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TRANSFORMATION OF PROTOBERBERINES INTO BENZINDENOAZEPINES A TOTAL SYNTHESIS OF FUMAROFINE AND *O*-METHYLFUMAROFINE

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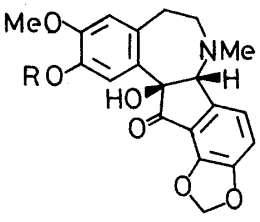
Acidic treatment of the 8,14-cycloberbine (12), derived from the protoberberine (8), effected regioselective ring cleavage to afford the *cis*-benzindenoazepine (15) along with a small amount of the *trans*-derivative (16) after *N*-methylation. Hydrogenolysis of 15 provided fumarofine (1), which was methylated with diazomethane to give *O*-methylfumarofine (2).

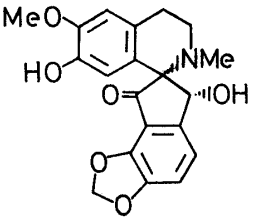
KEYWORDS—— fumarofine; *O*-methylfumarofine; benzindenoazepine; regioselective ring cleavage; 8,14-cycloberbine

The structure of fumarofine (1), an alkaloid from *Fumaria officinalis* L.[1] and *F. rostellata* Knaf,[2] had been initially assigned as the spirobenzylisoquinoline (3);[2,3] however, recently the same alkaloid was isolated from *F. microcarpa* Boiss.[4,5] and its structure was revised to be the benzindenoazepine (1)[4] by spectroscopic reinvestigation and synthesis of *O*-methylfumarofine (2) from the spirobenzylisoquinoline (4).

We have previously demonstrated an efficient transformation of the 8,14-cyclo-



1: R= H
2: R= Me



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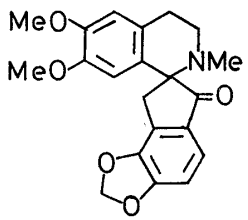

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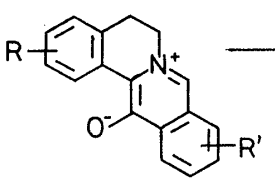

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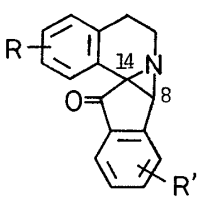

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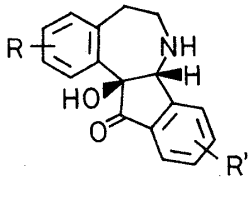

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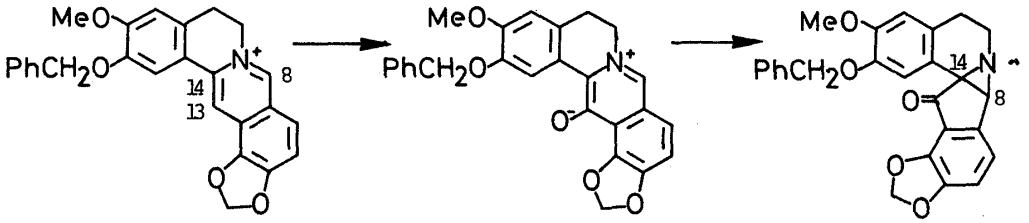
berbine (6),[6] derived readily from photochemical valence tautomerization of the phenolbetaine (5), into the *cis*-benzindenoazepine (7)[7,8] by regioselective C_{14}-N bond cleavage. This method was now applied to a total synthesis of a benzindenoazepine alkaloid, fumarofine, from the protoberberine (8) *via* the 8,14-cycloberbine (12).

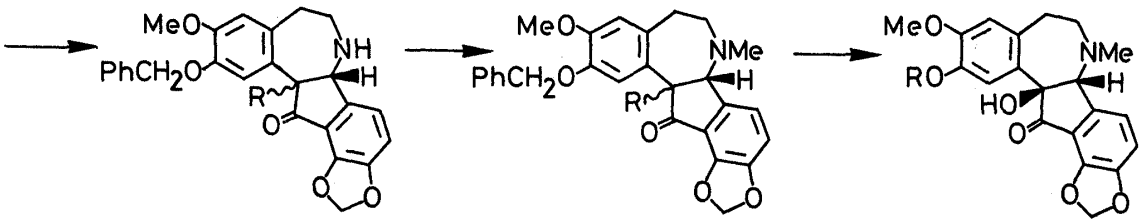
Dehydrogenation of the tetrahydroprotoberberine (8)[9] with iodine in the presence of potassium acetate in ethanol followed by reduction with lithium aluminum hydride afforded the dihydro derivative (10) in 92% yield *via* the quaternary salt (9). Oxidation of 10 with *m*-chloroperbenzoic acid in dichloromethane at -20~-30°C gave the phenolbetaine [11, *m/e* 427 (M^+), δ 9.37 (1H, s), 7.5-7.2 (8H, m), 6.59 (1H, s), 6.27 (2H, s), 5.26 (2H, s), 4.37 (2H, t, *J*=6 Hz), 3.85 (3H, s), 2.98 (2H, t, *J*=6 Hz)] in 82% yield. Irradiation (100 W high pressure Hg lamp, with a Pyrex filter) of 11 in methanol in a stream of nitrogen effected valence tautomerization to give the 8,14-cycloberbine [12, mp 144-145°C, *m/e* 427 (M^+), ν 1710 (C=O), δ 3.84 (1H, s, C_8-H)] in 64% yield.[10] On treatment with methanesulfonic acid in aqueous tetrahydrofuran at room temperature for 70 h, 12 was converted to the benzindenoazepines (13 and 14) as a mixture (*ca.* 2:1)[11] in 92% yield through regioselective C_{14}-N bond cleavage.[12] *N*-Methylation of the mixture (13 and 14) with methyl iodide in acetonitrile at room temperature for 1 h afforded *cis N*-methyl derivative [15, 51%, mp 96-98°C, *m/e* 459 (M^+), ν 3425 (OH), 1710 (C=O), δ 4.44 (1H, s, C_8-H), 2.48 (3H, s, N-CH_3)] and the unchanged *trans*-benzindenoazepine [14, 21%, mp 226-227°C, *m/e* 445 (M^+), ν 3425 (OH, NH), 1710 (C=O), δ 4.33 (1H, s, C_8-H)]. The latter was methylated with difficulty under this condition, and its *N*-methyl derivative (16) [*m/e* 459 (M^+), ν 3425 (OH), 1710 (C=O), δ 4.39 (1H, s, C_8-H), 2.83 (3H, s, N-CH_3)] was obtained only in 6% yield upon treatment of the above mixture with dimethyl sulfate in tetrahydrofuran at room temperature for 43 h.



8 : 7,8,13,14-tetrahydro 11 12

9

10 : 7,8-dihydro



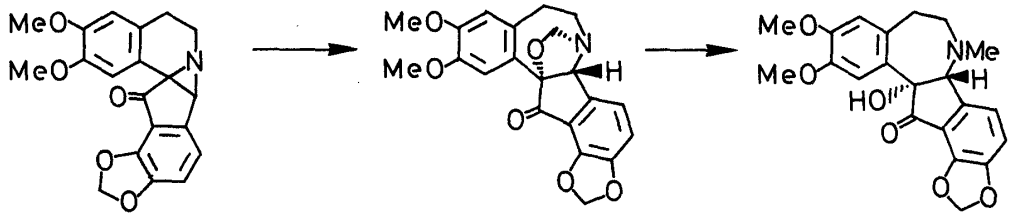
13 : R= ◀OH 15 : R= ◀OH 1 : R= H

14 : R= ···OH 16 : R= ···OH 2 : R= Me

In general acidic cleavage of 8,14-cycloberbines affords predominantly *cis*-benzindenoazepines as thermodynamically more stable isomers;[7,8] therefore, the stereochemistry of the major product (13) could be assigned to be *cis*. This assignment was further supported by the appearance of the *N*-methyl signal of 15 at higher field[7] than that of 16. However, efforts to isomerize 16 into 15 under various acidic conditions[7] went unrewarded.

Hydrogenolysis of 15 in methanol over 5% palladium on charcoal afforded fumarofine (1) [mp 255-256°C,[13] *m/e* 369 (M^+), ν 3450 (OH), 1700 (C=O), δ 7.28 (2H, s, C_9- and C_{10}-H), 7.14 (1H, s, C_1-H), 6.61 (1H, s, C_4-H), 6.18 (2H, s, OCH_2O), 4.44 (1H, s, C_8-H), 3.87 (3H, s, OCH_3), 2.54 (3H, s, N-CH_3), δ (DMSO-d_6)[14] 8.69 (1H, s, C_2-OH), 7.30, 7.16 (2H, AB-q, *J*= 8Hz, C_9- and C_{10}-H), 7.18 (1H, s, C_1-H), 6.63 (1H, s, C_4-H), 6.22 (2H, s, OCH_2O), 4.25 (1H, s, C_8-H), 3.74 (3H, s, OCH_3)] in 77% yield. The synthetic fumarofine was proved to be identical with natural fumarofine by spectral comparison and thin-layer chromatographic behavior. *O*-Methylation[3] of 1 with diazomethane provided *O*-methylfumarofine (2)[15] [mp 243-244°C,[16] *m/e* 383 (M^+), ν 3325 (OH), 1710 (C=O), δ 7.29 (1H, s, C_1-H), 7.15 (2H, s, C_9- and C_{10}-H), 6.62 (1H, s, C_4-H), 4.45 (1H, s, C_8-H), 3.92, 3.86 (each 3H, s, OCH_3 x 2), 2.54 (3H, s, N-CH_3)] in 82% yield, which was identical with the authentic sample derived from natural fumarofine by spectral and thin-layer chromatographic comparison.

In order to confirm unambiguously the stereochemistry of these alkaloids (1 and 2), we next tried to synthesize the *trans*-benzindenoazepine (19) according to Shamma's method.[8] Treatment of the 8,14-cycloberbine (17)[17] with 37% aqueous formaldehyde in methanol provided the oxazolidine (18) [87%, *m/e* 381 (M^+), ν 1720 (C=O), δ 4.99, 4.24 (2H, AB-q, *J*=6.5 Hz, OCH_2N), 4.69 (1H, s, C_8-H)], which was reduced with sodium cyanoborohydride to give the *trans*-benzindenoazepine (19) [58%, *m/e* 383 (M^+), ν 3400 (OH), 1710 (C=O), δ 4.39 (1H, s, C_8-H), 2.84 (3H, s, N-CH_3)]. As *O*-methylfumarofine (2) was not identical with this *trans* derivative (19),[18] the stereochemistry of 1 and 2 was established to be *cis* as depicted.



17 18 19

The present synthesis provides a general and convenient method for synthesis of benzindenoazepine alkaloids from protoberberines.

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REFERENCES AND NOTES

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2) The alkaloid was originally named as fumarostelline: H.G. Kiryakov and P.P. Panov, *C. R. Acad. Bulg. Sci.*, 25, 345 (1972) [*Chem. Abstr.*, 77, 58795u (1972)].
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4) G. Blaskó, N. Murugesan, S.F. Hussain, R.D. Minard, M. Shamma, B. Sener, and M. Tanker, *Tetrahedron Lett.*, 22, 3135 (1981).
5) The alkaloid isolated is racemic and the $[\alpha]_D$ value was not described in the literature;[1,2] therefore, the alkaloid isolated earlier might also be racemic.
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7) M. Hanaoka, M. Inoue, K. Nagami, Y. Shimada, and S. Yasuda, *Heterocycles*, 19, 313 (1982); M. Hanaoka, M. Inoue, S. Sakurai, Y. Shimada, and S. Yasuda, *Chem. Pharm. Bull.*, 30, 1110 (1982).
8) *Cf.* N. Murugesan, G. Blaskó, R.D. Minard, and M. Shamma, *Tetrahedron Lett.*, 22, 3131 (1981); G. Blaskó, V. Elango, N. Murugesan, and M. Shamma, *Chem. Commun.*, 1981, 1246.
9) The protoberberine (8) was prepared from 4-benzyloxy-3-methoxyphenethylamine and 2,3-methylenedioxyphenylacetic acid through conventional reaction sequence, and its details will be described in a separated paper.
10) 73% yield based on consumed starting material.
11) As separation of the mixture was very difficult, the mixture was used to the next step without separation. The benzindenoazepine (13) showed the following physical data: *m/e* 445 (M^+), ν 3325 (OH, NH), 1705 (C=O), δ 7.38-7.12 (7H, m, Ar-H), 6.90 (1H, s, C_1-H), 6.72 (1H, s, C_4-H), 6.21, 6.18 (2H, AB-q, *J*=1 Hz, OCH_2O), 5.05, 5.03 (2H, AB-q, *J*=12 Hz, $PhCH_2O$-), 4.26 (1H, s, C_8-H), 3.86 (3H, s, OCH_3).
12) Under other acidic conditions such as 10% HCl, *p*-TsOH, CF_3CO_2H *etc.*, 12 also gave the benzindenoazepines in rather low yields.
13) Natural fumarofine: mp 256°C,[1] mp 251-252°C,[2] mp 253-254°C.[15]
14) NMR spectra were measured in $CDCl_3$ solution unless otherwise stated.
15) *O*-Methylfumarofine and fumarofine were isolated from *Fumaria kralikii* Jord.: H.G. Kiryakov and P.P. Panov, *C. R. Acad. Bulg. Sci.*, 29, 677 (1976) [*Chem. Abstr.*, 85, 119633d (1976)].
16) Natural *O*-methylfumarofine: mp 248-249°C,[14] mp 245-246°C.[3]
17) M. Hanaoka, S. Yasuda, Y. Hirai, K. Nagami, and T. Imanishi, *Heterocycles*, 14, 1455 (1980).
18) Treatment of 19 with 10% HCl did not result in any isomerization to *O*-methylfumarofine.

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