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REVISED STRUCTURE FOR FUMAROFINE, AN INDENOBENZAZEPINE TYPE ALKALOID

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Fumarofine is not a spirobenzylisoquinoline. Rather, it is the first known reduced indenobenzazepine alkaloid, and possesses the cis B/C fused structure 7. Rearrangement of synthetic spirobenzylisoquinoline 12 using methanesulfonyl chloride furnished indenobenzazepine 14. Osmium tetroxide oxidation of 14 gave cis-glycol 15. O-Methylfumarofine (8) was then obtained through pyridinium chlorochromate oxidation of 15.

The thirty known spirobenzylisoquinoline alkaloids, all of which bear a methylenedioxy substituent in ring D, have been found only among the plant family Fumariaceae. More specifically, they occur within the genera Fumaria and Corydalis. A direct relationship obtains between the plant source and the oxygenation pattern of ring C. The genus Fumaria yields spirobenzylisoquinolines bearing only one oxygenated function in ring C in the form of an alcohol or a ketone located at C-8 (see 1 and 2 below). 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 is at C-8, while the ketone is at C-13 (3 and 4 below).[3]

The alkaloid fumarofine is unusual among the known spirobenzylisoquinolines in that it is found in Fumaria species, yet it has been claimed to incorporate a ketone at C-8 and an alcohol at C-13 as represented in expression 5 or its mirror image.[4]

As part of a general plan to study the alkaloidal content of the flora of Turkey, a quantity of Fumaria microcarpa Boiss. was collected in eastern Anatolia, in the vicinity of the village of Gevaş, south of Mount Ararat, and close to Lake Van. Work-up of the plant extract furnished a wide variety of isoquinoline alkaloids, one of which was recognized as fumarofine because of the identity of its nmr spectrum, its mass spectrum, and its melting point, to those reported for that alkaloid. Additionally, diazomethane O-methylation of our fumarofine yielded material identical with that previously described for O-methylfumarofine.[4]

The structural proof in favor of expression 5 for fumarofine and 6 for O-methylfumarofine appeared, initially at least, to be incontrovertible, especially since it was buttressed by an nmr analysis of O-methylfumarofine which included n.O.e. studies.[4] Nevertheless, a reinterpretation of the data available for fumarofine now indicates that this alkaloid is best represented by the cis-fused indenobenzazepine structure 7, so that O-methylfumarofine is described by expression 8.

It was first noted that the two methoxyl signals in the nmr spectrum of O-methylfumarofine (8) are close together (δ3.87 and 3.94). This is never the case in 2,3-dimethoxylated spirobenzylisoquinolines where the C-2 methoxyl usually appears between δ3.50 and 3.65, and the C-3 methoxyl is found in the δ3.70 to 3.94 range.[3] The N-methyl signal in 8 is at δ2.55 while in spirobenzylisoquinolines the corresponding signal is located between δ2.25 and 2.40. The H-1 absorption of

spirobenzylisoquinolines is normally found near δ6.25,[3] so that the downfield singlet in fumarofine (7) and O-methylfumarofine (8), found at δ7.15 and 7.28 respectively, cannot be associated with H-1 of a spiro structure. Rather, this signal should now be considered diagnostic of the H-1 proton within an indenobenzazepine skeleton. Again, the singlet at δ4.43 in O-methylfumarofine (8) had been originally associated with H-8, which is geminal to a hydroxyl in the old structure 6.[4] Among the true spirobenzylisoquinolines, however, such protons uniformly appear downfield from δ4.90.[3]

Finally, as a result of the O-acetylation of O-methylfumarofine (8) to yield O-methylfumarofine acetate (9), the singlet proton absorption at δ4.43 in 8, which is now assigned to H-8, is found at δ4.94 in 9, so that acetylation results in a downfield shift of 0.51 ppm. If this absorption were due to a hydrogen geminal to an alcohol group, as required in the old assignment, the downfield shift upon acetylation should have been in the order of 1.1 ppm. The n.O.e. results are also in concurrence with the new structure 8 for fumarofine since saturation of the methoxyl signal at C-3 (δ3.87) is known to cause a 25% increase in the area of H-4 (δ6.61), and saturation of H-8 (δ4.42) results in a 9% increase of the H-9 absorption (δ7.29-7.30).[4]

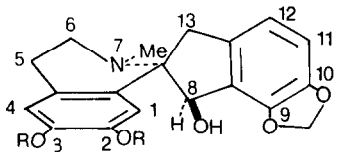
Ultraviolet spectroscopy is of assistance in establishing the position of the substituent in ring D of fumarofine (7) and O-methylfumarofine (8). Spirobenzylisoquinolines of type 2 show a characteristic shoulder near 260 nm, while compounds of type 4 show no maximum in that region.[3] Fumarofine and O-methylfumarofine have ultraviolet shoulders at 257 and 259 nm, respectively, thus their substitution pattern in ring D resembles alkaloids of type 2. A reliable test for differentiating between 8-ketospirobenzylisoquinolines on the one hand, and fumarofine analogs on the other, is that upon addition of acid, the 260 nm shoulder of the former becomes a distinct maximum between 265 and 267 nm, while fumarofine and its congeners demonstrate no such change.

Mass spectroscopy offers another criterion for differentiation. Fumarofine as well as O-methylfumarofine upon electron impact show a molecular ion which is also the base peak, and a strong $(M - 18)^+$ peak due to loss of water. The latter ion is absent in the mass spectra of type 4 such as raddeanone, sibiricine, yenhusomidine and corydaine.[3]

Treatment of O-methylfumarofine (8) with 18% hydrochloric acid at room temperature overnight did not result in any isomerization at C-14. Rather, O-demethylation at C-3 occurred to produce amorphous isofumarofine (10), $C_{20}H_{19}O_6N$, λ max 234, 258 sh, 286 sh and 349 nm (log ε 4.41, 4.02, 3.39 and 3.40), so that 8 must incorporate the thermodynamically more stable cis B/C fusion.[5] Additionally, O-methylfumarofine (8) acetylates slowly, over a period of three days.[4] Such behavior is indicative of a cis B/C fusion, since it is known that similar indenobenzazepine ketols with the trans B/C stereochemistry acetylate completely under identical conditions overnight.[5]

Conclusive evidence concerning the nature of the ring fusion is also furnished by ^1H as well as ^{13}C nmr spectroscopy. The acetoxyl methyl singlet in O-methylfumarofine acetate (9) is at δ2.22. This value is consonant with a cis B/C fusion, since in the alternate trans arrangement the corresponding absorption is at δ2.00.[5] The ^{13}C nmr spectrum of O-methylfumarofine has been summarized in expression 8a. Comparison of the chemical shifts for C-5 (δ33.05) and C-6 (δ50.12) with those for a known cis-ketol indenobenzazepine[5] clearly show that the two compounds belong to the same stereochemical series.

Final proof for the new structural assignments derives from a total synthesis of O-methylfumarofine (8). Spirobenzylisoquinoline 11, $C_{21}H_{21}O_5N$, mp 157-159° (MeOH), λ max 236, 292 and 314 nm (log ε 4.38, 3.96 and 3.82), prepared by us by a method similar to Irie's,[6] was reduced with sodium borohydride to furnish the anti-alcohol 12, $C_{21}H_{23}O_5N$, mp 177-179° (EtOH), in 52% yield, and the syn-alcohol 13, $C_{21}H_{23}O_5N$, mp 247-249° (MeOH), in 14% yield. Rearrangement of 12 with



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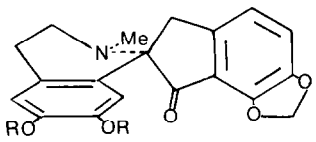

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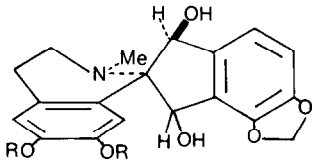

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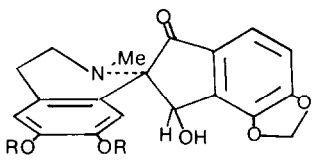

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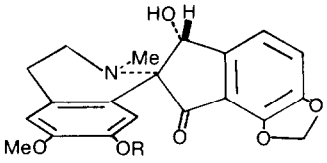
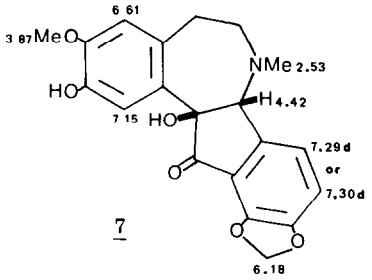


5, R = H

6, R = Me



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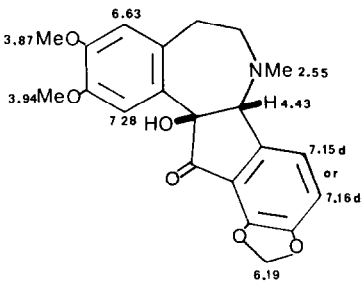

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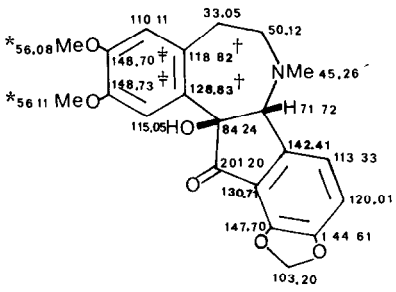
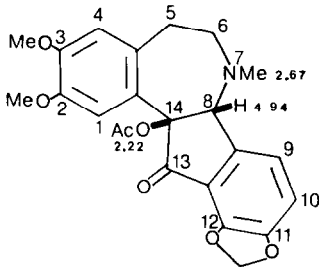


8a



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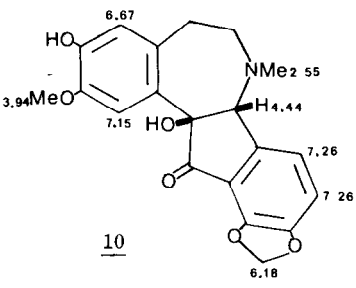

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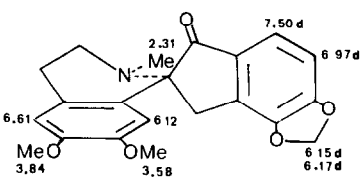

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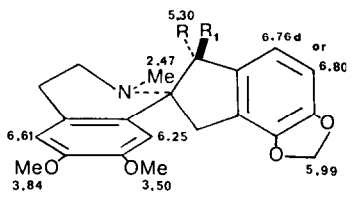
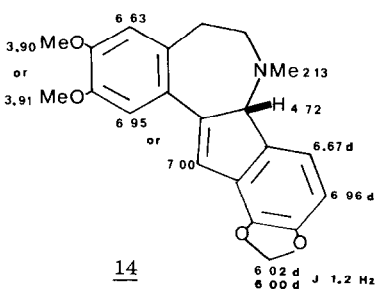


12, R = H, R_1 = OH

13, R = OH, R_1 = H

(NMR data above are for 12)



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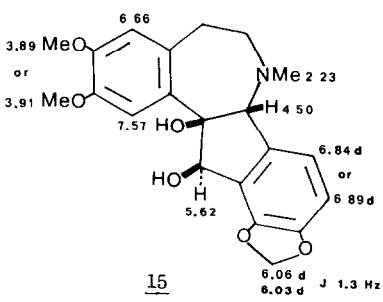

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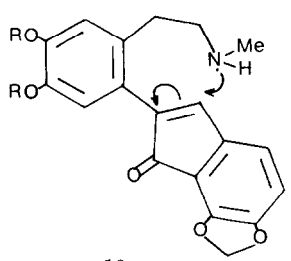

16

methanesulfonyl chloride in triethylamine and THF at 0° furnished amorphous indenobenzazepine 14 (68%), $C_{21}H_{21}O_4N$, λ max 225 and 332 nm (log ε 4.13 and 4.06). Treatment of this material with osmium tetroxide resulted in approach of the reagent from the less hindered side with formation of cis glycol 15 (71%), $C_{21}H_{23}O_6N$, mp 161-163° (EtOH). O-Methylfumarofine (8), spectrally and chromatographically identical with material derived from the natural product was then obtained by oxidation of 15 with pyridinium chlorochromate in methylene chloride at 5°. This synthetic sequence thus supplies interlocking evidence for the assignment of the cis B/C fusion to the alkaloid.

Fumarofine can be considered the first "reduced" indenobenzazepine alkaloid, and it bears a striking resemblance to the recently discovered and completely aromatic indenobenzazepines lahorine and lahoramine.[7] Whereas the last two alkaloids probably result from a direct rearrangement of spirobenzylisoquinoline alcohols of type 1 in the plant through an S_N2 process, followed by oxidation and aromatization,[7] it is likely that fumarofine could be formed in nature from a ketonic spirobenzylisoquinoline precursor of type 2. β-Elimination would give rise to indenone derivative 16, and intramolecular Michael addition followed by oxidation at C-14 would then supply fumarofine.

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References and Footnotes[8]

1. Permanent address: Central Research Institute for Chemistry, Hungarian Academy of Sciences, H-1025 Budapest, Hungary.
2. Permanent address: PCSIR Laboratories, Peshawar, Pakistan.
3. For a complete listing of spirobenzylisoquinolines and their spectral data, see R.M. Preisner and M. Shamma, J. Natural Products, 43, 305 (1980).
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6. H. Irie, S. Tani and H. Yamane, J. Chem. Soc. Perkin I, 2986 (1972).
7. G. Blaskó, S.F. Hussain, A.J. Freyer and M. Shamma, Tetrahedron Lett., in press.
8. The sample of fumarofine we worked with was racemic. There is a possibility, however, that this alkaloid may also be found in an optically active form. TLC R_f values on Merck silica gel F-254 plates using benzene-methanol (100:15 v/v) are as follows: 7, 0.23; 8, 0.30; 9, 0.47; 10, 0.24; 11, 0.41; 12, 0.17; 13, 0.11; 14, 0.34; 15, 0.24. The general numbering system adopted here for the indenobenzazepines corresponds to that followed for lahorine and lahoramine.[7] Ultraviolet spectra are in methanol. All ^1H nmr spectra, as summarized on the structures page, are in $CDCl_3$ solution at 360 MHz, with TMS as internal standard. All peaks are singlets except where indicated otherwise. For indenobenzazepines 7, 8, and 9, $J_{9,10}$ = 8.5 Hz; and for 14, $J_{9,10}$ = 7.8 Hz; and for 15, $J_{9,10}$ = 8.0 Hz. For spirobenzylisoquinolines 11 and 12, $J_{11,12}$ = 8.1 Hz. ^{13}C nmr data for O-methylfumarofine as summarized in expression 8a are in $CDCl_3$ at 90 MHz; chemical shift values with identical superscripts are interchangeable. Elemental analyses are by mass spectroscopy.

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