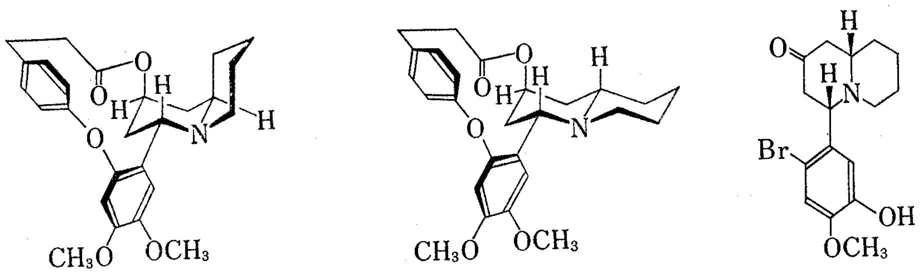
Chem. Pharm. Bull.
22(4) 973—974 (1974)

UDC 547.94.057 : 581.192

Total Synthesis of (±)-Vertaline

Vertaline,1) an alkaloid of *Decodon verticillatus* (L.) Ell. (Lythraceae), possesses a *cis*-fused quinolizidine ring with a biphenyl ether and a fourteen-membered lactone in its structure (I). Its epimeric alkaloid decaline (II) having a *trans*-fused quinolizidine ring was already synthesized.2,3) We now report the total synthesis of (±)-vertaline.



I II III

Chart 1

Previously we reported that condensation of isopelletierine with 6-bromoisovanillin in aqueous sodium hydroxide afforded only the *trans*-quinolizidine (III)2) whereas the reaction with benzaldehyde was reported to give a mixture of *cis*- and *trans*-4-phenylquinolizidin-2-one.4) The complete stereoselectivity in the former case would be interpreted as follows: this condensation reaction gave also a mixture of *cis*- and *trans*-isomer and then the resulting *cis*-isomer isomerized to *trans*-isomer under this reaction condition. The stereoselectivity in these condensation reactions would depend on solvents and solubilities of the starting aldehydes and the products.

Condensation of isopelletierine (IV)5) with 6-bromoveratraldehyde6) in tetrahydrofuran in the presence of aqueous sodium hydroxide gave the *cis*-quinolizidine (V) [*m*/*e*: 369, 367 (M$^+$, 1:1), $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 1712 (C=O), no Bohlmann bands,7) δ: 4.87 (1H, t, J=6.5 Hz, C$\underline{\text{H}}$Ar)] and the *trans*-quinolizidine (VI) in the ratio of 3:2 in 42% yield. The latter was identified with the authentic specimen2) derived from III. The former (V) isomerized to VI by treatment with aqueous sodium hydroxide in methanol. The stereochemsitry of V was verified from its spectral data and especially the presence of a *cis*-quinolizidine ring was confirmed by the lower chemical shift of the proton at C$_4$ in the nuclear magnetic resonance (NMR) spectrum of V.8)

Reduction of the *cis*-quinolizidine (V) with sodium borohydride in methanol afforded the axial alcohol (VII) [*m*/*e*: 371, 369 (M$^+$, 1:1), δ: 4.79 (1H, t, J=5.5 Hz, C$\underline{\text{H}}$Ar)] and the

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7) All the compounds except VI described for the synthesis of (±)-vertaline lack the Bohlmann bands due to *trans*-quinolizidine in their infrared (IR) spectra.

8) F. Bohlmann, D. Schumann and C. Arndt, *Tetrahedron Letters*, **1965**, 2705; J.P. Ferris, C.B. Boyce and R.C. Briner, *J. Am. Chem. Soc.*, **93**, 2942 (1971).

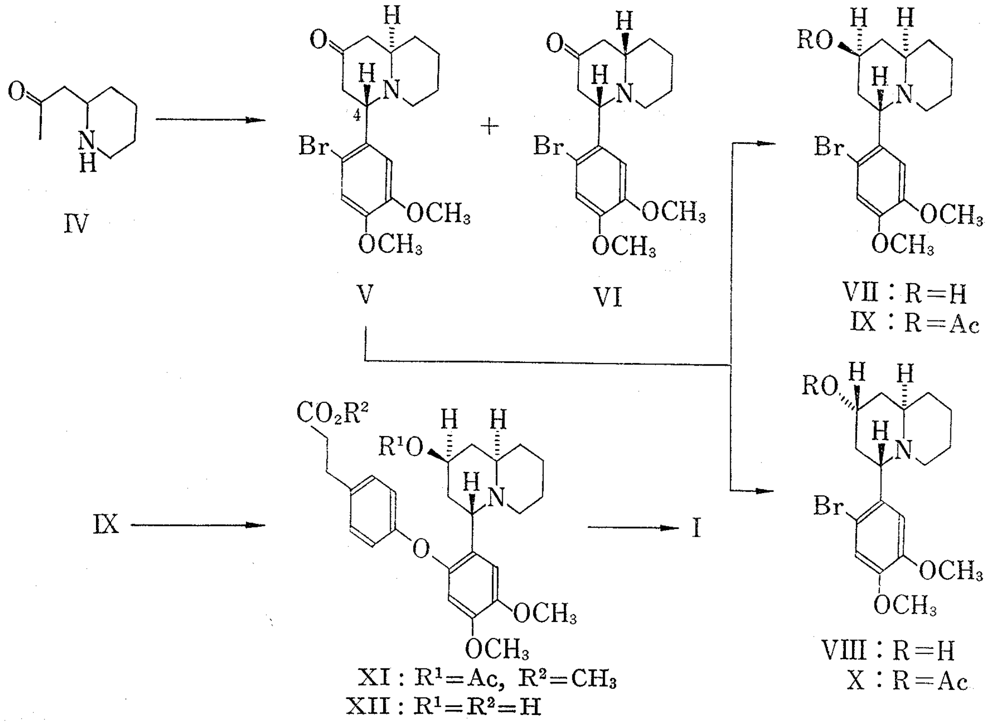

Chart 2

equatorial alcohol (VIII) [*m/e*: 371, 369 (M^+, 1:1), δ: 4.51 (1H, d-d, J=11.5; 3 Hz, C$\underline{\mathrm{H}}$Ar)] in the ratio of 3:1 in 96% yield. Both alcohols (VII and VIII) were acetylated with acetic anhydride in pyridine to give quantitatively the axial acetyl derivative (IX) [δ: 5.16 (1H, quin, J=4.5 Hz, C$\underline{\mathrm{H}}$OAc), 4.76 (1H, d-d, J=8; 4.5 Hz, C$\underline{\mathrm{H}}$Ar), 2.11 (3H, s, $OCOCH_3$)] and the equatorial acetyl derivative (X) [δ: 5.14 (1H, m, W_H=24 Hz, C$\underline{\mathrm{H}}$OAc), 4.57 (1H, d-d, J=11.5; 3 Hz, C$\underline{\mathrm{H}}$Ar), 2.04 (3H, s, $OCOCH_3$)], respectively.

Ullmann condensation of IX with methyl 4-hydroxyhydrocinnamate[9] in pyridine using copper oxide furnished the biphenyl ether (XI) [*m/e*: 511 (M^+), $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1727 (C=O), δ: 5.20 (1H, m, W_H=14 Hz, C$\underline{\mathrm{H}}$OAc), 4.62 (1H, t, J=6 Hz, C$\underline{\mathrm{H}}$Ar), 3.98, 3.84, 3.73 (each 3H, s, $OCH_3 \times 3$), 1.92 (3H, s, $OCOCH_3$)], which, on hydrolysis with aqueous sodium hydroxide, afforded the carboxylic acid (XII) [*m/e*: 455 (M^+), $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 2460 br. (N^+H), 1590 (COO^-)] in 28% yield from IX. A solution of XII in benzene was heated with *p*-toluenesulfonic acid to provide (±)-vertaline (I) [mp 224—225°, *m/e*: 437 (M^+), $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1720 (C=O), δ: 4.96 (1H, m, W_H=9 Hz, C$\underline{\mathrm{H}}$OCO), 3.97, 3.93 (each 3H, s, $OCH_3 \times 2$), 3.48 (1H, d-d, J=11; 3.5 Hz, C$\underline{\mathrm{H}}$Ar)[10]] in 41% yield.

The synthetic (±)-vertaline was proved to be identical with natural vertaline by IR (in $CHCl_3$), NMR and mass spectral comparison and thin-layer chromatographic behaviour.

Acknowledgement The authors are grateful to Prof. James P. Ferris, Department of Chemistry, Rensselaer Polytechnic Institute, for the sample of natural vertaline and its IR, NMR and mass spectra.

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Received December 17, 1973

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[9] E.N. Marvell, D. Sturmer and C. Rowell, *Tetrahedron*, 22, 861 (1966).

[10] The proton at C_4 of (±)-vertaline appeared *ca.* 1 ppm higher than the corresponding protons of other compounds. The diamagnetic shift of this proton was caused by the anisotropy of the benzene ring in the lactonized hydrocinnamate moiety.