Tetrahedron Letters Vol. 21, pp 1909 - 1912
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0040-4039/80/0502-1909$02.00/0

PARVIFLORINE, A GLYCOSIDIC SPIROBENZYLISOQUINOLINE ALKALOID

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(+)-Parviflorine (1), found in Fumaria parviflora Lam. (Fumariaceae), is the first known glycosidic spirobenzylisoquinoline alkaloid. Its acid hydrolysis yields (+)-parfumine (4) and D-glucose. Klyne's rule indicates that 1 is a β-D-glucoside. The absolute configuration shown in expressions 1-11 is predominant among spirobenzylisoquinolines. A generalization has been drawn between plant source and the oxygenation pattern of ring C for the spirobenzylisoquinoline alkaloids.

A detailed reinvestigation of the alkaloids of Fumaria parviflora Lam. (Fumariaceae)[2] has led to the isolation and characterization of parviflorine (1), the first known glycosidic spirobenzylisoquinoline alkaloid. Fractionation of the strongly basic extract from 8 kg of dried plant on a silica gel column yielded 70 mg of colorless and chloroform insoluble crystals of parviflorine (1), $C_{26}H_{29}NO_{10}$, mp 230-232° (MeOH), $[\alpha]_D$ +1° (c 0.0124, MeOH), ν_{max}^{KBr} 1700 and 3390 cm^{-1}. Upon treatment with acetic anhydride in pyridine, the alkaloid readily afforded the tetraacetate 2, $C_{34}H_{37}NO_{14}$, mp 225-226° (MeOH), $\nu_{max}^{CHCl_3}$ 1708 and 1778 cm^{-1}. Alternatively, the ketone function in 1 could be reduced with sodium borohydride in methanol to provide dihydroparviflorine (3), $C_{26}H_{31}NO_{10}$, mp $>$355° (MeOH). Finally, hydrolysis of parviflorine (1) with 3N H_2SO_4 at 70° for 12 hours gave, after work-up, the known alkaloid (+)-parfumine (4),[3] as well as D-glucose.

The stereochemistry of the anomeric center in parviflorine was assigned on the basis of Klyne's rule.[4] The molecular rotation of parviflorine (+5°) should be nearly equal to the sum of the molecular rotation of the aglycone parfumine (+64°) and that for either α-methyl-D-glucopyranoside (+309°) or for β-methyl-D-glucopyranoside (-66°). Since the sum of -2° obtained in the β-case is much closer to the required value of +5° than the sum of +373° derived from the α- case, it follows that parviflorine (1) is a β-D-glucoside. (+)-Parviflorine (1) thus corresponds to (+)-parfumine-β-D-glucoside.

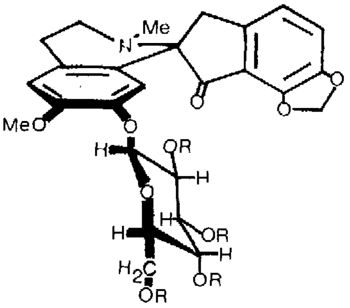
Further support for the β-anomeric stereochemistry comes from the pyridine-d_5 nmr spectrum of the alkaloid. The spin-spin coupling constant for the anomeric proton resonance located at δ5.35

is 7.3 Hz. This relatively large value is consonant with a trans diaxial relationship between the anomeric hydrogen and the hydrogen on the adjacent carbon atom in the sugar moiety as indicated in expression 1.

Spirobenzylisoquinoline alkaloids previously reported to be present in F. parviflora are (+)-parfumine (4), (+)-parfumidine (5), and (+)-fumariline (6).[2,3] Beside confirming the presence of these three bases in the plant, we have also found fumaritine (7) which was known to be present in other Fumaria species.[3]

The only spirobenzylisoquinoline alkaloids whose absolute configuration had been established prior to the present work were (+)-ochotensine (8), ochotensimine (9), (+)-ochrobirine (10), and (+)-fumariline (6). In each case, the CD curve of the alkaloid or of its dihydro derivative had shown a positive Davydov split, so that the aromatic chirality rule indicated the identical absolute configuration.[5] We have now recorded the CD curve for dihydroparfumine, the sodium borohydride reduction product of (+)-parfumine (4). This compound corresponds in all respects to the known alkaloid fumaritine (7). A positive Davydov split is evidenced between 277 and 294 nm, so that the absolute configuration of 7 is identical with that of the spirobenzylisoquinolines previously studied. It follows that (+)-parfumine (4), and the chemically related (+)-parfumidine (5), also possess the same absolute configuration. The C-14 chirality indicated in expressions 1-11 thus seems to be prevalent among the spirobenzylisoquinoline alkaloids.

The spirobenzylisoquinolines are found almost exclusively within the plant genera Fumaria and Corydalis belonging to the family Fumariaceae.[6] A telling generalization can at this stage be drawn which relates plant source to the oxygenation pattern of ring C. The genus Fumaria yields spirobenzylisoquinolines bearing only one oxygenated substituent in ring C in the form of an alcohol, an acetate, a methoxy ether or a ketone located at C-8. On the other hand, those bases originating from Corydalis species possess two oxygenated substituents in ring C, usually in the form of two alcohols or an alcohol plus a ketone. In those cases where an alcohol and a ketone are present, the alcohol will be at C-8 and the ketone at C-13.[3] An exception to this rule among the thirty spirobenzylisoquinoline alkaloids presently known is fumarofine (11) which occurs in Fumaria species, yet incorporates a ketone at C-8 and an alcohol at C-13.[3] The biogenesis of this alkaloid must, therefore, differ in some important respects from that for the other spirobenzylisoquinolines.[7]



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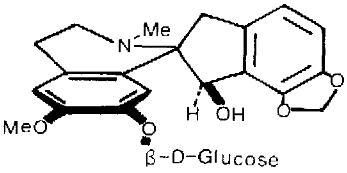

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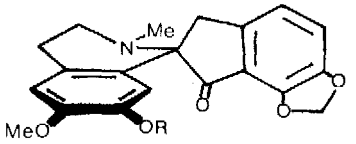

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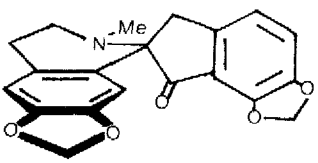
5, R = Me



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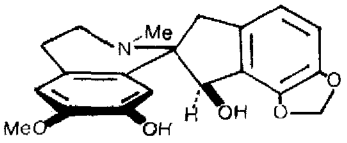

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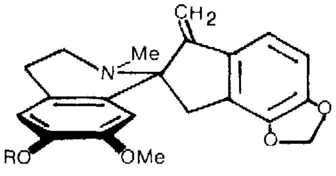

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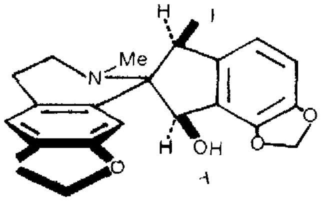
9, R = Me



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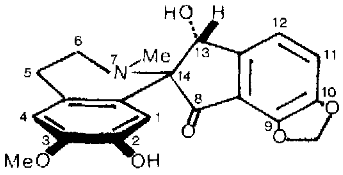

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Spectral Data for the Spirobenzylisoquinolines

Parviflorine (1): λ_{max}^{MeOH} 233, 260, 288sh and 352 nm (log ε 4.50, 4.18, 3.70 and 3.66); ms m/e 515 (M^+, 7), 353 (30), 338 (11), 325 (27) and 324 (100); nmr (pyridine-d_5) δ 2.45 (3H, s, NCH_3), 3.67 (3H, s, OCH_3), 5.35 (1H, d, J = 7.3 Hz, anomeric H), 6.13 (2H, apparent d, J = 7 Hz, OCH_2O), 6.73 (1H, s, H-4), 6.88 (1H, d, J = 7.9 Hz, H-12), 7.05 (1H, s, H-1) and 7.14 (1H, d, J = 7.9 Hz, H-11); CD (MeOH) $[\Delta\varepsilon]_{nm}$ $[+4.50]_{355}$, $[-4.88]_{293}$, $[-5.49]_{261}$, $[+4.90]_{240}$ and $[-4.85]_{229}$.

Parviflorine tetraacetate (2): ms m/e 683 (M^+, 8), 352 (20) and 324 (100); nmr ($CDCl_3$) δ 1.99 (3H, s, $OCOCH_3$), 2.00 (3H, s, $OCOCH_3$), 2.01 (3H, s, $OCOCH_3$), 2.04 (3H, s, $OCOCH_3$), 2.37 (3H, s, NCH_3), 3.78 (3H, s, OCH_3), 4.75 (1H, d, J = 7.6 Hz, anomeric H), 6.20 (2H, apparent d, J = 15.5 Hz, OCH_2O), 6.45 (1H, s, H-1), 6.63 (1H, s, H-4), 6.90 (1H, d, J = 7.9 Hz, H-12) and 7.09 (1H, d, J = 7.9 Hz, H-11).

Dihydroparviflorine (3): λ_{max}^{MeOH} 260, 278sh and 290sh nm (log ε 3.94, 3.66 and 3.53); ms m/e 517 (M^+, 4), 355 (40), 354 (30), 340 (58), 337 (60) and 192 (100).

Parfumine (4): nmr ($CDCl_3$) δ 2.37 (3H, s, NCH_3), 3.85 (3H, s, OCH_3), 6.16 (2H, s, OCH_2O), 6.30 (1H, s, H-1), 6.58 (1H, s, H-4), 6.89 (1H, d, J = 7.9 Hz, H-12) and 7.10 (1H, d, J = 7.9 Hz, H-11); CD (MeOH) $[\Delta\varepsilon]_{nm}$ $[+4.55]_{355}$, $[-4.67]_{295}$, $[-5.02]_{259}$ and $[+4.28]_{239}$.

Fumaritine (7): nmr ($CDCl_3$) δ 2.40 (3H, s, NCH_3), 3.29 (2H, d, J = 1.8 Hz, H-13), 3.86 (3H, s, OCH_3), 5.45 (1H, apparent d, J = 8.6 Hz, H-8), 5.96 (2H, apparent d, J = 4.6 Hz, OCH_2O), 6.48 (1H, s, H-1), 6.61 (1H, s, H-4), 6.69 (1H, d, J = 7.7 Hz, H-12) and 6.77 (1H, d, J = 7.7 Hz, H-11); CD (MeOH) $[\Delta\varepsilon]_{nm}$ $[+5.19]_{294}$, $[-4.66]_{277}$ and $[+4.77]_{236}$.

Acknowledgment: This research was supported by grant CA-11450 from the National Cancer Institute.

References and Notes

1. Permanent address: PCSIR Laboratories, Peshawar, NWFP, Pakistan.
2. *F. parviflora* was collected in the vicinity of Peshawar. This species is identical with *F. indica* Pugsley. For a lead reference on *Fumaria* alkaloids, see F. Šantavý in *The Alkaloids*, Vol. XVII, ed. by R.H.F. Manske and R. Rodrigo, Academic Press, New York (1979), p. 385.
3. For a complete listing of spirobenzylisoquinolines together with their physical constants, see R.M. Preisner and M. Shamma, *J. Natural Products*, in press. Present nmr data are at 200 MHz.
4. W. Klyne, *Biochem. J.*, *47*, xli (1950). See also A. Němečkova, F. Šantavý and D. Walterova, *Collect. Czech. Chem. Commun.*, *35*, 1733 (1970).
5. M. Shamma, J.L. Moniot, R.H.F. Manske, W.K. Chan and K. Nakanishi, *Chem. Commun.*, 310 (1972). A complete x-ray crystallographic study of ochrobirine methanolate has also been carried out, see M. Mathew and G.J. Palenik, *Acta Cryst.*, *B31*, 2899 (1975).
6. There is a report of the isolation of ochotensimine from *Dicentra cucullaria* Bernh. (Fumariaceae): R.H.F. Manske, *Can. J. Res.*, *16B*, 81 (1938).
7. The three *Corydalis* spirobenzylisoquinolines ochotensine (8), ochotensimine (9) and raddeanamine, which possess an exocyclic methylene or a methyl group at C-13, do not incorporate an oxygenated function at C-8, and fall outside the purview of our generalization.

(Received in USA 15 February 1980)