Tetrahedron Letters No. 39, pp 3749 - 3752.
©Pergamon Press Ltd. 1979. Printed in Great Britain.

0040-4039/79/0922-3749$02.00/0

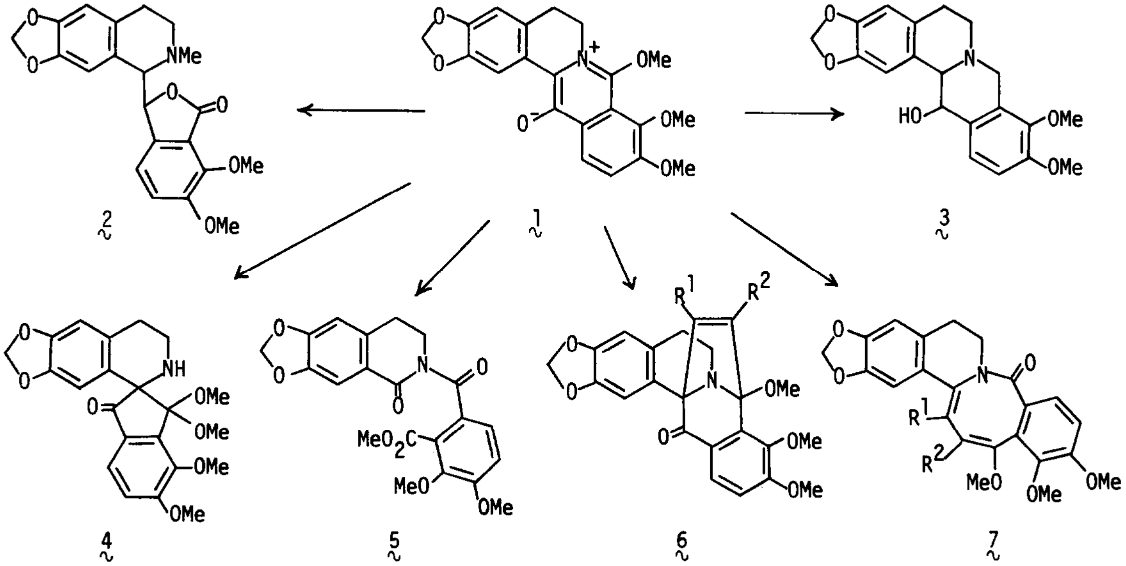
PHOTOCHEMICAL VALENCE TAUTOMERIZATION OF BERBERINEPHENOLBETAINES TO 8,14-CYCLOBERBINES, VERSATILE AZIRIDINE DERIVATIVES FOR SPIROBENZYLISOQUINOLINES

Miyoji Hanaoka,* Shingo Yasuda, Kazuyoshi Nagami, Keiko Okajima,
and Takeshi Imanishi

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

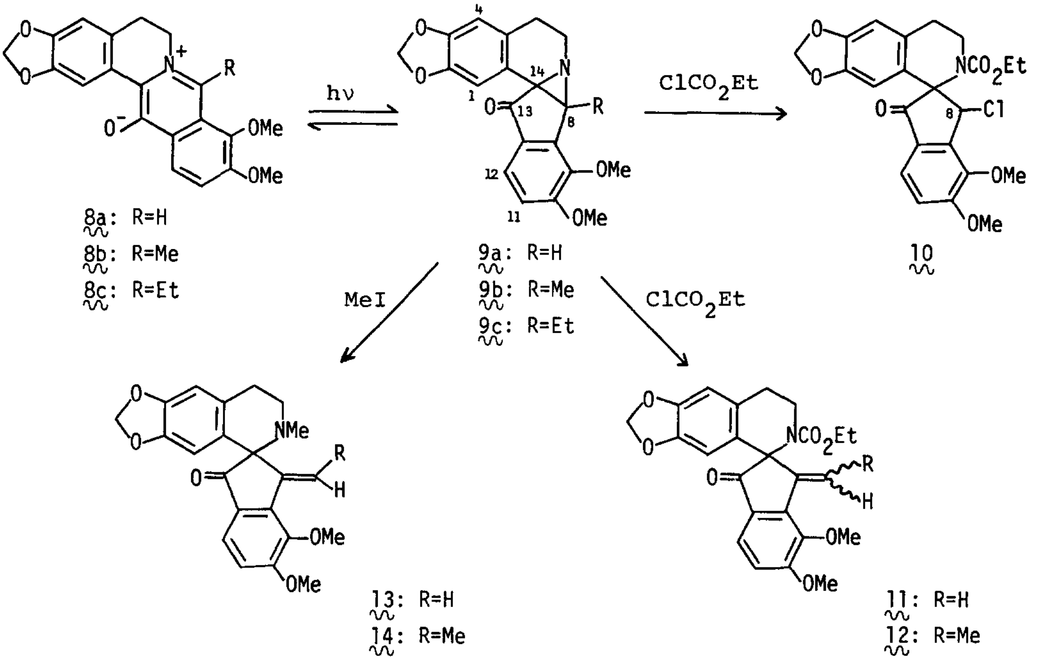
Summary: Irradiation of the berberinephenolbetaines (8a, 8b, and 8c) effected valence tautomerization to give the 8,14-cycloberbines (9a, 9b, and 9c), the aziridine derivatives, in high yield. The 8,14-cycloberbines were efficiently converted to the spirobenzylisoquinolines by regioselective C-N bond cleavage.

8-Methoxyberberinephenolbetaine (1),[1,2] derived from berberine, has been demonstrated to furnish a variety of ring systems such as the phthalideisoquinoline (2),[1] the 13-oxyberbine (3),[2] the spirobenzylisoquinoline (4),[3] methyl isoanhydroberberilate (5),[3,4] the 8,14-ethenoberbine (6),[5] and the 8*H*-isoquino[2,1-*b*][2]benzazocine (7).[5] This communication deals with a further trans-



formation of the berberinephenolbetaines (8) into the aziridine derivatives, 8,14-cycloberbines (9) by photochemical valence tautomerization and a synthesis of spirobenzylisoquinolines from 9 by regioselective bond cleavage.

Irradiation (100W high-pressure Hg lump, with Pyrex filter) of the betaine (8a)(6) in methanol in a stream of nitrogen for 50 min afforded 2,3-methylenedioxy-9,10-dimethoxy-13-oxo-8,14-cycloberbine (9a)[mp 182-183°, *m/e*: 351 (M^+), ν(7) 1715 cm^{-1}, δ(7) 7.56 (1H, d, J=8.5, H-12), 7.31 (1H, s, H-1), 6.91 (1H, d, J=8.5, H-11), 6.64 (1H, s, H-4), 5.92 (2H, s, OCH_2O), 4.00 (1H, s, H-8), 3.97, 3.93 (each 3H, s, OCH_3)] in 70% yield. The presence of the aziridine ring in 9a was further confirmed from its ^{13}C-nuclear magnetic resonance spectrum [δ 49.55 (s, C-14), 40.98 (d, C-8)]. Analogous irradiation of 8-methyl- and 8-ethylberberinephenolbetaine (8b and 8c)(8) for 30 min and 1 hr gave the 8-methyl-8,14-cycloberbine (9b)[85%, mp 176-178°, *m/e*: 365 (M^+), ν 1710 cm^{-1}, δ 1.65 (3H, s, $C\text{-}CH_3$)] and the 8-ethyl-8,14-cycloberbine (9c)[77%, mp 179-181°, *m/e*: 379 (M^+), ν 1705 cm^{-1}, δ 1.47 (2H, q, J=7, $C\underline{H}_2CH_3$), 1.00 (3H, t, J=7, $CH_2C\underline{H}_3$)], respectively. The present ready photochemical valence tautomerization was remarkable especially in the high yield in comparison with the tautomerization of 3-oxido-1-phenylpyridinium to the corresponding aziridine (6% yield).(9)

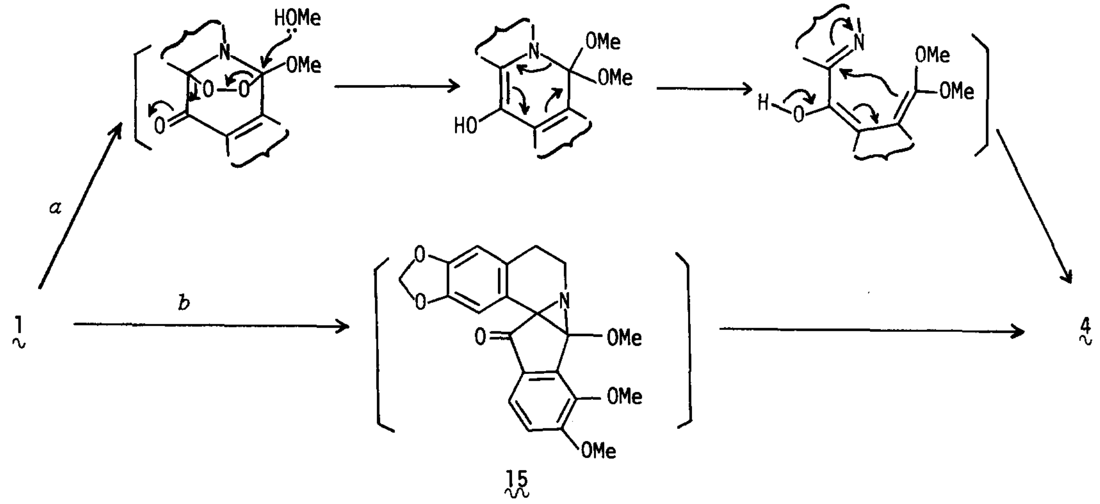


On the other hand, irradiation of the aziridine (9a) in methanol with 400W high-pressure Hg lump in a stream of nitrogen for 20 min produced the starting betaine (8a) in 55% yield. The existence of a photoequilibrium between the betaines (**8**) and the aziridines (**9**) was confirmed. Similar photoequilibrium has been reported on isoquinolinium betaine,[10)] isoquinolinium imide,[11)] and pyrylium oxide.[12)]

8,14-Cycloberbines would be expected to afford spirobenzylisoquinoline or benzazepine ring system *via* regioselective C-N bond cleavage of the aziridine ring.

Heating of **9a** in benzene with ethyl chloroformate provided regioselectively the amorphous spirobenzylisoquinoline (**10**)[*m/e*: 459, 461 (M^+, 3:1), ν 1720, 1673 cm^{-1}, δ 7.53 (1H, d, *J*=8.5, H-12), 7.03 (1H, d, *J*=8.5, H-11), 6.55 (1H, s, H-4), 6.06 (1H, s, H-1), 5.87 (1H, s, H-8), 5.78 (2H, AB-q, *J*=1.5, OCH_2O), 3.94, 3.91 (each 3H, s, OCH_3)] in 70% yield. On similar treatment with ethyl chloroformate, the aziridines (**9b** and **9c**) afforded the methylidene- and ethylidene-spiro compounds (**11** and **12**[13)]) in almost quantitative yields. Treatment of **9b** and **9c** in acetone with methyl iodide at room temperature effected both *N*-methylation and the Hofmann elimination resulting in the methylidene-spirobenzylisoquinoline (**13**) [mp 166-168°, *m/e*: 379 (M^+), ν 1705, 1640 cm^{-1}, δ 6.45, 5.56 (each 1H, s, $C=CH_2$), 2.28 (3H, s, NCH_3)] and the ethylidene derivative (**14**)[mp 167-169°, *m/e*: 393 (M^+), ν 1695 cm^{-1}, δ 7.00 (1H, q, *J*=7.5, C=CH), 2.24 (3H, s, NCH_3), 1.67 (3H, d, *J*=7.5, $C=CCH_3$)] in 72% and 66% yield, respectively.

Previously we reported a novel conversion of **1** into the spirobenzylisoquinoline (**4**, 40%) by photo-oxygenation and proposed its possible reaction mechanism as the route *a* shown below.[3)] The above ready tautomerization of betaines (**8**) strongly suggest the alternative mechanism (the route *b*) *via* the aziridine (**15**). The betaine (**1**) in methanol was irradiated for 20 min under the analogous condition described for **9a** from **8a** to afford the spiro compound (**4**) in 65% yield,



which was identified with the authentic specimen3) in all respects. The mechanism (the route *b*) was thus supported even though the aziridine (15) could not be isolated.14)

The present ready photochemical valence tautomerization of the berberine-phenolbetaines (8) to the 8,14-cycloberbines (9), followed by regioselective C_8-N bond cleavage, provides a novel and convenient method for the synthesis of the spirobenzylisoquinoline alkaloids. Transformation of 8,14-cycloberbines into benzazepine derivatives by selective C_{14}-N bond cleavage is now in progress

REFERENCES AND FOOTNOTES

1) J.L. Moniot and M. Shamma, *J. Am. Chem. Soc.*, 98, 6714 (1976).
2) M. Hanaoka, C. Mukai, and Y. Arata, *Heterocycles*, 6, 895 (1977).
3) M. Hanaoka and C. Mukai, *ibid.*, 6, 1981 (1977).
4) J.L. Moniot, A. Rahman H.A. Rahman, and M. Shamma, *Tetrahedron Letters*, 3787 (1977).
5) M. Hanaoka, A. Wada, S. Yasuda, C. Mukai, and T. Imanishi, *Heterocycles*, 12, 511 (1979).
6) T. Takemoto and Y. Kondo, *Yakugaku Zasshi*, 82, 1413 (1962).

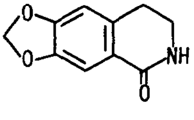
7) All infrared and nuclear magnetic resonance spectra were measured in chloroform and deuterochloroform, respectively.

8) Synthesis of the betaines (8b and 8c) will be published elsewhere.

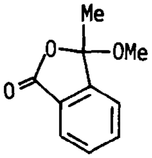
9) N. Dennis, A.R. Katritzky, and H. Wilde, *J. Chem. Soc. Perkin I*, 2338 (1976).
10) P.E. Hansen and K. Undheim, *ibid.*, 305 (1975).
11) J.W. Lown and K. Matsumoto, *J. Org. Chem.*, 36, 1405 (1971).
12) E.F. Ullman, *J. Am. Chem. Soc.*, 85, 3529 (1963).

13) This is an inseparable mixture of two geometric isomers at an ethylidene moiety.

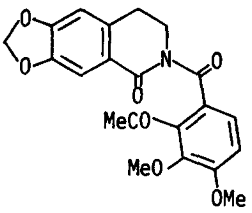
14) Irradiation of 8b in a stream of oxygen afforded the aziridine (9b, 23%) in addition to the oxygenated products, i (21%), ii (21%), iii (22%), and iv (30%).



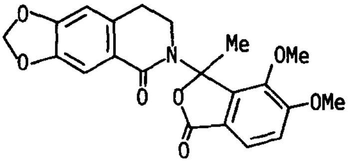
i



ii



iii



iv

(Received in Japan 21 June 1979)