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Syntheses and Reactions of N-Aminothiouracils and Thiadiazolo[3,2-*a*]pyrimidinones

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3-Amino-6-methyluracil and its thio analogs were synthesized. From these thio analogs, 7-methyl-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one, its 2-amino and 2- or 5-thio derivatives were prepared. Reflux of thiadiazolopyrimidines with chloroacetic acid or hydrochloric acid led to the ring opening of the thiadiazole moiety to give unexpected 3-amino-6-methyluracil.

Keywords——N-aminothiouracil; N-aminouracil; thiadiazolo[3,2-*a*]pyrimidinone; thiation; acid hydrolysis; ring opening reaction

In the preceding papers we have reported syntheses of N-aminopyrimidines and their reactions including the conversion into thiadiazolopyrimidines.[2] In continuation of the work, this paper describes syntheses of thio analogs of N-amino-6-methyluracil and their conversion into 5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one derivatives, and further concerns with some chemical properties of these compounds.

3-Amino-6-methyl-2-thiouracil (I) has been prepared by us[2a] from the reaction of thiosemicarbazide with ethyl acetoacetate in the presence of sodium ethoxide. Meanwhile, 1-amino-6-methyluracil has been synthesized by Kato and Katagiri[3] by the reaction of aliphatic ketone semicarbazone with diketene in acetic acid. In the application of the latter method, the condensation of acetone thiosemicarbazone with diketene in acetic acid, followed by hydrolysis gave I exclusively, without the formation of any amount of 1-amino isomer. When a suspension of I in chloroacetic acid was heated at refluxing temperature, 3-amino-6-methyluracil (II) was obtained.

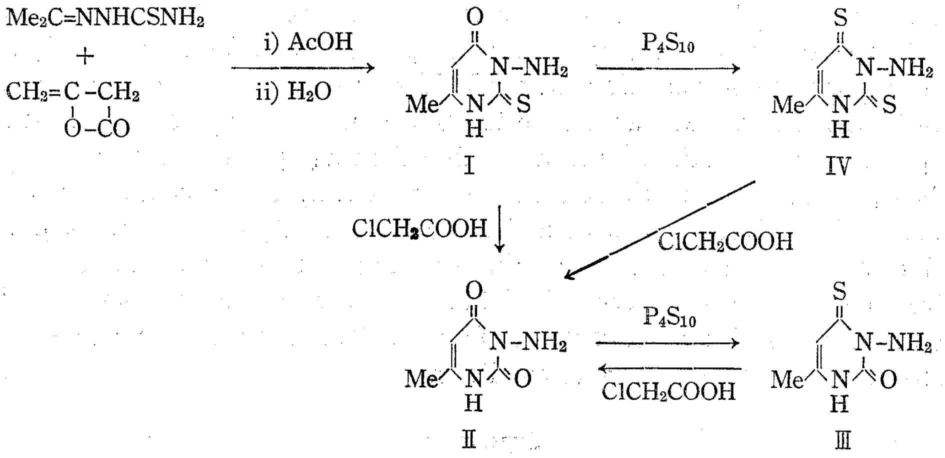

Chart 1

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[1] Location: *2-8-11 Mejirodai, Bunkyo-ku, Tokyo, 112, Japan.*

[2] *a*) T. Tsuji and T. Ueda (neé Yamaka), *Chem. Pharm. Bull.* (Tokyo), **19**, 2530 (1971); *b*) T. Tsuji and Y. Kamo, *Chem. Lett.*, **1972**, 641.

[3] T. Kato and N. Katagiri, *Chem. Pharm. Bull.* (Tokyo), **18**, 2278 (1970).

Thiation of II and I with phosphorus pentasulfide in 2-picoline yielded 3-amino-6-methyl-4-thiouracil (III) and 3-amino-6-methyl-2,4-dithiouracil (IV), respectively. The use of tetralin or pyridine as a solvent resulted in the recovery of starting materials. The ultraviolet spectra of III and IV were similar with those[4] of 4-thiouracil and 2,4-dithiouracil, respectively, and the treatment of III or IV with aqueous chloroacetic acid gave II.

Previously we reported that the treatment of 3-formamido-6-methyl-2-thiouracil with phosphorus oxychloride gave 7-methyl-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (V). Now compound V was obtained in good yield by the reflux of I with ethyl orthoformate, and further 2-amino-7-methyl-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (VI) was prepared from the reaction of the sodium salt of I with cyanogen bromide. The treatment of I with carbon disulfide and potassium hydroxide gave 2-mercapto derivative of V (VII). Reflux of IV with ethyl chloroformate afforded 7-methyl-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-thione (VIII) exclusively, which was unambiguously prepared from the thiation of V with phosphorus pentasulfide. No formation of isomeric thiadiazolopyrimidine compound (IX) was observed.

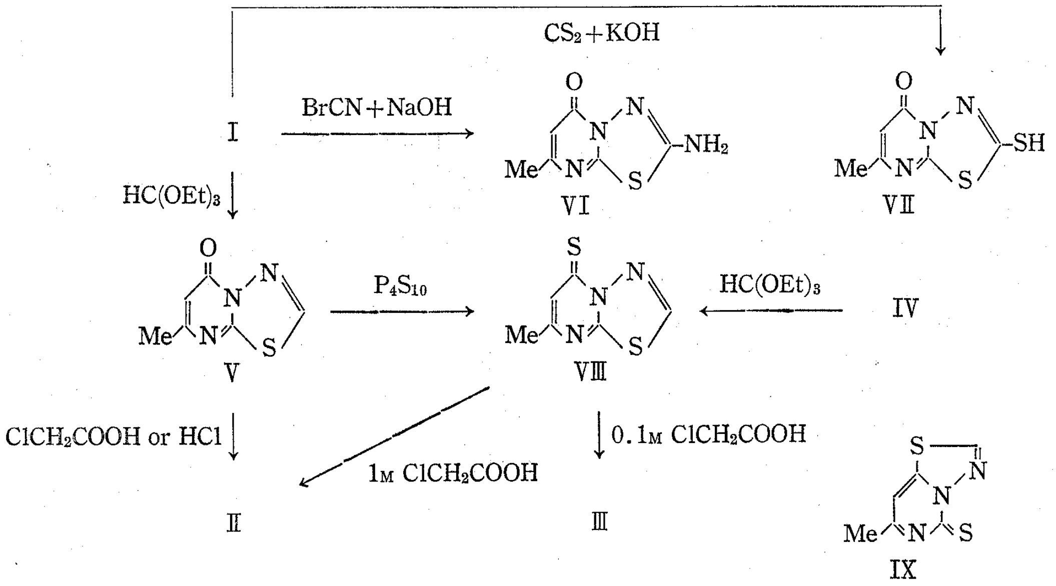

Chart 2

Aiming at obtaining V, an aqueous solution of VIII was refluxed with an equimolecular amount of chloroacetic acid. Unexpectedly the product was found to be II, and the use of 0.1 molar amount of chloroacetic acid for VIII resulted in the formation of III. Similar treatment of V with chloroacetic acid gave II. Since only a catalytic amount of chloroacetic acid was required for the reaction, we assumed that the ring opening reaction proceeds through acid hydrolysis, where chloroacetic acid acts as acid catalyst. In connection with this ring opening reaction, hydrolysis of V with hydrochloric acid was attempted. Reflux of V with 5% hydrochlotic acid for 6 hr led to the ring opening of thiadiazole moiety to afford II.

When referred the base-catalyzed N–N bond cleavage of thiadiazolopyrimidines which was reported by us[2b] and Okabe, *et al.*[5] it is of interest to note that the bond cleavage between S and C at 9-position took place in acid conditions.

Experimental

3-Amino-6-methyl-2-thiouracil (I)——A solution of 4.1 g of acetone thiosemicarbazone and 6.18 g of diketene in 27.4 ml of AcOH was refluxed for 1.5 hr, and then 30 ml of H_2O was added. After the mixture

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[4] G.B. Elion, W.S. Ide, and G.H. Hitchings, *J. Amer. Chem. Soc.*, **68**, 2137 (1946).
[5] T. Okabe, E. Taniguchi, and K. Maekawa, *Bull. Chem. Soc. Jpn.*, **47**, 2813 (1974).

was heated additional 0.5 hr, and cooled, the precipitate was purified by recrystallization from H_2O to give 3.6 g (73.2%) of colorless needles, mp 247—248°, which was identical in all respects with the authentic sample.[2a)]

3-Amino-6-methyluracil (II)——A suspension of 1.57 g of I in 19 ml of 5% $ClCH_2COOH$ was refluxed for 6 hr. The resulting solution was concentrated until a solid began to crystallize out, and kept in a refrigerator overnight after addition of 20 ml of EtOH. Recrystallization of the precipitate from EtOH yielded 720 mg (51%) of colorless fine needles, mp 269—272°. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (log ε) 260 (3.88). *Anal.* Calcd. for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.78. Found: C, 42.51; H, 4.99; N, 29.70. This compound was further obtained from the reaction of III, IV, V or VIII with $ClCH_2COOH$, after the similar work-up as that described above.

3-Amino-6-methyl-4-thiouracil (III)——a) To a solution of 1.64 g of II in 49.8 ml of 2-picoline, 2.59 g of P_4S_{10} and 0.1 ml of H_2O was added, and the whole was refluxed for 5 hr. After removal of the solvent *in vacuo*, the residue was treated with ice, and dissolved in 5% NaOH. After acidification with 5% HCl, the mixture was heated on a water bath and filtered while hot. The filtrate was cooled and the precipitate was recrystallized from H_2O to give pale yellow needles, mp 176—178°. Yield, 210 mg. UV $\lambda_{\max}^{H_2O}$ nm (log ε) 329.5 (4.14). *Anal.* Calcd. for $C_5H_7N_3OS$: C, 38.22; H, 4.49; N, 26.74. Found: C, 38.45; H, 4.30; N, 26.91.

b) A suspension of 915 mg of VIII in 4.73 ml of 1% $ClCH_2COOH$ was refluxed for 6 hr. The resulting solution was concentrated under reduced pressure, and kept in a refrigerator for 2 days after addition of 4 ml of EtOH. The precipitate was collected and recrystallized from H_2O to give 170 mg of colorless needles, mp 173—175°. This was identical with the above sample in all respects.

3-Amino-6-methyl-2,4-dithiouracil (IV)——A mixture of 0.97 g of I, 17 ml of 2-picoline and 0.41 g of P_4S_{10} was refluxed for 5 hr. The similar work-up with that described in the preparation of III gave a solid, which was recrystallized from H_2O to give 470 mg (44%) of pale yellow needles, mp 174—177°. UV $\lambda_{\max}^{H_2O}$ nm (log ε) 290 (4.36). *Anal.* Calcd. for $C_5H_7N_3S_2$: C, 34.68; H, 4.08; N, 24.24. Found: C, 34.79; H, 3.99; N, 24.02.

7-Methyl-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (V)——A mixture of 500 mg of I and 15 ml of ethyl orthoformate was refluxed for 14 hr. The solution was evaporated to dryness *in vacuo* and the residue was recrystallized from EtOH to give 0.41 g (77%) of colorless needles, mp 184—186°. This was identified with the authentic sample[2a)] by the comparison of mp and IR spectra.

2-Amino-7-methyl-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (VI)——To a solution of 1.57 g of I in 10 ml of 5% NaOH was added 1.06 g of cyanogen bromide in small portions at 0—5°. Stirring and cooling were continued for 3 hr, and then the precipitate was collected, washed with water, and recrystallized from EtOH to give colorless needles, mp>300°. Yield, 1.4 g (77%). UV $\lambda_{\max}^{\mathrm{MeOH}}$ nm (log ε): 218 (3.92), 255 (3.40), 306 (3.76). *Anal.* Calcd. for $C_6H_6N_4OS$: C, 39.56; H, 3.32; N, 30.76. Found: C, 39.45; H, 3.31; N, 30.35.

2-Mercapto-7-methyl-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (VII)——A solution of 314 mg of I, 112 mg of KOH and 2 ml of CS_2 in 2 ml of EtOH was gently refluxed for 24 hr. After removal of the solvent, the residue was dissolved in H_2O. To the solution was added 5% HCl and the precipitate was purified by recrystallization from H_2O to give colorless fine needles, mp 213—215°. UV $\lambda_{\max}^{H_2O}$ nm (log ε): 252 (4.30), 286.5 (3.96), 316 (4.02). *Anal.* Calcd. for $C_6H_5N_3OS_2$: C, 36.11; H, 2.68; N, 21.06. Found: C, 36.47; H, 2.78; N, 21.11.

7-Methyl-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-thione (VIII)——a) A suspension of 200 mg of IV in 5 ml of ethyl orthoformate was refluxed for 4 hr. The resulting solution was evaporated to dryness in vacuum and the residue was recrystallized from EtOH to give 0.19 g (89%) of yellow needles, mp 209—211°. UV $\lambda_{\max}^{H_2O}$ nm (log ε): 231.5 (3.92), 297 (3.79), 354.5 (4.14). *Anal.* Calcd. for $C_6H_5N_3S_2$: C, 39.35; H, 2.75; N, 22.95. Found: C, 39.33; H, 2.84; N, 23.16.

b) To a solution of 1.69 g of V in 49.8 ml of 2-picoline was added 2.59 g of P_4S_{10} and 0.1 g of H_2O, and the whole was refluxed for 5 hr. After evaporation of the solvent *in vacuo*, the residue was digested with 3% AcOH, collected by suction, and suspended in H_2O. The mixture was cooled, adjusted to pH 8.0 with 1% NaOH, and filtered. The filtrate was acidified with 5% AcOH and warmed on a water bath. The precipitate was filtered off while the mixture was hot. After being the filtrate cooled, the precipitate was recrystallized from H_2O to obtain 630 mg (32.7%) of pale yellow needles, mp 205—207°. This was identical with the sample obtained above.

Hydrolysis of V with HCl——A suspension of 1 g of V in 10 ml of 5% HCl was refluxed for 5 hr. After evaporation of the resulting solution to dryness, the residue was recrystallized from EtOH to give 450 mg of colorless prisms, mp 270—271°. UV $\lambda_{\max}^{\mathrm{EtOH}}$ 260 nm. *Anal.* Calcd. for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.78. Found: C, 42.73; H, 4.81; N, 29.57. This compound was identical with the sample of II in all respects.