[Chem. Pharm. Bull. 16(9)1700—1704(1968)]

UDC 547.831.6.04

Reaction of Aromatic Heterocyclic Nitro Compound with Potassium Cyanide. I.[1] 3-Nitroquinoline

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(Received December 20, 1967)

3-Nitroquinoline was reacted with potassium cyanide in methanol at refluxing temperature to give 3-methoxycinchoninonitrile (I) and 1-aminoisoxazolo[3,4-*c*]quinoline (II) in the yield of 62% and 30%, respectively. 3-Nitrocinchoninonitrile (III), which was prepared by the reaction of 3-nitroquinoline with potassium cyanide in the presence of potassium ferricyanide, was treated with potassium cyanide in methanol to from I, and III was converted into II by reduction with zinc dust and ammonium chloride.

It is well known that reaction of aromatic nitro compounds with potassium cyanide in alcohol or aqueous alcohol generally gives a carboxylic acid as the product in which the nitro group is lost and the carboxyl group is introduced *ortho* to the original position of the nitro group. This type of reaction is called "von Richter reaction" and the reaction mechanism was studied intensively by Bunnett, *et al.*,[3] and later by several other workers.[4] They reported, however, that some aromatic nitro compounds with bromo, chloro, methyl or phenyl group located at *meta* or *para*-position of the nitro group react with potassium cyanide to form carboxylic acids. The sum of the value of Hammett substituent constant of the substituents other than the nitro group for the *ortho* position of the nitro group falls in the range of -0.2 to $+0.6$[5] in these cases and this limitation is required of the starting compound for "von Richter reaction." A compound which has a more positive value of the Hammett substituent constant, for example *m*-dinitrobenzene[6] or 2,4-dinitrochlorobenzene,[7] affords *o*-alkoxybenzonitrile derivative by the reaction with potassium cyanide in alcoholic solution.

There are many papers discussing the polar effect of ring nitrogen in heterocyclic compounds. In pyridine and quinoline, the Hammett substituent constant of the nitrogen of the pyridine ring is calculated as $+0.6(m)$ and $+0.9(p)$.[8] Therefore, nitropyridine derivatives are suitable compounds for this reaction. In the present paper, the authors discuss the reaction of 3-nitroquinoline with potassium cyanide in alcohol solution.

The products obtained from the reaction of 3-nitroquinoline with 1.5—2.0 molar equivalent of potassium cyanide in methanol solution were purified by chromatography on alumina, and compounds I and II were separated in the yield of 62% and 30%, respectively. The infrared spectrum of I exhibited a sharp absorption peak characteristic of cyano group at 2220 cm^{-1}, and its nuclear magnetic resonance spectrum in deuteriochloroform showed

1) This paper constitutes Part IX of a series entitled "Reaction Mechanism in Aromatic Heterocyclic Compounds" by T. Okamoto. Part VIII: *Chem.Pharm. Bull.*(Tokyo), **14**, 512 (1966).
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3) J.F. Bunnett and M.M. Rauhut, *J. Org. Chem.*, **21**, 944 (1956).
4) K.M. Ibne-Rasa and E. Koubek, *J. Org. Chem.*, **28**, 3240 (1963).
5) J.F. Bunnett and M.M. Rauht, *J. Org. Chem.*, **21**, 934 (1956).
6) A. Russel and L.M. Addison, *J. Am. Chem. Soc.*, **65**, 2379 (1943).
7) W.J. van Heteren, *Rec. Trav. Chim.*, **20**, 107 (1901).
8) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Company, Amsterdam, London, New York, 1967, p. 124.

a signal (three protons, singlet) at 5.68 τ attributable to the methoxyl group. Therefore, the compound I was postulated as 3–methoxycinchoninonitrile.

The compound II, as described in the following, was concluded to be 1–aminoisoxazolo-[3,4–*c*]quinoline, in which the nitro group of the starting compound was reduced to hydroxyamino group and cyclized to an isoxazole ring between this hydroxyamino and the cyano group introduced into the *ortho* position.

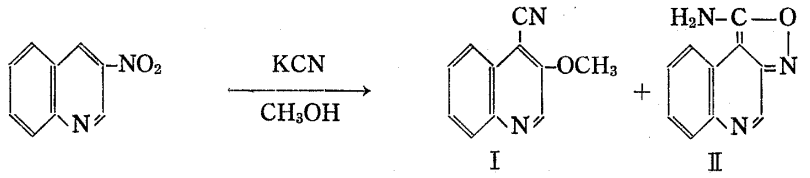

Chart 1

On the other hand, in the presence of potassium ferricyanide,[9] the reaction of 3–nitroquinoline with potassium cyanide in methanol solution at 15—20° gave 3–nitrocinchoninonitrile (III), in which the cyano group was introduced into 4–position of the quinoline ring. By treatment with potassium cyanide in methanol solution under the same condition as for obtaining I directly from 3–nitroquinoline, III was converted into I in a good yield. When III was heated with potassium hydroxide in aqueous methanol solution, 3–methoxycinchoninamide (IV) was produced. IV was also obtained from I by the same reaction. 3–Methoxycinchoninonitrile 1–oxide (V) was obtained by oxidation of I with hydrogen peroxide and acetic acid.

III was reduced catalytically with Pd–carbon to the amino compound (VI), and then treated with potassium hydroxide in aqueous methanol solution to form 3–aminocinchoninamide(VII). This compound was also obtained by the catalytic reduction of II. The reaction did not occur on refluxing II with potassium cyanide in methanol and merely the starting

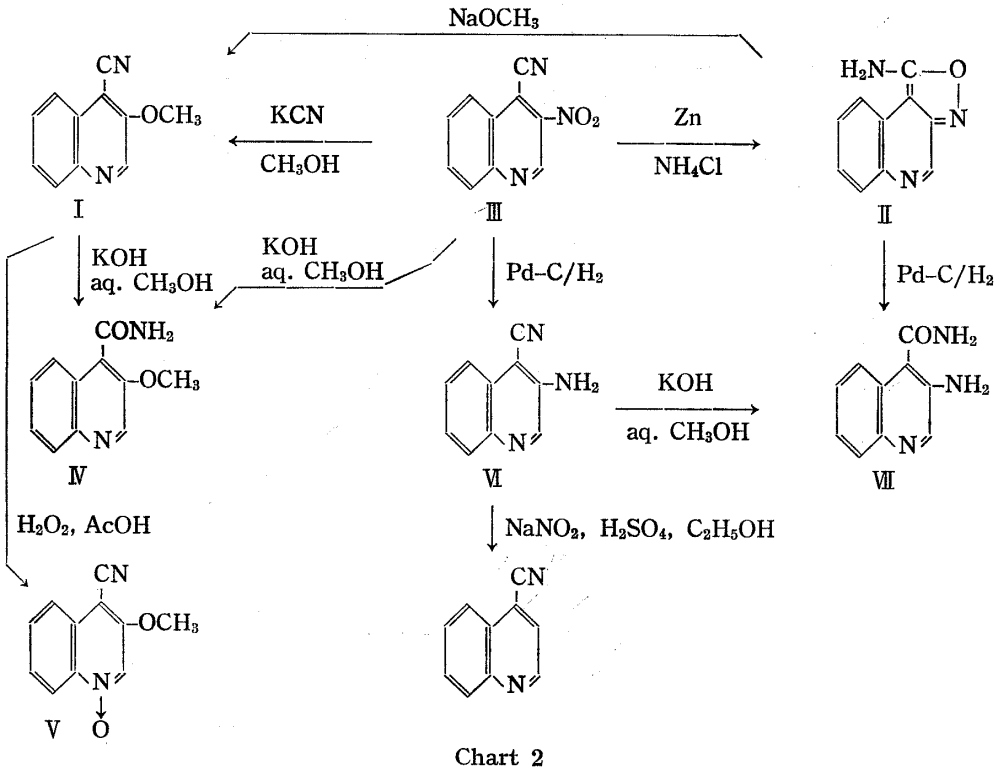

Chart 2

9) J.F. Bunnett and R.E. Zahler, *Chem. Rev.*, **49**, 273 (1951).

material was recovered. However, I was obtained from II on refluxing it with sodium methoxide in methanol solution. This reaction may be explained as follows; The isoxazole ring of II was attacked by the methoxide ion, opening the carbon–oxygen bond, and the hydroxyamino group produced was replaced by the methoxyl group because of the electronegative effect of the cyano group at *ortho* position.

3–Aminocinchoninonitrile (VI) was diazotized with sodium nitrite in sulfuric acid and ethanol solution, and deaminated to give a product, which was identical with the authentic specimen of cinchoninonitrile. This result confirms the position attacked by cyanide ion.

When III was reduced by the use of zinc dust in the presence of ammonium chloride, II was obtained in a moderate yield. The reduction of aromatic nitro compound with zinc dust in the presence of ammonium chloride or calcium chloride generally gives hydroxyamino derivative, so IIa seems to be the first product obtained in the reduction of III, and the hydroxyamino group will cyclize with the cyano group to give an isoxazole ring. The structure of II is represented by either IIb or IIc formula.

The infrared spectrum of II shows absorption bands at 3280 and 3110 cm^{-1} (KBr), assignable as that of amino group,[10] and IIc seems to be the most reasonable structure for II.

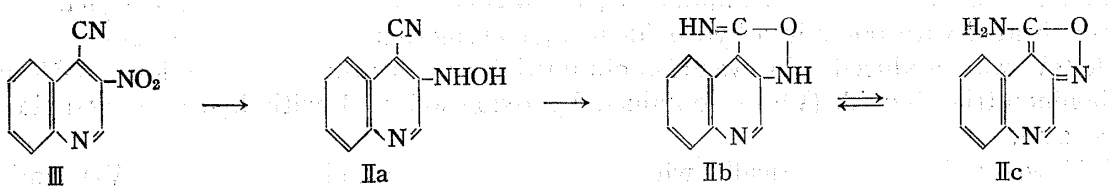

Chart 3

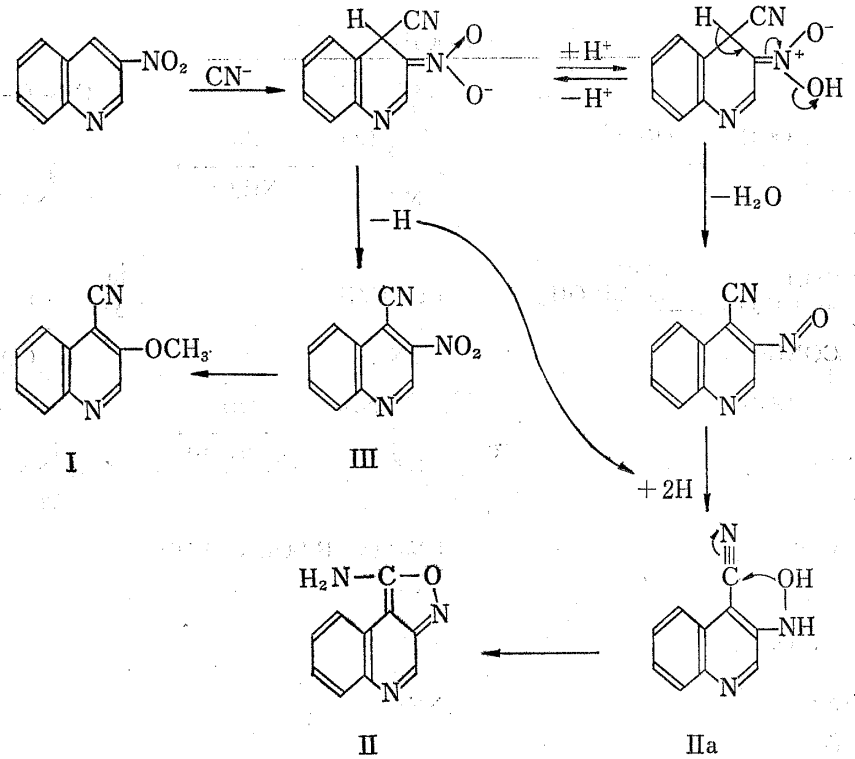

Chart 4

10) H. Musso and H. Schroder, *Chem. Ber.*, 98, 1562 (1965).

Summarizing the above data, it may be concluded that in the reaction of 3–nitroquinoline with potassium cyanide in methanol, the *ortho* position of the nitro group was attacked at first by the cyanide ion producing the intermediate dihydro compound, and through its dehydrogenation, III was formed. Next, this was converted into I, in which the nitro group was replaced by the methoxyl group under a rather mild condition. On the other hand, the dihydro–type intermediate was dehydrated to give the nitroso compound, successively reduced by the eliminated hydride ion to IIa, and then intramolecular cyclization took place to form II. The correlation of these reaction series is shown in Chart 4.

Experimental[10]

Reaction of 3-Nitroquinoline with KCN——To a solution of 3–nitroquinoline (1.0 g) in MeOH (25 ml), KCN (600 mg) was added and the mixture was refluxed for 4 hr. After addition of H_2O (*ca.* 25 ml), the reaction mixture was cooled to room temperature, whereupon needle crystals separated. The filtrate solution was extracted with ether and the extract was evaporated to dryness. The products were purified by chromatography on Al_2O_3. The first effluent gave 650 mg (62%) of 3–methoxycinchoninonitrile (I) as pale yellow scales (MeOH), mp 155—156°. *Anal.* Calcd. for $C_{11}H_8ON_2$: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.35; H, 4.53; N, 15.12. IR ν_{max}^{KBr} 2220 cm^{-1} (C≡N). NMR (in $CDCl_3$): singlet (3H) at 5.68 τ (OCH_3).

The second effluent gave 320 mg (30%) of 1–aminoisoxazolo[3,4–*c*]quinoline (II) as yellow silky needles (MeOH), mp 185—186° (decomp.). *Anal.* Calcd. for $C_{10}H_7ON_3$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.48; H, 3.76; N, 22.69. IR ν_{max}^{KBr} cm^{-1}: 3280, 3110 (NH_2).

Reaction of 3-Nitroquinoline with KCN in the Presence of $K_3Fe(CN)_6$——To a vigorously stirred solution of 3–nitroquinoline (1.0 g) in MeOH (45 ml), solutions of $K_3Fe(CN)_6$ (6.0 g) in H_2O (20 ml) and of KCN (1.0 g) in H_2O (10 ml) were separately added dropwise at 15—20°, the rate of addition being regulated. Addition of both solutions should be finished at the same time (*ca.* 15 min). The reaction mixture was stirred for 3 hr, the solution after separated from the precipitate was extracted with CH_2Cl_2, and the extract was evaporated to dryness. The precipitate was washed with H_2O and dried. The precipitate and the residue were combined and chromatographed on Al_2O_3 to give 702 mg (60%) of 3–nitrocinchoninonitrile (III) as slightly yellow plates (MeOH), mp 156—157°. *Anal.* Calcd. for $C_{10}H_5O_2N_3$: C, 60.30; H, 2.53; N, 21.10. Found: C, 60.39; H, 2.96; N, 20.85. IR ν_{max}^{KBr} cm^{-1}: 2240 (C≡N) (weak), 1545, 1355 (NO_2).

Reaction of 3-Nitrocinchoninonitrile (III) with KCN——To a solution of III (400 mg) in MeOH (20 ml), KCN (240 mg) was added and the mixture was refluxed for 1 hr. After addition of H_2O (20 ml), the solution was extracted with CH_2Cl_2, and the extract was evaporated to dryness. The residue was purified by chromatography on Al_2O_3 to give 281 mg of pale yellow scales, mp 155—156°. This compound was found to be identical with 3–methoxycinchoninonitrile (I) by mixed fusion and by the comparison of IR spectra.

3-Methoxycinchoninamide (IV)——i) From 3–Nitrocinchoninonitrile (III): III (180 mg) was dissolved in 10% KOH–MeOH (1:1) solution (40 ml), and refluxed for 3 hr. After removal of MeOH, the residual solution was adjusted to weak alkalinity and kept overnight at room temperature, whereupon needle crystals separated. The crude product was washed with water and dried (150 mg) to colorless prisms (MeOH), mp 217—218° (decomp.). *Anal.* Calcd. for $C_{11}H_{10}O_2N_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.33; H, 5.18; N, 13.63. IR ν_{max}^{KBr} cm^{-1}: 3240, 3100 (NH_2), 1665 (C=O).

ii) From 3–Methoxycinchoninonitrile (I): I (350 mg) was dissolved in 10% KOH–MeOH (1:1) solution (70 ml) and refluxed for 3 hr. Similar treatment of the reaction mixture as above gave 325 mg of a product whose melting point was not depressed when admixed with the reaction product of III, and its IR spectrum was identical with that of IV.

3-Methoxycinchoninonitrile 1-Oxide (V)——A solution of I (200 mg) and 30% H_2O_2 (4 ml) in AcOH (60 ml) was warmed at 70—75° for 3 hr, and then further 30% H_2O_2 (4 ml) was added, the warming being continued for 6 hr. The crude product obtained was purified by chromatography on Al_2O_3. Yield, 162 mg (75%) of pale yellow scales (MeOH), mp 236—237° (decomp.). *Anal.* Calcd. for $C_{11}H_8O_2N_2$: C, 65.99; H, 4.03; N, 13.99. Found: C, 65.89; H, 3.94; N, 14.14. IR ν_{max}^{KBr} 2220 cm^{-1} (C≡N).

3-Aminocinchoninonitrile (VI)——III (300 mg) was catalytically reduced over 10% Pd–C in MeOH (30 ml). When the absorption of H_2 (3 moles) ended, the reaction mixture was filtered to remove the catalyst and the filtrate was concentrated to dryness (180 mg). Slightly yellow needles (EtOH), mp 213—214° (decomp.). *Anal.* Calcd. for $C_{10}H_7N_3$: C, 70.99; H, 4.17; N, 24.84. Found: C, 71.16; H, 4.41; N, 24.45. IR ν_{max}^{KBr} cm^{-1}: 3330, 3220 (NH_2), 2210 (C≡N).

3-Aminocinchoninamide (VII)——i) From 3–Aminocinchoninonitrile (VI): VI (180 mg) was dissolved in 10% KOH–MeOH (1:1) solution (36 ml) and the solution was refluxed for 3 hr. After removal of MeOH,

11) All melting points are uncorrected. The IR spectra were taken with Koken Model DS–402 spectrophotometer, and the NMR spectra were measured with JEOL–60 spectrometer.

the residue was extracted with ether. Yield 126 mg (64%) of pale yellow needles (EtOH), mp 222–223°. *Anal.* Calcd. for $C_{10}H_9ON_3$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.20; H, 4.95; N, 22.73.

ii) Reduction of 1–Aminoisoxazolo[3,4–*c*]quinoline (II): II (180 mg) was catalytically reduced over 10% Pd–C in MeOH (30 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 (160 mg). The melting point of the product was undepressed on admixture with the product obtained from VI, and the IR spectra were identical.

Reduction of 3-Nitrocinchoninonitrile (III) to 1-Aminoisoxazolo[3,4-*c*]quinoline (II)——To a vigorously stirred suspension of III (480 mg) and NH_4Cl (260 mg) in aqueous MeOH (1:1) solution (12 ml), zinc dust (700 mg) was added in small portions during 40 min at 10—15°. After the addition, stirring was continued for 5 hr and the mixture was stood overnight at room temperature. The solution separated from the precipitate, was extracted with CH_2Cl_2, and the extract was evaporated to dryness. The precipitate was dissolved in MeOH, filtered, and the solvent was removed. The precipitate and the residue were combined and chromatographed on Al_2O_3 to give 320 mg (74%) of yellow silky needles, which were found to be identical with II by mixed fusion and by the comparison of IR spectra. Some starting material (3 mg) was recovered.

Reaction of 1-Aminoisoxazolo[3,4-*c*]quinoline (II) with Sodium Methoxide——To a solution of metallic sodium (130 mg) in MeOH (16 ml), II (160 mg) was added and the mixture was refluxed for 3 hr. The reaction mixture was concentrated and the residue was separated by chromatography on Al_2O_3 to give 16 mg (10%) of pale yellow needles, which were found to be identical with I by mixed fusion and by the comparison of IR spectra. Some starting material (58 mg) was recovered.

Deamination of 3-Aminocinchoninonitrile (VI) to Cinchoninonitrile——To a mixture of VI (150 mg) in EtOH (0.8 ml) and conc. H_2SO_4 (0.2 ml), $NaNO_2$ (85 mg) was added under good agitation at 10—15°. The reaction mixture was warmed on a water bath for 5 min. The crude product was purified by chromatography on Al_2O_3 to give 82 mg (60%) of cinchoninonitrile, whose melting foint was undepressed on admixture with an authentic sample, and the IR spectra were identical.