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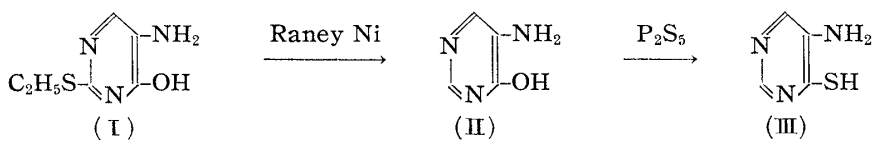
Previous papers of this series described the syntheses of thiazolo[5,4-*d*]pyrimidine derivatives, substituted especially in 2- and 5-positions. This paper deals with the syntheses of thiazolo[5,4-*d*]pyrimidines and related compounds containing substituted thiazole ring.



(I) (II) (III)

Chart 1.

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

NII-Electronic Library Service

4-Hydroxy-5-aminopyrimidine (II), obtained by the method of McOmie[2] was converted into 4-mercapto-5-aminopyrimidine (III) by treatment with phosphorus pentasulfide in xylene. The synthesis of (III) was also carried out by another route as shown in Chart 2.

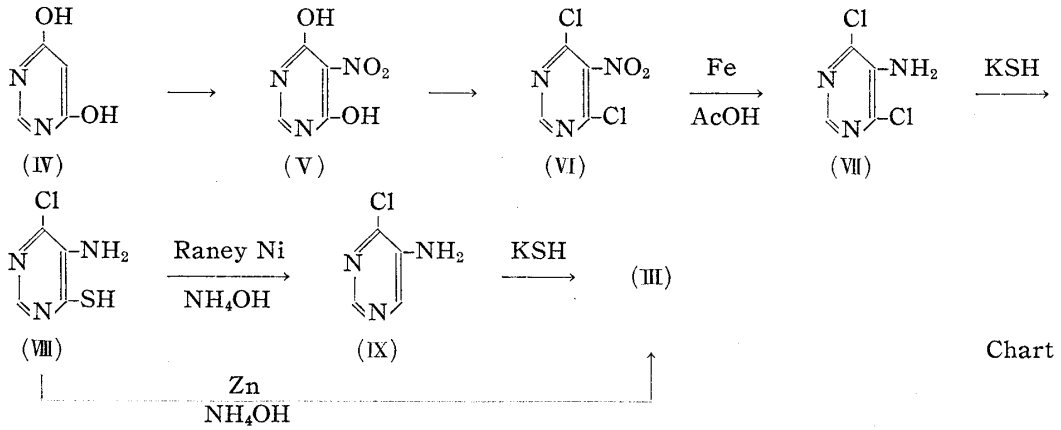

Chart 2.

In 1951, Boon[3] prepared 4,6-dihydroxypyrimidine (IV) from formamidine and diethyl malonate, and also obtained 4,6-dichloro-5-nitropyrimidine (VI) from (IV) through the nitro derivative (V). Reduction of (VI) with iron powder and acetic acid has now given 4,6-dichloro-5-aminopyrimidine (VII). The addition of 1 mole of potassium hydrogen sulfide to (VII) afforded the mono-substituted product, 4-mercapto-5-amino-6-chloropyrimidine (VIII). The reaction of (VIII) with Raney nickel in ammonia gave 5-amino-6-chloropyrimidine (IX), which was converted into (III) in the presence of potassium hydrogen sulfide in a good yield. When zinc powder was used instead of Raney nickel, the chlorine in 6-position was eliminated and (III) was obtained directly. Several thiazolo[5,4-*d*]pyrimidines were synthesized from this compound (III), an isomer of thiocytosin.

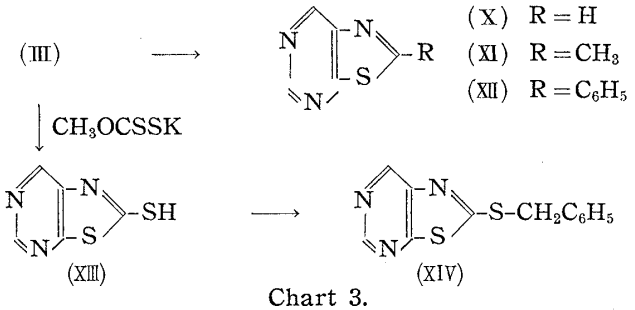

Chart 3.

The reaction of (III) with formic acid gave thiazolo[5,4-*d*]pyrimidine (X) which is the sulfur analog of purine. The chemical and physical properties of (X) will be reported in another paper. It would be quite interesting to study its biochemical activity from the point of view of its being an antagonist of purine. 2-Methylthiazolo[5,4-*d*]pyrimidine (XI) was obtained by treatment of (III) with acetic anhydride, and (XI) was identical with the compound prepared by the desulfurization of 2-methyl-5-mercaptothiazolo[5,4-*d*]pyrimidine with Raney nickel.[1] 2-Phenylthiazolo[5,4-*d*]pyrimidine (XII) was obtained by heating (III) with benzoyl chloride in pyridine. 2-Mercaptothiazolo[5,4-*d*]pyrimidine (XIII) was produced by the reaction of (III) with potassium methylxanthate. The sodium salt of (XIII) reacted with benzyl chloride and was converted into 2-benzylthio-thiazolo-[5,4-*d*]pyrimidine (XIV).

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

2) M.P.V. Boarland, J.F.W. McOmie : J. Chem. Soc., **1952**, 4942.
3) W.R. Boon, *et al.* : *Ibid.*, **1951**, 96.

NII-Electronic Library Service

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

Experimental

(All melting points are uncorrected)

4-Mercapto-5-aminopyrimidine (III)—i) Preparation from (II) : One gram of (II) and 3 g. of P_2S_5 were mixed well, 20 cc. of xylene was added to this mixture, and refluxed for 8 hrs. under thorough stirring. After cool, the reaction mixture was filtered, washed rapidly with a small amount of benzene, and dried. The filter cake was dissolved in 20 cc. of *N* NaOH, decolorized with charcoal, filtered, the filtrate was neutralized with AcOH, and extracted with AcOEt. From the extract there were obtained yellow crystals which recrystallized from EtOH to yellow needles, m.p. 207°(decomp.). Yield, 0.4~0.5 g. *Anal.* Calcd. for $C_4H_5N_3S$: C, 37.80; H, 3.97. Found : C, 38.02; H, 3.94.

ii) Preparation from (IX) : (IX) (0.13 g.) was dissolved in 5 cc. of H_2O, 0.2 g. of KSH was added to this solution, and the reaction mixture was heated for 2 hrs. at 60°. After cool, the reaction mixture was neutralized with AcOH and the separated crystals were collected by filtration. The filtrate was extracted with AcOEt, dried, the solvent was removed, and the yellow crystals were combined with the above crop of crystals. This was recrystallized from EtOH. Yield, 0.1 g.

iii) Preparation from (VIII) : To a solution of 1 g. of (VIII) in 3 cc. of 28% NH_4OH and 20 cc. of H_2O, 5 g. of Zn powder was added and the reaction mixture was refluxed for 3 hrs. under stirring. The residual Zn powder was filtered while hot and extracted with boiling water. The filtrate and the extract were combined, concentrated to one-fifth the original volume, neutralized with AcOH, and extracted several times with AcOEt. From the extract there were obtained yellow crystals which decomposed at 207°. Yield, 0.55 g.

4,6-Dichloro-5-aminopyrimidine (VII)—(VI) (5 g.) was dissolved in 100 cc. of MeOH containing 10 cc. of AcOH and 5 g. of iron powder was added to this solution. The reaction mixture was stirred for 1.5 hrs. (reduction occurred vigorously with generation of heat). After heating for a short time, it was filtered and the filtrate was evaporated to dryness *in vacuo*. The residue was taken up in AcOEt, the extract was washed with *N* NaOH, dried, and evaporated. The crystals thus obtained were recrystallized from MeOH to colorless needles, m.p. 142°. Yield, 3 g. *Anal.* Calcd. for $C_4H_3N_3Cl_2$: C, 29.23; H, 1.84. Found : C, 29.50; H, 2.11.

4-Mercapto-5-amino-6-chloropyrimidine (VIII)—To a hot solution of 5 g. of (VII) in 50 cc. of EtOH, a calculated amount of aq. KSH was added. After heating at 60° for 3 hrs., the mixture was cooled and the deposited yellow crystals were collected by filtration. The filtrate was concentrated to one-fifth the original volume and cooled. The separated crystals and the above-obtained yellow crystals were combined, washed with H_2O, and recrystallized from EtOH to yellow needles; this substance did not melt below 300°. Yield, 4.1 g. *Anal.* Calcd. for $C_4H_4N_3ClS$: C, 29.73; H, 2.47. Found : C, 29.83; H, 2.66.

5-Amino-6-chloropyrimidine (IX)—To 1 g. of (VIII) there was added 20 cc. of H_2O, 3 cc. of 28% NH_4OH, and then 5 g. of Raney Ni catalyst. This mixture was refluxed for 3 hrs. with stirring and filtered while hot. The residual Ni was washed 3 times with boiling water. The washings and the filtrate were combined and concentrated *in vacuo*, and the residual reaction mixture containing a small amount of the rest of the solvent was extracted with ether. From the dried extract there were obtained colorless needles which were recrystallized from ether-petr. ether, m.p. 123°(decomp.). Yield, 0.2 g. *Anal.* Calcd. for $C_4H_4N_3Cl$: C, 37.08; H, 3.11. Found : C, 37.60; H, 3.55.

Thiazolo[5,4-*d*]pyrimidine (X)—A mixture of 0.3 g. of (III) and 15 cc. of HCOOH was refluxed for 2 hrs. This was concentrated to one-fifth the original volume, basified with *N* NaOH, and extracted with AcOEt. The extract was dried, evaporated, and the residue was purified by sublimation *in vacuo* to give colorless needles, m.p. 144°. Yield, 0.1 g. *Anal.* Calcd. for $C_5H_3N_3S$: C, 43.80; H, 2.22; N, 30.65. Found : C, 43.48; H, 2.32; N, 30.18.

2-Metylthiazolo[5,4-*d*]pyrimidine (XI)—A mixture of 0.3 g. of (III) and 10 cc. of Ac_2O was refluxed for 2 hrs. After cool, the reaction mixture was treated with a small amount of H_2O in order to decompose excess Ac_2O. The subsequent treatment of this preparation was similar to the case of (X). Sublimation *in vacuo* gave 0.16 g. of white needles m.p. 77°, undepressed on admixture with the product obtained by desulfurization of 2-methyl-5-mercaptothiazolo[5,4-*d*]pyrimidine with Raney Ni.[1]

2-Phenylthiazolo[5,4-*d*]pyrimidine (XII)—0.4 g. of (III) was dissolved in 5 cc. of pyridine, 1.9 g. of BzCl was added to this solution, and the reaction mixture was refluxed for 3 hrs. After cool, it was poured into H_2O, basified with *N* NaOH, and extracted with ether. The extract was washed with *N* HCl to remove the free pyridine and dried. Removal of the solvent gave white needles which were recrystallized from EtOH to white scales, m.p. 119~120°. Yield, 0.55 g. *Anal.* Calcd. for $C_{11}H_7N_3S$: C, 61.97; H, 3.31. Found : C, 61.85; H, 3.43.

2-Mercaptothiazolo[5,4-*d*]pyrimidine (XIII)—0.15 g. of KOH was dissolved in 1 cc. of H_2O, and to this 5 cc. of MeOH and then 0.16 g. of CS_2 were added with shaking, to form a yellow solution of

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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-mercapto-thiazolo[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).

* Hagiyama-cho, Mizuho-ku, Nagoya (非公開).

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).

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