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).

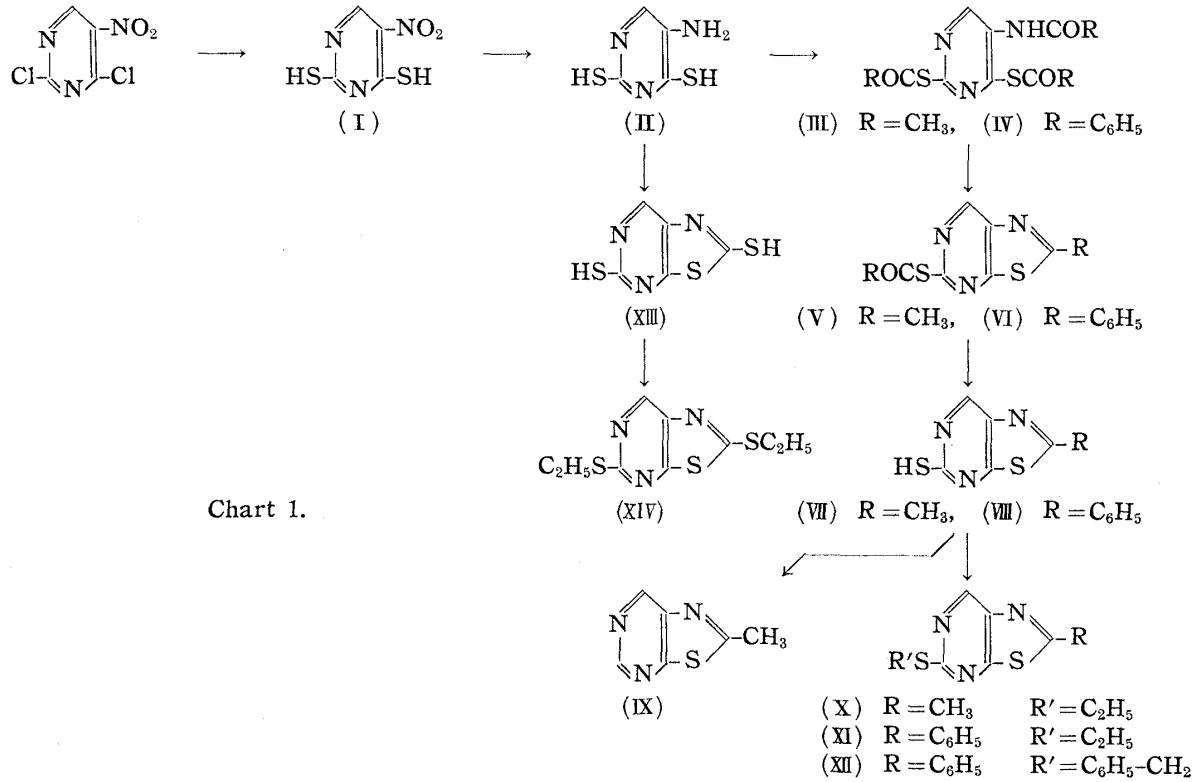

Chart 1.

mercaptothiazolo[5,4-*d*]pyrimidine (VIII) only after heating with *N* sodium hydroxide for more than one hour.

Condensation of (VIII) with ethyl bromide or benzyl chloride respectively gave compounds (XI) and (XII). Preparation of 2,5-dimercaptothiazolo[5,4-*d*]pyrimidine (XIII) from (II) and potassium methylxanthate proceeded in good yield, and (XIII) was converted into 2,5-bis(ethylthio)thiazolo[5,4-*d*]pyrimidine (XIV) by addition of 2 moles of ethyl bromide to the potassium salt of (XIII) in ethanol.

Subsequently, 2-ethylthio-4-hydroxy-5-aminopyrimidine (XV) was prepared according to the method of McOmie[3] and this was employed for the syntheses of thiazolo[5,4-*d*]-pyrimidine derivatives.

The reverse sequence, namely, acylation followed by ring closure, was studied in the present experiment and it was found to be satisfactory. The second stage presumably proceeds through the intermediate (XVII) shown in Chart 2, and the products, 5-ethylthio-thiazolo[5,4-*d*]pyrimidine (XIX) and 2-methyl-5-ethylthio-thiazolo[5,4-*d*]pyrimidine (X) are obtained by the liberation of one mole of hydrogen sulfide.

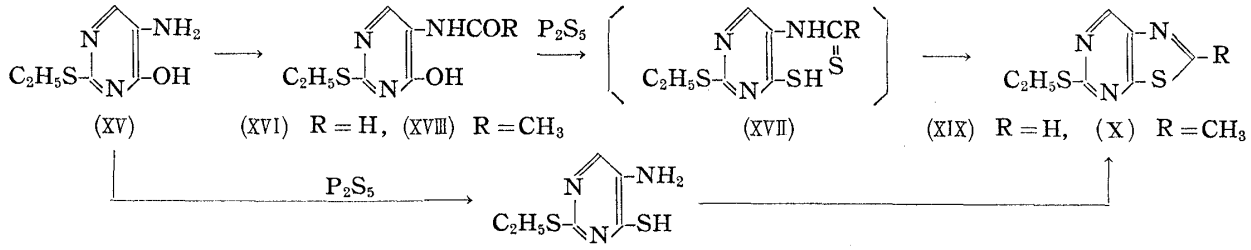

Chart 2.

The author expresses his gratitude to Prof. T. Takahashi, University of Kyoto, for his encouragement and to Prof. T. Naito, Nagoya City University, for his advices in this work. The author is indebted to Miss H. Iwata, University of Kyoto, and Mrs. M. Hasegawa, Nagoya City University, for the elemental microanalyses.

3) M.P.V. Boarland, J.F.W. McOmie : J. Chem. Soc., **1952**, 4942.

Experimental

(All melting points are uncorrected)

2,4-Dimercapto-5-nitropyrimidine (I)—To a solution of 5 g. of 2,4-dichloro-5-nitroyprimidine in 100 cc. of EtOH, 7.5 g. of KSH in 10 cc. of H_2O was added dropwise under stirring. After stirring for 1 hr. at room temperature, the solvent was removed by distillation *in vacuo*. To the residue, a small amount of H_2O was added, the orange yellow crystals were collected, and washed with H_2O. The product was taken up in hot EtOH to remove the insoluble material. Orange yellow prisms, m.p. 213~215°(decomp.), were obtained from the extract. Yield, about 3 g. *Anal.* Calcd. for $C_4H_3O_2N_3S_2$: C, 25.34; H, 1.59. Found: C, 25.73; H, 1.28.

2,4-Dimercapto-5-aminopyrimidine (II)—To a solution of 2 g. of (I) in 40 cc. of *N* NaOH, $Na_2S_2O_4$ was added under stirring until the red color had disappeared. The reaction mixture was warmed at 50° for 15 mins. and cooled. The separated yellow crystals were collected by filtration, washed with cold H_2O, and dried. The product (1.2 g.) was pure enough for further use. On heating, it decomposed gradually above 270° without melting. This substance was identical with the product prepared by Whittaker's method.[4]

2,4-Diacetylthio-5-acetamidopyrimidine (III)—(II) was converted into yellow scales upon heating with Ac_2O for a few mins. The crystals were collected and recrystallized from a large volume of H_2O to yellow scales. Yield, almost theoretical. The product did not melt below 300°. *Anal.* Calcd. for $C_{10}H_{11}O_3N_3S_2$: C, 42.11; H, 3.98. Found: C, 42.55; H, 4.01.

2-Methyl-5-acetylthio-thiazolo[5,4-*d*]pyrimidine (V)—A suspension of 2 g. of (II) in 60 cc. of Ac_2O was refluxed for 5 hrs. in an oil bath to form a red solution. After removal of excess Ac_2O under reduced pressure, the residue was extracted several times with hot ether. The solvent was removed and the residual product was recrystallized from petr. ether to colorless plates, m.p. 135°. Yield, 2 g. *Anal.* Calcd. for $C_8H_7ON_3S_2$: C, 42.67; H, 3.13. Found: C, 42.84; H, 3.22.

2-Methyl-5-mercaptothiazolo[5,4-*d*]pyrimidine (VII)—The residue obtained after removal of the solvent from acetylation of another 2 g. of (II) was dissolved in 10% NaOH, decolorized with charcoal, filtered, and the orange yellow filtrate was neutralized with AcOH. The product (1.5 g.) separated almost immediately as yellow scales or needles, and decomposed above 242°. This product was identified as the ethylthio derivative as described below.

2-Methyl-5-ethylthio-thiazolo[5,4-*d*]pyrimidine (X)—0.37 g. of (VII) was dissolved in a small amount of H_2O containing 0.12 g. of KOH and 10 cc. of EtOH, and 0.25 g. of EtBr was added to this. The mixture was heated at 60° for 30 mins. Removal of the solvent left an oily residue which soon solidified on addition of H_2O. The solid was collected and recrystallized from petr. ether to colorless prisms, m.p. 56°. This substance showed no m.p. depression on admixture with the product which was prepared from 5-chloro-2-methylthiazolo[5,4-*d*]pyrimidine and EtSNa as reported in Part III[1] of this series.

2-Methylthiazolo[5,4-*d*]pyrimidine (IX)—To 0.65 g. of (VII), 20 cc. of H_2O, 5 cc. of 25% NH_4OH, and 5 g. of Raney Ni catalyst were added. This mixture was heated under reflux for 3 hrs. and filtered. The residual Ni was washed 3 times with 50 cc. portions of boiling water. The washings and the filtrate were combined and concentrated *in vacuo* to one-half the original volume. The residue was extracted with ether and dried. Removal of the solvent furnished yellow crystals which melted at 60~65°. The crude product was sublimed *in vacuo* to colorless needles which melted at 76~77°. *Anal.* Calcd. for $C_6H_5N_3S$: C, 47.68; H, 3.34. Found: C, 48.26; H, 3.27.

2-Phenyl-5-benzoylthio-thiazolo[5,4-*d*]pyrimidine (VI)—To a solution of 1 g. of (II) in 20 cc. of pyridine, 8 cc. of BzCl was added slowly. The reaction was exothermic and the tribenzoyl derivative (IV) precipitated out. After refluxing for 3 hrs. in an oil bath, the dark red reaction mixture was poured on 100 g. of crushed ice and basified with *N* NaOH, upon which an oily material separated. To this reaction mixture, 50 cc. of ether was added, the insoluble crystals were collected, washed with ether, and dried. Recrystallization of the crude product (2 g.) from acetone yielded pale colored needles, m.p. 180~181°. *Anal.* Calcd. for $C_{18}H_{11}ON_3S_2$: C, 61.89; H, 3.17. Found: C, 61.46; H, 3.27.

2-Phenyl-5-mercaptothiazolo[5,4-*d*]pyrimidine (VIII)—A suspension of 0.5 g. of (VI) in 20 cc. of *N* NaOH was heated in a water bath for 2~3 hrs. to form a clear yellow solution. After the content was filtered and acidified with AcOH, the yellow crystals were converted into the 5-ethylthio derivative as described below.

2-Phenyl-5-ethylthio-thiazolo[5,4-*d*]pyrimidine (XI)—Prepared by the same way from the Na salt of (VIII) and EtBr in EtOH as in the case of (X). Colorless needles (from EtOH), m.p. 131°. *Anal.* Calcd. for $C_{13}H_{11}N_3S_2$: C, 57.14; H, 4.06. Found: C, 56.89; H, 4.02.

2-Phenyl-5-benzylthio-thiazolo[5,4-*d*]pyrimidine (XII)—(VIII) (0.24 g.) was added to a solution of 0.06 g. of KOH in a small amount of H_2O and 20 cc. of EtOH. To this solution, 0.12 g. of benzyl chloride was added and heated under reflux for 30 mins. After concentration of the reaction mixture,

4) N. Whittaker: J. Chem. Soc., **1951**, 1565.

the separated crystals were collected, washed with H_2O, and recrystallized from acetone to colorless needles, m.p. 184°, which weighed 0.3 g. *Anal.* Calcd. for $C_{18}H_{13}N_3S_2$: C, 64.47; H, 3.91. Found : C, 64.79; H, 4.01.

2,5-Dimercaptothiazolo[5,4-*d*]pyrimidine (XIII)—A solution of potassium methylxanthate was prepared by dissolving 0.6 g. of KOH in 4 cc. of H_2O and 20 cc. of MeOH, and subsequent addition of 0.64 g. of CS_2 with shaking. To this solution, 0.5 g. of (II) was added and the reaction mixture was refluxed for 15 hrs. The solution of the K salt was decolorized with charcoal, filtered, and the filtrate was neutralized with AcOH. The product separated as pale yellow crystals. Purification of this product was unsuccessful, and accordingly it was converted into the diethylthio derivative as described below.

2,5-Bis(ethylthio)thiazolo[5,4-*d*]pyrimidine (XIV)—Prepared from the dipotassium salt of (XIII) and 2 moles of EtBr in EtOH in the same way as in the case of (X). Recrystallization from petr. ether gave colorless prisms, m.p. 69°. *Anal.* Calcd. for $C_9H_{11}N_3S_3$: C, 42.03; H, 4.31. Found : C, 41.75; H, 4.31.

5-Ethylthio-thiazolo[5,4-*d*]pyrimidine (XIX)—(XVI), m.p. 269~270° (0.5 g.), prepared according to McOmie,[3] and 1.5 g. of P_2S_5 were mixed intimately, and 10 cc. of xylene was added to this mixture. The reaction mixture was refluxed in an oil bath for 5 hrs. with stirring, cooled, the filter cake was washed with a small amount of benzene, and dried. To this cake, 30 cc. of 5% NH_4OH was added with stirring, the mixture was left to stand for a short time, and extracted with ether. The ether layer was dried and evaporated. The residue thus obtained was recrystallized from petr. ether to colorless needles, m.p. 82°. Yield, 0.18~0.2 g. *Anal.* Calcd. for $C_7H_7N_3S_2$: C, 42.64; H, 3.58. Found: C, 42.78; H, 3.57.

2-Methyl-5-ethylthio-thiazolo[5,4-*d*]pyrimidine (X)—Prepared by the action of P_2S_5 on 0.5 g. of (XVIII), prepared from (XV) and Ac_2O in the usual way as in the case of (XIX). Recrystallization from petr. ether gave colorless prisms. This product was identical with the substance, m.p. 56°, prepared from (VII) and EtBr.

Summary

The reaction of 2,4-dimercapto-5-aminopyrimidine with acetic anhydride and benzoyl chloride gave 2-methyl-5-mercapto- (VII) and 2-phenyl-5-mercaptothiazolo[5,4-*d*]pyrimidine, respectively. By desulfurization of (VII) with Raney nickel, 2-methylthiazolo[5,4-*d*]pyrimidine was obtained. The corresponding thiazolo[5,4-*d*]pyrimidines were prepared from 2-ethylthio-4-hydroxy-5-acylamidopyrimidine in the presence of phosphorus pentasulfide.

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

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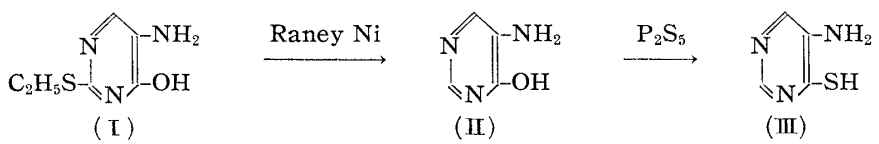
Previous papers of this series described the syntheses of thiazolo[5,4-*d*]pyrimidine derivatives, substituted especially in 2- and 5-positions. This paper deals with the syntheses of thiazolo[5,4-*d*]pyrimidines and related compounds containing substituted thiazole ring.



(I) (II) (III)

Chart 1.

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1) Part IV : This Bulletin, **6**, 346(1958).