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SHORT COMMUNICATION

7-EPIDEOXYNUPHARIDINE* FROM *NUPHAR LUTEUM* SUBSP. *VARIEGATUM*[1]

CHUN FOOK WONG and ROBERT T. LALONDE

Department of Chemistry, State University College of Forestry at Syracuse University, Syracuse, New York 13210, U.S.A.

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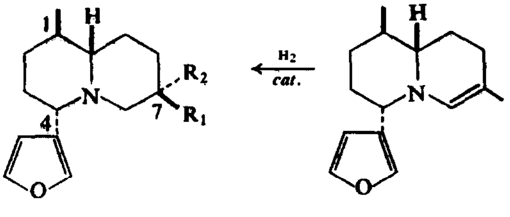
Abstract—7-Epideoxynupharidine has been isolated from *Nuphar luteum* subsp. *variegatum*.

7-EPIDEOXYNUPHARIDINE (I) has been encountered previously in connexion with the synthesis[2] of deoxynupharidine (II) and in a study[3] of the stereochemistry of nupharamine. Hitherto, 7-epideoxynupharidine has not been reported as a natural product. The isolation from a natural source and the identification of this alkaloid are now reported.

The hydrochloride salt of I gave a satisfactory analysis for $C_{15}H_{24}NOCl$. The structural similarity to deoxynupharidine was strongly suggested by the virtual identity of the mass spectra. The infrared spectrum (i.r.) corresponded to that reported[2] for synthetic (±)-7-epideoxynupharidine and was different in several respects from the spectra of the other synthesized "deoxynupharidines". Significantly, the i.r. displayed prominent Bohlmann bands,[4] in the region 3·5–3·7 μ, which pointed to the presence of a *trans*-quinolizidine ring system and accounted for the single nitrogen atom. In addition, the i.r. clearly revealed the presence of the furanyl group through display of bands at 6·68 and 11·45 μ. The NMR confirmed this structural feature by showing vinyl resonance bands at 3·69 (q, $J = 1·5$ and 1 Hz, 1 β-furanyl H) and 2·78 τ (m, 2 α-furanyl H).



(III)

(I) $R_1 = CH_3$, $R_2 = H$
(II) $R_1 = H$, $R_2 = CH_3$

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[3] I. KAWASAKI, S. MATSUTANI and T. KANEKO, *Bull. Chem. Soc. Japan* **36**, 1474 (1963).

[4] F. BOHLMANN, *Chem. Ber.* **91**, 2157 (1958).

NMR data also indicated that both methyl groups of I were equatorial. The spectrum displayed methyl resonance doublets at 9·08 ($J = 3$ Hz) and 9·26 τ ($J = 5·5$ Hz), both coupling constants being within the range usually exhibited by equatorial methyl groups in quinolizidines. In contrast, deoxynupharidine (II) displayed the C_1 equatorial methyl resonance at 9·08 τ, $J = 5·6$ Hz, but the C_7 axial methyl resonance at 9·01 τ, $J = 7·0$ Hz. Nuphenine, possessing a single axial methyl group,[5] gives a methyl doublet at 9·02 τ, $J = 6·6$ Hz. Both methyl resonances of the 7-epi-isomer correspond to the higher field chemical shift and lower coupling constant values exhibited by the C_1 equatorial methyl group of deoxynupharidine. The correlation[6] of axial methyl groups with lower field signals and larger splittings and equatorial methyl groups with higher field signals and smaller splittings is a well-known one in quinolizidine chemistry.

Solvent-induced shift experiments provided supporting evidence for two equatorial methyl groups. For deoxynupharidine, a change from deuterochloroform to benzene resulted in an up-field shift of 5·0 Hz for the C_1 equatorial methyl but a down-field shift of 4·2 Hz for the C_7 axial methyl. In contrast, the same solvent change induced an up-field shift of 3·0 Hz for both C_1- and C_7-methyls of the 7-epi isomer.

Finally, the structure was established conclusively by the observation that catalytic hydrogenation of Δ^6-dehydrodeoxynupharidine* (III), produced deoxynupharidine (II) and the 7-epi-isomer (I), the latter being identical in all respects with material secured directly from the plant source.

The absolute configuration of 7-epideoxynupharidine is that represented by structure I and follows from correlation through III with deoxynupharidine, whose stereochemistry has been established.[7]

EXPERIMENTAL

Isolation of 7-Epideoxynupharidine (I)

Rhizomes of *Nuphar luteum* subsp. *variegatum* were harvested from the southern shore of Green Lake, Onondaga County, New York, during July and August of 1967. Verification of plant material was made by Mr. Stanley Smith of the New York State Botanists Office, Albany, New York.

Dried powdered rhizomes (16 kg) were extracted with 150 l. of CH_3OH at room temperature over a period of 3 weeks. Removal of CH_3OH on the rotary evaporator furnished 4·98 kg of residue which was stirred with 12 l. of 10% acetic acid for 8 hr. The mixture was stored at 10° for 1 week, filtered through glass wool, extracted repeatedly with hexane, benzene then CH_2Cl_2. The hexane and benzene extracts were set aside for other investigations. The CH_2Cl_2 extract was dried, filtered, reduced in volume at the rotary evaporator and placed in the refrigerator. The precipitated acetic acid salt of nupharidine (226 g total) was removed in several batches by filtration and the combined filtrates were evaporated to dryness. The residue (6·64 g) was taken up in 30 ml of 1 N HCl and the resulting mixture was extracted with Et_2O. The aqueous layer was made basic ($pH > 12$) with NaOH and extracted with CH_2Cl_2. The combined CH_2Cl_2 extract was dried and evaporated to dryness, leaving 0·346 g of brown residue. TLC (Alumina-G, n-hexane–5 per cent Et_2O) of the residue showed three poorly separated spots, close to the solvent front, which corresponded in R_f values to deoxynupharidine, nuphenine, and 7-epideoxynupharidine (listed in decreasing order of mobility).

A neutral alumina column containing 332 mg of the residue was eluted with n-hexane–5 per cent Et_2O (fraction number and volume of eluant in milliliters are as follows: 1–3, 5; 4, 3; 5, 2; 6–7, 3; 8, 25; 9, 27; 10, 25; 11, 92; 12, 25 ml of CH_3OH). Fraction 8 contained 50·7 mg of a homogeneous (TLC, Alumina-G, n-hexane–5 per cent Et_2O) liquid material: $[\alpha]_D^{25} - 89°$ (*c*. 3·5, 95% EtOH); i.r. (CH_2Cl_2) 3·4, 3·58, 3·62,

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* A preliminary account of the preparation of Δ^6-dehydrodeoxynupharidine and its conversion to 7-epi- and deoxynupharidine has been given elsewhere.[8] Details will be disclosed in a subsequent publication.

[5] R. BARCHET and T. P. FORREST, *Tetrahedron Letters* 4229 (1965).

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·68, 6·6, 6·68, 8·62, 9·4, 9·75 and 11·45 μ; NMR ($CDCl_3$, 2%T MS, 10 τ) 9·26 (d, 5·5 Hz, 3 H, $CHCH_3$), 9·08 (d, 3 Hz, 3 H, $CHCH_3$), 8·9–7·8 (m, 12 H), 2·7–3·1 (m, 2 H), 3·69 (q, 1·5 and 1 Hz, 1 H, β-furanyl) and 2·78 τ (m, 2 H, α-furanyl); NMR (C_6H_6) 9·32 (d, 3 H), 9·13 (d, 3 H), 8·9–7·8 (m, 12 H), 6·3–6·9 τ; m.s. *m/e* 233 (M^+), 136, 107, 98 (base peak), 94 (RMU6 Hitachi-Perkin-Elmer, all glass heated inlet, 70 eV, chamber temperature 160–165°).

7-*Epideoxynupharidine Hydrochloride*

A 50 mg sample of 7-epideoxynupharidine was treated with 3 drops of conc. HCl in CH_3OH at 0°. The mixture was evaporated to dryness and the residue was recrystallized from a mixture of CH_3OH–Et_2O (3×) to afford 39 mg of crystals: m.p. 255–258°; admixture m.p. with 7-epideoxynupharidine hydrochloride[8] 255–258°; $[\alpha]_D^{25}$ – 39·7° (*c*. 0·79, 95% EtOH). The analytical sample was dried at 56° (0·05 mm) overnight. (Found: C, 66·56; H, 8·93; N, 5·17. Calc. for $C_{15}H_{24}NOCl$: C, 66·77; H, 8·97; N, 5·19%.)*

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* The elemental analysis was determined by Galbraith Laboratories, Knoxville, Tennessee.