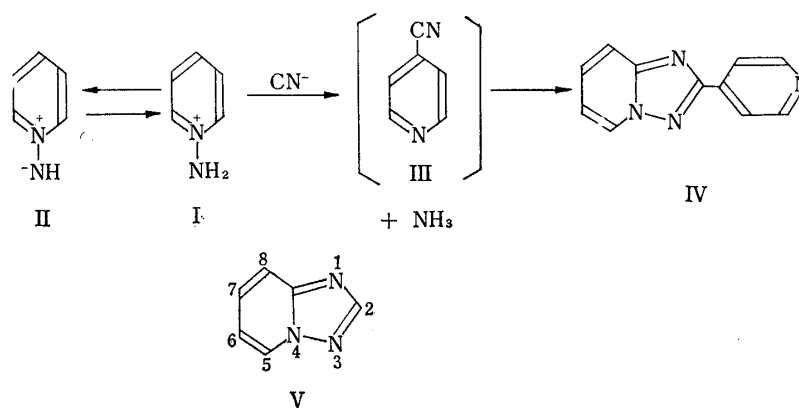


71. Toshihiko Okamoto, Masaaki Hirobe, Yasunobu Tamai, and Emiko Yabe\*<sup>1</sup>: Reaction of N-Aminopyridinium Derivatives. III.\*<sup>2</sup>  
Synthesis of *s*-Triazolo[1,5-*a*]pyridine Ring.

(Faculty of Pharmaceutical Sciences, University of Tokyo\*<sup>3</sup>)

The writers reported in the previous communication<sup>1)</sup> that the reaction of N-aminopyridinium iodide (I) with potassium cyanide in an aqueous medium at room temperature gave 2-(4-pyridyl)-*s*-triazolo[1,5-*a*]pyridine (IV) having *s*-triazolo[1,5-*a*]pyridine ring (V). It was assumed that the reaction would proceed *via* intermediate, 4-cyanopyridine (III) which would be converted into IV by the 1,3-dipolar cycloaddition with N-aminopyridine (II) which exists as an equilibrium mixture with I in the reaction solution.

In this paper, the writers wish to report whether 1,3-dipolar cycloaddition of II occurs with the nitrile of other types to produce *s*-triazolo[1,5-*a*]pyridine derivatives.



In the reaction of I with cyanide ion, III has not been isolated. But, from the fact that ammonia gas evolved when the reaction mixture was made strongly alkaline with potassium hydroxide and that IV was obtained when III was added at room temperature to an aqueous potassium hydroxide solution of I or to an alcoholic solution of II prepared by passing an alcoholic solution of I through the anion exchange resin (Amberlite IRA-400, treated with 10% sodium hydroxide), it could be assumed that III was produced as an intermediate which would be very short lived and soon reacted with II by the 1,3-dipolar cycloaddition mechanism to produce IV. Production of III and ammonia are quite reasonable from the reaction mechanism of N-aminopyridinium derivatives with cyanide ion which has previously been reported.<sup>2)</sup> The structure of IV was proved, by synthesizing it from 1,2-diaminopyridinium salt (IX) and isonicotinoyl chloride by the ring closure in pyridine.

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\*<sup>2</sup> Part II: This Bulletin, **11**, 780 (1963). This paper constitutes Part VII of a series entitled "Reaction Mechanism in Aromatic Heterocyclic Compounds" by T. Okamoto. Part VI: This Bulletin, **11**, 780 (1963).

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1) T. Okamoto, M. Hirobe, Y. Tamai: This Bulletin, **11**, 1089 (1963).

2) T. Okamoto, M. Hirobe, *et al.*: This Bulletin, **11**, 780 (1963).

In order to further investigate generality of this reaction, the writers tried to synthesize several *s*-triazolo [1,5-*a*] pyridine derivatives by 1,3-dipolar cycloaddition of II to several nitriles. As the nitriles, acetonitrile and benzonitrile were used. Hydrogen cyanide was also used for the purpose of synthesizing V. Since it was impossible to isolate II, an aqueous potassium hydroxide solution of I or an alcoholic solution of II obtained by the anion exchange resin treatment, was used in this experiment.

The reaction of II with acetonitrile gave 2-methyl-*s*-triazolo[1,5-*a*] pyridine (VI) (m. p. 49~50°) and with benzonitrile afforded 2-phenyl-*s*-triazolo[1,5-*a*] pyridine (VII) (m. p. 138~139°), both in 40~50% yield. But, in the reaction of II with liquid hydrogen cyanide, *s*-triazolo[1,5-*a*] pyridine (V) was obtained only in 2% yield, and IV and isonicotinamide (VIII) were obtained respectively in 22.2% and 6% yield. The reaction was effected by adding a large excess of hydrogen cyanide to an alcoholic solution of II prepared by treating I with the anion exchange resin. The reason why IV was obtained as a main product and V was obtained only in small amount is considered as follows: in this reaction, II would mostly react with hydrogen cyanide to form *N*-aminopyridinium cyanide (I'). Consequently, the same reaction as that of I with cyanide ion in an alcoholic medium would occur as a main reaction to produce IV through an intermediate (III). On the other hand, concentration of II, which would exist as an equilibrium mixture with I' is too low to produce a considerable amount of 1,3-dipolar cycloaddition products (V or IV). Consequently, a part of III would be converted into its hydrolyzed product (VIII).

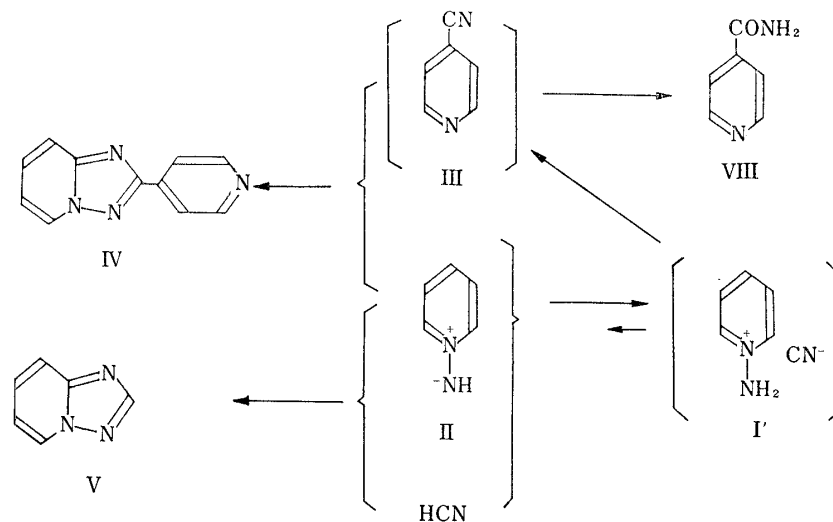


Chart 2.

This 1,3-dipolar cycloaddition of II to a nitrile is considered to proceed *via* dihydro-type intermediate. However, such has not been separated yet. In the reaction of II with acetonitrile and benzonitrile, a product having a molecular formula  $C_{10}H_{16}N_4$  (m. p. 182~183°) was obtained as a common by-product. The writers assumed that it would be tetrahydro-dimer of II, which was a product resulting from the dimer of II acted as a hydrogen acceptor. However, such assumption is not confirmed yet, since this product could not be isolated in the case of the reactions producing IV and V.

Structures of V, VI and VII were confirmed by IR spectra comparison and mixed melting point determination with those prepared by the method adopted to IV (ring closure of K with a carboxylic acid, acid chloride or acid anhydride).

As to syntheses of VI and VII, there is a report by Bower, *et al.*<sup>3)</sup> in which 2-aminopyridine is reacted with acetonitrile or benzonitrile in the presence of aluminum chloride to produce N-(2-pyridyl) acetamide or N-(2-pyridyl) benzamide, which is then subjected to oxidative ring closure with lead tetraacetate to produce VI or VII.

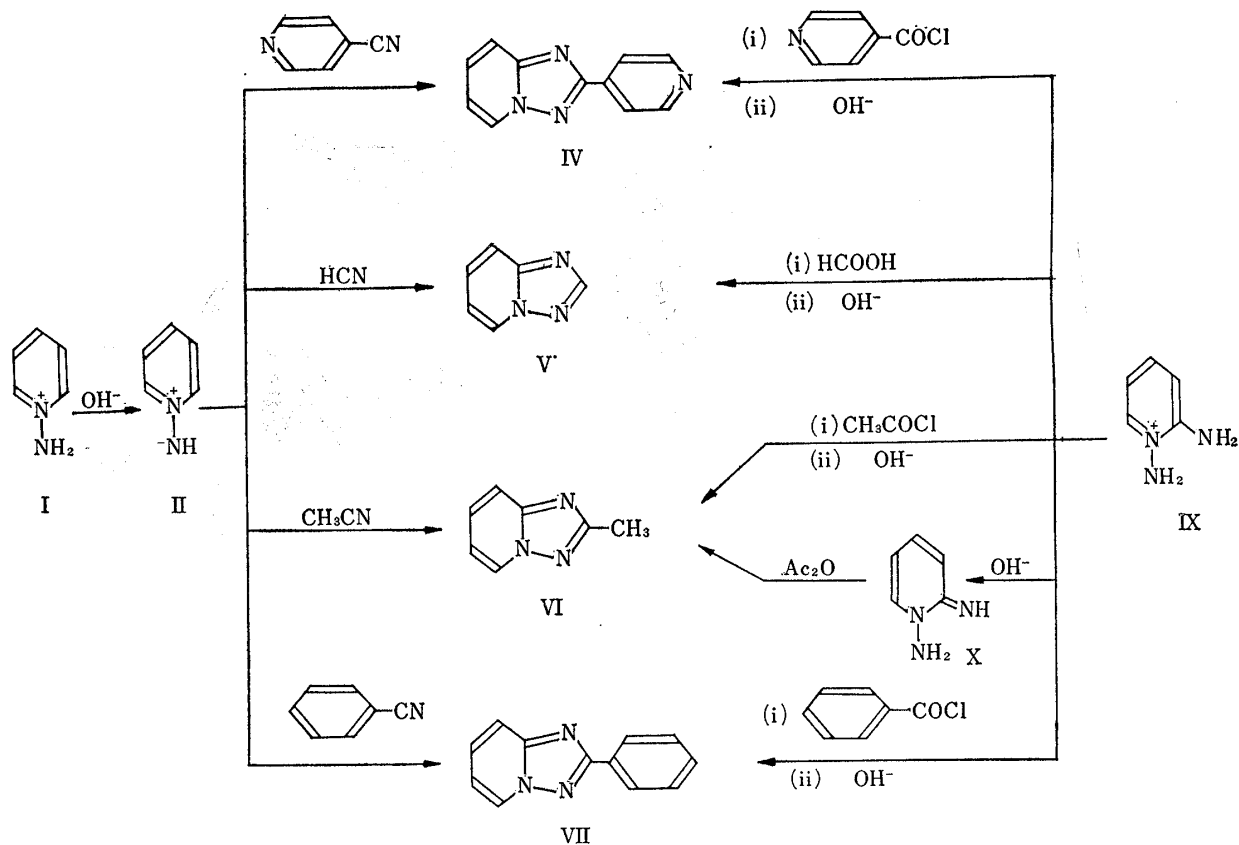


Chart 3.

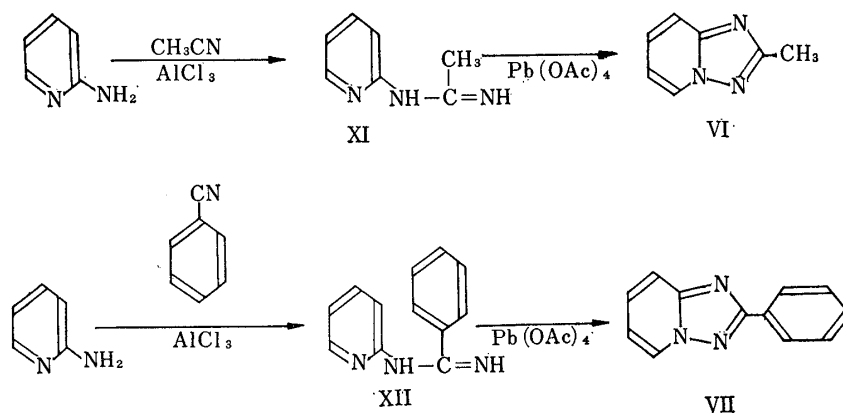


Chart 4.

Syntheses of IV and V have not been reported yet. VI and VII obtained by the writer's method were also identified with those prepared by the method of Bower, *et al.* When the reaction of I with cyanide ion was carried out in water, yield of IV was about 20 to 25%, while in aqueous alcohol (EtOH-H<sub>2</sub>O=2:1), it was increased to about 30 to 35%.

3) J.D. Bower, G.R. Ramage: *J. Chem. Soc.*, 1957, 4506.

In order to examine differences in reactivity of those which differ in substituents attached to the amino group, reactions of N-methylaminopyridinium salt (XIII) and N-acetamidopyridinium salt (XIV) with cyanide ion were carried out. The reaction of XIII with cyanide ion afforded 11.5% of III and traces of two kinds of by-products whose structures have not been made clear, but a compound corresponding to 1,3-dipolar cycloaddition product (XVI) of N-methyliminopyridine (XVIII) to III could not be obtained. The reaction of XIV with cyanide ion merely afforded N-acetyliminopyridine (XV), but neither III nor 1,3-dipolar cycloaddition product (XVII) of III to XV was isolated.

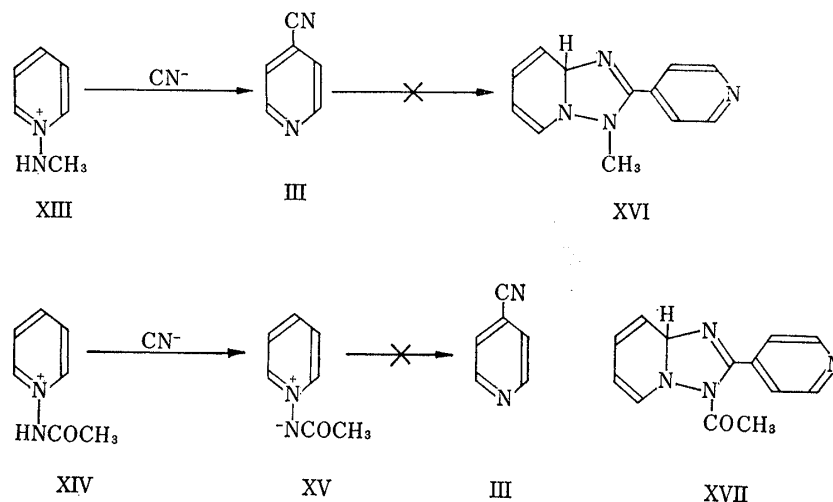


Chart 5.

For the purpose of explaining the above differences in reactivity, pK<sub>a</sub>' values of I, XIII and XIV were determined. The determination was carried out by titrating aqueous solutions of I, XIII and XIV with 5*N* sodium hydroxide solution at 15° and the pK<sub>a</sub>' values were obtained from their titration curves. The results were: pK<sub>a</sub>' (I); 11.2, pK<sub>a</sub>' (XIII), 12~13 (undeterminable) and pK<sub>a</sub>' (XIV); 3.6. The above results indicate that the order of basicity of these ylide compounds is XVIII > II ≫ XV and that XIV has acidity comparable to that of acetic acid (pK<sub>a</sub>'; 4.8 at 25°). The latter fact could easily be assumed from the study of its IR absorption spectrum previously been reported,<sup>4)</sup> which showed that XV has resonance structure quite similar to that of carboxylate. From these pK<sub>a</sub>' values, it is presumed that each I, XIII and XIV is in equilibrium with their ylide compounds (II, XVIII and XV) as shown in the following chart under the condition effecting cyanation (pH 11~12):

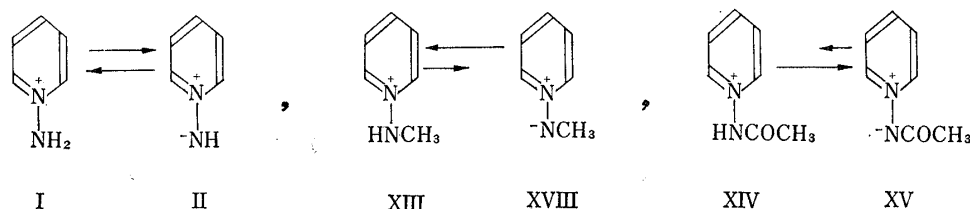


Chart 6.

In the present reaction, nucleophilic substitution of a pyridinium salt with cyanide ion and 1,3-dipolar cycloaddition of the resulting cyanopyridine to its ylide compound are considered to occur almost simultaneously. Thus, merely I which exists in almost equal concentration with II as an equilibrium mixture produced 2-substituted *s*-triazolo

4) T. Okamoto, M. Hirobe, *et al.*, *Yakugaku Zasshi*, **83**, 308 (1963).

[1,5-*a*]pyridine. In the reaction of XIII, concentration of whose ylide compound (XVIII) would be remarkably low, only the first nucleophilic substitution took place to produce III and in the reaction of XIV, even the nucleophilic substitution could not take place because of too lower concentration the quarternary form in the equilibrium mixture and the main product was its ylide compound (XV).

Only from the above reaction, it can not be concluded that XIV can not react with any other nucleophilic reagents and also that XVIII or XV do not have ability of 1,3-dipolar cycloaddition to any other dipolarophiles. The writers are still studying on this point. *s*-Triazolo[1,5-*a*]pyridine ring obtained in this experiment was quite stable and showed quite interesting reactivity, which will be reported in the succeeding paper.<sup>5)</sup>

### Experimental

#### 2-(4-Pyridyl)-*s*-triazolo[1,5-*a*]pyridine (IV)

a) **Reaction of N-Aminopyridinium Iodide (I) with Potassium Cyanide**—To a solution of 3.0 g. of I in 6 ml. of H<sub>2</sub>O, 12.0 g. of KCN dissolved in 15 ml. of H<sub>2</sub>O was added at a time with stirring. The reaction mixture (pale reddish violet) was heated at 35° for 2 hr., during the time, colorless needles were separated. After allowing the mixture to stand overnight at room temperature, 162 mg. of needles of IV were obtained by filtration. The filtrate was heated at 65~70° on a water bath for 30 min. and cooled to precipitate 168 mg. of amorphous product which was identical with IV, total yield, 24.7% (m.p. 193° recrystallized from CHCl<sub>3</sub>). *Anal.* Calcd. for C<sub>11</sub>H<sub>8</sub>N<sub>4</sub>: C, 67.33; H, 4.11; N, 28.56. Found: C, 67.09; H, 4.48; N, 28.78. Mol. wt. (Rast), 198 (Calcd. 215).

b) **Reaction of N-Iminopyridine (II) with 4-Cyanopyridine**—To a solution of 200 mg. of I dissolved in 1 ml. of 2*N* KOH, was added at a time 50 mg. of 4-cyanopyridine dissolved in 1 ml. of EtOH. The reaction mixture (bluish violet) was allowed to stand overnight at room temperature, distilled to remove EtOH, extracted with CHCl<sub>3</sub>. The CHCl<sub>3</sub> layer was dried over anhyd. Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. The resulting residue was chromatographed on alumina. From the fraction eluted with CHCl<sub>3</sub>, 80 mg. of colorless needles were obtained (m.p. 192~193° recrystallized from CHCl<sub>3</sub>), which were confirmed to be identical with IV obtained in a) by comparison of their IR and UV spectra and mixed melting point determination. Yield: 84.5% (calculated from 4-cyanopyridine).

c) **Reaction of 1,2-Diaminopyridinium Iodide (IX) with Isonicotinoyl Chloride**—In 1 ml. of pyridine were dissolved 244 mg. of IX and 152 mg. of HCl salt of isonicotinoyl chloride (m.p. 163~164°). The mixture was heated on a water bath for 3 min. to completely dissolve the solid, allowed to stand overnight at room temperature and evaporated to dryness under reduced pressure. The resulting residue was dissolved in 2*N* NaOH solution and extracted with CHCl<sub>3</sub>. The CHCl<sub>3</sub> layer was dried over anhyd. Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. The residue was chromatographed on alumina to give 30 mg. of colorless needles (m.p. 192~193°), which were confirmed to be identical with IV by IR and UV spectra comparison and mixed melting point determination.

c') **1,2-Diaminopyridinium Iodide (IX)**—To a solution of 9.36 g. of 2-aminopyridine in 20 ml. of H<sub>2</sub>O, 20 ml. of an aqueous H<sub>2</sub>NOSO<sub>3</sub>K solution (prepared by neutralizing 11.23 g. of H<sub>2</sub>NOSO<sub>3</sub>H with 5.59 g. of KOH) was added dropwise. The reaction mixture was heated at 85~88° on a water bath for 4 hr., and then 6.9 g. of K<sub>2</sub>CO<sub>3</sub> in 40 ml. of H<sub>2</sub>O was added. The resulting mixture was diluted with about three times its volume of MeOH, the separating K<sub>2</sub>SO<sub>4</sub> was filtered off and the filtrate was concentrated under reduced pressure. On adding 8 ml. of 57% HI to this concentrated filtrate and allowing the resulting solution to stand for a while, colorless needles were separated. The solution was further cooled in dry ice-acetone to give 11.03 g. of IX, m.p. 160~161° (decomp.) (recrystallized from EtOH), yield: 46.5%, Picrate; m.p. 182~184° (decomp.). *Anal.* Calcd. for C<sub>5</sub>H<sub>8</sub>N<sub>3</sub>I: C, 25.33; H, 3.40; N, 17.73. Found: C, 25.57; H, 3.48; N, 17.76.

#### *s*-Triazolo[1,5-*a*]pyridine (V)

a) **Reaction of N-Iminopyridine (II) with Liq. Hydrogen Cyanide**—In a flask equipped with KOH tube and placed in an ice bath, was put a solution (about 100 ml.) of II in MeOH (bluish violet) obtained by treating a solution of 2.5 g. of I in MeOH with the anion exchange resin treated with 10% NaOH. To this was added at a time a large excess of liq. HCN (15 ml.). The reaction mixture was allowed to stand overnight at room temperature. After evaporation of excess liq. HCN and MeOH, the resulting reddish brown tarry residue was dissolved in CHCl<sub>3</sub> and chromatographed on alumina. As the first fraction eluted with ether, 28 mg. of V were obtained as colorless needles, m.p. 107~108° (recrystallized from benzene-petr. ether).

5) Part VI of this series, This Bulletin, 14, 523 (1966).

Yield: 2% (calculated from I). *Anal.* Calcd. for  $C_6H_3N_3$ : C, 60.49; H, 4.23; N, 35.28. Found: C, 60.52; H, 4.58; N, 35.39. Picrate; m.p. 196~197° (decomp.). *Anal.* Calcd. for  $C_{12}H_8O_7N_6$ : C, 41.39; H, 2.32; N, 24.18. Found: C, 41.58; H, 2.89; N, 24.12. As the second fraction eluted with ether, 246 mg. of IV (yield: 22.2%) and as the third fraction eluted with  $CHCl_3$ -MeOH (20:1), 81 mg. of VIII (m.p. 155~156.5°; yield: 6%) were obtained, both of which were identified with authentic sample by mixed melting point determination respectively. In addition to the above three products, two kinds of products whose structures have not been confirmed yet were obtained in traces amount.

**b) Reaction of 1,2-Diaminopyridinium Iodide (IX) with Formic Acid**—To a solution of 820 mg. of IX in 1 ml. of 80% HCOOH, was added 0.4 ml. of conc. HCl. The reaction mixture was heated under reflux for 1.5 hr., cooled and evaporated to dryness under reduced pressure. The residue was recrystallized from EtOH to give 590 mg. of hydrochloride of V as colorless needles, m.p. 195~197° (decomp.), which were dissolved in 2 ml. of 28%  $NH_4OH$ , extracted with ether. The ether layer was dried over anhyd.  $Na_2SO_4$  and evaporated to dryness to give 270 mg. of V as colorless needles, m.p. 107~108° (recrystallized from benzene-petr. ether), which were identified with V obtained in a) by IR and UV spectra comparison and mixed melting point determination. Yield: 65.6% (calculated from IX).

### 2-Methyl-s-triazolo[1,5-a]pyridine (VI)

**a) Reaction of N-Iminopyridine (II) with Acetonitrile**—To a solution of 3.0 g. of I in 6 ml. of 2N KOH, 12 ml. of  $CH_3CN$  added. The mixture which showed first bluish violet and then reddish brown was allowed to stand overnight. The reaction mixture was concentrated to about half its volume under reduced pressure to remove excess of  $CH_3CN$ , extracted several times with  $CHCl_3$ . The  $CHCl_3$  layer was dried over anhyd.  $Na_2SO_4$  and evaporated to dryness. The resulting residue was dissolved in  $CHCl_3$  and chromatographed on alumina. As the first fraction, 0.86 g. of VI was obtained, as hygroscopic, colorless needles, m.p. 49~50° (yield: 48~50%). Picrate: m.p. 182°. *Anal.* Calcd. for  $C_7H_7N_3 \cdot C_6H_5O_7N_3$  (picrate): C, 43.09; H, 2.76; N, 23.20. Found: C, 43.28; H, 3.13; N, 23.16.

VI was identified with the product prepared according to the method of Bower, *et al.*<sup>3)</sup> by IR spectra comparison and by admixture. The second fraction provided 0.21 g. of colorless scaly crystals, m.p. 182~183° (recrystallized from benzene). *Anal.* Calcd. for  $C_{10}H_{10}N_4$ : C, 62.50; H, 8.33; N, 29.16. Found: C, 62.25; H, 8.11; N, 29.33. Mol. wt. (Rast), 183 (Calcd. 184).

**b) Reaction of 1,2-Diaminopyridinium Iodide (IX) with Acetyl Chloride**—To 5 ml. of  $CH_3COCl$ , was added 500 mg. of IX. The reaction mixture was allowed to stand overnight at room temperature. After evaporation of excess  $CH_3COCl$  under reduced pressure, the resulting residue was dissolved in MeOH and passed through anion exchange resin (Amberlite IRA-401) treated with 10% NaOH. The eluted solution was evaporated to dryness to afford pale brown oily residue, which was dissolved in  $CHCl_3$  and purified by alumina chromatography to give 194 mg. of colorless hygroscopic crystalline product from the fraction eluted with  $CHCl_3$ . Yield: 70%. This was identified with VI obtained in a) by IR and UV spectra comparison.

**c) Reaction of 1-Amino-2-iminopyridine (X) with Acetic Anhydride**—In 5 ml. of  $Ac_2O$  was dissolved 400 mg. of X prepared from 200 mg. of IX. The reaction mixture was heated on a boiling water bath for 2 hr., cooled and excess  $Ac_2O$  was distilled off under reduced pressure. The residue was chromatographed on alumina to give 360 mg. of colorless hygroscopic crystals from the fraction eluted with  $CHCl_3$ , which were identified with VI obtained in a) and b) by IR and UV spectra comparison and mixed melting point determination of their picrate (m.p. 176° (decomp.)). Yield: 73.8%.

**c') 1-Amino-2-iminopyridine (X)**—A solution of 200 mg. of IX in MeOH was treated with anion exchange resin (Amberlite IRA 401) activated with 10% NaOH solution to effect dehydroiodation. The resulting solution was then concentrated to about  $\frac{1}{3}$  of its volume, when white crystals were separated. The solution was further concentrated to dryness, washed with MeOH to give 92 mg. (almost quantitative yield) of colorless crystalline product X which was sparingly soluble in any organic solvent, m.p. 197°. From the fact that the product did not show characteristic coloration of N-iminopyridine derivatives and that its IR spectra showed an absorption at  $1670\text{ cm}^{-1}$  (KBr) due to  $>C=NH$  stretching vibration, 1-imino-2-aminopyridine is considered to be converted into the stable form, X.

### 2-Phenyl-s-triazolo[1,5-a]pyridine (VII)

**a) Reaction of N-Iminopyridine (II) with Benzonitrile**—To a solution of 6.66 g. of I in 15 ml. of 2N KOH was added 6.18 g. of benzonitrile dissolved in 15 ml. of EtOH. The mixture which showed first bluish violet and then reddish brown was allowed to stand overnight and then concentrated under reduced pressure to remove EtOH. The residual liquid was extracted several times with  $CHCl_3$ . The  $CHCl_3$  layer was dried over anhyd.  $Na_2SO_4$  and evaporated to dryness. The residue was separated by chromatography on alumina with  $CHCl_3$ . As the first fraction benzonitrile was recovered and the second fraction provided 2.42 g. of VII, m.p. 138~139° (recrystallized from a mixture of benzene and petr. ether), yield: 41%. *Anal.* Calcd. for  $C_{12}H_9N_3$ : C, 73.85; H, 4.61; N, 21.53. Found: C, 73.95; H, 4.85; N, 21.66. VII was identified by IR spectra comparison and by admixture with the product prepared by the method developed by Bower, *et al.*<sup>3)</sup> The third fraction provided 0.23 g. of colorless scaly crystal (m.p. 182°, recrystallized from benzene), which was identified with the compound obtained as by-product in the reaction of N-iminopyridine with

acetonitrile by IR spectra comparison and by mixed melting point determination.

**b) Reaction of 1,2-Diaminopyridinium Iodide (IX) with Benzoyl Chloride**—To 330 mg. of IX was added 2 ml. of benzoyl chloride. The reaction mixture was refluxed for 1 hr. and added dropwise to water to hydrolyze excess of benzoyl chloride. The resulting solution was made alkaline with 2*N* KOH and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The CH<sub>2</sub>Cl<sub>2</sub> layer was dried over anhyd. Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. The residue was purified by chromatography on alumina with CHCl<sub>3</sub> to give 166 mg. of VII as colorless needles, m.p. 137~138° (recrystallized from benzene-petr. ether), yield: 61.2%.

**Reaction of N-Methylaminopyridinium Chloride (XIII) with Cyanide Ion**—In 1 ml. of H<sub>2</sub>O was dissolved 340 mg. of XIII (hygroscopic colorless crystal) prepared by hydrolyzing N-methylacetamidopyridinium iodide<sup>4)</sup> with HCl (1:1) in order to effect deacetylation and then treating with anion exchange resin (Amberlite IRA-400) treated with saturated NaCl solution. To this was added a solution of 1.5 g. of KCN in 3 ml. of H<sub>2</sub>O at a time at room temperature (10~15°). The reaction mixture was allowed to stand overnight and extracted with CHCl<sub>3</sub>. The CHCl<sub>3</sub> layer was dried over anhyd. Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. The resulting residue was separated by chromatography on alumina to give 28 mg. of III as the first fraction eluted with ether, which was identified with the authentic sample prepared according to an alternative route by IR spectra comparison and by mixed melting point determination. Yield: 11.5%. In addition to III, 10 mg. of hygroscopic yellow crystals (IR: 2200 cm<sup>-1</sup>, UV λ<sub>max</sub><sup>EtOH</sup> mμ: 238, 343; m.p. 189~191° (picrate)) and 9 mg. of reddish brown oily product (IR: 1695 cm<sup>-1</sup>, UV λ<sub>max</sub><sup>EtOH</sup>: 265 mμ) were obtained as the fraction eluted with ether and CHCl<sub>3</sub>, respectively. However, both of which were not proposed *s*-triazolo[1,5-*a*]pyridine derivatives.

### Summary

N-Aminopyridinium salt (I) was reacted with cyanide ion in water at room temperature to give 2-(4-pyridyl)-*s*-triazolo[1,5-*a*]pyridine (IV). In alkaline medium I exists as an equilibrium mixture with the ylide type, N-iminopyridine (II) which was reacted with several nitrile compounds to produce *s*-triazolo[1,5-*a*]pyridine derivatives by 1,3 dipolarcyclo addition. This novel triazole ring could also be synthesized by ring closure of 1,2-diaminopyridinium salt with a carboxylic acid, acid chloride or acid anhydride. Reaction of N-methylaminopyridinium salt (XIII) or N-acetamidopyridinium salt (XIV) with cyanide ion did not afford any 1,3-dipolar cycloaddition products. Explanation for the difference in reactivity among I, XIII and XIV was attempted from each pKa' values.

(Received October 9, 1965)

[Chem. Pharm. Bull.]  
[14(5) 512 ~ 517 (1966)]

UDC 547.831.1.04.07

## 72. Toshihiko Okamoto, Masaaki Hirobe, and Tsuneyoshi Yamazaki : Reaction of N-Aminopyridinium Derivatives. IV.\*<sup>1</sup> Syntheses of N-Aminoquinolinium Salts and Their Reaction with Cyanide Ion.

(Faculty of Pharmaceutical Sciences, University of Tokyo\*<sup>2</sup>)

In the previous paper<sup>1)</sup> of this series, syntheses of N-aminopyridinium salts and their reaction with cyanide ion were reported as an example of the nucleophilic sub-

\*<sup>1</sup> This paper constitutes Part VIII of series entitled "Reaction Mechanism in Aromatic Heterocyclic Compounds" by T. Okamoto. Part VII: This Bulletin, 14, 506 (1966).

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1) T. Okamoto, M. Hirobe *et al.*: Yakugaku Zasshi, 83, 309 (1963); This Bulletin, 11, 780 (1963).