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Studies on the Reactions of Heterocyclic Compounds. XIII.[1] Basicity of 1,6-Naphthyridine and Its N-Oxides: Correlation to Peracid Oxidation[2]

Yoshiro Kobayashi, Itsumaro Kumadaki, and Haruo Sato

Tokyo College of Pharmacy[3]

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Selective protonation of 1,6-naphthyridine and its N-oxides was studied from the results of ultraviolet spectra in various concentrations of sulfuric acid. Nitrogen atom in 6-position was protonated preferentially to that in 1-position, which seems to be caused by the stability of 2,6-quinonoid structure. This point is also supported by the difference in the changes of effective nuclear charges on protonation, which are calculated by SCF–LCAO–MO method. It was also shown that protonation plays an important role in N-oxidation of some heteroaromatic amines with a peracid.

Oxidation reactions of 1,6-naphthyridine (I) have been described in our previous papers,[1,4] and the following two points were of interest about this oxidation reaction. One is the fact that oxidation with peracid gave 6-oxide (IV) and a ring-oxidized product (V), while oxidation with hydrogen peroxide in the presence of sodium tungstate as catalyst gave 1,6-dioxide (II) and 6-oxide (IV) without the formation of V. The other is the preferential oxidation of the nitrogen atom in 6-position rather than that in 1-position by both methods. It may be suggested from these facts that the mechanism of N-oxidation of 1,6-naphthyridine differs markedly according to the acidity of the medium, and that the nitrogen atom in 6-position has greater reactivity, *i.e.*, greater basicity, than that in 1-position.

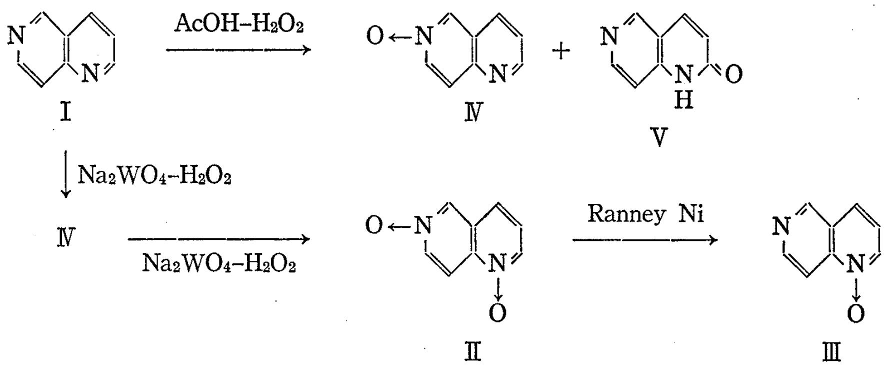

Chart 1

In the present series of work, selective protonation in the case of 1,6-naphthyridine and its N-oxides was examined with the data of ultraviolet (UV) spectra of these compounds in acidic solution. At the same time, these UV spectra were analyzed by molecular orbital theory, and the reaction mechanism of N-oxidation of 1,6-naphthyridine based on these results was proposed.

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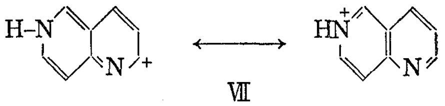
1) Part XII: Y. Kobayashi, I. Kumadaki, H. Sato, Y. Sekine, and T. Hara, *Chem. Pharm. Bull.* (Tokyo), **22**, 2097 (1974).

2) Presented at the 90th Annual Meeting of Pharmaceutical Society of Japan, Sapporo, July 1970.

3) Location: *Kitashinjuku 3-chome, Shinjuku-ku, Tokyo, 160, Japan.*

4) Y. Kobayashi, I. Kumadaki, and H. Sato, *Chem. Pharm. Bull.* (Tokyo), **17**, 1045 (1969).

First, variations in UV spectrum of 1,6-naphthyridine (I) were examined, as the concentration of sulfuric acid was changed. As shown in Fig. 1, the absorption at 223 nm in a neutral solution shows a blue shift in 0.001 N sulfuric acid, the absorption at 246 nm in a neutral solution splits into three characteristic bands (250, 260, and 270 nm), and α-band of Plat's nomenclature shows a red shift. This absorption curve in 0.001 N sulfuric acid agrees with that of 1,6-naphthyridine 6-methyl iodide (VI), which suggests that the first protonation of I occurs at 6-position (Fig. 2). Further, increase of the concentration of sulfuric acid results in the appearance of the β-band of Plat's nomenclature at 230 nm (log ε 4.238), the three absorption bands characteristic of the monocation disappear with the appearance of new bands at 255 and 264 nm, and α-band makes a further red shift. Thus, the first step in the protonation of I occurs in the nitrogen atom at 6-position and, since the characteristic absorption of that monocation at 250—270 nm also appears in the protonated 2-naphthylamine,[5] the monocation of I (VII) is thought to take also the para-quinonoid structure.



VII

Next, the variation in UV absorption curve of 1,6-naphthyridine 1-oxide (III) was examined. As shown in Fig. 3, a new absorption appears at 256 nm in 0.5—1.0 N sulfuric acid, and the molar extinction coefficient has a maximum value in this range of concentration. Further increase of the concentration of sulfuric acid results in the disappearance of this absorption band, so that it is considered to be an absorption characteristic of the monocation. The absorption curve in 0.5—1.0 N sulfuric acid agrees with that of 1,6-naphthyridine 1-oxide 6-methyl iodide (VIII), obtained by the reaction of III with methyl iodide (Fig. 4), which shows that protonation of III occurs at 6-position. Further increase of the concentration of sulfuric acid results in an absorption curve similar to that of I considered to be of dication.

Similar examinations were made on 1,6-naphthyridine 6-oxide (IV). As shown in Fig. 5, increase of the concentration of sulfuric acid results in the disappearance of the absorption at 246 nm and appearance of a new band at 260 nm, as in the case of III. This new band shows the maximum molar extinction-coefficient in 0.5—2.6 N sulfuric acid and is considered to be the absorption of a monocation. In the case of IV, the site of protonation in the first step is not clearly determined because the formation of its methyl iodide has not been achieved. In general, protonation on the N-oxide group occurs only in 60—70% sulfuric acid[5] and, in the case of IV, the protonation may have occurred at the nitrogen atom in 1-position rather than at the N-oxide group in 6-position. Further increase of the concentration of sulfuric acid gives a dication absorption band slightly different from those of I and III.

From the comparison of the protonation of III and IV, from the concentration of sulfuric acid to produce the absorption band thought to be that of a monocation, and from the formation of methyl iodides of III and IV, III is considered to have stronger basicity than IV.

Similar examination of UV spectra of 1,6-naphthyridine 1,6-dioxide (II) was made in various concentrations of sulfuric acid. As shown in Fig. 6, there was no distinct absorption band ascribable to monocation and, with the disappearance of the absorptions at 287 and 253 nm, a new absorption band appeared at 230 nm; the curve changed to that of a dication. This result seems to be due to the lack of selectivity in protonation of II. However, in catalytic deoxygenation of II, change of solvent from methanol to acetic acid results in predominant reduction of 6-oxide group, indicating selective protonation at this position: this fact seems to be an indirect evidence for the fact that the interaction with proton is stronger at 6-oxide group.

The interesting facts found from the foregoing experiments are that there is a difference in the basicity of the nitrogen atoms in 1- and 6-positions, and that there is a difference in the protonation of compounds with a free nitrogen and N-oxide group, such as III and IV.

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[5] E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., Amsterdam, 1967.

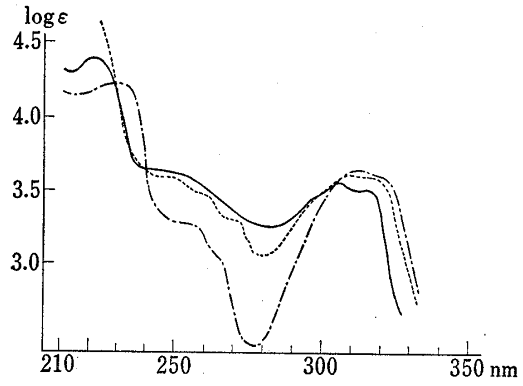
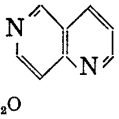


Fig. 1. 

——: in H_2O
------: in 0.01N H_2SO_4
—·—·—: in 92% H_2SO_4

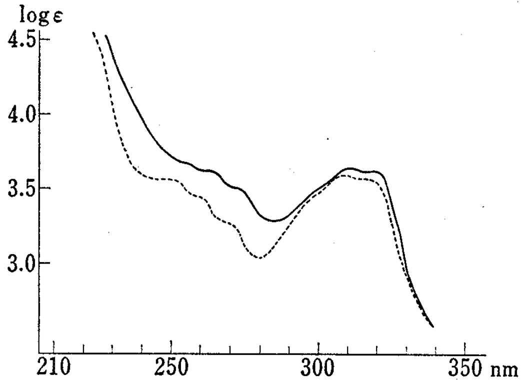
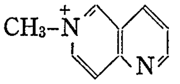
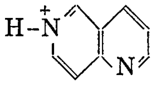


Fig. 2. ——: 

------: 

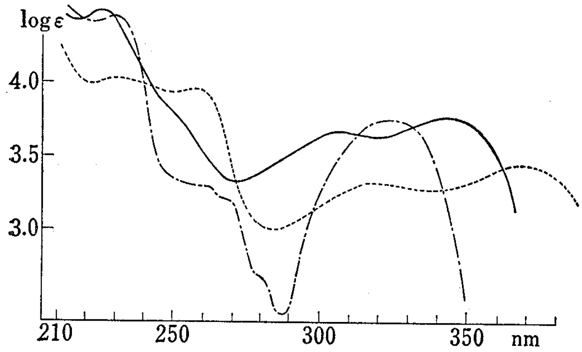
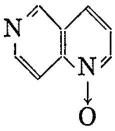


Fig. 3. 

——: in H_2O
------: in 0.5—1N H_2SO_4
—·—·—: in 92% H_2SO_4

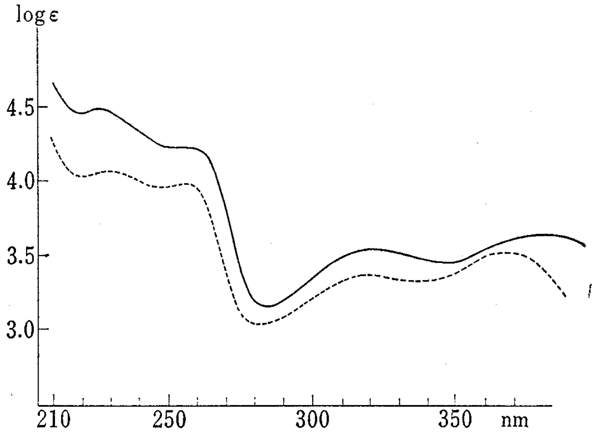
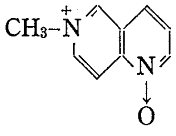
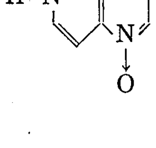


Fig. 4. ——: 

------: 

An attempt was, therefore, made to estimate quantitatively the basicity of these, 1,6-naphthyridine and its N-oxides.

As reported by Paudler and others,[6] basicity of I is the highest (pK_a' 3.78) among naphthyridines, but values of pK_a' of N-oxides of I have not been reported yet. Here, pK_a' values of III and IV are calculated from their UV absorption curves at various concentrations of sulfuric acid. Determination of pK_a' from UV spectra is carried out using the method used for the determination of pK_a' of weakly basic substances and is calculated from the following equation:

$$pK_a' = pH + \log \frac{\varepsilon_B - \varepsilon_{OH^-}}{\varepsilon_{H^+} - \varepsilon_B}$$

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[6] W.W. Paudler, *J. Heterocyclic. Chem.*, 5, 561 (1968).

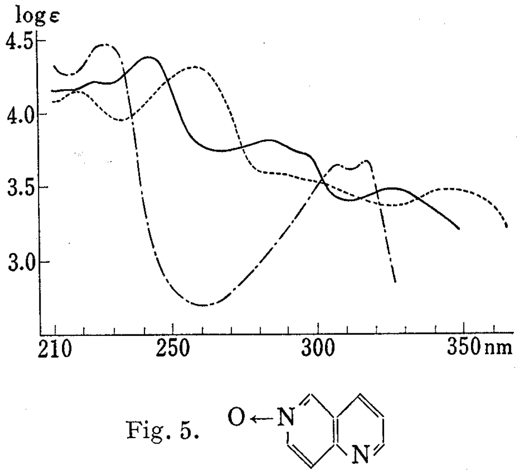

Fig. 5.

———: in H_2O
-----------: in 5—10% H_2SO_4
—·—·—: in 92% H_2SO_4

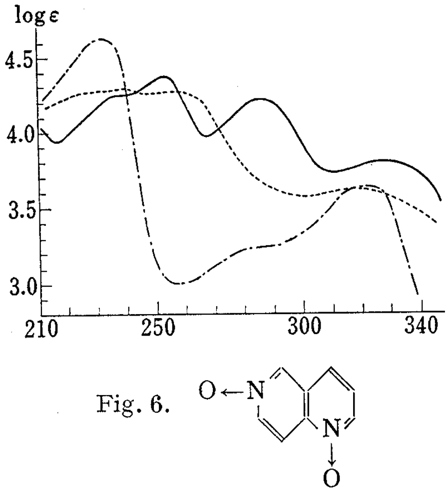

Fig. 6.

———: in H_2O
-----------: in 30% H_2SO_4
—·—·—: in 92% H_2SO_4

Here, pH is of the buffer solution, ε_B is the absorption coefficient in the buffer solution at given wave lengths, ε_{H^+} is the molar absorption coefficient of a cation, and ε_{OH^-} is that of a free base. Calculations made on III and IV gave the values of $pK_a'=1.87$ for III and $pK_a'=1.10$ for IV. These values indicate that in these N-oxides (III and IV), introduction of the N-oxide group has weakened the basicity of the nitrogen atom in the neighboring ring compared with the free base (I), and that III has stronger basicity than IV. If the electronic effect of the N-oxide group on the adjacent ring upon the basicity of the nitrogen atom were assumed to be equal in II and IV, the difference in the basicity of various N-oxides might originate from the difference in the basicity of nitrogen atoms in 1- and 6-positions of the 1,6-naphthyridine skeleton. It is of interest to know whether this difference in the basicity of nitrogen atoms at 1- and 6-positions is only due to the electronic effect of the 1,6-naphthyridine skeleton or steric hindrance against protonation of the nitrogen atom in 1-position by a proton in peri-position, as seen in the comparison of quinoline with isoquinoline.[7]

This point was examined by calculation of the energy level, π-electron density, and electron repulsion by protonation, according to the molecular orbital theory. The SCF-LCAO-MO calculation of the π-electron system of I gave the total electron density as 1.2789 eV for the nitrogen atom in 1-position and 1.2650 eV for that in 6-position, a reverse of the observed result. This fact indicates that the selectivity of I for protonation cannot be explained merely from its electron density, and the effect of the peri-position must be taken into consideration. An example of the quantitative expression of the effect of the peri-position and explanation of its basicity were made for heterocyclic compounds like purine derivatives by Pullmann and Nakajima,[8,9] which indicate that the order of basicity cannot be explained merely by the values of the negative charge of nitrogen atoms. They reported that the basicity depends on the whole charge distribution in the molecule and its effect cannot be ignored. The points of this theory are that the energy change, $\delta E = C^{te} + \Sigma Qp(NN/PP)\ \delta\ Zn$ and that a proportional relationship must exist between pK_a' and $\Sigma Qp(NN/PP)$. In the above equation, Qp is the formal charge of the p atom, NN/PP is the coulomb repulsion integral between the nitrogen atom in question and p atom, and δ Zn is the change in effective nuclear charge of the nitrogen atom by protonation. This theory was applied to 1,6-naphthyridine and $\Sigma Qp(NN/PP)\ \delta\ Zn$ was calculated for the protonation of nitrogen atoms in 1- and 6-positions. The values thereby

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[7] O. Chalvet, R. Daudel, and F. Peradejordi, *J. Chim. Phys.*, **59**, 709 (1962).
[8] T. Nakajima and A. Pullmann, *Compt. rend.*, **246**, 1047 (1958).
[9] T. Nakajima and A. Pullmann, *J. Chim. Phys.*, **55**, 782 (1958).

obtained were —1.8428 eV for 1-position and —1.8532 eV for 6-position, indicating that the nitrogen atom in 6-position has stronger basicity if electron repulsion is taken into consideration, and this explains the ease of protonation of this nitrogen atom.

Thus, the nitrogen atom in 6-position was found to have stronger basicity than that in 1-position of 1,6-naphthyridine and its N-oxides in their selectivity to protonation, and this fact was also endorsed from calculation by the SCF-LCAO-MO method. Thus, the behavior of I and its N-oxides (III and IV) in acid solution was explained by the results of the above treatments.

From such physical studies on I, an attempt was made to explain the selective N-oxidation of I at 6-position, as mentioned above. The priority of the 6-position is seen not only in protonation but also in the case of N-oxidation. As iterated above, N-oxidation of I with peracid gives IV and V, but that with hydrogen peroxide in the presence of sodium tungstate can yield IV alone at dilute concentration of hydrogen peroxide at lower temperatures, by which III is not formed. Further, in this reaction, raising of reaction temperature affords II almost quantitatively. V was not formed from III with peracid.

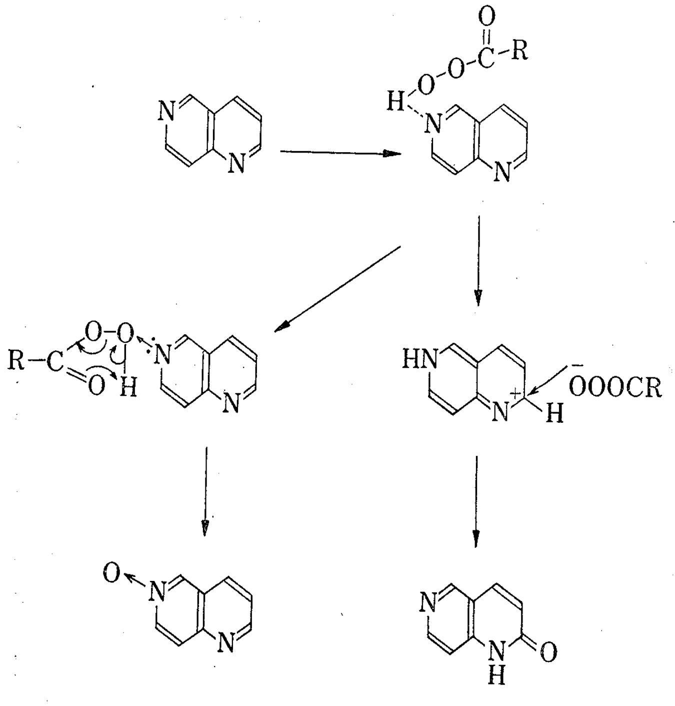

Chart 2

These differences between the products by N-oxidation with peracid and those with hydrogen peroxide in the presence of sodium tungstate will be explained as follows. The assumed selectivity of protonation of I in acidic solution is the cause of the ring-oxidation product (V) with peracid, as shown in Chart 2; namely, if the protonation with peracid is to determine the direction of the reaction, formation of IV and V can be understood. The *p*-quinonoid structure in Chart 2 was assumed from the fact that the absorption curve of the monocation of I had a characteristic bands in 260—290 nm region, as seen in the monocation of 2-naphthylamine, which was identified as of *p*-quinonoid structure. In the method using hydrogen peroxide-sodium tungstate, protonation occurs in much the less degree than in the case with acidic solution; and this *p*-quinonoid structure does not take part in it.

The concept of preferential protonation in the reaction mechanism of N-oxidation with peracid seems contrary to the known concept¹⁰⁾ that the lone-pair electrons of the nitrogen atom attack the oxygen atom in the peracid. However, the mechanism for the fomation of N-oxide after protonation may be described as shown in Chart 2; namely, it seems easier to consider that the first step in N-oxidation reaction is approaching of peracid through nitrogen-proton interaction rather than that of the oxygen atom to nitrogen atom.

In such a reaction mechanism of N-oxidation, it seems less contradictory to consider preferential protonation for the oxidation of I. The idea of taking protonation as the first step in the oxidation with peracid may also explain the fact that a peracid from a stronger acid is used for N-oxidation of weaker bases.

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10) A.R. Katritzky and J.M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press, London, 1971, p. 21.

Experimental

1,6-Naphthyridine 1-Oxide 6-Methyliodide——1,6-Naphthyridine 1-oxide (0.146 g) was dissolved in MeOH (5 ml) and methyl iodide (2 ml) was added to this solution. The reaction mixture was stirred at 23° for 5 hr and left at room temperature overnight. Yellow-brown crystals were collected and washed with ether. Yield, 0.234 g, mp 215—217° (decomp.). IR cm^{-1} (KBr): 1395, 1300, 1270, 1215. *Anal.* Calcd. for $C_9H_9ON_2I$: C, 37.52; H, 3.14; N, 9.73. Found: C, 37.46; H, 3.26; N, 9.43.

Measurement of UV Spectra——UV spectra were measured by Hitachi Spectrophotometer EPS-3. Silica cell: cell length, 10 mm; slit length, 1 mm. Samples (*ca.* 10 mg) were weighed accurately and dissolved in H_2O (50 ml). This solution (5 ml) was diluted to 100 ml with H_2O or a given concentration of H_2SO_4 (0.01N, 0.05N, 0.1N, 0.5N, 0.7N, 1.0N, 1.5N, 10%, 15%, 20%, 30%, 50%, 62%, and 92%).

pH of the solutions was measured by pH-meter: Model HM5A (Toa Dempa Kogyo).