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Studies on Pyrimidine Derivatives and Related Compounds. LXV.[1) On the Reactions of Thiamine with Carbon Disulfide[2)

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The action of CS_2 on B_1–HCl in MeOH after treatment with Et_3N gave B_1-methylxanthogenate (II). This reaction was applied to potassium xanthogenate as a new B_1 precipitant.

The reaction of II with primary amines gave thioureas, while the reaction with secondary amines yielded corresponding 2-methyl-4-amino-5-pyrimidinylmethylcarbodithioates by exchange with thiazole moiety of B_1. This substitution reaction was found to be caused by the reaction between B_1 and aminocarbodithioate.

On the other hand, the reaction of CS_2 with B_1–Na salt followed by the action of alkyl halides afforded the S-dithioalkoxycarbonylthiamines readily.

In previous papers,[4) the chemical reactivity of thiazolium C-2 position in thiamine (B_1) was clearly demonstrated obtaining the various kinds of adducts. These reactions were of interest from the point of view of carbene or ylide chemistry.

In order to investigate the behavior of thiamine in non-aqueous solvent in the presence of base, the reaction with carbon disulfide was carried out.

To a suspension of thiamine hydrochloride (I) in MeOH, two moles eq. of triethylamine was added giving yellow clear solution, and excess of carbon disulfide was allowed to react. Separated yellow crystals (II), mp 155° (decomp.), were found to be $CH_3OC{<}^{S}_{S}$ adduct of thiamine from elemental analysis, $C_{14}H_{20}O_2N_4S_3$. Ultraviolet (UV) spectrum of II showed absorption maxima at 229, 271, and 302.5 $m\mu$. However, ethanol-HCl solution showed maximum at 258.5 $m\mu$. Infrared (IR) spectrum exhibited bands at 3280, 3240, and 3000 cm^{-1} due to NH_2 group and characteristic strong bands at 1100, 1085, and 1055 cm^{-1} due to $O{-}C{<}^{S}_{S-}$ group. Nuclear magnetic resonance (NMR) spectrum in d_6-DMSO showed the signals assigned to thiamine structure and a singlet at 6.28 τ due to methyl group of $CH_3O{-}C{<}^{S}_{S}$ group. These facts suggested that II was thiamine methylxanthogenate.

After treatment of II with HCl, addition of KSCN gave thiamine thiocyanate (III). After treatment of II with NaOH, reaction with benzylthiosulfate afforded thiamine benzyldisulfide (IV).

Similarly, reaction with benzoyl chloride gave O,S-dibenzoylthiamine (V). The reaction of II with diethyl phosphite in MeOH afforded thiochrome (VI). These reactions supported

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1) Part LXIV: A. Takamizawa, K. Hirai, Y. Hamashima, and H. Sato, *Chem. Pharm. Bull.* (Tokyo), **17**, 1462 (1969).

2) A part of this paper was presented at the 20th Annual Meeting of the Vitamin Society of Japan at Kōchi, April, 1968.

3) Location: *Fukushima-ku, Osaka.*

4) A. Takamizawa, K. Hirai, Y. Hamashima, S. Matsumoto, and T. Ishiba, *Chem. Pharm. Bull.* (Tokyo), **16**, 1210 (1968); A. Takamizawa, K. Hirai, and Y. Hamashima, *ibid.*, **16**, 1758 (1968); A. Takamizawa, K. Hirai, Y. Hamashima, Y. Matsumoto, and S. Tanaka, *ibid.*, **16**, 1764 (1968); A. Takamizawa, K. Hirai, S. Matsumoto, and T. Ishiba, *ibid.*, **16**, 2130 (1968); A. Takamizawa, S. Matsumoto, and S. Sakai, *ibid.*, **17**, 128 (1969); A. Takamizawa, K. Hirai, S. Matsumoto, and T. Ishiba, *ibid.*, **17**, 462 (1969).

the structure of II. Potassium methylxanthogenate prepared from MeOH, CS_2, and KOH was added by thiamine hydrochloride to separate thiamine methylxanthogenate immediately, and the identity with II was confirmed by IR, UV spectra and mp comparison. Thus, the formation of II would be explained as follows: triethylamine treatment of thiamine in MeOH solution failed to abstract thiazolium C-2 proton in thiamine giving CS_2 adduct at this position, but anion exchange between chloride and methylxanthogenate formed in reaction mixture had preferably occurred to separate slightly soluble thiamine methylxanthogenate.

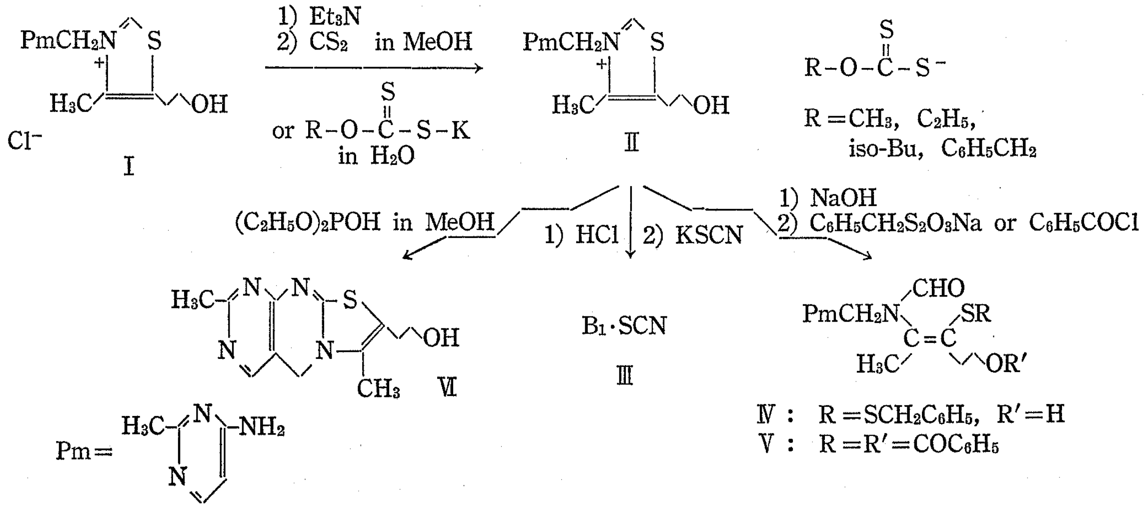

Chart 1

Various kinds of xanthogenate prepared from CS_2, KOH, and alcohol (EtOH, iso-BuOH, benzyl alcohol) were allowed to react with thiamine hydrochloride to give the corresponding thiamine xanthogenate.

Table I

II: R	Yield (%)	mp (°C) (decomp.)	UV λ_{max}^{EtOH} mμ (log ε)
CH_3	84	155	229, 271, 302.5 (3.96, 3.48, 3.75)
C_2H_5	74	134	230, 270, 303.5 (4.29, 3.93, 4.22)
iso-Bu	73	125	230, 272, 304 (4.24, 3.89, 4.16)
$C_6H_5CH_2$	68	124	230, 268, 306 (4.37, 3.37, 4.17)

II: R	Formula	Analysis (%)							
		Calcd.				Found			
		C	H	N	S	C	H	N	S
CH_3	$C_{13}H_{16}ON_4S_3\cdot CH_3OH$	45.16	5.41	15.05	25.80	45.30	5.34	15.28	25.83
C_2H_5	$C_{15}H_{22}O_2N_4S_3$	46.66	5.74	14.50	24.88	46.68	5.90	14.45	24.99
iso-Bu	$C_{17}H_{26}O_2N_4S_3\cdot C_2H_5OH$	49.55	7.00	12.17	20.89	49.09	6.92	12.44	21.10
$C_6H_5CH_2$	$C_{20}H_{24}O_2N_4S_3$	53.57	5.39	12.50	21.45	53.42	5.30	12.75	21.72

This reaction was also caried out in a following manner. Thiamine hydrochloride was added to the corresponding alcohol or aqueous solution of potassium xanthogenate and neutralized with K_2CO_3 giving the precipitate in quantitative yield.

Thiamine xanthogenates obtained here were stable and slightly soluble in H_2O or organic solvents. Therefore, it is practically useful to use this reagent as a new thiamine precipitant.

On heating of II with aniline or benzylamine, SB_1 (X) and thioureas were obtained. On the other hand, heating with secondary amines such as morpholine, piperidine, or N,N-methylbenzylamine gave the corresponding 2-methyl-4-amino-5-pyrimidinomethyl N,N-dialkylaminocarbodithioates (XII, XIII, XIV). In the case of morpholine, 1:1 molecular complex of morpholine morpholinocarbodithioate and carbodithioester XII was obtained as the crystals of mp 228° (decomp.). Carbodithioesters were isolated by Al_2O_3 column chromatography. Carbodithioesters showed characteristic UV absorption band at about 280 mμ. IR spectra exhibited thioureid second band at about 1470 cm^{-1}, and NMR spectra showed broad bands due to protons attaching to the carbon next to N showing the hindered rotation around the C–N bond in dithiocarbamate.[5]

The reaction of amine N,N-dialkylaminocarbodithioate with 2-methyl-4-amino-5-bromomethylpyrimidine gave carbodithioate and the identities with the products obtained from II and secondary amines were confirmed by UV, IR spectra and mp comparison. The formation of 4-methyl-5-β-hydroxyethylthiazole was confirmed by gas chromatography.

N,N-Dialkylamine N,N-dialkylaminocarbodithioates prepared by independent way from amines and CS_2 were allowed to react with thiamine hydrochloride to give the correspoding aminocarbodithioate ester from thiazole exchange reaction. A probable mechanism for this reaction involves the aminocarbodithioate anion formation. Aniline or primary amine gave ureas from the reaction with xanthogenate,[6] while secondary amines afforded aminocarbodithioates from the reaction with xanthogenate. These anion attacked to the methylene bridge of thiamine to result in the displacement of aminocarbodithioate with the thiazole portion of thiamine to give 2-methyl-4-amino-5-pyrimidinomethyl aminocarbodithioate (probably S_N2 type).

It is well known that sulfite decomposed thiamine to give 2-methyl-4-amino-5-pyrimidinylmethane sulfonic acid (XV) and 4-methyl-5-β-hydroxyethylthiazole (XVI).[7] Matsukawa and Yurugi reported that application of aromatic amines to thiamine hydrochloride in aqueous solution in the presence of sulfurous acid resulted in the substitution of amines added with the thiazole portion (XVI) of thiamine.[8]

These reactions were of interest from the similarlity with the reactions caused by thiamine decomposing enzyme (aneurinase).

Recently, sulpyrine (XVIII) was found to cause the decomposition of thiamine to give aminoantipyrine derivative (XIX) and this replacement reaction of thiamine with the basic moiety of sulpyrine was catalyzed by bisulfite from sulpyrine.[9–11]

As shown in this paper, however, it is interesting to note that thiamine undergoes the replacement reaction with aminocarbodithioate to give 2-methyl-4-amino-5-pyrimidinomethyl aminocarbodithioate (XII—XIV). These results would add the suggestive informations about the stability of thiamine as well as its biological action.

On the other hand, the reaction of thiamine sodium salt (XX) with CS_2 was carried out in DMF solution followed by the action of alkyl halides giving the corresponding dithioalkoxycarbonylthiamine (XXI) in good yield. S-Dithioethoxycarbonylthiamine (XXI: R=C_2H_5) was obtained previously by the reaction of thiamine sodium salt (XX) and ethyl dithiochloroformate.[12] The identity of both products was confirmed by UV, IR spectra and mp comparison.

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[5] J.L. Richards, D.S. Tarbell, and E.H. Hoffmerster, *Tetrahedron*, **24**, 6485 (1968).

[6] P.A. Aravindaksham, G.V. Nair, and C.N.V. Nambury, *Ind. J. Chem.*, **1**, 395 (1963).

[7] R.R. Williams, R.E. Waterman, J.C. Keresztesy, and E.R. Buchman, *J. Am. Chem. Soc.*, **57**, 536 (1935).

[8] T. Matsukawa and S. Yugugi, *Yakugaku Zasshi*, **71**, 1423, 1450 (1951); **72**, 33, 990 (1952).

[9] K. Inazu and R. Yamamoto, *Vitamins* (Japan), **34**, 328 (1966).

[10] M. Samejima, I. Sugimoto and I. Utumi, *Yakugaku Zasshi*, **86**, 900 (1966).

[11] Morpholine substituted thiazole (XVI) of thiamine in the presence of diethylbenzoylphosphonate (A. Takamizawa and Y. Hamashima, *Vitamins* (Japan)., **33**, 661 (1966)).

[12] A. Takamizawa, Y. Hamashima, and H. Sato, *Vitamins*, **29**, 26 (1964).

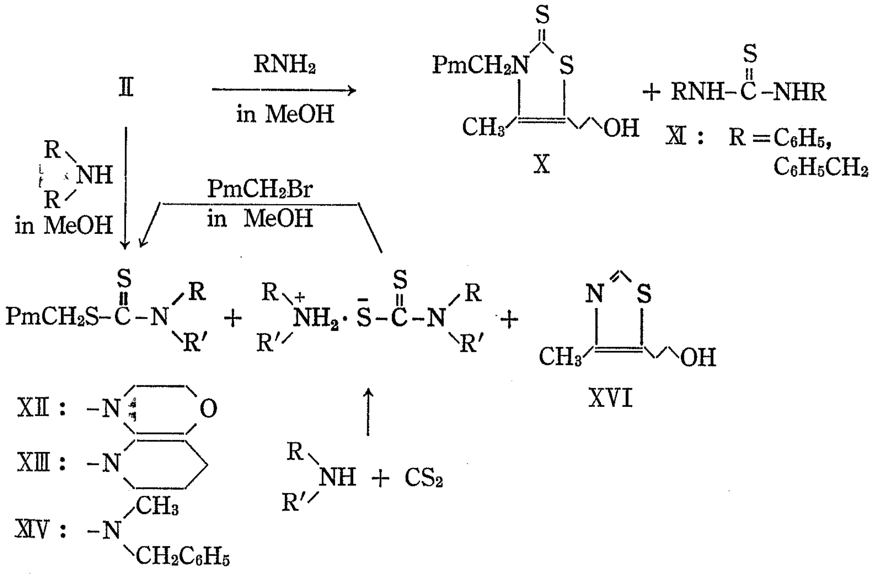


Chart 2

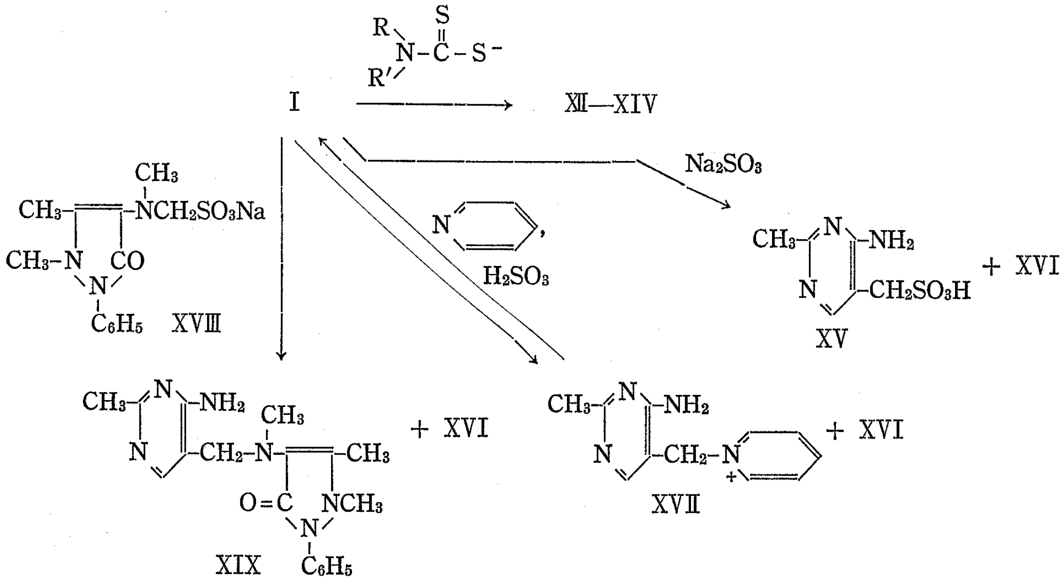
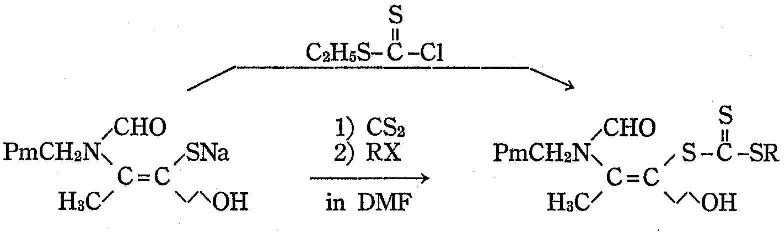


Chart 3

This method is very convenient for the preparation of S-dithioalkoxycarbonyl thiamine, because the operation is simple by using readily available materials and the yield is good. **S**-Dithioalkoxycarbonylthiamines obtained here were listed in Table II.



XX Chart 4 XXI

Table II. S-Dithioalkoxycarbonylthiamine

XXI: R	Yield (%)	mp (°C) (decomp.)	UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε)
CH_3	57	72	231, 270, 312 (4.08, 3.93, 4.10)
C_2H_5	68	124—125[12]	
$C_6H_5CH_2$	56	130—132	238^{sh}, 268, 314 (4.13, 3.97, 4.14)
CH_2=$CHCH_2$	75	124—125	236^{sh}, 268, 313 (4.09, 3.92, 4.09)

XXI: R	Formula	Analysis (%)							
		Calcd.				Found			
		C	H	N	S	C	H	N	S
CH_3	$C_{14}H_{20}O_2N_4S_3 \cdot \frac{1}{2}CH_3COOC_2H_5$	46.15	5.81	13.46	23.05	46.05	5.79	13.59	
$C_6H_5CH_2$	$C_{20}H_{24}O_2N_4S_3$	53.57	5.39	12.50	21.41	53.80	5.45	12.48	21.17
CH_2=$CHCH_2$	$C_{16}H_{22}O_2N_4S_3$	48.24	5.57	14.07	24.10	48.42	5.53	14.23	23.87

Experimental

All melting points were determined in capillary tube and are uncorrected. NMR spectra were taken on a Varian A-60 spectrometer in $CDCl_3$ or d_6-DMSO containing TMS as an internal reference and chemical shifts are presented in a τ value.

Thiamine Methylxanthogenate (II)——a) To a suspension of 16.6 g of B_1–HCl (I) in 160 ml of MeOH, 12 g of Et_3N was added to give yellow clear solution. Carbon disulfide (20 ml) was added to the above solution and allowed to stand at room temperature for two nights. Separated crystals were collected, washed with H_2O and EtOH to give 15.4 g (82%) of II. Recrystallization from MeOH gave colorless prisms, mp 153° (decomp.). *Anal.* Calcd. for $C_{13}H_{16}ON_4S_3$–CH_3OH: C, 45.16; H, 5.41; N, 15.05; S, 25.80. Found: C, 45.30; H, 5.34; N, 15.28; S, 25.83.

Recrystallization from H_2O gave pale yellow scales, mp 155° (decomp.). Found: C, 45.34; H, 5.46; N, 15.14; S, 25.51. UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 229 (3.96), 271 (3.48), 302.5 (3.75). $\lambda_{\max}^{\text{EtOH-HCl}}$ 258.5 mμ. IR cm^{-1}: 3280, 3240, 3000 (NH_2); 1100, 1085, 1055 ($O\text{–}\overset{\overset{S}{\|}}{C}\text{–}S^-$) (KBr). NMR ($d_6$-DMSO) τ: 7.63 (Pm-2-$CH_3$), 7.50 (Thiazole 4-$CH_3$), 6.95 (triplet, J=6 cps, Th-5-CH_2–), 6.33 (triplet, J=6, C$\underline{H}_2$–OH), 6.28 ($CH_3O\text{–}\overset{\overset{S}{\|}}{C}\text{–}S$), 4.80 (OH), 4.60 (Pm–$CH_2$–Th), 2.73 ($NH_2$), 1.92 (Pm-6-H), 0.47 (Th-2-H).

b) To a solution of 0.3 g of KOH in 10 ml of MeOH, 0.5 g of CS_2 was added. To this solution, 1.5 g of B_1–Cl was added and stirred at room temperature to precipitate the crystals in a few minutes. Separated crystals were collected, washed with H_2O and EtOH to yield 1.6 g (84%) of pale yellow crystals. The identity with B_1-methylxanthogenate obtained in a) was confirmed by IR, UV, and mp comparison.

General Procedure for the Preparation of Thiamine Xanthogenates (II)——To a solution of 0.3 g of KOH in 10 ml of alcohol (EtOH, iso-BuOH, $C_6H_5CH_2OH$), 0.5 g of CS_2 was added and 1.5 g of B_1–Cl was added. After stirring for 10 min, precipitates were collected, and washed with H_2O. Data were summarized in Table I.

Reactions of II with Benzylthiosulfate or Benzoyl Chloride in NaOH Solution——a) II (0.34 g) was dissolved in KOH solution (H_2O 5 ml and KOH 0.3 g), and 0.7 g of $C_6H_5CH_2S_2O_3Na$ was added with stirring. Separated oil was crystallized to give 0.2 g of cystals. Recrystallization from acetone–pet. ether gave thiamine benzyl disulfide[13] as colorless crystals of mp 154°.

b) To a solution of 0.2 g of II in 10% NaOH, C_6H_5COCl was added to give O,S-dibenzoylthiamine.[14]

Reactions of II with Diethyl Phosphite——A solution of 0.4 g of II and 0.2 g of diethyl phosphite in 20 ml of MeOH was refluxed for 5 hr. The reaction mixture was evaporated *in vacuo*, and the residue was washed with $CHCl_3$. The aqueous layer was extracted with iso-BuOH, and the separated yellow crystals from extract were collected. IR spectrum showed to be thiochrome (VI).[15]

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[13] T. Matsukawa and H. Kawasaki, *Yakugaku Zasshi*, **73**, 705, 709 (1953).

[14] T. Matsukawa and H. Kawasaki, *Yakugaku Zasshi*, **73**, 216 (1953).

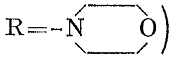
[15] A.R. Todd and F. Bergel, *J. Chem. Soc.*, **1936**, **1601**.

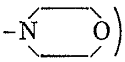
Reaction of II with Hydrochloric Acid——To a suspension of 0.11 g of II in 1 ml of H_2O, dil. HCl was added then 0.15 g of KSCN was added, and neutralized with $KHCO_3$ to separate colorless crystals. Collected, washed with H_2O, and dried to give 0.092 g (89%) of thiamine thiocyanate.

Reaction of II with Benzylamine or Aniline——a) A mixture of 1.0 g of II, 1.2 g of benzylamine, and 30 ml of MeOH was refluxed for 4 hr. After evaporation *in vacuo*, H_2O was added to the residue and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhyd. $MgSO_4$, and $CHCl_3$ was removed. The residue was subjected to Al_2O_3 column chromatography with $CHCl_3$. The first fraction gave oil which crystallized by ether treatment to give 0.3 g of crystals. Recrystallization from AcOEt gave dibenzylthiourea (XI: $R=C_6H_5CH_2$) as colorless prisms, mp 144—145°. *Anal.* Calcd. for $C_{15}H_{16}N_5S$: C, 70.29; H, 6.26; N, 10.93; S, 12.49. Found: C, 70.46; H, 6.21; N, 11.14; S, 13.17.

MeOH elution gave the crystals, which recrystallized from MeOH–AcOEt to give 25 mg of SB_1 (X).

b) A mixture of 0.5 g of II, 0.5 g of aniline, and 10 ml of MeOH was refluxed for 6 hr. The reaction mixture was treated as above a) giving 0.1 g of diphenylthiourea.

Reaction of II with Morpholine——a) A mixture of 0.5 g of II, 1.0 ml of morpholine, and 10 ml of MeOH was refluxed for 5 hr. After cooling, separated needles (0.28 g) were collected and recrystallized from MeOH to give colorless needles, mp 224—228° (decomp.). It was found to be a molecular complex of carbodithioester (XII: R=) and morpholine morpholinocarbodithioate in a 1:1 ratio. *Anal.* Calcd. for $C_{20}H_{34}O_3N_6S_4$: C, 44.92; H, 6.41; N, 15.72; S, 23.97. Found: C, 44.92; H, 6.40; N, 15.60; S, 24.09.

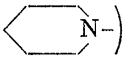
The filtrate was concentrated *in vacuo*, and the residue was added H_2O to give 0.02 g of crystals. Recrystallization from MeOH gave carbodithioester (XII: ) as colorless needles of mp 228—230° (decomp.).

Anal. Calcd. for $C_{11}H_{16}ON_4S_2$: C, 46.47; H, 5.67; N, 19.71; S, 22.56. Found: C, 46.82; H, 5.72; N, 19.92; S, 21.87. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 248 (4.17), 282 (4.18). IR $\nu_{\mathrm{C}\cdots\mathrm{N}+}^{\mathrm{Nujol}}$ 1469 cm^{-1}.

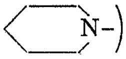
Above molecular complex (0.093 g) was suspended in H_2O and shaken with $CHCl_3$. $CHCl_3$ layer was dried over anhyd. $MgSO_4$, and evaporated to give carbodithioester (XII) (0.046 g). Identity with authentic sample was confirmed by IR comparison.

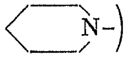
b) A mixture of 0.6 g of morpholine morpholinocarbodithioate prepared from morpholine and CS_2, 0.6 g of B_1–Cl (I), and 20 ml of MeOH was refluxed for 8 hr. After cooling separated needles (0.65 g) were collected. It was found to be identical with above molecular complex.

Reaction of II with Piperidine——a) A mixture of 0.8 g of II, 0.6 g of piperidine, and 20 ml of MeOH was refluxed for 4 hr. Reaction mixture was concentrated *in vacuo*, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over anhyd. $MgSO_4$, and evaporate to give 1.2 g of oil, which crystallized on treatment with ether. Recrystallization from MeOH–AcOEt gave 0.2 g of colorless prisms, mp 170° (decomp). *Anal.* Calcd. for $C_{11}H_{22}N_2S_2$: C, 53.64; H, 9.00; N, 11.37; S, 25.98. Found: C, 53.60; H, 9.19; N, 11.54; S, 25.84. Identity with piperidine piperidinocarbodithioate prepared from piperidine and CS_2 in MeOH was confirmed by IR comparison.

The filtrate and ether layer was concentrated and the residue was subjected to Al_2O_3 column chromatography with $CHCl_3$. Carbodithioseter (XIII: R = ) was obtained as colorless prisms of mp 180—181° (0.047 g) by recrystallization from AcOEt.

Anal. Calcd. for $C_{12}H_{18}N_4S_2$: C, 51.05; H, 6.43; N, 19.85; S, 22.67. Found: C, 50.97; H, 6.38; N, 19.87; S, 22.82. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 250 (4.19), 280 (4.26). IR $\nu_{\mathrm{C}\cdots\mathrm{N}+}^{\mathrm{Nujol}}$ 1462 cm^{-1}.

b) A mixture of 0.98 g of piperidine piperidinocarbodithioate, 0.6 g of B_1–Cl (I), and 20 ml of MeOH was refluxed for 2 hr. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over anhyd. $MgSO_4$, and evaporated. AcOEt was added to the residue to give 0.5 g of carbodithioester (XIII: R = ). Identity with the sample obtained above a) was confirmed by IR comparison.

c) A mixture of 0.3 g of 2-methyl-4-amino-5-bromomethylpyrimidine hydrobromide, 0.3 g of piperidine piperidinocarbodithioate, 0.4 g of Na_2CO_3, and 1 ml of DMF was warmed at 70° for 5 min. H_2O was added to the reaction mixture and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over anhyd. $MgSO_4$, and evaporated. The residue was recrystallized from AcOEt–MeOH to give 0.2 g of colorless prisms. IR spectrum showed to be identical with carbodithioester (XIII: R = ).

Reaction of II with N,N-Methylbenzylamine——A mixture of 0.6 g of II, 0.5 g of N,N-methylbenzylamine, and 20 ml of MeOH was refluxed for 7 hr. After concentartion *in vacuo*, the residue was subjected to Al_2O_3 column chromatography with $CHCl_3$. The crystals (0.4 g) obtained were recrystallized from AcOEt to give carbodithioester (XIV: R= $\genfrac{}{}{0pt}{}{CH_3}{C_6H_5CH_2}\!\!>\!N-$) as colorless prisms of mp 139°.

Anal. Calcd. for $C_{15}H_{18}N_4S_2$: C, 56.59; H, 5.70; N, 17.60; S, 20.10. Found: C, 56.67; H, 5.77; N, 17.81; S, 20.21. UV λ_{max}^{EtOH} mμ (log ε): 247 (4.28), 279 (4.25). IR $\nu_{C\cdots N+}^{Nujol}$ 1471 cm^{-1}.

General Procedure of the Preparation of S-Dithioalkoxycarbonylthiamine (XXI)——To a suspension of 2.25 g of B_1–Na (XX) in 20 ml of DMF, 1.14 g of CS_2 was added with sitrring, 0.7 g of CH_3I was added and stirred for 2 hr at room temp. Reaction mixture was concentrated *in vacuo*, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over anhyd. $MgSO_4$, and evaporated to give 1.3 g of oil, which crystallized on treatment with ether. The crystals were collected and recrystallized from AcOEt to give 1.05 g of yellow prisms, mp 72° (Table II). Similar manner using halides gave the corresponding S-dithioalkoxycarbonylthiamine (XXI) (Table II).