Communications to the Editor

[Chem. Pharm. Bull. 30(3)1110—1112(1982)]

EFFICIENT CONVERSION OF PROTOBERBERINES INTO BENZINDENOAZEPINES. A FORMAL SYNTHESIS OF (±)-*cis*-ALPINIGENINE AND (±)-*cis*-ALPININE

Miyoji Hanaoka,* Mitsuru Inoue, Shun-ichiro Sakurai,
Yasuji Shimada, and Shingo Yasuda
Faculty of Pharmaceutical Sciences, Kanazawa University
Takara-machi, Kanazawa 920, Japan

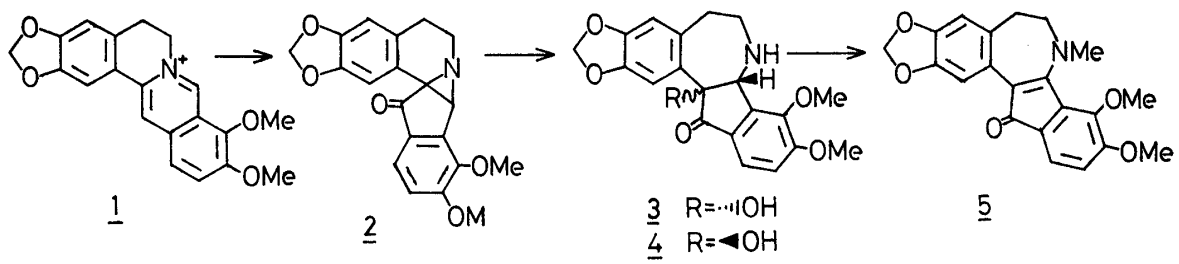
Acidic treatment of the 8,14-cycloberbine (2), derived from berberine (1), in methanol afforded the *cis*- and *trans*-benzindanoazepines (7 and 8), whereas the reaction of 2 with *p*-toluenesulfonic acid in benzene yielded the benzindenoazepine (6) in an excellent yield. This simple conversion method was applied to the synthesis of the benzindenoazepine (21), the key intermediate for the total synthesis of (±)-*cis*-alpinigenine (22) and (±)-*cis*-alpinine (23).

KEYWORDS——regioselective C-N bond cleavage; photochemical valence tautomerization; protoberberine alkaloid; benzindenoazepine alkaloid; rhoeadine alkaloid; benzindenoazepine skeleton; berberine; 8,14-cycloberbine; *cis*-alpinigenine; *cis*-alpinine

The benzindenoazepine skeleton has been shown to be the key intermediate in the total synthesis of rhoeadine alkaloids[1,2] and some alkaloids possessing this skeleton have recently been found.[3] In a previous paper,[4] we reported a convenient one-step conversion of the 8,14-cycloberbine (2),[5] derived from berberine (1), into the *trans*- and *cis*-benzindanoazepines (3 and 4) as the kinetically and thermodynamically controlled products, respectively. These were dehydrated to give the benzindenoazepine (5) *via* their *N*-methyl derivatives.[4]

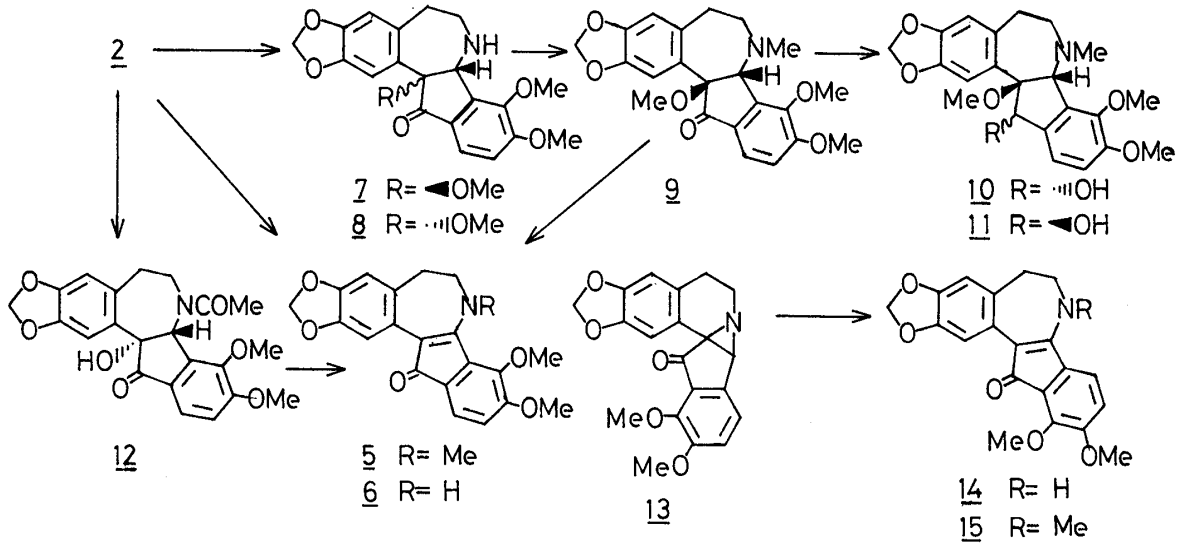
The recent communication[6] on similar conversion of 2 into this skeleton prompts us to publish our further results on the simple efficient synthesis of benzindenoazepines and its application to a formal synthesis of (±)-*cis*-alpinigenine and (±)-*cis*-alpinine, rhoeadine alkaloids.

A solution of 2 in methanol-benzene was treated with trifluoroacetic acid at room temperature for 3 h to give the *cis*-benzindanoazepine (7)[6] [94%, *m/e* 383(M^+), ν 3350, 1695, δ 7.61, 7.06 (2H, AB-q, *J*=8), 7.26, 6.70 (2 x 1H, s), 5.96, 5.90 (2H, AB-q, *J*=1.5), 4.41 (1H, s), 3.96, 3.95, 3.30 (3 x 3H, s)], which was also obtained



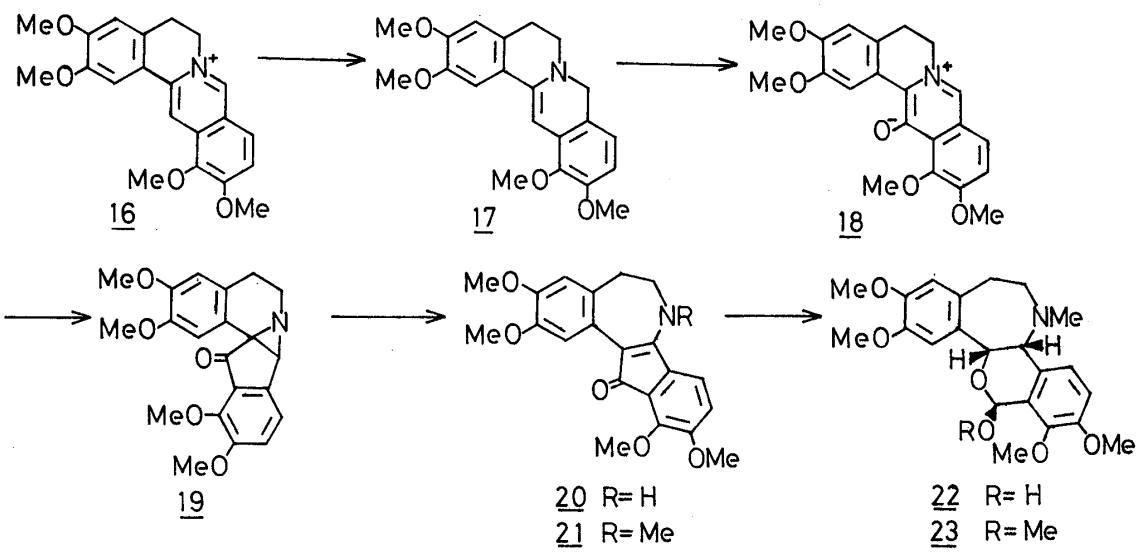
1 2 3 R=···OH 4 R=◀OH 5

in 81 and 92% yield by similar treatment with 35% hydrochloric acid and conc. sulfuric acid, respectively, as acidic catalysts. The reaction of 2 with hydrogen chloride in methanol for 1 h yielded 7 (70%) and its *trans* isomer (8)[6] [23%, *m/e* 383(M^+), ν 3350, 1700, δ 7.62, 6.99 (2H, AB-q, *J*=8.5), 7.40, 6.66 (2 x 1H, s), 5.95 (2H, s), 4.61 (1H, s), 3.94, 3.91, 3.21 (3 x 3H, s)], which with acid in methanol isomerized to 7. Methylation of 7 with methyl iodide in tetrahydrofuran (THF) afforded the *N*-methyl derivative (9) [94%, mp 193-194.5°C, *m/e* 397(M^+), δ 2.49 (3H, s)], sodium borohydride reduction of which furnished two diastereoisomers, 10 [60%, *m/e* 399(M^+)] and 11 [36%, *m/e* 399(M^+)]. The predominant alcohol (10) appears to be the product obtained by the hydride attack from the convex side of 9. Heating of 9 with boron trifluoride etherate in dichloromethane produced the known benzindenoazepine (5)[4,7] in 41% yield.



On treatment with acetic acid at room temperature for 3 h or under reflux for 2 h, 2 afforded the *N*-acetyl *trans*-benzindanoazepine (12)[4] or the benzindenoazepine (6)[8] [mp 238-240°C, *m/e* 351(M^+), ν 3375, 1660, δ 7.87 (1H, s), 7.21, 6.74 (2H, AB-q, *J*=8), 6.69 (1H, s), 5.90 (2H, s), 3.97, 3.89 (2 x 3H, s)], in 89 and 56% yield, respectively. The former was converted to the latter in 41% yield under reflux in acetic acid for 2 h. As one-step conversion of 2 to 6 was accomplished using an organic acid, reactions catalyzed with other organic acids were tried. Treatment of 2 with trifluoroacetic acid at room temperature for 1 h or with *p*-toluenesulfonic acid (*p*-TsOH) in benzene under reflux for 2 h gave 6 in 44 or 96% yield, respectively. Similarly, the 8,14-cycloberbine (13)[4] was converted to the benzindenoazepine (14) [67%, mp 237-239°C, *m/e* 351(M^+), ν 3275, 1650, δ 7.74 (1H, s), 7.28, 6.95 (2H, AB-q, *J*=8), 6.68 (1H, s), 5.93 (2H, s), 3.85, 3.80 (2 x 3H, s)] using *p*-TsOH in benzene. The secondary amines (6 and 14) thus obtained were methylated with dimethyl sulfate in hexamethylphosphoramide (HMPA) in the presence of sodium hydride to afford the *N*-methyl benzindenoazepines (5 and 15)[4,7] in 92 and 76% yield, respectively.

The above simple one-step method for the preparation of the benzindenoazepines was next applied to the synthesis of the benzindenoazepine (21),[1] the key intermediate for (±)-*cis*-alpinigenine and (±)-*cis*-alpinine. The protoberberine (16)[9] was reduced with lithium aluminum hydride in THF and then oxidized with *m*-chloroper-



benzoic acid in dichloromethane to afford the phenolbetaine (18) [overall 63%, mp 162-164°C, *m/e* 367(M^+)] *via* the dihydroprotoberberine (17). Irradiation (100W high-pressure Hg lamp, with a Pyrex filter)[5] of 18 in methanol in a stream of nitrogen gave the 8,14-cycloberbine (19) [78%, mp 157.5-158.5°C, *m/e* 367(M^+), ν 1710, δ 3.79 (1H, s)], which was heated with *p*-TsOH in benzene under reflux for 1.5 h to yield the benzindenoazepine (20) [58%, mp 234-237°C, *m/e* 367(M^+), ν 3425, 1655, δ 8.06 (1H, s), 6.76, 6.68 (2H, AB-q, *J*=8), 6.53 (1H, s), 4.03, 3.92, 3.87, 3.83 (4 x 3H, s)]. Methylation of 20 with dimethyl sulfate in HMPA in the presence of sodium hydride gave the *N*-methyl derivative (21) [78%, mp 164-166°C (lit.[1] mp 159-161°C), *m/e* 381(M^+), ν 1650, δ 7.81 (1H, s), 7.01, 6.66 (2H, AB-q, *J*=8), 6.54 (1H, s), 4.01 3.94, 3.87, 3.85, 3.40 (5 x 3H, s), 3.8-3.6, 3.0-2.8 (2 x 2H, m)].[10] Since 21 has already been converted to (±)-*cis*-alpinigenine (22) and (±)-*cis*-alpinine (23),[1] the present synthesis of 21 amounts to a formal synthesis of these alkaloids.

Thus, the present results provide an efficient method for the synthesis of benzindenoazepines and benzindanoazepines from 8,14-cycloberbines derived from protoberberines.

REFERENCES AND NOTES

1) K. Orito, R.H. Manske, and R. Rodorigo, *J. Am. Chem. Soc.*, 96, 1944(1974).
2) H. Irie, S. Tani, and H. Yamane, *J. Chem. Soc. Perkin I*, 1972, 2986.
3) G. Blaskó, S.F. Hussain, A.J. Freyer, and M. Shamma, *Tetrahedron Lett.*, 22, 3127(1981); G. Blaskó, N. Murugesan, S.F. Hussain, R.D. Minard, M. Shamma, B. Sener, and M. Tanker, *ibid.*, 22, 3135(1981); G. Blaskó, N. Murugesan, A.J. Freyer, R.D. Minard, and M. Shamma, *ibid.*, 22, 3143(1981).
4) M. Hanaoka, M. Inoue, K. Nagami, Y. Shimada, and S. Yasuda, *Heterocycles*, 19, 313(1982).
5) M. Hanaoka, S. Yasuda, K. Nagami, K. Okajima, and T. Imanishi, *Tetrahedron Lett.*, 1979, 3749.
6) G. Blaskó, V. Elango, N. Murugesan, and M. Shamma, *Chem. Commun.*, 1981, 1246.
7) H.L. Holland, M. Curcumelli-Rodostamo, and D.B. MacLean, *Can. J. Chem.*, 54, 1472(1976).
8) Independently 6 was obtained in 77% yield by treatment of 2 with iodine.[6]
9) H. Irie, K. Akagi, S. Tani, K. Yabusaki, and H. Yamane, *Chem. Pharm. Bull.*, 21, 855(1973); D. Greenslade and R. Ramage, *Tetrahedron*, 33, 927(1977).
10) The published pmr data for 21: δ 7.93 (1H, s), 7.13, 6.73 (2H, AB-q, *J*=8), 6.62 (1H, s), 4.04, 3.97, 3.40 (3 x 3H, s), 3.84 (6H, s), 3.9-3.6, 3.1-2.8 (2 x 2H, m).[1]

(Received February 9, 1982)