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ON THE STRUCTURE OF PIPLARTINE AND A SYNTHESIS OF DIHYDROPIPLARTINE*

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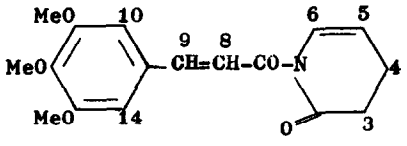
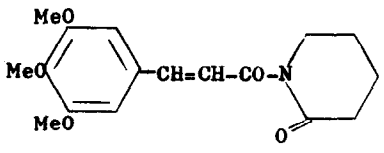
Recent reports on the isolation and structure determination of the alkaloid piplartine(1-5) from the stem bark and roots of Piper longum Linn. (Fam. Piperaceae) prompt us to record our findings on the structure of this compound‡. The alkaloid has been constituted as (I) on the basis of spectral and degradative evidence (4,5).



I



II

Piplartine $C_{17}H_{19}O_5N$ (M^+; m/e 317) m.p. 124°, isolated from the roots of Piper longum gave on reduction with Pd/C in ethanol, dihydropiplartine(II) $C_{17}H_{21}O_5N$ m.p. 116-7° λ max 206, 240(infl.), and 324 mμ (log ε 4.43, 4.05 and 3.99); ν max 1670, 1660(amide), 1610 (-CH=CH-) cm^{-1}. (Found : C, 64.0; H,6.8; $C_{17}H_{21}O_5N$ requires C, 63.9; H, 6.6%). Reduction of piplartine with PtO_2 in acetic acid gave the previously reported tetrahydro derivative(III) m.p.83-4°. Piplartine on ozonolysis gave 3,4,5-trimethoxybenzaldehyde and alkaline hydro-

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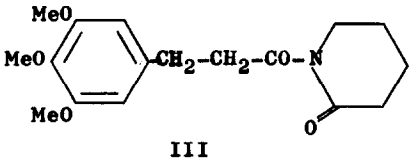
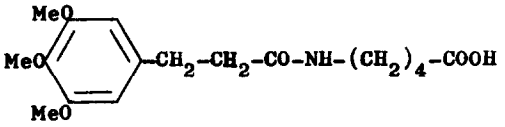
‡Since the alkaloid was first reported and designated as piplartine(1,2) and subsequently found to be identical with piperlongumine(5), we propose to retain the former name.

lysis provided 3,4,5-trimethoxycinnamic acid.



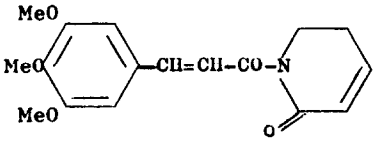
III



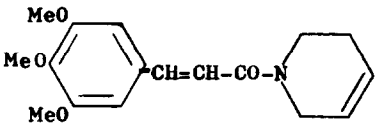
IV

Piplartine and dihydropiplartine resemble closely in their UV Spectra indicating that the cinnamoyl double bond is not reduced in the latter compound. The tetrahydro derivative does not show any UV absorption showing that both the olefinic double bonds are reduced. The structure of dihydropiplartine was confirmed by synthesis. Condensation of 3,4,5-trimethoxycinnamoyl chloride with α-piperidone gave (II), identical with dihydropiplartine in its TLC, mixed m.p. IR, and NMR Spectra.

Chatterjee and Dutta have formulated piplartine having a 5,6-double bond in the pyridone ring as in (I). Although their communication(5) is entitled "-----synthesis of piperlongumine-----", there is no report of this synthesis. On the other hand, tetrahydropiplartic acid(IV) has been synthesized and compared



V



VI

with the degradation product. The other evidence cited in support of a 5,6-double bond is the formation of succinaldehydic acid(identified as its DNPH derivative)* by ozonolysis of piplartic acid.

A careful examination of the NMR Spectra of piplartine and its derivatives suggests that the double bond in piplartine should be placed on carbon atoms 3,4 leading to the structure(V). Chatterjee and Dutta assign the multiplet

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*Piplartic acid(0.6 g) on ozonolysis is reported(5) to have furnished 0.925 g. of the DNPH derivative of succinaldehydic acid. The theoretical yield could be about 0.5 g. only.

around 2.5δ (Fig.1) to the 4 protons attached to the C-3 and C-4 carbon atoms of (I). The integrated area of the multiplet at 2.5δ however shows only two protons and these are found to be coupled with the two proton triplet at 4.1δ. The signal at 4.1δ which has been overlooked, should be assigned to the methylene protons α to the nitrogen atom and the numerous examples in the literature (6) and those in Table I would support this conclusion. Erroneous assignments have been made for the styryl protons and the olefinic protons of the pyridone ring. These authors have assigned the triplets at 6.0 and 6.18δ to the C-5 and C-8 protons and the signals at 7.65 and 7.9δ have been ascribed to the C-6, C-9 protons of structure (I). However the area between 5.8 and 6.2δ integrates to only one proton. This doublet centered at 6.03δ (J = 10 c/s) each signal being further split into triplets (J = 1.6 c/s) should be ascribed to the C-3 proton in structure (V). The further splitting of the doublet is caused by the C-5 methylene protons in the meta position(7). The ortho coupled C-4 proton appears as a complex multiplet (the doublet at 6.95δ J = 10 c/s can be clearly seen) centered at 6.9δ. The cinnamoyl protons C-8 and C-9 in structure (V) appear as an AB quartet at 7.38 and 7.75δ (J = 15 c/s). (see Table I for other examples).

A structure having double bond at 4,5-position in the pyridone ring is incompatible with the observed multiple splitting of the methylene and olefinic protons of the pyridone ring. As a model compound(VI) was synthesized by condensation of 3,4,5-trimethoxycinnamoyl chloride with 1,2,5,6-tetrahydropyridine (8), m.p. 126° (Found: C, 67.2; H, 7.1, N. 4.7; $C_{17}H_{21}O_4N$ requires: C, 67.3; H, 7.0; N, 4.6%). The C-3,C-4 protons show a broad signal (2H) at 5.85 and the methylene protons at C-2, α-to the nitrogen atom appear as a broad peak at 4.2δ.

A UV difference curve between piplartine(V) and dihydropiplartine(II) shows $\lambda_{max}^{ethanol}$ 225 mμ; ε, 11,000 which is in good agreement with an α,β-unsaturated lactam chromophore(9). The enamine lactam in (I) would be expected to absorb around 240 mμ. Piplartine should therefore be represented as (V).

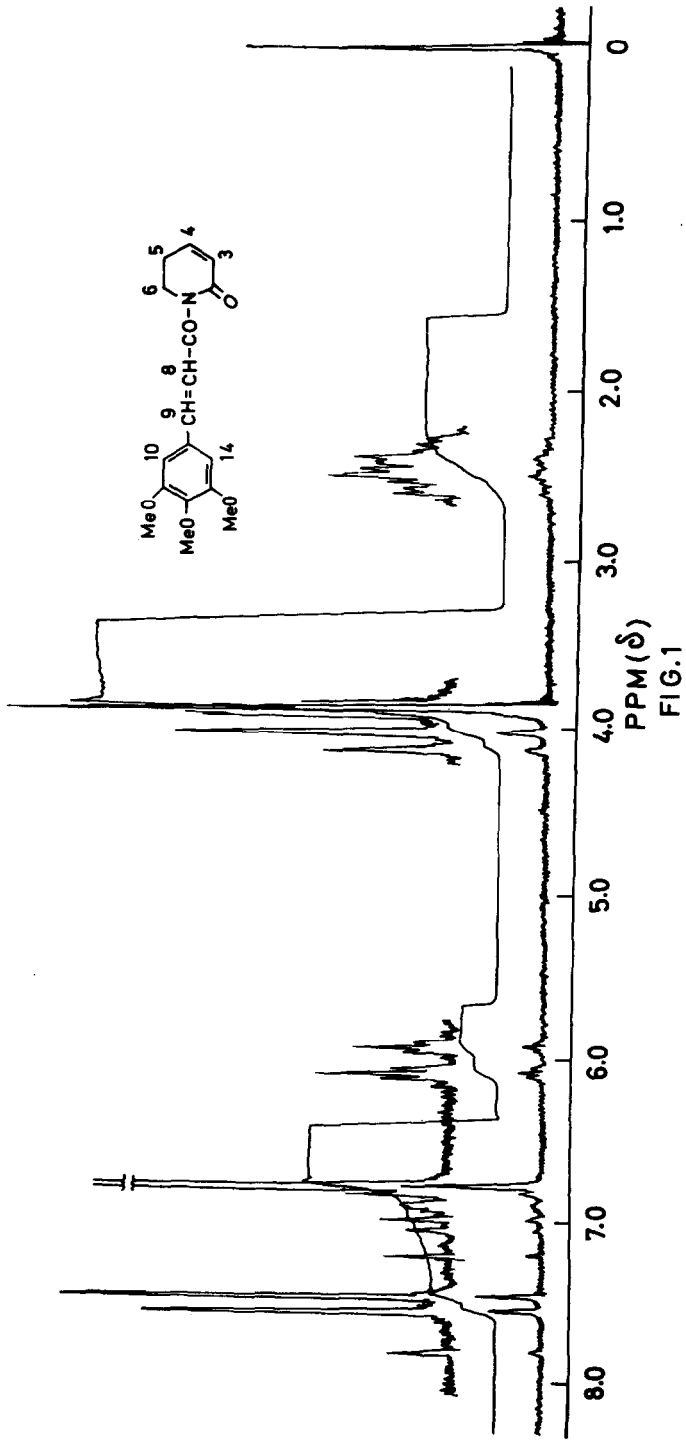

FIG.1

TABLE I

NMR Spectra($CDCl_3$; 60 mc) are taken with TMS as internal standard. Symbolss,d,t and m represent singlet,doublet,triplet and multiplet respectively. All signals are reported as ppm in δ values.

	δ	No. of protons	Multiplicity (J; c/s)	Proton assignment; see formula
Piplartine (V)	2.5	2	m	C-5
	3.9	9	s	C-11,12,13$(OCH_3)_3$
	4.1	2	t(7)	C-6
	6.03	1	d(10)	C-3
	6.8	2	s	C-10,14
	6.9	1	m	C-4
	7.38	1	d(15)	C-8
	7.75	1	d(15)	C-9
Dihydro-piplartine (II)	1.9	4	m	C-4,5
	2.65	2	m	C-3
	3.9	2	m	C-6
	3.95	9	s	C-11,12,13$(OCH_3)_3$
	6.85	2	s	C-10,14
	7.4	1	d(15)	C-8
	7.7	1	d(15)	C-9
Tetrahydro piplartine (III)	1.9	4	m	C-4,5
	2.55	2	m	C-3
	3.15	4	q(6)	C-8,9
	3.8	2	m	C-6
	3.9	9	s	C-11,12,13$(OCH_3)_3$
	6.5	2	s	C-10,14
Compound (VI)	2.25	2	(broad)	C-5
	3.8	2	t(6)	C-6
	3.9	9	s	C-11,12,13$(OCH_3)_3$
	4.2	2	(broad)	C-2
	5.85	2	(broad)	C-3,4
	6.8	2	s	C-10,14
	6.82	1	d(15)	C-8
	7.65	1	d(15)	C-9

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