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

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Purine antagonists have been one of the subjects of intensive study in cancer chemotherapy during the past few years. It seemed interesting to prepare compounds similar to purine and their derivatives, such as thiazolopyrimidine derivatives which may be obtained by the condensation of pyrimidine and thiazole rings. Only a few thiazolopyrimidine derivatives are known in the literature, i.e., 2-methyl-5,7-dihydroxy-thiazolo[5,4-*d*]pyrimidine has been prepared by Fischer,[1] and recently, several related compounds have been prepared by Hitchings,[2] Erlenmeyer,[3] and others.

The authors have prepared thiazolopyrimidine derivatives systematically to detect antagonistic property of precursors of nucleic acid components in biochemical field. For the syntheses of thiazolo[5,4-*d*]pyrimidines, it is necessary to prepare the intermediate compounds, 4-mercapto-5-aminopyrimidine, 4-thiocyano-5-nitropyrimidine, and their derivatives.

5-Nitrouracil[4] was employed as the starting material and this was converted into 2,4-dichloro-5-nitropyrimidine (I) by the action of phosphoryl chloride in the presence of dimethylaniline according to the method of Whittaker.[5] It was subsequently converted into 2-chloro-4-thiocyano-5-nitropyrimidine (II) by reacting 1 mole of potassium thiocyanate under cooling.

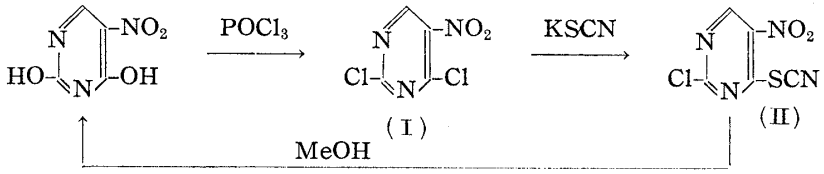

Chart 1.

When ethanol was used as the solvent in the second step, the yield of (II) decreased since ethanol reacted with (II); on the other hand, when acetic acid was used, the yield of (II) was satisfactory. Concerning the reaction of the thiocyano group with alcohols, Davies and Sexton[6] described in 1944 the formation of alkyl benzothiazole-thiocarbamates from 2-thiocyanobenzothiazole and alcohols. Takahashi and Ueda[7] recently reported that four kinds of derivatives, alkyl 3-nitro-4-pyridylthionocarbamates, 3-nitro-4-aminopyridine, the pyridyl disulfide, and the monosulfide derivative of 3-nitropyridine were produced by the reaction of 3-nitro-4-thiocyanopyridine with alcohols and interpreted the reaction mechanism as shown in Chart 2.

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1) E. Fisher, Ach : Ann., **288**, 167(1895).
2) G.H. Hitchings, G.B. Elion : J. Am. Chem. Soc., **78**, 2858(1956).
3) H.V. Hahn, H. Erlenmeyer : Helv. Chim. Acta, **39**, 1160(1956).
4) M.T. Bogert, D. Davidson : J. Am. Chem. Soc., **55**, 1667(1933).
5) N. Whittaker : J. Chem. Soc., **1951**, 1565.
6) W.H. Davies, W.A. Sexton : *Ibid.*, **1944**, 11.
7) T. Takahashi, K. Ueda : This Bulletin, **2**, 78(1954).

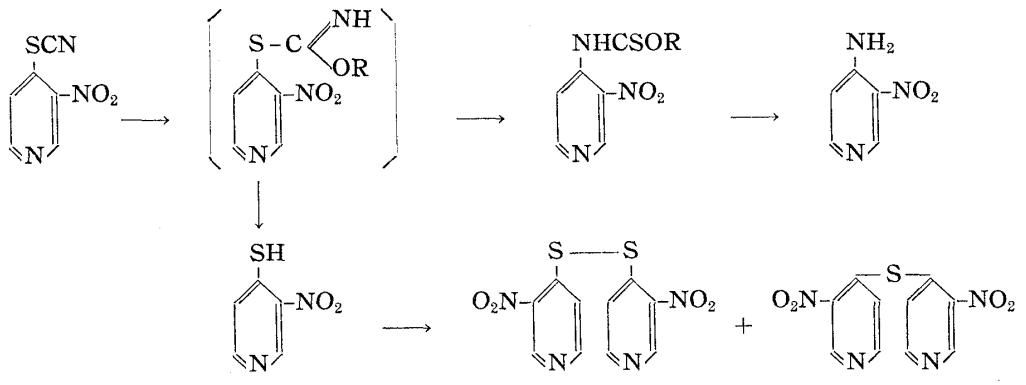

Chart 2.

The present authors tested the same reaction on (II) by using ethanol or methanol and heating for five hours, but unexpectedly the resulting product was identified as 5-nitrouracil, the starting material. The mechanism of this reaction has not been confirmed.

Ross,[8] in 1934, reported that the reaction of the thiocyano group in thiocyanobenzene with sodium ethoxide gave benzene disulfide, ethylthiobenzene, and thiophenol. Davies, *et al.*[6] similarly prepared 2-mercaptobenzothiazole and 2-ethylthiobenzothiazole from 2-thiocyanobenzothiazole, and Takahashi and Ueda[9] have also recently obtained a mercapto compound from 3-nitro-4-thiocyanopyridine in a good yield by the same method. The application of this method on (II) gave, besides 2-ethoxy-4-mercapto-5-nitropyrimidine (IV), the unexpected 2,4-diethoxy-5-nitropyrimidine (V).

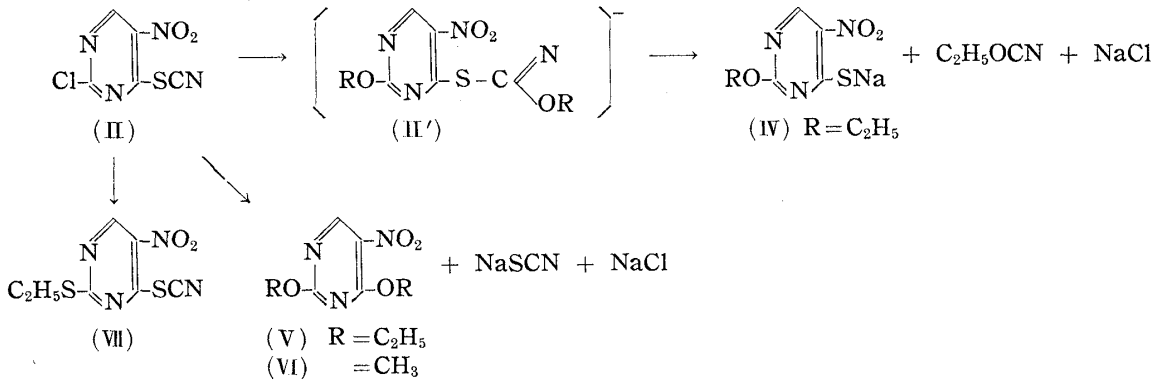

Chart 3.

It appears evident that the compound (IV) is formed through the intermediate (II'), the -S-C< bond of which is cleaved, and formation of the by-product (V) is regarded as being a simple substitution reaction. When methanol was used instead of ethanol, 2,4-dimethoxy-5-nitropyrimidine (VI) was obtained in a good yield and formation of the mercapto derivative decreased. 2-Ethylthio-4-thiocyano-5-nitropyrimidine (VII) was obtained from the reaction of (II) with 1 mole of sodium ethanethioxide in ethanol, the thiocyano group of (II) not being attacked.

Compound (IV) was reduced to (VIII) with sodium hydrosulfite in alkali solution, and (V) and (VI) were reduced to (IX) and (X) with iron powder and acetic acid. A similar reduction of (VII) with iron powder and acetic acid resulted in ring closure and the formation of 2-amino-5-ethylthio-thiazolo[5,4-*d*]pyrimidine (XI), which was subsequently acetylated to (XII).

The diformyl and diacetyl derivatives prepared from (VIII) with formic acid or acetic

8) J. Ross : J. Am. Chem. Soc., **56**, 727(1934).
9) T. Takahashi, K. Ueda : This Bulletin, **2**, 196(1954).

anhydride were converted into 5-ethoxythiazolo[5,4-*d*]pyrimidine (XIII) and 2-methyl-5-ethoxythiazolo[5,4-*d*]pyrimidine (XIV), respectively, by refluxing for further 2 hours.

Finally, 2-mercapto-5-ethoxythiazolo[5,4-*d*]pyrimidine (XV) was prepared from (VIII) with potassium methylxanthate, and (XV) in turn was converted into 2-ethylthio-5-ethoxythiazolo[5,4-*d*]pyrimidine (XVI) and 2-benzylthio-5-ethoxythiazolo[5,4-*d*]pyrimidine (XVII) as shown in Chart 4.

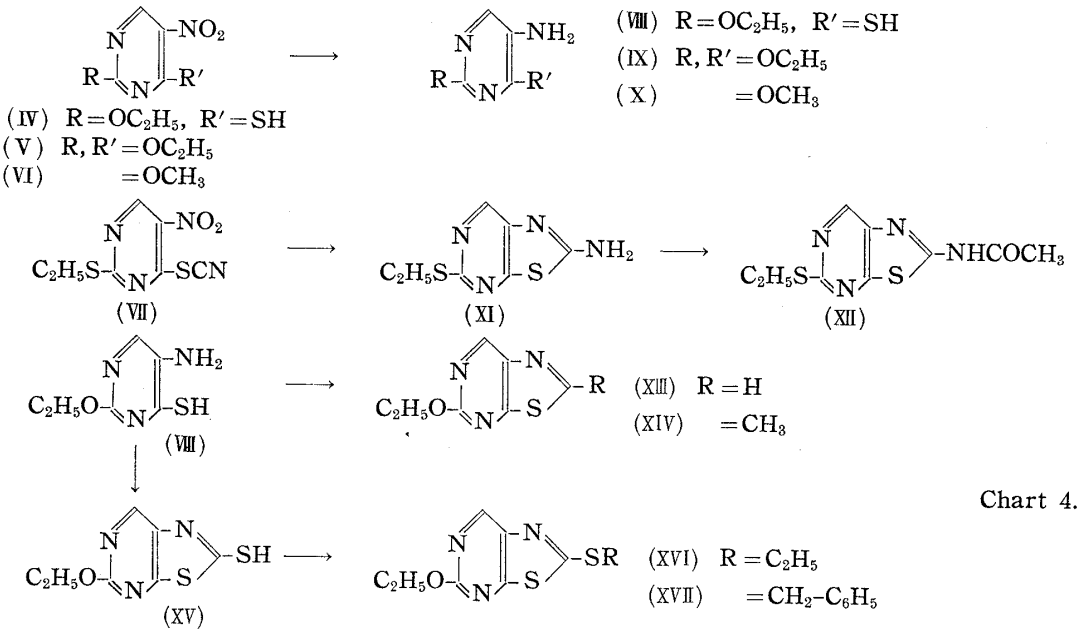

Chart 4.

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

Experimental

(All melting points are uncorrected)

2-Chloro-4-thiocyano-5-nitropyrimidine (II)—To a solution of 1.94 g. of (I) in 5 cc. of glacial AcOH 0.97 g. of KSCN was added and stirring was continued for 15 mins. at 10°. The reaction mixture was poured into ice water and the precipitate was recrystallized from benzene to greenish yellow prisms, m.p. 141°; yield, 1.84 g. *Anal.* Calcd. for $C_5HO_2N_4ClS$: C, 27.71; H, 0.41. Found: C, 27.55; H, 0.72.

Reaction of 2-Chloro-4-thiocyano-5-nitropyrimidine (II) with Methanol—A solution of 2 g. of (II) in 10 cc. of MeOH was refluxed on a water bath for 5 hrs. After cool, the deposited crystals were collected, the filtrate was concentrated, the residue and the above obtained crystals were combined, washed with H_2O, and recrystallized from H_2O to colorless needles. This substance did not melt below 300°, and it was also prepared by the treatment of (II) with EtOH in the same way. The product was identified as 5-nitrouracil as described above. *Anal.* Calcd. for $C_4H_3O_3N_4$: C, 30.56; H, 1.91; N, 26.75. Found: C, 30.74; H, 2.08; N, 26.72.

Reaction of (II) with Sodium Ethoxide—To a stirred solution of 100 cc. of EtOH containing 1.2 g. of Na, 5 g. of (II) was added and the mixture was maintained below 10°. The color of the solution changed to dark red. After continued stirring for 2 hrs., the solvent was removed by distillation, a small amount of H_2O was added to the residue, and the separated oily product (1.8~2.0 g.) was extracted with ether. This was identified as 2,4-diethoxy-5-nitropyrimidine, m.p. 45°, which was synthesized from 2,4-dichloro-5-nitropyrimidine with 2 moles of EtONa. Acidification of the aqueous layer with dil. H_2SO_4 gave reddish yellow crystals (2~2.5 g.), which recrystallized from EtOH to yellow scales, m.p. 133°. This substance is 2-ethoxy-4-mercapto-5-nitropyrimidine (IV). *Anal.* Calcd. for $C_6H_7O_3N_3S$: C, 35.82; H, 3.84. Found: C, 36.19; H, 3.52.

2,4-Dimethoxy-5-nitropyrimidine (VI) (Reaction of (II) with Sodium Methoxide)—To a solution of 0.25 g. of Na in 30 cc. of MeOH, 1.1 g. of (II) was added with stirring at 0°. After continued stirring for 2 hrs., the reddish yellow solution was poured into H_2O, the product was collected, and recrystallized from MeOH to pale yellow prisms, m.p. 95°; yield, 0.75 g. *Anal.* Calcd. for $C_6H_7O_4N_3$: C, 38.92; H, 3.81. Found: C, 38.58; H, 3.52.

2-Ethylthio-4-thiocyano-5-nitropyrimidine (VII) (Reaction of (II) with 1 Mole of Sodium Ethanethioxide)—A solution of 1 mole of EtSNa in 30 cc. of dehyd. EtOH was added dropwise to a suspension

of 4.3 g. (II) in 60 cc. of EtOH at 0° to 5°. The temperature was gradually raised to room temperature. After 2 hrs., the reaction mixture was concentrated to one-third the original volume without filtering. After cool, the separated yellow needles and NaCl were collected, washed with H_2O, and the filtrate was further concentrated until an oily product was observed. A small amount of ether was added to the residue, the insoluble crystals were collected and washed with ether. The collected crystals were combined and recrystallized from EtOH to yellow needles, m.p. 131°. *Anal.* Calcd. for $C_7H_6O_2N_4S$: C, 34.72; H, 2.50. Found : C, 34.33; H, 2.21.

2,4-Diethoxy-5-aminopyrimidine (IX)—A mixture of 3 g. of (V) in 15 cc. of AcOH and 3 g. of Fe powder was heated on a water bath at 60° for 1 hr. under vigorous stirring, the reaction mixture was filtered, and the filtrate was evaporated under reduced pressure to dryness. A small amount of H_2O was added to the residue, extracted with ether, the ether layer was washed with *N* NaOH and H_2O, dried, and 2.1 g. of an oily product was obtained by removal of the solvent. This was recrystallized from petr. ether to colorless prisms, m.p. 64°. *Anal.* Calcd. for $C_8H_{13}O_2N_3$: C, 52.44; H, 7.15. Found : C, 52.83; H, 6.86.

2,4-Dimethoxy-5-aminopyrimidine (X)—The preparation was carried out by reducing (VI) in AcOH with Fe powder as described above. Colorless needles (from petr. ether), m.p. 89°. *Anal.* Calcd. for $C_6H_9O_2N_3$: C, 46.44; H, 5.82. Found : C, 46.97; H, 5.92.

2-Amino-5-ethylthio-thiazolo[5,4-*d*]pyrimidine (XI)—To a hot solution of 0.3 g. of (VII) in 7 cc. of AcOH, 0.2 g. of Fe powder was added. After stirring for 2 hrs. at 60°, the reaction mixture was filtered, the filtrate was eveporated to dryness *in vacuo*, and the residue was extracted with hot AcOEt. Removal of the solvent afforded 0.24 g. of crystals which recrystallized to white needles or prisms from EtOH, m.p. 123°. *Anal.* Calcd. for $C_8H_7N_4S_2$: C, 39.26; H, 3.80; N, 26.41. Found : C, 39.69; H, 3.95; N, 26.30.

Acetate (XII) : (XI) was treated with Ac_2O in the usual way and the product was recrystallized from 50% EtOH to colorless needles, m.p. 125~126°. *Anal.* Calcd. for $C_9H_{10}ON_4S_2$: C, 42.52; H, 3.97. Found : C, 42.71; H, 4.12.

2-Ethoxy-4-mercapto-5-aminopyrimidine (VIII)—Sodium hydrosulfite (5~7 g.) was added in one batch to a stirred solution of 1.2 g. of (IV) in 5 cc. of 10% NaOH. The reaction proceeded exothermically and red color of the solution changed to yellow. Stirring was continued at 50° for another 15 mins. The solution was cooled and extracted with AcOEt to give orange yellow crystals, which were recrystallized from benzene to light yellow prisms or needles, m.p. 127°; yield, 0.7 g. *Anal.* Calcd. for $C_6H_9ON_3S$: C, 42.10; H, 5.30. Found : 42.48; H, 5.04.

5-Ethoxythiazolo[5,4-*d*]pyrimidine (XIII)—A solution of 0.2 g. of (VIII) in 5 cc. of HCOOH was refluxed for 2 hrs. and excess HCOOH was evaporated by distillation *in vacuo*. The residue was basified with 5% NaOH, extracted with ether, and dried. Removal of the solvent gave an oily product which soon solidified. Recrystallized from petr. ether to colorless needles, m.p. 95°. Yield, 0.09 g. *Anal.* Calcd. for $C_7H_7ON_3S$: C, 46.41; H, 3.90. Found : C, 46.18; H, 3.88.

2-Methyl-5-ethoxythiazolo[5,4-*d*]pyrimidine (XIV)—This was obtained by refluxing 0.2 g. of (VIII) with 5 cc. of Ac_2O, similar to the case of (XIII). Recrystallization from 20% EtOH gave 0.1 g. of white needles, m.p. 93°. *Anal.* Calcd. for $C_8H_9ON_3S$: C, 49.23; H, 4.65. Found : C, 49.31; H, 4.80.

2-Mercapto-5-ethoxythiazolo[5,4-*d*]pyrimidine (XV)—A solution of potassium methylxanthate was prepared by adding 0.32 g. of CS_2 under shaking to 0.3 g. of KOH in 2 cc. of H_2O and 10 cc. of MeOH, and 0.5 g. of (VIII) was added to this solution. The reaction mixture was refluxed for 15 hrs., the solvent was concentrated on a water bath, and treated with 5 cc. of H_2O. The solution was decolorized with charcoal, filtered, and the clear filtrate was neutralized with AcOH. The separated product was recrystallized from EtOH to pale yellow needles, which began to melt near 234° and to decompose at above 280°. Yield, 0.5 g. *Anal.* Calcd. for $C_7H_7ON_3S_2$: C, 39.44; H, 3.31. Found : C, 39.17; H, 3.24.

2-Ethythio-5-ethoxythiazolo[5,4-*d*]pyrimidine (XVI)—To a solution of 0.07 g. of KOH in a small amount of H_2O and 15 cc. of EtOH, 0.2 g. of (XV) was added. After addition of 0.11 g. of EtBr, the reaction mixture was refluxed for 30 mins. Removal of the solvent left an oily product which soon solidified upon addition of H_2O. This was extracted with ether, and the ether layer was dried and evaporated. The product was recrystallized from petr. ether to colorless needles or prisms, m.p. 66°. Yield, 0.19 g. *Anal.* Calcd. for $C_9H_{11}ON_3S_2$: C, 44.81; H, 4.60. Found : C. 44.71; H, 4.62.

2-Benzylthio-5-ethoxythiazolo[5,4-*d*]pyrimidine (XVII)—0.12 g. of benzyl chloride was added to a solution of 0.2 g. of (XV) and 0.07 g. of KOH in a small amount of H_2O and 15 cc. of EtOH, and the mixture was refluxed for 30 mins. After cool, the crystals (white needles) were collected by filtration, the filtrate was evaporated, the residue was treated with a small amount of H_2O, and the insoluble crystals were combined with the first crop of white needles. This was washed with H_2O and recrystallized from EtOH to white needles, m.p. 102°. Yield, 0.22 g. *Anal.* Calcd. for $C_{14}H_{13}ON_3S_2$: C, 55.44; H, 4.32. Found : C, 55.21; H, 4.29.

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.

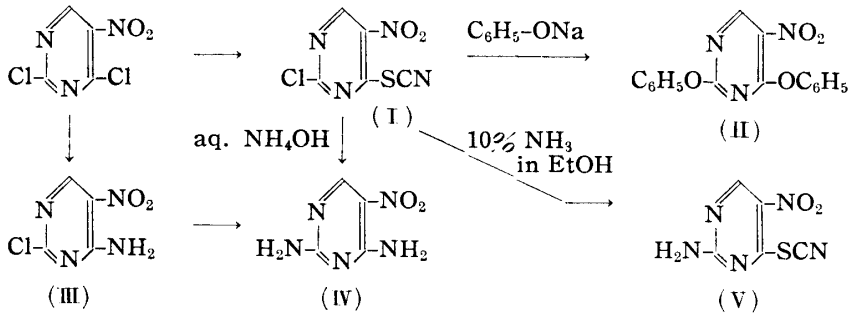

Chart 1.

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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1) Part I: This Bulletin, **6**, 334(1958).