Tetrahedron Letters Vol. 21, pp 1693 - 1696 0040-4039/80/0429-1693$02.00/0

THE CATABOLISM OF PHTHALIDEISOQUINOLINE ALKALOIDS

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Fumariflorine (1a), the only known alkaloidal o-(β-dimethylaminoethyl)benzoic acid, has been isolated as its ethyl ester 1 from Fumaria parviflora Lam. (Fumariaceae). Since alkaloids 2-6 are also present in the plant, it is probable that the biogenetic sequence for the catabolism of the lactonic phthalideisoquinolines involves initial quaternization to an N-metho salt, Hofmann elimination, and oxidative cleavage of the resulting olefin to supply a substituted o-(β-dimethylaminoethyl)benzoic acid.

Although the creeper Fumaria parviflora Lam. (Fumariaceae), of widespread occurrence in Pakistan, has already supplied seventeen isoquinoline bases,[2] we have undertaken a detailed reinvestigation of this plant[3] since thin layer chromatography of different fractions of the ethanolic extracts indicated that at least twice that many alkaloids were present.

From the strongly basic ethanolic extracts of 8 kg of the dried plant material, we have isolated 18 mg of the ethyl ester 1 of the new alkaloid fumariflorine (1a). Fumariflorine (1a) is the first substituted o-(β-dimethylaminoethyl)benzoic acid suspected to exist in nature.

The ethyl ester 1 was obtained as a colorless wax, λ_{max}^{EtOH} 218, 262 and 298 nm (log ε 4.45, 3.87 and 3.78), $\nu_{max}^{CHCl_3}$ 1710 cm^{-1}. The mass spectrum (70 eV) shows peaks m/e 265 (M^+, $C_{14}H_{19}NO_4$) (10), 220 $(M - OC_2H_5)^+$ (15), 134 $(C_8H_6O_2)^+$ (5), and 58 $(CH_2{=}N(CH_3)_2)^+$ (100). The presence of the m/e 58 base peak is diagnostic of a β-dimethylaminoethyl side chain. The nmr spectrum at 200 MHz (FT) in $CDCl_3$ is extremely informative and has peaks at δ1.38 (3H, t, J = 7 Hz, CH_3CH_2), 2.34 (6H, s, $2xNCH_3$), 2.53 (2H, m. CH_2N), 3.12 (2H, m, $ArCH_2$), 4.33 (2H, q, J = 7 Hz, CH_3CH_2), 5.99 (2H, s, OCH_2O), 6.74 (1H, s, H-3), and 7.39 (1H, s, H-6).

Significantly, alkaloids previously known to be present in F. parviflora and which were reisolated in the present study include the phthalideisoquinolines (+)-bicuculline (2), (+)-α-hydrastine (3),[4] N-methylhydrasteine (4), fumaridine (5)[5] and fumaramine (6).[5] Inspection of

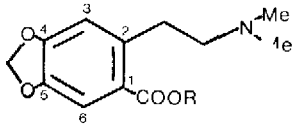
these structures suggests that in the living plant the metabolic sequence is such that the classical type phthalideisoquinolines which incorporate a γ-lactone, such as (+)-bicuculline (2) and (+)-α-hydrastine (3), are initially N-methylated to their quaternary analogs. These salts undergo Hofmann elimination to supply phthalideisoquinolines with an open ring B, e.g. N-methylhydrasteine (4) or its methylenedioxy analog 4a. Finally, 4 or 4a, or closely related alkaloids such as fumaridine (5) or fumaramine (6), can undergo oxidative cleavage to the amino acid 1a. Since ethyl esters are essentially unknown among alkaloids in general, and since ethanol was used during the extraction process, it is very likely that the true natural product is the amino acid 1a, rather than the ester 1.[6]

To prove conclusively the structure of our ester 1, the known quaternary salt hydrastinine iodide (7)[7] was treated with benzyl chloroformate in the presence of aqueous sodium hydroxide. The resulting aldehydo urethan 8, $C_{19}H_{19}NO_5$, mp 88-89° C ($CHCl_3$), $\nu_{max}^{CHCl_3}$ 1690 cm^{-1} (broad), obtained in 65% yield, was reduced in high yield with lithium aluminum hydride in THF to the amino alcohol 9, $C_{12}H_{17}NO_3$, mp 69-70° C ($CHCl_3$). Alternatively, direct lithium aluminum hydride reduction of the crude urethan 8 furnished an overall yield of 98% of the amino alcohol 9 from the isoquinolinium salt 7.

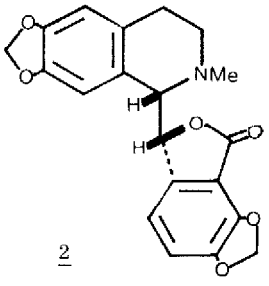
Oxidation of 9 with pyridinium chlorochromate provided a 30% yield of the oily amino aldehyde 10, $C_{12}H_{15}NO_3$, previously obtained as a degradation product of the alkaloid cryptopleurospermine (11).[8] Acid permanganate oxidation of the amino aldehyde 10 in aqueous acetone, immediately followed by esterification using absolute ethanol in the presence of thionyl chloride and sulfuric acid gave rise to fumariflorine ethyl ester (1) in 11% yield, identical with material R_f 0.44 in $CHCl_3$-$HN(C_2H_5)_2$ 95:5, obtained from the isolation.[9]

Another alkaloid we have found in F. parviflora is the hitherto unreported and amorphous fumaramidine (12) which is structurally isomeric with fumaridine (5). The 200 MHz nmr spectrum of fumaramidine in $CDCl_3$ exhibits peaks at δ2.31 (6H, s, 2×NCH_3), 3.89 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 6.20 (2H, s, 9,10-OCH_2O), 6.49 (1H, s, H-4), 6.79 (1H, s, H-1), 6.84 (1H, s, H-14), 7.07 (1H, dd, J = 8.1 Hz, H-12), and 7.31 (1H, dd, J = 8.1 Hz, H-11); while its mass spectrum has peaks m/e 396 (M^+, $C_{22}H_{24}N_2O_5$) (11), 220 (6), and 58 (100). It is probable, therefore, that an analog of fumariflorine (1a) yet to be found in nature is the amino acid 13.

Since fumariflorine (1a) is appreciably different in its structural features from such phthalideisoquinoline alkaloids as 2-6, it is pertinent to consider it as the first representative of a new but small group of isoquinoline derived alkaloids, namely the o-(β-dimethylaminoethyl)-benzoic acids.



1, R = C_2H_5
1a, R = H



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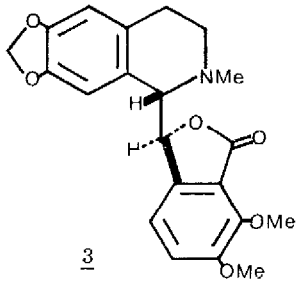

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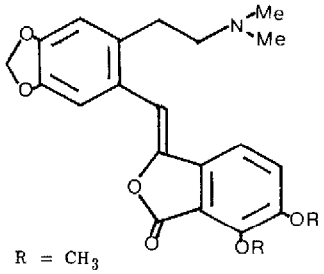
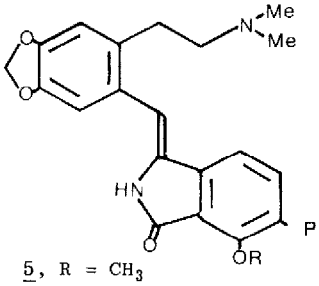
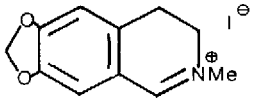


4, R = CH_3
4a, R + R = CH_2



5, R = CH_3
6, R + R = CH_2



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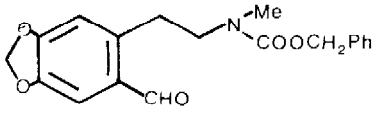

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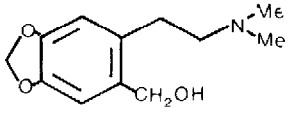

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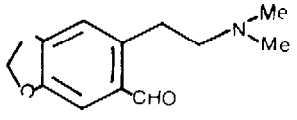

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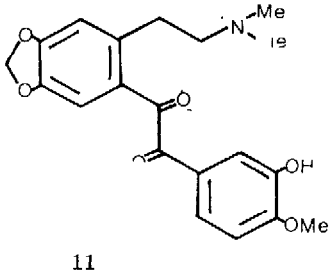

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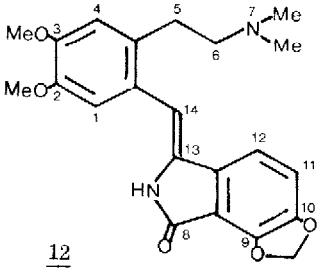

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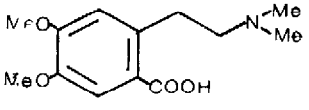

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Acknowledgments:- This research was supported by grant CA-11450 from the National Cancer Institute, National Institutes of Health, PHS/DHEW.

References and Notes

1. Permanent address: PCSIR Laboratories, Peshawar, Pakistan.
2. For lead references, see F. Šantavy in The Alkaloids, Vol. XVII, ed. by R.H.F. Manske and R. Rodrigo, Academic Press, New York (1979), p. 385.
3. F. parviflora was collected in the vicinity of Peshawar, NWFP, Pakistan.
4. I.A. Israilov, M.S. Yunusov and S. Yu. Yunusov, Khimiya Prirodnykh Soedinenii, 4, 194 (1968); and Chemistry of Natural Compounds, 167 (1968).
5. Fumaridine (5) corresponds to hydrastine imide, see M. Shamma and J.L. Moniot, Chem. Commun., 89 (1975).
6. It is relevant to point out that although nature provides a facile route, using methionine, for O-methylation to supply natural products incorporating aryl methyl ethers and methyl esters, an analogous mechanism for O-ethylation is lacking, so that aryl ethyl ethers and also ethyl esters are not of common occurrence among natural products.
7. Hydrastinine chloride is available from the Aldrich Chemical Co.
8. S.R. Johns, J.A. Lamberton, A.A. Sioumis and R.I. Willing, Aust. J. Chem., 23, 353 (1970).
9. Thin layer chromatography was on Merck silica gel F-254 plates. Melting points are uncorrected. The other large group of alkaloids, besides the phthalideisoquinolines, we have found in F. parviflora is composed of spirobenzylisoquinolines. These will be discussed in a separate paper.

(Received in USA 13 February 1980)