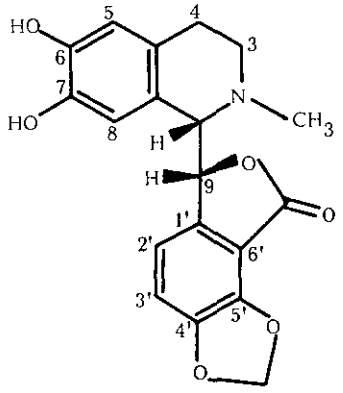
A NEW ISOQUINOLINE ALKALOID PAPRAINE FROM FUMARIA INDICA

Atta-ur-Rahman*, Mohammad Khalid Bhatti, Hussain Ahmad, and Habib-ur-Rehman
H.E.J. Research Institute of Chemistry, University of Karachi, Karachi-32, Pakistan.

David S. Rycroft,*
Department of Chemistry, University of Glasgow,
Glasgow G12 8QQ, Scotland.

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 diseases[1-3]. 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°. 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 alkaloids[6]. The ir spectrum showed absorption at 1750 cm^{-1} indicating the presence of a lactone carbonyl function[6]. Other intense absorptions were observed at 1120 cm^{-1} (C-O-C), 1600 cm^{-1}, (C=C,ar.) and 3520-3200 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-C<u>H</u>$_3$ (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-<u>C</u>H$_3$	44.71
3	49.07	O-<u>C</u>=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-<u>C</u>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 compounds[7].

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 ^{1}H-nmr spectrum was recorded at 400 MHz on a Bruker AM-400 NMR spectrometer, and ^{13}C-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 NH_4OH to pH~9. This solution was extracted with $CHCl_3$ dried with anhydrous Na_2SO_4 and evaporated to a gummy mass. This was loaded on silica gel column and eluted with increasing polarities of $CHCl_3$-MeOH. The fraction obtained with $CHCl_3$-MeOH (9.0:1.0) was dried (2.0 g) and subjected to preparative tlc on silica gel (GF-254, 02 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° (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 ($CHCl_3$) 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 ^{1}H-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 δ6.57 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 δ2.55 were assigned to the C-3 protons while the C-4 protons appeared at δ2.58 and δ2.87 as multiplets[8]. 1-H resonated as a doublet at δ3.97 ($J_{1,9}$ = 4.1Hz) while another doublet at δ5.54 ($J_{9,1}$ = 4.1Hz) was assigned to 9-H. 2'-H appeared at δ6.27 ($J_{2',3'}$ = 7.4Hz) as a doublet while 3'-H resonated at δ6.91 ($J_{3',2'}$ = 7.4Hz) as a doublet. A 3H singlet at δ2.53 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 δ6.48 (8-H) resulted in 3.4% NOE at δ5.54 (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 δ6.48 (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 δ2.53 (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 θ= 45°, 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 δ103.27 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-7[6]. The chemical shifts of C-5' (δ 144.53) and C-4' (δ 149.10) indicate that the methylenedioxy group is substituted at these carbons[6]. 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 (+)-corlumine[12].

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 papraine.

^{1}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, $J_{9,1}$ = 4.1Hz, 9-H), 6.27 (1H, d, J 2',3'=7.4Hz, 2'-H), 6.91 (1H, d, $J_{3',2'}$=7.4Hz, 3'-H), 6.13 (2H, s, O-$C\underline{H}_2$), 2.53 (3H, s, N-$C\underline{H}_3$). ^{13}C-NMR ($CDCl_3$, 100MHz) : (Table-II).

REFERENCES

1. E. Nasir and S.I.Ali, "Flora of West Pakistan," No. 73, Ferozsons Karachi, p. 39 (1974).
2. K.M. Nadkarni, "The Materia Medica" Popular Prakashan, Bombay, p. 560 (1976).
3. K.R. Kirtikar and B.D. Basu, "Indian Medicinal Plants", Indian Press, Allahabad, p. 86 (1918).
4. B. Dasgupta, K.K.Seth, V.B. Pandey, and A.B. Ray, Planta Medica, 481 (1984).
5. S.F. Hussain, R.D. Minard, A.J. Freyer and M. Shamma, J. Nat. Prod., 1981, **44**, 169.
6. G. Blasko, D.J. Gula, and M. Shamma, J. Nat. Prod., 1982, **45**, 105.
7. G. Blasko, S.F. Hussain, and M. Shamma, J. Nat. Prod., 1981, **44**, 475.
8. O. E. Edwards and K.L. Handa, Can. J. Chem., 1961, **39**, 1801.
9. V. Elango, A.J. Freyer, G. Blasko, and M. Shamma, J. Nat. Prod., 1982, **45**, 517.
10. Atta-ur-Rahman, "Nuclear Magnetic Resonance Spectroscopy", Springer Verlag, New York, 1986, p. 202.
11. W.P.Aue, J. Karhan, and R.R. Ernst, J. Chem. Phys., 1976, **64**, 4226.
12. D.W. Hughes, H.L.Holland, and D.B Maclean, Can J.Chem., 1976, **54**, 2252.
13. G. Snatzke and G. Wollenberg, Tetrahedron, 1969, **25**, 5059.

Received, 18th November, 1988