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SYLVATINE, A NEW ALKAMIDE FROM *PIPER SYLVATICUM* ROXB. (*PIPERACEAE*)

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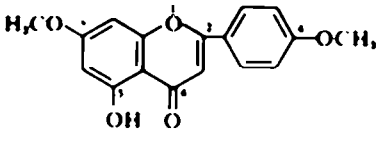
Abstract – The structure of sylvatine (1), a new alkamide from *Piper sylvaticum*, has been elucidated from spectroscopic studies, chemical reactions and correlation with compounds of known structures

The genus *Piper* has attracted considerable interest in recent years because of its reputation for producing a number of physiologically active compounds.[1] Among these mention may be made of the piperidine amides e.g. piperine,[2] lignans such as cubebin[3] and sesamin,[4] flavones and chalcones like 4',7-dimethoxy-5-hydroxyflavone[5] and flavokawain[6] and N-pyrrolidinyl-eicosa-*trans*-2-*trans*-4-dienamide.[7]

Exhaustive studies on the petrol (b.p. 60–80°) extract of the seeds of *Piper sylvaticum*, one of the forty-five *Piper* species indigenous to India, resulted in the isolation and structure elaboration of a new alkamide, sylvatine, in addition to the 4',7-dimethoxy-5-hydroxyflavone (2).



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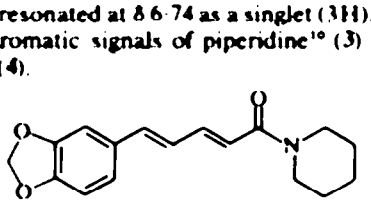
Sylvatine (1) $C_{24}H_{33}NO_3$ (M^+ 383), m.p. 112°, $[\alpha]_D^{25} \rightarrow 0°$ (EtOH) showed ultraviolet absorption [λ_{max}^{EtOH}: 304·5 and 259 nm (log ε: 3·97 and 4·69 respectively)] characteristic of a conjugated dienone system.[8] The IR spectrum indicated the presence of an >NH function (3279 cm^{-1}) typical of a monosubstituted α,β-unsaturated amide[9] (1603 cm^{-1}), a *trans*-configuration[9] of the double bond conjugated with the amide CO (strong single peak at 1000 cm^{-1}) and a methylenedioxy group (922 cm^{-1}). The 60 MHz NMR spectrum studied in $CDCl_3$, showed the presence of a gem-dimethyl group ($-CH(CH_3)_2$) at δ 0·90 (6H, d, J = 6 Hz) and eight methylene protons at δ 1·36 (s). The secondary amide proton (>NH) merged with those of the methylenedioxy resulting in a singlet (3H) at δ 5·91. The two proton triplet at δ 3·15 was assigned to the methylene proton adjacent to the amide nitrogen ($-\overset{\overset{O}{\|}}{C}-NH-CH_2-$). The allylmethylene and the methine proton appeared at δ 2·29 (5H, m) while the aromatic protons resonated at δ 6·74 as a singlet (3H), similar to the aromatic signals of piperidine[10] (3) and the amide[11] (4).



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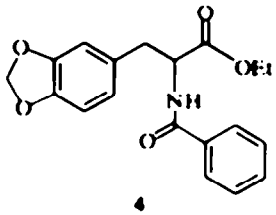

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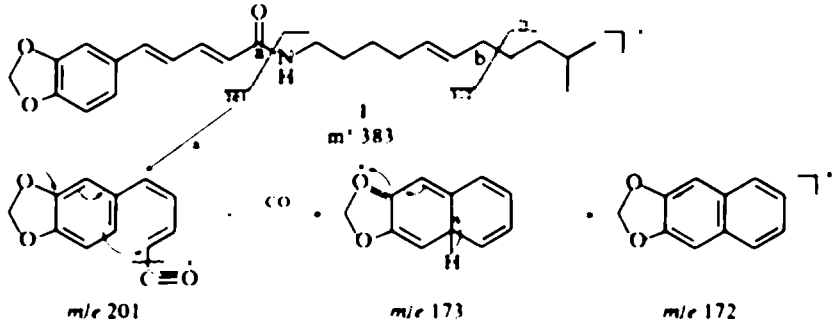
Hydrogenation of sylvatine with Adams catalyst in spectral alcohol afforded its hexahydroderivative (5), $C_{24}H_{39}NO_3$ (M^+ 389), m.p. 84°. The ultraviolet absorption spectrum of the reduced product [λ_{max}^{EtOH}: 233 and 285·5 nm (log ε: 3·88 and 3·81 respectively)] was comparable to that of methylenedioxybenzene[12] [λ_{max}^{EtOH}: 232 and 283 nm (log ε: 3·90 and 3·52 respectively)]. The IR spectrum lacked the olefinic absorption at 1603 cm^{-1} discernible in the IR spectrum of the parent compound. The 60 MHz NMR spectrum of hexahydrosylvatine, studied in $CDCl_3$, was akin to that of sylvatine except for the disappearance of the olefinic signals at δ 5·65 (2H, s), δ 6·05 (3H, m) and δ 6·88 (1H, s) and the appearance of twenty methylene protons at δ 1·25 (broad singlet). The $-N-CH_2-$ protons appeared at δ 3·08 (2H, t), the benzylic protons at δ 2·46 (2H, m) and those for keto-methylene merged with the methine proton resulting in a multiplet (3H) at δ 2·12.

Prolonged hydrolysis of hexahydrosylvatine (5) in a sealed tube with alcoholic hydrochloric acid yielded tetrahydropiperic acid (6) characterised from m.p., m.m.p. determination, co-TLC behaviour and superimposable IR spectra with an authentic sample. This not only confirmed the presence of an amide linkage but also proved the presence of a tetrahydropiperic acid (6) moiety in hexahydrosylvatine (5) and hence of piperic acid (7) unit in sylvatine (1).

Identified as its methylester, $C_8H_{16}O_2$ (M^+ 144) from GLC and mass spectral investigations. Based on these spectral and chemical evidences the structure of sylvatine has been settled as 10-methyl-5-undecenamide of piperic acid (1).

The 70 e.v. mass spectrum of sylvatine rendered diagnostic peaks at *m/e* 383 (M^+), 312, 201, 173, 172 and 71 all of which are consistent with the proposed structure (1). The genesis of these peaks can be readily rationalised as shown:

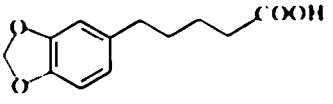


m/e 201 *m/e* 173 *m/e* 172

Of the three olefinic double bonds present in the parent compound two are incorporated in the piperic acid moiety. The third ethylenic bond was shown to be isolated and it readily formed a monoepoxide, $C_{24}H_{33}NO_4$ (M^+ 399) during the controlled epoxidation of sylvatine with *m*-chloroperbenzoic acid. In order to ascertain the location of this double bond the compound was oxidised with potassium meta-periodate and potassium permanganate to 5-methylhexanoic acid (8) which was

EXPERIMENTAL

The m.ps were determined in a Kofler block and are uncorrected. The UV absorption spectra were measured with a Beckman DK-2 spectrophotometer and a Carl Zeiss Universal spectrometer using 95% aldehyde-free EtOH, and the IR spectra with a Perkin-Elmer Infracord Spectrophotometer in Nujol mull. The NMR spectra were recorded with a Varian A-60D instrument with TMS as the internal standard. Preparative TLC was carried out with silica gel G as adsorbent, the developing system being petrol ether–glacial AcOH (80 : 20 : 1·5 v/v).



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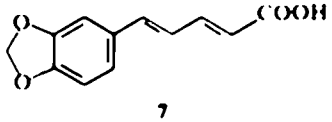

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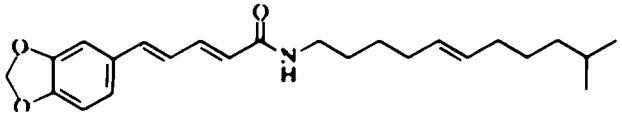

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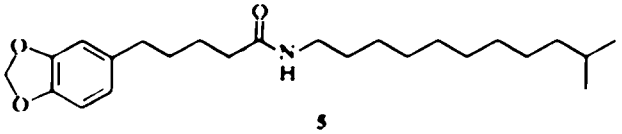

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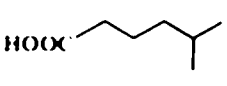

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The spots were detected with iodine vapour. The analytical samples were routinely dried *in vacuo* at 80° over P_2O_5 for 24 hr unless otherwise stated. The solvents were dried over Na_2SO_4.

Isolation of sylvatine. Air dried and finely pulverized seeds of *Piper sylvaticum* Roxb (500 g) were exhaustively extracted (32 hr) with petrol (b.p. 60–80°) in a Soxhlet apparatus. Removal of the solvent left a gummy mass which was subjected to column chromatography over silica gel (500 g). The column was eluted with solvents of increasing polarity using petrol (b.p. 60–80°), petrol–benzene mixture in varying proportions, benzene, benzene–chloroform mixture of different compositions and chloroform. The benzene–chloroform (3:1) eluates furnished sylvatine, $C_{21}H_{33}NO$, (M⁺ 383). Repeated crystallisation from petrol–benzene (3:1) yielded pure sylvatine in form of white flakes, m.p. 112° (yield 0.04%). R_f 0.72 [developing system EtOH–EtOAc (1:3)] and $[\alpha]_D^{28} = 0°$ (C_2H_5OH). (Found: C, 75.21; H, 8.57; O, 12.62; N, 3.73. $C_{21}H_{33}NO$, requires: C, 75.19; H, 8.62; O, 12.53; N, 3.66%).

Catalytic hydrogenation of sylvatine to hexahydrosylvatine. Sylvatine (300 mg) was dissolved in 95% aldehyde-free EtOH (20 ml) and magnetically stirred for 3 hr in an atmosphere of H_2 in presence of PtO_2 (30 mg), prereduced with H_2. The H_2 uptake corresponded to 3 mole-equiv per mole of sylvatine. The ethanolic soln was then filtered from the catalyst. The filtrate, on removal of the solvent under reduced pressure, furnished a colourless oil (278 mg). Hexhydrosylvatine, $C_{21}H_{39}NO$, (M⁺ 389), thus obtained, crystallised from petrol–benzene (3:1) as white needles, m.p. 84°. (Found: C, 73.98; H, 9.90; O, 12.50; N, 3.73. $C_{21}H_{39}NO$, requires: C, 74.04; H, 10.02; O, 12.34; N, 3.60%).

Acid hydrolysis of hexahydrosylvatine to tetrahydropiperic acid. A mixture of hexahydrosylvatine (200 mg), 10 N HCl (10 ml) and EtOH (10 ml) was taken in a hard glass tube which was evacuated and sealed. The contents of the tube were heated in an oil bath at 120–125° for 36 hr. The products were extracted with ether (4 × 25 ml). The ether extract was washed with $NaHCO_3$ aq. The resulting aqueous extract was acidified with dil. HCl and then extracted with ether (4 × 25 ml). The ether extract was washed with water, dried and evaporated to dryness when a reddish semi solid residue (80 mg) was obtained which could not be crystallised. This product was identified as tetrahydropiperic acid, $C_{13}H_{26}O_4$, (M⁺ 222) from its mass spectral fragmentation pattern, co-TLC behaviour and superimposable IR spectra with an authentic sample.

Epoxidation of sylvatine. Sylvatine (10 mg) dissolved in dichloromethane (10 ml) was treated with a molar proportion of *m*-chloroperbenzoic acid (5.2 mg) in dichloromethane (7 ml). The mixture was left for 7 hr. Excess *m*-chloroperbenzoic acid was decomposed with 5% Na_2SO_3 and the soln was washed with water until Na_2SO_3 was removed (till negative with starch–iodide paper). The organic layer was then washed with 10% $NaHCO_3$ aq to remove *m*-chlorobenzoic acid and dried. Removal of the solvent afforded an oil which solidified on keeping. The latter analysed for $C_{21}H_{33}NO_2$ (M⁺ 399). (Found: C, 72.20; H, 8.36; O, 16.08; N, 3.60. $C_{21}H_{33}NO_2$ requires: C, 72.18; H, 8.27; O, 16.04; N, 3.51%).

Oxidation of sylvatine with potassium meta-periodate and potassium permanganate. The stock soln used was prepared by dissolving potassium metaperiodate (0.45 g) and $KMnO_4$ (0.01 g) in distilled water (100 ml) with slight warming. A mixture of sylvatine (100 mg), *t*-BuOH (22 ml), oxidising stock soln (35 ml) and distilled water (10 ml) was brought to approximately pH 8–9 by addition of powdered K_2CO_3 and stirred for 19 hr. The resulting mixture was acidified with a drop of 10% H_2SO_4 and then treated with $NaHSO_3$ to convert the excess periodate into I_2 and then to iodide. The dark red colouration that formed initially soon disappeared and the soln became completely colourless. The soln was then made alkaline with 5% KOH aq. the *t*-BuOH was distilled off under reduced pressure and the remaining soln was acidified and extracted with ether (5 × 25 ml). The ether extract was dried. On removal of the solvent pale yellow oil was obtained. The resulting oil was found to be a mixture from which 5-methylhexanoic acid was separated by preparative TLC [developing system: petrol ether–glacial AcOH (80:20:1.5), spraying reagent – 0.25 g Rhodamine 6 G in alcohol (100 ml)]. This acid was converted to its methyl ester by treatment with diazomethane. The latter (1 μl) was then injected to the polyester column, the temp being maintained at 150°. N_2 was used as the carrier gas. An identical experiment was run with the authentic methylester of 5-methylhexanoic acid. The unknown compound and the standard sample exhibited the same retention time of 1.5 min thereby confirming their identities.

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REFERENCES

[1]K. R. Kirtikar and B. D. Basu, *Indian Medicinal Plants* 3, 2131 (1933).
[2]H. G. Boit, *Ergebnisse der Alkaloid-Chemie* (Akademie Verlag, Berlin), 130 (1961).
[3]T. Ishiguro, *J. Pharm. Soc. Japan* **56**, 68 (1936).
[4]C. K. Atal, R. N. Girotra and K. L. Dhar, *Indian J. Chem.* **4**, 252 (1966).
[5]K. L. Dhar, C. K. Atal and A. Pelter, *Planta Medica* **18**, 332 (1970).
[6]R. Hansel, G. Ranft and P. Dhar, *Z. Naturf.* **18b**, 370 (1963).
[7]J. Singh, K. L. Dhar and C. K. Atal, *Tetrahedron letters* 2119 (1971).
[8]K. L. Dhar and C. K. Atal, *Indian J. Chem.* **5**, 588 (1967).
[9]L. Crombie, *J. Chem. Soc.* 995, 997, 1007 (1955).
[10]*Varian NMR Spectra Catalog* 328 (1962).
[11]*Varian NMR Spectra Catalog* 334 (1962).
[12]W. J. Gensler and C. M. Camour, *J. Org. Chem.* **18**, 9 (1953).