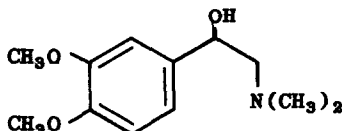


TWO NEW ALKALOIDS IN CACTI

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The plant Thelocactus macromeris (Engelm.) L. Benson, Coryphantha macromeris (Engelm.) Lem., Britton and Rose, has been found to contain three alkaloids by gas chromatography. The alkaloids were extracted on a large scale from the plant by standard methods.² The principal alkaloid was separated from the minor constituents by chromatography on alumina. The main alkaloid, "macromerine", gave mol. wt. 240 ± 25 GLC³, (213 vapor pressure lowering), m.p. 66-67.5° and rotation of ($[\alpha]_D^{25} - 147.01$, $c = 0.0390$ g/ml, CHCl_3 ; $[\alpha]_D^{25} - 42.61$, $c = 0.0200$ g/ml, absolute ethanol). The structure, according to spectral data discussed below, is (I):



The n.m.r. spectrum indicated three aromatic hydrogens, a benzylic hydrogen, and an alcohol hydrogen [singlet 3.91 δ (1H); shifts with concentration changes and disappears in deuterium oxide]. Two methoxyls were shown centered at 3.95 δ (6H), a doublet centered at 2.20 δ (2H) and a singlet 2.33 δ (6H). The latter two groups of hydrogens were determined to be a methylene group (2.20 δ) attached to nitrogen and not to an aromatic system by observing the chemical shift, to lower field, of these hydrogens by changing solvent from chloroform to deuterium oxide and finally to acidic deuterium oxide.⁴ The i.r. spectrum showed the hydroxyl to be strongly associated, in KBr pellet, by a broad band at 3125 cm^{-1} . Elemental analysis has confirmed the empirical formula (Calcd. for $\text{C}_{12}\text{H}_{19}\text{NO}_3$, Calcd. C, 63.96; H, 8.52; N, 6.22; mol. wt.

225.32), found C, 63.94; H, 8.57; N, 6.12).

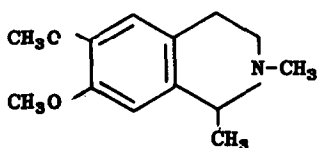
d,l-Macromerine⁵ has been obtained by two independent syntheses. The first was accomplished by a Friedel-Crafts acylation⁶ of veratrole with chloroacetyl chloride, then reacting the product with dimethylamine followed by reduction with sodium borohydride. The second, and most convenient, was via a Hoesch condensation⁷ of veratrole and dimethylaminoacetonitrile hydrochloride, prepared by the procedure for the synthesis of the monomethylamine derivative followed by reduction with sodium borohydride (m.p. 46-47°, picrate 146-147°). The i.r., n.m.r. and u.v. of synthetic d,l-macromerine and natural l-macromerine are in complete agreement.

We are presently attempting to synthesize l-macromerine from L(-)-adrenaline in order to establish its absolute configuration. L(-)-Normacromerine (N-demethyl) has been prepared in good optical purity.

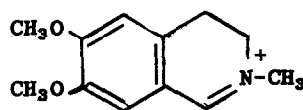
The cactus Carnegia gigantea (Engelm.), investigated by Heyl in 1928⁸, has been reinvestigated and found to contain in addition to carnegine (II), another alkaloid, m.p. 151-152°, $[\alpha]_D^{25} + 27.1$, (C = .02 g/ml, CHCl₃), 30% by wt. of total alkaloids.

The presence of an alcohol function was indicated by a band at 3540 cm⁻¹ in the infrared spectrum, by a peak at m/e 219 (m-18, 3% of the base peak) in the mass spectrum⁹, and by the formation of an acetate derivative as indicated by a shift in gas chromatographic retention time when injection of the alkaloid is followed immediately by injection of acetic anhydride¹⁰. The alkaloid gave a negative ferric chloride test. The nature of other substituent groups was deduced from the n.m.r. spectrum which exhibited signals indicating the presence of: (i) two OCH₃, singlet at 3.83 δ (6H); (ii) N-CH₃, singlet at 2.45 δ (3H); (iii) CH-CH₃, doublet (J = 6.9 cps) at 1.37 δ (3H); and (iv) two probable para aromatic hydrogens, singlet at 6.23 δ (2H).

The base peak in the mass spectrum of carnegine (II) was m/e 206, as expected for a tetrahydroisoquinoline alkaloid.¹¹ The base peak in the new alkaloid was found at m/e 222 (m-15). The molecular weight was determined from a molecular ion peak at m/e 237 (2.3% of the base peak), in

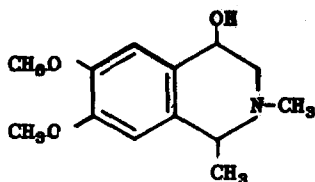


II



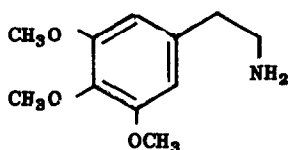
m/e 206

agreement with the empirical formula $C_{13}H_{19}NO_3$ also determined by elemental analysis. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.73; H, 8.15; N, 5.91.



III

The above results lead to structure III for the alkaloid, which we have named gigantine (1,2-dimethyl-4-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline). Synthesis of d-gigantine is presently being undertaken.



IV

The benzylic hydroxyl relationship between macromerine and mescaline (IV) and gigantine and carnegine may arise from related enzymatic reactions or by direct synthesis with oxygenated fragments. This relationship has been observed in other natural products.^{12,13}

Synthetic d,l-macromerine, natural macromerine and natural gigantine are physiologically active. Both alkaloids caused hallucinogenic reactions when tested on squirrel monkeys and cats (macromerine; 20 mg/kilo-I.P., hallucinogenic; gigantine, 20 mg/kilo-I.P., lethal; 5 mg/kilo-I.P., hallucinogenic).¹⁴ Macromerine shows "anti" adrenaline results in the turtle heart.¹⁵

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