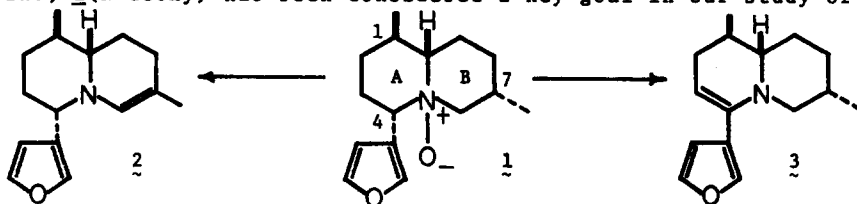


THE MEISENHEIMER TRANSFORMATION OF (+)-NUPHARIDINE*

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(Received in USA 28 February 1972; received in UK for publication 6 March 1972)

The selective introduction of functionality into rings A and B of deoxy-nupharidine, 1(N-deoxy) has been considered a key goal in our study of Nuphar

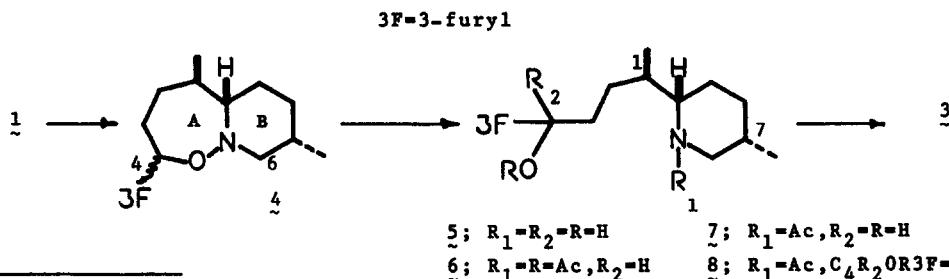


alkaloids because the quinolizidine system then could be degraded systematically for label location in biogenesis studies, labelled for ms studies, and employed in the conversion to other structural types. Earlier (1) we reported the one step, regioselective conversion of (+)-nupharidine, 1, to the Δ^6 -enamine, 2, which in turn was converted to the piperidine alkaloid, nupharamine, and deoxy-nupharidine-6 β ,7 β -d₂,1(N-deoxy). We report here the three step transformation of 1 to the Δ^3 -enamine, 3, which is converted to deoxynupharidine-4 β -d₁,1(N-deoxy). We also report the ms data for the two labelled compounds in order to establish the origin of the principal diagnostic peaks found in the spectra of quinolizidine Nuphar alkaloids.

* This work was supported by Grant A110188, National Institutes of Health, U.S. Public Health Service.

According to a modified procedure (2) for effecting Meisenheimer rearrangements (3), (+)-nupharidine, 1, was heated in refluxing dimethylacetamide for 1.5 hours to obtain, in 65% yield, the liquid, fused-ring, hexahydro-1,2-oxazepine, 4^{**}: ir (film, NaCl plate), 6.69(m, sp), 11.48 μ (s, sp); nmr (100 MHz) δ 0.97(d, 6Hz, 3H, HCCH₃), 1.10(d, 6Hz, 3H, HCCH₃), 1.2-2.3 (several m), 2.3-3.3(3d, ~10Hz, 2.5H, C₆ and/or C₁₀ NCH₂ and/or NCH), 4.53(q, 10 and 6.9Hz, 0.5H, 3FC₄H), 4.88(t, 6.0Hz, 0.5H, 3-FC₄H), 6.38(s, 0.5H, β -furyl H), 6.60(s, 0.5H, β -furyl H), 7.38(m, 2H, α -furyl H); ms 249(5)(M⁺), 114(100), 98(9). The spectral properties and deduced structural features most pertinent to establishing 4 from among three possible rearrangement products were: 1) the chemical shift, integrated intensities and splitting characteristics of δ 4.53 and 4.88 signals demonstrated the partial structure CH₂CH(C)ON<, 2) the base peak m/e 114 corresponded to the loss of ring A with transfer of a hydrogen to the charged fragment C₆H₁₂NO⁺ (ring B), and 3) the integrated intensities of δ 4.53 and 4.88 (C₄) as well as δ 6.38 and 6.60 (β -furyl) protons were both in a 1:1 ratio and indicated that the rearrangement product was a mixture of diastereoisomers present in equal amounts.

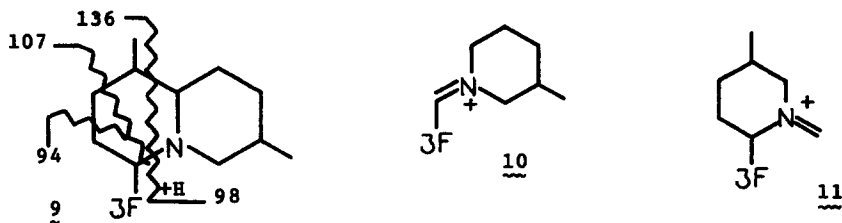
The rearrangement product was converted in 92% yield with zinc powder in water-acetic acid at 25° for 8 hours to the hydroxyamine 5: ir (film, NaCl plate) 2.95-3.20(m, w) 6.68(w, sp), 11.47 μ (s, sp); nmr δ 0.88(d, 6Hz, 3H, HCCH₃), 0.98(d, 6Hz, 3H, HCCH₃), 2.33(m, 1H, C₁₀H), 2.56(br s, 2H, OH and NH, removed



^{**} Satisfactory elemental analyses were obtained for all new compounds. Unless otherwise noted, nmr were run in CDCl₃, TMS 0.0 δ , Varian A-60; ms are given as m/e (% relative intensity) and were determined on a HPE-RMU-6 using an all glass heated inlet, a chamber temperature of 200° and ionizing voltage of 70v; hrms was determined by the HRMS Laboratory, Battelle Columbus Laboratories and where ions are assigned, the mass of the observed is within three millimass units of the calculated.

with D_2O), 2.72(ABq of d, 3 and 1Hz, 2H, C_6H_2), 4.64(t, 6Hz, 1H, C_4H), 6.42(m, 1H, β -furyl H), 7.35(m, 2H, α -furyl H); ms 251(3)(M^+), 98(100), 94(36). The hydroxyamine 5 gave the acetoxyamide 6[ir ($CHCl_3$) 5.79, 6.18, 8.08, 11.47 μ ; ms 335(23)(M^+), 293(47), 140(96), 98(100)] and the hydroxyamide 7[ir (film, NaCl plate) 2.17, 6.20, 6.69, 11.47 μ ; ms 293(66)(M^+), 149(50), 141(59), 140(100), 98(98)] which in turn was oxidized to the ketoamide 8[ir ($CHCl_3$) 5.96, 6.19, 6.40, 6.63, 11.46 μ , ms 291(2)(M^+), 140(100), 98(100), 95(100)]. The hydroxyamine, 5, in CH_2Cl_2 was shaken with an excess of activated MnO_2 for 18 hours at 25° and thereby afforded unstable Δ^3 -dehydrodeoxynupharidine, 3[ir ($CHCl_3$) 5.98(m), 6.22(w), 6.69(m), 11.48 μ (m); nmr δ 4.96(m, 1H, $>NC_4=C_3H$) ms 231(80)(M^+)], which was treated immediately with $NaBH_4$ in ethanol to obtain in 90% yield (-)-deoxynupharidine [α]_D²⁷ = -101° (c 25mg/ml, MeOH), whose ir, nmr and ms were identical with the spectra of an authentic sample.

Treatment of the Δ^3 -enamine with $NaBD_4$ in ethanol gave deoxynupharidine-4 β -d₁: nmr, no C_4H at δ 2.88; ms 234 (M^+ , 100% d₁). A sample of deoxynupharidine-6 β ,7 β -d₂ (ms 235 (M^+), 3% d₁, 97% d₂) was prepared from 2 as disclosed earlier (1). The ms of unlabelled deoxynupharidine was the same as reported (4) and displayed the most prominent peaks at m/e 233(M^+), 136, 98 and 94. M/e 136 and 94, but not 98, were shifted one unit higher in the ms of the 4-d₁ sample. M/e 98 was shifted to m/e 100 in the ms of the 6,7-d₂ sample while m/e 136 and 94 were retained. The fragmentations depicted below in 9 are consistent with the results. Likewise the much less intense m/e 107 is shifted



to 108 in the ms of the 4-d₁ sample but is retained in the ms of the 6,7-d₂ sample. M/e 178 is not a strong peak but is prominent in the ms of thiospirane Nuphar alkaloids. This ion is shifted to m/e 179 and 180 in the ms of 4-d₁ and

6,7-d₂ samples respectively and therefore can be assigned structure 10. However other labelling studies (5) have demonstrated that structure 11 is in agreement with m/e 178 when formed from thiospirane type alkaloids. Shift and retention values for all ions mentioned above were found to be greater than 90%. Finally, moderate intensity ions formed with the loss of C_nH_{2n+1} (n = 1,2,4,5) neutral fragments are shifted one and two units respectively in the ms of 4-d₁ and 6,7-d₂ samples. Shift values range from 70-85% and suggest that the above specified loss occurs chiefly with the removal of methyl groups and/or C₁-C₃ and C₈-C₉. Prominent among the peaks occurring by loss of C_nH_{2n+1} is m/e 190 (M⁺-C₃H₇) which is shifted to 192 (92%) in the ms of the 6,7-d₂ sample but is shifted to 191 to the extent of 35% in the ms of the 4-d₁ sample. This result is consistent with the loss of hydrogen from C₄ followed by a retro-Diels-Alder loss of C₃H₆ from ring A.

REFERENCES

1. R. T. LaLonde, E. Auer, C. F. Wong and V. P. Muralidharan, J. Am. Chem. Soc., 93, 2501 (1971).
2. L. D. Quin and F. A. Shelburne, J. Org. Chem., 30, 3135 (1965).
3. For a recent review of this rearrangement see: R. A. Y. Johnstone in "Mechanisms of Molecular Migrations," Vol. 2, B. S. Thyagarajan, Ed., Interscience, New York, N. Y. 1968, p. 249.
4. O. Achmatowicz, H. Banazek, G. Spitteller and J. T. Wrobel, Tetrahedron Letters, 927 (1964).
5. R. T. LaLonde, C. F. Wong and W. P. Cullen, Tetrahedron Letters, 4477 (1970).