

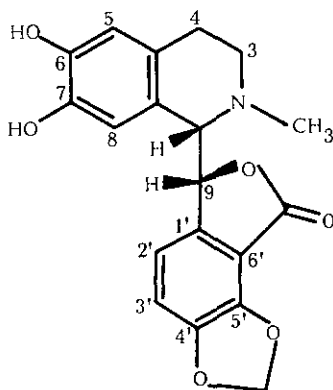
A NEW ISOQUINOLINE ALKALOID PAPRAINE FROM FUMARIA INDICA

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Abstract - A new phthalide isoquinoline alkaloid (+)-papraine (1) has been isolated from Fumaria indica and its structure and absolute configuration have been assigned.

Fumaria indica Hausskn. (Fumariaceae), locally known as 'papra', is a small herb which is widely distributed in northern Pakistan^{1,2}. It has long been used in the indigenous system of medicine for the treatment of various diseases¹⁻³. A number of alkaloids have been isolated previously from the plant^{4,5}. As a result of our investigations on Fumaria indica, we have isolated a new phthalide isoquinoline alkaloid, papraine (1) $[\alpha]_D^{24} + 25^\circ$. Its structure has been assigned on the basis of spectral studies.



(1)

RESULTS AND DISCUSSION

(+)-Papraine (1) was isolated from the crude alkaloids obtained from the alcoholic extract of Fumaria indica. The uv spectrum of the alkaloid was typical of phthalide isoquinoline alkaloids⁶. The ir spectrum showed absorption at 1750 cm^{-1} indicating the presence of a lactone carbonyl function⁶. Other intense absorptions were observed at 1120 cm^{-1} (C-O-C), 1600 cm^{-1} , (C=C, ar.) and $3520\text{-}3200\text{ cm}^{-1}$ (O-H). The high resolution mass spectrum showed the molecular ion peak at $m/z\ 355.1062$, corresponding to the molecular formula $C_{19}H_{17}NO_6$, indicating twelve degrees of

Table-1: NOE difference measurements on papraine (1)

Proton irradiated (δ)	proton enhanced (δ)	% NOE
1-H (4.16)	8-H (6.48)	3.2
	9-H (5.54)	3.2
	2'-H (6.27)	1.1
	N- $\underline{\text{C}}\text{H}_3$ (2.53)	1.2
8-H (6.48)	1-H (3.97)	3.2
	9-H (5.54)	3.4
9-H (5.54)	1-H (3.97)	3.1
	8-H (6.48)	3.6
	2'-H (6.27)	1.2
2'-H (6.27)	1-H (3.97)	1.0
	9-H (5.54)	1.0
	3'-H (6.91)	5.8

Table-II: ^{13}C -NMR chemical shift assignments of papraine (1)

Carbon No.	Chemical shift (δ)	Carbon No.	Chemical shift (δ)
1	65.41	N- $\underline{\text{C}}\text{H}_3$	44.71
3	49.07	O- $\underline{\text{C}}=\text{O}$	167.68
4	25.81	1'	140.51
4a	123.00 ⁺	2'	115.69 [*]
5	114.50	3'	115.16 [*]
6	143.49	4'	149.10
7	142.11	5'	144.53
8	113.37	6'	109.87
8a	128.90	O- $\underline{\text{C}}\text{H}_2$ -O	103.27
9	84.61		

* Values are interchangeable ⁺ Weak signal

unsaturation in the molecule. The peak at m/z 177 suggested the cleavage of the C-1/C-9 bond while the peak at m/z 149 corresponded to the cleavage around C-9/C-1' and lactone carbonyl/oxygen bonds. Other prominent peaks occurred at m/z 310, 256, 219, 179, 178, 148, 136 and 120. The mass fragmentation pattern of the alkaloid was found to be similar to that reported for other similar compounds⁷.

EXPERIMENTAL

The uv spectrum was recorded on a Shimadzu UV-240 spectrophotometer, the ir spectrum was recorded on a JASCO A-302 IR spectrophotometer, and the mass spectra were recorded on a Finnigan MAT-312 mass spectrometer connected to a PDP 11/34 (DEC) computer system. The ¹H-nmr spectrum was recorded at 400 MHz on a Bruker AM-400 NMR spectrometer, and ¹³C-nmr spectra were recorded at 100 MHz on the same instrument. The optical rotation was recorded on a Polartronic Universal Australian standard K-157 digital polarimeter. Tlc experiments were performed on silica gel (GF-254, 0.2 mm) precoated plates (E. Merck).

Plant Material: Mature whole plants (40 kg dry weight) of *Fumaria indica* were collected in March, 1987 from the wheat fields in the suburbs of Bhattian Chibban, 40 km from Gujrat City and their authenticity was verified by the Department of Botany, University of Karachi where a specimen sample is deposited.

Isolation of papraine (1)

The EtOH extract of the plant (40 kg dry weight) of *Fumaria indica* was concentrated, acidified with 5% HCl, filtered and basified with NH₄OH to pH ~9. This solution was extracted with CHCl₃ dried with anhydrous Na₂SO₄ and evaporated to a gummy mass. This was loaded on silica gel column and eluted with increasing polarities of CHCl₃-MeOH. The fraction obtained with CHCl₃-MeOH (9.0:1.0) was dried (2.0 g) and subjected to preparative tlc on silica gel (GF-254, 0.2 mm) precoated plates with acetone-chloroform (2.0:8.0). This afforded a Dragendorff's reagent active alkaloid papraine as an amorphous solid (1) $[\alpha]_D^{24} + 25^\circ$ (8.3 mg, 2.0×10^{-5} % yield).

Uv (MeOH) λ_{\max} nm (log ϵ): 220 (4.25), 233sh (3.98), 288 (3.60), 324 (3.61) λ_{\min} nm (log ϵ): 262 (3.29), 303 (3.48).

Ir (CHCl₃) λ_{\max} , cm⁻¹: 3520-3200 (O-H), 1750 (lactone C=O), 1600 (C=C) and 1120 (C-O-C).

Hrms m/z (%): 355 (2), 310 (3), 256 (2), 219 (3), 206 (3), 179 (12), 178 (96), 177 (45), 176 (28), 163 (4), 150 (11), 149 (100), 148 (20), 137 (6), 136 (9), 121 (11) and 120 (27).

The ^1H -nmr spectrum (CDCl_3 , 400MHz) indicated the presence of a methylenedioxy group by the presence of a singlet at δ 6.13. 5-H appeared as a singlet at δ 6.57 while another singlet at δ 6.48 was assigned to 8-H, indicating substitution at C-6 and C-7. The two multiplets at δ 2.24 and δ 2.55 were assigned to the C-3 protons while the C-4 protons appeared at δ 2.58 and δ 2.87 as multiplets⁸. 1-H resonated as a doublet at δ 3.97 ($J_{1,9} = 4.1\text{Hz}$) while another doublet at δ 5.54 ($J_{9,1} = 4.1\text{Hz}$) was assigned to 9-H. 2'-H appeared at δ 6.27 ($J_{2',3'} = 7.4\text{Hz}$) as a doublet while 3'-H resonated at δ 6.91 ($J_{3',2'} = 7.4\text{Hz}$) as a doublet. A 3H singlet at δ 2.53 was assigned to the N-CH_3 protons.

A series of NOE difference measurements were carried out to establish the relative stereochemistry at the asymmetric centres by comparison with the data in reference 9. Irradiation at δ 6.48 (8-H) resulted in 3.4% NOE at δ 5.54 (9-H) and 3.2% NOE at δ 3.97 (1-H). The NOE interactions between 8-H, 9-H and 1-H suggested their close proximities. Similarly irradiation at δ 3.97 (1-H) causes 3.2% NOE at δ 6.48 (8-H), 1.1% NOE at δ 6.27 (2'-H), 3.2% NOE at δ 5.54 (9-H) and 1.2% NOE at δ 2.53 (N-CH_3). These NOE interactions suggested the close proximities of H-1, H-2, H-8 and H-9. The NOE difference results are given in Table 1.

The ^{13}C -nmr spectrum (CDCl_3 , 100MHz) showed the presence of 19 carbon resonances in the molecule. The multiplicity assignments were made by carrying out the DEPT pulse sequence with the last polarization pulse angle $\theta = 45^\circ$, 90° and 135° ^{10,11}. C-1 appeared at δ 65.41 while C-3 resonated at δ 49.07, the downfield chemical shifts of C-1 and C-3 being due to the α -nitrogen function. The C-9 methine carbon appeared at δ 84.61, the downfield chemical shift of C-9 being due to the oxygen function on it. The methylene signal at δ 103.27 was assigned to the methylenedioxy carbon. Its chemical shift is consistent with the compound having the methylenedioxy group at C-5' and C-4' rather than at C-6 and C-7⁶. The chemical shifts of C-5' (δ 144.53) and C-4' (δ 149.10) indicate that the methylenedioxy group is substituted at these carbons⁶. The lactone carbonyl carbon resonated at δ 167.68 while the methyl carbon signal at δ 44.71 was assigned to the N-CH_3 carbon. The ^{13}C -NMR shift assignments are shown in Table II, on the basis of comparison with (+)-corlumine¹².

The 1S, 9R erythro configuration was established on the basis of the CD spectrum (EtOH) which showed close resemblance with that of corlumidine^{6,13} which also has erythro configuration. On the basis of the above spectroscopic data structure (1) has been assigned to papraïne.

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 3.97 (1H, d, $J_{1,9} = 4.1$ Hz, H-1), 2.24 (1H, m, 3-H), 2.55 (1H, m, 3-H), 2.58 (1H, m, 4-H), 2.87 (1H, m, 4-H), 6.57 (1H, s, 5-H), 6.48 (1H, s, 8-H), 5.54 (1H, d, $J_{9,1} = 4.1$ Hz, 9-H), 6.27 (1H, d, $J_{2',3'} = 7.4$ Hz, 2'-H), 6.91 (1H, d, $J_{3',2'} = 7.4$ Hz, 3'-H), 6.13 (2H, s, O- CH_2), 2.53 (3H, s, N- CH_3). $^{13}\text{C-NMR}$ (CDCl_3 , 100MHz) : (Table-II).

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