case of 5-hydroxy-7-amino- and 5,7-dihydroxy-*s*-triazolo[2.3-*a*]pyrimidines, reaction of bromine gave 6-bromo derivatives (VIIb and VIIIb) while that of chlorine gave 5-dichloroacetamido-*s*-triazole (IX) instead of 6-chloro derivatives (VIIa and VIIIa). 2-Halo-1,3-dicarbonyl compounds were condensed with 5-amino-*s*-triazole (X) into 6-chloro-*s*-triazolo[2,3-*a*]pyrimidines (VIa, VIIa, and VIIIa), but 6-bromo derivatives were not obtained due to resinification. Ultraviolet spectra of 19 kinds of 6-halo-*s*-triazolo[2,3-*a*]pyrimidines were measured and compared with those of the corresponding original compounds.

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[127] **Yasuo Makisumi** : Synthesis of Potential Anticancer Agents. VI.*2
Reactivity of 6-Bromo-*s*-triazolo[2,3-*a*]pyrimidines.

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In Part III of this series,[1] it was shown that the halogen atom at 7-position of *s*-triazolo[2,3-*a*]pyrimidines reacted readily with nucleophilic reagents, but the halogen atom at 6-position was very resistant to nucleophilic substitutions. For example, 6,7-dihalo-*s*-triazolo[2,3-*a*]pyrimidines reacted with acid or alkali, ammonia, thiourea, and hydrogen iodide to form 7-hydroxy-, 7-amino-, 7-mercapto-, and 7-iodo-6-halo-*s*-triazolo[2,3-*a*]-pyrimidines, respectively.

X=Cl or Br R=OH, NH_2, SH or I

It has been generally concluded that in the pyrimidine series halogens at 5-position of pyrimidines are quite stable and difficult to be displaced by nucleophilic reagents, except in a few cases.

However, Phillips[2] has reported that the 5-bromo derivatives of uracil and isocytosine react with several amines to give the corresponding 5-substituted amino derivatives. Barker and co-workers[3] have also reported that the 5-bromo derivatives of barbituric acid and 6-aminouracil react with thiourea to give the corresponding derivatives containing sulfur at their 5-position.

These facts suggested the possibility that, in *s*-triazolo[2,3-*a*]pyrimidines, the presence of groups capable of tautomerism at both 5- and 7-positions might activate the halogen at 6-position sufficiently to bring about a reaction. In order to clarify this point, the same reactions were carrried out with 6-bromo-*s*-triazolo[2,3-*a*]pyrimidines in the present series of work.

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*1 Fukushima-ku, Osaka (牧角徳夫).
*2 Part V : This Bulletin, **9**, 808 (1961).
1) Y. Makisumi, H. Kanō : *Ibid.*, **7**, 907 (1959).
2) A.P. Phillips : J. Am. Chem. Soc., **73**, 1061 (1951); *ibid.*, **75**, 4092 (1953).
3) G.R. Barker, N.G. Luthy, M.M. Dhar : J. Chem. Soc., **1954**, 4206.

In attempting this reaction with substituted amines, butylamine and cyclohexylamine were used as the primary amines, and piperidine and morpholine were used as the secondary amines. The reaction was carried out at the boiling temperature of these amines.

6-Bromo-7-hydroxy-*s*-triazolo[2,3-*a*]pyrimidine[1] (I) and its 5-methyl derivative[4] (II) failed to react with the primary or secondary amines. Although 5-hydroxy-6-bromo-7-amino-*s*-triazolo[2,3-*a*]pyrimidine*[2] (III) did not react with the primary amines, (III) was converted into the corresponding 6-piperidino and 6-morpholino derivatives (V and VI) by reaction with the secondary amines. Similarly, 5,7-dihydroxy-6-bromo-*s*-triazolo[2,3-*a*]-pyrimidine*[2] (IV) was also converted into the corresponding 6-piperidino and 6-morpholino derivatives (VII and VIII), but the reaction with the primary amines was unsuccessful.

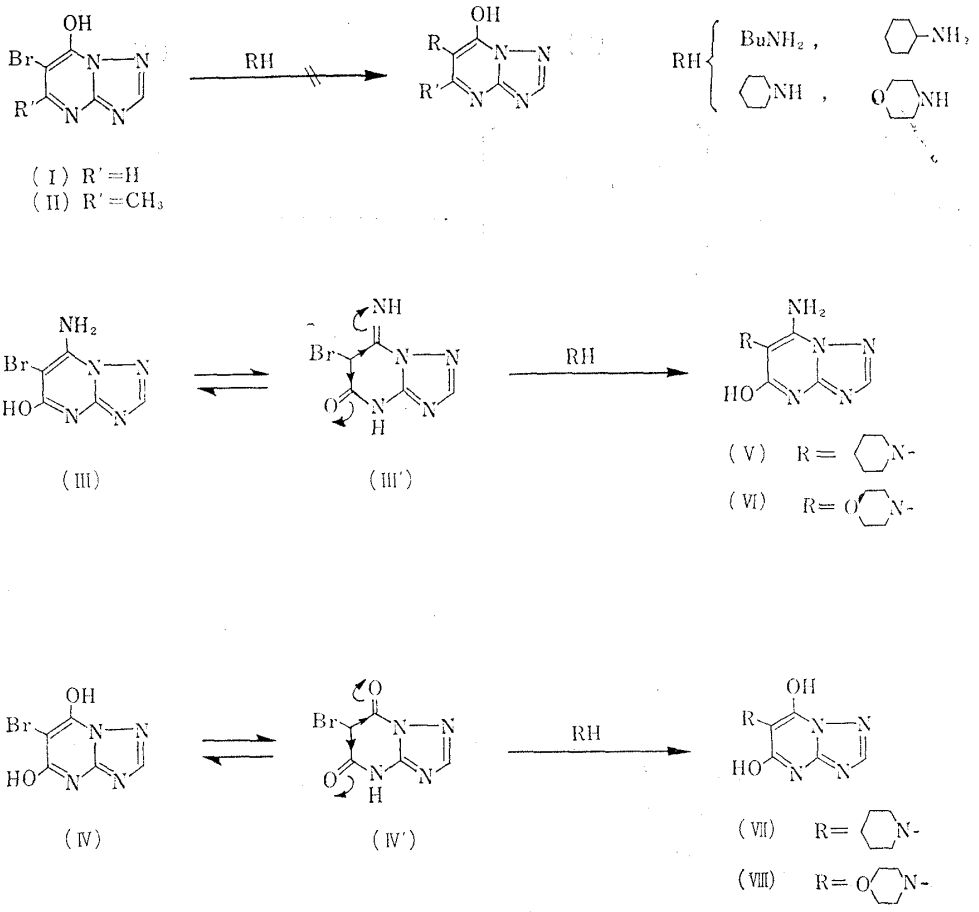

Chart 1.

In the reaction with thiourea, the 6-bromo-7-hydroxy compounds (I and II) also did not react, but (IV) reacted with thiourea in boiling ethanol. A white intermediate was formed which was assumed to be 5,7-dihydroxy-6-amidinothio-*s*-triazolo[2,3-*a*]pyrimidine (IX). It would appear that the compound (IX) is stabilized by internal salt formation or by hydrogen bonding. On hydrolysis with aqueous alkali, (IX) gave bis(5,7-dihydroxy-*s*-triazolo[2,3-*a*]pyrimidin-6-yl) disulfide (X), which was also obtained by the reaction of (IV) and thiourea in alkaline medium. Polarography of this compound (X) clearly demonstrated the presence of a disulfide linkage, its alkaline solution showing a cathodic wave, which confirms this structure.

Reaction of (III) with thiourea in boiling ethanol gave the known 5-hydroxy-7-amino-*s*-triazolo[2,3-*a*]pyrimidine (XII) and sulfur. In this reaction, it was assumed that the

4) H. Konō, Y. Makisumi, S. Takahashi, M. Ogata : This Bulletin, **7**, 903 (1959).

6-amidinothio derivative (XI), which would be produced as the intermediate, was decomposed to (XII) by the action of hydrogen bromide, produced as a by-product. Accordingly, the reaction of (III) with thiourea was carried out in alkaline medium and bis(5-hydroxy-7-amino-*s*-triazolo[2,3-*a*]pyrimidin-6-yl) sulfide (XIII) and (XII) were obtained, but a disulfide analogous to (X) was not isolated. The same difference in the behavior as that between (III) and (IV) is also known in pyrimidine derivatives.[3]

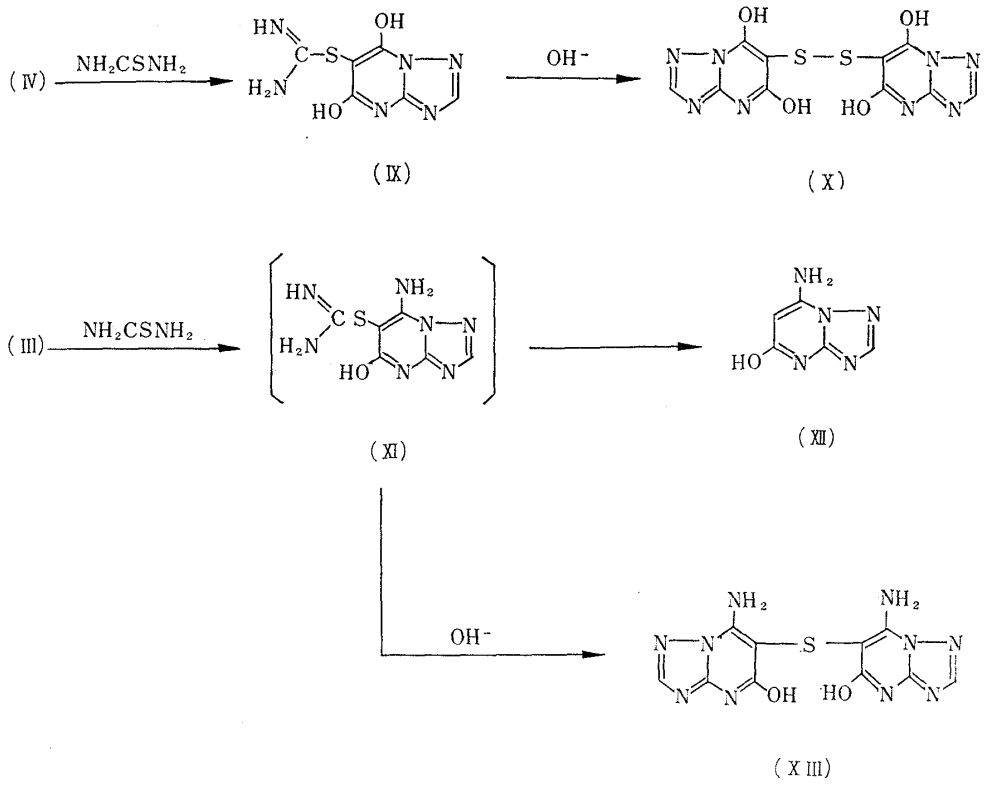

Chart 2.

From these experiments, it was clarified that 6-bromo-*s*-triazolo[2,3-*a*]pyrimidines which possessed groups capable of tautomerism (e.g. OH or NH_2) at both 5- and 7-position, reacted with some nucleophilic reagents and the bromine at 6-position was displaced by reactants.

Biological details of these compounds will be reported elsewhere.

Experimental*2

5-Hydroxy-6-piperidino-7-amino-*s*-triazolo[2,3-*a*]pyrimidine (V)——A mixture of 1.0 g. of (III) and 2.0 g. of piperidine was refluxed at 140~150° for 4 hr. The reaction mixture was diluted with 20 cc. of H_2O and AcOH was added to bring the pH to 6~7. After cool, the resulting crystals were collected and recrystallized from 50% EtOH to 0.8 g. of colorless needles, m.p. 259.5°(decomp.). *Anal.* Calcd. for $C_{10}H_{14}ON_6$: C, 51.27; H, 6.02; N, 35.88. Found: C, 50.94; H, 6.36; N, 35.74.

5-Hydroxy-6-morpholino-7-amino-*s*-triazolo[2,3-*a*]pyrimidine (VI)——A mixture of 0.5 g. of (III) and 1.0 g. of morpholine was refluxed for 4 hr. The reaction mixture was treated by the same method as above and the resulting product was recrystallized from 50% EtOH to 0.4 g. of colorless needles, m.p. 309°(decomp.). *Anal.* Calcd. for $C_9H_{12}O_2N_6 \cdot \frac{1}{2}H_2O$: C, 44.07; H, 5.34; N, 34.31. Found: C, 44.28; H, 5.55; N, 34.12.

5,7-Dihydroxy-6-piperidino-*s*-triazolo[2,3-*a*]pyrimidine (VII)——A mixture of 1.0 g. of (IV) and 2.0 g. of piperidine was refluxed for 3 hr. The reaction mixture was treated by the same method

*3 All melting points are uncorrected.

as above and the resulting crystals were recrystallized from hydr. EtOH to 0.9 g. of colorless needles, m.p. 320~321°(decomp.). *Anal.* Calcd. for $C_{10}H_{13}O_2N_5$: C, 51.05; H, 5.57; N, 29.77. Found: C, 50.70; H, 5.95; N, 29.81.

5,7-Dihydroxy-6-morpholino-*s*-triazolo[2,3-a]pyrimidine (VIII)——A mixture of 1.1 g. of (IV) and 2.2 g. of morpholine was refluxed for 3 hr. The reaction mixture was treated by the same way as above and the resulting crystals were recrystallized from hydr. EtOH to 1.0 g. of colorless scales, m.p. 295°(decomp.). *Anal.* Calcd. for $C_9H_{11}O_3N_5 \cdot H_2O$: C, 42.35; H, 5.13; N, 27.74. Found : C, 42.77; H, 5.42; N, 27.54.

5,7-Dihydroxy-6-amidinothio-*s*-triazolo[2,3-*a*]pyrimidine (IX)——To a solution of 0.6 g. of (IV) dissolved in 150 cc. of 90% EtOH, a solution of 0.2 g. of thiourea in 20 cc. of EtOH was added and the mixture was refluxed for 30 min. The white crystals deposited were collected by filtration, washed with hydr. EtOH, and dried to 0.47 g. of a white crystalline powder, m.p. above 320°. *Anal.* Calcd. for $C_6H_6O_2N_6S$: C, 31.86; H, 2.67; N, 37.16; S, 14.15. Found : C, 31.61; H, 3.01; N, 36.96; S, 13.80.

Bis(5,7-dihydroxy-*s*-triazolo[2,3-*a*]pyrimidin-6-yl) Disulfide (X)——a) To a solution of 1.1 g. of (IV) in 20 cc. of 1% NaOH, a solution of 0.38 g. of thiourea in 30 cc. of H_2O was added and the mixture was heated on a water bath for 3 hr. The yellowish white crystals deposited were collected by filtration, washed with H_2O, and dried. The resulting crystals (0.6 g.) were dissolved in dil. NaOH, filtered, and the filtrate was acidified with 10% HCl, giving a yellowish white crystalline powder, m.p. 234~235°(decomp.). *Anal.* Calcd. for $C_{10}H_6O_4N_8S_2 \cdot 2H_2O$: C, 29.85; H, 2.50; N, 27.85; S, 15.91. Found : C, 29.51; H, 2.83; N, 28.17; S, 15.89. Polarographic data : $E_{1/2}$=0.7 v.(3.96 mg./100 cc. in 0.05*N* KOH).

b) A solution of 0.5 g. of (IX) dissolved in 5 cc. of *N* NaOH was heated on a water bath for 30 min. and the hot reaction solution was filtered. After cool, an equal volume of EtOH was added to this filtrate and the resulting Na salt of (X) was collected, dissolved in H_2O, filtered with charcoal, and the filtrate was acidified with HCl to give 0.3 g. of a yellowish white crystalline powder, m.p. 234~235° (decomp.), which was identified with the compound prepared by method (a) by infrared spectrum. *Anal.* Calcd. for $C_{10}H_6O_4N_8S_2 \cdot 2H_2O$: C, 29.85; H, 2.50; N, 27.85; S, 15.91. Found : C, 29.64; H, 2.83; N, 27.78; S, 15.89.

Reaction of (III) with Thiourea——a) To a solution of 0.6 g. of (III) dissolved in 250 cc. of 85% EtOH, a solution of 0.2 g. of thiourea in 20 cc. of EtOH was added and the mixture was refluxed for 5 hr. The reaction mixture was concentrated to one-third the original volume and the resulting precipitate was collected, dissolved in dil. NaOH, and insoluble S was filtered off. The filtrate was acidified with AcOH and resulting crystals were collected, washed with H_2O, and recrystallized from hydr. EtOH to 0.23 g. of 5-hydroxy-7-amino-*s*-triazolo[2,3-*a*]pyrimidine (XII) as colorless prisms, m.p. above 320°. *Anal.* Calcd. for $C_5H_5ON_5$: C, 39.73; H, 3.33; N, 46.34. Found : C, 39.79; H, 3.43; N, 46.28.

b) 1.2 g. of (III) was suspended in 50 cc. of H_2O and dissolved by addition of 2 cc. of 10% NaOH. A solution of 0.4 g. of thiourea in 5 cc. of H_2O was added and the mixture was heated on a water bath for 2 hr. After cool, the precipitated crystals were collected, dissolved in dil. NaOH, filtered with charcoal, and the filtrate was acidified with AcOH to give 0.5g. of white crystals. Recrystallization from hydr. EtOH gave 0.1 g. of bis(5-hydroxy-7-amino-*s*-triazolo[2,3-*a*]pyrimidin-6-yl) sulfide (XIII) as a white crystalline powder, m.p. above 320°. *Anal.* Calcd. for $C_{10}H_8O_2N_{10}S \cdot H_2O$: C, 34.29; H, 2.85; N, 40.00. Found : C, 34.56; H, 3.17; N, 40.00. From the reaction solution and the filtrate of recrystallization, 0.4 g. of (XII) was obtained as colorless prisms, m.p. above 320°.

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Summary

5-Hydroxy-6-bromo-7-amino- and 5,7-dihydroxy-6-bromo-*s*-triazolo[2,3-*a*]pyrimidines (III and IV) reacted with piperidine or morpholine to form the corresponding 6-piperidino- (V and VII) or morpholino- (VI and VIII) derivatives. Reaction of (IV) with thiourea gave the 6-amidinothio derivative (IX), which was converted into disulfide compound (X) by the action of alkali. Reaction of (III) with thiourea gave the 5-hydroxy-7-amino derivative (XII) and this reaction in alkaline medium gave the sulfide compound (XIII).

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