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147. Akira Takamizawa, Yoshio Hamashima, Yoshiro Sato, and Hisao Sato: Studies on Pyrimidine Derivatives and Related Compounds. XLVI.*1 The Reactions of Diethyl Acetylphosphonate with Thiamine (Takamizawa Reaction (5)).

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3-(2-Hydroxy- and 2-acetoxy)ethyl-1,4,9-trimethyl-1,6-dihydropyrimido[4′,5′-4,5]pyrimido-[2,3-*c*][1,4]thiazine (Ⅲb and Ⅳb) were obtained by the reaction of thiamine (I) and diethyl acetylphosphonate (Ⅱb). Alkaline hydrolysis of Ⅲb or Ⅳb gave 2-methyl-4-(2-methyl-4-amino-5-pyrimidinyl)-methyl-5-methyl-6-(2-hydroxy)ethyl-2*H*-1,4-thiazin-3(4*H*)-one (Ⅴb), which was decomposed to give Ⅶb by conc. HCl. The structures of Ⅳb and Ⅶb were confirmed by the synthetic method.

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We have previously reported[1] that diethyl benzoylphosphonate (Ⅱa) reacted with thiamine after treatment with triethylamine to give 1-phenyl-3-(2-hydroxy)ethyl-4,9-dimethyl-1,6-dihydro[4′,5′-4,5]pyrimido[2,3-*c*][1,4]thiazine (Ⅲa) and 3-(2-benzoyloxy)ethyl derivative (Ⅳa) in good yield. These were hydrolyzed to give 2-phenyl-4-(2-methyl-4-amino-5-pyrimidinyl)methyl-5-methyl-6-(2-hydroxy)ethyl-2*H*-1,4-thiazin-3(4*H*)-one (Ⅴa) and 6-(2-benzoyloxy)ethyl derivative (Ⅵa), respectively.

In this paper, it was found that the reaction with diethyl-acetylphosphonate (Ⅱb) gave 3-(2-hydroxy)ethyl-1,4,9-trimethyl-1,6-dihydro[4′,5′-4,5]pyrimido[2,3-*c*][1,4]thiazine (Ⅲb) and 3-(2-acetyloxy)ethyl derivative (Ⅳb) similarly, and Ⅳb was synthesized by another route to confirm that structure. Four equivalent moles of triethylamine were added to the suspension of thiamine hydrochloride (I) in dimethylformamide (DMF), and two equivalent moles of Ⅱb were allowed to react with cooling. The reaction product was purified by alumina column chromatography to give the crystals of m.p. 120~123° in 30.4% yield from the first fraction. These crystals have a constitution of $C_{16}H_{20}O_2N_4S$, ultraviolet (UV) spectrum showed the maximum at 371 mμ (ε 10680), and infrared (IR) spectrum showed no NH band but showed C=O band at 1733 cm^{-1} and C-O band at 1246 cm^{-1}. Nuclear magnetic resonance (NMR) spectrum showed the signals as follows: 1.89τ (singlet, 1H) (pyrimidine C_6-H), 5.17τ (singlet, 2H), 5.76τ (triplet, 2H) (OCH_2-), 7.42τ (singlet, 3H) (pyrimidine C_2-CH_3), 7.87τ (singlet, 3H) (thiazole C_4-CH_3), 7.95τ (singlet, 3H) ($COCH_3$), 6.43τ (quartet, 1H, J=7.0) (-$\dot{C}$H-CH_3), and 8.52τ (doublet, 3H, J=7.0) (-$\dot{C}$H-CH_3). These results showed that this product had the structure Ⅳb, analogous to Ⅳa.

Following fraction gave pale yellow oil, which had a maximum at 371 mμ in UV spectrum, and no C=O and NH bands were shown in IR spectrum. Therefore, the structure of this oily product was considered to be Ⅲb. The heating of Ⅲb or Ⅳb in alcoholic sodium hydroxide gave the same product, the crystals of m.p. 159~161°. The constitution of this product was $C_{14}H_{20}O_2N_4S$, UV spectrum showed the maxima at 232.5 and 279 mμ, and IR spectrum showed NH_2 band at 3300~3200 and 1642 cm^{-1}, and C=O band at 1674 cm^{-1}. NMR spectrum exhibited the signals as follows: 2.07τ (singlet, 1H) (pyrimidine C_6-H), 3.98τ (singlet, 2H) (NH_2), 4.95 and 5.12τ (AB type quartet,

*1 Part XLV: This Bulletin, **15**, 816 (1967).

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1) A. Takamizawa, Y. Hamashima, Y. Sato, H. Sato, S. Tanaka, H. Ito, Y. Mori: J. Org. Chem., **31**, 2951 (1966).

2H), 5.95τ (triplet, 2H) (OCH_2CH_2-), 7.58τ (singlet, 3H) (pyrimidine C_2-CH_3), 7.93τ (singlet, 3H) (thiazole C_4-CH_3), 6.68τ (quartet, 1H, J=6.8) (-CH-CH_3), 8.59τ (doublet, 3H, J=6.8) (-CH-CH_3). These results showed that this product had the structure, 2-methyl-4-(2-methyl-4-amino-5-pyrimidinyl)methyl-5-methyl-6-(2-hydroxy)ethyl-2*H*-1,4-thiazin-3-(4*H*)-one (Vb), analogous to Va. Therefore, the oily product obtained above was confirmed to have the structure Ⅲb. The yield of Ⅲb was 23.6% (calculated from the yield of Vb). On heating Ⅳb in 50% MeOH, the crystals of m.p. 128~131° were obtained. The constitution of this product was $C_{16}H_{22}O_3N_4S$, UV spectrum had the maxima at 232 and 279 mμ, and IR spectrum showed two C=O band at 1734 and 1660 cm^{-1}. Treatment of this product with ethanolic sodium hydroxide gave Vb. Therefore, this product proved to be the O-acetate of Vb, 2-methyl-4-(2-methyl-4-amino-5-pyrimidinyl)methyl-5-methyl-6-(2-acetoxy)ethyl-2*H*-1,4-thiazin-3(4*H*)-one (Ⅵb). In the previous paper[2] it was reported that treatment of Va with conc. HCl gave S-(1-acetyl-3-chloro)-propyl-N-(2-methyl-4-amino-5-pyrimidinyl)methylthiomandelamide (Ⅶa) and treatment of Ⅶa with dil. NaOH gave S-(1-acetylcyclopropyl)-N-(2-methyl-4-amino-5-pyrimidinyl)methylthiomandelamide (Ⅷa). Similarly, treatment of Vb with conc. HCl afforded the crystals of m.p. 108~110°. The constitution of this product was $C_{14}H_{21}O_2N_4SCl$, and infrared spectrum showed two C=O bands at 1705 and 1665 cm^{-1} NMR spectrum showed the signals as follows : 2.13τ (singlet, 1H) (pyrimidine C_6-H), 3.61τ (singlet, 2H) (NH_2), 7.53τ (singlet, 3H) (pyrimidine C_2-CH_3), 7.73τ (singlet, 3H) (thiazole C_4-CH_3), 2.14τ (triplet, J=7.0) (-NH-CH_2), 5.76τ (doublet, 2H, J=7.0) (-NH-CH_2-), 6.68τ (quartet, 1H, J=7.0) (-$CHCH_3$), and 8.52τ (doublet, 3H, J=7.0) (-CH-CH_3). Therefore, the structure of this product was found to have the structure, N-(2-methyl-4-amino-5-pyrimidinyl)methyl-2-(1-acetyl-3-chloro)propylthiopropionamide (Ⅶb), analogous to Ⅶa. Treatment of Ⅶb with alkali gave the crystals of m.p. 168~170°. The constitution was $C_{14}H_{20}O_2N_4S$, and in agreement with the value less HCl than Ⅶb. IR spectrum showed two C=O bands at 1690 and 1662 cm^{-1}. NMR spectrum showed the signals as follows : 2.18τ (singlet, 1H) (pyrimidine C_6-H), 3.8τ (singlet, 2H) (NH_2), 7.57τ (singlet, 3H) (pyrimidine C_2-CH_3), 7.80τ (singlet, 3H) (thiazole C_4-CH_3), 5.77τ (doublet, 2H) (-NH-CH_2-), 6.55τ (quartet, 1H, J=7.5) (-CH-CH_3), 8.52τ (doublet, 3H, J=7.5) (-CH-CH_3), and about 8.7τ (A_2B_2 type quartet, 4H). These results showed that this product had the structure, N-(2-methyl-4-amino-5-pyrimidinyl)methyl-2-(1-acetylcyclopropyl)thiopropionamide (Ⅷb).

Based upon the method described in the previous paper, Ⅳb and Ⅷb were synthesized by alternative route.

The reaction of 2-bromopropionylbromide (X) with 2-methyl-4-amino-5-aminomethylpyrimidine (Ⅸ) gave N-(2-methyl-4-amino-5-pyrimidinyl)methyl-2-bromopropionamide (Ⅺ). Ⅺ reacted with benzylmercaptan in EtOH-EtONa solution to give N-(2-methyl-4-amino-5-pyrimidinyl)methyl-2-benzylthiopropionamide (XIII). After treatment of XIII with metallic sodium in liquid ammonia, 3-acetyl-3-chloropropanol acetate (XIV) was allowed to react to give N-(2-methyl-4-amino-5-pyrimidinyl)methyl-2-(1-acetyl-3-acetoxypropyl)thiopropionamide (XV). Treatment of XV with dil. HCl gave N-(2-methyl-4-amino-5-pyrimidinyl)methyl-2-(1-acetyl-3-hydroxy)propylthiopropionamide (XVI). The structures of the products obtained above were confirmed by elemental analysis, UV, IR, and NMR spectra. Acetylation of XVI gave XV. When XVI was treated with conc. HCl, the crystals of m.p. 108~110° were obtained and were identified with Ⅷb. Furthermore, treatment of XV with phosphoryl chloride afforded tricyclic compound (Ⅳb) and this result also gave the chemical evidence for the structure of Ⅳ. At the same time, the chemical evidence for the structure of Ⅵb was gained.

2) A. Takamizawa, Y. Sato, S. Tanaka, H. Ito : This Bulletin, **14**, 407 (1966).

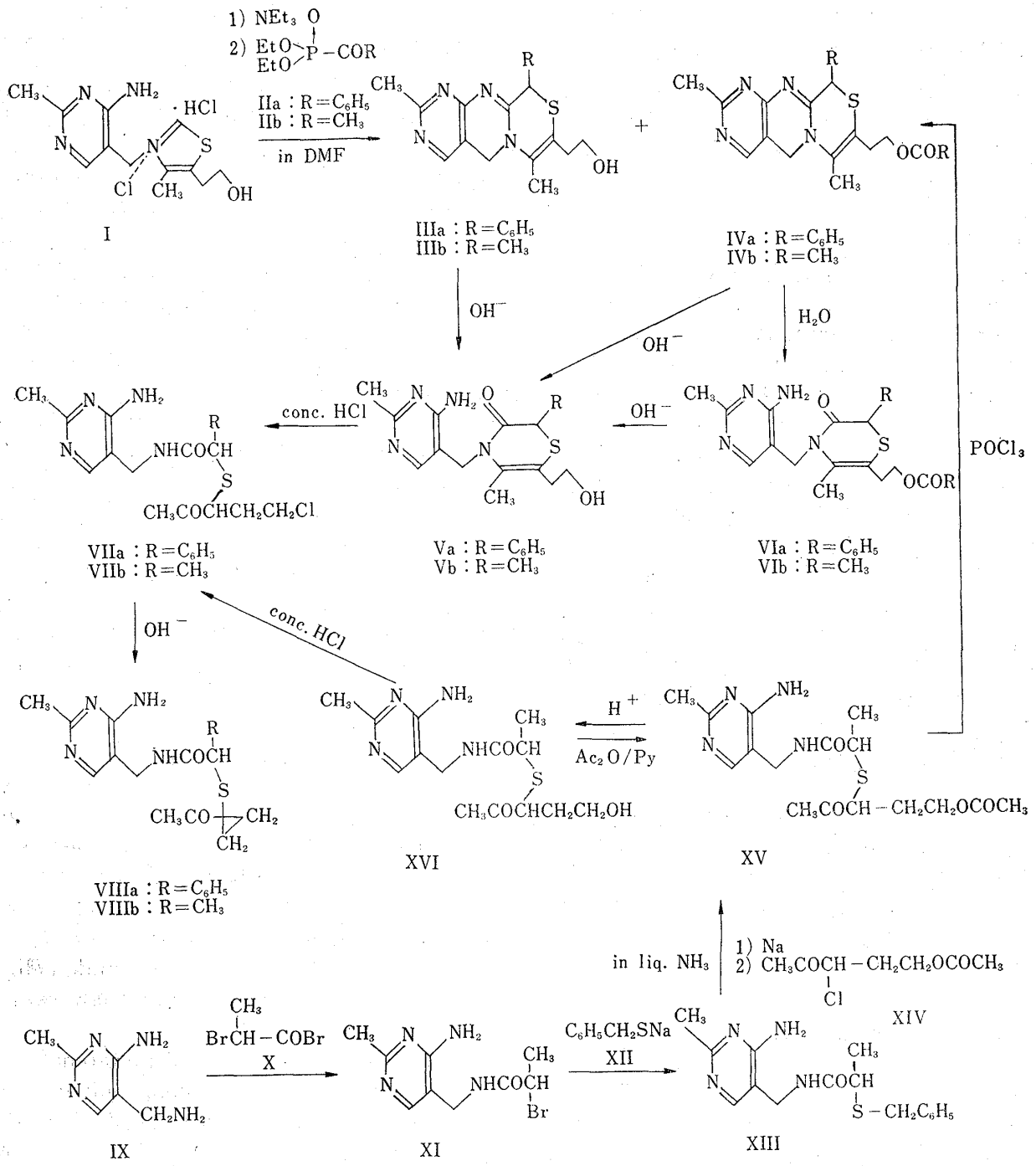

Chart 1.

Experimental

3-(2-Hydroxy- and 2-acetoxy)ethyl-1,4,9-trimethyl-1,6-dihydropyrimido[4′,5′-4,5]pyrimido[2,3-*c*][1,4]-thiazine (IIIb and IVb)——To a suspension of I (dried over P_2O_5 at 110° *in vacuo*, 5.0 g., 14.8 mmol.) in 25 ml. of dimethylformamide was added dropwise 6.0 g. (59.3 mmol.) of triethylamine below 10°, and the mixture was stirred for 1 hr. under cooling during the time. Then 4.4 g. (29.6 mmol.) of IIb was added dropwise, and the stirring was continued under cooling until heat generation ceased (*ca.* 60 min.), then at room temperature for 3 hr. The mixture was then allowed to stand overnight, and heated at 70~80° for 4 hr. After removal of the solvent *in vacuo*, the residue was dissolved in $CHCl_3$, and the $CHCl_3$ solution was successively washed with aqueous $NaHCO_3$, H_2O, dried and evaporated. The oily residue was chromatographed on alumina. Elution with EtOAc gave 1.5 g. of yellow crystals, which were recrystallized from

EtOAc–ether to give IVb as yellow sticks, m.p. 120~123°. Yield, 1.5 g. (30.4%). UV λ_{max}^{EtOH} mμ : 371 (ε 10680). *Anal.* Calcd. for $C_{16}H_{20}O_2N_4S$: C, 57.81; H, 6.06; N, 16.86; O, 9.63; S, 9.65. Found : C, 58.00; H, 6.27; N, 17.17; O, 9.77; S, 9.76. Further elution gave IIIb as a viscous orange oil, of which crystallization was difficult. UV λ_{max}^{EtOH} mμ : 371. IIIb was dissolved in 50 ml. of 75% EtOH containing 2.5 g. of KOH and heated at 60° for 2 hr. After being evaporated to dryness, the residue was extracted with $CHCl_3$, which was successively washed with H_2O, dried and evaporated. The residue was recrystallized from EtOH to give Vb as colorless needles, m.p. 159~161°(decomp.). Yield, 1.08 g. (23.6%). UV λ_{max}^{EtOH} mμ (log ε) : 232.5 (4.18), 279 (3.86). *Anal.* Calcd. for $C_{14}H_{20}O_2N_4S$: C, 54.53; H, 6.54; N, 18.17; S, 10.38. Found : C, 54.48; H, 6.74; N, 18.05; S, 10.30.

2-Methyl-4-(2-methyl-4-amino-5-pyrimidinyl)methyl-5-methyl-6-(2-acetoxy)ethyl-2*H*-1,4-thiazin-3(4*H*)-one (VIb)——A solution of IVb (0.1 g.) in 3 ml. of 50% MeOH was heated to reflux on a steam bath for 2 hr. Disappearance of absorption maximum at 370 mμ in UV spectrum was pointed out the completion of the reaction. The solution was concentrated to dryness and the residue was extracted with $CHCl_3$. The residue after evaporation of the solvent was recrystallized from EtOAc to give VIb as colorless needles, m.p. 128~131°. Yield, 0.09 g. (85.3%). IR ν_{max}^{Nujol} cm^{-1} : 1734 (C=O), 1660 (C=O), 1632 (NH_2). UV λ_{max}^{EtOH} mμ (ε) : 232 (15500), 279 (7390). *Anal.* Calcd. for $C_{16}H_{22}O_3N_4S$: C, 54.81; H, 6.33; N, 15.98; O, 13.69; S, 9.15. Found : C, 54.77; H, 6.34; N, 16.03; O, 13.40; S, 9.26.

Hydrolysis of IVb——A solution of 0.5 g. of IVb in 30 ml. of 70% EtOH containing 3 g. of NaOH was refluxed on a steam bath for 30 min. The brown solution was concentrated and extracted with $CHCl_3$, the $CHCl_3$ extract was washed with H_2O, dried and evaporated. Recrystallization of the residue from EtOH afforded colorless needles, m.p. 159~161°, which was proved to be identical with Vb by the mixture melting point determination and their IR comparison.

Hydrolysis of VIb——Treatment of VIb (0.7 g.) by the similar method described above gave gave colorless needles, m.p. 159~160°, undepressed by admixture with Vb. They also gave identical IR spectra. Yield, 90%.

S-(1-Acetyl-3-chloro)propylthio-N-(2-methyl-4-amino-5-pyrimidinyl)methylpropionamide (VIIb)——A solution of 1.5 g. of Vb in 17 ml. of conc. HCl was allowed to stand at room temperature for 24 hr. The reaction mixture was diluted with two times of H_2O, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extract was successively washed with H_2O, dried, and evaporated. The oily residue was chromatographed on silica gel. Elution with Me_2CO afforded colorless crystals, which were recrystallized from benzene to give VIIb as colorless needles, m.p. 108~110°. Yield, 0.72 g. (43%). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1705 (C=O), 1665 (C=O), 1635 (NH). *Anal.* Calcd. for $C_{14}H_{21}O_2N_4ClS$: C, 48.75; H, 6.14; N, 16.24; O, 9.28; S, 9.29; Cl, 10.28. Found : C, 48.96; H, 6.17; N, 16.03; O, 9.73; S, 9.31; Cl, 9.76.

N-(2-Methyl-4-amino-5-pyrimidinyl)methyl-2-(1-acetylcyclopropyl)thiopropionamide (VIIIb)——To 5 ml. of 5% NaOH in dil. EtOH was added 0.35 g. of VIIb, mixture was heated at 80° for 1 hr. Evaporation of the solvent afforded brown residue, which was extracted with $CHCl_3$. The $CHCl_3$ extrct was successively washed with H_2O, dried and evaporated. Recrystallization of the residue from EtOAc gave VIIIb as colorless plates, m.p. 168~170°. Yield, 0.112 g. (35.8%). IR ν_{max}^{Nujol} cm^{-1} : 1690 (C=O), 1662 (C=O), 1639 (NH). *Anal.* Calcd. for $C_{14}H_{20}O_2N_4S$: C, 54.52; H, 6.51; N, 18.17; O, 10.38, S, 10.40. Found : C, 55.39; H, 6.54; N, 17.96; O, 11.42; S, 9.92.

N-(2-Methyl-4-amino-5-pyrimidinyl)methyl-2-bromo-propionamide (XI)——Twenty grams of IX was dissolved in 650 ml. of tetrahydrofuran by warming. To the solution after being cooled was added dropwise 15.7 g. of 2-bromopropionyl bromide (X) under cooling and stirring. The precipitated solids were filtered off, and the filtrate and the washings were concentrated *in vacuo* to give colorless crystals. Recrystallization from Me_2CO gave XI as colorless needles, m.p. 268~270°(decomp.). Yield, 11.7 g. (59%). *Anal.* Calcd. for $C_9H_{13}ON_4Br$: C, 39.57; H, 4.79; N, 20.51; Br, 29.25. Found : C, 39.83; H, 4.71; N, 20.78; Br, 28.95.

N-(2-Methyl-4-amino-5-pyrimidinyl)methyl-2-benzylthio-propionamide (XIII)——To a solution of 0.927 g. of Na, 5.0 g. of benzylmercaptan in 80 ml. of EtOH was added 11 g. of XI in a portion under ice-water cooling. The reaction occurred immediately separating sodium bromide. After being refluxed for 1.5 hr., the reaction mixture was concentrated *in vacuo*. The residue was extracted with $CHCl_3$, the $CHCl_3$ extract was successively washed, dried and evaporated. Recrystallization of the residue from acetone gave XIII as colorless needles, m.p. 150°. Yield, 11.2 g. (88%). *Anal.* Calcd. for $C_{16}H_{20}ON_4S$: C, 60.72; H, 6.35; N, 17.70; S, 10.12. Found : C, 60.81; H, 6.55; N, 17.71; S, 9.78.

N-(2-Methyl-4-amino-5-pyrimidinyl)methyl-2-(1-acetyl-3-acetoxypropyl)thiopropionamide (XV)——To a suspension of 9.0 g. of XIII in 350 ml. of liquid ammonia was added 1.3 g. of Na in small pieces. The solution was stirred more 15 min., after disappearance of blue color, to become pink violet solution. To the solution was added dropwise 10.2 g. of 3-chloro-3-acetopropanol acetate to become almost clear solution. After being stirred for 2 hr., ammonia was removed to leave light green residues, which were extracted with $CHCl_3$. The $CHCl_3$ extract was washed and dried. Evaporation of the solvent afforded oily residue, which was submitted to alumina chromatography. Elution with EtOAc recovered 3.2 g. of the starting material as the first fraction. Further elution yielded 3.1 g. of oily product, of which crystallization was difficult. This oil was used for the next reaction without further purification. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3425, 3280,

3175, 1731, 1656, 1628.

N-(2-Methyl-4-amino-5-pyrimidinyl)methyl-2-(1-acetyl-3-hydroxy)propylthiopropionamide (XVI)——To a solution of 12 ml. of conc. HCl and 24 ml. of H_2O was added 1.8 g. of XV under cooling to give the solution. After stirring at room temperature for 2 hr., the reaction mixture was washed with $CHCl_3$, and neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The oily residue after removal of the solvent was chromatographed on silica gel. Elution with acetone afforded XVI as viscous oil, which was solidified gradually during several weeks. Recrystallization from EtOAc gave colorless needles, m.p. 126~127°. Yield, 1.2 g. (75.3%). IR ν_{max}^{Nujol} cm^{-1}: 3300, 3136, 1710, 1677, 1645. UV λ_{max}^{EtOH} mμ (ε): 235.5 (9000), 277 (5550). *Anal.* Calcd. for $C_{14}H_{22}O_3N_4S$: C, 51.52; H, 6.80; N, 17.17. Found: C, 51.27; H, 7.07; N, 16.89.

Acetylation of XVI——A mixture of 1 g. of XVI, 5 ml. of pyridine, and 2.5 ml. of acetic anhydride was stirred at room temperature for 3 hr. After that the mixture was concentrated *in vacuo* to leave brown oil, which was extracted with $CHCl_3$. The $CHCl_3$ extract was successively washed with $NaHCO_3$, H_2O, dried and evaporated. The oily residue was chromatographed on silica gel. Elution with acetone gave 0.9 g. of oily product, which was proved to be identical with XV by the comparison of their IR spectra and thin-layer chromatography.

Treatment of XVI with conc. HCl——To 3 ml. of conc. HCl was dissolved 0.3 g. of XVI. The solution was allowed to stand at room temperature for 20 hr. After dilution with 6 ml. of H_2O, the solution was washed with $CHCl_3$, and neutralized with $NaHCO_3$, and then extracted with $CHCl_3$. The extract was washed with H_2O, dried and evaporated. The residue was chromatographed on silica gel. Elution with acetone gave colorless rocks, m.p. 108~110°, undepressed by admixture with VIIb. Direct comparison of their IR spectra also showed them to be identical.

The Cyclization Reaction of XV with Phosphoryl Chloride——The solution of 1 g. of XV in 30 ml. of $POCl_3$ was heated at 110° for 17 hr. under N_2 stream until an absorption curve of UV spectrum became constant. The reaction mixture was concentrated *in vacuo*, crushed ice was added to the dark brown residue, neutrallized with $NaHCO_3$, and extracted with $CHCl_3$. The brown oily residue after removal of the solvent was chromatographed on alumina (*Merck, standerdized*). Elution with EtOAc afforded yellow solids, which were recrystallized from EtOAc–ether to give yellow sticks (0.245 g., 27%), m.p. 121~123°, undepressed by admixture with IVb. Direct comparison of their IR spectra also showed them to be identical.