removal of the solvent, H_2O was added, decolorized with charcoal, filtered, and the filtrate was acidified with AcOH. The separated yellow crystals were collected, and recrystallized from EtOH. The results of these experiments are shown in Table I.

2-Ethylthio-5-aminothiazolo[5,4-*d*]pyrimidine (XXX)—0.24 g. of the K salt of (XXVIII) was dissolved in 15 cc. of 70% EtOH, 0.15 g. of EtBr was added, and the reaction mixture was heated for 20 mins. Removal of the solvent (without filtering) left white needles upon addition of H_2O. These were recrystallized from EtOH to white needles, m.p. 168°. Yield, 0.22 g. *Anal.* Calcd. for $C_7H_8N_4S_2$: C, 39.62; H, 3.80. Found : C, 39.69; H, 3.51.

2-Benzylthio-5-anilinothiazolo[5,4-*d*]pyrimidine (XXXI)—To a solution of 0.31 g. of the K salt of (XXIX) in 20 cc. of 70% EtOH, 0.12 g. of benzyl chloride was added, and the reaction mixture was heated for 20 mins. After the solvent was removed by distillation, the product obtained was recrystallized from EtOH to white needles, m.p. 154°. Yield, 0.32 g. *Anal.* Calcd. for $C_{18}H_{14}N_4S_2$: C, 61.71; H, 4.03. Found : C, 61.68; H, 4.27.

Summary

1) The reaction of 2-chloro-4-thiocyano-5-nitropyrimidine (I) with aq. NH_4OH, $EtNH_2$, thiourea, or sodium phenoxide gave 2,4-disubstituted derivatives. The reaction of (I) with ethanolic NH_4OH and aniline respectively gave 2-amino-4-thiocyano-5-nitropyrimidine (V) and 2-anilino-4-thiocyano-5-nitropyrimidine (IX), and the reaction of (V) or (IX) with sodium alkoxide gave 2-amino-4-mercapto- (XIV) and 2-anilino-4-mercapto-5-nitropyrimidine (XV).

2) The reduction of (V) and (IX) afforded the corresponding 2-aminothiazolo[5,4-*d*]-pyrimidines, and the reduction of (XIV) and (XV) gave 2,5-diamino-4-mercapto- (XVII) and 2-anilino-4-mercapto-5-aminopyrimidine (XVIII), respectively. The cyclization of (XVII) and (XVIII) with formic acid, acetic anhydride, benzoyl chloride, or potassium methylxanthate, gave the corresponding 2-substituted(H, CH_3, C_6H_5, SH) thiazolo[5,4-*d*]-pyrimidines.

3) In the presence of alkali, 2-aminothiazolo[5,4-*d*]pyrimidines were hydrolysed to the 4-mercapto-5-aminopyrimidine derivatives via the (4-mercapto-5-pyrimidyl)ureas.

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60. Shoji Inoue : Studies on Pyrimidine Derivatives. III.[1] Synthesis of Thiazolo[5,4-*d*]pyrimidines and Related Compounds. (3).

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This paper deals especially with the synthesis of 2-chloro-4-thiocyano-5-aminopyrimidine and 2-chloro-4-mercapto-5-aminopyrimidine, and their reactivities.

As described in the previous report,[1] the reduction of 2-ethylthio-, 2-amino-, and 2-anilino-4-thiocyano-5-nitropyrimidine with iron powder and acetic acid gave 2-amino-5-ethylthio-, 2,5-diamino-, and 2-amino-5-anilino-thiazolo[5,4-*d*]pyrimidines through the corresponding 5-amino derivatives.

On the other hand, the compound which was obtained by the reduction of (I) was only sparingly soluble in alkali solution and retained the chemical activity of thiocyano group. Accordingly, this compound was assumed to be 2-chloro-4-thiocyano-5-aminopyrimidine (II). From this compound (II), 2,4-diethoxy-5-aminopyrimidine (III) was produced on heating with sodium ethoxide. In this reaction, if the reduced compound

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1) Part II : This Bulletin, **6**, 338(1958).

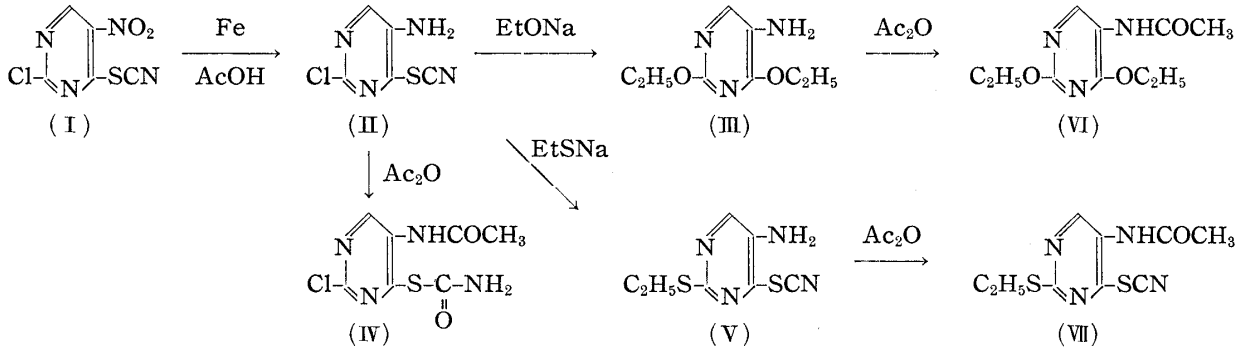

Chart 1.

(II) was 2-amino-5-chlorothiazolo[5,4-*d*]pyrimidine, the resulting product would have been 2-amino-5-ethoxythiazolo[5,4-*d*]pyrimidine, and if the cleavage of the thiazole ring had taken place, the resulting product would have been 2-ethoxy-4-mercapto-5-aminopyrimidine. Furthermore, the acetate of (II) (Chart 1) prepared by conventional methods analysed for 2-chloro-5-acetamidopyrimidine-4-thiocarbamide (IV) in which the thiocyano group had been converted into a thiocarbamate group. Heating of (II) with sodium ethanethioxide for 20 hours gave 2-ethylthio-4-thiocyano-5-aminopyrimidine (V) which is isomeric with 2-amino-5-ethylthio-thiazolo[5,4-*d*]pyrimidine reported in Part I[2] of this series. Upon acetylation of (V) with acetic anhydride, contrary to the behavior of (II), (V) retained its thiocyano group and merely formed its acetate (VII).

Since it was disclosed that the reduction of (II) which contains a 2-chloro group did not result in cyclization to a thiazole ring, and its thiocyano group was affected by the action of sodium ethoxide or acetic anhydride, the synthesis of 2-chloro-4-mercapto-5-aminopyrimidine (IX) was undertaken in order to see whether the action of acetic anhydride would cause cyclization to a thiazole ring. The routes of the synthesis are shown in Chart 2.

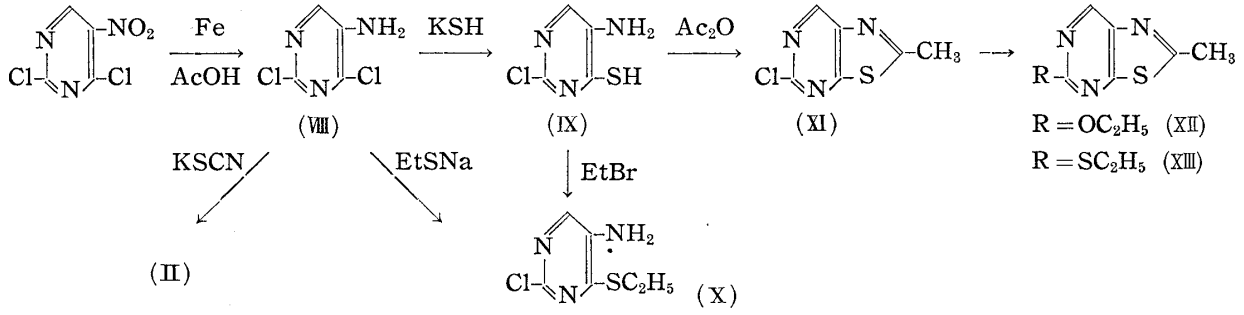

Chart 2.

Though 2,4-dichloro-5-aminopyrimidine (VIII) has already been synthesized from the corresponding 5-nitro derivative with barium hydroxide and ferrous sulfate,[3] the method is complicated in operation; (VIII) was, instead, obtained by the reduction with iron powder and acetic acid in a good yield, the halogen atoms being left intact. (II) was obtained by heating (VIII) with 1 mole of potassium thiocyanate in acetic acid, and 2-chloro-4-mercapto-5-aminopyrimidine (IX) was produced by the reaction of (VIII) with the calculated amount of potassium hydrogen sulfide. Furthermore, the reaction of (VIII) with 1 mole of sodium ethanethioxide gave 2-chloro-4-ethylthio-5-aminopyrimidine (X), which was identical with the compound prepared from the sodium salt of (IX) and ethyl bromide. The heating of (IX) in acetic anhydride resulted in ring closure to afford 2-methyl-5-chlorothiazolo[5,4-*d*]pyrimidine (XI); the yield was, however, rather low. The reaction of (XI)

2) Part I: *Ibid.*, **6**, 334(1958).
3) N. Whittaker: J. Chem. Soc., **1951**, 1565.

with sodium ethoxide or sodium ethanethioxide gave 2-methyl-5-ethoxythiazolo[5,4-*d*]-pyrimidine (XII) and 2-methyl-5-ethylthio-thiazolo[5,4-*d*]pyrimidine (XIII), respectively.

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Experimental

(All melting points are uncorrected)

2-Chloro-4-thiocyano-5-aminopyrimidine (II)—Two grams of (I) was dissolved in 50 cc. of AcOH, and to this solution, 1.5 g. of Fe powder was added. The reaction mixture was heated at 60° for 2 hrs. with stirring. After filtration, the solvent was evaporated to dryness *in vacuo*, the residue was treated with 50 cc. of H_2O, the insoluble portion was collected, washed with H_2O, and recrystallized from EtOH to white needles. Yield, 1.5 g. This substance did not melt below 300°. *Anal.* Calcd. for $C_5H_3N_4SCl$: C, 32.18; H, 1.62. Found: C, 32.45; H, 1.83.

2,4-Diethoxy-5-aminopyrimidine (III) (Reaction of (II) with Sodium Ethoxide)—0.05 g. of Na was dissolved in 30 cc. of EtOH, and 0.18 g. of (II) was added to this solution. The reaction mixture was refluxed for 15 hrs. After cool, the insoluble substance was filtered off, the filtrate was evaporated to dryness, a small amount of H_2O was added to the residue, and the product was extracted with ether. Removal of the dried solvent left an oily product which soon solidified. This was recrystallized from petr. ether to colorless prisms, m.p. 64°, which showed no depression on admixture with the same product described in Part I.[2] Yield, 0.03 g.

Acetyl derivative (VI): White needles (from H_2O), m.p. 136°. *Anal.* Calcd. for $C_{10}H_{15}O_3N_3$: C, 53.32; H, 6.71. Found: C, 53.36; H, 6.55.

2-Ethylthio-4-thiocyano-5-aminopyrimidine (V) (Reaction of (II) with Sodium Ethanethioxide)—A solution of EtSNa was prepared by adding 0.08 g. of EtSH to 0.03 g. of Na in 30 cc. of dehyd. EtOH, and 0.15 g. of (II) was added to this solution. After refluxing for 20 hrs., the solvent was removed by distillation and the crystals obtained were recrystallized from EtOH to white needles, m.p. 234°. Yield, 0.1 g. *Anal.* Calcd. for $C_7H_8N_4S_2$: C, 39.62; H, 3.80; N, 26.41. Found: C, 39.86; H, 3.74; N, 26.37.

Acetyl derivative (VII): Recrystallized from hydr. EtOH to white scales, m.p. 185~186°. *Anal.* Calcd. for $C_9H_{10}ON_4S_2$: C, 42.52; H, 3.97; N, 22.04. Found: C, 42.34; H, 4.04; N, 21.89.

Reaction of (II) with Acetic Anhydride—One gram of (II) was added to 15 cc. of Ac_2O and the reaction mixture was refluxed for 15 mins. Removal of excess Ac_2O left crystals which were recrystallized from EtOH to colorless plates, m.p. 224°. Yield, 1.2 g. The analysis of this substance agreed with these for 2-chloro-5-acetamidopyrimidine-4-thiocarbamide (IV). *Anal.* Calcd. for $C_7H_7O_2N_4ClS$: C, 34.08; H, 2.86; N, 22.71. Found: C, 33.97; H, 3.00; N, 23.00.

2,4-Dichloro-5-aminopyrimidine (VIII)—To a solution of 5 g. of 2,4-dichloro-5-nitropyrimidine in 100 cc. of AcOH, 5 g. of Fe powder was added. The reaction proceeded exothermically. After filtration, the filtrate was evaporated *in vacuo*. A small amount of H_2O was added to the residue and the insoluble crystals were recrystallized from hydr. EtOH or $CHCl_3$ to colorless prisms, m.p. 122°. Yield, 3.2 g.

2-Chloro-4-ethylthio-5-aminopyrimidine (X)—(VIII) (0.32 g.) was dissolved in 15 cc. of dehyd. EtOH and to this, a solution of EtSNa (prepared from 0.05 g. of Na in 25 cc. of dehyd. EtOH and 0.13 g. of EtSH) was added and the reaction mixture was refluxed for 15 mins. After removal of the solvent, the residual oily product soon solidified upon addition of H_2O. It was recrystallized from petr. ether to colorless needles, m.p. 94°. Yield, 0.3 g. *Anal.* Calcd. for $C_6H_8N_3SCl$: C, 37.90; H, 4.22. Found: C, 38.01; H, 4.46.

2-Chloro-4-mercapto-5-aminopyrimidine (IX)—(VIII) (1.64 g.) was dissolved in 50 cc. of EtOH, 1.6 g. of KSH in 5 cc. of H_2O was added to this solution, and the mixture was heated on a water bath for 2 hrs. at 60°. After removal of excess solvent by distillation, 20 cc. of H_2O was added to the residue and the solution was acidified with AcOH. The separated yellow crystals were collected by filtration. Recrystallization from EtOH gave yellow needles which did not melt below 300°. Yield, 1.1~1.3 g.

4-Ethylthio Derivative—Prepared from (IX) with EtBr, showed no m.p. depression with the above-mentioned sample (X), m.p. 94°.

2-Methyl-5-chlorothiazolo[5,4-*d*]pyrimidine (XI)—One gram of (IX) was added to 50 cc. of Ac_2O and the mixture was refluxed for 5 hrs. After removal of excess Ac_2O *in vacuo*, a small amount of H_2O was added, this was basified with *N* NaOH, and extracted with ether. The ether extract was dried and evaporated to yield colorless prisms (from EtOH), m.p. 135~136°. Yield, 0.4 g. *Anal.* Calcd. for $C_6H_4N_3ClS$: C, 38.79; H, 2.17. Found: C, 38.76; H, 2.41.

2-Methyl-5-ethoxythiazolo[5,4-*d*]pyrimidine (XII)—To a solution of 20 cc. of dehyd. EtOH containing 0.03 g. of Na, 0.18 g. of (XI) was added. After refluxing for 1 hr., the solvent was evaporated. To the residue, a small amount of H_2O was added and extracted with ether. The ether extract was dried and evaporated to give an oily product, which was recrystallized from 20% EtOH to colorless needles, m.p. 93°, undepressed on admixture with a sample prepared as described in Part I.[2] Yield, 0.14 g.

2-Methyl-5-ethylthio-thiazolo[5,4-*d*]pyrimidine (XIII)—A solution of EtSNa was prepared from 0.03 g. of Na in 20 cc. of EtOH and 0.07 g. of EtSH. To this solution, 0.18 g. of (XI) was added. After refluxing for 1 hr., the product was obtained by the same manner as in the case of (XII) as colorless prisms of m.p. 56°. Yield, 0.16 g. *Anal.* Calcd. for $C_8H_9N_3S_2$: C, 45.50; H, 4.30. Found: C, 45.70; H, 4.24.

Summary

The reduction product of 2-chloro-4-thiocyano-5-nitropyrimidine (I) was found to be 2-chloro-4-thiocyano-5-aminopyrimidine (II). Reaction of (II) with sodium ethoxide or ethanethioxide gave 2,4-diethoxy-5-aminopyrimidine and 2-ethylthio-4-thiocyano-5-aminopyrimidine. 2-Chloro-4-mercapto-5-aminopyrimidine reacted with acetic anhydride and the resulting product was 2-methyl-5-chlorothiazolo[5,4-*d*]pyrimidine, the chlorine of which is reactive.

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61. Shoji Inoue: Studies on Pyrimidine Derivatives. IV.[1] Synthesis of Thiazolo[5,4-*d*]pyrimidines and Related Compounds. (4).

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In a previous paper,[2] formation of 2,4-dimercapto-5-nitropyrimidine (I) from 2-chloro-4-thiocyano-5-nitropyrimidine and 2 moles of thiourea was described, and this was compared and found to be identical with a specimen prepared from 2,4-dichloro-5-nitropyrimidine and 4 moles of potassium hydrogen sulfide.

The present paper first deals with the latter synthesis; a by-product with a high melting point is produced in these two syntheses, the property of which has not been further investigated owing to the difficulty of its purification.

The synthesis of 5-mercaptothiazolo[5,4-*d*]pyrimidines and related compounds are then described.

A reduction of (I) with sodium hydrosulfite in alkaline solution yielded 2,4-dimercapto-5-aminopyrimidine (II) as shown in Chart 1.

The triacetyl derivative (III) was prepared by heating (II) with acetic anhydride. 2-Methyl-5-acetylthio-thiazolo[5,4-*d*]pyrimidine (V) was produced on heating (II) with acetic anhydride for a longer time and was easily crystallized from ethanol. This was then hydrolysed with diluted alkali and converted into 2-methyl-5-mercaptothiazolo-[5,4-*d*]pyrimidine (VII) which was confirmed by the preparation of its 5-ethylthio derivative (X).

The desulfurization of (VII) with Raney nickel in ammonia gave 2-methylthiazolo-[5,4-*d*]pyrimidine (IX). 2-Phenyl-5-benzoylthio-thiazolo[5,4-*d*]pyrimidine (VI) was obtained through the tribenzoyl derivative (IV) by refluxing (II) with excess of benzoyl chloride in pyridine. The benzoylthio group in 5-position of (VI) was more stable against alkaline hydrolysis than the acetylthio group in (V) and it was debenzoylated to 2-phenyl-5-

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1) Part III: This Bulletin, **6**, 343(1958).

2) Part II: *Ibid.*, **6**, 338(1958).