[Chem. Pharm. Bull. 24(7)1506—1509(1976)]

UDC 547.853.3.04 : 547.494.04

An Improved Synthesis of Pyrimido[5,4-*d*]pyrimidine Derivatives substituted by Mercapto Groups

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(Received September 30, 1975)

5-Amino-6-hydroxy-2-methlythiopyrimidine-4-carboxamide (VII) was prepared from methyl 6-hydroxy-2-methylthiopyrimidine-4-carboxylate (V) by bromination, followed by amino-amidation. VII was also prepared by a similar treatment of 6-hydroxy-2-methylthiopyrimidine-4-carboxamide (VIII) which was synthesized by half-amidation of sodium salt of ethyl methyl oxalacetate (IV), followed by treatment with S-methylisothiourea sulfate. 4,8-Dihydroxy-2-mercapto-6-methylthio-pyrimido[5,4-*d*]pyrimidine (I) was synthesized with quantitative yields by reacting VII with sodium or potassium ethylxanthogenate or with diethylammonium N,N-diethyldithiocarbamate in suitable solvents, such as pyridine, water, *etc.*, under refluxing condition. I was converted to 4,8-dihydroxy-2,6-dimercapto-pyrimido[5,4-*d*]pyrimidine (II) by treating sodium salt of I in ethylene glycol at about 125° in passing of hydrogen sulfide.

4,8-Dihydroxy-2-mercapto-6-methylthio-pyrimido[5,4-*d*]pyrimidine (I) and 4,8-dihydroxy-2,6-dimercapto-pyrimido[5,4-*d*]pyrimidine (II) were very important intermediates for the synthesis of dipyridamole (=2,6-bis[bis(2-hydroxyethyl)amino]-4,8-dipiperidinopyrimido[5,4-*d*]pyrimidine) and its analogues which were well known as the useful remedies for angina pectoris.[2,3] As one of the general methods for the synthesis of I, a method that 5-amino-6-hydroxy-2-methylthiopyrimidine-4-carboxylic acid (III) was fused with thiourea or ammonium thiocyanate at about 150° was considered.[4,5] However, this method was not suitable for the synthesis of I, because many decomposed compounds, especially desulfurized compounds which were resulted with the heavy evolution of hydrogen sulfide during the reaction, were accompanied with I on account of the drastic reaction condition and the isolation of I was practically impossible.[6] Therefore, we have investigated on many routes for the synthesis of I and II, and we found an useful new method that 5-amino-6-hydroxy-2-methylthiopyrimidine-4-carboxamide (VII) was reacted with potassium or sodium ethylxanthogenate or with diethylammonium N,N-diethyldithiocarbamate as shown in Chart 1. This new method was especially advantageous for the industrial synthesis of I and II.

VII was prepared by two methods. One of them was the use of methyl 6-hydroxy-2-methylthiopyrimidine-4-carboxylate (V) which was prepared by the method of Daves, *et al.*[7] V was brominated with one equivalent of bromine in acetic acid and methyl 5-bromo-6-hydroxy-2-methylthiopyrimidine-4-carboxylate (VI) obtained was converted to VII by

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2) *a*) M. Murakami, S. Kawahara, N. Inukai, S. Ishida, K. Imai, and T. Ozasa, Japan Patent 12734 (1971) [*C.A.*, **75**, 36100*v* (1971)]; *idem, ibid.*, 12735 (1971) [*C.A.*, **75**, 36114*c*(1971)]; *idem, ibid.*, 12736 (1971) [*C.A.*, **75**, 36112*a* (1971)]; *idem, ibid.*, 12737 (1971) [*C.A.*, **75**, 36099*b* (1971)]; *idem, ibid.*, 12738 (1971) [*C.A.*, **75**, 36113*b* (1971)]; *idem, ibid.*, 29000 (1972); *idem, ibid.*, 31320 (1972); *idem, ibid.*, 44755 (1972) [*C.A.*, **78**, 58453*b* (1973)]; *b*) Ger. Offen 2146440 (1972) [*C.A.*, **77**, 126676*h* (1972)].
3) K. Imai, N. Inukai, T. Ishida, T. Ozasa, S. Kawahara, and M. Murakami, *Yakugaku Zasshi*, **96**, 593 (1976).
4) G.F. Fischer, J. Roch, and A. Koffler, Ger. Patent 1093801 (1960).
5) "Heterocyclic Compounds," Vol. 7, ed. by R.C. Elderfield, John Wiley and Sons, Inc., New York, 1961.
6) M. Murakami, N. Inukai, and Y. Ishii, Japan Patent 40 (1975).
7) G.D. Daves, Jr., F. Baiocchi, R.K. Robins, and C.C. Cheng, *J. Org. Chem.*, **26**, 2755 (1961).

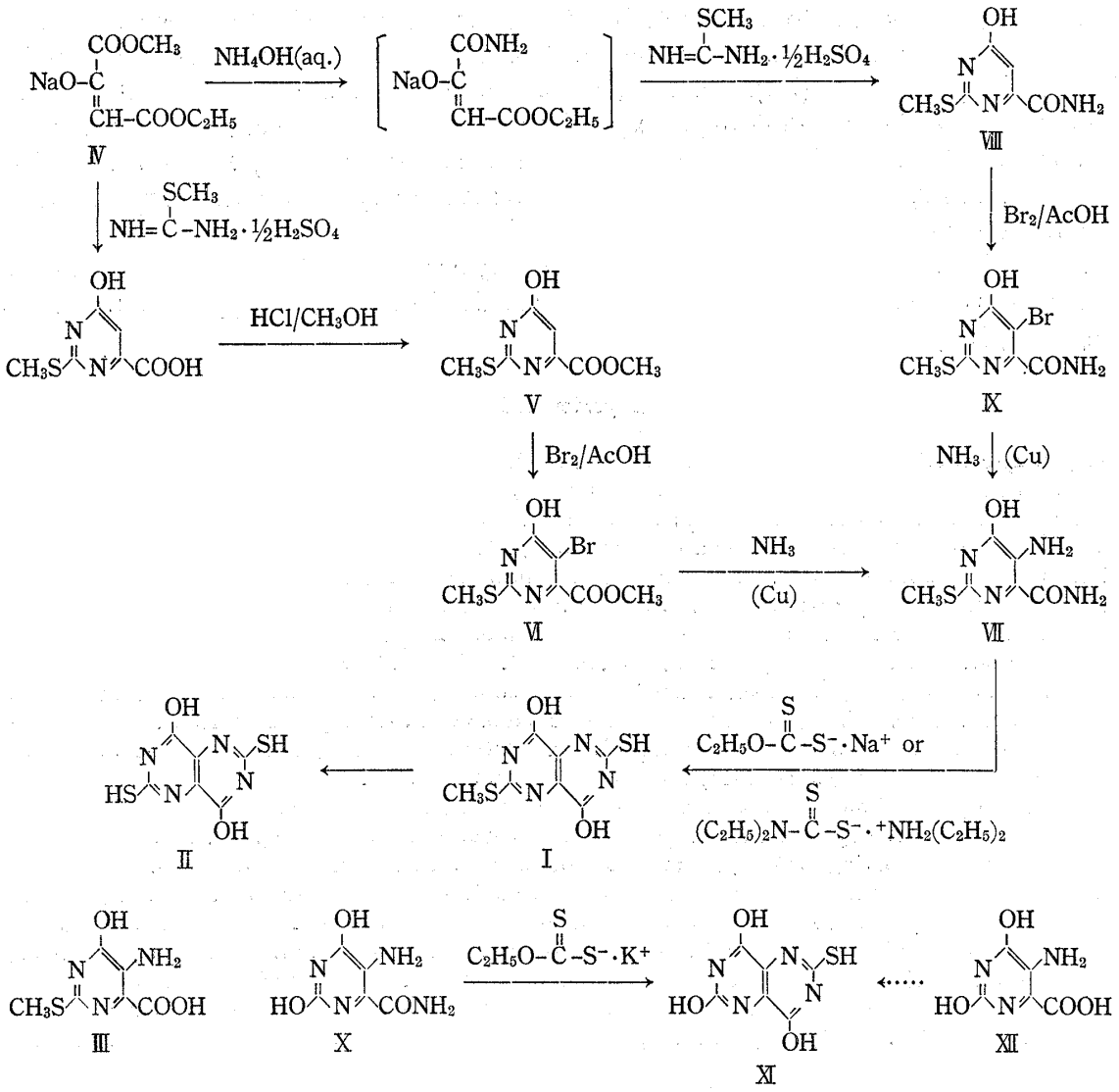

Chart 1

treatment with concentrated aqueous ammonia in the presence of catalytic amounts of copper powder.[8] The other was the use of 6-hydroxy-2-methylthiopyrimidine-4-carboxamide (VIII) which was prepared by half amidation of sodium salt of ethyl methyl oxalacetate (IV) with concentrated aqueous ammonia below 5°, followed by treatment with S-methylisothiourea sulfate. The synthesis of VII from VIII was carried out by bromination, followed by amination, which were the similar procedures as described above. The latter method was more excellent than the former on the convenience of procedures and on the total yield of VII from IV.

I was easily obtained in a 98% yield by reacting VII with potassium or sodium ethylxantogenate or with diethylammonium N,N-diethyldithiocarbamate in suitable solvents, such as pyridine, water, *etc.*, under refluxing condition. This new method is very useful for the industrial synthesis of I, because the reaction condition was comparatively mild and I was obtained with quantitative yields. Other dithio derivatives, such as dithioformate, were also usefully applied for the purpose. However, carbon disulfide did not react with VII under the same condition.

8) M. Murakami, T. Osono, K. Yano, S. Kawahara, S. Ishida, and H. Horiguchi, Japan Patent 29666 (1970) [*C.A.*, **74**, 22869*v* (1971)].

This method was able to be used satisfactorily for the synthesis of analogous compounds which have the mercapto groups as the substituent, such as 2-mercapto-4,6,8-trihydroxypyrimido[5,4-*d*]pyrimidine (XI). Fischer, *et al.* synthesized XI with only a 30% yield by fusing a mixture of 5-amino-2,6-dihydroxypyrimidine-4-carboxylic acid (XII) and ammonium thiocyanate at about 150°[9] We synthesized the same compound (XI) with a 97.2% yield by treating 5-amino-2,6-dihydroxypyrimidine-4-carboxamide (X) with potassium ethylxanthogenate in water under refluxing condition.

II was synthesized with about 86% yields from I by a modified method of the literatures.[7,10] Namely, I was converted to II by treating sodium salt of I in ethylene glycol at about 125° in passing of hydrogen sulfide.

Experimental[11]

6-Hydroxy-2-methylthiopyrimidine-4-carboxamide (VIII)——a) To 50 ml of 14% NH_4OH cooled in an ice bath was added 5.0 g of the sodium salt of ethyl methyl oxalacetate (IV) and the mixture was stirred for 1 hr under ice-cooling. To the solution thus prepared was added 3.8 g of S-methylisothiourea sulfate and the mixture was further stirred for 3 hr under ice-cooling. After the reaction, the pH of the solution was adjusted to 4—5 by adding AcOH. The solution was allowed to stand for a while, whereby white crystals were precipitated. The crystals were collected by filtration and washed with a small amount of H_2O and recrystallized from EtOH. The amount of the product was 3.2 g (yield 68%) and the melting point was 275—276°. *Anal.* Calcd. for $C_6H_7O_2N_3S$: N, 22.69; S, 17.31. Found: N, 22.82; S, 17.10.

b) To 50 ml of 14% NH_4OH cooled below 5° was added 5.0 g of IV and the mixture was stirred for 1 hr at the same temperature. Then, to the solution was added 5.3 g of S-methylisothiourea sulfate and the mixture was stirred for further 3 hr at the same temperature. After the reaction, the reaction solution was treated as a). 3.7 g (79%) of white crystals (VIII) was obtained: mp 270—271°.

5-Bromo-6-hydroxy-2-methylthiopyrimidine-4-carboxamide (IX)——In 400 ml of AcOH was suspended 50 g of VIII and 49.3 g of Br_2 was added dropwise to the suspension with stirring. Then the suspension was heated to 50° and after stirring for 1 hr, the inner temperature of it was further raised to 100° and stirring was continued for 1 hr. The reaction mixture was allowed to cool at room temperature. The crystals precipitated were collected by filtration and washed with a small amount of AcOH. Then, the crystals obtained were suspended in 125 ml of benzene and the suspension was boiled for 30 min. After cooling, the crystals were collected by filtration and washed with a small amount of MeOH. 61.6 g (yield 86%) of IX was obtained. The crystals which were recrystallized from a dimethylformamide–MeOH mixture had a melting point of 244—245°. *Anal.* Calcd. for $C_6H_6O_2N_3SBr$: N, 15.96; S, 12.14; Br, 30.25. Found: N, 15.93; S, 12.02; Br, 29.97.

Methyl 5-Bromo-6-hydroxy-2-methylthiopyrimidine-4-carboxylate (VI)——Methyl 6-hydroxy-2-methylthiopyrimidine-4-carboxylate (V)[7] was brominated by the same procedure as described above. The yield of VI was 83% and the melting point of the needle crystals of VI which were recrystallized from MeOH showed 207—208°. *Anal.* Calcd. for $C_7H_7O_3N_2SBr$: C, 30.12; H, 2.53; N, 10.04; S, 11.49. Br, 28.63; Found: C, 29.85; H, 2.57; N. 9.83; S, 12.01. Br, 28.24;

5-Amino-6-hydroxy-2-methylthiopyrimidine-4-carboxamide (VII)——a) To 180 ml of 28% NH_4OH was added 50 g of IX and after adding 0.5 g of Cu powder to the solution, the mixture was heated for 3 hr to 90—100° in a sealed tube. After the reaction, the reaction mixture was cooled, and the yellow crystals precipitated were collected by filtration. The crude crystals were dissolved in 800 ml of 2% NH_4OH by heating and the hot solution was treated with active carbon. The solution was cooled and the pH of the solution was adjusted to 6 with the addition of AcOH, whereby yellow crystals were precipitated. The crystals thus formed were collected by filtration, washed with H_2O and then MeOH, and dried *in vacuo*. 29.2 g (yield 77%) of VII was obtained: mp 280°. The filtrate and the washing solution were combined and concentrated to about 400 ml and then, pH of the concentrated solution was adjusted to 6 with AcOH. The yellow crystals precipitated were collected by filtration, washed with a small amount of H_2O and then MeOH, and dried *in vacuo*. 4.05 g (yield 10.7%) of the second crop of VII was obtained: mp 280° (lit.,[8] mp 278—279°). The combined amount of the product was 33.25 g (yield 87.7%). *Anal.* Calcd. for $C_6H_8O_2N_4S$: C, 35.99; H, 4.03; N, 27.98; S, 16.01. Found: C, 35.41; H, 4.10; N, 27.19; S, 15.63.

b) VII was also obtained from VI with a 76.9% yield by the same procedure as described above.

4,8-Dihydroxy-2-mercapto-6-methylthio-pyrimido[5,4-*d*]pyrimidine (I)——a) To a mixture of 10 ml of pyridine and 6 ml of EtOH were added 100 mg of VII and 1.6 g of potassium ethylxanthogenate and then,

9) G.F. Fischer and J. Roch, Ger. Patent 845940 (1952).
10) F.H.S. Curd and D.N. Richardson, *J. Chem. Soc.*, **1955**, 1853.
11) All melting points are not corrected.

the mixture was refluxed overnight. After the solvent was distilled off, 3 ml of H_2O was added to the residual yellow crystals, and the pH of the mixture was adjusted to 4—5 with AcOH. The crystals precipitated were collected by filtration and washed twice with 0.5 ml each of H_2O. The crystals thus obtained were dissolved in 10 ml of 3 N NH_4OH. After the solution was treated with activated carbon, the pH of the solution was adjusted to 4—5 with the addition of AcOH and the creamy colored crystals thus precipitated were collected by filtration, washed twice with 1 ml each of H_2O, and dried. 96 mg (yield 74%) of I having a melting point of higher than 300° was obtained. Mass Spectrum *m/e*: 242 (M^+). *Anal.* Calcd. for $C_7H_6O_2N_4S_2 \cdot H_2O$: C, 32.23; H, 3.21; N, 21.48; S, 24.66. Found: C, 32.30; H, 3.10; N, 21.52; S, 24.64.

The same sample was dried over P_2O_5 *in vacuo*. *Anal.* Calcd. for $C_7H_6O_2N_4S_2$: C, 34.70; H, 2.50; N, 23.13; S, 26.47. Found: C, 34.49; H, 2.44; N, 22.75; S, 26.22.

When the reaction was carried out in H_2O instead of pyridine under refluxing for 6 hr, I was also obtained in a 98% yield. Furthermore, when the reaction was carried out in dimethylformamide at 110—115° for 19 hr, the yield of I was 75.4%.

b) In 10 ml of pyridine were dissolved 100 mg of VII and 2.2 g of N,N-diethyldithiocarbamic acid diethylamine salt and the solution was refluxed overnight. The reaction mixture was concentrated and then 3 ml of H_2O was added to the residue. After the pH of the mixture was adjusted to 4—5 by adding AcOH, the mixture was washed with 10 ml of ether. The mixture was allowed to stand for about 1 hr at room temperature. The crystals precipitated were collected by filtration and washed twice with 0.5 ml each of H_2O. The crystals thus obtained were dissolved in 10 ml of 3 N NH_4OH. Activated carbon was added to the mixture, and then the carbon and an insoluble material were filtered off. The filtrate was weakly acidified with AcOH and the yellow crystals thus precipitated were collected by filtration and washed twice with 1 ml each of H_2O, followed by dry. 80 mg (yield 61.5%) of I was obtained.

c) To a mixture of 5 ml of pyridine and 3 ml of EtOH were added 50 ml of VII and 1 g of potassium dithioformate and the mixture was refluxed for 22 hr under heating. The reaction mixture was concentrated and the residue was treated as described above. 38 mg of the yellow crystal of I was obtained with a yield of 58.5%.

4,8-Dihydroxy-2,6-dimercapto-pyrimido[5,4-*d*]pyrimidine (II)——To a sodium methylate solution which was prepared from 16 g of Na and 200 ml of absolute MeOH, 28 g of dried H_2S was introduced. MeOH was distilled off and 1 liter of anhydrous ethylene glycol was added to the residue. The mixture was concentrated at the pressure of 70—80 mmHg until the inner temperature of the mixture was reached at about 135° and then cooled to room temperature. 80 g of I was suspended to the mixture. The suspension was stirred for 30 min in passing of H_2S and the temperature of the slurry thus formed was gradually raised to 120—135° with stirring and then the stirring was continued for 9 hr at the same temperature in passing of H_2S through the reaction mixture. The reaction mixture was cooled and after adding thereto 800 ml of MeOH, the mixture was stirred for 10 min. The precipitates thus formed were collected by filtration and then washed with 200 ml of MeOH. The product, sodium salt of II, was dissolved in 2 liter of 1% NaOH at 30—40° and the hot solution was treated with activated carbon. The pH of the solution was adjusted to 3—4 with the addition of AcOH below 40°, whereby precipitates were formed. The precipitates were collected by filtration and washed with 320 ml of H_2O and 160 ml of MeOH. 65 g (yield 86.2%) of the yellow fine powder of II having a melting point of higher than 300° was obtained. Mass Spectrum *m/e*: 228 (M^+). *Anal.* Calcd. for $C_6H_4O_2N_4S_2$: C, 31.57; H, 1.77; N, 24.55; S, 28.10. Found: C, 31.65; H, 1.51; N, 24.22; S, 27.80.

Acknowledgement The authors wish to express their thanks to the Measurement Division of the Central Research Laboratories for Measurements of NMR and mass spectra and for elemental microanalyses.