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A NEW SYNTHESIS OF (±)-7-EPIDEOXYNUPHARIDINE AND (±)-1-EPI-7-EPIDEOXYNUPHARIDINE

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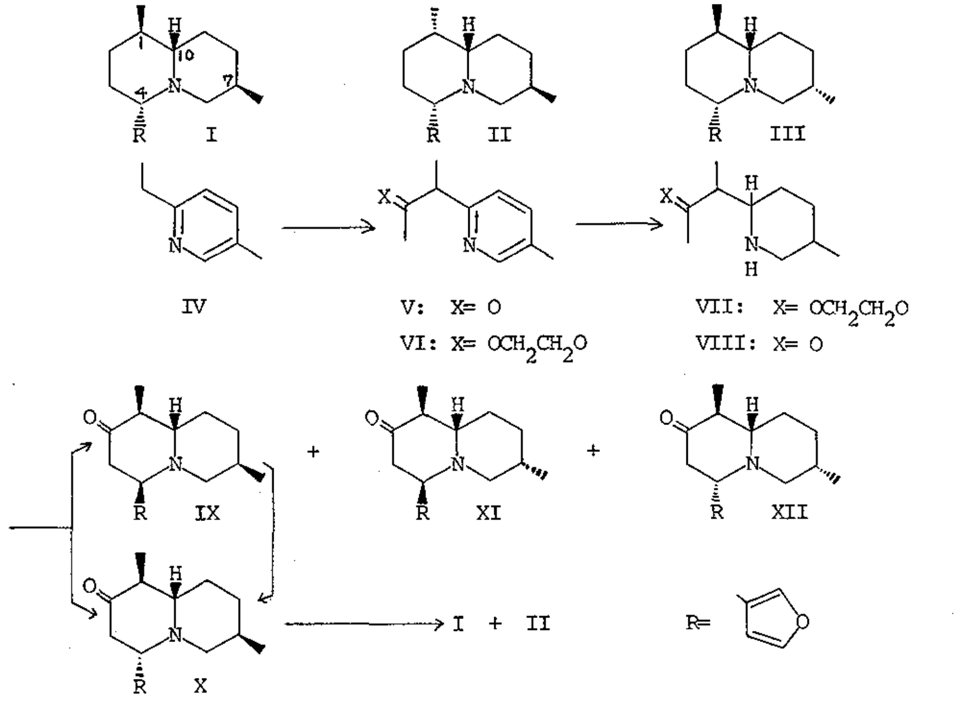
The Mannich reaction of the amino-ketone (VIII) with 3-furylaldehyde followed by the isomerization afforded stereoselectively the trans-quinolizidine (X), the Wolff-Kishner reduction of which provided (±)-7-epi- and (±)-1-epi-7-epideoxynupharidine (I and II).

(±)-7-Epideoxynupharidine (I) and (±)-1-epi-7-epideoxynupharidine (II) accompanied with other four stereoisomers including (±)-deoxynupharidine (III) had been synthesized without the consideration of stereoselectivity.[1] Recently (-)-I and (-)-II were isolated from the rhizomes of Nuphar luteum subsp. variegatum[2] and the scent glands of Canadian beaver.[3] The present communication deals with a new convenient synthesis of I and II.

Condensation of 2-ethyl-5-methylpyridine (IV)[4] with acetonitrile in the presence of phenyllithium followed by acidic treatment gave the ketone (V) [$\nu_{max}^{CHCl_3}$ cm^{-1}: 1715 (C=O), picrate: mp 123-124°] in 35% yield. Ketalization of V with ethylene glycol afforded the ketal (VI) (76%, picrate: mp 127-128°), which was hydrogenated over 5% rhodium on alumina in acetic acid to give the piperidine (VII) [90%, bp 135-138°/ 17mmHg, $\nu_{max}^{CHCl_3}$ cm^{-1}: 3325 (NH)].

Acidic hydrolysis of VII provided the amino-ketone (VIII) [bp 125-130°/ 17mmHg, $\nu_{max}^{CHCl_3}$ cm^{-1}: 3320 (NH), 1705 (C=O)] in 87% yield.



The Mannich reaction^5 of VIII with 3-furylaldehyde in aqueous methanol in the presence of sodium hydroxide afforded the four stereoisomeric quinolizidin-2-ones, IX [$\nu_{max}^{CHCl_3}$ cm^{-1}: 1708 (C=O), δ: 0.86 (3H, d, J=5.5 Hz, C_7-CH_3), 1.10 (3H, d, J=6.5 Hz, C_1-CH_3), 4.24 (1H, d-d, J=7;2 Hz, C_4-H), m/e: 247 (M^+), picrate: mp 181-183°], X [$\nu_{max}^{CHCl_3}$ cm^{-1}: 2790, 2770 (Bohlmann bands), 1712 (C=O), δ: 0.77 (3H, d, J=6 Hz, C_7-CH_3), 1.05 (3H, d, J=6.5 Hz, C_1-CH_3), 3.31 (1H, d-d, J=12;3 Hz, C_4-H), m/e: 247 (M^+), mp 76.5-77°], XI [$\nu_{max}^{CHCl_3}$ cm^{-1}: 1700 (C=O), δ: 0.96 (3H, d, J=6 Hz, C_7-CH_3), 1.03 (3H, d, J=6.5 Hz, C_1-CH_3), 4.20 (1H, br-d, J=6 Hz, C_4-H), picrate: mp 185-

186.5°], and XII [$\nu_{max}^{CHCl_3}$ cm^{-1}: 2790, 2765 (Bohlmann bands), 1710 (C=O), δ: 1.03 (6H, d, J=7.5 Hz, C_1- and C_7-CH_3), 3.52 (1H, d-d, J=11.5;3.5 Hz, C_4-H), picrate: mp 93-95°] in 45, 14, 3, and 1% yield, respectively.

The stereochemistry at C_4 and C_{10} of X and XII was verified from the presence of the Bohlmann bands in their IR spectra and C_4-H signals in their NMR spectra. The equatorial methyl group on C_1 in X and XII was suggested from the fact that no epimerization occurred at C_1 in X and XII, on treatment with sodium ethoxide in ethanol. The trans-quinolizidines (X and XII) are, therefore, epimeric at C_7 with each other. The higher chemical shift and smaller coupling constant of C_7-methyl signal of X in comparison with that of XII in their NMR spectra indicated that C_7-methyl group in X is equatorial and that in XII, axial.[6] Thus, the stereochemistry of X and XII was established as depicted.

The presence of the cis-quinolizidine ring in IX and XI was confirmed by the lower chemical shift[7] of the C_4-H in their NMR spectra. As the major product (IX) isomerized to X in 60% yield by treatment with aqueous sodium hydroxide in methanol, the stereochemistry of IX was assumed to be as depicted. Similarly, the possible stereochemistry of XI was shown to be as depicted.

Thus, the above Mannich condensation followed by the isomerization gave stereoselectively the most stable trans-quinolizidine (X).

The Wolff-Kishner reduction of X afforded I [$\nu_{max}^{CHCl_3}$ cm^{-1}: 2790, 2770 (Bohlmann bands), δ: 0.72 (3H, d, J=6.5 Hz, C_7-CH_3), 0.90 (3H, d, J=6 Hz, C_1-CH_3), m/e: 233 (M^+), picrate: mp 188-189°] and II [$\nu_{max}^{CHCl_3}$ cm^{-1}: 2790, 2765 (Bohlmann bands), δ: 0.73 (3H, d, J=6.5 Hz,

C_7-CH_3), 1.07 (3H, d, J=6.5 Hz, C_1-CH_3), m/e: 233 (M^+), picrate: mp 180-182.5°] in 45 and 15% yield, respectively. The higher chemical shift of C_1-methyl signal of I in comparison with that of II in their NMR spectra indicated that C_1-methyl group in I is equatorial and that in II, axial.[6]

The synthetic (±)-7-epideoxynupharidine (I) and (±)-1-epi-7-epideoxynupharidine (II) were proved to be completely identical with the corresponding natural alkaloids by IR, NMR, and mass spectral comparison and thin layer chromatographic behavior.

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