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115. Hideo Kanō and Yasuo Makisumi: Synthesis of Potential Anticancer Agents. I. 5-Substituted 7-Methyl-*s*-triazolo[4,3-*a*]- and -tetrazolo[1,5-*a*]-pyrimidines.

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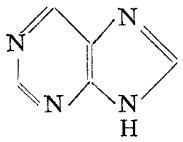
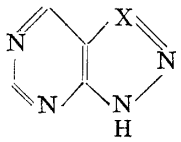
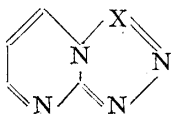
Various purine derivatives[1] have been shown to have tumor-inhibiting and antileukemic activity in experimental animals and in man, and certain derivatives having closely related ring systems to purine, for example, 8-azaguanine[2] and 4-aminopyrazolo[3,4-*d*]pyrimidine,[3] are also known to exhibit similar activity.



Purine



(I) X=CH
(II) X=N



(III) X=CH
(IV) X=N

The structural resemblance between pyrazolo[3,4-*d*]pyrimidine (I) and *s*-triazolo[4,3-*a*]pyrimidine (III), and between 8-azapurine (II) and tetrazolo[1,5-*a*]pyrimidine (IV) promoted the synthesis of compounds having the condensed ring systems of (III) and (IV).

This paper deals with the synthesis of some 5-substituted 7-methyl-*s*-triazolo[4,3-*a*]-pyrimidines and 5-substituted 7-methyltetrazolo[1,5-*a*]pyrimidines. The starting compounds, 5-hydroxy derivatives (V and VI) were prepared by the method of Bülow[4] by the condensation of ethyl acetoacetate with the appropriate aminoazoles. Treatment of 5-hydroxy derivatives with phosphoryl chloride gave 5-chloro derivatives (VII and VIII) which were proved to be very useful intermediates in the synthesis of this series. When (VII) and (VIII) were treated with the usual nucleophilic reagents under relatively mild conditions, the corresponding 5-substituted derivatives, e.g. ethoxy (IX and XII), amino (XI and XII), diethylamino (XIII and XIV), piperidino (XV and XVI), hydrazino (XVII and XVIII), thiocyanato (XXI), and mercapto (XXII and XXIII) derivatives were obtained (Table I). 5-Furfurylamino derivatives (XIX and XX), which are related to Kinetin[5] (6-furfurylaminopurine), were prepared by the condensation of (VII) and (VIII) with furfurylamine. 5-Methylthio derivatives (XXIV and XXV) were obtained by the reaction of (XXII) and (XXIII) with methyl iodide. 5-Carboxymethylthio derivatives (XXVI and XXVII) were prepared by reacting (XXII) and (XXIII) with chloroacetic acid.

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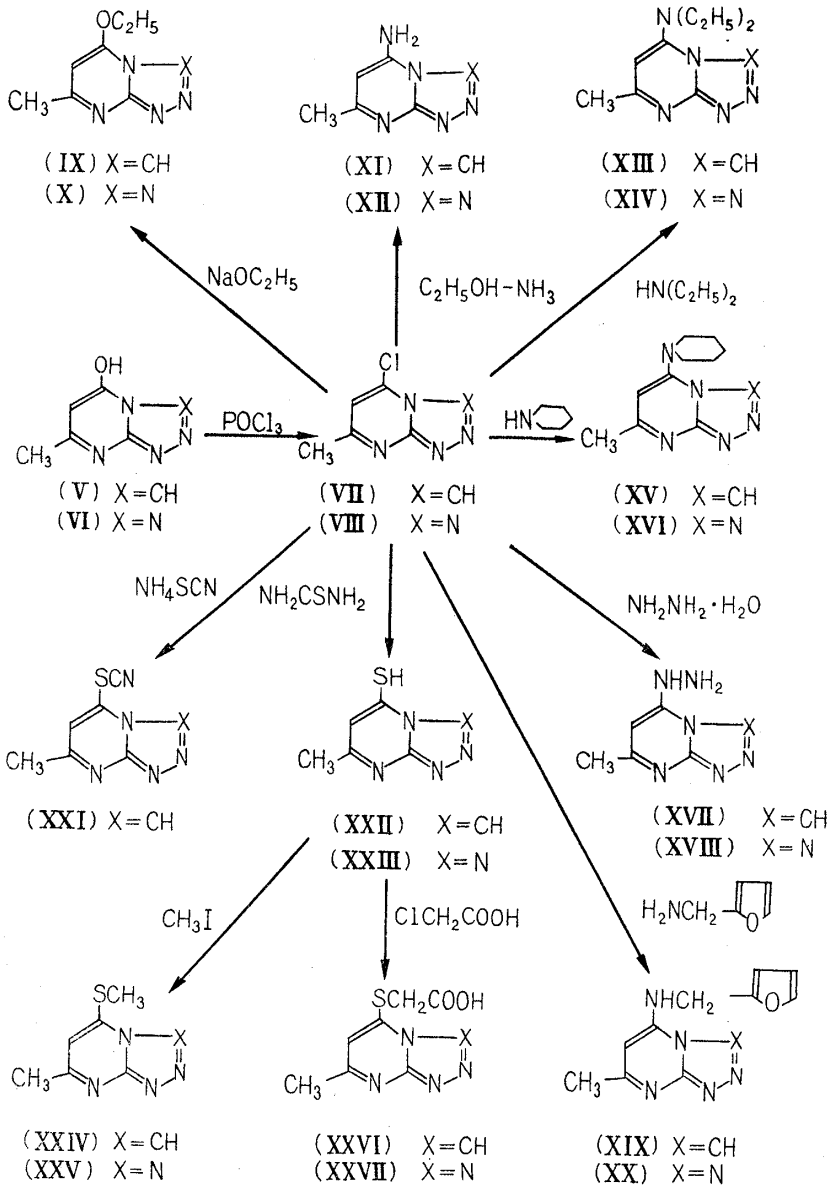
1) G. H. Hitchings, G. B. Elion: 3éme Congrés International de Biochimie Rapports, 185 (1955).
2) K. Sugiura, *et al.*: Cancer Research, **10**, 178 (1950).
3) R. W. Brockman, F. M. Schabel, Jr.: *Ibid.*, **17**, 579 (1957).
4) C. Bülow, K. Haas: Ber., **42**, 4429, 4638 (1909).
5) C. O. Miller, *et al.*: J. Am. Chem. Soc., **77**, 1392 (1955).



In preliminary biological tests, three of these compounds, (VII), (XXI), and (XXII), inhibited the growth of *Lactobacillus casei* and *Streptococcus faecalis*. The biological details will be published elsewhere.

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Experimental

5-Chloro-7-methyl-*s*-triazolo[4,3-a]pyrimidine (VII)—5 g. of 5-hydroxy-7-methyl-*s*-triazolo[4,3-*a*]pyrimidine (V) was refluxed with 40 cc. of $POCl_3$ for 2 hrs. The excess $POCl_3$ was removed under reduced pressure on a steam bath and the residual syrup was poured with stirring into ice water. The solution was neutralized with conc. NH_4OH and extracted with $CHCl_3$. The extract was dried, evaporated, and the residue was recrystallized from EtOH to 4.5 g. of (VII) as colorless plates, m. p. 154~155°. *Anal.* Calcd. for $C_6H_5N_4Cl$: C, 42.72; H, 2.97; N, 33.23. Found: C, 43.03; H, 3.17; N, 33.04.

5-Chloro-7-methyltetrazolo[1,5-a]pyrimidine (VIII)—(VIII) was obtained from 5 g. of 5-hydroxy-

7-methyltetrazolo[1,5-*a*]pyrimidine (VI) by the same treatment as for (VII). Colorless needles (4.3 g.), m.p. 115~116° (from benzene-benzine). *Anal.* Calcd. for $C_5H_4N_5Cl$: C, 35.40; H, 2.36; N, 41.30. Found, C, 35.28; H, 2.40; N, 41.57.

5-Ethoxyl-7-methyl-*s*-triazolo[4,3-*a*]pyrimidine (**IX**)—To a solution of 0.1 g. of Na dissolved in 15 cc. of dehyd. EtOH 0.7 g. of (VII) was added. The solution was heated on a steam bath for 1 hr. and neutralized with AcOH. NaCl was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in water and extracted with $CHCl_3$. The extract was dried, evaporated, and the residue was recrystallized from benzene to white needles (0.5 g.), m.p. 149~150°. *Anal.* Calcd. for $C_8H_{10}ON_4$: C, 53.93; H, 5.62; N, 31.46. Found: C, 54.21; H, 5.91; N, 31.29.

5-Ethoxy-7-methyltetrazolo[1,5-*a*]pyrimidine (**X**)—To a solution of 0.2 g. of Na dissolved in 20 cc. of dehyd. EtOH, 1.5 g. of (VIII) was added. The solution was warmed on a steam bath for 5 mins. NaCl was filtered off and the filtrate was evaporated to dryness under reduced pressure. Water was added to the residue, the precipitate was collected, washed with water, and recrystallized from water to colorless needles (1.0 g.), m.p. 125~126°. *Anal.* Calcd. for $C_7H_9ON_5$: C, 46.93; H, 5.03; N, 39.11. Found: C, 46.92; H, 5.06; N, 39.15.

5-Amino-7-methyl-*s*-triazolo[4,3-*a*]pyrimidine (**XI**)—In a bomb were placed 2 g. of (VII) and 25 cc. of dehyd. EtOH saturated with dry NH_3 at 0°. The bomb was heated to 160° for 8 hrs. After cool, the solution was filtered and the residue was crystallized from dehyd. EtOH to 1.8 g. of white needles, m.p. 246~247°. *Anal.* Calcd. for $C_6H_7N_5$: C, 48.32; H, 4.70; N, 46.98. Found: C, 48.18; H, 5.18; N, 47.19.

5-Amino-7-methyltetrazolo[1,5-*a*]pyrimidine (**XII**)—(XII) was obtained from 2 g. of (VIII) by the same procedure as for (XI). Colorless needles (1.8 g.), m.p. 270° (decomp.). *Anal.* Calcd. for $C_5H_6N_6$: C, 40.00; H, 4.00; N, 56.00. Found: C, 40.15; H, 4.29; N, 56.29.

5-Diethylamino-7-methyl-*s*-triazolo[4,3-*a*]pyrimidine (**XIII**)—To a solution of 0.75 g. of diethylamine dissolved in 30 cc. of dehyd. EtOH, 1 g. of (VII) was added and the mixture was refluxed for 5 hrs. After the volatile portion was removed, the residue was dissolved in water and extracted with benzene. The extract was dried and evaporated to dryness. The residue was recrystallized from benzene-benzine (1:1) to 1.1 g. of colorless needles, m.p. 105~106°. *Anal.* Calcd. for $C_{10}H_{15}N_5$: C, 58.54; H, 7.32; N, 34.15. Found: C, 58.71; H, 7.53; N, 33.81.

5-Diethylamino-7-methyltetrazolo[1,5-*a*]pyrimidine (**XIV**)—To a solution of 0.8 g. of diethylamine dissolved in 40 cc. of dehyd. EtOH, 1 g. of (VIII) was added, and the mixture was refluxed for 3 hrs. After the volatile portion was removed to one-half the volume, the solution was cooled and the resulting crystals were collected, washed with water, and recrystallized from EtOH to 0.95 g. of colorless pillars, m.p. 179°. *Anal.* Calcd. for $C_9H_{14}N_6$: C, 52.43; H, 6.80; N, 40.78. Found: C, 52.24; H, 7.18; N, 40.43.

5-Piperidino-7-methyl-*s*-triazolo[4,3-*a*]pyrimidine (**XV**)—This compound was prepared from 1 g. of (VII) and 1.2 g. of piperidine in the same manner as for (XIII). The residue obtained by evaporation of the solvent was recrystallized from acetone-benzine (1:5) to 1 g. of colorless plates, m.p. 112~113°. *Anal.* Calcd. for $C_{11}H_{15}N_5$: C, 60.83; H, 6.91; N, 32.26 Found: C, 60.97; H, 7.07; N, 32.48.

5-Piperidino-7-methyltetrazolo[1,5-*a*]pyrimidine (**XVI**)—This compound was prepared from 1 g. of (VIII) and 1 g. of piperidine in a similar manner as for (XIV). The resulting crystals were collected, washed with water, and recrystallized from EtOH to 1.1 g. of colorless pillars, m.p. 203° (decomp.). *Anal.* Calcd. for $C_{10}H_{14}N_6$: C, 55.05; H, 6.42; N, 38.53. Found: C, 54.82; H, 6.67; N, 38.37.

5-Hydrazino-7-methyl-*s*-triazolo[4,3-*a*]pyrimidine (**XVII**)—A mixture of 1 g. of (VII), 1 cc. of 80% $NH_2NH_2 \cdot H_2O$, and 10 cc. of EtOH was heated on a steam bath for 1 hr. After cool, the separated crystals were collected by suction and recrystallized from EtOH to 0.9 g. of white needles, m.p. 260~261° (decomp.). *Anal.* Calcd. for $C_6H_8N_6$: C, 43.90; H, 4.88; N, 51.22. Found: C, 44.37; H, 5.13; N, 51.42.

5-Hydrazino-7-methyltetrazolo[1,5-*a*]pyrimidine (**XVIII**)—A mixture of 2 g. of (VIII), 3 cc. of 80% $NH_2NH_2 \cdot H_2O$, and 20 cc. of EtOH was heated on a steam bath for 5 mins. After cool, the separated crystals were collected and recrystallized from EtOH to 1.9 g. of white needles, m.p. 237~238° (decomp.). *Anal.* Calcd. for $C_5H_7N_7$: C, 36.36; H, 4.24; N, 59.39. Found: C, 36.33; H, 4.30; N, 59.09.

5-Furfurylamino-7-methyl-*s*-triazolo[4,3-*a*]pyrimidine (**XIX**)—A mixture of 0.3 g. of (VII), 0.36 g. of furfurylamine, and 15 cc. of dehyd. EtOH was refluxed for 6 hrs. The solution was evaporated to dryness, and the residue was diluted with water, the resulting crystals were collected, washed with water, and recrystallized from hot water to 0.6 g. of white needles, m.p. 126~127°. *Anal.* Calcd. for $C_{11}H_{11}ON_5$: C, 57.64; H, 4.80; N, 30.57. Found: C, 57.72; H, 5.26; N, 30.27.

5-Furfurylamino-7-methyltetrazolo[1,5-*a*]pyrimidine (**XX**)—A mixture of 1 g. of (VIII), 1.2 g. of furfurylamine, and 50 cc. of dehyd. EtOH was refluxed for 6 hrs. After cool, the separated crystals were collected, washed with EtOH, and recrystallized from EtOH to 1.3 g. of white scales, m.p. 195° (decomp.).

Anal. Calcd. for $C_{10}H_{10}ON_6$: C, 52.17; H, 4.35; N, 36.52. Found: C, 52.32; H, 4.50; N, 36.27.

5-Thiocyanato-7-methyl-*s*-triazolo[4,3-*a*]pyrimidine (XXI)—To a solution of 1 g. of (VII) in 20 cc. of EtOH a solution of 0.5 g. of NH_4CNS in 10 cc. of water was added and the mixture was allowed to stand overnight at room temperature. The resulting crystals were collected, washed with EtOH, and recrystallized from EtOH to 0.6 g. of white needles, m.p. 170° (decomp.). *Anal.* Calcd. for $C_7H_5N_5S$: C, 43.98; H, 2.62; N, 36.65. Found: C, 43.91; H, 2.99; N, 36.43.

5-Mercapto-7-methyl-*s*-triazolo[4,3-*a*]pyrimidine (XXII)—0.5 g. of (VII) and 0.5 g. of thiourea were added to 20 cc. of dehyd. EtOH and the solution was refluxed for 20 mins. After cool, the separated crystals were collected and washed with EtOH to give 0.47 g. of almost pure product. A sample was recrystallized from EtOH to yellow needles, m.p. 297~298° (decomp.). *Anal.* Calcd. for $C_6H_6N_4S$: C, 43.37; H, 3.61; N, 33.74. Found: C, 43.50; H, 3.97; N, 33.41.

5-Mercapto-7-methyltetrazolo[1,5-*a*]pyrimidine (XXIII)—This compound was prepared from 0.5 g. of (VIII) and 0.5 g. of thiourea in the same manner as for (XXII). The obtained crystals were recrystallized from EtOH to 0.2 g. of yellow needles, m.p. 189° (decomp.). *Anal.* Calcd. for $C_6H_5N_5S$: C, 35.93; H, 3.00; N, 41.92. Found: C, 36.12; H, 3.18; N, 42.25.

5-Methylthio-7-methyl-*s*-triazolo[4,3-*a*]pyrimidine (XXIV)—A solution of 1.5 g. of (XXII) dissolved in 7.5 cc. of 2*N* NaOH was shaken at room temperature with 1.35 g. of MeI. After 30 mins., the solution was acidified with 10% AcOH and extracted with $CHCl_3$. The extract was dried, evaporated to dryness, and the residue was recrystallized from benzene to 1.2 g. of white needles, m.p. 181~182°. *Anal.* Calcd. for $C_7H_8N_4S$: C, 46.67; H, 4.44; N, 31.11. Found: C, 46.58; H, 4.60; N, 31.05.

5-Methylthio-7-methyltetrazolo[1,5-*a*]pyrimidine (XXV)—A solution of 1 g. of (XXIII) dissolved in 10 cc. of 1*N* NaOH was shaken at room temperature with 0.9 g. of MeI for 30 mins. The resulting precipitate was collected and recrystallized from EtOH to 0.8 g. of pale yellow scales, m.p. 151~152°. *Anal* Calcd. for $C_6H_7N_5S$: C, 39.78; H, 3.78; N, 38.67. Found: C, 39.77; H, 4.15; N, 38.45.

5-Carboxymethylthio-7-methyl-*s*-triazolo[4,3-*a*]pyrimidine (XXVI)—A mixture of 0.2 g. of (XXII) and 0.12 g. of chloroacetic acid in 10 cc. of water was heated on a steam bath for 3 hrs. After cool, the resulting crystals were collected and recrystallized from hot water to 0.2 g. of colorless pillars, m.p. 236° (decomp.). *Anal.* Calcd, for $C_8H_8O_2N_4S$: C, 42.86; H, 3.57; N, 25.00. Found: C, 43.13; H, 4.38; N, 24.73.

5-Carboxymethylthio-7-methyltetrazolo[1,5-*a*]pyrimidine (XXVII)—This compound was prepared from 0.2 g. of (XXIII) and 0.12 g. of chloroacetic acid in the same manner as for (XXVI). The resulting crystals were recrystallized from hot water to 0.18 g. of white scales, m.p. 182~182.5°. *Anal.* Calcd. for $C_7H_7O_2N_5S$: C, 37.33; H, 3.11; N, 31.11. Found: C, 37.23; H, 3.51; N, 31.37.

Summary

A number of 5-substituted 7-methyl-*s*-triazolo[4,3-*a*]- and -tetrazolo[1,5-*a*]pyrimidines were prepared by nucleophilic displacement of the corresponding chloro compounds (VII and VIII). These compounds are being screened for antimetabolite and anticancer activity.

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