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26. Morizo Ishidate and Hidetaka Yuki: Rearrangement Reaction of 7-Mercaptoöxazolo[5,4-*d*]pyrimidine to 7-Hydroxythiazolo[5,4-*d*]pyrimidine.

(*Faculty of Pharmaceutical Sciences, University of Tokyo*[*1])

The authors previously reported that heating of 5-acylamino-6-mercaptopyrimidine (A) with dilute hydrochloric acid resulted in cyclization to form 2-substituted thiazolo-[5,4-*d*]pyrimidine (B).[1] On the other hand, Hitchings[2] reported that 5,7-diamino-2-*p*-chlorophenyloxazolo[5,4-*d*]pyrimidine (C) underwent cleavage by the action of hydrochloric acid, forming 2-amino-4,6-dihydroxy-5-*p*-chlorobenzamidopyrimidine (D). It was therefore assumed that heating of 7-mercaptoöxazolo[5,4-*d*]pyrimidine (E) with hydrochloric acid would first effect opening of the oxazole ring to form 4-hydroxy-5-acylamino-6-mercaptopyrimidine (F), which would be cyclized toward the mercapto group to form (G), and thereby effecting rearrangement of oxazolo[5,4-*d*]pyrimidine to thiazolo-[5,4-*d*]pyrimidine (Chart 1).

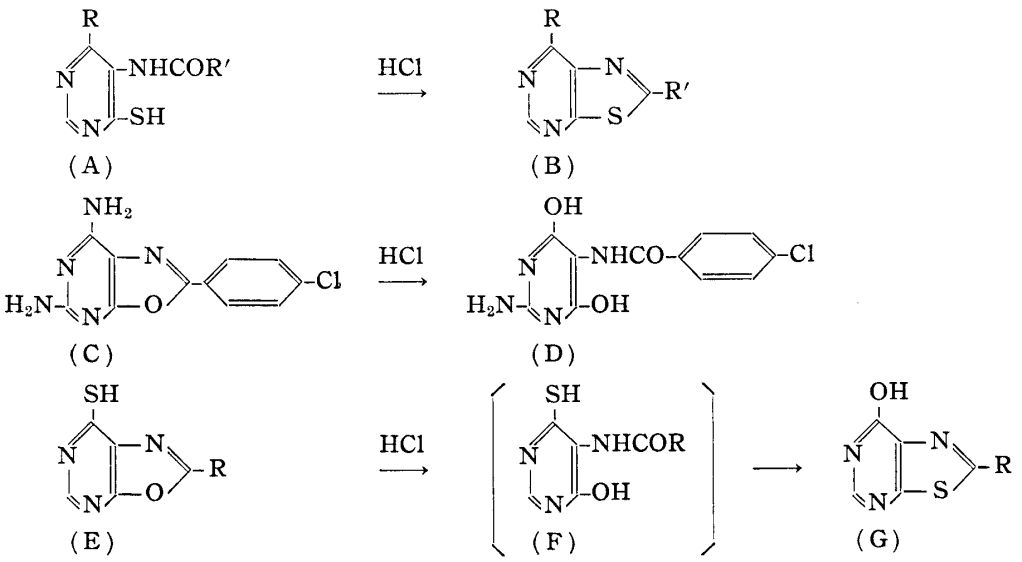

Chart 1.

In order to examine this reaction, an attempt was first made to prepare 2-methyl-7-mercaptoöxazolo[5,4-*d*]pyrimidine (Ⅷ). 4,6-Dihydroxy-5-nitropyrimidine (I) was reduced with stannous chloride to (Ⅱ) and this was boiled with acetic anhydride, forming 7-hydroxy-2-methyloxazolo[5,4-*d*]pyrimidine (Ⅲ). To change this hydroxyl in 7-position to thiol, (Ⅲ) was treated with phosphorus pentasulfide, but even under mild conditions, the compound formed was identified as 7-mercapto-2-methylthiazolo[5,4-*d*]pyrimidine[1] (Ⅳ), the product in which both oxygens in the hydroxyl and the oxazole ring were substituted with sulfur.

(Ⅲ) was then boiled with phosphoryl chloride and the reaction mixture was poured on ice, from which a crystalline precipitate (Ⅵ) was obtained. When this mixture without isolation was allowed to stand over night, the oxazole ring was opened by the action of acid to form (Ⅴ), showing the oxazole ring to be labile to acids. Reaction of

*1 Hongo, Tokyo (石館守三, 由岐英剛).

1) M. Ishidate, H. Yuki: This Bulletin, **8**, 131(1960).
2) G. H. Hitchings, *et al.*: J. Am. Chem. Soc., **74**, 4897(1952).

(V) with phosphoryl chloride effected reclosure of the ring to form (VI). Treatment of (VI) with sodium hydroxide solution saturated with hydrogen sulfide afforded 7-mercapto-2-methyloxazolo[5,4-*d*]pyrimidine (VII), m.p. 342°(decomp.). It was positive to SH test with sodium azide-iodine reagent.

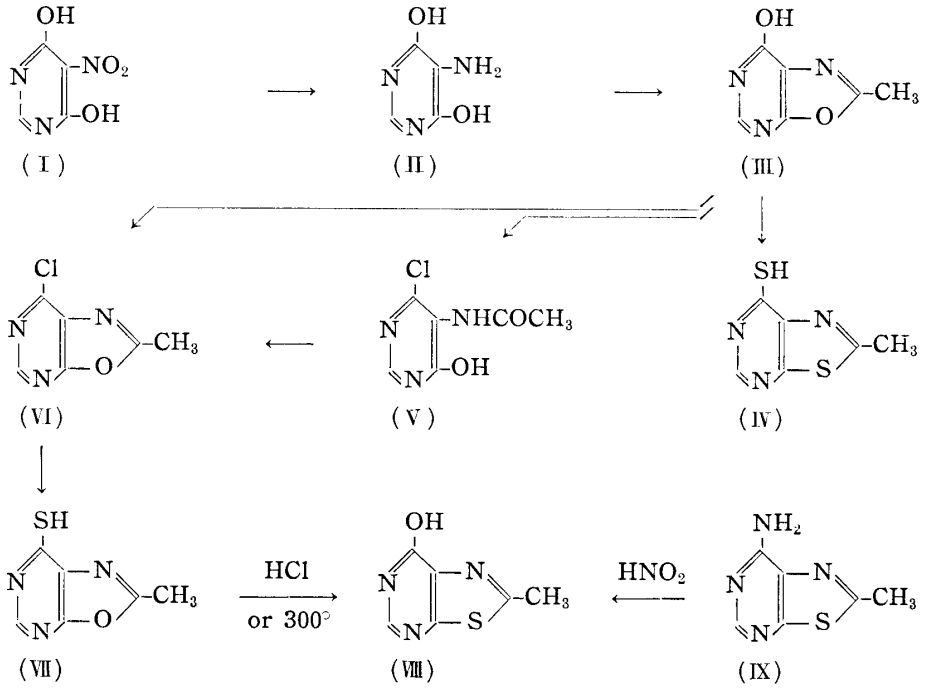

Chart 2.

(VII) was boiled with hydrochloric acid and the reaction product (VIIIa) so obtained was positive to sulfur test but negative to SH test. It was identified with 7-hydroxy-2-methylthiazolo[5,4-*d*]pyrimidine (VIIIb) obtained by the reaction of nitrous acid with 7-amino-2-methylthiazolo[5,4-*d*]pyrimidine (IX). However, (VII) and (VIII) showed the same decomposition point (342°) and there seemed to be a possibility that one of these would transit to the other by rearrangement by heat during determination of the melting point. Therefore, (VII) was heated to 300° and cooled, and the substance (VIIIc) so formed was examined. This was found to be positive to sulfur test but negative to SH test, which indicated that (VII) undergoes rearrangement to (VIII) whether heated in hydrochloric acid or as crystals without the acid. Ultraviolet and infrared spectra of (VIIIa), (VIIIb), and (VIIIc) were completely identical, but were different from that of (VII), further confirming the rearrangement. This rearrangement does not occur when (VII) is boiled in water and consequently the rearrangement of (VII) by heating with hydrochloric acid is not the effect of heat but that of acid. Reverse rearrangement of (VIII) to (VII) by alkali did not take place.

Experimental*2

5-Amino-4,6-dihydroxypyrimidine (II) Hydrochloride—A suspension of 4,6-dihydroxy-5-nitropyrimidine (20 g.) in a mixture of EtOH (75 cc.) and conc. HCl (80 cc.) was warmed on a water bath gradually and $SnCl_2$ (75 g.) was added to the suspension in small portions to effect complete dissolution. After warming on a water bath for a few min., the reaction mixture was treated with 250 cc. of EtOH and left overnight in a refrigerator. The colorless needles (18 g.), which deposited, were collected, dissolved in a small amount of water, and precipitated by adding EtOH. m.p. 247~249°

*2 All m. p. s are uncorrected.

(decomp.). *Anal.* Calcd. for $C_4H_5O_2N_3 \cdot HCl$: C, 28.18; H, 4.25; N, 25.76. Found : C, 28.89; H, 4.17; N, 25.15.

7-Hydroxy-2-methyloxazolo[5,4-*d*]pyrimidine (III)—A mixture of (II)·HCl (5 g.) and Ac_2O (40 cc.) was boiled for 1 hr. Unreacted Ac_2O was distilled off, the residue was cooled, precipitate formed was collected, dissolved in NaOH, and acidified with AcOH to give colorless needles (3.25 g.), which were recrystallized from water; m.p. 281~282° (decomp.). *Anal.* Calcd. for $C_6H_5O_2N_3$: C, 47.70; H, 3.31; N, 27.81. Found : C, 47.85; H, 3.41; N, 27.67.

7-Mercapto-2-methylthiazolo[5,4-*d*]pyrimidine (IV)—A mixture of (III) (0.5 g.) and P_2S_5 (2 g.) in tetralin (10 cc.) was heated for 2 hr. at a bath temperature of 170~180° and cooled. Precipitate formed was collected, washed with EtOH, dissolved in dil. NH_4OH, insoluble matter was filtered off, and the filtrate was acidified with AcOH. The precipitate (0.15 g.) formed was recrystallized from water. m.p. 306° (decomp.). SH, positive. *Anal.* Calcd. for $C_6H_5N_3S_2$: C, 39.35; H, 2.75; N, 22.95. Found : C, 39.13; H, 2.73; N, 23.92.

5-Acetamido-6-chloro-4-hydroxypyrimidine (V)—A suspension of (III) (10 g.) in $POCl_3$ (100 cc.) was refluxed for 30 min., unreacted $POCl_3$ was distilled off, and the residue was poured onto crushed ice under stirring. White crystals separated and then dissolved after being stood overnight. The solution was adjusted to pH 5, concentrated on a water bath, and cooled. Crystals formed were recrystallized from water to give square crystals, m.p. 212~213°. *Anal.* Calcd. for $C_6H_6O_2N_3Cl \cdot H_2O$: C, 35.04; H, 3.80; N, 20.44; H_2O, 8.76. Found : C, 35.30; H, 3.95; N, 20.65; H_2O, 9.30.

7-Chloro-2-methyloxazolo[5,4-*d*]pyrimidine (VI)—a) A suspension of (III) (3 g.) in $POCl_3$ (30 cc.) was refluxed until in solution, unreacted $POCl_3$ was distilled off under a reduced pressure, and the residue was poured onto crushed ice under stirring. Precipitate was collected immediately, washed with water, and recrystallized from 100 cc. of water to 1.5 g. of colorless crystals, m.p. 101~101.5°. *Anal.* Calcd. for $C_6H_4ON_3Cl$: C, 42,48; H. 2.36; N, 24.78. Found : C, 42.80; H, 2.87; N, 23.68.

b) A mixture of (V) (5.5 g.) and $POCl_3$ (50 cc.) was treated as above and 0.6 g. of (VI) was obtained. No depression of m.p. was observed on admixture with the product prepared by method (a).

7-Mercapto-2-methyloxazolo[5,4-*d*]pyrimidine (VII)—A solution of 50% EtOH (50 cc.) containing 1 g. of NaOH was saturated with H_2S, (VI) (1.5 g.) was added to the solution, and the mixture was warmed on a water bath for several min., during which (VI) dissolved completely under generation of H_2S. After cool, acidification with AcOH precipitated colorless crystals, which were recrystallized from water. Yield, 1.1 g. m.p. 342° (decomp.). SH, positive. *Anal.* Calcd. for $C_6H_5ON_3S$: C, 43.12; H, 3.02. Found : C, 43.72; H, 2.93.

7-Hydroxy-2-methylthiazolo[5,4-*d*]pyrimidine (VIII)—a) A solution of $NaNO_2$ (0.3 g.) in 3 cc. of H_2O was dropped into a solution of 7-amino-2-methylthiazolo[5,4-*d*]pyrimidine (IX) (0.6 g.) in 10% HCl (10 cc.) under stirring and the mixture was stood overnight. The precipitate formed was collected, dissolved in dil. NH_4OH, activated carbon was added, and the solution was filtered. The filtrate was acidified with AcOH to give colorless needles. Recrystallization from water gave 0.32 g. of (VIII), m.p. 342~343° (decomp.). S, positive; SH, negative. *Anal.* Calcd. for $C_6H_5ON_3S$: C, 43.12; H, 3.00; N, 25.15. Found : C, 43.46; H, 3.66; N, 24.27.

b) A mixture of (VII) (0.2 g) and 10% HCl (5 cc.) was refluxed for 20 min. and evaporated to dryness on a water bath. The residue was dissolved in NaOH solution and precipitated by acidification with AcOH. Recrystallization from water gave (VIII), m.p. 342° (decomp.). S, positive; SH, negative.

c) (VII) (0.2 g) was heated in a salt bath at 270~300° for 1 hr. and recrystallized from H_2O. m.p. 342° (decomp.). S, positive; SH, negative.

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Summary

7-Mercapto-2-methyloxazolo[5,4-*d*]pyrimidine was found to undergo rearrangement to 7-hydroxy-2-methylthiazolo[5,4-*d*]pyrimidine either by boiling with dilute hydrochloric acid or by heating the crystals to 270~300°.

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