Biomimetic Synthesis of Nazlinin: a Structural Revision

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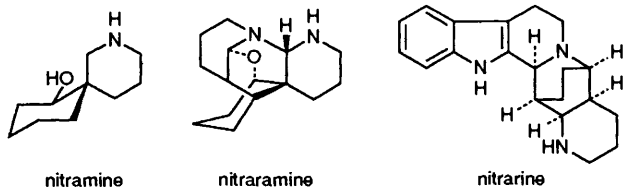
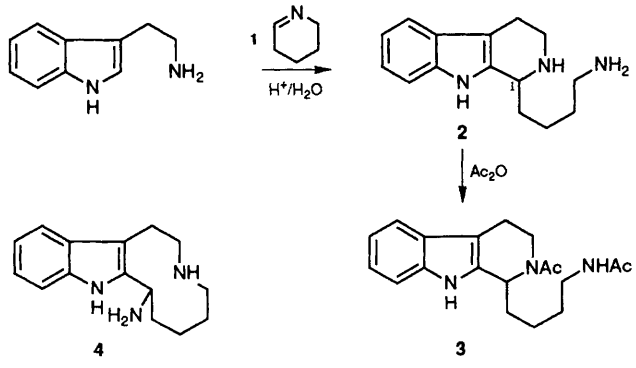
A one-step synthesis of the β-carboline alkaloid nazlinin **2** from its likely biochemical precursors tryptamine and 2,3,4,5-tetrahydropyridine has resulted in a revision of its structure.

Piperidine alkaloids that are present in plants of the genus *Nitraria* are formed *via* biosynthetic pathways that are different from those that are established for *e.g.* Lupine and Lycopodium alkaloids. This has resulted in the isolation and identification of several new spirocyclic[1,2] and indole[2,3] alkaloids, showing a variety of pharmacologically interesting properties[4] (Scheme 1). A recent publication[5] describes the structure elucidation of nazlinin, an indole alkaloid possessing vasorelaxing properties. This serotonin-like amine was isolated from *Nitraria schoberi*, *via* bioassay-guided fractionation. To this racemic† alkaloid a ten-membered indole ring system **4** was assigned on the basis of its NMR and mass spectra. Although the reported spectral data are not in contradiction with structure **4**, an alternative tetrahydro-β-carboline ring system cannot be excluded. The isomeric 1-(3-propylamino)-1,2,3,4-tetrahydro-β-carboline **2** not only possesses more chemical stability, but also fits well in the biosynthesis proposed by us for the Nitraria indole alkaloids, like nitramine.[2]



Scheme 1

To verify this assumption, a one-step synthesis of **2** from the presumed bioprecursors tryptamine and 2,3,4,5-tetrahy-



Scheme 2

† All of the indole alkaloids and some of the spiroalkaloids obtained from *Nitraria* species, are racemic.

Table 1 ^1H and ^{13}C NMR chemical shifts of protonated and unprotonated nazlinin

	Synthetic **2**[a]	**2** TFA-salt[a]	Natural **2**[a]	Diacetate **3**[b]
H-1/δ	4.02	4.72	4.72	5.77
C-1/δ	53.95	54.60	54.60	48.8

[a] CD_3OD. [b] $CDCl_3$.

dropyridine **1**‡ was performed, using trifluoroacetic acid as a catalyst for a Pictet Spengler reaction in water (2 equiv. **1**, 5 h, 95 °C). Compound **2**§ was obtained as a slowly crystallizing syrup in 72% yield. Comparison of the ^1H and ^{13}C NMR spectra of **2** with those reported for the natural product[5] showed large differences in chemical shifts (see Table 1). However, addition of more than 2 equiv. of deuteriated trifluoroacetic acid (TFA) to the NMR sample in CD_3OD produced spectra that were completely identical with those described in the literature.[5] The origin of the acid that protonates natural nazlinin remains unclear.

‡ 2,3,4,5-Tetrahydropyridine **1** (Δ^1-piperidine) is not stable under neutral conditions, due to irreversible imine/enamine dimerization reactions[6] (C–C bond formation). The corresponding symmetric trimer of **1** which contains only intermolecular N–C–N bonds, is an easy to handle, crystalline substance.[7] Dissolving this trimer in water containing one or more equiv. of acid results in a rapid hydrolysis into the protonated monomeric form of **1**, which is stable in solution. **1** has been used before in the biomimetic syntheses of several piperidine alkaloids.[8]

§ *Selected spectroscopic data* for **2**: m.p. 75–78 °C; EIMS *m/z* (% rel. int.): 243 (77), 197 (9), 171 (100), 169 (13), 144 (14). Mass calc. 243.1735; obs. 243.1706. ^1H NMR (300 MHz; CD_3OD): δ 1.5 (4H, m), 1.71 (1H, m), 1.99 (1H, m), 2.67 (4H, m), 2.95 (1H, d × d × d, *J* 12.3, 8.9, 5.2 Hz), 3.31 (1H, m), 4.02 (1H, m, *J* 8.4, 3.5, 1.8 Hz), 6.98 (2H, m), 7.27 (1H, m), 7.36 (1H, d × d, *J* 7.1, 1.3 Hz). ^{13}C NMR (75.5 MHz; CD_3OD): δ 23.00, 24.00, 33.65, 35.26, 42.28, 43.62 (6 × CH_2); 53.95 (CH); 108.73 [C (aromatic)]; 111.78, 118.48, 119.58, 121.88 [4 × CH (aromatic)]; 128.64, 136.91, 137.75 [3 × C (aromatic)].

Nazlinin **2** was further analysed by converting it into its diacetate **3** (acetic anhydride, 80 °C), to differentiate between the CH–NH_2 and the CH_2–NH_2 functionalities that are present in **4** and **2**, respectively. In contrast to the ^1H NMR spectrum of nazlinin **2** (recorded in CD_3OD), the spectrum of diacetate **3** in $CDCl_3$ clearly showed the proton–proton coupling in the CH_2–NHAc system.

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