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125. Yasuo Makisumi : Synthesis of Potential Anticancer Agents. IV.[*2] 5,7-Disubstituted *s*-Triazolo[2,3-*a*]pyrimidines.

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In the previous paper of this series,[1] the authors described the synthesis of 7-substituted *s*-triazolo[2,3-*a*]pyrimidines as tumor inhibiting agents, with some of them showing biological activity.[2,3]

The present paper describes the synthesis of some 5,7-disubstituted *s*-triazolo[2,3-*a*]-pyrimidines for biological evaluation, including the reactivity and transformation of these substituents.

It has been reported by Heimbach and Kelly[4] that the condensation of ethyl malonate and ethyl cyanoacetate with 5-amino-*s*-triazole (I) gave 5,7-dihydroxy- and 5-amino-7-hydroxy-*s*-triazolo[2,3-*a*]pyrimidines (II and III′), but the reaction conditions and the physical character of these compounds were not described. Moreover, the possibility of formation of another isomer (III) as the condensate of ethyl cyanoacetate and (I) was not considered.

The condensation of ethyl malonate and ethyl cyanoacetate with (I) did not proceed in ethanol or glacial acetic acid at refluxing temperature, and only 5-acetamido-*s*-triazole was obtained in the latter solvent. In the presence of sodium ethoxide in ethanol, however, the condensation furnished 5,7-dihydroxy-*s*-triazolo[2,3-*a*]pyrimidine (II) and 5-hydroxy-7-amino-*s*-triazolo[2,3-*a*]pyrimidine(III). These condensation products proved to be *s*-triazolo[2,3-*a*]pyrimidines, and not *s*-triazolo[4,3-*a*]pyrimidines (V) by the transformation reaction described below. The Heimbach's structure (III′) for the condensate of ethyl cyanoacetate with (I) was also rejected by the following experimental evidence.

Similarly, condensation of methyl ethoxycarbonyldithioacetate[5] with (I) in the presence of sodium exthoxide in ethanol gave 5-hydroxy-7-mercapto-*s*-triazolo[2,3-*a*]pyrimidine (IV) and the structure of (IV) was also determined by the following reactions.

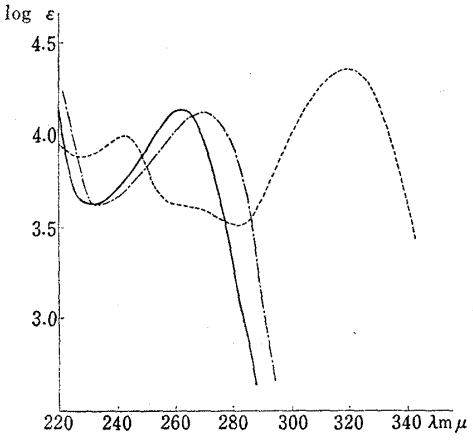
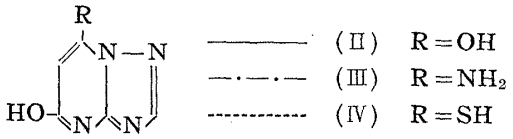


Fig. 1. Ultraviolet Absorption Spectra (in EtOH)



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*2 Part III : This Bulletin, **7**, 907 (1959).

1) H. Kano, Y. Makisumi : *Ibid.*, **6**, 583 (1958).
2) T. Okabayashi, H. Kanō, Y. Makisumi : *Ibid.*, 8, 157 (1960).
3) T. Okabayashi : *Ibid.*, 8, 162 (1960).
4) N. Heimbach, W. Kelly : U.S. Pat. 2,444,605 (1948).
5) P.V. Laakso : Suomen Kemistilehti, **17B**, 1 (1944)(C.A., **40**, 4671 (1946)).

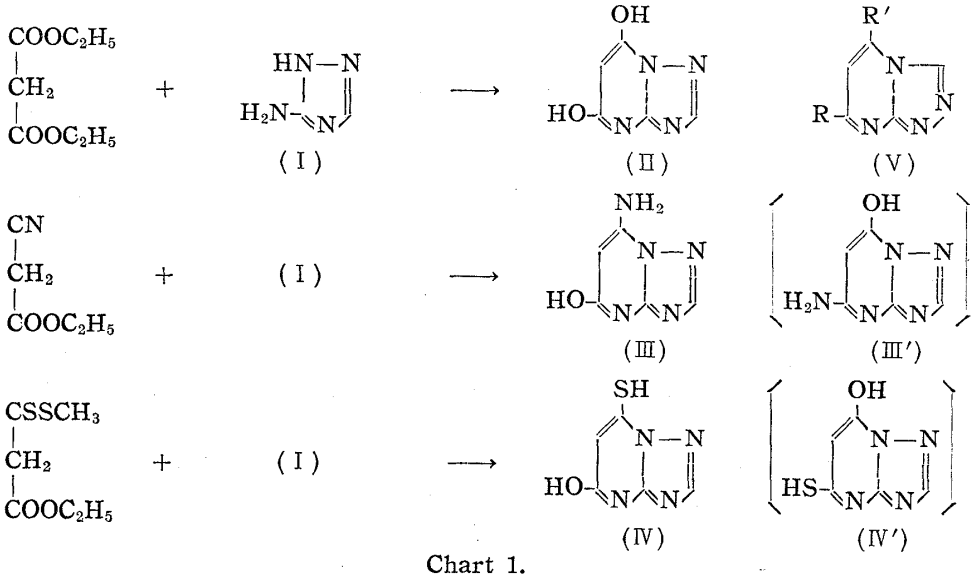

Chart 1.

Treatment of the 5,7-dihydroxy derivative (II) with phosphoryl chloride at 100° gave the 5,7-dichloro derivative (VI). Dehalogenation of (VI) using palladium-charcoal as a catalyst in hydrogen stream gave *s*-triazolo[2,3-*a*]pyrimidine (VII), which was identified with the authentic sample.*2 Heating of (VI) with ethanolic ammonia solution in a sealed tube at 160° gave the 5,7-diamino derivative (VIII) and reaction of (VI) with two molar amounts of thiourea produced the 5,7-dimercapto derivative (IX), which was methylated with methyl iodide in alkaline solution into the 5,7-dimethylthio derivative (X).

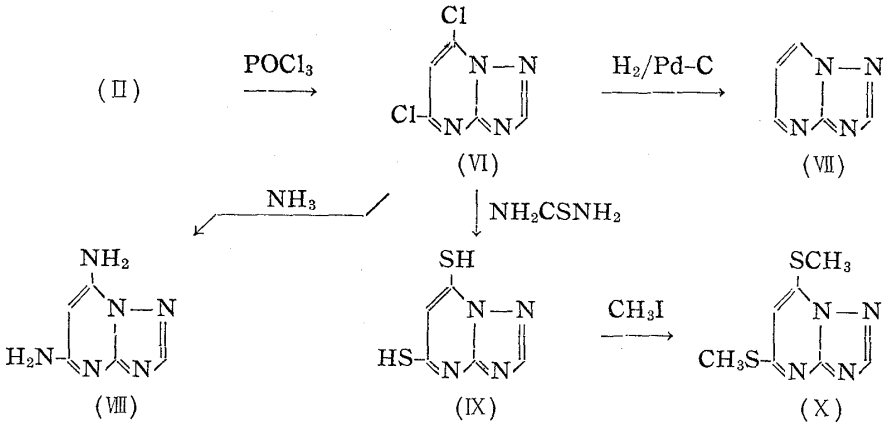

Chart 2.

However, hydrolysis of (VI) with aqueous acid or alkaline solution gave, not the 5,7-dihydroxy derivative (II), but a monochloro-monohydroxy derivative (XI), which was dehalogenated by means of catalytic reduction into the hydroxyl derivative (XIII'). (XIII') was identified with 7-hydroxy-*s*-triazolo[2,3-*a*]pyrimidine obtained by the condensation of malic acid with (I) in the preceding work.*2 Therefore, the hydrolyzed product of (VI) was determined as 5-chloro-7-hydroxy-*s*-triazolo[2,3-*a*]pyrimidine. Attempts to displace the chlorine atom of (XI) with ammonia or thiourea and further hydrolysis into (II) were unsuccessful.

From the result of these reactions, it was assumed that the two chlorine atoms in (VI) are somewhat different in their reactivity. In the case of (XI), the chlorine atom at 5-position is stabilized by the —M effect of hydroxyl group at 7-position and therefore is resistant to the displacement.

For comparison of the reactivity of two halogens in 5- and 7-positions, partial dehalogenation of (VI) was carried out and a monochloro derivative (XII) was obtained. This product was not identified with the known 7-chloro-*s*-triazolo[2,3-*a*]pyrimidine*[2] (XII′) and (XII) was considered to be 5-chloro-*s*-triazolo[2,3-*a*]pyrimidine. (XII) was converted into 5-hydroxy (XIII), 5-amino (XIV), and 5-mercapto (XV) derivatives respectively by the action of hydrochloric acid, ammonia, and thiourea under mild conditions. (XIV) was acetylated with acetic anhydride into the 5-acetamido derivative (XVI), and (XV) was also methylated with methyl iodide into the 5-methylthio derivative (XVII). These products were compared with the corresponding 7-substituted *s*-triazolo[2,3-*a*]pyrimidines, by mixed melting point and ultraviolet absorption spectra.

Table I. Ultraviolet Absorption Spectra of Monosubstituted *s*-Triazolo[2,3-*a*]pyrimidines

Compd. No.	Substituent	m.p. (°C)	λ_{max}^{EtOH} mμ (log ε)		
(XII)	5-Cl	173~173.5			277 (3.67)
(XII′)	7-Cl	175~176			279.5 (3.69)
(XIII)	5-OH	274~275		247 (3.56)[a]	272 (3.67)
(XIII′)	7-OH	288~289		242 (3.67)	274 (3.96)
(XIV)	5-NH_2	266~267	223 (4.49)	243 (3.66)[a]	293.5 (3.62)
(XIV′)	7-NH_2	278~279		263.5 (3.72)[a]	292 (4.10)
(XV)	5-SH	259~260[b]	254.5 (3.96)	279 (3.76)[a]	348 (4.00)
(XV′)	7-SH	294~295[b]	236 (3.84)	278 (3.21)[a]	341 (4.34)
(XVII)	5-SCH_3	157~158.5		243.5 (4.15)	305 (3.96)
(XVII′)	7-SCH_3	207~208			303 (4.11)

a) shoulder *b*) m.p. (decomp.)

(XII) was dehalogenated by catalytic reduction into *s*-triazolo[2,3-*a*]pyrimidine (VII).

Treatment of (VI) with concentrated ammonium hydroxide at room temperature gave monochloro-monoamino derivative (XVIII), which was converted by catalytic reduction into a monoamino derivative (XIV′). This compound was identified with 7-amino-*s*-triazolo-[2,3-*a*]pyrimidine, obtained by the amination of 7-chloro derivative (XII′) in the preceding work.*[2] Therefore, (XVIII) was determined as 5-chloro-7-amino-*s*-triazolo[2,3-*a*]pyrimidine. Treatment of (XVIII) with ethanolic ammonia solution in a sealed tube at 160° gave the 5,7-diamino derivative (VIII) and hydrolysis of (XVIII) with dilute alkaline solution gave a 5-hydroxy-7-amino derivative, which was identified with the condensation product (III). Therefore, it was proved that the condensation product of ethyl cyanoacetate with (I) has not Heimbach's structure (III′) but is 5-hydroxy-7-amino-*s*-triazolo[2,3-*a*]pyrimidine (III). (XVIII) did not react with thiourea to form the 5-mercapto-7-amino derivative (XIX), probably because the chlorine atom at 5-position is stabilized by the effect of the amino group at 7-position.

From the results of the above experiments, it has been clarified that the halogens at 5- and 7-position of *s*-triazolo[2,3-*a*]pyrimidine ring are both extremely active towards nucleophilic substitution and the activity of halogen at 7-position is greater than that at 5-position, and hydroxyl or amino group at 7-position stabilizes the halogen atom at 5-position.

Hydroxy-mercapto derivative (IV), which was obtained by the condensation, was methylated with methyl iodide in dilute alkali solution into the hydroxy-methylthio derivative (XX), which was treated with ethanolic ammonia solution in a sealed tube at 160° to give a hydroxy-amino derivative. This compound was identified with 5-hydroxy-7-amino-*s*-triazolo[2,3-*a*]pyrimidine (III) by the infrared spectrum. Therefore, it was proved that the condensation product (IV) of methyl ethoxycarbonyldithioacetate with (I) is 5-hydroxy-7-mercapto-*s*-triazolo[2,3-*a*]pyrimidine and its methylated product (XX), the 5-hydroxy-7-methylthio derivative.

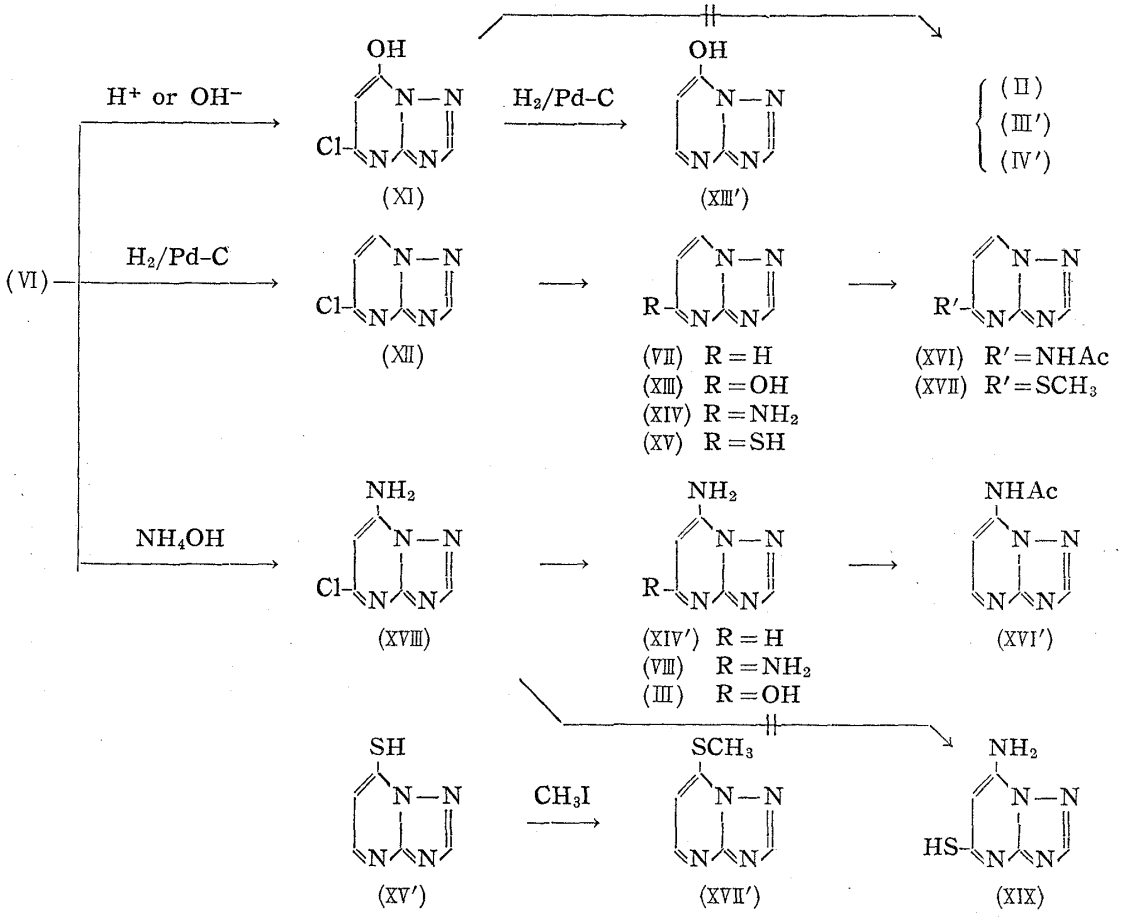

Chart 3.

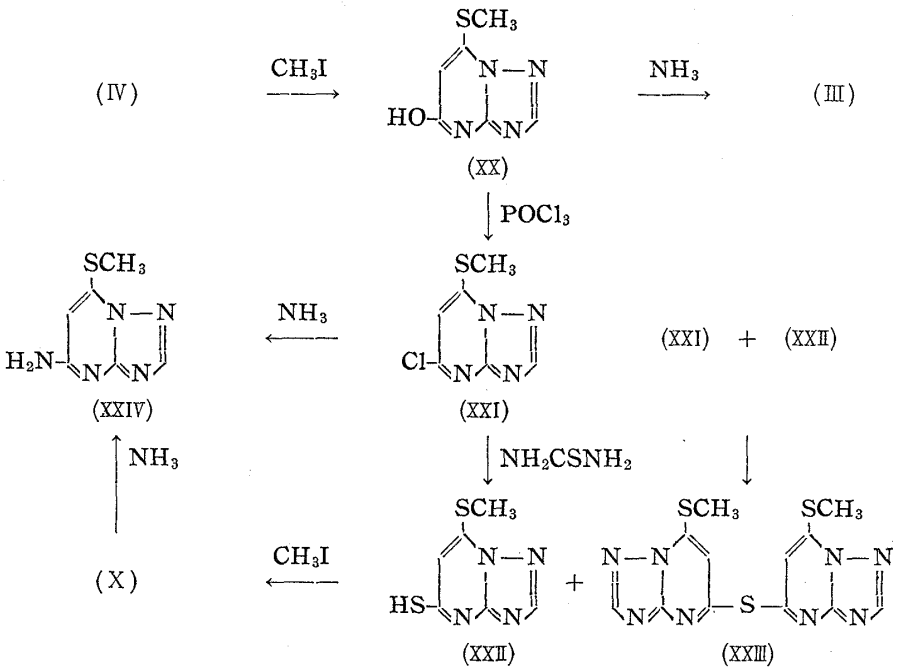

Chart 4.

(XX) was converted into the 5-chloro-7-methylthio derivative (XXI) by the action of phosphoryl chloride in the presence of N,N-dimethylaniline. Reaction of (XXI) with thiourea in boiling ethanol gave two products, alkali-soluble yellow crystals (XXII) and alkali-insoluble white crystals (XXIII), in the ratio of 3 to 1. (XXII) was determined as 5-mercapto-7-methylthio-*s*-pyrimidine by the result of elemental analysis and the fact that (XXII) was converted by the action of methyl iodide in aqueous alkaline solution into the 5,7-dimethylthio derivative (X). (XXIII) was identified with bis(7-methylthio-*s*-triazolo[2,3-*a*]-pyrimidin-5-yl) sulfide which was prepared by the reaction of (XXI) and (XXII) in aqueous alkaline solution. Heating of the 5,7-dimethylthio derivative (X) with ethanolic ammonia solution in a sealed tube at 160° gave a methylthio-amino compound (XXIV), which was identified with 5-amino-7-methylthio-*s*-triazolo[2,3-*a*]pyrimidine prepared by reaction of (XXI) with ethanolic ammonia solution.

Biological details of these compounds will be published elsewhere.

Experimental*3

5,7-Dihydroxy-*s*-triazolo[2,3-*a*]pyrimidine (II)——To a solution of 4.6 g. of Na in 150 cc. of dehyd. EtOH, 32 g. of ethyl malonate and 16.8 g. of 5-amino-*s*-triazole (I) were added and the mixture was refluxed for 8 hr. After cool, the precipitated white Na salt was collected, dissolved in H_2O, filtered with charcoal, and the filtrate was acidified with conc. HCl. The resulting precipitate was collected, washed with H_2O, and dried to 15.2 g. of white crystals, m.p. 236~237°(decomp.). Recrystallization from hydr. EtOH gave colorless needles, m.p. 238°(decomp.). *Anal.* Calcd. for $C_5H_4O_2N_4$: C, 39.41; H, 2.63; N, 36.84. Found : C, 39.46; H, 2.61; N, 36.63. UV : λ_{max}^{EtOH} 261 mμ (log ε 4.14). IR (in Nujol) cm^{-1} : 1710 (broad) (lactam C=O).

5-Hydroxy-7-amino-*s*-triazolo[2,3-*a*]pyrimidine (III)——a) To a solution of 2.3 g. of Na in 70 cc. of dehyd. EtOH, 11.3 g. of ethyl cyanoacetae and 8.4 g. of (I) were added. The mixture was refluxed for 8 hr. After cool, the precipitated Na salt was treated as described above to 8.0 g. of white crystals, m.p. above 320°. Recrystallization from hydr. EtOH gave colorless prisms, m.p. above 320°. *Anal.* Calcd. for $C_5H_5ON_5$: C, 39.73; H, 3.33; N, 46.34. Found : C, 39.81; H, 3.43; N, 46.54. UV: λ_{max}^{EtOH} 269 mμ (log ε 4.13). IR (in Nujol) cm^{-1} : 3486 (lactim N-H), 1642 (broad) (lactam C=O).

b) A mixture of 0.5 g. of 5-chloro-7-amino-*s*-triazolo[2,3-*a*]pyrimidine (XVIII) and 10 cc. of 10% NaOH was heated on a water bath for 2 hr. After cool, the reaction mixture was filtered and the filtrate was acidified with dil. HCl. The resulting precipitate was recrystallized from hydr. EtOH to 0.35 g. of colorless prisms, m.p. above 320°. *Anal.* Calcd. for $C_5H_5ON_5$: C, 39.73; H, 3.33; N, 46.34. Found: C, 40.01; H, 3.51; N, 45.92. This was identified by the infrared and ultraviolet spectra.

c) A mixture of 0.3 g. of 5-hydroxy-7-methylthio-*s*-triazolo[2,3-*a*]pyrimidine (XX) and 20 cc. of EtOH-NH_3 in a sealed tube was heated at 150~160° for 10 hr. After cool, the resulting crystals were collected and recrystallized from hydr. EtOH to 0.15 g. of colorless prisms, m.p. above 320°. *Anal.* Calcd. for $C_5H_5ON_5$: C, 39.73; H, 3.33; N, 46.34. Found : C, 39.84; H, 3.57; N, 46.28. This was also identified with the samples described in (a) and (b), by the infrared and ultraviolet spectra.

5-Hydroxy-7-mercapto-*s*-triazolo[2,3-*a*]pyrimidine (IV)——To a solution of 3.7 g. of Na in 80 cc. of dehyd. EtOH, 14.2 g. of methyl ethoxycarbonyldithioacetate and 6.7 g. of (I) were added and the mixture was refluxed for 15 hr. with stirring. After cool, the precipitated Na salt of (IV) was dissolved in H_2O, filtered with charcoal, and the filtrate was acidified with dil. HCl to 8.6 g. of slightly colored product, m.p. above 320°, which was recrystallized from 50% EtOH to colorless scales, m.p. above 320°. *Anal.* Calcd. for $C_5H_4ON_4S$: C, 35.72; H, 2.40; N, 33.33. Found : C, 36.01; H, 2.43; N, 33.50. UV λ_{max}^{EtOH} mμ (log ε) : 242 (4.00), 265 (shoulder), 319 (4.36). IR (in Nujol) cm^{-1} : 1643 (lactam C=O).

5,7-Dichloro-*s*-triazolo[2,3-*a*]pyrimidine (VI)——A mixture of 4.0 g. of (II) and 20 cc. of $POCl_3$ was heated at 100° for 4 hr., forming a clear solution. The solution was concentrated in a reduced pressure to a syrup, which was poured with stirring on crushed ice. The aqueous solution was extracted with $CHCl_3$, the extract was washed with H_2O, dried over $CaCl_2$, and evaporation of the solvent gave 4.2 g. of pale yellow crystals, m.p. 129~130°. Recrystallization from dehyd. EtOH gave colorless needles, m.p. 131~132°. *Anal.* Calcd. for $C_5H_2N_4Cl$: C, 31.77; H, 1.07; N, 29.64. Found: C, 31.98; H, 1.30; N, 29.42.

*3 All melting points are uncorrected. Infrared spectra were measured with the Kōken Infrared Spectrophotometer, Model DS-301, and ultraviolet spectra were taken with the Hitachi Recording Spectrophotometer, EPS-2.

Catalytic reduction of (VI)——a) To a solution of 0.5 g. of (VI) in 60 cc. of dehyd. EtOH, 0.3 g. of 5% Pd-C and 0.3 g. of Na_2CO_3 were added and the mixture was shaken in H_2 stream at ordinary temperature and pressure. The reaction almost came to a stop after absorption of ca. 2 moles of H_2. The catalyst was filtered off, the solvent was evaporated in a reduced pressure to dryness, and the residue was recrystallized from benzene to 0.2 g. of colorless prisms, m.p. 145~146°. *Anal.* Calcd. for $C_5H_4N_4$: N, 46.66. Found: N, 46.58. This was identified with the authentic sample of *s*-triazolo[2,3-*a*]pyrimidine (VII).

b) A solution of 1.0 g. of (VI) in 100 cc. of dehyd. EtOH was reduced with 0.3 g. of 5% Pd-C and 0.3 g. of Na_2CO_3 by the same method as above and the reaction stopped after absorption of ca. 1 mole of H_2. The reaction mixture was treated as above and the resulting product was recrystallized from benzene to 0.5 g. of 5-chloro-*s*-triazolo[2,3-*a*]pyrimidine (XII) as colorless needles, m.p. 173~173.5°, mixed m.p. 148~150° with the sample of 7-chloro-*s*-triazolo[2,3-*a*]pyrimidine (XII') of m.p. 175~176°. *Anal.* Calcd. for $C_5H_3N_4Cl$: C, 38.87; H, 1.97; N, 36.27. Found: C, 39.04; H, 2.26; N, 36.15.

This product (0.5 g.) was also reduced by the same method as above to 0.35 g. of (VII) as colorless prisms, m.p. 145~146°(from benzene).

Amination of (VI)——a) A mixture of 0.5 g. of (VI) and 20 cc. of EtOH-NH_3 was heated in a sealed tube at 160° for 8 hr. After cool, the resulting crystals were collected by filtration and recrystallized from H_2O to 0.25 g. of 5,7-diamino-*s*-triazolo[2,3-*a*]pyrimidine (VIII), colorless pillars, m.p. 300.5°(decomp.). *Anal.* Calcd. for $C_5H_6N_6$: C, 39.99; H, 4.03; N, 55.98. Found: C, 40.10; H, 4.23; N, 56.06.

b) Five g. of (VI) was added in small portions to 100 cc. of conc. NH_4OH at room temperature with stirring. After stirring for 2 hr., the resulting precipitate was collected by filtration and recrystallized from hydr. EtOH to 3.9 g. of 5-chloro-7-amino-*s*-triazolo[2,3-*a*]pyrimidine (XVIII) as white needles, m.p. above 320°. *Anal.* Calcd. for $C_5H_4N_5Cl$: C, 35.40; H, 2.36; N, 41.30. Found: C, 35.61; H, 2.63; N, 41.59. UV λ_{max}^{EtOH} mμ (log ε): 257 (shoulder), 287 (4.08).

This compound (0.3 g.) and 20 cc. of EtOH-NH_3 were heated in a sealed tube at 160° for 10 hr. After cool, the solvent was evaporated and the residue was recrystallized from H_2O to 0.2 g. of (VIII), colorless pillars, m.p. 300.5°(decomp.). This was identified with the sample prepared by the method (a).

5,7-Dimercapto-*s*-triazolo[2,3-*a*]pyrimidine (IX)——To a solution of 1.5 g. of (VI) in 50 cc. of dehyd. EtOH, 1.5 g. of thiourea was added and the mixture was refluxed for 1 hr., depositing a yellow precipitate. After cool, the resulting yellow crystals were collected by filtration, dissolved in dil. NaOH, filtered with charcoal, and the filtrate was acidified with dil. HCl to give 1.25 g. of yellow crystalline powder, m.p. above 320°(coloring from 273°). *Anal.* Calcd. for $C_5H_4N_4S_2$: C, 32.59; H, 2.19; N, 30.41. Found: C, 32.65; H, 2.31; N, 30.26.

5,7-Dimethylthio-*s*-triazolo[2,3-*a*]pyrimidine (X)——a) To a solution of 0.4 g. of (IX) dissolved in 16 cc. of 1% NaOH, 0.65 g. of MeI was added and the mixture was shaken at room temperature for 2 hr. The resulting precipitate was collected by filtration, washed with H_2O, and recrystallized from benzene to 0.35 g. of colorless needles, m.p. 221~222°. *Anal.* Calcd. for $C_7H_8N_4S_2$: C, 39.62; H, 3.80; N, 26.41. Found: C, 39.83; H, 3.98; N, 26.62. UV λ_{max}^{EtOH} mμ (log ε): 253 (4.40), 301 (4.26).

b) To a solution of 0.3 g. of 5-mercapto-7-methylthio-*s*-triazolo[2,3-*a*]pyrimidine (XXII) dissolved in 6.6 cc. of 1% NaOH, 0.25 g. of MeI was added. The mixture was treated as above to 0.3 g. of (X). Recrystallization from benzene gave colorles needles, m.p. 221~222°. This was identified with the sample prepared by the method (a).

5-Chloro-7-hydroxy-*s*-triazolo[2,3-*a*]pyrimidine (XI)——a) A mixture of 0.4 g. of (VI) and 4 cc. of 5% NaOH was heated on a water bath for 30 min. to form a clear solution. After cool, the precipitated Na salt was collected by filtration, dissolved in H_2O, filtered with charcoal, and the filtrate was acidified with dil. HCl to 0.3 g. of white crystals, m.p. 256°(decomp.). Recrystallization from hydr. EtOH gave colorless needles, m.p. 257°(decomp.). *Anal.* Calcd. for $C_5H_2ON_4Cl$: C, 35.19; H, 1.76; N, 32.85. Found: C, 35.48; H, 2.03; N, 32.62. UV λ_{max}^{EtOH} mμ (log ε): 256.5 (3.77), 283 (4.04).

b) A mixture of 0.4 g. of (VI) and 4 cc. of 10% HCl was heated on a water bath for 20 min. After cool, the resulting crystals were collected by filtration, washed with H_2O, and dried to 0.3 g. of white crystals, m.p. 255~256°(decomp.). Recrystallization from EtOH gave colorless needles, m.p. 257°(decomp.). This was identified with the sample prepared by the method (a).

Reduction of (XI)——A solution of 0.7 g. of (XI) in 60 cc. of 50% EtOH containing 1 cc. of conc. NH_4OH was shaken in H_2 stream with 0.4 g. of 5% Pd-C. After absorption of one mole of H_2, the catalyst was filtered off and the filtrate was concentrated to dryness in a reduced pressure. The residue was recrystallized from H_2O to 0.4 g. of colorless needles, m.p. 288~289°. This sample showed no depression on admixture with the authentic sample of 7-hydroxy-*s*-triazolo[2,3-*a*]pyrimidine (XIII').

Reduction of (XVIII)——A solution of 0.5 g. of (XVIII) in 80 cc. of dil. EtOH containing 1 cc. of conc. NH_4OH was shaken in H_2 stream with 0.2 g. of 5% Pd-C. After absorption of one mole of H_2, the

reaction mixture was treated as above and the resulting residue was recrystallized from H_2O to 0.3 g. of colorless needles, m.p. 278~279°. *Anal.* Calcd. for $C_5H_5N_5$: C, 44.44; H, 3.73; N, 51.83. Found : C, 44.45; H, 3.81; N, 51.75. This was identified with the authentic sample of 7-amino-*s*-triazolo[2,3-*a*]pyrimidine (XIV') by mixed melting point and infrared spectra.

Acetylation of this compound with Ac_2O gave white needles (XVI'), m.p. 238~238.5°. *Anal.* Calcd. for $C_7H_7ON_5$: C, 47.45; H, 3.98; N, 39.53. Found : C, 47.53; H, 3.85; N, 39.62.

5-Amino-*s*-triazolo[2,3-*a*]pyrimidine (XIV)——A mixture of 0.5 g. of (XII) and 20 cc. of EtOH-NH_3 was heated in a sealed tube at 120° for 10 hr. After cool, the solvent was evaporated to dryness and the residue was recrystallized from H_2O to 0.2 g. of colorless pillars, m.p. 266~267°. *Anal.* Calcd. for $C_5H_5N_5$: C, 44.44; H, 3.73; N, 51.83. Found : C, 44.65; H, 4.07; N, 51.78.

This compound was heated with Ac_2O on a water bath for 4 hr. and the resulting crystals were recrystallized from H_2O to colorless prisms, m.p. 296~297°. *Anal.* Calcd. for $C_7H_7ON_5$ (5-acetamido-*s*-triazolo[2,3-*a*]pyrimidine (XVI)) : C, 47.45; H, 3.98; N, 39.53. Found : C, 47.62; H, 4.15; N, 39.54.

5-Mercapto-*s*-triazolo[2,3-*a*]pyrimidine (XV)——To a solution of 0.4 g. of (XII) in 20 cc. of dehyd. EtOH, 0.4 g. of thiourea was added, and the mixture was refluxed for 1 hr. After cool, the resulting crystals were collected, dissolved in hot dil. NaOH, filtered with charcoal, and the filtrate was acidified with dil. HCl. The precipitated yellow crystals were collected, washed with H_2O, and dried to 0.25 g. of yellow needles, m.p. 258~259°(decomp.). Recrystallization from EtOH gave yellow needles, m.p. 259~260°(decomp.). *Anal.* Calcd. for $C_5H_4N_4S$: C, 39.46; H, 2.65; N, 36.82. Found : C, 39.56; H, 2.84; N, 36.85.

5-Methylthio-*s*-triazolo[2,3-*a*]pyrimidine (XVII)——To a solution of 0.1 g. of (XV) dissolved in 2.8 cc. of 1% NaOH, 0.1 g. of MeI was added. The mixture was shaken for 30 min. and allowed to stand for 2 hr. at room temperature. The resulting white crystals were collected by filtration, washed with H_2O, and recrystallized from H_2O to 60 mg. of colorless needles, m.p. 157~158.5°. *Anal.* Calcd. for $C_6H_6N_4S$: C, 43.37; H, 3.64; N, 33.73. Found : C, 43.51; H, 3.84; N, 33.79.

7-Methylthio-*s*-triazolo[2,3-*a*]pyrimidine(XVII')——To a solution of 0.5 g. of 7-mercapto-*s*-triazolo-[2,3-*a*]pyrimidine (XV') dissolved in 13.4 cc. of 1% NaOH, 0.5 g. of MeI was added and the mixture was treated as above. The resulting product was recrystallized from EtOH to 0.4 g. of white prisms, m.p. 207~208°. *Anal.* Calcd. for $C_6H_6N_4S$: C, 43.37; H, 3.64; N, 33.73. Found : C, 43.53; H, 3.77; N, 33.53.

5-Hydroxy-*s*-triazolo[2,3-*a*]pyrimidine (XIII)——A mixture of 0.2 g. of (XII) and 2 cc. of 10% HCl was heated on a water bath for 1 hr. After cool, the reaction solution was adjusted to pH 5~6 with NH_4OH, the precipitated crystals were collected by filtration, washed with H_2O, and recrystallized from hydr. EtOH to 0.15 g. of colorless needles, m.p. 274~275°. *Anal.* Calcd. for $C_5H_4ON_4$: C, 44.12; H, 2.96; N, 41.17. Found : C, 43.96; H, 3.17; N, 41.20.

5-Hydroxy-7-methylthio-*s*-triazolo[2,3-*a*]pyrimidine(XX)——To a solution of 0.8 g. of (IV) dissolved in 20 cc. of 1% NaOH, 0.75 g. of MeI was added and the mixture was shaken for 1 hr. at room temperature. The resulting crystals were collected, washed with H_2O, and dried. This product (0.8 g.) was recrystallized from 50% EtOH to colorless needles, m.p. 283°. *Anal.* Calcd. for $C_6H_6ON_4S$: C, 39.56; H, 3.32; N, 30.76. Found : C, 39.63; H, 3.42; N, 30.71.

5-Chloro-7-methylthio-*s*-triazolo[2,3-*a*]pyrimidine (XXI)——To a mixture of 4.5 g. of (XX) and 45 cc. of $POCl_3$, 9 cc. of dimethylaniline was added and the mixture was refluxed for 2 hr. The excess $POCl_3$ was removed in a reduced pressure on a water bath, the syrupy residue was poured with stirring into ice water, the resulting crystals were collected by filtration, and washed with H_2O. The filtrate was extracted with $CHCl_3$, which was dried over $CaCl_2$ and evaporation of $CHCl_3$ gave a crude product. Both products were combined and recrystallized from dichloroethane to 3 g. of colorless needles, m.p. 207~208°. *Anal.* Calcd. for $C_6H_5N_4ClS$: C, 35.91; H, 2.49; N, 27.93. Found : C, 36.25; H, 2.70; N, 27.87.

Reaction of (XXI) with thiourea——To a solution of 0.8 g. of (XXI) in 80 cc. of dehyd. EtOH, 0.31 g. of thiourea was added and the mixture was refluxed for 3 hr. After cool, the precipitate was collected by filtration, washed with EtOH, and dried to 0.78 g. of yellow crystalline product, which was added to dil. NaOH and the mixture was stirred for 10 min. The insoluble portion was collected and washed with H_2O to 0.18 g. of slightly yellow needles, m.p. 287~288°(decomp.). Recrystallization from dimethylformamide gave (XXIII) as white needles, m.p. 288~289°(decomp.). *Anal.* Calcd. for $C_{12}H_{10}N_8S_3$: C, 39.78; H, 2.87; N, 30.93. Found : C, 39.98; H, 2.96; N, 30.90.

The filtrate (alkali-soluble portion) was acidified with dil. HCl, the precipitate was collected, washed with H_2O, and dried to 0.54 g. of yellow crystalline product, m.p. 245°(decomp.). Recrystallization from a large amount of EtOH gave 5-mercapto-7-methylthio-*s*-triazolo[2,3-*a*]pyrimidine (XXII) as yellow needles, m.p. 245~246°(decomp.). *Anal.* Calcd. for $C_6H_6N_4S$: C, 36.37; H, 3.53; N, 28.28. Found : C, 36.66; H, 3.14; N, 28.11.

Bis(7-methylthio-*s*-triazolo[2,3-*a*]pyrimidin-5-yl) Sulfide (XXIII)——To a solution of 0.2 g. of (XXII) dissolved in 4 cc. of 1% NaOH, a solution of 0.2 g. of (XXI) in 30 cc. of 60% EtOH was added and the mixture was refluxed for 3 hr. After cool, the resulting crystals were collected by filtration,

washed with H_2O, and dried to 0.35 g. of white needles, m.p. 288~289°(decomp.). *Anal.* Calcd. for $C_{12}H_{10}N_8S_3$: C, 39.78; H, 2.87. Found: C, 39.98; H, 3.01.

5-Amino-7-methylthio-*s*-triazolo[2,3-*a*]pyrimidine (XXIV)——a) A mixture of 2.0 g. of (XXI) and 30 cc. of EtOH-NH_3 was heated in a sealed tube at 150~160° for 10 hr. The reaction mixture was evaporated to dryness, the residue wes dissolved in dil. HCl, filtered with charcoal, and the filtrate was neutralized with dil. NaOH to form 1.3 g. of white crystalline product. Recrystallization from EtOH gave colorless needles, m.p. 230~231°. *Anal.* Calcd. for $C_6H_7N_5S$: C, 39.77; H, 3.89; N, 38.65. Found: C, 40.06; H, 4.18; N, 38.58.

b) A mixture of 0.4 g. of (X) and 15 cc. of EtOH-NH_3 was reacted as above and the product was recrystallized from EtOH to 0.35 g. of colorless needles, m.p. 230~231°, which showed no depression on admixture with (XXIV), prepared by the method (a).

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Summary

The products of the condensation of 5-amino-*s*-triazole (I) with ethyl malonate, ethyl cyanoacetate, and methyl ethoxycarbonyldithioacetate were proved to be respectively 5,7-dihydroxy-, 5-hydroxy-7-amino-, and 5-hydroxy-7-mercapto-*s*-triazolo[2,3-*a*]pyriminines (II, III, and IV). (II) was converted into the 5,7-dichloro derivative (VI), and the reactivity of the two halogens in (VI) towards the usual nucleophilic reagents was examined. (IV) was also transformed into the 5-chloro-7-methylthio derivative (XXI), which was converted into 5-substituted 7-methylthio derivatives by nucleophilic substitution. Ultraviolet absorption spectra of 5-substituted and 7-substituted *s*-triazolo[2,3-*a*]pyrimidines were compared.

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126. Yasuo Makisumi: Synthesis of Potential Anticancer Agents. V.*2 6-Halo-*s*-triazolo[2,3-*a*]pyrimidines.

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In the previous paper[1] of this series, it was reported that the reaction of 5-methyl-7-hydroxy-*s*-triazolo[2,3-*a*]pyrimidine (I) with phosphoryl chloride gave 5-methyl-7-chloro derivative (II), but that the reaction of (I) with a mixture of phosphorus pentachloride and phosphoryl chloride resulted in the formation of the 5-methyl-6,7-dichloro derivative (IIa). In the latter reaction, it was assumed that the 6-position of (I) was activated for electrophilic substitution by the hydroxyl group at 7-position and consequently was chlorinated with phosphorus pentachloride into the 5-methyl-6-chloro-7-hydroxy derivative (Ia) and then chlorination of the hydroxyl group of (Ia) followed to give (IIa). In order to prove this assumption, the halogenation of 7-hydroxy- or 7-amino-*s*-triazolo[2,3-*a*]pyrimidine and its 5-methyl derivative with chlorine or bromine was carried out, and the expected 6-halo derivatives were obtained.[1,2]

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*2 Part IV: This Bulletin, **9**, 801 (1961).

1) H. Kanō, Y. Makisumi, S. Takahashi, M. Ogata: *Ibid.*, **7**, 903 (1959).

2) Y. Makisumi, H. Kanō: *Ibid.*, **7**, 907 (1959).