

Total Synthesis of (\pm)-Lagerine¹⁾

(\pm)-Lagerine was synthesized from isopelletierine (IV) in 6 steps. This total synthesis corroborates the revised structure II for lagerine.

The initially proposed structure (I) for lagerine,²⁾ an alkaloid of *Lagerstroemia indica* L. (Lythraceae), was confirmed to be revised from the non-identity of the synthetic racemic compound (I)³⁾ with lagerine. The revised structure (II) was then proposed⁴⁾ on the basis of

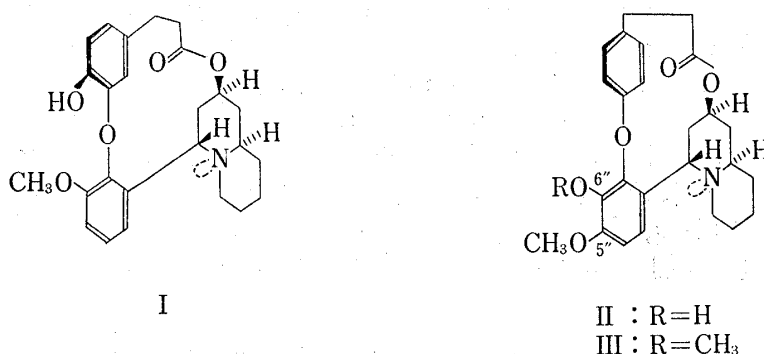


Chart 1

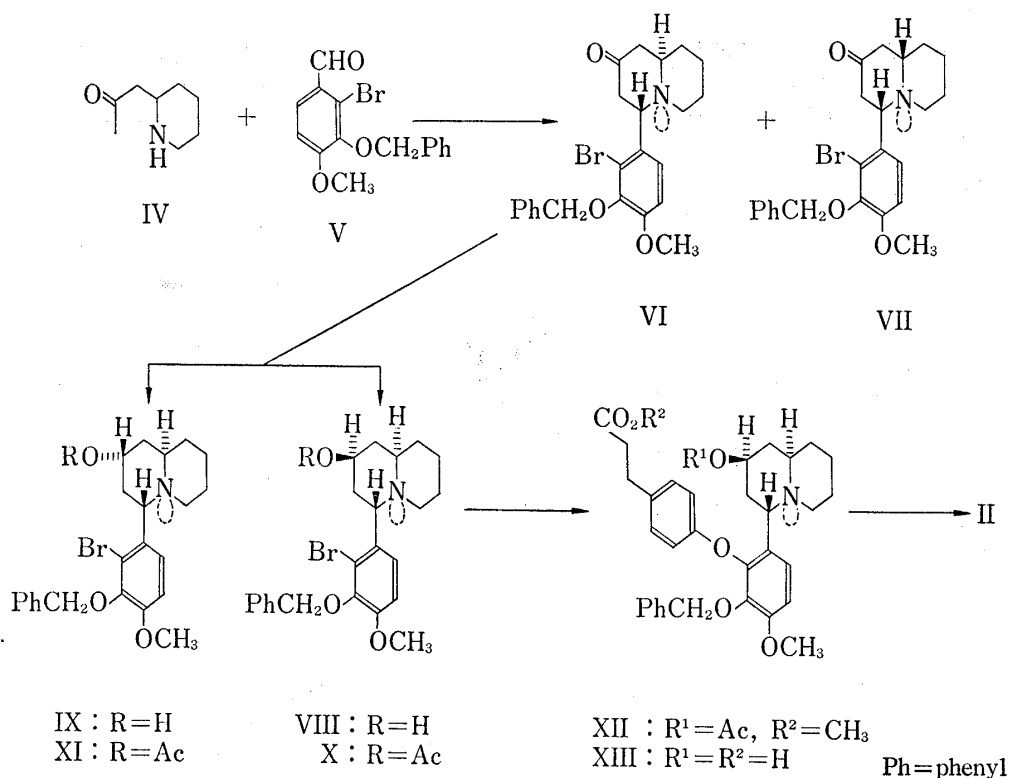


Chart 2

- 1) Presented at the 40th Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Kanazawa, June 1975.
- 2) J.P. Ferris, R.C. Briner, and C.B. Boyce, *J. Am. Chem. Soc.*, **93**, 2958 (1971).
- 3) M. Hanaoka, N. Hori, N. Ogawa, and Y. Arata, *Chem. Pharm. Bull.* (Tokyo), **22**, 1684 (1974).
- 4) M. Hanaoka, H. Sassa, N. Ogawa, Y. Arata, and J.P. Ferris, *Tetrahedron Letters*, **1974**, 2533.

the total synthesis of (\pm)-methyllagerine (III),⁴⁾ lagerine methyl ether, and biogenetic considerations.⁵⁾ However, it has not yet been established whether the phenolic hydroxyl group in lagerine exists at C-5" or C-6". The present communication deals with the total synthesis of (\pm)-lagerine, which corroborates the revised structure (II).

Condensation of isopelletierine (IV)⁶⁾ with the benzyl ether (V) of 2-bromoisovanillin⁷⁾ in aqueous tetrahydrofuran in the presence of sodium hydroxide afforded the *cis*-quinolizidine (VI) [Mass Spectrum *m/e*: 445, 443 (M^+ , 1:1), NMR δ : 4.92 (1H, t, $J=5.5$ Hz, CHAr)] and the *trans*-quinolizidine (VII) [Mass Spectrum *m/e*: 445, 443 (M^+ , 1:1), IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1} : 2790, 2750 (Bohlmann bands)]. Reduction of VI with sodium borohydride furnished the axial alcohol (VIII) [Mass Spectrum *m/e*: 447, 445 (M^+ , 1:1)] along with the equatorial alcohol (IX) [Mass Spectrum *m/e*: 447, 445 (M^+ , 1:1)]. Both alcohols (VIII and IX) were acetylated with acetic anhydride in pyridine to give the corresponding acetyl derivatives (X and XI).

The Ullmann condensation of X with methyl 4-hydroxyhydrocinnamate⁸⁾ afforded the biphenyl ether (XII) [Mass Spectrum *m/e*: 587 (M^+)]. Alkaline hydrolysis of XII and subsequent heating of the resulting hydroxy acid (XIII) [Mass Spectrum *m/e*: 531 (M^+)] with *p*-toluenesulfonic acid in benzene provided (\pm)-lagerine (II) [Mass Spectrum *m/e*: 423 (M^+), IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1} : 3540 (OH), 1720 (C=O), δ : 4.87 (1H, m, $W_H=9$ Hz, CHOCO), 3.92 (3H, s, OCH₃)].

The synthetic (\pm)-lagerine was proved to be completely identical with natural lagerine by infrared (IR) (CHCl₃) and mass spectral comparison and thin-layer chromatographic behaviour.

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5) J.P. Ferris, C.B. Boyce, and R.C. Briner, *Tetrahedron Letters*, **1966**, 5129; S.H. Koo, R.N. Gupta, I.D. Spencer, and J.T. Wrobel, *Chem. Comm.*, **1970**, 396; M. Hanaoka, N. Ogawa, H. Sassa, N. Hori, C. Shimezawa, K. Shimizu, and Y. Arata, Symposium Papers, 18th Symposium on the Chemistry of Natural Products, Kyoto, October 1974, p. 195.

6) M. Hanaoka, N. Ogawa, and Y. Arata, *Yakugaku Zasshi*, **94**, 531 (1974).

7) S.E. Hazlet and R.J. Brotherton, *J. Org. Chem.*, **27**, 3253 (1962).

8) E.N. Marvell, D. Strumer, and C. Rowell, *Tetrahedron*, **22**, 861 (1966).