[Chem. Pharm. Bull. 19(11)2222—2228(1971)]

UDC 547.855.04 : 547.789.04

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

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(Received January 11, 1971)

Reaction of thiamine anhydride (I) with CH_3COSH gave acetylthioethyl SB_1 (II), which was converted into acetylthioethylthiamine (IV). Mercaptoethylthiamine (V), a S-analogue of thiamine, was obtained from IV. A munber of reactions of IV and V were carried out to give a variety of S-analogues of thiamine derivatives. Thiol type S-acyl derivatives, disulfides, perhydrothieno[2,3-*d*]thiazole derivatives, and hexahydrothienothiachromine derivatives were synthesized.

In previous papers,[1,4] thiamine anhydride (I) was found to be a reactive compound giving various types of thiamine derivatives. This stimulated us to prepare some new thiamine derivatives involving thiamine S-analogues from the chemical and biological points of view.

Thiamine anhydride (I) reacted with thiolacetic acid in dimethylformamide (DMF) to give the thiazolinethione (SB_1) having the acethylthioethyl group in the C-5 position (acethylthioethyl SB_1, II) mp 149—151° (decomp.), which was identical with the product obtained from chloroethyl SB_1 (III)[5] and thiolacetic acid. The action of hydrogen peroxide on II followed by treatment with barium chloride gave acetylthioethylthiamine hydrochloride (IV), mp 228—231° (decomp.), which was hydrolized to mercaptoethylthiamine hydrochloride (V),[6] mp 216—218° (decomp.), in high yield. PPC[7] of V showed a single spot at *Rf* 0.48, which was positive for the thiochrome test. The nuclear magnetic resonance (NMR)[8] spectrum of V agreed well with the corresponding protons signals in thiamine.

Mercaptoethylthiamine (V) is a compound having the CH_2CH_2SH group instead of CH_2CH_2OH in the thiamine molecule. Therefore, V is interesting as a thiamine S-analogue. The compound has been reported by Schultz,[6] who, however, reported only that it has no thiamine activity, and gave no detailed report on the synthesis and physical properties, the only value listed being the mp of 180°.[6] The chemical reactivity of V was investigated as follows. Oxidation of V with hydrogen peroxide gave sulfoethylthiamine monochloride (VI), mp 234—237° (decomp.). A number of thiol type of thiamine derivatives have been prepared from thiamine. This prompted us to synthesize some thiol type of thiamine derivatives S-analogues. Acetylthioethylthiamine (IV) was dissolved in sodium hydroxide solution to give the sodium salt of the thiol (VII), and reaction with iodine-potassium iodide gave a mixture of compounds VIII, mp 151—154°, and IX, mp 164—166°, in 33 and 30%

1) Part LXXI: A. Takamizawa, K. Hirai, and T. Ishiba, *Chem. Pharm. Bull.* (Tokyo), **19**, 2009 (1971).
2) This work was presented at the 19th General Meeting of Kinki Branch, Pharmaceutical Society of Japan, Osaka, Oct., 1969.
3) Location: *Sagisu, Fukushima-ku, Osaka.*
4) A. Takamizawa, K. Hirai, and T. Ishiba, *Chem. Pharm. Bull.* (Tokyo), **19**, 1022 (1971).
5) S. Yoshida and M. Unoki, *Yakugaku Zasshi*, **72**, 1431 (1952).
6) F. Schultz, *Z. Physiol. Chem.*, **265**, 113 (1940).
7) PPC: iso-PrOH, HCl, H_2O (170: 41: 39), Ascending Method, Toyo Roshi # 50.
8) NMR spectra were taken with a Varian A-60 Spectrometer in D_2O or $CDCl_3$ containing DDS or TMS as an internal references. Chemica shifts are given as τ values.

yields, respectively. Compound VIII, $C_{28}H_{38}O_4N_8S_4 \cdot H_2O$, was considered to be an intermolecular disulfide from its NMR spectrum, showing peaks at τ 7.98[s] (3H, CH_3-Ċ=), 7.67[s] (3H, $SCOCH_3$), 7.55[s] (3H, Pm-CH_3), 5.60[b] (2H, Pm-CH_2), 3.86[b] (2H, NH_2), and 2.22[s] (2H, Pm-6 H, NCHO). Compound IX has the formula $C_{12}H_{16}ON_4S_2$ (M^+: *m/e* 296) and ultraviolet (UV) absorption maxima at 237, 273, and 343 mμ, the weak absorption at 343 mμ (log ε 2.70) being ascribable to a strained 5-membered disulfide ring.[9] These facts suggest that IX has a structure containing a 1,2-dithiolanylidene ring.

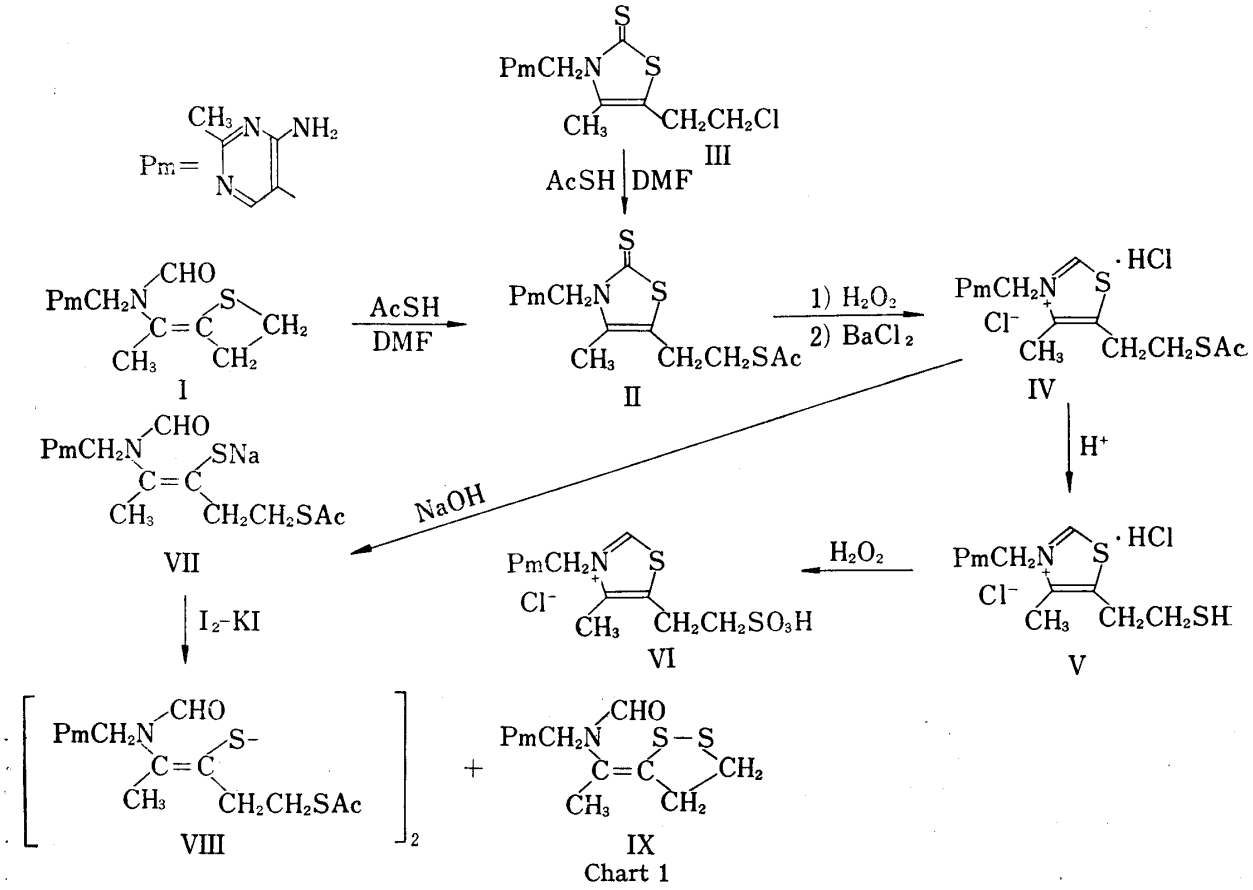

Chart 1

Oxidation of thiol type of mercaptoethylthiamine with iodine-potassium iodide in sodium hydroxide solution gave the disulfide IX and the compound X, mp 128—230°, in 50 and 18% yields, respectively. The elemental analysis value and mass spectrum of X are identical with those of IX suggesting that IX and X are N,S-*cis* and *trans* isomers around the C=C bond. The thiol type of thiamine is easily converted into its geometrical isomer, the N,S-*trans* isomer, by alkali-sulfur.[10] When the thiol type of V was treated under these isomerization reaction conditions, then oxidized with iodine-potassium iodide, the product contained a much higher proportion of X than IX. Therefore, X is the N,S-*trans* isomer and IX the *cis* isomer. The NMR spectra of IX and X are similar but showed some peaks with different chemical shifts. In these spectra, it is notable that the methylene bridge protons showed a sharp singlet at about τ 5.55 probably due to the small effective bulkiness of the 1,2-dithiolanylidene ring,[11] and the CH_3-Ċ= signals appeared at τ 8.10 (IX) and 8.00 (X) as triplets (J=1.2 and 1.7 Hz) long range coupled with the methylene protons in the 1,2 dithiolanylidene ring.

9) J.A. Barltrop, P.M. Hayes, and M. Calvin, *J. Am. Chem. Soc.*, **76**, 4348 (1954).
10) M. Murakami, K. Takahashi, M. Iwanami, and H. Iwamoto, *Yakugaku Zasshi*, **85**, 752 (1965).
11) S. Arakawa, M. Hashimoto, J. Nakano, and H. Nishimura, Abstracts of Papers, 7th NMR Symposium, Nagoya, Nov. 1968, p. 87.

Reaction of thiol type of acetylthioethylthiamine (VII) with sodium benzylthiosulfate in sodium hydroxide solution gave the corresponding benzyl disulfide XI, mp 102°. Similarly, reaction with diethyl pyrocarbonate gave the S-ethoxycarbonyl derivative XII, mp 88—90°. Reaction of VII with *p*-tolyl dithiochlorocarbonate gave the S-dithio-*p*-tolyloxycarbonyl derivative XIII, mp 60—65°.

Mercaptoethylthiamine hydrochloride (V), dissolved in 4 molar equivalents of sodium hydroxide solufion and treated with benzoyl chloride, afforded the dibenzoyl derivative XIV, mp 115—118°, as the hydrochloride. Similarly, reaction with diethyl pyrocarbonate gave the bisethoxycarbonyl derivative XV, mp 95—105°, as the hydrochloride. Reaction with ethyl chloroformate gave a mixture of XV and trisethoxycarbonyl derivative XVI, mp 118—120°.

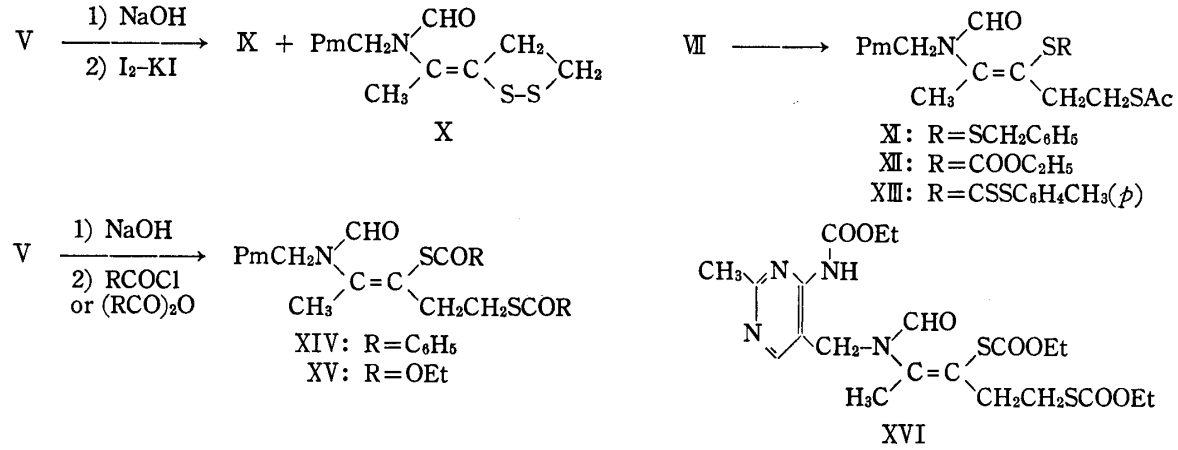

Chart 2

Reaction of thiol type of V with *p*-tolyl dithiochlorocarbonate in NaOH solution gave the compound XVII, mp 180—183° (decomp.), which showed UV absorption maxima at 236, 313, and 351.5 mμ (log ε 4.10, 3.97, 4.08) and an elemental analysis: $C_{13}H_{16}ON_4S_3 \cdot H_2O$, suggesting that it is the dithio-derivative of cyclocarbothiamine. This was confirmed by obtaining XVII from the reaction of thiol type of V with thiophosgene in sodium hydroxide solution. When phosgene was used instead of thiophosgene in this reaction, cyclocarbothiamine S-analogue XVIII, mp 167—169° (decomp.), which showed UV absorprtion maxima at 236 and 265 mμ, was obtained.

After treatment of V with triethylamine in DMF, it was treated with morpholine to give the compound XIX, mp 165—169° (decomp.), which showed UV absorption maxima at 237 and 280 mμ. The elemental analysis, $C_{16}H_{25}ON_5S_2$, suggests that this compound is 2-morpholinodihydrothiamine. The NMR spectrum showed the presence of an isomer. When a solution of XIX in dil. acetic acid was neutralized with sodium bicarbonate the compound XX, $C_{12}H_{16}N_4S_2$, mp 177—180° (decomp.), separated in 72% yield, this compound was also obtained in 60% yield by heating XIX in aqueous solution. The UV spectrum of XX showed absorption maxima at 244 and 286 mμ. The NMR spectrum showed signals at τ 8.15^s (8.23^s) (CH_3-C$\langle$), 7.50^s (Pm-2-CH_3), 4.20^s (4.08^s) (N-CH-S), 2.00 (2.08^s) (Pm-6-H) suggesting contamination with the diastereoisomer (signals at the values in parentheses show about 10% contamination). The presence of diastereoisomers due to C-2 asymmetry in the thiazolidine ring has been observed in thiamine free base,[12] and the compound XX is considered to be the thiamine free base S-analogue.

Reaction of XX with phenyl isocyanate gave the phenylcarbamoyl derivative XXI, mp 177—180°, as a mixture of diastereoisomers, and treatment of XX with ethanolic hydro-

12) A. Takamizawa, K. Hirai, T. Ishiba, and I. Makino, *Chem. Pharm. Bull.* (Tokyo), **19**, 759 (1971).

chloric acid afforded the compound XXII, mp 193—194° (decomp.), as the hydrochloride The UV spectrum of XXII showed absorption maximum at 271 mμ. The elemental analysis, $C_{12}H_{17}N_4S_2Cl \cdot HCl$, agreed with the value of mercaptoethylthiamine hydrochloride (V), however, the infrared (IR) and NMR spectra were different from those of V. Th-C_2-H appeared at τ 0.65 and Th-C_4-CH_3 appeared at a higher field (τ 7.93) than that for V (τ 7.42). Therefore, XXII was an isomer of V containing the tetrahydrothiophene ring. After heating XXII with 5% hydrochloric acid at 80° for 15 min only the starting material was recovered.

Thus mercaptoethylthiamine was found to show similar reactivity to thiamine in some cases, but it also exhibited specific reactivity ascribed to the mercapto group.

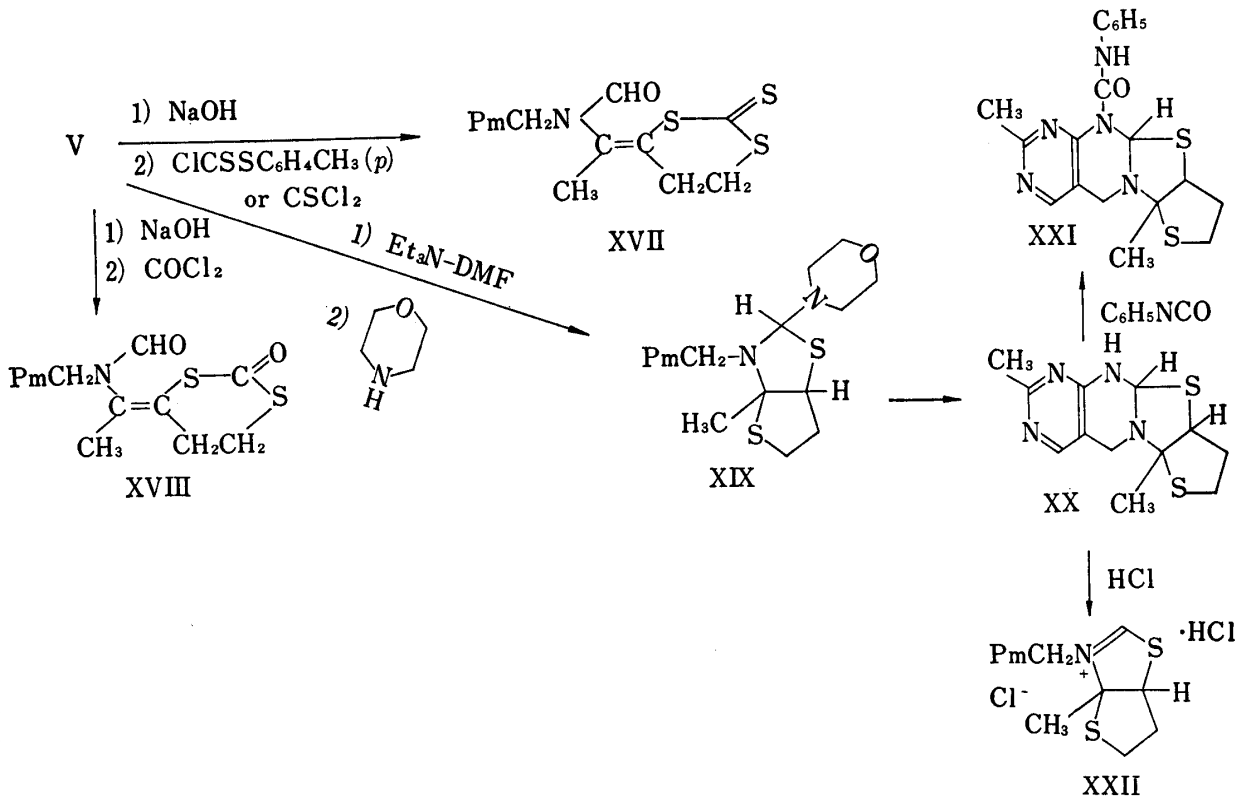

Chart 3

Experimental[13]

5-(2-Acetylthioethyl)-3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-4-methyl-4-thiazoline-2-thione(II)—a) To a solution of 1.5 g of I in 10 ml of DMF was added 2.3 g of CH_3COSH and the mixture was stirred for 5 hr at room temperature. After being kept 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, the eluate with AcOEt giving 0.65 g (34%) of II. Recrystallization from AcOEt gave colorless prisms of mp 149—151° (decomp.). *Anal.* Calcd. for $C_{14}H_{18}ON_4S_3 \cdot 1/3CH_3COOC_2H_5$: C, 47.97; H, 5.43; N, 14.60; S, 25.06; O, 6.96. Found: C, 47.52; H, 5.12; N, 14.41; S, 25.11; O, 6.61. UV λ_{max}^{EtOH} mμ (log ε): 233, 279, 325 (4.21, 3.79, 4.18). NMR ($CDCl_3$)τ: 7.80[s] (3H, CH_3-C=), 7.67[s] (3H, $COCH_3$), 7.52[s] (3H, Pm-2-CH_3), 4.57[s] (2H, NCH_2), 3.75[b] (2H, NH_2), 1.83[s] (1H, Pm-6-H). Mass Spectrum *m/e*: 354 (M^+).

b) To a solution of 6.3 g of III in 100 ml of DMF was added 3 g of CH_3COSH 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 extracted with $CHCl_3$. The $CHCl_3$ extract was washed with dil. $NaHCO_3$ and H_2O, dried, and evaporated. The residue was treated with ether to give 5.4 g (71%) of II. Recrystallization from AcOEt gave crystals which were identical with II obtained above a).

13) All melting points are uncorrected.

5-(2-Acetylthioethyl)-3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-4-methylthiazolium Chloride Hydrochloride (IV)——To a suspension of 3.84 g of II in 80 ml of H_2O was added 3.8 g of 30% H_2O_2 and the mixture was stirred for 5 hr. To this solution was added 2.44 g of saturated $BaCl_2$ solution and the mixture was filtered over Norit "A". The filtrate was concentrated *in vacuo* and to the residue was added EtOH. After it had been kept overnight in a refregerater, 3.0 g (76%) of colorless pillars (IV) were separated from the mixture. *Anal.* Calcd. for $C_{14}H_{19}ON_4S_2Cl\cdot HCl$: C, 42.53; H, 5.10; N, 14.17; S, 16.22; Cl, 17.93. Found: C, 42.24; H, 5.02; N, 14.09; S, 15.95; Cl, 18.08. UV $\lambda_{max}^{H_2O}$ mμ (log ε): 234.5, 263.5 (4.18, 3.89). NMR (D_2O) τ: 7.65^s (3H, $COCH_3$), 7.43^s (3H, CH_3-C=), 7.37^s (3H, Pm-2-CH_3), 6.75^s (4H, CH_2CH_2SAc), 4.42^s (2H, NCH_2), 2.02^s (1H, Pm-6-H), 0.30^s (1H, Th-2-H). *Rf*[7]: 0.53.

3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-5-(2-mercaptoethyl)-4-methylthiazolium Chloride Hydrochloride (V)——A solution of 0.395 g of IV in 0.7 ml of 10% HCl was stirred for 30 min at 80° under N_2 stream. EtOH was added to this solution and separated V was collected to give 0.31 g (82%) of crystals. Recrystallization from EtOH gave colorless pillars of mp 216—218° (decomp.). *Anal.* Calcd. for $C_{12}H_{17}N_4S_2Cl\cdot HCl\cdot\frac{1}{2}H_2O$: C, 39.78; H, 5.29; N, 15.47; S, 17.70; Cl, 19.57. Found: C, 40.15; H, 5.30; N, 15.43; S, 17.72; Cl, 19.47. UV λ_{max}^{EtOH} mμ (log ε): 235, 268 (4.14, 3.96), NMR (D_2O) τ: 7.42^s (3H, CH_3-C=), 7.33^s (3H, Pm-2-CH_3), 4.38^s (2H, NCH_2), 1.97^s (1H, Pm-6-H), 0.30^s (1H, Th-2-H). *Rf*[7]: 0.45.

3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-4-methyl-5-(2-sulfoethyl)thiazolium Chloride (VI)——To a solution of 0.76 g of V in 5 ml of 2% H_2SO_4 was added 1.13 g of 30% H_2O_2 and the mixture was allowed to stand for 7 days. A saturated solution of $BaCl_2$ in H_2O was added to the reaction mixture which was then filtered over Norit "A". The filtrate was concentrated *in vacuo*, and to the residue was added EtOH causing the separation of 0.6 g (78%) of VI. Recrystallization from EtOH gave colorless prisms of mp 234—237° (decomp.). *Anal.* Calcd. for $C_{12}H_{17}O_3N_4S_2Cl\cdot H_2O$: C, 37.64; H, 5.00; N, 14.63; S, 16.75; Cl, 9.26. Found: C, 37.71; H, 5.43; N, 14.30; S, 16.31; Cl, 9.78. UV $\lambda_{max}^{H_2O}$ mμ (log ε): 241, 260 (4.05, 4.02). NMR (D_2O) τ: 7.43^s (3H), 7.37^s (3H), 4.42^s (2H), 2.05^s (1H), 0.30^s (1H). *Rf*[7]: 0.38.

N,N'-[Dithiobis[2-(2-acetylthioethyl)-1-methylvinylene]]bis[N-[(4-amino-2-methyl-5-pyrimidinyl)methyl]formamide] (VIII) and N-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-N-[1-(*cis*-1,2-dithiolan-3-ylidene)ethyl]formamide (IX)——To a solution of 0.79 g of IV in 96 ml of H_2O was added 1.5 ml of 4N NaOH and the mixture was stirred for 30 min under ice-cooling. A solution of 0.26 g of I_2 and 0.6 g of KI in 20 ml of H_2O was added dropwise. After stirring for 1 hr under ice-cooling, the mixture was allowed to stand in a refregerater. Separated VIII (0.23 g, 33%) was collected and recrystallized from AcOEt to give colorless needles of mp 151—154°. *Anal.* Calcd. for $C_{28}H_{38}O_4N_8S_4\cdot H_2O$: C, 48.24; H, 5.78; N, 16.08; S, 18.40. Found: C, 48.44; H, 5.92; N, 15.94; S, 18.12. UV λ_{max}^{EtOH} mμ (log ε): 233.5, 277 (4.52, 4.06). NMR ($CDCl_3$) τ: 7.98^s (3H), 7.67^s (3H), 7.55^s (3H), 5.60^b (2H), 3.85^b (2H), 2.22^s (2H).

The filtrate was extracted with AcOEt and the AcOEt extract was dried and evaporated. The residue was treated with Et_2O to give 0.18 g of IX. Recrystallization from AcOEt gave pale yellow needles of mp 164—166°. *Anal.* Calcd. for $C_{12}H_{16}ON_4S_2$: C, 48.64; H, 5.44; N, 18.91; S, 21.60. Found: C, 48.98; H, 5.51; N, 18.62; S, 21.56. UV λ_{max}^{EtOH} mμ (log ε): 237, 273, 343 (4.00, 3.83, 2.70). Mass Spectrum *m/e*: 296 (M^+). NMR ($CDCl_3$) τ: 8.10^t (3H, J=1.2 Hz), 7.55^s (3H), 5.55^s (2H), 3.92^b (2H), 2.17^s (1H), 1.92^s (1H).

N-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-N-[1-(*trans*-1,2-dithiolan-3-ylidene)ethyl]formamide (X)——a) To a solution of 4.95 g of V in 670 ml of H_2O was added 10.5 ml of 4N NaOH and the mixture was allowed to stand for 30 min. A solution of 1.82 g of I_2 and 4.2 g of KI in 140 ml of H_2O was added dropwise. After being kept for 2 days at room temperature, the reaction mixture was extracted with AcOEt. The AcOEt extract was dried, evaporated, and to the residue was added acetone to give 1.9 g (49.5%) of IX. The acetone solution was chromatographed on silica gel and the eluate with acetone gave 0.68 g (17.5%) of X. Recrystallization from AcOEt gave pale yellow prisms of mp 128—130°. *Anal.* Calcd. for $C_{12}H_{16}ON_4S_2$: C, 48.64; H, 5.44; N, 18.91; S, 21.60. Found: C, 48.64; H, 5.53; N, 18.76; S, 21.49. UV λ_{max}^{EtOH} mμ (log ε): 238.5, 258, 275(sh), 344 (4.02, 3.95, 3.90, 2.54). NMR ($CDCl_3$) τ: 8.00^t (3H, J=1.7 Hz), 7.53^s (3H), 5.57^s (2H), 3.77^b (2H), 2.08^s (1H), 1.92^s (1H). Mass Spectrum *m/e*: 296 (M^+).

b) A solution of 0.71 g of V in 100 ml of 0.24% NaOH was allowed to stand for 30 min under ice-cooling. Sulfur (0.064 g) was added to this solution which was then stirred for 2.5 hr at room temperature. A solution of 0.26 g of I_2 and 0.6 g of KI in 20 ml of H_2O was added and the mixture was allowed to stand for 2 days in a refrigerator. The solution was extracted with AcOEt and the extract was dried and evaporated. The residue was treated with acetone to give 0.085 g of IX. The acetone solution was chromatographed on silica gel and the eluate with acetone was shown by thin layer chromatography (TLC) to contain more X then was found in experiment a).

N-[4-(Acetylthio)-2-(benzyldithio)-1-methyl-1-butenyl]-N-[(4-amino-2-methyl-5-pyrimidinyl)methyl]formamide (XI)——A solution of 1 g of IV in 3 ml of 10% NaOH was allowed to stand under ice-cooling. To this solution was added 1 g of $C_6H_5CH_2S_2O_3Na\cdot NaBr$ and the mixture was stirred for 30 min under ice-cooling then extracted with $CHCl_3$. The $CHCl_3$ extract was dried, evaporated, and the residue was treated with ether–pet. ether to give 0.85 g (74%) of XI. Recrystallization from AcOEt gave colorless prisms of mp 102°. *Anal.* Calcd. for $C_{21}H_{26}O_2N_4S_3$: C, 54.54; H, 5.67; N, 12.12; S, 20.76; O, 6.92. Found: C, 54.42; H, 5.73; N, 12.03; S, 20.49; O, 7.38. UV λ_{max}^{EtOH} mμ (log ε): 227, 270 (4.37, 3.82). NMR ($CDCl_3$) τ:

8.00^{s}(3H), 7.67^{s} (6H), 7.22^{t} (2H, J=4 Hz), 7.17^{t} (2H, J=4 Hz), 6.43^{s} (2H), 3.92^{b} (2H), 2.17^{s} (1H), 2.12^{s} (1H).

N-[4-(Acetylthio)-2-(ethoxycarbonylthio)-1-methyl-1-butenyl]-N-[(4-amino-2-methyl-5-pyrimidinyl)methyl]formamide (XII)——A solution of 0.73 g of IV in 2.4 ml of 10% NaOH was allowed to stand under ice–cooling. To this solution was added 0.27 g of $(C_2H_5OCO)_2O$ and the mixture was stirred for 30 min under ice–cooling. The reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was dried, evaporated, and the residue was chromatographed on silica gel. The eluate with acetone gave 0.2 g (26.4%) of XII as colorless prisms of mp 88—90°. *Anal.* Calcd. for $C_{17}H_{24}O_4N_4S_2$: C, 49.51; H, 5.86; N, 13.59; S, 15.52. Found: C, 49.72; H, 5.83; N, 13.44; S, 15.37. UV λ_{max}^{EtOH} mμ (log ε): 235, 277 (4.18, 3.68).). NMR ($CDCl_3$) τ: 8.73^{t} (3H, J=7 Hz), 7.90^{s} (3H), 7.67^{s} (3H), 7.55^{s} (3H), 5.50^{s} (2H), 4.07^{b} (2H), 2.18^{s} (1H), 2.07^{s} (1H).

N-[4-(Acetylthio)-1-methyl-2-(*p*-tolylthiothiocarbonylthio)-1-butenyl]-N-[(4-amino-2-methyl-5-pyrimidinyl)methyl]formamide (XIII)——To a solution of 0.73 g of IV in 2.4 ml of 10% NaOH was added 0.4 g of *p*-tolyl chlorodithioformate and the mixture was then treated as above. An amorphous powder XIII, mp 60—65°, was obtained. Yield, 0.23 g (24.6%). *Anal.* Calcd. for $C_{22}H_{26}O_2N_4S_4$: C, 52.17; H, 5.18; N, 11.06; S, 25.28. Found: C, 51.95; H, 5.36; N, 10.65; S, 25.44. UV λ_{max}^{EtOH} mμ (log ε): 228, 274, 315 (4.44, 4.07, 4.10). NMR ($CDCl_3$) τ: 7.85^{s} (3H), 7.68^{s} (3H), 7.57^{s} (6H), 5.57^{b} (2H), 4.10^{b} (2H), 2.23^{b} (1H), 2.07^{s} (1H).

N-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-N-[2,4-(dibenzoylthio)-1-methyl-1-butenyl]formamide (XIV)——After a solution of 0.76 g of V in 3.2 ml of 10% NaOH had been allowed to stand for 30 min under ice–cooling, 0.56 g of PhCOCl was added and the mixture was stirred for 1 hr under ice–cooling. The reaction mixture was extracted with AcOEt. The AcOEt extract was dried and evaporated, and the residue was chromatographed on silica gel. The eluate with acetone gave a syrup which was dissolved in $CHCl_3$ and shaken with 10% HCl. The $CHCl_3$ later was dried and evaporated, and the residue was treated with ether to give 0.53 g (43%) of XIV. Recrystallization from acetone gave colorless prisms of mp 115—118°. *Anal.* Calcd. for $C_{26}H_{26}O_3N_4S_2\cdot HCl\cdot 1/3CH_3COCH_3$: C, 58.11; H, 5.69; N, 9.04; S, 10.34; Cl, 5.72. Found: C, 57.89; H, 5.67; N, 9.04; S, 10.57; Cl, 5.74. UV λ_{max}^{EtOH} mμ (log ε): 241.5, 268.5 (4.52, 4.36). NMR ($CDCl_3$) τ: 7.67^{s} (3H), 7.52^{s} (3H), 5.33^{b} (2H), 2.07^{s} (1H), 1.58^{s} (1H).

N-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-N-[2,4-(bisethoxycarbonylthio)-1-methyl-1-butenyl]formamide (XV) and N-[[4-(Ethoxycarbonylamino)-2-methyl-5-pyrimidinyl]methyl]-N-[2,4-(bisethoxycarbonylthio)-1-methyl-1-butenyl]formamide (XVI)——a) After a solution of 0.57 g of V in 2.4 ml of 10% NaOH had been allowed to stand under ice–cooling, 0.326 g of ethyl chloroformate was added and the mixture was stirred for 45 min under ice–cooling. The reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was dried and evaporated, and the residue was chromatographed on silica gel. The eluate with acetone gave 0.043 g (6%) of colorles pillarss (XVI). *Anal.* Calcd. for $C_{21}H_{30}O_7N_4S_2$: C, 49.01; H, 5.87; N, 10.89; S, 12.46. Found: C, 48.87; H, 5.84; N, 10.39; S, 12.60. UV λ_{max}^{EtOH} mμ (log ε): 235(sh), 266(sh) (4.16, 3.88). NMR ($CDCl_3$) τ: 8.77^{t} (3H, J=7 Hz), 8.72^{t} (3H, J=7 Hz), 8.65^{t} (3H, J=7 Hz), 7.88^{s} (3H), 7.35^{s} (3H), 5.50^{b} (2H), 2.07^{s} (1H), 1.85^{s} (1H), 0.73^{b} (1H).

Subsequent elution with acetone gave a syrup which was dissolved in $CHCl_3$ and shaken with 10% HCl. The $CHCl_3$ layer was dried and evaporated, and the residue was treated with Et_2O to give 0.16 g (22%) of colorless prisms (XV), mp 95—105°. *Anal.* Calcd. for $C_{18}H_{26}O_5N_4S_2\cdot HCl\cdot H_2O$: C, 43.50; H, 5.88; N, 11.27; S, 12.90; Cl, 7.13. Found: C, 44.02; H, 6.02; N, 11.00; S, 13.05; Cl, 7.15. UV λ_{max}^{EtOH} mμ (log ε): 241, 277(sh) (4.09, 3.66). NMR ($CDCl_3$) τ: 8.73^{t} (3H, J=7 Hz), 8.70^{t} (3H, J=7 Hz), 7.70^{s} (3H), 7.30^{s} (3H), 2.03^{s} (1H), 1.37^{s} (1H).

b) After a solution of 0.76 g of V in 3.2 ml of 10% NaOH had been allowed to stand for 30 min under ice–cooling, 0.54 g of $(C_2H_5OCO)_2O$ was added and the mixture was stirred for 1 hr under ice–cooling. The reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was shaken with 10% HCl. The $CHCl_3$ layer was dried and evaporated, and the residue was treated with ether to give 0.43 g of XV.

N-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-N-[1-(2-thioxo-1,3-dithian-4-ylidene)ethyl]formamide (XVII)——a) After a solution of 0.76 g of V in 3.2 ml of 16% NaOH had been allowed to stand under ice–cooling, 0.81 g of *p*-tolyl chlorodithioformate was added and the mixture was stirred for 1.5 hr then extracted with $CHCl_3$. The $CHCl_3$ extract was dried and evaporated, and the residue was chromatographed on silica gel. The eluate with acetone gave 0.13 g (18%) of XVII. Recrystallization from AcOEt gave pale yellow prisms of mp 180—183° (decomp.). *Anal.* Calcd. for $C_{13}H_{16}ON_4S_3\cdot H_2O$: C, 43.52; H, 4.88; N, 15.98; S, 27.51. Found: C, 43.57; H, 5.06; N, 15.64; S, 26.78. UV λ_{max}^{EtOH} mμ (log ε): 236, 313, 351.5 (4.10, 3.97, 4.08). Mass Spectrum *m/e*: 340 (M^+). NMR ($CDCl_3$) τ: 8.07^{s} (3H), 7.55^{s} (3H), 5.53^{s} (2H), 3.92^{b} (2H), 2.17^{s} (1H), 2.02^{s} (1H).

b) After a solution of 1.9 g of V in 40 ml of 2% NaOH had been allowed to stand for 30 min under ice–cooling, 2 g of $CSCl_2$ was added dropwise, the pH being kept above 10 by addition of NaOH solution. The mixture was then stirred for 45 min. The reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was dried and evaporated, and the residue was chromatographed on silica gel. The eluate with Me_2CO gave 0.075 g of XVII.

N-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-N-[1-(2-oxo-1,3-dithian-4-ylidene)ethyl]formamide (XVIII)——After a solution of 1.9 g of V in 40 ml of 2% NaOH had been allowed to stand for 30 min under

ice-cooling, 1.75 g of $COCl_2$ was added, the pH being kept above 10 by addition of NaOH solution. The mixture was then stirred for 30 min. The reaction mixture was extracted with $CHCl_3$, and the $CHCl_3$ extract was dried and evaporated, and the residue was chromatographed on silica gel. The eluate with acetone gave 0.355 g (22%) of XVIII. Recrystallization from AcOEt gave pale yellow prisms of mp 167—169° (decomp.). *Anal.* Calcd. for $C_{13}H_{16}O_2N_4S_2$: C, 48.15; H, 4.97; N, 17.28; S, 19.74. Found: C, 48.48; H, 5.21; N, 17.02; S, 19.36. UV λ_{max}^{EtOH} mμ (log ε): 236, 265 (4.17, 3.93). Mass Spectrum *m/e*: 324 (M^+). NMR ($CDCl_3$) τ: 8.03^s (3H), 7.55^s (3H), 5.50^s (2H), 4.02^b (2H), 2.17^s (1H), 2.05^s (1H).

3-(4-Amino-2-methyl-5-pyrimidinyl)methyl-3a-methyl-2-morpholinoperhydrothieno[2,3-d]thiazole (XIX)——To a suspension of 0.9 g of V in 5 ml of DMF was added 1 g of Et_3N, and the mixture was stirred for 30 min. To this solution was added 0.45 g of morpholine and the mixture was stirred for 3.5 hr. 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 treated with ether to give 0.35 g (40%) of XIX. Recrystallization from acetone gave colorless prisms of mp 165—169° (decomp.). *Anal.* Calcd. for $C_{16}H_{25}ON_5S_2$: C, 52.30; H, 6.86; N, 19.06; S, 17.42. Found: C, 52.09; H, 6.58; N, 19.02; S, 17.43. UV λ_{max}^{EtOH} mμ (log ε): 237, 280 (3.93, 3.77). Mass Spectrum *m/e*: 280 (M^+-NH⌒O). NMR ($CDCl_3$) τ: 8.30^s, 8.35^s (3H, 6:1), 7.53^s (3H), 4.93^s, 4.83^s (1H, 6:1) 4.33^b, 4.07s (2H, 6:1), 1.98^b, 2.08^s (1H, 6:1).

2,6a-Dimethyl-6a,8,9,9a,10a,11-hexahydro-5H-thieno[2,3-*h*]thiachromine (XX)——a) To a suspension of 0.08 g of XIX in 1.8 ml of H_2O was added 10% AcOH to give a clear solution. The reaction mixture was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ extract was dried and evaporated to give 0.044 g (72%) of XX. Recrystallization from acetone gave colorless prisms of mp 177—180° (decomp.). *Anal.* Calcd. for $C_{12}H_{16}N_4S_2$: C, 51.42; H, 5.75; N, 19.99; S, 22.83. Found: C, 51.37; H, 5.55; N, 19.73; S, 23.06. UV λ_{max}^{EtOH} mμ (log ε): 244, 286 (3.94, 3.83). Mass Spectrum *m/e*: 280 (M^+). NMR ($CDCl_3$) τ: 8.15^s, 8.23^s (3H), 7.50^s (3H), 4.20^s, 4.08^s (1H), 2.00^s, 2.08^s (1H).

b) A suspension of 0.07 g of XIX in 2 ml of H_2O was heated on a steam bath for 15 min. After being cooled, the reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was dried and evaporated to give 0.032 g (60%) of XX.

2,6a-Dimethyl-11-phenylcarbamoyl-6a,8,9,9a,10a,11-hexahydro-5H-thieno[2,3-*h*]thiachromine (XXI)—— To a solution of 0.076 g of XX in 2 ml of DMF was added 0.097 g of C_6H_5NCO and the mixture was stirred for 4 hr at room temperature. After the mixture had been allowed to stand overnight, DMF was removed *in vacuo*, and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was dried and evaporated, and the residue was treated with acetone to give 0.085 g (79%) of XXI. Recrystallization from acetone gave colorless pillars of mp 177—180° (decomp.). *Anal.* Calcd. for $C_{19}H_{21}ON_5S_2$: C, 57.13; H, 5.30; N, 17.54; S, 16.03. Found: C, 57.41; H, 5.30; N, 17.45; S, 16.24. Mass Spectrum *m/e*: 399 (M^+). NMR ($CDCl_3$) τ: 8.13^s, 8.23^s (3H), 7.28^s (3H), 3.67^s, 3.42^s (1H), 1.72^s, 1.82^s (1H).

3-(4-Amino-2-methyl-5-pyrimidinyl)methyl-3a-methyl-3a,5,6,6a-tetrahydrothieno[2,3-d]thiazolium Chloride Hydrochloride (XXII)——To a suspension of 0.3 g of XX in 2 ml of abs. EtOH was added 0.5 ml of 10% EtOH-HCl to give a clear solution. Crystals separated gradually to give 0.35 g (89.5%) of XXII as colorless prisms of mp 193—194° (decomp.). *Anal.* Calcd. for $C_{12}H_{17}N_4S_2Cl \cdot HCl$: C, 40.79; H, 5.14; N, 15.86; S, 18.15. Found: C, 40.79; H, 4.96; N, 15.87; S, 18.09. UV λ_{max}^{EtOH} mμ (log ε): 271 (4.02). NMR (D_2O) τ: 7.93^s (3H), 7.37^s (3H), 4.92^s (2H), 1.63^s (1H), 0.65^s (1H).

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