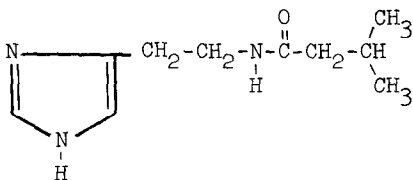


DOLICHTHELINE, A NOVEL IMIDAZOLE ALKALOID FROM DOLICHTHELE SPHAERICA

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A new imidazole alkaloid named dolichotheline has been isolated from Dolichothele sphaerica (Dietrich) Britton and Rose, a small cactus indigenous to southern Texas and northern Mexico. From the data discussed below we propose that the alkaloid is 4(5)-[2-N-isovalerylaminoethyl]imidazole (N-isovalerylhistamine) (I).



I

Alkaloids were extracted by the method previously reported and separated into phenolic and non-phenolic fractions (1). Crystallization of dolichotheline was accomplished by treating the condensed non-phenolic fraction with benzene-acetone (1:1). The crystalline base (0.02% on the basis of dry weight) melted at 130-131°, was homogeneous on TLC and gave the characteristic red color of nonsubstituted ring-nitrogen imidazoles with a modified Pauly's reagent (2-4). Elemental analysis supports the empirical formula C₁₀H₁₇N₃O (Calcd.: C, 61.51; H, 8.77; N, 21.52. Found: C, 61.57; H, 8.73; N, 21.55).

The picrate melted at 150-152° and elemental analysis supports the empirical formula C₁₆H₂₀N₆O₈ (Calcd.: C, 45.28; H, 4.75; N, 19.80. Found: C, 44.69;

H, 4.68; N, 19.55). The acetate melted at 76-78° and elemental analysis supports the empirical formula $C_{12}H_{19}N_3O_2$ (Calcd.: C, 60.74; H, 8.07; N, 17.71. Found: C, 60.65; H, 8.09; N, 17.70).

No characteristic absorption maxima were present in the u.v. spectrum of dolichotheleine. This is in accord with the general behavior of imidazoles not possessing a carbonyl function in conjugation with the imidazole ring (5). The i.r. spectrum displayed a strong band at 1640 cm^{-1} suggestive of a mono-substituted amide. The n.m.r. spectrum (6) in deuterated methanol showed a doublet of doublets centered at 0.88 δ ($J = 5$ cps) and 0.95 δ ($J = 3$ cps) corresponding to two methyl groups. Two singlets, 7.52 δ and 6.78 δ , were indicative of two aromatic protons which were assigned to the 2 and 4(5) positions respectively (7). A broad band at 7.93 δ , which exchanged with D_2O , corresponded to the imino hydrogen. The methylene and methine groups of the isovaleryl radical were evidenced by a multiplet centered at 1.97 δ and the methylene group adjacent to the ring showed a triplet centered at 2.77 δ ($J = 7$ cps). The remaining methylene group and the amido hydrogen showed a multiplet centered at 3.40 δ .

On acid hydrolysis of the alkaloid, an odor characteristic of short-chain fatty acids was detected. The acid was water distilled and the sodium salt prepared. The i.r. spectrum of the salt was identical with that of sodium isovalerate. The amine, isolated as the dihydrochloride, displayed an i.r. spectrum identical with that of histamine dihydrochloride, melted at 227-231°, and showed no melting point depression when mixed with authentic histamine dihydrochloride. Elemental analysis supports the empirical formula $C_5H_9N_3 \cdot 2HCl$. (Calcd.: C, 32.62; H, 6.02; N, 22.83; Cl, 38.53. Found: C, 32.63; H, 6.01; N, 22.74; Cl, 38.55).

The high resolution mass spectrum (8) of dolichotheleine showed a strong molecular ion peak at m/e 195, corresponding to I and confirmed the empirical formula $C_{10}H_{17}N_3O$, with an accurate mass of 195.1382 (Calcd., 195.1372). The isovaleryl side chain led to simple acyl cleavage ($M - C_4H_9$) and a McLafferty rearrangement ($M - C_3H_6$) (9). Further there was a strong peak at m/e 85

corresponding to the isovaleryl portion and one at m/e 111 corresponding to the amine. The fragmentation pattern of the isolated amine was identical with that reported for histamine (10) and confirmed the empirical formula $C_5H_9N_3$ with an accurate mass of 111.0792 (Calcd., 111.0796).

Dolichotheleine was synthesized by refluxing histamine with isovaleric anhydride (11). The crystalline product obtained melted at 130° and showed no melting point depression when mixed with natural dolichotheleine. The R_f value on TLC and the i.r. spectra of the free base and the picrate derivatives were also identical with natural dolichotheleine.

This constitutes the first report of the occurrence of an imidazole alkaloid in the Cactaceae. Known cactus alkaloids are either of the β -phenethylamine or tetrahydroisoquinoline structures. With the exception of the jaborandi alkaloids, no other imidazole alkaloids have been reported to occur in higher plants.

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