UDC 547.789.6.07

25. **Morizo Ishidate and Hidetaka Yuki :** Syntheses of Thiazolo[5,4-*d*]pyrimidine Derivatives and Related Compounds.

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The authors reported previously[1] that fusion of 4,5-diamino-6-mercaptopyrimidine (I) with oxalic acid afforded 7-aminothiazolo[5,4-*d*]pyrimidine (XI). This type of reaction was further examined and a novel method for the synthesis of thiazolo[5,4-*d*]pyrimidine derivatives was found. Several new derivatives thereby obtained are described in the present paper.

There are many reports on the synthetic method for thiazolo[5,4-*d*]pyrimidine. Cook and others adopted cyclization of a pyrimidine ring from thiazole ring,[2] while Fischer,[3] Childress,[4] Hitchings,[5] and Erlenmeyer[6] started with 5-amino-6-mercaptopyrimidine, using acetic anhydride, benzoic anhydride, or formic acid to effect cyclization. Hitchings[7] also used phosphorus pentasulfide for ring closure. However, nothing has been reported on the preparation of derivatives posessing optional substituent in the 2-position. Therefore, examinations were made on the preparation of 2-substituted thiazolo[5,4-*d*]pyrimidine derivatives in connection with the synthesis of 8-substituted purine derivatives reported earlier.[1]

Reaction of 4,5-diamino-6-mercaptopyrimidine (I) with acetic anhydride at room temperature results in acylation of the amino group in 5-position to form (II). Boiling of (I) or (II) with acetic anhydride affords a compound assumed to be (III) and its hydrolysis with alkali gives a compound soluble in acid, insoluble in alkali, and giving positive reaction for sulfur by fusion with sodium but negative to SH or C=S test by sodium azide-iodine reagent. Its analytical values showed the compound to be 7-amino-2-methylthiazolo[5,4-*d*]pyrimidine (IV), which is also obtained directly from (II) by heating in dilute hydrochloric acid.

Fusion of (I) with cyanoacetic acid afforded (IV), which was assumed to have been formed through reaction of the cyano group with the amino in 5-position, followed by deammoniation and decarboxylation to form (IV), being isolated as cyanoacetic acid salt (V) by formation of a salt with excess of cyanoacetic acid.

In order to obtain evidence for the formation of thiazolo[5,4-*d*]pyrimidine by the reaction of (I) and a nitrile, a mixture of (I) and acetonitrile was boiled at the boiling point of the latter (80°) but no such product was obtained. Heating of the same mixture in a sealed tube at 160° finally afforded (IV), though in an extremely poor yield, recovering most of the starting material. These results suggest that the reaction with cyanoacetic acid is not effected by acetonitrile formed by its decomposition by heat but cyanoacetic acid itself reacts with (I), with subsequent decarboxylation.

Boiling of (VII)[1] with acetic anhydride affords square crystals of m.p. 300~330° (decomp.) (VIII) which show positive reaction to SH test and dissolve in sodium hydrogen-

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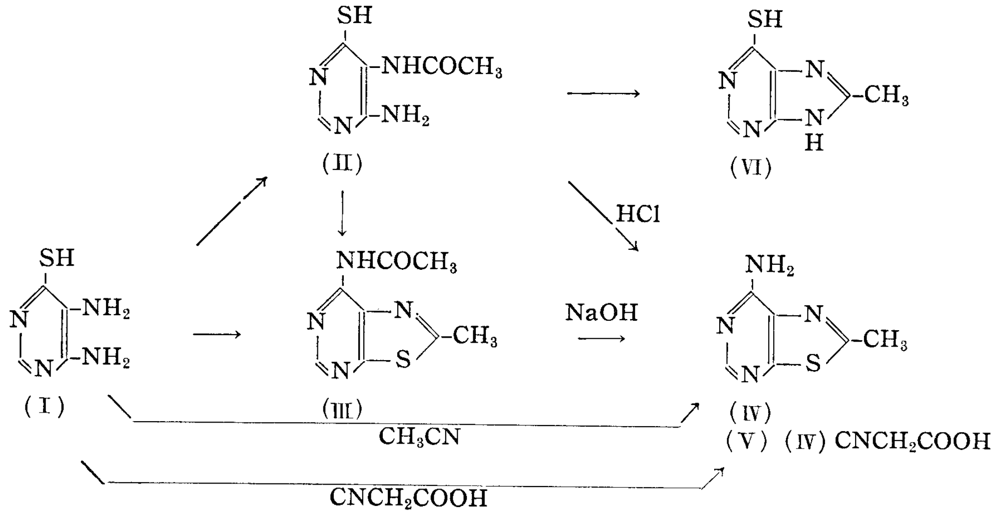
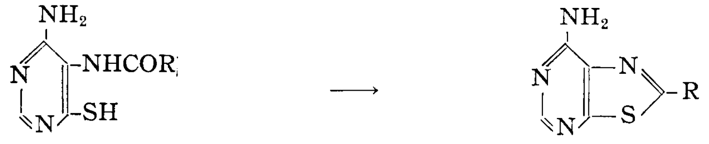


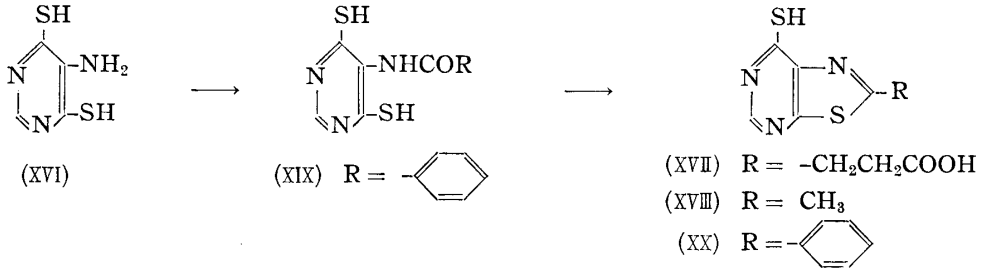
(I) (II) (III) (IV) (VI)

(V) (IV) $CNCH_2COOH$



(VII) R = $-CH_2CH_2COOH$
(X) R = H
(XII) R = $-CH_2OH$
(XIV) R = $-(CHOH)_4CH_2OH$
(XV) R = $-CH_2OCOCH_3$

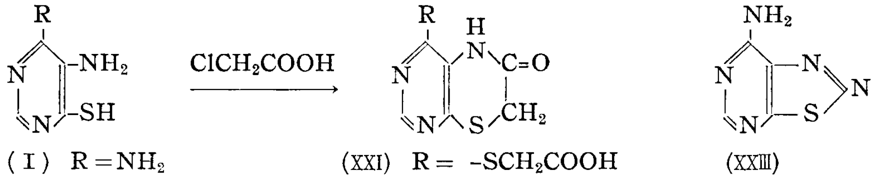
(IX) R = $-CH_2CH_2COOH$
(XI) R = H
(XIII) R = $-CH_2OH$



(XVI)

(XIX) R =

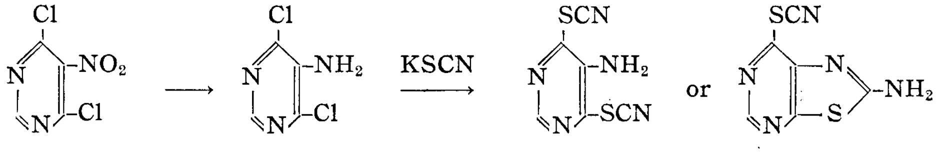
(XVII) R = $-CH_2CH_2COOH$
(XVIII) R = CH_3
(XX) R =



(I) R = NH_2
(XVI) R = SH

(XXI) R = $-SCH_2COOH$
(XXII) R = NH_2

(XXIII)



(XXIV) (XXV) (XXV')

carbonate solution. Its analytical values are not in agreement with the assumed structure for this product, but its transformation product (IX), obtained by heating with dilute hydrochloric acid, showed no depression of the melting point on admixture with the compound obtained by treatment of (VII) with hydrochloric acid, proving the compound to be (IX). Hitchings and others[8] obtained (XI) by formylation of (I) with 50% formic acid and boiling its product (X) with 90% formic acid. (XI) was obtained in a more simple manner by boiling (X) with dilute hydrochloric acid. Heating of (XII)[1] with dilute hydrochloric acid similarly affords (XIII) but the boiling with acetic anhydride results in exchange reaction with glycolic acid to form (IV). Boiling of acetic anhydride with (XV), formed by fusion of (I) with acetoxyacetic acid, also gives (IV), similar to the case of (XII). Only (XIV)[1] failed to undergo cyclization on being heated with hydrochloric acid and underwent hydrolysis to form (I).

Heating of the sodium salt of (II) effects cyclization, not with the thiol group but with the amino group, and 6-mercapto-8-methylpurine (VI) is produced. It was therefore found that heating of 4-amino-5-acylamino-6-mercaptopyrimidine with hydrochloric acid affords thiazolo[5,4-*d*]pyrimidine, while heating of its sodium salt gives a purine derivative, making it possible to effect cyclization in optional direction. The mechanism of this reaction was assumed as follows: In the case of the sodium salt, thiol group is inactivated by forming SNa group, making it impossible to be dehydrated, and dehydrative cyclization occurs with amino group. In heating with hydrochloric acid, the amino group is inactivated by forming a hydrochloride, while the thiol group remains free and the reaction occurs with SH group to form thiazolo[5,4-*d*]pyrimidine. The same result is obtained by the use of dilute sulfuric acid in place of hydrochloric acid.

Examinations were then made to see if the 5-acylated compound of 4,6-dimercapto-5-aminopyrimidine (XVI) would also undergo cyclization with hydrochloric acid. Fusion of (XVI) with succinic acid or cyanoacetic acid, or reaction with cold acetic anhydride, results in immediate cyclization to respective products (XVII) and (XVIII), and intermediate acylated compounds were not isolated. (XVI) failed to react with oxalic, glycolic, lactic, or benzoic acid by fusion. Thus, (XVI) is less readily acylated than (I) but once it has been acylated, the acylation product is more easily cyclized than the acylated compound of (I).

Reaction of (XVI) with benzoyl chloride in pyridine affords (XIX) which undergoes cyclization on being heated with dilute hydrochloric acid to form (XX).

Reaction of (XVI) with monochloroacetic acid gives the pyrimido[4,5-*b*][1,4]thiazine derivative (XXI) as well as (XXII), as in the case of (I). Cyclization of pyrimido[4,5-*b*][1,4]-thiazine was effected by Rose[9] with sodium hydrogencarbonate. Infrared spectrum of (XXII) in Nujol exhibits absorption of a carbonyl at $1665\,cm^{-1}$ but no absorption of a hydroxyl, so that the carbonyl at 3-position has not been enolized.

Reduction of 4,6-dichloro-5-nitropyrimidine with zinc dust gives (XXIV) and its reaction with potassium thiocyanate produces a compound whose infrared spectrum indicates the presence of $C{\equiv}N\,(2150\,cm^{-1})$, but whether this is (XXV) or (XXV′) has not been established yet.

The reaction of (I) with nitrous acid results in cyclization at the thiol group, forming 7-amino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (XXIII). (XVI) does not react with nitrous acid.

The compounds prepared in the present series of experiments and described in this paper have been submitted to screening test with Yoshida sarcoma, giving almost negative results, which will be reported elsewhere.

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8) G. G. Hitchings, *et al.*: J. Am. Chem. Soc., **78**, 2858(1956).

9) F. L. Rose: J. Chem. Soc., **1952**, 3448.

Experimental[*2]

5-Acetamido-4-amino-6-mercaptopyrimidine (II)—To 2 g. of finely powdered (I), 10 cc. of Ac_2O was added and shaken for several min. to result in coagulation. After gently warming on a water bath for about 5 min. the reaction mixture was cooled, filtered, and the residue was recrystallized from 50 cc. of water to give 2 g. of needles, m.p. 280°(decomp.). SH, positive. *Anal.* Calcd. for $C_6H_8ON_4S$: C, 39.13; H, 4.38; S, 17.49. Found : C, 38.78; H, 4.30; S, 17.02.

7-Acetamido-2-methylthiazolo[5,4-*d*]pyrimidine (III)—A mixture of 1 g. of (I) and 10 cc. of Ac_2O was refluxed for 2 hr., the excess Ac_2O was distilled off under a reduced pressure, 5 cc. of water was added, and the mixture was left to stand overnight. Crystals formed were recrystallized from water to give 0.9 g. of white needles, m.p. 157°, after being dried at 100°. S, positive; SH, negative. *Anal.* Calcd. for $C_8H_8ON_4S$: C, 46.15; H, 3.87; S, 15.40. Found : C, 46.00; H, 3.85; S, 16.32.

This substance was obtained in the same way using (II) instead of (I).

7-Amino-2-methylthiazolo[5,4-*d*]pyrimidine (IV)—a) A mixture of 0.7 g. of (III) and 7 cc. of 5% NaOH solution was boiled for several sec., then a crystalline precipitate was produced. Recrystallization from water gave 0.5 g. of colorless crystals, m.p. 213~214°. S, positive; SH, negative. *Anal.* Calcd. for $C_6H_6N_4S$: C, 43.37; H, 3.61; N, 33.73. Found : C, 43.78; H, 3.76; N, 33.67.

b) A mixture of 0.1 g. of (II) and 1 cc. of 10% HCl was boiled for several min., during which (II) dissolved in the solution. After cool, the solution was made alkaline with NaOH to give a white precipitate. Recrystallization from water gave 0.06 g. of (IV), m.p. 212~213°. S, positive; SH, negative. No depression of m.p. was observed on admixture with the product prepared by the method a).

c) A mixture of 1.5 g. of (I) and 4 g. of cyanoacetic acid was heated on a bath of about 140°. The mixture melted once, then resolidified during the heating. Hot water was added to dissolve the product while hot and colorless crystals separated after cooling, were recrystallized from water to give (V), m.p. 176°(decomp.). S, positive; SH, negative. *Anal.* Calcd. for $C_6H_6N_4S \cdot CNCH_2COOH$: C, 43.03; H, 3.61. Found : C, 43.97; H, 3.46.

On addition of NaOH solution to a suspension of (V) in H_2O, colorless plates precipitated immediately after the suspension became clear. After sublimation at 220°(bath temp.), 0.8 g. of (IV) was obtained as colorless needles, m.p. 213~214°. S, positive; SH, negative. No depression of m.p. was observed on admixture with the product prepared by the method a). Recrystallization of (IV) from an aqueous solution of $CNCH_2COOH$ gave (V) again.

d) A suspension of 0.3 g. of (I) in 5 cc. of CH_3CN was heated at 160° for 4.5 hr. in a sealed tube and left to stand overnight. Crystals formed were collected by filtration, warmed with 15 cc. of EtOH, and filtered while hot. The insoluble fraction was the starting material (I). The filtrate was evaporated to dryness and the residue was recrystallized from water to give 15 mg. of colorless crystals, m.p. 213~214°. S, positive; SH, negative. No depression of m.p. was observed on admixture with the product prepared by the method a).

6-Mercapto-8-methylpurine (VI)—A solution prepared by dissolving 0.8 g. of (II) in an equimolar amount of 10% NaOH solution was evaporated to dryness under a reduced pressure and the residue was heated at 230~240° for 30 min. After cool, water was added to dissolve the residue, acidified with AcOH, and a precipitate formed was recrystallized from 100 cc. of water to yield 0.4 g. of m.p. 250~300° (decomp.). SH, positive. *Anal.* Calcd. for $C_6H_6N_4S$: C, 43.37; H, 3.64; N, 33.73; S, 19.24. Found : C, 43.16; H, 4.14; N, 32.91; S, 18.40.

Compound (VIII)—A mixture of 1.2 g. of finely powdered (VII) and 12 cc. of Ac_2O was refluxed for 3~5 min., during which crystalline precipitate separated. Recrystallization from water gave 0.35 g. of square crystals, m.p. 300~330°(decomp.). SH, positive. *Anal.* Found : C, 42.42; H, 4.00; N, 24.33; S, 15.33.

7-Amino-2-(2-carboxyethyl)thiazolo[5,4-*d*]pyrimidine (IX)—a) A mixture of 0.3 g. of (VII) and 8 cc. of 10% HCl was boiled until in solution and cooled. The solution was made alkaline with NaOH and acidified with AcOH again. The precipitate formed was recrystallized from water to 0.2 g. of colorless crystals, m.p. 380°(decomp.), which dissolves in $NaHCO_3$ solution. *Anal.* Calcd. for $C_8H_8O_2N_4S$: C, 42.86; H, 3.60; N, 24.99; S, 14.25. Found : C, 43.04; H, 3.90; N, 24.96; S, 14.54.

b) To 2 cc. of 10% HCl, 0.2 g. of (VIII) was added and the same after-treatment gave 0.12 g. of (IX). No depression of m.p. was observed on admixture with the product prepared by method a).

7-Aminothiazolo[5,4-*d*]pyrimidine (XI)—A suspension of 0.24 g. of (X) in 2.5 cc. of 10% HCl was boiled until in solution and cooled. NaOH was added to the solution to render alkaline and the precipitate that separated was recrystallized from water to 0.14 g. of (XI), m.p. 209~210°. S, positive; SH, negative. No depression of m.p. was observed on admixture with an authentic sample of (XI).

[*2] All m.p.s are uncorrected.

7-Amino-2-hydroxymethylthiazolo[5,4-*d*]pyrimidine (XIII)—A suspension of 0.2 g. of (XII) in 2 cc. of 10% HCl was boiled until in solution and cooled. Neutralization with NaOH gave slightly yellow precipitate which recrystallized from water. Yield, 0.12 g. m.p. 212~213°. S, positive; SH, negative. *Anal.* Calcd. for $C_6H_6ON_4S \cdot H_2O$: C, 36.00; H, 4.00; S, 17.55; H_2O, 9.00. Found : C, 35.89; H, 4.35; S, 17.88; H_2O, 9.23. The m.p. was depressed to about 190° on admixture with (IV) (m.p. 213~214°) and (XI) (m.p. 209~210°).

Reaction of (XII) with Ac_2O—A suspension of 0.5 g. of (XII) in 5 cc. of Ac_2O was refluxed for 5 min., concentrated under a reduced pressure, and 3 cc. of water was added to the residue. This solution was basified with NaOH and left to stand overnight. The precipitate that separated was recrystallized from H_2O to give 75 mg. of colorless crystals, m.p. 213~214°. S, positive; SH, negative. No depression of m.p. was observed on admixture with the authentic sample of (IV).

Reaction of (XIV) with dil. HCl—A suspension of 0.35 g. of (XIV) in 3.5 cc. of 10% HCl was boiled, during which the reaction mixture became clear once and then a precipitate formed. Recrystallization of the precipitate from water gave only (I).

5-Acetoxyacetamido-4-amino-6-mercaptopyrimidine (XV)—A mixture of 1 g. of (I) and 3 g. of acetylglycolic acid was heated gradually to 180° (bath temp.), during which the mixture became clear. Hot water (10 cc.) was added to the hot reaction mixture and cooled. The precipitate that separated was recrystallized from water to give 0.7 g. of (XV) as colorless needles, m.p. 222~223° (decomp.). SH, positive. *Anal.* Calcd. for $C_8H_{10}O_3N_4S$: C, 39.67; H, 4.16; N, 23.41. Found : C, 39.97; H, 4.55; N, 23.44.

Reaction of (XV) with Ac_2O—A mixture of 0.3 g. of (XV) and 3 cc. of Ac_2O was refluxed for 10 min. and evaporated to dryness under a reduced pressure. The residue was dissolved in water and basified with NaOH, affording plate crystals. Recrystallization from water gave 0.12 g. of colorless crystals, m.p. 213~214°. S, positive; SH, negative. No depression of m.p. was observed on admixture with an authentic sample of (IV).

2-(2-Carboxyethyl)-7-mercaptothiazolo[5,4-*d*]pyrimidine (XVII)—To 5 g. of fused succinic acid in a bath at a temperature of 210°, 1 g. of (XVI) was added and the reaction mixture melted to a clear solution under foaming. After cool, the product was dissolved in dil. NaOH and precipitated by acidification with HCl. Recrystallization from 300 cc. of water gave 0.55 g. of yellow needles, m.p. 266° (decomp.). SH, positive. *Anal.* Calcd. for $C_8H_7O_2N_3S_2$: C, 39.84; H, 2.93; N, 17.43. Found : C, 39.73; H, 3.22; N, 18.17.

7-Mercapto-2-methylthiazolo[5,4-*d*]pyrimidine (XVIII)—a) A mixture of 1 g. of (XVI) and 5 g. of cyanoacetic acid was heated at a bath temperature of 145°. The reaction mixture melted once and resolidified. After cool, the product was dissolved in NaOH and acidification with AcOH gave 0.55 g. of orange-yellow crystals, which became pale yellow after recrystallization from water, m.p. 305~306° (decomp.). SH, positive. *Anal.* Calcd. for $C_6H_5N_3S_2$: C, 39.35; H, 2.75; N, 22.95; S, 34.96. Found : C, 39.46; H, 3.17; N, 22.74; S, 34.81.

b) A mixture of 0.8 g. of (XVI) and 8 cc. of Ac_2O was refluxed for 1 hr. After cool, crystals that separated were collected and recrystallized from water to 0.6 g. of pale yellow needles, m.p. 305~306° (decomp.). SH, positive.

c) A mixture of 0.5 g. of finely powdered (XVI) and 5 cc. of Ac_2O was allowed to stand overnight. Water was added to the coagulated product to decompose Ac_2O and crystals that separated were recrystallized from water to 0.6 g. of pale yellow needles, m.p. 305~306° (decomp.). SH, positive.

5-Benzamido-4,6-dimercaptopyrimidine (XIX)—To a suspension of 0.5 g. of (XVI) in 5 cc. of pyridine, 0.5 cc. of BzCl was added and the mixture was warmed gently on a water bath until in solution. After addition of 50 cc. of EtOH, the reaction mixture was cooled and crystals that separated were recrystallized from hydrous EtOH to 0.7 g. of (XIX), m.p. 146~147° (decomp.). SH, positive. *Anal.* Calcd. for $C_{11}H_9ON_3S_2$: C, 50.19; H, 3.45; N, 15.97; S, 24.33. Found : C, 50.52; H, 4.19; N, 15.82; S, 24.61.

7-Mercapto-2-phenylthiazolo[5,4-*d*]pyrimidine (XX)—A suspension of 0.5 g. of (XIX) in 10 cc. of 10% HCl was boiled for several min., during which appearance of the precipitate changed somewhat. After cool, 0.44 g. of product was collected and recrystallized from water, m.p. 252~253°. SH, positive. *Anal.* Calcd. for $C_{11}H_7N_3S_2$: C, 53.88; H, 2.88; N, 16.09. Found : C, 53.00; H, 3.36; N, 16.41.

4-Carboxymethylthio-5*H*-pyrimido[4,5-*b*][1,4]thiazin-6(7*H*)-one (XXI)—a) A mixture of 1 g. of (XVI) and 3 g. of monochloroacetic acid was heated at 140° for 10 min. After cool, 20 cc. of water was added to the mixture, the precipitate formed was collected and recrystallized from water to 0.7 g. of pale yellow plates, m.p. 215~217° (decomp.). S, positive; SH, negative. *Anal.* Calcd. for $C_8H_7O_3N_3S$: C, 37.36; H, 2.74; N, 16.34; S, 24.90. Found : C, 37.26; H, 3.15; N, 16.04; S, 24.26.

b) To a solution of 3 g. of monochloroacetic acid in 70 cc. of water, 1 g. of (XVI) was added and the mixture was refluxed for 1 hr. Activated carbon was added to the solution, filtered, and cooled, giving 1.15 g. of yellow plates, m.p. 213~214° (decomp.). S, positive; SH, negative. *Anal.* Calcd.

for $C_8H_7O_3N_3S$: N, 16.34. Found : N, 15.54.

4-Amino-5*H*-pyrimido[4,5-*b*][1,4]thiazin-6(7*H*)-one (XXII)—A mixture of 1 g. of (I) and 3 g. of monochloroacetic acid was heated for several min. at 140°, during which the reaction mixture melted once and solidified again. After cool, unreacted monochloroacetic acid was dissolved by addition of 20 cc. of water and the insoluble product was recrystallized from water to 3 g. of colorless needles, m.p. 270~300°(decomp.). S, positive; SH, negative. *Anal.* Calcd. for $C_6H_6ON_4S$: C, 39.56; H, 3.32; N, 30.76. Found : C, 39.17; H, 3.98; N, 31.07.

7-Amino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (XXIII)—A solution of 0.8 g. of (I) dissolved in 60 cc. of hot water was cooled rapidly, and after addition of 5 cc. of 10% H_2SO_4, $NaNO_2$ soln. (0.5 g. in 3 cc. of H_2O) was dropped in before the crystals of (I) separated. A fine yellow precipitate that formed was recrystallized from 1 L. of water to 0.5 g. of (XXIII), m.p. >250°(decomp.). S, positive; SH, negative. *Anal.* Calcd. for $C_4H_3N_5S$: C, 31.38; H, 1.98; N, 45.75. Found : C, 31.83; H, 2.69; N, 45.67.

5-Amino-4,6-dichloropyrimidine (XXIV)—To boiling water containing 30 g. of Zn powder, finely powdered 4,6-dichloro-5-nitropyrimidine was added in small portions and boiled further for 10 min. The reaction mixture was filtered while hot and the filtrate was brought to pH 10 by addition of NH_4OH. After cool, crystals that separated were recrystallized from water to colorless needles, m.p. 145°. *Anal.* Calcd. for $C_4H_3N_3Cl_2$: C, 29.27; H, 1.81; N, 25.61. Found : C, 29.89; H, 2.44; N, 25.61.

Compound (XXV) or (XXV′)—A mixture of 0.3 g. of (XXIV), 0.3 g. of KSCN, and 5 cc. of 2*N* HCl was boiled for several min., during which the mixture dissolved once and then bulky precipitate formed. After cool, the precipitate was collected by filtration and recrystallized twice from EtOH, m.p. >250°. S, positive; SH, negative. *Anal.* Calcd. for $C_6H_3N_5S_2$: C, 34.46; H, 1.45; N, 33.97; S, 30.62. Found : C, 34.83; H. 1.60; N, 32.68; S, 27.57.

The authors are indebted to Messrs. E. Kimura and M. Endo, and to Miss N. Shinriki for elemental analyses, and to Mr. K. Tanikawa for infrared spectral measurement. The authors are also grateful to Dr. H. Sato for the animal test of these compounds. A part of expenses of this work was supported by Grant-in-Aid for Scientific Research from the Ministry of Education which is gratefully acknowledged.

Summary

Heating of the sodium salt of 4-amino-5-acylamino-6-mercaptopyrimidine results in the formation of a purine derivative but its heating with dilute hydrochloric or sulfuric acid was found to give thiazolo[5,4-*d*]pyrimidine derivatives. 5-Amino-6-mercaptopyrimidine derivatives react with nitrile to form thiazolo[5,4-*d*]pyrimidine derivatives, while they react with monochloroacetic acid to form pyrimido[4,5-*b*][1,4]thiazine derivatives, and with nitrous acid to form thiadiazolo[5,4-*d*]pyrimidine derivatives.

(Received July 21, 1959)