl function. The alkaloid forms a crystalline hydrochloride, $C_{18}H_{19}O_4N$, HCl, $2H_2O$, $[\alpha]_D^{22}$ $+169^{\circ}$ (in MeOH), m. p. 200° (decomp.).

Lindcarpine shows OH and NH infrared absorption at 3490, 3330, and 3125 cm.⁻¹ and no carbonyl absorption. Its ultraviolet spectrum in ethanol shows λ_{max} . at 218, 267, and 303 mµ (log ε 4.57, 4.14, and 3.82), which is almost superposable on that of isocorydine (III) ⁵ and is characteristic of 1,2,10,11-tetrasubstituted noraporphines.6

The alkaloid is unstable and tends to darken on exposure to air or light. Although phenolic it gives, like isocorydine (III), a negative test with ferric chloride in ethanol. It gives a reddish-brown coloration with concentrated nitric acid; a positive Gibb's test; ⁷ but a negative Gaebel's test and a negative Quastel test.⁸

The n.m.r. spectrum of lindcarpine (in deuteriodimethyl sulphoxide) confirms the presence of two methoxyl groups (τ 6.22, 6.42) and three aromatic protons, and the absence of an N-methyl function. The spectrum of the crude acetate (in CDCl₃) shows the presence of three aromatic protons (a pair of AB doublets at $\tau 2.80$ and 3.03 with J = 8 c./sec., and a singlet at 3.08); two methoxyl groups (τ 6.12, 6.62); and two O-acetyl and one N-acetyl functions (τ 7.66, 7.76, and 7.81). The AB doublets in the aromatic region have the coupling constant characteristic of two aromatic protons in ortho positions. The high chemical shift of the protons of one of the methoxyl groups is characteristic for a methoxyl group situated in the C-1 or C-11 position of aporphine alkaloids.⁹ The other methoxyl group is, therefore, at C-2 or C-10.

Methylation of lindcarpine with formaldehydesodium borohydride at room temperature yields *N*-methyl-lindcarpine (IV), $C_{19}H_{21}O_4N$, $[\alpha]_D^{22} + 222^\circ$ (in MeOH), m. p. 196° (decomp.). Both N-methyllindcarpine and lindcarpine hydrochloride react with diazomethane to give NO-dimethyl-lindcarpine, which is identical with authentic isocorydine. This reaction and the positive Gibb's test given by lindcarpine establish the presence of a hydroxyl group at C-11, and consequently a methoxyl group at C-1 in the alkaloid. Since lindcarpine gives a negative Quastel test for a catechol system, it can be assigned the structure (II).

Besides hernovine,¹⁰ lindcarpine is the only other 1,2,10,11-tetrasubstituted dihydroxydimethoxynoraporphine that has been isolated from a natural source.



EXPERIMENTAL

Melting points were determined on a Hoover capillary melting point apparatus.

Isolation of Lindcarpine.-(a) Dried powdered root wood of Lindera pipericarpa (1.84 kg.) was continuously extracted with (i) ether to remove linderone and methyllinderone³ and then with (ii) methanol for 1 week. The methanol extract was concentrated to a thick sticky residue (400 ml.). The residue was stirred with 2N-sodium carbonate solution (1.2 l) and the mixture was extracted with chloroform $(7 \times 1 l)$. The chloroform extracts were washed with water, dried (Na_2SO_4) , and evaporated in vacuo to give a dark grey alkaloid solid (21.2 g.). The crude alkaloid (1.0 g) was rubbed with dilute hydrochloric acid (80 ml.) and the mixture was extracted with benzene $(4 \times 25 \text{ ml.})$ to remove a non-alkaloidal gummy material. The acid layer was basified with sodium carbonate solution and extracted with chloroform (6 \times 30 ml.). The combined chloroform extracts were washed with water and dried (Na₂SO₄), and, on evaporation in vacuo, gave a light brown solid which crystallised from ethyl acetate in colourless needles (0·1 g.), m. p. 195° (decomp.), $[\alpha]_{D}^{22} + 166°$ (c 1·35 in ethanol) (Found: C, 69.0; H, 6.2; N, 4.25; OMe, 19.9; NMe, nil. C₁₈H₁₉O₄N requires C, 69.0; H, 6.1;

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⁴ Personal communication from Dr. H. H. Lee.

⁵ R. H. F. Manske, Canad. J. Res., 1942, 20B, 57.

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N, 4.5; 20Me, 19.8%). Lindcarpine gave a crystalline hydrochloride in colourless needles (from dilute hydrochloric acid), m. p. 200° (decomp.), $[\alpha]_{D}^{22} + 169^{\circ}$ (c 1.59 in methanol) (Found: C, 56.2; H, 6.4; N, 3.7.

C₁₈H₁₉O₄N,HCl,2H₂O requires C, 56.0; H, 6.3; N, 3.6%).

(b) By a similar procedure $11\cdot 2$ g. of dark grey crude alkaloid was obtained from $2\cdot 2$ kg. of dried powdered root bark.

N-Methyl-lindcarpine. A mixture of lindcarpine (0.4 g.), 40% formaldehyde solution (0.4 ml.), sodium borohydride (100 mg.), and 95% ethanol (30 ml.) was kept at room temperature, with occasional swirling, for 5 hr. After the removal of the solvent under reduced pressure the residue was heated with water (10 ml.) on a steam-bath for 15 min., and carbon dioxide was passed into the cooled mixture. The colourless precipitate (0.32 g.) was collected and crystallised from acetone-methanol in colourless *needles*, m. p. 196° (decomp.), $[\alpha]_{D}^{22} + 222°$ (c 0.80 in methanol) (Found: C, 69.9; H, 6.7; N, 4.6. $C_{19}H_{21}O_4N$ requires C, 69.7; H, 6.5; N, 4.3%).

N-Methyl-lindcarpine gave a *methiodide*, colourless needles from aqueous methanol, m. p. 187° (decomp.),

 $[\alpha]_{D}^{22} + 151^{\circ}$ (c 0.49 in methanol) (Found, for specimen dried at 80°/0.2 mm. for 8 hr.: C, 48.6, 48.6; H, 5.9, 5.8. C₂₀H₂₄O₄N, 1.5H₂O requires C, 48.4; H, 5.5%).

NO-Dimethyl-lindcarpine. Lindcarpine hydrochloride (0.5 g.) in methanol (5 ml.) was treated with ethereal diazomethane (from 3 g. nitrosomethylurea) and the mixture was left at 10° for 4 days. The solvents were removed and the residue, dissolved in benzene, was chromatographed on alumina (25 g.). Elution with benzene gave NO-dimethyl-lindcarpine (44 mg.), which crystallised from methanol in prisms, m. p. 184–186°, $[\alpha]_D^{22} + 207^\circ$ (c 0.87 in methanol). It was found to be identical with authentic isocorydine (mixed m. p. and infrared spectra).

Treatment of N-methyl-lindcarpine with diazomethane also furnished isocorydine in quantitative yield.

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