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Studies on the Reactions of Heterocyclic Compounds. I. Syntheses and Some Reactions of 1,6-Naphthyridine N-Oxides

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N-Oxidation of 1,6-naphthyridine was carried out in various ways and 6-oxide and 1,6-dioxide were obtained. Reduction of the latter afforded 1-oxide. Reactions of these oxides with acetic anhydride and with phosphoryl chloride were carried out and the structure of each product was determined.

The synthesis of 1,6-naphthyridine, which is a chemically and biochemically interesting compound when compared with pteridine bases, has been tried by various methods without any satisfactory result, but, recently, Paudler and others[2] reported that they succeeded in obtaining this compound in a good yield by using sulfo–mix in the Skraup reaction. On the other hand, there is no report on 1,6-napthyridine N-oxides except that of Kato and others[3] that 1,6-naphthyridine 6-oxide was obtained in a poor yield from 4-aminopyridine 1-oxide by the Skraup reaction.

By following Paudler's method, we synthesized 1,6-naphthylidine (I) and, by carrying out various experiments on its N-oxidation, succeeded in obtaining its 1-oxide, 1,6-dioxide, and 6-oxide. Some reactions of these oxides are also reported in this paper.

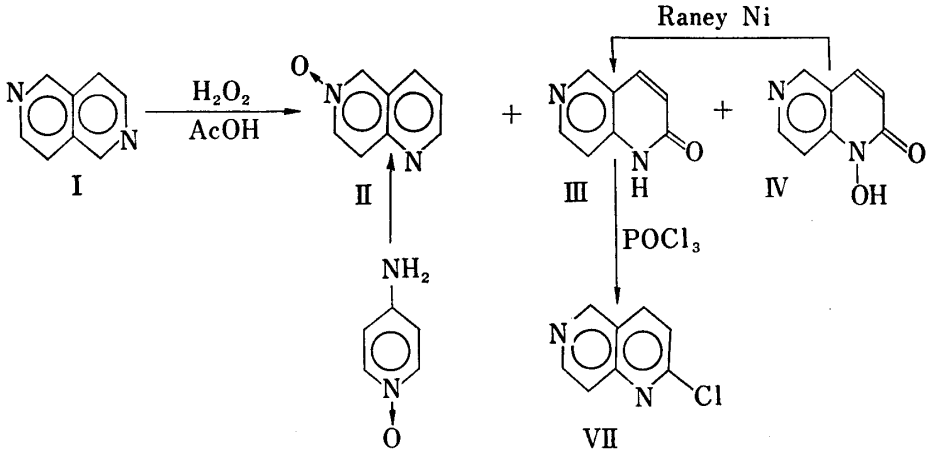

Chart 1

N-Oxidation of I was carried out in the usual way using hydrogen peroxide and acetic acid and heating on a water bath. When the reaction mixture was heated at 45° for 2 hours, 1,6-naphtyridine 6-oxide (II) was obtained in 0.6% yield, with 1,6-naphthyridin-2(1*H*)-one (III) in 1.0% yield and 30% of the starting material was recovered. II was identified with the product obtained by the method of Kato and others[3] by the mixed melting point determination and comparison of their infrared specrta. Its structure was also supported

1) Location: *Kashiwagi 4-chome, Shinjuku-ku, Tokyo.*
2) T.J. Kress and W.W. Paudler, *Chem. Commun.*, **1967**, 3.
3) T. Kato, F. Hamaguchi, and T. Oiwa, *Chem. Pharm. Bull.* (Tokyo), **4**, 178 (1956).

by its NMR spectrum indicating the shift of the protons at 5- and 7-positions to a higher magnetic field and marked increase of J_{7-8} from 5.1 to 8.2 cps.

Identification of III was made from its elemental analysis indicating the addition of one atom of oxygen to the naphthyridine molecule. The oxygen atom was presumed to be at 2- or 5-position because the carbonyl absorption band appeared at 1705 cm^{-1} in its infrared spectrum. The structure was confirmed from the fact that the signal of 2-H did not appear in the NMR spectrum when III was converted to its chloro derivative (VII) by treatment with phosphoryl chloride.

Next, N-oxidation of I was carried out at 60° for 9 hours with the same reagent as above; 1-hydroxy-1,6-naphthyridin-2(1*H*)-one (IV) was obtained in 27% yield and III in 3% yield, and the starting material was hardly detected.

The structure of IV was confirmed by elemental analysis showing addition of two oxygen atoms to the naphthyridine molecule, from the appearance of the carbonyl absorption band at 1688 cm^{-1} and the hydroxy absorption band at 2800—3150 cm^{-1} in its infrared spectrum, from its solubility in sodium hydrogencarbonate, and coloration of its solution on addition of ferric chloride, suggesting a hydroxamic acid-type compound. Further proof was supplied by its derivation to III by catalytic hydrogenation over Raney nickel.

As stated above, N-oxidation of these compounds with hydrogen peroxide and acetic acid did not give a satisfactory result and this was thought to be due to the electron-withdrawing effect by the presence of two nitrogen atoms in the ring system, making the ring more susceptible to oxidation than the nitrogen atoms. Therefore, N-oxidation was attempted with monoperphthalic acid and maintaining the reaction mixture at 2° for 18 days. The reaction afforded the 6-oxide (II) and the naphthyridin-2(1*H*)-one (III), both in 9% yield, together with 27% recovery of the starting material. This result proved that oxidation of the ring depends on the reaction temperature and that oxidation in an acidic medium does not give a satisfactory result.

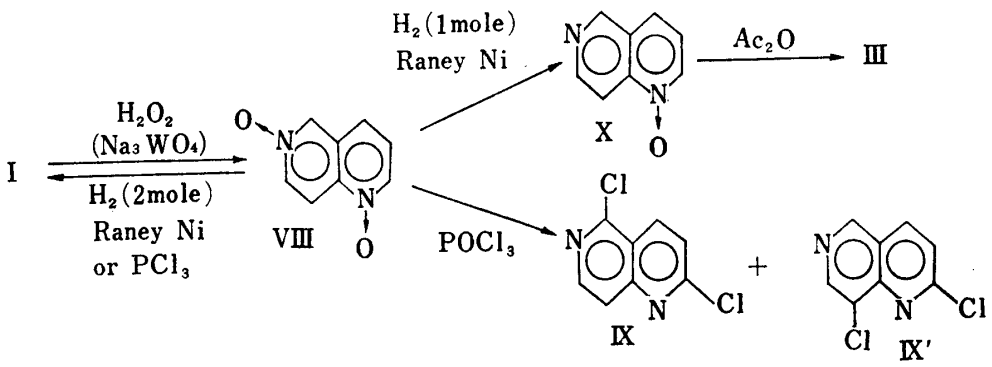

Chart 2

Another method was then tried by carrying out the oxidation without an acid, in the presence of sodium tungstate,[4] by heating the reaction mixture at 55—60° with hydrogen peroxide and 1,6-naphthyridine 1,6-dioxide (VIII), mp 279—280°, was obtained in 85.5% yield. The elemental analysis of VIII agreed with addition of two oxygen atoms to the naphthyridine molecule and its infrared spectrum exhibited two strong N–O stretching bands at 1290 and 1270 cm^{-1}. NMR spectrum of VIII showed the signals of all the six protons; although the chemical shift cannot be compared with the value accurately because its NMR was measured by using sodium 2,2-dimethyl-2-silapentan-5-sulfonate as the standard in heavy water in the order of 2-H 7-H 4-H 5-H, they shifted to a higher magnetic field. Only 8-H shifted considerably to a lower field, and J_{2-3} increased from 4.0 to 6.0 cps. All these facts support the structure of VIII.[5]

4) R.C. Witman, U.S. Patent 3047579 [*Chem. Abstr.*, **58**, 7916].

As naphthyridine 1-oxide could not be obtained even under the above conditions, we examined the method of deriving VIII to 1-oxide by catalytic hydrogenation. VIII absorbed 1 mole of hydrogen by hydrogenation over Raney nickel in methanol. Chromatographic separation of its product afforded 12% of I, 9.4% of the starting material VIII, and 30% of the objective 1,6-naphthyridine 1-oxide (X), mp 155—156°. Elemental analytical values of X agreed with the addition of one oxygen atom to the naphthyridine molecule, and its infrared spectrum showed the N–O stretching band at 1310 cm^{-1}. Because this compound did not agree with the 6-oxide (II), it was presumed to be the expected 1-oxide. The NMR spectrum of X showed the shift of 2-H and 4-H to a higher magnetic field and 8-H to a lower field, and increase of J_{2-3} from 4.0 to 5.2 cps. All these facts support our assumption that this compound is the 1-oxide.[5]

Thus, 1-oxide, 6-oxide, and 1,6-dioxide of naphthyridine were all synthesized by N-oxidation. Results of NMR spectra of these compounds are interesting. With the 1-oxide, 2-H and 4-H shifted to a higher magnetic field by about 0.6 ppm; with the 6-oxide, 5-H and 7-H similarly shifted to a higher field by 0.5—0.7 ppm. These facts show that electrophilic substitution of naphthyridine, which has been thought impossible, might become possible if the reaction conditions were set right. The fact that J_{2-3} changed from 4.0 to 5.2—6.0 cps by N-oxidation at 1-position and J_{7-8} greatly from *ca.* 5 to 8 cps by N-oxidation at 6-position agrees with the tendency of the change of J_{2-3} from 3—4 cps to 6—8 cps by quaternarization of the ring nitrogen in pyridine.[5]

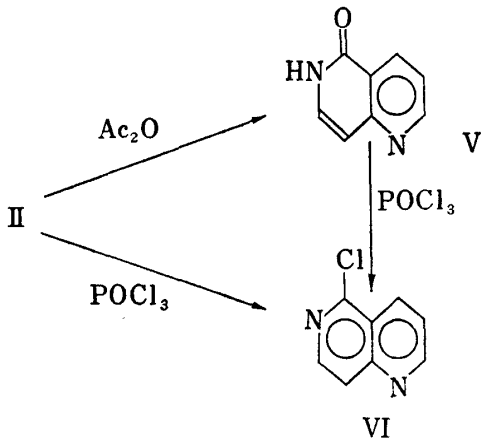

Chart 3

Reaction of the naphthyridine oxides so obtained with acetic anhydride and phosphoryl chloride was examined. Boiling of the 1-oxide with acetic anhydride produced III which was determined from its infrared spectrum. Treatment of the 6-oxide (II) in the same way in acetic anhydride afforded 1,6-naphthyridin-5(6*H*)-one (V) in 23% yield. The structure of V was determined by elemental analysis, presence of a carbonyl absorption band at 1645—1655 cm^{-1} in its infrared spectrum, and formation of 5-chloro-1,6-naphthyridine (VI) by chlorination with phosph-

Table I. Chemical Shifts[a] and Coupling Constants[b] of Nucleous Protons of 1,6-Naphthyridine Derivatives

	Position of proton						J_{2-3}	J_{7-8}	J_{3-4}
	2	3	4	5	7	8			
Naphthyridine	9.22	7.63	8.41	9.39	8.88	8.04	4.0	5.1	8.2
1-Oxide	8.63	7.45	7.85	9.30	8.78	8.46	5.2	5.8	8.8
6-Oxide	9.05	7.63	8.42	8.86	8.16	8.04	4.2	8.2	8.2
1,6-Dioxide[c]	8.84	7.85	8.27	9.23	8.57	8.57	6.0	—	8.2
2-Chloride	—	7.52	8.24	9.26	7.78	7.84	—	5.2	6.2
5-Chloride	9.12	7.63	8.62	—	7.50	7.88	4.0	5.1	8.1
2,5-Dichloride	—	7.58	8.55	—	8.52	7.87	—	5.2	8.8
2,8-Dichloride	—	7.85	8.50	8.98	8.56	—	—	—	6.2

a) in $CDCl_3$: internal standard: tetramethylsilane *b*) *J*: cps
c) in D_2O: internal standard: sodium 2,2-dimethyl-2-silapentane-5-sulfonate

5) Private communication from Dr. K. Tori.

oryl chloride. Structure of VI was determined by elemental analysis and from its NMR spectrum. VI was also obtained in 32.5% yield by boiling II with phosphoryl chloride.

Although 1,6-dioxide was decomposed when boiled with acetic anhydride, it formed 13.5% of 2,5-dichloride (IX) and 15% of 2,8-dichloride (IX') when boiled with phosphoryl chloride. Presence of only two peaks in its gas chromatogram shows that other isomers were not formed. Formation of 8-chloro compound is reasonable since treatment of isoquinoline 2-oxide with phosphoryl chloride produces 4-chloro compound.[6] The fact that only the 5-chloro compound was formed in the reaction of naphthyridine 6-oxide with phosphoryl chloride is rather interesting (checked by gas chromatography). The reaction of the 1-oxide with phosphoryl chloride produced 2-chloride, which was too labile to be isolated.

Experimental

Oxidation of 1,6-Naphthyridine with H_2O_2-AcOH——a) To a solution of 1,6-naphthyridine (5 g) in AcOH (25 ml), 24% H_2O_2 (6.3 g) was added and the mixture was warmed at 45° on a water bath for 2 hr; then H_2O_2 (6.3 g) was added further, warming being continued for 3 hr. The reaction mixture was concentrated *in vacuo* to about half the volume and, after the same amount of water was added, the solution was concentrated to half the volume; the same procedure was repeated three times. Then the solution was concentrated to about 5 ml, made alkaline with solid Na_2CO_3, and extracted with $CHCl_3$. After being dried over Na_2SO_4, the solvent was evaporated and the residue was chromatographed over alumina. Elution with CCl_4 afforded the starting material (I, 1.5 g), and elution with $CHCl_3$–MeOH (100:1) gave light-yellow prisms of 1,6-naphthyridine 6-oxide (II), mp 150°, by recrystallization from acetone. Yield, 33 mg (0.6%). II was identified by mixture melting point and comparing IR spectra with the authentic sample, which was obtained by Skraup reaction of 4-aminopyridine 1-oxide. And NMR spectra also agreed.

Elution with $CHCl_3$–MeOH (10:1) gave faintly orange sands of 1,6-naphthyridin-2(1*H*)-one (III), mp 290—291°, by recrystallization from MeOH. Yield, 56 mg (1.0%). IR cm^{-1}: $\nu_{C=O}$ 1705, ν_{N-H} 2854 (Nujol). *Anal.* Calcd. for $C_8H_6ON_2$: C, 65.72; H, 4.13; N, 19.17. Found: C, 65.60; H, 4.30; N, 18.97.

The structure of III was confirmed from NMR spectra of VII, chlorinated derivative of III.

b) To a solution of I (1.5 g) in AcOH (5 ml), 30% H_2O_2 (3 ml) was added and the mixture was heated at 60° on a water bath for 9 hr. After half the amount of water was added, the reaction mixture was concentrated *in vacuo* to half the volume. After the same amount of water was added, the solution was concentrated *in vacuo*. The same procedure was repeated five times, and the precipitated solid was collected by filtration, washed with water, dried, and recrystallized from MeOH to obtain colorless needles of 1-hydroxy-1,6-naphthyridin-2(1*H*)-one (IV). Melting Point is higher than 350°. Yield, 0.5 g (27%). $FeCl_3$ test: positive. IR cm^{-1}: $\nu_{C=O}$ 1688, ν_{OH} 2800—3150 (KBr). *Anal.* Calcd. for $C_8H_6O_2N_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 58.83; H, 3.93; N, 16.97.

The filtrate was made alkaline with Na_2CO_3 and extracted with $CHCl_3$. After it was dried over Na_2SO_4, $CHCl_3$ was evaporated. The water layer was evaporated *in vacuo* to dryness and extracted with hot $CHCl_3$–MeOH; and the solvent was evaporated. The both residues above were treated together and chromatographed over silicagel.

Elution with $CHCl_3$ afforded I (0.1 g) and elution with $CHCl_3$–MeOH (20:1) afforded III (0.05 g, 3%).

Catalytic Reduction of IV——IV (0.2 g) was suspended in MeOH (20 ml) and in the presence of Raney Ni (prepared from 0.1 g Al-Ni alloy) shaken in H_2, and 20 ml of H_2 was absorbed. The catalyst was filtered off and the filtrate was concentrated *in vacuo*, made alkaline with Na_2CO_3, and extracted with $CHCl_3$. After being dried over Na_2SO_4, $CHCl_3$ was evaporated and the residue was chromatographed. Elution with $CHCl_3$–MeOH (100:1) afforded faintly yellow powder (0.02 g), which was recrystallized from benzene. The compound was identified with III by comparing IR spectra.

Oxidation of 1,6-Naphthyridine with Monoperphtharic Acid——To an ice-cooled solution of I (3 g) in ether (50 ml), a solution of monoperphtharic acid (4.5 g) in ether (50 ml) was added. After allowing it to stand for 18 days at 2°, the ether layer was removed and the precipitated solid was dissolved in water (100 ml) made alkaline with K_2CO_3, and extracted with $CHCl_3$. After it was dried over Na_2SO_4, $CHCl_3$ was evaporated. The water layer was evaporated to dryness and extracted with $CHCl_3$–MeOH (100:1), and the solvent was evaporated. The both residues above were treated together and chromatographed over silicagel.

Elution with $CHCl_3$ afforded I (0.8 g), elution with $CHCl_3$–MeOH (100:1) afforded II (0.3 g, 8.9%), and elution with $CHCl_3$–MeOH (10:1) afforded III (0.3 g, 8.9%).

6) Private communication from Dr. M. Hamana.

1,6-Naphthyridin-5(6*H*)-one (V)——A mixture of II (180 mg) and Ac_2O (4 ml) was refluxed at 140—160° (bath-temperature) for 3 hr. After Ac_2O was removed *in vacuo*, a small amount of EtOH was added and the solvent was removed *in vacuo*. The residue was made alkaline with Na_2CO_3 and extracted with $CHCl_3$. The water layer was concentrated *in vacuo* and extracted with $CHCl_3$. Both $CHCl_3$ solutions were dried together over Na_2SO_4 and the sovent was evaporated. The residue was recrystallized from MeOH to give colorless needles of mp 242°. Yield, 42 mg (23%). IR cm^{-1}: $\nu_{C=O}$ 1645—1655, ν_{N-H} 2800—3100 (KBr). *Anal.* Calcd. for $C_8H_6ON_2$: C, 65.72; H, 4.13; N, 19.17. Found: C, 65.30; H, 3.95; N, 19.04.

The structure was determined as V from NMR spectrum of a chlorinated derivative (VI). This compound has been reported in an old literature[7] (mp, 236—238°), but no proof is given.

5-Chloro-1,6-naphthyridine (VI)——a) A mixture of V (82 mg), $POCl_3$ (5 ml), and $(C_2H_5)_3N$ (3 drops) was refluxed at 140° (bath-temperature) for 3 hr. After $POCl_3$ was removed *in vacuo*, ice was added to the residue to decompose the remaining $POCl_3$; then it was made alkaline with K_2CO_3, extracted with ether, and dried over Na_2SO_4, and the solvent was evaporated. The residue was recrystallized from *n*-hexane to give colorless needles of VI, mp 107° (36 mg, 39%). Beilstein test was positive with this compound and $\nu_{C=O}$ was not found in IR spectrum. *Anal.* Calcd. for $C_8H_5N_2Cl$: C, 58.38; H, 3.06; N, 17.02. Found: C, 58.13; H, 3.25; N, 17.25.

The position of Cl was determined from NMR (Table I).

The starting material V (16 mg) was obtained as an insoluble residue to *n*-hexane.

b) A mixture of V (100 mg) and $POCl_3$ (5 ml) was refluxed at 130—150° (bath-temperature) for 6 hr and worked up as above. VI (35 mg, 32.5%) was recrystallized from *n*-hexane. Beilstein test was positive. The structure was identified with VI by mixture melting point and comparing IR spectrum.

2-Chloro-1,6-naphthyridine (VII)——A mixture of III (200 mg) and $POCl_3$ (8 ml) was refluxed at 140—160° (bath-temperature) for 6 hr and worked up as for VI. Colorless needles, mp 88°, were obtained by recrystallization from *n*-hexane. Yield, 43 mg (19.2%). Beilstein test was positive. *Anal.* Calcd. for $C_8H_5N_2Cl$: C, 58.38; H, 3.06; N, 17.02. Found: C, 57.99; H, 3.13; N, 16.59.

$\nu_{C=O}$ was not found in IR spectrum and the position of Cl was determined from NMR.

1,6-Naphthyridine 1,6-Dioxide (VIII)——A mixture of I (2.6 g), Na_3WO_4 (0.2 g), and 30% H_2O_2 (15 ml) was heated at 55—60° for 7 hr under stirring. After the reaction was completed, the same amount of distilled water was added to the reaction mixture and it was concentrated to half the volume. After the same procedure was repeated three times, the solution was made alkaline with a small amount of $NaHCO_3$; the same procedure as above was repeated until H_2O_2 was not detected by KI test. Finally the solution was concentrated to 20 ml and the crystals were precipitated by adding acetone. The yellow needles, mp 278° (decomp.), were recrystallized from MeOH. Yield, 2.77 g(85.5%). IR cm^{-1}: ν_{N-O} 1270, 1290 (KBr). *Anal.* Calcd. for $C_8H_6O_2N_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.12; H, 3.85; N, 17.34.

Chlorination of 1,6-Naphthyridine 1,6-Dioxide——A suspension of VIII (1 g) in $POCl_3$ (20 ml) was gently refluxed for 1 hr and worked up as for VI. The ether extract was dissolved in $CHCl_3$ and passed through a silicagel column. The gas chromatograph of the elute shows two peaks. Fractional recrystallization from *n*-hexane gave two kinds of needles. First crystals (IX): mp 173—174°; yield, 168 mg (13.5%); no $\nu_{C=O}$ absorption in IR. *Anal.* Calcd. for $C_8H_4N_2Cl_2$: C, 48.27; H, 2.13; N, 14.08. Found: C, 48.05; H, 2.02; N, 14.13. Second crystals (IX'): mp 93—94°; yield, 184 mg (15%); no $\nu_{C=O}$ absorption in IR. *Anal.* Calcd. for $C_8H_4N_2Cl_2$: C, 48.27; H, 2.13; N, 14.08. Found: C, 48.58; H, 2.07; N, 13.81.

Dehydrogenation of 1,6-Naphthyridine 1,6-Dioxide——a) A mixture of Raney Ni (prepared from 2.6 g of Al-Ni alloy by Hayashi's method,[8]) VIII (3.2 g), and MeOH (500 ml) was shaken in H_2. When 460 ml of H_2 was absorbed, the reaction was stopped, the catalyst was filtered off, and the filtrate was evaporated to dryness. The residue was chromatographed over silicagel.

Elution with $CHCl_3$ afforded oil (0.3 g, 11.5%), which was identified with 1,6-naphthyridine (I) by mixture melting point of picrate with the authentic sample.

Elution with $CHCl_3$–MeOH (100:1) afforded pale yellow needles, mp 155—156°, which were recrystallized from acetone. Yield, 0.85 g (30%). The mixture melting point with 1,6-naphthyridine 6-oxide (II, mp 150—151°) showed depression. IR cm^{-1}: ν_{N-O} 1301 (KBr). *Anal.* Calcd. for $C_8H_6ON_2$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.83; H, 4.16; N, 19.32. The structure was determined as 1,6-naphthyridine 1-oxide (X) by NMR. (Table I).

Elution with $CHCl_3$–MeOH (10:1) afforded VIII (0.3 g, 9.4%).

b) A mixture of Raney Ni (Al-Ni alloy, 300 mg), VIII (324 mg, 2 mmole), and MeOH (100 ml) was shaken in H_2. When 90 ml(2 mmole) of H_2 was absorbed, the reaction was stopped and the mixture was worked up as usual. An oily product was distilled *in vacuo* to give I (120 mg, 46%). Picrate: mp 220°.

c) To a solution of VIII (130 mg) in $CHCl_3$ (50 ml), a solution of PCl_3 (130 mg) in $CHCl_3$ (1.3 ml) was added with ice-cooling and stirring. After refluxing it for 30 min, the reaction mixture was poured into ice water and $CHCl_3$ layer was extracted with H_2O. The water solution was made alkaline with K_2CO_3, ex-

7) O. Rosenheim and J. Tafel, *Ber.*, **26**, 1501 (1893).

8) E. Hayashi, H. Yamanaka, and K. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **7**, 145 (1959).

tracted with $CHCl_3$, and dried over Na_2SO_4. The solution was concentrated and chromatographed over alumina. Elution with $CHCl_3$ afforded I. (Picrate: mp 220°; yield, 32 mg). Elution with $CHCl_3$–MeOH (10:1) afforded VIII, the starting material (4 mg).

1,6-Naphthyridin-2(1*H*)-one (III)——A mixture of X (50 mg) and Ac_2O (1 ml) was heated at 160° for 3 hr, and then Ac_2O was distilled off *in vacuo*; a small amount of EtOH was added and the solvent was removed *in vacuo*. To the residue ice was added and it was made alkaline with K_2CO_3 and evaporated to dryness. The residue was extracted with hot $CHCl_3$–MeOH (10:1) and after the solvent was evaporated, the residue was chromatographed over silicagel. Elution with $CHCl_3$–MeOH (30:1) afforded pale yellow crystals, which were recrystallized from MeOH, mp 290°. Yield, 5 mg (10%).

The product was identified with III by mixture melting point and comparing IR spectrum with the sample obtained by oxidation of I.

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