Tetrahedron Letters, Vol.22, No.33, pp 3127 - 3130, 1981
Printed in Great Britain

0040-4039/81/333127-04$02.00/0

A NEW CLASS OF ISOQUINOLINE ALKALOIDS: THE INDENOBENZAZEPINES

Gábor Blaskó,[1] S. Fazal Hussain,[2] Alan J. Freyer and Maurice Shamma*,

Department of Chemistry, The Pennsylvania State University,

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

The dark yellow indenobenzazepine alkaloids lahorine (1) and lahoramine (2) have been found in Fumaria parviflora Lam. (Fumariaceae). In a transformation with biogenetic implications, treatment of the spirobenzylisoquinolines dihydrofumariline (4) and dihydroparfumidine (7) with methanesulfonyl chloride and triethylamine in dry THF, followed by iodine oxidation, provided 1 and 2, respectively.

It is known that plants can convert benzylisoquinolines into protoberberines[3,4] which in turn are the probable precursors of spirobenzylisoquinolines.[5] We now wish to describe two new alkaloids, lahorine (1) and lahoramine (2) which represent the first members of the novel class of indenobenzazepines,[6] and which are most probably derived biogenetically from spirobenzylisoquinolines.

The creeping plant Fumaria parviflora Lam. (Fumariaceae), which is identical with F. indica Pugsley, is a rich repository of isoquinoline alkaloids, and is of widespread distribution in Pakistan where, under the name of "Pit Papra", it is used as an anthelmintic and in the treatment of skin diseases. Previous investigations had shown that this plant is an abundant source of spirobenzylisoquinolines as well as phthalideisoquinolines.[7]

As part of a reinvestigation of F. parviflora, we had occassion to place on a silica gel column 46 g of plant extract, originating from the extraction of 12 Kg of the dried whole plant. Elution was first with chloroform, and then with 1% methanol in chloroform.

In one of the middle fractions which contained the known spirobenzylisoquinolines (+)-fumariline (3) (55 mg) and (+)-parfumidine (6) (309 mg), it was noticed that tlc also showed a light yellow spot which turned to a darker yellow upon evaporation of the solvent from the plate.[8] Additionally, this spot became dark brown upon spraying with the chloroplatinic acid reagent, rather than dark purple as with most spirobenzylisoquinolines. Further purification of the yello material by tlc gave the optically inactive lahorine (1) (16 mg) and lahoramine (2) (0.5 mg).[9]

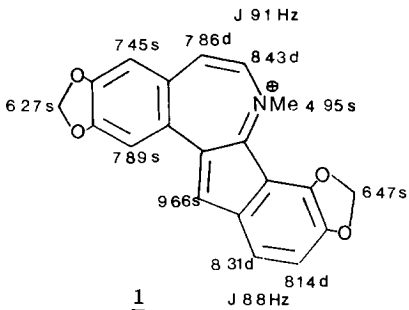
Lahorine chloride (1), $C_{20}H_{14}O_4N^+ Cl^-$, mp 253-255° C (decomp.) ($CHCl_3$), is a yellow salt whose mass spectrum shows a molecular cation peak m/e 332 which is also the base peak. Other peaks are m/e 317 (23), 260 (3.0), 201 (4.1), 190 (4.2), 167 (7.0), 149 (24), 137 (6), 111 (7.0) and 97 (11.0). The uv spectrum of the material that had been freshly purified by tlc shows λ_{max}^{MeOH} 233, 283, 323 and 349 sh nm (log ε 3.94, 3.92, 3.57 and 3.14), λ_{min}^{MeOH} 256 and 310 nm (log ε 3.62 and 3.50), which denotes a highly conjugated system different from that of any other known isoquinoline alkaloid. There is no change in the absorption pattern in basic solution, but a substantial modification occurs in acid. The alkaloid turns to a darker yellow, and exhibits $\lambda_{max}^{MeOH-H^+}$ 257, 274, 328 and 346 nm (log ε 3.91, 3.94, 3.84 and 3.67), $\lambda_{min}^{MeOH-H^+}$ 264 and 299 nm (log ε 3.90 and 3.46). This behavior indicates that lahorine tends to solvate in a neutral or basic medium, but reverts back to the ionic form in acid.

The nmr of lahorine chloride proved to be extremely informative and has been summarized in expression 1.[10] The most salient feature is the absence of any aliphatic protons with the exception of those associated with the N-methyl and the two methylenedioxy substituents. Of particular import are the downfield one proton singlets at δ7.89 and 9.66 representing H-1 and H-13, respectively, and the pair of aromatic doublet of doublets denoting H-5 and H-6, and H-11 and H-12.[6]

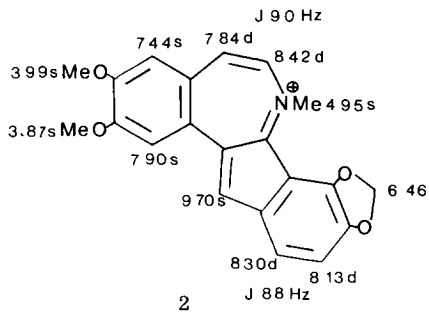
Attempted reduction of lahorine using either Adams catalyst or sodium borohydride resulted in the ephemeral formation of a partially reduced species. This material could not be adequately characterized since it readily reverted to the starting alkaloid upon purification by tlc.

The second yellow alkaloid, lahoramine (2), $C_{21}H_{18}O_4N^+ Cl^-$, was obtained in too small an amount to allow for crystallization. But its mass spectrum indicates that it is the ring A dimethoxy analog of 1. There is a molecular cation peak m/e 348 (19.2), and the base peak is m/e 347. Other peaks are m/e 333 (39.5), 332 (58.7), 317 (61.6), 289 (11.6), 206 (12.8), 163 (14.0), 158 (11.6), 111 (17.4), and 97 (31.4). The uv spectrum bears a similarity to that of lahorine and exhibits λ_{max}^{MeOH} 234, 286, 323 and 350 sh nm (log ε 3.90, 3.85, 3.48 and 3.21); λ_{min}^{MeOH} 256 and 312 nm (log ε 3.59 and 3.45); $\lambda_{max}^{MeOH-H^+}$ 257, 277, 327 and 348 sh nm (log ε 3.76, 3.82, 3.65 and 3.47), $\lambda_{min}^{MeOH-H^+}$ 262 and 300 nm (log ε 3.75 and 3.43).

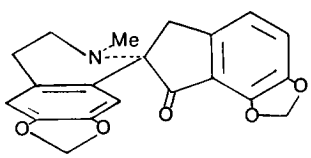
In order to prove the structures of the two alkaloids, and in particular to show that the substituents in ring D are located at C-9,10 rather than at C-11,12, the known dihydroparfumidine (7), obtained by sodium borohydride reduction of parfumidine (6),[11] was dissolved in dry THF, and treated with methanesulfonyl chloride and triethylamine at 0° C for 6-7 h.[12] Work-up provided the amorphous indenobenzazepine 8 in 75% yield, $C_{21}H_{21}O_4N$, ms m/e 351 (95.8, M^+) and 336 (base), λ_{max}^{MeOH} 219, 240 sh, 308 sh and 338 nm (log ε 4.33, 4.16, 4.07 and 4.18). The nmr spectrum has been summarized in expression 8. Formation of 8 may be rationalized through the intermediacy of the azi*ridinium cation* 7a and the quinone methide cation 7b. Oxidation of 8 with iodine in ethanol at



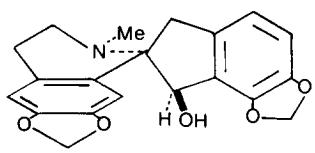
1



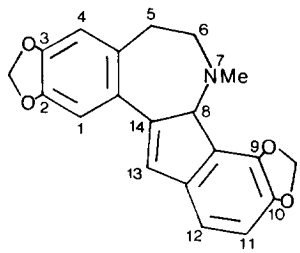
2



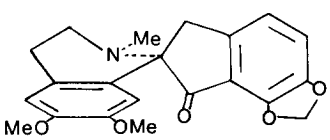
3



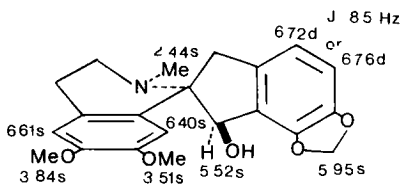
4



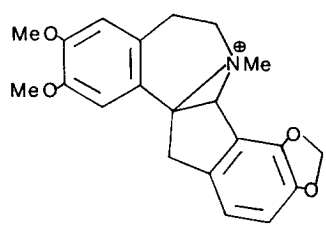
5



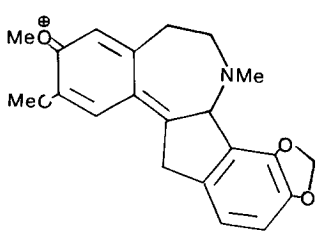
6



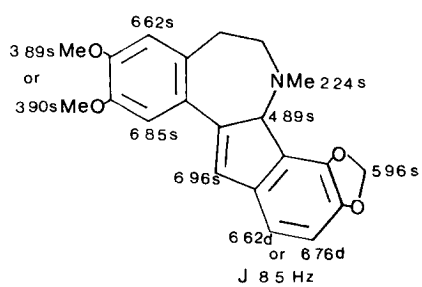
7



7a



7b



8

reflux for 6-7 h provided lahoramine (2) in 20% yield. In like fashion, dihydrofumariline (4) was converted into lahorine (1), but without full characterization of the intermediate indenobenzazepine 5 due to the paucity of starting dihydrofumariline in our possession.[13]

It is likely that indenobenzazepine alkaloids originate in plants from the rearrangement of spirobenzylisoquinolines, so that the present conversions of dihydrofumariline (4) and dihydroparfumidine (7) into lahorine and lahoramine, repectively, can be considered to be biogenetically patterned transformations.

Acknowledgments: This research was supported by grant CA-11450 from the National Cancer Institute, USPHS. G.B. is the recipient of an IREX fellowship.

References and Footnotes

1. Permanent address: Central Research Institute for Chemistry, Hungarian Academy of Sciences, H-1025 Budapest, Hungary.
2. Permanent address: PCSIR Laboratories, Peshawar, NWFP, Pakistan.
3. D.H.R. Barton, Proc. Chem. Soc., London, 293 (1963).
4. A.R. Battersby, Proc. Chem. Soc., London, 189 (1963).
5. H.L. Holland, M. Castillo, D.B. MacLean and I.D. Spenser, Can. J. Chem., 52, 2818 (1974). See also M. Shamma and C.D. Jones, J. Am. Chem. Soc., 92, 4943 (1970).
6. The IUPAC name for this totally aromatic ring system is benz[d]indeno[1,2-b]azepine. The numbering adopted here is in accord with that for protoberberines and spirobenzylisoquinolines.
7. For a lead reference, see F. Šantavy in The Alkaloids, Vol. XVII, ed. by R.H.F. Manske and R. Rodrigo, Academic Press, New York (1979), p. 385. See also S.F. Hussain and M. Shamma, Tetrahedron Lett., 1693 and 1909 (1980).
8. Under long-wave uv light, this yellow spot becomes a bright, fluorescent yellow.
9. TLC was on silica gel F-254 plates. In benzene-methanol (100:12 v/v) 1 has R_f 0.64 and 2 has R_f 0.60. In ether-methanol (100:5 v/v), the respective values are 0.67 and 0.56.
10. All nmr data were collected on a Bruker 360 MHz (FT) spectrometer, in $CDCl_3$ solution. In the case of alkaloids 1 and 2, a drop of TFA-d was added to the $CDCl_3$.
11. For a listing of spirobenzylisoquinolines, see R.M. Preisner and M. Shamma, J. Natural Products, 43, 305 (1980).
12. H. Irie, S. Tani and H. Yamane, J. Chem. Soc., Perkin I, 2986 (1972).
13. To insure against the possibility of lahorine and lahoramine being artefacts of isolation, parfumidine (6) and dihydroparfumidine (7) were independently allowed to stand overnight in $CHCl_3$ solution in the presence of silica gel. No lahoramine could be detected as a result.

(Received in USA 4 March 1981)