UDC 547.821.2-261.07

173. Toshihiko Okamoto*1 and Hideo Tani*2 : Reaction Mechanism in Aromatic Heterocyclic Compound. I. The Reactions of N-Alkoxypyridinium Derivatives. (1).*3

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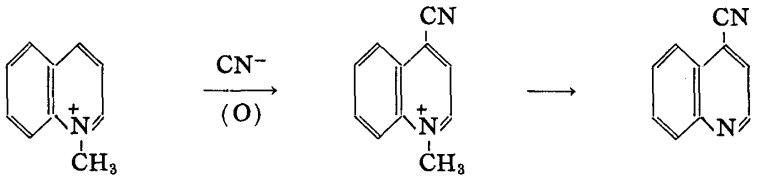
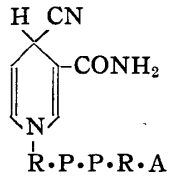
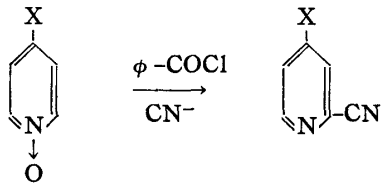
Several methods are known for the direct introduction of cyano group into the 2- or 4-position of the pyridine ring. Kaufmann[1] reported that the reaction of quinoline methiodide with cyanide ion and subsequent oxidation produced 4-cyanoquinoline methiodide and pyrolysis of this compound gave 4-cyanoquinoline. This reaction proceeds in a good yield with quinoline but is not available for pyridine derivatives.



However, some pryidinium derivatives form addition compounds with cyanide ion which have dihydro-type structures and these have been discussed in relation to the addition compound of diphosphopyridine nucleotide with cyanide ion.[2]



Another method for the direct introduction of a cyano group, the Reissert reaction, has also been intensively investigated by many workers.[3] Quinoline series compounds gave 2-cyano derivatives in considerable yield but again this reaction did not proceed with pyridine derivatives except with 4-halopyridine 1-oxide.[4]



Pyridine and quinoline 1-oxides easily form their quaternary salts on reaction with alkyl halides, dialkyl sulfate, or alkyl sulfonate.[5] These quaternary salts of the N-

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*3 A preliminary communication appeared in this Bulletin, **7**, 130(1959).

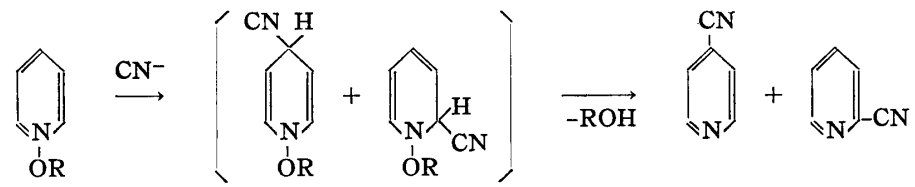
1) A. Kaufmann, *et al.* : Ber., **42**, 3776(1909); **44**, 2058(1911); **45**, 1805(1912); **51**, 116(1918).
2) O. Meyerhof, *et al.* : Biochem. Z., **297**, 113(1938); S. P. Colowick, *et al* : J. Biol. Chem., **191**, 447 (1951); N. O. Kaplan, *et al.* : J. Am. Chem. Soc., **79**, 6173(1957); P. Karrer, *et al.* : Helv. Chim. Acta, **39**, 1451(1956).
3) A. Reissert : Ber., **38**, 1603, 3415(1905); W. E. McEwen, R. L. Cobb : Chem. Revs., **55**, 511(1955).
4) E. Ochiai, I. Nakayama : Yakugaku Zasshi, **65** B, 582(1945).
5) E. Ochiai, *et al.* : *Ibid.*, **64**, 210(1944). A. R. Katritzky : J. Chem. Soc., **1956**, 2404; **1957**, 191; W. Feely, W. L. V. Boekelheide : J. Org. Chem., **32**, 1135(1957).

oxides should be quite reactive toward nucleophilic reagents at the 2- and 4-positions of the pyridine ring. Further, pyridines should be more easily recovered from these quaternary N-oxides than pyridinium salts. From these assumptions, a novel synthesis of 2- and 4-cyanopyridines was developed.

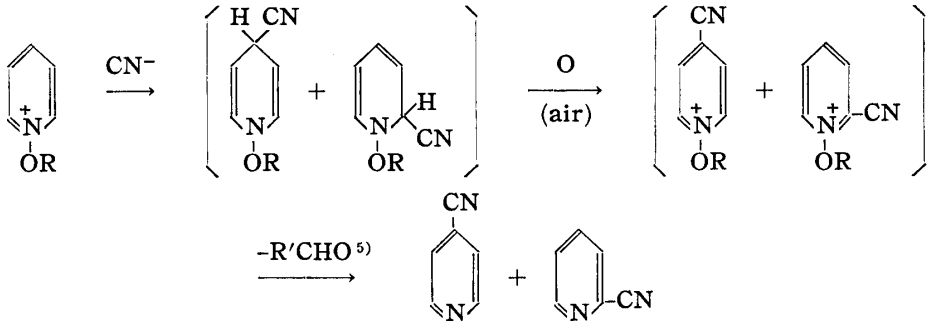
Pyridine 1-oxide was reacted with an excess of methyl iodide or dimethyl sulfate by standing at room temperature for a few days. Quaternary salt of the N-oxides generally separated out as hygroscopic crystals, which were washed with ether and used for the reaction with cyanide without further purification.

Potassium cyanide was added to a solution of the quaternary salts of pyridine 1-oxides in water or other solvents containing water, the reaction took place at room temperature, and the products, 2- and 4-cyanopyridines, separated out from the reaction solution when water was used as the solvent. After standing the mixture for about one hour at room temperature, the reaction product was extracted with chloroform and separated by vacuum distillation or alumina chromatography. 4-Cyanopyridines were also separated from the isomers by precipitation as a picrate or by extraction with acids. Thus deoxygenated 2- and 4-cyano derivertives were obtained.

The possible mechanism of this reaction is considered as follows :



The first step of this reaction should be a nucleophilc attack of cyanide ion at 2- or 4-position of the pyridine ring and in the next step, the dihydropyridine-type intermediate would loose alcohol, giving the final product. The alcohol was actually isolated from the reaction solution in a good yield. Further, this reaction proceeded in hydrogen atmosphere. From these facts, above-mentioned mechanism seems more plausible than the following mechanism which is similar to the Kaufmann reaction.



The results of the reaction with quaternary salts of N-oxides of pyridine, quinoline, isoquinoline, and their derivatives are summarized in Table I.

In the case of lutidine 1-oxide, ω-cyano derivative was isolated in a considerable amount. This is an example of the reactivity of 2-methyl group of pyridine toward nucleophilic reagents.

The present experiments were limited to the cyanide addition but these results suggest the possibility of nucleophilic addition of other reagents including ketones and amines to these quaternary salts.

The authors wish to express their deep appreciations to Dr. E. Ochiai for encouragement. The authors also thank Misses K. Ito and M. Yamaguchi for microanalyses.

Table I. Reactions of N-Methoxypyridinium Derivatives with Potassium Cyanide (in 70% dioxane at 23°)

N-Oxide	Product	Total yield[a] (%)	Each yield[a] (%)	m.p.(°C) b.p.(°C/mm. Hg)	Picrate m.p.(°C)
Pyridine	4-Cyanopyridine	86	24	78~80 (79)[b]	197~199 (198~199)[b]
	2-Cyanopyridine		48	111~113/20 (118~120/25)[f]	—
2-Picoline	4-Cyano-2-picoline	77	18	— (44~46)[e]	164~165 (165~167)[d]
	6-Cyano-2-picoline		45	70~72 (69~71)[c]	—
3-Picoline	4-Cyano-3-picoline	66	15	— (50~52)[d]	154~156 (154~156)[d]
	2-Cyano-3-picoline		30	85~86 (87~88)[c]	—
4-Picoline	2-Cyano-4-picoline	41	30	88~91 (88~89)[c]	—
2,6-Lutidine	4-Cyano-2,6-lutidine	61	13	80~83 (81~82)[b]	175~178 (175~177.5)[b]
	6-Cyanomethyl-2-picoline		33	125~133/22 (40~41)[g]	176~179 (179~180)[g]
Quinoline	4-Cyanoquinoline	98	trace	— (100~101.5)[b]	175~177 (175~177)[b]
	2-Cyanoquinoline		71	93~95 (93)[e]	—
Isoquinoline	1-Cyanoisoquinoline	86	49	90~92.5 (89~89.5)[h]	—

a) Calculated from N-oxides.
b) E. Ochiai, Y. Suzuki: This Bulletin, **2**, 247(1954).
c) Y. Suzuki: *Ibid.*, **5**, 13(1957).
d) Y. Suzuki: *Ibid.*, **5**, 78(1957).
e) M. Henze: Ber., **69**, 1566(1936).
f) L. C. Craig: J. Am. Chem. Soc., **56**, 231(1934).
g) W. Baker, *et al.*: J. Chem. Soc., **1958**, 3594.
h) J. J. Padbury, H. G. Lindwall: J. Am. Chem. Soc., **67**, 1268(1945).

Experimental

Reaction of 1-methoxypyridinium Iodide with KCN—A mixture of 2 cc. of MeI added to 1.0 g. of pyridine 1-oxide ($b.p_{16}$ 145~148°) was allowed to stand for 20 hr. at room temperature. The resulting quaternary salt was washed with AcOEt and Et_2O, and dried over P_2O_5 *in vacuo* at room temperature. Yield, 2.4 g. of m.p. 78~83° (hygroscopic).

To the solution of this salt in 10 cc. of 70% dioxane, KCN solution (1.3 g. of KCN in 3 cc. of H_2O) was added dropwise during 10 min. at 23°. The reaction solution was stirred for another 45 min. at this temperature and then extracted with $CHCl_3$. After evaporation of the solvent the crude product was distilled *in vacuo* to give 0.94 g. (86% as calcd. from the N-oxide) of an oil ($b.p_{21}$ 100~125°).

The product mixture was dissolved in Et_2O and picric acid solution (in EtOH) was added. Precipitated picrate was recrystallized from EtOH-acetone mixture to needles of m.p. 197~199°. Yield, 0.83 g. (23.7%). By admixture with 4-cyanopyridine picrate (m.p. 198~199°), it showed no depression. *Anal.* Calcd. for $C_6H_4N_2 \cdot C_6H_3O_7N_3$: C, 43.25; H, 2.12; N, 21.02. Found: C, 43.94; H, 2.56; N, 20.69.

The free base was recrystallized from isopropyl ether to needles, m.p. 78~80°, which showed no depression when mixed with 4-cyanopyridine (m.p. 79°). *Anal.* Calcd. for $C_6H_4N_2$: C, 69.22; H, 3.87; N, 26.91. Found: C, 69.21; H, 4.24; N, 27.31.

The mother liquor of the picrate was treated with NH_4OH and extracted with $CHCl_3$. This solution was passed through Al_2O_3 column and, after evaporation of the solvent, the residue was purified by vacuum distillation to give 0.52 g. (47.5%) of oil, $b.p_{20}$ 111~113°. It solidified on cooling to prisms, m.p. 28~29°, 0.4 g. of which was hydrolysed with NaOH solution to the corresponding carboxylic acid. This was recrystallized from EtOH-ether mixture to needles, m.p. 136~139°. Yield, 0.25 g. On admixture with picolinic acid (m.p. 138~139°) it showed no depression. *Anal.* Calcd. for $C_6H_5O_2N$: N, 11.38. Found: N, 10.80.

Rection of 1-Methoxypyridinium Iodide with KCN in Hydrogen Atmosphere—To a solution of 2.5 g. of N-methoxypyridinium iodide dissolved in 5 cc. of 70% dioxane, KCN solution (1.3 g. of KCN in 3 cc. of H_2O) was added in H_2 stream at 0° and the solution was allowed to stand for 45 min. in H_2 atmosphere at 2°. The reaction product was taken up in $CHCl_3$ and after evaporation of the solvent, the residue (a mixture of 2- and 4-cyanopyridine) was distilled *in vacuo* to give 0.98 g. (89%) of oil ($b.p_{20}$ 95~125°).

Isolation of the Alcohol from the Reaction Product—6.0 g. of pyridine 1-oxide was heated with 14.4 g. of butyl *p*-toluenesulfonate at 100~110° for 4 hr. and the resulting quaternary salt was recrystallized from EtOH-AcOEt mixture to needles, m.p. 80~84°. Yield, 15 g. (73.5%). *Anal.* Calcd. for $C_{16}H_{21}O_4NS$: C, 59.42; H, 6.54; N, 4.33. Found: C, 60.09; H, 6.95; N, 4.17.

To a solution of 3.3 g. of the above quaternary salt dissolved in H_2O (6 cc.), 1.3 g. of KCN in H_2O (2 cc.) was added dropwise at 40~43° The reaction solution was stirred at this temperature for 30 min. This was distilled at reduced pressure on a steam bath, 5 cc. of H_2O was added to the residue and distillation was repeated. The combined distillate was extracted with CH_2Cl_2 after saturating with $(NH_4)_2SO_4$. After evaporation of the solvent, the residue was distilled to give a fraction of b.p. 100~120°; yield, 0.37 g. (49% calcd. as BuOH). Undistilled residue, 0.46 g.

This fraction was dissolved in ether and treated with HCl gas. After filtering off the precipitate the solvent was evaporated and the residue was distilled to yield 0.27 g. (35.7%) of a fraction of b.p. 100~118°. 0.2 g. of this compound was reacted with 0.35 g. of phenyl isocyanate on a steam bath and the reaction product was recrystallized from petr. benzine to needles, m.p. 63~64°. Yield, 0.44 g. (84%). This showed no depression on admixture with butyl phenylcarbamate, m.p. 63~64°. *Anal.* Calcd. for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.29; H, 8.11; N, 7.83. Above-mentioned undistilled oesidue (0.46 g.) and the precipitate obtained with HCl gas was identified as 4-cyanopyridine and its HCl salt, respectively, after purification.

Reaction of 1-Methoxy-2-methylpyridinium Iodide with KCN—A mixture of 1.0 g. of 2-picoline 1-oxide ($b.p_3$ 103~106°) and 2 cc. of MeI was reacted at room temperature and 2.3 g. of hygroscopic quaternary salt was obtained. This salt was dissolved in 10 cc. of 70% dioxane and KCN solution (1.15 g. of KCN in 3 cc. of H_2O) was added at 23°. After standing for 45 min. at this temperature, the reaction solution was treated as usual and 0.83 g. (76.8%) of product mixture ($b.p_{22}$ 100~125°) was obtained. The solution of this mixture was extracted with 6% HCl and the extract was basified to give 0.37 g. of oil. This oil was treated with picric acid solution (EtOH) and 0.58 g. (18.2%) of needles (from acetone-EtOH mixture) was obtained. The picrate melted at 164~165° and showed no depression on admixture with 4-cyano-2-picoline picrate (m.p. 165~167°). *Anal.* Calcd. for $C_7H_6N_2 \cdot C_6H_3O_7N_3$: C, 44.96; H, 2.61; N, 20.17. Found: C, 45.15; H, 2.72; N, 19.86.

The above solution was evaporated to dryness and the residue was recrystallized to give 0.36 g. of prisms (m.p. 70~72°). The free base, obtained from the mother liquor of the picrate, formed prisms, m.p. 70~72°, after recrystallization from isopropyl ether. Both crystals showed no depression when mixed with 6-cyano-2-picoline (m.p. 69~71°). Total yield, 0.49 g. (45.4%).

Reaction of 1-Methoxy-3-methylpyridinium Iodide with KCN—One g. of 3-picoline 1-oxide ($b.p_4$ 113~114°) was reacted with 2 cc. of MeI as usual. The resulting quaternary salt was extracted with 4 cc. of water and 9 cc. of dioxane was added. This was reacted with 1.15 g. of KCN (in 3 cc. of water) at 23° and the reaction product was purified by vacuum distillation.

Fraction (1)	$b.p_{22}$ 110~125°	0.20 g.
(2)	$b.p_{22}$ 125~135°	0.36
(3)	$b.p_7$ 130°	0.15
	Total	0.71 g. (65.7%)

Fraction (1) gave a picrate of needles (from MeOH-acetone mixture), m.p. 154~156°, which showed no depression on admixture with 4-cyano-3-picoline picrate (m.p. 154~156°). Yield, 0.47 g. (14.8%). *Anal.* Calcd. for $C_7H_6N_2 \cdot C_6H_3O_7N_3$: C, 44.96; H, 2.61; N, 20.17. Found: C, 44.36; H, 2.41; N, 19.90.

Fraction (2) was recrystallized from isopropyl ether to prisms, m.p. 85~86°; yield, 0.32 g. (29.6%), which showed no depression when mixed with 2-cyano-3-picoline, m.p. 87~88°. *Anal.* Calcd. for $C_7H_6N_2$: C, 71.16; H, 5.11; N, 23.72. Found: C, 71.40; H, 5.11; N, 23.62.

From the mother liquor of Fraction (2), a small amount of 4-cyano-3-picoline was isolated as its picrate (m.p. 154~156°).

Fraction (3) was converted to a picrate (m.p. 131~134°) and this was identified as 3-picoline 1-oxide picrate by admixture.

Reaction of 1-Methoxy-3-methylpyridinium Methosulfate with KCN—1.0 g. of 3-picoline 1-oxide (m.p. 181~184°) was reacted with Me_2SO_4 at room temperature, 2.3 g. of the resulting quaternary salt was reacted with 1.19 g. of KCN in 70% dioxane as usual, and the product was purified by vacuum distillation.

Fraction (1)	b.p_{13}	~115°	0.05 g.
(2)	b.p_{13}	115~125°	0.33
(3)	b.p_4	~130°	0.06
		Total	0.44 g. (40.7%)

Fraction (1) was purified as a picrate of m.p. 162~164° and this was identified as 4-picoline picrate by admixture. Fraction (2) was recrystallized from isopropyl ether to prisms, m.p. 88~91°. Yield, 0.32 g. (29.6%). On admixture with 2-cyano-4-picoline (m.p. 88~89°) it showed no depression. *Anal.* Calcd. for $C_7H_6N_2$: C, 71.16; H, 5.12; N, 23.72. Found: C, 71.40; H, 5.22; N, 24.07.

Picrate of Fraction (3) melted at 155~156° and was identified as 4-picoline 1-oxide picrate.

Reaction of 1-Methoxy-2,6-dimethylpyridinium Iodide with KCN—1.0 g. of 2,6-lutidine 1-oxide (b.p_5 96~98°) was reacted with MeI as usual and 2.1 g. of the quaternary salt was obtained. The salt was reacted with 1.0 g. of KCN in 70% dioxane as usual and the product mixture was distilled *in vacuo*.

Fraction (1)	b.p_{25}	~100°	0.05 g.
(2)	b.p_{25}	110~130°	0.35
(3)	b.p_9	~130°	0.25
		Total	0.65 g. (60.7%)

Fraction (1) gave a picrate of m.p. 158~162° and this was identified as 2,6-lutidine picrate by admixture. Fraction (2) was recrystallized from isopropyl ether-petr. ether mixture to needles, m.p. 80~83°; yield, 0.14 g. (13.1%), which was identified as 4-cyano-2,6-lutidine by admixture with the sample synthesized by a different route. *Anal.* Calcd. for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.90; H, 6.30; N, 20.63. It gave a picrate of m.p. 175~178°.

Fraction (3) was combined with the mother liquor of Fraction (2) and submitted to alumina chromatography. The residue from petr. benzine-$CHCl_3$ (9:1) eluate was converted to a picrate of needles (from MeOH-acetone mixture), m.p. 176~179°, which showed no depression on admixture with' 6-cyanomethyl-2-picoline picrate, obtained by a different route. *Anal.* Calcd. for $C_8H_8N_2 \cdot C_6H_3O_7N_3$: C, 46.54; H, 3.07; N, 19.39. Found: C, 46.25; H, 3.06; N, 18.96.

From $CHCl_3$-MeOH eluate a small amount of 2,6-lutidine 1-oxide was isolated as a picrate of m.p. 123~125°.

Reaction of 1-Methoxyquinolinium Methosulfate with KCN—1.2 g. of quinoline 1-oxide (b.p_6 166~169°) was reacted with 1.1 g. of Me_2SO_4 as usual. Resulting quaternary salt was reacted with 0.85 g. of KCN in 70% dioxane and the reaction product was separated by alumina chromatography.

Fraction No.	Solvent	Yield (g.)
(1)	petr. benzine (b.p. 55~65°):$CHCl_3$ (8:2)	0.25
(2)	〃	0.80
(3)	〃	0.10
(4)	$CHCl_3$:MeOH (9:1)	0.10
	Total	1.25 (98.4%)

Fraction (1) was treated with picric acid and 0.02 g. of a picrate of needles (from EtOH-acetone mixture), m.p. 175~177°, was obtained. It showed no depression on admixture with 4-cyanoquinoline picrate (m.p. 175~176°) synthesized by a different route.

The free base obtained from the picrate was combined with Fractions (2) and (3), and recrystallized from isopropyl ether to 0.9 g. of needles, m.p. 93~95° (70.6%), which showed no depression when mixed with 2-cyanoquinoline (m.p. 95~96°) obtained by the Reissert reaction of quinoline 1-oxide. *Anal.* Calcd. for $C_{10}H_6N_2$: C, 77.90; H, 3.92; N, 18.17. Found: C, 77.99; H, 4.10; N, 17.49.

Fraction (4) was identified as quinoline 1-oxide by its picrate (m.p. 135~140°).

Reaction of 2-Methoxyisoquinolinium Methosulfate with KCN—One g. of isoquinoline 2-oxide (b.p_1 170~172°) was reacted with 3 cc. of MeI as usual and 1.6 g. of quaternary salt was obtained. The salt was reacted in 70% dioxane with 0.72 g. of KCN as usual and the reaction product was separated by alumina chromatography.

Fraction No.	Solvent	Yield (g.)
(1)	petr. benzine (b.p. 76~80°):$CHCl_3$ (8:2)	0.03
(2)	〃	0.25
(3)	〃	0.15
(4)	〃	0.08
(5)	〃	0.05
(6)	$CHCl_3$	0.05
(7)	$CHCl_3$:MeOH (9:1)	0.30
	Total	0.91 (85.8%)

Fractions (1)~(5) melted at 90~92.5°. These fractions were combined and were recrystallized from isopropyl ether to needles of m.p. 90~92.5° (0.52 g.: 49.1%). It showed no depression on admixture with 1-cyanoisoquinoline (m.p. 90~92°), obtained by the Reissert reaction of isoquinoline 2-oxide. *Anal.* Calcd. for $C_{10}H_6N_2$: C, 77.90; H, 3.92; N, 18.17. Found: C, 77.85; H, 3.65; N, 17.82.

Fractions (6) and (7) were converted to a picrate which was recrystallized from EtOH-acetone mixture to needles, m.p. 165~166°, and was identified as isoquinoline 1-oxide by admixture.

Summary

N-Alkoxypyridinium derivatives were reacted with potassium cyanide and 2- and 4-cyanopyridines were obtained as the reaction product. This reaction was proved to be a universal reaction for quaternary salts of N-oxides of pyridine and substituted pyridines including quinoline and isoquinoline. A mechanism for this reaction was proposed.

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174. **Hideo Tani**: The Reaction of N-Alkoxypyridinium Derivatives. (2).[1]

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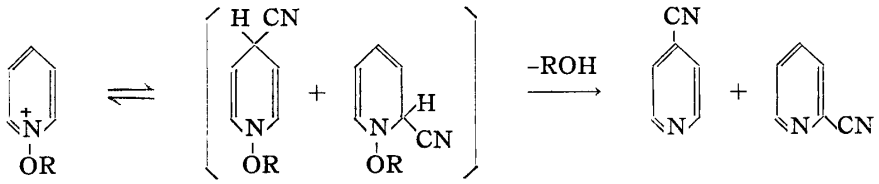
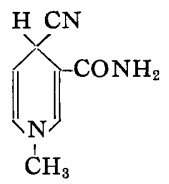
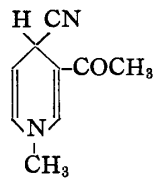
In the preceding paper[1] the author tentatively proposed the mechanism of the reaction of N-alkoxypyridinium derivatives with cyanide ion as shown below and this paper deals further with this mechanism.



The ultraviolet spectra of the addition compounds of nicotinamide methiodide and analogous compounds with cyanide ion were investigated by many workers.[2] These addition compounds show strong absorptions between 340 and 360 mμ and these absorptions were proved to be characteristic to the grouping of –N–C=C–CO–.



λ_{max}^{EtOH} 340 mμ



λ_{max}^{EtOH} 355 mμ

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1) This paper constitutes Part II of a series entitled "Reaction Mechanism in Aromatic Heterocyclic Compounds" by T. Okamoto. Part I: This Bulletin, **7**, 925(1959).

2) S. P. Colowick, *et al.*: J. Biol. Chem., **191**. 447(1951); P. Karrer, *et al.*: Helv. Chim. Acta, **39**, 1451(1956); N. O. Kaplan, *et al.*: J. Am. Chem. Soc., **79**, 6173(1957).