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PIPERMETHYSTINE, A NOVEL PYRIDONE ALKALOID FROM *PIPER METHYSTICUM*

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Abstract—A new alkaloid, pipermethystine, isolated from the leaves of *Piper methysticum* is shown to be 5-acetoxy-5,6-dihydro-1-(3-phenylpropanoyl)-2(1H)-pyridone (1) by PMR, CMR and mass spectrometry and by its conversion to phenylpropanoic acid and 5-acetoxy-5,6-dihydro-2-(1H)-pyridone (5).

The tropical shrub *Piper methysticum* Forst, (Piperaceae) is widely cultivated in the South Pacific for its roots and stems, which are used in folk medicine and in the ceremonial and social drink, known as kawa, kava, 'awa, and yanqona.[1] The plant contains a series of α-pyrones, which have been shown to possess pharmacological activity with anticonvulsive, antiepileptic, fungistatic and local anaesthetic effects.[1,2]

Despite earlier reports[3] that alkaloids were present in the roots, in concentrations up to 0.22% based on colour tests, attempts to isolate alkaloids were unsuccessful until 1970, when the amides N-cinnamoylpyrrolidine (0.002%) and N-(*m*-methoxycinnamoyl)pyrrolidine (0.002%) were isolated and identified from a methanolic extract.[4] However, a report that the α-pyrones will give immediate positive "alkaloid" reactions with Dragendorff's reagent suggests that the earlier colour responses may have been misleading.[5] In the present work we report the isolation and structural determination of the novel amide alkaloid, pipermethystine (1), a major constituent (0.17%) of the leaves of *Piper methysticum*.

Freshly collected leaves of *P. methysticum* were dried and extracted with ethyl acetate. Fractionation of the extract by tlc yielded pipermethystine (1) as an oil, homogeneous by tlc and glc, as well as a series of α-pyrones.[6] 1 was lost on column chromatography on alumina and showed decomposition of tlc on freshly activated alumina. It was also present as a minor component in the roots and stems on glc analysis.

The MS of 1 contained a molecular ion at *m/e* 287, $C_{16}H_{17}NO_4$, and a strong fragment ion at *m/e* 227, $C_{14}H_{13}NO_2$, suggesting the presence of an acetoxyl group. The IR spectrum of 1 contained bands at 3070, 3035 (ArH), 1740 (C=O ester), 1700 and 1690 (C=O amide) and 1630 (C=C) cm^{-1}.

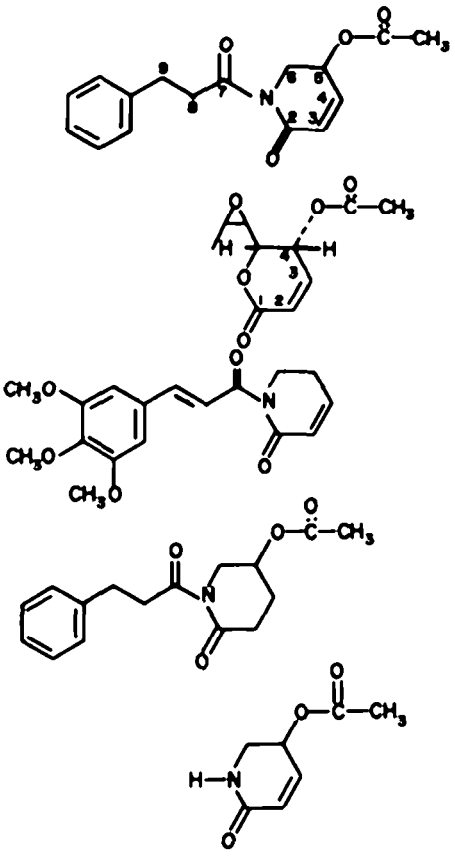
The UV spectrum, λ_{max} 210, 243 nm, indicated the presence of a conjugated system. The PMR spectrum was unchanged on the addition of D_2O and contained signals for an acetyl group (δ 2.06, 3H, s) and an aromatic ring (δ 7.2, 5H, bs). A series of coupled signals were assigned to the pyridone ring, C-3H (δ 6.15, d, $J_{3,4}$ = 10 Hz slightly broadened by long range coupling), C-4H (δ 6.84, ddd, $J_{3,4}$ = 10, $J_{4,5}$ = 5, $J_{4,6}$ = 1 Hz), C-5H (δ 5.42, q, $J_{4,5} = J_{5,6}$ = 5 Hz), C-6H_2 (AB system δ 3.86, dd, J_{AB} = 15, $J_{5,6}$ = 5 Hz and 4.32, ddd, J_{AB} = 15, $J_{5,6}$ = 5, $J_{4,6}$ = 1 Hz). The chemical shifts and couplings were similar to those of C-2H (δ 6.21, d, $J_{2,3}$ = 10 Hz), C-3H (δ 7.08, dd, $J_{2,3}$ = 10, $J_{3,4}$ = 5.5 Hz), and C-4H (δ 5.33, dd, $J_{3,4}$ = 5.5, $J_{4,5}$ = 3 Hz) in the acetyl-δ-lactone, asperline (2)[7] and to C-3H (δ 6.03, d, $J_{2,3}$ = 10 Hz) and C-4H (δ 6.9, m) in the alkaloid, piperlongumine (piplartine) 3 from *Piper longum*.[8,9] The assignments in the spectrum of 1 were confirmed by double irradiation at 5.30 ppm (C-5H) when the signals at 3.86 and 4.32 ppm collapsed to an AB quartet (J_{AB} = 15 Hz) and the signal at 6.77 ppm collapsed to a doublet (J = 10 Hz). Irradiation at 4.30 ppm (C-6H) caused a partial collapse of the signal at 5.30 ppm (C-5H). The remaining signals in the spectrum appeared as an A_2B_2 system and were assigned to C-8H_2 (δ 3.01, slightly broadened) and C-9H_2 (δ 3.38), similar to the $-CH_2CH_2-$ system in 3-phenylpropanoic acid, (δ 2.80, 4H, A_2B_2 multiplet). The long-range coupling between C-4H and one of the C-6 protons suggests that these two protons are in a coplanar W-configuration.

An attempt to confirm the relationships between the protons using Eu(fod)$_3$ shift reagent was unsuccessful as the interaction of 1 with the reagent was non-specific and there were no clear differences in contact shifts.

The CMR spectrum (Table 1) was in agreement with the proposed structure. It contained signals for three carbonyl groups at 163.8, 169.9 and 175.3 ppm, an acetyl methyl at 20.8 ppm, (q) and an oxygenated methine C-5 at 63.4 (d) ppm. The C-8 (40.9, t) and C-9 (30.9 ppm, t) signals were similar to those of C-2 (35.5) and C-3 (30.5 ppm) in 3-phenylpropanoic acid.[10] The remaining methylene group corresponded to C-6 (45.1 ppm, t) and there was a group of olefinic and aromatic carbon signals between 126.1 and 140.9 ppm.

Hydrogenation of 1 over Pd/C gave the dihydroderivative 4 as an oil. The UV spectrum contained only the aromatic band at 213 nm. The IR spectrum contained bands at 1740 and 1690 cm^{-1} for the ester and amide groups but lacked the olefinic band at 1630 cm^{-1} present in the spectrum of 1. The PMR spectrum contained the signals for the acetyl (δ 2.03 s) and aromatic groups (δ 7.23 s). The C-5H signal appeared at δ 5.25 m and no olefinic signals were present. The remaining protons were present as a complex series of multiplets 3.7–1.9 ppm.

On standing for some months at room temperature 1 partially decomposed to give a mixture of compounds, which could be separated on tlc on silica gel. If 1 was chromatographed by tlc on activated alumina a similar degradation occurred. The two principal products were isolated and identified as 3-phenylpropanoic acid and the dihydropyridone 5, m.p. 130–131.5, $C_7H_9NO_3$. The UV spectrum of 5, λ_{max} 207, 241 nm (log ε 4.10, 3.30) was similar to that of 5,6-dihydro-2(1H)-pyridone, λ_{max} 204,



(1) (2) (3) (4) (5)

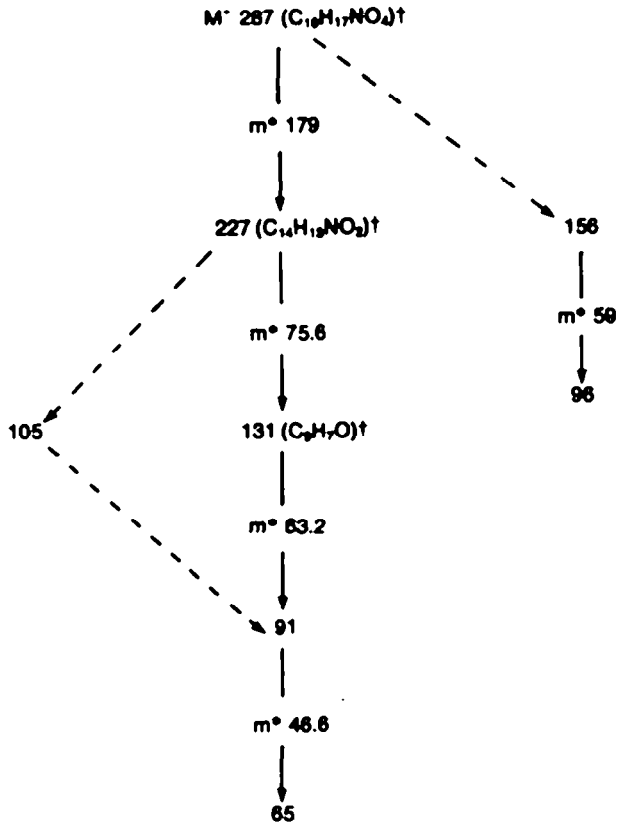
Table 1. CMR spectrum of pipermethystine (1)

δ ppm (relative to TMS)	Splitting[a]	
20.8	q	$\underline{C}H_3$-C=O
30.9	t	C-9
40.9	t	C-8
45.1	t	C-6
63.4	d	C-5
126.1	d	C=C and Ar C=C
127.6	d	
128.4	d	
128.8	d	
140.2	d	
140.9	s	C-1′
163.8	s	C=O
169.9	s	C=O
175.3	s	C=O

[a] From off-resonance decoupling study

240 nm (log ε 3.92, 3.08.[11] The IR spectrum contained bands for a secondary amide, (3420 NH and 1680 C=O cm^{-1}), an ester (1732 cm^{-1}), and an olefinic group (1615 cm^{-1}).

The PMR spectrum contained a signal for an acetyl group (δ 2.10 s) and series of coupled signals assigned to



†HRMS measurements.

Scheme 1. MS fragmentation of 1.

C-3H (δ 6.13, dd, $J_{3,4}$ = 10, $J_{3,6}$ = 2 Hz) C-4H (6.66, dd, $J_{3,4}$ = 10, $J_{4,5}$ = 5 Hz), C-5H (5.38, q, $J_{4,5}$ = $J_{5,6}$ = 5 Hz), C-6H_2 (2H, 3.70, m) similar to those in the spectrum of 1. The C-3H signal was apparently coupled across the carbonyl group to the NH group (δ 6.42, bs). The assignments were confirmed by double irradiation studies. Irradiation at 6.12 ppm collapsed the signal at 6.66 ppm to a doublet, at 6.66 ppm collapsed 6.13 and 5.38 ppm to multiplets, at 3.70 ppm collapsed 5.38 ppm to a multiplet, and at 5.38 ppm collapsed the signal at 3.70 ppm.

The MS of 1 (Scheme 1) contained an unexpected ion at *m/e* 131, C_9H_7O, and a corresponding M^+-131 ion at *m/e* 156, which were absent from the spectrum of 4. The fragmentation appears to correspond to cleavage of the amide –CO–N bond with double hydrogen transfer to the pyridone ring, to give $(Ph–CH_2–C{=}C{=}O)^{\cdot+}$ or $(Ph–CH{=}CH–C{=}O)^{\cdot+}$.

Amide alkaloids are typical constituents of members of the *Piperaceae* family, most of the compounds known being based on piperidine, pyrrolidine, or isobutylamine.[12] 1 and 3 are both unusual in also containing a second carbonyl group present as an imide system. 1, which potentially could undergo ready elimination to a pyridone, appears to be the first report of a 5-acyl-5,6-dihydro-2-(1H)-pyridone structure either naturally occurring or synthetic.

Although 1 is also present in small amounts in the stems and roots of *P. methysticum*, its instability on standing or on alumina chromatography probably explains why it has not previously been isolated. Most of the earlier studies used roots or the commercially available *P. methysticum*, which is exported as dried ground roots or stems and contains no leaves.

EXPERIMENTAL

M.ps were measured on a Koller block, UV spectra were measured on a Unicam SP 800 spectrometer and IR spectra on a Perkin Elmer 177 spectrometer. PMR spectra were determined on Perkin Elmer R 10 and R 32 spectrometers in $CDCl_3$ soln. CMR spectra were measured on a JEOL FX-60 spectrometer in $CDCl_3$ soln. GLC was carried out on a Perkin Elmer F 33 chromatograph with a F.I.D. detector, carrier gas N_2 (30 ml min^{-1}), on a 3% OV-101 on Gas Chrom Q glass column (2 m × 3 mm) at 215°. MS were recorded on A.E.I. MS10 and MS902 spectrometers and microanalysis was carried out at the University of Belfast.

Isolation of pipermethystine (1). Dried leaves of *Piper methysticum* Forst. (18 g) collected in Suva, Fiji were extracted with EtOAc in a Soxhlet extractor to give a gum (2.82 g) on evaporation of the solvent. The gum was dissolved in EtOAc and filtered through silica gel. The eluate was fractionated by tlc on silica gel GF_{254} (EtOAc:light petroleum, 1:1). A major UV absorbing band, R_f 0.55 was eluted to give a greenish oil (178 mg). The oil was purified by tlc on silica gel and then on deactivated alumina to give as a colourless oil, homogeneous by tlc and glc, pipermethystine (1, 128 mg, 0.17% yield), glc R_t 8.4 min, λ_{max} 210, 243 nm, ν_{max} (film) 3070, 3035 (ArH), 2940, 1740 (C=O ester), 1700 and 1690 (C=O amide), 1630 (C=C) 825, 750, 703, (mono sub. ArH) cm^{-1}, ν_{max} ($CHCl_3$) 1732 (C=O ester), 1687 (b, C=O amide), 1630 (C=C) cm^{-1}, ν_{max} (CCl_4 3070, 3015, 2930, 1740 (C=O ester), 1695 (C=O amide), 1630 (w) cm^{-1} MS *m/e* (M^+) 287.1157 (9%) ($C_{16}H_{17}NO_4$ requires: *m/e* 287.1157), 227.0942 (23) ($C_{14}H_{13}NO_2$ requires: 227.0946), 156 (9), 150 (6), 131.0498 (53) (C_9H_7O requires: 131.0497), 105 (34), 104 (100), 96 (47), 91 (75), 65 (11).

Dihydropipermethystine (4). A sample of 1 (15 mg) in EtOAc was hydrogenated over 10% Pd/C to yield as an oil 4 (11.8 mg) glc R_t 9.5 min, λ_{max} 214 nm, ν_{max} (film), 3090, 3060, 3030, 2930, 2860, 1740 (C=O ester), 1690 (C=O amide), 1600 (w), 750, 703, (ArH) cm^{-1}, MS *m/e* (M^+) 289 (1%), 178 (9), 150 (36), 104 (62), 97 (45), 91 (100), 43 (43).

Dihydropyridone 5. On standing for 3–4 months at r.t. 1 gave a mixture of compounds which were separated by tlc on silica gel (EtOAc–light petroleum, 2:1) to give 1 (10 mg) R_f 0.90, 3-phenylpropanoic acid (1.9 mg) R_f 0.6–0.3, identified by IR, NMR, and MS and as its methyl ester by glc comparison with an authentic sample, and a crystalline solid (12 mg) R_f 0.3, which on recrystallisation from EtOAc–light petroleum gave the dihydropyridone 5, m.p. 130–131.5°, glc, R_t 0.8 min, λ_{max} 207, 241 nm (log ε 4.10, 3.30), ν_{max} (Nujol) 3180, 1727, 1690, 1615 cm^{-1}, ν_{max} ($CHCl_3$) 3420, 1732, 1680, 1615 cm^{-1}, MS *m/e* (M^+) 155 (1%), 126 (5), 113 (1), 95 (24), 84 (27), 67 (4). (Found: C, 54.35; H, 5.71; N, 9.13. $C_7H_9NO_3$ requires: C, 54.19; H, 5.85; N, 9.03%).

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REFERENCES

[1]A. T. Sbulgin, *Bull. Narc.* 25, 59 (1973); R. Hänsel, *Pacific Sci.* 22, 293 (1968); R. Kämpf, *Schweiz Apoth. Ztg.* 108, 520 (1970); and refs. therein.
[2]W. B. Mors, M. T. Magalhaes and O. R. Gottlieb, *Fortschritte der Chemie Organischer Naturstoffe* 20, 131 (1962).
[3]E. Winzheimer, *Arch. Pharm.* 246, 338 (1908); *Chem. Abstr.* 3, 429 (1908); C. E. Swanholm, H. St. John and P. J. Scheuer, *Pacific Sci.* 13, 295 (1959).
[4]H. Achenbach and W. Karl, *Chem. Ber.* 103, 2535 (1970).
[5]N. R. Farnsworth, N. A. Pilewski and F. J. Draus, *Lloydia* 25, 312 (1962).
[6]R. M. Smith, Unpublished observations.
[7]A. P. Argoudelis and J. F. Zieserl, *Tetrahedron Letters* 1969 (1966).
[8]A. Chatterjee and C. P. Dutta, *Tetrahedron* 23, 1769 (1967); *Sci. Cult.* 29, 568 (1963).
[9]B. S. Joshi, V. N. Kamat and A. K. Saksena, *Tetrahedron Letters* 2395 (1968).
[10]L. F. Johnson and W. C. Jankowski, *Carbon-13 NMR Spectra.* Wiley, New York (1972).
[11]R. H. Mazur, *J. Am. Chem. Soc.* 81, 1454 (1959).
[12]C. K. Atal, K. L. Dhar and J. Singh, *Lloydia* 38, 256 (1975); R. Hegnauer, *Chemotaxonomie der Pflanzen*, Vol. 5, p. 314. Birkhäuser Verlag, Basel (1969).