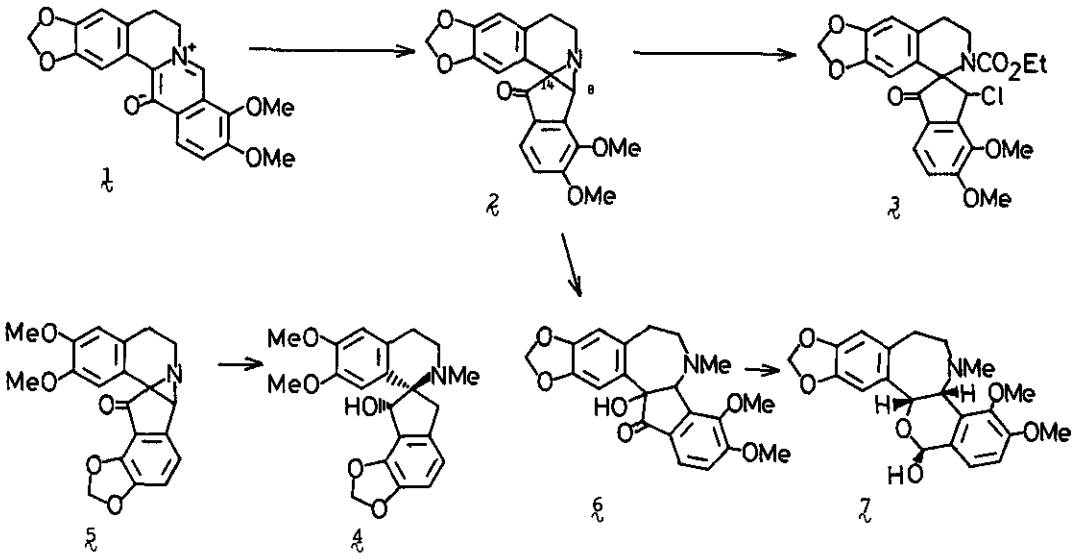
CONVERSION OF BERBERINE INTO BENZINDANOAZEPINES VIA 8,14-CYCLOBERBINES

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

Abstract—— Acidic treatment of the 8,14-cycloberbine (2) effected regioselective C_{14}-N bond cleavage to give the *trans*- and *cis*-benzindanoazepine (8a and 8b) as the kinetically and thermodynamically controlled product, respectively. Dehydration of their *N*-methyl derivatives (11a and 11b) afforded the unsaturated benzindanoazepine (13). Similarly the 11,12-oxygenated cycloberbine (19) was converted to the benzindanoazepines (20a, 20b, 21b, and 22). All these benzindanoazepines have been shown to be the key intermediates for the rhoeadine skeleton.

Previously we reported[1] the simple photochemical valence tautomerization of berberinephenolbetaine (1),[2] derived from berberine, into the 8,14-cycloberbine (2), which type of compound would be one of the most versatile intermediates for transformation of protoberberine alkaloids to spirobenzylisoquinoline and rhoeadine alkaloids through regioselective C_8-N and C_{14}-N bond cleavage, respectively. The potentiality of 8,14-cycloberbines was demonstrated by conversion of 2 into the spirobenzylisoquinoline (3)[1] and synthesis of (±)-fumaricine (4)[3] from the corresponding 8,14-cycloberbine (5). The recent communication[4] on conversion of 2 into the rhoeadine skeleton (7) *via* the benzindanoazepine (6) prompted us to report our own results on regioselective C_{14}-N bond cleavage of 2 to benzindanoazepines. Treatment of 2 with 10% hydrochloric acid at room temperature (r.t.) for 30 min afforded two diastereomeric benzindanoazepines,[5] 8a [41%, mp 199.5-200.5°, *m/e* 369 (M^+), ν 3200, 1700, δ 7.46 (1H, d, *J*=8), 7.24 (1H, s), 6.87 (1H, d, *J*=8), 6.47 (1H, s), 5.76 (2H, s), 4.18 (1H, s, H-8), 3.86 (3H, s), 3.80 (3H, s)] and 8b [41%,



mp 112-114°, *m/e* 369 (M^+), ν 3200, 1710, δ 7.53 (1H, d, *J*=8), 6.98 (1H, d, *J*=8), 6.95 (1H, s), 6.56 (1H, s), 5.86, 5.80 (2H, AB-q, *J*=1.5), 4.37 (1H, s, H-8), 3.93 (6H, s)]. The B/C ring junctures of 8a and 8b were assigned to be *trans* and *cis*, respectively, from comparison of their chemical shifts due to H-8 signal in PMR spectra.[6] These assignments were confirmed by isomerization of 8a into the more stable *cis* isomer 8b, namely, treatment of 8a with 10% hydrochloric acid at 70°C for 3 hr gave 8a (17%) and 8b (65%). Regioselective C_{14}-N bond cleavage of 2 was

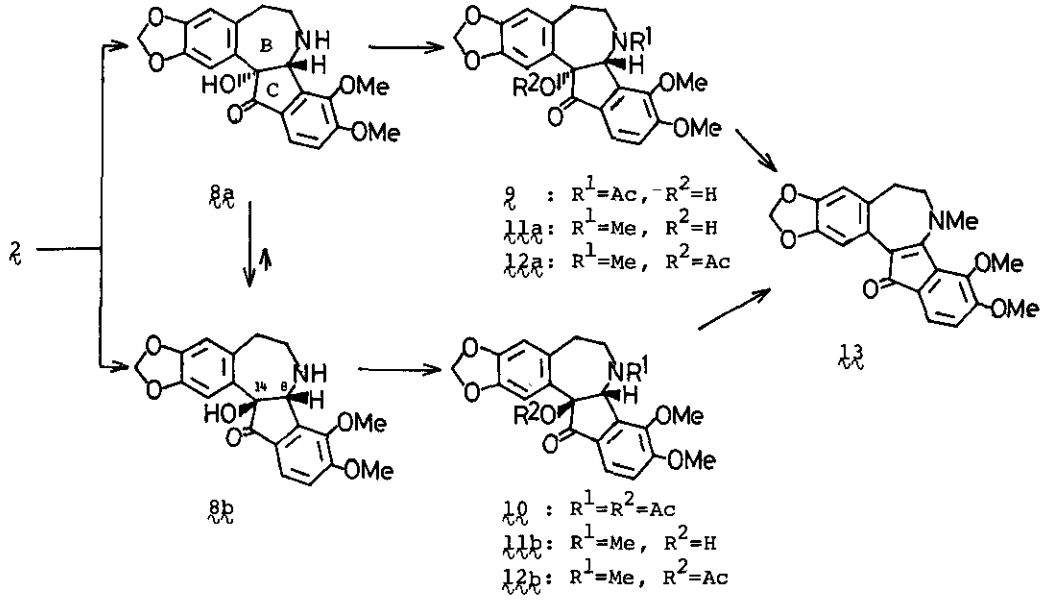
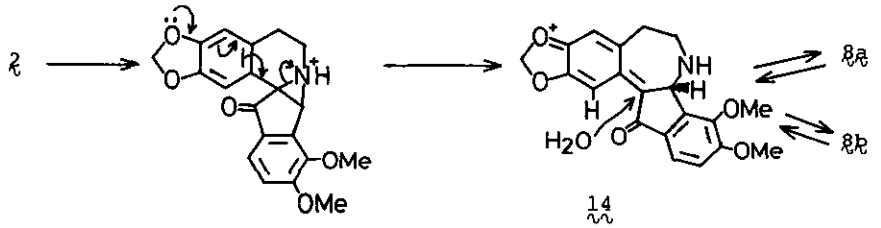


Table. Regioselective C_{14}-N bond cleavage of the cycloberbine (2) to the benzindanoazepines (8a and 8b).

Reaction Condition			Yield (%) of 8a	Yield (%) of 8b
10% HCl	70°C	1 hr	18	61
10% HCl	70°C	3 hr	12	66
10% H_2SO_4	r.t.	30 min	44	30
10% H_2SO_4	70°C	3 hr	19	71
35% HCl	r.t.	5 min	21	60
20% $HClO_4$/THF	reflux	44 hr	30	51

also achieved under various acidic conditions and the results were summarized in Table. And the benzindanoazepines (8a and 8b) isomerized to each other under acidic conditions; product ratio of 8a/8b (reaction condition): *from* 8a; 7/10 (10% HCl, r.t., 14 hr), *from* 8b; 1/32 (10% HCl, r.t., 14 hr), 1/10 (10% HCl, 70°C, 3 hr), 1/5 (20% $HClO_4$/THF, reflux, 48 hr).

The above results suggest that 8a and 8b are the kinetically controlled product and the thermodynamically controlled product, respectively, and there exists an equilibrium between them. The formation and equilibrium reaction would proceed *via* the intermediate (14),[7] to which water attacked preferentially from α-side to avoid the steric hindrance caused by H-1 and H-8 under kinetically controlled conditions.

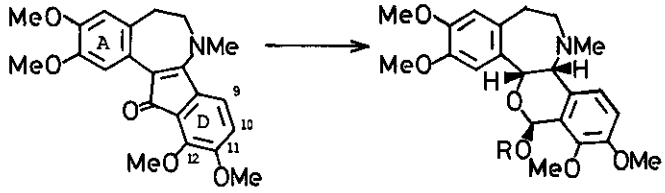


14

On treatment with acetic anhydride in pyridine at 75°C for 4 hr, 8a furnished the *N*-acetyl derivative [9, 78%, *m/e* 411 (M^+), ν 3300, 1710, 1630, δ 7.69 (1H, d, *J*= 8.5), 7.38 (1H, s), 7.02 (1H, d, *J*=8.5), 6.69 (1H, s), 5.92 (2H, s), 4.81 (1H, s), 3.93 (3H, s), 3.79 (3H, s), 2.29 (3H, s)], whereas 8b yielded the *N*,*O*-diacetyl derivative [10, 66%, *m/e* 453 (M^+), ν 1735, 1720, 1640, δ 7.60 (1H, d, *J*=8.5), 7.39 (1H, s), 7.10 (1H, s), 7.07 (1H, d, *J*=8.5), 6.35 (1H, s), 5.97, 5.92 (2H, AB-q, *J*= 1.5), 3.99 (3H, s), 3.82 (3H, s), 2.24 (3H, s), 2.09 (3H, s)]. Methylation of 8a and 8b with methyl iodide in tetrahydrofuran produced the *N*-methyl derivatives, 11a [97%, mp 157.5-158.5° (lit[4] mp 182-183°), *m/e* 383 (M^+), ν 3300, 1710, δ 7.52 (1H, d, *J*=8), 7.00 (1H, s), 6.93 (1H, d, *J*=8), 6.49 (1H, s), 5.73 (2H, s), 4.33 (1H, s,

H-8), 3.88 (3H, s), 3.77 (3H, s), 2.74 (3H, s)] and 11b [90%, mp 187-189° (lit[4] mp 192-193°), *m/e* 383 (M^+), ν 3300, 1700, δ 7.58 (1H, d, *J*=8.5), 7.21 (1H, s), 6.96 (1H, d, *J*=8.5), 6.48 (1H, s), 5.87 (2H, s), 4.48 (1H, s, H-8), 3.96 (3H, s), 3.90 (3H, s), 2.56 (3H, s)], respectively, which have been converted to the rhoeadine skeleton (7).[4] These products (11a and 11b) also isomerized to each other under acidic conditions and an equilibrium between them lies appreciably to 11b.[8] Acetylation of 11a and 11b with acetic anhydride in pyridine at 70°C gave the *O*-acetyl derivatives, 12a [mp 192-194° (lit.[4] mp 186-187°), *m/e* 425 (M^+), ν 1750, 1700, δ7.67 (1H, d, *J*=8.5), 7.59 (1H, s), 7.05 (1H, d, *J*=8.5), 6.64 (1H, s), 5.92, 5.91 (2H, AB-q, *J*=1.5), 4.91 (1H, s), 3.96 (3H, s), 3.84 (3H, s), 2.83 (3H, s), 2.00 (3H, s)] and 12b [mp 172-174° (lit[4] mp 178-181°), *m/e* 425 (M^+), ν 1735, 1710, δ 7.60 (1H, d, *J*=8.5), 7.32 (1H, s), 7.04 (1H, d, *J*=8.5), 6.48 (1H, s), 5.94, 5.90 (2H, AB-q, *J*=1.5), 4.98 (1H, s), 3.99 (3H, s), 3.94 (3H, s), 2.77 (3H, s), 2.21 (3H, s)], respectively.

On treatment with titanium tetrachloride in refluxing methylene chloride both 11a and 11b gave the unsaturated benzindanoazepine (13)[9] [mp 185-186° (lit.[9] mp 185-187°), *m/e* 365 (M^+), ν 1660, δ 7.64 (1H, s), 7.16 (1H, d, *J*=8), 6.69 (1H, d, *J*=8), 6.47 (1H, s), 5.83 (2H, s), 3.85 (3H, s), 3.76 (3H, s), 3.13 (3H, s)] in 30 and 42% yield, respectively. The product has the same structure except the substituents on ring A and D as that of the key intermediate (15), which has already been led to (±)-*cis*-alpinine (16) and (±)-*cis*-alpinigenene (17).[10]



15

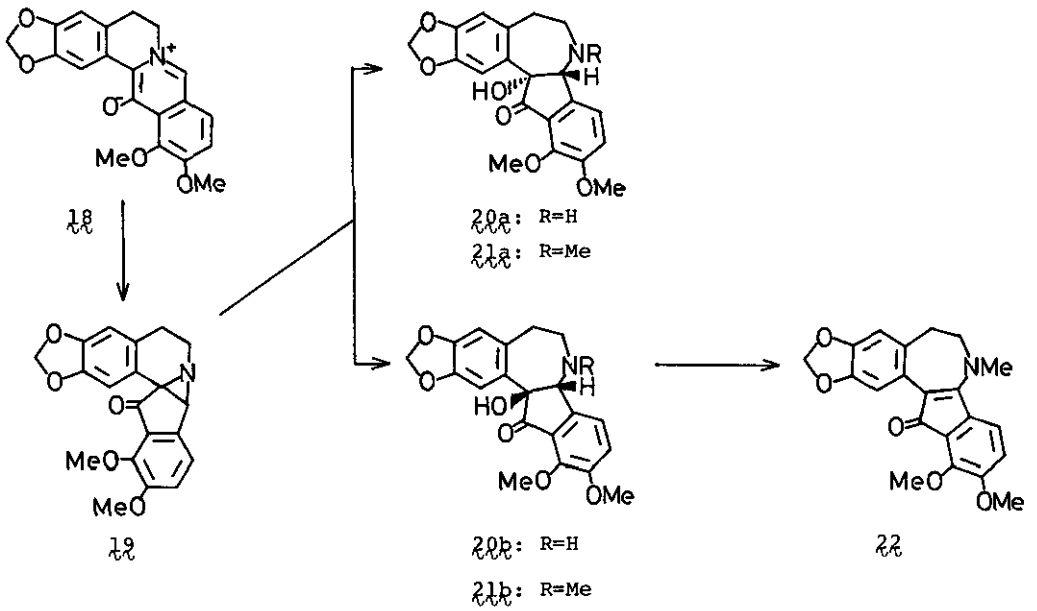
16: R=Me

17: R=H

In order to convert protoberberine alkaloids into natural rhoeadine alkaloids according to the above method, it is necessary to change the substitution pattern on ring D in protoberberines from 9,10- to 11,12-substitution. In previous paper,[11] we developed efficient methods for conversion of naturally occurring 9,10-oxygenated protoberberines into non-natural 11,12-oxygenated protoberberines *via* ring D inversion, and berberine has been transformed into the 11,12-oxygenated betaine (18).[11]

Irradiation (100W high-pressure Hg lamp, with Pyrex filter) of 18 in methanol

afforded the 8,14-cycloberbine [19, 82%, mp 187.5-188.5°, *m/e* 351 (M^+), ν 1700, δ 7.23 (1H, s), 7.00 (2H, s), 6.55 (1H, s), 5.86 (2H, s), 4.00 (3H, s), 3.82 (3H, s), 3.70 (1H, s)], which was treated with 10% hydrochloric acid at 70°C for 3 hr to yield the benzindanoazepines, 20a and 20b (1: 11),[12] as an inseparable mixture. The mixture was methylated with dimethyl sulfate in tetrahydrofuran in the presence of 10% sodium hydroxide to give the *N*-methyl derivative [21b, overall 46%, mp 191-192°, *m/e* 383 (M^+), ν 3300, 1705, δ 7.33-7.24 (3H), 6.57 (1H, s), 5.95, 5.93 (2H, AB-q, *J*=1.5), 4.40 (1H, s), 4.01 (3H, s), 3.93 (3H, s), 2.54 (3H, s)], and 20a [overall 7%, *m/e* 369 (M^+), ν 3300, 1705, δ 7.41 (1H, s), 7.27-7.25 (2H), 6.65 (1H, s), 5.93 (2H, s), 4.30 (1H, s), 4.08 (3H, s), 3.90 (3H, s)], which was difficult to be methylated to 21a under this condition. The pure indanoazepine (20b) [mp 205-207°, *m/e* 369 (M^+), ν 3300, 1705, δ 7.38, 7.27 (2H, AB-q, *J*=8.5), 6.70 (1H, s), 6.68 (1H, s), 5.90, 5.87 (2H, AB-q, *J*=1.5), 4.20 (1H, s), 4.11 (3H, s), 3.89 (3H, s)] was obtained by isomerization of 20a or the above mixture with 10% hydrochloric acid at 70°C for 3 hr and subsequent recrystallization. Treatment of 21b with boron trifluoride etherate effected dehydration to produce the unsaturated benzindanoazepine (22)[9] [25%, mp 189-190° (lit.[9] 188-189°), *m/e* 365 (M^+), ν 1660, δ 7.60 (1H, s), 7.06, 6.66 (2H, AB-q, *J*=8), 6.53 (1H, s), 5.90 (2H, s), 4.03 (3H, s), 3.88 (3H, s), 3.40 (3H, s)], which has the same substitution pattern on ring D in its molecule as that in 15.



Thus, we developed a novel convenient synthesis of benzindanoazepines, the key compounds for rhoeadines, from berberine *via* regioselective C_{14}-N bond cleavage of the 8,14-cycloberbines. The present simple conversion coupled with ring D inversion method[11] will provide a new convenient route for synthesis of rhoeadine alkaloids from protoberberine alkaloids. The application of this method to transformation of palmatine into alpinigenine is now in progress.

Acknowledgement: The authors are grateful for a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture of Japan.

REFERENCES AND FOOTNOTES

1. M. Hanaoka, S. Yasuda, K. Nagami, K. Okajima, and T. Imanishi, *Tetrahedron Lett.*, 1979, 3749.
2. T. Takemoto and Y. Kondo, *Yakugaku Zasshi*, 1962, 82, 1413.
3. M. Hanaoka, S. Yasuda, Y. Hirai, K. Nagami, and T. Imanishi, *Heterocycles*, 1980, 14, 1455.
4. N. Murugesan, G. Blaskó, R.D. Minard, and M. Shamma, *Tetrahedron Lett.*, 1981, 22, 3131.
5. The numbering of benzindanoazepines in this report is in accord with that for protoberberines and spirobenzylisoquinolines.
6. The H-8 signals of *trans*- and *cis*-5,6,7,8,13,14-hexahydro-7-methyl-2,3-methylenedioxybenz[*d*]indeno[1,2-*b*]azepine appeared at 4.38 and 4.77 ppm, respectively: T. Kametani, S. Hirata, S. Hibino, H. Nemoto, M. Ihara, and K. Fukumoto, *Heterocycles*, 1975, 3, 151.
7. Similar intermediate, *N*-methyl derivative of 14, was proposed for isomerization of 11a to 11b.[4]
8. Although 11a was reported to isomerize irreversibly to 11b,[4] we found that the isomerization is reversible in the following conditions; product ratio of 11a/11b (reaction condition): *from 11a*; 1/1 (10% HCl, 70°C, 3 hr), *from 11b*; 1/20 (10% HCl, 70°C, 3 hr), 1/35 (20% $HClO_4$/THF, reflux, 37 hr).
9. This compound has been obtained from a phthalideisoquinoline alkaloid, β-hydrastine: H.L. Holland, M. Curcumelli-Rodostamo, and D.B. MacLean, *Can. J. Chem.*, 1976, 54, 1472.
10. K. Orito, R.H. Manske, and R. Rodrigo, *J. Am. Chem. Soc.*, 1974, 96, 1944.
11. M. Hanaoka, M. Inoue, M. Takahashi, and S. Yasuda, *Heterocycles*, in press.
12. Other acidic treatment of 19 gave a mixture of 20a and 20b in the ratio of 1:3 (10% HCl, r.t., 30 min) or 1:5 (20% $HClO_4$/THF, reflux, 37 hr).

Received, 5th October, 1981