[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]

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(Received January 11, 1971)

A number of new thiamine derivatives in which the OH group of thiamine Th-5-CH_2CH_2OH is replaced by $CH_2CH_2N\langle^{R}_{R}$, CH_2CH_2SR, CH_2CH_2SOR, or $CH_2CH_2SO_2R$ 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-CH_2CH_2OH 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 SB_1) reacted with morpholine and piperidine in dimethylformamide (DMF) giving morpholinoethyl and piperidinoethyl SB_1 (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 SB_1 (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 $C_{13}H_{24}O_3N_4S_2Cl_2$. Several forms of the crystals containing different mole of water of crystallization were obtained. From this value the possibility of methylsulfonylethyl thiamine (VII) or methylthioethyl thiamine (VIII) could not be excluded. However, the infrared (IR) spectrum of VIa showed a ν_{SO} band at 1030 cm^{-1} and the nuclear magnetic resonance (NMR) spectrum showed an $SOCH_3$ signal at τ 7.22. These facts supported the methylsulfinylethylthiamine structure for VIa.

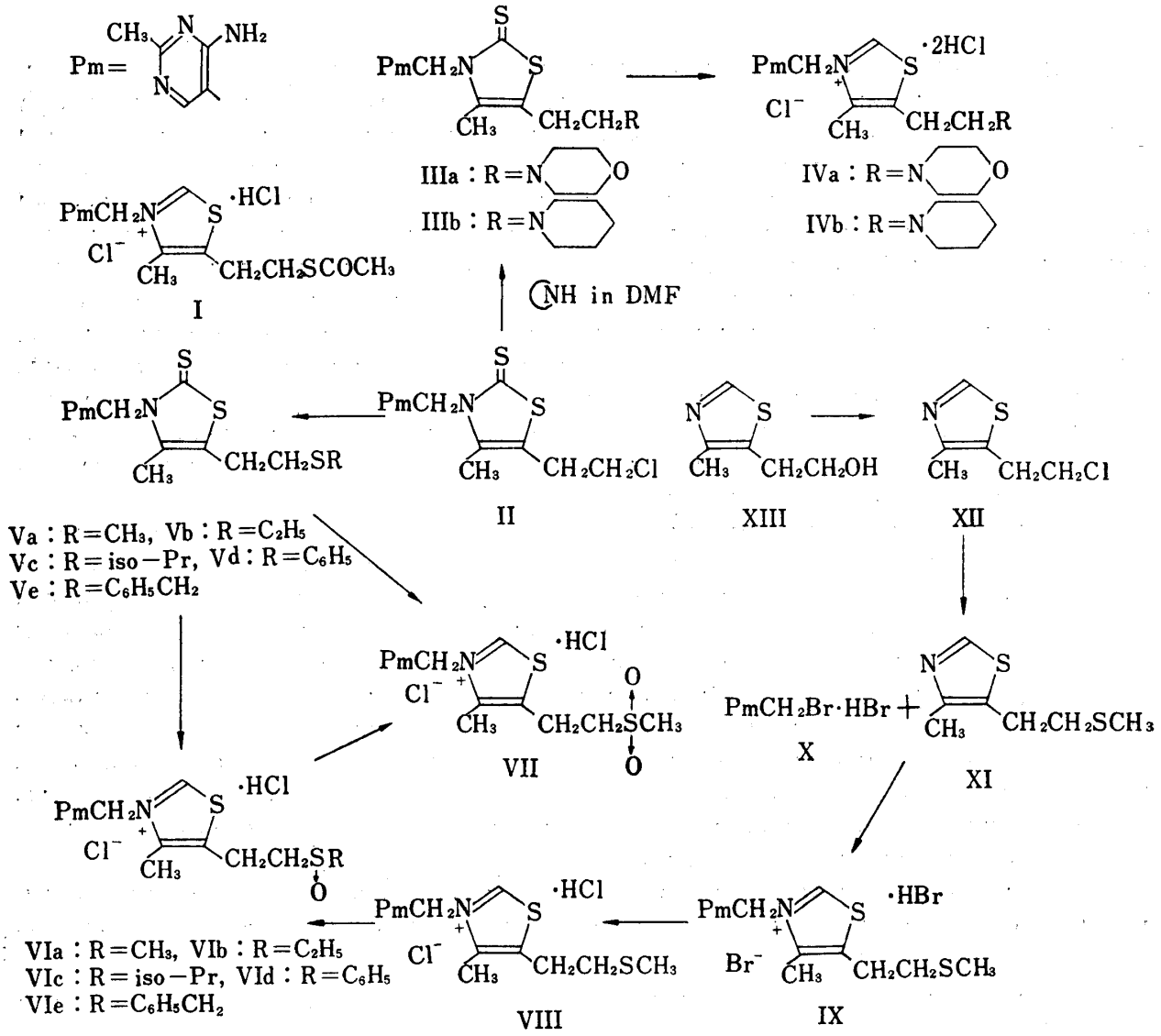
When 5.5 molar equivalents of hydrogen peroxide were allowed to react with Va, followed by treatment with barium chloride, the sulfone VII, mp 239—241° (decomp.), was

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).

obtained as the hydrochloride in 85% yield. The IR spectrum showed an antisymmetric ν_{SO_2} band at 1290 cm^{-1} and a symmetric ν_{SO_2} band at 1110 cm^{-1}. The NMR spectrum showed an SO_2CH_3 signal at the lower field (τ 6.82) than $SOCH_3$ signal of VIa. Compound VII was also obtained from VIa by hydrogene peroxide oxidation.

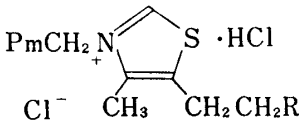
Methylthioethylthiamine hydrobromide (IX), mp 226—228° (decomp.), was prepared from (4-amino-2-methyl-5-pyrimidinyl)methyl bromide hydrobromide (X) and 4-methyl-5-(2-methylthioethyl)thiazole (XI). Compound XI was obtained from the reaction of 5-(2-chloroethyl)-4-methylthiazole (XII) with methanethiol in DMF. The hydrobromide IX was converted into hydrochloride VIII, mp 215—217° (decomp.), by silver chloride. Compound VIII showed an SCH_3 NMR signal at the higher field (τ 7.85) than $SOCH_3$ signal of VIa. Treatment of VIII with hydrogen peroxide gave the sulfoxide VIa.

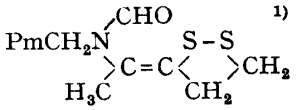
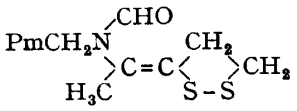
The monothiocyanate, mp 186—187° (decomp.), and mononitrate, mp 150—153° (decomp.), of methylsulfinylethylthiamine were prepared by treatment with ammonium thiocyanate and sodium nitrate, respectively, after the action of hydrogen peroxide on Va.



Reaction of II with ethyl-, isopropyl-, phenyl-, and benzylmercaptan gave the corresponding mercaptoethyl SB_1 (Vb—e). The action of hydrogen peroxide on Vb—e followed by treatment with barium chloride afforded the corresponding sulfinylethylthiamine hydrochloride VIb—e. The compounds prepared here were tested their anticoccidial activities

Table 1. ACI Values of Thiamine Derivatives



	R	ACI[a]		R	ACI[a]
IVa		133	VId	SOC_6H_5	110
			VIe	$SOCH_2C_6H_5$	100
IVb		123	VII	SO_2CH_3	121
	SH[1]	114		 [1]	180
	SO_3H[1]	61			
VIII	SCH_3	168			
I	$SCOCH_3$[1]	191		 [1]	204
VIa	$SOCH_3$	225			
VIb	SOC_2H_5	176			
VIc	$SOCH(CH_3)_2$	125			

a) ACI=(relative weight gains+viavility)−(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 sulonyl derivatives were also ineffective. Two isomers having an intramolecular disulfide linkage were obtained in the preceding report[1] 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.

Experimental[9]

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 $CHCl_3$, 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 $C_{16}H_{23}ON_5S_2$: 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 λ_{max}^{EtOH} mμ (log ε): 234, 280, 324 (4.10, 3.76, 4.17). NMR ($CDCl_3$) 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 IIIb. Recrystallization from Me_2CO gave colorless pillars of mp 188—189°. *Anal.* Calcd. for $C_{17}H_{25}N_5S_2$: 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 λ_{max}^{EtOH} mμ (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 $BaCl_2 \cdot 2H_2O$ 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 $C_{16}H_{24}ON_5SCl \cdot 2HCl \cdot 2.5H_2O$: 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 $\lambda_{max}^{H_2O}$ mμ (log ε): 237, 261 (3.81, 3.74). PPC[10]: *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 $BaCl_2 \cdot 2H_2O$ 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 $C_{17}H_{26}N_5SCl \cdot 2HCl \cdot H_2O$: 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 $\lambda_{max}^{H_2O}$ mμ (log ε): 236, 260 (4.05, 3.97). PPC[10]: *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 $C_{13}H_{18}N_4S_3$: 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 λ_{max}^{EtOH} mμ (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 C_2H_5SH 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 $C_{14}H_{20}N_4S_3$: 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 λ_{max}^{EtOH} mμ (log ε): 234, 279, 325 (4.12, 3.76, 4.18). NMR ($CDCl_3$) τ: 8.77[t] (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 $C_{15}H_{22}N_4S_3 \cdot CH_3COCH_3$: 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 λ_{max}^{EtOH} mμ (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 C_6H_5SH gave 3.3 g of Vd. Recrystallization from Me_2CO gave colorless pillars of mp 138—139°. *Anal.* Calcd. for $C_{18}H_{20}N_4S_3$: 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 λ_{max}^{EtOH} mμ (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 $C_6H_5CH_2SH$ gave 3.45 g (86%) of Ve. Recrystallization from Me_2CO gave colorless pillars of mp 134—135°. *Anal.* Calcd. for $C_{19}H_{22}N_4S_3$: 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 λ_{max}^{EtOH} mμ (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 $BaCl_2 \cdot 2H_2O$ 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 $C_{13}H_{19}ON_4S_2Cl \cdot HCl \cdot H_2O$: 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 $\lambda_{max}^{H_2O}$ mμ (log ε): 237, 262.5 (4.05, 3.99). PPC[11]: *Rf* 0.45. NMR (D_2O) 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 P_2O_5 for 6 hr *in vacuo* gave crystals of mp 216—218° (decomp.). *Anal.* Calcd. for $C_{13}H_{19}ON_4S_2Cl \cdot HCl$: 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 $C_{13}H_{19}ON_4S_2Cl \cdot HCl \cdot 2H_2O$: 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 repeatedlly 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 $C_{13}H_{19}ON_4S_2Cl \cdot 1.5H_2O$: C, 38.04; H, 5.65; N, 13.65; S, 15.62; Cl, 17.28; H_2O, 6.58. Found: C, 38.23; H, 5.70; N, 13.70; S, 15.29; Cl, 17.28; H_2O, 6.41.

b) To a solution of 0.367 g of VIII in 4 ml of H_2O was added 0.117 g of 30% H_2O_2 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 H_2O 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 $C_{14}H_{21}ON_4S_2Cl \cdot HCl \cdot H_2O$: 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 $\lambda_{max}^{H_2O}$ mμ (log ε): 238, 262.5 (4.07, 4.02). PPC[11]: *Rf* 0.46. NMR (D_2O) τ: 8.68[t] (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 H_2O 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 $C_{15}H_{23}ON_4S_2Cl \cdot HCl \cdot H_2O$: 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 $\lambda_{max}^{H_2O}$ mμ (log ε): 237, 262 (4.07, 4.01). PPC[11]: *Rf* 0.46. NMR (D_2O) 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 (VId)——A suspension of 1.94 g of Vd in 300 ml of H_2O was treated as above giving 1.8 g (75.5%) of VId. Recrystallization from dil. EtOH gave colorless prisms of mp 198—200° (decomp.). *Anal.* Calcd. for $C_{18}H_{21}ON_4S_2Cl \cdot HCl \cdot H_2O \cdot 1/2C_2H_5OH$: 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 $\lambda_{max}^{H_2O}$ mμ (log ε): 236.5, 260 (4.22, 4.09). PPC[11] *Rf* 0.56. NMR (D_2O) 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 H_2O 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 $C_{19}H_{23}ON_4S_2Cl \cdot HCl \cdot H_2O$: 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 $\lambda_{max}^{H_2O}$ mμ (log ε): 223.5, 262 (4.20, 4.02). PPC[11], *Rf* 0.56. NMR (D_2O) 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 H_2O was added 0.38 g of NH_4SCN and the mixture was stirred for 3 min. This solution was neutralized with 0.712 g of $Na_2CO_3 \cdot 10H_2O$ to give 1.5 g (81%) of VIa monothiocyanate. Recrystallization from 80% EtOH gave colorless prisms of mp 186—187° (decomp.). *Anal.* Calcd. for $C_{13}H_{19}ON_4S_2 \cdot SCN$: 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 $\lambda_{max}^{H_2O}$ mμ (log ε): 231.5, 267 (4.13, 3.90). PPC[11]: *Rf* 0.58.

VIa Mononitrate——a) To a suspension of 6.52 g of Va in 15 ml of H_2O was added 9.1 g of 30% H_2O_2 and the mixture was stirred for 2 hr below 35°. To this solution was added 1.77 g of $NaNO_3$ then 1.68 g of $NaHCO_3$ 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 $C_{13}H_{19}ON_4S_2 \cdot NO_3 \cdot H_2O$: 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 $\lambda_{max}^{H_2O}$ mμ (log ε): 232, 266 (4.10, 3.95).

b) To a solution of 4 g of VIa hydrochloride in 8 ml of H_2O was added 0.84 g of NH_4NO_3 then 1.43 g of $Na_2CO_3 \cdot 10H_2O$. 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 H_2O and 0.6 ml of conc. HCl was added 3.12 g of 30% H_2O_2 and the mixture was stirred for 6 hr. After standing for 2 days at room tomperature, a saturated solution of 1.21 g of $BaCl_2 \cdot 2H_2O$ 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.

11) iso-PrOH, conc. HCl. H_2O, (170:41:39), Ascending method, Toyo Roshi #50.

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 $\lambda_{max}^{H_2O}$ mμ (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 bp_6 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, bp_7 120—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 $\lambda_{max}^{H_2O}$ mμ (log ε): 236.5, 265 (4.03, 3.97). PPC[11]: *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. PPC[11]: *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.