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REVISED STRUCTURES FOR FUMARITRIDINE AND FUMARITRINE: TWO INDENOBENZAZEPINE TYPE ALKALOIDS

Gábor Blaskó,[1] Natesan Murugesan, Alan J. Freyer, Robert D. Minard and Maurice Shamma*,

Department of Chemistry, The Pennsylvania State University,

University Park, Pennsylvania 16802, U.S.A.

Fumaritridine and fumaritrine are not spirobenzylisoquinolines. Rather, they are indenobenzazepines so that fumaritridine is represented by expression 10 and fumaritrine by 11. Treatment of dihydroparfumine (6) and dihydroparfumidine (7) with trifluoroacetic anhydride followed by quenching with methanol gives 10 and 11, respectively.

Following the finding that fumarofine (1) is an indenobenzazepine alkaloid rather than a spirobenzylisoquinoline,[2] a search was undertaken for other indenobenzazepines which could have been erroneously assigned spirobenzylisoquinoline structures. Two prime suspects for such a misassignment appeared to be fumaritridine and fumaritrine.[3] The former is found in Fumaria rostellata Knaf. and was assigned spiro structure 2,[4,5] while the latter is present in both F. rostellata Knaf. and F. officinalis L. and was stated to be represented by expression 3, a claim partially supported by the finding that diazomethane O-methylation of fumaritridine affords fumaritrine.[4,5]

Besides the fact that fumaritridine and fumaritrine possess aliphatic methoxyl groups, a feature with no analogy among the naturally occurring spirobenzylisoquinolines of established structure, three characteristics of their nmr spectra aroused our suspicions. Firstly, in the reported spectrum of fumaritrine (see expression 3), the two aromatic methoxyl singlets appear close together at δ3.90 and 3.95.[4,5] This is never the case with true spirobenzylisoquinolines where the methoxyl signals are separated by more than 0.2 ppm,[3] and is suggestive instead of an indenobenzazepine system.[2] Secondly, H-1 in fumaritridine (see expression 2) and fumaritrine appears at δ6.90 and 7.11, respectively. Such downfield proton singlets are again diagnostic of indenobenzazepines rather than spirobenzylisoquinolines.[2] Thirdly, the singlets at δ4.49 and 4.68 in fumaritridine and fumaritrine cannot be assigned to H-8 which is geminal to the aliphatic methoxyl group, since such a proton would be expected to appear instead further downfield in the δ5.40 to 5.55 range.

As a rapid check on the veracity of our suspicions, O-methylfumarofine (4)[2] was treated with thionyl chloride in pyridine, and the reaction quenched with methanol. The expected product 5, $C_{22}H_{23}O_6N$, λmax 235, 260sh, 286sh and 354 nm (log ε 4.22, 3.88, 3.30 and 3.22), υmax ($CHCl_3$) 1710 cm^{-1}, has an nmr spectrum (summarized in expression 5) which shows a significant similarity to that for fumaritrine. Specifically, the two aromatic methoxyl singlets are situated closely together at δ3.87 and 3.93, the H-1 singlet is downfield at δ7.40, the H-8 singlet is at δ4.61, and the aliphatic methoxyl appears at δ3.36.

The next endeavor was to synthesize both fumaritridine and fumaritrine, and thus prove their structures. For this purpose, dihydroparfumine (6) and dihydroparfumidine (7), derived from the sodium borohydride reduction of naturally occurring (+)-parfumine and (+)-parfumidine,[3] were

treated separately with trifluoroacetic anhydride in methylene chloride at -20° C for 4 hours. After quenching with methanol, the mixture was refluxed for another 4 hours. Evaporation of the solvent and purification by tlc supplied a 40-45% yield (corrected for recovered starting materials) of indenobenzazepines 10, $C_{21}H_{23}O_5N$, mp 189-193° C (EtOH), λmax 208, 230 and 291 nm (log ε 4.12, 3.81 and 3.37), and 11, $C_{22}H_{25}O_5N$, mp 151-153° C (EtOH), λmax 210, 230 and 284 nm (log ε 4.36, 3.95 and 3.57), respectively. The nmr spectrum of 10 was found to correspond to that for fumaritridine, while that of 11 was congruent with that for fumaritrine. It follows that fumaritridine is represented by expression 10, while fumaritrine corresponds to 11. Our nmr spectral values obtained at 360 MHz (FT) for fumaritridine and fumaritrine have been summarized in expressions 10 and 11, respectively; and should be compared to those given in expressions 2 and 3.

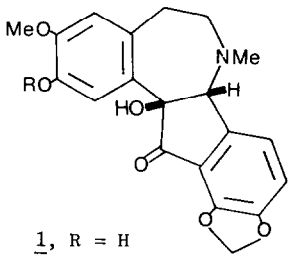
The transformation of 6 into 10, and 7 into 11, must proceed through the intermediacy of aziridinium cation 8 which is in turn converted to benzylic cation 9. The latter species then adds methanol to produce indenobenzazepines 10 and 11 which incorporate the thermodynamically more stable cis B/C fusion.[6] Proof for the cis fusion is forthcoming from the finding that treatment of 11 with methanolic hydrogen chloride did not result in any isomerization, and gave only starting material.[6]

As further evidence for the position of the methylenedioxy substituent in ring D of fumaritridine (10) and fumaritrine (11), the known synthetic and racemic spirobenzylisoquinoline 12[2] was also rearranged using TFAA followed by methanol quenching. The main product proved to be racemic indenobenzazepine 13, $C_{22}H_{25}O_5N$, mp 147-149° C (EtOH), λmax 211, 235 and 283 nm (log ε 4.24, 3.76 and 3.46), whose nmr spectrum shows a significant divergence from that of fumaritrine (11). Salient features in the spectrum of 13 are the relatively upfield N-methyl singlet at δ2.21, and the very close splitting of the ring D methylenedioxy protons into a doublet of doublets.

Pyrolysis of the synthetic indenobenzazepine 13 at 190° C for 15 minutes readily provided indenobenzazepine enamine 14 whose nmr spectrum shows a characteristically downfield N-methyl singlet at δ3.14. This pyrolytic elimination parallels that originally reported for fumaritrine, in which an indenobenzazepine enamine was also obtained.[4,5] The facile loss of methanol from fumaritridine and fumaritrine is also observed in their mass spectra.[7]

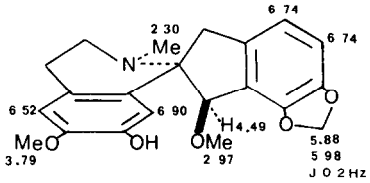
It is known that naturally occurring spirobenzylisoquinolines monohydroxylated in ring C bear their C-8 substituent anti to the nitrogen atom.[3] An effort was, therefore, made to synthesize species 15 which would be the first spirobenzylisoquinoline truly methoxylated in ring C. O-Methylation of synthetic spirobenzylisoquinoline 12 using diazomethane in the presence of aluminum isopropoxide[8] and methylene chloride generated the desired spirobenzylisoquinoline 15, $C_{22}H_{25}O_5N$ (amorphous), λmax 215, 234 and 284 nm (log ε 4.13, 3.87 and 3.55), whose nmr spectrum bears little resemblance to that for fumaritrine (11). In particular, the proton geminal to the aliphatic methoxyl and syn to the nitrogen atom is found downfield at δ5.52.

Natural fumaritridine has $[\alpha]_D^{22}$ +18° (c = 1% $CHCl_3$), while no rotation has been given for fumaritrine.[4,5] Our semi-synthetic fumaritridine (10) and fumaritrine (11) should also be optically active, and should possess the absolute configuration indicated, since the asymmetric center at C-8 is not racemized during the spirobenzylisoquinoline-indenobenzazepine rearrangement. Using a Perkin-Elmer Model 241 high performance automatic polarimeter, it was established that 10 has $[\alpha]_D^{25}$ +12° ±2° (c = 0.045 $CHCl_3$), while 11 shows $[\alpha]_D^{25}$ +14 5° ±1° (c = 0.055 $CHCl_3$). The similarity in the specific rotation quoted in the literature for fumaritridine with that for our semi-synthetic 10 makes it clear that the alkaloid possesses the absolute configuration denoted in expression 10. It follows that the chirality of the related fumaritrine is most likely as shown in 11. This stereochemical assignment is consistent with the idea that fumaritridine and fumaritrine are probably derived in nature from 6 and 7, respectively, of established absolute configuration.[9,10]



1, R = H

4, R = Me



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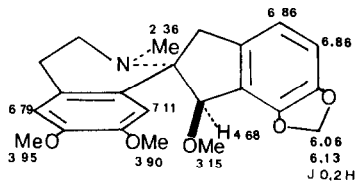
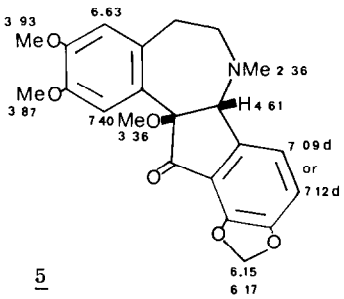


3

(60 MHz ^{1}H nmr data above are from refs. 4 and 5)



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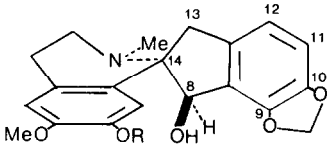
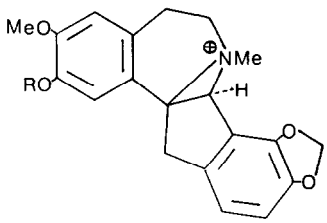


6, R = H

7, R = Me



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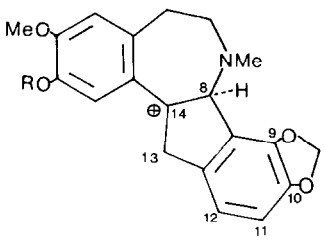

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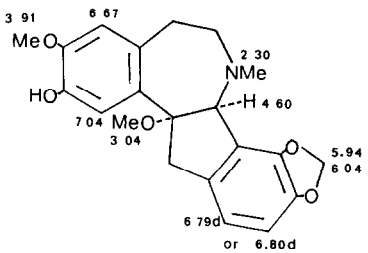

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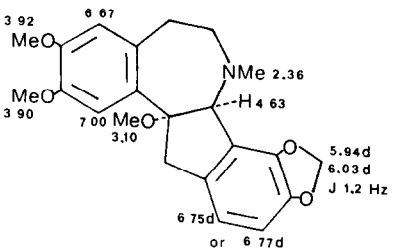

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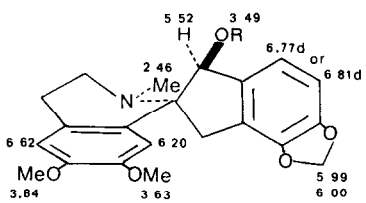
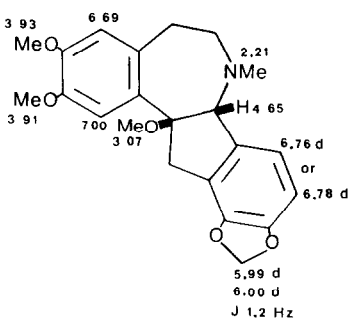


12, R = H

15, R = Me

(^{1}H nmr data above are for 15)



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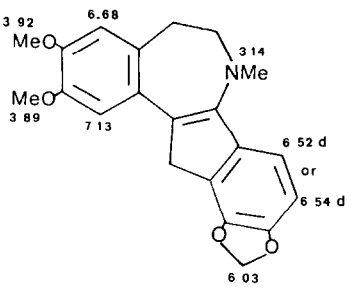

14

With the characterization of lahorine, lahoramine,[11] fumarofine,[2] and presently fumaritridine and fumaritrine, it becomes apparent that the indenobenzazepines will eventually emerge as a major group of isoquinoline alkaloids on a par with the protopines, phthalideisoquinolines and rhoeadines.

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References and Footnotes[12-15]

1. Permanent address: Central Research Institute for Chemistry, Hungarian Academy of Sciences, H-1025 Budapest, Hungary.
2. G. Blaskó, N. Murugesan, S.F. Hussain, R.D. Minard, M. Shamma, B. Şener and M. Tanker, Tetrahedron Lett., in press.
3. For a complete listing of spirobenzylisoquinoline alkaloids and their spectral data, see R.M. Preisner and M. Shamma, J. Natural Products, 43, 305 (1980).
4. N.M. Mollov, H.G. Kirjakov and G.I. Yakimov, Phytochemistry, 11, 2331 (1972).
5. H.G. Kirjakov and P.P. Panov, C.R. Acad. Bulg. Sci., 25, 345 (1972).
6. N. Murugesan, G. Blaskó, R.D. Minard and M. Shamma, Tetrahedron Lett., in press.
7. Elemental analyses are by high resolution mass spectroscopy. The low resolution mass fragmentations are as follows: 5, m/e 397 (32, M^+), 382 (39), 365 (20), 354 (34), 352 (23), 351 (59), 350 (20), 338 (17), 336 (23), 323 (11), 311 (12), and 193 (100); 10, m/e 369 (9, M^+), 354 (15), 337 (100), and 322 (83); 11, m/e 383 (39, M^+), 368 (61), 351 (100), 336 (80), 325 (32), 309 (7), 293 (13), 278 (8), and 193 (34); 13, m/e 383 (13, M^+), 368 (37), 351 (100), 336 (79), 325 (11), 306 (3), and 293 (7); 15, m/e 383 (14, M^+), 368 (100), 351 (9), 336 (7), 255 (2) and 206 (13).
8. A. Popelak and G. Lettenbauer, Arch. Pharm., 295, 427 (1962).
9. There is a possibility that fumaritridine (10) and fumaritrine (11) may be artefacts of isolation, originating from the rearrangement of dihydroparfumine (6) and dihydroparfumidine (7) which are present in F. officinalis and other Fumaria species. However, in our hands, when dihydroparfumidine (7) was placed in refluxing methanolic hydrogen chloride overnight, no fumaritrine (11) was obtained.
10. The alkaloid fumarostelline is identical with fumarofine, and is therefore an indenobenzazepine, see ref. 3 above.
11. G. Blaskó, S.F. Hussain, A.J. Freyer and M. Shamma, Tetrahedron Lett., in press.
12. Thin layer chromatography was on Merck silica gel F-254 plates. The R_f values using benzene-methanol (100:15 v/v) are: 5, 0.51; 10, 0.26; 11, 0.54; 13, 0.41; 14, 0.75; and 15, 0.43.
13. All nmr spectra were obtained at 360 MHz (FT) in $CDCl_3$ with TMS as internal standard. Chemical shifts are shown on the structural expressions. Unless otherwise indicated, all absorptions are singlets. Coupling constants for the ortho aromatic protons of ring D are as follows: 5, 8.2 Hz; 10, 8.0 Hz; 11, 8.0 Hz; 13, 8.0 Hz; 14, 8.0 Hz; and 15, 8.5 Hz. UV spectra are in methanol.
14. The numbering system adopted here for the indenobenzazepines is in accord with that for the protoberberines and spirobenzylisoquinolines.
15. The CD curves in MeOH for 10 and 11 show $\Delta\epsilon_{nm}$ -1.90_{280} and $-8\ 25_{238}$, and -1.82_{286} and -8.06_{241}, respectively.

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