The authors express their gratitude to Dr. Yo Ueda for his kind suggestion on the IR spectral analysis. They are indebted to Mr. M. Shido and Miss S. Indo for the microanalyses, and also to Messrs. H. Matsui and K. Hikita and Miss Y. Soeda for the spectral measurements.

Summary

A crystalline dye was separated from the reaction mixture of anthrone with furfural or xylose in sulfuric acid, and its probable structure was presented. The same dye was also yielded by condensing anthrone to another dye which was separated from the reaction mixture of the same reagents in phosphoric acid.

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214. Akira Takamizawa, Kentaro Hirai, Yoshio Hamashima, and Hisao Sato : Studies on the Pyrimidine Derivatives. XXIV.*1 Syntheses of Several Thiol-type Thiamine Derivatives and their Primary Screening Tests.

(*Shionogi Research Laboratory, Shionogi & Co., Ltd.**2)

The synthesis of O-chlorocarbonylthiamine (II) by the action of phosgene on thiamine hydrochloride (I), and its conversion into O-alkoxycarbonylthiamine (III) or O-carbamoylthiamine (IV) were recently reported from this laboratory.[1] S-Ethoxycarbonylthiamine (CET) (V), S-butoxycarbonylthiamine (CBT) (VI) and O,S-bis(ethoxycarbonyl)thiamine (DCET) (VII)[2] exhibit a thiamine acitvity to approximately the same extent as thiamine hydrochloride (I), and when administered orally, they are highly absorbed and maintain their thiamine levels for a longer period than thiamine hydrochloride.[3] Of these compounds, VII is most stable.[4] Thiamine propyl disulfide (VIII) is also known for its good intestinal absorption. We were also interested in studying the reaction of VIII with phosgene and also the biological activity of its O-substituted derivatives.

VIII reacted in chloroform solution with phogene to give O-chlorocarbonylthiamine propyl disulfide (IX) as a syrupy product. IX, on treatment with ethanol, yielded O-ethoxycarbonylthiamine propyl disulfide (X) as a hydrochloride, m.p. 149~151°. As X could not be obtained by the action of ethyl chloroformate on VIII, it is evident that X was produced through IX in this reaction.

X was also obtained by the action of sodium propyl thiosulfate (Bunte's salt*3) on S-ethoxycarbonylthiamine (V) in alkaline solution. O-Dimethylcarbamoylthiamine propyl

*1 Part XXIII : Ann. Rep. Shionogi Research Lab., **12**, 48 (1962).
*2 Sagisu, Fukushima-ku, Osaka (高見沢 映, 平井健太郎, 浜島好男, 佐藤久夫).
*3 Organic thiosulfate (XXVII). cf. H. Bunte : Ber. **7**, 646 (1874).
1) A. Takamizawa, K. Hirai, Y. Hamashima : This Bulletin, **11**, 882 (1963).
2) A. Takamizawa, K. Hirai : *Ibid.*, **10**, 1102 (1962).
3) *a*) T. Minesita, M. Morita, T. Iwata : Ann. Rep. Shionogi Research Lab., **12**, 6 (1962). *b*) Vitamin B_1 New Deriv. Research sub Comm., Japan : Vitamins, **25**, 516 (1962).
4) R. Yamamoto, T. Kubota, K. Inazu : Ann. Rep. Shionogi Research Lab., **12**, 17 (1962).

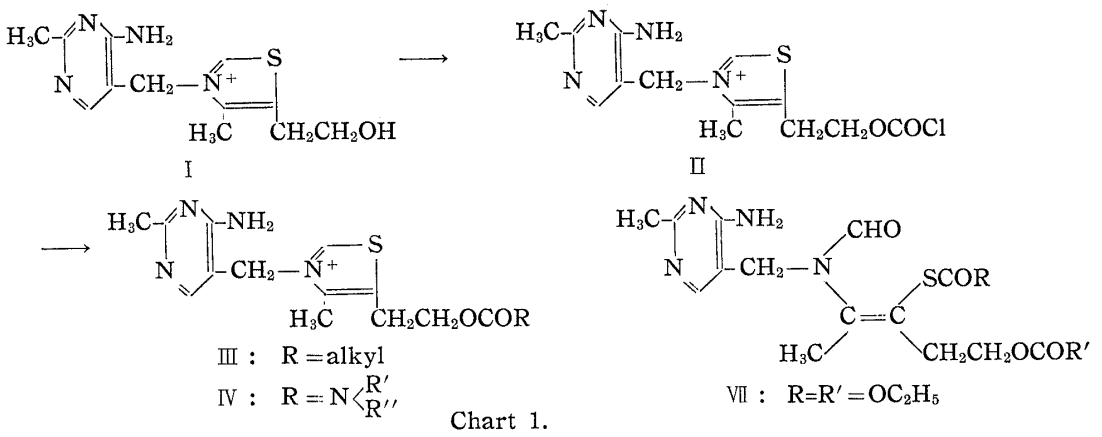
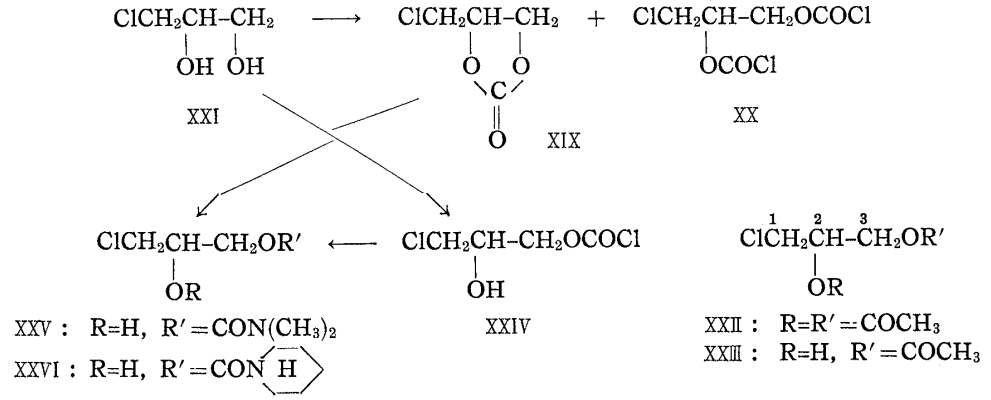


Chart 1.

disulfide (XI), O-piperidinocarbonylthiamine propyl disulfide (XII) and O-morpholinocarbonylthiamine propyl disulfide (XIII) were prepared in a similar manner from S-dimethylcarbamoylthiamine (XIV), S-piperidinocarbonylthiamine (XV) and S-morpholinocarbonylthiamine (XVI)[1] by the action of sodium propyl thiosulfate in alkaline solution, respectively.

Although Yurugi, *et al.*[5,6] synthesized several thiamine monohydroxyalkyl disulfide derivatives, no report on thiamine polyhydroxyalkyl disulfide derivatives seemed to have appeared so far. In an attempt to synthesize thiamine 2,3-dihydroxypropyl disulfide (XVII), thiamine sodium salt was allowed to react with sodium 2,3-dihydroxypropyl thiosulfate (XXVII : R=$CH_2CH(OH)CH_2OH$). However, the expected XVII was not obtained but thiamine thiazolone (XVIII) was isolated from the reaction mixture. Next, it was investigated to protect their hydroxyl groups by the action of phosgene. Contardi, *et al.*[7] obtained chlorohydrin carbonate (XIX) and dichloroformate (XX) by the action of phosgene on α-monochlorohydrin (XXI). We also carried out the reaction of XXI with phosgene



and treated the resulted product with dimethylamine, whereby an oil, $b.p_{1.0}$ 105~106°, was obtained. The elemental analysis indicated that one dimethylcarbamoyl group was introduced into XXI. The position of this group was confirmed by the nuclear magnetic resonance spectra (Fig. 1). Acetylation of XXI gave a monoacetate and a diacetate,[8] and the nuclear magnetic resonance spectrum of the diacetate (XXII) showed signals at 4.75, 5.7, and 6.37 τ due to the protons at 2-C, 3-C, and 1-C, respectively. However, since the monoacetate (XXIII) did not show a signal at about 4.75 τ, its acetoxyl group should be

5) S. Yurugi : Yakugaku Zasshi, **74**, 1157 (1954).
6) S. Yurugi, T. Fushimi : *Ibid.*, **77**, 16 (1957); **78**, 602 (1958).
7) A. Contardi, A. Ercoli : Gazz. Chem. Ital., **64**, 522 (1934). (C. A., **29**, 1392³. (1935)).
8) E. Abderhalden, E. Eichwald : Ber., **47**, 1859 (1914).

at 3-C. The nuclear magnetic resonance spectrum of dimethylcarbamoyl compound had resemblance to that of XXIII and hence the dimethylcarbamoyl group in the molecule should be at 3-C. Accordingly, the chloro compound obtained by the action of phosgene should be 1-chloro-3-chlorocarbonyloxy-2-propanol (XXIV) or XIX. However, no detailed examination of this intermediate was made. Similarly, 1-chloro-3-piperidinocarbonyloxy-2-propanol (XXVI) was prepared.

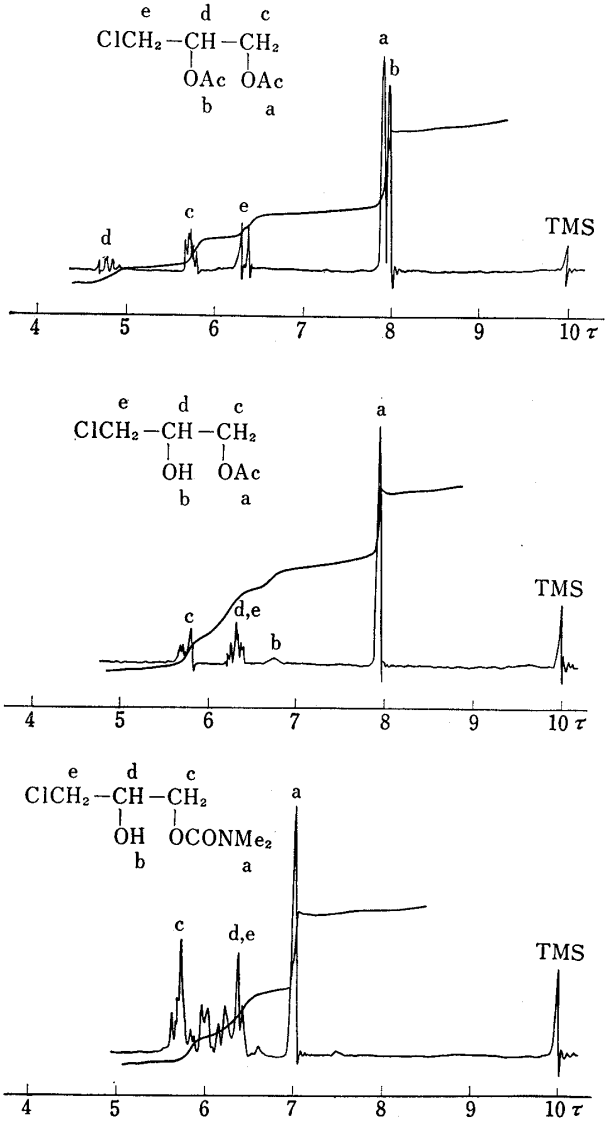


Fig. 1. Nuclear Magnetic Resonance Spectra

The NMR spectra were measured with a Varian A-60 Spectrometer at 60 MC. in $CHCl_3$ containing tetramethylsilane as an internal reference.

Yurugi, *et al.* reported that in the reaction to obtain Bunte's salt, 2-hydroxy-3-alkoxy bromide hardly reacts with sodium thiosulfate. However, Bunte's salt (XXVII: $R=CH_2CH(OH)CH_2OCON(CH_3)_2$) was prepared from 1-chloro-3-dimethylcarbamoyloxy-2-propanol (XXV), and XXVII reacted with thiamine sodium salt to give thiamine 2-hydroxy-3-dimethylcarbamoyloxypropyl disulfide (XXVIII) as the crystalline hydrochloride. O-Ethoxycarbonylthiamine 2-hydroxy-3-dimethylcarbamoyloxypropyl disulfide (XXIX) and thiamine 2-hydroxy-3-piperidinocarbonyloxypropyl disulfide (XXX′) were obtained as a syrup, and attempts to crystallize them as the hydrochlorides were unsuccessful. Yurugi, *et al.*[8] also obtained thiamine alkoxycarbonylmethyl disulfide (XXXI) as an oil. We prepared the higher homologues, thiamine ethoxycarbonylethyl disulfide (XXXII) and O-ethoxycarbonyl derivative (XXXIII).

Thiamine 2-hydroxyethyl disulfide (XXXIV), which is known for its good intestinal absorption, was prepared by Yurugi.[5] The syntheses of acyl derivatives of XXXIV were also reported; the monobenzoate (XXXV′) was obtained in the crystalline form, whereas the mono and diacetates and the dibenzoate were obtained as an oil. We obtained O′- and O-ethoxycarbonyl compounds (XXXV: R′=$COOC_2H_5$ and XXXV″) and O,O′-bis(ethoxycarbonyl) compound (XXXVI) as the hydrochloride. 1-Chloro-2-ethoxycarbonyloxyethane (XXX) was prepared from the reaction of phosgene with ethylenechlorohydrin followed by treatment with ethanol, and converted into Bunte's salt (XXVII: R=$CH_2CH_2OCOOC_2H_5$) by treatment with sodium thiosulfate.

Recently, N. Yoshida, *et al.*[9] prepared S-acylthiamine O-acetal, but S. Yoshida[10] reported that these compounds did not give the expected effect for conversion into thiamine in the living body when administered orally or injected intravenouly. We prepared S-ethoxycarbonyl-O-(2-tetrahydropyranyl)thiamine (XXXVII). S-butoxycarbonyl-O-(2-tetrahydropyranylthiamine (XXXVIII), S-(ethylthio)carbonyl-O-(2-tetrahydropyranylthiamine (XXXIX) and O-(2-tetrahydropyranyl)thiamine propyl disulfide (XL) by the action of 2,3-dihydro-4*H*-pyran on V, VI, XLI, and VIII, respectively.

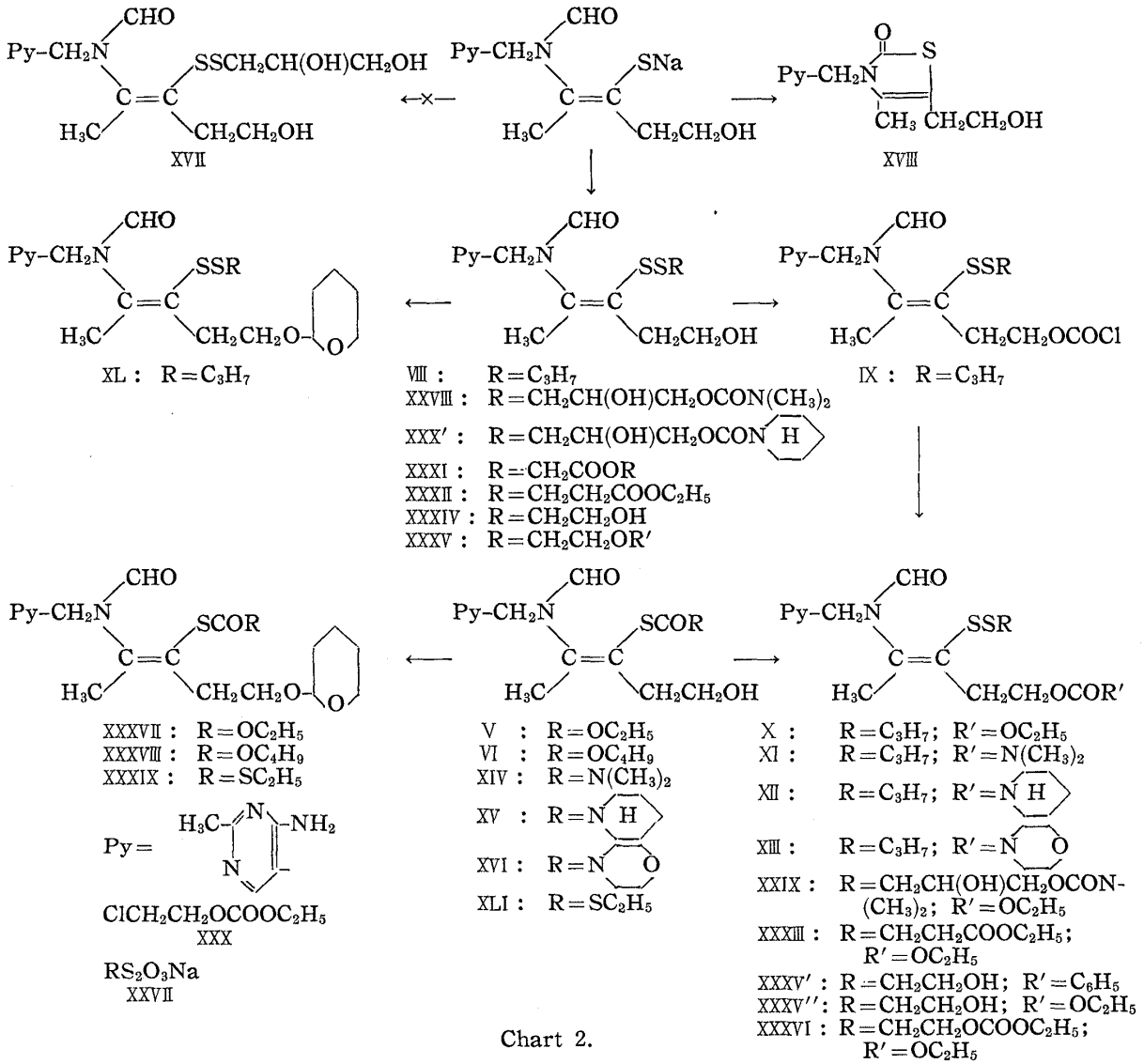
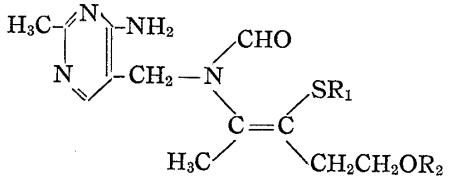


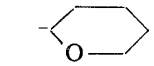
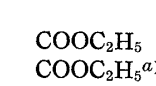
Chart 2.

9) N. Yoshida, Y. Nakamura : Ann. Rep. Takamine Lab., **13**, 37 (1961).
10) S. Yoshida, *Ibid.*, **13**, 16 (1961).

Of these compounds, thiamine alkyl disulfide derivatives, when orally administered, were absorbed to approximately the same or somewhat less extent as compared with thiamine propyl disulfide (VIII), but S-ethoxycarbonyl derivatives showed an extremely high absorption and maintained their blood thiamine levels to the same extent as in the case of DCET (VII). Some of these results are listed in Table I.*4

Table I. Blood Thiamine Levels Following Oral Administration of Thiamine Derivatives to Rabbits (Equimolar Amount to 5 mg./kg. of Thiamine Hydrochloride)



	R_1	R_2	Total B_1 γ/dl.(hr.)				
			0	1	3	5	8
I	Thiamine hydrochloride		22.2	27.5	32.9	34.4	28.7 (standard)
VIII	$S-C_3H_7$	H	23.6	52.9	59.5	51.5	43.6 (〃)
X	〃	$COOC_2H_5$ a)	25.4	46.5	58.6	54.9	42.3
XL	〃		22.5	51.6	59.2	48.7	42.5
XXVIII	$S-CH_2CH(OH)-CH_2OCON(CH_3)_2$	H a)	22.5	27.9	32.7	32.7	28.5
XXXV''	$S-CH_2CH_2OH$	$COOC_2H_5$	27.6	46.9	53.1	48.5	44.4
XXXVI	$S-CH_2CH_2OCOOC_2H_5$	$COOC_2H_5$ a)	24.0	33.2	39.4	39.4	37.2
VII	$COOC_2H_5$	$COOC_2H_5$ a)	24.8	55.1	89.4	81.1	62.4 [2,3]
XXXVII	$COOC_2H_5$		25.2	80.8	87.8	74.8	61.4

a) Hydrochloride

Experimental*5

O-Ethoxycarbonylthiamine Propyl Disulfide (X) Hydrochloride——a) To a solution of 3.0 g. of VIII[11] in 100 ml. of dry $CHCl_3$, 200 ml. of liquid $COCl_2$ was added at −25° under stirring. The mixture was gradually brought to room temperature and then refluxed for 4 hr., at which time syrupy substances were separated. After removing the excess $COCl_2$, the $CHCl_3$ was evaporated *in vacuo* at 30°. The residue was taken up in 200 ml. of $CHCl_3$ and treated with a solution of 5.0 g. of $N(C_2H_5)_3$ in 20 ml. of $CHCl_3$ and 20 ml. of abs. EtOH at −45° under stirring. After standing overnight in a refrigerator, the reaction mixture was concentrated to about 100 ml. *in vacuo*, washed successively with H_2O, 2% AcOH, and 10% HCl, dried over anhyd. $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was triturated with petr. ether and recrystallized from Me_2CO to yield 0.05 g. of colorless prisms, m.p. 149~151°(decomp.), which gave a negative, but, after treatment with cysteine, a positive thiochrome reaction. Rf*6 0.79. *Anal.* Calcd. for $C_{18}H_{28}O_4N_4S_2 \cdot HCl$: C, 46.55; H, 6.25; N, 12.06. Found : C, 46.18; H, 6.54; N, 11.84.

b) To 10 ml. of 2.8% NaOH, 1.0 g. of V was added under cooling and stirring. After 10 min. at room temp., 2.5 g. of sodium propyl thiosulfate[11] was added with continued stirring. The separated oil was extracted with $CHCl_3$, and the $CHCl_3$ extract was washed successively with H_2O, 2% AcOH, and 10% HCl, dried over anhyd. $MgSO_4$, and evaporated to dryness. The residue was crystallized from Et_2O to give 0.3 g. of colorless crystals, which, after recrystallization from Me_2CO, showed m.p. 151~152° (decomp.). The identity was confirmed by comparison of the IR spectra and Rf values with the sample obtained as above (see section a)).

O-Dimethylcarbamoylthiamine Propyl Disulfide (XI)——To a solution of 0.23 g. of NaOH in 10 ml. of H_2O, 1.0 g. of XIV[1] was added and the mixture was stirred for 15 min. at 25°. After having become

*4 Biological tests were undertaken by Dr. T. Minesita, *et al.* of this laboratory. A more detailed report will be presented elsewhere.

*5 All melting points are uncorrected.

*6 Paper chromatography, BuOH-AcOH-H_2O(4:1:5). Ascending method.

11) T. Matsukawa, T. Iwatsu, H. Kawasaki : Yakugaku Zasshi, **73**, 497 (1953).

clear, the solution was cooled to 8~10°, and 0.5 ml. of 10% NaOH and 1.0 g. of sodium propyl thiosulfate were added under stirring. The separated oily product, after solidifying, was extracted with $CHCl_3$ and the extract was washed with H_2O, dried over anhyd. $MgSO_4$, and evaporated to dryness. The residue was crystallized from H_2O and recrystallized from dil. EtOH to afford 0.9 g. of colorless plates, m.p. 73~78°, which gave a negative, but, after treatment with cysteine, a positive thiochrome reaction. Rf 0.81. IR ν_{max}^{Nujol} cm^{-1}: 1708(C=O), 1650(C=C), 1183(C-O). *Anal.* Calcd. for $C_{18}H_{27}O_3N_5S_2 \cdot H_2O$: C, 48.53; H, 7.01; N, 15.72; H_2O, 4.04. Found: C, 48.27; H, 7.04; N, 15.41; H_2O, 4.00.

O-Piperidinocarbonylthiamine Propyl Disulfide (XII)——To a solution of 0.3 g. of NaOH in 15 ml. of H_2O, 1.5 g. of XV[1] was added. After the solution became clear, 1 ml. of 10% NaOH and 1.5 g. of sodium propyl thiosulfate were added under cooling and stirring, whereupon the separated oil gradually solidified. Filtration, washing with a small amount of H_2O, and recrystallization from dil. EtOH yielded 1.3 g. of colorless plates, m.p. 92~94°, which gave a negative, but, after treatment with cysteine, a positive thiochrome reaction. Rf 0.73. *Anal.* Calcd. for $C_{21}H_{33}O_3N_5S_2 \cdot H_2O$: C, 51.95; H, 7.27; N, 14.43; H_2O, 3.71. Found: C, 52.19; H, 7.27; N, 14.19; H_2O, 3.62.

O-Morpholinocarbonylthiamine Propyl Disulfide (XIII)——XIII was prepared from 0.4 g. of NaOH, 17 ml. of H_2O and 1.75 g. of XVI.[1] Colorless rhombics, m.p. 82~85°. Yield 1.6 g. Thiochrome reaction was negative, but positive after treatment with cysteine. Rf 0.78. *Anal.* for $C_{20}H_{31}O_4N_5S_2 \cdot H_2O$: C, 49.27; H, 6.82; N, 14.37. Found: C, 49.10; H, 6.94; N, 14.69.

Thiamine Thiazolone (XVIII)——To a solution of 2.4 g. of NaOH in 12 ml. of H_2O, 6.7 g. of B_1-HCl (I) was added and saturated with NaCl. 4.6 g. of 2,3-dihydroxypropyl thiosulfate (XXVII: $R=CH_2CH(OH)CH_2OH$) (prepared from α-monochlorohydrine (XXI) and sodium thiosulfate by the usual manner) was added under stirring. The oil was separated immediately, and allowed to stand for several days. The crystals separated from the oil were filtered and recrystallized from dil. EtOH to afford 0.1 g. of colorless needles, m.p. 233~235°(decomp.), which was identified with thiamine thiazolone (XVIII).

1-Chloro-3-dimethylcarbamoyloxy-2-propanol (XXV)——Under stirring and cooling in an ice bath, $COCl_2$ was passed into 110.5 g. of 1-chloro-2,3-propanediol for 4.5 hr., and the solution was kept overnight. The excess $COCl_2$ and the generated HCl were removed *in vacuo*. The residue was dissolved in 250 ml. of dry $CHCl_3$ and a solution of 40 g. of $N(C_2H_5)_3$ in 50 ml. of dry $CHCl_3$ was added. Into this solution, dry $(CH_3)_2NH$ was passed during 4 hr. and the solution was allowed to stand overnight in a refrigerater. This solution, after washing with H_2O and 2% AcOH, was dried overanhyd. $MgSO_4$ and evaporated. The oily residue was distilled at 106~108°/1.0 mm. Hg. Yield, 83.4 g. *Anal.* Calcd. for $C_6H_{12}O_3NCl$: C, 39.70; H, 6.62; N, 7.72; Cl, 19.55. Found: C, 39.26; H, 6.40; N, 6.11; Cl, 20.42.

1-Chloro-3-piperidinocarbonyloxy-2-propanol (XXVI)——XXVI was prepared in the same manner as above, except that piperidine was used instead of dimethylamine. A colorless oil was distilled at 135~140°/0.65 mm. Hg (Yield, 68.5%).

Thiamine 2-Hydroxy-3-dimethylcarbamoyloxypropyl Disulfide (XXVIII) Hydrochloride——To a solution of 30 g. of XXV in 60 ml. of EtOH, a solution of 40.9 g. of $Na_2S_2O_3 \cdot H_2O$ in 41 ml. of H_2O was added and the mixture was boiled for 5 hr. under stirring. Evaporation of the solvent gave crude Bunte's salt as a syrup. A portion (18.8 g.) of this syrup was added under stirring and cooling to 18 ml. of an aqueous solution of the Na salt of thiamine (prepared from 12.5 g. of I and 4.4 g. of NaOH). $CHCl_3$ (130 ml.) was then added and the solution was stirred for 1 hr. The $CHCl_3$ layer was separated, washed with H_2O, dried over anhyd. $MgSO_4$, and evaporated to dryness. The oily residue was washed with Et_2O, treated with EtOH-HCl to afford the hydrochloride, which, after crystallization from Me_2CO-Et_2O and then from AcOEt-MeOH, formed colorless prisms, m.p. 122~123°(decomp.)(2.0 g.). This gave a negative, but, after treatment with cysteine, a positive thiochrome reaction. IR: ν_{max}^{Nujol} 1700 cm^{-1}(C=O). *Anal.* Calcd. for $C_{18}H_{29}N_5O_5S_2 \cdot HCl$: C, 43.59; H, 6.05; N, 14.13; S, 12.92; Cl, 7.17. Found: C, 43.27; H, 6.17; N, 13.97; S, 13.26; Cl, 7.20.

O-Ethoxycarbonylthiamine 2-Hydroxy-3-dimethylcarbamoyloxypropyl Disulfide (XXIX) Hydrochloride——This compound was obtained as a colorless syrup from 10 g. of V, 46 ml. of 5% NaOH and 20 g. of the thiosulfate (XXVII: $R=CH_2CH(OH)CH_2OCON(CH_3)_2$). Yield, 3.0 g. Rf 0.74. Thiochrome reaction was negative but became positive after teratment with cysteine. IR ν_{max}^{film} cm^{-1}: 1735(C=O at $O-\overset{O}{\overset{\|}{C}}-O$), 1703(C=O at $O-\overset{O}{\overset{\|}{C}}-N$). UV: λ_{max}^{EtOH} mμ 230,275.

Thiamine 2-Hydroxy-3-piperidinocarbonyloxypropyl Disulfide (XXX′) Hydrochloride——Prepared from 13.5 g. of I, NaOH 4.8 g., H_2O 20 ml. and 20 g. of the thiosulfate (XXVII: $R=CH_2CH(OH)CH_2OCON$ ) (prepared from XXVI and sodium thiosulfate). Colorless syrup; yield, 9.0 g. Rf 0.75. Thiochrome reaction was negative but positive after treatment with cysteine.

Thiamine 2-Ethoxycarbonylethyl Disulfide (XXXII)——To a cooled solution of 20 g. of I in 20 ml. of H_2O, a solution of 7.13 g. of NaOH in 10 ml. of H_2O was added. After 30 min. the solution was

saturated with NaCl, and treated with 250 ml. of $CHCl_3$ and 20.5 g. of sodium 2-ethoxycarbonylethyl thiosulfate. (XXVII: $R=CH_2CH_2COOC_2H_5$) (prepared from ethyl 3-chloropropionate and sodium thiosulfate). After 40 min., the $CHCl_3$ layer was separated, washed with H_2O, dried over anhyd. $MgSO_4$, and evaporated to dryness. The oily residue was crystallized from Et_2O; yield, 17.0 g. Recrystallization from Me_2CO gave colorless prisms, m.p. 110~111°(decomp.); yield, 13.0 g. Rf 0.70. Thiochrome reaction was negative but positive after treatment with cysteine. *Anal.* Calcd. for $C_{17}H_{26}O_4N_4S_2$: C, 49.27; H, 6.32; N, 13.52. Found: C, 49.49; H, 6.49; N, 13.14.

O-Ethoxycarbonylthiamine 2-Ethoxycarbonylethyl Disulfide (XXXIII) Hydrochloride——To a solution of 2.3 g. of NaOH in 48 ml. of H_2O, 10 g. of V was added and the solution was stirred for 10 min. at room temperature. After saturation with NaCl, 1 ml. of 10% NaOH and 9 g. of sodium 2-ethoxycarbonylethyl thiosulfate (XXVII: $R=CH_2CH_2COOC_2H_5$) were added under cooling and stirring. The separated oil was extracted with 130 ml. of $CHCl_3$. The extract was washed successively with H_2O, 2% AcOH, and 10% HCl and, after drying over anhyd. $MgSO_4$, evaporated to dryness. The oily residue was crystallized from Et_2O and then from Me_2CO to form colorless needles, m.p. 105~110° (decomp. at 125°); yield, 0.7 g. Rf 0.86. Thiochrome reaction was negative, but positive after treatment with cysteine. *Anal.* Calcd. for $C_{20}H_{30}N_4O_6S_2 \cdot HCl \cdot H_2O$: C, 45.20; H, 6.21; N, 10.54. Found: C, 45.39; H, 6.21; N, 10.36.

1-Chloro-2-ethoxycarbonyloxyethane (XXX)——$COCl_2$ was passed under stirring and cooling into 175 g. of ethylenechlorohydrin for 7 hr. After standing overnight at room temperature, the excess $COCl_2$ and the generated HCl were removed *in vacuo*. The residue was treated with 150 ml. of abs. EtOH and the solution was stirred for 5 hr. and allowed to stand for 2 days. Evaporation of the EtOH gave a brown oily residue, which was taken up in benzene and washed with 5% $NaHCO_3$ then H_2O, dried over anhyd. $MgSO_4$, and evaporated. The oily residue was distilled at 92~98°/40 mm. Hg (86.9 g.) and 100°/40 mm. Hg (91.5 g.). *Anal.* Calcd. for $C_5H_9O_3Cl$: C, 39.40; H, 5.90; Cl, 23.30. Found: C, 39.44; H, 5.86; Cl, 23.46.

Thiamine 2-Ethoxycarbonyloxyethyl Disulfide (XXXV: $R'=COOC_2H_5$) Hydrochloride——A solution of 47.8 g. of $Na_2S_2O_3 \cdot 5H_2O$ in 50 ml. of H_2O was treated with a solution of 29.4 g. of XXX in 60 ml. of EtOH in the usual manner. Crude Bunte's salt (XXVII: $R=CH_2CH_2OCOOC_2H_5$) was obtained as a colorless crystalline mass (27.4 g.). A portion (5 g.) of this was added to a solution of thiamine sodium salt (prepared from 3.37 g. of I and 1.2 g. of NaOH) in 6 ml. of H_2O. The separated oil was extracted with 80 ml. of $CHCl_3$, and the extract was washed with H_2O, dried over anhyd. $MgSO_4$, and evaporated to dryness. The residue was washed with Et_2O and treated with EtOH-HCl to convert it into the hydrochloride, which, after crystallization from MeOH-Me_2CO, formed colorless prisms, m.p. 158~160° (decomp.); yield, 0.6 g. Rf 0.70. Thiochrome reaction was negative but positive after treatment with cysteine. *Anal.* Calcd. for $C_{17}H_{26}O_5N_4S_2 \cdot HCl$: C, 43.80; H, 5.79; N, 12.00. Found: C, 43.76; H, 5.90; N, 11.55.

O-Ethoxycarbonylthiamine 2-Ethoxycarbnoyloxyethyl Disulfide (XXXVI) Hydrochloride——Prepared from 10 g. of V, 2.4 g. of NaOH, 49 ml. of H_2O and 10 g. of crude Bunte's salt (XXVII: $R=CH_2CH_2OCOOC_2H_5$) as described above. Colorless needles, m.p. 105° (decomp. at 155°); yield, 0.55 g. Rf 0.81. Thiochrome reaction was negative but positive after treatment with cysteine. *Anal.* Calcd. for $C_{20}H_{30}O_7N_4S_2 \cdot HCl$: C, 44.60; H, 5.76; N, 10.40. Found: C, 44.13; H, 5.98; N, 9.96.

O-Ethoxycarbonylthiamine 2-Hydroxyethyl Disulfide (XXXV″)——To a solution of 2.3 g. of NaOH in 50 ml. of H_2O, 10 g, of V was added and the solution was stirred for 15 min. at room temperature. After saturation with NaCl, 1 ml. of 10% NaOH and 13 g. of sodium 2-hydroxyethyl thiosulfate (XXVII: $R=CH_2CH_2OH$)[5] were added under cooling and stirring. The separated oil was extracted with 70 ml. of $CHCl_3$. The extract was successivey washed with H_2O and 2% AcOH, after drying over anhyd. $MgSO_4$, evaporated to dryness. The oily residue was crystallized from Et_2O and from Me_2CO to form colorless prisms, m.p. 125~126°(decomp.); yield, 1.9 g. Rf 0.71. Thiochrome reaction was negative but positive after treatment with cysteine. *Anal.* Calcd. for $C_{17}H_{26}O_5N_4S_2$: C, 47.50; H, 6.05; N, 13.02. Found: C, 47.35; H, 6.29; N, 13.19.

S-Ethoxycarbonyl-(2-O-tetrahydropyranyl)thiamine (XXXVII)——To a suspension of V in 10 ml. of 2,3-dihydropyran, 0.35 ml. of conc. HCl was added. After exothermic reaction had subsided, stirring was continued for 2.5 hr. at room temperature. Separated crystals were filtered, washed with Et_2O and dissolved in H_2O. When this solution was made alkaline by addition of aq. NH_4OH, crystals were separated. Recrystallization from dil. EtOH gave 0.85 g. of colorless prisms, m.p. 73~74°. Rf 0.81. Thiochrome reaction was negative but positive after treatment with NaOH. *Anal.* Calcd, for $C_{20}H_{30}O_5N \cdot H_2O$: C, 52.62; H, 7.04; N, 12.22. Found: C, 52.24; H, 7.18; N, 12.22.

S-Butoxycarbonyl-O-(2-tetrahydropyranyl)thiamine (XXXVIII) Hydrochloride——To a suspension of 0.5 g. of S-butoxycarbonylthiamine (VI) in 5 ml. of 2,3-dihydropyran, 0.17 ml. of conc. HCl was added under stirring. After exothermic reactionhad ended, stirring was continued for 4 hr. Separated crystals were filtered and recrystallized from EtOH-Et_2O to form colorless prisms m.p. 125°; yield, 0.4 g. Rf 0.81. *Anal.* Calcd. for $C_{22}H_{34}O_5N_4S \cdot HCl$: C, 52.50; H, 7.01; N, 11.14. Found: C, 52.10; H, 7.22; N, 11.36.

S-(Ethylthio)carbonyl-O-(2-tetrahydropyranyl)thiamine(XXXIX)——To a solution of 0.5 g. of S-(ethyl-

thio)carbonylthiamine (XLI) in 5 ml. of dihydropyran, 0.18 ml. of conc. HCl was added under stirring. After exothermic reaction had subsided, stirring was continued for 3 hr. Separated crystals were filtered, dissolved in a small amount of H_2O, and the solution was made alkaline and extracted with $CHCl_3$. The extract was dried over anhyd. $MgSO_4$ and evaporated. The oily residue was purified by chromatography on alumina and crystallized from petr. ether to form colorless prisms, m.p. 102~103°; yield, 0.3 g. Rf 0.76. *Anal.* Calcd. for $C_{20}H_{30}O_4N_4S_2$: C, 52.85; H, 6.65; N, 12.33. Found : C, 52.66; H, 6.98; N, 12.42.

O-(2-Tetrahydropyranyl)thiamine Propyl Disulfide (XL)——Prepared from 0.5 g. of Ⅷ, 5 ml. of 2,3-dihydropyran and 0.18 ml. of conc. HCl as described above. Colorless prisms, m.p. 80°; yield, 0.3 g, Rf 0.84. *Anal.* Calcd. for $C_{20}H_{32}O_3N_4S_2$: C, 54.53; H, 7.32; N, 12.72. Found : C, 54.45; H, 7.55; N, 12.35.

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Summary

The new thiamine derivatives, O-substituted derivatives of thiamine propyl disulfide, disulfide derivatives of thiamine and 2-hydroxy-3-carbamoyloxypropyl, 2-ethoxycarbonylethyl, 2-ethoxycarbonyloxyethyl, and their O-substituted derivatives were prepared. Also, O-2-tetrahydropyranyl derivatives of S-alkoxycarbonyl thiamine and thiamine propyl disulfide were prepared, and their primary screening tests were made.

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215. Shirō Takahashi and Hideo Kanō : Benzimidazole N-Oxides. I. The Structure of Benzimidazole N-Oxide and Synthesis of its Derivatives.

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Since the report by Ochiai[1] in 1942 on the synthesis and characterisic reactivity of pyridine N-oxide, many interesting studies on six-membered heteroaromatic N-oxides have been carried out. However, there are only a few reports on five-membered N-oxides. It appeared of interest to investigate syntheses and reactivities of benzimidazole N-oxide, the structure of which involves a five-membered heteroaromatic N-oxide. This paper, the first of a series, deals with the structure of benzimidazole N-oxide and synthesis of its derivatives.

Benzimidazole N-oxide was first synthesized by reduction of 2′-nitroformanilide with ammonium sulfide by von Niementowski.[2] He also prepared 2,6-dimethylbenzimidazole 3-oxide by dehydrobromination of 2,3-dibromo-2,6-dimethyl-2,3-dihydrobenzimidazole with potassium hydroxide.[3] Recently, Hayashi and Iijima[4] obtained 2-phenylbenzimidazole 3-oxide from 2-phenylquinoxaline 4-oxide by treatment with hydrogen

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