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Reaction of 6-Nitroquinoxalines with Potassium Cyanide

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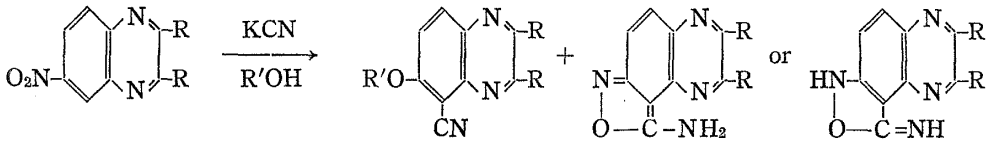
2,3-Disubstituted 6-nitroquinoxalines were reacted with potassium cyanide in alcoholic solutions to form 2,3-disubstituted 6-alkoxyquinoxaline-5-carbonitriles (I, III and IV) and 2,3-disubstituted-5-aminoisoxazolo[4,3-*f*]quinoxalines (II and V) at the yield of about 50 and 30%, respectively. The reaction of 2,4-dinitroaniline with potassium cyanide in methanolic solution gave *o*-methoxybenzonitrile compounds (VII and VIII). The same reaction was carried out in the presence of potassium ferricyanide and only dinitrobenzonitrile (VI) was obtained. Each VI and VII were reduced catalytically to *o*-phenylenediamine compounds and then condensed with benzil to yield the corresponding quinoxaline compounds. These were identical with the direct alkoxycyanation products of 2,3-disubstituted 6-nitroquinoxaline.

It was previously reported by Okamoto, *et al.*[2] that nitroquinolines reacted with potassium cyanide in alcoholic solution producing *o*-alkoxyquinolinecarbonitriles and 1-aminoisoxazoloquinolines in good yields. Concerning the mechanism of this reaction, they suggested that the former compound was given as the result of the introduction of cyano group at the position *ortho* to nitro group and the subsequent replacement of the nitro group by alkoxyl group, while the latter was produced by the reduction of intermediary *o*-nitrocarbonitrile into *o*-hydroxylaminocarbonitrile, followed by an intramolecular cyclization. These reactions were regarded as a different type of "von Richter reaction".[3]

Insofar as this same type reaction is expected to take place not only at nitroquinolines but aromatic N-heterocyclic nitro compounds in general, the authors attempted in the present work the reactions of nitroquinoxalines with potassium cyanide, and observed the formations of *o*-alkoxycarbonitriles and aminoisoxazolo compounds as in the case of the reaction of nitroquinolines. Moreover, in order to confirm the structures of these products, the reaction of 2,4-dinitroaniline under the same condition was carried out, and the products were treated with benzil to give the corresponding quinoxaline compounds. These results are also reported.

2,3-Disubstituted 6-nitroquinoxalines were allowed to react with two molar equivalent of potassium cyanide in methanolic solution and the reaction mixtures were purified by chromatography on alumina. 2,3-Disubstituted 6-methoxyquinoxaline-5-carbonitriles (I, IV) and 2,3-disubstituted 5-aminoisoxazolo[4,3-*f*]quinoxalines (II, V) were obtained in the yield of



i) R=Ph, R'=Me	I	II	IIa
ii) R=Ph, R'=Et	III	II	IIa
iii) R=Me, R'=Me	IV	V	Va

Chart 1

1) Location: *Ebara 2-4-41, Shinagawa-ku, Tokyo.*
2) T. Okamoto and H. Takahashi, *Chem. Pharm. Bull.* (Tokyo), **16**, 1700 (1968); T. Okamoto, H. Takahashi, H. Takayama, T. Kitagawa, and M. Ikeda, *ibid.*, **17**, 140 (1969).
3) J.F. Bunnett, J.F. Cormack, and F.C. McKay, *J. Org. Chem.*, **15**, 481 (1950).

about 50 and 30%, respectively. In the similar reaction, using ethanol in place of methanol as solvent, the corresponding *o*-ethoxycarbonitrile compound (III) along with aminoisoxazoloquinoxaline (II) was afforded. These results were shown in Chart 1.

2,4-Dinitroaniline was reacted with potassium cyanide in methanolic solution, and the products were purified by chromatography on alumina. Orange red needles, mp 212—213° (VII) and yellow needles, mp 173—174° (VIII) were separated with the yield of 4:5 ratio. The infrared spectra (IR) of both VII and VIII exhibited a sharp absorption peak characteristic of cyano group at 2225 cm^{-1} and the nuclear magnetic resonance spectra (NMR) of each VII and VIII in deuterochloroform showed a signal (singlet, three proton) at 4.29 and 4.10 ppm, respectively, both of which are attributable to the methoxyl group.

There are two facts so far known concerning the alkoxycyanation of nitrobenzenes, that is, *m*-dinitrobenzene[4] and 2,4-dinitrochlorobenzene[5] reacted with alcoholic potassium cyanide to give 2-alkoxy-6-nitrobenzonitrile and 2-alkoxy-5-chloro-6-nitrobenzonitrile, respectively. By analogy with these reaction, the above two products (VII, VIII) were assumed to be the correlated isomer of each other, where the cyano group introduced at 3-position of 2,4-dinitroaniline and one of the nitro group was replaced by the methoxy group.

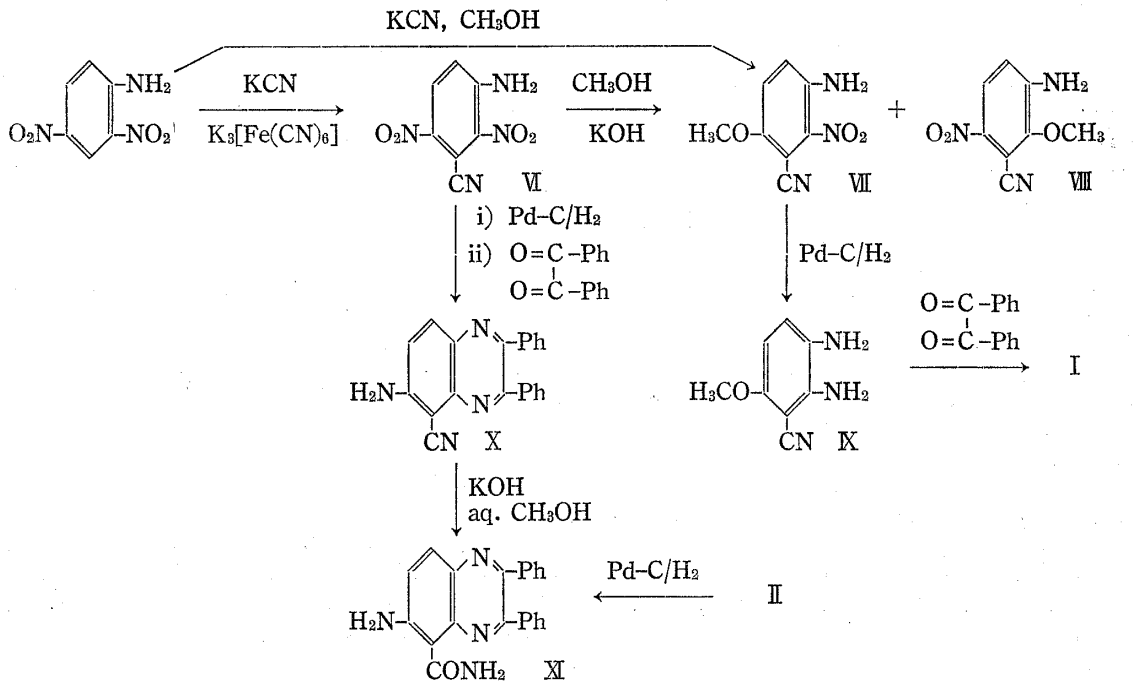


Chart 2

When VII was reduced catalytically with paradized carbon to amino compound (IX) and then condensed with equivalent mole of benzil in methanolic solution, the quinoxaline compound which was identical with the methoxycyanation product of 2,3-diphenyl-6-quinoxaline was obtained. Accordingly, the other product having mp 173—174° (VIII) must be 2-methoxy-3-cyano-4-nitroaniline.

On the other hand, when the reaction of 2,4-dinitroaniline with potassium cyanide was carried out under the presence of potassium ferricyanide as a mild oxydative reagent, 2,6-dinitro-3-aminobenzonitrile (VI) in which the cyano group introduced at 3-position and the nitro group not replaced by the methoxyl group, was obtained. But by the treatment of VI with potassium hydroxide in alcoholic solution, the foregoing isomers VII and VIII were resulted similar to the case of direct reaction of 2,4-dinitroaniline with potassium cyanide.

4) A. Rusell and L.M. Addison, *J. Am. Chem. Soc.*, **65**, 2379 (1943).
5) W.J. van Heteren, *Rec. Trav. Chim.*, **20**, 107 (1901); J.J. Blanksma, *ibid.*, **21**, 424 (1902).

VI was reduced catalytically to triamino compound and then reacted with benzil to form 2,3-diphenyl-6-aminoquinoxaline-5-carbonitrile (X) as in the case of I from VII. By refluxing with alkali solution, X was easily hydrolyzed to carboxamide (XI), which was prepared also by the hydrogenation of foregoing product II.

From the results so far described, it can be concluded that the two products obtained from the reaction of 2,3-diphenyl-6-nitroquinoxaline with potassium cyanide are represented by the structure of I and II. Concerning the structure of isoxazoloquinoxalines, the most reasonable structure is not decided either amino (II and V) or imino type (IIa and Va) from the results of IR spectra.

In addition, connecting with the present work, a similar reaction with 2-substituted 5-nitrobenzimidazoles was attempted, but merely the starting material was recovered.

Experimental[6]

Reaction of 2,3-Diphenyl-6-nitroquinoxaline with KCN—i) In MeOH Solution: To a solution of 2,3-diphenyl-6-nitroquinoxaline (1.31 g) in MeOH (150 ml), KCN (520 mg) was added and the mixture was refluxed for 4 hr. The reaction mixture was cooled to room temperature, whereupon needle crystals separated. The filtrate was diluted with about 100 ml of water, extracted with CH_2Cl_2, and the CH_2Cl_2 solution after drying was concentrated to dryness. The separated crystals and evaporation residue were combined and chromatographed on Al_2O_3 using CH_2Cl_2 as solvent. The effluent gave 350 mg (52%) of 2,3-diphenyl-6-methoxyquinoxaline-5-carbonitrile (I) as colorless needles (MeOH), mp 237—238°. *Anal.* Calcd. for $C_{22}H_{15}ON_3$: C, 78.32; H, 4.48; N, 12.46. Found: C, 78.54; H, 4.70; N, 12.71. IR ν_{max}^{KBr} cm^{-1}: 2225 (C≡N). NMR (in $CDCl_3$) δ: 4.12 (3H, singlet, OCH_3). The chromatogram was developed with 50% MeOH–CH_2Cl_2, and 240 mg (35%) of 2,3-diphenyl-5-aminoisoxazolo[4,3-*f*]quinoxaline (II) as slightly yellow plates (MeOH), mp 262—263° (decomp.) was obtained. *Anal.* Calcd. for $C_{21}H_{14}ON_4$: C, 74.54; H, 4.17; N, 16.56. Found: C, 74.58; H, 4.39; N, 16.69.

ii) In EtOH solution: A Solution of 2,3-diphenyl-6-nitroquinoxaline (1.3 g) in EtOH (150 ml), and KCN (520 mg) was heated under reflux for 4 hr. By a similar treatment of the reaction mixture, 710 mg (51%) of 2,3-diphenyl-6-ethoxyquinoxaline-5-carbonitrile (III), pale yellow needles (MeOH), mp 213—214° and 520 mg (39%) of II were obtained. *Anal.* Calcd. for $C_{23}H_{17}ON_3$ (III): C, 78.61; H, 4.88; N, 11.96. Found: C, 78.95; H, 4.81; N, 12.28. IR ν_{max}^{KBr} cm^{-1}: 2225 (C≡N). NMR (in $CDCl_3$) δ: 1.69 (3H, triplet, J=7Hz, CH_3), 4.64 (2H, quartet, J=7Hz, OCH_2Me). II was found to be identical with the compound obtained from methanol solvent.

Reaction of 2,3-Dimethyl-6-nitroquinoxaline with KCN——To a solution of 2,3-dimethyl-6-nitroquinoxaline (2.03 g) in MeOH (100 ml), KCN (1.3 g) was added and the mixture was refluxed for 4 hr. By a similar treatment of the reaction mixture, 2,3-dimethyl-6-methoxyquinoxaline-5-carbonitrile (IV) was obtained as pale yellow needles (MeOH) of mp 194°. Yield, 842 mg (40%). *Anal.* Calcd. for $C_{12}H_{11}ON_3$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.56; H, 5.31; N, 20.14. IR ν_{max}^{KBr} cm^{-1}: 2220 (C≡N). NMR (in $CDCl_3$) δ: 4.15 (3H, singlet, OCH_3). Another product was 2,3-dimethyl-5-aminoisoxazolo[4,3-*f*]quinoxaline (V) as yellow needles (MeOH), mp 225—226° (decomp.). Yield, 282 mg (13%). *Anal.* Calcd. for $C_{11}H_{10}ON_4$: C, 61.67; H, 4.71; N, 26.16. Found: C, 61.36; H, 4.85; N, 26.27.

Reaction of 2,4-Dinitroaniline with KCN——i) At the refluxing Condition: To a solution of 2,4-dinitroaniline (3.1 g) in MeOH (90 ml), KCN (2.6 g) was added and refluxed for 3 hr. After addition of water (*ca.* 100 ml), the solution was extracted with CH_2Cl_2, and the extract was condensed to dryness. The residue in CH_2Cl_2 solution was chromatographed on Al_2O_3, and an orange yellow chromatogram containing two substances was gradually separated. The first effluent gave 240 mg of 2-nitro-3-amino-6-methoxybenzonitrile (VII) as orange red needles (MeOH), mp 212—213°. *Anal.* Calcd. for $C_8H_7O_3N_3$: C, 49.74; H, 3.64; N, 21.76. Found: C, 49.88; H, 3.59; N, 22.05. IR ν_{max}^{KBr} cm^{-1}: 3500, 3360 (NH_2), 2225 (C≡N). NMR (in $CDCl_3$) δ: 4.29 (3H, singlet, OCH_3), 7.62 (1H, doublet, J=11Hz), 8.28 (1H, doublet, J=11Hz). The second effluent gave 300 mg of 2-methoxy-3-amino-6-nitrobenzonitrile (VIII) as yellow needles (MeOH), mp 173—174°. *Anal.* Calcd. for $C_8H_7O_3N_3$: C, 49.74; H, 3.64; N, 21.76. Found: C, 49.88; H, 3.72; N, 22.18. IR ν_{max}^{KBr} cm^{-1}: 3490, 3355 (NH_2), 2225 (C≡N). NMR (in $CDCl_3$) δ: 4.10 (3H, singlet, OCH_3), 7.10 (1H, doublet, J=10Hz), 8.06 (1H, doublet, J=10Hz).

ii) In the Presence of $K_3[Fe(CN)_6]$ Condition: To a vigorously stirred solution of 2,4-dinitroaniline (3.1 g) in MeOH (250 ml), solution of $K_3[Fe(CN)_6]$ (30 g) in H_2O (150 ml) and of KCN (5.2 g) in H_2O (30 ml) were separately added dropwise at 40—45°, the rate of addition being regulated. Addition of both solutions

6) All melting points are uncorrected. The IR spectra were taken with JASCO Model DS-301 spectrophotometer, and the NMR spectra were measured with Hitachi–Parkin–Elmer Model R-20 spectrometer.

should be finished at the same time (*ca.* 30 min) and stirring continued for 3 hr. The precipitate that separated was washed with H_2O, and dried. The crude product 2.35 g (51%) was recrystallized from acetone to yield 2,6-dinitro-3-aminobenzonitrile (VI) as yellow crystals, mp 187—188°. *Anal.* Calcd. for $C_7H_4O_4N_4$: C, 40.39: H, 1.94; N, 26.92. Found: C, 40.65; H, 2.22; N, 26.67. IR ν_{max}^{KBr} cm^{-1}: 3460, 3340 (NH_2), 2240 (C≡N).

Reaction of 2,6-Dinitro-3-aminobenzonitrile (VI) to VII and VIII——To a solution of VI (416 mg) in MeOH (40 ml), KOH (500 mg) was added and the mixture was refluxed for 1 hr. After the addition of H_2O (*ca.* 40 ml), the solution was extracted with CH_2Cl_2, and the extract was evaporated to dryness (290 mg). The residue was purified by chromatography on Al_2O_3, and VII and VIII were obtained at the yield of 30 and 36%, respectively.

2,3-Diamino-6-methoxybenzonitrile (IX)——VII (386 mg) was catalytically reduced over 10% Pd–C in MeOH (50 ml). When the absorption of H_2 (3 mole) ended, the reaction mixture was filtered to remove the catalyst and the filtrate was concentrated to dryness (245 mg). Colorless plates (*n*–hexane), mp 158°. *Anal.* Calcd. for $C_8H_9ON_3$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.93; H, 5.25; N, 25.30. IR ν_{max}^{KBr} cm^{-1}: 2220 (C≡N).

Formation of I from IX and Benzil——A solution of IX (125 mg) and benzil (162 mg) in MeOH (*ca.* 10 ml) was added conc. HCl (2 ml) and the mixture was refluxed for 1 hr. After removal of the solvent, the residue was recrystallized from MeOH to colorless needles of mp 237—238. Yield, 188 mg. This was found to be identical with 2,3-diphenyl-6-methoxyquinoxaline-5-carbonitrile (I) by mixed fusion and by the comparison of IR spectra.

2,3-Diphenyl-6-aminoquinoxaline-5-carbonitrile (X)——VI (1.04 g) was catalytically reduced over 10% Pd–C in EtOH (50 ml). When the absorption of H_2 (6 mole) ended, the reaction mixture was filtered to remove the catalyst. And to the filtrate, benzil (1.05 g) and conc. HCl (3 ml) were added and the mixture was stirred at 60—65° for 2 hr. After addition of 5% K_2CO_3 solution, the reaction mixture was cooled to room temperature, whereupon needles crystals separeted. The crude product was purified by chromatography on Al_2O_3, and 2,3-diphenyl-6-aminoquinoxaline-5-carbonitrile (X) as pale yellow needles (MeOH), mp 264° was obtained. Yield, 970 mg (57%). *Anal.* Calcd. for $C_{21}H_{14}N_4$: C, 78.24; H, 4.38; N, 17.38. Found: C, 78.17; H, 4.47; N, 17.52. IR ν_{max}^{KBr} cm^{-1}: 3460, 3355 (NH_2), 2215 (C≡N).

2,3-Diphenyl-6-aminoquinoxaline-5-carboxamide (XI)——i) From 2,3-Diphenyl-6-aminoquinoxaline-5-carbonitrile (X): X (161 mg) was dissolved in 10% KOH–EtOH (1:1) solution (200 ml) and refluxed for 4 hr. After removal of EtOH, the residual solution cooled to room temperature, whereupon needle crystals (150 mg) separated. Yellow needles, mp 236—237°. *Anal.* Calcd. for $C_{21}H_{16}ON_4$: C, 74.10; H, 4.74; N, 16.46. Found: C, 74.14; H, 4.98; N, 16.50. IR ν_{max}^{KBr} cm^{-1}: 1640 (C=O).

ii) From 2,3-Diphenyl-5-aminoisoxazolo[4,3-*f*]quinoxaline (II): II (170 mg) was catalytically reduced over 10% Pd–C in MeOH (50 ml). The reaction mixture after removed from the catalyst was concentrated to give yellow neeldes of mp 236—237°. Yield, 155 mg (91%). This compound was found to be identical with the above described XI by mixed fusion and by the comparison of IR spectra.

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