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168. Hideo Kanō, Yasuo Makisumi, Shirō Takahashi, and Masaru Ogata : Synthesis of Potential Anticancer Agents. II.[1] Halogenation of 7-Substituted 5-Methyl-*s*-triazolo[2,3-*a*]pyrimidines.

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Birr and Walther[2] showed that the reaction of formic acid and 2-hydrazino-4-hydroxy-6-methylpyrimidine (IV) gave the same compound as that previously designated as 5-methyl-7-hydroxy-*s*-triazolo[2,3-*a*]pyrimidine (III), prepared by Bülow and Haas[3] by the reaction of ethyl acetoacetate (I) and 3-amino-*s*-triazole (II). The former workers proposed the structure of 5-hydroxy-7-methyl-*s*-triazolo[4,3-*a*]pyrimidine (III′) in preference to the isomeric structure (III).

More recently, a surprising evidence concerning the structure of this compound was provided by Shirakawa[4] who disclosed that (III′) could be obtained from (IV) by heating with formic acid for a short time, but that this (III′) was readily rearranged to (III) on boiling with formic acid for a long period or by fusion, and that the condensate (I) with (II) was identical with (III).

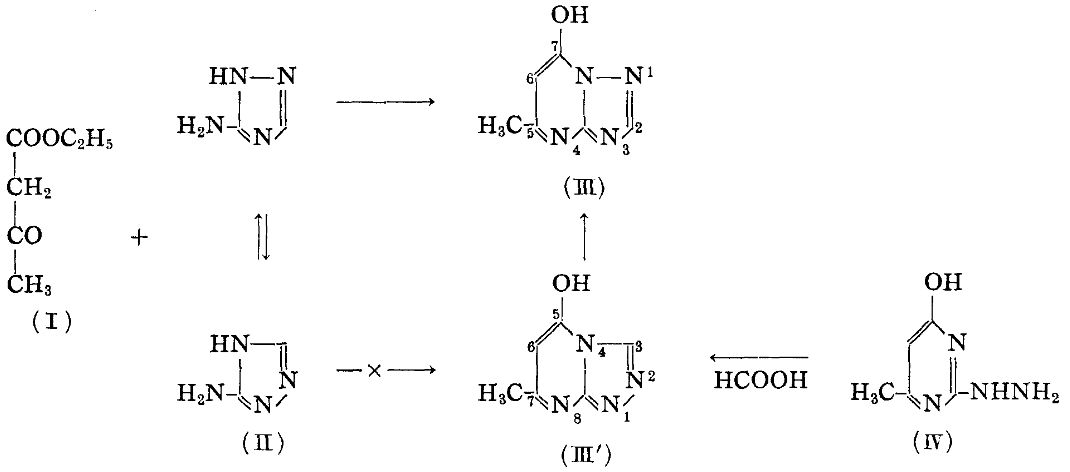

Chart 1.

Although the starting compound was formulated as (III′) according to Birr's structure in the first paper of this series,[1] which described the synthesis of derivatives of triazolopyrimidine, the structure (III) provided by Bülow and proved by Shirakawa should have more preference. Therefore, the starting compound and its derivatives mentioned in the foregoing paper should be corrected to 7-substituted 5-methyl-*s*-triazolo[2,3-*a*]-pyrimidines.

In continuation of the foregoing work, the present study deals with the halogenation of 7-substituted 5-methyl-*s*-triazolo[2,3-*a*]pyrimidines.

As described in the first paper, the reaction of (III) with phosphoryl chloride gave 5-methyl-7-chloro derivative (V). On the other hand treatment of (III) with a mixture of phosphoryl chloride and phosphorus pentachloride resulted in the formation of a dichloro derivative (VI) in about 50% yield. The catalytic reduction of (VI) with pallad-

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[1] Part I : This Bulletin, **6**, 583(1958).

[2] E. J. Birr, W. Walther : Chem. Ber., **86**, 1421(1953).

[3] C. Bülow, K. Haas : Ber., **42**, 4638(1909).

[4] K. Shirakawa : Yakugaku Zasshi, 78, 1395(1958).

ium-carbon catalyst yielded another monochloro derivative (VIII), while (V) was converted into 5-methyl-*s*-triazolo[2,3-*a*]pyrimidine (VII) by the same reduction. (VII) was also obtained from (VIII) by refluxing with Raney nickel in ammonia solution. These experiments and the analogy of halogenation in pyrimidine series suggest that the position of two chlorines in (VI) must be at 6- and 7-positions of this ring system.

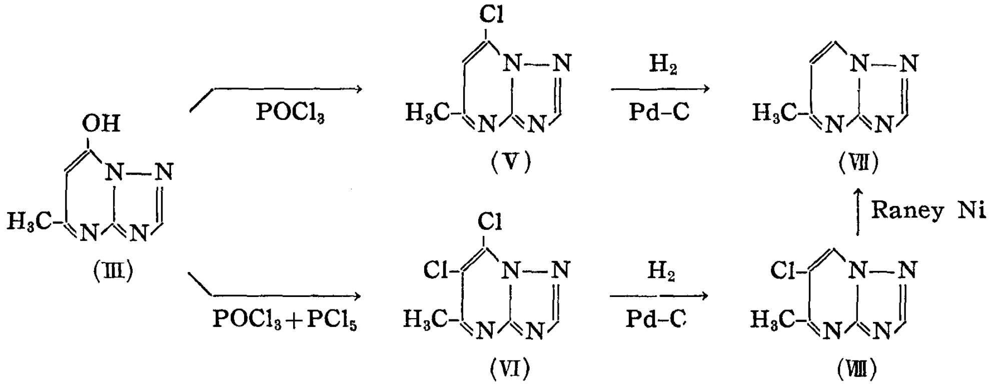

Chart 2.

Confirmation of the structure assigned to (VI) was obtained by the treatment of 5-methyl-6-chloro-7-hydroxy-*s*-triazolo[2,3-*a*]pyrimidine (IX) with phosphoryl chloride to yield the same dichloro derivative. (IX) and its bromo homolog (X) were prepared by the condensation of ethyl 2-haloacetoacetate with (II) in glacial acetic acid. Treatment of (X) with phosphoryl chloride in the presence of dimethylaniline gave 6-bromo-7-chloro derivative (XI). (VI) and (XI) were conversely hydrolysed to the corresponding 7-hydroxy derivatives (IX and X) on heating with dilute hydrochloric acid.

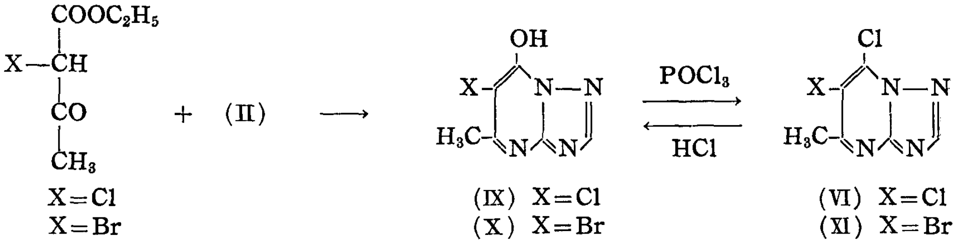

Chart 3.

It was further found that the halogenation of (III) with chlorine or bromine in acetic acid or water gave the corresponding 6-halo-7-hydroxy derivatives (IX and X). The application of this method to 5-methyl-7-amino-*s*-triazolo[2,3-*a*]pyrimidine (XII)1) gave the corresponding 6-halo-7-amino derivatives (XIII and XIV). As the chlorine at 7-position is very reactive, (VI) and (XI) were readily converted into the corresponding 7-amino derivatives (XIII and XIV) on heating with ethanolic ammonia in a sealed tube. Heating of (VI) and (XI) with thiourea in ethanol gave the corresponding 7-mercapto compounds (XV and XVI). Methylation of (XV) with methyl iodide afforded 7-methylthio derivative (XVII), which was hydrolysed to (IX) with 25% sulfuric acid.

In preliminary biological tests, (XIII), (XIV), (XV), (XVI), and (XVII) were found to have growth-inhibitory activity against *Lactobacillus casei* and *Streptococcus faecalis*, and (VI) and (XI) inhibited the growth of *Escherichia coli*. Some of these derivatives, especially 5,6-dihalogen derivatives (VI and XI), were effective against transplantable tumor in animals. The biological details will be published elsewhere.

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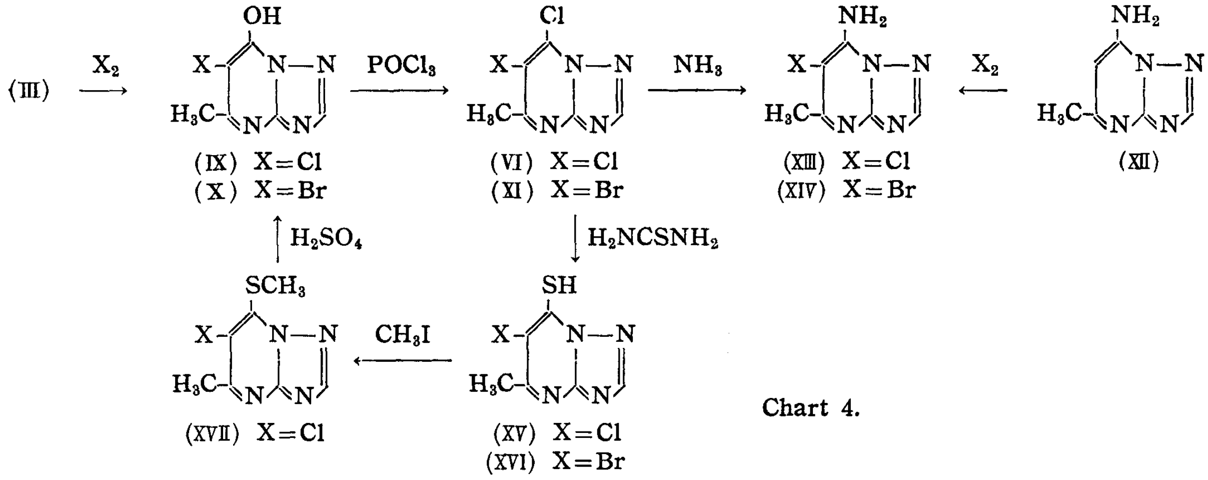

Chart 4.

Experimental*[2]

6,7-Dichloro-5-methyl-*s*-triazolo[2,3-*a*]pyrimidine (VI)—a) A mixture of 33 g. of (III), 55 g. of PCl_5, and 280 cc. of $POCl_3$ was refluxed for about 25 hr., during which time the mixture turned into a deep brown solution. The excess $POCl_3$ was removed *in vacuo* on a water bath and the residual syrup was extracted with 300 cc. of $CHCl_3$. The extract was washed with water and 10% K_2CO_3 solution, and dried over $CaCl_2$. After evaporation of 150 cc. of $CHCl_3$, the solution was purified by chromatography through an alumina column and 22.5 g. of pale yellow crystals, m.p. 135~136°, was obtained. The sample for analysis was recrystallized from water, m.p. 135~137°. *Anal.* Calcd. for $C_6H_4N_4Cl_2$: C, 35.50; H, 1.99; N, 27.60. Found : C, 35.62; H, 2.17; N, 27.74.

b) 1.5 g. of (IX) was refluxed with 20 cc. of $POCl_3$ for 25 hr. After removal of excess $POCl_3$, the residual syrup was treated as in a) to give 0.7 g. of (VI).

c) To a mixture of 1.2 g. of (IX) and 6 cc. of $POCl_3$, 2.4 cc. of dimethylaniline was added and the mixture was refluxed for 2 hr. After removal of excess $POCl_3$ *in vacuo*, the syrupy residue was poured into ice-water. The resulting crystals were collected, washed with water, and recrystallized from water to 0.7 g. of (VI).

5-Methyl-6-chloro-*s*-triazolo[2,3-*a*]pyrimidine (VIII)—A solution of 1 g. of (VI) in 50 cc. of MeOH was hydrogenated in the presence of 5% Pd-C. When 1 mole of hydrogen per mole of the compound had been absorbed, the mixture was worked up as usual to 0.65 g. of (VIII), m.p. 133~135° (from $CHCl_3$ + CCl_4). *Anal.* Calcd. for $C_6H_5N_4Cl$: C, 42.75; H, 2.99; N, 33.24. Found : C, 43.09; H, 3.12; N, 33.34.

5-Methyl-*s*-triazolo[2,3-*a*]pyrimidine (VII)—a) A solution of 1 g. of (V) in 30 cc. of EtOH containing 1 cc. of conc. NH_4OH was hydrogenated in the presence of 0.3 g. of 5% Pd-C. One mole of H_2 per mole of (V) was absorbed during 2 hr., after which time the uptake of H_2 decreased. The mixture was worked up as usual to give 0.6 g. of (VII) as colorless pillars, m.p. 185~186° (from $CHCl_3$ + benzene). *Anal.* Calcd. for $C_6H_6N_4$: C, 53.73; H, 4.48; N, 41.79. Found : C, 53.65; H, 4.26; N, 42.00.

b) A mixture of 0.2 g. of (VIII) in 7 cc. of water, 0.5 g. of Raney Ni, and 0.2 cc. of conc. NH_4OH was heated under reflux for 3 hr. After cool, the solution was extracted with $CHCl_3$ and the extract was purified by chromatography through an alumina column to 0.03 g. of (VII).

5-Methyl-6-chloro-7-hydroxy-*s*-triazolo[2,3-*a*]pyrimidine (IX)—a) A mixture of 15 cc. of glacial AcOH, 5 cc. of ethyl 2-chloroacetoacetate, and 2.4 g. of (II) was refluxed for 2 hr. After cool, the resulting pale yellow crystals were collected and recrystallized from water to colorless pillars, m.p. 343° (decomp.); yield, 2.6 g. *Anal.* Calcd. for $C_6H_5ON_4Cl$: C, 39.04; H, 2.73; N, 30.35. Found : C, 39.29; H, 2.98; N, 30.63.

b) Into a solution of 0.5 g. of (III) in 20 cc. of water, 0.25 g. of chlorine gas was absorbed, and the solution was warmed at 70° for 2 hr. After cool, the precipitate was collected and recrystallized from water to 0.45 g. of (IX). *Anal.* Calcd. for $C_6H_5ON_4Cl$: C, 39.04; H, 2.73; N, 30.35. Found: C, 38.98; H, 2.94; N, 30.02.

c) 0.2 g. of (VI) was heated with 20 cc. of 0.2% HCl on a water bath for 20 min. After cool, the precipitated crystals were collected and recrystallized from water to colorless pillars, m.p. 343° (decomp.). *Anal.* Calcd. for $C_6H_5ON_4Cl$: C, 39.10; H, 2.93; N, 30.46.

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

d) A suspension of 0.5 g. of (XVII) in 4 cc. of 25% H_2SO_4 was heated on a water bath, by which the compound dissolved and white crystals precipitated out. After cool, the product was collected and recrystallized from water to colorless pillars, m.p. 343°(decomp.). *Anal.* Calcd. for $C_6H_5ON_4Cl$: C, 39.04; H, 2.73; N, 30.35. Found: C, 39.10; H, 3.17; N, 30.45.

5-Methyl-6-bromo-7-hydroxy-*s*-triazolo[2,3-*a*]pyrimidine (X)—a) To a mixture of 10 cc. of dehyd. EtOH, 2.1 g. of ethyl 2-bromoacetoacetate, and 0.84 g. of (II) 2 drops of piperidine were added, the mixture was refluxed for 6 hr., and evaporated to dryness. The residue was recrystallized from water to (X) as white needles, m.p. 280°(decomp.). *Anal.* Calcd. for $C_6H_5ON_4Br$: C, 31.44; H, 2.19; N, 24.45. Found : C, 31.50; H, 2.28; N, 24.79.

b) To a solution of 0.5 g. of (III) dissolved in 20 cc. of glacial AcOH, a solution of 0.55 g. of Br_2 in 10 cc. of glacial AcOH was added dropwise. After standing for several hr., the crystals separated were collected, washed with water, and recrystallized from water to 0.7 g. of (X), m.p. 280° (decomp.), undepressed by admixture with the sample obtained by the procedure a).

5-Methyl-6-bromo-7-chloro-*s*-triazolo[2,3-*a*]pyrimidine (XI)—To 1.5 g. of (X) and 15 cc. of $POCl_3$, 4 cc. of dimethylaniline was added and the mixture was refluxed for 2 hr. The excess $POCl_3$ was removed *in vacuo* and the syrupy residue was poured into ice-water. The crystals that precipitated out were collected, washed with water, and recrystallized from EtOH to 1.6 g. of (XI) as white needles, m.p. 141~142°. *Anal.* Calcd. for $C_6H_4N_4BrCl$: C, 29.11; H, 1.63; N, 22.64. Found : C, 29.00; H, 1.73; N, 22.58.

5-Methyl-6-chloro-7-amino-*s*-triazolo[2,3-*a*]pyrimidine (XIII)—a) Into a suspension of 0.5 g. of (XII) in 10 cc. of glacial AcOH, 0.25 g. of chlorine was absorbed. After standing for several hr., the crystals that precipitated out were collected and neutralized with dil. NaOH to give 0.4 g. of (XIII). Recrystallization from EtOH gave colorless scales, m.p. 289°. *Anal.* Calcd. for $C_5H_6N_5Cl$: C, 39.24; H, 3.27; N, 38.15. Found : C, 39.54; H, 3,37; N, 36.38.

b) In a sealed tube were placed 3 g. of (VI) and 25 cc. of ethanolic ammonia, and heated at 160° for 6 hr. After cool, crystals that precipitated out were collected, washed with water, and recrystallized from EtOH to 2.5 g. of (XIII).

5-Methyl-6-bromo-7-amino-*s*-triazolo[2,3-*a*]pyrimidine (XIV)—a) To a suspension of 1.3 g. of (XII) in 20 cc. of glacial AcOH, 1.4 g. of bromine in 10 cc. of glacial AcOH was added dropwise. After several hr., the crystals that precipitated out were treated by the same procedure as for (XIII) to furnish colorless scales, m.p. 248°(decomp.). *Anal.* Calcd. for $C_6H_6N_5Br$: C, 31.58; H, 2.63; N, 30.70. Found : C, 31.75; H, 2.98; N, 30.60.

b) In a sealed tube 0.2 g. of (XI) and 15 cc. of ethanolic ammonia were placed and heated at 160° for 7 hr. After cool, the reaction mixture was treated by the same procedure as for (XIII) to give (XIV).

5-Methyl-6-chloro-7-mercapto-*s*-triazolo[2,3-*a*]pyrimidine (XV)—To a solution of 0.5 g. of thiourea in 10 cc. of EtOH 0.5 g. of (VI) was added and the mixture was refluxed for 20 min. The crystals that precipitated out were collected and recrystallized from a large amount of EtOH to pale yellow needles, m.p. 274~275°(decomp.). *Anal.* Calcd. for $C_6H_5N_4ClS$: C, 35.94; H, 2.51; N, 27.95. Found : C, 35.99; H, 2.75; N, 28.03.

5-Methyl-6-bromo-7-mercapto-*s*-triazolo[2,3-*a*]pyrimidine (XVI)—This was prepared from (XI) and thiourea in EtOH by the same procedure as for (XV). Pale yellow prisms (from EtOH), m.p. 262° (decomp.). *Anal.* Calcd. for $C_6H_5N_4BrS$: C, 29.39; H, 2.04; N, 22.86. Found : C, 29.81; H, 2.38; N, 22.91.

5-Methyl-6-chloro-7-methylthio-*s*-triazolo[2,3-*a*]pyrimidine (XVII)—To a solution of 2 g. of (XV) in 45 cc. of 1% NaOH, 1.6 g. of MeI was added and the mixture was shaken at room temperature for several hr. The crystals that precipitated out were collected and recrystallized from EtOH to white needles, m.p. 141~142.5°. *Anal.* Calcd. for $C_7H_7N_4ClS$: C, 39.16; H, 3.26; N, 26.11. Found : C, 39.43; H, 3.50; N, 26.52.

Summary

Halogenation of 5-methyl-7-hydroxy- and 5-methyl-7-amino-*s*-triazolo[2,3-*a*]pyrimidines with chlorine or bromine gave the corresponding 6-halogeno derivatives (IX), (X), (XIII), and (XIV). 5-Methyl-6-halo-7-hydroxy derivatives (IX and X) were transformed to the corresponding 6-halo-7-chloro derivatives (VI and XI), which were converted into some 7-substituted 6-halogeno derivatives (XIII, XIV, XV, and XVI) by the usual nucleophilic substitution. Some of these compounds showed biological activity.

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