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# STRUCTURE AND SYNTHESIS OF METHYLLAGERINE

Miyoji Hanaoka, Hironori Sassa, Nobuo Ogawa and Yoshio Arata

Faculty of Pharmaceutical Sciences, Kanazawa University

Takara-machi, Kanazawa 920, Japan

James P. Ferris

Department of Chemistry, Rensselaer Polytechnic Institute

Troy, New York 12181, U. S. A.

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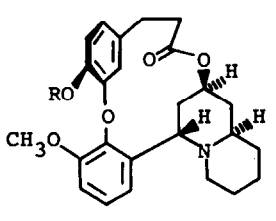
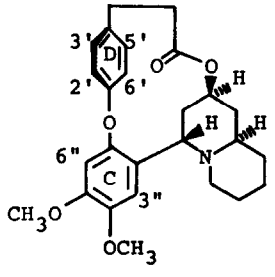
The proposed structure (I) for lagerine (1), an alkaloid of Lagerstroemia indica L. (Lythraceae), requires revision because the synthetic racemic compound (I) (2) was found not to be identical with lagerine. From the spectroscopic comparison of methyllagerine (1) with vertaline (III) (3), structure IV was assigned to methyllagerine, which was now isolated as a natural product from Lagerstroemia indica L. grown in Japan. The total synthesis of (±)-methyllagerine confirmed this assignment.

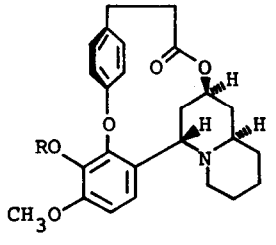


I R=H

II R=$CH_3$



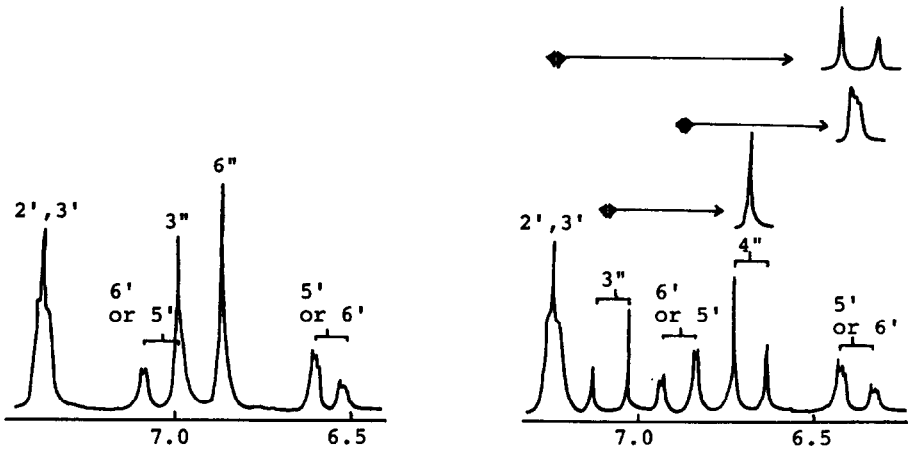
III



IV R=$CH_3$

V R=H

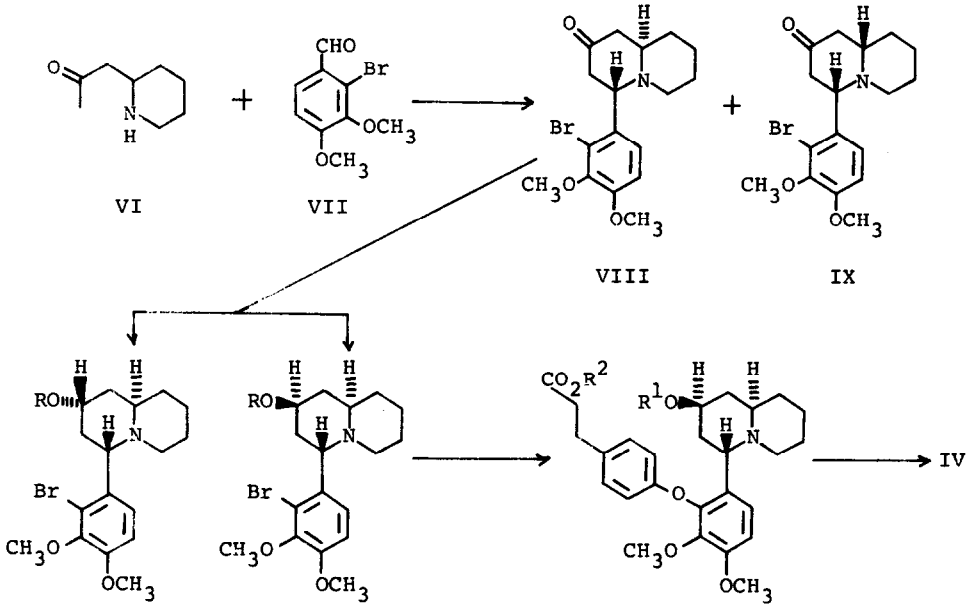
Both the mass and NMR spectra of methyllagerine were almost identical with those of vertaline (III) except for the aromatic region in the NMR spectra. The NMR spectra of both alkaloids in the aromatic region are shown below.




In the NMR spectrum of vertaline H-3" and H-6" of the ring C appear as a singlet [δ: 7.00 and 6.86, respectively], two protons (probably H-2' and H-3') of the ring D resonate as a broad singlet with a fine structure at the same chemical shift [δ: 7.39] because of the influence of the anisotropy caused presumably by the carbonyl grouping and/or the phenyl ring C, and other two protons (H-5' and H-6') appear as a AB-quartet [δ: 7.04; 6.58 ($J$=8 Hz)] with a fine structure. The exactly same pattern of four protons of the ring D is observed in the NMR spectrum of methyllagerine [δ: 7.23 (2H, br-s), 6.87; 6.42 (2H, AB-q, $J$=8 Hz)] and the remaining signals form a sharp AB-quartet [δ: 7.07; 6.68 ($J$=8 Hz)], suggesting that in methyllagerine four protons exist in the ring D as in the case of vertaline and two protons of the ring C are located ortho to each other. These assignments were proved by the decoupling experiment shown in the figure.

The above NMR data coupled with biogenetic considerations led the structure IV for methyllagerine. In order to corroborate this assignment, the synthesis of IV was performed according to the method reported for the total synthesis of (±)-vertaline (4).

Condensation of isopelletierine (VI) (5) with 2-bromoveratraldehyde (VII) (6) in aqueous tetrahydrofuran in the presence of sodium hydroxide gave the cis-quinolizidine (VIII) [m/e: 369, 367 ($M^+$, 1:1), δ: 4.91 (1H, t, J=6 Hz, CHAr)] and the trans-quinolizidine (IX) [m/e: 369, 367 ($M^+$, 1:1), $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 2790, 2750 (Bohlmann bands)] in the ratio of 3:1. Reduction of VIII with sodium borohydride afforded the equatorial alcohol (X) [m/e: 371, 369 ($M^+$, 1:1)] and the axial alcohol (XI) [m/e: 371, 369 ($M^+$, 1:1)] in the ratio of 1:3. Both alcohols (X and XI) were acetylated with acetic anhydride in pyridine to give the corresponding acetyl derivatives (XII and XIII).



VI VII VIII IX

X R=H XI R=H XIV $R^1$=Ac, $R^2$=$CH_3$

XII R=Ac XIII R=Ac XV $R^1$=$R^2$=H

The Ullmann condensation of XIII with methyl 4-hydroxyhydrocinnamate (7) afforded the biphenyl ether (XIV) [m/e: 511 ($M^+$)]. Hydrolysis of XIV and subsequent heating of the resulting hydroxy acid (XV) [m/e: 455 ($M^+$)] in benzene with p-toluenesulfonic acid provided (±)-methyllagerine (IV) [m/e: 437 ($M^+$), $\nu_{max}^{CHCl_3}$

$cm^{-1}$: 1720 (C=O), δ: 4.83 (1H, m, $W_H$=9 Hz, CHOCO), 3.86, 3.90 (each 3H, s, $OCH_3$), 3.35 (1H, d-d, J=11; 3.5 Hz, CHAr)], which was proved to be identical with natural methyllagerine by IR (in $CHCl_3$), NMR and mass spectral comparison and thin-layer chromatographic behaviour.

This synthesis confirms that IV (R=$CH_3$) is the correct structure of methyllagerine. Structure II (R=$CH_3$) was assigned mainly on the basis of the isolation of p-methoxycinnamyl alcohol in the Emde degradation of methyllagerine methiodide (1). However, p-hydroxycinnamyl alcohol was obtained when the same Emde degradation was performed on the lithium aluminum hydride cleavage product of methyllagerine (1). It was assumed that the latter reaction product was formed as a result of O-methyl cleavage. Instead the Emde cleavage of methyllagerine must proceed with O-methyl transfer.

The synthesis of lagerine (V, R=H) is now in progress.

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