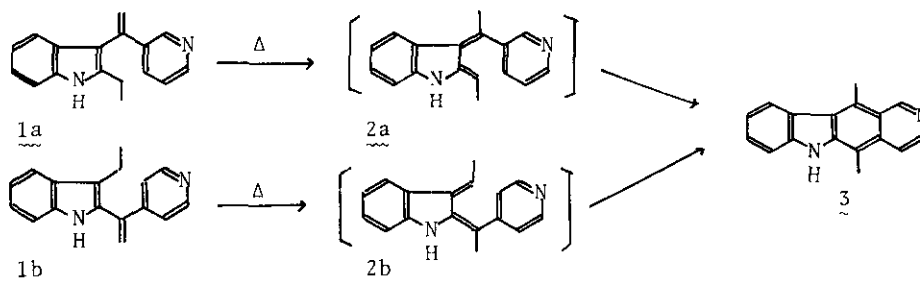


A NEW SYNTHESIS OF ELLIPTICINE AND OLIVACINE THROUGH  
PYRIDINE-3,4-QUINODIMETHANE INTERMEDIATES

Shinzo Kano\*, Eiichi Sugino, and Satoshi Hibino  
Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji,  
Tokyo 192-03, Japan

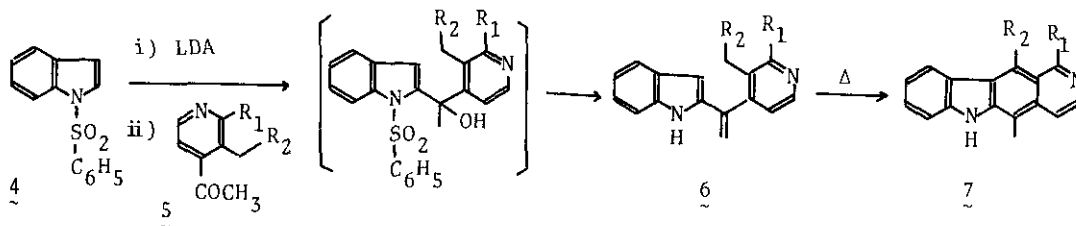
**Abstract** — Thermolysis of 2-[3-methyl- $\alpha$ -(4-pyridyl)vinyl]indole (6a) at 500°C for 3 min gave 11-demethylellipticine (7a). The similar reaction by using 2-[2,3-dimethyl- $\alpha$ -(4-pyridyl)vinyl]indole (6b) afforded olivacine (7b). Ellipticine and 11-demethylellipticine were obtained by thermolysis of 2-[3-ethyl- $\alpha$ -(4-pyridyl)vinyl]indole (6c)

Cyclization of the pyridyl indole-2,3-quinodimethane intermediate (2a)<sup>1</sup> and its isomer (2b)<sup>2</sup>, generated by thermal reaction of the corresponding 2-[ $\alpha$ -(pyridyl)-vinyl]indoles (1a) and (1b), provided the effective method yielding the significant antitumor carbazole alkaloid, ellipticine (3)<sup>1-4</sup>.



Our interest in the use of reactive heterocyclic *o*-quinodimethane intermediates for the synthesis of biologically active heterocyclic compounds led us to investigate the synthetic utility of pyridine analogue of *o*-quinodimethane intermediates. We now examined a new and facile synthesis of ellipticine and olivacine through intramolecular cyclization of pyridine-3,4-quinodimethane intermediates<sup>5</sup> formed *in situ* by thermolysis of 2-[3-alkyl- $\alpha$ -(4-pyridyl)vinyl]indoles. Condensation of 2-lithio-1-benzenesulfonylindole<sup>6</sup> (4, LDA, THF, 0°C, 1 h) with 3-methyl-4-acetylpyridine (5a)<sup>7</sup>, 2,3-dimethyl-4-acetylpyridine (5b)<sup>7</sup> and 3-ethyl-4-acetylpyridine (5c)<sup>7,8</sup>

(-78°C-room temperature, 14 h) afforded the corresponding 2-vinylindoles (6a<sup>9</sup>: 34.8 % yield), (6b<sup>9</sup>: 14.3 % yield) and (6c<sup>9</sup>: 24.3 % yield), respectively.



a:  $R_1=R_2=H$ ; b:  $R_1=CH_3$ ,  $R_2=H$ ; c:  $R_1=H$ ,  $R_2=CH_3$

The compound (6a) was heated at 490-500°C for 3 min to give 11-demethylellicine (7a<sup>2</sup>: 57.2 % yield<sup>10</sup>) in addition to the starting material (6a: 10 % yield). In a similar fashion, thermolysis of 6b (470-480°C, 3 min) yielded olivacine (7b<sup>11</sup>: 57.4 % yield<sup>10</sup>) and 6b (1.2 % yield). Olivacine, thus obtained, was identified with the authentic sample by comparison with the spectral data donated from Professor Ichiya Ninomiya. Thermal reaction of 6c (450-460°C, 3 min) resulted in the formation of ellipticine (3: 30.1 % yield<sup>10</sup>) and (7a: 43.0 % yield) accompanied by the recovery of 11.9 % of 6c. The formation of 7a would be caused by elimination of methyl group as methane by radical chain reaction on aromatization of the cyclization intermediate.

The thermolysis presented in this paper should be effective for the synthesis of olivacine.

Acknowledgement We are grateful to Professor Ichiya Ninomiya, Kobe Women's College of Pharmacy, for donating spectral data of synthetic sample of olivacine.

#### References and Note

1. J. Bergman and R. Carlsson Tetrahedron Lett., 4663 (1977).
2. S. Kano, E. Sugino, S. Shibuya, and S. Hibino, J. Org. Chem., 46, 2979 (1981).
3. For Reviews: (a) M. Sainsbury, Synthesis, 437 (1977); (b) R. Barone and M. Chanone, Heterocycles, 16, 1357 (1981), and references cited therein.
4. M. Sainsbury, D. Weerasighe, and D. Dolman, J. C. S. Perkin I, 587 (1982).
5. Intermolecular cyclization of the pyridine-3,4-quinodimethane intermediate with

- indole gave olivacine: T. Kametani, T. Suzuki, and K. Fukumoto, Heterocycles, 8, 465 (1977).
6. S. Kano, E. Sugino, S. Shibuya, and S. Hibino, J. Org. Chem., 46, 3856 (1981).
7. 4-Acetylpyridines were prepared by methyllithium treatment of the corresponding 4-cyanopyridines: 5a, bp 93-95°C/1 torr, m/e 135 ( $M^+$ ),  $^1\text{HNMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.57 (3H, s), 2.67 (3H, s), 7.70 (1H, d,  $J$  5 Hz), 8.48 (1H, d,  $J$  5 Hz), 8.48 (1H, s); 5b, oil, m/e 149.0819 ( $M^+$ , Calcd  $\text{C}_9\text{H}_{11}\text{NO}$  149.0839),  $^1\text{HNMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.31 (3H, s), 2.53 (3H, s), 7.11 (1H, d,  $J$  5 Hz), 8.38 (1H, d,  $J$  5 Hz); 5c, bp 123-214°C/2 torr.
8. K. N. Kilminster and M. Sainsbury, J. C. S. Perkin I, 2265 (1972).
9. 6a, mp 149-150°C, m/e 234 ( $M^+$ ),  $^1\text{HNMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.18 (3H, s), 5.13 (1H, s), 5.81 (1H, s); 6b, mp 178-179°C, m/e 248 ( $M^+$ ),  $^1\text{HNMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.13 (3H, s), 2.53 (3H, s), 5.10 (1H, s), 5.79 (1H, s); 6c, mp 172-173°C, m/e 248 ( $M^+$ ),  $^1\text{HNMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.13 (3H, t,  $J$  7.4 Hz), 2.58 (2H, q,  $J$  7.4 Hz), 5.17 (1H, s), 5.81 (1H, s).
10. On the basis of the recovery of the starting materials, yields of 7 and 3 are as follows: 7a (63.5 % yield from 6a, 50.0 % yield from 6c), 7b (58.1 % yield), 3 (33.0 % yield).
11. (a) T. Naito, N. Iida, and I. Ninomiya, J. C. S. Chem. Commun., 563 (1981);  
 (b) J. P. Kutney, M. Noda, N. G. Lewis, B. Monteriro, D. Mostowicz, and B. R. Worth, Heterocycles, 16, 1469 (1981).

Received, 14th May, 1982