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UDC 547.821.04.07

73. **Toshihiko Okamoto, Masaaki Hirobe, and Akio Ohsawa :**

Reaction of N-Aminopyridinium Derivatives. V.[*1] Syntheses of 1-(N-Methylacetamido)alkylpyridinium Salts and Their Reaction with Cyanide Ion.

(*Faculty of Pharmaceutical Sciences, University of Tokyo*[*2])

As a method for directly introducing cyano group into 2- or 4-position of pyridine ring, the nucleophilic substitution of N-alkoxypyridinium salt (I) with cyanide ion has been reported.[1] In this reaction, 2-cyano and 4-cyanopyridine are obtained as a mixture. This reaction is considered to proceed through the following dihydro-type intermediates (II).

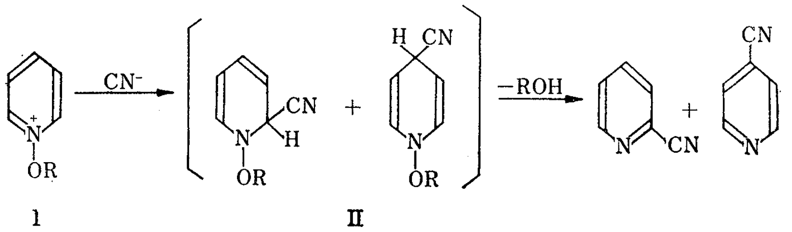


Chart 1.

In our recent study,[2] it was found that an 1-(N-acylalkylamino)pyridinium derivative (III) gave predominantly 4-cyanopyridine and the corresponding amide (V) by the reaction with cyanide ion in water at room temperature. Of the attempted derivatives, 1-(N-methylacetamido) pyridinium iodide (IIIa) gave a stable crystalline intermediate, 1-(N-methylacetamido)-4-cyano-1,4-dihydropyridine (IVa), which was decomposed to 4-cyanopyridine and N-methylacetamide (Va).

From the above facts, it is concluded that the mechanism of this reaction is also analogous to that of N-alkoxypyridinium derivatives, but the reactivity of 4-position of pyridine ring to cyanide ion is remarkable in N-aminopyridinium derivatives as compared with N-alkoxypyridinium derivatives.

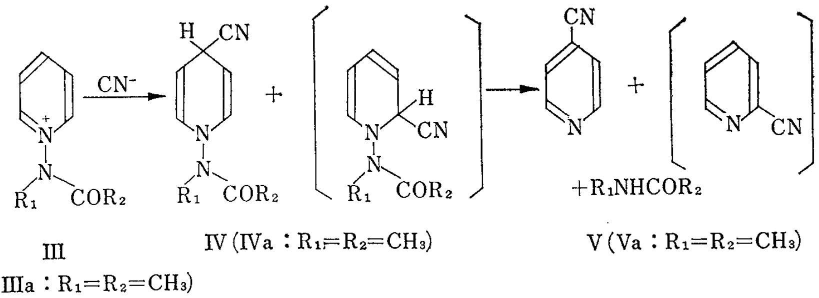


Chart 2.

The present paper relates to syntheses of 1-(N-methylacetamido)alkylpyridinium salts and their reaction with cyanide ion which was carried out to confirm the above conclusion.

[*1] Part IV : This Bulletin, **14**, 512 (1966).

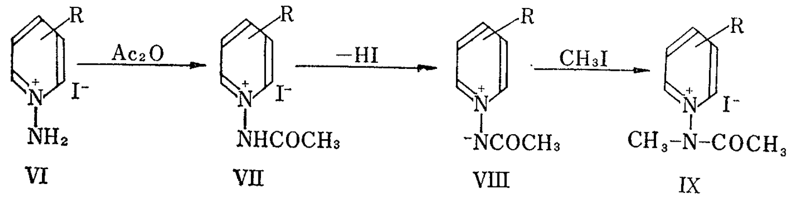
[*2] Hongo, Bunkyo-ku, Tokyo (岡本敏彦, 広部雅昭, 大沢昭緒).

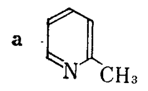
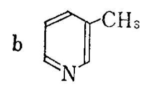
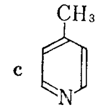
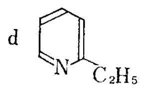
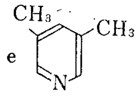
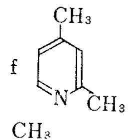
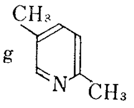
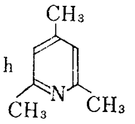
1) T. Okamoto, H. Tani : This Bulletin, **7**, 130, 925, 930 (1959). W.E. Feely, E.M. Beavers : J. Am. Chem. Soc., **81**, 4008 (1959).

2) T. Okamoto, M. Hirobe, C. Mizushima, A. Ohsawa : This Bulletin, **11**, 780 (1963).

N-Aminoalkylpyridinium salt (VI) was prepared from the corresponding alkylpyridine and hydroxylamine-O-sulfonic acid by the method of Gösl, *et al.*[3] Reaction of VI with acetic anhydride provided 1-(N-acetamido)alkylpyridinium salt (VII), which was then converted into its ylide compound 1-(N-acetimido)alkylpyridine (VIII) by the treatment with anion exchange resin (Amberlite IRA 410 treated with 10% sodium hydroxide). VIII was further reacted with methyl iodide to finally give 1-(N-methylacetamido)alkylpyridinium salt (IX). Cyanation was effected by adding an aqueous potassium cyanide solution to an aqueous solution of thus obtained IX at room temperature.

Table I. Physical Properties of N-Aminoalkylpyridinium Derivatives



	VI	VII	VIII	IX
a 	m.p. 155.5° pale yellowish needles (151°)	m.p. 188° yellowish flake (167°)	hygroscopic colorless needles (167°)	m.p. 172.5° yellowish needles
b 	hygroscopic yellowish needles (149°)	m.p. 162.2° yellowish flake (148.5°)	hygroscopic colorless needles (149～150°)	m.p. 152.8° hygroscopic yellowish powder
c 	hygroscopic yellowish needles (165°)	monoacetate(hygroscopic) diacetate(colorless needles) m.p. 175° (166°); monoacetate	hygroscopic yellowish flake (166°)	tar
d 	m.p. 107° yellowish needles (116.5°)	tar (163°)	hygroscopic yellowish needles (163°)	m.p. 139° brown powder
e 	m.p. 137.5° colorless needles (164.5°)	m.p. 217° pale yellowish prism (175°)	hygroscopic yellowish needles (175°)	m.p. 215° yellowish needles
f  g 	mixture	mixture	oily mixture VIIIf:VIIIg(=2:1) by NMR	brown amorph
h 	m.p. 203° colorless needles (171.5°)	m.p. 168° colorless needles (193°)	m.p. 84° yellowish flake (193°)	m.p. 66° hygroscopic yellowish needles

( ); melting point of picrate

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[3] R. Gösl, A. Meuwsen : Ber., **92**, 2521 (1959).

Synthesized 1-(N-methylacetamido)alkylpyridinium iodide are summarized in Table I.

Acetylation of Ⅵ with acetic anhydride mostly provided monoacetate (Ⅶ), but in the case of Ⅵc gave a mixture of mono- and di-acetate(Ⅶ'c). However, by passing through the anion exchange resin, deacetylation of Ⅶ'c also took place and the same ylide compound (Ⅷc) was obtained.

Ⅷ showed characteristic IR absorption band at 1600~1500 cm^{-1} due to $C=O$ stretching vibration which was observed at 1720~1750 cm^{-1} in Ⅶ and at 1700 cm^{-1} in Ⅸ.

The above shift of $C=O$ stretching absorption is characteristic of ylide compounds, N-acylimidopyridines, which has previously been reported.[4]

As for 2,4- and 2,5-dimethylpyridine, it was so difficult to isolate each of them that the commercially available mixture containing the above two compounds was used for this reaction and the ratio of the resulting quaternary salts (Ⅸf) and (Ⅸg) was calculated from the ratio of their ylide compounds (Ⅷf) and (Ⅷg) which was determined by the NMR (nuclear magnetic resonance) spectra of their mixture.

The results of the reaction of 1-(N-methylacetamido)alkylpyridinium salts (Ⅸ) with cyanide ion are summarized in the following Table Ⅱ.

In any case, the substitution of cyano group occurred predominantly at 4-position of the pyridine ring as compared with its 2- or 6-positions.

In the reaction of N-alkoxyalkylpyridinium salt with cyanide ion,[1] the substitution occurred almost equally at 4- and 2- or 6-positions and in some cases, it occurred at α-methyl group to give cyanoalkylpyridines. Such substitution has not been occurred in the present reaction.

In N-amino derivatives of di- or monoalkylpyridine whose α- and γ-positions are free from alkylsubstituents γ-cyano compounds were obtained nearly in quantitative yields without producing α-cyano compounds. From the N-amino derivative of 4-methylpyridine (Ⅸc), 2-cyano compound was obtained only in 13% yield and a compound having the molecular formula of $C_{10}H_{13}ON_3$ (m.p. 178~179°) was obtained, structure of which is under investigation.

Cyanation of the N-amino derivative of 2,4-dimethylpyridine (Ⅸf) gave only 7% of 6-cyano compound. In the case of N-amino derivative of 3,5-dimethylpyridne (Ⅸe), whose 4-position is hindered by the adjacent two methyl groups, yield of 4-cyano compound was decreased to some extent (82%). In this case, a crystalline intermediate could be separated, which would have 1,4-dihydro-structure (Ⅹe) and which was easily converted into N-methylacetamide and 4-cyano compound (Ⅺe) as described in the experimental part. A small amount of 2-cyano compound (Ⅻe) was also obtained, though a dihydro-type intermediate (Ⅹ'e) could not be isolated in this case. As for the N-amino derivative of 2,4,6-collidine (Ⅸh) whose α- and γ-positions are all occupied with methyl groups, cyanation did not take place and the starting material was recovered.

Experimental

1-(N-Acetamido)-2-methylpyridinium Iodide (VIIa)——A solution of 11.8 g. of Ⅵa in 100 ml. of acetic anhydride was heated in an oil bath at 95~100° for 2 hr. Excess of acetic anhydride was then evaporated under reduced pressure. The residue was washed with ether and recrystallized from EtOH to give 12 g. of Ⅶa as pale yellowish flakes, m.p. 188°, yield; 86%. *Anal.* Calcd. for $C_8H_{11}ON_2I$: C, 34.53; H, 3.95; N, 10.08. Found: C, 34.76; H, 4.20; N, 10.32. Picrate; m.p. 167°. *Anal.* Calcd. for $C_{14}H_{13}O_8N_5$: C, 44.33; H, 3.43; N, 18.47. Found: C, 44.24; H, 3.46; N, 18.56.

1-(N-Acetimido)-2-methylpyridine (VIIIa)——A solution of 2.0 g. of Ⅶa in 50 ml. of EtOH was passed through a column of anion exchange resin (Amberlite IRA 410) treated with 10% NaOH solution. The eluted

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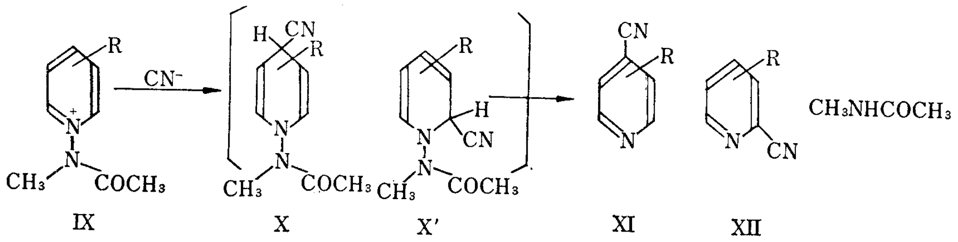
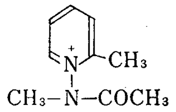
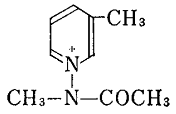
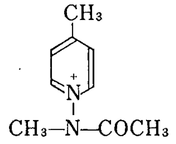
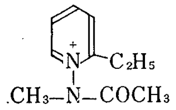
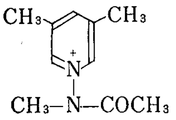
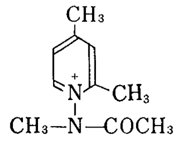
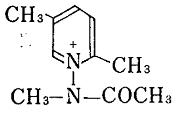
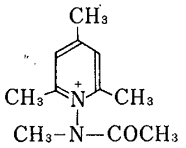
[4] T. Okamoto, M. Hirobe, C. Mizushima, A. Ohsawa: Yakugaku Zasshi, **83**, 308 (1963).

TABLE II. Results of the Reaction of 1-(N-Methylacetamido)-alkylpyridinium Derivatives (IX) with Cyanide Ion



	IX	Reaction condition			Reaction products			Derivatives of XI or XII synthesized for identification
		[IX] mol./L.	[KCN] mol./L.	Temp. (°C)	XI	XII	$CH_3NHCOCH_3$ (%)	
a		0.49	11.0	27	m.p.[a] 45~46.5° 88%	—	64	picrate[a,b] m.p. 166°
b		0.79	10.25	10	m.p. 51°[a] 92%	—	65	picrate[a,b] m.p. 156.5°
c		1.10	8.9	28	—	m.p. 89°[a,b] 13%	13	
d		0.66	5.1	30	b.p.[c,d] (28 mm.) 105~110° 90%	—	93	picrate m.p. 134~135° amide[d] m.p. 132.5° thioamide[c,d] m.p. 163°
e		0.98	9.2	27	m.p. 88~89° 82.7%	m.p. 64~65° 1.2%	81.8	XIe picrate m.p. 174~175° XIe amide m.p. 222~223° XIIe amide m.p. 146~148°
f		1.58	7.7	27	m.p. 39~41° 90.9%	m.p. 50°[a] 7%	22	XIg picrate m.p. 152~154° XIg amide m.p. 199~200° XIIf amide[e] m.p. 108~113° XIIf carboxylic acid[e] m.p. 145~150°
g								
h		0.26	7.0	15	—	—	—	

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[a] W.E. Feely, E.M. Beavers: J. Am. Chem. Soc., **81**, 4004 (1959).
[b] T. Okamoto, H. Tani: This Bulletin, **7**, 925 (1959).
[c] N. F. Kucherova: Zhur. Obshchei. Khim., **29**, 915 (1959).
[d] D. Liebermann: Bull. soc. chim. France, **1958**, 687.
[e] M. Häring: Helv. Chim. Acta, **37**, 147 (1953).

solution was evaporated under reduced pressure and the residue was purified by alumina chromatography with $CHCl_3$ to give 1.1 g. of VIIIa as hygroscopic colorless needles, which afforded the same picrate as that of VIIa. IR $\nu_{C=O}$ cm^{-1}: 1571 ($CHCl_3$).

1-(N-Methylacetamido)-2-methylpyridinium Iodide (IXa)——To 1.1 g. of VIIIa was added 30 ml. of CH_3I. The mixture was allowed to stand at room temperature for 8 hr. Excess of CH_3I was removed to give 1.8 g. of IXa as pale yellowish needles, m.p. 172.5°(recrystallized from EtOH), yield; 86%. *Anal.* Calcd. for $C_9H_{13}ON_2I$: C, 36.99; H, 4.45; N, 9.59. Found: C, 37.37; H, 4.49; N, 9.53.

1-(N-Acetamido)-4-methylpyridinium Iodide (VIIc) and 1-(N,N-Diacetamido)-4-methylpyridinium Iodide (VIIc′)——15 g. of VIc was treated with acetic anhydride in the same manner as described above to give 16.5 g. of tarry product composed of a mixture of mono- and di-acetate. IR $\nu_{C=O}$ cm^{-1}(Cap.): 1709, 1725, 1745 (sh). However, the mixture gave only picrate of mono-acetate (VIIc), m.p. 166°. *Anal.* Calcd. for $C_{14}H_{13}O_8N_5$: C, 44.33; H, 3.43; N, 18.47. Found: C, 44.51; H, 3.49; N, 18.44.

By recrystallization of the tarry product from EtOH, a small amount of diacetate (VIIc′) was obtained as white needles (m.p. 175°, IR $\nu_{C=O}$ cm^{-1}(KBr): 1742, 1709), which did not afford picrate. *Anal.* Calcd. for $C_{10}H_{13}O_2N_2I$: C, 37.53; H, 4.10; N, 8.76. Found: C, 37.99; H, 4.19; N, 8.93. By the treatment with anion exchange resin, VIIc′ was easily deacetylated to VIIc.

Reaction of 1-(N-Methylacetamido)-2-methylpyridinium Iodide (IXa) with Cyanide Ion——To a solution of 1.0 g. of IXa in 1 ml. of water was added 5.0 g. of KCN dissolved in 6 ml. of H_2O. The reaction mixture was allowed to stand for 10 min. at room temperature and extracted first with ether and then with $CHCl_3$. Each layer was dried over anhyd. Na_2SO_4 and evaporated to dryness. A large excess of picric acid dissolved in EtOH was added to the residue of ether extract to give 1.0 g. of the picrate of 2-methyl-4-cyano-pyridine (XIa), m.p. 165~166°(yield: 83% as picrate), which was converted into XIa (m.p. 45~46°) by chromatography on alumina with $CHCl_3$. 20% NH_4OH was added to the combined filtrate and washings of the picrate, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and evaporated to dryness. The residue was chromatographed on alumina to give 20 mg. of XIa and 80 mg. of N-methylacetamide, but 2-methyl-6-cyano-pyridine (XIIa) was not obtained. On the other hand, the residue of $CHCl_3$ extract from the above reaction mixture was chromatographed on alumina to give 70 mg. of N-methylacetamide. Total yield: XIa; 88%, N-methylacetamide; 64%. *Anal.* Calcd. for $C_7H_6N_2$(XIa): C, 71.16; H, 5.12; N, 23.72. Found: C, 71.12; H, 5.06; N, 22.96. *Anal.* Calcd. for $C_{13}H_9O_7N_5$ (picrate of XIa): C, 44.96; H, 2.61; N, 20.17. Found: C, 44.96; H, 2.92; N, 20.47.

Reaction of 1-(N-Methylacetamido)-4-methylpyridinium Iodide (IXc) with Cyanide Ion——To a solution of 95 g. of IXc in 100 ml. of water was added 150 g. of KCN dissolved in 200 ml. of water. The reaction mixture was allowed to stand for several minutes and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and evaporated to dryness. The residue was chromatographed on alumina to give 5.0 g. of 2-cyano-4-methylpyridine (XIIc) (m.p. 89°, yield; 13%), 3.3 g. of N-methylacetamide (yield; 13%), 5.4 g. of a compound having an empirical formula $C_{10}H_{13}ON_3$ and a small amount of red product. Structures of the latter two by-products are under investigation.

Determination of the Ratio of 1-(N-Acetimido)-2,4-dimethylpyridine (VIIIf) and 1-(N-Acetimido)-2,5-dimethylpyridine (VIIIg)——A mixture of VIIIf and VIIIg was obtained by the general procedure described above from the mixture of VIf and VIg. The NMR spectrum of this mixture in $CDCl_3$ showed the following signals (τ-value) corresponding to the methyl groups of each position; 7.45 (α-$C\underline{H}_3$), 7.52 (γ-$C\underline{H}_3$), 7.60 (β-$C\underline{H}_3$), 8.03 (-$NCOC\underline{H}_3$).

It was assumed that the ratio (2:1) of the integrated intensity of signals at 7.52 and 7.60 corresponded to the ratio of VIIIf and VIIIg in this mixture.

Reaction of 1-(N-Methylacetamido)-3,5-dimethylpyridinium Iodide (IXe) with Cyanide Ion——To a solution of 14.990 g. of IXe in 20 ml. of H_2O was added, at a time, 30 g. of KCN dissolved in 30 ml. of H_2O. The reaction mixture soon became cloudy and then the precipitate was separated, which was filtered, washed with H_2O and dried to give 7.7 g. of colorless crystalline product. The filtrate was extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over anhyd. Na_2SO_4 and evaporated to dryness. The residue was chromatographed on alumina to give 0.074 g. of 2-cyano-3,5-dimethylpyridine (XIIe), m.p. 64~65°, 0.370 g. of 4-cyano-3,5-dimethylpyridine (XIe), m.p. 88~89°, and 0.171 g. of N-methylacetamide. The above crystalline product was quite unstable and easily decomposed to XIe and N-methylacetamide in air. It was also easily decomposed by dissolving in an organic solvent to XIe and N-methylacetamide almost in quantitative yield. If the above crystalline product was not filtered from the reaction mixture, it disappeared in a short time. Hence, it was impossible to purify the product and to determine the melting point. From the above facts, the crystalline product was considered as an intermediate, 1-(N-methylacetamido)-4-cyano-3,5-dimethyl-1,4-dihydropyridine (Xe). Total yields of this reaction; XIe; 5.33 g. (82.7%), XIIe; 0.074 g. (1.2%), $CH_3NHCOCH_3$; 2.91 g. (81.8%).

Reaction of the Mixture of 1-(N-Methylacetamido)-2,4-dimethylpyridinium Iodide (IXf) and 1-(N-Methylacetamido)-2,5-dimethylpyridinium Iodide (IXg) with Cyanide Ion——The mixture of IXf and IXg was obtained by the reaction of the mixture of VIIIf and VIIIg with CH_3I according to the general procedure described above. To a solution of 29.1 g. of the above mixture in 30 ml. of H_2O was added 30 g. of KCN dissolved in 30 ml. of H_2O. The reaction mixture was allowed to stand at room temperature for 1 hr. and extracted first with ether and then with $CHCl_3$. Each layer was dried over anhyd. Na_2SO_4 and evaporated to dryness. Their resulting residue were each chromatographed on alumina. As for ether extract, the fraction eluted with ether was dissolved in EtOH and excess of picric acid solution was added to this. The precipitated picrate was dissolved in $CHCl_3$ and chromatographed on alumina to convert to 2.8 g. of XIg. The combined filtrate and washings of the picrate were dissolved in 20% NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and evaporated to dryness. The resulting residue was chromatographed on alumina to give 250 mg. of XIIf. On the other hand, from the fraction eluted with $CHCl_3$, 760 mg. of N-methylacetamide was obtained. The $CHCl_3$ extract was also treated as described above to give 871 mg. of XIg 324 mg. of XIIf and 720 mg. of N-methylacetamide. Total yields : XIg; 3.67 g. (30% calculated from the mixture; 90.9% calculated from IXg), XIIf; 0.58 g. (4.6% calculated from the mixture; 7% calculated from IXf),[*3] N-methylacetamide; 1.48 g. (22% calculated from the mixture).

Summary

1-(N-Methylacetamido)alkylpyridinium salt was also quite reactive to cyanide ion at its 4-position as showed in the reaction of N-methylacetamidopyridinium salt. In this paper, was reported syntheses of various N-amino derivatives of alkylpyridines and the results of the reaction of them with cyanide ion. By utilizing this reaction, it would be possible to obtain various 4-cyanoalkylpyridines without by-producing 2- or 6-cyanoalkylpyridines.

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[*3] The Ratio of IXf and IXg in reaction mixture was assumed to be equal to the ratio (2:1) of VIIIf and VIIIg.

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74. Toshihiko Okamoto, Masaaki Hirobe, and Emiko Yabe[*1] :
Reaction of N-Aminopyridinium Derivatives. VI.[*2]
Properties of s-Triazolo[1,5-a]pyridine Ring.

*(Faculty of Pharmaceutical Sciences, University of Tokyo[*3])*

In the previous paper,[1] the writers reported that 2-(4-pyridyl)-*s*-triazolo[1,5-*a*]pyridine (II) was obtained in the reaction of an N-amino pyridinium salt (I) with cyanide ion and further that 2-substituted *s*-triazolo[1,5-*a*]pyridine (III) can be obtained by the reaction of I with a nitrile (RCN) in an alkaline medium.

The compound of the structure (III) obtained according to this reaction was quite stable to the action of acid, alkali, or reducing agent. From this fact and by studies of its UV and nuclear magnetic resonance (NMR) spectra, it is considered that the compound has properties quite similar to those of aromatic compounds. However, it was quite unstable to oxidation.

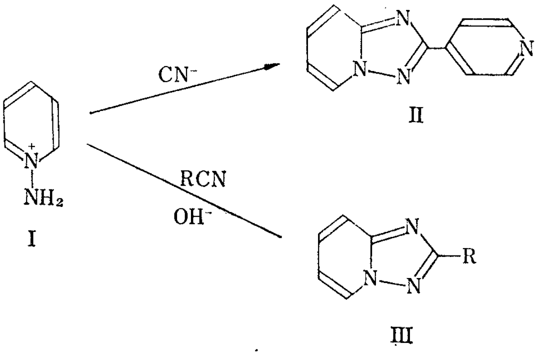

Chart 1.

In order to further study the properties of this compound, the writers studied nitration and oxidation reactions of III. In this experiment, 2-methyl-*s*-triazolo[1,5-*a*]pyridine (IV) was em-

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[1] Part III of this series : This Bulletin, **14**, 506 (1966).