1,5-NAPHTHYRIDINES AND THEIR N-OXIDES

I. 2-AMINO- AND 2-HYDROXY-1,5-NAPHTHYRIDINE N-OXIDES

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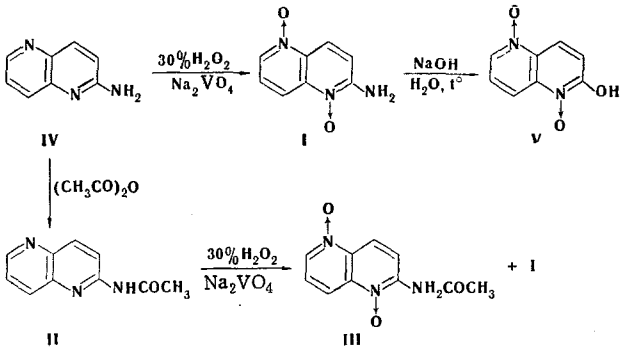
The N-oxidation reactions of 2-hydroxy- and 2-amino-1,5-naphthyridines were investigated. 2-Hydroxy-1,5-naphthyridine 5-oxide and 2-hydroxy-, 2-amino-, and 2-acetamido-1,5-naphthyridine 1,5-dioxides were obtained. The structures of the compounds obtained were proved by means of IR and PMR spectroscopy.

In a continuation of our search for biologically active compounds among the N-oxides of aromatic nitrogen-containing heterocycles, we have accomplished the synthesis of 1,5-naphthyridine N-oxides, which can be considered to be analogs of antibiotics of the aspergillic acid group. It is known that aspergillic acid analogs in the pyridine series have antibacterial activity [1].

It has been demonstrated [1,2] that the oxidation of a ring nitrogen adjacent to a hydroxyl group gives rise to considerable difficulties. In addition, it is known that, in contrast to 2-aminopyridine and quinoline N-oxides, the amino group adjacent to the N → O group in 2-aminoquinoxaline N-oxides is readily hydrolyzed in alkaline media to the N-oxides of the corresponding hydroxy derivatives [3].

In order to study the analogous reaction in the 1,5-naphthyridine series, we undertook the synthesis of 2-amino-1,5-naphthyridine 1,5-dioxide (I). Heating 2-acetamido-1,5-naphthyridine (II) with hydrogen peroxide in acetic acid gave a difficult-to-separate mixture of oxidation products. A mixture of I and 2-acetamido-1,5-naphthyridine 1,5-dioxide (III) in a ratio of 2 : 1 was formed in the oxidation of II with hydrogen peroxide in the presence of sodium vanadate. Since it has been shown that the acetamido group is partially hydrolyzed under the conditions of the N-oxidation reaction, we investigated the oxidation of 2-amino-1,5-naphthyridine (IV) and obtained I in 68.4% yield.



Like the amino group of the corresponding quinoxaline derivatives, the amino group in I was relatively easily replaced by a hydroxyl group on heating in alkali solutions, and 2-hydroxy-1,5-naphthyridine 1,5-dioxide (V) was formed.

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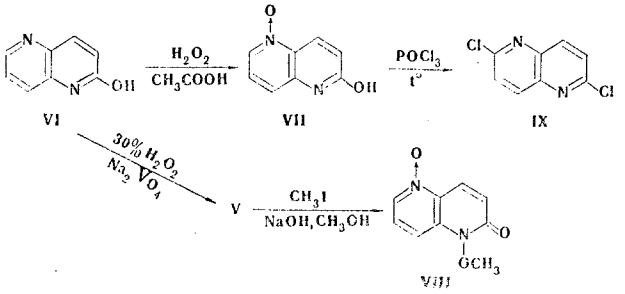
TABLE 1. PMR Spectra of 1,5-Naphthyridine Derivatives*

Comp.	Solvent	δ, ppm					J, Hz				
		H_3	H_4	H_6	H_7	H_8	3,4	4,8	6,7	6,8	7,8
IV	DMSO	7,05	7,99	8,54	7,47	7,86	9,5	0,75	4,2	1,8	8,4
I	DMSO	7,36	8,24	8,36	7,57	8,11	9,8	1,0	6,0	1,0	8,5
I	H_2O	7,59	8,4	8,53	7,73	8,4	9,6	—	6,0	—	8,0
VI	DMSO	6,70	7,87	8,43	7,43	7,69	9,0	1,0	4,2	2,0	8,0
VII	DMSO	6,67	8,35	8,09	7,33	7,21	9,9	0,5	6,0	1,0	8,7

*The spectra were recorded with a JNM-4H-100 spectrometer with an operating frequency of 100 MHz with tetramethylsilane and tert-butyl alcohol as the internal standards. The spectrum of 2-hydroxy-1,5-naphthyridine N,N'-dioxide was not examined, since V undergoes irreversible transformations in DMSO.

The possibility of the direct N-oxidation of 2-hydroxy-1,5-naphthyridine (VI) was also investigated. Resinification occurred when VI was heated with 10% peracetic acid, and a difficult-to-separate mixture of oxidation products was obtained. Heating of VI with hydrogen peroxide in acetic acid led to oxidation of the nitrogen in the 5 position to form 2-hydroxy-1,5-naphthyridine 5-oxide (VII) in 87% yield. Compound V could be obtained in high yield (72.8%) by heating VI with hydrogen peroxide in the presence of sodium vanadate (a mixture of V and VII was isolated at 20°).

The presence of an intense band of the stretching vibrations of an amide carbonyl group in the IR spectra of V and VII attests to the predominant existence of these compounds in the oxo form in the crystalline state.



1-Methoxy-2-oxo-1,5-naphthyridine 5-oxide (VIII) was isolated in the methylation of V with methyl iodide in alkaline media. Deoxidation of the N → O group accompanied by chlorination of the ring occurred when VII was heated with $POCl_3$; the 2-hydroxy (oxo) group was simultaneously replaced by chlorine, and 2,6-dichloro-1,5-naphthyridine (IX) was obtained.

The PMR spectra of unsubstituted 1,X-naphthyridines and their N-oxides have been previously examined [4]. It seemed of interest to examine the PMR spectra of the 1,5-naphthyridine derivatives that we obtained.

As in the case of N-oxides of other six-membered aromatic heterocycles [5,6], in the PMR spectra of I and VII one observes shielding of the proton adjacent to the N → O group ($\Delta\delta$ H_6 = +0.18 and +0.34, respectively*) and a considerable increase in the $J_{6,7}$ spin–spin coupling constant as compared with the constant of the unoxidized compounds (see Table 1). Just as in the N-oxides of unsubstituted naphthyridine [4], the protons in the peri position relative to the N → O group in I and VII are deshielded. However, the signals of the H_4 and H_8 protons of I, which simultaneously occupy the para and peri positions with respect to the N → O groups, are shifted to weak field to a considerably lesser degree ($\Delta\delta$ $H_4 = \Delta\delta$ $H_8 = -0.25$) than the signal of the H_4 proton in VII, which is situated only in the peri position relative to the N → O group

*$\Delta\delta$ is the difference between the chemical shifts of the signals of the protons of 2-hydroxy- or 2-amino-1,5-naphthyridines and the corresponding N-oxides. A positive $\Delta\delta$ means a shift of the proton signals to strong field, while a negative $\Delta\delta$ means a shift to weak field.

($\Delta\delta H_4 = -0.47$). The H_8 proton of VII, which is in the para position relative to the N → O group, is shifted to strong field ($\Delta\delta H_8 = +0.48$), just like the para protons in pyridine N-oxide and 1,5-naphthyridine N-oxide [4,5]. The H_3 proton of I is shifted to weak field as compared with the H_3 proton of IV. In comparison with unsubstituted 1,5-naphthyridine N,N'-dioxide, the signals of the ring protons of I lie at stronger field, which can be explained by the effect of the NH_2 group.

The N-oxides of the 1,5-naphthyridine derivatives had weak in vitro activity with respect to staphylococcus, Escherichia coli, and the dysentery bacillus.

EXPERIMENTAL

2-Amino-1,5-naphthyridine N,N'-Dioxide (I). A mixture of 3.62 g (25 mmole) of IV, 0.5 g of $Na_2VO_4 \cdot 2H_2O$, and 20 ml of 30% H_2O_2 was stirred at 20-25° for 5 days. It was then cooled, and 3.8 g of a precipitate with mp 169-171° was removed by filtration. The precipitate was added with stirring to a mixture of 10 ml of concentrated hydrochloric acid and 10 ml of a 23% alcohol solution of hydrogen chloride. The mixture was cooled to 15°, and 4.35 g of the hydrochloride of I was removed by filtration. The hydrochloride yielded 3.0 g (68.4%) of I with mp 280-282° (from alcohol). The bright yellow needles were only slightly soluble in most organic solvents, had R_f 0.125* (bright yellow spot), and gave a dark violet coloration with $FeCl_3$. Found: C 54.4; H 4.1; N 23.7%. $C_8H_7N_3O_2$. Calculated: C 54.2; H 4.0; N 23.7%.

Oxidation of 2-Acetamido-1,5-naphthyridine (II). A mixture of 3.67 g (19.6 mmole) of II, 0.4 g of $Na_2VO_4 \cdot 2H_2O$, and 15 ml of 30% H_2O_2 was stirred at 20-25° for 72 h. It was then cooled to 5°, and 3.1 g of a mixture of I and III was removed by filtration. The mixture was treated with hot acetone, and the insoluble material was removed by filtration and recrystallized from alcohol to give 1.1 g of I with mp 275-278°; an additional 0.8 g of I was obtained from the mother liquor. The yield of I was 1.9 g (10.7 mmole) or 54.7%. The acetone mother liquor was vacuum-evaporated to a small volume, and 1.1 g (4.9 mmole or 25%) of III was removed by filtration. The light yellow needles had mp 230-230.5° (from alcohol), were soluble in most organic solvents, and had R_f 0.178 (light green spot). Found: C 54.4; H 4.1; N 19.2%. $C_{10}H_9N_3O_3$. Calculated: C 54.8; H 4.1; N 19.2%.

2-Hydroxy-1,5-naphthyridine 1,5-Dioxide (V). A. A mixture of 0.45 g (30.8 mmole) of VI, 0.8 g of $Na_2VO_4 \cdot 2H_2O$, and 3.5 ml of 30% H_2O_2 was stirred at 60-65° for 8 h. It was then cooled to 10°, and the precipitate was removed by filtration to give 0.4 g (72.8%) of light yellow crystals of V with mp 286° (from water) and R_f 0.182 (yellow-brown spot). The crystals were only slightly soluble in organic solvents and water, gave a dark cherry-red coloration with $FeCl_3$, and liberated CO_2 from $NaHCO_3$ solutions. Found: C 53.7; H 3.4; N 15.8%. $C_8H_6N_2O_3$. Calculated: C 53.9; H 3.4; N 15.7%. IR spectrum: 1665 cm^{-1} (amide CO).

B. A mixture of 2.5 g (14.1 mmole) of I and 110 ml of 2 N NaOH was refluxed for 45 min, treated with activated charcoal, and filtered. The filtrate was cooled to 20° and acidified to pH 1. The resulting precipitate was removed by filtration to give 1.35 g (53.7%) of V with mp 286°.

2-Hydroxy-1,5-naphthyridine 5-Oxide (VII). A mixture of 1.76 g (12 mmole) of VI, 3.52 ml of 30% H_2O_2, and 30 ml of glacial acetic acid was stirred at 55-60° for 14 h. Water (30 ml) was added to the reaction mass, and the mixture was evaporated to half its original volume. The operation was repeated until the unchanged hydrogen peroxide had been completely decomposed, after which the solution was vacuum-evaporated to a minimal volume and cooled, and 1.7 g (87%) of VII with mp 308° (from alcohol) was removed by filtration. The pale yellow crystals had R_f 0.27 (bright blue spot) and did not give a color reaction with $FeCl_3$. Found: C 59.2; H 3.6; N 17.1%. $C_8H_6N_2O_2$. Calculated: C 59.3; H 3.7; N 17.3%. IR spectrum: 1665 cm^{-1} (amide CO).

1-Methoxy-2-oxo-1,5-naphthyridine 5-Oxide (VIII). A mixture of 0.3 g (1.68 mmole) of V, 4.9 ml of 10% NaOH, 5 ml of CH_3I, and 10 ml of methanol was stirred at 20-25° for 28 h, after which the solution was vacuum-evaporated to dryness. The residue was dissolved in 3 ml of water and extracted with $CHCl_3$. The chloroform was removed to give 0.25 g (77.5%) of VIII with mp 239-240° (from alcohol). The colorless crystals had R_f 0.28 (violet spot). Found: C 56.3; H 4.5; N 14.3%. $C_9H_8N_2O_3$. Calculated: C 56.2; H 4.2; N 14.6%. IR spectrum: 1670 cm^{-1} (amide CO).

*Here and elsewhere, by paper chromatography with isoamyl alcohol–6% CH_3COOH (1 : 1) and development in UV light.

2,6-Dichloro-1,5-naphthyridine (IX). A mixture of 1.8 g (11.1 mmole) of VII and 30 ml of $POCl_3$ was refluxed for 25 min, after which the $POCl_3$ was removed by distillation. The residue was treated with ice and ammonium hydroxide, and the precipitate was removed by filtration to give 1.8 g (81.5%) of IX with mp 259-259.5° (from heptane). PMR spectrum (DMSO): $\delta H_3 = \delta H_7$ 7.82 ppm, $\delta H_4 = \delta H_8$ 8.38 ppm, $J_{3,4} = J_{7,8} =$ 10 Hz. 2,6-Dichloro-1,5-naphthyridine, previously obtained by the reaction of 1,5-naphthyridine 1,5-dioxide with $POCl_3$, had mp 236-238° [7]. The substance that we obtained by the Hart method [7] was identical to IX with respect to the melting point (259.5°) and the PMR spectrum.

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