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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 reported¹⁾ 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 C₁₆H₂₀O₂N₄S, 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 C₆-H), 5.17τ (singlet, 2H), 5.76τ (triplet, 2H) (OCH₂-), 7.42τ (singlet, 3H) (pyrimidine C₂-CH₃), 7.87τ (singlet, 3H) (thiazole C₄-CH₃), 7.95τ (singlet, 3H) (COCH₃), 6.43τ (quartet, 1H, J=7.0) (-CH-CH₃), and 8.52τ (doublet, 3H, J=7.0) (-CH-CH₃). 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 C₁₄H₂₀O₂N₄S, UV spectrum showed the maxima at 232.5 and 279 mμ, and IR spectrum showed NH₂ 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 C₆-H), 3.98τ (singlet, 2H) (NH₂), 4.95 and 5.12τ (AB type quartet,

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2H), 5.95 τ (triplet, 2H) (OCH₂CH₂-), 7.58 τ (singlet, 3H) (pyrimidine C₂-CH₃), 7.93 τ (singlet, 3H) (thiazole C₄-CH₃), 6.68 τ (quartet, 1H, J=6.8) (-CH-CH₃), 8.59 τ (doublet, 3H, J=6.8) (-CH-CH₃). 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-2H-1,4-thiazin-3-(4H)-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 Nb in 50% MeOH, the crystals of m.p. 128~131° were obtained. The constitution of this product was C₁₆H₂₂O₃N₄S, UV spectrum had the maxima at 232 and 279 m μ , 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-2H-1,4-thiazin-3-(4H)-one (VIb). In the previous paper²⁾ 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 C₁₄H₂₁O₂N₄SCl, and infrared spectrum showed two C=O bands at 1705 and 1665 cm⁻¹. NMR spectrum showed the signals as follows: 2.13 τ (singlet, 1H) (pyrimidine C₆-H), 3.61 τ (singlet, 2H) (NH₂), 7.53 τ (singlet, 3H) (pyrimidine C₂-CH₃), 7.73 τ (singlet, 3H) (thiazole C₄-CH₃), 2.14 τ (triplet, J=7.0) (-NH-CH₂), 5.76 τ (doublet, 2H, J=7.0) (-NH-CH₂-), 6.68 τ (quartet, 1H, J=7.0) (-CHCH₃), and 8.52 τ (doublet, 3H, J=7.0) (-CH-CH₃). 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 C₁₄H₂₀O₂N₄S, 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: 2.18 τ (singlet, 1H) (pyrimidine C₆-H), 3.8 τ (singlet, 2H) (NH₂), 7.57 τ (singlet, 3H) (pyrimidine C₂-CH₃), 7.80 τ (singlet, 3H) (thiazole C₄-CH₃), 5.77 τ (doublet, 2H) (-NH-CH₂-), 6.55 τ (quartet, 1H, J=7.5) (-CH-CH₃), 8.52 τ (doublet, 3H, J=7.5) (-CH-CH₃), and about 8.7 τ (A₂B₂ 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, Nb and VIIb were synthesized by alternative route.

The reaction of 2-bromopropionylbromide (X) with 2-methyl-4-amino-5-aminomethylpyrimidine (K) 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 VIIb. Furthermore, treatment of XV with phosphoryl chloride afforded tricyclic compound (Vb) and this result also gave the chemical evidence for the structure of V. 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).

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 P₂O₅ 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 CHCl₃, and the CHCl₃ solution was successively washed with aqueous NaHCO₃, H₂O, 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 **Vb** as yellow sticks, m.p. 120~123°. Yield, 1.5 g. (30.4%). UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ : 371 (ϵ 10680). *Anal.* Calcd. for $\text{C}_{16}\text{H}_{20}\text{O}_2\text{N}_4\text{S}$: 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 $\lambda_{\text{max}}^{\text{EtOH}}$ m μ : 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 $\lambda_{\text{max}}^{\text{EtOH}}$ m μ ($\log \epsilon$): 232.5 (4.18), 279 (3.86). *Anal.* Calcd. for $\text{C}_{14}\text{H}_{20}\text{O}_2\text{N}_4\text{S}$: 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-2H-1,4-thiazin-3(4H)-one (VIb)—A solution of **Vb** (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 m μ 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 $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1734 (C=O), 1660 (C=O), 1632 (NH_2). UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (ϵ): 232 (15500), 279 (7390). *Anal.* Calcd. for $\text{C}_{16}\text{H}_{22}\text{O}_3\text{N}_4\text{S}$: 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 **Vb** 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 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 $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1705 (C=O), 1665 (C=O), 1635 (NH). *Anal.* Calcd. for $\text{C}_{14}\text{H}_{21}\text{O}_2\text{N}_4\text{ClS}$: 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 extract 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 $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1690 (C=O), 1662 (C=O), 1639 (NH). *Anal.* Calcd. for $\text{C}_{14}\text{H}_{20}\text{O}_2\text{N}_4\text{S}$: 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 **X** 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 $\text{C}_9\text{H}_{13}\text{ON}_4\text{Br}$: 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 $\text{C}_{16}\text{H}_{20}\text{ON}_4\text{S}$: 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-acetoxypentyl)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 $\nu_{\text{max}}^{\text{CHCl}_3}$ 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 H₂O 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 CHCl₃, and neutralized with NaHCO₃ and extracted with CHCl₃. 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 $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3300, 3136, 1710, 1677, 1645. UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (ϵ): 235.5 (9000), 277 (5550). *Anal.* Calcd. for C₁₄H₂₂O₃N₄S: 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 CHCl₃. The CHCl₃ extract was successively washed with NaHCO₃, H₂O, 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 H₂O, the solution was washed with CHCl₃, and neutralized with NaHCO₃, and then extracted with CHCl₃. The extract was washed with H₂O, dried and evaporated. The residue was chromatographed on silica gel. Elution with acetone gave colorless rocks, m.p. 108~110°, undepressed by admixture with VIb. 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 POCl₃ was heated at 110° for 17 hr. under N₂ 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, neutralized with NaHCO₃, and extracted with CHCl₃. The brown oily residue after removal of the solvent was chromatographed on alumina (*Merck, standardized*). 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 VIb. Direct comparison of their IR spectra also showed them to be identical.