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Reaction of Aromatic Heterocyclic Nitro Compounds with Potassium Cyanide. II[1]

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On the reaction of 5-, 6-, 7-, and 8-nitroquinoline with potassium cyanide in methanol solution, always two kinds of compound were obtained in a moderate yield. The one was *o*-methoxyquinoline–carbonitrile, in which the cyano group is introduced in *ortho*–position to the nitro group and then the nitro group is replaced by a methoxyl group, and the other was 1–aminosoxazoloquinoline, in which the nitro group was reduced to hydroxyamino group and this hydroxyamino group was cyclized to an isoxazole ring with the cyano group introduced at *ortho*–position of the original nitro group. However, in the reaction of 4-nitroquinoline, 4-methoxyquinoline was obtained as a sole product.

In the preceding paper,[1] the reaction products of 3-nitroquinoline with potassium cyanide and their reaction mechanism were reported. In this connection, the cyanation reaction of mononitroquinoline compounds, whose nitro group is located at 4-, 5-, 6-, 7-, or 8-position of quinoline ring, were successively examined in order to find the nucleophillic reactivity of aromatic heterocyclic nitro compounds.

6-Nitroquinoline was allowed to react with potassium cyanide in methanol[3] and the reaction products were separated by chromatography on alumina. 6-Methoxyquinoline-5-carbonitrile (I) and an other product (II) were obtained in 53 and 26% yield, respectively.

6-Methoxyquinoline-5-carbonitrile (I) gave the corresponding carbonamide (III) on hydrolysis with potassium hydroxide in aqueous methanol solution and 6-methoxyquinoline-5-carbonitrile 1-oxide (IV) was obtained in a good yield by hydrogen peroxide-acetic acid oxidation.

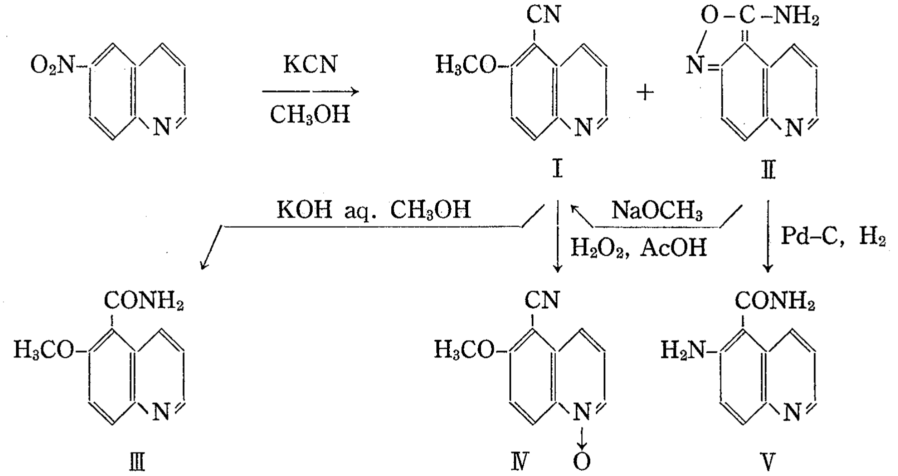

Chart 1

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[1] Part I: T. Okamoto and H. Takahashi, *Chem. Pharm. Bull.* (Tokyo), **16**, 1700 (1968).

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[3] R. Huisgen had reported the formation of 6-methoxyquinoline-5-carbonitrile (I) in 75% yield (*Ann.*, **559**, 142 (1948)).

The product II was formulated as 1-aminoisoxazolo[4,3-*f*]quinoline, because the infrared spectra of II was very similar to that of 1-aminoisoxazolo[3,4-*c*]quinoline[1] prepared from 3-nitroquinoline. Actually, II was converted into I on refluxing with sodium methoxide in methanol solution, the carbon–oxygen bond of isoxazole ring being cleaved, and II was reduced catalytically over palladium–carbon to form 6-aminoquinoline-5-carbonamide (V) by cleavage of the nitrogen–oxygen bond in isoxazole.

From the reaction of 5-nitroquinoline with potassium cyanide in methanol solution, 5-methoxyquinoline-6-carbonitrile (VI) and 1-aminoisoxazole[3,4-*f*]quinoline (VII) were obtained in a respective yield of 39 and 30%. The methoxynitrile compound (VI) was treated with potassium hydroxide to form 5-methoxyquinoline-6-carbonamide (VIII) and, by the hydrogen peroxide–acetic acid oxidation, VI was converted into 5-methoxyquinoline-6-carbonitrile 1-oxide (IX). The isoxazoloquinoline compound (VII) reacted with sodium methoxide in methanol to give VI and was reduced catalytically over palladium–carbon to form 5-aminoquinoline-6-carbonamide (X).

Similar reaction with 7-nitroquinoline gave 7-methoxyquinoline-8-carbonitrile (XI) and 1-aminoisoxazolo[3,4-*h*]quinoline (XII) in respective yield of 54 and 35%.

The compound XII was changed to XI by methanolysis as in the cases of II and VII. The cyanated position in 7-nitroquinoline is assumed to be either 6- or 8-position of the quinoline ring. In the nuclear magnetic resonance spectrum in deuteriochloroform, XI shows two doublet (J=9 cps) singnals at 2.66 τ and 2.00 τ attributable to the protons of 5- and 6-positions of the quinoline ring and, therefore, the substitution is assumed to have occurred at 8-position.

From a similar reaction of 8-nitroquinoline, 8-methoxyquinoline-7-carbonitrile (XIII) and 1-aminoisoxazolo[4,3-*h*]quinoline (XIV) were obtained. However, the yield of the product of this alkoxycyanation was exceptionally low.

The results thus obtained are summarized in Table I.

TABLE I. Products and Yield of the Reaction of Some Nitroquinolines with Potassium Cyanide in Methanol

Quinolines	Products	Yield (%)	
3-Nitro	3-methoxycinchoninonitrile[a]	62	92
	1-aminoisoxazolo[3,4-*c*]quinoline[a]	30	
4-Nitro	4-methoxyquinoline	78	
5-Nitro	5-methoxyquinoline-6-carbonitrile (VI)	39	69
	1-aminoisoxazolo [3,4-*f*] quinoline (VII)	30	
7-Nitro	6-methoxyquinoline-5-carbonitrile (I)	53	89
	1-aminoisoxazolo [3,4,-*h*]quinoline (XII)	35	
8-Nitro	8-methoxyquinoline-7-carbonitrile (XIII)	0.5	7.4
	1-aminoisoxazolo [4,3-*h*] quinoline (XIV)	6.9	

a) Part I: T. Okamoto and H. Takahashi, *Chem. Pharm. Bull.* (Tokyo), **16**, 1700 (1968)

The reaction of these nitro compounds with nucleophilic reagents such as chloride or methoxide ion does not give products and merely the starting material is recovered,[4] while these nitro compounds are reactive for cyanide ion and the characteristic alkoxycyanation reaction always takes place.

The reaction of 4-nitroquinoline with potassium cyanide in methanol solution, however, only gave 4-methoxyquinoline in which the nitro group was replaced by a methoxyl group. The nitro group in the 4-position is much more activated than that in other positions of quinoline[5] and nucleophilic substitution by a methoxide ion will take place.

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4) T. Okamoto, *Yakugaku Zasshi*, **71**, 279 (1951).
5) I. Nakayama, *Yakugaku Zasshi*, **71**, 1088 (1951).

Examination of this reaction procedure was made under various condition and the results are summarised in Table II.

Table II. Reaction of 6-Nitroquinoline with Potassium Cyanide in Various Condition

Solvent	KCN (mg)	Adding matter	Time (hr)	Methoxynitrile comp. (mg)	Aminoisoxazole comp. (mg)
MeOH	650	—	5	490	230
MeOH	650	—	10	490	140
MeOH	650	—	2.5	510	170
MeOH	3260	—	5	480	220
MeOH	650	2 N KOH 0.5 ml	5	500	210
MeOH	650	Na 580 mg	5	470	210
MeOH, H_2O (1:1)	650	—	5	465	85
MeOH, H_2O (3:7)	650	—	5	470	10
EtOH	650	—	5	460[a]	290
EtOH,H_2O (1:1)	650	—	5	420[a]	65

Procedure: To a solution of 870 mg of 6-nitroquinoline in 50 ml of the solvent, the potassium cyanide was added and refluxed. The reaction products were purified by chromatography on alumina.
a) 6-ethoxyquinoline-5-carbonitrile

The reaction is completed generally in about 2.5 hours, and evern further refluxing for 10 hours does not reduce the yield of the product. The amount of potassium cyanide usually taken is 1.5—2.0 molar equivalent of the nitro compound, and it is not necessary to use excess of potassium cyanide. Yield of the products was not influenced by the presence of an alkali such as sodium methoxide or potassium hydroxide. In ethanol solution, the alkoxycyanation reaction gave ethoxylated quinoline–carbonitrile derivative in a good yield together with 1-aminoisoxazolo[4,3-*f*]quinoline (II) as in the use of methanol as a solvent. However, the use of aqueous alcohol as the reaction solvent markedly reduces the yield of aminoisoxazoloquinoline compound.

Experimental[6]

Reaction of 6-Nitroquinoline with KCN——To a solution of 6-nitroquinoline (4.0 g) in MeOH (140 ml), KCN (3.0 g) was added and refluxed for 4 hr. After addition of H_2O (*ca.* 200 ml), the reaction mixture was cooled to room temperature, whereupon a precipitate separated. The filtered solution was extracted with CH_2Cl_2, the extract was evaporated to dryness, and the combined precipitate and the evaporation residue was submitted to chromatography on Al_2O_3, using CH_2Cl_2 as the solvent. The first effluent gave 2.25 g (53%) of 6-methoxyquinoline-5-carbonitrile (I) as colorless needles (MeOH), mp 178—179°. *Anal.* Calcd. for $C_{11}H_8ON_2$: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.73; H, 4.23; N, 15.09. IR ν_{max}^{KBr}: 2220 cm^{-1} (C≡N).

The second effluent gave 1.10 g (26%) of 1–aminoisoxazolo [4,3-*f*]quinoline (II) as slightly yellow needles (MeOH), mp 199—200° (decomp.). *Anal.* Calcd. for $C_{10}H_7ON_3$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.92; H, 3.66; N, 22.66.

6-Methoxyquinoline-5-carbonamide (III)——I (200 mg) was dissolved in 10% KOH–aq. MeOH (1:1) solution (40 ml) and refluxed for 3 hr. After evaporation of MeOH, the residual solution was adjusted to weak alkaline and kept overnight at room temperature, whereupon a precipitate separated. The precipitate was collected washed with water and dried (180 mg) to colorless needles (MeOH), mp 232—233° (decomp.). *Anal.* Calcd. for $C_{11}H_{10}O_2N_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 64.95; H, 5.14; N, 13.80. IR ν_{max}^{KBr} cm^{-1}: 3320, 3110 (NH_2), 1660 (C=O).

6-Methoxyquinoline-5-carbonitrile 1-Oxide (IV)——A Solution of I (1.2 g) and 30% H_2O_2 (4 ml) in AcOH (20 ml) was heated at 65—70° for 3 hr, then further 30% H_2O_2 (2 ml) was added, and the heating was continued for 3 hr. The reaction mixture was concentrated *in vacuo.* The precipitated product was

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[6] All melting points are uncorrected. The IR spectra were taken with Koken Model DS-402 spectrophotometer, and the NMR spectra were measured with JEOL–3H–60 spectrometer.

separated to pale yellow needles (MeOH), mp 256—257° (decomp.). Yield 1.05 g. *Anal.* Calcd. for $C_{11}H_8O_2N_2$: C, 65.99; H, 4.03; N, 13.99. Found: C, 65.65; H, 4.20; N, 13.66. IR ν_{max}^{KBr} : 2220 cm^{-1} (C=N).

6-Aminoquinoline-5-carbonxamide (V)——**II** (200 mg) was catalytically reduced over 10% Pd-C in MeOH (25 ml). When the absorption of H_2 (1 mole) ended, the reaction mixture was filtered to remove the catalyst, and the filtrate was concentrated to dryness (170 mg). Slightly yellow needles (EtOH), mp 220—221° (decomp.). *Anal.* Calcd. for $C_{10}H_9ON_3$: C, 64.16; H, 4.85; N, 22.45. Found: C, 63.98; H, 4.80; N, 21.96.

Reaction of 1-Aminoisoxazolo[4,3-*f*]quinoline (II) with Sodium Methoxide——To a solution of metallic sodium (180 mg) in MeOH (18 ml), II (185 mg) was added and the mixture was refluxed for 3 hr. The reaction mixture was evaporated to half the original volume, poured into H_2O (*ca.* 40 ml), extracted with CH_2Cl_2, and the extract was evaporated to dryness. The residue was chromatographed on Al_2O_3 to give 42 mg (23%) of colorless needles, confirmed to be identical with I by mixed fusion and by the comparison of IR spectra. Some starting material (60 mg) was recovered.

Reaction of 5-Nitroquinoline with KCN——To a solution of 5-nitroquinoline (2. 0 g) in MeOH (60 ml), KCN (1.2 g) was added and refluxed for 4 hr. After addtion of H_2O (*ca.* 150 ml), the reaction mixture was extracted with ether and the extract was evaporated to dryness. The residue was submitted to chromatography on Al_2O_3. The first effluent gave 286 mg (39%) of 5-methoxyquinoline-6-carbonitrile (VI) as colorless needles (MeOH), mp 96—96.5°. *Anal.* Calcd. for $C_{11}H_8ON_2$: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.80; H, 4.32; N, 15.00. IR ν_{max}^{KBr}: 2220 cm^{-1} (C=N). NMR (in $CDCl_3$): singlet (3H) at 5.62 (OCH_3).

The second effluent gave 650 mg (30%) of 1-aminoisoxazolo [3,4-*f*]quinoline (VII) as yellow needles (MeOH), mp 197—199° (decomp.). *Anal.* Calcd. for $C_{10}H_7ON_3$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.94; H, 3.87; N, 22.30.

5-Methoxyquinoline-6-carbonamide (VIII)——To a solution of VI (2.0 g) in MeOH (200 ml), 2 N KOH (20 ml) and 30% H_2O_2 (20 ml) were added and the mixture was warmed at 50—55° for 3 hr. The reaction mixture was concentrated, extracted with CH_2Cl_2, and the extract was evaporated to dryness. The crude product (1.2 g) was recrystallized from MeOH to colorless prisms, mp 203—204° (decomp.) *Anal.* Calcd. for $C_{11}H_{10}O_2N_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.58; H, 5.25; N, 13.40. IR ν_{max}^{KBr} cm^{-1}: 3380, 3160 (NH_2), 1660 (C=O).

5-Methoxyquinoline-6-carbonitrile 1-Oxide (IX)——A solution of VI (800 mg) and 30% H_2O_2 (3 ml) in AcOH (20 ml) was warmed at 60° for 5 hr reaction mixture was concentrated *in vacuo*, extracted with CH_2Cl_2, and the extract was evaporated to dryness. The crude product was chromatographed on Al_2O_3 to give 730 mg (84%) of pale yellow needles (MeOH), mp 171—172° (decomp.). *Anal.* Calcd. for $C_{11}H_8O_2N_2$: C, 65.99; H, 4.03; N, 13.99. Found: C, 66.28; H, 4.32; N, 13.17. IR ν_{max}^{KBr} cm^{-1}: 2220 (C≡N).

5-Aminoquinoline-6-carbonamide (X)——VII (400 mg) was dissolved in MeOH (40 ml) and reduced catalytically over 10% Pd-C. After the catalyst was removed and MeOH evaporated, the residue was chromatographed on Al_2O_3 and the product was recrystallized from MeOH to slightly yellow needles, mp 179—180°. *Anal.* Calcd. for $C_{10}H_9ON_3$: C, 64.16; H, 4.85; N, 22.45. Found: C, 63.83; H, 4.80; N, 22.31.

Reaction of 1-Aminoisoxazolo[3,4-*f*]quinoline (VII) with Sodium Methoxide——To a solution of methallic Na (800 mg) in MeOH (20 ml), VII (185 mg) was added and the mixture was refluxed for 5 hr. The product was obtained as colorless needles, identified with VI by mixed fusion and by the comparison of IR spectra. Yield, 45 mg (24%). Some starting material (42 mg) was recovered.

Reaction of 7-Nitroquinoline with KCN——7-Nitroquinoline (1.0 g) in MeOH (50 ml) was allowed to reacted with KCN (800 mg), as described above for 5-nitroquinoline. By a similar treatment of the reaction mixture, 7-methoxyquinoline-8-carbonitrile (XI) was obtained as colorless needles (MeOH), mp 139—140°. Yield, 571 mg (54%). *Anal.* Calcd. for $C_{11}H_8ON_2$: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.81; H, 4.54; N, 15.12. IR ν_{max}^{KBr} : 2220 cm^{-1} (C=N). NMR (in $CDCl_3$): singlet (3H) at 5.90 (OCH_3), doublet (1H) at 2.66 ($J=9$ cps), 1-Aminoisoxazolo [3,4-*h*] quinoline (XII) was obtained in a yield of 377mg (35.1) slightly yellow plates (MeOH) 147—148° (decomp.). *Anal.* Calcd. for $C_{10}H_7ON_3$: C, 64.86; H, 3.81; N, 22.68. Found: C, 64.95; H, 3.77; N, 22.69. UV λ_{max}^{MeOH} mμ (log ε) 242 (4.55), 270 (3.81) (shoulder), 323 (3.86), 360 (3.76).

Reaction of 1-Aminosoxazolo[3,4-*h*]quinoline (XII) with Sodium Methoxide——To a solution of metallic Na (300 mg) in MeOH (30 ml), XI (300 mg) was added and the mixtured was refluxed for 3 hr. The reaction mixture was treated as described above to give 92 mg (31%) of colorless needles, which were indentified with XI by mixed fusion and by the comparison of IR spectra.

Reaction of 8-Nitroquinoline with KCN——A solution of 8-nitro quinoline (2.0 g) in MeOH (60 ml) added with KCN (1.68 g) was refluxed for 12 hr. After addition of H_2O (*ca.* 80 ml), the reaction mixture was extracted with ether and the extract was evaporated to dryness. The residue was chromatographed on Al_2O_3 to give 8-methoxyquinoline-7-carbonitrile (XIII) as colorless needles (MeOH), mp 118—119°. Yield, 10 mg (0.5%). *Anal.* Calcd. for $C_{11}H_8ON_2$: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.40; H, 4.55; N, 14.97; IR ν_{max}^{KBr} 2220 cm^{-1} (C=N). Another product was 1-aminoisoxazolo [4,3-*h*] quinoline (XIV) (yield 145 mg (6.9%)) as yellow needles (MeOH), mp 163—165° (decomp.). *Anal.* Calcd. for $C_{10}H_7ON_3$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.77; H, 3.85; N, 22.25. Some starting material (100 mg) was recovered.

Reaction of 1-Aminoisoxazolo [4,3-*h*]quinoline (XIV) with Sodium Methoxide——To a solution of methallic Na (2.5 g) in MeOH (60 ml), XIV (460 mg) was added and the mixture was refluxed for 7 hr. The product was obtained as colorless needles in 30 mg yield, which was identified as XIII by mixed fusion and by the comparison of IR spectra.

Reaction of 4-Nitroquinoline with KCN——To a solution of 4-nitroquinoline (1.0 g) in MeOH (50 ml), KCN (650 mg) was added and the mixture was refluxed for 3 hr. By a similar treatment of the reaction mixture, 710 mg (78%) of 4-methoxyquinoline was obtained, which was identified by the comparison of IR spectra and by the mixed fusion of its picrate.