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Reaction of Aromatic Heterocyclic Nitro Compounds with Potassium Cyanide. III.[1] Some Nitroquinoline 1-Oxides

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The reaction of 3-nitroquinoline 1-oxide with potassium cyanide in methanol was carried out producing 3-methoxycinchoninonitrile 1-oxide (I) and 3-methoxy-1*H*-pyrazolo[4,3-*b*]quinoline-9-carboxamide (II). 5-Nitroquinoline 1-oxide gave 5-methoxyquinoline-6-carbonitrile 1-oxide (XIII) and 7-aminoisoxazolo[3,4-*f*]quinoline 1-oxide (XIV), whereas 6-nitroquinoline 1-oxide gave methyl 5-cyano-6-methoxyquinaldimidate 1-oxide (VI), 5-cyano-6-methoxyquinaldamide 1-oxide (VII), and 1-hydroxy-6-nitrocarbostyril (VIII) by the similar type reactions. 4-Nitroquinoline 1-oxide produced 4-methoxyquinoline 1-oxide.

It was previously reported that aromatic heterocyclic nitro compounds were reacted with potassium cyanide in alcohol producing *o*-alkoxycarbonitriles and aminoisoxazoles in good yields. The aromatic heterocyclic nitro compounds used in these reactions were mono azine compounds such as nitroquinolines,[1,3] and diazine compounds such as nitroquinoxalines.[4] Insofar as these same type reactions are expected to take place at aromatic N-oxides, the authors attemped in the present work the reactions of some nitroquinoline 1-oxides with potassium cyanide, and studied the effect of N-oxide group.

3-Nitroquinoline 1-oxide was allowed to reflux with 1.5—2.0 molar equivalent of potassium cyanide in methanol, and 3-methoxycinchoninonitrile 1-oxide (I) and 3-methoxy-1*H*-pyrazolo [4,3-*b*]quinoline-9-carboxamide (II) were obtained. The former compound (I) was pale yellow scales, mp 236—237° (decomp.), and was found to be identical with the N-oxide compound obtained by the hydrogen peroxide-acetic acid oxidation of 3-methoxycinchonino-

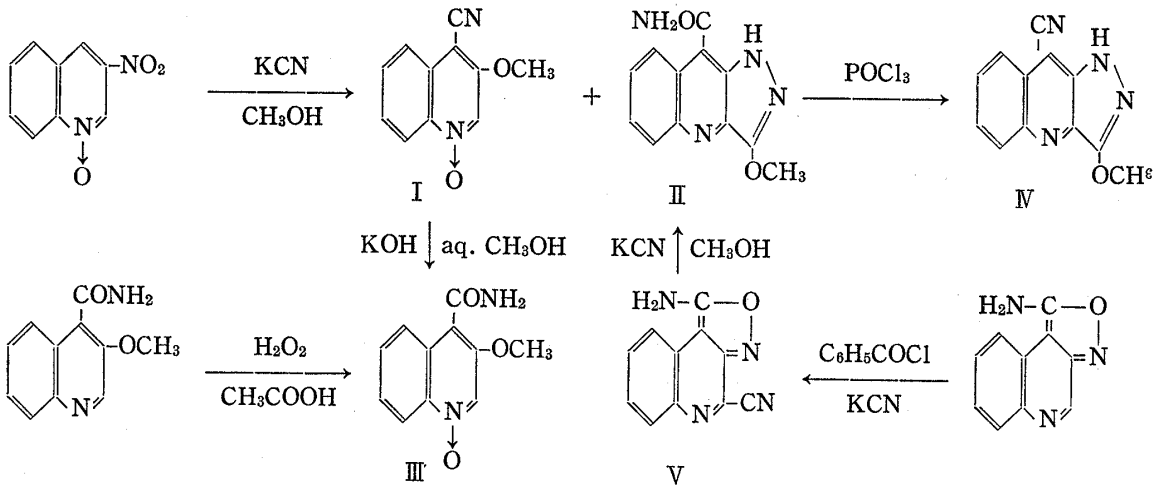

Chart 1

1) Part II: T. Okamoto, H. Takahashi, H. Takayama, T. Kitagawa, and M. Ikeda, *Chem. Pharm. Bull.* (Tokyo), **17**, 140 (1969).
2) Location: *Hongo 7-3-1, Bunkyo-ku, Tokyo*; *a*) Present address: *Hoshi College of Pharmacy, Ebara* 2-4-41, *Shinagawa-ku, Tokyo.*
3) T. Okamoto and H. Takahashi, *Chem. Pharm. Bull.* (Tokyo), **16**, 1700 (1968).
4) H. Takahashi and H. Otomasu, *Chem. Pharm. Bull.* (Tokyo), **18**, 22 (1970).

nitrile.[3] When I was heated with potassium hydroxide in aqueous methanolic solution, 3-methoxycinchoninamide 1-oxide (III) was produced. This compound was identified with the N-oxide obtained by the oxidation of 3-methoxycinchoninamide.

The latter compound (II) was yellow needles, mp 283—285° (decomp.), stable in dil. sulfuric acid and potassium hydroxide solution, and resistant to the catalytic reduction with paradized carbon. II was heated in phosphorus oxychloride and dehydroxylated to form 3-methoxy-1*H*-pyrazolo[4,3-*b*]quinoline-9-carbonitrile (IV). The infrared (IR) spectrum of the product (IV) showed the typical cyano group absorption at 2220 cm^{-1} and exhibited lack of absorptions of amide group. With the purpose of confirming the structure of II, the synthesis of alternative compound and some other experiments for the circumstantial evidence were attempted. 1-Aminoisoxazolo[3,4-*c*]quinoline was subjected to cyanation under the condition of Reissert reaction producing 1-aminoisoxazolo[3,4-*c*]quinoline-4-carbonitrile (V). V was converted into II by the reaction of methanol in presence of potassium cyanide.

With regard to the reaction mechanism of the producing of II, it can probably be concluded that, as shown in Chart 2, 3-nitroquinoline 1-oxide was reacted firstly with potassium cyanide to give 5-aminoisoxazolo[3,4-*c*]quinoline 1-oxide (IIa), which was then converted into a dihydro compound (IIb) by the entrance of one more cyano group, as the result of the activated 2-position of the quinoline ring by the effect of N-oxide group.[5] IIb thus yielded was subjected to dehydroxylation to form the nitrile compound (V). The compound (II) was finally derived by the addition of methanol upon the cyano group of V, followed by the subsequent intramolecular recyclization from isoxazole to pyrazole ring.

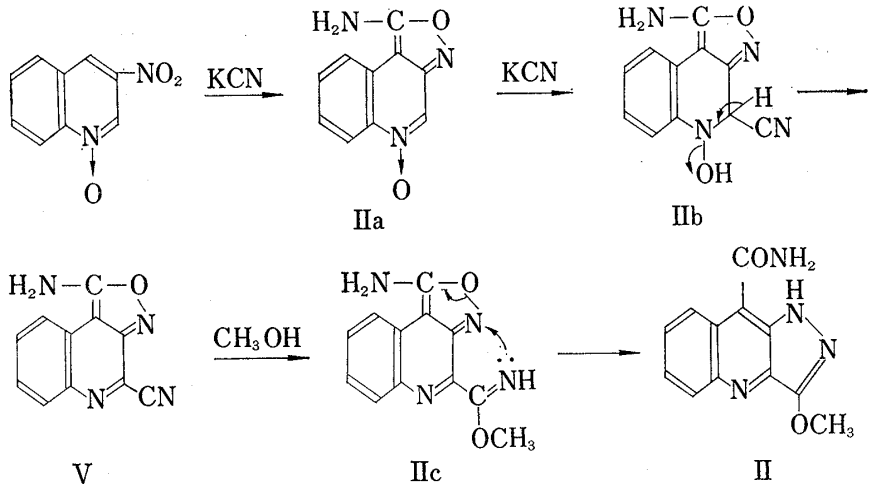

Chart 2

6-Nitroquinoline 1-oxide was refluxed with potassium cyanide in methanol, and the reaction mixture was purified by chromatography on almina. Methyl 5-cyano-6-methoxyquinaldimidate 1-oxide (VI), 5-cyano-6-methoxyquinaldamide 1-oxide (VII), and 1-hydroxy-6-nitrocarbostyril (VIII) were obtained. Even at room temperature, the reaction of 6-nitroquinoline 1-oxide with potassium cyanide occured giving rise to methyl 6-nitroquinaldimidate 1-oxide (IX) and 6-nitroquinaldamide 1-oxide (X), due to the nucleophilic activation at the 2-position of the quinoline ring enhanced by both the nitro and the N-oxide groups.[5] On the other hand, in the presence of the oxidizing agent potassium ferricyanide, the reaction of 6-nitroquinoline 1-oxide with potassium cyanide at low temperature (3—5°) resulted 6-nitroquinaldonitrile 1-oxide (XI), where the cyano group was introduced into the 2-posi-

5) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Company, Amsterdam, London, New York, 1967, pp. 340—423.

tion of the quinoline ring. XI was converted, at room temperature, into IX and X in methanolic potassium cyanide solution, and the iminomethyl ether compound (IX) was hydrolyzed to the amide compound (X).

At refluxing temperatue, IX, X, and XI obtained at mild condition so far described were finally reacted with potassium cyanide in methanol to form VI and VII, respectively, when cyano group was introduced into 5-position and nitro group replaced by methoxyl group. 1-Hydroxy-6-nitrocarbostyril (VIII) was obtained by moderate heating of either X and XI in methanolic potassium hydroxide aqueous solution. From the above described experimental results, it was concluded that IX, X, and XI were intermediate compounds in the reaction of the 6-nitroquinoline 1-oxide with potassuim cyanide, and that VI, VII, and VIII were produced through the route shown in Chart 3.

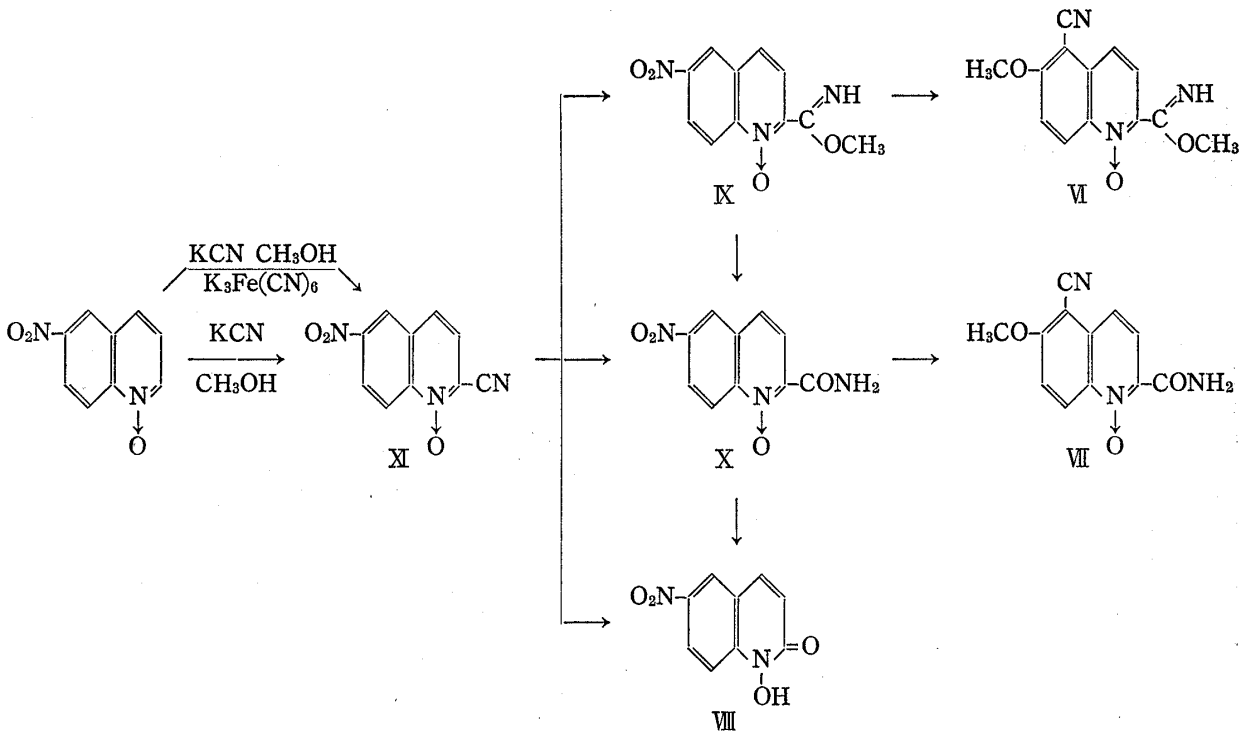

Chart 3

1-Hydroxy-6-nitrocarbostyril (VIII) was found to be identical with the mono nitro compound obtained by the nitration of 1-hydroxycarbostyril with fuming nitric acid in acetic acid at room temperature. VIII was converted into 1-methoxy-6-nitrocarbostyril (XII) by methylation with diazomethane.

By the reaction of 5-nitroquinoline 1-oxide with potassium cyanide, 5-methoxyquinoline-6-carbonitrile 1-oxide (XIII) and 7-aminoisoxazolo[3,4-*f*]quinoline 1-oxide (XIV) were obtained in the respective yield of 25 and 29%. XIII was identified with the N-oxide obtained by hydrogen peroxide-acetic acid oxidation of 5-methoxyquinoline-6-carbonitrile.[1] XIV was converted into XIII by refluxing with sodium methoxide in methanol, when the carbon–oxygen bond of the isoxazole ring was cleaved.[3]

The reaction of 4-nitroquinoline 1-oxide with potassium cyanide in methanol gave only 4-methoxyquinoline 1-oxide, due to the activation of the nitro group at the 4-position of the quinoline ring by the effect of N-oxide group.[5]

From the experimental results so far described, it was disclosed that *o*-alkoxycarbonitrile compounds (I, VI, VII, and XIII) and aminoisoxazole compound (XIV) were produced by the reaction of nitroquinoline 1-oxides with potassuim cyanide, and this same type reactions

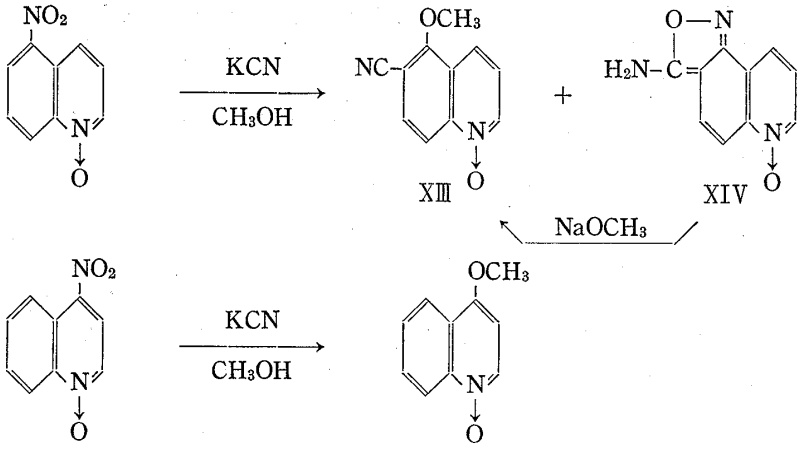

Chart 4

took place not only at nitroquinolines but their N-oxides. However, by the effect of the N-oxide group the structural formula of the reaction products were somewhat different from those of nitroquinolines, as shown in the compounds II, VI, VII, and VIII, respectively.

Experimental[6)]

Reaction of 3-Nitroquinoline 1-Oxide with KCN——To a solution of 3-nitroquinoline 1-oxide (1.0 g) in MeOH (50 ml), KCN (500 mg) was added and refluxed for 4 hr. After addition of water (*ca.* 50 ml), the reaction mixture was cooled to room temperature, and then needle precipitate was separated from the solution. A soluble portion of the product with $CHCl_3$ (*ca.* 60 ml) was purified by chromatography on Al_2O_3 to give pale yellow scales, mp 236—237° (decomp.). Yield, 398 mg (38%). This compound was found to be identical with 3-methoxycinchoninonitrile 1-oxide[2)] by mixed fusion and comparison of IR spectra. The insoluble portion in $CHCl_3$ was chromatographed on Al_2O_3 using CH_2Cl_2–MeOH (1:1) as solvent. The effluent gave 255 mg (20%) of 3-methoxy-1*H*-pyrazolo[4,3-*b*]quinoline-9-carboxamide (II) as yellow needles (MeOH), mp 283—285° (decomp.). *Anal.* Calcd. for $C_{12}H_{10}O_2N_4$: C, 59.40; H, 4.16; N, 23.13. Found: C, 59.53; H, 3.86; N, 22.97. UV λ_{max}^{MeOH} mμ (log ε): 248 (4.85), 322 (3.68, shoulder), 335 (3.80), 398 (3.72). IR ν_{max}^{KBr} cm^{-1}: 3370, 3210 (NH_2), 1670 (C=O).

3-Methoxycinchoninamide 1-Oxide (III)——i) From 3-Methoxycinchoninonitrile 1-Oxide (I): I (200 mg) was dissolved in MeOH (20 ml), 20% KOH aqueous solution (20 ml) was added, warmed to reflux for 3 hr. After removal of MeOH, the residual solution was adjusted to weak alkaline and kept overnight at room temperature, and then needle precipitate was separated. The crude product obtained was recrystallized from MeOH to give colorless needles, mp 246—247° (decomp.). Yield, 150 mg (69%). *Anal.* Calcd. for $C_{11}H_{10}O_3N_2$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.24; H, 4.38; N, 12.73. IR ν_{max}^{KBr} cm^{-1}: 3310, 3140 (NH_2), 1665 (C=O).

ii) N-Oxidation of 3-Methoxycinchoninamide: A solution of 3-methoxycinchoninamide (200 mg) and 30% H_2O_2 (4 ml) in AcOH (20 ml) was warmed at 70—75° for 5 hr. The reaction mixture was concentrated *in vacuo*. After addition of water, colorless needle precipitate was separated from solution. Yield, 106 mg (49%). This compound was identified with III by mixed fusion and comparison of IR spectra.

3-Methoxy-1*H*-pyrazolo[4,3-*b*]quinoline-9-carbonitrile (IV)——II (140 mg) was heated with $POCl_3$ (4 ml) at 120—130° for 3 hr. After standing overnight at room temperature, the reaction mixture was poured into water and extracted with CH_2Cl_2. The extract was evaporated to dryness and the residue was purified by chromatography on Al_2O_3 to give yellow needles (MeOH) of mp 243—244° (decomp.). Yield, 105 mg (80%). *Anal.* Calcd. for $C_{12}H_8ON_4$: C, 64.29; H, 3.60; N, 24.99. Found: C, 64.46; H, 3.61; N, 24.68. IR ν_{max}^{KBr} cm^{-1}: 2220 (C≡N).

1-Aminoisoxazolo[3,4-*c*]quinoline-4-carbonitrile (V)——To a solution of 1-aminoisoxazolo[3,4-*c*]quinoline (100 mg) in MeOH (10 ml), a solution of KCN (160 mg) in water (2 ml) was added, then benzoyl chloride (1 ml) was added dropwise under good agitation at 40—50°. The reaction mixture was stirred for 1 hr. After standing overnight at room temperature, the solution separated orang-red precipitate. The crude product thus obtained was purified by chromatography on Al_2O_3 with CH_2Cl_2–MeOH (9:1) as solvent, yield

6) All melting points were uncorrected. The IR spectra were taken with JASCO Model DS-402 spectrophotometer, and the NMR spectra were measured with JEOL-3H-60 spectrometer.

58 mg (51%), orange-red needles (MeOH), mp 206—207° (decomp.). *Anal.* Calcd. for $C_{11}H_6ON_4$: C, 62.85; H, 2.88; N, 26.66. Found: C, 63.02; H, 3.01; N, 26.77. IR ν_{max}^{KBr} cm^{-1}: 2240 (C≡N, weak).

Conversion of 1-Aminoisoxazolo[3,4-*c*]quinoline-4-carbonitrile (V) to 3-Methoxy-1*H*-pyrazolo[4,3-*b*]quinoline-9-carboxamide (II)——To a solution of V (60 mg) in MeOH (10 ml), KCN (60 mg) was added and stirred at 15—20° for 4 hr. After addition of water (20 ml), the solution was extracted with CH_2Cl_2, and evaporated to dryness. The residue was purified by chromatography on Al_2O_3 to give yellow needles (44 mg), which was identified with II by mixed fusion and comparison of IR spectra.

Reaction of 6-Nitroquinoline 1-Oxide with KCN——i) At Refluxing Temperature: To a solution of 6-nitroquinoline 1-oxide (1.0 g) in MeOH (100 ml), KCN (700 mg) was added and refluxed for 2 hr. After addition of water (*ca.* 100 ml), the alkaline reaction mixture was extracted with CH_2Cl_2, evaporated to dryness, and the residue was separated by chromatography on Al_2O_3. The first effluent (CH_2Cl_2 solvent) gave 210 mg (16%) of methyl 5-cyano-6-methoxyquinaldimidate 1-oxide (VI), pale yelow needles (MeOH), mp 239° (decomp.). *Anal.* Calcd. for $C_{13}H_{11}O_3N_3$: C, 60.69; H, 4.31; N, 16.34. Found: C, 60.62; H, 4.48; N, 16.16. IR ν_{max}^{KBr} cm^{-1}: 2220 (C≡N). The second effluent (CH_2Cl_2–MeOH solvent) gave 240 mg (19%) of 5-cyano-6-methoxyquinaldamide 1-oxide (VII), slightly yellow needles (EtOH), mp 264—265° (decomp.). *Anal.* Calcd. for $C_{12}H_9O_3N_3$: C, 59.26; H, 3.73; N, 17.29. Found: C, 59.24; H, 3.88; N, 16.90. IR ν_{max}^{KBr} cm^{-1}: 3260, 3100 (NH_2), 2220 (C≡N), 1690 (C=O). The residual aqueous solution from CH_2Cl_2 extraction was acidified and extracted with CH_2Cl_2. The crude product (160 mg) was recrystallized from MeOH to give 1-hydroxy-6-nitrocarbostyril (VIII), colorless needles, mp 203—205°. *Anal.* Calcd. for $C_9H_6O_4N_2$: C, 52.43; H, 2.93; N, 13.59. Found: C, 52.77; H, 3.17; N, 13.55. IR ν_{max}^{KBr} cm^{-1}: 1650 (C=O).

ii) At Room Temperature: To a solution of 6-nitroquinoline 1-oxide (1.0 g) in MeOH (60 ml), KCN (600 mg) was added and stirred vigorously at 15—20° for 3 hr. After addition of water (*ca.* 100 ml), the reaction mixture was extracted with $CHCl_3$ (300 ml). From the extract, 555 mg (43%) of methyl 6-nitroquinaldimidate 1-oxide (IX) was obtained as slightly yellow silky needles (MeOH), mp 215—216° (decomp.). *Anal.* Calcd. for $C_{11}H_9O_4N_3$: C, 53.44; H, 3.67; N, 17.00. Found: C, 53.23; H, 3.60; N, 17.01. The residual solution form $CHCl_3$ extraction was neutralized and extracted with $CHCl_3$. From the extract, 568 mg (46%) of 6-nitroquinaldamide 1-oxide (X) was obtained as yellow needles (acetone), mp 287—288° (decomp.). *Anal.* Calcd. for $C_{10}H_7O_4N_3$: C, 51.51; H, 3.03; N, 18.02. Found: C, 51.36; H, 3.22; N, 17.76. IR ν_{max}^{KBr} cm^{-1}: 3270, 3100 (NH_2), 1690 (C=O).

iii) Under the Presence of $K_3Fe(CN)_6$: To a vigorously stirred solution of 6-nitroquinoline 1-oxide (1.0 g) in MeOH (60 ml), solution of $K_3Fe(CN)_6$ (9.0 g) in water (30 ml) and of KCN (600 mg) in water (10 ml) were separately added dropwise at 3—5°, the rate of addition being regulated so that addition of both solutions were finished at the same time (*ca.* 15 min). The reaction mixture was stirred for 2 hr, and then the solution was separated from the precipitate. The crude product was purified by chromatography on Al_2O_3 to give 360 mg (32%) of 6-nitroquinaldonitrile 1-oxide (XI), with recovery of 580 mg of the starting material. XI was slightly yellow needles ($CHCl_3$), mp 257—258° (decomp.). *Anal.* Calcd. for $C_{10}H_5O_3N_3$: C, 55.82; H, 2.84; N, 19.53. Found: C, 56.00; H, 2.52; N, 19.29. IR ν_{max}^{KBr} cm^{-1}: 2230 (C≡N).

Reaction of Methyl 6-Nitroquinaldimidate 1-Oxide (IX) with KCN——i) At Refluxing Temperature: To a solution of IX (300 mg) in MeOH (40 ml), KCN (200 mg) was added and refluxed for 2 hr. After addition of water (40 ml), the reaction mixture was extracted with CH_2Cl_2. The residue after removal of solvent was chromatographed on Al_2O_3 to give 145 mg (47%) of pale yellow needles, which was confirmed to be identical with VI.

ii) At Room Temperature: To a solution of IX (200 mg) in MeOH (20 ml), KCN (200 mg) was added. The mixture was stirred for 2 hr, and kept for 5 days at room temperature. By the similar treatment of the reaction mixture as described above, 145 mg (77%) of the needles identified with X, was obtained.

Reaction of 6-Nitroquinaldamide 1-Oxide (X)——i) At Refluxing Temperature with KCN: To a solution of X (200 mg) in MeOH (20 ml), KCN (150 mg) was added and refluxed for 2 hr. After addition of water (30 ml), the reaction mixture was extracted with CH_2Cl_2. The residue after removal of solvent was recrystallized to give 95 mg (46%) of slightly yellow needles, which was confirmed to be identical with VII.

ii) Reaction with KOH: 5% KOH aqueous solution (15 ml) was added to X (150 mg), the mixture was warmed at 85—90° for 3 hr. By the similar treatment of the reaction mixture as described above, 65 mg (50%) of colorless needles was obtained. This compound was identified with VIII.

Reaction of 6-Nitroquinaldoinitrile 1-Oxide (XI)——i) At Refluxing Temperature with KCN: To a solution of XI (300 mg) in MeOH (30 ml), KCN (150 mg) was added and refluxed for 2 hr. From the reaction mixture, 83 mg (23%) of pale yellow needles and 75 mg (21%) of slightly yellow needles were obtained. These compounds were identified with VI and VII, respectively.

ii) At Room Temperature with KCN: To a solution of XI (300 mg) in MeOH (30 ml), KCN (300 mg) was added and stirred at 15—20° for 2 hr. After standing overnight at room temperature, 81 mg (24%) of slightly yellow needles and 60 mg(18%) of yellow needles were obtained. These compounds were identified with IX and X, respectively, and the starting material (45 mg) was recovered.

iii) Reaction with KOH: To a solution of XI (300 mg) in MeOH (15 ml), 5% KOH aqueous solution (30 ml) were added and heated to reflux for 1 hr. The reaction mixture was acidified with 10% HCl and

extracted with CH_2Cl_2. The residue after evaporation of solvent was recrystallized to give 245 mg (86%) of colorless needles, which was identified with VIII.

1-Methoxy-6-nitrocarbostyril (XII)——To a solution of VIII (770 mg) in $CHCl_3$ (120 ml), excess of diazomethane ether solution was added. After standing overnight at room temperature, the residue after removal of solvent was purified by chromatography on Al_2O_3 to give 510 mg (62%) of colorless needles (benzene), mp 204—206°. *Anal.* Calcd. for $C_{10}H_8O_4N_2$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.52; H, 3.76; N, 12.57. IR ν_{max}^{KBr} cm^{-1}: 1668 (C=O). NMR (in $CDCl_3$) δ: 5.79 (3H, singlet, OCH_3), 3.01 (1H, doublet, $J=10$ Hz), 2.15 (1H, doublet, $J=10$ Hz), 2.10 (1H, doublet, $J=10$ Hz), 1.43 (1H, doublet, $J=10$ Hz), 1.35 (1H, singlet).

Reaction of 5-Nitroquinoline 1-Oxide with KCN——To a solution of 5-nitroquinoline 1-oxide (1.0 g) in MeOH (50 ml), KCN (700 mg) was added and refluxed for 3.5 hr. After addition of water (*ca.* 50 ml), the reaction mixture was extracted with CH_2Cl_2. The extract was purified by chromatography on Al_2O_3 to give 260 mg (25%) of pale yellow needles. This compound (XIII) was found to be identical with 5-methoxyquinoline-6-carbonitrile 1-oxide[1] by mixed fusion and comparison of IR spectra. The residual aqueous solution after CH_2Cl_2 extraction was kept overnight at room temperature, and then precipitate was separated from the solution. The crude product thus obtained was recrystallized from MeOH to give tarnished yellow needles, mp 241—242° (decomp.), of 7-aminoisoxazolo[3,4-*f*]quinoline 1-oxide (XIV). *Anal.* Calcd. for $C_{10}H_7O_2N_3$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.32; H, 3.57; N, 20.84.

Reaction of 7-Aminoisoxazolo[3,4-*f*]quinoline 1-Oxide (XIV) with Sodium Methoxide——To a solution of metallic sodium (1.0 g) in MeOH (30 ml), XIV (140 mg) was added and refluxed for 6.5 hr. The reaction mixture was evaporated to half as much as the original volume, poured into water (*ca.* 30 ml), and extracted with CH_2Cl_2. The residue after evaporation of solvent was chromatographed on Al_2O_3 giving 42 mg (31%) of pale yellow needles. This was identical with XIII. Starting material (32 mg) was recovered.

Reaction of 4-Nitroquinoline 1-Oxide with KCN——To a solution of 4-nitroquinoline 1-oxide (2.0 g) in MeOH (120 ml), KCN (1.2 g) was added and refluxed for 5 hr. After addition of water (*ca.* 120 ml), the reaction mixture was extracted with CH_2Cl_2. The extract was chromatographed on Al_2O_3 to give 970 mg (52%) of 4-methoxyquinoline 1-oxide, which was identified with the authentic sample.