[Chem. Pharm. Bull.]
19(11):2229-2234 (1971)

UDC 547.853.3.04 : 547.789.04 : 615.356.011.5

Studies on Pyrimidine Derivatives and Related Compounds. LXXIII.¹⁾
Syntheses and Reactions of Thiamine Sulfur Analogues and
Related Derivatives. (2)²⁾

AKIRA TAKAMIZAWA, KENTARO HIRAI, and TERUYUKI ISHIBA

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

(Received January 11, 1971)

A number of new thiamine derivatives in which the OH group of thiamine Th-5-CH₂CH₂OH is replaced by CH₂CH₂N^R_R, CH₂CH₂SR, CH₂CH₂SOR, or CH₂CH₂SO₂R groups were prepared. Some of these compounds showed marked anticoccidial activity in chickens. Structure-activity relationship was discussed and methylsulfinylethylthiamine showed the highest activity.

In the preceding paper,¹⁾ a number of derivatives of thiamine S-analogues were prepared. In the course of biological screening tests on these compounds, acetylthioethylthiamine (I) and some derivatives were found to have potential anticoccidial activity. This prompted us to prepare some related derivatives in a search for a more potent coccidiostatic compounds.

Currently, some compounds related to thiamine are widely used for the prevention and treatment of coccidiosis in poultry and are also of interest in connection with antithiamine activity.⁴⁻⁶⁾ In this connection, we have prepared some new thiamine derivatives, replacing the hydroxy group in thiazolium 5-CH₂CH₂OH group with amino or mercapto groups.

3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-4-methyl-5-(2-chloroethyl)-4-thiazoline-2-thione (II, chloroethyl SB₁) reacted with morpholine and piperidine in dimethylformamide (DMF) giving morpholinoethyl and piperidinoethyl SB₁ (IIIa, b), respectively. Action of hydrogen peroxide on IIIa, b followed by treatment with barium chloride gave morpholinoethylthiamine (IVa), mp 243—245° (decomp.), and piperidinoethylthiamine (IVb), mp 241—242° (decomp.), as dihydrochlorides, respectively.

Reaction of methanethiol with II in DMF afforded methylthioethyl SB₁ (Va), mp 166—167°, in 85% yield. Four molar equivalents of hydrogen peroxide were allowed to react with Va in water suspension and the mixture was then treated with barium chloride to give hydrochloride VIa, mp 186° (decomp.), in 85% yield. The ultraviolet (UV) spectrum of VIa showed absorption maxima at 237 and 262.5 mμ, and elemental analysis gave the formula of C₁₃H₂₄O₃N₄S₂Cl₂. Several forms of the crystals containing different mole of water of crystallization were obtained. From this value the possibility of methylsulfonyethyl thiamine (VII) or methylthioethyl thiamine (VIII) could not be excluded. However, the infrared (IR) spectrum of VIa showed a ν₈₀ band at 1030 cm⁻¹ and the nuclear magnetic resonance (NMR) spectrum showed an SOCH₃ signal at τ 7.22. These facts supported the methylsulfinylethylthiamine structure for VIa.

When 5.5 molar equivalents of hydrogen peroxide were allowed to react with Va, followed by treatment with barium chloride, the sulfone VII, mp 239—241° (decomp.), was

- 1) Part LXXII: A. Takamizawa, K. Hirai, and T. Ishiba, *Chem. Pharm. Bull.* (Tokyo), **19**, 2222 (1971).
- 2) This work was presented at the 22nd Annual Meeting of the Vitamin Society of Japan, Hiroshima, Oct., 1970.
- 3) Location: *Sagisu, Fukushima-ku, Osaka.*
- 4) E.F. Rogers, *Ann. N.Y. Acad. Sci.*, **98**, 412 (1962).
- 5) T. Matsuzawa, M. Nagawa, and Y. Suzuki, *Vitamins* (Kyoto), **42**, 22 (1970).
- 6) Z. Suzuoki, K. Furuno, K. Murakami, and T. Fujita, *J. Nutr.*, **94**, 427 (1968).

The monothiocyanate, mp 186—187° (decomp.), and mononitrate, mp 150—153° (decomp.), of methylsulfinylethylthiamine were prepared by treatment with ammonium thiocyanate and sodium nitrate, respectively, after the action of hydrogen peroxide on Va.

TABLE 1. ACI Values of Thiamine Derivatives

$$\begin{array}{c} \text{PmCH}_2\text{N}^+ \text{---} \text{S} \cdot \text{HCl} \\ | \quad \quad | \\ \text{CH}_3 \quad \text{CH}_2\text{CH}_2\text{R} \\ | \\ \text{Cl}^- \end{array}$$

	R	ACI ^{a)}		R	ACI ^{a)}
IVa		133	VId	SOC ₆ H ₅	110
IVb		123	VIe	SOCH ₂ C ₆ H ₅	100
	SH ¹⁾	114	VII	SO ₂ CH ₃	121
	SO ₃ H ¹⁾	61			180
VIII	SCH ₃	168			204
I	SCOC ₃ H ₇ ¹⁾	191			
VIa	SOCH ₃	225			
VIb	SOC ₂ H ₅	176			
VIc	SOCH(CH ₃) ₂	125			

a) ACI = (relative weight gains + viability) - (lesion score + oocysts score)

against avian coccidiosis caused by *Eimeria tenella*.⁷⁾ Some of these showed anticoccidial activities as summarized in Table I.

The anticoccidial activities of the thiamine derivatives examined may be compared on the basis of the Anticoccidial index (ACI)⁸⁾ values, compounds having an ACI of 180 or more were considered as effective and those with values 160—179 as less effective.

Replacement of thiamine hydroxy group with an amino group gave inactive compounds, however, replacement with acetylthio or methylthio group gave active compounds. Methyl- and ethylsulfinyl derivatives were also active and the activity of the former was the highest in this series, while isopropyl-, benzyl-, and phenylsulfinyl were not active. Sulfo- and sulfonyl derivatives were also ineffective. Two isomers having an intramolecular disulfide linkage were obtained in the preceding report¹⁾ and these compounds showed high activity, but less than that of methylsulfinylethyl thiamine. Of these isomers, it is interesting to note that the S,N-*trans* compound was more active than the *cis* compound. Further biological tests are now in progress.

Experimental⁹⁾

3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-4-methyl-5-(2-morpholinoethyl)-4-thiazoline-2-thione (IIIa)—To a solution of 3.15 g of II in 40 ml of DMF was added 1.75 g of morpholine and the mixture was stirred for 3 hr at room temperature, then stirred for 1.5 hr at 60°. After the mixture had been kept overnight at room temperature, 0.87 g of morpholine was added and the mixture was stirred for 5 hr at 60°. The reaction mixture was allowed to stand overnight at room temperature, concentrated *in vacuo*, and extracted with CHCl₃, dried, and evaporated. The residue was chromatographed on silica gel and the eluate with acetone gave 1.8 g of IIIa. Recrystallization of IIIa from acetone gave colorless prisms of mp 184—185°. Anal. Calcd. for C₁₈H₂₃ON₅S₂: C, 52.59; H, 6.35; N, 19.17; S, 17.52. Found: C, 52.59; H, 6.38; N, 19.40; S, 17.32. UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (log ϵ): 234, 280, 324 (4.10, 3.76, 4.17). NMR (CDCl₃) τ : 7.82^s (3H), 7.55^s (3H), 4.57^s (2H), 3.42^b (2H), 1.88^s (1H).

3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-4-methyl-5-(2-piperidinoethyl)-4-thiazoline-2-thione (IIIb)—To a solution of 3.15 g of II in 40 ml of DMF was added 1.7 g of piperidine and the mixture was stirred for 3 hr at 60°. After the mixture had been kept overnight at room temperature, 0.85 g of piperidine

7) Detailed experiments will be reported in other report by Drs. H. Oikawa and T. Minesita of Aburahi Laboratories of this company.

8) Marck Sharp and Dohme: International "Veterinary and Agricultural Technical Service- Anticoccidial Index."

9) All melting points are uncorrected.

was added and the mixture was stirred for 6 hr at 60° then allowed to stand overnight at room temperature. 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, and evaporated. The residue was chromatographed on silica gel and the eluate with Me_2CO gave 0.8 g (22%) of IIb. Recrystallization from Me_2CO gave colorless pillars of mp 188—189°. *Anal.* Calcd. for $\text{C}_{17}\text{H}_{25}\text{N}_5\text{S}_2$: C, 56.18; H, 6.93; N, 19.27; S, 17.61. Found: C, 55.93; H, 6.89; N, 19.09; S, 17.81. UV $\lambda_{\text{max}}^{\text{EtOH}}$ $m\mu$ (log ϵ): 233.5, 280, 324.5 (4.11, 3.77, 4.18). NMR (CDCl_3) τ : 7.82^s (3H), 7.52^s (3H), 4.55^s (2H), 3.55^b (2H), 1.83^s (1H).

3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-4-methyl-5-(2-morpholinoethyl)thiazolium Chloride Dihydrochloride (IVa)—To a suspension of 0.91 g of IIIa in 20 ml of H_2O was added 0.9 g of 30% H_2O_2 and the mixture was stirred for 8.5 hr under ice-cooling. After the mixture had been kept overnight in a refrigerator, a saturated solution of 0.61 g of $\text{BaCl}_2 \cdot 2\text{H}_2\text{O}$ was added and the mixture was filtered on Norit "A". The filtrate was concentrated *in vacuo*, and the residue was treated with cold EtOH to give 0.52 g (43%) of IVa. Recrystallization from dil. EtOH gave colorless scales of mp 243—245° (decomp.). *Anal.* Calcd. for $\text{C}_{16}\text{H}_{24}\text{ON}_5\text{S}_2 \cdot 2\text{HCl} \cdot 2.5\text{H}_2\text{O}$: C, 39.39; H, 6.40; N, 14.35; S, 6.57; Cl, 21.80. Found: C, 38.96; H, 5.21; N, 14.49; S, 6.22; Cl, 22.62. UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ $m\mu$ (log ϵ): 237, 261 (3.81, 3.74). PPC¹⁰: *Rf* 0.115. NMR (D_2O) τ : 7.38^s (3H), 7.35^s (3H), 4.40^s (2H), 1.87^s (1H).

3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-4-methyl-5-(2-piperidinoethyl)thiazolium Chloride Dihydrochloride (IVb)—To a suspension of 0.91 g of IIIb in 20 ml of H_2O was added 0.9 g of 30% H_2O_2 and the mixture was stirred for 3.5 hr at room temperature. A saturated solution of 0.61 g of $\text{BaCl}_2 \cdot 2\text{H}_2\text{O}$ was added and the mixture was filtered on Norit "A". The filtrate was concentrated *in vacuo* and the residue was treated with cold EtOH to give 0.52 g of IVb. Recrystallization from dil. EtOH gave colorless prisms of mp 241—242° (decomp.). *Anal.* Calcd. for $\text{C}_{17}\text{H}_{26}\text{N}_5\text{S}_2 \cdot 2\text{HCl} \cdot \text{H}_2\text{O}$: C, 44.98; H, 6.59; N, 15.26; S, 6.99; Cl, 23.18. Found: C, 45.50; H, 6.71; N, 14.92; S, 6.88; Cl, 22.40. UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ $m\mu$ (log ϵ): 236, 260 (4.05, 3.97). PPC¹⁰: *Rf* 0.135. NMR (D_2O) τ : 7.42^s (3H), 7.37^s (3H), 4.42^s (2H), 1.88^s (1H), 0.27^s (1H).

3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-4-methyl-5-(2-methylthioethyl)-4-thiazoline-2-thione (Va)—To a solution of 0.5 g of powdered NaOH in 40 ml of DMF was added 2.8 g of CH_3SH then 3.15 g of II and the mixture was allowed to stand overnight. 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, and evaporated to give 2.8 g of Va. Recrystallization from Me_2CO gave colorless pillars of mp 166—167°. *Anal.* Calcd. for $\text{C}_{18}\text{H}_{18}\text{N}_4\text{S}_3$: C, 47.85; H, 5.56; N, 17.17; S, 29.42. Found: C, 47.79; H, 5.63; N, 17.01; S, 28.96. UV $\lambda_{\text{max}}^{\text{EtOH}}$ $m\mu$ (log ϵ): 234, 279, 325 (4.12, 3.76, 4.18). NMR (CDCl_3) τ : 7.92^s (3H), 7.83^s (3H), 7.55^s (3H), 4.60^s (2H), 3.63^b (2H), 1.90^s (1H).

3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-5-(2-ethylthioethyl)-4-methyl-4-thiazoline-2-thione (Vb)—To a solution of 0.5 g of powdered NaOH in 40 ml of DMF was added 1.92 g of $\text{C}_2\text{H}_5\text{SH}$ then 3.15 g of II and the mixture was treated as above to give 2.6 g (76.5%) of Vb. Recrystallization from Me_2CO gave colorless pillars of mp 150—152°. *Anal.* Calcd. for $\text{C}_{14}\text{H}_{20}\text{N}_4\text{S}_3$: C, 49.40; H, 5.92; N, 16.46; S, 28.21. Found: C, 49.25; H, 5.99; N, 16.20; S, 27.98. UV $\lambda_{\text{max}}^{\text{EtOH}}$ $m\mu$ (log ϵ): 234, 279, 325 (4.12, 3.76, 4.18). NMR (CDCl_3) τ : 8.77^c (3H, $J=7$ Hz), 7.82^s (3H), 7.53^s (3H), 4.58^s (2H), 3.67^b (2H), 1.87^s (1H).

3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-5-(2-isopropylthioethyl)-4-methyl-4-thiazoline-2-thione (Vc)—A reaction similar to the above using 2.3 g of *iso*-PrSH gave 2.7 g of Vc. Recrystallization from Me_2CO gave colorless prisms of mp 127—129°. *Anal.* Calcd. for $\text{C}_{15}\text{H}_{22}\text{N}_4\text{S}_3 \cdot \text{CH}_3\text{COCH}_3$: C, 52.41; H, 6.84; N, 13.59; S, 23.28. Found: C, 52.48; H, 6.86; N, 13.55; S, 23.40. UV $\lambda_{\text{max}}^{\text{EtOH}}$ $m\mu$ (log ϵ): 234, 279, 325 (4.12, 3.77, 4.18). NMR (CDCl_3) τ : 8.78^d (6H, $J=7$ Hz), 7.83^s (3H), 7.57^s (3H), 4.60^s (2H), 3.65^b (2H), 1.90^s (1H).

3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-4-methyl-5-(2-phenylthioethyl)-4-thiazoline-2-thione (Vd)—A similar reaction using 3.3 g of $\text{C}_6\text{H}_5\text{SH}$ gave 3.3 g of Vd. Recrystallization from Me_2CO gave colorless pillars of mp 138—139°. *Anal.* Calcd. for $\text{C}_{18}\text{H}_{20}\text{N}_4\text{S}_3$: C, 55.66; H, 5.19; N, 14.43; S, 24.72. Found: C, 55.74; H, 5.28; N, 14.23; S, 24.66. UV $\lambda_{\text{max}}^{\text{EtOH}}$ $m\mu$ (log ϵ): 235, 325 (4.20, 4.19). NMR (CDCl_3) τ : 7.95^s (3H), 7.53^s (3H), 4.65^s (2H), 3.73^b (2H), 1.90^s (1H).

3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-5-(2-benzylthioethyl)-4-methyl-4-thiazoline-2-thione (Ve)—A reaction similar to the above using 3.75 g of $\text{C}_6\text{H}_5\text{CH}_2\text{SH}$ gave 3.45 g (86%) of Ve. Recrystallization from Me_2CO gave colorless pillars of mp 134—135°. *Anal.* Calcd. for $\text{C}_{19}\text{H}_{22}\text{N}_4\text{S}_3$: C, 56.71; H, 5.51; N, 13.92; S, 23.86. Found: C, 56.60; H, 5.54; N, 13.72; S, 23.57. UV $\lambda_{\text{max}}^{\text{EtOH}}$ $m\mu$ (log ϵ): 231, 280, 325.5 (4.15, 3.77, 4.18). NMR (CDCl_3) τ : 7.93^s (3H), 7.53^s (3H), 6.30^s (2H), 4.62^s (2H), 3.60^b (2H), 1.88^s (1H).

3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-4-methyl-5-(2-methylsulfinylethyl)thiazolium Chloride Hydrochloride (VIa)—a) To a suspension of 1.63 g of Va in 30 ml of H_2O was added 2.3 g of 30% H_2O_2 and the mixture was stirred for 3 hr at room temperature. To this solution was added a saturated solution of 1.21 g of $\text{BaCl}_2 \cdot 2\text{H}_2\text{O}$ and the mixture was filtered on Norit "A". The filtrate was concentrated *in vacuo* and the residue was treated with cold EtOH to give 1.7 g (85%) of VIa. Recrystallization from 95% EtOH gave colorless pillars of mp 209—211° (decomp.). *Anal.* Calcd. for $\text{C}_{13}\text{H}_{19}\text{ON}_4\text{S}_2 \cdot \text{HCl} \cdot \text{H}_2\text{O}$: C, 38.90;

10) AcOH , *n*-BuOH, H_2O (1:4:5), Ascending method, Toyo Roshi #50.

H, 5.53; N, 13.96; S, 15.98; Cl, 17.67. Found: C, 39.85; H, 5.40; N, 13.92; S, 16.08; Cl, 17.64. UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ m μ (log ϵ): 237, 262.5 (4.05, 3.99). PPC¹¹: Rf 0.45. NMR (D₂O) τ : 7.40^s (3H), 7.35^s (3H), 7.22^s (3H), 4.40^s (2H), 1.93^s (1H), 0.28^s (1H). IR (Nujol): ν_{SO} 1030 cm⁻¹.

These crystals were treated as below. Heating at 80° over P₂O₅ for 6 hr *in vacuo* gave crystals of mp 216–218° (decomp.). Anal. Calcd. for C₁₃H₁₉ON₄S₂Cl·HCl: C, 40.73; H, 5.26; N, 14.62; S, 16.73; Cl, 18.50. Found: C, 40.49; H, 5.44; N, 14.06; S, 16.24; Cl, 18.29.

Standing at room temperature for several days in air gave crystals of mp 186° (decomp.). Anal. Calcd. for C₁₃H₁₉ON₄S₂Cl·HCl·2H₂O: C, 37.22; H, 5.77; N, 13.36; S, 15.29; Cl, 16.90. Found: C, 37.39; H, 5.81; N, 13.30; S, 15.26; Cl, 17.05.

These crystals were recrystallized repeatedly from 99% EtOH and allowed to stand in air at room temperature for a week to give the crystals of mp 187–189° (decomp.). Anal. Calcd. for C₁₃H₁₉ON₄S₂Cl·1.5H₂O: C, 38.04; H, 5.65; N, 13.65; S, 15.62; Cl, 17.28; H₂O, 6.58. Found: C, 38.23; H, 5.70; N, 13.70; S, 15.29; Cl, 17.28; H₂O, 6.41.

b) To a solution of 0.367 g of VIII in 4 ml of H₂O was added 0.117 g of 30% H₂O₂ and the mixture was stirred for 3 hr at room temperature. The reaction mixture was concentrated *in vacuo* and the residue was treated with cold EtOH to give 0.27 g (77%) of VIa.

3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-5-(2-ethylsulfinylethyl)-4-methylthiazolium Chloride Hydrochloride (VIb)—A suspension of 1.7 g of Vb in 30 ml of H₂O was treated as above a) giving 1.42 g (68.5%) of VIb. Recrystallization from EtOH gave colorless pillars of mp 185–188° (decomp.). Anal. Calcd. for C₁₄H₂₁ON₄S₂Cl·HCl·H₂O: C, 40.48; H, 5.83; N, 13.49; S, 15.44; Cl, 17.07. Found: C, 40.88; H, 5.95; N, 13.18; S, 15.24; Cl, 16.72. UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ m μ (log ϵ): 238, 262.5 (4.07, 4.02). PPC¹¹: Rf 0.46. NMR (D₂O) τ : 8.68^s (3H, $J=7.5$ Hz), 7.42^s (3H), 7.37^s (3H), 4.42^s (2H), 1.95^s (1H).

3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-5-(2-isopropylsulfinylethyl)-4-methylthiazolium Chloride Hydrochloride (VIc)—A suspension of 2.06 g of Vc in 30 ml of H₂O was treated as above giving 1.68 g (78%) of VIc. Recrystallization from EtOH gave colorless pillars of mp 201–202° (decomp.). Anal. Calcd. for C₁₅H₂₃ON₄S₂Cl·HCl·H₂O: C, 41.95; H, 6.10; N, 13.05; S, 14.93; Cl, 16.51. Found: C, 42.08; H, 6.16; N, 12.84; S, 14.76; Cl, 16.79. UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ m μ (log ϵ): 237, 262 (4.07, 4.01). PPC¹¹: Rf 0.46. NMR (D₂O) τ : 8.69^d (6H, $J=7$ Hz), 7.40^s (3H), 7.35^s (3H), 4.40^s (2H), 1.95^s (1H), 0.28^s (1H).

3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-4-methyl-5-(2-phenylsulfinylethyl)thiazolium Chloride Hydrochloride (VIId)—A suspension of 1.94 g of Vd in 300 ml of H₂O was treated as above giving 1.8 g (75.5%) of VIId. Recrystallization from dil. EtOH gave colorless prisms of mp 198–200° (decomp.). Anal. Calcd. for C₁₈H₂₁ON₄S₂Cl·HCl·H₂O·1/2C₂H₅OH: C, 46.91; H, 5.60; N, 11.52; S, 13.19; Cl, 14.58. Found: C, 46.56; H, 5.69; N, 11.28; S, 13.64; Cl, 14.35. UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ m μ (log ϵ): 236.5, 260 (4.22, 4.09). PPC¹¹ Rf 0.56. NMR (D₂O) τ : 7.52^s (3H), 7.35^s (3H), 4.45^s (2H), 2.30^s (5H), 1.92^s (1H), 0.30^s (1H).

3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-5-(2-benzylsulfinylethyl)-4-methylthiazolium Chloride Hydrochloride (VIe)—A suspension of 2.01 g of Ve in 30 ml of H₂O was treated as above to give 1.8 g (75.5%) of VIe. Recrystallization from dil. EtOH gave colorless pillars of mp 202–204° (decomp.). Anal. Calcd. for C₁₉H₂₃ON₄S₂Cl·HCl·H₂O: C, 47.79; H, 5.49; N, 11.74; S, 13.43; Cl, 14.86. Found: C, 46.93; H, 5.61; N, 11.48; S, 13.68; Cl, 14.80. UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ m μ (log ϵ): 223.5, 262 (4.20, 4.02). PPC¹¹, Rf 0.56. NMR (D₂O) τ : 7.42^s (3H), 7.32^s (3H), 5.97, 5.75, 5.70, 5.48 (2H, AB q), 4.42^s (2H), 1.93^s (1H), 0.27^s (1H).

VIa Monothiocyanate—To a solution of 2 g of VIa hydrochloride in 4 ml of H₂O was added 0.38 g of NH₄SCN and the mixture was stirred for 3 min. This solution was neutralized with 0.712 g of Na₂CO₃·10H₂O to give 1.5 g (81%) of VIa monothiocyanate. Recrystallization from 80% EtOH gave colorless prisms of mp 186–187° (decomp.). Anal. Calcd. for C₁₃H₁₉ON₄S₂·SCN: C, 45.50; H, 5.18; N, 18.95; S, 26.03. Found: C, 45.46; H, 5.11; N, 18.77; S, 26.01. UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ m μ (log ϵ): 231.5, 267 (4.13, 3.90). PPC¹¹: Rf 0.58.

VIa Mononitrate—a) To a suspension of 6.52 g of Va in 15 ml of H₂O was added 9.1 g of 30% H₂O₂ and the mixture was stirred for 2 hr below 35°. To this solution was added 1.77 g of NaNO₃ then 1.68 g of NaHCO₃ causing the separation of crystals. After the mixture had been cooled in an ice bath for 30 min, the separated mononitrate (6.2 g, 79%) was collected and recrystallized from dil. EtOH to give colorless pillars of mp 150–153° (decomp.). Anal. Calcd. for C₁₃H₁₉ON₄S₂·NO₃·H₂O: C, 39.88; H, 5.41; N, 17.89; S, 16.38. Found: C, 40.19; H, 4.87; N, 18.28; S, 15.95. UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ m μ (log ϵ): 232, 266 (4.10, 3.95).

b) To a solution of 4 g of VIa hydrochloride in 8 ml of H₂O was added 0.84 g of NH₄NO₃ then 1.43 g of Na₂CO₃·10H₂O. After the mixture had been cooled for 1 hr, the separated mononitrate (2.75 g, 70.5%) was collected.

3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-4-methyl-5-(2-methylsulfonylethyl)thiazolium Chloride Hydrochloride (VII)—a) To a solution of 1.632 g of II in 6 ml of H₂O and 0.6 ml of conc. HCl was added 3.12 g of 30% H₂O₂ and the mixture was stirred for 6 hr. After standing for 2 days at room temperature, a saturated solution of 1.21 g of BaCl₂·2H₂O was added and the mixture was filtered on Norit "A". The filtrate was concentrated *in vacuo*, and the residue was treated with cold EtOH to give 1.78 g (85%) of VII.

Recrystallization from EtOH gave colorless prisms of mp 239—241° (decomp.). *Anal.* Calcd. for $C_{13}H_{19}O_2N_4S_2Cl \cdot HCl \cdot H_2O$: C, 37.40; H, 5.32; N, 13.42; S, 15.36; Cl, 16.99. Found: C, 37.88; H, 5.50; N, 13.01; S, 15.51; Cl, 16.58. UV $\lambda_{max}^{H_2O}$ m μ (log ϵ): 237.5, 260 (4.12, 3.99). IR (Nujol): ν_{SO_2} 1290, 1110 cm^{-1} . NMR (D_2O) τ : 7.42^s (3H), 7.30^s (3H), 6.82^s (3H), 4.40^s (2H), 2.00^s (1H), 0.25^s (1H).

b) To a solution of 1.03 g of VIa in 3 ml of H_2O and 1.03 g of conc. HCl was added 0.6 g of 30% H_2O_2 and the mixture was stirred for 7 hr at room temperature. After being kept overnight at room temperature, the reaction mixture was concentrated *in vacuo*, and the residue was treated with EtOH to give 0.99 g of a 1:1 mixture of VIa and VII.

5-(2-Chloroethyl)-4-methylthiazole (XII)—To a solution of 14 g of 5-(2-hydroxyethyl)-4-methylthiazole (XIII) in 9 ml of pyridine was added 12.5 g of $SOCl_2$ and the mixture was stirred for 45 min at room temperature. The reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O , dried, and evaporated. The residue was distilled to give 6.2 g (40%) of colorless liquid of bp₆ 96—98°. *Anal.* Calcd. for C_6H_8NSCl : C, 44.69; H, 4.99; N, 9.24; S, 19.83; Cl, 21.93. Found: C, 44.51; H, 5.06; N, 8.49; S, 19.81; Cl, 22.06. NMR (CCl_4) τ : 7.65^s (3H), 1.53^s (1H).

4-Methyl-5-(2-methylthioethyl)thiazole (XI)—To a solution of 1.5 g of powdered NaOH in 60 ml of DMF was added 4 g of CH_3SH then 5 g of XII. The reaction mixture was stirred for 6 hr and allowed to stand overnight at room temperature. After evaporation *in vacuo*, the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O , dried, and evaporated. The residue was distilled *in vacuo* to give 4.4 g (84%) of oil, bp₇ 120—121°. *Anal.* Calcd. for $C_7H_{11}NS_2$: C, 48.55; H, 6.40; N, 8.09; S, 36.96. Found: C, 48.06; H, 6.56; N, 8.12; S, 34.57. NMR (CCl_4) τ : 7.93^s (3H), 7.65^s (3H), 1.60^s (1H).

3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-4-methyl-5-(2-methylthioethyl)thiazolium Bromide Hydrobromide (IX)—A solution of 5.7 g of (4-amino-2-methyl-5-pyrimidinyl)methyl bromide hydrobromide (X) and 4.2 g of XI in 5 ml of DMF was heated at 110—115° for 10 min. To this reaction mixture was added 50 ml of EtOH to give 1.9 g (20%) of IX. Recrystallization from EtOH gave colorless prisms of mp 226—228° (decomp.). *Anal.* Calcd. for $C_{13}H_{19}N_4S_2Br \cdot HBr \cdot H_2O$: C, 33.77; H, 4.58; N, 12.12; S, 13.87; Br, 34.57. Found: C, 33.96; H, 4.54; N, 12.04; S, 13.98; Br, 34.40. UV $\lambda_{max}^{H_2O}$ m μ (log ϵ): 236.5, 265 (4.03, 3.97). PPC¹¹: Rf 0.58. NMR (D_2O) τ : 7.83^s (3H), 7.43^s (3H), 7.35^s (3H), 4.42^s (2H), 1.97^s (1H), 0.32^s (1H).

3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-4-methyl-5-(2-methylthioethyl)thiazolium Chloride Hydrochloride (VIII)—To a solution of 1 g of IX in 3.5 ml of H_2O was added 1.07 g of AgCl and the mixture was stirred for 1 hr at 98—99° then filtered. The filtrate was concentrated *in vacuo*, and the residue was treated with cold EtOH to give 0.65 g (80%) of VIII. Recrystallization from EtOH gave colorless prisms of mp 215—217° (decomp.). *Anal.* Calcd. for $C_{13}H_{19}N_4S_2Cl \cdot HCl \cdot H_2O$: C, 40.51; H, 5.76; N, 14.54; S, 16.64; Cl, 18.40. Found: C, 40.62; H, 6.03; N, 14.25; S, 16.76; Cl, 18.15. PPC¹¹: Rf 0.58. NMR (D_2O) τ : 7.85^s (3H), 7.45^s (3H), 7.37^s (3H), 4.42^s (2H), 1.97^s (1H), 0.30^s (1H).

Acknowledgement The authors express their deep gratitude to Dr. K. Takeda, Director of this laboratory, for his encouragement, and to Drs. T. Minesita and H. Oikawa for biological assay. Thanks are also due to the members who undertook the elemental analyses, and NMR and UV spectra measurements.