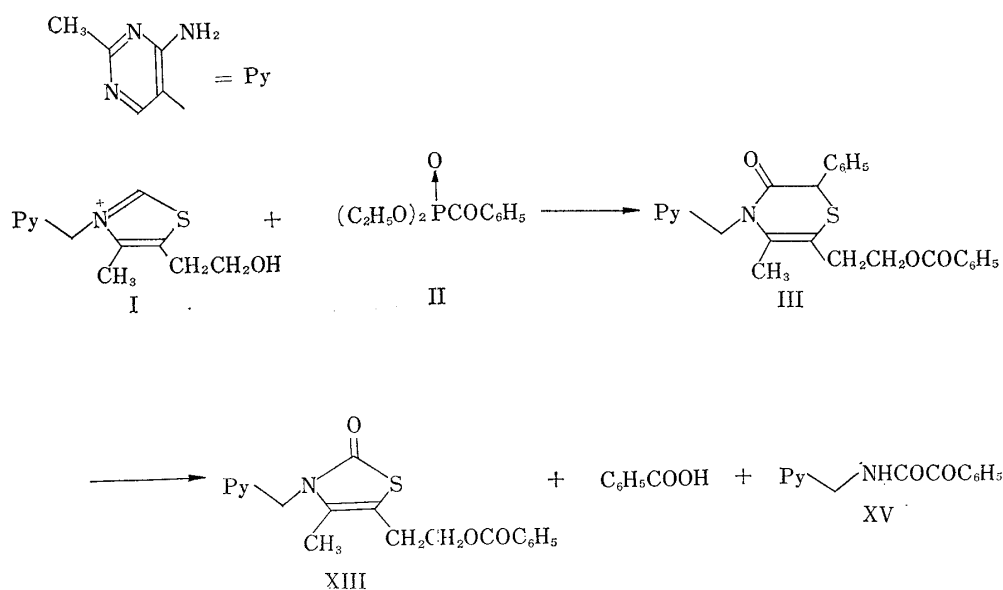


83. Akira Takamizawa, Yoshiro Sato, and Sachiko Tanaka: Studies on the Pyrimidine Derivatives and Related Compounds. XXXX.\*<sup>1</sup>On the Oxidation Products of 2-Phenyl-4-(2-methyl-4-amino-5-pyrimidyl)methyl-5-methyl-6-(2-benzoyloxy or hydroxy)-ethyl-4*H*-1,4-thiazin-3(2*H*)-one.(Shionogi Research Laboratory, Shionogi & Co., Ltd.\*<sup>2</sup>)

We have previously reported<sup>1)</sup> a new type of the reaction between thiamine (I) and diethyl benzoylphosphonate (II) to give 2-phenyl-4-(2-methyl-4-amino-5-pyrimidyl)methyl-5-methyl-6-(2-benzoyloxy)ethyl-4*H*-1,4-thiazin-3(2*H*)-one (III). At that time, oxidation of III with permanganic acid or chromium trioxide in acetic acid, in relation to determination of the structure, afforded thiamine thiazolone O-benzoate (XIII), benzoic acid and 2-methyl-4-amino-5-phenyl-glyoxyloylaminomethylpyrimidine (XV). However, the rearrangement of 1,4-thiazine to thiazoline, in order to form thiamine thiazolone from III, should be taken place in the course of the reaction. This paper deals with the oxidation reactions of III and 2-phenyl-4-(2-methyl-4-amino-5-pyrimidyl)methyl-5-methyl-6-(2-hydroxy)ethyl-4*H*-1,4-thiazin-3(2*H*)-one (IV) with various oxidizing agents.



When III was treated with an equimolar of hydrogen peroxide in acetic acid, a product (VIII), m.p. 174~174.5° (decomp.), C<sub>26</sub>H<sub>26</sub>O<sub>4</sub>N<sub>4</sub>S was obtained. The component of VIII shows increase of an atom of oxygen in comparison with III. On the other hand, the same treatment of IV gave a product (IX), m.p. 197~198° (decomp.), C<sub>19</sub>H<sub>22</sub>O<sub>3</sub>N<sub>4</sub>S, increased of an atom oxygen as compared with IV. Since VIII, on hydrolysis with alcoholic potassium hydroxide, was derived to IX, both have to be the same fundamental structure which is stable in alkali. Acetylation of IX afforded diacetate (X), m.p. 160~162° (decomp.), C<sub>23</sub>H<sub>26</sub>O<sub>5</sub>N<sub>4</sub>S. In its nuclear magnetic resonance\*<sup>3</sup> spectrum (Fig. 1.), the signal for the

\*<sup>1</sup> Part XXXVIII: A. Takamizawa, K. Hirai, S. Sumimoto: This Bulletin, 14, 238 (1966).\*<sup>2</sup> Fukushima-ku, Osaka (高見沢 映, 佐藤義朗, 田中幸子).

1) A. Takamizawa, Y. Sato, S. Tanaka, H. Itoh: This Bulletin, 14, 407 (1966).

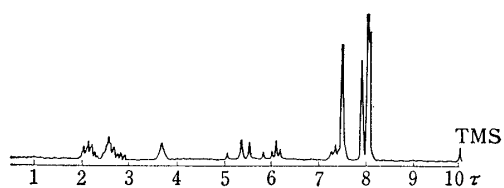


Fig. 1. Nuclear Magnetic Resonance Spectrum of 2-Acetoxy-2-benzoyl-3-(2-methyl-4-amino-5-pyrimidyl)methyl-4-methyl-5-(2-acetoxy)ethylthiazoline (X) in Deuteriochloroform at 60 Mc. p.s.

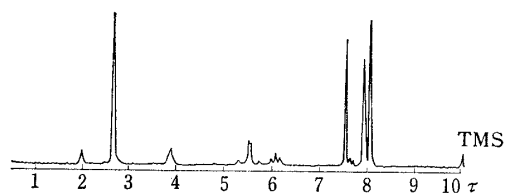


Fig. 2. Nuclear Magnetic Resonance Spectrum of 2-Phenyl-3-oxo-4-(2-methyl-4-amino-5-pyrimidyl)methyl-5-methyl-6-(acetoxy)ethyl-2,3-dihydro-4H-1,4-oxazin-3(2H)one (XVI) in Deuteriochloroform at 60 Mc. p. s.

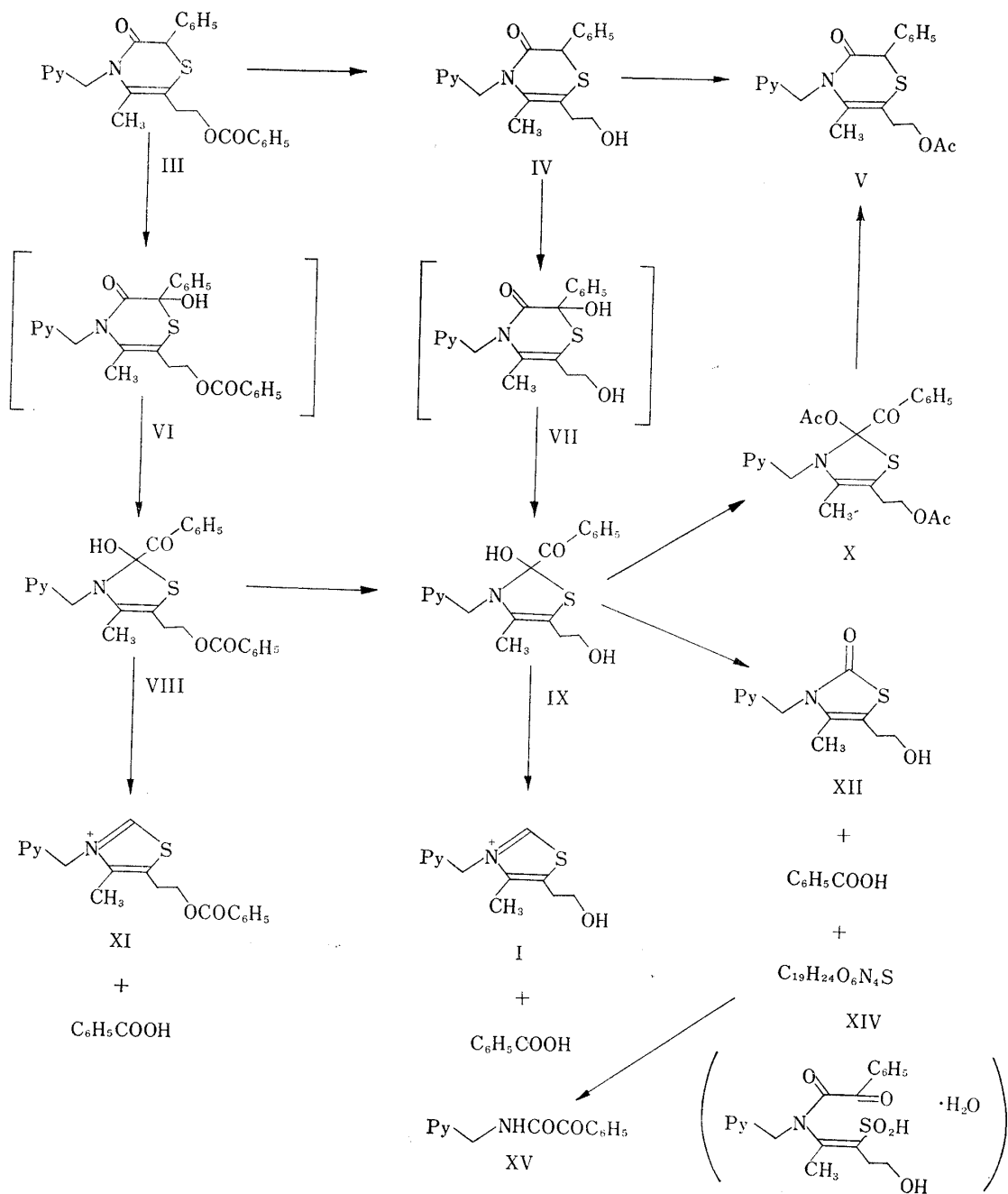


Chart 2.

amino protons appeared and the tertiary proton linked 2-position of thiazine ring of III or IV disappeared. Therefore, acetylation should be proceeded on two hydroxyl groups, not on amino group; one is on the 2-hydroxyethyl group and another is on the hydroxyl group originated from the tertiary hydrogen atom. For the structure of this dihydroxy compound, therefore, 2-hydroxy-2-phenyl-4-(2-methyl-4-amino-5-pyrimidyl)methyl-5-methyl-6-(2-hydroxy)ethyl-4*H*-1,4-thiazin-3(2*H*)-one (VII) may be possible. But the proton signals for the phenyl group of X showed typical benzoic acid-like pattern contrast to V. If the structure of the dihydroxy compound was VII, signal pattern for the phenyl protons should be singlet, even if broad. Therefore 2-benzoyl-2-hydroxy-3-(2-methyl-4-amino-5-pyrimidyl)methyl-4-methyl-5-(2-hydroxy)-ethylthiazoline (X) which formed by the rearrangement of VII is a reasonable structure.

On treatment with either sodium borohydride or lithium aluminum hydride, the diacetate (X) underwent hydrogenation accompanied by the rearrangement to yield 2-phenyl-4-(2-methyl-4-amino-5-pyrimidyl)methyl-5-methyl-6-(2-acetoxy)ethyl-4*H*-1,4-thiazin-3(2*H*)-one (V). This result supports the structure (X) having a benzoyl ketone, because lactams are not attacked by sodium borohydride. It is sure, from these results, that VIII, IX and X are derivatives of "pseudo-thiamine".<sup>2)</sup> In the alternative exchange between thiamine and thiol type thiamine, pseudo-thiamine has been considered as an intermediate. But isolation of this intermediate does not yet succeed.

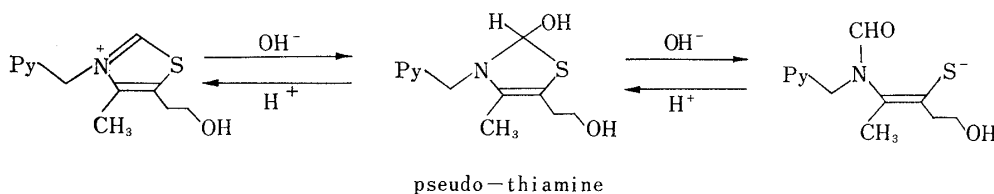


Chart 3.

VIII and IX are unstable in an acidic medium. When their aqueous hydrochloric acid solution were allowed to stand at room temperature, O-benzoylthiamine (XI) and benzoic acid from VIII, and from IX thiamine (I) and benzoic acid were obtained in high yield respectively. These facts lend some support to pseudo-thiamine hypothesis and furthermore present an experimental proof for the structure of the dihydroxy derivatives. Hydroxylation of III or IV gave a similar result also using per acids.

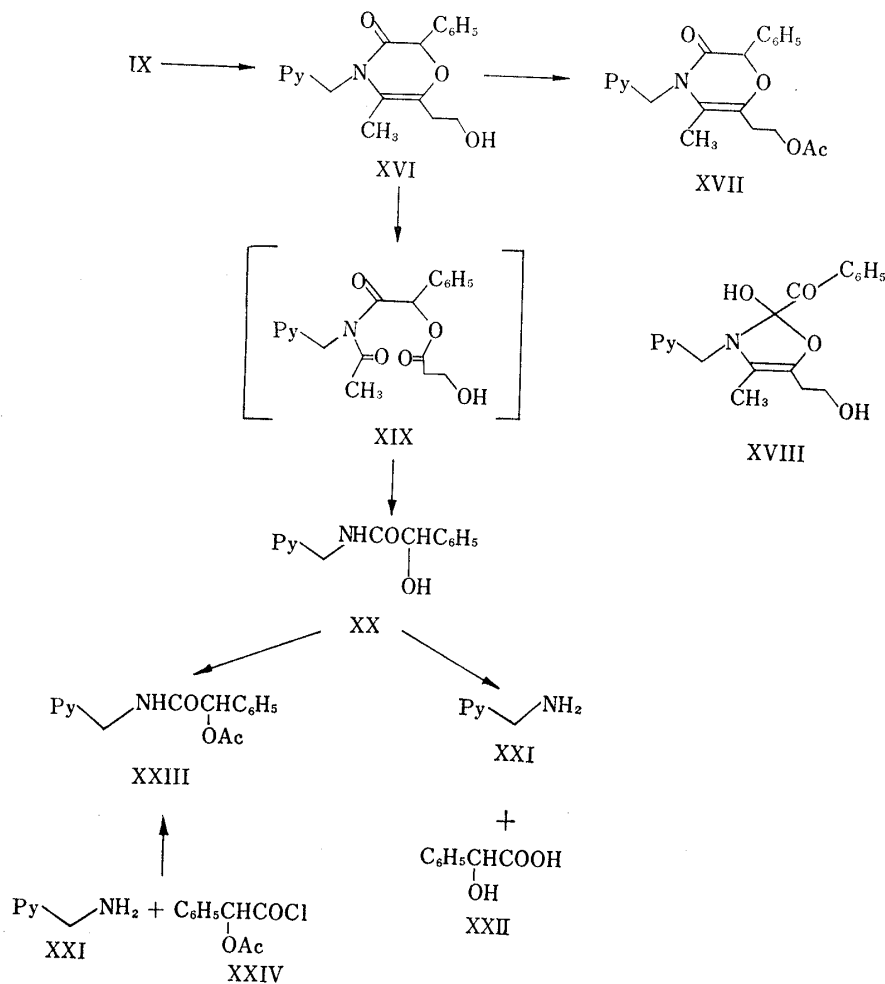
X, on oxidation with permanganic acid in 10% acetic acid, gave thiamine thiazolone (XII), benzoic acid and unstable crystals (XIV), m.p. 212~213° (dcomp.),  $C_{10}H_{24}O_6N_4S$ . XIV was rapidly decomposed to 2-methyl-4-amino-5-phenylglyoxyloylaminomethylpyrimidine<sup>1)</sup> (XV) on treatment with an alkali. Accordingly, it is undoubtedly that oxidation of III to XIII is accompanied by the rearrangement from six member to five member ring at the first step of the reaction. For the structure of XIV, N-(2-methyl-4-amino-5-pyrimidyl)methyl-N-(1-methyl-2-sulfinyl-4-hydroxy-1-butenyl)phenylglyoxylamide may be conceivable, but further investigation was not carried out.

On the contrary above, when X was oxidized with potassium permanganate in N-potassium hydroxide, quite a different product (XVI), m.p. 108~110°,  $C_{10}H_{22}O_3N_4$ , was obtained. This substance having no sulfur is soluble in a caustic alkali. Its infrared spectrum showed carbonyl ( $1703\text{ cm}^{-1}$ ), amino ( $3232, 3347\text{ cm}^{-1}$ ) and hydroxyl group ( $3452\text{ cm}^{-1}$ ), respectively. Acetylation of XVI with acetic anhydride gave monoacetate (XVII), m.p. 195~196° (decomp.). The nuclear magnetic resonance spectrum (Fig. 2) of XVII

\*3 All NMR spectra were taken on Varian Associates A-60 recording spectrometer with tetramethylsilane as an internal standard.

2) R. R. Williams: *Ergeb. Vitamin u. Hormon Forsch.*, **1**, 256 (1938).

showed proton signals comparable with X, but that of phenyl group changed to a sharp singlet pattern again. If the structure of this desulfurication product followed by recyclization was 2-hydroxy-2-benzoyl-3-(2-methyl-4-amino-5-pyrimidyl)methyl-4-methyl-5-(2-hydroxy)ethyloxazoline (XVIII), the signal patterns of the phenyl protons should be benzoic acid-like multiplet. For that reason, 1,4-oxazinone (XVI), in this case, rather than oxazoline (XVIII) is preferable formula.



Ozonolysis of XVI afforded colorless crystals, m.p. 234~235° (decomp.),  $C_{14}H_{16}O_2N_4$ . The ultraviolet absorption spectrum of this substance in ethyl alcohol exhibited maxima at 234  $m\mu$  ( $\epsilon$  8,710) and 276  $m\mu$  ( $\epsilon$  5,180) due to the pyrimidine nucleus. Its infrared spectrum has absorption bands for carbonyl (1663, 1676  $cm^{-1}$ ), amino (3040, 3260  $cm^{-1}$ ) and hydroxy (3350  $cm^{-1}$ ) groups. The nuclear magnetic resonance spectrum in dimethylsulfoxide contained the following proton signals: phenyl (singlet, 2.66 $\tau$ ), amino (singlet, 3.26 $\tau$ ), tertiary hydrogen (singlet, 5.03 $\tau$ ), NH (triplet, 1.4 $\tau$ ) and the two methylene protons (doublet, 5.93 $\tau$ ,  $J=6.1$  c.p.s.) indicating the presence of the  $-CH_2NH-$  group. Heating of XX with hydrochloric acid furnished 2-methyl-4-amino-5-aminomethylpyrimidine (XXI) and an acidic substance, m.p. 182~183°,  $C_8H_8O_3$ , which was identified as *d* 1-mandelic acid. The identity of XXIII which is the acetate of XX, with 2-methyl-4-amino-5-(O-acetyl)mandeoylaminomethylpyrimidine was confirmed by synthesizing it from XXI and O-acetylmandeoyl chloride (XXIV). A  $>N-CO-CH\begin{matrix} \searrow C_6H_5 \\ \searrow O \end{matrix}$  system, therefore, exists

actually in a molecule of XVI. That is, XX must be formed from 2-phenyl-4-(2-methyl-4-amino-5-pyrimidyl)methyl-5-methyl-6-(2-hydroxy)ethyl-4*H*-1,4-oxazin-3(2*H*)-one(XVI) via O-(3-hydroxy)propionoyl-N-acetyl-N-(2-methyl-4-amino-5-pyrimidyl)methylmande-loylamide (XX) as an intermediate.

The progress of these reactions may occur by way of the following mechanisms.

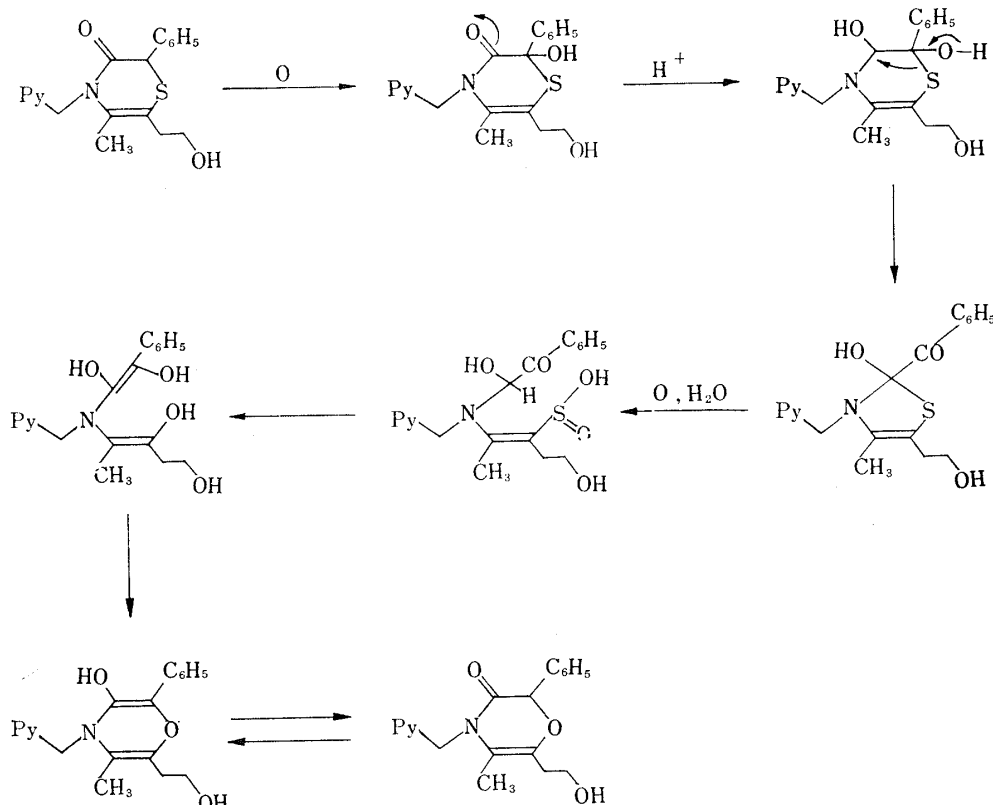


Chart 5.

#### Experimental\*4

**2-Benzoyl-2-hydroxy-3-(2-methyl-4-amino-5-pyrimidyl)methyl-4-methyl-5-(2-benzoyloxy)ethylthiazoline (VIII)**—A solution of 10.0 g. of 2-phenyl-4-(2-methyl-4-amino-5-pyrimidyl)methyl-5-methyl-6-(2-benzoyloxy)ethyl-4*H*-1,4-thiazin-3(2*H*)-one (III) in a mixture of 40 ml. of AcOH and 4.6 g. of 30%  $H_2O_2$  was stirred for 20hr. at 18~20°. After evaporation of the solvent *in vacuo* at room temperature the residue was dissolved in  $CHCl_3$  and washed with 10%  $Na_2CO_3$  and  $H_2O$ , then dried over  $Na_2SO_4$ . The residue after removal of the solvent was dissolved in a small portion of AcOEt, and allowed to stand. The crystals which precipitated were recrystallized from EtOH to yield 3.4 g. (34%) of VIII as colorless crystals, m.p. 174~174.5°(decomp.). *Anal.* Calcd. for  $C_{26}H_{26}O_4N_4S$ : C, 63.65; H, 5.34; N, 11.42; S, 6.53. Found: C, 64.00; H, 5.60; N, 11.40; S, 6.29.

**2-Benzoyl-2-hydroxy-3-(2-methyl-4-amino-5-pyrimidyl)methyl-4-methyl-5-(2-hydroxy)ethylthiazoline (IX)**—i) A solution of 13.7 g. of 2-phenyl-4-(2-methyl-4-amino-5-pyrimidyl)methyl-5-methyl-6-(2-hydroxy)ethyl-4*H*-1,4-thiazin-3(2*H*)-one (IV) in a mixture of 58.8 g. of AcOH and 4.2 g. of 30%  $H_2O_2$  was stirred for 16hr. at 18~20°. After evaporation of the solvent *in vacuo* at room temperature the residue was dissolved in  $CHCl_3$  and extracted with 10% KOH under cooling. To the KOH solution washed with  $CHCl_3$ ,  $CO_2$  was passed and saturated under ice cooling. The product which precipitated was recrystallized from EtOH to yield 5.5 g. (38.5%) of IX as colorless crystals, m.p. 197~198°(decomp.). *Anal.* Calcd. for  $C_{19}H_{22}O_3N_4S$ : C, 59.04; H, 5.74; N, 14.50; S, 8.30. Found: C, 59.06; H, 6.23; N, 14.46; S, 8.13. From the  $CHCl_3$  layer 6.7 g. of IV- $CHCl_3$  was recovered.

ii) A solution of 100 mg. of VIII in 5 ml. of 5% KOH in aq. MeOH was heated at 50° for 30 min. MeOH was removed under reduced pressure. To the resulting aqueous layer,  $CO_2$  was saturated under cooling.

\*4 All melting points are uncorrected. IR spectra were measured in Nujol.

The precipitate was collected and recrystallized from EtOH to give 54 mg. (68.5%) of colorless crystals, m.p. 196~198°(decomp.), which were identical with obtained above.

**2-Acetoxy-2-benzoyl-3-(2-methyl-4-amino-5-pyrimidyl)methyl-4-methyl-5-(2-acetoxy)ethylthiazoli-  
ne (X)**—To a solution of 263 mg. of **X** in 6 ml. of dry pyridine, 0.5 ml. of  $\text{Ac}_2\text{O}$  was added. The solution was stirred for 4 hr. at room temperature. After evaporation of the solvent *in vacuo* the residue was treated with *N*  $\text{NaHCO}_3$  and extracted with  $\text{CHCl}_3$ . The  $\text{CHCl}_3$  solution was washed with  $\text{H}_2\text{O}$ , dried over  $\text{Na}_2\text{SO}_4$  and evaporated. The resulting crystals were recrystallized from  $\text{AcOEt}$  to yield 198 mg. (62%) of **X**, m.p. 160~162°(decomp.). *Anal.* Calcd. for  $\text{C}_{23}\text{H}_{26}\text{O}_5\text{N}_4\text{S}$ : C, 58.70; H, 5.57; N, 11.91; S, 6.81. Found: C, 58.67; H, 5.63; N, 11.69; S, 6.87.

**Reduction of X with Sodium Borohydride**—To a solution of 375 mg. of **X** in 30 ml. of abs. EtOH, 45 mg. of  $\text{NaBH}_4$  was added. The solution was stirred for 3 hr. and then allowed to stand overnight at room temperature. After evaporation of the solvent the residue was dissolved in  $\text{CHCl}_3$  and washed with  $\text{H}_2\text{O}$ , then dried over  $\text{Na}_2\text{SO}_4$ . Removal of the  $\text{CHCl}_3$  and crystallization from ether gave colorless crystals, m.p. 125~127°, which were identical with 2-phenyl-4-(2-methyl-4-amino-5-pyrimidyl)methyl-5-methyl-6-(2-acetoxy)ethyl-4*H*-1,4-thiazin-3(2*H*)-one (**V**) by mixed melting point determination and IR spectra comparison. Yield, 223 mg. (68%).

**Reduction of X with Lithium Aluminum Hydride**—To a stirred solution of 31 mg. of  $\text{LiAlH}_4$  in tetrahydrofuran (THF), a solution of 250 mg. of **X** in 10 ml. of THF was added dropwise under ice cooling. The reaction mixture was stirred for 4.5 hr. under cooling, and then at 30° for 1 hr. After the reaction mixture was treated with  $\text{H}_2\text{O}$ , the precipitate was removed by means of centrifuge. After evaporation of the supernatant *in vacuo* the residue was dissolved in  $\text{CHCl}_3$ , and washed with  $\text{H}_2\text{O}$ , then dried over  $\text{MgSO}_4$ . The IR spectrum (in  $\text{CHCl}_3$ ) of the residue which the solvent was removed agreed completely with that of **V**.

**Treatment of VIII with Hydrochloric Acid**—A solution of 340 mg. of **VIII** in a mixture of 7 ml. of *N*  $\text{HCl}$  and 3 ml. of EtOH was allowed to stand for 2 days at room temperature. After distillation of the EtOH *in vacuo* the  $\text{HCl}$  solution was extracted with ether. Evaporation of ether gave 19 mg. (22.6%) of benzoic acid. The  $\text{HCl}$  fraction was neutralized to pH 6.2 with *N*  $\text{NaHCO}_3$  and washed with  $\text{CHCl}_3$ , then 200 mg. of  $\text{NH}_4\text{CNS}$  was added. The crystals which precipitated were identical with authentic specimen of *O*-benzoyl thiamine thiocyanate by mixed melting point determination and IR spectra comparison, m.p. 136.5~139°(decomp.), Yield, 109 mg. (35.4%).

**Treatment of IX with Hydrochloric Acid**—A solution of 305 mg. of **IX** in 8 ml. of *N*  $\text{HCl}$  was heated at 40° for 24 hr., and then extracted with ether. From the ether solution, 25 mg. of benzoic acid was obtained. The  $\text{HCl}$  fraction was concentrated under reduced pressure to about half volume, and then neutralized to pH 6.4 with *N*  $\text{NaHCO}_3$ . The precipitated crystals, identified with **K**, were filtered off, 14 mg. (4.6%). To the filtrate, 200 mg. of  $\text{NH}_4\text{CNS}$  was added. The solution was allowed to stand under cooling. The product which precipitated was collected and recrystallized from  $\text{H}_2\text{O}$  to yield 234 mg. (87.0%) of colorless crystals, which were identical with authentic specimen of thiamine thiocyanate. *Anal.* Calcd. for  $\text{C}_{13}\text{H}_{17}\text{ON}_4\text{S}\cdot\text{H}_2\text{O}$ : C, 45.72; H, 5.61; N, 20.51; S, 18.78;  $\text{H}_2\text{O}$ , 5.28. Found: C, 45.73; H, 5.78; N, 20.05; S, 18.98;  $\text{H}_2\text{O}$ , 5.23.

**Oxidation of IX with Potassium Permanganate in 10% Acetic Acid**—To a stirred solution of 272 mg. of **IX** in 10 ml. of 10%  $\text{AcOH}$ , a cold solution of 89 mg. of  $\text{KMnO}_4$  in 10 ml. of 10%  $\text{AcOH}$  was added portion-wise under 5°. The mixture was stirred for 2 hr. under ice cooling. The precipitated crystals were collected and recrystallized from aq. EtOH to yield 126 mg. (38.6%) of colorless crystals (**XIV**). m.p. 212~213°(decomp.). *Anal.* Calcd. for  $\text{C}_{19}\text{H}_{24}\text{O}_6\text{N}_4\text{S}\cdot\frac{1}{2}\text{H}_2\text{O}$ : C, 49.23; H, 5.87; N, 12.09; S, 6.92;  $\text{H}_2\text{O}$ , 5.83. Found: C, 48.92; H, 5.91; N, 12.16; S, 7.04;  $\text{H}_2\text{O}$ , 6.06

The filtrate was extracted with ether. From the ether solution, 27 mg. (31.4%) of benzoic acid was obtained. The aqueous layer was neutralized with aq.  $\text{KOH}$ . The  $\text{MnO}_2$  which precipitated was removed by means of centrifuge, and washed with EtOH. The supernatant and the washings were combined. After distillation of the EtOH under reduced pressure the resulting aqueous solution was extracted with  $\text{CHCl}_3$ . The  $\text{CHCl}_3$  fraction was washed with  $\text{H}_2\text{O}$ , dried and evaporated. The residual oil was crystallized with ether to yield 70 mg. (35.5%) of colorless crystals, m.p. 233~235°(decomp.), which were identical with authentic specimen of thiamine thiazolone (**XI**).

$\text{C}_{19}\text{H}_{24}\text{O}_6\text{N}_4\text{S}\cdot\frac{1}{2}\text{H}_2\text{O}$  (**XIV**) (464 mg.) was dissolved in 23 ml. of *N*  $\text{KOH}$  at room temperature, and the solution was rapidly extracted with  $\text{CHCl}_3$ . The extract was washed with  $\text{H}_2\text{O}$ , dried over  $\text{Na}_2\text{SO}_4$ . Evaporation of the solvent gave 221 mg. (81.8%) of colorless crystals, m.p. 210~211°(decomp.). Its IR spectrum was identified with that of 2-methyl-4-amino-5-phenylglyoxyloylaminomethylpyrimidine (**XV**).

**2-Phenyl-4-(2-methyl-4-amino-5-pyrimidyl)methyl-5-methyl-6-(2-hydroxy)ethyl-4*H*-1,4-oxazin-3(2*H*)-one (XVI)**—A solution of 1.23 g. of  $\text{KMnO}_4$  in 123 ml. of  $\text{H}_2\text{O}$  was added gradually to a vigorously stirred solution of 2.25 g. of **X** in 40 ml. of *N*  $\text{KOH}$ . After 5 min.,  $\text{MnO}_2$  which precipitated was removed by means of centrifuge, and washed with EtOH. The supernatant and the washings were combined and neutralized to pH 8.4 with  $\text{HCl}$  (or  $\text{CO}_2$  was saturated under cooling). After distillation of the EtOH *in vacuo* the resulting aqueous solution was extracted with  $\text{CHCl}_3$ . The  $\text{CHCl}_3$  solution was dried over  $\text{Na}_2\text{SO}_4$  and evaporated. The residue was recrystallized from EtOH to yield 1.82 g. (78.1%) of colorless crystals

(XVI), m.p. 128~130°(efferv.). *Anal.* Calcd. for  $C_{19}H_{22}O_3N_4 \cdot C_2H_5OH$ : C, 62.98; H, 7.05; N, 13.99; O, 15.98%. Found: C, 62.81; H, 7.22; N, 13.65; O, 16.33. It was recrystallized from water to yield  $C_{19}H_{22}O_3N_4 \cdot \frac{3}{2}H_2O$ , m.p. 108~110°(efferv.).

When a solution of  $BaCl_2$  was added to the aqueous fraction which extracted with  $CHCl_3$ , 1.01 g. (79.7%) of  $BaSO_3$  was given.

**2-Phenyl-4-(2-methyl-4-amino-5-pyrimidyl)methyl-5-methyl-6-(2-acetoxy)ethyl-4H-1,4-oxazin-3(2H)-one (XVII)**—To a solution of 383 mg. of XVI in 6 ml. of dry pyridine, 0.5 ml. of  $Ac_2O$  was added under stirring. The solution was stirred for 4 hr. at room temperature. After evaporation of the solvent under reduced pressure the residue was treated with aq.  $NaHCO_3$  and extracted with  $CHCl_3$ . The  $CHCl_3$  solution was washed with  $H_2O$  and dried over  $Na_2SO_4$ , then evaporated. The remained oil was crystallized from ether and was recrystallized from a mixture of  $AcOEt$  and  $MeOH$  to yield 243 mg. (63.5%) of XVII, m.p. 195~196° (decomp.). *Anal.* Calcd. for  $C_{21}H_{26}O_4N_4$ : C, 63.30; H, 6.58; N, 14.06; O, 16.06. Found: C, 62.88; H, 6.48; N, 13.71; O, 16.17.

**Ozonization of XVI**—One mole equivalent of  $O_3$  (78 mg. of  $O_3/100$  ml. of  $O_2$ , gas flow: 54 ml./min.) was passed through a solution of 1.22 g. of XVI ( $C_{19}H_{22}O_3N_4 \cdot C_2H_5OH$ ) in 20 ml. of  $AcOH$  at 7~8° for 35 min. The mixture which small amount of Zn powder and water were added was stirred for 30 min. at room temperature. The mixture was filtered and evaporated under reduced pressure. The  $H_2O$  solution of the residue was neutralized with aq.  $NaHCO_3$  and extracted with  $CHCl_3$ . The  $CHCl_3$  solution was again extracted with 10%  $KOH$ . Then  $CO_2$  was saturated in the  $KOH$  solution under ice cooling. The solution was extracted with  $CHCl_3$  after filtration. The  $CHCl_3$  layer was dried and evaporated. The residue was crystallized by the aid of ether to yield 179 mg. (21.5%) of 2-methyl-4-amino-5-mandeloylaminomethylpyrimidine (XX), m.p. 234~236°(decomp.). *Anal.* Calcd. for  $C_{14}H_{16}O_2N_4$ : C, 61.75; H, 5.92; N, 20.58; O, 11.75. Found: C, 61.06; H, 6.27; N, 20.01; O, 12.65.

**Hydrolysis of XX**—A solution of 35 mg. of XX in 5 ml. of 10%  $HCl$  was heated at 70° for 5 hr.; and then extracted with ether. The ether solution was washed with  $H_2O$ , dried and evaporated. The remained crystals were recrystallized from benzene to yield 14 mg. (75%) of colorless crystals. m.p. 115~117°, which were identical with *dl*-mandelic acid by mixed melting point measurement and IR spectra comparison.

The  $HCl$  fraction was concentrated and neutralized, then treated with picric acid to give 2-methyl-4-amino-5-aminomethylpyrimidine dipicrate.

**2-Methyl-4-amino-5-(O-acetyl)mandeloylaminomethylpyrimidine (XXIII)**—i) To a suspension of 50 mg. of XX in 4 ml. of dry pyridine, 38 mg. of  $Ac_2O$  was added with stirring. The mixture was stirred for 2 hr. at room temperature, and then at 40 to 50° for 3.5 hr. A few drops of  $H_2O$  were added to the residue which the pyridine was removed under reduced pressure. The product which crystallized was collected and recrystallized from benzene to yield 37 mg. (64.5%) of XXIII, m.p. 182~183°. *Anal.* Calcd. for  $C_{16}H_{18}O_3N_4$ : C, 61.13; H, 5.77; O, 15.27. Found: C, 60.88; H, 5.91; O, 15.32.

ii) To a stirred solution of 600 mg. of 2-methyl-4-amino-5-aminomethylpyrimidine (XXI) in 30 ml. of dry pyridine, 615 mg. of O-acetylmandeloyl chloride was added at room temperature. After 30 min. the pyridine was removed under reduced pressure. The  $CHCl_3$  solution of the residue was washed with  $H_2O$ , dried and evaporated. The resulting crystals were recrystallized from benzene to yield 207 mg. (22.8%) of XXIII, m.p. 182~183°, which were identical with the product obtained at i).

The authors thank Prof. Emeritus E. Ochiai and Prof. S. Nagakura of Tokyo University for valuable discussions.

### Summary

It has revealed that 2-benzoyl-2-hydroxy-3-(2-methyl-4-amino-5-pyrimidyl)methyl-4-methyl-5-(2-benzoyloxy or hydroxy)-ethylthiazoline (VIII) or (IX) of pseudo-thiamine type was produced from the oxidation reaction of 2-phenyl-4-(2-methyl-4-amino-5-pyrimidyl)methyl-5-methyl-6-(2-benzoyloxy or hydroxy)ethyl-4H-1,4-thiazin-3(2H)one (III) or (IV). In addition, several reactions of these new compounds have been studied.

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