TOTAL SYNTHESES OF (±)-SINACTINE AND (±)-CAVIDINE (BASE II)[1)]

Ichiya Ninomiya*, Hisashi Takasugi, and Takeaki Naito

Kobe Women's College of Pharmacy

Motoyama, Higashinada, Kobe, Japan.

Sinactine (VIa) and cavidine (VIb) were synthesized by a route which included enamide photocyclization.

During the course of investigation of enamide photocyclization,[2)] we found that the photocyclization occurred predominantly at the root of an ortho-methoxyl group[3)] and could apply to berbine synthesis[4)]. By taking advantage of the above results, we have now accomplished facile total syntheses of two protoberberine alkaloids, (±)-sinactine[5)] and hitherto unexploited (±)-cavidine[6)].

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline (Ia) was acylated with 2-methoxy-5,6-methylenedioxybenzoyl chloride[7)] to afford the enamide (IIa), m.p. 207-208°, in an 80 % yield. Irradiation[2)] of the enamide (IIa) in methanol with a low pressure mercury lamp at room temperature was carried out, and two photoproducts (IIIa and IVa) were obtained in 44 % and 21 % yields respectively. The desired product (IIIa), m.p. 247-249° (lit.[5a)] 240-241°), NMR $\delta(CDCl_3)$ 7.2-6.72 (5H, four aromatic and one olefinic H), 6.28 (2H, s, OCH_2O) and 3.98, 3.93 (3H×2, each s, OMe×2), had the structure as shown.

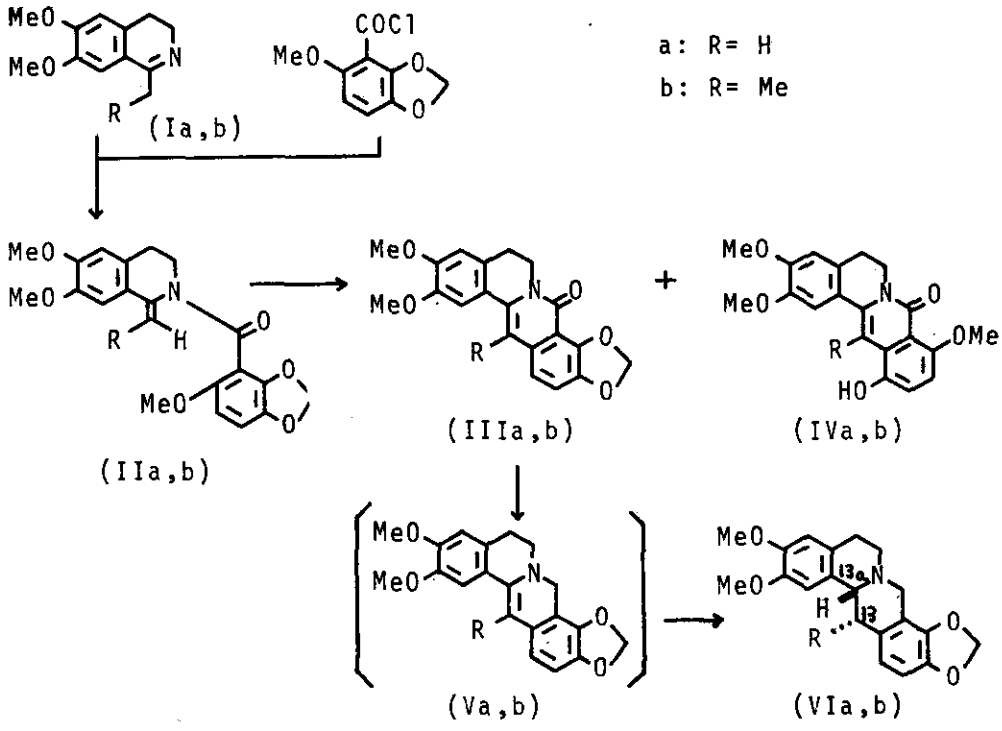
The second product (IVa), m.p. 280-281°(dec), IR ν_{max}(Nujol) ~3100 cm^{-1}(br, OH), NMR δ(DMSO-d_6) 9.58 (1H, br, OH), 7.08, 6.79 (2H, each d,J=8.5Hz, C_{10}-, C_{11}- H), 3.88,3.83,3.78 (3H×3, each s, OMe×3), had the structure as shown which suggested that the cyclization occurred at the root of a methylenedioxy group followed by cleavage and elimination.

Lithium aluminum hydride reduction of the photoproduct (IIIa) afforded the intermediary enamine (Va), which, without further purification, was reduced with sodium borohydride to yield the tertiary amine (VIa), m.p. 169-170°(lit.[5a] 169-170°) in a 54 % yield from IIIa, which was found to be identical with natural (-)-sinactine[5] upon comparisons of their IR and NMR spectra.

This facile synthesis of sinactine had a wide applicability as exemplified by the first total synthesis of cavidine[6c], which is an alkaloid of Corydalis plants.[6]

Starting from 1-ethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (Ib), cavidine[6c], a stereoisomer of thalictrifoline, was readily synthesized by a route completely analogous to the above.

Acylation of the 1-alkyl-3,4-dihydroisoquinoline (Ib) with 2-methoxy-5,6-methylenedioxybenzoyl chloride[7] afforded the corresponding enamide (IIb), m.p. 165-167°, in a 77 % yield, which was then irradiated to afford two photoproducts (IIIb and IVb) in 41 % and 29 % yields respectively. The structure of the former (IIIb) was clearly established from the following data; NMR $\delta(CDCl_3)$ 6.21 (2H, s, OCH_2O), 3.93, 3.90 (3H×2, each s, OMe×2) and 2.53 (3H, s, C_{13}-Me). Thus, it is clear that the cyclization occurred at the



root of an ortho-methoxyl group, which was then subjected to elimination to afford the above product (IIIb). The second product had the structure (IVb) as shown from its spectral data; IR ν_{max}(Nujol) ~3200 cm^{-1}(OH), NMR $\delta(CDCl_3)$ 9.41 (1H, br, OH), 7.10, 6.87 (2H, each d, J=8Hz, C_{10}-,C_{11}-H), 3.83, 3.79, 3.75 (3H×3, each s, OMe×3).

Lithium aluminum hydride reduction of the photoproduct (IIIb) afforded the enamine (Vb) which was further reduced with sodium borohydride to the corresponding tertiary amine (VIb), m.p. 194-195°(lit.190-191°[6b]; 192°[6c]), in a 37 % yield from IIIb. The structure of the tertiary amine (VIb) was established from the following data; IR $\nu_{max}(CHCl_3)$ 2800-2750 cm^{-1}(distinct Bohlmann bands) NMR $\delta(CDCl_3)$ 3.73 (1H, br d, W1/2=6Hz, C_{13a}-H), 0.93 (3H, d, J=7Hz, C_{13}-Me) and Rf value close to that of Base II[6b]. This evidence proved the stereochemistry of VIb as having B/C trans-fused juncture

and two hydrogens at C_{13} and C_{13a} in cis relationship.

Further, upon direct comparisons, this tertiary amine (VIb) was found to be identical with Base II. Since Base II had been converted into thalictrifoline[6b], this synthesis formally completed the total synthesis of thalictrifoline.

ACKNOWLEDGEMENT We thank Dr. J.Kunitomo of Mukogawa Women's University, and Drs. Taguchi and Imaseki of Tsumura Institute(Tokyo) for their precious samples of sinactine and base II.

REFERENCES

* All compounds gave satisfactory analyses and physical data.

1 Base II, an alkaloid first isolated by Taguchi and Imaseki,[6b] was later identified and designated as cavidine by Manske et al.[6c]

2 I. Ninomiya, T. Naito, and T. Mori, J. Chem. Soc. Perkin I, 1973, 505.

3 I. Ninomiya, T. Kiguchi, and T. Naito, unpublished data.

4 I. Ninomiya, and T. Naito, J. Chem.Soc. Chem. Comm., 1973, 137.

5 a) R.D. Haworth, and W.H. Perkin, J. Chem.Soc., 1926, 1769; b) C.K. Bradsher, and N.L. Dutta, J. Org. Chem., 26, 2231 (1961)

6 a) R.H.F. Manske, Can. J. Res., 21B, 111 (1943); b) H. Taguchi and I. Imaseki, J. Pharm. Soc. Japan, 84, 955 (1964); C) C.K. Yu, D.B. MacLean, R.G.A. Rodrigo, and R.H.F. Manske, Can. J. Chem., 48, 3673 (1970).

7 F.P. Doyle, K. Hardy, J.H.C. Nayler, M.J.Soulal, E.R. Stove, and H.R.J. Waddington, J. Chem. Soc., 1962, 1453.

Received, 4th June, 1973