[Chem. Pharm. Bull. 15(6) 816~821 (1967)]

UDC 547.853.07

100. Akira Takamizawa, Kentaro Hirai, Yoshio Hamashima, and Hisako Ito : Studies on Pyrimidine Derivatives and Related Compounds. XLV.*1 On Some Synthetic Methods of N-[1-(2-Oxo-1,3-oxathian-4-ylidene)ethyl]-N-[(2-methyl-4-amino-5-pyrimidinyl)-methyl]formamide.*2

(*Shionogi Research Laboratory, Shionogi & Co., Ltd.**3)

The reaction of phosgene with thiamine chloride (IIa) or nitrate (IIb) gave O-chlorocarbonylthiamine (IX) in good yield. Treatment of IX with alkali afforded N-[1-(2-oxo-1,3-oxathian-4-ylidene)ethyl] -N-[(2-methyl-4-amino-5-pyrimidinyl)methyl]formamide (XIII). The reaction of thiamine sodium salt (III) with aryloxycarbonyl chloride (phenoxy-, *p*-methylphenoxy, *p*-methoxyphenoxy) gave corresponding S-aryloxycarbonylthiamine (XIIa~c), and further treatment of XIIa~c with alkali afforded XIII in good yield. On the other hand, IX reacted with sodium salts of phenol, *p*-cresol, and *p*-methoxyphenol to give corresponding O-aryloxycarbonylthiamine (XIa~c). Treatment of XIa~c with alkali also gave XIII in low yield. Therefore, it was assumed that XI and XII gave XIII in independent way by alkali treatment.

(Received August 27, 1966)

It has been reported[1] that the reaction of thiamine sodium salt (III) with phosgene gave S-chlorocarbonylthiamine (IV) and O,S-bis(chlorocarbonyl)thiamine (V), and treatment of IV and V with ethanol afforded S-ethoxycarbonylthiamine (VII) and O,S-bis-(ethoxycarbonyl)thiamine (VI), respectively.

Recently, Murakmi, *et al.*[2] reported the synthesis of N-[1-(2-oxo-1,3-oxathian-4-ylidene)ethyl]-N-[(2-methyl-4-amino-5-pyrimidinylmethyl)]formamide (XIII) from the reaction of phosgene with thiamine in alkaline solution. It would be reasonable to consider the route *via* IV as an intermediate in this reaction. Then isolated IV was treated with alkali to give XIII as expected. The structure of IV was also confirmed by the fact that IV reacted with morpholine to give S-morpholinocarbonylthiamine (VIII). Previously,[1] it was found that the reaction of thiamine hydrochloride (I) with phosgene in chloroform gave O-chlorocarbonylthiamine hydrochloride (IX). It was also expected to form XIII from IX, therefore, IX was treated with alkali to give XIII as expected.

Since this method was considered to be useful for obtaining XIII industrially from I, an attempt to improve the yield of IX was made. I was sparingly soluble in organic solvents and had a tendency to remain unreacted, but the reaction of thiamine chloride (IIa) with phosgene in acetic anhydride gave pure IX as the crystals of m.p. 225° (decomp.). The elemental analyses of these crystals were in agreement with the value of $C_{13}H_{17}O_2N_4SCl_3$, infrared (IR) spectrum showed the bands at 1765 ($\nu_{C=O}$) and 1149 cm^{-1} ($\nu_{O-C=O}$), and the reaction with ethanol gave O-ethoxycarbonylthiamine (X). Treatment of this product with alkali gave pure XIII in good yield. Similarly, thiamine nitrate (IIb) gave IX in good yield.

---

*1 Part XLIV, A. Takamizawa, K. Hirai, T. Ishiba, Y. Matsumoto : This Bulletin, **15**, 731 (1967).

*2 A part of this paper was presented at 19th Annual Meeting of Vitamin Society of Japan, Osaka, May, 1966.

*3 Fukushima-ku, Osaka (高見沢 映, 平井健太郎, 浜島好男, 伊藤寿子).

1) A. Takamizawa, K. Hirai, Y. Hamashima : This Bulletin, **11**, 882 (1963).

2) M. Murakami, K. Takahashi, Y. Hirata, H. Iwamoto : Vitamin, **34**, 71 (1966).

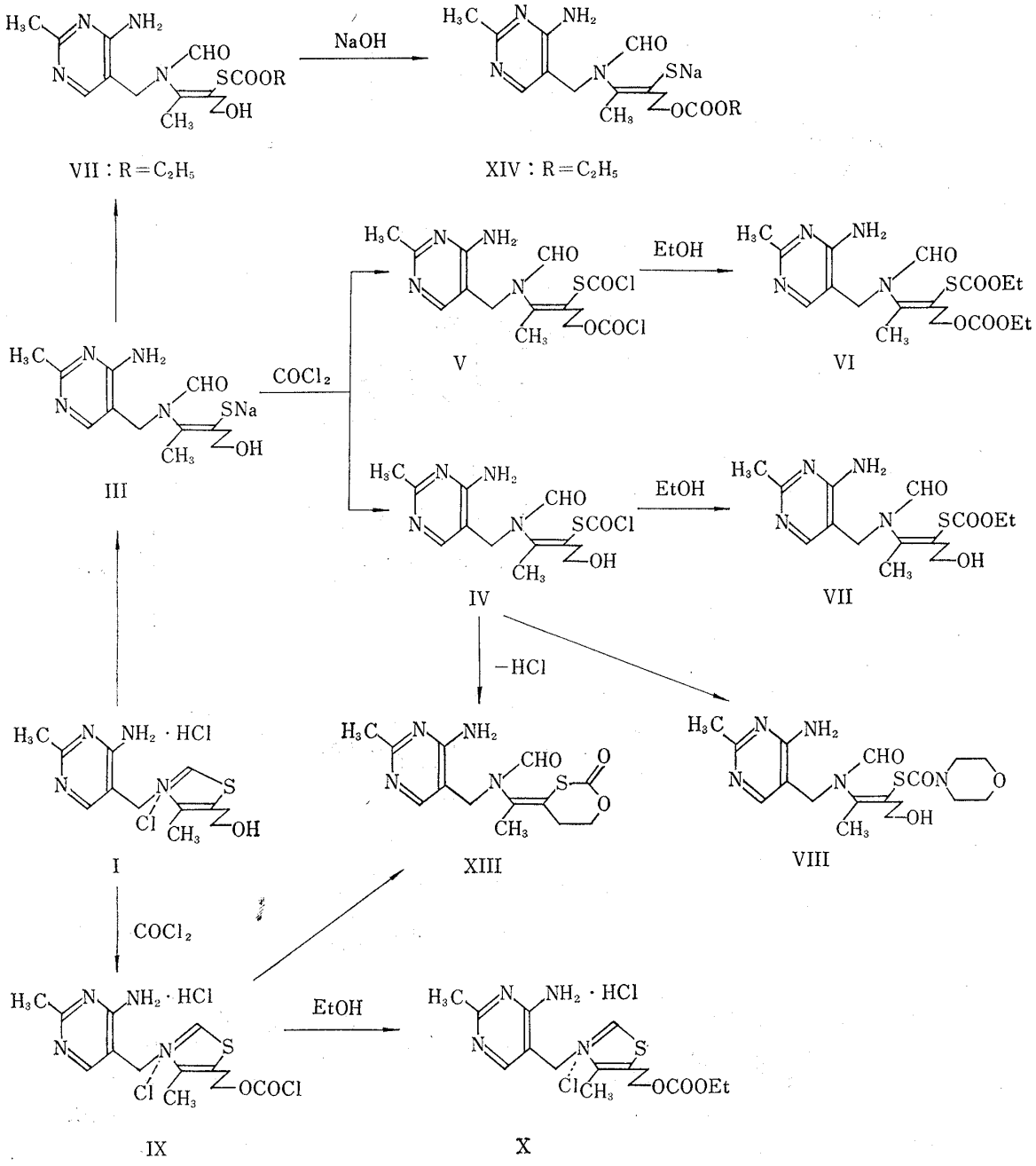

Chart 1.

It was previously reported[3] that the reaction of III with alkyl chloroformate gave S-alkoxycarbonylthiamine and its rearrangement to O-alkoxycarbonylthiamine by alkaline catalysis. In this rearrangement, the intermediate XVI′ was assumed to be present in the course of the reaction. It should be possible to form XIII by the preferential removal of the alkoxyl group of XVI′ (route B), and the scission of the C-S bond of XVI′ should give O-alkoxycarbonylthiamine (route A). When R of OR group was alkyl group, the reaction proceeded through route A. However, when R is aryl group, its electron-attracting effect and resonance effect would make it possible to take route B. The reaction of III with phenoxycarbonyl chloride gave S-phenoxycarbonylthiamine (XIIa) as the crystals of m.p. 112° (decomp.). The structure of this product was

3) A. Takamizawa, K. Hirai : This Bulletin, **10**, 1102 (1962).

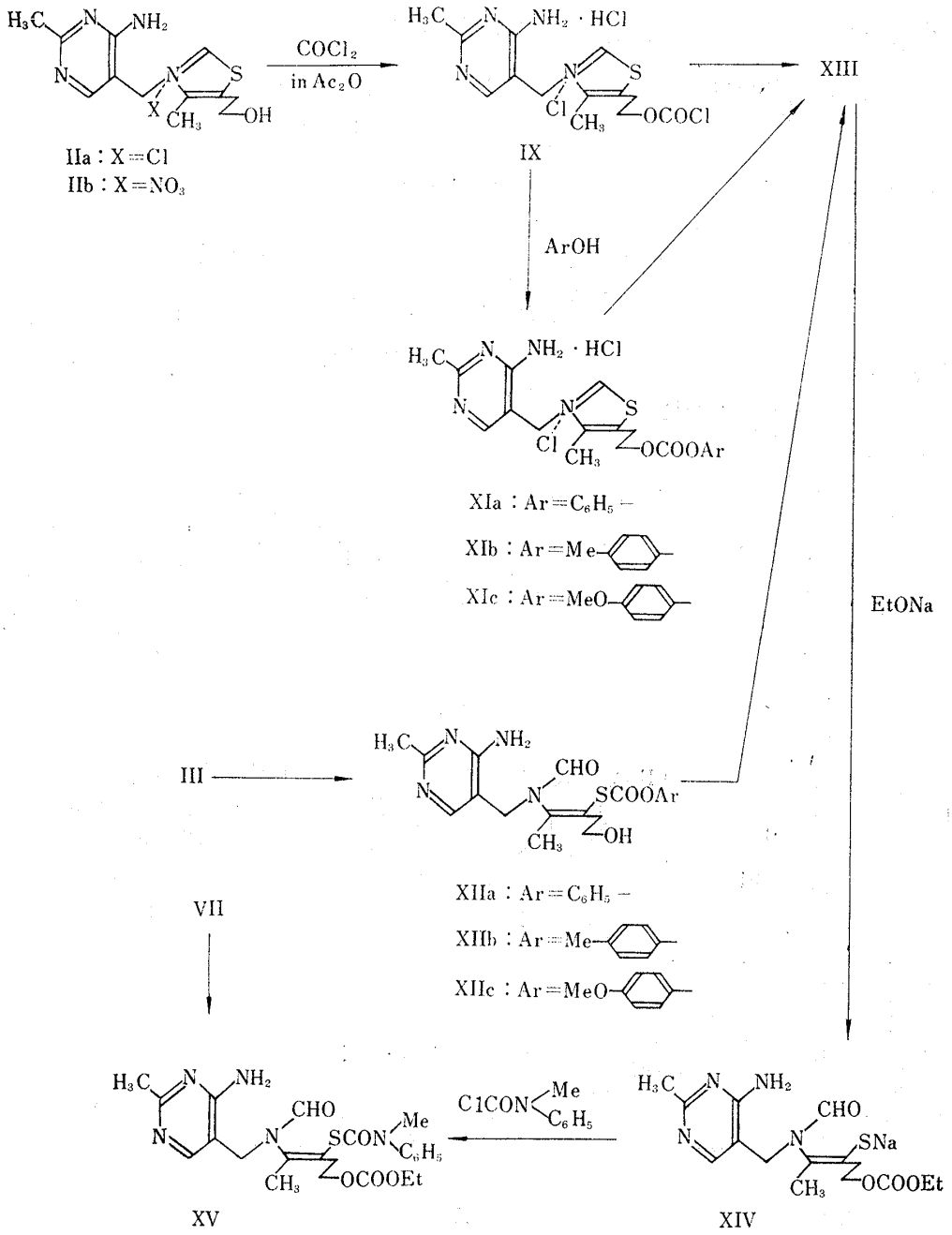

Chart 2.

confirmed by its elemental analysis and IR spectrum showing the band at 1730 cm^{-1} due to S-C=O group. Treatment of XIIa with sodium ethoxide followed by the reaction with methylphenylcarbamoyl chloride gave the crystals of m.p. 143°. The elemental analysis of this product was in agreement with the value of $C_{23}H_{29}O_5N_5S$. The IR comparison with O-ethoxycarbonyl-S-methylphenylcarbamoylthiamine (XV) obtained from VII and methylphenylcarbamoyl chloride by sodium ethoxide catalyzed reaction showed the identical spectra. It was assumed that XIII was first formed from XIIa and then converted into O-ethoxycarbonylthiamine sodium salt (XIV). Then XIIa was treated with 5% sodium bicarbonate in chloroform to give XIII in high yield. The reaction with *p*-methylphenoxycarbonyl chloride and *p*-methoxyphenoxycarbonyl chloride gave S-*p*-methylphenoxycarbonylthiamine (XIIb) and S-*p*-methoxyphenoxycarbonylthiamine

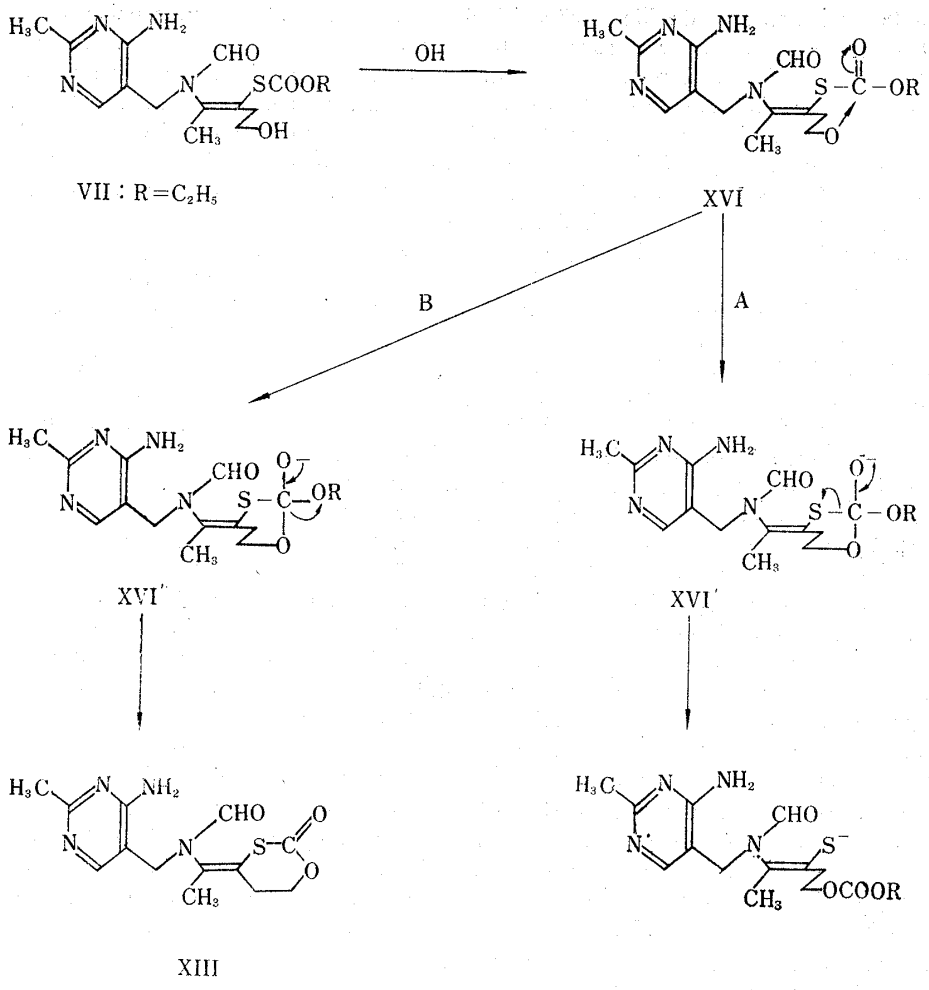

Chart 3.

(XIIc), respectively. Similar treatment of XIIb, c with sodium bicarbonate also gave XIII in high yield.

In the course of this reaction, the route *via* O-aryloxycarbonylthiamine (XI) from S-aryloxycarbonylthiamine (XIIa~c) would not be eliminable. Then O-phenoxycarbonylthiamine (XIa) obtained from IX by the action of sodium phenolate was treated with alkali to give XIII. Similarly, O-*p*-methylphenoxycarbonylthiamine (XIb) and O-*p*-methoxyphenoxycarbonylthiamine (XIc), which were obtained from the reactions of IX with sodium salts of *p*-cresol and *p*-methoxyphenol, were treated with alkali to afford XIII. However, the yields of XIII from XIa~c were worse than those from XIIa~c. Therefore, it was concluded that XIa~c and XIIa~c gave XIII independently.

Experimental*4

S-Chlorocarbonylthiamine (IV)——Into a suspension of 3.22 g. of thiamine sodium salt (III) in 30 ml. of MeCN, 1.0 g. of phosgene was passed through with stirring at −40~−45°. After 2 hr., the reaction mixture was concentrated *in vacuo* to give crystalline solid IV. It was failed to detect XIII (Rf 0.35) on TLC (SiO_2, Me_2CO). IR ν_{max}^{Nujol} cm^{-1} : 1708 (S-C=O).

S-Morpholinocarbonylthiamine (VIII)——To a solution of IV obtained above in 30 ml. of MeCN, 3 g. of morpholine was added with cooling, then stirred for 2 hr. at 20°. The reaction mixture was concentrated *in vacuo*, and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on SiO_2 with Me_2CO to give 0.8 g. of colorless prisms, m.p. 169~170°(decomp.), which proved to be identical with VIII by IR comparison with an authentic sample.[1]

*4 All melting points are uncorrected.

O-Chlorocarbonylthiamine Chloride Hydrochloride (IX)——a) Into a suspension of 1.5 g. of IIa in 20 ml. of Ac_2O, excess of phosgene was passed through with stirring at −5～−10°. After 2 hr. in cooling, stirring was continued for 15 hr. at room temperature. The reaction mixture was concentrated *in vacuo* to give 1.7 g. (85%) of crystalline (IX), m.p. 225°(decomp.). *Anal.* Calcd. for $C_{13}H_{17}O_2N_4SCl_3$: C, 39.03; H, 4.28; N, 14.02. Found: C, 39.35; H, 4.56; N, 14.31. IR ν_{max}^{Nujol} cm^{-1}: 1765 (C=O), 1147 (O-C=O).

b) Into a suspension of 1.7 g. of thiamine nitrate (IIb) in 20 ml. of Ac_2O, excess of phosgene was passed through at −10°, and worked up as above to give 1.65 g. (88%) of IX. IR spectrum of this product was completely in accordance with that of IX obtained above a).

O-Ethoxycarbonylthiamine Chloride Hydrochloride (X)——A suspension of 4 g. of IX in 20 ml. of EtOH was stirred for 3 hr. at 50～60°. The reaction mixture was concentrated *in vacuo*, and the residue was recrystallized from EtOH to give 3.2 g. (74.8%) of X, m.p. 206～207°(decomp.), which showed identical spectrum with that of an authentic sample.[4]

O-Phenoxycarbonylthiamine Chloride Hydrochloride (XIa)——To a solution of 1 g. of IX in 10 ml. of H_2O, 100 ml. of Me_2CO was added. To this solution, the solution of 0.87 g. of sodium phenolate in 3 ml. of H_2O was added dropwise at −40°. The reaction mixture showed pH 7 after stirring for 4 hr., and was adjusted to pH 2 with addition of conc. HCl at −20°. The solvent was removed *in vacuo*, the concentrate was adjusted to pH 4.5 with 10% NaOH, and extracted with $CHCl_3$. The aqueous layer was adjusted to pH 1.5 with dil. HCl and concentrated *in vacuo*. The residue was recrystallized from EtOH to give 0.5 g. (51.8%) of colorless scales, m.p. 210～211°(decomp.). *Anal.* Calcd. for $C_{19}H_{22}O_3N_4SCl_2$: C, 49.88; H, 4.85; N, 12.25; Cl, 15.50. Found: C, 49.52; H, 5.04; N, 12.36; Cl, 15.80. IR ν_{max}^{Nujol} cm^{-1}: 1767 (C=O), 1245 (O-C=O). The $CHCl_3$ extract was dried over Na_2SO_4, evaporated, and the residue was added ether to give the crystals. Recrystallization from AcOEt gave 0.2 g. (3.7%) of XIII, m.p. 182～183°(decomp.).

O-*p*-Methylphenoxycarbonylthiamine Chloride Hydrochloride (XIb)——To a solution of 1 g. of IX in 10 ml. of H_2O, 100 ml. of Me_2CO was added and a solution of 0.98 g. of sodium *p*-cresolate in 4 ml. of H_2O was added dropwise at −40～−50°. After stirring for 2.5 hr., the reaction mixture was worked up as above to give 0.51 g. (43%) of colorless prisms, m.p. 206～207.5°(decomp.). *Anal.* Calcd. for $C_{20}H_{24}O_3N_4SCl_2$: N, 11.84; S, 6.80. Found: N, 11.40; S, 6.88. IR ν_{max}^{Nujol} cm^{-1}: 1767 (C=O), 1255 (O-C=O).

O-*p*-Methoxyphenoxycarbonylthiamine Chloride Hydrochloride (XIc)——To a solution of 3 g. of IX in 30 ml. of H_2O, 300 ml. of Me_2CO was added and a solution of 3.36 g. of sodium *p*-methoxyphenolate in 10.5 ml. of H_2O was added dropwise at −40～−50°. Treatment of this reaction mixture as above gave 1.768 g. (48.4%) of colorless prisms, m.p. 195～196.5°(decomp.). *Anal.* Calcd. for $C_{20}H_{24}O_4N_4SCl_2$: N, 11.50; Cl, 14.55. Found: N, 12.08; Cl, 14.71. IR ν_{max}^{Nujol} cm^{-1}: 1768 (C=O), 1251 (O-C=O).

S-Phenoxycarbonylthiamine (XIIa)——To a solution of 32 g. of III in 250 ml. of EtOH, 17.5 g. of $ClCOOC_6H_5$ was added dropwise at −10° and stirred for 30 min. After stirring was continued for 1.5 hr. at 20°, the reaction mixture was concentrated *in vacuo* to give crystalline residue. The crystals were collected and washed with a small amount of cold water to give 20.8 g. (quantitative) of colorless prisms, m.p. 80. IR ν_{max}^{Nujol}: 1730 (S-C=O). This product was unstable and used in the following step without further purification.

S-*p*-Methoxyphenoxycarbonylthiamine (XIIc)——To a solution of 3.04 g. of III in 25 ml. of EtOH, 1.87 g. of *p*-methoxyphenylchloroformate was added and stirred for 30 min. After stirring for 1 hr. at 20°, the reaction mixture was concentrated *in vacuo* and the separated crystals were collected to give 3.8 g. (87%) of crystalline powder, m.p. 96～97°(decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1731 (S-C=O). This product was unstable and used in the following step without further purification.

O-Ethoxycarbonyl-S-methylphenylcarbamoylthiamine (XV)——a) To a solution of 0.127 g. of metalic Na in 20 ml. of EtOH, 2.01 g. of XIIa was added and stirred for 10 min. at 20°. Methylphenylcarbamoyl chloride (0.94 g.) was added and stirred for 1 hr. at 40～45°. The reaction mixture was concentrated *in vacuo* and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4, and evaporated. The crystalline residue was recrystallized from Me_2CO-ether to give 2 g. (82.2%) of colorless rhombs, m.p. 143°. *Anal.* Calcd. for $C_{23}H_{29}O_5N_5S$: C, 56.66; H, 6.00; N, 14.37; S, 6.57. Found: C, 56.78; H, 6.15; N, 14.07; S, 6.52. IR ν_{max}^{Nujol} cm^{-1}: 3325, 3180, 1746, 1662, 1654, 1251.

b) To a solution of 0.253 g. of metalic Na in 30 ml. of EtOH, S-ethoxycarbonylthiamine (VII, 3.544 g.) was added to become yellow solution. To this solution, 1.867 g. of methylphenylcarbamoyl chloride was added to separate NaCl. After 2 hr., the reaction mixture was concentrated *in vacuo* and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with dil. $NaHCO_3$ solution, dried over Na_2SO_4, and evaporated. The residue was recrystallized from Me_2CO to give 3.903 g. (80%) of colorless rhombs, which were identified in IR spectrum with XV obtained above a).

N-[1-(2-oxo-1,3-oxathian-4-ylidene)ethyl]-N-[(2-methyl-4-amino-5-pyrimidinyl)methyl] formamide (XIII)——a) To a suspension of IV obtained from 4.5 g. of III and 1.0 g. of phosgene in $CHCl_3$, saturated solution of $NaHCO_3$ was added and shaked. The $CHCl_3$ layer was dried over Na_2SO_4, and evaporated. The residual crystals were recrystallized from AcOEt to give 0.6 g. of colorless prisms, m.p. 182～183°(decomp.).

4) A. Takamizawa, K. Hirai, Y. Hamashima: This Bulletin, **10**, 1107 (1962).

Anal. Calcd. for $C_{13}H_{16}O_3N_4S$: C, 50.64; H, 5.23; N, 18.18. Found : C, 50.70; H, 5.18; N, 17.79. IR ν_{max}^{Nujol} cm^{-1} : 1686 (C=O), 1167, 1027.

b) Ⅸ (4 g.) was dissolved in a solution of 10 ml. of H_2O and 30 ml. of Me_2CO was added at −30～−40°, and a solution of 1.2 g. of NaOH in 2 ml. of H_2O was added. After stirring for 1.5 hr. at −40°, the reaction mixture was concentrated *in vacuo* (at <30°). The residue was extracted with $CHCl_3$, and the $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4, and evaporated. The residual crystals were recrystallized from AcOEt to give 1 g. of colorless prisms, m.p. 182～183°(decomp.), which were identified in IR spectrum with XIII obtained above a).

c) To a solution of 0.4 g. of XIIa in 25 ml. of $CHCl_3$, 10 ml. of 5% $NaHCO_3$ (or 5% Na_2CO_3) was added and shaked for 30 min. The $CHCl_3$ layer was dried over Na_2SO_4, and evaporated. The crystalline residue was recrystallized from AcOEt to give 0.26 g. (84%) of colorless prisms, m.p. 182～183°(decomp.), which were identified in IR spectrum with XIII obtained above a).

d) XIIb (0.4 g.) was treated as above c) to give 0.26 g. (88%) of XIII. Identity was confirmed by IR comparison with an authentic sample.

e) XIIc (0.4 g.) was treated as above c) to glve 0.25 g. (87.5%) of XIII. Identity was confirmed by IR comparison with an authentic sample.

f) XIa (0.8 g.) was dissolved in a solution of 2 ml. of H_2O and 6 ml. of Me_2CO, and a solution of 0.2 g. of NaOH in 0.5 ml. of H_2O was added at −30～−35°. After stirring for 3 hr. at 0～7°, Me_2CO was removed *in vacuo* (at 25°) and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and evaporated. The residual crystals were recrystallized from AcOEt to give 0.11 g. (20%) of XIII. Identity was confirmed by IR comparison with an authentic sample.

g) XIb (0.975 g.) was treated as above f) to give 0.135 g. (21.2%) of XIII. Identity was confirmed by IR comparison with an authentic sample.

h) XIc (1 g.) was treated as above f) to give 0.114 g. (18%) of XIII, m.p. 182～183°(decomp.).

The authors wish to thank to the member of analytical section of this laboratory for elemental analyses.