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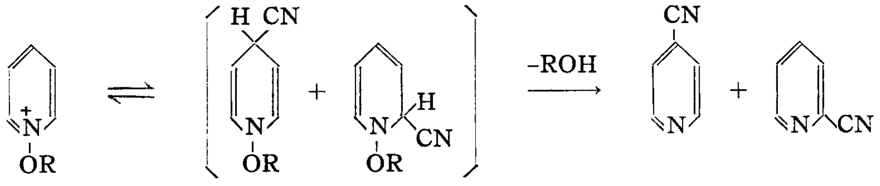
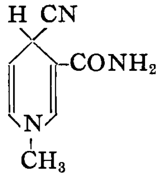
174. **Hideo Tani**: The Reaction of N-Alkoxypyridinium Derivatives. (2).[1]

(*Kowa Chemical Laboratories*[*1])

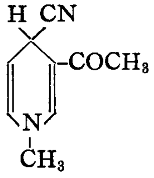
In the preceding paper[1] the author tentatively proposed the mechanism of the reaction of N-alkoxypyridinium derivatives with cyanide ion as shown below and this paper deals further with this mechanism.



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

[*1] Shimotakaido, Suginami-ku, Tokyo (谷 英郎).

[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).

Considering these facts, the reaction of 1-methoxy-3-ethoxycarbonylpyridinium methosulfate with cyanide ion was carefully followed by ultraviolet spectrum and results obtained are shown in Fig. 1.

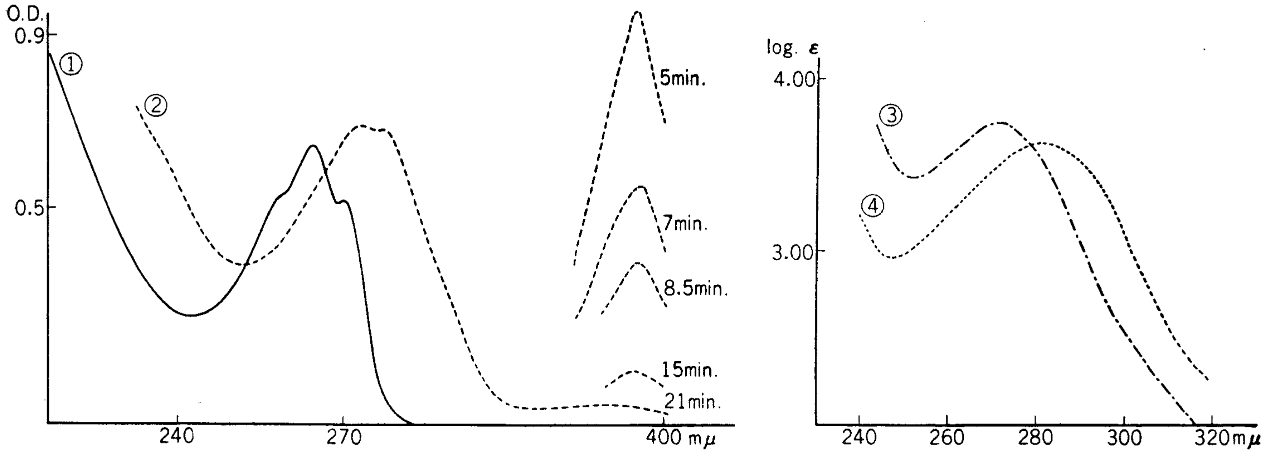
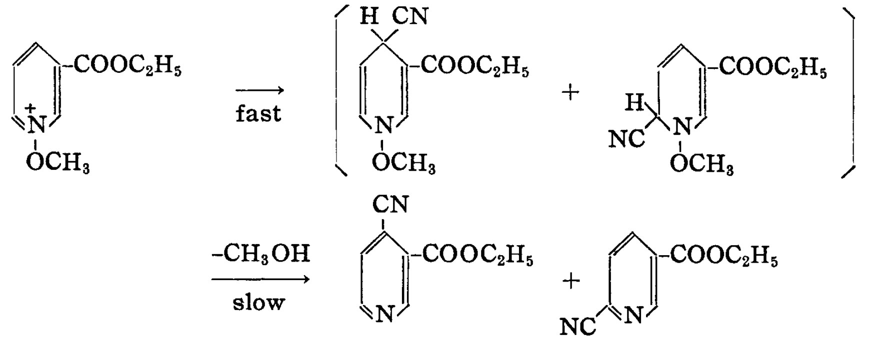


Fig. 1. UV Spectra of 1-Methoxy-3-ethoxycarbonylpyridinium Methosulfate and its Reaction Products with KCN

① 1.66×10^{-4} mole 1-methoxy-3-ethoxycarbonylpyridinium methosulfate (in H_2O)
② Reaction of 1-methoxy-3-ethoxycarbonylpyridinium methosulfate (1.66×10^{-4} mole) with KCN (1 mole) in H_2O at 15°
③ 3-Ethoxycarbonyl-6-cyanopyridine in ethanol
④ 3-Ethoxycarbonyl-4-cyanopyridine in ethanol

An absorption at 382 mμ appeared immediately when aqueous solution of the N-methoxypyridinium salt was mixed with potassium cyanide solution. This absorption band gradually disappeared and turned into the spectrum of the product. The reaction product was separated by alumina chromatography, and 3-ethoxycarbonyl-4-cyanopyridine (m.p. 53~55°) and 3-ethoxycarbonyl-6-cyanopyridine (m.p. 55.5~56.5°) were isolated in respective yield of 31.6% and 19.0%.

Consequently, the absorption at 382 mμ should be considered as that of 1,4- and 1,6-dihydro-type structures,[3] and this absorption should be considered as characteristic of that of the R-O-N-C=C-CO- structure.



Further, the step of formation of the dihydro-type intermediate should be relatively fast and decomposition of the intermediates should be a slow step. As already mentioned, alcohol was obtained as the reaction product and this novel reaction should be considered in some relation to the Reissert reaction.

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[3] Absorption spectra of the two dihydro compounds may be overlapped. Cf. M. B. Mathens: J. Biol. Chem., **176**, 229(1948); F. Bohlmann, M. Bohlmann: Ber., **86**, 1419(1953); W. Traber, P. Karrer: Helv. Chim. Acta, **41**, 2066(1958).

From the above reaction mechanism it is easily considered that the ratio of isomers in the product should be affected by reaction conditions. The effect of the change of reaction temperature, solvent, and also basicity of the reaction solution were examined as well as change in the size of the N–OR group.

Effect of the Reaction Temperature

1-Alkoxypyridinium compounds were reacted at various temperatures and the product was examined.[*2] Table I shows the results.

Table I. Reaction of 1-Methoxypyridinium Iodide with KCN at Various Temperature

No.	Temp. (°C)	Total yield		4-Cyanopyridine picrate		2-Cyanopyridine		Ratio of 4-/2-
		(mg.)	(%)	(mg.)	(%)	(mg.)	(%)	
1	2	810	80.2	145	4.5	765	75.7	0.06
2	10	920	91.1	290	9.0	829	82.1	0.11
3	20	900	89.1	540	16.7	731	72.4	0.23
4	30	950	94.1	1240	38.3	563	55.8	0.69
5	40	900	89.1	1700	52.5	369	36.6	1.43
6	50	840	83.2	1800	55.6	277	27.6	2.01
7	60	700	69.3	1500	46.4	232	22.9	2.03
8	reflux	410	40.6	820	25.3	154	15.3	1.65

To the solution of 1-methoxypyridinium iodide (2.30 g.) in dil. EtOH (EtOH:H_2O=8:2 cc.), KCN (1.3 g. in 3 cc. of H_2O) was added dropwise and the mixture was stirred for 30 min.

At a low temperature, the reaction product consisted mainly of 2-cyanopyridine and at a higher temperature, 4-cyano derivative was obtained predominantly. However, at higher temperatures over 60°, the total yield decreased and this may be due to the decomposition of the starting material.[4]

Solvent Effect

The reaction proceeded in various kinds of solvent and the result is summarized in Tables II and III. The ratio of the amount of isomers in the product was greatly

Table II. Reaction of 1-Methoxypyridinium Iodide with KCN in Various Solvents

No.	Solvent	Total yield		4-Cyanopyridine picrate		2-Cyanopyridine		Ratio of 4-/2-
		(mg.)	(%)	(mg.)	(%)	(mg.)	(%)	
9	H_2O	350	34.7	350	10.8	241	23.9	0.45
10	H_2O:EtOH (1:1)	700	69.3	460	14.2	556	55.1	0.26
11	H_2O:EtOH (3:7)	870	86.1	410	12.7	742	73.4	0.17
12	H_2O:EtOH (2:8)	920	91.1	290	9.0	829	82.1	0.11
13	EtOH	840	83.2	200	6.2	777	77.0	0.08
14	Dioxane	890	88.1	280	8.7	802	79.4	0.11

To the solution of 2.3 g. of the quaternary salt in the solvent, 1.3 g. of KCN (in 3 cc. of H_2O) was added at 10° and the mixture was stirred for 30 min. at this temperature.

Table III. Reaction of 1-Methoxy-3-ethoxycarbonylpyridinium Methosulfate with KCN

No.	Solvent	Total yield		3-COOEt-4-CN-pyridine		3-COOEt-6-CN-pyridine		Ratio of 4-/6-
		(mg.)	(%)	(mg.)	(%)	(mg.)	(%)	
15	H_2O	1000	63.3	500	31.6	300	19	1.66
16	EtOH	990	62.7	trace		800	50.6	0.00

To the solution of the salt (2.5 g.) in the solvent (10 cc.), 0.9 g. of KCN (in 2 cc. of H_2O) was added at 20° and the mixture was stirred for 30 min. at this temperature.

[*2] Separation of the products was effected as described in Part I of this series.

4) cf. E. Ochiai, *et al.* : Yakugaku Zasshi, **64**, 210(1944).

affected by the polarity of the solvent. The yield of 4-cyanopyridine increased in a polar solvent and decreased in non-polar solvent.

Effect of pH of the Reaction Solution

The results are shown in Table IV. The reaction takes place at above pH 8 and the optimum pH is about 11. In this case, some effect was also observed on the ratio of 4-cyano to 2-cyano derivative in the product.

TABLE IV. Reaction of 1-Methoxypyridinium Iodide with KCN at Various pH

No.	pH	Total yield		4-Cyanopyridine picrate		2-Cyanopyridine		Ratio of 4-/2-
		(mg.)	(%)	(mg.)	(%)	(mg.)	(%)	
17	11.91	650	64.4	690	21.3	434	43.1	0.49
18	11.58	610	60.4	1110	34.3	263	26.1	1.31
19	10.99	570	56.4	1120	34.6	220	21.8	1.59
20	10.07	370	36.6	740	22.9	138	13.7	1.67
21	9.03	80	7.9	140	4.3	36	3.6	1.19
22	8.06	trace	—	—	—	—	—	—

To the solution of the salt (2.3 g. in 10 cc. of the buffer), 1.3 g. of KCN (in 12 cc. of the buffer) was added at 40° and stirred at this temperature for 30 min.

Britton-Robinson buffer (H. T. S. Britton, R. A. Robinson: J. Chem. Soc., **1931**, 1456) was used and pH value was determined immediately after the addition of KCN.

Steric Effect of N-OR Group

From the steric consideration, the ratio of 4-substituted to 2-substituted derivative was checked by changing the size of a substituent group of the quaternary salt. The result is shown in Table V. Changing of methyl to ethyl or butyl increased this ratio and this must be interpreted as the steric inhibition of a large group to the attack of cyanide ion at 2-position.

TABLE V. Reaction of KCN with the Quaternary Salts having Various Substituent Groups

No.	Quat. salt	(g.)	Total yield		4-Cyanopyridine picrate		2-Cyanopyridine		Ratio of 4-/2-
			(mg.)	(%)	(mg.)	(%)	(mg.)	(%)	
23	1-Methoxypyridinium iodide	2.30	900	89.1	540	16.7	731	72.4	0.23
24	1-Ethoxypyridinium iodide	2.30	820	78.8	1940	58.3	214	20.5	2.84
25	1-Butoxypyridinium *p*-toluenesulfonate	3.20	750	72.8	1640	49.8	237	23.0	2.17

To the solution of the quaternary salt in EtOH (8 cc.)-H_2O (2 cc.) mixture, 1.3 g. of KCN (in 2 cc. of H_2O) was added at 20° and the mixture was stirred for 30 min. at this temperature.

By considering such a factor affecting the 4/2 ratio, best conditions for obtaining 4-cyano- or 2-cyano-pyridine can be selected. Thus 4-cyanopyridine was obtained with over 70% yield and 2-cyanopyridine with over 80% yield, calculated from the N-oxides.

The author is grateful to Dr. E. Ochiai and also to Mr. T. Teshigawara, Director of this Laboratories, for their encouragement and for giving him facilities for the present study. A part of the experiments was carried out by Miss S. Suzuki, microanalyses were carried out by Mr. A. Nara and Miss Y. Urushibata of this Laboratory, and UV spectra were determined by Dr. E. Ohki, Institute of Applied Microbiology, University of Tokyo, to all of whom the author's thanks are due.

Experimental

Reaction of 1-Methoxy-3-ethoxycarbonylpyridinium Methosulfate with KCN—A mixture of 3.0 g. of ethyl nicotinate 1-oxide (m.p. 103~104°) and 2.3 g. of Me_2SO_4 was heated at 100° for 1 hr. and allowed to stand for 20 hr. at room temperature. Resulting quaternary salt (oil) was washed with ether and dried *in vacuo*. Yield, 5.0 g.

To a solution of 2.5 g. of the above salt dissolved in 10 cc. of H_2O, 1.1 g. of KCN (in 2 cc. of H_2O) was added dropwise at 20° and the mixture was stirred at this temperature for 30 min. The reaction solution was saturated with NaCl, extracted with $CHCl_3$, which was dried over anhyd. Na_2SO_4 and the solvent was distilled off. The residue was distilled *in vacuo*, affording Fractions (1) b.p$_{10}$ ∼100°, 0.17 g., and (2) b.p$_5$ 115∼121°, 1.00 g. (63.3% calcd. from the N-oxide).

Fraction (1) was converted to its picrate and recrystallized from EtOH to needles, m.p. 144∼146°. This was identified as ethyl nicotinate picrate by admixture.

Fraction (2) was separated by alumina chromatography and the first fraction eluted with isopropyl ether-petr. benzine mixture (2:8) was recrystallized from petr. benzine to needles (A), m.p. 55.5∼56.5°. Yield, 0.3 g. (18.0%, calcd. from the N-oxide). *Anal.* Calcd. for $C_9H_8O_2N_2$: C, 61.36; H, 4.58; N, 15.90. Found : C, 61.83; H, 4.40; N, 15.81. UV $\lambda_{\max}^{\mathrm{EtOH}}$ 272 mμ (log ε 3.75).

The second fraction eluted with isopropyl ether-$CHCl_3$ mixture (5:5) gave an oil (0.61 g.), which was distilled *in vacuo* and the fraction of b.p$_6$ 125∼129° was collected (0.55 g.). This was recrystallized from petr. benzine-isopropyl ether mixture to needles (B), m.p. 53∼55°. Yield, 0.5 g. (31.6%, calcd. from the N-oxide). *Anal.* Calcd. for $C_9H_8O_2N_2$: C, 61.36; H, 4.58; N, 15.90. Found : C, 61.91; H, 4.39; N, 15.42. UV $\lambda_{\max}^{\mathrm{EtOH}}$ 282 mμ (log ε 3.64).

Further, a small amount of oily product was obtained from $CHCl_3$-MeOH elution but this fraction was not investigated further.

Compound A (m.p. 55.5∼56.5°) was identified as 3-ethoxycarbonyl-6-cyanopyridine as follows : 0.3 g. of the compound A was refluxed with 1.5 cc. of 2*N* NaOH solution for 2 hr., acidified with HCl, and crystals that precipitated were recrystallized from H_2O to needles, m.p. 260∼263° (decomp.). This was treated with CH_2N_2 in ether solution and the resulting methyl ester was recrystallized from MeOH-isopropyl ether mixture to needles, m.p. 162.5∼164°. This showed no depression when mixed with methyl isocinchomeronate (m.p. 163∼164°). *Anal.* Calcd. for $C_9H_9O_4N$: C, 55.38; H, 4.65. Found : C, 55.01; H, 4.87.

Compound B (m.p. 53∼55°) was identified as 3-ethoxycarbonyl-4-cyanopyridine in a similar way as above : 0.3 g. of compound B was hydrolyzed with 1.5 cc. of 2*N* NaOH solution and resulting acid was recrystallized from H_2O as needles, m.p. 249∼252° (decomp.). Yield, 0.2 g. from the acid, 0.15 g. of methyl ester, b.p$_6$ 130∼131°, was obtained.

Picrate, m.p. 127∼129° (needles from EtOH). The picrate showed no depression on admixture with methyl cinchomeronate picrate (m.p. 127∼129°). *Anal.* Calcd. for $C_9H_9O_4N \cdot C_6H_3O_7N_3$: C, 42.46; H, 2.85; N, 13.21. Found : C, 42.74; H, 2.84; N, 13.32.

Summary

The mechanism of the reaction of 1-alkoxypyridinium compounds with cyanide ion was studied and as the intermediate of this reaction, dihydropyridine-type compounds were confirmed by ultraviolet spectra. Several factors affecting the ratio of the amount of 2- and 4-cyanopyridines in the reaction products were also investigated.

(Received August 10, 1959)

〔Added in proof〕 After this paper was submitted for publication, the paper of W.E. Feely and E.M. Beavers (J. Am. Chem. Soc., **81**, 4008(1959)) became available in this Library. They described a synthesis of cyanopyridines by a method similar to the present one.