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Syntheses of New Thiamine Derivatives[1]

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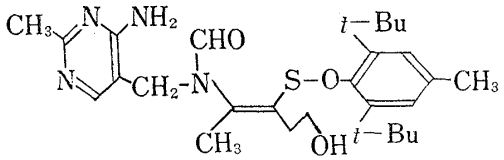
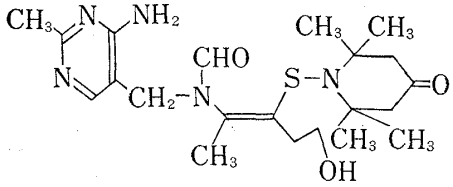
Oxidation of thiamine sodium salt (I) with iodine in the presence of amines (II) gave S-aminothiamines (III). When III was treated with weak acids, oxathiolane derivative (VIII) was obtained. From VIII, some new thiamine derivatives, pyrimido [4,5-*c*] [1,2,6]-10H-thiadiazocine (XIII), S-phosphate (XVI) derivatives and so forth, were derived. An analogue of XVI, cyclic O, S-phosphate (XVIII) was also synthesized.

Although many kinds of thiol type thiamine derivatives have been synthesized, there have been few reports concerning compounds having S-N,[3] S-O, or S-P[4] bonds of thiol type thiamine. The authors undertook the syntheses of this group of compounds in search of biological activity. Recently, Yoshioka and Murayama[5] reported that the reactions of the S-anion of thiamine with potassium ferricyanide in the presence of 4-methyl-2,6-di-*t*-butylphenoxy and 4-oxo-2,2,6,6-tetramethylpiperidine-1-oxyl radical gave the sulfenic acid derivative, S-(4-methyl-2,6-di-*t*-butylphenoxy)thiamine (a), and the sulfenamide derivative, S-(4-oxo-2,2,6,6-tetramethylpiperidino)thiamine (b), respectively.



a



b

Chart 1

On oxidation of thiol type thiamine and its derivatives (I) with iodine in the presence of amine (II) such as dimethylamine, piperidine and morpholine, the corresponding S-aminothiamines (III) were obtained accompanied by disulfides as shown in Chart 2 and Table I. Unsuccessful results were obtained on the reaction with aniline. O-acyl derivatives(IIIf—h) were obtained *via* the S→O rearrangement[6] of the corresponding S-acyl derivatives with alkali followed by oxidation as mentioned above.

The nuclear magnetic resonance (NMR) spectrum of S-dimethylaminothiamine (IIIa) is representative of these products and is showin in Fig. 1.

1) This work was presented at the 88th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1968.
2) Location: *Kami-Ebie 2, Fukushima-Ku, Osaka.*
3) R. G. Cooks and P. Sykes proposed that the sulphenamides would be one of the intermediates on the reaction of thiamine disulfide with amines. R. G. Cooks and P. Sykes, *J. Chem. Soc. (C)*, **1968**, 2871.
4) Some S-phosphates of thiamine were presented by A. Takamizawa and S. Sakai at the 18th General Meeting of Kinki Branch, Pharmaceutical Society of Japan, Kyoto, November 1968.
5) K. Murayama and T. Yoshioka, *Chem. Pharm. Bull.* (Tokyo), **15**, 723 (1967); C. Tamura, S. Sato and T. Yoshioka, *Tetrahedron Letters*, **1969**, 547; K. Murayama and T. Yoshioka, *Bull. Chem. Soc. Japan*, **42**, 1942 (1969).
6) A. Takamizawa, K. Hirai, Y. Hamashima and H. Ito, *Chem. Pharm. Bull.* (Tokyo), **15**, 816 (1967).

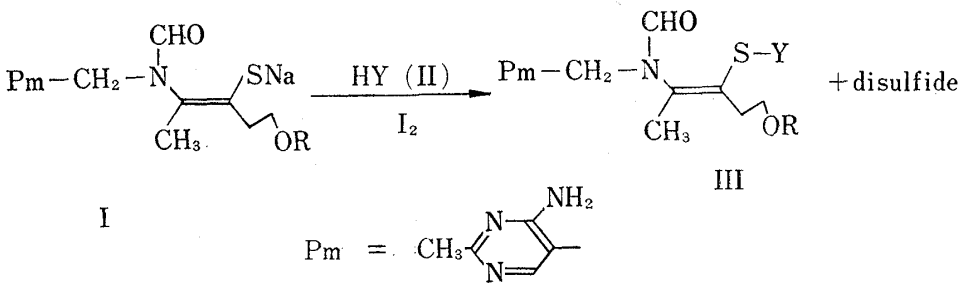
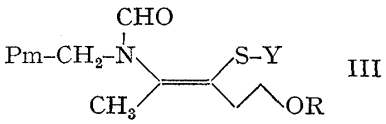


Chart 2

TABLE I. Melting Point and Yield of III



III	Y	R	mp °C	Yield %
a	$(CH_3)_2N-$	H	143—145	17
b	$(C_2H_5)_2N-$	H	112—113	11
c		H	173—176	21
d		H	130—132	22
e		H	152—154	27
f	$(CH_3)_2N-$	$(CH_3)_2CHCO-$	112—114	18
g	$(CH_3)_2N-$	C_6H_5CO-	98—100	12
h		$(CH_3)_2CHCO-$	130—133	14

The data on the NMR spectrum indicated that the compound was a thiol type thiamine lerivative[7] and that the dimethylamine group was mostly certainly to bind the S or alcholic) atom.

It is generaelly well known that the sulfenamide derivative (IV) reacts with H_2SO_3, HCl ınd excess mercaptan to give S-sulfonic acid,[8] disulfide[9] and mercaptan[10] derivative res-)ectively.

The reaction of IIIa with H_2SO_3 gave S-sulfothiamine (V),[11] and moreover on the treat- nent with HCl and excess thioglycol, IIIa gave thiamine difulfide[12] (VII) and thiamine (VI) 'espectively.

These results establish the structure of IIIa as reasonable. All other aminothiamines howed similar NMR spectra and chemical behavior. The treatment of aminothiamine (III) vith weak acid such as silicic acid or acetic acid gave a crystalline product (VIII), mp 139

7) K. Kotera, *Chem. Pharm. Bull.* (Tokyo), **13**, 440 (1965).
8) H. Z. Lecher and E. M. Hardy, *J. Org. Chem.*, **20**, 475 (1955).
9) J. A. Barltrop and K. J. Morgan, *J. Chem. Soc.*, **1957**, 3072.
10) D. Brandenburg, *Tetrahedron Letters*, **1966**, 6201.
11) H. Hirano, M. Hieda, Y. Oka and K. Takiura, *Vitamin*, **33**, 444 (1966).
12) O. Zima and R. R. Williams, *Chem. Ber.*, **73**, 941 (1940).

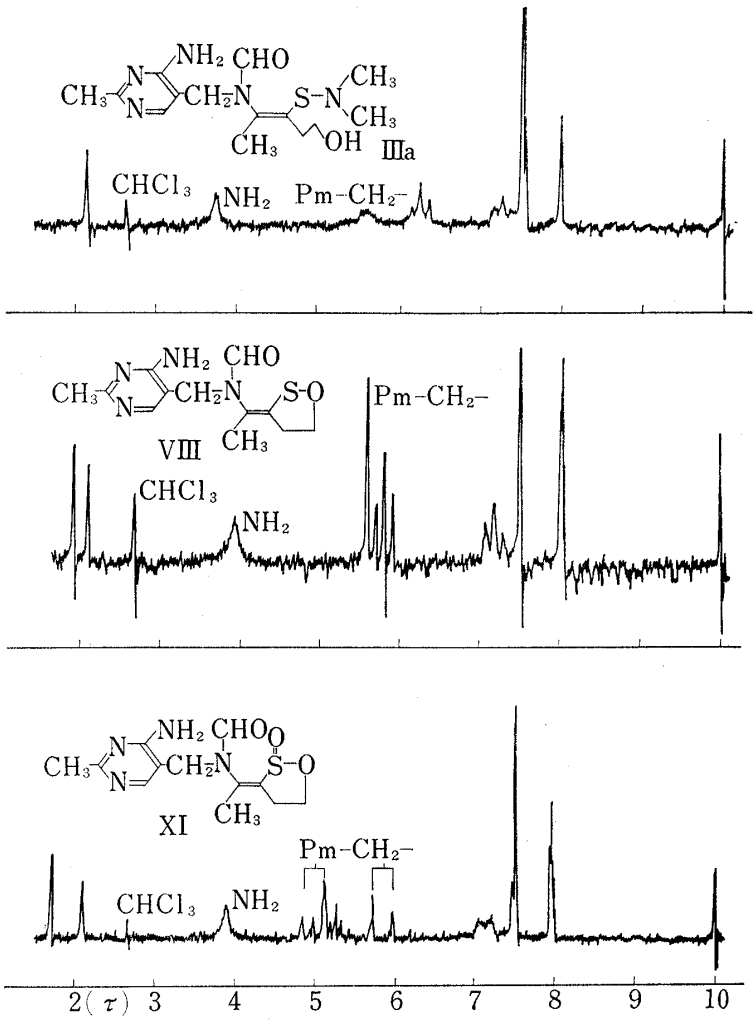


Fig. 1. NMR Spectra of IIIa, VIII and XI

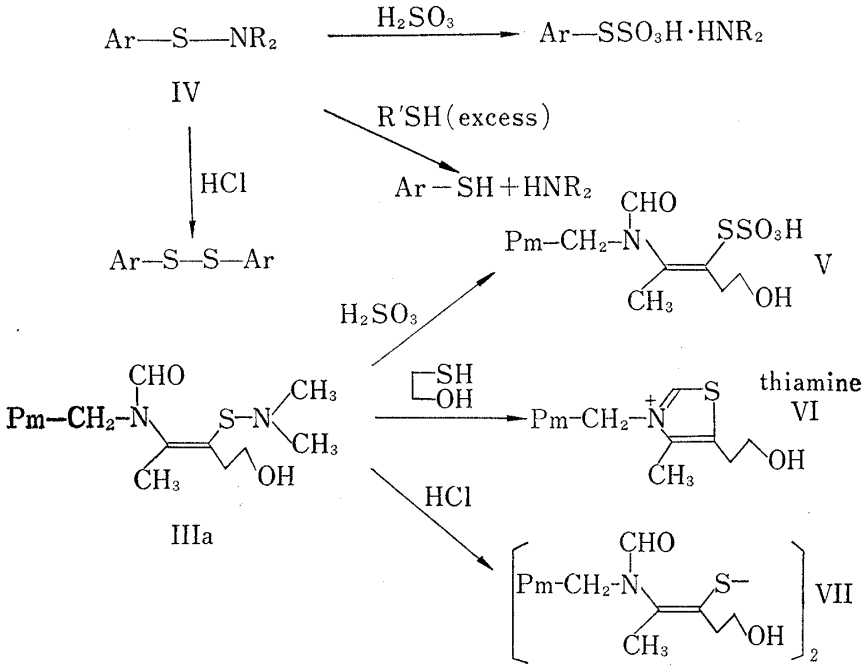


Chart 3

—141°. Elemental analysis showed the composition $C_{12}H_{16}O_2N_4S$, which was consistent with that of deaminated starting material.

As shown in Fig. 1, the NMR spectrum is characterized by the fact that the oxymethylene signals of VIII (5.82 τ, triplet, J=6.5 cps) is shifted to lower field than that of aminothiamine (IIIa: 6.23 τ, triplet, J=6.5 cps). From these findings the presence of S-O bond in VIII was suggested.

On warming VIII with morpholine or aniline, S-morpholinothiamine (IIIe) and S-anilinothiamine (X) respectively were obtained. X was not obtained by the reactin of I with aniline under the same condition mentioned above. VIII also was treated with two equivalents of propylmercaptan to yield thiaminepropyldisulfide[13] (IX) and with a large excess of thioglycol to give thiamine. Oxidation of VIII with an excess of benzoyl peroxide gave sulfinic acid ester[14] (XI) in which the chemical shift of the oxymethylene signal shift to lower field than that of VIII as shown in Fig. 1. The results described above establish the structure of VIII.

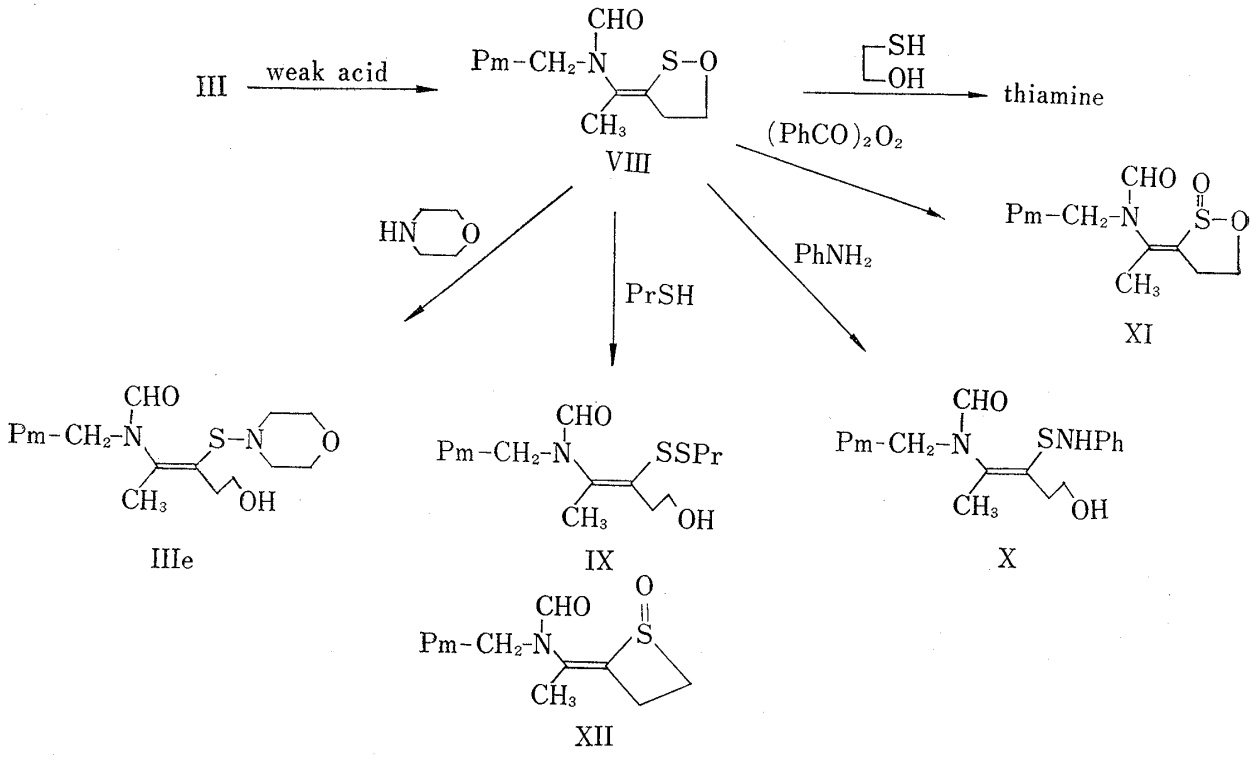


Chart 4

VIII was able to be distinguished by IR [VIII: 1000—1100 cm^{-1}, no strong absorption, XII: 1050 cm^{-1}, (S=O)] and NMR spectra (pyrimidine-CH_2-N, VIII: 5.6 τ, singlet, XII: 4.88 and 5.92 τ, quartet, J=15 cps) from thiamine anhydride S-oxide (XII), an isomer of VIII, which had already been synthesized by Kawasaki.[15] One of essential differences between VIII and the isomer XII is that only VIII gave thiamine on the treatment with excess thioglycol.

The interesting behavior of methylene protons between the pyrimidine and N-formyl moiety of these thiamine derivatives on NMR spectra was discussed at the 7th NMR symposium.[16]

13) T. Matsukawa and H. Kawasaki, *Yakugaku Zasshi*, 73, 216 (1953); T. Matsukawa, T. Iwatsu and H. Kawasaki, *Yakugaku Zasshi*, 73, 497 (1953).
14) G. Tsukamoto, T. Watanabe and I. Utsumi, *Bull. Chem. Soc. Japan*, 42, 2686 (1969).
15) C. Kawasaki, I. Tomita and T. Motoyama, *Vitamin*, 13, 57 (1957).
16) S. Arakawa, M. Hashimoto, J. Nakano and H. Nishimura, Abstracts of the 7th NMR symposium (Japan), Nagoya, November, 1968, p. 87.

When VIII was dissolved in warm H_2O followed by standing in the refrigerator, crystals (XIII), mp 167—168°, were precipitated. From the elemental analysis, the composition of XIII is identical to that of VIII. The reaction of XIII with acetylchloride and triethylamine for a short time afforded the monoacetate, which was proved to be O-acetyl derivative (XIV) by its IR spectrum (1730 cm^{-1} and 1240 cm^{-1}) and the NMR spectrum (Fig. 2). Although the NMR spectrum of XIV showed it was a thiol type thiamine derivative, the amino group attached to the pyrimidine ring had only one hydrogen differing from that observed for other thiol type thiamine derivatives. This fact suggested that the amino group was linked to the S-atom.

Treatment of XIII with excess thioglycol gave thiamine and with acetyl chloride-triethylamine yielded diacetate (XV), having no IR absorption attributable to NH and OH.

Based on the findings mentioned above, it may be reasonable to assume that the compound (XIII) possesses an eight membered ring structure in which the amino group is bound to the S-atom.

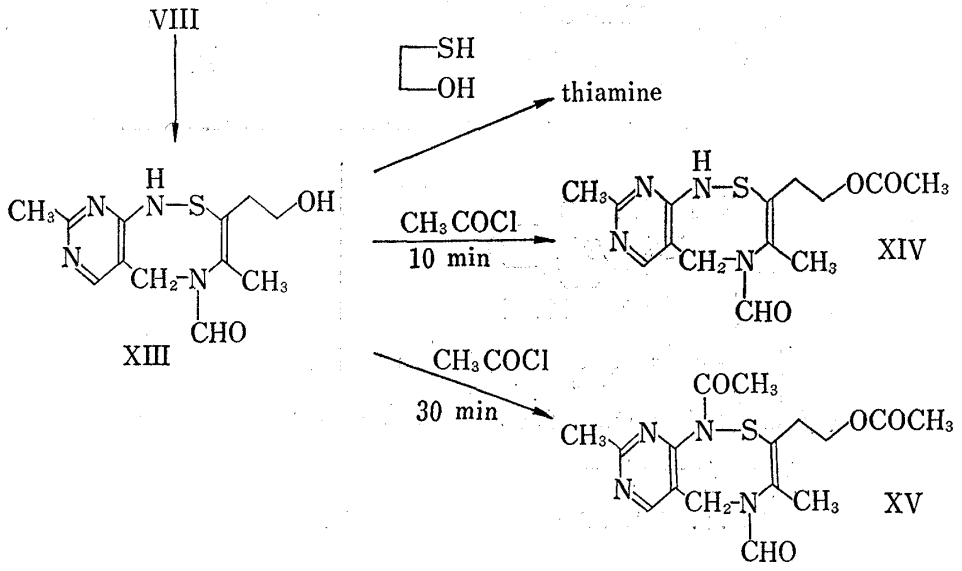


Chart 5

VIII, on standing, with diethyl hydrogen phosphite at room temperature in the presence of triethylamine, gave crystalline XVI, mp 133—134.° The IR spectrum showed strong absorption bands at 1255 and 1030 cm^{-1} due to P=O and P-O-C, respectively. In the NMR spectrum (Fig. 2) the chemical shift assigned to oxymethylene was at 6.15 τ. From this it may be concluded that the oxygen is not combined with any electro-attractive group but exists as the free OH. These results show that the structure of the compound is XVI, having an S-P bond. From the melting point and thin-layer chromatography it was also evident that XVI was distinguishable from O-diethylphosphothiamine disulfide (XVII) which had previously been synthesized by Mushika,[17] *et al.*

In an attmpt to obtain analogous thiophosphate derivatives, the sodium salt[12] of thiamine (I), on treatment with morpholinophosphodichloridate, gave crystaline XVIII, mp 103—107°, possessing $C_{16}H_{24}O_4N_5PS$. The NMR spectrum (Fig. 2) and IR spectrum supported the structure of XVIII. On acetylation of XVIII with acetic anhydride in the presence of *p*-toluene sulfonic acid, the N,N-diacetyl derivative (XIX) was obtained.

Attempts to eleminate the morpholine group from XVIII with hydrogen chloride under various conditions were unsuccessful and only the acetone adduct of 4-amino-5-aminomethyl-2-metyl-pyrimidine was isolated.

17) Y. Mushika and T. Fujita, *Yakugaku Zasshi*, **87**, 33 (1967).

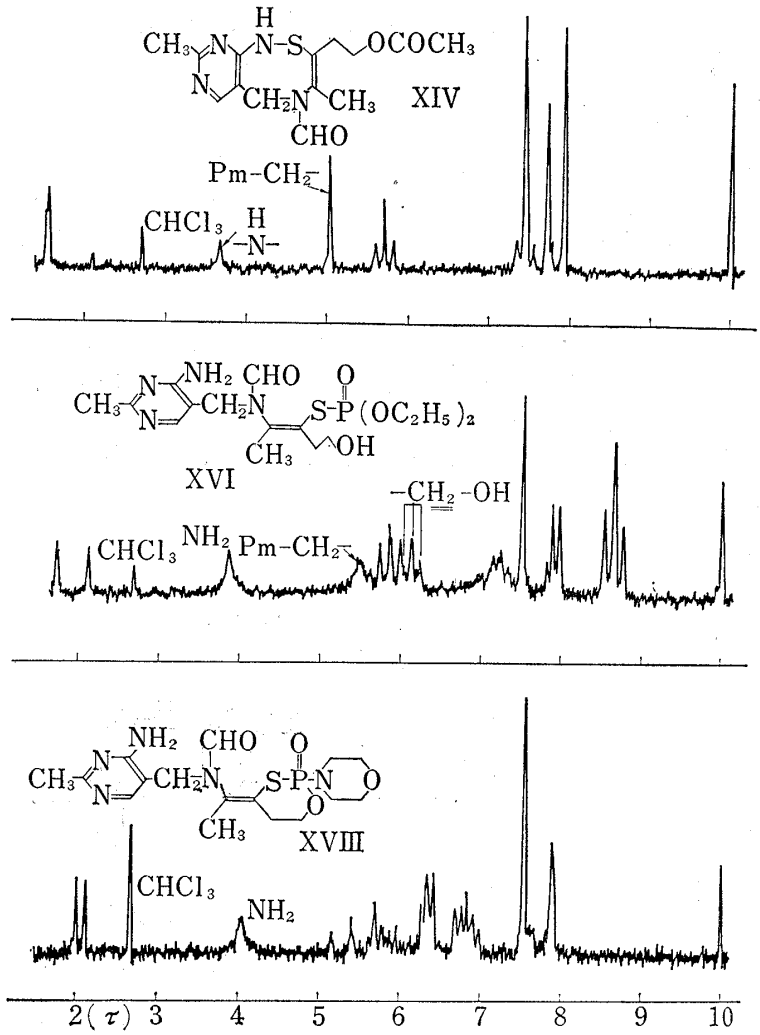


Fig. 2. NMR Spectra of XIV, XVI and XVIII

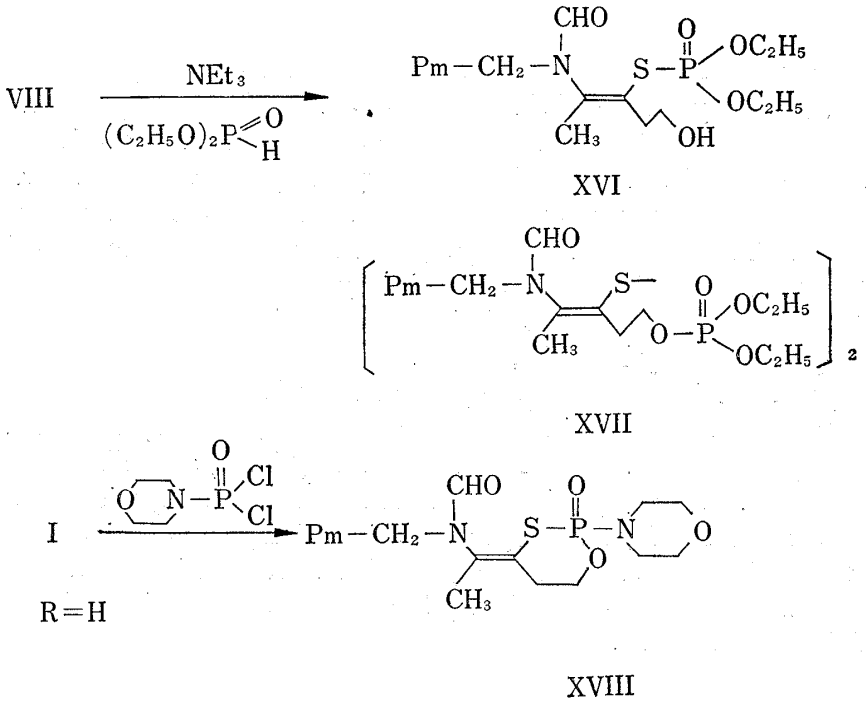


Chart 6

Experimental

All melting points were determined in capillary tubes and are uncorrected. NMR spectra were taken on a Varian A-60 recording spectrometer in $CDCl_3$ with tetramethylsilan as internal standard. Chemical shifts are presented in τ values.

All evaporations were carried out *in vacuo* below 50°. Silicic acid was used for thin-layer chromatography (TLC) and developed with $CHCl_3$–MeOH.

S-Dimethylaminothiamine (IIIa)——Thiamine chloride hydrochloride (10.1 g) in aqueous solution (76 ml) containing NaOH (3.6 g) was set aside at room temperature for 30 min.

After addition of an 40% aqueous solution of dimethylamine with stirring, the reaction mixture was gradually added with an aqueous solution (30 ml) of I_2 (7.6 g)–KI (8.0 g).

Excess amine was removed and the aqueous solution was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with a small amount of H_2O, dried over anhyd. Na_2SO_4, evaporated to dryness to afford crude crystals (3.1 g). Recrystallization from acetone gave 2.1 g of IIIa as prisms, mp 143—145°. IR ν_{max}^{KBr} cm^{-1}: 1655 (C=O), 1060 (C–O). NMR τ: 8.00 (3H, singlet, C=C–CH_3), 7.52 (6H, singlet, –$N(CH_3)_2$), 2.17 (2H, singlet, pyrimidine-6-H and CHO). *Anal.* Calcd. for $C_{14}H_{23}O_2N_5S$: C, 51.67; H, 7.12; N, 21.52; S, 9.85. Found: C, 51.93; H, 7.28; N, 21.18; S, 9.71.

Extraction of the residual solution with *n*-butanol gave thiamine disulfide,[12] mp 170° (2.0 g), which was identified with the authentic material by IR.

S-Diethylaminothiamine (IIIb)——Thiamine chloride hydrochloride (3.37 g) was treated with an aqueous solution (12 ml) of NaOH (1.2 g), diethylamine (4 g) and an aqueous solution of I_2 (2.5 g)–KI (3 g) as described above.

Recrystallization from acetone gave 400 mg of IIIb, mp 112—113°. *Anal.* Calcd. for $C_{16}H_{27}O_2N_5S$: C, 54.36; H, 7.70; N, 19.81; S, 9.07. Found: C, 54.45; H, 7.99; N, 19.46; S, 9.23.

S-Pyrrolidinothiamine (IIIc)——Thiamine chloride hydrochloride (3.3 g) was treated with an aqueous solution (1.2 g) and pyrrolidine (3.5 g). The solution was oxidized with an aqueous I_2 (2.5 g)–KI (2.5 g) solution at 45° as described above. Recrystallization from acetone gave 750 mg of IIIc, mp 173—176°. IR ν_{max}^{KBr} cm^{-1}: 1660 (C=O), 1055 (C–O). *Anal.* Calcd. for $C_{16}H_{25}O_2N_5S$: C, 54.68; H, 7.17; N, 19.93; S, 9.12. Found: C, 54.54; H, 7.33; N, 19.60; S, 9.05.

S-Piperidinothiamine (IIId)——Thiamine chloride hydrochloride (3.37 g) was treated with an aqueous solution (12 ml) of NaOH (1.2 g) and piperidine (4.0 g). The solution was oxidized with an aqueous solution of I_2 (2.5 g)–KI (2.5 g) at 45° as described above. 800 mg of IIId was obtained, mp 130—132° (from acetone). *Anal.* Calcd. for $C_{17}H_{27}O_2N_5S$: C, 55.86; H, 7.45; N, 19.16; S, 8.77. Found: C, 56.02; H, 7.57; N, 19.15; S, 8.77.

S-Morpholinothiamine(IIIe)——Thiamine chloride hydrochloride (10.1 g) was treated with an aqueous solution (36 ml) of NaOH (3.6 g), morpholine (50 g) and an aqueous solution (30 ml) of I_2 (7.8 g)–KI (8.0 g) as described above.

Recrystallization from acetone gave 3.1 g of IIIe, mp 152—154°. IR ν_{max}^{KBr} cm^{-1}: 1655 (C=O), 1050 (C–O). NMR τ: 7.98 (3H, singlet, C=C–CH_3), 7.58 (3H, singlet, pyrimidine-2-CH_3), 3.8(2H, broad, NH_2), 2.19 (2H, singlet, pyrimidine-6-H and CHO). *Anal.* Calcd. for $C_{16}H_{25}O_3N_5S$: C, 52.30; H, 6.86; N, 19.06; S, 8.73. Found: C, 52.55; H, 7.03; N, 18.99; S, 8.85.

O-Isobutyroyl-S-dimethylaminothiamine (IIIf)——S-Isobutyroylthiamine (3.5 g) was treated with an aqueous solution (14 ml) of NaOH (0.4 g) at 5°. After the addition of 40% aqueous dimethylamine solution, a solution of I_2 (2.5 g)–KI (2.5 g) in H_2O (10 ml) was added gradually at room temperature. The mixture was extracted with ether. The ether extract was washed with a diluted sodium thiosulfate solution, dried over anhyd. Na_2SO_4 and evaporated to dryness to give 1.5 g of crude IIIf. Recrystallization from acetone–ether gave 700 mg of IIIf as prisms, mp 112—114°. IR ν_{max}^{KBr} cm^{-1}: 1730 and 1660 (C=O). NMR: τ:8.84 (6H, doublet, isopropyl –CH_3), 8.0 (3H, singlet, C=C–CH_3), 7.54 (6H, singlet, $-N\langle^{CH_3}_{CH_3}$). *Anal.* Calcd. for $C_{18}H_{29}O_3N_5S$: C, 54.66; H, 7.39; N, 17.71; S, 8.11. Found: C, 54.19; H, 7.50; N, 17.50; S, 8.31.

The residual aqueous solution was extracted with $CHCl_3$, the $CHCl_3$ extract was shown by TLC to contain O-isobutyroylthiamine disulfide[18] and IIIf.

O-Benzoyl-S-dimethylaminothiamine (IIIg)——S-Benzoylthiamine (3.8 g) was treated with an aqueous solution of NaOH (0.4 g), 40% aqueous dimethylamine solution (20 ml) and a solution of I_2 (2.5 g)–KI (2.5 g) in H_2O (10 ml) as described above. After chromatography of the ethereal extract on silicic acid and elution with $CHCl_3$, crystallization from ether gave 500 mg of IIIg, mp 98—100°. IR ν_{max}^{KBr} cm^{-1}: 1730 and 1660 (C=O). *Anal.* Calcd. for $C_{21}H_{27}O_3N_5S$: C, 58.72; H, 6.34; N, 16.31; S, 7.46. Found: C, 58.12; H, 6.34; N, 15.76; S, 7.59.

O-Isobutyroyl-S-morpholinothiamine (IIIh)——O-Isobutyroylthiamine (3.5 g) was treated with an aqueous solution of NaOH (0.4 g), morpholine (10 ml) and an aqueous solution of I_2 (2.5 g)–KI (2.5 g) as

18) T. Ammo, T. Sakai, E. Fujihira and T. Aizawa, *Vitamin*, 32, 260 (1965).

described above. After chromatography of the ethereal extract on silicic acid and elution with $CHCl_3$, recrystallization from acetone gave 600 mg of IIIh, mp 130—133°. IRν_{max}^{KBr} cm^{-1}: 1730 and 1660 (C=O). *Anal.* Calcd. for $C_{20}H_{31}O_4N_5S$: C, 54.90; H, 7.14; N, 16.01; S, 7.33. Found: C, 54.82; H, 7.29; N, 15.90; S, 7.37.

From the aqueous solution, O-isobutyroylthiamine disulfide[18] (1.5 g) mp 140—145° was obtained.

Oxidation of Thiamine Sodium Salt and Aniline with Iodine——Thiamine chloride hydrochloride (6.7 g) was treated with a aqueous solution (24 ml) of NaOH (2.4 g), aniline (2.5 g), EtOH (10 ml) and an aqueous solution (20 ml) of I_2(5 g)–KI (5 g) as described above. From $CHCl_3$ extract tarry substance (3.5 g) was obtained which gave many spots on TLC. No crystalline product was obtained from this residue.

S-Sulfothiamine (V)——A solution of IIIe (2 g) in H_2O (5 ml) was saturated with SO_2 and allowed to stand for 3 days. Fraction gave 1.4 g (63%) of crystalline V, mp 215—218°. *Anal.* Calcd. for $C_{12}H_{11}O_5N_4S_2$: C, 39.77; H, 5.01; N, 15.46; S, 17.69. Found: C, 39.83; H, 5.10; N, 15.69; S, 17.53.

Thiamine from S-Dimethylaminothiamine (IIIa)——To a solution of IIIa (1.0 g) in EtOH (10 ml) was added thioglycol (500 mg). After stirring for 30 min at room temperature, addition of EtOH–HCl gave thiamine chloride hydrochloride (650 mg), mp 255° (decomp.), which was identified with the authentic material by IR.

Thiamine Disulfide from S-Dimethylaminothiamine (IIIa)——A solution of IIIa (200 mg) in $CHCl_3$ (30 ml) was treated with a small amount of EtOH–HCl. After 30 min, the reaction mixture was washed with an aqueous solution of $NaHCO_3$, dried over anhyd. Na_2SO_4 and evaporated to dryness to give 100 mg of thiamine disulfide, mp 170°, which was identical with the authentic material by IR.

N-1-(1,2-Oxathiolane-3-ylidene)ethyl-N-(4-amino-2-methyl-5-pyrimidinyl)methyl Formamide (VIII)——A) A solution of IIIa (19 g) in $CHCl_3$ (150 ml) was treated with silicic acid (58 g) with vigorous stirring for 4 hr. The silicic acid was filtered off and washed well with $CHCl_3$. Evaporation of the $CHCl_3$ gave crude VIII (12 g). Chromatography of the crude product on silicic acid (30 g) and elution with 1% MeOH–$CHCl_3$ gave 7.7 g (47%) of VIII, mp 139—141°. Recrystallization was carried out from ethylacetate.

B) A solution of IIIa (1.0 g) in $CHCl_3$ (30 ml) was treated with AcOH (0.2 ml) for *ca.* 2 hr at room temperature. After washing with an $NaHCO_3$ solution, chromatography of the $CHCl_3$ solution on silicic acid gave 150 mg of VIII, mp 139—141°. IRν_{max}^{KBr} cm^{-1}: 3100 and 3300 (NH_2), 1675 (C=O). NMR τ: 8.02 (3H, triplet, J=1 cps, C=C–CH_3), 7.52 (3H, singlet, pyrimidine-6-CH_3), 5.60 (2H, singlet, pyrimidine–CH_2–N). *Anal.* Calcd. for $C_{12}H_{16}O_2N_4S$: C, 51.41; H, 5.75; N, 19.99; S, 11.44. Found: C, 51.71; H, 5.89; N, 19.69; S, 11.45.

S-Morpholinothiamine (IIIe) from VIII——VIII (1 g) was heated with morpholine (5 ml) at 60° for 2 hr. After the addition of $CHCl_3$, the $CHCl_3$ solution was washed with H_2O, dried and evaporated to dryness. The residue was triturated with ether to give 400 mg of IIIe, mp 153—154°, which was identical with the above mentioned IIIe by IR and TLC.

Thiamine Propyldisulfide (IX)——A solution of VIII (560 mg) in $CHCl_3$ (30 ml) was treated with propylmercaptan (150 mg) and allowed to stand over night. Crude crystals (510 mg) were obtained after evaporation of solvent and trituration with ether. Chromatography on silicic acid on elution with MeOH–$CHCl_3$ (1:50) gave 250 mg of IX. Recrystallization from benzene gave 220 mg of IX, mp 131°, which was identical with the authentic material by IR, and mixed mp.

Thiamine from VIII——A solution of VIII (500 mg) and thioglycol (500 mg) in MeOH (30 ml) was allowed to stand for 10 min.

After addition of EtOH–HCl, the solvent was evaporated to dryness and recrystallization of the residue from EtOH gave 550 mg of thiamine chloride hydrochloride, mp 254—255°, which was identical with the authentic material by IR.

S-Anilinothiamine (X)——A solution of VIII (500 mg) in aniline (2 ml) was heated at 60° for 3 hr. The reaction mixture was cooled and triturated with ether to give crude crystals which were recrystallized from acetone to give 700 mg of X, mp 164—165°. IR ν_{max}^{KBr} cm^{-1}: 1660 (C=O), 1050 (C–O). *Anal.* Calcd. for $C_{18}H_{22}O_2N_5S$: C, 57.89; H, 6.21; N, 18.75; S, 8.59. Found: C, 57.78; H, 6.14; N, 18.40; S, 8.60.

Sulfinic Acid Ester (XI)——A solution of VIII (560 mg) and benzoylperoxide (774 mg) in $CHCl_3$ (30 ml) was allowed to stand over night. The $CHCl_3$ extract obtained on extraction of reaction mixture with 10% HCl followed by neutralization with $NaHCO_3$ and extraction with $CHCl_3$ was evaporated to dryness. The crystals (500 mg) were recrystallized from ethyl acetate to give 270 mg of XI, mp 154—155°. IRν_{max}^{KBr} cm^{-1}: 1105 (S=O). NMR τ: 8.09 (3H, broad, C=C–CH_3), 7.52 (3H, singlet, pyrimidine–2–CH_3), 5.92 and 5.12 (2H, quartet, J=15 cps, pyrimidine–CH_2–N). *Anal.* Calcd. for $C_{12}H_{16}O_3N_4S$: C, 48.63; H, 5.44; N, 18.91; S, 10.82. Found: C, 48.53; H, 5.53; N, 19.24; S, 10.79.

5,6-Dihydro-2,7-dimethyl-6-formyl-8-(2-hydroxyethyl)-pyrimido[4,5-*c*][1,2,6]-10H-thiadiazocine (XIII)——VIII (1.0 g) was dissolved in H_2O (5 ml) on heating and the resulting solution on standing in a refrigerator gave 550 mg of XIII, mp 175—178°. IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O), 1040 (C–O). NMR[19] τ: 1.64

19) This spectrum was taken in DMSO-D_6 with tetramethylsilan as internal standard.

(1H, singlet) and 1.70 (2H, broad singlet, N-CHO and pyrimidine-5-H), 7.63 (3H, singlet, pyrimidine-CH_3), 7.82 (3H, singlet, C=C-CH_3). *Anal.* Calcd. for $C_{12}H_{16}O_2N_4S$: C, 51.41; H, 5.75; N, 19.99; S, 11.44. Found: C, 51.40; H, 6.00; N, 20.08; S, 11.26.

Monoacetyl XIII (XIV)——A suspension of XIII in $CHCl_3$ (20 ml) was treated with Et_3N and acetyl chloride (0.2 ml) at O° for 10 min. After removal of solvent, a solution of the residue in $CHCl_3$ (50 ml) was washed fully with H_2O, dried with anhyd. Na_2SO_4 and evaporated to dryness to yield 120 mg of XIV, mp 159—161°. IR ν_{max}^{KBr} cm^{-1}: 1730, 1665 (C=O), 1240 (C-O). NMR τ: 7.94 (3H, singlet, $COCH_3$), 7.45 (3H, singlet, pyrimidine-2-CH_3), 5.02 (2H, singlet, pyrimidine-CH_2-N). *Anal.* Calcd. for $C_{14}H_{18}O_3N_4S$: C, 52.16; H, 5.64; N, 17.38; S, 9.95. Found: C, 52.27; H, 5.70; N, 17.03; S, 9.79.

Thiamin from XIII——A solution of XIII (150 mg) in MeOH (10 ml) was treated with thioglycol (0.5 ml) at room temperature for 30 min. After addition of EtOH–HCl the solvent was removed and the residue was recrystallized from EtOH–H_2O to give 100 mg of thiamine, mp 250—253°, which was identical with the authentic material by IR.

Diacetyl XIV (XV)——A solution of XIII (200 mg), $CHCl_3$ (10 mg) and Et_3N (1 ml) was treated with acetyl chloride (200 mg) at 0° for 30 min. The solution was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. Chromatography of the residue on silicic acid on elution with $CHCl_3$ gave XV, mp 93—95° (from ether). IR ν_{max}^{KBr} cm^{-1}: 1735, 1700, 1675 (C=O), 1225 (C-O). NMR τ: 7.95, 7.91, 7.76 (each 3H, singlet, $2\times COCH_3$ and C=C-CH_3), 1.30 and 1.73 (each 1H, singlet, N-CHO and pyrimidine-6-H). *Anal.* Calcd. for $C_{16}H_{20}O_4N_4S$: C, 52.73; H, 5.53; N, 15.38; S, 8.80. Found: C, 52.79; H, 5.39; N, 15.16; S, 9.06.

S-Diethyl Phosphothiamine (XVI)——A solution of VIII (1 g) in $CHCl_3$ (20 ml) was treated with triethylamine (1 ml) and diethylhydrogenphosphite (1 g) and stirred at O° for 5 hr. After extraction with 10% HCl solution, the 10% HCl extract was neutralized with $NaHCO_3$ and extracted with $CHCl_3$.

Crystals (160 mg) were obtained by evaporation of the solvent followed by standing in a small amount of acetone in a refrigerator, mp 133—134°. NMR τ: 7.53 (3H, singlet, pyrimidine-2-CH_3), 6.15 (2H, triplet, -CH_2-O-). *Anal.* Calcd. for $C_{16}H_{27}O_5N_4PS$: C, 45.90; H, 6.50; N, 13.39; P, 7.40. Found: C, 45.64; H, 6.26; N, 13.36, P, 7.03.

O,S-Cyclophosphate (XVIII)——A suspension of thiamine sodium salt (I, 35 g), dichlorophosphoromorpholidate (17 g) and K_2CO_3 (11 g) in CH_3CN (330 ml) was stirred over night at room temperature. The solvent was removed, the residue dissolved in H_2O and extracted with $CHCl_3$. The $CHCl_3$ solution was extracted with 10% HCl solution and the 10% HCl extract was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ solution was dried over anhyd. Na_2SO_4, evaporated to dryness. Standing the residue in a small amount of CH_3CN gave 8 g of XVIII, mp 103—107°. NMR τ: 7.90 (3H, broad, C=C-CH_3), 7.55 (3H, singlet, pyrimidine-2-CH_3). *Anal.* Calcd. for $C_{16}H_{24}O_4N_5PS$: C, 46.48; H, 5.85; N, 16.94; P, 7.45. Found: C, 46.34; H, 6.13; N, 17.39; P, 7.31. HCl salt, mp 140—143°. *Anal.* Calcd. for $C_{16}H_{24}O_4N_5PS$-$HClH_2O$: C, 41.07; H, 5.81; N, 14.97; Cl, 7.57; P, 6.67. Found: C, 41.23; H, 5.82; N, 14.55; Cl, 7.81; P, 6.20.

Diacetate (XIX)——A solution of XVIII (1.0 g), acetic anhydride (50 ml) and *p*-toluenesulfonic acid (50 ml) was heated at 70° for 4 hr. The acetic anhydride was removed and a $CHCl_3$ solution of the residue was washed with 10% HCl and $NaHCO_3$ solutions, dried over anhyd. Na_2SO_4 and evaporated to dryness. Recrystallization of the residue from acetone–ether gave 100 mg of XIX, mp 125—128°. IR ν_{max}^{KBr} cm^{-1}: 1725 and 1700 (C=O). NMR τ: 7.87 (3H, broad, C=C-CH_3), 7.69 (6H, singlet, $COCH_3$), 7.25 (3H, singlet, pyrimidine-2-CH_3), 2.00 (1H, singlet, N-CHO), 1.33 (1H, singlet, pyrimidine-5-H). *Anal.* Calcd. for $C_{20}H_{28}O_6N_5PS$: C, 48.28; H, 5.67; N, 14.08; P, 6.46. Found: C, 48.17; H, 5.90; N, 14.26; P, 6.67.

Reaction of (XVIII) with HCl——A solution of XVIII (300 mg) and conc. HCl (0.3 ml) in EtOH (15 ml) was refluxed for 2 hr. After cooling, the solvent was removed. On addition of acetone to the residue, crystals (50 mg) were obtained having the following elemental analysis, C, 40.70; H, 6.53; N, 21.07; Cl, 26.71; which was considered to be the acetone adduct of 4-amino-5-amino-methyl-2-methylpyrimidine, Calcd. for $C_9H_{18}ON_4Cl_2$: C, 40.15; H, 6.74; N, 20.81; Cl, 26.34.

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