potassium methylxanthate. 0.2 g. of (III) was added to it and refluxed for 15 hrs. The reaction mixture was then evaporated, the residual K salt of the product was dissolved in 10 cc. of H_2O, filtered, and acidified with AcOH. The separated crystals were recrystallized from EtOH to yellow needles, m.p. 287°(decomp.). Yield, 0.21 g. *Anal.* Calcd. for $C_5H_3N_3S_2$: C, 35.51; H, 1.97. Found : C, 35.19; H, 1.87.

2-Benzylthio-thiazolo〔5,4-*d*〕pyrimidine (XIV)—0.2 g. of K salt of (XIII) was dissolved in 20 cc. of 70% EtOH and treated with 0.12 g. of benzyl chloride. After refluxing for 30 mins., the solvent was distilled off, and 5 cc. of *N* NaOH was added to the residue. This was extracted with ether, dried, and the solvent was removed. The oily product which soon solidified was recrystallized from petr. ether to white prisms, m.p. 101°. Yield, 0.21 g. *Anal.* Calcd. for $C_{12}H_9N_3S_2$: C, 55.60; H, 3.50. Found : C, 55.80; H, 3.60.

Summary

4-Mercapto-5-aminopyrimidine (III) was prepared by the following two reactions.

1) The reaction of phosphorus pentasulfide on 4-hydroxy-5-aminopyrimidine.
2) The dehalogenation of 4-mercapto-5-amino-6-chloropyrimidine.

Thiazolo〔5,4-*d*〕pyrimidine and 2-methyl-, 2-phenyl-, and 2-mercaptothiazolo〔5,4-*d*〕-pyrimidines were prepared from (III).

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63. **Shoji Inoue** : Studies on Pyrimidine Derivatives. VI.[1] Synthesis of Thiazolo〔5,4-*d*〕pyrimidines and Related Compounds. (6).

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Harn and Erlenmeyer[2] reported in 1956 the synthesis of 2-methyl-7-mercaptothiazolo〔5,4-*d*〕pyrimidine (II) by the cyclization of 4,6-dimercapto-5-aminopyrimidine (I) with acetic anhydride. The author prepared (II) according to their method and derived several new compounds from it. In Part IV of this series,[3] it was shown that 2-methyl-5-acylthio-thiazolo〔5,4-*d*〕pyrimidines were isolated from the reaction mixture and that the acylthio groups were rather stable. Though the cyclization of (I) with acetic anhydride was expected to give 2-methyl-7-acetylthio-thiazolo〔5,4-*d*〕pyrimidine, the resulting product was only 7-mercapto derivative (II).

2-Methyl-7-methylthio-thiazolo〔5,4-*d*〕pyrimidine (III) was obtained by the action of methyl iodide on (II), and this was hydrolysed with conc. hydrochloric acid and converted into 2-methyl-7-hydroxythiazolo〔5,4-*d*〕pyrimidine (IV). On the other hand, compound (IV) was also prepared by the oxidation of (II) with hydrogen peroxide in alkaline solution. By treatment with phosphoryl chloride in the presence of dimethylaniline, (IV) was converted into 2-methyl-7-chlorothiazolo〔5,4-*d*〕pyrimidine (V), the chlorine group of which was reactive.

Condensation of (V) with sodium ethoxide, sodium phenoxide, ethylamine, or aniline respectively gave 7-ethoxy- (VI), 7-phenoxy- (VII), 7-ethylamino- (VIII), or 7-anilino-2-methylthiazolo〔5,4-*d*〕pyrimidine (IX).

2,7-Dimercaptothiazolo〔5,4-*d*〕pyrimidine (X) was produced by the reaction of (II) with potassium methylxanthate. The sodium salt of (X) reacted with 2 moles of benzyl chloride to be converted into 2,7-bis(benzylthio)thiazolo〔5,4-*d*〕pyrimidine (XI).

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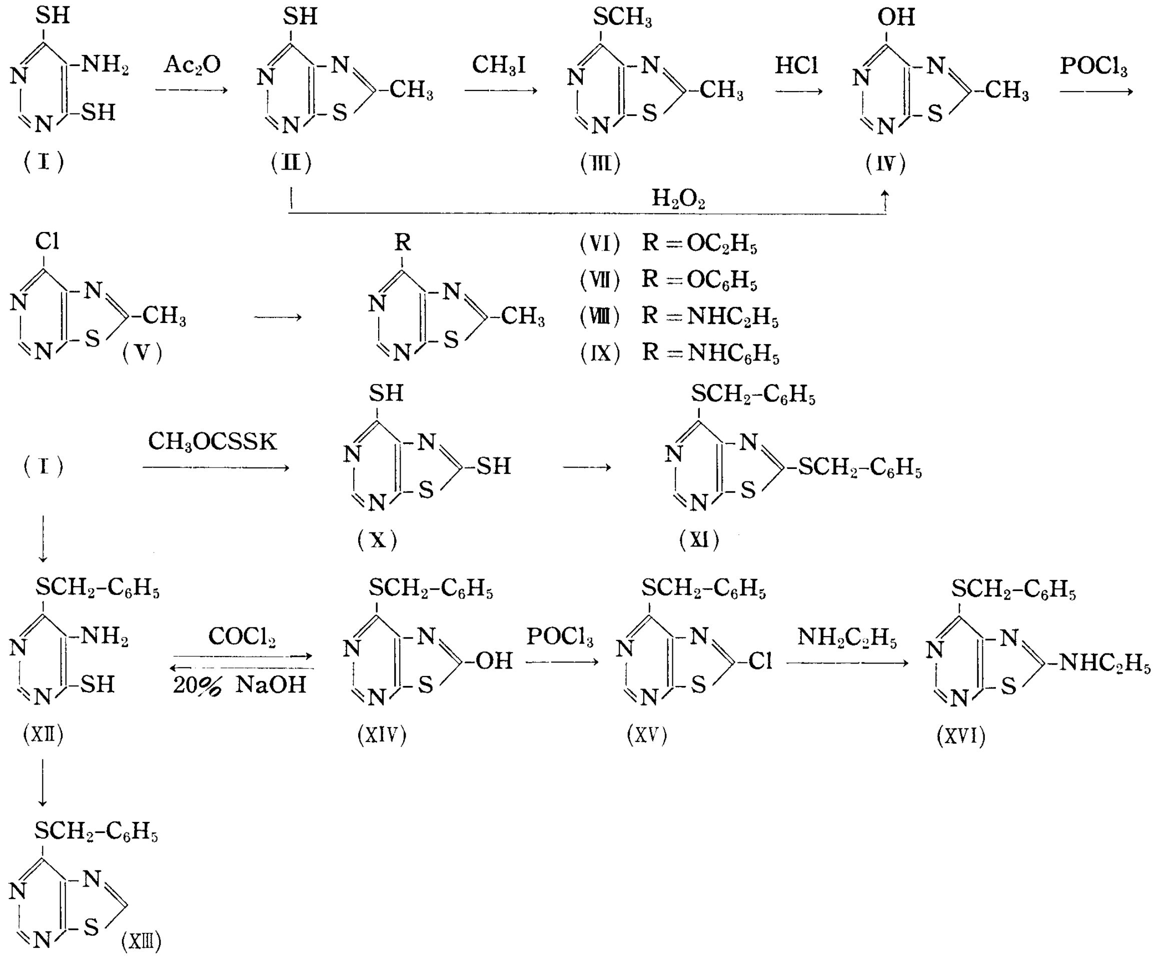
[1] Part V : This Bulletin, **6**, 349(1958).

[2] H.V. Hahn, H. Erlenmeyer : Helv. Chim. Acta, **39**, 1160(1956).

[3] Part IV : This Bulletin, **6**, 346(1958).



The addition of 1 mole of benzyl chloride to (I) afforded the mono-substituted product, 4-mercapto-5-amino-6-benzylthio-pyrimidine (XII). The heating of (XII) with formic acid resulted in ring closure to afford 7-benzylthio-thiazolo[5,4-*d*]pyrimidine (XIII), and the heating of (XII) with phosgene in chloroform also resulted in ring closure to afford 2-hydroxy-7-benzylthio-thiazolo[5,4-*d*]pyrimidine (XIV) in a good yield. The hydroxyl group in (XIV) was easily converted into chlorine to form 2-chloro-7-benzylthio-thiazolo-[5,4-*d*]pyrimidine (XV) by the action of phosphoryl chloride in the presence of dimethylaniline. The reaction of (XV) with ethylamine gave 2-ethylamino-7-benzylthio-thiazolo-[5,4-*d*]pyrimidine (XVI).

As described in a previous paper of this series,[4] cleavage of the thiazole ring possesing an amino group at 2-position of the thiazolopyrimidine ring was examined. The cleavage was effected by heating for one hour with sodium hydroxide solution and the corresponding (4-mercapto-5-pyrimidyl)urea thus obtained was hydrolysed to 4-mercapto-5-aminopyrimidine by further heating for 15 hours.

A similar cleavage of the thiazolo[5,4-*d*]pyrimidine possessing a hydroxyl group at 2-position was then examined. The heating of (XIV) in 20% sodium hydroxide for 30 minutes only gave 4-mercapto-5-amino-6-benzylthio-pyrimidine (XII), the starting material. One mole of carbon dioxide was generated in this reaction and accordingly the reaction proceeds by cleavage of the S-C bond to a carbamine derivative (not isolated) which is immediately decarboxylated to give the 4-mercapto-5-amino derivative.

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[4] Part II : This Bulletin, **6**, 338(1958).

indebted to Miss H. Iwata, University of Kyoto, and Mrs. M. Hasegawa, Nagoya City University, for carrying out the elemental microanalyses.

Experimental

(All m.p.s are uncorrected)

2-Methyl-7-mercaptothiazolo[5,4-*d*]pyrimidine (II)—This was prepared from 4,6-dimercapto-5-aminopyrimidine (I) and Ac_2O by the method of Erlenmeyer.2)

2-Methyl-7-methylthio-thiazolo[5,4-*d*]pyrimidine (III)—To a solution of 1.83 g. of (II) in 50 cc. of slightly hydrated EtOH containing 0.56 g. of KOH, there was added 1.5 g. of CH_3I. After the reaction mixture was refluxed for 30 mins., it was cooled, and the separated crystals were collected by filtration. The filtrate was concentrated, the residue was treated with a small amount of H_2O, and cooled. The separated crystals were combined, washed with H_2O, and recrystallized from EtOH to white needles, m.p. 137°. Yield, 1.7 g. *Anal.* Calcd. for $C_7H_7N_3S_2$: C, 42.64; H. 3.58. Found : C, 42.29; H, 3.80.

2-Methyl-7-hydroxythiazolo[5,4-*d*]pyrimidine (IV)—i) A mixture of 5 g. of (III) and 20 cc. of conc. HCl was heated on a water bath for 3 hrs., when a rapid evolution of MeSH occurred at first. After heating, the reaction mixture was evaporated *in vacuo*, a small amount of H_2O was added to the residue, and the solution was neutralized with aq. NH_4OH. The separated crystals were collected and recrystallized from H_2O to white needles which decomposed gradually, giving no distinct docomposition point. *Anal.* Calcd. for $C_6H_5ON_3S$: C, 43.12; H, 3.02. Found : C, 43.70; H, 3.27.

ii) To a solution of 1.5 g. of (II) in 15 cc. of 0.5*N* NaOH, 10 cc. of H_2O_2 was added under cooling and, after standing for a short time, the reaction mixture was acidified with AcOH, The separated crystals were collected and recrystallized from H_2O to white needles. Yield, 1.1 g.

2-Methyl-7-chlorothiazolo[5,4-*d*]pyrimidine (V)—A mixture of 1 g. of (IV), 15 cc. of $POCl_3$), and a small amount of dimethylaniline was refluxed for 1.5 hrs. After removal of excess $POCl_3$, the residual solution was poured on crushed ice and extracted with ether. The ether extract was dried and evaporated, and the residual crystals were recrystallized from petr. ether to 0.8 g. of colorless plates or needles, m.p. 105°. *Anal.* Calcd. for $C_6H_4N_3ClS$: C, 38.79; H, 2.17. Found : C, 39.37; H, 2.40.

2-Methyl-7-ethoxythiazolo[5,4-*d*]pyrimidine (VI)—To a solution of 20 cc. of dehyd. EtOH containing 0.05 g. of Na, 0.37 g. of (V) was added. After refluxing for 1 hr., the solvent was evaporated, a small amount of H_2O was added to the residue, the separated crystals were collected, and recrystallized from H_2O to colorless needles, m.p. 110°. Yield, 0.28 g. *Anal.* Calcd. for $C_8H_9ON_3S$: C, 49.23; H, 4.65. Found : 49.07; H. 4.86.

2-Methyl-7-phenoxythiazolo[5,4-*d*]pyrimdine (VII)—0.18 g. of (V) was dissolved in 20 cc. of EtOH, a solution of 0.13 g. of PhONa in 5 cc. of EtOH was added to this and the mixture was heated for 1 hr. Removal of the solvent yielded an oily product which soon solidified. It was extracted with ether, the ether extract was dried and evaporated, and the residual crystals were recrystallized from petr. ether to white needles, m.p. 99°. Yield, 0.18 g. *Anal.* Calcd. for $C_{12}H_9ON_3S$: C, 59.26; H, 3.73. Found : C, 59.69; H, 3.94.

2-Methyl-7-ethylaminothiazolo[5,4-*d*]pyrimidine (VIII)—To a solution of 0.18 g. of (V) in 20 cc. of EtOH, a slight excess of aq. $EtNH_2$ was added and the mixture was heated for 1 hr. at 40°. The reaction mixture was treated similary as described for (VI). Recrystallization from petr. ether gave colorless needles, m.p. 112°. *Anal.* Calcd. for $C_8H_{10}N_4S$: C, 49.48; H, 5.19. Found : C, 49.02; H, 5.42.

2-Methyl-7-anilinothiazolo[5,4-*d*]pyrimidine (IX)—A solution of 0.3 g. of (V) and 0.3 g. of aniline in 20 cc. of EtOH was refluxed for 2 hrs. and the solvent was removed by distillation. To the residue, a small amount of dil. HCl was added, the insoluble crystals were collected, washed with H_2O, and dried. These were recrystallized from EtOH to colorless needles, m.p. 185°. Yield, 0.35 g. *Anal.* Calcd. for $C_{12}H_{10}N_4S$: C, 59.50; H, 4.16. Found : C, 59.36; H, 4.29.

2,7-Dimercaptothiazolo[5,4-*d*]pyrimidine (X)—To a solution of 0.6 g. of KOH dissolved in 4 cc. of H_2O and 10 cc. of MeOH, and then 0.64 g. of CS_2 was added with shaking to form a yellow solution of potassium methylxanthate. (I) (0.5 g.) was added to it and the mixture refluxed for 15 hrs. The reaction mixture was then evaporated, the residual K salt of the product was dissolved in 15 cc. of H_2O, filtered, and the filtrate acidified with AcOH. The product separated as pale yellow crystals. Purification of this product was unsuccessful and accordingly it was converted into the dibenzylthio compound as described below.

2,7-Bis(benzylthio)thiazolo[5,4-*d*]pyrimidine (XI)—It was prepared from dipotassium salt of (X) and 2 moles of benzyl chloride in EtOH in the usual way. Recrystallization from EtOH gave colorless needles, m.p. 109°. *Anal.* Calcd. for $C_{19}H_{15}N_3S_3$: C, 59.48; H, 3.97. Found : C, 59.93; H, 4.10.

4-Mercapto-5-amino-6-benzylthio-pyrimidine (XII)—A solution of 4 g. of (I) dissolved in a solution of 2.9 g. of KOH in 5 cc. of H_2O and 50 cc. of EtOH was treated with 3.2 g. of benzyl chloride, the reaction mixture was refluxed for a short time, and evaporated to dryness. To the residue, 10 cc.

of *N* NaOH was added and this was extracted with ether to remove the dibenzyl derivative. The aq. layer was acidified with AcOH, the separated crystals were collected, and recrystallized from EtOH to yellow prisms, m.p. 183°. Yield, ca. 4.5 g. *Anal.* Calcd. for $C_{11}H_{11}N_3S_2$: C, 53.01; H, 4.45. Found : C, 52.69; H, 4.65.

7-Benzylthio-thiazolo[5,4-*d*]pyrimidine (XIII)—A mixture of 1 g. of (XII) and 50 cc. of HCOOH was heated on a water bath. After 2 hrs., the reaction mixture was evaporated *in vacuo,* 15 cc. of H_2O was added to the residue and the solution was basified with aq. NaOH. The separated alkali-insoluble crystals were collected by filtration and recrystallized from petr. ether to colorless scales, m.p. 91°. Yield, 0.75 g. *Anal.* Calcd. for $C_{12}H_9N_3S_2$: C, 55.60; H, 3.50. Found : C, 55.92; H, 3.73.

2-Hydroxy-7-benzylthio-thiazolo[5,4-*d*]pyrimidine (XIV)—To a solution of (XII) (2.5 g.) dissolved in 50 cc. of $CHCl_3$, $COCl_2$ gas was introduced under heating for 15 mins. After the solvent was removed by distillation, the residue was dissolved in 30 cc. of 10% NH_4OH, the solution was decolorized with charcoal, filtered, the filtrate was acidified with AcOH, and the separated white scales were collected. Recrystallization from EtOH gave 2.3 g. of colorless needles, m.p. 242°. *Anal.* Calcd. for $C_{12}H_9ON_3S_2$: C, 52.37; H, 3.30. Found : C, 52.18; H, 3.53.

2-Chloro-7-benzylthio-thiazolo[5,4-*d*]pyrimidine (XV)—A mixture of 1.1 g. of (XIV), 7 cc. of $POCl_3$, and 1.5 cc. of dimethylaniline was refluxed for 3 hrs. The reaction mixture was treated similarly to the case described under (V). The product was recrystallized from petr. ether giving 0.7 g. of colorless prisms, m.p. 74°. *Anal.* Calcd. for $C_{12}H_8N_3ClS_2$: C, 49.05; H, 2.74. Found : C, 49.36; H, 3.07.

2-Ethylamino-7-benzylthio-thiazolo[5,4-*d*]pyrimidine(XVI)—To a solution of 0.29 g. of (XV) in 30 cc. of EtOH, a slight excess of aq. $EtNH_2$ was added and the mixture was heated at 60° for 1 hr. On removal of the solvent, there were obtained 0.23 g. of colorless crystals which were recrystallized from EtOH to colorless needles, m.p. 188°. *Anal.* Calcd. for $C_{14}H_{14}N_4S_2$: C, 55.62; H, 4.67. Found: C, 55.36; H, 4.77.

Cleavage of 2-Hydroxy-7-benzylthio-thiazolo[5,4-*d*]pyrimidine with NaOH—A mixture of 0.25 g. of (XIV) and 5 cc. of 20% NaOH was heated on a water bath for 30 mins. After cool the resulting clear yellow solution was acidified with AcOH and the separated precipitate (0.2 g.) was recrystallized from EtOH to yellow prisms, m.p. 183°, undepressed on admixture with a sample prepared as described for (XII).

Summary

By treatment with hydrogen peroxide 2-methyl-7-mercaptothiazolo[5,4-*d*]pyrimidine was easily oxidized to the 7-hydroxy compound, and it was converted into the 7-chloro derivative. 7-Substituted($-OC_2H_5$, $-OC_6H_5$, $-NHC_2H_5$ and $-NHC_6H_5$) 2-methylthiazolo-[5,4-*d*]pyrimidines were synthesized from 7-chloro-2-methylthiazolo[5,4-*d*]pyrimidine.

2,7-Dimercaptothiazolo[5,4-*d*]pyrimidine was prepared from 4,6-dimercapto-5-aminopyrimidine and potassium methylxanthate. The heating of 4-mercapto-5-amino-6-benzylthio-pyrimidine (XII) with formic acid or phosgene also resulted in ring closure to afford 7-benzylthio-thiazolo[5,4-*d*]pyrimidine or 2-hydroxy-7-benzylthio-thiazolo[5,4-*d*]-pyrimidine (XIV).

Cleavage of (XIV) with sodium hydroxide solution was examined and (XII), the starting material, was recovered by the liberation of CO_2.

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