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137. Toshihiko Okamoto, Masaaki Hirobe, Chieko Mizushima, and Akio Ohsawa[*1]:

Reaction of N-Aminopyridinium Derivatives. II.[*2] The Reactions of 1-(N-Acylalkylamino)pyridinium Salt Derivatives with Cyanide Ion. (A New Synthesis of Primary Amines).

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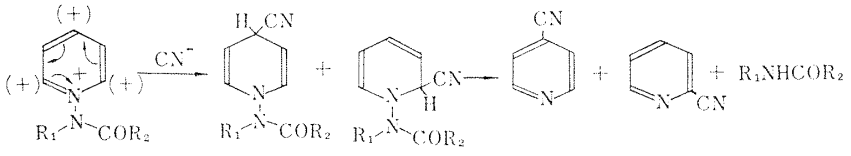
In the previous paper,[*3] it was shown that a new quaternary salt of pyridine, N-aminopyridinium salt could be converted into an "ylide" type compound, N-acyliminopyridine which could further be converted into various stable 1-(N-acylalkylamino)-pyridinium salts.

It has been found in our recent study that the pyridine ring of the 1-(N-acylalkylamino)pyridinium salt was quite reactive nucleophilic reagents at 2- and 4-positions, especially at 4-position. The 1-(N-acylalkylamino)pyridinium salt (1) reacted, for example, with cyanide ion to give cyanopyridines and an amide of a primary amine, both in good yields.

The possible mechanism of this reaction is considered as follows :

The first step of this reaction should be a nucleophilic attack of cyanide ion at 2- or 4-position of the pyridine ring and in the next step, the dihydro-type intermediates (2) would decompose to cyanopyridines (3) and an amide of a primary amine (4).



1 2 3 4

A method for direct introduction of cyano group at 2- or 4-position in pyridine ring by the reaction of N-alkoxypyridinium derivatives with cyanide ion was reported by Okamoto and Tani,[1)] and also by Felly and Beavers.[2)] The reaction was considered to proceed also *via* dihydropyridine-type intermediates, which are quite unstable and their existence could be confirmed only by ultraviolet absorption spectra.

In the reaction of the 1-(N-acylalkylamino)pyridinium salt with cyanide ion, however, one dihydro-type intermediate was obtained as a comparatively stable crystalline.

An aqueous potassium cyanide solution was added to an aqueous 1-(N-methylacetamido)pyridinium iodide solution (I) at one time at room temperatures. On allowing to stand the reaction mixture for a few minutes, colorless needles were crystallized out. The crystalline was filtered out, rinsed with water and dried (m.p. 98~99°, comparatively stable crystalline). It was soluble both in organic solvents and in a large quantity of water. However, it was unstable in solution and gradually decomposed to 4-cyanopyridine (III) and N-methylacetamide (V) quantitatively.

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[*2] The paper reported at the Kanto Local Meeting of the Pharmaceutical Society of Japan, March 17, 1962.

[*3] Part I: Yakugaku Zasshi 83, 308 (1963). This paper constitutes Part VI. of a series entitled "Reaction Mechanism in Aromatic Heterocyclic Compounds" by T. Okamoto. Part V : This Bulletin, **11**, 784 (1963).

1) T. Okamoto, H. Tani : This Bulletin **7**, 130, 925, 930 (1959).

2) W.E. Feely, E.M. Beavers : J. Am. Chem. Soc., **81**, 4008 (1959).

When the above crystalline was not separated from the reaction mixture, it gradually disappeared and 4-cyanopyridine, traces of 2-cyanopyridine (IV) and N-methylacetamide were obtained from the reaction mixture.

As seen from the above fact, it was impossible to purify the intermediate by recrystallization. Also, in the reaction of the 1-(N-acylalkylamino) pyridinium salt with cyanide ion in a large quantity of water or in an organic solvent, 4-cyanopyridine, traces of 2-cyanopyridine and an N-alkylamide were obtained directly without crystallizing out an intermediate. The decomposition of the intermediate to 4-cyanopyridine and N-methylacetamide was promoted in an alkaline medium. This fact is clearly shown by ultraviolet spectra in Fig. 1.

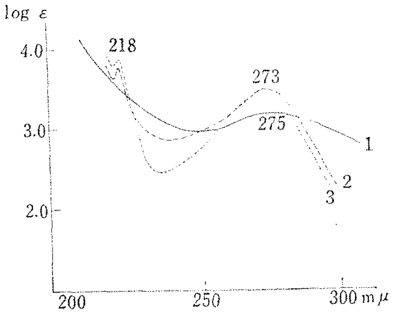


Fig. 1. Ultraviolet Spectra of the Intermediate (II)

1 : intermediate (II) in EtOH
2 : intermediate (II) in EtOH added a drop of 30% aqueous NaOH solution
3 : 4-cyanopyridine in EtOH

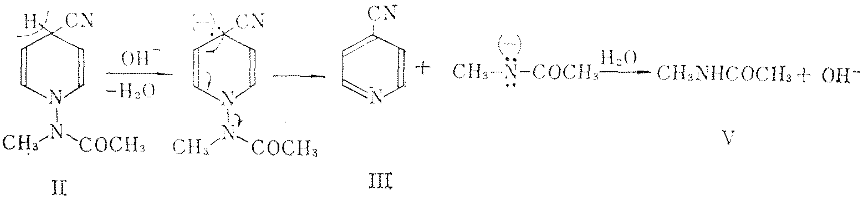
An absorption band which was quite similar to that of 4-cyanopyridine (λ_{max}^{EtOH} mμ (log ε) : 273 (3.45)) appeared immediately when a drop of 30% aqueous sodium hydroxide solution was mixed with the intermediate solution (λ_{max}^{EtOH} mμ (log ε) : 275 (3.15)) in a cell.

Other features of the intermediate are as follows :

The intermediate possessed characteristic infrared absorption band at 2230 cm^{-1} and 1683 cm^{-1} corresponding to C≡N and C=O stretching vibrations respectively, but did not show absorption bands near 1500 cm^{-1} and 1600 cm^{-1} due to aromatic ring vibrations. An aqueous potassium permanganate solution was decolorized immediately by addition of an aqueous solution of the intermediate.

Considering from the above facts, the most probable structure of the intermediate would be 1-(N-methylacetamido)-4-cyano-1,4-dihydropyridine (II), which would decompose to 4-cyanopyridine (III) and N-methylacetamide (V).

The decomposition would be catalized by bases as shown in the following :



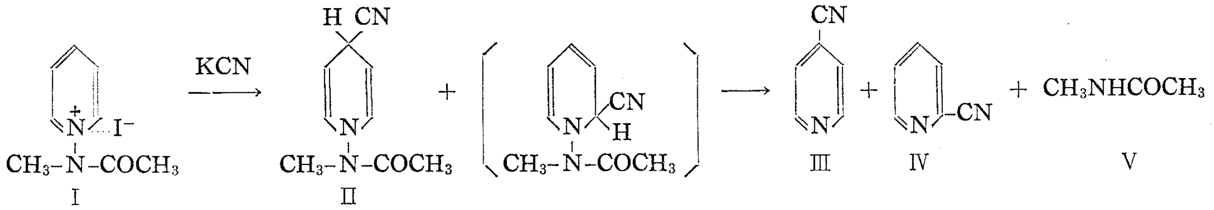
More detailed discussion for the structure of this intermediate will be made in the near future.

Although traces of 2-cyanopyridine were also obtained from the reaction mixture, 1,2-dihydro-type intermediate could not be isolated.

Results of the reaction of 1-(N-methylacetamido)pyridinium salt with cyanide ion are summarized in Table I.

It was shown in Table I that the ratio of the yield of 4-cyanopyridine to 2-cyanopyridine was about 10/1, whereas in the reaction of N-alkoxypyridinium derivatives with cyanide ion it was about 2~1/1. Under suitable conditions, the formation of 2-cyanopyridine could be further decreased.

Table I. Reaction of 1-(N-Methylacetamido)pyridinium Iodide with Potassium Cyanide (in water at room temperature)



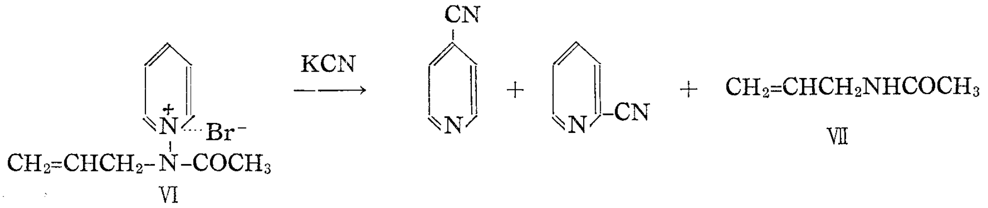
No.	Iodide (I)	KCN	Iodide (I)	KCN	Dihydropyridine(II)		4-Cyanopyridine (III)		II + III[a]	2-Cyanopyridine (IV)		Amide(V)		II + V[a]
	(g./cc. H_2O)	(g./cc. H_2O)	(*M*)	(*M*)	(g.)	(%)	(picrate, g.)	(%)	(%)	(g.)	(%)	(g.)	(%)	(%)
1[b]	1.023/1	6.01/6	0.526	13.21	0	0	0.900	76.2	76.2	0.028	7.0	0.140	52.2	52.2
2	1.952/4	6.00/10	0.502	6.59	0	0	1.681	72.1	72.1	0.050	6.0	0.271	52.6	52.6
3	1.878/10	6.84/10	0.338	5.26	0.381	31.8	0.547	24.5	56.3	0.025	3.6	0.160	32.4	64.2
4	1.251/10	5.65/10	0.225	4.35	0.145	19.3	0.600	40.3	59.6	0	0	0.105	31.4	50.7

a) II + III, and II + V could be considered as the total yield of 4-cyanopyridine and N-Methylacetamide respectively.

b) These data were described in Experimental.

Thus, in the reaction of 1-(N-allylacetamido)pyridinium bromide (VI) with cyanide ion, 4-cyanopyridine could be obtained with or even without by-producing traces of 2-cyanopyridine. The results are summarized in Table II.

Table II. Reaction of 1-(N-Allylacetamido)pyridinium Bromide with Potassium Cyanide (in water at room temperature)[a]



No.	[Bromide (IV)] (*M*)	[KCN] (*M*)	4-CN-Pyridine (yield %)	2-CN-Pyridine (yield %)	Total yield (%)	Amide(VII) (yield %)
1	0.385	12.46[b]	33.9	24.7	58.6	64.1
2	0.390	12.31[b]	34.1	24.7	58.8	61.8
3	0.390	9.23	50.4	0	50.4	59.7
4	0.392	6.15	50.3	0	50.3	56.7
5	0.387	6.15	52.4	0	52.4	58.6
6	0.390	3.08	53.4	0	53.4	57.1
7	0.390	1.55	54.9	0	54.9	61.9
8	0.390	0.77	46.4	0	46.4	52.2
9	0.780	6.15	78.6	1.0	79.6	88.8
10	1.170	6.15	81.7	2.0	83.7	90.8
11[c]	1.971	6.15	88.5	2.5	91.0	93.3

a) About 10°

b) Saturated solutions with undissolved excessive KCN crystalline, the concentrations show the total amount of KCN.

c) These data were described in Experimental.

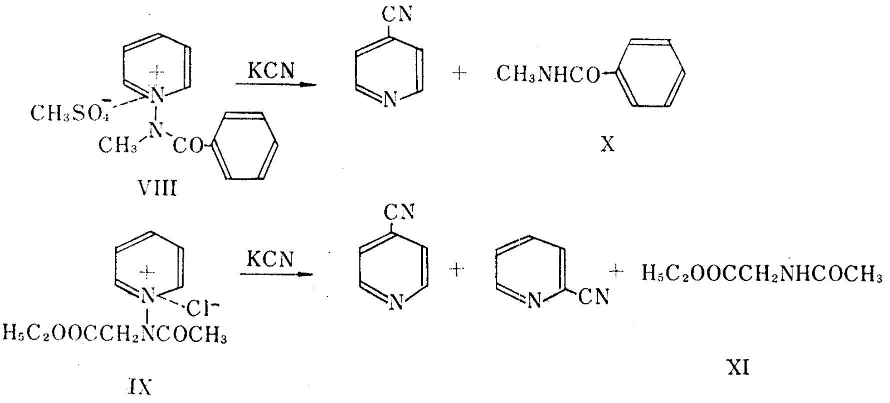
Examination of the data in Table II reveals the following facts:

(a) At constant concentration of the pyridinium salt (Nos. 1~8): The production of 2-cyanopyridine could not be observed with various concentrations of cyanide ion, but with saturated solution of cyanide ion (Nos. 1~2) 2-cyanopyridine was obtained in considerable amount. The yield of 4-cyanopyridine could not be correlated with the concentration of cyanide ion as shown in Nos. 3~7. In the experiment No. 8, the yield of 4-cyanopyridine was decreased owing to the extremely low concentration of cyanide ion.

(b) At constant concentration of cyanide ion (Nos. 9~11): The yield of 4-cyanopyridine was remarkably increased by increasing the concentration of the pyridinium salt. In this case, the yield of 2-cyanopyridine was also slightly increased. However, it was negligible as compared with that of 4-cyanopyridine. The yield of N-allylacetamide (VII) coproduced, was increased in parallel with increasing total yield of cyanopyridines.

In the reaction of 1-(N-allylacetamido)pyridinium bromide with cyanide ion, any substance which was considered as an intermediate, was not crystallized out. However, an oily product which might be the intermediate, was first produced and thereafter gradually disappeared.

Analogous to the above reaction, 1-(N-methylbenzamido)pyridinium methosulfate (VIII) was reacted with cyanide ion to produce 4-cyanopyridine and N-methylbenzamide (X), and 1-(N-ethoxycarbonylmethylacetamido)pyridinium chloride (IX) gave 4-cyanopyridine, traces of 2-cyanopyridine and N-acetylglycine ethyl ester (XI) in the same reaction.



By utilizing the above reaction, it would be possible to introduce a cyano group at 4-position of various pyridine derivatives without by-producing 2-cyanopyridine derivatives. Further, the above reaction may be used for the preparation of primary amines which could not easily be obtained by alternative methods. Infrared spectra of four kinds of amides obtained by the present experiments are shown in Fig. 2.

Experimental

Reaction of 1-(N-Methylacetamido)pyridinium Iodide with Potassium Cyanide in Water——1.023 g. of 1-(N-methylacetamido) pyridinium iodide was dissolved in 1 cc. of H_2O. On adding 6.0 g. of KCN in 6 cc. of H_2O to the above solution all at once, an intermediate was crystallized out. Without filtration of the crystalline, the reaction mixture was allowed to stand for about 1 hr. at room temperature for completion of the reaction. The reaction products were taken up in $CHCl_3$ and after evaporation of the solvent, separated by alumina chromatography.

28 mg. of 2-cyanopyridine (yield: 7.0%), 900 mg. of 4-cyanopyridine (yield: 76.2%) and 140 mg. of N-methylacetamide (yield: 52.2%) were thus obtained. Table I shows the results obtained under different reaction conditions.

When the above crystallized intermediate was filtered out, rinsed with H_2O and dried, it was obtained as a stable crystalline of m.p. 98~99°. *Anal.* Calcd. for $C_9H_{11}N_3O$: C, 61.08; H, 5.98; N, 24.10. Found: C, 61.02; H, 6.21; N, 23.73.

Reaction of 1-(N-Allylacetamido)pyridinium Bromide with Potassium Cyanide in Water——750 mg. of 1-(N-allylacetamido)pyridinium bromide were dissolved in 0.5 cc. of H_2O. On adding 600 mg. of KCN in 1 cc. of H_2O to the above solution at room temperature, a cloudy solution with oily products was produced. However, the solution became soon clear. After allowing the solution to stand for about

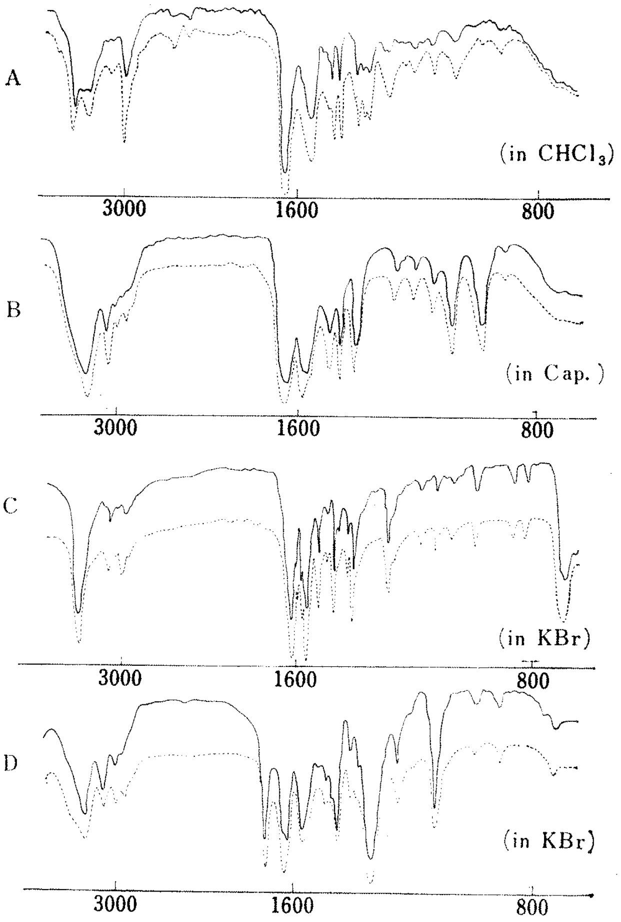


Fig. 2. Infrared Spectra of amides (wave number : cm^{-1})

A : N-methylacetamide
B : N-allylacetamide
C : N-methylbenzamide
D : N-acetylglycine ethylester

—— synthetic amide obtained by our new method
········ authentic sample prepared by alternative methods

1 hr., the reaction products were taken up in CHCl$_3$. The products obtained on removal of the solvent, were separated by alumina chromatography.

7 mg. of 2-cyanopyridine (yield : 2.5%), 262 mg. of 4-cyanopyridine (yield : 88.5%) and 271 mg. of N-allylacetamide (yield : 93.3%) were thus obtained. Table II showed the results obtained under different reaction conditions.

Reaction of 1-(N-Methylbenzamido)pyridinium Methosulfate with Potassium Cyanide in Water——265 mg. of 1-(N-methylbenzamido)pyridinium methosulfate were dissolved in 0.5 cc. of H$_2$O. On adding a solution of 300 mg. of KCN in 1 cc. of H$_2$O at room temperature, a cloudy solution was first produced and then became gradually clear. After about 1 hr., the reaction products were taken up in CHCl$_3$ and treated in the same manner as hereinbefore described.

50 mg. of 4-cyanopyridine (yield : 56.8%) and 66 mg. of N-methylbenzamide (yield : 60%) were thus obtained. Under this condition, 2-cyanopyridine was not obtained.

Reaction of 1-(N-Ethoxycarbonylmethylacetamido)pyridinium Chloride with Potassium Cyanide in Water——To a solution of 4.5 g. of 1-(N-ethoxycarbonylmethylacetamido)pyridinium chloride in 2 cc. of H$_2$O, a solution of 5.80 g. of KCN in 8 cc. of H$_2$O are added. After allowing the resulting solution to stand at room temperature for about 1 hr., the reaction products were taken up in CHCl$_3$ and treated in the same manner as hereinbefore described.

7 mg. of 2-cyanopyridine (yield : 0.5%), 520 mg. of 4-cyanopyridine (yield : 34.7%) and 401 mg. of N-acetylglycine ethylester (yield : 19.8%) were thus obtained.

In the above experiments, 2-cyanopyridine (m.p. 24~26°) and 4-cyanopyridine (m.p. 78~79°) were identified by admixture with the samples synthesized by different routes and also confirmed by comparing the IR spectra. Amides are identified by IR spectra comparison as shown in Fig. 2. N-acetylglycine ethylester (m.p. 48°) was also identified by admixture with an authentic sample prepared by an alternative method.

The authors are grateful to the members of the Central Analysis Room of this Faculty for elementary analyses and spectral measurements. This study was partly supported by the Grant-in-Aid for Scientific Research provided by the Ministry of Education, which is gratefully acknowledged.

Summary

1-(N-Monosubstituted amido)pyridinium compounds derived from novel quaternary salts of pyridine, N-aminopyridinium compounds, were quite reactive to nucleophilic agents at 2- and 4-positions of their pyridine rings, especially at 4-position. The 1-(N-monosubstituted amido)pyridinium salts were reacted with cyanide ion to give N-monosubstituted amides and cyanopyridines, (predominantly 4-cyanopyridine), both in good yields. The reaction may involve dihydro-type intermediates and one intermediate 1-(N-methylacetamino)-4-cyano-1,4-dihydropyridine could be obtained stably.

By utilizing this reaction, it would be possible to introduce a cyano group at 4-position of various pyridine derivatives and to obtain various primary amines.

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138. **Toshihiko Okamoto and Michiya Itoh** : Reaction Mechanism in Aromatic Heterocyclic Compounds. V.*1 Kinetics of the Reaction of 4-Nitroquinoline 1-Oxide and Related Compounds with Thioglycolic Acid.*2

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The 4-nitro or 4-halo groups in quinoline 1-oxides are easily replaced by alkoxydes, phenoxydes or amines,1) and these 4-substituents in quinoline are reactive toward nucleophlic reagents. Thus, some attempts have been made to correlate the reactivities of aromatic substitution reactions with the effects of heteroaromatic N-oxide groups.2,3) 4-Nitroquinoline 1-oxide reacts readily with the SH groups of thioglycolic acid, of cystein and of glutathion to afford the corresponding sulfides of quinoline 1-oxide.4)

On the other hand, 4-nitroquinoline 1-oxide has been known to be a skin cancer producing agent, and W. Nakahara, *et al.* have suggested that the carcinogenic action of this compound might be due to the nucleophlic reactivity at 4-position.5)

In 4-nitroquinoline 1-oxide and its related compounds, H. Endo reported that there was a certain relationship between the chemical structure and carcinogenic activity.6) But kinetic studies on the reactivities of these compounds have not been made, thus comparative data for the reactivities of 4-nitro groups in the 4-nitroquinoline 1-oxide and its related compounds are needed.

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*1 Part IV. This Bulletin, **11**, 514 (1963).

*2 A part of this work was reported at the 19th general meeting of the Japanese Cancer Association (Dec. 1960).

*3 Hongo, Bunkyo-ku, Tokyo (岡本敏彦, 伊藤道也).

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