

STRUCTURE OF PIPERLONGUMININE, AN ALKALOID OF PIPER LONGUM LINN.

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In our earlier publication (1) we have reported the occurrence of piperine and piperlongumine, a new piperidone alkaloid in Piper longum Linn. (Piperaceae). Piperlongumine has been shown to be a N-(3,4,5-trimethoxy cinnamoyl)- $\Delta^5$ -piperidine-2-one (I). The present communication concerns the isolation and structure elucidation of their congener alkaloid piperlonguminine.

Piperlonguminine,  $C_{16}H_{19}O_3N$ , (yield, 0.002%; M, 273), m.p. 166-68°, is neutral in character and does not form any crystalline salt or adduct with  $CH_3I$ . The alkaloid contains an active hydrogen atom and a methylenedioxy group (two proton singlet at 5.90 $\delta$ ). Kuhn-Roth determination corresponds to more than one C-methyl but its NMR spectrum (six proton doublet at 1.05 $\delta$ ; J = 6 cps) reveals the presence of two such groupings associated with an isopropyl side chain.

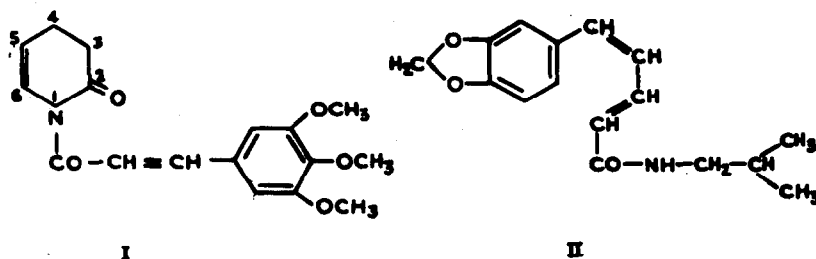
The ultraviolet absorption spectrum,  $\lambda_{\max}^{EtOH}$  245, 256, 307 and 340 m $\mu$  ( $\log \epsilon$  3.99, 4.02, 4.33 and 4.52) of piperlonguminine is comparable with that of its congener alkaloid piperine (256, 310 and 344 m $\mu$ ;  $\log \epsilon$  4.04, 4.29 and 4.49) which evidently indicates the presence of similar chromophoric system in the alkaloid. The infrared absorption spectrum of the alkaloid

exhibits bands for monosubstituted  $\alpha,\beta$ -unsaturated amide (3.05 and 3.25  $\mu$ , 6.10  $\mu$ ) (2), isopropyl (7.25 and 7.35  $\mu$ ) (3), methylenedioxy group (10.80  $\mu$ ) and trans configuration of an olefinic double bond (10.10  $\mu$ ) (3).

Piperlongumine develops a yellow colouration with tetra-nitromethane and readily decolourises bromine in glacial acetic acid. This observation in conjunction with four olefinic proton signals (6.01, 6.32, 6.75 and 7.50 $\delta$ ) in the NMR spectrum of the alkaloid reveals the presence of two olefinic unsaturation in its molecule. Accordingly piperlongumine upon catalytic hydrogenation furnishes a tetrahydroderivative,  $C_{16}H_{23}O_3N$  (M, 277), m.p. 66°. The infrared absorption spectrum of tetrahydro-piperlongumine, as expected, lacks the intense peaks at 6.20 and 10.10  $\mu$  for olefinic double bonds discernible in the spectrum of the parent alkaloid. In conformity with the above physical and chemical data the ultraviolet absorption spectrum of tetrahydro-piperlongumine shows typical absorption at 234 and 290 m $\mu$  (log  $\epsilon$  3.60 and 3.59) comparable with the ultraviolet spectrum of methylenedioxy benzene (4).

Piperlongumine, which is shown to be an amide undergoes hydrolysis with ethanolic concentrated hydrochloric acid in a sealed tube and produces several products from which only isobutylamine hydrochloride,  $C_4H_{11}N$ , HCl, m.p. 172-74° could be isolated and identified. Ozonolysis of the alkaloid yields piperonal,  $C_8H_6O_3$  (isolated as its DNPH, m.p. 264-66°) the formation of which shows that one of the two double bonds remains conjugated to the phenyl nucleus. Summing up, it may therefore be concluded that piperlongumine is an isobutylamide of a carboxylic acid, the structure of which can only be represented

as (II), which immediately proves that it is an isobutylamide of piperic acid.



It has been further observed that the proton signals associated with piperic acid residue in piperine (5) are essentially the same as that in the NMR spectrum of piperlonguminine (II).

The structure (II) thus derived for piperlonguminine fits excellently with its mass spectrum. This alkaloid amide exhibits the molecular ion peak at  $m/e$  273 and other intense peaks at  $M-72$ , [loss of  $(CH_3)_2.CH.CH_2.NH$ ],  $M-100$  [M-72-CO] and at  $m/e$  135 and 115. As expected, tetrahydropiperlonguminine shows the molecular ion peak at  $m/e$  277 and the peaks at  $m/e$  205 and  $m/e$  204 are due to the loss of [  $(CH_3)_2.CH.CH_2.NH$  ] and [  $(CH_3)_2.CH.CH_2.NH_2$  ] residues. The peak at  $m/e$  135 which is common to both the parent alkaloid and its tetrahydroderivative is diagnostic of piperonylidene or piperonyl grouping (6). Thus the mass spectrum provides an independent structure proof for the proposed structure of the alkaloid.

The above formulation (II) of piperlonguminine has been further substantiated by an unambiguous synthesis. Piperic acid on treatment with  $PCl_3$  furnishes the corresponding acid chloride. The latter with isobutylamine in dry benzene and pyridine at room temperature gave piperlonguminine which was identical with the natural product.

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#### REFERENCES

- (1) A. Chatterjee and C.P. Dutta, Science & Culture, 29, 568 (1963); A. Chatterjee and C.P. Dutta, IUPAC Symposium on "The Chemistry of Natural Products", Kyoto, Japan, Abstracts, p.81 (1964).
- (2) L. Crombie, J. Chem. Soc., 995, 997, 1007 (1955).
- (3) K.R. Varma, M.L. Maheswari and S.C. Bhattacharyya, Tetrahedron, 21, 115 (1965).
- (4) W. J. Genster and C.M. Camour, J. Org. Chem., 18, 9 (1953).
- (5) N.S. Bhacca, L.F. Johnson and J.N. Shoolery, "NMR Spectra Catalog", Varian Associates, U.S.A. (1962).
- (6) B. Willhalm, A.F. Thomas and F. Gautschi, Tetrahedron, 20, 1185 (1964).

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Melting points are uncorrected. Satisfactory analyses were obtained for all compounds reported in this communication.