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SYNTHESIS AND MOLECULAR STRUCTURE OF PIPLARTINE (=PIPERLONGUMINE)

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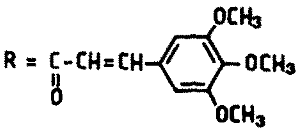
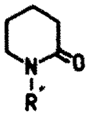
Abstract-The structure of piplartine (=piperlongumine) was established as (E)-N-3',4',5'-trimethoxycinnamoyl-5,6-dihydro-2(1H)-pyridone (13) by synthesis and by an X-ray crystallographic analysis. Model condensation of (E)-3,4,5-trimethoxycinnamoyl chloride and crotonamide gave not the expected cinnamoylcrotonamide, but (E)-N-3',4',5'-trimethoxycinnamoyl-3-chlorobutyramide (12).

The bark[1,2] and roots[3,4] of Piper longum L. have among other alkaloids afforded piplartine[‡] originally formulated as 1. The constitution has been changed to 2 on the basis of spectral and degradative evidence;[3,4] but more recently reexamination of NMR and UV spectra of piplartine and its derivatives suggests that the double bond should be placed at the 3,4-position leading to structure 3.[5]





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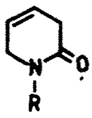

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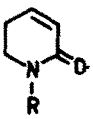

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In the light of this it was of interest to study the synthesis of piplartine and carry out an X-ray study of the compound. The work on both these aspects is reported in the present paper.

Synthetic Experiments

It is reported that vinylacrylic acid (4) and sorbic acid (5) upon heating with ammonia under pressure give 5,6-dihydro-2(1H)-pyridone (6)[6,7] and 6-methyl-5,6-dihydro-2(1H)-pyridone (8),[8-10] respectively. Our experiments were not in agreement with the above findings, but showed that vinylacrylic acid (4) upon heating with ammonia consistently gives a mixture of isomeric lactams 6 (65 %) and 7 (35 %), whereas sorbic acid (5) gives a mixture of the lactams 8 (85 %) and 9 (15 %). The existence of the isomers was recognized by two sets of signals in the ^{13}C NMR spectrum and the relative amounts of isomers were estimated from the integrals in the ^{1}H NMR spectra. It has to be added that the assignment of signals in the ^{13}C NMR spectrum of 9 was somewhat complicated,

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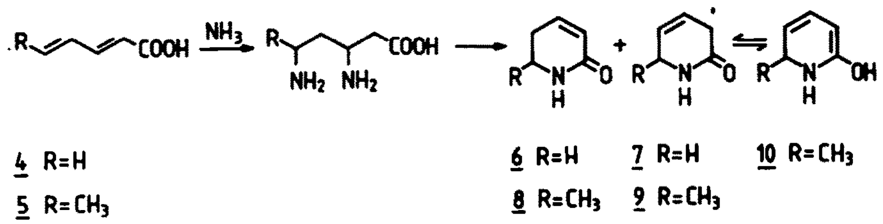
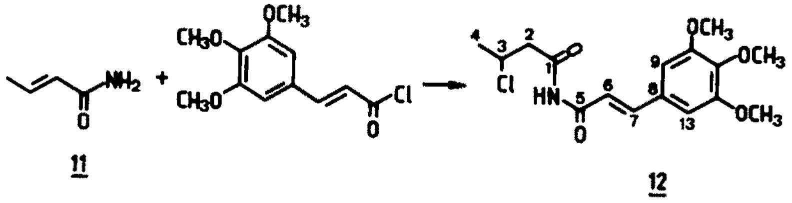
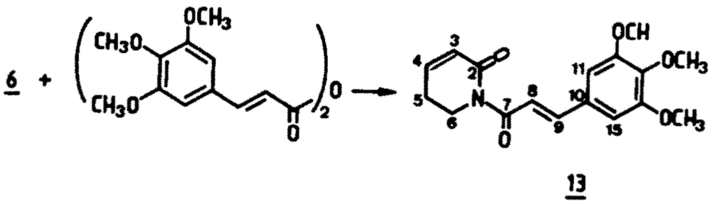
[‡] The name piperlongumine has also been used for piplartine.[3,4]

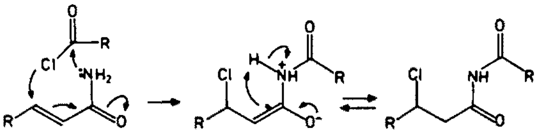
since more signals appeared than expected for a mixture of two isomers. We believe that it can be explained by keto-enol tautomerism giving rise to signals from three isomers 8, 9 and 10. Compound 6 was obtained by fractional crystallization.







Model condensations of (E)-3,4,5-trimethoxycinnamoyl chloride with crotonamide (11) in either toluene or pyridine surprisingly afforded not the expected (E)-N-3',4',5'-trimethoxycinnamoylcrotonamide, but (E)-N-3',4',5'-trimethoxycinnamoyl-3-chlorobutyramide (12). Apparently, a nucleophilic attack of the amide nitrogen group on the carbonyl carbon of the acid chloride and a Michael-type addition of the chlorine atom,to the double bond of crotonamide take place in a concerted manner.



Attempts to condense (E)-3,4,5-trimethoxycinnamoyl chloride with 5,6-dihydro-2(1H)-pyridone (6) were not successful, whereas reaction of (E)-3,4,5-trimethoxycinnamic anhydride with 6 afforded (E)-N-3',4',5'-trimethoxycinnamoyl-5,6-dihydro-2(1H)-pyridone (13). This compound was in all respects identical with piplartine isolated from Piper longum L., and piplartine, therefore, shall be represented as 13.

X-Ray Crystallography

To substantiate the synthetic evidence for the structure of piplartine (13) the structure was determined by a single crystal X-ray analysis. The bond distances and bond angles found in the lactam ring show unequivocally that C3-C4 (1.322(2) Å) is a double bond. International Tables for Crystallography^{11} quote 1.337(6) Å for a "simple" double bond.

The system O2,C2,N1,C7,O7 constitutes a "double" amide with an unequal contribution from the mesomeric forms A: $^{-}\text{O2-C2=}\overset{+}{\text{N}}\text{1-C7=O7}$ and B: $\text{O2=C2-}\overset{+}{\text{N}}\text{1=C7-O7}^{-}$. The significant difference between the two N-C bonds N1-C2: 1.389(2) Å, N1-C7: 1.420(2) Å and the two C-O bonds C2-O2: 1.223(2) Å, C7-O7: 1.209(2) Å indicates that form A is predominating. The distances C2-O2: 1.223(2) Å and C2-N1: 1.389(2) Å compare well with the corresponding bonds in acetamide investigated by electrom diffraction (gas phase),^{12} C-O: 1.220(3) Å, C-N: 1.380(4) Å, but differ somewhat from the acetamide distances determined by an X-ray investigation,[13] C-O: 1.243(4) Å; C-N: 1.336(4) Å. This is probably caused by hydrogen bond effects which play a role in crystalline acetamide, but not in crystals of 13 or acetamide in the gas phase.

The three methoxy groups adopt a configuration similar to that observed for mescaline hydrobromide,[14] *i.e.* the two outer methoxy groups are approximately coplanar with the benzene ring and the center group is nearly perpendicular to the plane of the ring (dihedral angles C11,C12,O12,C16 = 1.6(2)°; C15,C14,O14, C18 = 2.0(2)° and C12,C13,O13,C17 = 76.4(2)°). Calculations associated with the least squares plane (I) defined by C2,C3,C4,C5 show that the lactam ring is bent around the line C5-N1. Distances from the least squares plane (I) are: C2: 0.006 Å; C3: -0.013 Å; C4: 0.013 Å; C5: 0.006 Å; C6: -0.660 Å; N1: -0.116 Å. The lactam ring system is twisted almost fifty degrees out of the benzene ring plane, as plane (I) and the benzene ring make a dihedral angle of 48.5(5)°.

EXPERIMENTAL

M.ps are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Jeol Fx60 spectrometer with TMS as an internal standard. IR spectra were recorded on a Perkin Elmer spectrometer 580. MS were recorded on a Varian 311A mass spectrometer. TLC were preformed on silica gel 60F 254 Merck in 2-propanol-petrol ether 50-70°C (1:3). Microanalyses were carried out by Novo Microanalytical Laboratory, Novo Allé, DK-2880 Bagsvaerd.

Isolation of piplartine. Air dried roots of *Piper longum* L. obtained from Sandhan Organics, P.K. Biswas Rd, P.O. Khardah, Calcutta, India, were Soxhlet-extracted with petrol ether 50-70 °C for 24 h and worked up according to ref.4. Yield 2.1 g, m.p. 123-124 °C (EtOH-ether (3:1)) (lit. 124[4]). ^1H NMR ($CDCl_3$, δ): 2.45 (m,2H, C5), 3.88 (s, 3H, C12 OCH_3), 3.89 (s, 6H, C11, C13 OCH_3), 4.03 (t, *J*= 7.5, 2H, C6), 6.03 (dq, *J*= 9.6, 1.8, H, C3), 6.80 (s, 2H, C10, C14), 6.94 (m/d, *J*= 9.6, H, C4), 7.37 (d, *J*= 15.6, H, C8), 7.73 (d, *J*= 15.6, H, C9). ^{13}C NMR ($CDCl_3$, δ): 24.74 (t, C5), 41.51 (t, C6), 56.02 (q, 2 OCH_3), 60.74 (q, OCH_3), 105.26 (d, C11, C15), 120.1 (s, C10), 120.77 (d, C8), 125.40 (d, C3), 139.65 (s, C13), 143.25 (d, C4), 144.57 (s, C12, C14), 145.02 (d, C9), 165.27 (s, C2), 168.27 (s, C7). ν_{max} (KBr, cm^{-1}): 1613, 1672. MS identical to that reported.[4]

5,6-Dihydro-2(1H)-pyridone (6) and 3,6-dihydro-2(1H)-pyridone (7). The method used is essentially that reported

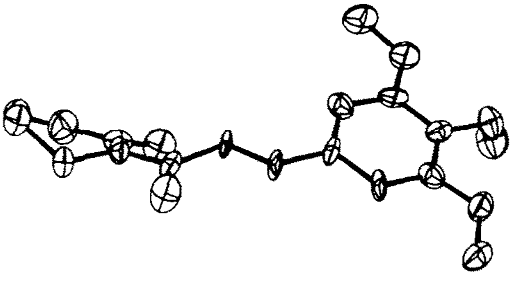


Fig. 1. Computer-generated perspective drawing of the X-ray model of 13.

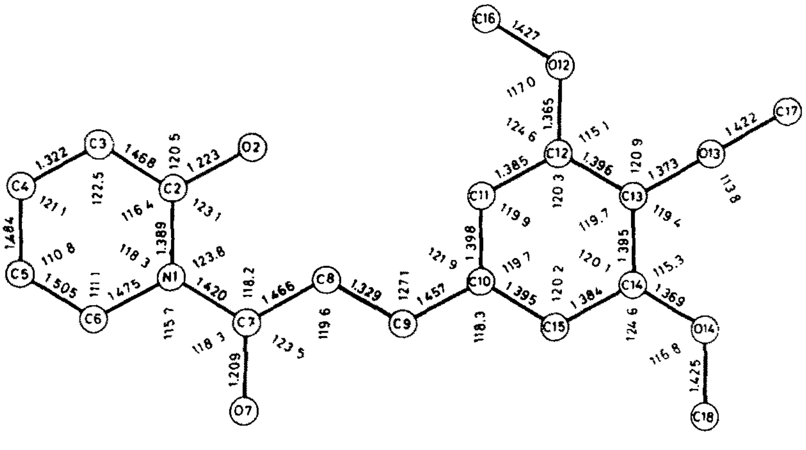


Fig. 2. Bond distances (Å), angles (°) and atom-numbering scheme for 13. Estimated standard deviations for the bond distances and angles are 0.002-0.003 Å and 0.1-0.2° respectively. C-H bond distances (not shown) range from 0.95(2) to 1.12(2) Å.

elsewhere.[6,7] Vinylacrylic acid (4)(25 g, 0.255 mol) reacted with ammonia to give 4.40 g (17 %) of a mixture of 6 (65 %) and 7 (35 %), b.p. 120-125 °C/1 mmHg, m.p. 50-53 °C (lit. 51-53,[6] 65-67[7]). MS: M^+ 97.052153 (calcd for C_5H_7NO: 97.052761). ^1H NMR ($CDCl_3$,δ): (6): 2.34 (t, *J*= 7.0, dd, *J*= 4.4, 1.6, 2H, C5), 3.43 (t, *J*= 7.0, d, *J*~ 2.6, 2H, C6), 5.65 - 6.0 (m/d, *J* ~10, H, C3 admixed 2H from C4 and C5 of 7), 6.66 (d, *J*= 9.9, t, *J*~ 4.2, *J*= ?), 6.8 -7.8 (br, NH admixed NH of 7). (7): 2.90 (m, 2H, C3), 3.97 (m, 2H, C6) + 2 signals mentioned above under 6. ^{13}C NMR ($CDCl_3$,δ): (6): 23.77 (t, C5), 39.37 (t, C6), 124.47 (d, C3), 141.11 (d, C4), 166.30 (s, C2). (7): 31.02 (t, C3), 43.45 (t, C6), 120.45 (d, C4 or C5), 121.49 (d, C5 or C4), 170 (s, C2). ν_{max}: 3210, 3270 (amide). TLC: R_F ~ 0.1, 0.2.

Crystallization from ether to which petrol ether was carefully added gave upon 3 recrystallization large crystals of 6, m.p. 63-65 °C, which deteriorated upon standing. NMR and TLC indicated about 90 % purity.

6-Methyl-5,6-dihydro-2(1H)-pyridone (8), *6-methyl-3,6-dihydro-2(1H)-pyridone* and *6-methyl-1,6-dihydropyridin-3-ol*(10). The method used is essentially that reported elsewhere.[6,7,9] Sorbic acid (5) (20 g, 0.18 mol) reacted with ammonia to give 5.42 g (27 %) of a mixture of 8 (85 %) and 10 + 11 (15 %), b.p. 130-136 °C/6 mmHg, m.p. 95-98 °C (lit. 93-98 and 103,[9] 108-109[10]). MS: M^+ 111.067380 (calcd for C_6H_9NO:111.068410). ^1H NMR ($CDCl_3$,δ): (8): 1.30 (d, *J*= 7, 3H, CH_3 admixed 3H from CH_3 of 9), 2.0-2.6 (m, br, 2H, C5), 3.5 - 4.25 (m, H, C6 admixed equivalent signals of 9), 5.65 - 6.1 (m/d, *J*= 10, H, C3 + 2H from C4,C5 of 9), 6.62 (t, *J*= 4.5, d, *J*= 10, H, C4), 7.2 - 7.9 (br, H, NH admixed equivalent signals of 9). (9): 2.90 (m, 2H, C3) + 4 signals mentioned above under 8. ^{13}C NMR ($CDCl_3$, δ): (8): 21.05 (q, CH_3), 31.60 (t, C5), 46.50 (d, C6), 124.01 (d, C3), 140.27 (d, C4), 166.56 (s, C2). (9): 23.25 (q, CH_3 admixed equivalent signal of 10), 30.76 (t, C3?), 49.35 (d, C6 admixed equivalent signal of 10), 120.38 (d, C4 o4 C5 admixed equivalent signal of 10), 126,60 (d, C5 or C4 admixed equivalent signal of 10). (10): 104.97 (d, C3), 136.77 (s, C2) + signals mentioned above under 9.

(E)-N-3',4',5'-Trimethoxycinnamoyl-3-chlorobutyramide (12). a) (E)-3,4,5-trimethoxycinnamoyl chloride (1.28 g, 5 mmol) and crotonamide (11) (0.43 g, 5 mmol) in toluene (50 ml) were stirred for 6 h at 70 °C. Upon evaporation and recrystallization from EtOH-ether (3:1) 0.76 g (45 %) of 12 was isolated, m.p. 190 - 191.5 °C. ^1H NMR (DMSO-d_6,δ): 1.54 (d, *J*= 6.6, 3H, C4), 3.11 (d, *J*= 7.7, 2H C2), 3.71 (s, C11, OCH_3), 3.82 (s, C10, C12, OCH_3), 4.3 - 4.7 (m, *J*= 6.6, *J*= ?, H, C3), 6.93 (d, *J*= 15.6, H, C6), 6.97 (s, 2H, C9, C13), 7.65 (d, *J*= 15.6, H, C7). ^{13}C NMR ($CDCl_3$,δ): 25.13 (q, C4), 47.69 (t, C2), 52.20 (d, C3), 55.98 (q, 2 OCH_3), 60.77 (q, OCH_3), 105.49 (s, C9, C13); 118.18 (d, C6), 124.03 (s, C8), 140.20 (s, C11), *ca* 145 (s, C9, C13), 145.67 (d, C7), 165.33 (s, C1), 171.93 (s, C5). MS |*m/e* (% rel. int.)|: 41 (37), 69 (100), 163 (10), 177 (15), 193 (35), 194 (10), 203 (13), 205 (10), 208 (63), (209 (11), 221 (37), 222 (18), 236 (15), 305 (45), 341 (22), 343 (8). (Found: C, 55.98; H, 5.89. $C_{16}H_{20}ClNO_5$ requires: C, 56,27, H, 5.93. ν_{max} (KBr, cm^{-1}): 1587, 1656.

b) The reaction was repeated by allowing the two reactants to stand in pyridine (5 ml) instead of toluene for 7 days at 45 °C. The reaction mixture was worked up as described below for 13. Yield 0.27 g (16 %), m.p. 190 - 191.5 °C. NMR data in agreement with those recorded under a).

(E)-N-3',4',5'-Trimethoxycinnamoyl-5,6-dihydro-2(1H)-pyridone (13). (E)-3,4,5-Trimethoxycinnamic anhydride (5.56 g, 0.02 mol) prepared according to ref. 15 and 5,6-dihydro-2(1H)-pyridone (0.97 g, 0.01mol were reacted in pyridine (3 ml) and toluene (50 ml) for 7 days at 45 °C. Upon evaporation *in vacuo* the resultant residue was extracted with ether (5 x 75 ml). The combined ether extract was shaken successively with four 30-ml portions of 1 M $NaHCO_3$, with four 40-ml portions of N HCl and with saturated NaCl, and dried. The ether was removed *in vacuo* and the resultant semi-crystalline mass was carefully recrystallized from EtOH-ether (3:1) in fine needles, m.p. 120 - 121 °C, yield 1.37 g (43 %). M.p. admixed authentic piplartine 120 - 121 °C. IR, ^1H and ^{13}C NMR identical with those recorded for piplartine.

X-Ray diffraction. The crystals of 13 used in the X-ray investigation were obtained upon voluntarily evaporation of a 2-methoxyethanol soln of the compound. A crystal with the dimensions 0.16 x 0.30 x 0.50 mm was selected. Space group $P2_1/c$ (No. 14), and preliminary unit-cell dimensions were deduced from Weissenberg and precession photographs. Refined cell constants were obtained from setting angles for 17 reflections, using graphite-monochromatized MoKα radiation (λ= 0.71073 Å) and the Enraf - Nonius CAD-4F diffractometer. This instrument was also used for the data collection. The reflections +h,+k,±l, in the range $2^\circ < \Theta < 30^\circ$ were measured with a mixed ω/Θ-scan technique. A reflection was designated not observed if $I \leq 2.5\ \sigma\ (I)$. With this criterion 1866 out of 2755 (independent measured) reflections were regarded as observed. Lorentz and polarization corrections were applied, but no extinction or absorption corrections were made.

The structure was solved by direct methods using MULTAN[16] and an IBM 3033-U computer.

Refinement and analyses of the structure was performed with the X-RAY program system[17] on an Univac 1110 computer. The quantity minimized was $\Sigma w(F_o-F_c)^2$. The weighting scheme was $w = 1.0/\{1 + [(F_o - b)/a]^2\}$ with a = 45.0 and b = 8.0, as this choice gave an acceptable weight analysis. Contributions from unobserved reflections were included, if $F_c > F_o$. The positional H-parameters were calculated and then refined separately ($\sin \Theta/\lambda < 0.40\ Å^{-1}$). The position of the methyl H-atoms were

Table 1. Fractional atomic coordinates and thermal parameters with estimated standard deviations in parantheses.

Atom	x	y	z	B_{eq}
O2	0.33130(6)	-0.76570(26)	0.39652(4)	5.17(8)
O7	0.05300(5)	-0.58888(28)	0.33258(3)	5.08(8)
O12	0.42124(5)	0.25375(24)	0.58712(3)	4.85(7)
O13	0.33554(6)	0.18261(22)	0.65116(3)	4.40(7)
O14	0.16569(6)	-0.09558(24)	0.61489(3)	4.71(7)
N1	0.18599(6)	-0.66758(25)	0.32281(3)	3.62(7)
C2	0.28059(8)	-0.76634(31)	0.34703(5)	4.27(9)
C3	0.31863(10)	-0.87115(43)	0.30978(7)	6.53(14)
C4	0.27027(14)	-0.83838(47)	0.25609(7)	7.97(17)
C5	0.17170(13)	-0.70758(39)	0.23012(5)	6.36(14)
C6	0.12400(9)	-0.76737(34)	0.26580(4)	4.50(10)
C7	0.13837(7)	-0.55450(31)	0.35264(4)	3.58(8)
C8	0.19470(7)	-0.38716(30)	0.40478(4)	3.59(8)
C9	0.15688(7)	-0.33233(31)	0.43839(4)	3.67(8)
C10	0.20325(7)	-0.18155(28)	0.49237(4)	3.37(8)
C11	0.29119(7)	-0.02402(30)	0.51152(4)	3.69(8)
C12	0.33559(7)	0.09617(29)	0.56446(4)	3.53(8)
C13	0.29250(7)	0.06353(28)	0.59865(4)	3.40(8)
C14	0.20330(7)	-0.08430(28)	0.57885(4)	3.45(8)
C15	0.15869(7)	-0.20369(30)	0.52591(4)	3.59(8)
C16	0.46619(9)	0.30335(39)	0.55296(6)	5.56(12)
C17	0.41193(10)	-0.01419(42)	0.68835(5)	5.71(12)
C18	0.07547(9)	-0.25083(37)	0.59640(5)	5.09(11)

calculated under the assumption that one H-atom in each methyl group is part of a H-C-O-C= trans configuration. Atomic scattering factors for the neutral atoms were taken from International Tables for X-ray Crystallography.[18] The final R index ($R = \Sigma||F_o|-|F_c||/\Sigma|F_o|$) was 0.047.

Supplementary material available. Crystallographic data including positional and thermal parameters as well as bond distance and angle calculation have been deposited with the Cambridge Crystallographic Data Centre in England.

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