Revised Structures for Fumaridine and Fumaramine

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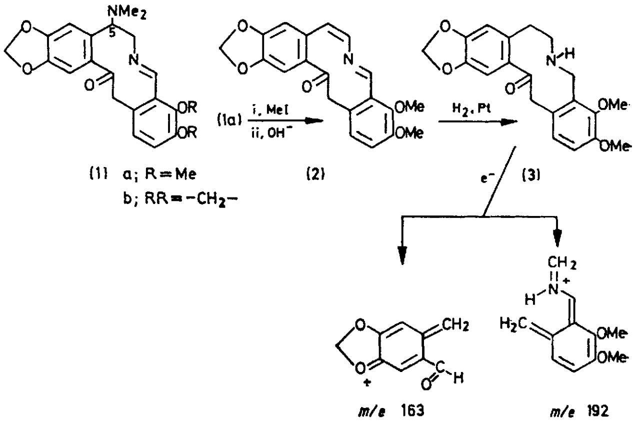
Summary The old structural assignments (**1a**) and (**1b**) for fumaridine and fumaramine are now replaced by structures (**4**) and (**7**), respectively; compound (**4**) corresponds to the known hydrastine imide.

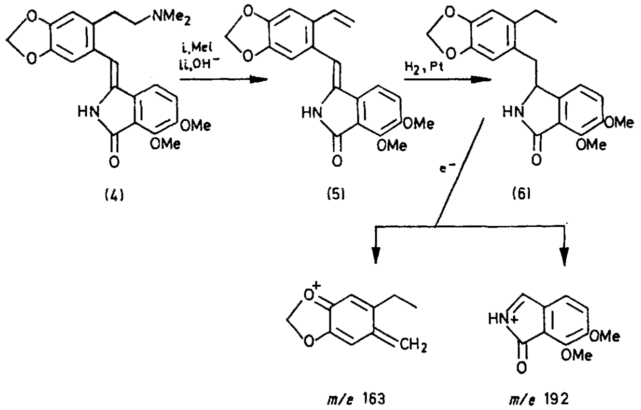
Two alkaloids found in *Fumaria parviflora* and *F. vaillanti* (Fumariaceae) are fumaridine, $C_{22}H_{24}O_5N_2$, and fumaramine, $C_{21}H_{20}O_5N_2$, which were recently ascribed structures (**1a**) and (**1b**), respectively.[1] If this assignment were correct, these two compounds would be of great importance among protopine bases. No protopine is known to incorporate either a conjugated imine function or a C-5 dimethylamino-group, so that a reconsideration of the biogenetic steps understood to lead to the protopines would be warranted.[2] The structural assignment did not appear to be secure, however, since both alkaloids are described as yellow, whereas (**1a**) or (**1b**) do not contain a chromophoric group. Additionally, structures (**1a**) and (**1b**) are chiral at C-5, yet no mention of optical activity was made.

Since the alkaloids were unavailable to us, we reappraised the published structural data.[1] Fumaridine, ν_{max} ($CHCl_3$) 1705 cm^{-1}, λ_{max} (EtOH) 228, 297, and 368 nm (log ϵ 4·43, 4·02, and 4·35), was originally treated first with MeI and then with base to furnish dedimethylaminofumaridine,



Scheme 1

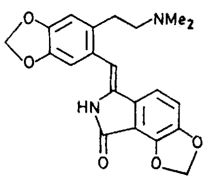
$C_{20}H_{17}O_5N$, supposedly (**2**). Subsequent reduction of this compound with Pt in HOAc led to tetrahydrodedimethylaminofumaridine, $C_{20}H_{21}O_5N$, formulated as (**3**) and giving intense mass spectral ions at *m/e* 163 and 192 (100%) which were assigned the structures indicated in Scheme 1.[1]



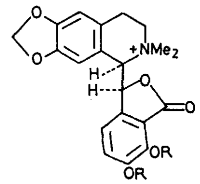
Scheme 2

It seemed to us that representation of ions *m/e* 163 and 192 as in Scheme 2, arising from structural assignments (**4**) (**5**), and (**6**), for fumaridine, and its dedimethylamino- and tetrahydrodedimethylamino-derivatives, respectively, was more credible. Structure (**4**) for fumaridine, which fulfils all the spectral requirements, seemed particularly attractive since its high degree of conjugation would explain the apparent inconsistency in the alkaloid being yellow. Structure (**4**) has been known since 1891 and corresponds to hydrastine imide.[3] Indeed, treatment of (—)-β-hydrastine methiodide (**8**) with hot conc. NH_4OH[4] yielded yellow hydrastine imide (**4**) whose m.p. as well as u.v., i.r., and n.m.r. spectra are identical with those described for fumaridine.† The name fumaridine should, therefore, be replaced by the older name hydrastine imide.

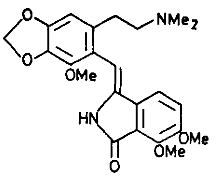
Similary, we found that treatment of the known (—)-bicuculline methiodide (**9**) with hot, conc. NH_4OH afforded yellow crystals, m.p. 218—219° (EtOH), reported m.p. for fumaramine 220—221° (EtOH),[2] spectrally identical with fumaramine.‡ The correct structure for fumaramine is, therefore, (**7**).



(7)



(8) R = Me
(9) R,R = -CH₂-



(10)

A related compound recently isolated from *Papaver somniferum* L. (Papaveraceae) is narceine imide which was correctly characterized as (**10**).[5] It was pointed out that narceine imide may not necessarily be a true alkaloid, but could conceivably be an artifact formed during work-up. Such a possibility should also be considered for hydrastine imide (**4**) and fumaramine (**7**), especially so since the required biogenetic precursors, namely hydrastine and bicuculline, have been reported to be present in the two *Fumaria* species in question.[6]

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† The 60 MHz $CDCl_3$ n.m.r. spectrum of hydrastine imide (**4**) is superimposable on that reproduced in ref. 1 above, and shows peaks at δ 2·27 (6H, s, NMe_2) 3·93 (3H, s, OMe), 4·10 (3H, s, Me), 5·93 (2H, s, OCH_2O), 6·38, 6·73 and 6·85 (3H, 3s, Ar- and vinyl-H), 7·10 (1H, d, *J* 8 Hz, lower ring Ar-H), and 7·43 (1H, d, *J* 8 Hz, lower ring Ar-H). The m.p.s. of the hydrochloride and methiodide salts of authentic hydrastine imide were identical with those reported for fumaridine.

‡ In particular, the n.m.r. spectrum of bicuculline imide in $CDCl_3$ was superimposable on that for fumaramine reproduced in ref. 1 above.

[1] I. A. Ismailov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 1970, **6**, 588 (*Chem. Abs.*, 1971, **74**, 42,528m); *Chem. Natural Compounds*, 1973, **6**, 603.

[2] D. H. R. Barton, R. H. Hesse, and G. W. Kirby, *Proc. Chem. Soc.*, 1963, 267; A. R. Battersby, R. J. Francis, E. A. Ruveda, and J. Staunton, *Chem. Comm.*, 1965, 89.

[3] M. Freund and M. Helm, *Friedlanders Fortschritte der Teerfarbenfabrikation*, 1891, **3**, 971; *Chem. Ber.*, 1890, **23**, 2909; M. Freund, *Annalen*, 1892, **271**, 360; see also Beilstein-Prager-Jacobson-Richter Organische Chemie, Bd. 27, System 4462, p. 536, 1937.

[4] The procedure used was a modification of that utilized for the preparation of phthalimide, W. A. Noyes and P. K. Porter, *Org. Synth.*, 1941, Coll. Vol. I, 457.

[5] J. Hodková, Z. Veselý, Z. Koblicová, J. Holubek, and J. Trojánek, *Lloydia*, 1972, **35**, 61. No specific geometry about the olefinic bond in (**4**), (**5**), (**7**), and (**10**) is intended.

[6] I. A. Israilov, M. S. Yunusov, and S.Yu. Yunusov, *Khim. Prir. Soedin.*, 1968, **4**, 194; *Chem. Natural Compounds*, 1971, **4**, 167.