[Chem. Pharm. Bull. 12 (5) 558 ~ 564] UDC 577.164.11:547.853

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-Alkoxycarbonylthiamine.

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

During the course of an investigation of S-alkoxycarbonyl and S-carbamoyl-thiamine derivatives (I), the authors[1] found that the alkoxycarbonyl 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 (SB_1) (IV) with hydrogen peroxide. The course of this reaction was applied to the syntheses of II and III.

Upon treatment of SB_1 (IV) with 2,3-dihydro-4*H*-pyran in the presence of hydrochloric acid, O-(2-tetrahydropyranyl)SB_1 (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 SB_1 in acetic acid solution, however, gave an unfavorable result.[3]

SB_1 (IV) reacted with trityl chloride in pyridine to give O-trityl SB_1 (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 previously[4] from S-ethoxycarbonylthiamine (Ia).

This route is a new and convenient method to prepare XVII, which has already been reported[4] 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).

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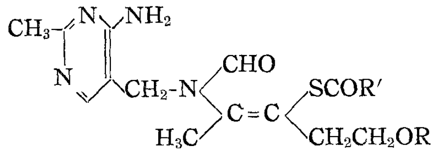
*1 Part XXIX. A. Takamizawa, K. Hirai, Y. Sato, K. Tori : J. Org. Chem., in contribution (to be published in July, 1964).

*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. C	H	N	S	Found C	H	N	S
XII	$C(C_6H_5)_3$	OC_2H_5	89	29	0.79	Et_2O	68.43	6.08	9.38	5.37	68.53	6.00	9.80	5.66
XIII	〃	OC_4H_9	102～103	30	0.90	Et_2O–EtOH	69.20	6.45	8.97	5.13	69.02	6.22	8.91	5.03
XIV	〃	$OCH_2CH{=}CH_2$	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_2O	69.94	6.65	9.89	5.66	69.64	6.55	9.36	5.58
XVI	〃	C_6H_5	135～136	36	0.73	Et_2O–EtOH	74.48	5.92	9.14	5.23	74.40	5.91	9.27	5.66
XVII	–⟨O⟩ (tetrahydrofurfuryl ring)	OC_2H_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_6H_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 obtained[6] by the action of alkyl chloroformate on the thiol type thiamine, but it is known[7] 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 hydrochloride[8] and thiamine alkyl disulfide[4] were previously reported from this laboratory. This reaction was applied to Ia[1] 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).

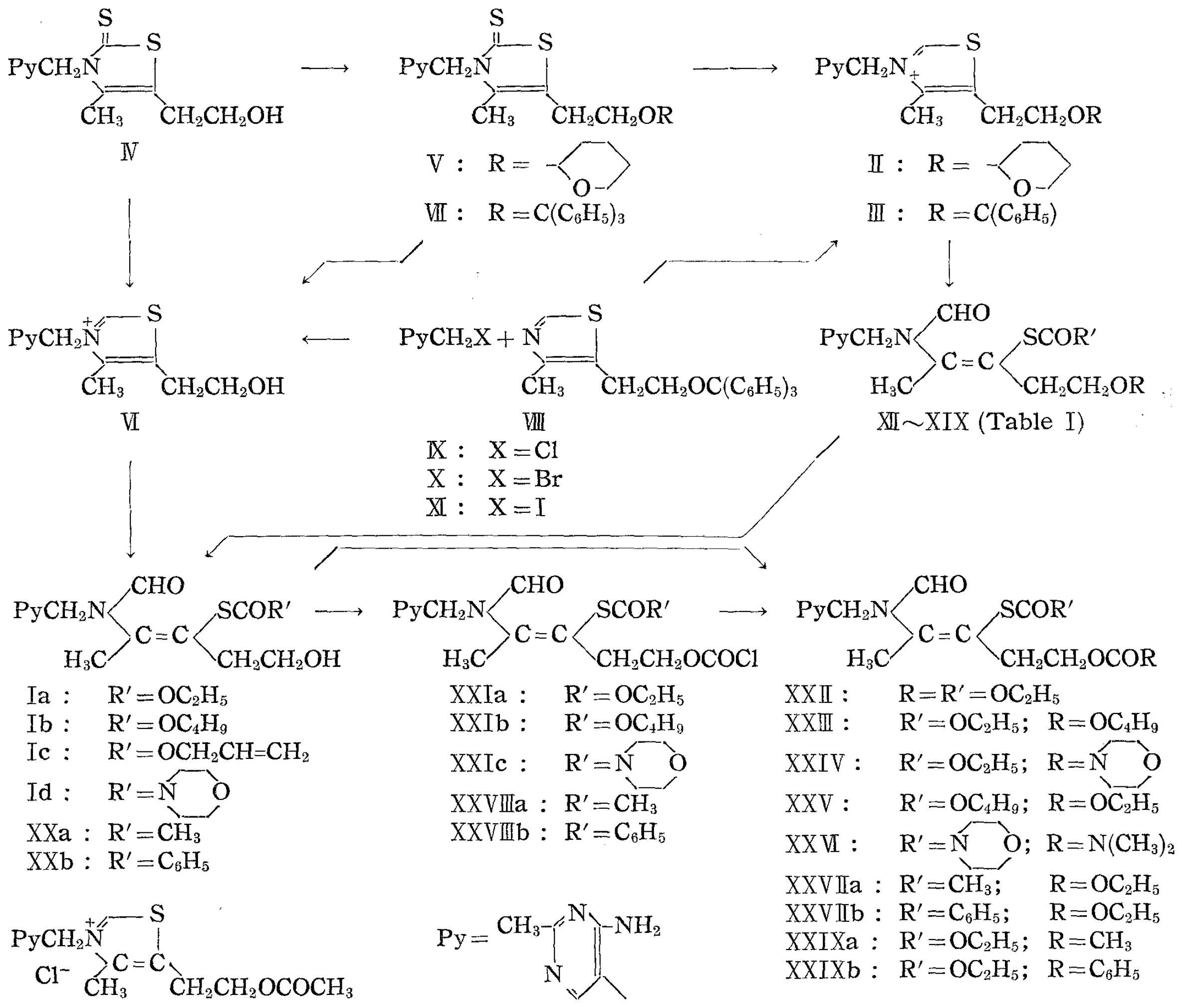


Chart 1.

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)SB$_1$ (V)——To a suspension of 3 g. of SB$_1$ (IV) in 9 g. of 2,3-dihydro-4*H*-

*[3] All melting points are uncorrected. Paper chromatography, Toyo Roshi No. 50, BuOH-AcOH-H_2O (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 H_2O and the solution was made basic with NH_4OH, and extracted with $CHCl_3$. The undissolved material (Ⅳ, 0.5 g.) was filtered off. The $CHCl_3$ extract was washed with H_2O, dried over $MgSO_4$ and evaporated to leave a syrup. Et_2O 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 λ_{max}^{EtOH} mμ (log ε): 232 (4.09), 278 (3.76), 322 (4.17). *Anal.* Calcd. for $C_{17}H_{24}N_4O_2S_2$: 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 H_2O, 0.325 ml. of 34.5 w/v % H_2O_2 was added under stirring and cooling. After 4 hr., a solution of 0.244 g. of $BaCl_2 \cdot 2H_2O$ in 1 ml. of H_2O was added to the reaction mixture. To remove excess $BaCl_2$, 10% H_2SO_4 was added and separated $BaSO_4$ 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 $Ba(OH)_2 \cdot 8H_2O$ was added. Under stirring and cooling, 2.0 ml. of 34.5 w/v % H_2O_2 was added to the solution. After 4 hr., $BaSO_4$ 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 NH_4SCN 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 $C_{18}H_{25}N_5O_2S_2 \cdot H_2O$: 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 SB_1 (VII)——A mixture of 3.6 g. of SB_1 (Ⅳ), 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 H_2O, and the separated oil was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and evaporated to leave a syrup. Et_2O 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 $C_{31}H_{30}ON_4S_2$: 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 $Ba(OH)_2 \cdot 8H_2O$ in 100 ml. of 50% AcOH, 4.6 ml. of 34.5 w/v % H_2O_2 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 NH_4SCN in 30 ml. of H_2O 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. 148°. Rf 0.79 (positive thiochrome reaction). *Anal.* Calcd. for $C_{32}H_{31}ON_5S_2 \cdot H_2O$: 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 H_2O, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ 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 $C_{25}H_{23}ONS$: 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 $C_{31}H_{26}O_8N_4S$: 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 $MeOH-Et_2O$ gave 2.4 g. of colorless prisms, m.p. 212°(decomp.). Rf 0.62. *Anal.* Calcd. for $C_6H_9N_3I_2$: C, 19.11; H, 2.41; 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 Et_2O were added to the reaction mixture and the separated crystals (1 g.) were filtered. On washing with H_2O, 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 H_2O solution was concentrated and the residue was recrystallized from $MeOH-Et_2O$ 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 chloroformate 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) hydrochloride[6] 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. 138~139° (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. 141~142° (colorless needles, from MeOH-AcOEt), was obtained by a similar procedure. *Anal.* Calcd. for $C_{16}H_{22}O_4N_4S \cdot HCl$: 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. 136~137° (decomp.). *Anal.* Calcd. for $C_{14}H_{20}O_3N_4S$: 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 $-5\sim-10°$. 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. 120~125° (decomp.)), dissolved in dil. EtOH, and neutralized with $NaHCO_3$ solution. XXb was obtained as colorless prisms, m.p. 145~146° (decomp.). Yield, 0.39 g. (62%). Rf 0.86. *Anal.* Calcd. for $C_{19}H_{22}O_3N_4S$: 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 $-5\sim-10°$. 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 $-5\sim-10°$. 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 ν_{max}^{Nujol} cm^{-1}: 1732, 1662, 1241, 1222. *Anal.* Calcd. for $C_{14}H_{19}O_2N_4SCl$: 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 $\lambda_{max}^{CHCl_3}$ cm^{-1}: 1767, 1143 (OCOCl), 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 Me_2CO-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 XXIa 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 XXIa prepared from 1.5 g. of Ia in 30 ml. of $CHCl_3$, 1.7 g. of morpholine was added under cooling. After standing at room temperature for 2 hr., the $CHCl_3$ solution was shaken with 15% HCl. The $CHCl_3$ layer was dried over $MgSO_4$ and evaporated to give 0.75 g. (31%) of XXIV hydrochloride hydrate. Recrystallization from Me_2CO-Et_2O 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 $CHCl_3$, 30% $COCl_2$-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 $\lambda_{max}^{CHCl_3}$ 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 $CHCl_3$, shaken with 15% HCl, and the $CHCl_3$ layer concentrated after drying over $MgSO_4$. The residue was recrystallized from AcOEt-Et_2O 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 Id[8] in 30 ml. of $CHCl_3$, 30% $COCl_2$-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 $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1152) was dissolved in $CHCl_3$ and a $CHCl_3$ solution of dimethylamine was added dropwise until the solution became alkaline. After stirring at room temperature for 2 hr., the solution was washed with H_2O, dried over $MgSO_4$, and evaporated. To the residue Me_2CO was added, and separated crystals were filtered (0.9 g., 51%). Recrystallization from Me_2CO gave colorless needles, m.p. 156°. Rf 0.58. IR cm^{-1}: $\nu_{C=O}$ 1710, 1660 (Nujol). *Anal.* Calcd. for $C_{20}H_{30}O_5N_6S$: 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. K_2CO_3 was added to the residue. The separated crystal (3.6 g., 91%, m.p. 128～129°) was filtered and recrystallized from Me_2CO-Et_2O to give 3.2 g. of colorless plates, m.p. 131°. IR $\lambda_{max}^{CHCl_3}$ cm^{-1}: 3420, 3280, 1740, 1701, 1262, 1118. *Anal.* Calcd. for $C_{17}H_{24}O_5N_4S$: 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 $CHCl_3$, 5 ml. of 30% $COCl_2$-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 $\lambda_{max}^{CHCl_3}$ 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 $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$, and then evaporated. The residue was recrystallized from Me_2CO-Et_2O 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 H_2O and Et_2O. Yield, 5.9 g. Recrystallization from Me_2CO gave colorless rhombics, m.p. 138° (decomp.). Rf 0.81. IR λ_{max}^{Nujol} cm^{-1}: 1745, 1669, 1655, 1263, 1020. *Anal.* Calcd. for $C_{22}H_{26}O_5N_4S$: 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 $CHCl_3$, 10 ml. of 30% $COCl_2$-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 λ_{max}^{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 K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$, and evaporated to give the coloress crystals. Washing with Et_2O 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 K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was shaken with 15% HCl and dried over $MgSO_4$. Evaporation of the solvent gave the crystals, which was recrystallized from Me_2CO to give 0.25 g. (36%) of colorless plates, m.p. 99～103°. IR λ_{max}^{Nujol} cm^{-1}: 3375, 3280, 3195, 1745, 1718, 1220, 1157. *Anal.* Calcd. for $C_{17}H_{24}O_5N_4S \cdot HCl \cdot H_2O$: 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 H_2O. Recrystallization from Me_2CO 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 $C_{22}H_{26}O_5N_4S$: 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)SB_1 (V) and O-trityl SB_1 (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, $[X_2M(\leftarrow HON=CH-R)_n]$,[2] where n is 2 or 4, but in the simple aliphatic series, only acetaldoxime,[2] acetoxime[3] and isobutyraldoxime[2] 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.

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

1) M. Bartusec, A. Okac : Collection Czech. Chem. Commun., **26**, 52, 883, 2174 (1961).
2) W. Hieber, F. Leutert : Ber., **60B**, 2296 (1927).
3) *Idem* : *Ibid.*, **60B**, 2310 (1927).