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

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The action of CS₂ on B₃HCl in MeOH after treatment with Et₃N gave B₃-methyl-
Xanthogenate (II). This reaction was applied to potassium Xanthogenate as a new B₃  
precipitant.

The reaction of II with primary amines gave thioureas, while the reaction with sec-

ondary amines yielded corresponding 2-methyl-4-amino-5-pyrimidinymethyl-carboxidithioates  
by exchange with thiazole moiety of B₃. This substitution reaction was found to be  
caused by the reaction between B₃ and aminocarboxidithioate.

On the other hand, the reaction of CS₂ with B₃-\(\text{Na}\) salt followed by the action of alkyl  
halides afforded the S-dithioalkoxycarbonylthiamines readily.

In previous papers, the chemical reactivity of thiazolidine C-2 position in thiamine (B₃)  
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 \(\text{CH₃OC₆S₂}\) adduct of thia-

mine from elemental analysis, C₁₄H₂₆O₂N₄S₂. 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\(_₆S₂\) group.  
Nuclear magnetic resonance (NMR) spectrum in \(\text{d₆-DMSO}\) showed the signals assigned to  
thiamine structure and a singlet at 6.28 \(\tau\) due to methyl group of \(\text{CH₃O-C₆S₂}\) 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 benzyl-
disulfide (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

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: \(\text{Fukushima-ku, Osaka}\).
16, 1210 (1968); A. Takamizawa, K. Hirai, and Y. Hamashima, \(\text{ibid.}\), 16, 1758 (1968); A. Tanaka,  
A. Takamizawa, K. Hirai, Y. Hamashima, Y. Matsumoto, and S. Tanaka, \(\text{ibid.}\), 16, 1764 (1968); A. Takamizawa,  
K. Hirai, S. Matsumoto, and T. Ishiba, \(\text{ibid.}\), 16, 2130 (1968); A. Takamizawa, S. Matsumoto, and S. Sakai,  
\(\text{ibid.}\), 17, 128 (1969); A. Takamizawa, K. Hirai, S. Matsumoto, and T. Ishiba, \(\text{ibid.}\), 17, 462 (1969).
the structure of II. Potassium methylxanthogenate prepared from MeOH, CS₂, 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 CS₂ 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 CS₂, KOH, and alcohol (EtOH, iso-BuOH, benzyl alcohol) were allowed to react with thiamine hydrochloride to give the corresponding thiamine xanthogenate.

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
<th>mp (°C) (decomp.)</th>
<th>UV λ₉₀₀nm (μm (log ε))</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>84</td>
<td>155</td>
<td>229, 271, 302.5 (3.96, 3.48, 3.75)</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>74</td>
<td>134</td>
<td>230, 270, 303.5 (4.29, 3.95, 4.22)</td>
</tr>
<tr>
<td>iso-Bu</td>
<td>73</td>
<td>125</td>
<td>230, 272, 304 (4.24, 3.89, 4.16)</td>
</tr>
<tr>
<td>C₆H₄CH₂</td>
<td>68</td>
<td>124</td>
<td>230, 268, 306 (4.37, 3.37, 4.17)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R</th>
<th>Formula</th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>S</th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>C₁₉H₂₀N₅S₅CH₂OH</td>
<td>45.16</td>
<td>5.41</td>
<td>15.05</td>
<td>25.80</td>
<td>45.30</td>
<td>5.34</td>
<td>15.28</td>
<td>25.83</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>C₁₉H₂₀N₅S₅</td>
<td>46.66</td>
<td>5.74</td>
<td>14.50</td>
<td>24.88</td>
<td>46.68</td>
<td>5.90</td>
<td>14.45</td>
<td>24.99</td>
</tr>
<tr>
<td>iso-Bu</td>
<td>C₁₅H₂₀N₅S₅CH₂OH</td>
<td>49.55</td>
<td>7.00</td>
<td>12.17</td>
<td>20.89</td>
<td>49.09</td>
<td>6.92</td>
<td>12.44</td>
<td>21.10</td>
</tr>
<tr>
<td>C₆H₄CH₂</td>
<td>C₂₀H₂₄N₅S₅</td>
<td>53.57</td>
<td>5.39</td>
<td>12.50</td>
<td>21.45</td>
<td>53.42</td>
<td>5.30</td>
<td>12.75</td>
<td>21.72</td>
</tr>
</tbody>
</table>

This reaction was also carried out in a following manner. Thiamine hydrochloride was added to the corresponding alcohol or aqueous solution of potassium xanthogenate and neutralized with K₂CO₃ giving the precipitate in quantitative yield. Thiamine xanthogenates obtained here were stable and slightly soluble in H₂O or organic solvents. Therefore, it is practically useful to use this reagent as a new thiamine precipitant.
On heating of II with aniline or benzyamine, SB₁ (X) and thiourea 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 228⁰ (decomp.). Carboxidithioesters were isolated by Al₂O₃ 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 N₂ showing the hindered rotation around the C–N bond in dithiocarbamate.⁵

The reaction of amine N,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 CS₂ were allowed to react with thiamine hydrochloride to give the corresponding 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 S₈₂ 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 sulfuric acid resulted in the substitution of amines added with the thiazole portion (XVI) of thiamine.⁸

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

Recently, sulpyrine (XVIII) was found to cause the decomposition of thiamine to give aminoantipyrrine 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 CS₂ was carried out in DMF solution followed by the action of alkyl halides giving the corresponding dithiaoalkoxygenylthiamine (XXI) in good yield. S-Dithioethoxycarbonylthiamine (XXI: R = C₂H₅) 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.

⁸ T. Matsukawa and S. Yaguchi, Yakugaku Zasshi, 71, 1423, 1450 (1951); 72, 33, 990 (1952).
⁹ K. Inazu and R. Yamamoto, Vitamins (Japan), 34, 228 (1966).
¹¹ Morpholine substituted thiazole (XVI) of thiamine in the presence of diethylbenzyolphosphonate (A. Takamizawa and Y. Hamashima, Vitamins (Japan), 33, 661 (1966)).
This method is very convenient for the preparation of S-dithioalkoxy carbonyl thiamine, because the operation is simple by using readily available materials and the yield is good. S-Dithioalkoxy carbonylthiamines obtained here were listed in Table II.
Table II. S-Dithioalkoxy carbonylthiamine

<table>
<thead>
<tr>
<th>XXI: R</th>
<th>Yield (%)</th>
<th>mp (°C) (decomp.)</th>
<th>UV $\lambda_{\text{max}}$ (m$\mu$ (log e))</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$</td>
<td>57</td>
<td>72</td>
<td>231, 270, 312 (4.08, 3.93, 4.10)</td>
</tr>
<tr>
<td>C$_2$H$_5$</td>
<td>68</td>
<td>124—125$^{13}$</td>
<td></td>
</tr>
<tr>
<td>C$_4$H$_9$CH$_2$</td>
<td>56</td>
<td>130—132</td>
<td>238$^{18}$, 268, 314 (4.13, 3.97, 4.14)</td>
</tr>
<tr>
<td>CH$_3$=CHCH$_3$</td>
<td>75</td>
<td>124—125</td>
<td>236$^{18}$, 268, 313 (4.09, 3.92, 4.09)</td>
</tr>
</tbody>
</table>

Analysis (%)

<table>
<thead>
<tr>
<th>XXI: R</th>
<th>Formula</th>
<th>Calcd.</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>C$<em>{19}$H$</em>{26}$O$_2$N$_2$S$_2$.1/2CH$_2$COOC$_2$H$_5$</td>
<td>46.15</td>
<td>5.81</td>
</tr>
<tr>
<td>C$_2$H$_5$CH$_2$</td>
<td>C$<em>{20}$H$</em>{26}$O$_2$N$_2$S$_2$</td>
<td>53.57</td>
<td>5.39</td>
</tr>
<tr>
<td>CH$_3$=CHCH$_3$</td>
<td>C$<em>{19}$H$</em>{26}$O$_2$N$_2$S$_2$</td>
<td>48.24</td>
<td>5.57</td>
</tr>
</tbody>
</table>

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 $\tau$ value.

Thiamine Methylxanthogenate (II)—a) To a suspension of 16.6 g of B$_2$-HCl (I) in 160 ml of MeOH, 12 g of Et$_2$N 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$_2$O 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$_{18}$ON$_2$S$_2$-CH$_2$OH: 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$_2$O gave pale yellow scales, mp 155° (decomp.). Found: C, 45.34; H, 5.46; N, 15.14; S, 25.51. UV $\lambda_{\text{max}}$ (m$\mu$ (log e)): 229 (3.96), 271 (3.48), 302.5 (3.75). $\lambda_{\text{max}}$ (m$\mu$ (log e)): 283.5 m$\mu$. IR cm$^{-1}$: S 3280, 3240, 3000 (NH$_2$); 1100, 1055, 1055 (O-C-S) (KBr). NMR (d$_6$-DMSO): r: 7.63 (Pm-2-CH$_2$), 7.50

(Thiazole 4-CH$_3$), 6.95 (triplet, J = 6 cps, Th-5-CH$_2$), 6.33 (triplet, J = 6, CH$_3$-OH), 6.28 (CH$_2$O-C-S), 4.80 (OH), 4.00 (Pm-4-CH$_2$-Th). 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$_2$-Cl was added and stirred at room temperature to precipitate the crystals in a few minutes. Separated crystals were collected, washed with H$_2$O and EtOH to yield 1.6 g (84%) of pale yellow crystals. The identity with B$_2$-methylxanthogenate obtained in a) was confirmed by IR, UV, and mp comparison.

General Procedure for the Preparation of Thiamine Xanthogenate (II)—To a solution of 0.3 g of KOH in 10 ml of alcohol (EtOH, iso-ButOH, C$_4$H$_9$CH$_2$OH), 0.5 g of CS$_2$ was added and 1.5 g of B$_2$-Cl was added. After stirring for 10 min, precipitates were collected, and washed with H$_2$O. Data were summarized in Table I.

Reactions of II with Benzylsulfinylate or Benzoyl Chloride in NaOH Solution—
a) II (0.34 g) was dissolved in KOH solution (H$_2$O 5 ml and KOH 0.3 g), and 0.7 g of C$_6$H$_5$CH$_2$SO$_2$Na was added with stirring. Separated oil was crystallized to give 0.2 g of crystals. Recrystallization from acetone-pet ether gave thiamine benzyl disulfide$^{10}$ as colorless crystals of mp 154°.

b) To a solution of 0.2 g of II in 10% NaOH, C$_6$H$_5$COCl was added to give O,S-dibenzoylthiamine.$^{14}$

Reactions of II with Diethyl Phosphone—
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-ButOH, and the separated yellow crystals from extract were collected. IR spectrum showed to be thiochromic (VI).$^{15}$

13) T. Matsukawa and H. Kawasaki, Yakugaku Zasshi, 73, 705, 709 (1953).
14) T. Matsukawa and H. Kawasaki, Yakugaku Zasshi, 73, 216 (1953).
Reaction of II with Hydrochloric Acid—To a suspension of 0.11 g of II in 1 ml of H₂O, dil. HCl was added then 0.15 g of KSCN was added, and neutralized with KHCO₃ to separate colorless crystals. Collected, washed with H₂O, and dried to give 0.092 g (89%) of thiamine thiocyanate.

Reaction of II with Benzylamine or Aniline—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, H₂O was added to the residue and extracted with CHCl₃. The CHCl₃ extract was dried over anhyd. MgSO₄, and CHCl₃ was removed. The residue was subjected to Al₂O₃ column chromatography with CHCl₃. The first fraction gave oil which crystallized by ether treatment to give 0.3 g of crystals. Recrystallization from AcOEt gave dibenzylthioiurea (XI): R=CH₂CH₃ as colorless prisms, mp 144—145°. Anal. Calcd. for C₂₅H₂₅N₂S: 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 SB₃ (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 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 carbodiithioester (XII: R=—N—O) and morpholine morpholinocarbodiithioate in a 1:1 ratio. Anal. Calcd. for C₈H₈O₄N₄S₄: 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 H₂O to give 0.02 g of crystals. Recrystallization from MeOH gave carbodiithioester (XII: R=—N—O) as colorless needles of mp 228—230° (decomp.).


Above molecular complex (0.093 g) was suspended in H₂O and shaken with CHCl₃. CHCl₃ layer was dried over anhyd. MgSO₄, and evaporated to give carbodiithioester (XII) (0.046 g). Identity with authentic sample was confirmed by IR comparison.

b) A mixture of 0.6 g of morpholine morpholinocarbodiithioate prepared from morpholine and CS₂, 0.6 g of B₃Cl-I (l), 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 mixture of 0.6 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 CHCl₃. The CHCl₃ layer was washed with H₂O, dried over anhyd. MgSO₄, and evaporated 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 C₁₄H₂₄N₂S₂: C, 53.64; H, 6.00; N, 11.37; S, 25.88. Found: C, 53.60; H, 6.19; N, 11.54; S, 25.84. Identity with piperidine piperidinocarbodiithioate prepared from piperidine and CS₂ in MeOH was confirmed by IR comparison.

The filtrate and ether layer was concentrated and the residue was subjected to Al₂O₃ column chromatography with CHCl₃. Carbodiithioester (XIIΙ: R=—N—) was obtained as colorless prisms of mp 180—181° (0.047 g) by recrystallization from AcOEt.

Anal. Calcd. for C₁₄H₂₄N₂S₂: C, 51.05; H, 6.49; N, 19.85; S, 22.67. Found: C, 50.97; H, 6.38; N, 19.87; S, 22.82. UV λₘₚₐₓ mₜ (log ε): 250 (4.19), 280 (4.26). IR νₚₐₓ mₜ cm⁻¹: 1462 cm⁻¹.

b) A mixture of 0.98 g of piperidine piperidinocarbodiithioate, 0.6 g of B₃Cl-I (l), and 20 ml of MeOH was refluxed for 2 hr. The reaction mixture was concentrated in vacuo, and the residue was dissolved in CHCl₃. The CHCl₃ layer was washed with H₂O, dried over anhyd. MgSO₄, and evaporated. AcOEt was added to the residue to give 0.5 g of carbodiithioester (XIII: R=—N—). 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-bromomethylpyrimidin hydrobromide, 0.3 g of piperidine piperidinocarbodiithioate, 0.4 g of Na₂CO₃, and 1 ml of DMF was warmed at 70° for 5 min. H₂O was added to the reaction mixture and extracted with CHCl₃. The CHCl₃ extract was washed with H₂O, dried over anhyd. MgSO₄, and evaporated. The residue was recrystallized from AcOEt–MeOH to give 0.2 g of colorless prisms. IR spectrum showed to be identical with carbodiithioester (XIII: R=—N—). Identity with the sample obtained above a) was confirmed by IR comparison.

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 concentaration in vacuo, the residue was subjected to Al₂O₃ column chromatography with CHCl₃. The crystals (0.4 g) obtained were recrystallized from AcOEt to give carbodiithioester (XIV: R=CH₃CH₂CH₃N−) as colorless prisms of mp 139°.
Anal. Calcd. for C₁₃H₁₆N₅S₂: C, 56.60; H, 5.70; N, 17.60; S, 20.10. Found: C, 56.67; H, 5.77; N, 17.81; S, 20.21. UV λmax μm (log ε): 247 (4.28), 279 (4.25). IR ν$_{\text{C=O}}$ 1471 cm$^{-1}$.

General Procedure of the Preparation of S-Dithioalkoxycarbonylthiamine (XXI)—To a suspension of 2.25 g of B$_2$-Na (XX) in 20 ml of DMF, 1.14 g of CS$_2$ was added with stirring, 0.7 g of CH$_2$I was added and stirred for 2 hr at room temp. Reaction mixture was concentrated to nucle, and the residue was dissolved in CHCl$_3$. The CHCl$_3$ layer was washed with H$_2$O, 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).