

Naphthyridine Chemistry. XII. Syntheses of *N*-Oxides

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The syntheses of the various 1,*X*-naphthyridine mono- and di-*N*-oxides as well as the 2-mono- and 2,7-di-*N*-oxides of 2,7-naphthyridine are reported. The PMR spectra of these compounds have been analyzed in detail.

One of the logical extensions of our recent studies dealing with the syntheses of various naphthyridines (1) involves the preparation and study of some of the spectral properties of the various mono- and di-*N*-oxides of these compounds. This investigation becomes especially intriguing when one considers the different possible interactions that might occur between the oxidized and the non-oxidized nitrogen atom in the mono-*N*-oxides. The most eminently suitable technique for examining these interactions clearly lies in the domain of proton magnetic resonance spectroscopy.

The only parent naphthyridine-*N*-oxides that were known at the outset of these studies were those of 1,5-naphthyridine which had been prepared by Hart (2). Since completion of this work, a paper by Kobayashi, Kumadaki and Soto (3) appeared, describing the syntheses of the various 1,6-naphthyridine *N*-oxides. These workers prepared the 6-oxide in yields of 0.6 to 9.0 percent and the 1,6-di-oxide in 85.5 percent yield by direct oxidation of the parent naphthyridine. Reduction of the di-oxide afforded the 1-oxide of 1,6-naphthyridine.

The Skraup reaction on 4-aminopyridine *N*-oxide is reported (2) to yield the 1,6-naphthyridine-6-oxide in less than five percent yield. Several other substituted derivatives of various naphthyridine *N*-oxides have also been reported (4). Among these compounds, the described formation of the 4,5-dimethyl-7-ethoxy-1,8-naphthyridine 1,8-di-oxide warrants some attention in view of the highly hindered environment in which two such oxygen atoms have to exist.

We now wish to report the syntheses and NMR spectral properties of all of the 1,*X*- and 2,7-naphthyridine-mono- and di-*N*-oxides (5). After considerable experimentation it was found that the most suitable *N*-oxidizing agents for all of the naphthyridines are either *m*-chloroperbenzoic or perbenzoic acid itself. The mixtures of mono-*N*-oxides were obtained by allowing the peracids to stay in contact with the appropriate naphthyridine dissolved in chloroform for 8 hours at room temperature. The isomeric mono-*N*-oxides were then separated by chromatography on neutral Grade III alumina. In order to extend the

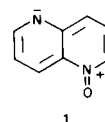
oxidation to the formation of the di-*N*-oxides it is necessary to reflux the chloroform solutions for one hour.

The establishment of the site of substitution of the oxygen atoms in the isomeric 1,6- and 1,7-naphthyridine *N*-oxides is readily accomplished by NMR spectroscopy. The chemical shift assignment of H₂ and H₄ in the various 1,*X*-naphthyridine 1-oxides is based upon the fact that H₄ is not only coupled to H₂ and H₃, but also to H₈, while H₂ is only coupled to H₃ and H₄. The identification of H₄ vs H₈ in the 1,5-naphthyridine 1-oxide is based upon the observation that H₈ in those 1-oxides where no ambiguity of assignment exists, is considerably more shielded than H₄. The assignments of the chemical shifts of H₂ and H₄ in the 1,8-naphthyridine 1-oxide is based upon the observation that H₂ in the 1,5-naphthyridine 1-oxide is more deshielded than is H₄. The same trend must exist in the 1,8-naphthyridine series. The multiplicities of the remaining protons in the various 1-oxides define their chemical shifts in an unambiguous manner. The assignments of the H₂ and H₄ chemical shifts of the 1,5-naphthyridine 1,5-di-oxide are determined by a comparison of J₂₃ and J₃₄ of the 1,5-naphthyridine 1-oxide with the corresponding values of the di-oxide.

Because of the multitude of resonance and inductive effects that can be envisioned to be operating in the various compounds, it is of some interest to discuss the NMR spectra by comparing the differences between the chemical shifts of the appropriate parent naphthyridine with its *N*-oxide.

The H₂ and H₄ Protons in Naphthyridine Mono-*N*-oxides.

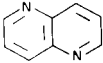
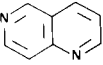
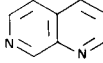
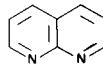
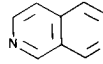
One of the resonance contributing structures of the ground-state of 1,5-naphthyridine 1-oxide might be 1.



If this is in fact the case, we would expect that the chemical shift difference between the parent compound and H₂

TABLE I (Part 1)

NMR Spectral Data of Various Naphthyridine *N*-Oxides (δ (ppm))

	H ₁	H ₂	H ₃	H ₄	H ₅	H ₆	H ₇	H ₈	Solvent
	---	8.97	7.59	8.40	---	8.97	7.58	8.40	CDCl ₃
	---	8.63	7.52	7.80	---	8.63	7.52	7.80	D ₂ O
1-oxide	---	8.55	7.52	8.00	---	9.03	7.68	9.03	CDCl ₃
1,5-di-oxide	---	8.86	7.92	8.70	---	8.86	7.92	8.70	D ₂ O
	---	9.10	7.52	8.28	9.28	---	8.76	7.93	CDCl ₃
	---	9.08	7.73	8.28	8.96	---	8.60	7.60	D ₂ O
1-oxide	---	8.64	7.45	7.87	9.34	---	8.82	8.49	CDCl ₃
6-oxide	---	8.94	7.51	8.04	8.76	---	8.32	7.92	CDCl ₃
1,6-di-oxide	---	8.80	7.78	8.24	9.20	---	8.50	8.58	D ₂ O
	---	9.14	7.67	8.26	7.72	8.73	---	9.66	CDCl ₃
	---	8.68	7.52	8.04	7.48	8.24	---	8.78	D ₂ O
1-oxide	---	8.56	7.53	7.74	7.72	8.75	---	10.07	CDCl ₃
7-oxide	---	8.98	7.51	8.18	7.74	8.22	---	8.94	CDCl ₃
1,7-di-oxide	---	8.80	7.70	8.28	8.23	8.46	---	9.47	D ₂ O
	---	9.22	7.48	8.22	8.22	7.48	9.22	---	CDCl ₃
	---	8.80	7.43	7.99	7.99	7.43	8.80	---	D ₂ O
1-oxide	---	8.81	7.44	7.81	8.40	7.71	9.12	---	CDCl ₃
	9.26	---	8.61	7.51	7.51	8.61	---	9.26	CDCl ₃
	9.02	---	8.44	7.53	7.53	8.44	---	9.02	D ₂ O
2-oxide	8.84	---	8.27	7.67	7.61	8.65	---	9.16	CDCl ₃
2,7-di-oxide	9.07	---	8.38	8.12	8.12	8.38	---	9.07	D ₂ O

in this isomer should be modified in a manner different from that observed for H₂ in all of the other 1,X-naphthyridine 1-oxides. Since there is no such difference observed, we conclude, that this structure is not a major contributor. In fact, the *N*-oxide linkage causes shielding (0.4-0.6 ppm.) of H₂ in all of the instances examined. A similar shielding effect (0.4-0.5 ppm.) is evident in all of the H₄ nuclei. Because these differences are essentially identical for H₂ and H₄ in the individual compounds one can suggest that similar increases in the ground-state densities occur at these two positions.

The H₈ Protons in Naphthyridine *N*-Oxides.

The anisotropy effect of the oxygen atom on N₁ in the different 1,X-naphthyridine 1-oxides expresses itself by

causing substantial *deshielding* (0.41-0.63 ppm.) of the proton on C₈. This observation should be a very useful aid in the structure determination of related compounds.

The "Remaining" Protons in Naphthyridine 1-Oxides.

The major effects caused by the *N*-oxide linkages are not expected to go beyond the *ortho*-, *para*-, and *peri*-situated protons and consequently only minor differences in the chemical shifts between the related parent naphthyridine protons and the 1-oxides are to be expected. The data presented in Table I are in agreement with this estimate.

The *ortho*-Protons of the 1,X-Naphthyridine X-oxides.

The shielding effect of the *N*-oxide grouping is also

TABLE I (Part 2)

Spin-Spin Coupling Constants

	J ₁₃	J ₁₄	J ₁₅	J ₂₃	J ₂₄	J ₃₄	J ₄₈	J ₅₆	J ₅₇	J ₅₈	J ₆₇	J ₆₈	J ₇₈
1,5-Naph.	---	---	---	4.1	1.8	8.0	0.6	---	---	---	4.1	1.8	8.0
1-oxide	---	---	---	6.0	1.0	9.0	0.7	---	---	---	3.5	1.0	8.5
1,5-di-oxide	---	---	---	6.0	---	9.0	---	---	---	---	6.0	---	9.0
1,6-Naph.	---	---	---	4.1	1.9	8.2	0.9	---	---	0.9	---	---	6.0
1-oxide	---	---	---	6.0	1.0	8.0	0.6	---	---	0.6	---	---	6.0
6-oxide	---	---	---	4.2	1.4	8.2	0.6	---	2.0	0.6	---	---	7.3
1,6-di-oxide	---	---	---	6.0	1.2	8.5	0.5	---	1.8	---	---	---	(a)
1,7-Naph.	---	---	---	4.1	1.6	8.4	0.9	5.6	---	0.9	---	---	---
1-oxide	---	---	---	6.0	1.5	8.5	0.6	6.0	---	---	---	---	---
7-oxide	---	---	---	4.2	1.8	8.5	0.7	7.0	---	---	---	1.5	---
1,7-di-oxide	---	---	---	6.0	1.0	8.5	0.8	7.5	---	---	---	1.8	---
1,8-Naph.	---	---	---	4.2	2.0	8.0	---	8.0	2.0	---	4.2	---	---
1-oxide	---	---	---	6.0	1.5	8.0	---	8.0	1.9	---	4.2	---	---
2,7-Naph.	---	0.8	0.8	---	---	6.0	0.8	6.0	---	0.8	---	---	---
2-oxide	1.4	---	0.6	---	---	7.2	0.2	6.0	---	---	---	---	---
2,7-di-oxide	1.8	---	0.6	---	---	7.0	0.6	7.0	---	0.6	---	1.8	---

(a) This coupling constant cannot be evaluated since the outer members of the AB system are not discernible.

TABLE II

Analytical Data of the Naphthyridine *N*-Oxides:

Compound	M.p.	% Yield	Anal. Calcd. for: C ₈ H ₆ N ₂ O		
			%C, 65.74	%H, 4.13	%N, 19.17
			Found:		
			%C	%H	%N
1,6-Naph.-1-oxide (a)	158-160 (b)	12	65.69	3.98	19.42
1,6-Naph.-6-oxide	158 (c)	38	65.55	4.13	19.20
1,7-Naph.-1-oxide	190-191	3	65.92	4.13	19.20
1,7-Naph.-7-oxide	150-151	45	65.70	3.99	19.14
1,8-Naph.-1-oxide	132-133	47	65.89	4.07	19.26
2,7-Naph.-2-oxide	228-229	72	65.91	4.08	19.09
1,5-Naph.-1-oxide	127-128 (d)	67	65.64	4.08	19.05
			Anal. Calcd. for: C ₈ H ₆ N ₂ O ₂		
			%C, 59.26	%H, 3.73	%N, 17.29
			Found:		
			%C	%H	%N
1,6-Naph.-1,6-dioxide	285 dec. (e)	53	59.46	3.55	17.10
1,7-Naph.-1,7-dioxide	275 dec.	47	59.36	3.82	17.40
2,7-Naph.-2,7-dioxide	> 300	20	59.50	3.96	17.09

(a) Naph. = Naphthyridine. (b) M.p. (reported) (3) 155-156°. (c) No observable melting range, m.p. (reported) (3) 150°. (d) M.p. (reported) (2) 125-127°. (e) M.p. (reported) (3) 278°.

reflected in the differences between the chemical shifts of the protons situated *ortho* to the *N*-oxide linkage in the parent 1,X-naphthyridines and their corresponding X-oxides, along with the corresponding protons of the 2,7-naphthyridine 2-oxide, where an average shielding of 0.4 ppm. is evident, (see Table I). The only exception to this is observed in the instance where H₈ is *peri*- to a nitrogen atom, as is the case in the 1,7-naphthyridine 7-oxides, in which the shielding effect is even more severe (0.71 ppm.). The 1,X-Naphthyridine Di-*N*-oxides.

Unfortunately, these compounds are insufficiently soluble, as a group, in deuteriochloroform to enable their spectra to be obtained in this solvent. It is because of this that deuterium oxide was used. Since this solvent introduces considerable complexity because of, as yet not understood, hydrogen bonding in these compounds, we consider it meaningless to attempt to draw any conclusions from an examination of the chemical shifts of the various protons. The only outstanding feature involves those protons which are situated *peri*- to the *N*-oxide linkages, where, again, substantial chemical shift differences between the parent compounds and their respective di-*N*-oxides are apparent. This is reflected by the considerable deshielding (0.69-0.98 ppm.) noted for these protons in comparison to the related atoms in the parent compounds. Attempted Synthesis of the 1,8-Naphthyridine 1,8-Di-oxide.

All attempts at preparing the highly elusive and potentially most interesting 1,8-naphthyridine 1,8-di-oxide have, unfortunately, so far failed. Nevertheless, in view of the fact that we have been able to di-protonate 1,8-naphthyridine under highly acidic conditions and at low temperatures (6), it appears potentially feasible that the 1,8-di-oxide may still be capable of being coaxed into existence. Relative Yields of the Two Isomeric Mono-*N*-oxides.

The relative amounts of the two isomeric mono-*N*-oxides of 1,6- and 1,7-naphthyridine obtained are considerably different. Thus, the 7-oxide of the 1,7-naphthyridine is formed in a 15:1 ratio over the isomeric 1-oxide, while the 6-oxide of the 1,6-naphthyridine is formed in a ratio of 3:1 over the corresponding 1-oxide. These differences reflect the relative basicities of the two nitrogen atoms, where the isoquinoline-like nitrogen in these naphthyridines is the more basic of the two heteroatoms.

Comments Regarding the Reported NMR Data of the 1,6-Naphthyridine Oxides.

The reported (4) nmr spectral analyses of the 1,6-naphthyridine 1-oxide and 1,6-di-oxide are in general agreement with our data. However, the reported chemical shift

assignments of H₄ (δ 8.4 ppm.) and H₇ (δ 8.16 ppm.) in the 6-oxide must be reversed in order to coincide with J₃₄ and J₇₈. Furthermore, the reported analyses do not include the *meta*- (H₂-H₄) and the cross-ring (H₄-H₈) spin-spin coupling constants as well as J₅₆ in the 6-oxide and the 1,6-di-oxide. These values further substantiate our H₄ and H₇ chemical shift assignments of the 1,6-naphthyridine-6-oxide.

Spin-Spin Coupling Constants.

We have noted in earlier papers, dealing with the mono-protonated and *N*-alkylated naphthyridines, that whenever there is developed a positive charge on a nitrogen atom of the naphthyridines, the protons situated on the two *ortho*-carbon atoms will be spin-spin coupled. This same behavior is observed in the different naphthyridine *N*-oxides where this atom arrangement (HC=N-CH=) is present. These coupling constants (for example, J₁₃ in the 2,7-naphthyridine *N*-oxides) are about 1.6 cps. This observation can also be used in further confirmation of the site of *N*-oxidation in some of these substances.

Another, rather drastic, change occurs in the vicinal coupling constants where an *N*-oxide linkage is directly bonded to one of these carbon atoms. In these cases, *N*-oxidation increases the coupling constant by about 2 cps (J₂₃, for example, in 1,5-naphthyridine 1,5-di-oxide changes from 4.1 in the parent compound to 6.0 in the oxidized material). This change may well reflect a bond-shortening of the adjacent C-C bonds (C₂-C₃ in the 1,X-naphthyridines 1-oxides, C₅-C₆ and C₇-C₈ in the 1,X-naphthyridine X-oxides).

EXPERIMENTAL (7).

General Procedure for the Preparation of the Mono-*N*-oxides.

Equimolar amounts of the appropriate naphthyridine in 1 g. amounts (7.7 moles) and the perbenzoic acid were dissolved in 100 ml. each of chloroform and the solutions were combined at room temperature. The reaction mixture was then allowed to stand at room temperature for a period of 8 hours. During this time the mixture became pale yellow. After this period of time, the chloroform was carefully removed under vacuum at 0°. To the remaining residue was then added 40 ml. of a saturated aqueous solution of sodium carbonate and the resulting solution was continuously extracted with chloroform for a period of 12 hours. The dried chloroform extract (anhydrous magnesium sulfate) was then evaporated onto about 5 g. of neutral alumina. This alumina mixture was placed on top of an alumina-packed chromatographic column (75 g. of neutral, Grade III, Brockman scale) which had been prepared with dried benzene. Elution with a mixture of 90 ml. of methanol and 1800 ml. of ethyl acetate afforded the separated isomers in different fractions. The material thus obtained was then sublimed at 100°/0.05 mm. This procedure is applicable for the isolation of the 1,6- and the 1,7-naphthyridine mono-*N*-oxides.

1,8-Naphthyridine 1-Oxide.

The solution of the 1,8-naphthyridine and perbenzoic acid (20 percent excess) prepared as described above was heated under reflux for one hour and worked-up in a manner identical to that described above except that the water extract was freeze-dried and the remaining solid was extracted with chloroform by means of a Soxhlet extractor. The extracted mono-*N*-oxide was then further purified by recrystallization from dry benzene.

General Procedure for the Preparation of the Di-*N*-oxides.

The same general procedure as described for the preparation of the mono-*N*-oxides was employed except that the reaction mixture was refluxed for one hour and that twice the equimolar amount of peracid was used. The water solution is then continuously extracted for three days and the di-*N*-oxides isolated in this manner are recrystallized from absolute ethanol.

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(5) The content of this paper has been delivered by W. W. Paudler as part of several lectures on Naphthyridine Chemistry presented at various European Universities during the months of April-July, 1969.

(6) These studies will be the content of a forthcoming paper to be published in this journal.

(7) PMR spectra were obtained as dilute (5w/v) solutions with a Varian HA-100 spectrometer. Elemental analyses were done by Mrs. K. Decker of this department. Mass spectra were obtained on all compounds with a Hitachi-Perkin Elmer RMU-6E mass spectrometer, with an ionization potential of 80 eV and an inlet system temperature of 180°. The experimental molecular weights of the various *N*-oxides are in agreement with the theoretical molecular weights. After loss of 16 mass units (oxygen), the compounds fragmented as "normal" naphthyridines. Melting points are corrected.

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