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.

(Received October 9, 1965)

[*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.

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-

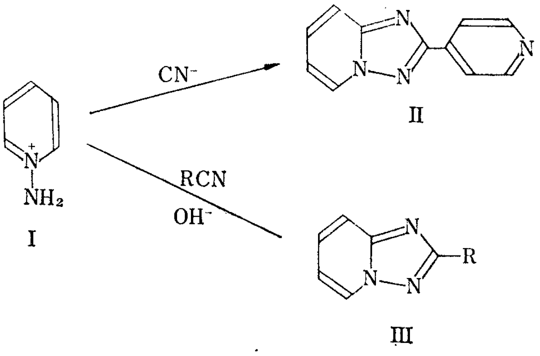


Chart 1.

[*1] Present address : Faculty of Pharmaceutical Sciences, University of Tōho, Narashino, Chiba.

[*2] Part Ⅴ : This Bulletin, **14**, 518 (1966).

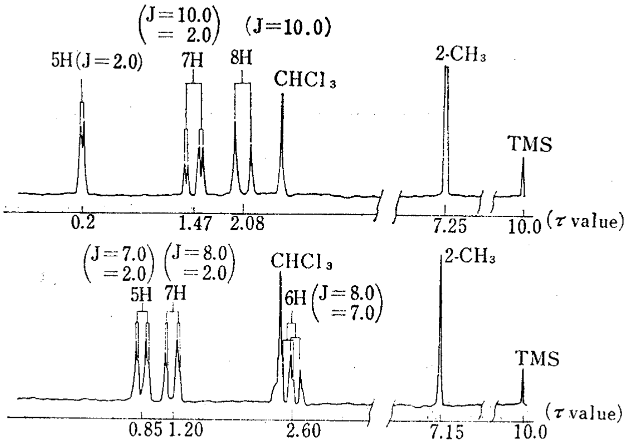
[*3] Hongo, Bunkyo-ku, Tokyo (岡本敏彦, 広部雅昭, 矢部恵美子).

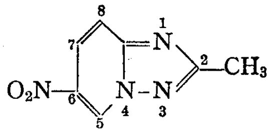
1) Part Ⅲ of this series : This Bulletin, **14**, 506 (1966).

ployed, which can easily be synthesized by reacting I with methyl cyanide.

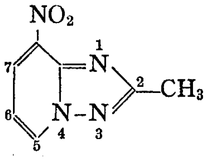
Nitration of IV was effected by the usual method of reacting IV with potassium nitrate in concentrated sulfuric acid at 120~130°. On separating the reaction product by chromatography or by fractional crystallization from benzene, two kinds of mononitro compounds (V), m.p. 211~212°, and (VI), m.p. 193~194°, were obtained in 14% and 37% yield, respectively. Catalytic reduction of V and VI over palladium-carbon afforded the corresponding amino derivatives (VII) and (VIII) which were further converted to the corresponding bromo derivatives (IX and X) by diazotization of VII and VIII with sodium nitrite in hydrogen bromide, followed by reaction with cuprous brom ide.

In order to know the position of the nitro group in V and VI their nuclear magnetic resonance spectra were measured in deuterochloroform (Fig. 1). In each of the spectra, it was assumed that the lowest field signal corresponds to C_5 proton adjacent to the hetero atom, nitrogen, and the small coupling constant (2.0 c.p.s.) is due to "meta-coupling". According to this assumption, V and VI were considered to be 6-nitro and 8-nitro derivative, respectively. In the spectra of V, the signal corresponding to C_5 proton had shifted to a lower field than that of VI, because of the shielding effect of neighboring nitro group.





V



VI

Fig. 1. Nuclear Magnetic Resonance Spectra measured at 60 Mc. in Deuterochloroform

Based on this assumption, the writers attempted to verify the structure of V and VI by their synthesis. For preparing the 2-methyl-*s*-triazolo[1,5-*a*]pyridine ring, there are the following methods (a) and (b) previously reported by the writers[1] and the method (c) of Bower, *et al.*[2]

(a) 1,3-Dipolarcycloaddition of N-aminopyridinium salt with methyl cyanide in an alkaline medium.

(b) Ring closure of 1,2-diaminopyridinium salt with acetyl chloride in the presence of pyridine.

(c) Oxidative ring closure of N-2-pyridylacetamidine with the use of lead tetra-acetate.

If V and VI are respectively 6-nitro and 8-nitro derivatives, their reduction products, 6-amino (VII) and 8-amino (VIII) derivatives, would simultaneously be obtained from 1,3-diaminopyridinium salt (XI) according to the method (a). Thus, 3-aminopyridine was reacted with hydroxylamine-O-sulfonic acid according to the usual method to its 1-amino derivative (XI), which was further reacted with methyl cyanide in an alkaline medium.[3] On separating the reaction product by chromatography on alumina, a sub-

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[2] J.D. Bower, G.R. Ramage: J. Chem. Soc., **1957**, 4506.

stance corresponding to VIII was obtained, but not that corresponding to VII.

Since VIII would be the 8-amino derivative from the NMR spectrum of its corresponding nitro derivative (VI), attempts were made to synthesize the 6-substituted derivative by an alternative route, but none of the following methods gave the desired product and the starting materials were recovered. Synthesis of 1,2-diamino-5-nitropyridinium salt from 2-amino-5-nitropyridine and hydroxylamine-O-sulfonic acid in an attempt to prepare V according to the method (b); synthesis of N-2-(5-nitropyridyl)acetamidine from 2-amino-5-nitropyridine and methyl cyanide in the presence of aluminum chloride in an attempt to produce V according to the method (c), and 1-amination of 2,5-diaminopyridine with hydroxylamine-O-sulfonic acid in an attempt to produce VII according to the method (b). Also, in the reaction of 2-amino-5-bromopyridine with hydroxylamine-O-sulfonic acid in an attempt to prepare IX according to the method (b), purification of the reaction product was quite difficult and the desired 5-bromo-1,2-diamino pyridinium salt could not be obtained in a pure state. Synthesis of IX according to the method (c) was finally attempted. Reaction of 2-amino-5-bromopyridine with methyl cyanide in the presence of aluminum chloride afforded N-2-(5-bromopyridyl)acetamidine (XII) which was subjected to ring closure with the use of lead tetraacetate to 2-methyl-6-bromo-*s*-triazolo[1,5-*a*]pyridine. This product was confirmed to be identical with IX by IR spectral comparison and mixed melting point determination. Consequently, V was proved to be 2-methyl-6-nitro-*s*-triazolo[1,5-*a*]pyridine and at the same time VI was confirmed as 2-methyl-8-nitro-*s*-triazolo[1,5-*a*]pyridine. The above results are summarized in Chart 2.

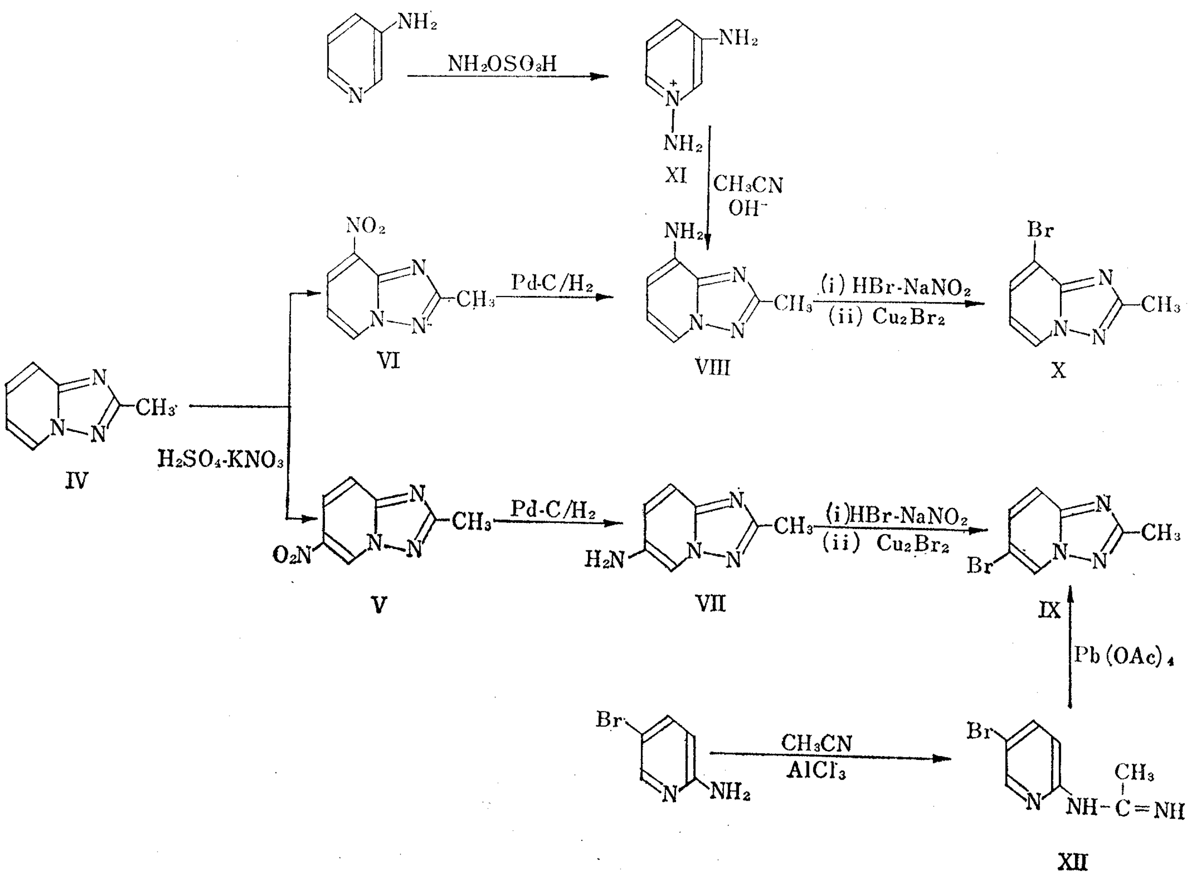

Chart 2.

Nature of *s*-triazolo[1,5-*a*]pyridine ring against oxidation was also investigated. When IV and 2-phenyl-*s*-triazolo[1,5-*a*]pyridine[1] (XIII) were each reacted with potassium permanganate in an aqueous solution at a room temperature, about 3 moles of potassium permanganate was consumed, From the reaction mixture, 3-methyl-*s*-triazole-5-carboxylic acid (XIV) and 3-phenyl-*s*-triazole-5-carboxylic acid (XV) were respectively separated as a copper salt. Decarboxylation of XIV and XV provided 3-methyl-*s*-triazole[3] (XVI) and 3-phenyl-*s*-triazole[4] (XVII), respectively, which were both confirmed by IR spectral comparison and by admixture with an authentic sample prepared by an alternative route. It was thus clear that *s*-triazolo[1,5-*a*]pyridine ring is quite unstable to oxidation and fission of the pyridine ring occurs.

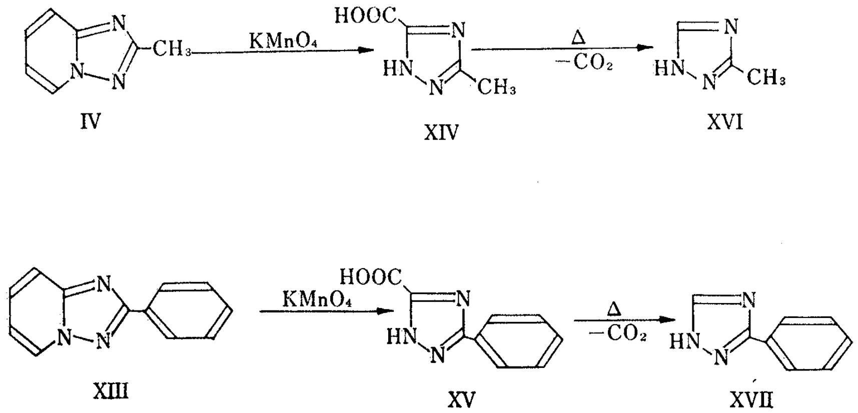

Chart 3.

Experimental

Nitration of IV——To a solution of 7.98 g. of IV dissolved in 200 g. of conc. H_2SO_4, 12.12 g. of KNO_3 was added in small portions as a fine powder. The mixture was heated at 120~130° for 10 hr. After cool, the reaction mixture was poured into ice water and neutralized with Na_2CO_3. The separated product was extracted several times with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and the solvent was evaporated. The residue recrystallized twice from benzene and 3.94 g. (37%) of VI was obtained as light yellow needles, m.p. 193~194°. *Anal.* Calcd. for $C_7H_6O_2N_4$: C, 47.19; H, 3.37; N, 31.46. Found : C, 47.03; H, 3.34; N, 31.15.

The recrystallization filtrate was concentrated to about one half its volume, and V separated as white cotton-like crystals; yield, 1.48 g. (14%). m.p. 211~212° (recrystallized from EtOH). *Anal.* Calcd. for $C_7H_6O_2N_4$: C, 47.19; H, 3.37; N, 31.46. Found : C, 47.35; H, 3.30; N, 31.24.

Catalytic Reduction of V over Palladium-carbon——In 20 ml. of MeOH was suspended 0.33 g. of V. Catalytic reduction was effected with the use of 1 g. of 10% Pd-C at room temperature and 130 ml. of H_2 was absorbed. After completion of the reduction, Pd-C was filtered off and the filtrate was evaporated to dryness under reduced pressure to give 0.21 g. of crude crystals, which were recrystallized from a mixture of benzene and petr. ether to 0.19 g. of VII as colorless needles, m.p. 166~167°. *Anal.* Calcd. for $C_7H_8N_4$: C, 56.75; H, 5.41; N, 37.83. Found : C, 56.50; H, 5.40; N, 37.86.

Catalytic Reduction of VI over Palladium-carbon——In 30 ml. of MeOH was suspended 0.53 g. of VI. Catalytic reduction was effected with the use of 1 g. of 10% Pd-C at room temperature and 237 ml. of H_2 was absorbed. After completion of the reduction, Pd-C was filtered off and the filtrate was evaporated to dryness under reduced pressure to give 0.39 g. of crude crystals, which were recrystallized from a mixture of benzene and petr. ether to 0.23 g. of VIII as colorless needles, m.p. 116~117°. *Anal.* Calcd. for $C_7H_8N_4$: C, 56.75; H, 5.41; N, 37.83. Found : C, 56.56; H, 5.32; N, 37.96.

Sandmeyer Reaction of VII——To 0.5 g. of VII was added 2 ml. of 47% HBr and hydrobromide of VII separated out. A solution of 0.40 g. of $NaNO_2$ in 1 ml. of water was added to this mixture at a temperature below 0°; by which the hydrobromide of VII disappeared. The resulting diazotized solution was added dropwise into a solution of 1.5 g. of KBr, 0.58 g. of Cu_2Br_2, 0.5 ml. of 47% HBr, and 2.5 ml. of water at 90~

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3) R.G. Jones, C. Ainsworth : J. Am. Chem. Soc., **77**, 1538 (1955).

4) E. Hoggarth : J. Chem. Soc., **1949**, 1160.

95° with stirring. The reaction mixture was stirred further for 30~40 min. until the evolution of N_2 ceased, cooled, neutralized with 2*N* NaOH, and extracted with ether. The ether layer was dried over anhyd. K_2CO_3 and evaporated to leave 0.23 g. of crude crystals, which were recrystallized from benzene to 0.13 g. (18%) of IX as colorless needles, m.p. 153~155°. By comparison of IR spectra and by mixed melting point determination, IX was proved as 2-methyl-6-bromo-*s*-triazolo[1,5-*a*]pyridine obtained by ring closure of XII.

Sandmeyer Reaction of VIII——To 0.60 g. of VIII was added 2 ml. of 47% HBr and hydrobromide of VIII separated out. A solution of 0.40 g. of $NaNO_2$ in 1 ml. of water was added to this mixture at a temperature below 0° and hydrobromide of VIII disappeared. The resulting diazotized solution was added dropwise with stirring into a solution of 1.5 g. of KBr, 0.58 g. of Cu_2Br_2, 0.5 ml. of 47% HBr, and 2.5 ml. of water at a temperature between 60 and 70°. The reaction mixture was stirred for 30~40 min. until the evolution of N_2 ceased, cooled, neutralized with 2*N* NaOH, and extracted with ether. The ether layer was dried over anhyd. K_2CO_3 and evaporated to leave 0.57 g. of crude crystals, which were recrystallized from benzene-petr. ether to 0.56 g. (65%) of X as light yellow pillar-shaped crystals, m.p. 122~123°. *Anal.* Calcd. for $C_7H_6N_3Br$: C, 39.64; H, 2.85; N, 19.82. Found : C, 40.06; H, 3.06; N, 19.77.

1,3-Diaminopyridinium Iodide (XI)——To a solution of 9.4 g. (0.1 mole) of 3-aminopyridine[5] in 20 ml. of water, 0.1 mole of H_2NOSO_3K dissolved in 30 ml. of water (an aqueous solution prepared by neutralizing an aqueous solution of 11.30 g. of H_2NOSO_3H with an aqueous solution of an equal mole of KOH at 0°) was added dropwise at 40° during 10 min. with stirring. After reacting the mixture at 55° for 2 hr., a solution of 6.9 g. (0.05 mole) of K_2CO_3 in 30 ml. of water was added. The resulting solution was concentrated at 40~50° to about one-half its volume under a reduced pressure and 2~3 volumes of EtOH was added. The precipitated K_2SO_4 was filtered off and the filtrate was concentrated under a reduced pressure. To this was added 14 ml. of 57% aqueous HI solution and the resulting solution was evaporated to dryness under a reduced pressure to give crude crystals, which were recrystallized from EtOH to 7.03 g. (30%) of XI as light yellow leaf-like crystals, m.p. 140~141°. *Anal.* Calcd. for $C_5H_8N_3I$: C, 25.33; H, 3.40; N, 17.73. Found : C, 25.57; H, 3.60; N, 17.65.

Reaction of 1,3-Diaminopyridinium Iodide (XI) with Acetonitrile——To a solution of 4.74 g. of XI in 40 ml. of 2*N* KOH, 40 ml. of CH_3CN was added. The reaction mixture was allowed to stand overnight at room temperature and concentrated to about one-half its volume under a reduced pressure to remove excess of CH_3CN. The residual liquid was extracted several times with $CHCl_3$, the $CHCl_3$ layer was dried over anhyd. Na_2SO_4, and the solvent was evaporated to dryness. The residue was dissolved in $CHCl_3$ and separated by chromatography on Al_2O_3 with $CHCl_3$-acetone (7:3). The first fraction provided 0.87 g. (25%) of VIII which was recrystallized from a mixture of benzene-petr. ether as colorless needles, m.p. 116~117°.

N-2-(5-Bromopyridyl)acetamidine (XII)——To a mixture of 1.73 g. of 2-amino-5-bromopyridine[6] and 1.6 g. of CH_3CN, 2.6 g. of $AlCl_3$ was added and the reaction mixture was heated for 50 min. at 200°. After cool, 20 g. of ice was added little by little with external cooling to hydrolyze $AlCl_3$ and washed the aqueous solution with ether. The aqueous layer was further cooled and made strongly alkaline by adding 50% NaOH at below 5°. The separated product was extracted several times with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and evaporated under a reduced pressure to give 1.60 g. (74%) of XII as colorless needles, m.p. 124~126°. Recrystallization was made by dissolving the residue in a small amount of benzene at below 40° and adding an appropriate amount of petr. ether to the solution. *Anal.* Calcd. for $C_7H_8N_3Br$: C, 39.28; H, 3.77; N, 19.63. Found : C, 39.39; H, 3.79; N, 19.14. When XII was chromatographed on Al_2O_3 with $CHCl_3$, it was hydrolyzed to 5-bromo-2-acetamidopyridine, m.p. 175°.

Synthesis of 2-Methyl-6-bromo-*s*-triazolo[1,5-*a*]pyridine (IX) by the Ring Closure of XII——To a solution of 0.64 g. of XII in 10 ml. of AcOH, 1.52 g. of lead tetraacetate was added and the reaction mixture was heated under reflux for 15 min. After cool, the reaction mixture was poured into ice water and neutralized with Na_2CO_3. The separating product was extracted several times with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. K_2CO_3 and evaporated to dryness. The residue was recrystallized from benzene to give 0.34 g. (54%) of IX, m.p. 153~155°. *Anal.* Calcd. for $C_7H_6N_3Br$: C, 39.64; H, 2.85; N, 19.82. Found : C, 39.61; H, 3.10; N, 19.42.

Oxidation of IV with Potassium Permanganate——To a solution of 2.4 g. of IV in 30 ml. of water, 12 g. of $KMnO_4$ dissolved in 400 ml. of water was added dropwise at room temperature, with stirring during one hour. The reaction mixture was stirred further for 3 hr. The excess of $KMnO_4$ was decomposed by adding 20 ml. of EtOH and the resulting MnO_2 was filtered off after warming the mixture. The filtrate was concentrated to 100 ml. under a reduced pressure and adjusted at pH 3~4 by adding 2*N* HCl. To this was added a saturated solution of copper acetate. After filtering, washing, and drying the separated bluish white copper salt, it was suspended in 100 ml. of EtOH and the suspension was saturated with H_2S. The resulting CuS was filtered off and the filtrate was evaporated to dryness to give 1.5 g. of XIV, m.p. 131~132° (decomp.). One gram of XIV was heated at 120~130° in an oil bath and XIV was decomposed with evolution of CO_2 gas. The pyrolysis product was extracted with $CHCl_3$ and the solvent was evaporated

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[5] C. S. Hamilton, M. D. Brunner : Org. Syntheses, **30**, 3.

[6] H. L. Bradlow, C. A. Vanderwerf : J. Org. Chem., **16**, 81 (1951).

to give the residue which was recrystallized from benzene to provide 0.32 g. of XVI as hygroscopic white needles, m.p. 98°(picrate, 148~149°). ***Anal.*** Calcd. for $C_3H_5N_3 \cdot C_6H_3O_7N_3$ (picrate): C, 34.61; H, 2.56; N, 26.92. Found: C, 34.72; H, 2.70; N, 26.77. XVI was identified by IR spectral comparison and by admixture with an authentic sample prepared according to the method of Jones, ***et al.***[3] and also by admixture of the picrate with that of the authentic sample.

Oxidation of XIII with Potassium Permanganate——To a suspension of 1.2 g. of XIII in 30 ml. of water, 4 g. of $KMnO_4$ dissolved in 200 ml. of water was added dropwise at 40~50° with stirring during one hour. After allowing the mixture to stand overnight with stirring, 1 g. of $KMnO_4$ dissolved in 50 ml. of water was further added. The mixture was allowed to stand overnight and the resulting MnO_2 was filtered off. The filtrate was concentrated to about ⅔ of its volume under a reduced pressure and extracted several times with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and evaporated to recover 0.34 g. of XIII. The aqueous layer was further concentrated to 100 ml. under a reduced pressure and adjusted to pH 3~4 with 2*N* HCl. By adding a saturated solution of copper acetate to this solution, bluish white precipitate was obtained, which was filtered, washed with water and dried. It was then suspended in 100 ml. of EtOH and the suspension was saturated with H_2S. The resulting CuS was filtered off and the filtrate was evaporated to dryness to give 0.75 g. of XV, m.p. 114°(decomp.). 0.5 g. of XV was heated in an oil bath, whereupon decomposition took place with evolution of CO_2 gas. The pyrolysis product was extracted with $CHCl_3$ and the solvent was evaporated to give the residue which was recrystallized from benzene to provide 0.24 g. of XVII as colorless needles, m.p. 117~118°. XVII was identified by IR spectral comparison and by admixture with an authentic sample prepared according to the procedure of Hoggarth, ***et al.***[4]

Summary

s-Triazolo[1,5-*a*]pyridine ring was quite stable and showed properties similar to those of aromatic compounds. Nitration of 2-methyl-*s*-triazolo[1,5-*a*]pyridine (IV) with potassium nitrate and sulfuric acid gave two mononitro compounds (V) and (VI). Catalytic reduction of V and VI gave the corresponding amino derivatives (VII) and (VIII) which were further converted to the corresponding bromo derivatives (IX) and (X) by the Sandmeyer reaction. But this ring was quite unstable against oxidation and fission of the pyridine ring occurred to give *s*-triazole derivatives.

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75. Atsusuke Terada, Hiroo Itō, and Masatoshi Nagawa: Syntheses of 1-(*p*-Nitrophenyl)-3-(2,2-dichloroacetamido)-1,2-propanediols.[*1]

(*Central Research Laboratories, Sankyo Co., Ltd.*[*2])

Kollonitsch[1] obtained an isomer of 1-(*p*-nitrophenyl)-3-(2,2-dichloroacetamido)-1,2-propanediol (I), as a crystalline substance of m.p. 163~165°, but he has not revealed that the substance is either DL-*threo* or DL-*erythro* form in which I exists.

In the present paper we wish to report that the two isomers of I were obtained by a method different from the Kollonitsch procedure.

Rebstock[2] reported that 2-bromo-3-methoxypropiophenone (II) was reacted with potassium phthalimide to yield 2-phthalimido-3-methoxypropiophenone (III), from

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[*1] Reported at the 80th (1960) and 82th (1962) Annual Meeting of the Pharmaceutical Society of Japan.

[*2] Hiromachi, Shinagawa-ku, Tokyo (寺田敦祐, 伊藤博雄, 名川方敏).

1) J. Kollonitsch, A. Hajos, M. Kraut, V. Gabor: Acta Chim. Acad. Sci. Hung., **6**, 381 (1955).

2) M.C. Rebstock: J. Org. Chem., **19**, 851 (1955).