

RACEMIC AND CHIRAL SYNTHESSES OF THE ALANGIUM ALKALOID ALANCINE

Tozo Fujii,^{*,†} Masashi Ohba,[†] Asako Yonezawa,[†] Jun Sakaguchi,[†]
 Sunil K. Chattopadhyay,[‡] David J. Slatkin,[‡] Paul L. Schiff, Jr.,[‡]
 and Anil B. Ray[§]

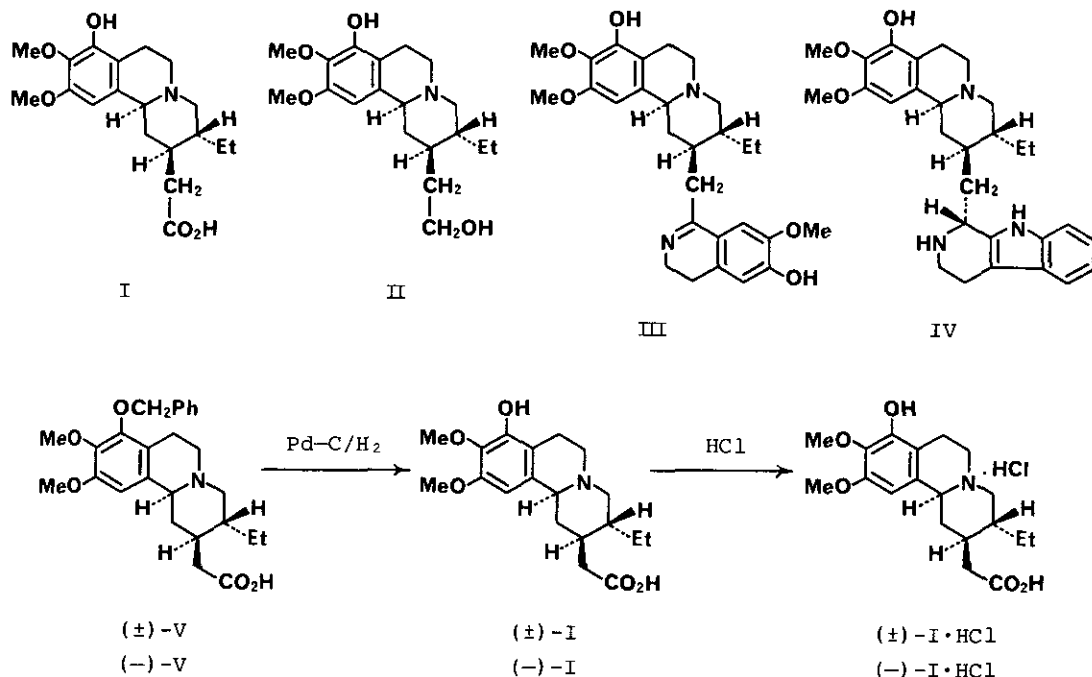
[†]*Faculty of Pharmaceutical Sciences, Kanazawa University, Takaramachi, Kanazawa 920, Japan*

[‡]*Department of Pharmaceutical Sciences, School of Pharmacy, University of Pittsburgh, Pittsburgh, PA 15261, U. S. A.*

[§]*Department of Medicinal Chemistry, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005, India*

Abstract — (±)-Alancine [(±)-I] has been synthesized in good yield from the tricyclic amino acid (±)-V by catalytic hydrogenolysis. Treatment of (±)-I with aqueous HCl gave the hydrochloride salt (±)-I·HCl. A parallel synthesis starting with (-)-V produced (-)-alancine [(-)-I] as well as its hydrochloride (-)-I·HCl in good yields. The synthetic (-)-I·HCl was found to be identical with a sample isolated from Alangium lamarckii Thw.

(-)-Alancine (I)¹ is a phenolic benzo[a]quinolizidine alkaloid isolated quite recently from the stem bark of Alangium lamarckii Thw. (Alangiaceae) by Schiff and co-workers.² Its tricyclic amino acid structure, unique in all the known benzo[a]quinolizidine-type alkaloids,³ has been determined² by spectral evidence and chemical correlation with (-)-ankorine (II),⁴ another Alangium alkaloid with established absolute stereochemistry. In the present work, we have achieved the racemic and chiral syntheses of alancine from the (±)- and (-)-tricyclic amino acids V,⁵ which were key intermediates in the previous racemic and chiral syntheses of alangicine (III)⁵ and alangimarckine (IV),⁶ two other Alangium alkaloids. Catalytic hydrogenolysis of (±)-V using hydrogen and 10% Pd-C catalyst in EtOH at 24°C for 3 h produced racemic alancine [(±)-I] [mp 217–218°C (dec.)]⁷ in 82% yield. Treatment of (±)-I with aqueous HCl afforded the corresponding hydrochloride salt



(±)-I·HCl [mp 241.5–245°C (dec.)] in quantitative yield. A parallel transformation of (-)-V gave (-)-alancine [(-)-I] [82% yield; mp 216–220.5°C (dec.); $[\alpha]_{\text{D}}^{20} -29.3^\circ$ (c 0.097, MeOH); cd (c 2.66×10^{-4} M, MeOH) $[\theta]_{280}^{18} -1000$ (neg. max.); uv $\lambda_{\text{max}}^{\text{MeOH}}$ nm (log ϵ) 230 (shoulder) (3.97), 273 (3.01), 280 (shoulder) (2.99); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) 287 (3.43); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 273 (3.02), 279 (shoulder) (3.01); ir $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} 3430 (broad, OH), 2530 (broad, N^+H), 1707 (weak, broad, CO_2H), 1566 (CO_2^-)]⁷ as well as its hydrochloride (-)-I·HCl [85% yield; mp 247.5–248.5°C (dec.); $[\alpha]_{\text{D}}^{22} -27.9^\circ$ (c 0.101, MeOH); cd (c 4.72×10^{-4} M, MeOH) $[\theta]_{280}^{22} -1080$ (neg. max.); uv $\lambda_{\text{max}}^{\text{MeOH}}$ 230 (shoulder) (3.98), 273 (3.04), 280 (shoulder) (3.01); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) 287 (3.42); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 273 (3.02), 279 (shoulder) (3.01); ir $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} 3325 (broad, OH), 2710–2620 (N^+H), 1725 (CO_2H)]. The spectral identity of (-)-I with (±)-I and that of (-)-I·HCl with (±)-I·HCl were confirmed by comparison of their ^1H nmr (CD_3OD), ^{13}C nmr (CD_3OD or $\text{CD}_3\text{OD}-\text{D}_2\text{O}$), and mass spectra. To our surprise, the previously reported ir (KBr), ^1H nmr (CD_3OD), and ^{13}C nmr (CD_3OD) spectra of "natural alancine"² did not match those of the synthetic (-)-I, but matched those of its hydrochloride salt [(-)-I·HCl] instead. Thus, the physical, chemical, and spectral data reported for "natural alancine" in the previous communication² are in reality those for the hy-

drochloride salt $[(-)-I \cdot HCl]$ of alancine. Since the "natural alancine" had been isolated from the plant by a procedure utilizing the Mayer's complex formation and subsequent treatment with anion-exchange resin (Cl^-),² it is not unreasonable to consider that the alkaloid had actually been obtained in the form of the hydrochloride salt.

ACKNOWLEDGMENT One (T. F.) of the authors is pleased to acknowledge the support of this work by a grant from the Japan Research Foundation for Optically Active Compounds.

REFERENCES

1. Unless otherwise stated, the structural formulas of optically active compounds in this paper represent their absolute configurations.
2. S. K. Chattopadhyay, D. J. Slatkin, P. L. Schiff, Jr., and A. B. Ray, Heterocycles, 1984, 22, 1965.
3. For recent reviews and information on the benzo[a]quinolizidine-type alkaloids as well as the Alangium alkaloids, see (a) T. Fujii and M. Ohba, 'The Alkaloids,' Vol. XXII, ed. by A. Brossi, Academic Press, New York, Chapter 1, 1983; (b) T. Fujii, Yakugaku Zasshi, 1983, 103, 257; (c) W. Wiegrebe, W. J. Kramer, and M. Shamma, J. Nat. Prod., 1984, 47, 397; (d) S. C. Pakrashi, R. Mukhopadhyay, R. R. Sinha, P. P. Ghosh Dastidar, B. Achari, and E. Ali, Indian J. Chem., 1985, 24B, 19; (e) T. Ravao, B. Richard, M. Zeches, G. Massiot, and L. Le Men-Olivier, Tetrahedron Lett., 1985, 26, 837.
4. (a) B. Dasgupta, J. Pharm. Sci., 1965, 54, 481; (b) A. R. Battersby, R. S. Kapil, D. S. Bhakuni, S. P. Popli, J. R. Merchant, and S. S. Salgar, Tetrahedron Lett., 1966, 4965; (c) T. Fujii and S. Yoshifuji, J. Org. Chem., 1980, 45, 1889.
5. T. Fujii, K. Yamada, S. Minami, S. Yoshifuji, and M. Ohba, Chem. Pharm. Bull., 1983, 31, 2583.
6. T. Fujii, H. Kogen, S. Yoshifuji, and M. Ohba, Chem. Pharm. Bull., 1985, 33, 1946.
7. The elemental analysis pointed to the formula $C_{19}H_{27}NO_5 \cdot 1/2 H_2O$.

Received, 4th October, 1985