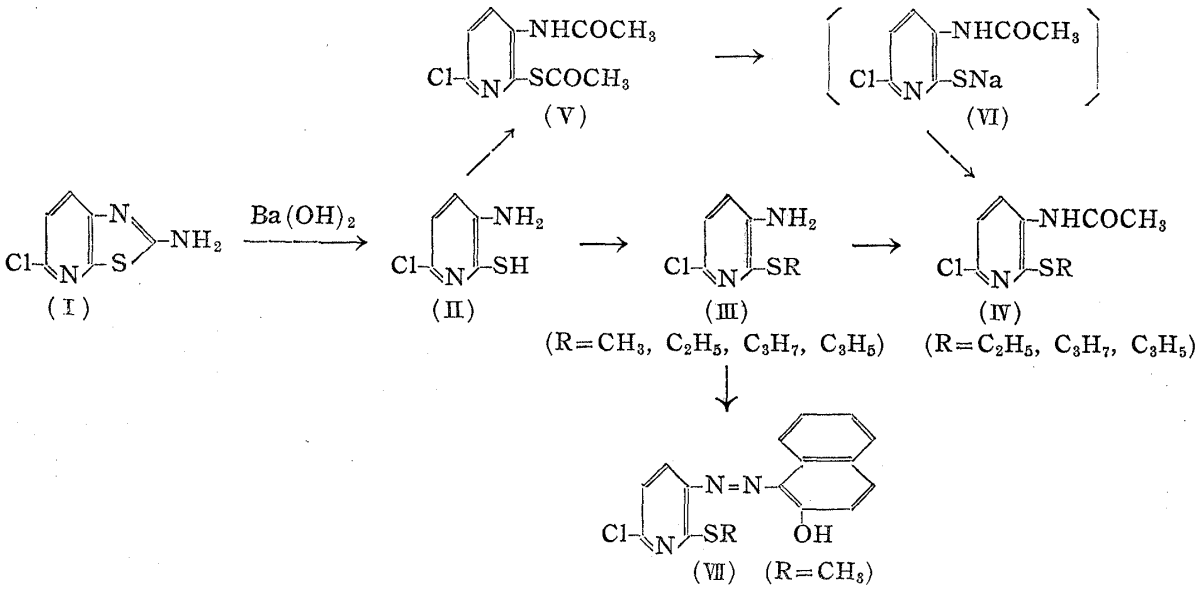
71. Torizo Takahashi and Yoshifumi Maki: Sulfur-containing Pyridine Derivatives. XLV.* Synthesis of 2-Mercapto-3-amino-6-chloropyridine Derivatives.

(*Pharmaceutical Institute, Medical Faculty, University of Kyoto***)

In an earlier paper of this series, we reported the synthesis of 6-chloropyrido[2,3: 2′,3′]-*p*-thiazine derivatives by the condensation of 2-mercapto-3-amino-6-chloropyridine (II) with *α*-halocarbonyl compounds, and some of their chemical properties, especially their behavior to acids and alkalis.

In addition to the foregoing paper, this communication describes the synthesis of the thioethers (alkyl, pyridyl) of (II) and their related compounds, in which the rearrangements of the pyridyl thioether is also included.



The preparation of (II)[1] can be carried out by the alkaline hydrolysis of 6-chloro-2′-aminopyrido[2,3 : 5′,4′]thiazole (I) with either barium hydroxide (product IIb) or sodium hydroxide (Product IIs). In the previous paper, however, it was pointed out that the application of the latter method (IIs) was found to be unfavorable from the stand-point of purity of (II) obtained, bringing about an undesirable side reaction to yield a product with higher melting point and of unknown constitution.

One of the authors (T) and his collaborator[2] demonstrated that the alkylation of (IIs) with alkyl halides furnished none of the expected thioethers but unknown, high-melting substances. However, by employment of (IIb), as reported in our previous paper, the synthesis of the thioethers of (II) and their derivatives was successfully carried out with good yields.

Although the structures of the above-mentioned, high-melting substances remains still to be determined, based on facts described below they are considered to be molecular compounds of impurities contained in (IIs) and the expected thioethers.

1) Their melting points are remarkably higher than those of the expected thioethers and vary according to the circumstances.

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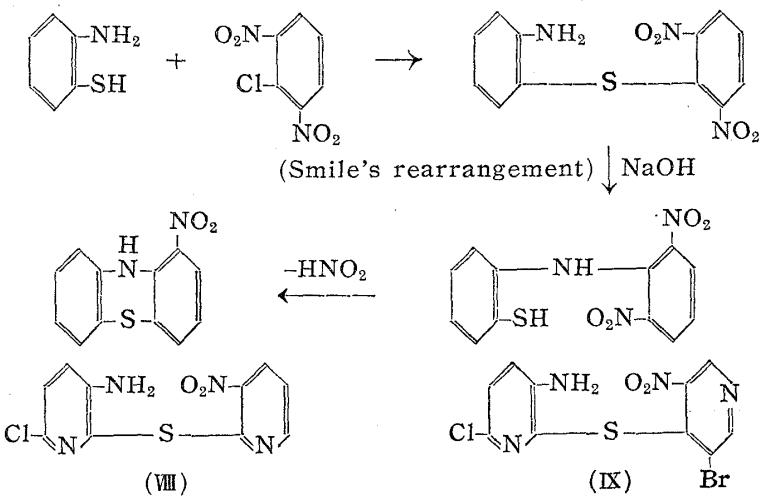
** Yoshida-Konoe-cho, Sakyo-ku, Kyoto (高橋酉蔵, 牧 敬文).
1) T. Takahashi, Y. Yamamoto: J. Pharm. Soc. Japan, **71**, 916(1951).
2) T. Takahashi, K. Ueda: *Ibid.*, **73**, 442(1953).

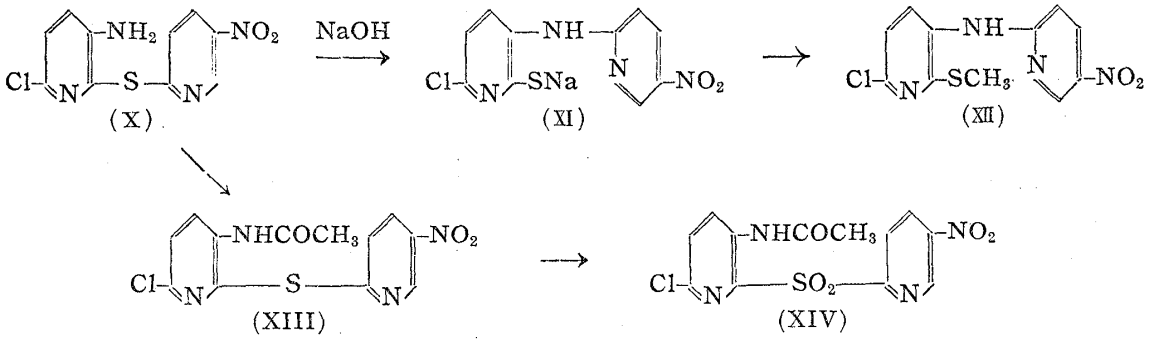
2) Their acetylation products[3] can be separated into the acetyl derivatives of the expected thioethers and other components by purification through chromatography.

As the alkyl thioethers, except the methyl thioether, could not be obtained in the crystalline state, they were confirmed by conversion to their acetyl derivatives (IV), which were also prepared by dissolving 2-acetylthio-3-acetylamino-6-chloropyridine (V) in methanolic potash solution, and by allowing the resulting 2-sodiothio-3-acetylamino-6-chloropyridine (VI) to react with alkyl halides.

As an example of the synthetic methods of phenothiazines, the following route with Smile's rearrangement[4] was previously reported by several workers.[5]



For the purpose of extending this reaction to the pyridine homologs, synthesis of azaphenothiazines was attempted by using 2-[3'-nitropyridyl-(2')]thio-3-amino-6-chloropyridine (VIII) and 2-[3'-nitro-5'-bromopyridyl-(4')]thio-3-amino-6-chloropyridine (IX) as starting materials, but neither the rearrangement products nor the expected azaphenothiazines could be isolated.



On the other hand, a phenomenon analogous to the Smile's rearrangement was recognized in 2-[5'-nitropyridyl-(2')]thio-3-amino-6-chloropyridine (X), which, differing from (VIII) and (IX), has no possibility of forming azaphenothiazine ring by elimination of nitrous acid.

The rearrangement from (X) to 2-sodiothio-3-[5'-nitropyridyl-(2')]amino-6-chloropyridine (XI) was brought about by heating (X) in caustic alkaline medium. The identity of the rearrangement product (XI) was established by the fact that it was soluble in water, showed a negative diazo reaction for primary arylamines, and could be con-

3) T. Takahashi, K. Ueda: Unpublished.
4) S. Smile: J. Chem. Soc., **1935**, 181, 340, 1263.
5) F. Kehrmann: Ber., **44**, 3011(1911); **46**, 2809(1913); R. Baltzly: J. Am. Chem. Soc., **68**, 2673 (1946); F. Ullman: Ann., **366**, 79(1909).

verted by the action of methyl iodide into 2-methylthio-5-[5′-nitropyridyl-(2′)]-amino-6-chloropyridine (XII). The reaction of (II) with 2-chloro-5-nitropyridine[6] in methanolic caustic alkali gave (X) at room temperature. However, when this reaction was conducted while heating in methanolic caustic alkali, another product was obtained, which, after methylation with methyl iodide, gave no m.p. depression on admixture with (XII) obtained above. Taking these facts into consideration, it may well be concluded that in the condensation of (II) with 2-chloro-5-nitropyridine in boiling alkaline solution, (X) formed in the first step of the reaction and underwent rearrangement to yield (XI) in the presence of alkali and heat.

This interesting rearrangement may also be expected in 2-[5′-nitropyridyl-(2′)]-thio-3-acetoamino-6-chloropyridine (XIII) and 2-[5′-nitropyridyl-(2′)]sulfone-3-acetamino-6-chloropyridine (XIV). Further results will be reported in the near future.

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Experimental[7]

2-Alkylthio-3-amino-6-chloropyridine (III)—To a solution of NaOH (1.2 moles) in a small amount of water were added (II) (1 mole), EtOH, and alkyl halide (1.2 moles), and the mixture was refluxed on a water bath for 30~50 mins. After removal of the solvent, the residue was taken up in ether, the ether extract was dried, and evaporated, leaving an oily product (III). Because of difficulty in crystallization, (III) was characterized by conversion into its acetyl derivative (IV). The methyl thioether formed colorless needles, m.p. 54°, from MeOH, undepressed on admixture with the compound previously obtained by Takahashi and Ueda by another method.

2-Alkylthio-3-acetamino-6-chloropyridine (IV)—1) A mixture of (III) with several volumes of Ac_2O was refluxed for 5~10 mins. After the solvent was distilled off, the residue was recrystallized from MeOH to give (IV).

2) To a clear solution of (V) (1 mole) dissolved in MeOH containing NaOH (1.2 moles) an alkyl halide (1 mole) was added and the mixture was kept standing for 2 hrs. After the solvent was evaporated to dryness in vacuum, the residue was washed with water and recrystallized from MeOH yielding the substance which was found to be identical by the mixed melting point determination with (IV) obtained above.

R	m.p.(°C)	Appearance	Formula	N%	
				Calcd.	Found
Ethyl	134	Colorless needles	$C_9H_{11}ON_2ClS$	12.14	12.15
Propyl	113	〃	$C_{10}H_{13}ON_2ClS$	11.41	11.56
Allyl	104	〃	$C_{10}H_{11}ON_2ClS$	11.50	11.64

2-Methylthio-6-chloropyridine[3-azo-1]-2-naphthol (VII)—A solution of 0.3 g. of $NaNO_2$ in 10 cc. of water was gradually added to a suspension of 2-methylthio-3-amino-6-chloropyridine in 10 cc. of 35% HCl, keeping the temperature between 0° and 5°. An excess of $NaNO_2$ was decomposed by urea and a solution of 0.4 g. of β-naphthol dissolved in 10 cc. of 20% NaOH was added with stirring to the reaction mixture. The color of the solution changed to dark red, and when the solution was allowed to stand at room temperature, crystals separated out. The dark red crystals thereby obtained were collected, washed with water, and after treating with charcoal, recrystallized from EtOAc to blood red needles, m.p. 189°(decomp.). Yield, 0.3 g. *Anal.* Calcd. for $C_{16}H_{12}ON_3ClS$: C, 58.27; H, 3.64. Found: C, 58.43; H, 3.98.

2-[3′-Nitropyridyl-(2′)]thio-3-amino-6-chloropyridine (VIII)—A mixture of (II) (0.3 g.) and 2-chloro-3-nitropyridine[8] (0.3 g.) in EtOH (10 cc.) was refluxed on a water bath for about 10 mins. The red solution obtained was cooled to precipitate dark red crystals, which were recrystallized from EtOAc to red needles, m.p. 205°(decomp.). Yield, 0.4 g. *Anal.* Calcd. for $C_{10}H_7O_2N_4ClS$: C, 42.47; H, 2.47. Found: C, 42.50; H, 2.63.

2-[3′-Nitro-5′-bromopyridyl-(4′)]thio-3-amino-6-chloropyridine (IX)—To a suspension of (II) (0.35 g.) in anhyd. MeOH (10 cc.) was added dropwise an anhyd. MeOH solution of 3-nitro-

6) M. A. Phillips: J. Chem. Soc., **1941**, 9.
7) All melting points are uncorrected.
8) T. Takahashi, H. Saikachi: J. Pharm. Soc. Japan, **64**, 202(1944).

4-chloro-5-bromopyridine[9] (0.55 g.), with stirring at room temperature. The reaction proceeded with distinct color change from yellow to red. The red solution deposited prisms, which were recrystallized from EtOAc, giving light brown prisms, m.p. 187~188° (decomp.). Yield, 0.1 g. *Anal.* Calcd. for $C_{10}H_6O_2N_2N_4BrClS$: N, 15.48. Found: N, 15.78. Both (Ⅷ) and (Ⅸ) easily dissolved in 35% HCl to present a positive diazo reaction of primary amines, and when treated with NaOH in the usual manner, gave a black resinous mass when heated on a water bath.

2-[5'-Nitropyridyl-(2')]thio-3-amino-6-chloropyridine (Ⅹ)—0.3 g. of (Ⅱ) was dissolved in 10 cc. of MeOH containing 0.2 g. of KOH and 0.3 g. of 2-chloro-5-nitropyridine in a few cc. of MeOH were added. The mixture was allowed to stand at room temperature with occasional shaking, whereby a yellow solid separated out. The product was recrystallized from EtOH to yellow needles, m.p. 195°. Yield, 0.45 g. *Anal.* Calcd. for $C_{10}H_7O_2N_4ClS$: C, 42.47; H, 2.47. Found: C, 42.13; H, 2.40.

Acetate (XIII): (Ⅹ) was refluxed with Ac_2O for 30 mins., and after evaporation of the reaction mixture in vacuum to dryness, the residue was recrystallized from EtOH to colorless needles, m.p. 170°. *Anal.* Calcd. for $C_{12}H_9O_3N_4ClS$: C, 44.45; H, 2.78. Found: C, 44.70; H, 3.16.

Rearrangement of (Ⅹ)—A mixture of (Ⅹ) (0.4 g.) and methanolic KOH (KOH 0.2 g., water 2 cc., MeOH 10 cc.) was refluxed on a water bath until a red solution formed. Partial removal of the solvent separated needles (Ⅺ), which were water soluble and showed a negative diazo reaction for primary amines. Subsequently, to the solution containing (Ⅺ) was added MeI and refluxing was continued for several mins. The residue left by evaporation of the solvent was washed with water and recrystallized from MeOH to light yellow needles (Ⅻ), m.p. 183~184°. *Anal.* Calcd. for $C_{11}H_9O_2N_4ClS$: C, 44.51; H, 3.04. Found: C, 44.70; H, 3.35. (Ⅻ) was also obtained by refluxing a mixture of 2-chloro-5-nitropyridine (0.3 g.), (Ⅱ) (0.3 g.) dissolved in methanolic KOH (KOH 0.2 g., MeOH 10 cc.), and MeI (0.2 g.).

2-[5'-Nitropyridyl-(2')]sulfone-3-acetamino-6-chloropyridine (XIV)—To a solution of (XIII) (0.35 g.) in glacial HOAc (10 cc.) was added dropwise an aqueous solution of $KMnO_4$ (0.25 g.), with stirring, at a room temperature. After continued stirring for 2 hrs. 30% H_2O_2 was added slowly to the reaction mixture to dissolve MnO_2 in the resulting precipitate. The crystals were collected, washed with water, dried, and recrystallized from EtOH to colorless needles, m.p. 178°. *Anal.* Calcd. for $C_{12}H_9O_5N_4ClS$: C, 40.39; H, 2.53. Found: C, 40.37; H, 2.68.

Summary

1) 2-Mercapto-3-amino-6-chloropyridine obtained by barium hydroxide hydrolysis of 6-chloro-2'-aminopyrido[2,3 : 5',4']thiazole afforded its thioethers (aikyl, pyridyl) and their derivatives in good yield.

2) A phenomenon analogous to the Smile's rearrangement was recognized in 2-[5'-nitropyridyl-(2')]thio-3-amino-6-chloropyridine.

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9) O. Bremes: Ann., **529**, 290 (1937).