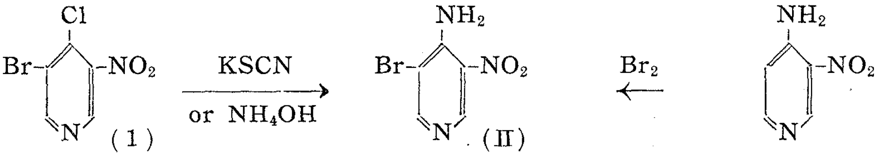
U.D.C. 547.822.5:547.789.61

6. **Torizo Takahashi and Osamu Yamashita** : Sulfur-containing Pyridine Derivatives. XLVI.* Synthesis of 7-Bromopyrido[3,4-*d*]thiazoles.

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

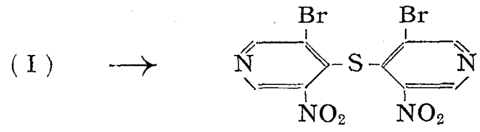
In the earlier papers of this series,[1,2] Takahashi and Ueda reported the synthesis of pyrido[3,4-*d*]thiazoles from 3-nitro-4-chloropyridine. The present paper is concerned with the synthesis of 7-bromopyrido[3,4-*d*]thiazoles from 3-nitro-4-chloro-5-bromopyridine[3] (I) and with some differerence in reactivity between these reagents at their respective stages.

It has been shown that 3-nitro-4-chloropyridine, when allowed to react with potassium thiocyanate in glacial acetic acid at room temperature, produced 3-nitro-4-thiocyanopyridine. On the other hand, however, the action of potassium thiocyanate upon (I) under the same conditions did not give rise to the expected thiocyano compound, but instead 3-nitro-4-amino-5-bromopyridine (II) in a good yield. (II) was also not obtained by treating (I) with potassium thiocyanate in benzene or dioxane even at its boiling temperature. This may be accounted for by the assumption that in a polar solvent, such as glacial acetic acid, the thiocyano compound once formed underwent isomerization to the corresponding isocyanate, and the latter combined with the solvent to yield the urethane type, which in turn was hydrolyzed to the amino compound. Moreover, (II) was obtained not only by the condensation of (I) with conc. ammonium hydroxide in a sealed tube at 100° but also by the bromination[4] of 3-nitro-4-aminopyridine.



Treatment of (I) with thiourea in dehydrated methanol at room temperature did not afford the thiuronium compound but 3,3′-dinitro-5,5′-dibromo-4,4′-dipyridyl monosulfide (III), which was also obtained by the condensation of (I) with the potassium salt of (IV), as well as that of (I) with potassium hydrosulfide in hot methanol. On the other hand, however, when a methanolic solution of (I) was added to a stirring methanolic solution of potassium hydrosulfide at such a rate that the temperature did not rise, 3-nitro-4-mercapto-5-bromopyridine (IV) soluble in alkalis was obtained in a good yield. The rise of temperature resulted in the increasing formation of (III).

On reduction with stannous chloride and hydrochloric acid at room temperature, (IV) yielded 3-amino-4-mercapto-5-bromopyridine (V) in about 50% yield, and in this case, the more rapidly (IV) was added to the acidic stannous chloride solution, the more violently the reaction proceeded, and the formation of a brown resinous mass increased.



(III)

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* Part XLV : This Bulletin, **5**, 361(1955).

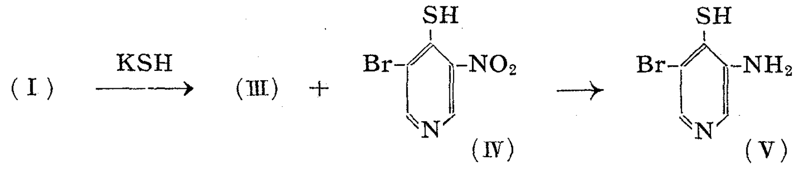
** Yoshida-konoe-cho, Sakyo-ku, Kyoto (高橋酉蔵, 山下 脩).

[1] T. Takahashi, K. Ueda : This Bulletin, **2**, 34(1954).

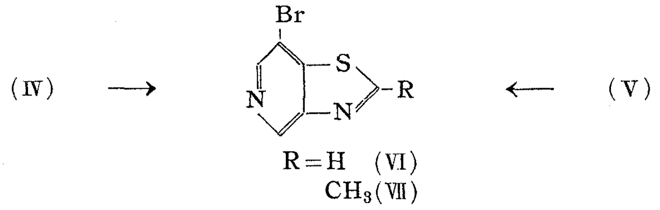
[2] T. Takahashi, K. Ueda : *Ibid.*, **2**, 196(1954).

[3] O. Bremer : Ann., **529**, 290(1937).

[4] O. Bremer : *Ibid.*, **518**, 274(1935).

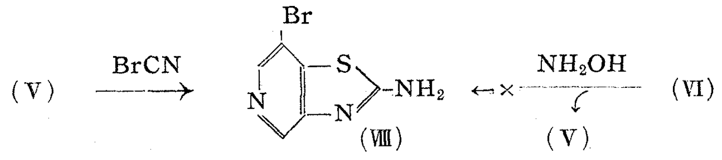


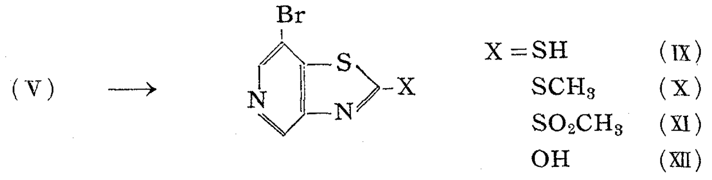
(IV) was reduced and cyclized by means of iron powder and formic acid to give 7-bromopyrido[3,4-*d*]thiazole (VI), and similarly 2-methyl-7-bromopyrido[3,4-*d*]thiazole (VII) was prepared. However, these yields were poor, and the products obtained showed no sharp melting points in spite of repeated recrystallization. On the other hand, when treated with formic acid in the presence of zinc dust, (V) afforded (VI), and similarly with acetic anhydride, (VII) in pure state and higher yields than in the former case.



Skraup5) reported the synthesis of 2-aminobenzothiazole by the reaction of benzothiazole with hydroxylamine in alkaline solution. However, when (VI) was allowed to react with hydroxylamine under the same conditions as employed by Skraup, the expected amino compound was not obtained at all, but (V) was formed instead, by the cleavage of its thiazole ring by alkali. The synthesis of 2-amino-7-bromopyrido[3,4-*d*]thiazole (VIII) was successfully achieved by the condensation of (V) with cyanogen bromide in an aqueous solution at room temperature.

Condensation of (V) with potassium methylxanthate afforded 2-mercaptopyrido[3,4-*d*]thiazole (IX) in a very good yield, which gave the methyl thioether (X) by treatment with methyl iodide. Subsequent oxidation with potassium permanganate led to methyl 7-bromopyrido[3,4-*d*]thiazolyl-2 sulfone (XI). The fusion of (V) with urea afforded 2-hydroxy-7-bromopyrdio[3,4-*d*]thiazole (XII), though in a poor yield.





On being treated with *p*-nitrobenzoyl chloride in pyridine, (V) yielded a product forming yellow crystals, m.p. 267°. It was insoluble in alkali though it showed a negative diazo reaction because of the ring closure being brought about in the hydrochloric acid medium, and therefore the above product was assumed to have the structure of the thioether (XIII). This supposition may be justified by the fact that on cyclization with hydrochloric acid, (XIII) gave (XIV), which was then reduced with stannous chloride to *p*-amino derivative (XV), obtainable also by direct reduction of (XIII).

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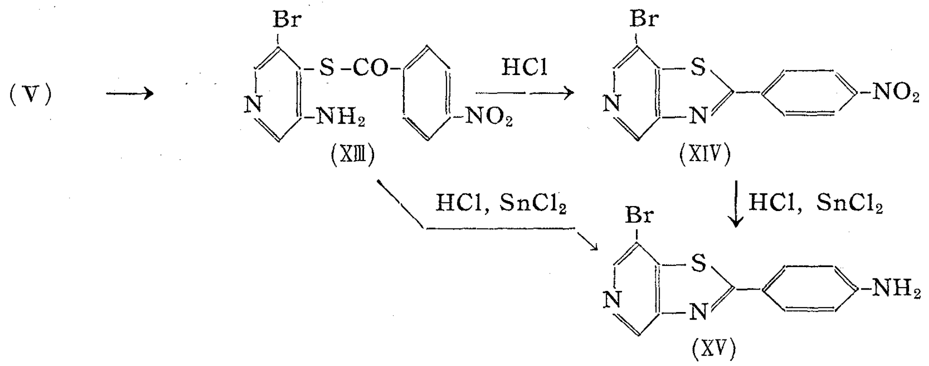
5) S. Skraup : Ann., **419**, 1(1919).

When (XIV) was recrystallized from benzene, it separated at first as yellow needles, which gradually changed into yellow granules in benzene solution. On reduction with stannous chloride and hydrochloric acid, (XIV) furnished the amino compound, which was also obtainable from (XIII) by an analogous mode of reduction.



The preparation of 3-nitro-4-alkylthiopyridine was readily accomplished in a fairly high yield by the alkylation with alkyl halides, whose oxidation furnished alkyl-3-nitropyridyl-4 sulfones. However, the alkylation of the mercapto groups of (IV) and (V) did not afford the corresponding alkyl thioethers, only resulting in the formation of a resinous mass. (III) did not undergo oxidation with potssium permanganate.

This work was supported by a Grant in Aid of Scientific Research from the Ministry of Education, to which the authors are greatly indebted.

Experimental

3-Nitro-4-amino-5-bromopyridine (II)—a) To a solution of 3-nitro-4-chloro-5-bromopyridine (I) (1.5 g.) in glacial AcOH (20 cc.), KSCN (1.5 g.) was added and the mixture was allowed to stand at room temperature over night. The color of the solution changed from pale yellow to orange. On being poured into water, the solution became muddy and yellow resin gradually formed. On neutralization with aq. Na_2CO_3, a yellow solid instantly deposited out, which was filtered with suction, washed with water, dried, and recrystallized from benzene to yellow needles, m.p. 179~180°. Yield, 1.35 g. *Anal.* Calcd. for $C_5H_4O_2N_3Br$: C, 27.55; H, 1.85; N, 19.28. Found : C, 27.83; H, 1.90; N, 18.98.

b) (I) (0.9 g.) in conc. NH_4OH (10 cc.) was heated in a sealed tube in a boiling water bath for 7 hrs. The yellow crude (I) began gradually to form yellow needles while heating. After cooling, the yellow needles were collected by filtration, washed with water, dried, and recrystallized from benzene. Yield, 0.64 g.

3,3-Dinitro-5,5-dibromo-4,4-dipyridyl Monosulfide (III)—a) To a solution of (I) (1.0 g.) in abs. MeOH was added thiourea (0.8 g.). The solution, after being stirred, was set aside at room temperature, whereupon yellow needles separated out, which were collected (0.6 g.). Upon concentration of the mother liquor *in vacuo* to one-third of the original volume, additional amount (0.12 g.) of (III) was obtained. Recrystallization from abs. MeOH afforded yellow needles, m.p. 185°. Yield, 0.72 g. *Anal.* Calcd. for $C_{10}H_4O_4N_4Br_2S$: C, 27.39; H, 0.93; N, 12.82. Found : C, 27.35; H, 1.13; N, 12.85.

b) To a solution of KOH (1.2 moles) in a small amount of water, (IV) (1.0 g.), MeOH, and (I) (1.2 moles) were added and the solution was refluxed for 1 hr. The color of the solution changed gradually from dark red to reddish yellow. The solvent was removed *in vacuo*, and water was added to the residue, whereupon yellow precipitate (III) formed. Yield, 0.31 g.

3-Nitro-4-mercapto-5-bromopyridine (IV)—To a stirred solution of KSH (6.0 g.) in MeOH (50 cc.), a solution of (I) (9.0 g.) in MeOH was added dropwise at room temperature during 4 hrs. The resultant blood red solution deposited white inorganic precipitate, which was filtered off, and the filtrate was evaporated *in vacuo* to dryness, leaving a red solid (6.3 g.). After addition of aq. NaOH (20 %) to the solid, insoluble yellow crystals (III) were removed (1.2 g.). The filtrate was neutralized with conc. HCl, blood red crystals that separated out were washed and dried. The solid could not be purified owing to autoxidation during recrystallization. m.p. 130~135°. Yield, 5.1 g.

3-Amino-4-mercapto-5-bromopyridine (V)—To a stirred solution of an excess of $SnCl_2$ in conc. HCl, (IV) was added at such a rate that the temperature did not rise. After a continued stirring for 3 hrs., the reactant was evaporated to dryness, a large amount of water was added to the residue, H_2S was bubbled through the solution, and black precipitate was removed. After evaporation of the filtrate *in vacuo*, the residue was dissolved in conc. NH_4OH and the solution was concentrated to one-fifth the original volume. The precipitate which separated was collected, washed, and recrystallized from a mixture of H_2O and MeOH to yellow prisms, m.p. 215°. Yield, 48%. *Anal.* Calcd. for $C_5H_5N_2BrS$: N, 13.66. Found : N, 13.92.

7-Bromopyrido[3,4-*d*]thiazole (VI)—To a solution of (V) (0.5 g.) in 80% HCO_2H(7 cc.), zinc dust (0.1 g.) was added in small portions. The reaction proceeded with the rise of temperature, and the reactant was refluxed in an oil bath for 30 mins. The solution was then concentrated to one-third the original volume and diluted with 50 cc. water. After neutralization with Na_2CO_3, the solution was extracted with ether and the extract was dried over anhyd. Na_2SO_4. Removal of the solvent left a white solid which was recrystallized from MeOH to white needles, m.p. 163~165°. Yield, 0.33 g. *Anal.* Calcd. for $C_6H_3N_2BrS$: C, 33.46; H, 1.41; N, 13.03. Found: C, 33.76; H, 1.65; N, 13.33.

2-Methyl-7-bromopyrido[3,4-*d*]thiazole (VII)—On treating (V) (1.0 g.) with Ac_2O(7 cc.), the reaction proceeded exothermally and yellow crystals separated out. After cooling, zinc dust (0.1 g.) was added in small portions to the content, and the mixture refluxed for 6 hrs.. After addition of water (15 cc.), the mixture was refluxed for a further 15 mins., after which it was evaporated to dryness *in vacuo*. The residue was extracted with ether and the extract was dried over anhyd. Na_2SO_4. Removal of the solvent furnished crude (VII), which was recrystallized from a mixture of petr. ether and ether, yielding colorless needles, m.p. 76~78°. Yield, 0.41 g. *Anal.* Calcd. for $C_7H_5N_2BrS$: N, 12.23. Found : N, 12.27.

2-Amino-7-bromopyrido[3,4-*d*]thiazole (VIII)—(V) (0.5 g.) was added in small portions to a solution of BrCN(0.28 g.) in H_2O(150 cc.) with stirring. After continued stirring for 3 hrs., the content was refluxed for 10 mins. and filtered with charcoal. Neutrallization of the filtrate with 50% aq. NaOH deposited white precipitate, which was collected, washed with H_2O, and recrystallized from MeOH to colorless crystals, m.p. 312°(decomp.). Yield, 0.31 g. *Anal.* Calcd. for $C_6H_4N_3BrS$: C, 31.35; H, 1.75. Found : C, 31.27; H, 2.00.

2-Mercapto-7-bromopyrido[3,4-*d*]thiazole (IX)—To a solution of KOH(1.2 moles) in several drops of water were added MeOH(1.0 cc.), CS_2(0.32 g.), and (V) (0.6 g.). The mixture was refluxed on a water bath for 15 hrs., cooled, and neutralized with AcOH(50%). A white solid precipitate was collected, washed, and dried. This substance could not be recrystallized due to its insolubility in solvents, but was assumed to be (IX) from the fact that it was converted to (X) by treatment with MeI and alkali. Yield, 0.65 g. m.p. 227°(decomp.).

2-Methylthio-7-bromopyrido[3,4-*d*]thiazole [X]—MeOH(1.0 cc.) and (IX) (0.65 g.) were added to a solution of KOH(1.1 moles) in a small amount of water. After treating with MeI (1.2 moles) and shaking, the reaction mixture was allowed to stand for 5 hrs. at room temperature. The depositing crystals were collected and recrystallized from MeOH to colorless needles, m.p. 147~149°. Yield, 0.58 g. *Anal.* Calcd. for $C_7H_5N_2BrS_2$: C, 32.19; H, 1.93. Found : C, 32.41; H, 1.97.

Methyl 7-Bromopyrido[3,4-*d*]thiazolyl-2′ Sulfone (XI)—To a stirred solution of (X) (0.41 g.) in AcOH(20 cc.) an aq. solution of $KMnO_4$ was added dropwise at room temperature. After stirring for 8 hrs., the solution was treated with aq. 30% H_2O_2 to dissolve MnO_2 and concentrated. Addition of water to the solution gave crude white (XI), which was recrystallized from MeOH to colorless pillars, m.p. 167~168°. Yield, 0.33 g. *Anal.* Calcd. for $C_7H_5O_2N_2BrS_2$: N, 9.56. Found : N, 9.84.

2-Hydroxy-7-bromopyrido[3,4-*d*]thiazole (XII)—A mixture of (V) (0.5 g.) and urea (0.5 g.) was heated in a test tube in an oil bath at 160°. The content changed into a brown liquid with evolution of NH_3. Heating was continued until the evolution of the gas ceased, after which the reactant was dissolved in 5% aq. NaOH(180 cc.) on a water bath and filtered with charcoal. The neutralization of the filtrate with 50% AcOH afforded crude (XII), which was collected, washed, and dried. Recrystallization from MeOH yielded colorless prisms, m.p. 264~265°. Yield, 0.12 g. *Anal.* Calcd. for $C_6H_3ON_2BrS$: C, 31.18; H, 1.13 Found : C, 31.47; H, 1.50.

***p*-Nitrobenzoyl 3-Amino-5-bromopyridyl-4 Thioether (XIII)**—(V) (0.45 g.) was dissolved in pyridine (8 cc.) and treated with *p*-nitrobenzoyl chloride (0.45 g). The color of the solution turned from yellow to orange, and a yellow solid separated out with rising of temperature. The reaction mixture was heated on a water bath for 10 mins. to form a red liquid, from which a solid deposited again on cooling. The solid was collected and recrystallized from pyridine to yellow granules, m.p. 267°(decomp.). Yield, 0.65 g. *Anal.* Calcd. for $C_{12}H_8O_3BrS$: N, 11.86. Found: N, 11.63.

2-(*p*-Nitrophenyl)-7-bromopyrido[3,4-*d*]thiazole (XIV)—(XIII) (0.7 g.) was heated with conc. HCl on a water bath for 1 hr. The yellow crystals changed into a white solid, which was collected after cooling and washed with water. After being dried and recrystallized from benzene, it formed pale yellow needles, m.p. 229°. Yield, 0.58 g. *Anal.* Calcd. for $C_{12}H_6O_2N_3BrS$:

C, 42.87; H, 1.80; N, 12.50. Found : C, 43.05; H, 2.08; N, 12.32.

2-(*p*-Aminophenyl)-7-bromopyrido[3,4-*d*]thiazole (XV) — To a solution of an excess $SnCl_2$ in conc. HCl solution was added (XIV) (0.5 g.) and the mixture was heated on a water bath for 2 hrs. The reaction mixture was evaporated to dryness and the residue was extracted with acetone. After evaporation of the extract, the residue was recrystallized from benzene to pale yellow crystals, m.p. 222~223°. Yield, 0.23 g. *Anal.* Calcd, for $C_{12}H_8N_3BrS$: C, 47.07; H, 2.63; N, 13.73. Found : C, 47.28; H, 2.89; N, 13.72.

Summary

1) 3-Nitro-4-chloro-5-bromopyridine (I) reacted with KSCN in glacial acetic acid to give 3-nitro-4-amino-5-bromopyridine, and 3-nitro-4-mercapto-5-bromopyridine was obtained by the reacion of (I) and KSH in methanol.

2) 7-Bromopyrido[3, 4-*d*]thiazole derivatives were synthesized from 3-nitro-4-mercapto-5-bromopyridine through reduction followed by cyclization.

(Received November 2, 1955)

U.D.C. 547.972.2 :

7. **Yasuo Kishimoto** : Phamaceutical Studies on Ferns. XI.* Flavonoids of Cyrtomium Species. (3). Constitution of Cyrtominetin and Cyrtopterinetin.

(*Shizuoka College of Pharmacy***)

It was shown in the previous paper of this series,[1] that two new kinds of flavanone, cyrtominetin (I) and cyrtopterinetin (II) had been isolated besides kaempferol and quercetin as flavonoid aglycones in *Cyrtomium falcatum* Presl, *C. Fortunei* J. Sm., and *C. Fortunei* J. Sm. var. *clivicola* Tagawa. Analysis agreed with the formula $C_{17}H_{16}O_6$ for (I) and $C_{17}H_{16}O_5$ for (II) and gave tetra- and triacetate, respectively. Each has optical activity and no methoxyl group.

Methylation of (I) with diazomethane gave trimethyl ether which shows a green coloration with ferric chloride, and it is presumed that one phenolic hydroxyl group is still left in the 5-position. On gentle alkali fusion of (I), 2,4-dimethylphloroglu-

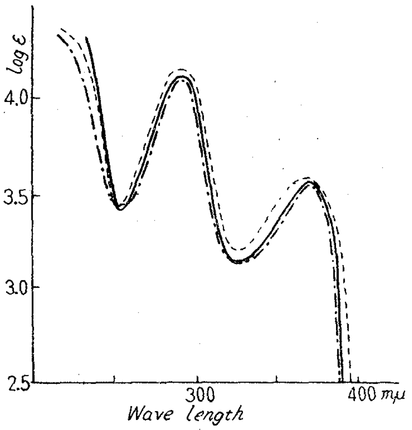


Fig. 1.

Ultraviolet Absorption Spectra ($^1/_{10000}$ *M.* EtOH solution)

·· ····· Cyrtominetin trimethyl ether

—·—·— Cyrtopterinetin dimethyl ether

——— Matteucinol monomethyl ether

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* This work constitutes a part of a series entitled "Pharmaceutcal Studies on Ferns" by Toshikazu Harada. Part X : J. Pharm. Soc. Japan, **76**, in press (1956).

** Oshika, Shizuoka (岸本安生).

[1] Part IX. Y. Kishimoto : *Ibid.* **76**, in press (1956).