THE STRUCTURE OF SUBULACINE-N-OXIDE

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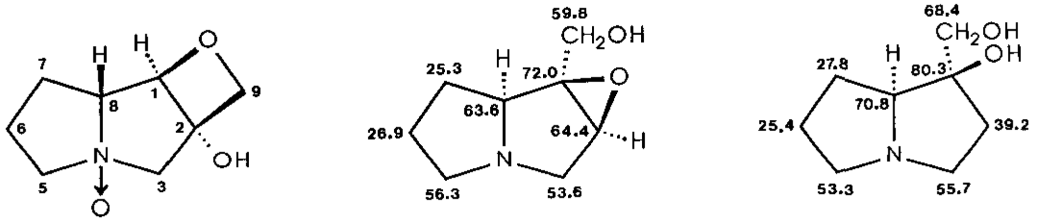
Abstract — The nmr spectra reported for subulacine-N-oxide are shown to be those of 1β,2β-epoxy-1α-hydroxymethyl-8α-pyrrolizidine.

Subulacine-N-oxide, the major alkaloid of Heliotropium subulatum, was recently reported[1] in this journal to possess structure 1, a pyrrolizidine system with an anellated oxetane ring. But the chemical shifts given for the oxetane protons (3.55 and 3.77 ppm) and the geminal coupling constant (12.7 Hz) for the oxetane OCH_2 group indicate immediately, that structure 1 cannot be correct (for a summary of ^{1}H-nmr characteristics of oxetanes see e.g. lit.[2]).

Scheme



1 2 3

Instead, a comparison of the reported[1] ^{1}H-nmr data of subulacine-N-oxide with those of 1β,2β-epoxy-1α-hydroxymethyl-8α-pyrrolizidine (2)[3] (table) shows that the two spectra are identical.

Table ^{1}H-nmr chemical shifts of 1β,2β-epoxy-1α-hydroxymethyl-8α-pyrrolizidine (2) in $CDCl_3$.

	H-2	H-3	H-5	H-6,7 (average)	H-8	H-9
authentic 2[3]	3.60	2.93; 3.09	2.6; 3.0	1.8	3.52	3.81
subulacine-N-oxide[1]	3.55	2.89; 3.03	2.54; 2.93	1.7	3.48	3.77

The small, constant shift difference of ca. 0.06 ppm is probably due to the higher temperature and concentration used in a 60 MHz instrument with an iron magnet as compared to a 400 MHz instrument with a superconducting magnet.

The carbon chemical shifts reported for subulacine-N-oxide (cf. scheme, data and signal assignments from lit.[1]) are in good agreement with **2** as can be seen by a comparison with those of the related compound **3**[4]. Moreover, N-oxidation would cause a downfield shift of C(3), C(5) and C(8) of 15-20 ppm[5] as compared with the shifts of these carbons in the tertiary base[4,5]. The absence of this downfield shift again rules out N-oxide structure **1**. As N-oxidation imparts high crystallinity and water solubility to pyrrolizidine alkaloids[5], an N-oxide group is also improbable for chemical reasons (subulacine-N-oxide was isolated as a chloroform-soluble oil[1]). Furthermore, the reported absorption in the ir spectrum at 1180-1280 cm^{-1} (typical rather for heteroaromatic N-oxides) can not be attributed to an $N^{+}-O^{-}$ group since aliphatic N-oxides absorp at 950-970 cm^{-1} (cf. lit.[6]).

Thus, the origin of the peak at 171 m/z in the mass spectra reported[1] for subulacine-N-oxide and the cause of the resistance of this hydroxymethylated alkaloid to acetylation and oxidation[1] remain open. Since the N-oxide of **2** as well as its acetate have not been described in the literature, continuation of the research on the alkaloids of *Heliotropium subulatum* seems warranted.

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