Naphthyridine Chemistry. XVI. A Literature Correction – The Preparation of 2,4-Dimethyl-7-ethoxy-1,8-naphthyridine 1-Oxides

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The *N*-oxidation of 2,4-dimethyl-7-ethoxy-1,8-naphthyridine has been shown to afford the 1-oxide rather than the 1,8-dioxide as reported by others.

We have recently been interested in the study of naphthyridine *N*-oxides and have observed, that the *N*-oxidation of 1,8-naphthyridine with peracids affords only the mono-*N*-oxides (1-3). Thus, a report that the oxidation of 2,4-dimethyl-7-ethoxy-1,8-naphthyridine (**1**) affords the 1,8-dioxide (**2**) created some skepticism and caused us to repeat this synthesis.

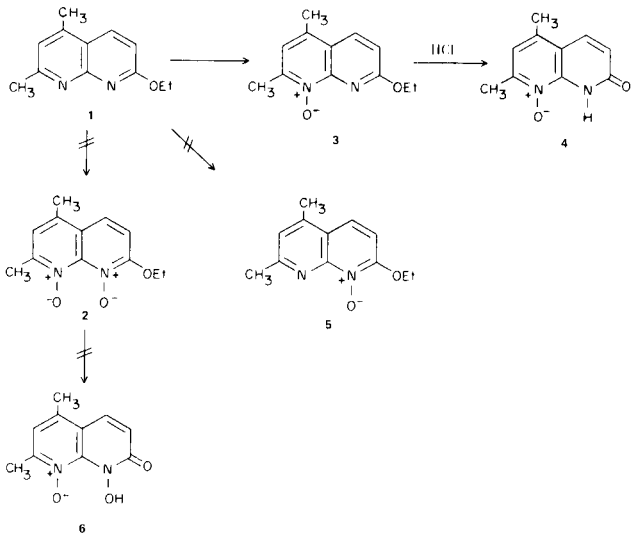
We now wish to report that the oxidation of 2,4-dimethyl-7-ethoxy-1,8-naphthyridine (**1**), under the reported conditions, affords a mixture, as shown by tlc, of the starting material (**1**) and 2,4-dimethyl-7-ethoxy-1,8-naphthyridine 1-oxide (**3**). The reported melting point 105° (4) of the "di-*N*-oxide" is, in fact, the melting point of a mixture of the mono-*N*-oxide and the starting material. Thus, we have ample proof of the incorrectness of the report.

The pure *N*-oxide (**3**) was obtained by chromatography on a neutral alumina column and gave the correct elemental analysis and mass spectrometric molecular weight for a mono-*N*-oxide. An examination of the papers by Colonna and coworkers revealed that they only reported an elemental analysis in terms of the percent carbon and nitrogen rather than a total analysis (4).

We have already shown that the N_1-oxidation of naphthyridines causes considerable shielding of H-2 (0.4-0.6 ppm) and H-4, (0.4-0.5 ppm) while having little effect on the chemical shift of H-3.

Thus, we can apply this information to differentiate between structures **3** and **5** (see Scheme I). If we are dealing with the N_8-oxide (**5**), we would anticipate a shielding effect of 0.4-0.5 ppm on H-4 upon going from the free base (**1**) to the *N*-oxide (**5**). In fact, there is little change in the chemical shifts of any of the protons in the *N*-oxide as compared to the non-oxidized precursor (**1**) (see Table I). Consequently, we can conclude that the *N*-oxidation of the naphthyridine (**1**) under the reported conditions affords the 1-oxide (**3**), exclusively.

SCHEME I



Colonna and coworkers also reported that the hydrolysis of their "di-*N*-oxide" affords the hydroxamic acid (**6**). We find that hydrolysis of the *N*-oxide (**3**) does indeed form a compound with a melting point as that reported for compound **6** (m.p. 250-251°). However, again an elemental analysis and mass spectrometric molecular weight shows it to have the elemental composition in agreement with structure **4**. The correctness of this assigned structure is confirmed by a comparison of its pmr spectrum with that of 1,2-dihydro-2-oxo-1,8-naphthyridine (**1**) whose H-3 and H-4 chemical shifts are essentially identical to the corresponding protons in compound **4**.

The statement that the hydrolysis product is a hydroxamic acid, because it forms a colored complex with ferric chloride is also in error, since 1,8-naphthyridine 1-oxide also forms a colored complex with ferric chloride.

TABLE I

Nmr Spectral Data (δ (ppm)) of some 1,8-Naphthyridines (b)

Compound	Solvent	H-3	H-4	H-5	H-6	H-7	2-CH_3	4-CH_3	$J_{3,4}$	$J_{5,6}$	$J_{5,7}$	$J_{6,7}$
1	$CDCl_3$	7.00	---	8.06	6.86	---	2.68	2.55	---	9.0	---	---
3	$CDCl_3$	7.04	---	8.10	7.00	---	2.68	2.56	---	9.0	---	---
	D_2O	7.05	---	7.84	6.78	---	2.63	2.32	---	9.0	---	---
4	D_2O	7.38	---	8.10	6.74	---	2.72	2.60	---	9.0	---	---
	DMSO	7.40	---	8.20	6.78	---	2.64	2.54	---	8.5	---	---
7(a)	DMSO	6.58	7.98	8.12	7.23	8.50	---	---	8.5	8.0	2.0	6.0

(a) The reader is reminded, that the numbering rules require compound **7** to be numbered differently than compounds **1**, **3**, and **4**. Thus, H-3 in compound **7** corresponds, structurally, to H-6 in compound **4**. (b) Obtained as dilute solutions, in the solvents indicated, with a Varian HA-100 spectrometer.

These data, unfortunately, still leave us without the established existence of a 1,8-naphthyridine 1,8-dioxide, a compound, which, if ever prepared, should have some rather intriguing properties.

EXPERIMENTAL

The compounds were prepared as described in reference 4 with the following modifications:

2,4-Dimethyl-7-ethoxy-1,8-naphthyridine 1-Oxide (**3**).

The crude oxidation product, (0.9 g.) now identified as compound **3**, was purified by chromatography on (7.0 g.) neutral Grade III alumina. Elution with ether afforded 0.4 g. of compound **1**. Further elution with chloroform affords 0.5 g. of compound **3** (134-135°, mass spec. mol. wt. 218).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.06; H, 6.42; N, 12.84. Found: C, 66.10; H, 6.51; N, 12.79.

1,2-Dihydro-5,7-dimethyl-2-oxo-1,8-naphthyridine 8-Oxide (**4**).

This compound (m.p. 250°; mass spec. mol. wt. 190) was prepared as described in reference 4.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.16; H, 5.26; N, 14.74. Found: C, 63.06; H, 5.40; N, 14.83.

2-Hydroxy-1,8-naphthyridine (**7**).

To 2-chloro-1,8-naphthyridine (**3**) (164 mg., 1 mmole) was added 5% of sodium hydroxide (10 ml.) and the resulting mixture was heated under reflux for 12 hours. The solution was acidified to *p*H 5 with dilute hydrochloric acid and continuously extracted (24 hours) with chloroform. The extracts were evaporated to dryness and the residue was sublimed (150°/0.05 mm) to afford the pure product **7** (100 mg., 0.69 mmole, 69%; m.p. 198°).

Anal. Calcd. for $C_8H_6N_2O$: C, 65.74; H, 4.13; N, 19.17. Found: C, 65.51; H, 3.99; N, 19.42.

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