Summary

The reaction of 2-chloro-4-thiocyano-5-nitropyrimidine with alcohol, sodium alkoxide, or sodium ethanethioxide was studied, and 5-nitrouracil, 2-ethoxy-4-mercapto-5-nitropyrimidine (IV), and 2-ethylthio-4-thiocyano-5-nitropyrimidine (VII) were obtained from the above reagents, while (IV) was reduced to the corresponding amino derivative (VIII). 2-Amino-5-ethylthio-thiazolo[5,4-*d*]pyrimidine was synthesized by the reduction of (VII). Treatment of (VIII) with formic acid, acetic anhydride, or potassium methylxanthate, gave 5-ethoxy-, 2-methyl-5-ethoxy-, and 2-mercapto-5-ethoxythiazolo[5,4-*d*]pyrimidine, respectively.

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59. Takio Naito and Shoji Inoue: Studies on Pyrimidine Derivatives. II.[1] Synthesis of Thiazolo[5,4-*d*]pyrimidines and Related Compounds. (2).

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In the foregoing paper,[1] the authors reported that the heating of 2-chloro-4-thiocyano-5-nitropyrimidine (I) with alcohols gave 5-nitrouracil, and that (I) reacted with sodium alkoxide to give 4-mercapto and 2,4-dialkoxy derivatives.

In the present paper, the reaction of (I) with sodium phenoxide to give diphenoxy derivative (II) is described.

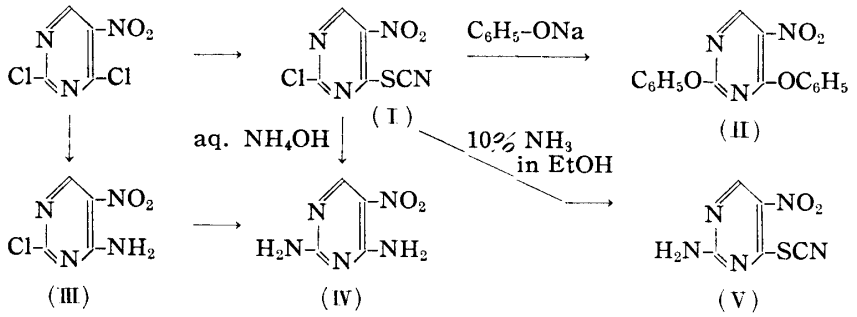

Chart 1.

The reaction of the thiocyano group of (I) with several amines was also examined. In the reaction of (I) with conc. aq. ammonia, surprisingly enough, (II) was converted directly into 2,4-diamino-5-nitropyrimidine (IV) which was identified with an authentic sample prepared from 2,4-dichloro-5-nitropyrimidine with ammonia through (III). Compound (IV) is presumably formed by a direct substitution of the thiocyano group and not through an intermediate rearrangement of the type such as $-SCN \longrightarrow SC\overset{O}{\underset{NH_2}{\diagup\diagdown}} \longrightarrow -NH-\overset{\overset{S}{\|}}{C}-OH \longrightarrow NH_2$.

On the other hand, the addition of 10% ethanolic ammonia instead of aq. ammonia to the benzene solution of (I) resulted in a substitution only at 2-position of (I), and 2-amino-4-thiocyano-5-nitropyrimidine (V) was obtained as the reaction product.

In the reaction of (I) with thiourea, 2,4-dimercapto-5-nitropyrimidine (VII) was produced

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by treatment of the intermediary salt (VI) with sodium hydroxide. Compound (VII) was identical with the substance synthesized from 2,4-dichloro-5-nitropyrimidine and thiourea (Chart 2).

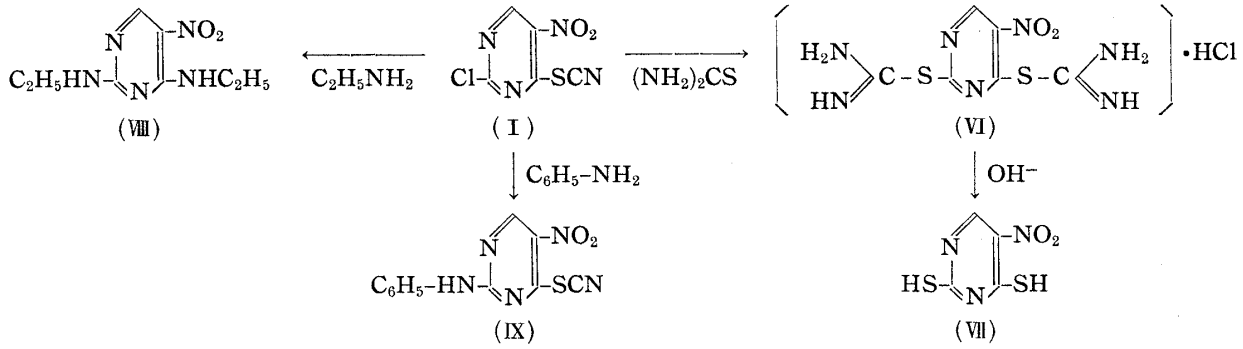


Chart 2.

Reaction of (I) with ethylamine gave 2,4-diethylamino-5-nitropyrimidine(VIII). However, the reaction of (I) with aniline gave a product identified as 2-anilino-4-thiocyano-5-nitropyrimidine (IX) which was rather stable like (V). Compounds (V) and (IX) were converted into the methoxyl derivatives, (X) and (XI), by treating with sodium methoxide in methanol.

In the case of sodium ethoxide in ethanol, the corresponding ethoxyl derivatives, (XII) and (XIII), and the mercapto derivatives, (XIV) and (XV), were respectively obtained.

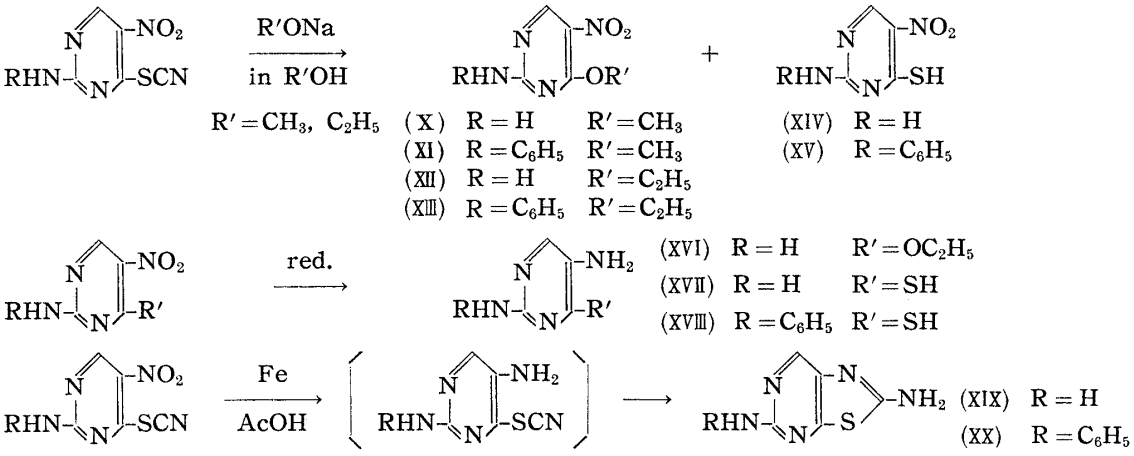


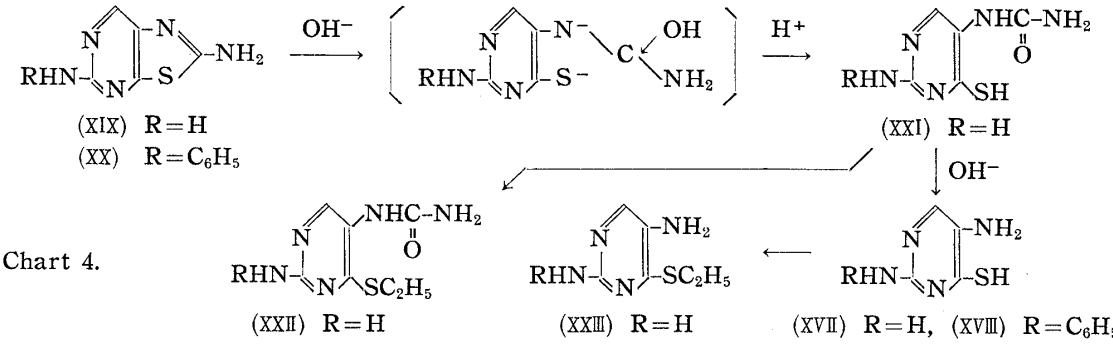
Chart 3.

The reduced compounds, 2,5-diaminothiazolo[5,4-*d*]pyrimidine (XIX), 2,5-diamino-4-ethoxypyrimidine(XVI), and 2-amino-5-anilinothiazolo[5,4-*d*]pyrimidine(XX) were obtained by reduction of the corresponding nitro derivatives with iron powder and acetic acid. 2,5-Diamino-4-mercaptopyrimidine (XVII) and 2-anilino-5-amino-4-mercaptopyrimidine (XVIII) were obtained similarly by reduction with sodium hydrosulfite and sodium hydroxide.

Ueda[2] reported that 2-mercapto-3-aminopyridine was formed during the alkaline cleavage of 2-aminothiazolopyridine and proposed a mechanism for this reaction.

The authors examined the cleavage of 2-aminothiazolo[5,4-*d*]pyrimidine with alkaline solution. Compound (XIX) was heated in 10% sodium hydroxide solution on a water bath for 1 hour to give (2-amino-4-mercapto-5-pyrimidyl)urea (XXI) which was further transformed into the S-ethyl derivative (XXII) by ethylation. Compound (XXI) was hydrolysed to (XVII) by further heating in 15% sodium hydroxide for 15 hours and this was also converted into the corresponding S-ethyl derivative, 2,5-diamino-4-ethylthiopyrimidine (XXIII).

2) K. Ueda : This Bulletin, **4**, 396(1956).



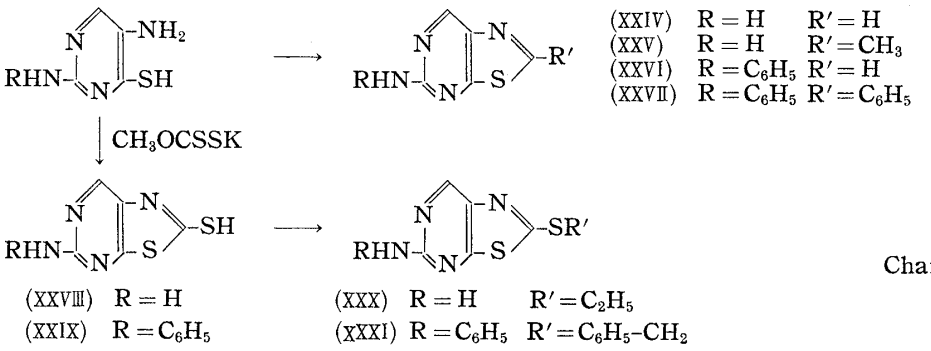
(XIX) R=H
(XX) R=C_6H_5

(XXI) R=H

(XXII) R=H (XXIII) R=H (XVII) R=H, (XVIII) R=C_6H_5

Chart 4.

These experiments suggest that the reaction follows a mechanism in which the attack of the hydroxide ion on 2-aminothiazolo[5,4-*d*]pyrimidines induces cleavage of the S–C bond in the thiazole ring to give the mercaptopyrimidylureas. Compounds (XVII) and (XVIII) were cyclized with formic acid, acetic anhydride, or potassium methylxanthate to give the corresponding thiazolo[5,4-*d*]pyrimidines. Finally, 2-ethylthio-5-aminothiazolo[5,4-*d*]pyrimidine (XXX) and 2-benzylthio-5-anilinothiazolo[5,4-*d*]pyrimidine (XXXI) were produced by the reaction of the potassium salt of (XXVIII) and (XXIX) with ethyl bromide and benzyl chloride as shown in Chart 5.



(XXIV) R=H R′=H
(XXV) R=H R′=CH_3
(XXVI) R=C_6H_5 R′=H
(XXVII) R=C_6H_5 R′=C_6H_5

(XXVIII) R=H
(XXIX) R=C_6H_5

(XXX) R=H R′=C_2H_5
(XXXI) R=C_6H_5 R′=C_6H_5-CH_2

Chart 5.

The authors express their gratitude to Prof. T. Takahashi, University of Kyoto, for his encouragement in this work. The authors are 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)

Reaction of 2-Chloro-4-thiocyano-5-nitropyrimidine (I) with Sodium Phenoxide—To an ice-cooled suspension of 0.2 g. of (I) in 30 cc. of EtOH there was added dropwise and under stirring 0.27 g. of PhONa dissolved in a small amount of EtOH. The stirring was continued for 1 hr., the solvent was removed, a small amount of H_2O was added to the oily residue, and this was extracted with benzene. Evaporation of the dried extract gave pale yellow crystals, which were recrystallized from EtOH to colorless needles, m.p. 105°. This substance analysed as 2,4-diphenoxy-5-nitropyrimidine (II). *Anal.* Calcd. for $C_{16}H_{11}O_4N_3$: C, 62.13; H, 3.59. Found : C, 62.53; H, 3.38.

Reaction of (I) with concentrated aq. NH_4OH—One gram of (I) was added to 50 cc. of 28% NH_4OH with stirring at 15°. After standing for a short time, the reaction mixture was cooled, the separated crystals were collected, washed with water, and dried. This product was identical with 2,4-diamino-5-nitropyrimidine (IV)[3] prepared from 2,4-dichloro-5-nitropyrimidine with ammonia through the monoaminated compound (III).

Reaction of (I) with 10% Ethanolic Ammonia—To a solution of 5 g. of (I) in 50 cc. of benzene, a slight excess of 10% ethanolic ammonia was added dropwise with stirring. After stirring for 20 mins., the deposited crystals were filtered, the filtrate was concentrated to one-fifth the original volume. After cool, the deposited crystals were combined, washed with H_2O, and recrystallized from EtOH to pale green-yellow prisms, m.p. 209~210°(decomp.). Yield, 4.2 g. This substance is 2-amino-4-thiocyano-5-nitropyrimidine (V). *Anal.* Calcd. for $C_5H_3O_2N_5S$: C, 30.47; H, 1.53. Found : C, 31.04; H, 1.62.

3) O. Isay : Ber., **39**, 250(1906).

Reaction of (I) with Thiourea—1.6 g. of thiourea was dissolved in 60 cc. of hot water. To this solution, 4.3 g. of powdered (I) was added and the reaction mixture was stirred for 30~40 mins. to a yellow solution. After cooling for 20 mins., the clear yellow solution was treated with excess alkali; at the neutralization point separation of yellow crystals of the intermediate (VI) was observed. The alkaline solution was decolorised with charcoal, filtered, and the filtrate was acidified with AcOH. The deposited crystals were collected, dried, and taken up in hot EtOH to remove some insoluble matter. The solution was concentrated, and the crystals were recrystallized from EtOH to orange-yellow prisms. This product is 2,4-dimercapto-5-nitropyrimidine (VII) which decomposed at 213° and was identical with the product obtained from the action of 2 moles of thiourea or 4 moles of KSH on 2,4-dichloro-5-nitropyrimidine.

Reaction of (I) with Ethylamine—To a solution of 0.43 g. of (I) in 5 cc. of benzene, a slight excess of $EtNH_2$ in 3 cc. of EtOH was added dropwise with stirring. The reaction mixture was treated similarly as described under reaction of (I) with alcoholic ammonia. Recrystallization from EtOH gave 2,4-diethylamino-5-nitropyrimidine (VIII) as pale yellow scales, m.p. 170°. *Anal.* Cald. for $C_8H_{13}O_2N_5$: C, 45.49; H, 6.20. Found: C, 45.94; H, 6.41.

Reaction of (I) with Aniline—A solution of 1.9 g. of aniline in EtOH was added to a solution of 2.1 g. of (I) in 30 cc. of benzene; the reaction was exothermic and yellow crystals separated, which were collected by filtration. The filtrate was concentrated, and after cooling, the separated crystals were combined, washed with dil. HCl and H_2O, dried, and recrystallized from benzene to yellow needles, m.p. 199~200°. This is 2-anilino-4-thiocyano-5-nitropyrimidine (IX). The yield was almost theoretical. *Anal.* Calcd. for $C_{11}H_7O_2N_5S$: C, 48.35; H, 2.58. Found: C, 47.77; H, 2.96.

2-Amino-4-methoxy-5-nitropyrimidine (X)—0.05 g. of Na was dissolved in 20 cc. of dehyd. MeOH, and 0.19 g. of (V) was added at once to this solution, and the reaction mixture was stirred for 2 hrs. at 0°. The separated crystals were collected and recrystallized from EtOH to colorless needles, m.p. 227°. Yield, 0.14 g. (a small amount of crystals were obtained from the filtrate). *Anal.* Calcd. for $C_5H_6O_3N_4$: C, 35.30; H, 3.55. Found: C, 35.70; H, 3.88.

2-Anilino-4-methoxy-5-nitropyrimidine (XI)—This was synthesized by the reaction of 0.27 g. of (IX) with 0.05 g. of Na in 30 cc. of MeOH in the same way as described above. Pale yellow needles (from MeOH), m.p. 183°. Yield, 0.23 g. *Anal.* Calcd. for $C_{11}H_{10}O_3N_4$: C, 53.66; H, 4.09. Found: C, 53.34; H, 3.98.

Reaction of 2-Amino-4-thiocyano-5-nitropyrimidine (V) with Sodium Ethoxide—Two grams of (V) was added in one portion to a stirred solution of 0.7 g. of Na in 100 cc. of EtOH at 0°. After 2 hrs., the solvent was removed by distillation. A small amount of H_2O was added to the residue to yield two kinds of reaction products. The alkali-insoluble product was 2-amino-4-ethoxy-5-nitropyrimidine (XII), colorless needles (from EtOH), m.p. 227°. Yield, 1.0~1.1 g. *Anal.* Calcd. for $C_6H_8O_3N_4$: C, 39.13; H, 4.38. Found: C, 39.82; H, 4.65.

The alkali-soluble product obtained from the filtrate was acidified with AcOH to give 2-amino-4-mercapto-5-nitropyrimidine (XIV) as yellow scales (from EtOH). It decomposed gradually without melting when heated. *Anal.* Calcd. for $C_4H_4O_2N_4S$: C, 27.91; H, 2.34. Found: C, 27.83; H, 2.73.

Reaction of (IX) with Sodium Ethoxide—The reaction was carried out in the manner described above and two kinds of product were also obtained.

The alkali-insoluble product: Recrystallized from EtOH to pale yellow needles, m.p. 150°. This substance is 2-anilino-4-ethoxy-5-nitropyrimidine (XIII). *Anal.* Calcd. for $C_{12}H_{12}O_3N_4$: C, 55.38; H, 4.65. Found: C, 55.44; H, 4.59.

The alkali-soluble product: This was 2-anilino-4-mercapto-5-nitropyrimidine (XV), yellow crystals. Since no suitable recrystallization could be found, the product was reduced to the corresponding amino compound.

2-Anilino-4-mercapto-5-aminopyrimidine (XVIII)—One gram of (XV) was dissolved in 30 cc. of H_2O and 5 cc. of 10% NaOH, and $Na_2S_2O_4$ was added to this under stirring until the red color changed to yellow. After 15 mins., the reaction mixture was heated for a short time, cooled, and the separated crystals were collected by filtration. The filtrate was extracted with AcOEt, dried, and evaporated. The above crystals and the residue were combined and recrystallized from EtOH to yellow needles, m.p. 218°(decomp.). Yield, 0.65 g. *Anal.* Calcd. for $C_{10}H_{10}N_4S$: C, 55.04; H, 4.62. Found: C, 54.81; H, 4.77.

2,5-Diamino-4-ethoxypyrimidine (XVI)—A mixture of 1.5 g. of (XII) in 30 cc. of AcOH and 1.5 g. of Fe powder was heated at 60° for 2 hrs. with stirring. After filtration, the filtrate was evaporated to dryness *in vacuo*, the residue was taken up in AcOEt, the extract was evaporated, and the residual crystals were recrystallized from benzene to 1 g. of slightly colored prisms, m.p. 128~129°. *Anal.* Calcd. for $C_6H_{10}ON_4$: C, 46.74; H, 6.54. Found: C, 46.19; H, 6.54.

2,5-Diamino-4-mercaptopyrimidine (XVII)—One gram of (XIV) was reduced similarly as in the case of (XVIII) to give (XVII) (0.6 g.) and this was purified from H_2O to yellow needles, m.p. 235°(decomp.). *Anal.* Calcd. for $C_4H_6N_4S$: C, 33.80; H, 4.26. Found: C, 33.53; H, 4.33.

2,5-Diaminothiazolo[5,4-*d*]pyrimidine (XIX)—1.5 g. of (V) was reduced by the method described

for (XVI). The product was recrystallized from EtOH to white crystals, which did not melt below 270° and decomposed gradually on further heating. Yield, 1.1 g. *Anal.* Calcd. for $C_5H_5N_5S$: C, 35.93; H, 3.02. Found : C, 36.41; H, 3.22.

2-Amino-5-anilinothiazolo[5,4-*d*]pyrimidine (XX)—This was obtained in the same way as in the case of (XIX) as white needle-like crystals, m.p. 243°. Yield, 1.15 g.(from 1.5 g. of (IX)). *Anal.* Calcd. for $C_{11}H_9N_5S$: C, 54.32; H, 3.73. Found : C, 54.56; H, 3.48.

Reaction of 2,5-Diaminothiazolo[5,4-*d*]pyrimidine (XIX) with aq. NaOH (Cleavage of 2-Aminothiazole Ring in Thiazolo[5,4-*d*]pyrimidine)—0.5 g. of (XIX) was added to 5 cc. of 10% NaOH and the mixture was heated on a water bath to a yellow solution. After 1 hr., the clear yellow solution was acidified with AcOH and the separated crystals were collected. Recrystallization from H_2O gave 0.4 g. of yellow needles, (2-amino-4-mercapto-5-pyrimidyl)urea (XXI), which decomposed gradually around 270° giving no distinct decomposition point. *Anal.* Calcd. for $C_5H_7ON_5S$: C, 32.43; H, 3.81. Found: C, 32.18; H, 3.83.

4-Ethylthio Derivative (XXII) of (XXI)—This was prepared from the K salt of (XXI) with EtBr in EtOH by the usual method. Colorless needles (from EtOH), m.p. 223~224°(decomp.). *Anal.* Calcd. for $C_7H_{11}ON_5S$: C, 39.43; H, 5.20; N, 32.85. Found : C, 39.83; H, 5.50; N, 32.98.

Hydrolysis of (2-Amino-4-mercapto-5-pyrimidyl)urea (XXI)—A solution of 1 g. of (XXI) in 20 cc. of 15% NaOH was heated in a water bath for 15 hrs. The reaction mixture was neutralized with AcOH and the separated yellow crystals were collected by filtration. The filtrate was extracted with AcOEt, the crystals obtained from the extract and the above-separated yellow crystals were combined, and recrystallized from H_2O to yellow needles, m.p. 235°(decomp.). This product was identical with 2,5-diamino-4-mercaptopyrimidine (XVII) prepared by the reduction of (XIV).

4-Ethylthio Derivative (XXIII)—Prepared by the usual way as described for (XXII). Recrystallization from benzene gave colorless scales, m.p. 87°. *Anal.* Calcd. for $C_6H_{10}N_4S$: C, 42.35; H, 5.92. Found: C, 42.21; H, 5.64.

Reaction of 2-Amino-5-anilinothiazolo[5,4-*d*]pyrimidine (XX) with aq. NaOH—The reaction was carried out in the same way as described for (XXI). By heating 1 g. of (XX) with 15% NaOH for 15 hrs., 0.5 g. of 2-anilino-4-mercapto-5-aminopyrimidine (XVIII) was obtained through the corresponding intermediate. Recrystallization from EtOH afforded yellow needles, m.p. 218°(decomp.), which were identical with the above-mentioned reduction product of (XV).

Synthesis of some 2-Substituted Thiazolo[5,4-*d*]pyrimidines from (XVII) and (XVIII)—The cyclization of (XVII) and (XVIII) was carried out by the following three methods :

(a) The materials were refluxed with HCOOH or Ac_2O, the reaction mixture was evaporated *in vacuo*, a small amount of H_2O was added to the residue, and basified with *N* NaOH. The separated crystals were collected and recrystallized from organic solvents.

(b) A solution of the material in pyridine was treated with excess BzCl and refluxed for 3 hrs. After addition of H_2O and basification with *N* NaOH the separated product was collected, washed with a small amount of ether, and recrystallized from EtOH.

(c) The materials were refluxed with potassium methylxanthate for 15 hrs. in MeOH. After

Table I.

Compd. No.	R	R′	Reagent	Method	Time (hr.)	m.p. (°C)	Appearence (recrstn. solvent)
(XXIV)	H	H	HCOOH	(a)	2	248~249	Colorless prisms (EtOH)
(XXV)	H	CH_3	Ac_2O	(a)	3	223	Colorless needles (EtOH)
(XXVI)	C_6H_5	H	HCOOH	(a)	3	152	White needles (petr. ether)
(XXVII)	C_6H_5	C_6H_5	C_6H_5COCl	(b)	3	187	Colorless needles (EtOH)
(XXVIII)	H	SH	CH_3OCSSK	(c)	15	>300	Light yellow needles (EtOH)
(XXIX)	C_6H_5	SH	CH_3OCSSK	(c)	15	267~268	Yellow needles (EtOH)

Compd. No.	Yield (g.) from 1 g.	Formula	Analyses (%) Calcd. C	Calcd. H	Found C	Found H
(XXIV)	0.6	$C_5H_4N_4S$	39.48	2.65	39.49	2.87
(XXV)	0.8	$C_5H_6N_4S$	43.37	3.64	43.21	3.85
(XXVI)	0.75	$C_{11}H_8N_4S$	57.89	3.53	57.29	3.53
(XXVII)	1.4	$C_{24}H_{16}ON_4S$*	70.57	3.95	70.10	4.26
(XXVIII)	1.05	$C_5H_4N_4S_2$	32.62	2.19	32.84	2.40
(XXIX)	1.09	$C_{11}H_8N_4S_2$	50.77	3.10	50.72	3.35

* Obtained as monobenzoyl derivative.

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).