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55. Yoshikazu Oka, Eikô Imamiya, and Hiroshi Hirano : Studies on Vitamin B_1 and Related Compounds. CVII.*1 Synthesis of Hydroxyethylthiamine Homologs.

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Two types of dihydrothiamine derivatives, IV, VI, VIII, and V, VII, IX, were obtained by the reaction of I, II, and phenylglyoxal derivatives. On treatment with mineral acids both of those underwent hydrolysis in the presence of water, but in non-aqueous solutions thiamine was afforded under room temperature. Treatments of them with weak acids such as phosphoric acid, formic acid and acetic acid effected the conversion to the aryl homologs of hydroxyethylthiamine, XI, XII and XIII.

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Several hydroxyalkylthiamines have been synthesized[1~3] and their biological activities have been recorded.[2,4]

With hydroxyaralkylthiamines, however, only one report has hitherto been made, which recorded the synthesis of α-hydroxy-3-hydroxybenzylthiamine by the reaction of 3-hydroxybenzaldehyde with free thiamine base,[2] but little has been mentioned about the experimental conditions and the properties of the compound obtained. Our attempts to obtain α-hydroxybenzylthiamine by the reaction of benzaldehyde with thiamine under a variety of conditions thus far met with failure, and the reaction always gave rise to a large amount of benzoin together with some degradation products.*3

In the preceding paper*1 we reported a new synthetic method of hydroxyethylthiamine, which involved the molecular rearrangement of 7-acetyl-2,9a-dimethyl-9-(2-hydroxyethyl)-5,9,9a,10-tetrahydro-7*H*-pyrimido[4,5-*d*]thiazolo[3,4-*a*]pyrimidine under acidic conditions.

The present paper is an extention of the preceding paper and describes the synthesis of some hydroxyaralkylthiamines which have so far been unrecorded.

The reaction of 4-amino-5-aminomethyl-2-methylpyrimidine (I), phenylglyoxal and 3-acetyl-3-mercapto-1-propanol (II) gave two isomers of the dihydrothiamine derivative substituted with benzoyl group at the 2-position of the thiazolidine ring in a total yield of 70~80%. These two compounds, which presumably had arisen from an initially formed common intermediate (III), were assigned the structure IV and V respectively on the basis of the arguments given below : In the nuclear magnetic resonance (NMR) spectrum (Fig. 1) the isomer which melted at 178~179° (decomp.) showed its methyl signal at 8.46τ, which indicated that the methyl was located on a saturated quarternary carbon. The 3.26τ signal of the same compound was reasonably ascribed to the amino group attached to the pyrimidine ring. The infrared (IR) spectrum (Fig. 2) showed an absorption band at 1650 cm^{-1} which was attributable to

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*3 Among the products were isolated 4-amino-2,5-dimethylphyrimidine, 2-benzoyl-4-methyl-5-(2-hydroxyethyl)thiazole and some other substances, of which we will report in the future.

1) L. O. Krampitz, G. Greull, C. S. Miller, J. M. Sprague : J. Am. Chem. Soc., **80**, 5893 (1958).
2) C. S. Miller, J. M. Sprague, L. O. Krampitz : Ann. N. Y. Acad. Sci., **98**, 401 (1962).
3) Y. Oka, S. Yurugi : Vitamins, **32**, 570 (1965).
4) Y. Shiobara, N. Sato, H. Homma, R. Hattori, M. Murakami : J. Vitaminol., **11**, 302 (1965).

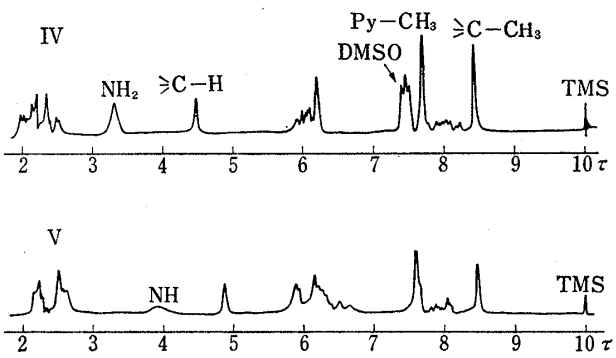

Fig. 1. Nuclear Magnetic Resonance Spectra of Ⅳ (in DMSO-d_6) and Ⅴ (in $CDCl_3$) at 60 Mc.

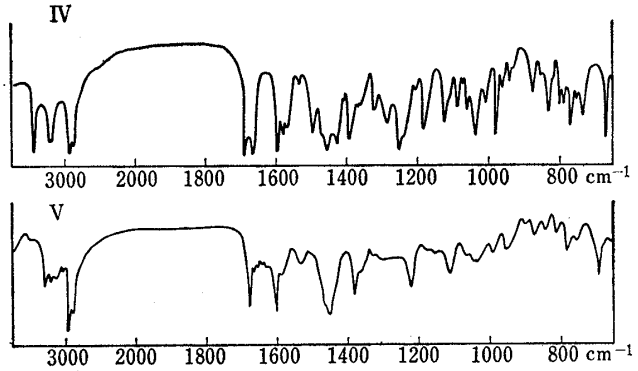

Fig. 2. Infrared Spectra of Ⅳ and Ⅴ in Nujol

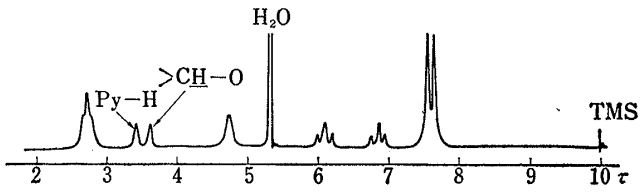

Fig. 3. Nuclear Magnetic Resonance Spectrum of Ⅺ Chloride Hydrochloride in D_2O at 60 Mc.

N-H deformation of the amino group as evidenced in many thiamine derivatives.[5] These observations indicate that 4-position of the thiazoline ring was saturated by the addition of adjacent hydroxyethyl group in Ⅲ giving rise to a thiazolinotetrahydrofuran ring as can be seen in Ⅳ. Moreover a carbonyl band in the region 1690 cm^{-1} in the infrared spectrum as well as a singlet (one proton) at 4.37τ in the NMR spectrum which is ascribed to the proton at the 2-position of the thiazoline ring suggest the presence of a benzoyl group attached to a secondary carbon. These results together with further chemical evidences led us

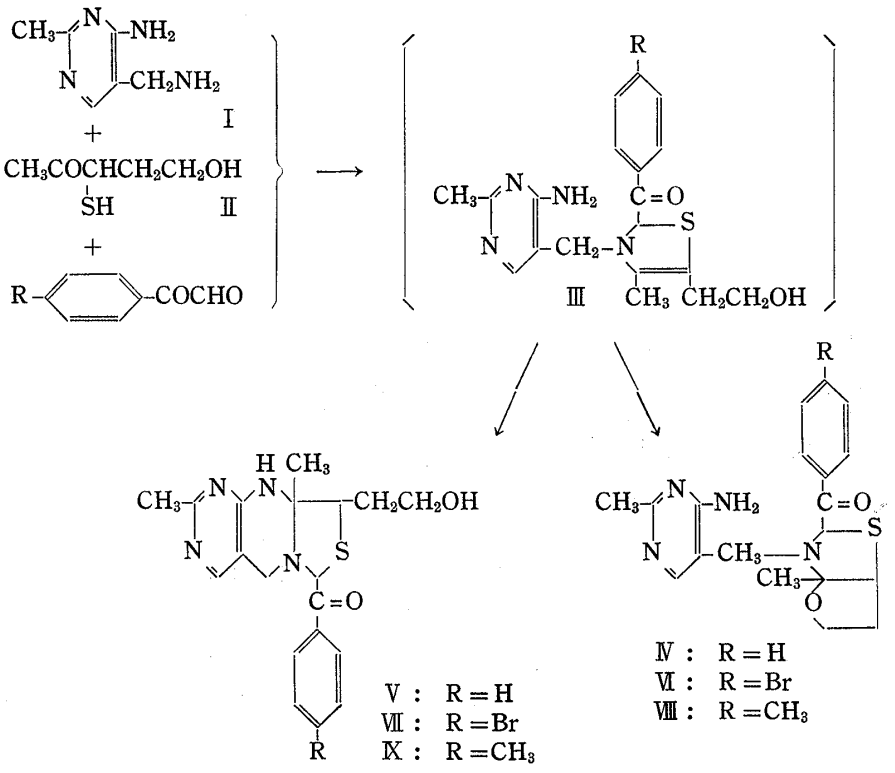

Chart 1.

5) S. Yoshida, M. Kataoka : This Bulletin, **6**, 577 (1958).

to assign the structure Ⅳ to the compound, which bears close analogy to the structure of so-called normal-dihydrothiamine.[6] The NMR spectrum of the second isomer, obtained as amorphous powder of m.p. 113~118° (decomp.), showed very similar peaks to those for Ⅳ except that a signal due to secondary amine was present in place of the peak due to the primary amine in Ⅳ. Furthermore, the IR spectrum showed no absorption band in the region 1650 cm^{-1}. This isomer therefore should be assigned the structure Ⅴ, which bears close resemblance to that of pseudo-dihydrothiamine.[6]

It was found that in a solution an equilibrium existed between Ⅳ and Ⅴ possibly *via* an intermediate (Ⅲ), the position of the equilibrium was somewhat on the side of Ⅳ in alkaline media and in an acidic media it was on the opposite side. These two isomers therefore behaved like a single compound during the reactions. On treatment with hydrochloric acid in aqueous solution, Ⅳ or Ⅴ easily underwent hydrolysis to give I and other fragments. In a non-aqueous solution, however, the treatment of Ⅳ or Ⅴ with mineral acid gave mainly thiamine. On the other hand when the compound (Ⅳ or Ⅴ) was warmed with weak acid like formic acid, acetic acid or phosphoric acid, the expected conversion to hydroxyethylthiamine homolog (Ⅺ) was effected in fairly good yields. The best conversion was attained when Ⅳ or Ⅴ was treated with 8.5% ethanolic phosphoric acid at 80°, affording the diphosphoric acid salt of Ⅺ in 65% yield. This reaction would be probably explained by the same mechanism as in the case of hydroxyethylthiamine synthesis reported previously;[*1] *e.g.* the protonation to the carbonyl oxygen, the enolization to Ⅹ and finally the transformation to the thiazolium compound (Ⅺ) (Chart 2).

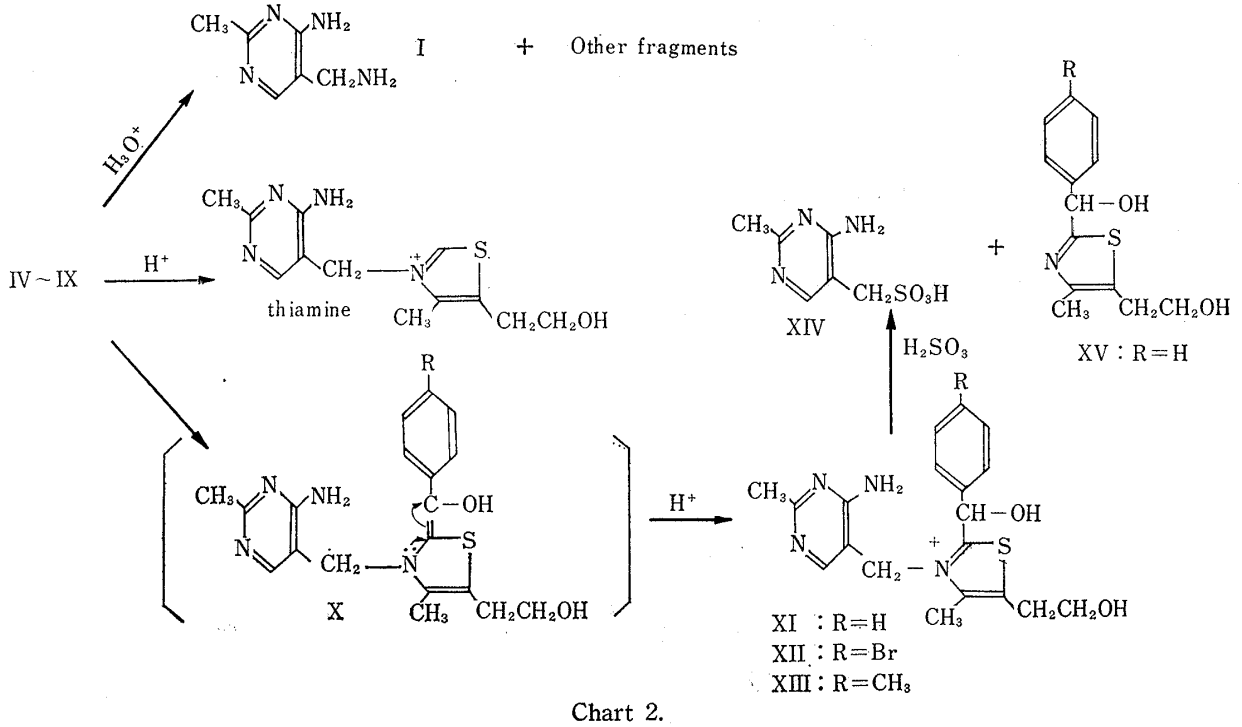

Chart 2.

The structure of Ⅺ was confirmed by the NMR spectrum, IR spectrum and elemental analysis. In the NMR spectrum (Fig. 3) it was observed that the proton signal of the 6-position in the pyrimidine ring appeared at 3.34τ,[*4] a region strikingly

[*4] The adjacent peak at 3.59τ (1H) might reasonably be ascribed to the α-hydrogen in the α-hydroxybenzyl group, because 3,4-dimethyl-2-(α-hydroxybenzyl)-5-(2-hydroxyethyl)thiazolium iodide shows the corresponding signal at 3.56τ (in D_2O).

6) H. Hirano, T. Iwatsu, S. Yurugi : Yakugaku Zasshi, **77**, 244 (1957).

up-field shifted from that for other thiamine derivatives, where the signals used to appear at 1.9~2.5τ.[3,7] This anomaly is presumably due to a long range shielding by the benzene ring which may stand over the pyrimidine ring when the thiazole moiety rotates around the C-N bond.

Further confirmation of the structure was made by the chemical cleavage of XI with sulfurous acid to yield 2-methyl-4-amino-5-pyrimidinylmethane sulfonic acid (XIV) and 2-(α-hydroxybenzyl)-5-(2-hydroxyethyl)-4-methylthiazole (XV).

Two other homologs of hydroxyethylthiamine, XII and XIII, were also synthesized *via* VI and VIII, or VII and IX, employing *p*-bromophenylglyoxal and *p*-methylphenylglyoxal as the starting materials, respectively, and by the similar procedure as described above.

While all these hydroxyaralkylthiamines were found to be fairly stable under acidic or neutral conditions, in alkaline solutions they rapidly underwent the ring opening to give the thiol compound as has been known with thiamine, hydroxyethylthiamine and other thiazolium compounds. Beside the above cleavage, however, X also underwent cleavage into thiamine and benzaldehyde or some other interesting cleavages and rearrangements, which will be discussed elsewhere.

Experimental[*5]

2-Benzoyl-3-(2-methyl-4-amino-5-pyrimidinylmethyl)-3a-methylperhydrofuro[2,3-*d*]thiazole (IV)——To an aqueous solution of 3-acetyl-3-chloro-1-propanol (14 g.), prepared by heating its dimer[8] in 50 ml. of H_2O at 80° for 15 minutes, were added 40 ml. of 10% NaOH solution saturated with H_2S and 50 ml. of EtOH. A solution of 2-methyl-4-amino-5-aminomethylpyrimidine·2HCl (21 g.) in 50 ml. of H_2O was neutralized with 80 ml. of 10% NaOH solution and then added to the above solution. To this mixture 14 g. of phenylglyoxal dissolved in 100 ml. of EtOH was added dropwise with stirring. The stirring was continued at room temperature for 3 hr. and the resulting precipitate was filtered to give 12 g. (34%) of crude product (IV).[*6] Recrystallization from EtOH gave colorless needles, m.p. 178~179°(decomp.), yield 6 g. (16%).[*7] UV λ_{max}^{EtOH} mμ (ε): 243 (20900). IR cm^{-1}: $\nu_{C=O}$ 1690 (Nujol), δ_{N-H} 1665 (Nujol). *Anal.* Calcd. for $C_{19}H_{22}O_2N_4S$: C, 61.59; H, 5.99; N, 15.12. Found: C, 61.61; H, 6.10; N, 15.01.

7-Benzoyl-2,9a-dimethyl-9-(2-hydroxyethyl)-5,9,9a,10-tetrahydro-7*H*-pyrimido[4,5-*d*]thiazolo[3,4-*a*]pyrimidine (V)——The filtrate of crude IV in the above experiment was evaporated to dryness. The residue was extracted with 50 ml. of AcOEt, dried over Na_2SO_4 and evaporated to dryness again. The residue was triturated with 50 ml. of ether and the resulting amorphous powder was filtered to give 17 g. (46%) of crude V. Upon purification by chromatography on alumina using benzene-acetone-MeOH (15:15:1) as developing solvent colorless amorphous powder, m.p. 113~118°(decomp.), was obtained. UV λ_{max}^{EtOH} mμ (ε): 246 (16560), 285 (7140). IR ν_{max}^{Nujol} cm^{-1}: 1690 (C=O). *Anal.* Calcd. for $C_{19}H_{22}O_2N_4S$: C, 61.59; H, 5.99; N, 15.13. Found: C, 61.41; H, 6.17; N, 14.71.

2-(*p*-Bromobenzoyl)-3-(2-methyl-4-amino-5-pyrimidinylmethyl)-3a-methylperhydrofuro[2,3-*d*]thiazole (VI)——To a solution of 8 g. of 3-acetyl-3-chloro-1-propanol in 28 ml. of H_2O and 23 ml. of 10% NaOH solution saturated with H_2S, was added a solution of I·2HCl (12 g.) in 29 ml. of H_2O neutralized with 10% NaOH (45.6 ml.). To this mixture was added dropwise with stirring a solution of *p*-bromophenylglyoxal (12 g.) in 85 ml. of EtOH. The stirring was further continued at room temperature for 3 hr. and the resulting crystalline substance (15 g.) was collected. Recrystallization from EtOH gave 7 g. (25%) of colorless needles, m.p. 153~155°(decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O). *Anal.* Calcd. for $C_{19}H_{21}O_2N_4BrS$: C, 50.78; H, 4.71; N, 12.47. Found: C, 50.44; H, 4.99; N, 12.31.

7-(*p*-Bromobenzoyl)-2,9a-dimethyl-9-(2-hydroxyethyl)-5,9,9a,10-tetrahydro-7*H*-pyrimido[4,5-*d*]thiazolo[3,4-*a*]pyrimidine (VII)——The mother liquor of the crude VI in the above experiment was evaporated to dryness and the residue was chromatographed on silica gel with a solvent system of benzene-acetone-MeOH (5:5:1) to afford needles, m.p. 120~123°(decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1695 (C=O). *Anal.* Calcd. for $C_{19}H_{21}O_2N_4BrS$: C, 50.78; H, 4.71; N, 12.47. Found: C, 50.36; H, 5.00; N, 12.48.

2-(*p*-Methylbenzoyl)-3-(2-methyl-4-amino-5-pyrimidinyl)-3a-methylperhydrofuro[2,3-*d*]thiazole (VIII)——3-Acetyl-3-chloro-1-propanol (1.4 g.), I·2HCl (1.2 g.) and *p*-tolylglyoxal (1.5 g.) were reacted as

*5 All melting points are uncorrected.
*6 This was pure enough to be used for the subsequent reaction without further purification.
*7 On every repeated recrystallization, about a half of IV was isomerized to V.
7) K. Kotera: This Bulletin, **13**, 440 (1965).
8) T. Matsukawa, T. Iwatsu: Yakugaku Zasshi, **71**, 720 (1951).

described before to give 0.7 g. of Ⅷ. Recrystallization from EtOH gave 0.3 g. of fine needles, m.p. 165～166°(decomp.). *Anal.* Calcd. for $C_{20}H_{24}O_2N_4S$: C, 62.50; H, 6.29; N, 14.57. Found: C, 62.81; H, 6.06; N, 14.28.

7-(*p*-Methylbenzoyl)-2,9a-dimethyl-9-(2-hydroxyethyl)-5,9,9a,10-tetrahydro-7*H*-pyrimido[4,5-*d*]thiazolo[3,4-*a*]pyrimidine (IX)——The mother liquor of the crude Ⅷ in the above experiment was taken to dryness and the residue was purified with chromatography on silica gel using benzene-acetone-MeOH (10:10:1) as developing solvent to give 0.2 g. of amorphous powder, m.p. 121～127°(decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1688 (C=O). *Anal.* Calcd. for $C_{20}H_{24}O_2N_4S$: C, 62.50; H, 6.29; N, 14.57. Found: C, 62.19; H, 6.41; N, 14.21.

Acid Hydrolysis of IV——To a suspension of 1.85 g. of Ⅵ in H_2O (1ml.) was added 5.4 ml. of 10% HCl and the mixture was allowed to stand for 40 hr. at room temperature. After extraction with ether the aqueous layer was evaporated *in vacuo* to dryness. The residue was washed with EtOH and recrystallized from dil. EtOH to give 0.8 g. (76%) of I·2HCl as colorless needles, m.p. 260～262°(decomp.). *Anal.* Calcd. for $C_6H_{10}N_4 \cdot 2HCl$: C, 34.14; H, 5.73; N, 26.54. Found: C, 34.41; H, 5.88; N, 26.56.

3-(2-Methyl-4-amino-5-pyrimidinylmethyl)-4-methyl-5-(2-hydroxyethyl)thiazolium Chloride Hydrochloride (Thiamine)——i) To a solution of 3.7 g. of Ⅳ in 10 ml. of EtOH and 30 ml. of acetone, was added 5 ml. of 20% EtOH-HCl and the mixture was allowed to stand for a week at room temperature. The resulting precipitate was collected and recrystallized from EtOH-H_2O (5:1) to afford colorless needles, m.p. 245° (decomp.), yield 1.3 g. (39%). This substance was positive to the thiochrome test. The mixed melting point with authentic thiamine chloride hydrochloride showed no depression and IR and NMR spectra of the two samples were identical in every respect.

ii) To a solution of Ⅴ (1.8 g.) in 3 ml. of EtOH was added 10% EtOH-HCl (0.3 ml.) and the mixture was allowed to stand for 40 hr. at room temperature. Working up as described in i) gave colorless needles, m.p. 245°(decomp.), yield 0.84 g. (52%); the compound thus obtained was identical with authentic thiamine chloride hydrochloride in every respect.

2-(α-Hydroxybenzyl)-3-(2-methyl-4-amino-5-pyrimidinylmethyl)-4-methyl-5-(2-hydroxyethyl)thiazolium (XI)——i) One gram of Ⅳ and 2 g. of 85% phosphoric acid were dissolved in 20 ml. of EtOH and the solution was refluxed for 1 hr. The solution was diluted with 10 ml. of MeOH and allowed to stand overnight. The resulting crystals were filtered and recrystallized from EtOH-H_2O (5:1) to afford di-phosphoric acid salt of Ⅺ as needles, m.p. 161～163°(decomp.), yield 1.0 g. (65%). *Anal.* Calcd. for $C_{19}H_{23}O_2N_4S \cdot H_3PO_4 \cdot H_2PO_4$: C, 40.11; H, 4.97; N, 9.89. Found: C, 40.15; H, 5.31; N, 9.65.

ii) The treatment of Ⅴ (1 g.) with 85% phosphoric acid (2 g.) in 20 ml. of EtOH in a similar manner as described in i) gave 1.0 g. (65%) of di-phosphoric acid salt of Ⅺ, m.p. 161～163°(decomp.).

iii) A solution of 7.4 g. of Ⅳ in 60 ml. of AcOH was warmed at 60～62° for 5 hr. AcOH was removed *in vacuo* and the residue was dissolved in 20 ml. of H_2O containing 12 ml. of 10% HCl. After extraction with AcOEt the aqueous layer was evaporated to dryness. The resulting crystalline residue was suspended in EtOH and filtered. Recrystallization from EtOH-H_2O gave Ⅺ·Cl·HCl as needles, m.p. 181～183°(decomp.), yield 3.1 g. (34%). UV λ_{max}^{EtOH} mμ (ε): 238 (9450), 270 (10200). *Anal.* Calcd. for $C_{19}H_{24}O_2N_4Cl_2S \cdot H_2O$: C, 49.45; H, 5.68; N, 12.14. Found: C, 49.53; H, 5.72; N, 12.18.

The filtrate of the crude crystals described above was evaporated to dryness and the residue was dissolved in 5 ml. of H_2O. To this solution was added 1.3 g. of potassium thiocyanate dissolved in 1 ml. of H_2O. After two hours, the precipitate was filtered*8 and recrystallized from MeOH-ether to give Ⅺ·SCN·HSCN as colorless prisms, m.p. 175～176°(decomp.), yield 1.9 g. (19.5%) (total yield: 53.5%). *Anal.* Calcd. for $C_{21}H_{24}O_2N_6S_3$: C, 51.61; H, 4.95; N, 17.20. Found: C, 51.56; H, 5.35; N, 16.92.

2-(4-Bromo-α-hydroxybenzyl)-3-(2-methyl-4-amino-5-pyrimidinylmethyl)-4-methyl-5-(2-hydroxyethyl)thiazolium (XII)——A solution of Ⅵ (1 g.) and 85% phosphoric acid (2 g.) in 20 ml. of EtOH was refluxed for 1 hr., diluted with 10 ml. of MeOH and allowed to stand overnight. The resulting precipitate was collected and recrystallized from EtOH-H_2O to give 0.7 g. (48%) of Ⅻ di-phosphoric acid salt as needles, m.p. 160～163°(decomp.). *Anal.* Calcd. for $C_{19}H_{22}O_2N_4BrS \cdot H_2PO_4 \cdot H_3PO_4 \cdot H_2O$: C, 34.40; H, 4.41; N, 8.45. Found: C, 34.61; H, 4.80; N, 8.14.

Dithiocyante: needles, m.p. 192～193° (decomp.). *Anal.* Calcd. for $C_{19}H_{22}O_2N_4BrS \cdot SCN \cdot HSCN$: C, 44.44; H, 4.08; N, 14.81. Found: C, 44.09; H, 3.96; N, 14.88.

2-(4-Methyl-α-hydroxybenzyl)-3-(2-methyl-4-amino-5-pyrimidinylmethyl)-4-methyl-5-(2-hydroxyethyl)thiazolium (XIII)——A solution of Ⅷ (1 g.) in 10 ml. of AcOH was heated to 60～63° for 4 hr. After evaporation *in vacuo*, the residue was treated with 10 ml. of H_2O and the mixture was extracted with 10 ml. of AcOEt. The aqueous layer was evaporated to 2 ml., to which was added a solution of potassium thiocyanate (0.2 g.) in 0.5 ml. of H_2O. The resulting precipitate was collected and recrystallized from EtOH to give 0.2 g. (15%) of XIII dithiocyanate. *Anal.* Calcd. for $C_{20}H_{25}O_2N_4S \cdot SCN \cdot HSCN$: C, 52.57; H, 5.21; N, 16.72. Found: C, 52.59; H, 5.53; N, 16.42.

*8 From the filtrate 0.5 g. (7.5%) of thiamine monothiocyanate was obtained upon addition of 0.5 g. of sodium bicarbonate.

Sulfite Cleavage of XI——To a solution of XI·Cl·HCl (3 g.) in 30 ml. of H_2O, 5 g. of sodium bisulfite was added and the mixture was heated at 80° for 1 hr. The solution was chilled, adjusted with 10% NaOH to pH 9~10 and extracted with AcOEt. After drying over Na_2SO_4, the organic solvent was removed under reduced pressure and the residue was dissolved in 20 ml. of ether. On cooling colorless crystals appeared, which were filtered and recrystallized from acetone–ether to give 1.25 g. (77%) of thiazole (XV), as prisms, m.p. 101~102°. UV λ_{max}^{EtOH} mμ (ε): 259 (7140). *Anal.* Calcd. for $C_{13}H_{15}ONS$: C, 62.62; H, 6.06; N, 5.62. Found: C, 62.62; H, 5.85; N, 5.48.

The aqueous layer was adjusted with HCl to pH 3.5 and allowed to stand overnight. The resulting crystals were filtered and washed with acetone to afford 0.9 g. (70%) of XIV as needles, which showed complete identity with an authentic sample.[9]

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9) K. Masuda: Yakugaku Zasshi, **81**, 533 (1961).