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Synthesis of (±)-Methyldecamine[1]

The Mannich condensation of the amide (VII) with isopelletierine (VIII) gave stereoselectively the *cis*-quinolizidine (IX), which was converted to (±)-methyldecamine (II) in 4 steps.

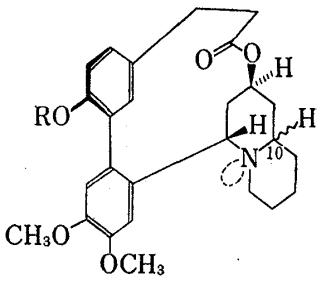
Lactonic Lytheaceae alkaloids[2] are classified into two groups, the biphenyl and biphenyl ether type, each of which is further subdivided into the *cis*- and *trans*-quinolizidine type, as shown in I, III, IV, and V. Only the biphenyl-*cis*-quinolizidine type alkaloids have remained unsynthesized, though the other types of alkaloids were already synthesized.[3] This communication deals with the synthesis of (±)-methyldecamine (II), the methyl ether of decamine (I),[4] which is an alkaloid of *Decodon verticillatus* (L.) ELL. and *Lagerstroemia indica* L. and the representative of the biphenyl-*cis*-quinolizidine type alkaloids.

The Mannich condensation of the biphenyl ester (VI)[5] with isopelletierine (VIII)[6] was shown to give stereoselectively the *trans*-quinolizidine derivative, because VI was readily hydrolyzed to the corresponding alkali-soluble carboxylic acid during the reaction.[5,7] In order to get the *cis*-quinolizidine, therefore, VI was converted to the alkali-insoluble amide (VII) [*m/e*: 371 (M^+), $\nu_{max}^{CHCl_3}$ cm^{-1}: 1675 (CHO), 1632 (CON)], which would not be hydrolyzed during the Mannich condensation.

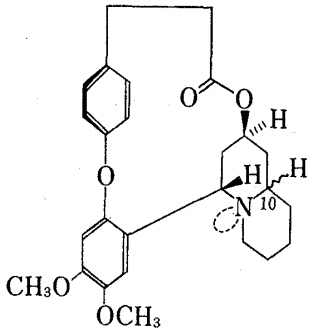
Condensation of VII with VIII in benzene-tetrahydrofuran in the presence of aqueous sodium hydroxide afforded the expected *cis*-quinolizidine (IX) [*m/e*: 494 (M^+), $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (C=O)] and the *trans*-quinolizidine (X) [*m/e*: 494 (M^+), $\nu_{max}^{CHCl_3}$ cm^{-1}: 2790, 2750 (Bohlmann bands), 1715 (C=O)] in the ratio of 6: 1. Reduction of IX with sodium borohydride, followed by the acetylation with acetic anhydride in pyridine furnished the axial acetyl derivative (XI) [*m/e*: 538 (M^+)] and the equatorial acetyl derivative (XII) [*m/e*: 538 (M^+)]. Each of the biphenyl derivatives (IX, X, XI, and XII) was found to be a mixture of two atropisomers from their dynamic nuclear magnetic resonance (NMR) spectra.[5]

Alkaline hydrolysis of XI and subsequent heating of the resulting hydroxy acid (XIII) [*m/e*: 469 (M^+)] with *p*-toluenesulfonic acid in benzene provided (±)-methyldecamine (II) [*m/e*: 451 (M^+), $\nu_{max}^{CHCl_3}$ cm^{-1}: 1719 (C=O), δ: 5.02 (1H, m, W_H=8 Hz, CHOCO), 4.09 (1H, d-d, J=10; 1 Hz, ArCH), 3.93, 3.88, 3.74 (each 3H, s, $OCH_3 \times 3$)[8]].

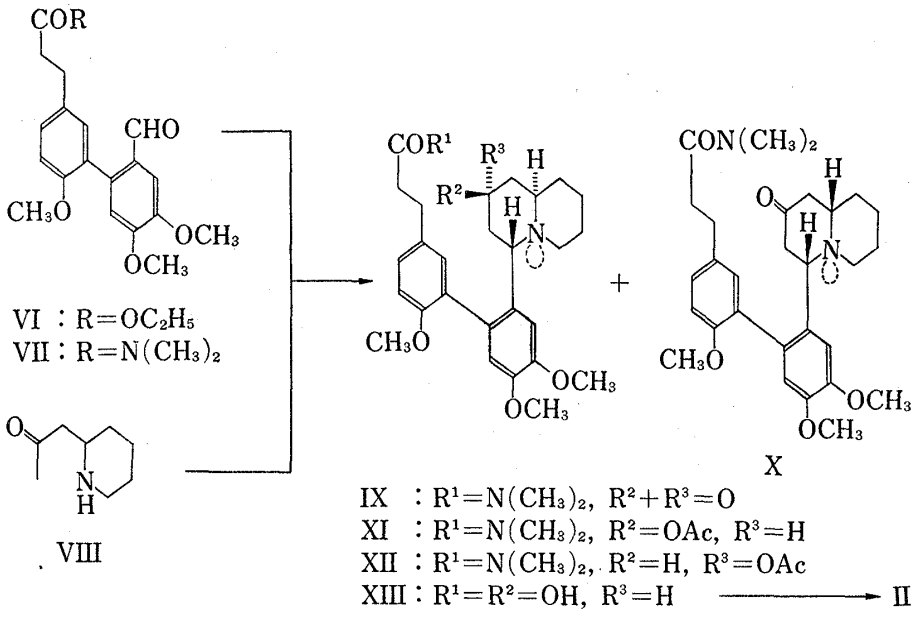
1) Presented at the 42nd Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Toyama, June 1976.
2) J.P. Ferris, C.B. Boyce, R.C. Briner, U. Weiss, I.H. Qureshi, and N.E. Sharpless, *J. Am. Chem. Soc.*, **93**, 2963 (1971) and references therein.
3) M. Hanaoka, N. Ogawa, and Y. Arata, *Chem. Pharm. Bull.* (Tokyo), **24**, 1045 (1976) and references therein.
4) J.P. Ferris, C.B. Boyce, and R.C. Briner, *J. Am. Chem. Soc.*, **93**, 2942 (1971); J.P. Ferris, R.C. Briner, and C.B. Boyce, *ibid.*, **93**, 2958 (1971).
5) M. Hanaoka, H. Sassa, C. Shimezawa, and Y. Arata, *Chem. Pharm. Bull.* (Tokyo), **23**, 2478 (1975).
6) M. Hanaoka, N. Ogawa, and Y. Arata, *Yakugaku Zasshi*, **94**, 531 (1974).
7) M. Hanaoka, N. Ogawa, K. Shimizu, and Y. Arata, *Chem. Pharm. Bull.* (Tokyo), **23**, 1573 (1975).
8) The published NMR data for methyldecamine[4]: 4.07 (1H, d-d, ArCH), 3.90, 3.86, 3.74 (each 3H, s, $OCH_3 \times 3$).



I : C_{10}⁻⁻⁻H, R=H (decamine)
II : C_{10}⁻⁻⁻H, R=CH_3
III : C_{10}—H, R=H (decinine)



IV : C_{10}⁻⁻⁻H (vertaline)
V : C_{10}—H (decaline)



VI : R=OC_2H_5
VII : R=$N(CH_3)_2$

VIII

IX : R^1=$N(CH_3)_2$, R^2+R^3=O
XI : R^1=$N(CH_3)_2$, R^2=OAc, R^3=H
XII : R^1=$N(CH_3)_2$, R^2=H, R^3=OAc
XIII : $R^1=R^2$=OH, R^3=H ⟶ II

Chart 1

Though we have not yet obtained the authentic natural decamine or methyldecamine for the comparison with the synthetic product (II), the above-mentioned synthesis will provide a general synthetic method for the biphenyl-*cis*-quinolizidine type of Lythraceae alkaloids.

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