[Chem. Pharm. Bull. 17(11)2614—2619(1969)]

UDC 547.865.4.04

Studies on the Reactions of Heterocyclic Compounds. III.[1] Cyanation of 1,6-Naphthyridine N-Oxides

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(Received August 21, 1969)

The Reissert reaction with 1,6-naphthyridine occurs at the nitrogen atom of 6-position. In the same reaction with 1,6-naphthyridine 1-oxide, 6-oxide, and 1,6-dioxide, N-oxide group reacts and gives 2-cyano-, 5-cyano-, and 2,5-dicyano-derivatives as expected. And 1,6-dioxide reacts with KCN in MeOH to give 2-methoxy-5-cyano-1,6-naphthyridine, 2-methoxy-1,6-naphthyridine-5-carboxamide, 2-methoxy-1,6-naphthyridine 6-oxide. The same recation with 1-oxide gives 1,6-naphthyridine and 2-methoxy-1,6-naphthyridine or 2-methoxy-1,6-naphthyridine-5-carboxamide. The mechanism of these novel reactions was proposed.

In the previous paper,[3] we reported the preparation of 1,6-naphthyridine N-oxide (1-oxide, 6-oxide, and 1,6-dioxide) and the reactions of these N-oxides with acetic anhydride or phosphoryl chloride.

In the present paper, we first discuss the Reissert reaction in which we found that some of these N-oxides were very sensitive to potassium cyanide, and then the discovery that a novel S_N reaction took place in this series of N-oxides upon a more precise examination of the reaction with potassium cyanide in methanol.

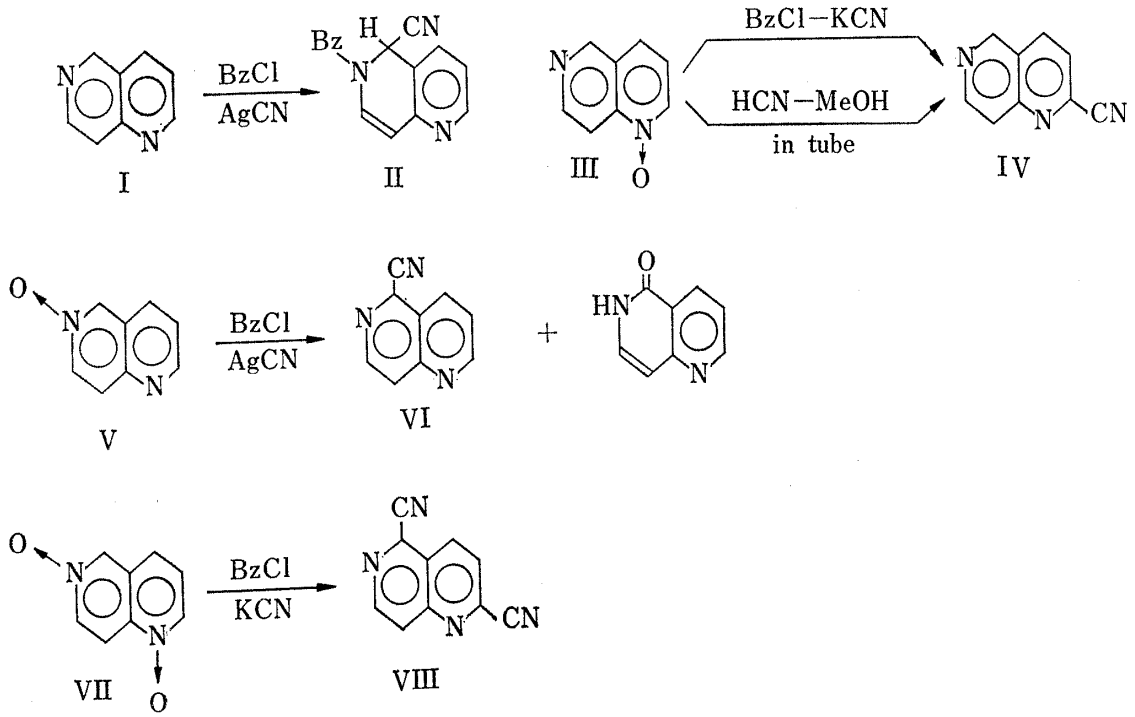

Chart 1

1) Part II: Y. Kobayashi, I. Kumadaki, and K. Morinaga, *Chem. Pharm. Bull.* (Tokyo), **17**, 1511 (1969).
2) Location: *Kashiwagi 4-chome, Shinjuku-ku, Tokyo.*
3) Y. Kobayashi, I. Kumadaki, and H. Sato, *Chem. Pharm. Bull.* (Tokyo), **17**, 1045 (1969).

First, we tried the Reissert reaction[4] of a free base. Addition of silver cyanide to a solution of 1,6-naphthyridine (I) and benzoyl chloride in chloroform afforded the Reissert compound, whose structure was determined as 5-cyano-6-benzoyl-5,6-dihydro-1,6-naphthyridine (II) by elemental analysis, nuclear magnetic resonance (NMR) spectrum and infrared (IR) spectrum. When potassium cyanide was used instead of silver cyanide, the products were rather complicated and the yield was low. This result shows that 6-nitrogen is more reactive to electrophile than 1-nitrogen; this is comparable to the iodomethylation of I, which gave 6-methyl-1,6-naphthyridinium iodide.

Then, the Reissert reaction of N-oxides[5] was examined, and the results are summerized in Chart 1 together with the result mentioned above.

1,6-Naphthyridine 1-oxide (III) afforded 2-cyano-1,6-naphthyridine (IV), showing that N-oxide group is more reactive to electrophile than ring nitrogen. The structure of IV was determined by elemental analysis, NMR spectrum, and IR spectrum. IV was also obtained by heating III with hydrogen cyanide in methanol in a sealed tube. The latter reaction also occurs in quinoxaline 3-oxide,[6] and shows that 1,6-naphthyridine ring has a reactivity comparable to quinoxaline. This will be discussed fully later. 1,6-Naphthyridine 6-oxide (V) and 1,6-naphthyridine 1,6-dioxide (VII) gave 5-cyano-1,6-naphthyridine (VI) and 2,5-dicyano-1,6-naphthyridine (VIII), respectively, as expected. But V gave 5,6-dihydro-1,6-naphthyridin (6*H*)-5-one as by-product, which shows that benzoyl adduct of V is very reactive to nucleophile.[1] In the reaction of VII, the reaction mixture was markedly colored when VII and potassium cyanide were mixed in water and the yield of VIII was very low. As this fact suggested that VII is too reactive in water, we attempted cyanation of VII with only potassium cyanide in methanol under reflux.

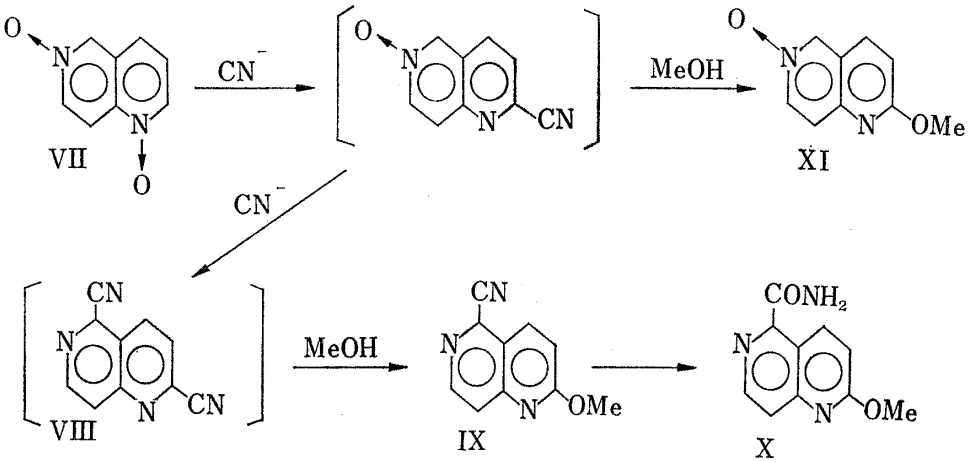

Chart 2

In this condition, VII gave 2-methoxy-5-cyano-1,6-naphthyridine (IX), 2-methoxy-1,6-naphthyridine-5-carboamide (X) and 2-methoxy-1,6-naphthyridine 6-oxide (XI) in the respective yields of 10, 5, and 15%. From the consideration of these products, XI was deduced to be an intermediate in this reaction, but we could not obtain IX or X from XI under the same reaction condition; XI was not obtained from VII with potassium carbonate or potassium hydroxide in methanol under reflux, while IX was obtained from VIII with potassium cyanide in methanol. These results are shown in Chart 2 with an estimated mechanism.

In the first step of the reaction, 2-cyano-1,6-naphthyridine 6-oxide is obtained and in the second, the reaction proceeds in either of these two directions: 2-cyano group is substituted

4) A. Reissert, *Chem. Ber.*, **38**, 1610, 3415 (1905).
5) M. Henze, *Chem. Ber.*, **69**, 1566 (1936).
6) T. Higashino, *Chem. Pharm. Bull.* (Tokyo), **9**, 638 (1961).

by methoxy group, which protects XI from nucleophile, or cyanide anion attacks this intermediate further, the product of which (VIII), being more reactive to a nucleophile, gives IX, which is partly hydrolysed to X. In this assumption, 2-position must be more reactive than 5-position. This assumption was supported by the reactions shown below.

1,6-Naphthyridine 6-oxide (V) was almost entirely recovered in the above condition, giving a trace of deoxygenated product (I), while 1-oxide (III) gave 2-methoxy-1,6-naphthyridine (XII) with deoxygenated product (I). Increased concentration of potassium cyanide gave 2-methoxy-1,6-naphthyridine-5-carboxamide (X), the same product as that of 1,6-dioxide (VII), in a poor yield. From these results, we could assume that the mechanism of these reactions was similar to that of VII as shown in Chart 3.

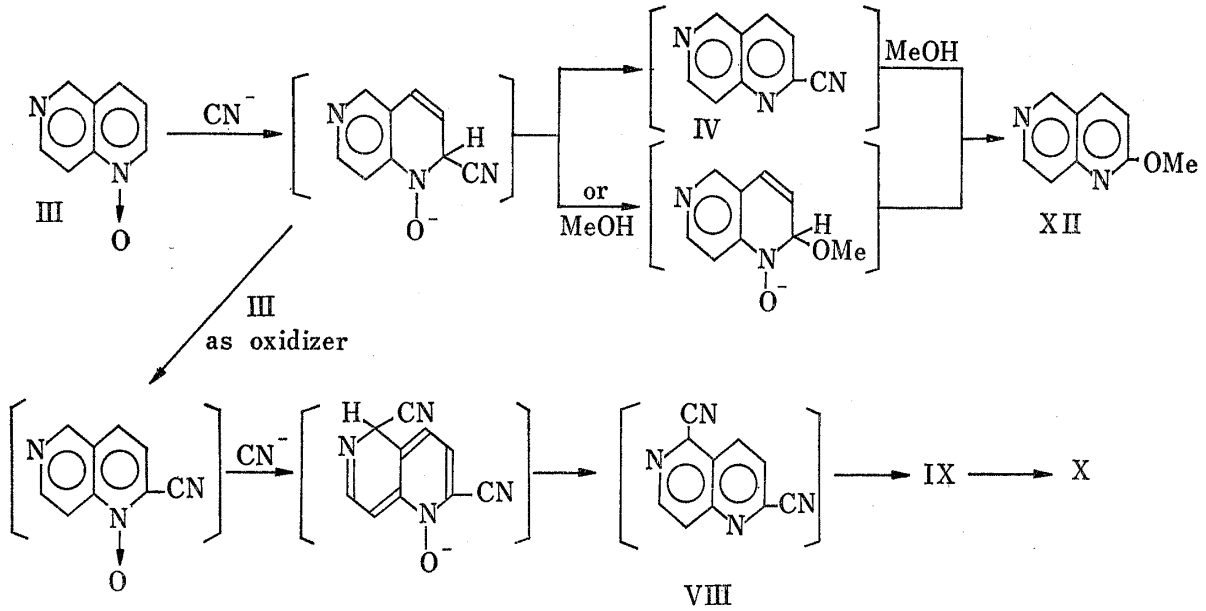

Chart 3

In the above scheme, III also seemed to react as an oxidizer; adding potassium ferricyanide to the reaction mixture we could obtain IX, but none of deoxygenated products (I andXII). This shows that our assumption was correct.

This cyanation reaction without acylating reagents is a quite new type of reaction of N-oxide, and application of this reaction to other nucleophiles is very interesting. The activity of cyano group for S_N reaction was observed by Higashino in quinoxaline series.[7] This fact suggests, as well as the reaction of hydrogen cyanide in methanol referred to above, that 1,6-diazanaphthalene (I) has the same reactivity to some nucleophile as 1,3-diazanaphthalene, as expected from the fact that both nitrogen atoms occupy the starred positions of the alternant hydrocarbon system. Reduction of N-oxide group by alcohol and alkali observed in the reactions of III and V will be discussed in the following paper.

The structures of these reaction products were determined from the following reactions. IX was obtained by the Reissert reaction of XI, and X was obtained by the hydrolysis of IX with hydrogen peroxide in the presence of potassium carbonate. Catalytic reduction of XI over Raney Ni gave XII, which was hydrolysed to 1,2-dihydro-1,6-naphthyridin(1*H*)-2-one[3] by conc. hydrochloric acid in a sealed tube at 140°. These reactions are summarized in Chart 4. XI was assumed to be either 2-methoxy-1,6-naphthyridine 1-oxide or 6-oxide, but it was found to be the 6-oxide from its NMR absorptions of C_5–H, C_7–H, and C_8–H which were almost identical with those of 1,6-naphthyridine 6-oxide. NMR spectra of N-oxide were discussed in the previous paper.[3]

7) T. Higashino, *Yakugaku Zasshi*, **80**, 1404 (1960).

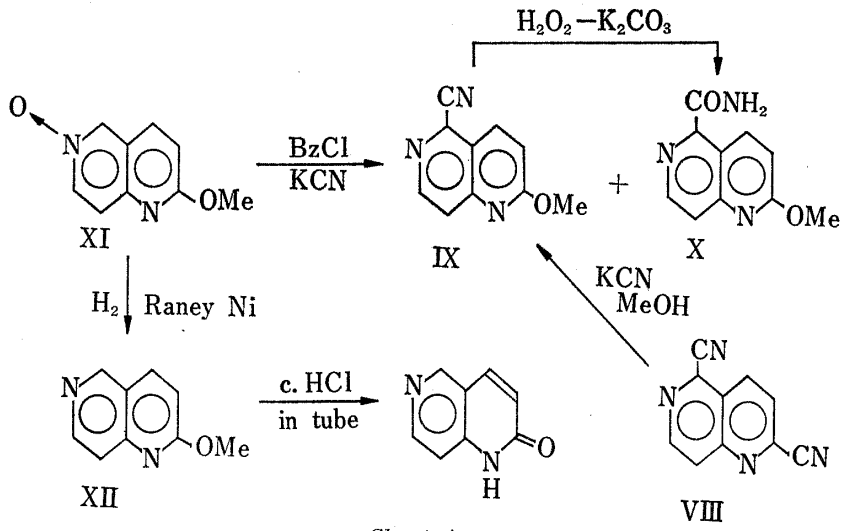

Chart 4

In order to examine the reactivity of 1,6-naphthyridine N-oxides more quantitatively, π-electron charge distribution was calculated from simple Hückel molecular orbital theory and shown in Chart 5. In this calculation the parameters were taken to be $\alpha_{N\delta+}=\alpha+\beta$, $\alpha_O=\alpha+1.5\beta$, and $\alpha_N=\alpha+0.5\beta$ from the assumption that, in this reaction, O atom of N-oxides makes a hydrogen bond with protic solvents. As a result, 1,6-naphthyridine 1-oxide and 1,6-dioxide were found to be active to nucleophilic attack, especially at 2-, 4-, and 5-positions. The results of above experiments were in approximate agreement with the results of the calculation.

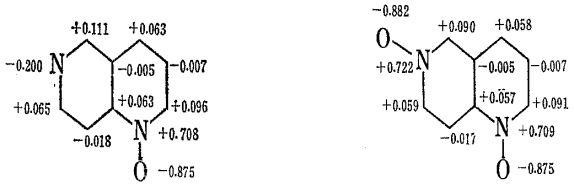

Chart 5. π-Electron Charge Distribution

Experimental

Reissert Reaction of 1,6-Naphthyridine (I)——To a solution of I (0.5 g) and benzoyl chloride (0.55 g) in $CHCl_3$ (20 ml), AgCN (0.6 g) was added and stirred for 4 hr at 15°. The solid substance was filtered off, the filtrate was washed with 1 N NaOH solution, and the $CHCl_3$ layer was dried over K_2CO_3. After $CHCl_3$ was evaporated, the residue was dissolved in C_6H_6 and purified through silica gel (20 g) column. The first elute with C_6H_6 contained oily substance, mainly BzCl, and from the second elute with CH_2Cl_2–MeOH (100:1) colorless crystals were obtained. Recrystallization from C_6H_6 gave colorless needles (II), mp 186—187°; yield, 0.4 g (40%). IR cm^{-1}: $\nu_{C=O}$ 1665 (KBr). NMR ($CDCl_3$) τ: 3.75 (1H, doublet, J=7.5 cps, C_8–H), 3.4 (1H, singlet, C_5–H), 3.05 (1H, doublet, J=7.5 cps, C_7–H), 2.7 (1H, C_3–H), 1.35 (1H, double doublet, J=5 cps, J=1.3 cps, C_2–H). *Anal.* Calcd. for $C_{16}H_{11}ON_3$ (5-cyano-6-benzoyl-5,6-dihydro-1,6-naphthyridine): C, 73.55; H, 4.24; N, 16.08. Found: C, 73.84; H, 4.27; N, 16.09.

Reissert Reaction of 1,6-Naphthyridine 1-Oxide (III)——To a mixture of III(0.27 g) in $CHCl_3$ (3 ml) and KCN (0.2 g) in H_2O (2 ml), a solution of BzCl (0.3 g) in $CHCl_3$ (2 ml) was added and stirred for 3 hr at 20°. The $CHCl_3$ layer was washed with 10% K_2CO_3 solution and dried over Na_2SO_4. The extracted residue was chromatographed over silica gel. The column was eluted with $CHCl_3$ to remove oily substance, mainly BzCl, and from the second elute colorless crystals were obtained. Recrystallization from *n*-hexane gave colorless needles (IV), mp 154—155°; IR cm^{-1}: $\nu_{C\equiv N}$ 2280 (KBr). NMR ($CDCl_3$) τ: 2.15 (1H, doublet, J=8.8 cps, C_3–H), 2.01 (1H, doublet, J=6.3 cps, C_8–H), 1.48 (1H, doublet, J=8.8 cps, C_4–H), 1.1 (1H, doublet, J=6.3 cps, C_7–H), 0.6 (1H, singlet, C_5–H). *Anal.* Calcd. for $C_9H_5N_3$ (2-cyano-1,6-naphthyridine): C, 69.67; H, 3.25; N, 27.09. Found: C, 69.43; H, 2.85; N, 27.32.

The following elution with CH_2Cl_2 gave the starting material (0.1 g, 33%).

Reissert Reaction of 1,6-Naphthyridine 6-Oxide (V)——To a solution of V (0.1 g) and BzCl (0.12 g) in $CHCl_3$ (4 ml), AgCN (0.2 g) was added and stirred for 3 hr at 15°. The reaction mixture was treated as in the case of I. The extracted residue was chromatographed over silica gel. The colorless crystals were obtained from elute with CH_2Cl_2. The recrystallization from *n*-hexane gave colorless needles (VI)

of mp 142—143°. Yield, 0.01 g(9.4%). This substance is so easily sublimated that its elemental analysis was difficult to carry out. IR cm^{-1}: $\nu_{C\equiv N}$ 2290 (KBr). NMR ($CDCl_3$) τ: 2.36 (1H, quartet, $J=4.5$ cps, C_3–H), 1.82 (1H, doublet, $J=6.3$ cps, C_8–H), 1.33 (1H, doublet, $J=8.8$ cps, C_4–H), 1.12 (1H, doublet, $J=6.3$ cps, C_7–H), 0.77 (1H, double doublet, $J=4.5$ cps, $J=2.5$ cps, C_2–H). Mass spectrum: *M/e* Calcd. for $C_9H_5N_3$ (5-cyano-1,6-naphthyridine): 155. Found: 155.

The elute with CH_2Cl_2–MeOH (10:1) gave 5,6-dihydro-1,6-naphthyridin(6*H*)-5-one[3] in the yield of 0.05 g (50%).

Reissert Reaction of 1,6-Naphthyridine 1,6-Dioxide (VII)——To a mixture of VII (0.5 g) in H_2O (5 ml) and BzCl (3 g) in $CHCl_3$ (10 ml), KCN (2 g) in H_2O (5 ml) was added and stirred for 2 hr at 23°. The following procedure was the same as in the case of III. The extracted residue was chromatographed over silica gel (10 g). The column was eluted with CCl_4 to remove oily substance, mainly BzCl. Recrystallization of the elute with $CHCl_3$ from *n*-hexane gave colorless needles (VIII) of mp 150—152°; yield, 0.02 g (3.6%). IR cm^{-1}: $\nu_{C\equiv N}$ 2280 (KBr). NMR ($CDCl_3$) τ: 1.97 (1H, doublet, $J=8.8$ cps, C_3–H), 1.73 (1H, doublet, $J=5$ cps, C_8–H), 1.16 (1H, doublet, $J=8.8$ cps, C_4–H), 0.96 (1H, doublet, $J=5$ cps, C_7–H). *Anal.* Calcd. for $C_{10}H_4N_4$ (2,5-dicyano-1,6-naphthyridine): C, 66.66; H, 2.24; N, 31.10. Found: C, 66.28; H, 2.38; N, 31.08.

Reaction of VII with KCN in MeOH——To a solution of VII (1 g) in MeOH (200 ml), KCN (2 g) was added and heated under reflux with stirring, and then the solution gradually became brown. After 6 hr's continuous reflux, MeOH was evaporated to dryness *in vacuo* and the residue was extracted with $CHCl_3$. The $CHCl_3$ solution was concentrated to *ca.* 10 ml, which was chromatographed over silica gel (30 g). The column was eluted with $CHCl_3$ to collect each band that showed fluorescence in UV ray. Colorless crystals were obtained from the first blue fluorescent fraction. Recrystallization from MeOH gave colorless needles (IX) of mp 193°; yield, 0.124 g (10.8%). IR cm^{-1}: $\nu_{C\equiv N}$ 2280 (KBr). NMR ($CDCl_3$) τ: 5.83 (3H, singlet, $-OCH_3$), 2.85 (1H, doublet, $J=8.8$ cps, C_3–H), 2.11 (1H, doublet, $J=6.3$ cps, C_8–H), 1.61 (1H, doublet, $J=8.8$ cps, C_4–H), 1.27 (1H, doublet, $J=6.3$ cps, C_7–H). *Anal.* Calcd. for $C_9H_8ON_2$ (2-methoxy-5-cyano-1,6-naphthyridine): C, 64.86; H, 3.81; N, 22.69. Found: C, 64.98; H, 4.07; N, 22.53.

The next fluorescent elute with $CHCl_3$ gave pale pink crystals and the recrystallization from MeOH gave colorless needles of mp 236° (X); yield, 0.065 g (5%). IR cm^{-1}: ν_{NH} 3430, 3280 (KBr); $\nu_{C=O}$ 1700 (KBr). NMR (CF_3COOH) τ: 5.53 (3H, singlet, $-OCH_3$), 2.35 (1H, doublet, $J=10$ cps, C_3–H), 1.61 (1H, doublet, $J=6.3$ cps C_8–H), 1.13 (1H, doublet, $J=6.3$ cps, C_7–H), 0.66 (1H, doublet, $J=10$ cps, C_4–H). *Anal.* Calcd. for $C_{10}H_9O_2N_3$ (2-methoxy-1,6-naphthyridine-5-carboxamide): C, 59.10; H, 4.46; N, 20.68. Found: C, 58.90; H, 4.03; N, 20.95.

The elute with $CHCl_3$–MeOH (20:1) gave pale green crystals, recrystallization of which from acetone gave colorless needles of mp 193° (XI); yield, 0.153 g (14.1%). IR cm^{-1}: ν_{N-O} 1210 (KBr). NMR ($CDCl_3$) τ: 5.95 (3H, singlet, $-OCH_3$), 2.99 (1H, doublet, $J=8.8$ cps, C_3–H), 2.40 (1H, doublet, $J=7.5$ cps, C_8–H), 2.14 (1H, doublet, $J=8.8$ cps, C_4–H), 1.75 (1H, double doublet, $J=7.5$ cps, $J=2.5$ cps, C_7–H), 1.34 (1H, doublet, $J=2.5$ cps, C_5–H). *Anal.* Calcd. for $C_9H_8O_2N_2$ (2-methoxy-1,6-naphthyridine 6-oxide); C, 61.36; H, 4.58; N, 15.90. Found: C, 60.93; H, 4.80; N, 16.02.

Reaction of III with KCN in MeOH——a) To a solution of III (0.8 g) in MeOH (200 ml), KCN (2 g) was added with stirring and heated under reflux for 1.5 hr. The solvent was evaporated to dryness *in vacuo* and the residue was extracted with CH_2Cl_2. The extracted solution was concentrated to *ca.* 10 ml and chromatographed over silica gel. The column was eluted with CH_2Cl_2 to collect oily substance (0.54 g). Gas chromatography of the oil showed two peaks in the ratio of 87.5:12.5 from their areas.[8] The first peak was assigned to I and the second to XII from the retention time, respectively. NMR spectrum of this oil showed the mixture of I and XII in the ratio of 84:16.

b) To a solution of III (0.6 g) in MeOH (20 ml), KCN (2 g) was added and heated with stirring under reflux for 9 hr. The following procedure was the same as in the case of the former reaction. The chromatography of this reaction residue gave colorless crystals from the elute with CH_2Cl_2. Recrystallization from MeOH gave colorless needles of mp 236°; yield, 0.03 g (3.6%). This substance was identified with X by IR spectra and mixture melting point.

Reaction of VIII with KCN in MeOH——To a solution of VIII (45 mg) in MeOH (10 ml), KCN (100 mg) was added and heated with stirring at 50° for 30 min. The solvent was evaporated to dryness *in vacuo* and the residue was extracted with CH_2Cl_2. This solution was chromatographed over silica gel and the column was eluted with CH_2Cl_2, colorless crystals being obtained. Recrystallization from MeOH gave colorless needles of mp 193°; yield, 10 mg (22%). This substance was identified with IX by IR spectra and the mixture melting point.

Cyanation of III with HCN——To a solution of III (0.3 g) in MeOH (20 ml), HCN–MeOH solution (10 ml: prepared from 1 g of KCN) was added and heated in a sealed tube at 100° for 10 hr. The reaction mixture was evaporated to dryness *in vacuo* and the residue was dissolved in CH_2Cl_2 and chromatographed

8) A. Shimazu GC-3AF was used. Column; DEGS (15%) 3 m. Column temp.; 188°. Carrier; N_2. Inlet press.; 1.8 atm.

over silica gel. The column was eluted with CH_2Cl_2 to collect colorless crystals of mp 155—156°; yield, 0.02 g (6.3%). This substance was identified with IV by IR spectra and mixture melting point. The second fraction gave 0.2 g of the starting material.

Reissert Reaction of 2-Methoxy-1,6-Naphthyridine 6-Oxide (XI)——To a mixture of XI (0.3 g, 1.7 mmole) in $CHCl_3$ (2 ml) and KCN (0.3 g) in H_2O (5 ml), BzCl (0.3 g) in $CHCl_3$ (2 ml) was added under ice cooling and stirred at 18° for 6 hr. The reaction mixture was extracted with CH_2Cl_2; the CH_2Cl_2 layer was washed with a solution of 10% K_2CO_3 and the CH_2Cl_2 layer was dried over Na_2SO_4. The CH_2Cl_2 was evaporated and the residue was dissolved in $CHCl_3$ and chromatographed over silica gel. The column was eluted with $CHCl_3$ to collect colorless crystals and recrystallization from MeOH gave colorless needles of mp 191—193°; yield, 0.17 g (54%). This substance was identified with IX by IR spectra and mixture melting point. The second elute with $CHCl_3$ gave 0.01 g (2.9%) of crystals, which were identified with X by IR spectra and mixture melting point.

2-Methoxy-1,6-naphthyridine (XII)——To a solution of XI (0.176 g, 1 mmole) in MeOH (30 ml), Raney Ni (prepared from Ni–Al alloy, 0.5 g) was added and the mixture was shaken with H_2 (24 ml) under 1 atm. at 15°. When the reduction was over, Ni was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was dissoved in $CHCl_3$ and chromatographed over silica gel. The elute with $CHCl_3$ gave colorless crystals and recrystallization from *n*-hexane gave colorless needles of mp 65—67°; yield, 0.08 g (50%). IR cm^{-1}: ν_{C-O-C} 1340 (KBr). NMR ($CDCl_3$) τ: 5.9 (3H, singlet, $-OCH_3$), 3.14 (1H, doublet, J=8.8 cps, C_3–H), 2.36 (1H, doublet, J=6.3 cps, C_8–H), 1.98 (1H, doublet, J=8.8 cps, C_4–H), 1.38 (1H, doublet, J=6.3 cps, C_7–H), 0.96 (1H, singlet, C_5–H). *Anal.* Calcd. for $C_9H_8ON_2$ (2-methoxy-1,6-naphthyridine): C, 67.48; H, 5.03; N, 17.49. Found: C, 66.69; H, 5.29; N, 17.09. Mass spectrum: *M/e* Calcd.: 160. Found: 160.

The elution with $CHCl_3$ (containing 2—5% MeOH) gave the starting material, 0.01 g (5.7%).

Hydrolysis of 2-Methoxy-1,6-naphthyridine (XII)——A solution of XII (0.2 g) in conc. HCl (5 ml) was heated in a sealed tube at 140° for 8 hr. The reaction mixture was evaporated *in vacuo* and 1ml of H_2O was added to the residue. When the solution was basified with Na_2CO_3, crystals appeared. Recrystallization from MeOH gave colorless needles of mp 291°; yield, 0.12 g (67%). This substance was identified with 1,2-dihydro-1,6-naphthyridin(1*H*)-2-one[3] by IR spectra and mixture melting point.

Reaction of 1,6-Naphthyridine 6-Oxide with KCN in MeOH——To a solution of V (0.3 g) in MeOH (20 ml), KCN (0.6 g) was added and heated under reflux for 3hr. It was treated in the same way as III. The residue was chromatographed over alumina. The elute with CH_2Cl_2 gave 40 mg (15%) of oil. The picrate of this oil melted at 210°. It was identified with 1,6-naphthyridine picrate by mixture melting point. The second elute with CH_2Cl_2 (containing 2% MeOH) gave 0.15 g (50%) of the starting material.

Reaction of VII with KCN and $K_3Fe(CN)_6$ in MeOH——To a solution of VII (0.5 g) in MeOH (150 ml), KCN (1 g) and $K_3Fe(CN)_6$(11 g) were added and heated under reflux for 3 hr. The solid substance of the reaction mixture was filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and chromatographed over silica gel. The elute with CH_2Cl_2 gave colorless crystals. Recrystallization from MeOH gave colorless needles of mp 193°; yield, 0.1 g (17.5%). This substance was identified with IX by IR spectra and mixture melting point.

Reaction of III with KCN and $K_3Fe(CN)_6$ in MeOH——To a solution of III (0.3 g) in MeOH (30 ml), KCN (0.3 g) and $K_3Fe(CN)_6$ (1.8 g) were added and heated under reflux for 2 hr. It was treated in the same way as VII. The elute with CH_2Cl_2 gave colorless crystals of mp 193°; yield, 0.02 g (5.3%). This substance was identified with IX by IR spectra and mixture melting point.

Acknowledgement We express our sincere gratitude to Sankyo Co., for elemental analyses, to Mr. T. Ono for the measurement of NMR spectra, and to Dr. C. Nagata and Dr. A. Imamura of National Cancer Research Center for letting us use the computor.