

78. Akira Takamizawa, Kentaro Hirai, Yoshio Hamashima, and
Machiko Hata : Studies on the Pyrimidine Derivatives. XXX.*¹
Syntheses and Reactions of O-(2-Tetrahydropyranyl)-
thiamine, O-Tritylthiamine, S-Acylthiamine,
and S-Alkoxy carbonylthiamine.

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

During the course of an investigation of S-alkoxycarbonyl and S-carbamoyl-thiamine derivatives (I), the authors¹⁾ found that the alkoxy carbonyl or carbamoyl group readily migrate to the hydroxyl group in the molecule. To prevent this migration, the syntheses of O-(2-tetrahydropyranyl)thiamine (II) and O-tritylthiamine (III), in which the substituents would be readily removed by acid, were attempted.

Previously,²⁾ it has been reported some information about the synthesis of thiamine by treatment of 3-(2-methyl-4-amino-5-pyrimidyl)methyl-4-methyl-5-(2-hydroxyethyl)-4-thiazoline-2-thione (SB₁) (IV) with hydrogen peroxide. The course of this reaction was applied to the syntheses of II and III.

Upon treatment of SB₁ (IV) with 2,3-dihydro-4H-pyran in the presence of hydrochloric acid, O-(2-tetrahydropyranyl)SB₁ (V) was produced. The latter reacted with hydrogen peroxide in hydrochloric acid solution to produce thiamine hydrochloride (VI) in almost quantitative yield. When the oxidation was carried out in acetic acid solution in the presence of barium acetate to remove the forming sulfuric acid as barium sulfate, O-(2-tetrahydropyranyl)thiamine (II) was produced and separated as the thiocyanate, m.p. 119°, in good yield. A similar procedure on SB₁ in acetic acid solution, however, gave an unfavorable result.³⁾

SB₁ (IV) reacted with trityl chloride in pyridine to give O-trityl SB₁ (VII), which was oxidized with hydrogen peroxide in the presence of barium acetate to produce O-tritylthiamine (III), which was separated from the solution as its thiocyanate, m.p. 148°.

The condensation of 4-methyl-5-(2-trityloxyethyl)thiazole (VIII) with 2-methyl-4-amino-5-chloromethylpyrimidine (IX) or the bromomethyl compound (X) gave thiamine accompanied with elimination of the trityl group, but condensation with the 5-iodomethyl compound (XI) gave O-tritylthiamine (III), the thiocyanate of which was found to be identical with the product derived from VII.

Reaction of III with alkyl chloroformate or acyl chloride in alkaline solution gave S-alkoxycarbonyl-O-tritylthiamine (XII~XIV) and S-acyl-O-tritylthiamine (XV, XVI), respectively. In a similar way, S-ethoxycarbonyl-O-(2-tetrahydropyranyl)thiamine (XVII) and S-acyl-O-(2-tetrahydropyranyl)thiamine (XVIII, XIX) were prepared from III. XVII was found to be identical with the product obtained previously⁴⁾ from S-ethoxycarbonylthiamine (Ia).

This route is a new and convenient method to prepare XVII, which has already been reported⁴⁾ to show a high absorption from intestine and high thiamine level in blood for a long time, to the same extent as in the case of O,S-bis(ethoxycarbonyl)thiamine (XXII).

*¹ Part XXIX. A. Takamizawa, K. Hirai, Y. Sato, K. Tori : J. Org. Chem., in contribution (to be published in July, 1964).

*² Fukushima-ku, Osaka (高見沢 映, 平井健太郎, 浜島好男, 畠 町子).

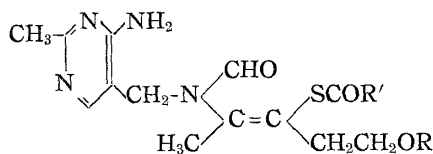
1) A. Takamizawa, K. Hirai, Y. Hamashima : This Bulletin, **10**, 1107 (1962).

2) A. Takamizawa, Y. Sato, S. Nakajima, T. Ishiba : Ann. Rep. Shionogi Res. Lab., **12**, 48 (1962).

3) T. Matsukawa, T. Iwatsu : Yakugaku Zasshi, **71**, 1215 (1951).

4) A. Takamizawa, K. Hirai, Y. Hamashima, H. Sato : This Bulletin, **11**, 1368 (1963).

TABLE I.



Compd.	R	R'	m.p. (decomp.) (°C)	Yield (%)	Rf ^{a)}	Solvent of cryst.	Analyses (%)							
							Calcd.				Found			
							C	H	N	S	C	H	N	S
XII	C(C ₆ H ₅) ₃	OC ₂ H ₅	89	29	0.79	Et ₂ O	68.43	6.08	9.38	5.37	68.53	6.00	9.80	5.66
XIII	"	OC ₄ H ₉	102~ 103	30	0.90	Et ₂ O- EtOH	69.20	6.45	8.97	5.13	69.02	6.22	8.91	5.03
XIV	"	OCH ₂ CH =CH ₂	156~ 157	36	0.90	"	69.06	5.96	9.21	5.27	68.62	6.51	9.36	5.57
XV	"	CH ₃	118~ 119	37	0.80	Et ₂ O	69.94	6.65	9.89	5.66	69.64	6.55	9.36	5.58
XVI	"	C ₆ H ₅	135~ 136	36	0.73	Et ₂ O- EtOH	74.48	5.92	9.14	5.23	74.40	5.91	9.27	5.66
XVII		OC ₂ H ₅ ⁴⁾	72~ 74	78	0.83	dil. EtOH								
XVIII	"	CH ₃	102~ 104	60	0.85	"	55.81	6.91	13.71	7.85	55.58	6.94	13.88	7.86
XIX	"	C ₆ H ₅ ⁵⁾	152~ 154	64	0.88	"	61.25	6.43	11.91	6.81	61.30	6.41	11.94	6.99

^{a)} See experimental.

Upon treatment on XII~XVI with hydrochloric acid, S-alkoxycarbonylthiamine (Ia, Ib, Ic) and S-acylthiamine (XXa, XXb) were readily obtained, respectively.

S-Alkoxycarbonylthiamine has been previously obtained⁶⁾ by the action of alkyl chloroformate on the thiol type thiamine, but it is known⁷⁾ that treatment with acid chloride yields mostly O,S-diacylthiamine and in a few cases S-acylthiamine (XX). Therefore, this seems to be a convenient method to obtain XX. On the other hand, XX was also successfully obtained by careful treatment of the sodium salt of thiamine in ethanol with acyl chloride at a low temperature. By this reaction, S-acetylthiamine (XXa) and S-benzoylthiamine (XXb) was also obtained, but by some changing the treatment of the reaction mixture, O-acetylthiamine chloride (XX') was yielded because of the large migrative activity of the S-acetyl group into the hydroxyl group in the molecule. XX' reacted with ethyl chloroformate yield O-acetyl-S-ethoxycarbonylthiamine (XXIXa).

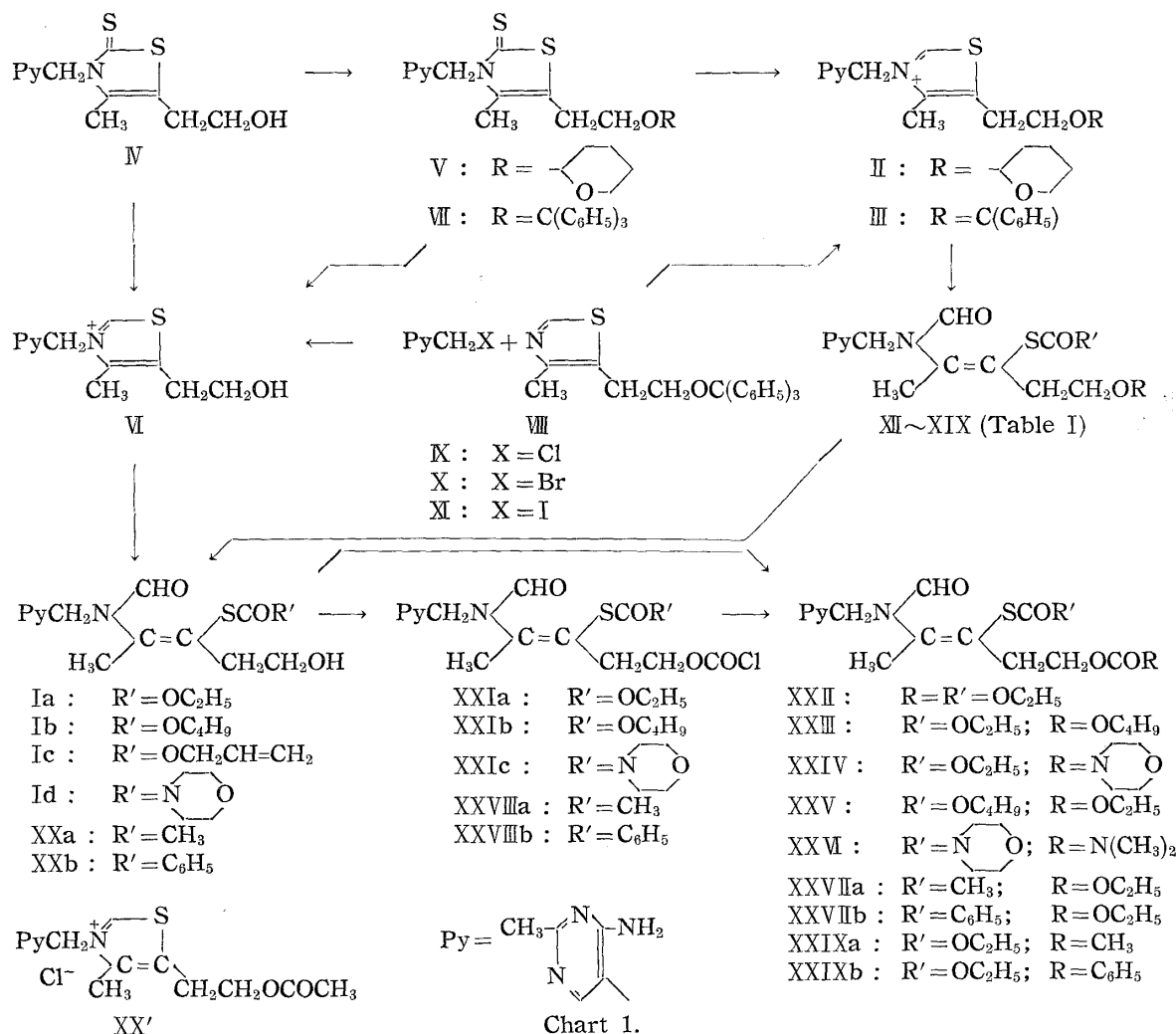
The reactions of phosgene with thiamine hydrochloride⁸⁾ and thiamine alkyl disulfide⁴⁾ were previously reported from this laboratory. This reaction was applied to Ia¹⁾ at ordinary pressure. Infrared spectrum of the product exhibited C=O and C-O bands arising from the OCOCl and the SCOO groups at 1767, 1722, and 1143 cm⁻¹, respectively, therefore it should be O-chlorocarbonyl-S-ethoxycarbonylthiamine (XXIa). Upon treatment with ethanol, butanol, and morpholine, it gave respectively O,S-bis(ethoxycarbonyl)thiamine (XXII),⁶⁾ O-butoxycarbonyl-S-ethoxycarbonylthiamine (XXIII),¹⁾ and O-morpholinocarbonyl-S-ethoxycarbonylthiamine (XXIV),⁸⁾ in good yield. In a similar fashion, phosgene reacted with S-butoxycarbonylthiamine (Ib)¹⁾ to give O-chlorocarbonyl-S-butoxycarbonylthiamine (XXIb), which was converted into O-ethoxycarbonyl-S-butoxycarbonylthiamine (XXV)¹⁾ by treatment with ethanol. Similarly, S-morpholinocarbonyl-

5) Japan patent publication No. 13482/1963.

6) A. Takamizawa, K. Hirai : This Bulletin, **10**, 1102 (1962).

7) T. Matsukawa, H. Kawasaki : Yakugaku Zasshi, **73**, 705 (1953); H. Kawasaki : *Ibid.*, **74**, 588, 1189 (1954); S. Yoshida : *Ibid.*, **74**, 933 (1954).

8) A. Takamizawa, K. Hirai, Y. Hamashima : This Bulletin, **11**, 882 (1963).



thiamine (Id)⁸⁾ reacted with phosgene to yield O-chlorocarbonyl-S-morpholinocarbonylthiamine (XXIc), which was converted into O-dimethylcarbamoyl-S-morpholinocarbonylthiamine (XXVI) by treatment with dimethylamine. XX was also converted into S-acyl-O-alkoxycarbonylthiamine (XXVII) *via* S-acyl-O-chlorocarbonylthiamine (XXVIII). This is a convenient method to introduce the alkoxycarbonyl or carbamoyl group into the hydroxyl group in S-alkoxycarbonyl, S-carbamoyl, or S-acylthiamine without S→O rearrangement. In alkaline solution, however, S-acylthiamine (XX) reacted with alkyl chloroformate to give O-acyl-S-alkoxycarbonylthiamine (XXIX) by S→O rearrangement of the acyl group. XXVII was also obtained from S-alkoxycarbonylthiamine (I) by the action of acyl chloride in alkaline solution and the identity with the product obtained from XX was confirmed.

O,S-Bis(ethoxycarbonyl)thiamine (XXII) was also readily obtained from XVII directly by the reaction of phosgene in chloroform solution with subsequent treatment with ethanol. It should be noted that this method is useful in obtaining pure XXII in a good yield.

Experimental^{*3}

O-(2-Tetrahydropyranyl)SB₁ (V)—To a suspension of 3 g. of SB₁ (IV) in 9 g. of 2,3-dihydro-4H-

^{*3} All melting points are uncorrected. Paper chromatography, Toyo Roshi No. 50, BuOH-AcOH-H₂O (4:1:5), ascending method.

pyran, 1.05 ml. of conc. HCl was added under cooling. After the exothermic reaction had subsided, stirring was continued for 0.5 hr. and the separated crystals were filtered. The crystals were dissolved in a small amount of H₂O and the solution was made basic with NH₄OH, and extracted with CHCl₃. The undissolved material (N, 0.5 g.) was filtered off. The CHCl₃ extract was washed with H₂O, dried over MgSO₄ and evaporated to leave a syrup. Et₂O was added to the residue and the mixture allowed to stand at room temperature to give V (2.55 g., 66%) as crystalline powder. Recrystallization from EtOH gave colorless prisms, m.p. 172° (decomp.). Rf 0.78. UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (log ϵ): 232 (4.09), 278 (3.76), 322 (4.17). *Anal.* Calcd. for C₁₇H₂₄N₄O₂S₂: C, 53.66; H, 6.36; N, 14.73; S, 16.85. Found: C, 53.64; H, 6.43; N, 14.84; S, 16.74.

Thiamine Hydrochloride (VI)—To a solution of 0.38 g. of V in 0.2 ml. of 20% HCl and 2.0 ml. of H₂O, 0.325 ml. of 34.5 w/v % H₂O₂ was added under stirring and cooling. After 4 hr., a solution of 0.244 g. of BaCl₂·2H₂O in 1 ml. of H₂O was added to the reaction mixture. To remove excess BaCl₂, 10% H₂SO₄ was added and separated BaSO₄ was filtered off. The filtrate was concentrated at below 30°, and 30 ml. of 99% EtOH was added to the concentrated solution. After standing overnight in a refrigerator, the separated crystals were filtered. Yield, 0.333 g. (98%), m.p. 241~244° (decomp.). This was proved to be identical with the authentic sample of thiamine hydrochloride (VI) by comparison of IR spectra.

O-(2-Tetrahydropyranyl)thiamine (II) Thiocyanate—To a solution of 2.29 g. of V in 25 ml. of 25% AcOH, 2.1 g. of Ba(OH)₂·8H₂O was added. Under stirring and cooling, 2.0 ml. of 34.5 w/v % H₂O₂ was added to the solution. After 4 hr., BaSO₄ was separated out by centrifugation. The supernatant clear solution was separated and adjusted to pH 5 by addition of saturated NaOH solution. To this solution, 1.1 g. of NH₄SCN was added and stirred. The separated crystals were collected and recrystallized from EtOH to give 2.18 g. (85%) of colorless needles, m.p. 119° (decomposed at 150°). Rf 0.49 (positive thiochrome reaction). *Anal.* Calcd. for C₁₈H₂₅N₅O₂S₂·H₂O: C, 50.80; H, 6.39; N, 16.46; S, 15.07. Found: C, 50.35; H, 6.53; N, 16.25; S, 15.08.

O-Trityl SB₁ (VII)—A mixture of 3.6 g. of SB₁(N), 3.4 g. of triphenyl chloromethane and 20 ml. of anhyd. pyridine was heated at 120~130° for 1 hr. The reaction mixture was poured into 150 ml. of ice H₂O, and the separated oil was extracted with CHCl₃. The CHCl₃ extract was dried over MgSO₄ and evaporated to leave a syrup. Et₂O was added to the residue and the solidified crystals were filtered. Yield, 5.2 g. (80%). Recrystallization from EtOH gave colorless needles, m.p. 185°. Rf 0.83. *Anal.* Calcd. for C₃₁H₃₆ON₄S₂: C, 69.11; H, 5.51; N, 10.40. Found: C, 69.28; H, 5.85; N, 10.13.

O-Tritylthiamine (III) Thiocyanate—To a solution of 5.39 g. of VII, 4.8 g. of Ba(OH)₂·8H₂O in 100 ml. of 50% AcOH, 4.6 ml. of 34.5 w/v % H₂O₂ was added under cooling and stirring. After 6 hr., the reaction mixture was adjusted to pH 5 by addition of 50% NaOH solution, and a solution of 26.5 g. of NH₄SCN in 30 ml. of H₂O was further added under stirring. The separated crystals were filtered and recrystallized from EtOH to give 2.553 g. (43.7%) of colorless needles, m.p. 145°. Rf 0.79 (positive thiochrome reaction). *Anal.* Calcd. for C₃₂H₃₁ON₅S₂·H₂O: C, 65.84; H, 5.70; N, 12.00; S, 10.99. Found: C, 65.68; H, 5.77; N, 11.49; S, 10.67.

4-Methyl-5-(2(trityloxyethyl)thiazole (VIII)—A mixture of 2.9 g. of 4-methyl-5-(2(hydroxyethyl)thiazole, 5.6 g. of triphenylchloromethane, and 35 ml. of anhyd. pyridine was heated at 110~120° for 1 hr. The reaction mixture was poured into ice H₂O, and extracted with CHCl₃. The CHCl₃ extract was dried over MgSO₄ and evaporated. The residue was recrystallized from benzene-petr. benzin to give 4.8 g. of colorless needles, m.p. 128~129°. *Anal.* Calcd. for C₂₅H₂₃ONS: C, 77.90; H, 6.01; N, 3.63; S, 8.32. Found: C, 77.63; H, 6.08; N, 3.84; S, 7.96. Picrate (from EtOH), yellow needles, m.p. 192~193°. *Anal.* Calcd. for C₃₁H₂₈O₈N₄S: C, 60.59; H, 4.27; N, 9.11; S, 5.21. Found: C, 60.57; H, 4.60; N, 9.33; S, 5.58.

2-Methyl-4-amino-5-iodomethylpyrimidine (XI) Hydriodide—To a solution of 5.2 g. of hydriodic acid in 50 g. of AcOH, 1.7 g. of 2-methyl-4-amino-5-ethoxymethylpyrimidine was added and refluxed for 2 hr. Separated crystals were filtered to yield 3.1 g. of colorless crystals, m.p. 210° (decomp.). Recrystallization from MeOH-Et₂O gave 2.4 g. of colorless prisms, m.p. 212° (decomp.). Rf 0.62. *Anal.* Calcd. for C₈H₉N₃I₂: C, 19.11; H, 2.41; N, 11.15; I, 67.31. Found: C, 19.27; H, 2.62; N, 11.07; I, 67.37.

Condensation of VIII and XI—A suspension of 1.6 g. of VIII and 0.8 g. of XI in 2 ml. of BuOH was heated at 120~125° for 15 min. Benzene and Et₂O were added to the reaction mixture and the separated crystals (1 g.) were filtered. On washing with H₂O, 0.5 g. of undissolved material was obtained. The undissolved material was recrystallize from EtOH to give colorless prisms, m.p. 186~187° (decomp.). Rf 0.70 (positive thiochrome reaction). This was converted into thiocyanate, m.p. 149~150°, which was proved to be identical with O-tritylthiamine (III) thiocyanate by comparison of IR spectra.

The H₂O solution was concentrated and the residue was recrystallized from MeOH-Et₂O to give 0.35 g. of thiamine hydriodide, m.p. 229° (decomp.).

General Procedure for Syntheses of O-Trityl-S-alkoxycarbonylthiamine (XII~XIV), O-Trityl-S-acylthiamine (XV, XVI), O-(2-Tetrahydropyranyl)-S-ethoxycarbonylthiamine (XVII), and O-(2-Tetrahydropyranyl)-S-acylthiamine (XVIII, XIX)—Under cooling, 0.01 mole of O-(2-tetrahydropyranyl)thiamine (II) thiocyanate or O-tritylthiamine (III) thiocyanate was dissolved in 10% NaOH containing 0.025 mole of NaOH and allowed to stand for 0.5 hr. at room temperature. To the solution, 0.02 mole of alkyl chloro-

formate or acyl chloride was added under cooling and stirring. An NaOH solution was added to maintain a basic reaction mixture. The separated oil was extracted with CHCl_3 , and the CHCl_3 extract was washed successively with H_2O , 5% AcOH , and H_2O . The CHCl_3 layer was dried over MgSO_4 ; CHCl_3 was evaporated and the residue was recrystallized from a suitable solvent. This reaction was similarly carried out in EtOH and EtONa solutions to give the products.

S-Ethoxycarbonylthiamine (Ia)⁶⁾—a) To 20 ml. of 20% HCl , 1.00 g. of XII was added under cooling and the separated crystals (triphenylcarbinol, m.p. 160°) were extracted with Et_2O . The HCl solution was neutralized with 10% NaOH and extracted with CHCl_3 . The CHCl_3 extract was dried over MgSO_4 , evaporated, and the residue was suspended in 4 ml. of EtOH . To this suspension, 1 ml. of conc. HCl was added and the clear solution evaporated *in vacuo* below 30° . The residue was added to 15 ml. of Me_2CO and the mixture allowed to stand overnight in a refrigerator to give colorless prisms, m.p. 176° (decomp.). Yield, 0.52 g. (80%). This was proved to be identical with S-ethoxycarbonylthiamine (Ia) hydrochloride⁶⁾ by comparison of IR spectrum.

b) To a solution of 0.457 g. of XVII in 2 ml. of EtOH , 0.18 ml. of 20% HCl was added and stirred for 2 hr. at room temperature. The solution was neutralized with 10% NaOH and extracted with CHCl_3 . CHCl_3 extract was dried over MgSO_4 , evaporated, and the residue was recrystallized from AcOEt to give 0.15 g. (42.2%) of Ia (free, m.p. $138\sim139^\circ$ (decomp.)).

S-Butoxycarbonylthiamine (Ib)⁶⁾—From 1.6 g. of XIII and 20 ml. of 20% HCl , 0.76 g. (71%) of Ib· HCl (m.p. 175° (decomp.)) was obtained by a similar procedure.

S-Allyloxycarbonylthiamine (Ic)⁶⁾—From 1.55 g. of XIV and 20 ml. of 20% HCl , 0.66 g. (47.8%) of Ic· HCl , m.p. $141\sim142^\circ$ (colorless needles, from MeOH-AcOEt), was obtained by a similar procedure. *Anal.* Calcd. for $\text{C}_{16}\text{H}_{22}\text{O}_4\text{N}_4\text{S}\cdot\text{HCl}$: C, 47.70; H, 5.75; N, 13.92. Found: C, 47.23; H, 5.88; N, 14.10.

S-Acetylthiamine (XXa)—a) One gram of XV was dissolved in 20 ml. of 5% EtOH-HCl and allowed to stand overnight in a refrigerator. The separated crystals were filtered, dissolved in dil. EtOH , neutralized with saturated NaHCO_3 solution, and allowed to stand in a refrigerator overnight. The separated needles were filtered to afford 0.23 g. (40%) of XXa, m.p. $136\sim137^\circ$ (decomp.). *Anal.* Calcd. for $\text{C}_{14}\text{H}_{20}\text{O}_3\text{N}_4\text{S}$: C, 51.84; H, 6.21; N, 17.27; S, 9.91. Found: C, 51.35; H, 6.50; N, 16.99; S, 9.87. NMR: 2.34 τ (NCHO), 2.11 τ (pyrimidine-H), (CDCl_3).

b) To a suspension of 5 g. of the Na salt of thiamine in 20 ml. of EtOH , AcCl was added dropwise under cooling at $-5\sim-10^\circ$. After 3 min., the reaction mixture was filtered, and Et_2O was added to the filtrate and allowed to stand at -20° , whereupon 1.25 g. of XXa was obtained.

S-Benzoylthiamine (XXb)⁹⁾—a) The solution of 1.00 g. of XVI in 10 ml. of 20% EtOH-HCl was allowed to stand overnight in a refrigerator. Separated crystals were filtered (m.p. $120\sim125^\circ$ (decomp.)), dissolved in dil. EtOH , and neutralized with NaHCO_3 solution. XXb was obtained as colorless prisms, m.p. $145\sim146^\circ$ (decomp.). Yield, 0.39 g. (62%). *Rf* 0.86. *Anal.* Calcd. for $\text{C}_{19}\text{H}_{22}\text{O}_3\text{N}_4\text{S}$: C, 59.05; H, 5.74; N, 14.50; S, 8.30. Found: C, 58.65; H, 5.01; N, 14.20; S, 8.35.

b) To a suspension of 5 g. of the Na salt of thiamine in 30 ml. of EtOH , BzCl was added under cooling at $-5\sim-10^\circ$. After 30 min., the mixture was filtered and washed with dil. EtOH to give 3.5 g. of XXb.

O-Acetylthiamine Chloride (XX')—To a suspension of 5 g. of the Na salt of thiamine in 20 ml. of EtOH , 0.93 g. of AcCl was added dropwise at $-5\sim-10^\circ$. After stirring for 5 min., the mixture was filtered and Et_2O added to the filtrate to separate the colorless oil, which gradually solidified. This was dissolved in MeOH and precipitated by the addition of Et_2O to give 3.2 g. of colorless crystals, m.p. 245° (decomp.). IR $\nu_{\text{max}}^{\text{NaCl}}$ cm^{-1} : 1732, 1662, 1241, 1222. *Anal.* Calcd. for $\text{C}_{14}\text{H}_{19}\text{O}_2\text{N}_4\text{SCl}$: C, 49.04; H, 5.59; N, 16.34; Cl, 10.34. Found: C, 48.30; H, 5.81; N, 16.68; Cl, 10.57.

O-Chlorocarbonyl-S-ethoxycarbonylthiamine (XXIa)—a) To a solution of 1.5 g. of Ia in 25 ml. of CHCl_3 , 10 ml. of 30% COCl_2 -toluene was added dropwise under cooling in an ice bath. After stirring at room temperature for 1.5 hr., the reaction mixture was concentrated *in vacuo* to give a syrupy product. IR $\lambda_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1767, 1143 (OCOC), 1722 (SCOO). This was used without purification in next process.

b) To a solution of 0.5 g. of XVII in 5 ml. of CHCl_3 , 2 ml. of 30% COCl_2 -toluene was added dropwise and the mixture treated as above to afford XXIa as a syrupy product.

O,S-Bis(ethoxycarbonyl)thiamine (XXII)—a) To crude XXIa obtained from 1.5 g. of Ia, 15 ml. of abs. EtOH was added, the mixture warmed at 75° for 1 hr. and allowed to stand overnight at room temperature. The reaction mixture was concentrated *in vacuo* and the residue was extracted with CHCl_3 . The CHCl_3 extract was shaken with 10 ml. of 15% HCl and the CHCl_3 layer was dried over MgSO_4 . Evaporation of CHCl_3 gave a syrupy product, which was gradually solidified by addition of Me_2CO . Recrystallization from $\text{Me}_2\text{CO-AcOEt}$ gave XXII hydrochloride hydrate,⁶⁾ m.p. 121° (decomp.). Yield, 1.55 g. (71%).

b) The same procedure from 1.5 g. of XVII as described above gave 1.23 g. (78%) of XXII hydrochloride hydrate.

9) S. Yoshida: Yakugaku Zasshi, **74**, 993 (1954); A. Ito: *Ibid.*, **82**, 883 (1962).

O-Butoxycarbonyl-S-ethoxycarbonylthiamine (XXIII)¹⁾—Ten milliliter of BuOH was added to crude XXIIa prepared from 1.5 g. of Ia, the mixture heated at 100° for 1 hr., and allowed to stand overnight at room temperature. The same treatment as described in the synthesis of XXII gave 0.7 g. (30.5%) of XXIII HCl, m.p. 126~127°. This was identical with the sample prepared by another method.¹⁾

O-Morpholinocarbonyl-S-ethoxycarbonylthiamine (XXIV)⁸⁾—To a solution of crude XXIIa prepared from 1.5 g. of Ia in 30 ml. of CHCl₃, 1.7 g. of morpholine was added under cooling. After standing at room temperature for 2 hr., the CHCl₃ solution was shaken with 15% HCl. The CHCl₃ layer was dried over MgSO₄ and evaporated to give 0.75 g. (31%) of XXIV hydrochloride hydrate. Recrystallization from Me₂CO-Et₂O gave colorless prisms, m.p. 116~117°.

O-Ethoxycarbonyl-S-butoxycarbonylthiamine (XXV)¹⁾—To a solution of 1.5 g. of Ib in 30 ml. of CHCl₃, 30% COCl₂-toluene was added under cooling. After stirring at room temperature for 1.5 hr., the solution concentrated *in vacuo* below 40°. To the oily residue (IR $\lambda_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1771, 1718, 1150, 1127), 20 ml. of EtOH was added and warmed at 60~70° for 1.5 hr. The residue obtained by removal of EtOH was dissolved in CHCl₃, shaken with 15% HCl, and the CHCl₃ layer concentrated after drying over MgSO₄. The residue was recrystallized from AcOEt-Et₂O to give 1.2 g. (61.7%) of XXV hydrochloride hydrate, m.p. 104~105° (decomp.).

O-Dimethylcarbamoyl-S-morpholinocarbonylthiamine (XXVI)—To a solution of 1.5 g. of Id⁸⁾ in 30 ml. of CHCl₃, 30% COCl₂-toluene was added under cooling. After stirring at room temperature for 2 hr., the reaction mixture was concentrated *in vacuo* below 40°.

The residue (IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1770, 1152) was dissolved in CHCl₃ and a CHCl₃ solution of dimethylamine was added dropwise until the solution became alkaline. After stirring at room temperature for 2 hr., the solution was washed with H₂O, dried over MgSO₄, and evaporated. To the residue Me₂CO was added, and separated crystals were filtered (0.9 g., 51%). Recrystallization from Me₂CO gave colorless needles, m.p. 156°. Rf 0.58. IR cm⁻¹: $\nu_{\text{C=O}}$ 1710, 1660 (Nujol). Anal. Calcd. for C₂₀H₃₀O₅N₆S: C, 51.49; H, 6.48; N, 18.02. Found: C, 51.38; H, 6.65; N, 17.61.

O-Ethoxycarbonyl-S-acetylthiamine (XXVIIa)—a) To a solution of 0.23 g. of Na in 30 ml. of EtOH, 3.54 g. of Ia was added and further 0.785 g. of AcCl was added under cooling. After 10 min. the reaction mixture (neutral) was concentrated *in vacuo* and dil. K₂CO₃ was added to the residue. The separated crystal (3.6 g., 91%, m.p. 128~129°) was filtered and recrystallized from Me₂CO-Et₂O to give 3.2 g. of colorless plates, m.p. 131°. IR $\lambda_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3420, 3280, 1740, 1701, 1262, 1118. Anal. Calcd. for C₁₇H₂₄O₅N₄S: C, 51.51; H, 6.10, N, 14.14. Found: C, 51.48; H, 6.25; N, 13.89.

b) To a solution of 0.5 g. of XXa in 30 ml. of CHCl₃, 5 ml. of 30% COCl₂-toluene was added under cooling. After stirring at room temperature for 30 min., the reaction mixture was concentrated *in vacuo* below 40°. To the residual hygroscopic crystals (IR $\lambda_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1774, 1705, 1665, 1152) 20 ml. of EtOH was added and the mixture warmed at 50° for 3 hr. The reaction mixture was concentrated *in vacuo* to a mass which was extracted with CHCl₃. The CHCl₃ extract was dried over MgSO₄, and then evaporated. The residue was recrystallized from Me₂CO-Et₂O to give 0.09 g. of colorless plates, m.p. 128°, which was proved to be identical with the sample obtained in a) by comparison of IR spectrum.

O-Ethoxycarbonyl-S-benzoylthiamine (XXVIIb)—a) To a solution of 0.325 g. of Na in 50 ml. of EtOH, 5 g. of Ia was added. After 10 min. BzCl was added dropwise under stirring, and stirring was continued for 1 hr. at 40°. The reaction mixture was concentrated *in vacuo*. The residue was washed successively with H₂O and Et₂O. Yield, 5.9 g. Recrystallization from Me₂CO gave colorless rhombics, m.p. 138° (decomp.). Rf 0.81. IR $\lambda_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1745, 1669, 1655, 1263, 1020. Anal. Calcd. for C₂₂H₂₆O₅N₄S: C, 57.63; H, 5.72; N, 12.22. Found: C, 57.39; H, 5.79; N, 12.10.

b) To a solution of 1.5 g. of XXb in 30 ml. of CHCl₃, 10 ml. of 30% COCl₂-toluene was added under cooling, and the mixture stirred for 1.5 hr. at room temperature. The reaction mixture was concentrated *in vacuo* to give colorless crystals, m.p. 59° (decomp.), (IR $\lambda_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3275, 1770, 1660, 1205, 1150). To the crude product, 20 ml. of EtOH was added and warmed at 50° for 1 hr. After standing overnight at room temperature, the solution was made basic by K₂CO₃ and extracted with CHCl₃. The CHCl₃ extract was dried over MgSO₄, and evaporated to give the colorless crystals. Washing with Et₂O gave 0.9 g. (50.5%) of colorless rhombics, which was identical with the sample prepared by the a) method.

O-Acetyl-S-ethoxycarbonylthiamine (XXIXa)—To a solution of 0.036 g. of Na in 10 ml. of EtOH, 0.5 g. of XXa was added and stirred for 5 min. at room temperature. To this solution, 0.167 g. of ethyl chloroformate was added and stirred for 1 hr. at room temperature. After concentration, the residue was made basic by K₂CO₃ and extracted with CHCl₃. The CHCl₃ extract was shaken with 15% HCl and dried over MgSO₄. Evaporation of the solvent gave the crystals, which was recrystallized from Me₂CO to give 0.25 g. (36%) of colorless plates, m.p. 99~103°. IR $\lambda_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3375, 3280, 3195, 1745, 1718, 1220, 1157. Anal. Calcd. for C₁₇H₂₄O₅N₄S·HCl·H₂O: C, 45.28; H, 6.04; N, 12.42. Found: C, 45.39; H, 6.35; N, 12.30.

O-Benzoyl-S-ethoxycarbonylthiamine (XXIXb)¹⁰⁾—To a solution of 0.071 g. of Na in 30 ml. of EtOH, 1.0 g. of XXb was added under cooling. To this solution, 0.337 g. of ethyl chloroformate was added and

10) K. Shirakawa: Yakugaku Zasshi, 74, 367 (1954).

stirred for 2 hr. at 45~48°. The separated crystals were filtered and washed with dil. NaOH and H₂O. Recrystallization from Me₂CO gave 1.0 g. of pale yellow rhombics, m.p. 146~148°. Rf 0.82. IR cm⁻¹: $\nu_{C=O}$ 1728, 1710 (Nujol). Anal. Calcd. for C₂₂H₂₆O₅N₄S: C, 57.63; H, 5.72; N, 12.22. Found: C, 57.86; H, 5.97; N, 11.98.

The authors are grateful to Prof. M. Tomita, Prof. S. Uyeo of Kyoto University, and Dr. K. Takeda, Director of this laboratory, for their encouragement throughout this work. The authors also thank Drs. Y. Matsui and K. Tori for IR and NMR spectral measurements, and the members of Analysis Room of this laboratory for elemental analyses.

Summary

O-(2-Tetrahydropyranyl)thiamine (II) and O-tritylthiamine (III) were prepared from O-(2-tetrahydropyranyl)SB₁ (V) and O-trityl SB₁ (VII), respectively. II and III were converted into S-alkoxycarbonyl or S-acyl derivatives, and removal of the trityl group gave S-acylthiamine. S-Alkoxycarbonyl and S-acylthiamine reacted with phosgene to give O-chlorocarbonyl derivatives, which were converted into O-alkoxycarbonyl- and O-carbamoylthiamine. These compounds were also obtained from S-alkoxycarbonyl- and S-carbamoylthiamine by S→O rearrangement. The combination of these reactions gave various kinds of thiol type thiamine derivatives.

(Received December 3, 1963)

[Chem. Pharm. Bull.]
12 (5) 564 ~ 569

UDC 547.288.4-38

79. Masaichiro Masui and Keiko Hotta: *n*-Butyraldoxime Complexes of Copper (II), Nickel (II), Cobalt (II), and Manganese (II).

(Faculty of Pharmaceutical Sciences, Osaka University*¹)

A simple aldoxime, except formaldoxime,¹⁾ and a ketoxime are said to react with copper, nickel and cobalt salts to form an addition compound, [X₂M(←HON=CH-R)_n],²⁾ where *n* is 2 or 4, but in the simple aliphatic series, only acetaldoxime,²⁾ acetoxime³⁾ and isobutyraldoxime²⁾ are the examples reported, and only very little have been studied on the compounds. We found that *n*-butyraldoxime reacts with not only copper (II), nickel (II) and cobalt (II) chlorides, but also with manganese (II) chloride under an exothermic reaction, and forms a crystalline complex with relatively low melting point. The color and the solubility of the complexes, which are non-electrolytes, are quite similar to those described,²⁾ and the value of *n* in the above equation is 4. Further has been studied spectroscopically.

Experimental

Reagents—*n*-Butyraldoxime was prepared by usual method and purified by repeating distillation. Extra pure grade Cu (II), Ni (II), Co (II) and Mn (II) chlorides with crystalline water were dehydrated by gentle heating in a casserole with a small flame, and used as soon as possible after being cool.

*¹ Toneyama, Toyonaka, Osaka-fu (榑井雅一郎, 堀田恵子).

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3) *Idem*: *Ibid.*, 60B, 2310 (1927).