A Novel and Efficient Synthesis of 13-Methylprotoberberine Alkaloids

Miyoji Hanaoka,* Shuji Yoshida, and Chisato Mukai

Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan

13-Methylberberine (**6a**), dehydrocorydaline (**6b**), and corysamine (**6c**), and their tetrahydro derivatives (**9a**—**c**) were efficiently synthesised from the corresponding protoberberines (**1**) through photochemical electrocyclic reaction of 13-methylene-8,14-cycloberbines (**3**).

Introduction of an alkyl group at the C-13 position of protoberberines (**1**) has so far been accomplished by the reaction[1] of 8-acetonyl-7,8-dihydro derivatives of (**1**) with alkyl halides, though yields are not always satisfactory. On the other hand, treatment of 7,8-dihydroprotoberberines with formaldehyde[2] has been found to furnish 13-methylprotoberberines (**6**), however, this method cannot be applied to ethylation with acetaldehyde.[2a] We describe herein a novel and efficient transformation of protoberberines (**1**) into 13-alkylprotoberberines (**6**)—(**8**) through the Wittig reaction of the 8,14-cycloberbin-13-ones (**2**),† followed by photochemical electrocyclic reaction.

The Wittig reaction of (**2a**),[3] (**2b**),[4] (**2c**),[5] derived from (**1a**—**c**), with methylidenetriphenylphosphorane in refluxing dry tetrahydrofuran produced the 13-methylene-8,14-cycloberbines (**3a**) [95%; m.p. 175—176 °C; ^{1}H n.m.r. δ 5.77, 5.16 (each 1H, each s)], (**3b**) [97%; m.p. 164—165 °C; ^{1}H n.m.r. δ 5.78, 5.21 (each 1H, each s)], and (**3c**) [94%; m.p. 173—174 °C; ^{1}H n.m.r. δ 5.76, 5.15 (each 1H, each s)], respectively. Similar treatment of (**2a**) with ethylidenetriphenylphosphorane or triphenylpropylidenephosphorane afforded 13-(*Z*)-ethylidene-8,14-cycloberbine (**4a**) [96%; m.p. 181—182 °C; ^{1}H n.m.r. δ 6.19 (1H, q, *J* 7.5 Hz), 1.58 (3H, d, *J* 7.5 Hz)] or 13-(*Z*)-propylidene-8,14-cycloberbine (**5a**) [92%; m.p. 175—176 °C; ^{1}H n.m.r. δ 6.08 (1H, t, *J* 7.5 Hz), 1.95 (2H, quin, *J* 7.5 Hz), 0.94 (3H, t, *J* 7.5 Hz)] as a single stereoisomer,‡ respectively.

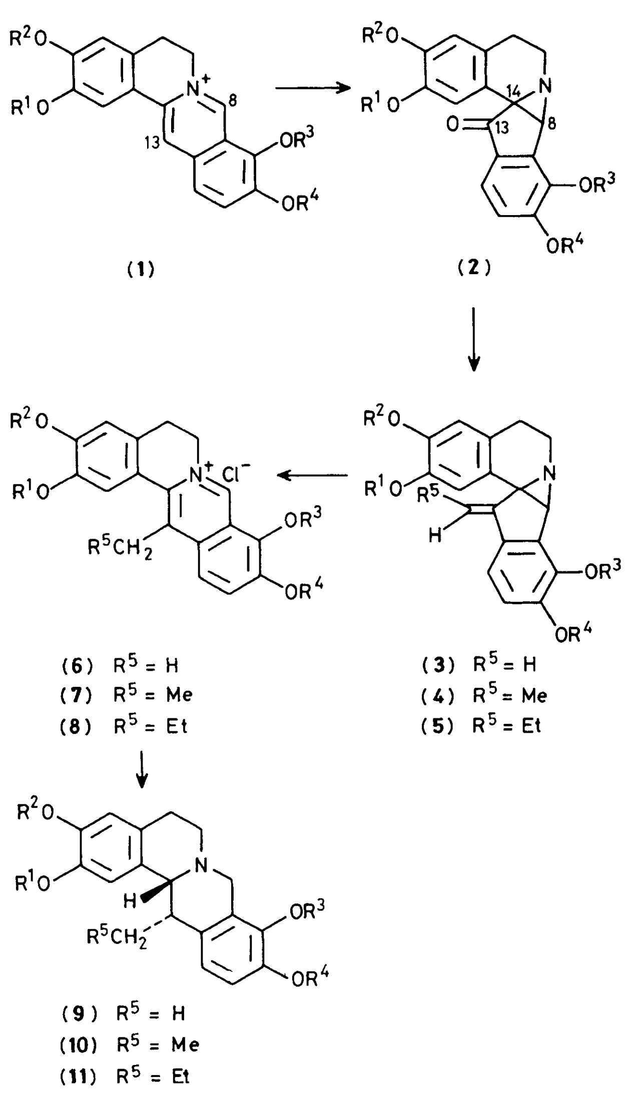
On irradiation with a high-pressure mercury lamp through a Pyrex filter in a stream of nitrogen at −20 °C in aqueous EtOH, the methylene cycloberbines (**3**) underwent photochemically induced electrocyclic reaction§ to yield 13-methylberberine (**6a**) (80%; m.p. 187—189 °C), dehydrocorydaline (**6b**) (85%; m.p. 162—163 °C), and corysamine (**6c**) (86%; m.p. 210—211 °C), respectively, after treatment with HCl. 13-Methylprotoberberines (**6**), thus obtained, were identical with the authentic specimens. Reduction of (**6**) with

---

† The 8,14-cycloberbines (**2**) have been shown to be versatile intermediates for spirobenzylisoquinolines and benzindenoazepines, ref. 10.

‡ The (*Z*)-configuration of (**4a**) and (**5a**) was determined by appearance of the vinylic protons at rather lower field in their ^{1}H n.m.r. spectra.

§ No change occurs with (**3**) in the absence of light. In fact, heating of (**3a**) in EtOH(aq.) under reflux did not afford (**6a**).



a; $R^1R^2 = CH_2$, $R^3 = R^4 = Me$
b; $R^1 = R^2 = R^3 = R^4 = Me$
c; $R^1R^2 = R^3R^4 = CH_2$

$NaBH_4$ in refluxing EtOH[6] gave (±)-thalictricavine (**9a**) [95%; m.p. 209—210 °C (lit.[7] m.p. 204—206 °C)], (±)-corydaline (**9b**) [97%; m.p. 135—136 °C (lit.[8] m.p. 133—134 °C)], and (±)-tetrahydrocorysamine (**9c**) [94%; m.p. 207—209 °C (lit.[9] m.p. 210—211 °C)]. In the same manner, (**4a**) and (**5a**) were also transformed into 13-ethylberberine (**7a**)[1d,e] [42%; m.p. 235—240 °C (decomp.)] and 13-propylberberine (**8a**)[1d,e] (86%; m.p. 215—217 °C), both of which were subsequently reduced with $NaBH_4$ to provide the tetrahydro derivatives (**10a**) [85%; m.p. 135—136 °C (lit.[1d] m.p. 135—136 °C); ^1H n.m.r. δ 3.69 (1H, br s), 0.80 (3H, t, *J* 7.5 Hz)] and (**11a**)[1d,e] [82%; ^1H n.m.r. δ 3.67 (1H, br s), 0.74 (3H, t, *J* 6 Hz)], respectively.

Thus we have developed a novel and convenient method for the preparation of 13-alkylprotoberberines and this procedure provides a general method for a synthesis of 13-methylprotoberberine alkaloids.

We are very grateful to Dr. S. Naruto, Dainippon Pharmaceutical Co. Ltd., for a generous supply of dehydrocorydaline.

Received, 29th May 1985; Com. 745

References

1 (a) F. V. Bruchhausen, *Arch. Pharm.*, 1923, **261**, 28; (b) C. Tani, N. Takao, and S. Takao, *Yakugaku Zasshi*, 1962, **82**, 748; (c) C. Tani, N. Takao, S. Takao, and K. Tagahara, *ibid.*, 1962, **82**, 751; (d) T. Takemoto and Y. Kondo, *ibid.*, 1962, **82**, 1408; (e) S. Naruto and H. Kaneko, *ibid.*, 1972, **92**, 1017.

2 (a) H. W. Bersch, *Arch. Pharm.*, 1950, **283**, 192; (b) Z. Kiparissides, R. H. Fichtner, J. Poplawski, B. C. Nalliah, and D. B. MacLean, *Can. J. Chem.*, 1980, **58**, 2770.

3 M. Hanaoka, C. Mukai, K. Nagami, K. Okajima, and S. Yasuda, *Chem. Pharm. Bull.*, 1984, **32**, 2230.

4 M. Hanaoka, K. Nagami, Y.Hirai, S. Sakurai, and S. Yasuda, *Chem. Pharm. Bull.*, 1985, **33**, 2273.

5 M. Hanaoka, S. Sakurai, T. Ohshima, S. Yasuda, and C. Mukai, *Chem. Pharm. Bull.*, 1982, **30**, 3446.

6 P. W. Jeffs, 'The Alkaloids,' Vol. 9, ed. R. H. F. Manske, Academic Press, New York, 1967, p.41.

7 M. Cushman and F. W. Dekow, *J. Org. Chem.*, 1979, **44**, 407.

8 M. Cushman and F. W. Dekow, *Tetrahedron*, 1978, **34**, 1435.

9 H. Kaneko, S. Naruto, and N. Ikeda, *Yakugaku Zasshi*, 1968, **88**, 235.

10 M. Hanaoka, S. K. Kim, M. Inoue, K. Nagami, Y. Shimada, and S. Yasuda, *Chem. Pharm. Bull.*, 1985, **33**, 1434 and references cited therein.