

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

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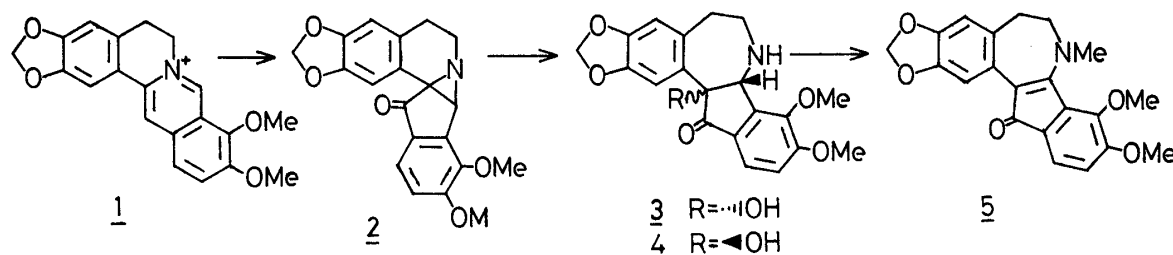
Acidic treatment of the 8,14-cycloberbine (2), derived from berberine (1), in methanol afforded the *cis*- and *trans*-benzindanoazepines (7 and 8), whereas the reaction of 2 with *p*-toluenesulfonic acid in benzene yielded the benzindenoazepine (6) in an excellent yield. This simple conversion method 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

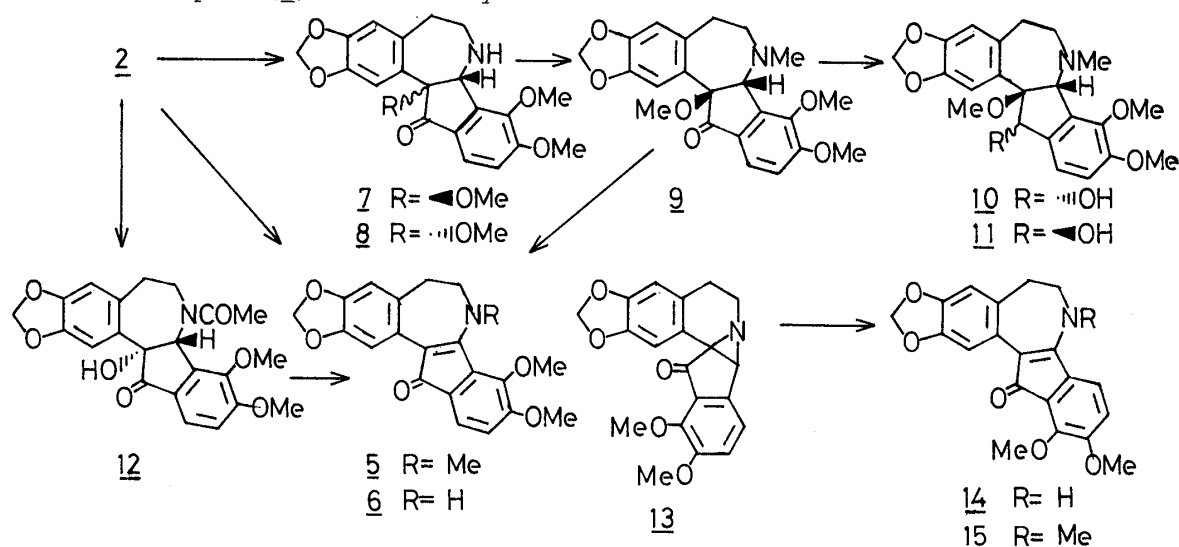
The benzindenoazepine skeleton has been shown to be the key intermediate in the total synthesis of rhoeadine alkaloids^{1,2)} and some alkaloids possessing this skeleton have recently been found.³⁾ In a previous paper,⁴⁾ we reported a convenient one-step conversion of the 8,14-cycloberbine (2),⁵⁾ derived 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 communication⁶⁾ 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*-alpinine 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

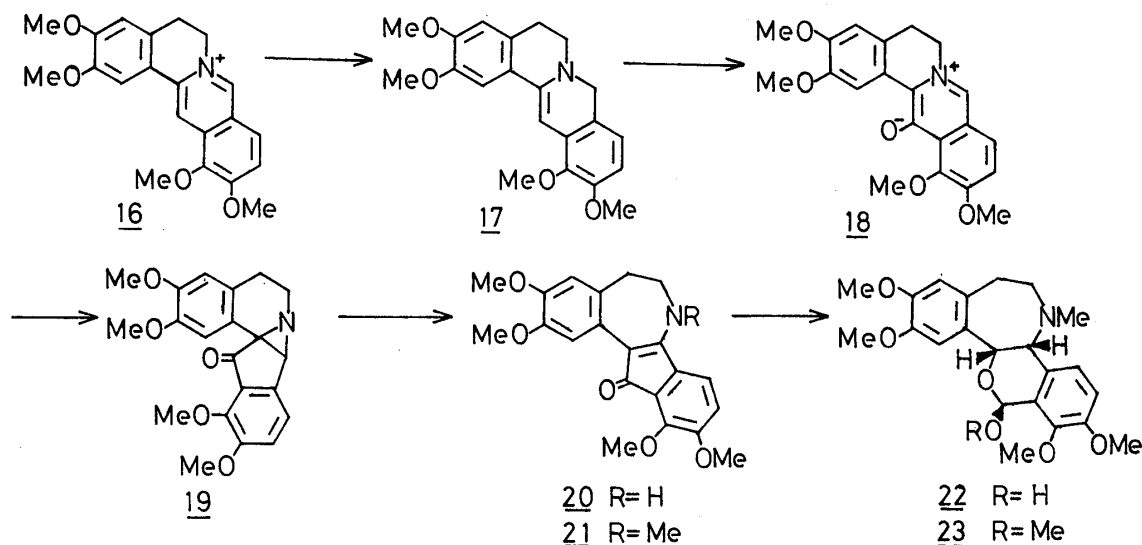


in 81 and 92% yield by similar treatment with 35% hydrochloric acid and conc. sulfuric acid, respectively, as acidic catalysts. The reaction of **2** with hydrogen chloride in methanol for 1 h yielded **7** (70%) and its *trans* isomer (**8**)⁶⁾ [23%, m/e 383(M^+), ν 3350, 1700, δ 7.62, 6.99 (2H, AB-q, $J=8.5$), 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 dihydropprotoberberine (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.

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- 8) Independently 6 was obtained in 77% yield by treatment of 2 with iodine.⁶⁾
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- 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)