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Studies on Pyrimidine Derivatives and Related Compounds. LIV.[1] Reactions of Thiamine with α-Ketoaldehydes[2]

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Reaction of thiamine-sodium salt (III) with phenylglyoxal in the presence of carbon dioxide yielded 2-phenyloxalylthiamine (Va) which underwent facile air oxidation to thiamine thiazolone (VI) and phenylglyoxylic acid. Thiamine hydrochloride (I) was also condensed with phenylglyoxal in the presence of triethylamine or sodium hydroxide to give Va. The reaction was applied to a number of α-ketoaldehydes including some heterocyclic glyoxals to give corresponding 2-oxalylthiamine derivatives (Vb–l) which were shown to be convertible into stable acyl derivatives (XIa–r).

In relation to the mechanism of thiamine action, considerable attention has been directed to the chemical reactivities of thiazolium 2-position of thiamine in recent years.[4] Krampitz and coworkers[5] first described that the reaction of thiamine hydrochloride (I) with acetaldehyde in the presence of alkali gave hydroxyethylthiamine (II) (HET).[6] On the other

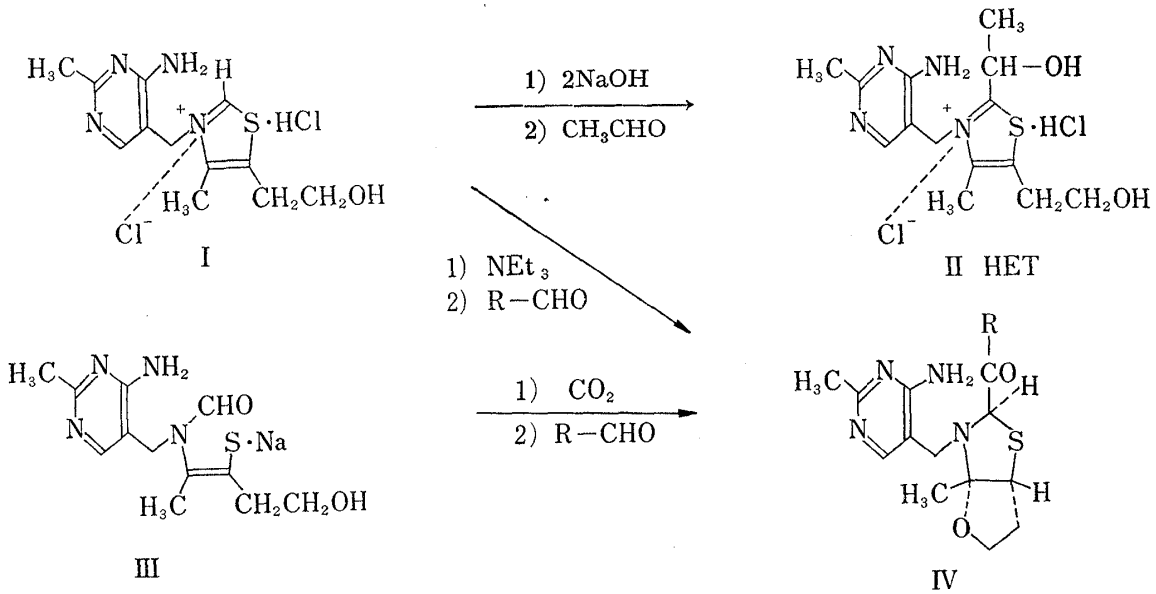


Chart 1

1) Part LIII: A. Takamizawa, Y. Mori, H. Sato, and S. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **16**, 1773 (1968).
2) A part of this work was preliminarily reported in *Tetrahedron Letters*, **1968**, 2189.
3) Location: *Fukushima-ku, Osaka.*
4) *a*) R. Breslow, *J. Am. Chem. Soc.*, **79**, 1762 (1957); *idem*, *Chem. Ind.* (London), 893 (1957); *idem*, *Ann. N.Y. Acad. Sci.*, **98**, 445 (1962); R. Breslow and E. McNelis, *J. Am. Chem. Soc.*, **81**, 3080 (1959); *b*) B. L. Carlson and B. M. Brown, *J. Biol. Chem.*, **236**, 2099 (1961); *c*) H. Holzer and K. Beaukamp, *Angew. Chem.*, **71**, 776 (1959); *idem*, *Biochim. Biophys. Acta*, **46**, 225 (1961).
5) C. S. Miller, J.M. Sprague, and L. O. Krampitz, *Ann. N.Y. Acad. Sci.*, **98**, 401 (1962).
6) L.O. Krampitz, G. Greull, C.S. Miller, J.B. Bicking, H.R. Skeggs, and J.M. Sprague, *J. Am. Chem. Soc.*, **80**, 5893 (1958).

hand, the authors[7] have previously reported that the reaction of thiamine-sodium salt (III) with a variety of aldehydes in the presence of carbon dioxide gave 2-acyl-3-(2-methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-*d*]thiazoles (IV) involving anomalous C-acylations at the 2-position of the thiazolium moiety, and the same type of acylation was also found to occur in the reaction of thiamine hydrochloride (I) with aldehydes in the presence of triethylamine under anhydrous condition.

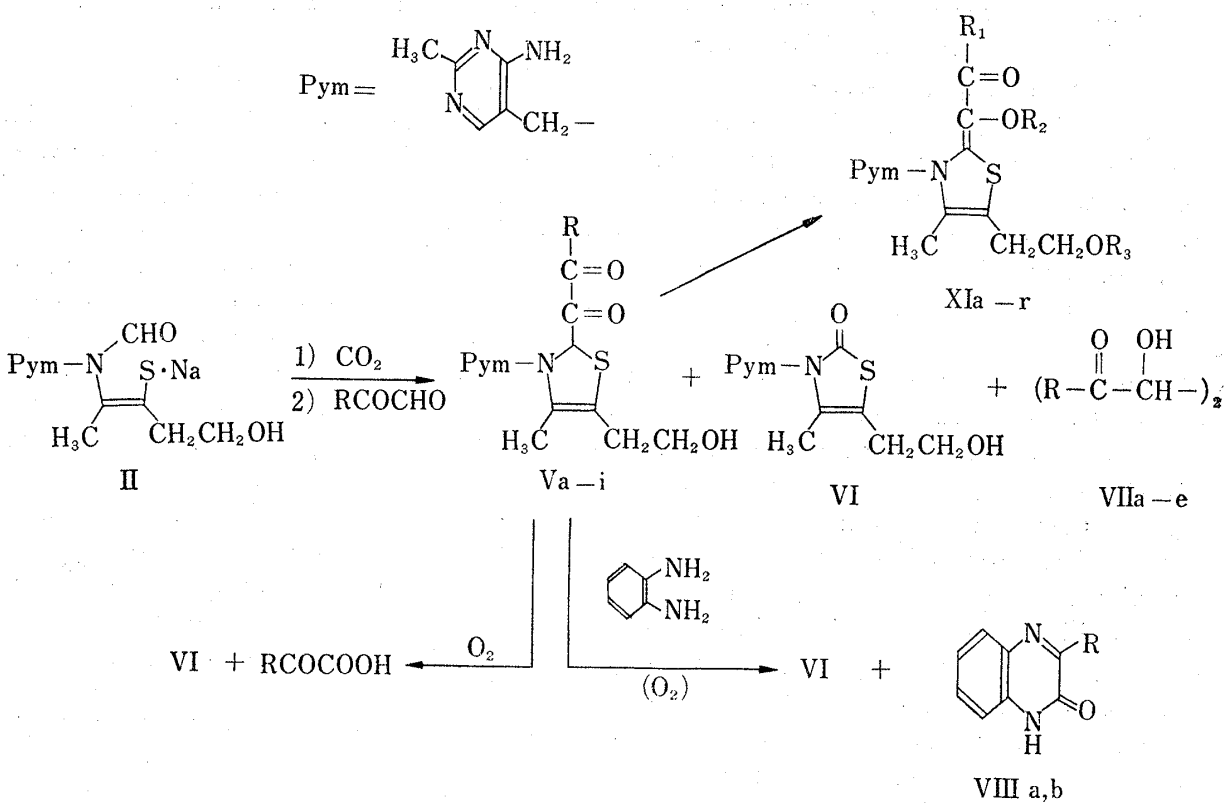
The present paper describes the reactions of thiamine with α-ketoaldehydes.

Ethanolic suspension of thiamine–sodium salt (III) was saturated with dry carbon dioxide, then an excess amount of phenylglyoxal was allowed to react at room temperature. The reaction mixture was gradually turned to green, and after two hours 2-phenyloxalyl-3-(2-methyl-4-aminopyrimidin-5-yl)methyl-4-methyl-5β-hydroxyethylthiazoline (or 2-phenyloxalylthiamine) (Va) was isolated as hemihydrate, mp 150—158° (decomp.), $C_{20}H_{22}N_4O_2S \cdot \frac{1}{2}H_2O$, in 50—60% yield accompanied with thiamine thiazolone (VI) and a compound (VIIa), mp 116—118°, as minor products. The major product Va was obtained as bright yellow crystalline powder in wet state, but it became to be dark green when dried *in vacuo* over phosphorous pentoxide, and it was gradually decomposed to an unidentified resinous substance by the atmospheric moisture. When it was dissolved in pyridine or dimethylsulfoxide (DMSO), a deep green solution first resulted, then it gradually fainted out along with the progress of air oxidation, and thiamine thiazolone (VI) and phenylglyoxylic acid were obtained from the final pale yellow solution. In these solvents, Va was found to absorb readily an approximately equimolar amount of oxygen to give VI and phenylglyoxylic acid. When the air oxidation was carried out in ethanol in the presence of *o*-phenylenediamine, VI and 3-phenylquinoxalin-2-one (VIIIa, R=phenyl)[8] were obtained. In aqueous alkaline solution, Va exhibited deep red coloring and the air oxidation was remarkably facilitated to give VI in almost quantitative yield. These properties of facile air oxidation indicate that phenyloxalyl group must be located on the 2-position of thiazoline moiety of Va, for an analogous oxidative C-C bond cleavage has been exemplified by the ready air oxidation of benzylphenyl-α-diketone to benzaldehyde and phenylglyoxylic acid.[9]

In the infrared (IR) spectrum, Va exhibited no carbonyl absorption besides 1660 cm^{-1}, whereas its ethanol solution exhibited a strong absorption maximum at 420 mμ (log $\varepsilon > 4$), which was rapidly disappeared within few minutes. In ethanolic hydrogen chloride, it exhibited no absorption in the visible region, and only single absorption maximum was observed at 250 mμ. These spectral properties indicate that Va exists predominantly in the enolic form (IX) whereas in the acidic medium the thiazolium form (X) may predominate. In fact, acetylation of Va with acetic anhydride and pyridine under nitrogen stream at room temperature afforded a stable diacetate (XIa, $R_1=C_6H_5$, $R_2=R_3=Ac$) which was found to be no longer vulnerable on the air oxidation. IR spectrum of XIa exhibited three different carbonyl absorptions at 1763 cm^{-1} (enol acetate), 1730 cm^{-1} (alcohol acetate) and 1636 cm^{-1} (α,β-unsaturated ketone), and its UV spectrum showed a strong absorption at 391 mμ (log $\varepsilon=4.40$). These spectral data as well as its nuclear magnetic resonance (NMR) spectrum (Fig. 1) clearly confirmed the structure represented by the formula, although the geometry around the exocyclic double bond on the thiazoline ring remained unknown. In particular, the formation of this diacetate excluded an alternative structure (XII) for Va, because the hydrofuran ring of the perhydrofuro[2,3-*d*]thiazole ring system of some compounds of the type IV was found to be stable on the acetylation condition described above, which is notable as compared with the previous results of the reactions of thiamine with aldehydes (ref. 7).

7) A. Takamizawa, K. Hirai, Y. Hamashima, and S. Matsumoto, *Tetrahedron Letters*, **1967**, 5071; A. Takamizawa, K. Hirai, Y. Hamashima, S. Matsumoto, and T. Ishiba, *Chem. Pharm. Bull.* (Tokyo), **16**, 1210 (1968).
8) J. Buraczewski and L. Marchlewski, *Chem. Ber.*, **34**, 4008 (1901).
9) E.P. Kohler and R.P. Barnes, *J. Am. Chem. Soc.*, **56**, 211 (1934).

The fact that the hydroxyethyl side chain of Va is not cyclized to form hydrofuran ring is possibly attributable to the stabilization of the thiazoline double bond by the resonance contributions such as XIII or XIV.



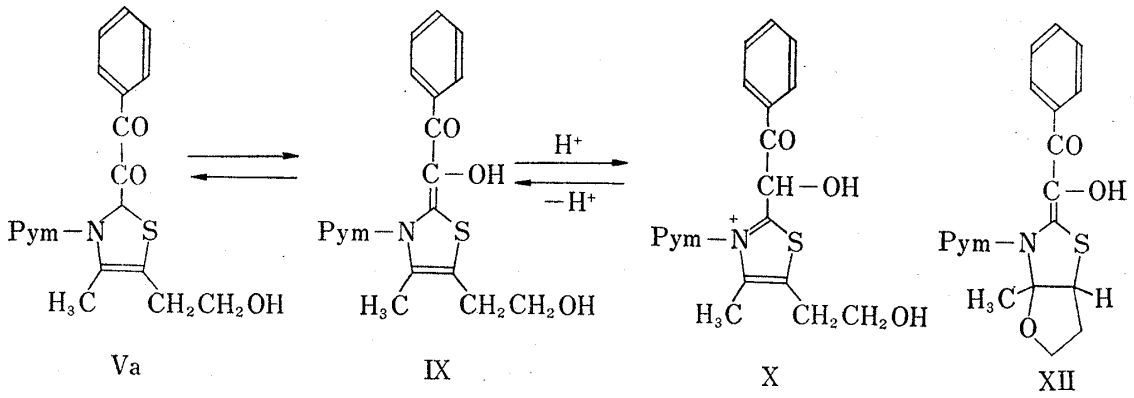


Chart 2

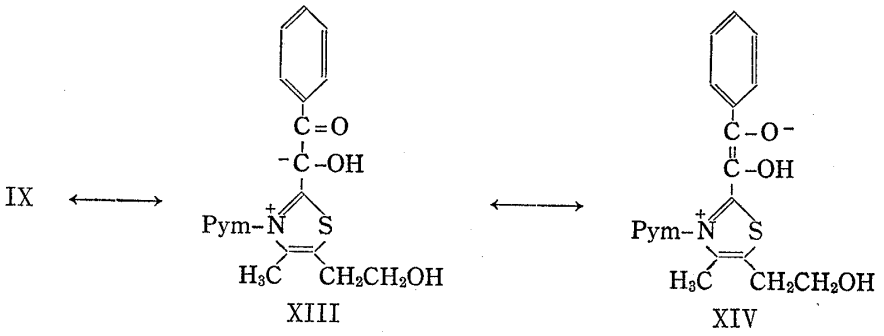


Chart 3

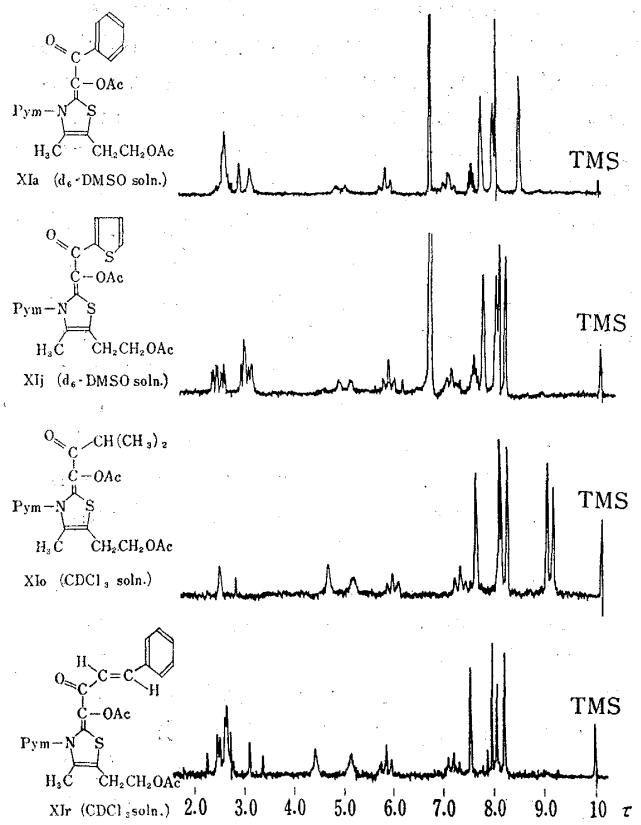


Fig. 1. NMR Spectra of 2-Oxalylthiamine Diacetates XIa, XIj, XIo and XIr

When acetylation was carried out in aqueous pyridine containing acetic anhydride, Va afforded an enol monoacetate (XIb, $R_1=C_6H_5$, $R_2=Ac$, $R_3=H$) predominantly. The structure of the monoacetate XIb was confirmed by the IR absorptions at 1770 cm^{-1} and 1665 cm^{-1} as well as the presence of UV absorption maximum at 392 mμ ($\log \varepsilon=4.38$). Benzoylation of Va with benzoyl chloride in aqueous pyridine also afforded a stable enol monobenzoate (XId, $R_1=C_6H_5$, $R_2=COC_6H_5$, $R_3=H$), whereas in pyridine solution a dibenzoate (XIc, $R_1=C_6H_5$, $R_2=R_3=COC_6H_5$) was preferentially formed.

The minor product VIIa($R=C_6H_5$) was assigned as 1,2-dibenzoylethylene glycol on the basis of the following data. Its elementary analysis and molecular weight determination corresponded to the molecular formula $C_{16}H_{14}O_4$. IR spectrum of VIIa showed a OH band at 3480 cm^{-1} and a C=O band at 1695 cm^{-1}. The NMR spectrum (Fig. 2) showed a broad doublet at 4.64 τ ($J=ca.$ 4 cps) and a broad signal at 6.10 τ with equal intensity, and by deuterium exchange the former signal was turned out to a sharp singlet, whereas the latter was disappeared, and moreover, the signal pattern of aromatic region was quite similar to that of benzoyl group. These facts apparently show that the two $C_6H_5COCH(OH)$- groups must be combined symmetrically. 1,2-Dibenzoylethylene glycol, however, has been reported to have two isomers melting at 126—127° and 118—119°,[10] and the higher melting isomer has been shown to be meso-form.[11] The melting point of VIIa is agreeable with that of the lower melting isomer, hence it may be considered to be racemic-form.

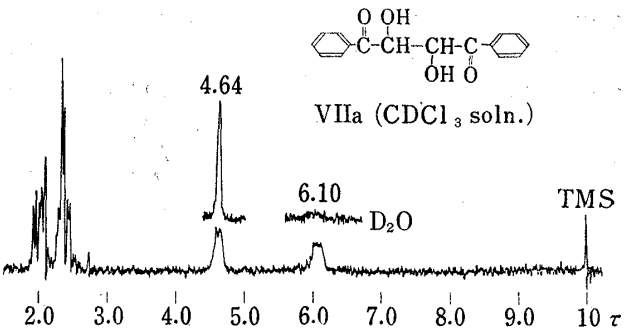


Fig. 2. NMR Spectrum of VIIa

Reaction of thiamine hydrochloride (I) with phenylglyoxal in the presence of triethylamine in 99% ethanol was found to proceed analogously providing Va in ca. 40% yield accompanied with small amount of VI and VIIa, and it is notable that the reaction was found to proceed even in 50% aqueous ethanol solution containing two equimolar amounts of sodium hydroxide, because the reaction of I with benzaldehyde under this condition has been shown to give hydroxybenzylthiamine without formation of the acylated product (ref. 7).

10) R.C. Fuson, C.H. McBurney, and W.E. Holland, *J. Am. Chem. Soc.*, **61**, 3246 (1939).
11) P. Ruggi, H. Dahn, and P. Fries, *Helv. Chim. Acta*, **29**, 302 (1946).

p-Bromo and *p*-methoxyphenylglyoxals also reacted readily with thiamine-sodium salt (III) in the presence of carbon dioxide in ethanol to give corresponding 2-oxalylthiamine derivatives (Vb, R=*p*-Br-C_6H_4) and (Vc, R=*p*-MeO-C_6H_4) accompanied with a trace amount of VIIb (R=*p*-Br-C_6H_4) and VIIc (R=*p*-MeO-C_6H_4) respectively besides VI. These products Vb and Vc were also found to be unstable and it was difficult to obtain in completely pure state, however by treating with benzoyl chloride in aqueous pyridine, they were convertible into stable enol monobenzoates XIe (R_1=*p*-Br-C_6H_4, R_2=COC_6H_4, R_3=H) and XIf (R_1=*p*-MeO-C_6H_4, R_2=COC_6H_4, R_3=H) respectively, which were able to be fully characterized. Similarly, reactions of *α*-furyl and *α*-thienyl glyoxals with III in the presence of carbon dioxide gave the expected products Vd (R=*α*-furyl) and Ve (R=*α*-thienyl) respectively accompanied with a trace quantity of the corresponding 1,2-diacylethylene glycols VIId (R=*α*-furyl) and VIIe (R=*α*-thienyl) besides VI. Vd and Ve were also susceptible to the air oxidation, for example, Vd was converted into VI and 3-*α*-furylquinoxalin-3-one (VIIIb, R=*α*-furyl)[12] by the action of *o*-phenylenediamine in ethanol. *β*-Naphthylglyoxal also gave the 2-oxalylthiamine derivative (Vf, R=*β*-naphthyl), although in this case, the corresponding ethylene glycol derivative could not be isolated. These 2-oxalylthiamine derivatives Vd-f afforded corresponding stable acyl derivatives on acetylation or benzoylation under appropriate conditions (See experimental section).

The reaction was able to be extended to some aliphatic *α*-ketoaldehydes. Thus, *t*-butyl, isopropyl, isobutyl and *sec*-butylglyoxals afforded corresponding 2-oxalylthiamine derivatives Vg-j (R=*t*-butyl, isopropyl, isobutyl, *sec*-butyl respectively), although their yields were less satisfactory as compared to those of Va-f. This may be attributable to the decomposition of the products by air oxidation during the reaction, because these compounds were found to be more soluble in ethanol than Va-f. In fact, considerable amounts of thiamine thiazolone (VI) was isolated from the reaction mixtures, however the 1,2-diacylethylene glycol derivatives could not be obtained. Although Vg-j were also unstable and could not be fully purified, they were easily convertible into stable diacetates XIn-q.

To extend the scope of the reaction, it was applied to olefinic *α*-ketoaldehydes. Thus, *trans*-cinnamyl glyoxal and *trans-p*-chlorocinnamyl glyoxal[13] were allowed to react with III similarly, and the reactions were shown to proceed quite analogously providing Vk (R=*trans*-cinnamyl) and Vl (R=*trans-p*-chlorocinnamyl) respectively as deep red crystals.

Table I. 2-Oxalylthiamine Derivatives (Va-l)

V		mp (°C)	Yield[b] (%)	λ_{max}^{EtOH} (visible region) (mμ)
a	C_6H_5	150—158 (d)[a]	55	420
b	C_6H_5	126—130 (d)	31	425
c	C_6H_4-OMe (*p*)	amorph.[c]	73	423
d	*α*-Furyl	140—144 (d)	49	433
e	*α*-Thienyl	138—145 (d)	67	437
f	*β*-Naphthyl	amorph.	46	434
g	$C(CH_3)_3$	157—166 (d)	30	384
h	$CH(CH_3)_2$	162—169 (d)	23	384
i	$CH_2CH(CH_3)_2$	amorph.	7	385
j	$CH(CH_3)CH_2CH_3$	168—170 (d)	34	385
k	*t*-[d]CH=CH-C_6H_5	120—125 (d)	41	468
l	*t*-CH=CH-C_6H_4-Cl(*p*)	110—115 (d)	68	466

a) d=decomposition *b*) Yields were calculated for thiamine-sodium salt. c) amorph.=amorphous d) *t*=*trans*

12) A. Gómez-Sánchez and M. Yruelá-Antinõlo, *Chem. Abstr.*, **50**, 10108 (1956).
13) These glyoxals were obtained by the selenium dioxide oxidation of corresponding methylketones (See experimental section).

Table II. Physical Constants of Acyl Derivative of 2-Oxalylthiamine (XIa-r)

XI	R_1	R_2	R_3	mp (°C)	IR ν_{max}^{Nujol} (CO) cm^{-1}	λ_{max}^{EtOH} (visible region) $m\mu$ (log ε)
a	C_6H_5	Ac[a]	Ac	176—178 (d)[b]	1763, 1730, 1636	391 (4.40)
b	C_6H_5	Ac	H	184—186 (d)	1770, 1665	392 (4.41)
c	C_6H_5	Bz[c]	Bz	173—174 (d)	1749, 1723, 1673	394 (4.41)
d	C_6H_5	Bz	H	189.5—190 (d)	1749, 1680	394 (4.40)
e	C_6H_4–Br(*p*)	Bz	H	165—170 (d)	1746, 1672	398 (4.38)
f	C_6H_4–OMe(*p*)	Bz	H	174—178 (d)	1740, 1680	397 (4.44)
g	α-Furyl	Ac	Ac	124—127 (d)	1775, 1740, 1675	409 (4.46)
h	α-Furyl	Ac	H	199—200 (d)	1765, 1665	410 (4.41)
i	α-Furyl	Bz	H	179—180 (d)	1730, 1665	412 (4.45)
j	α-Thienyl	Ac	Ac	166—168 (d)	1778, 1734, 1680	414 (4.36)
k	α-Thienyl	Ac	H	166—168 (d)	1775, 1680	415 (4.43)
l	α-Thienyl	Bz	H	207—209 (d)	1740, 1695	413 (4.47)
m	β-naphthyl	Bz	H	171—174 (d)	1740, 1665	402 (4.39)
n	$C(CH_3)_3$	Ac	Ac	179—183 (d)	1779, 1742, 1670	363 (4.42)
o	$CH(CH_3)_2$	Ac	Ac	178—180 (d)	1780, 1750, 1675	362 (4.41)
p	$CH_2CH(CH_3)_2$	Ac	Ac	169—170 (d)	1770, 1730, 1665	373 (4.42)
q	$CH(CH_3)CH_2CH_3$	Ac	Ac	180—181 (d)	1780, 1750, 1674	373 (4.42)
r	*trans*-CH=CH–C_6H_5	Ac	Ac	178—179 (d)	1770, 1750, 1630	438 (4.40)

a) Ac=acetyl *b*) d=decomposition *c*) Bz=benzoyl

The reaction was thus confirmed to be applicable to the various types of α-ketoaldehydes, and these results are summerized in Table I. In Table II the physical constants of the acyl derivatives of 2-oxalylthiamine are listed, and in Fig. 1 the NMR spectra of some 2-oxalylthiamine diacetates are shown.

Foregoing results disclose that α-ketoaldehydes in general are readily condensed with thiamine to give 2-oxalylthiamine derivatives under mild conditions, and in particular, it is notable that these products undergo facil air oxidation to generate α-ketoacids. As cocarboxylase, thiamine has been known to play an important role in the pyruvate metabolism which involves hydroxyethylthiamine diphosphate (HETDP) as a significant intermediate.[4a,b] The intermediate is found to be oxidised to acetate by an enzyme pyruvate oxidase, and the oxidation has been shown to proceed non enzymatically in the presence of 2,6-dichlorophenol indophenol as an electron acceptor.[14] Hydroxymethylthiamine diphosphate (HMTDP, active formaldehyde) is known also to undergo non enzymatic oxidation to formic acid in the presence of the electron acceptor.[15] The oxidation of 2-oxalylthiamine derivatives to α-ketoacids is partly similar to these oxidations, however in the present case, it proceeds almost spontaneously without presence of any special electron acceptor when oxygen is present (Chart 4).

$$\text{thiamine} + \text{RCOCHO} \xrightarrow{O_2} \text{thiamine thiazolone} + \text{RCOCOOH}$$

Chart 4

The remarkable catalitic activity of thiamine for the acyloin condensation reactions of aldehydes has been found first by Ugai and coworkers.[16] In this respect, it appears to be anomalous that the present reactions afforded 1,2-diacylethylene glycols which correspond to the dihydroderivatives of the expected acyloin condensation products, although their yields were poor. For a plausible mechanism of the present reaction, the following scheme may

14) L.O. Krampitz, I. Suzuki, and G. Gruell, *Ann. N.Y. Acad. Sci.*, **98**, 466 (1962).
15) G. Kohlhaw, B. Deus, and H. Holzer, *J. Biol. Chem.*, **240**, 2135 (1965).
16) T. Ugai, T. Dokawa, and S. Tsubokawa, *Yakugaku Zasshi*, **64**, 7A 3 (1944).

provide a reasonable explanation (Chart 5). The thiazolium ylid (A), or nucleophilic carbene,[17] initially resulted from thiamine (sodium salt or hydrochloride) would first add to α-ketoaldehyde to form carbanion (B) from which the major product (V) would be formed by a simple isomerization *via* path a). While the carbanion (B) might possibly undergo further condensation with the second molecule of α-ketoaldehyde to give an intermediate (1:2) adduct (C) *via* path b), and hydrolytic cleavage of the intermediate would result the minor products VI and VII.

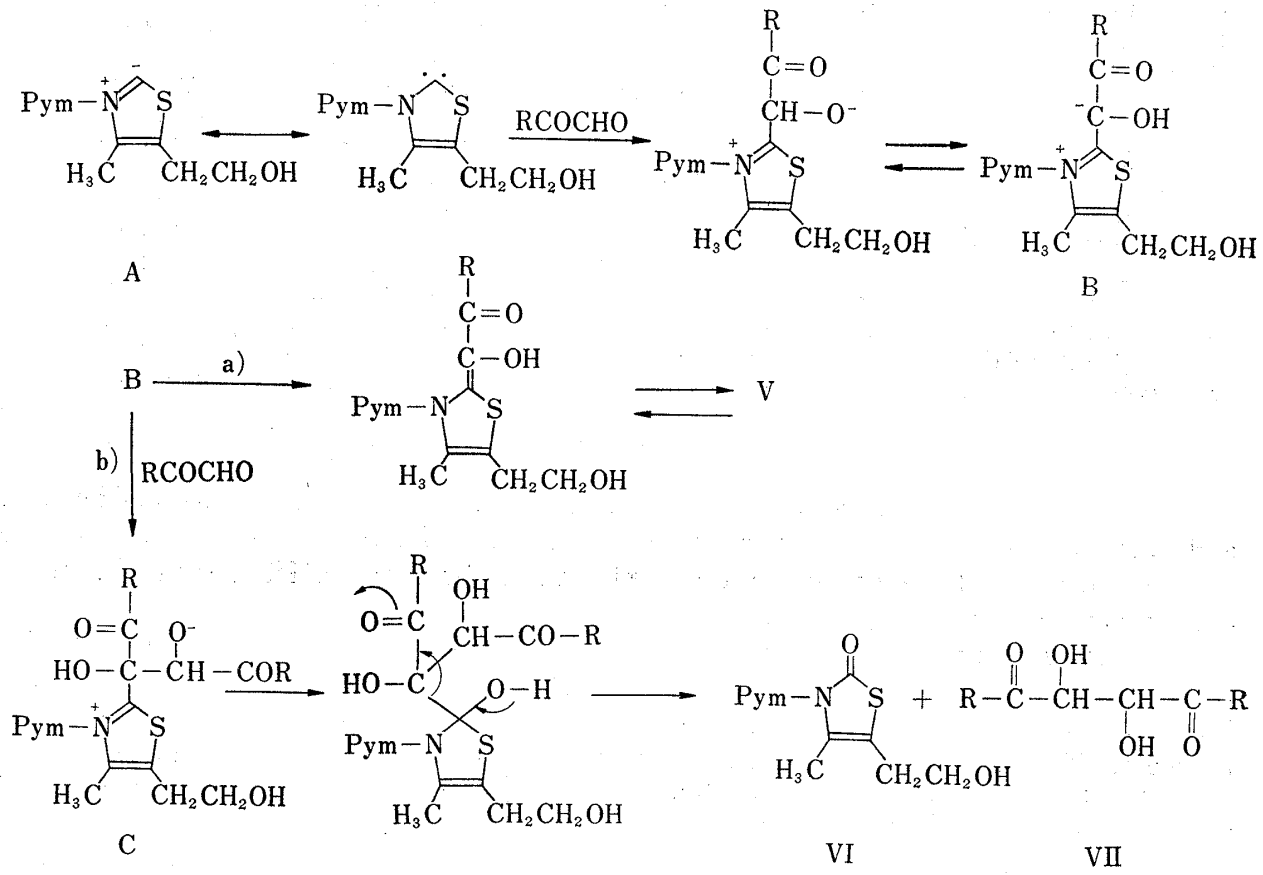


Chart 5

Experimental

All melting points were determined in capillary tube and are uncorrected. NMR spectra were taken on a Varian-Associates A-60 recording spectrometer in $CDCl_3$ or d_6-DMSO solution with tetramethylsilane (TMS) as an internal standard. Following abbreviations are used for the representation of NMR data: pym=pyrimidine, s=singlet, d=doublet, t=triplet, q=quartet, d.d=double doublet, sext=sextet and m=multiplet. IR spectra were taken in nujol mull on a Japan Spectroscopic Company IR-S infrared spectrophotometer using a NaCl prism, and UV spectra were taken on a Hitachi EPS-3 recording spectrophotometer in 99% EtOH. Silica Gel (Davision, Grade 950) was used for column chromatography, and eluted with acetone unless otherwise stated.

General Procedure for the Reaction of Thiamine-sodium Salt (III) with α-Ketoaldehyde——To a stirred suspension of III (0.01M) in 99% EtOH, CO_2 gas is introduced for *ca.* 1 hr at room temperature, then α-ketoaldehyde (0.01—0.02M) is added to the reaction mixture. After having been stirred for 2—3 hr under nitrogen stream at room temperature, the reaction mixture is concentrated under reduced pressure, and the resulting residue is washed adequately with H_2O, then it is suspended in $CHCl_3$ and filtered to give crude 2-oxalylthiamine which is dried *in vacuo* at room temperature.

Reaction of Phenylglyoxal with III——III (4.25 g, 0.01M, containing two equimolar amounts of NaCl) and phenylglyoxal (2.68 g, 0.02M) were allowed to react in 100 ml of 99% EtOH according to the general

17) H.W. Wanzlick, *Angew. Chem.*, **74**, 129 (1962).

procedure. The crude product was suspended in $CHCl_3$ and filtered by suction to give yellow powder which was repeatedly washed with H_2O, then with ether and dried overnight at 20°, 0.1 mmHg to give Va as green powder, mp 150—158° (decomp.). Yield 2.6 g (56.2%). *Anal.* Calcd. for $C_{20}H_{22}N_4O_3S \cdot 1/2H_2O$: C, 58.97; H, 5.68; N, 13.93; S, 7.88. Found: C, 58.70; H, 5.85; N, 13.52; S, 8.13. IR ν_{max}^{Nujol} cm^{-1}: 1660 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 233 (4.09), 274 (3.83), 4.20 (>3.90). The $CHCl_3$ filtrate, after concentration under reduced pressure, gave a brown gummy substance which was subjected to the column chromatography, and from benzene eluate VIIa was obtained as colorless prisms, mp 116—118°. Yield 42 mg. *Anal.* Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22; O, 23.68. Found: C, 71.12; H, 5.45; O, 24.31. Mol. wt. Calcd. for $C_{16}H_{14}O_4$: 270.27. Found (vapor pressure lowering method): 258. IR ν_{max}^{Nujol} cm^{-1}: 1695 (C=O), 3480 (OH). NMR ($CDCl_3$) τ: 1.9—2.5 (1OH, m, phenyl), 4.64 (2H, broad d, 2X-C<u>H</u>-OH), 6.10 (2H, broad, 2XOH). The column was then eluted with acetone to give thiamine thiazolone (VI) which was identified with authentic sample by IR comparison. Yield 130 mg.

Reaction of Phenylglyoxal with Thiamine Hydrochloride (I)——a) To a stirred suspension of I (3.37 g, 0.01M) in 50 ml of EtOH, NEt_3 (2.5 g) was added and stirred for 30 min at room temperature. To the solution, phenylglyoxal (2.68 g, 0.02M) was added and stirred for 3 hr at room temperature under N_2 stream. The reaction mixture was concentrated under reduced pressure to leave a brown residue which was treated quite similarly as stated in the general procedure to give Va. Yield 2.2 g (42.5%). From the filtrate of Va, VI (32 mg) and VIIa (110 mg) were isolated by column chromatography in similar way.

b) To a stirred solution of I (3.37 g, 0.01M) in 100 ml of 50% aqueous EtOH, 10% aqueous NaOH solution was added dropwise to adjust pH *ca.* 9.0, then phenylglyoxal (2.68 g, 0.02M) was added. After having been stirred for 2 hr at room temperature under N_2 stream, the resulting deposits were collected and washed with H_2O, subsequently with ether to give Va as yellow powder. Yield 0.9 g (17.4%).

Air Oxidation of 2-Phenyloxalylthiamine (Va)——a) Va (400 mg) was dissolved in 10 ml of pyridine, and the resulting deep green solution was stirred for 6 hr at room temperature. After evaporation of the reaction mixture under reduced pressure, the residue was dissolved in $CHCl_3$ and extracted with 10% aq. Na_2CO_3 solution. The aqueous layer after acidification with 10% HCl was extracted with ether, and on evaporation the ether layer gave phenylglyoxylic acid (60 mg). The $CHCl_3$ layer, on the other hand, was washed, dried over anhyd. Na_2SO_4 and concentrated to dryness, and the residual gummy material was subjected to column chromatography to give VI (180 mg). By the similar procedure, 400 mg of Va was oxidized in DMSO solution to give phenylglyoxylic acid (75 mg) and VI (200 mg). To a solution of Va (400 mg) in abs. pyridine (5 ml), oxygen was introduced with stirring. The amount of oxygen absorbed was determined after 1 hr to be 20.5 ml at 17°, 760 mmHg (86% of the theoretical).

b) Va (400 mg) was dissolved in 50 ml of 10% NaOH to give deep red solution which was vigorously stirred for 10 hr at room temperature. Thiamine thiazolone (VI) gradually deposited as white needles which were collected and weighed (268 mg, 95%).

c) To a solution of *o*-phenylenediamine (130 mg) in 20 ml of EtOH, Va (200 mg) was added and the mixture was warmed for few minutes with stirring, then it was allowed to stand overnight at room temperature. After evaporation of EtOH under reduced pressure, the residue was recrystallized from EtOH to give 3-phenylquinoxalin-2-one (VIIIa) (160 mg, 36%) which was identified with authentic sample by IR comparison. From the mother liquor of the recrystallization, brown gummy substance was obtained on evaporation under reduced pressure, and it was subsequently subjected to column chromatography to give VI (110 mg, 39%).

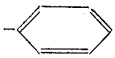
Acyl Derivatives of 2-Phenyloxalylthiamine (Va)——a) Diacetate (XIa): Va (1.5 g) was dissolved in 10 ml of pyridine and Ac_2O (2 ml) was added gradually under N_2 stream while cooling in an ice bath, then the solution was stirred for 4 hr at room temperature. After concentration of the reaction mixture under reduced pressure, the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4 and concentrated to give crystalline residue which was recrystallized from MeOH to give XIa as yellow prisms, mp 176—178° (decomp.). Yield 1.1 g (57%). *Anal.* Calcd. for $C_{24}H_{26}N_4O_5S$: C, 59.74; H, 5.43; N, 11.61; S, 6.62. Found: C, 59.72; H, 5.47; N, 11.41; S, 6.83. IR ν_{max}^{Nujol} cm^{-1}: 1763 (C=O), 1730 (C=O), 1636 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 234 (4.32), 272 (3.90), 391 (4.40). NMR (d_6-DMSO) τ: 2.65 (5H, m, phenyl), 2.82 (1H, s, pym-6-H), 3.11 (2H, broad, NH_2), 4.90 (2H, broad d, pym-5-CH_2), 5.77, 7.04 (each 2H, t, =C-CH_2-CH_2-O), 7.68, 7.91 (each 3H, s, pym-2-CH_3, =C-CH_3 respectively), 7.97 and 8.43 (each 3H, s, 2XOAc).

b) Enol Monoacetate (XIb): Va (2.0 g) was dissolved in 10 ml of (1:1) aqueous pyridine and Ac_2O (1 g) was added gradually under N_2 stream while cooling in an ice bath. After having been stirred for *ca.* 30 min at 10—15°, the reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4 and concentrated to give crystalline residue which was recrystallized from acetone to give XIb as yellow prisms, mp 184—186° (decomp.). Yield 1.23 g (56%). *Anal.* Calcd. for $C_{22}H_{24}N_4O_4S$: C, 59.98; H, 5.49; N, 12.72; S, 7.28. Found: C, 59.81; H, 5.51; N, 12.61; S, 7.12. IR ν_{max}^{Nujol} cm^{-1}: 1770 (C=O), 1665 (C=O), UV λ_{max}^{EtOH} mμ (log ε): 229 (4.31), 271 (3.92), 392 (4.41).

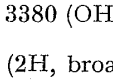
c) Dibenzoate (XIc): Va (900 mg) was dissolved in 10 ml of pyridine and benzoyl chloride (*ca.* 600 mg) was added dropwise while cooling in an ice bath, then the reaction mixture was stirred for 4 hr at room tem-

perature. After concentration of the reaction mixture under reduced pressure, the resulting residue was extracted with $CHCl_3$, and the $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4 and concentrated to give crystalline residue which was recrystallized from MeOH to give XIc, as yellow prisms, mp 173—174° (decomp.). Yield 750 mg (53%). *Anal.* Calcd. for $C_{34}H_{30}N_4O_5S$: C, 67.32; H, 4.99; N, 9.24; S, 5.27. Found: C, 67.13; H, 4.80; N, 9.01; S, 5.02. IR ν_{max}^{Nujol} cm^{-1}: 1749 (C=O), 1723 (C=O), 1673 (C=O). UV λ_{max}^{EtOH} $m\mu$ (log ε): 232 (4.30), 270 (3.89), 394 (4.41). NMR (d_6-DMSO)τ: 1.9—2.9 (6H, m, 3X phenyl and pym-6-H), 3.5 (2H, broad, NH_2), 4.7—5.7 (4H, m, pym-5-CH_2 and -C<u>H</u>$_2$-OCO-), 6.95 (2H, t, =C-C<u>H</u>$_2$-), 7.89 and 7.97 (each 3H, s, pym-2-CH_3 and =C-CH_3 respectively).

d) Enol Monobenzoate (XId): Va (500 mg) was dissolved in 10 ml of (1:1) aqueous pyridine and benzoyl chloride (*ca.* 400 mg) was added dropwise under N_2 stream while cooling in an ice bath, then the mixture was stirred for 1hr at room temperature. After addition of H_2O (50 ml) to the reaction mixture, the deposited crystals were collected and recrystallized from MeOH to give XIc as yellow prisms, mp 189.5—190° (decomp.). Yield 340 mg (54%). *Anal.* Calcd. for $C_{27}H_{26}N_4O_4S \cdot 1/2H_2O$: C, 63.41; H, 5.32; N, 10.96; S, 6.20. Found: C, 63.69; H, 5.02; N, 10.67; S, 6.31. IR ν_{max}^{Nujol} cm^{-1}: 1749 (C=O), 1680 (C=O). UV λ_{max}^{EtOH} $m\mu$ (log ε): 232 (4.47), 273 (3.92), 394 (4.40). NMR (d_6-DMSO)τ: 2.1—2.9 (11H, m, 2X phenyl and pym-6-H), 3.58 (2H, broad, NH_2) 5.14 (1H, difused t, OH), 6.1—6.4 (4H, m, -C<u>H</u>$_2$-O- and pym-5-CH_2), 7.22 (2H, t, =C-C<u>H</u>$_2$-), 7.90 and 7.98 (each 3H, s, pym-2-CH_3 and =C-CH_3 respectively).

Reaction of *p*-Bromophenylglyoxal with III——III (4.25 g) and *p*-bromophenylglyoxal (4 g) were allowed to react in 100 ml of EtOH according to the general procedure, and the resulting crude product was suspended in $CHCl_3$ and filtered to give Vb as yellow crystalline powder, mp 126—130° (decomp.). Yield 1.58 g (31%). IR ν_{max}^{Nujol} cm^{-1}: 1660 (C=O), UV ν_{max}^{EtOH} $m\mu$: 237, 272, 425. The $CHCl_3$ filtrated was concentrated under reduced pressure to give oily residue which was subsequently subjected to column chromatography and eluted with benzene to give 1,2-di-(*p*-bromobenzoyl)ethylene glycol (VIIb) which on recrystallization from MeOH gave colorless prisms, mp 197—200°. Yield 520 mg. *Anal.* Calcd. for $C_{16}H_{12}O_4Br_2$: C, 44.99; H, 2.83. Found: C, 44.70; H, 2.83. IR ν_{max}^{Nujol} cm^{-1}: 3370 (OH), 1670 (C=O). NMR (d_6-DMSO)τ: 2.15 (8H, AB q, J_{AB}=9 cps, Δ_{AB}=15 cps, 2X -  - Br), 4.05 (2H, broad, 2XOH), 4.88 (2H, difused d, J≒5 cps, 2X-C<u>H</u>-OH).

2-(*p*-Bromophenyloxalyl)thiamine Monobenzoate (XIIe)——Vb (1.5 g) was dissolved in 10 ml of (1:1) aqueous pyridine, and benzoyl chloride (1 g) was added gradually with stirring while cooling in an ice bath, then the reaction mixture was stirred for 1 hr at room temperature. To the reaction mixture, 20 ml of H_2O was added and after standing for 30 min the deposited crystals were collected and recrystallized from MeOH to give XIIe as yellow prisms, mp 165—167° (decomp.). Yield 1.02 g (56%). *Anal.* Calcd. for $C_{27}H_{25}N_4O_4SBr$: C, 56.25; H, 4.38; N, 9.74; S, 5.58. Found: C, 56.52; H, 4.43; N, 9.30; S, 5.43. IR ν_{max}^{Nujol} cm^{-1}: 1746 (C=O), 1672 (C=O). UV λ_{max}^{EtOH} $m\mu$ (log ε): 232 (4.45), 270 (4.01), 398 (4.38). NMR (d_6-DMSO)τ: 1.7—2.9τ (10H, m, aromatic protons), 2.90 (2H, broad, NH_2), 6.04 and 7.14 (each 2H, t, =C-C<u>H</u>$_2$-C<u>H</u>$_2$O), 7.53 and 8.05 (each 3H, s, pym-2-CH_3 and =C-CH_3 respectively).

Reaction of *p*-Methoxyphenylglyoxal with III——III (4.25 g) and *p*-methoxyphenylglyoxal (4 g) were allowed to react in 100 ml of EtOH according to the general procedure and the resulting crude product was suspended in $CHCl_3$ and filtered to give Vc as yellow-green amorphous powder. Yield 3.14 g (73%). UV λ_{max}^{EtOH} $m\mu$: 236, 273, 423. The $CHCl_3$ filtrate after concentration and column chromatography gave 1,2-di-(*p*-methoxybenzoyl)ethylene glycol (VIIc) from benzene eluate which was recrystallized from acetone to give colorless prisms, mp 78—80°. Yield 120 mg. *Anal.* Calcd. for $C_{18}H_{18}O_6$: C, 63.15; H, 5.35. Found: C, 64.53; H, 5.44. IR ν_{max}^{Nujol} cm^{-1}: 3380 (OH), 1680 (C=O). NMR (d_6-DMSO)τ: 2.00 and 2.92 (each 4H, d, J=9 cps, 2X -  -OMe), 4.72 (2H, broad d, J≒5 cps, 2X-C<u>H</u>-OH), 6.14 (6H, s, 2XOMe).

2-(*p*-Bromophenyloxalyl)thiamine Monobenzoate (XIIf)——Vc (1.2 g) was dissolved in 10 ml of (1:1) aqueous pyridine and benzoyl chloride (*ca.* 1 g) was added gradually with stirring in an ice bath. After stirring for 30 min at room temperature, 50 ml of H_2O was added to the reaction mixture and the resulting crystalline deposits were collected and recrystallized from EtOH to give XIIf as yellow prisms, mp 174—178° (decomp.). Yield 520 mg. *Anal.* Calcd. for $C_{28}H_{28}N_4O_5S \cdot H_2O$: C, 61.08; H, 5.49; N, 10.18; S, 5.81. Found: C, 60.68; H, 5.96; N, 9.51; S, 5.78. IR ν_{max}^{Nujol} cm^{-1}: 1740 (C=O), 1680 (C=O). UV λ_{max}^{EtOH} $m\mu$ (log ε): 227 (4.45), 272 (4.15), 397 (4.44).

Reaction of α-Furylglyoxal with III——III (4.25 g) and α-furylglyoxal were allowed to react according to the general procedure, and the resulting crude product was suspended in $CHCl_3$ and filtered to giveVd as green powder, mp 140—144° (decomp.). Yield 1.91 g (49%). IR ν_{max}^{EtOH} cm^{-1}: 1650 (C=O), UV λ_{max}^{EtOH} $m\mu$: 234, 277, 433. The $CHCl_3$ filtrate, after concentration under reduced pressure, was subjected to column chromatography and eluted with acetone to give VIId which on recrystallization from acetone afforded colorless prisms, mp 125—127°. Yield 70 mg. *Anal.* Calcd. for $C_{12}H_{10}O_6 \cdot 1/4H_2O$: C, 56.60; H. 4.15; O, 39.25. Found: C, 56.23; H, 3.83; O, 39.46. IR ν_{max}^{Nujol} cm^{-1}: 3440 (OH), 1675 (C=O). NMR ($CDCl_3$)τ: 2.27 (2H, d,

J=1.6 cps, 2X furan-α-H), 2.51 (2H, d, J=3.7 cps, 2X furan-γ-H), 3.34 (2H, d.d, J=1.6 and 3.7 cps, 2X furan-β-H) 4.55 (2H, braod, 2X–$\dot{C}$H-OH), 4.22 (2H, broad, 2XOH).

Air Oxidation of Vd in the Presence of *o*-Phenylenediamine——A mixture of Vd (1.2 g) and *o*-phenylenediamine (300 mg) in 20 ml of MeOH was warmed for 1 hr at 60—70° with stirring, and it was allowed to stand overnight at room temperature. After concentration of the reaction mixture under reduced pressure, the resulting residue was dissolved in $CHCl_3$ and extracted with 5% HCl. From the acid layer, after neutralization with aq. Na_2CO_3, thiamine thiazolone VI (420 mg) was deposited.

The $CHCl_3$ layer, after washing ,drying over Na_2SO_4 and concentration under reduced pressure, gave crystalline residue which was recrystallized from EtOH to give 3-α-furylquinoxalin-2-one (VIIIb) (90 mg) as pale yellow needles, mp >250°.

Acyl Derivatives of 2-(α-Furyloxalyl)thiamine (Vd)——a) Diacetate (XIIg): To a solution of Vd (320 mg) in 5 ml of pyridine, Ac_2O (1 ml) was added while cooling in an ice bath, then the mixture was stirred for 3 hr at room temperature. After addition of H_2O (50 ml), the reaction mixture was extracted with $CHCl_3$ and the $CHCl_3$ was washed, dried and evaporated to leave crystalline residue which was recrystallized from acetone to give XIIg (230 mg) as yellow prisms, mp 124—127° (decomp.). *Anal.* Calcd. for $C_{22}H_{24}N_4O_6S\cdot H_2O$: C, 53.83; H, 5.34; N, 11.42; S, 6.30. Found: C, 53.96; H, 5.20; N, 11.45; S, 6.63. IR ν_{max}^{Nujol} cm^{-1}: 1780 (C=O), 1742 (C=O), 1675 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 231 (4.16), 277 (4.14), 409 (4.46). NMR (d_6-DMSO)τ: 2.27 (1H, d, J=1.8 cps, furan-α-H), 2.93 (1H, s, pym-6-H), 3.07 (1H, d, J=4.5 cps, furan-γ-H), 3.47 (1H, d.d, J=1.8 and 4.5 cps, furan-β-H), 4.94 (2H, broad d, pym-5-CH_2), 5.08 and 7.06 (each 2H, t, =$\dot{C}$–CH_2CH_2-O), 7.80 and 7.94 (each 3H, s, pym-CH_3, =$\dot{C}$–CH_3) 8.00 and 8.10 (each 3H, s, 2XOAc).

b) Monoacetate (XIh): To a solution of Vd (1 g) in 10 ml of (1:1) aqueous pyridine, Ac_2O (2 ml) was added dropwise with stirring in an ice bath, then the reaction mixture was stirred for 30 min at 5—10°. After addition of H_2O (20 ml), the resulting deposits were collected and recrystallized from EtOH to give XIh as yellow prisms, mp 199—200° (decomp.). Yield 820 mg. *Anal.* Calcd. for $C_{20}H_{22}N_4O_5S\cdot H_2O$: C, 53.53; H, 5.39; N, 12.50; S, 7.14. Found: C, 53.39; H, 5.45; N, 12.32; S, 7.54. IR ν_{max}^{Nujol} cm^{-1}: 1765 (C=O), 1665 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 231.5 (4.18), 276.5 (4.09), 410 (4.41). NMR (d_6-DMSO)τ: 2.25 (1H, d, J= 1.8 cps, furan-α-H, 2.87 (1H, s, pym-H), 3.10 (2H, broad, NH_2), 3.12 (1H, d, J=4.5 cps, furan-γ-H), 3.47 (1H, d.d, J=1.8 and 4.5 cps, furan-β-H), 4.95 (2H, broad d. pym-CH_2), 6.40 and 7.23 (each 2H, t, =$\dot{C}$–CH_2-CH_2O-), 7.69 and 7.97 (each 3H, s, pym-CH_3 and =$\dot{C}$–CH_3 respectively) 8.13 (3H, s, Ac).

c) Monobenzoate (XIi): To a solution of Vd (1.2 g) in 10 ml of (1:1) aqueous pyridine, benzoyl chloride (1.0 g) was added dropwise with stirring in an ice bath, then the reaction mixture was stirred for 1 hr at room temperature. After addition of H_2O (50 ml), the reaction mixture was extracted with $CHCl_3$ and the $CHCl_3$ layer was washed, dried and concentrated under reduced pressure, then the resulting crystalline residue was recrystallized from EtOH to give XIi as yellow prisms, mp 179—180° (decomp.). Yield 790 mg. *Anal.* Calcd. for $C_{25}H_{24}N_4O_5S\cdot H_2O$: C, 58.82; H, 5.13; N, 10.98; S, 6.27. Found: C, 58.99; H, 5.06; N, 10.47; S, 6,66. IR ν_{max}^{Nujol} cm^{-1}: 1730 (C=O), 1655 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 230 (4.48), 276 (4.19), 412 (4.45). NMR (d_6-DMSO)τ: 2.20 (1H, d, J=1.8 cps, furan-α-H), 2.87 (1H, s, pym-H), 2.3—2.7 (5H, m, phenyl), 3.25 (1H, d, J=4.8 cps, furan-γ-H), 3.58 (3H, broad, NH_2 and furan-β-H), 5.02 (2H, broad d, pym-5-CH_2), 6.37 and 7.36 (each 2H, t, =$\dot{C}$–CH_2-CH_2-O), 7.90 and 8.07 (each 3H, s, pym-CH_3 and =$\dot{C}$–CH_3 respectively).

Reaction of α-Thienylglyoxal with III——According to the general procedure, III (4.25 g) was allowed to react with α-thienylglyoxal(3.2 g) and the resulting crude product was suspended in $CHCl_3$ and filtered to give Ve as green powder, mp 138—140° (decomp.). Yield 2.83 g (67%). IR ν_{max}^{Nujol} cm^{-1}; 1660 (C=O). UV λ_{max}^{EtOH} mμ: 235, 269, 437. The $CHCl_3$ filtrate was washed, dried and concentrated to dryness under reduced pressure, then the resulting residue was subjected to column chromatography and acetone eluate gave 1,2-di-(α-thienyl)ethylene glycol (VIIe) as colorless prisms, mp 94—95°. Yield 21 mg. *Anal.* Calcd. for $C_{12}H_{10}O_4S_2\cdot H_2O$: C, 48.01; H, 4.03; S, 21.32. Found: C, 47.98; H, 3.95; S, 20.95. IR ν_{max}^{Nujol} cm^{-1}: 3300 (OH), 1660 (C=O).

Acyl Derivatives of 2-(α-Thienyloxalyl)thiamine (Ve)——a) Diacetate (XIj): To a solution of Ve (500 mg) in 10 ml of (1:1) aqueous pyridine, Ac_2O (2 ml) was added dropwise with stirring in an ice bath, then the reaction mixture was stirred for 4 hr at room temperature. After addition of H_2O (50 ml), the reaction mixture was extracted with $CHCl_3$, and the $CHCl_3$ extracts were washed, dried and evaporated under reduced pressure to give XIj which on recrystallization from MeOH–acetone (1:1) gave yellow prisms, mp 166—168° (decomp.). Yield 390 mg. *Anal.* Calcd. for $C_{22}H_{24}N_4O_5S_2\cdot H_2O$: C, 52.17; H, 5.18; N, 11.06; S, 12.64. Found: C, 52.53; H, 5.34; N, 11.07; S, 12.85. IR ν_{max}^{Nujol} cm^{-1}: 1778 (C=O), 1734 (C=O), 1680 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 232.5 (4.23), 274 (4.0), 414 (4.36). NMR (d_6–DMSO) τ: 2.32 (1H, d.d, J=3.6 and 1.2 cps, thiophene–α–H), 2.48 (1H, d.d, J=4.8 and 1.2 cps, thiophene–γ–H), 2.94 (1H, d.d, J=4.8 and 3.6 cps, thiophene–β–H), 2.93 (1H, singlet, pym-H), 3.40 (2H, broad, NH_2), 4.90 (2H, difused d, pym-CH_2), 5.77 and 7.05 (each 2H, t, =$\dot{C}$–CH_2CH_2–O), 7.67 and 7.94 (each 3H, s, pym–CH_3 and =$\dot{C}$–CH_3 respectively), 7.99 and 8.11 (each 3H, s, 2XAc).

b) Monoacetate (XIk): To a solution of Ve (1.0 g) in 5 ml of (1:1) aqueous pyridine, Ac_2O (2 ml) was added dropwise with stirring in an ice bath, then the reaction mixture was stirred for 1 hr at 5—10°. After-

addition of H_2O (50 ml), the deposited crystals were collected and recrystallized from MeOH to give XIk as yellow prisms, mp 166—168° (decomp.). Yield 800 mg. *Anal.* Calcd. for $C_{20}H_{22}N_4O_4S_2 \cdot H_2O$: C, 51.72; H, 5.21; N, 12.06; S, 13.86. Found: C, 51.44; H, 5.19; N, 11.70; S, 13.63. IR ν_{max}^{Nujol} cm^{-1}: 1775 (C=O), 1680 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 232 (4.26), 274 (4.10), 415 (4.43). NMR (d_6-DMSO) τ: 2.33 (1H, d.d, J=1.0 and 6.0 cps, thiophene-α-H), 2.50 (1H, d.d, J=4 and 1 cps, thiophene-γ-H), 2.85 (1H, s, pym-H), 2.9—3.3 (3H, m, NH_2 and thiophene-β-H), 4.93 (2H, broad d, pym-CH_2), 6.39 and 7.25 (each 2H, t, =C-CH_2CH_2O), 7.68 and 7.94 (each 3H, s, pym-CH_3 and =C-CH_3 respectively) 8.13 (3H, s, Ac).

c) Monobenzoate (XIl): To a solution of Ve (1.5 g) in 5 ml of (1:1) aqueous pyridine, benzoyl chloride (*ca.* 1 g) was added dropwise with stirring in an ice bath, then the reaction mixture was stirred for 30 min at room temperature, and the resulting deposits were collected and recrystallized from EtOH–DMSO (1:1) to give XIl as yellow prisms, mp 207—209° (decomp.). Yield 1.1 g. *Anal.* Calcd. for $C_{25}H_{24}N_4O_4S_2 \cdot 3H_2O$: C, 53.40; H, 5.38; N, 9.96; S, 11.40. Found: C, 54.01; H, 5.05: N, 10.04; S, 11.43. IR ν_{max}^{Nujol} cm^{-1}: 1740 (C=O), 1695 (C=O)), UV λ_{max}^{EtOH} mμ (log ε): 230 (4.47), 276 (3.80), 413 (4.47).

2-β-Naphthyloxalylthiamine (Vf) and Monobenzoate (XIm)——III (4.25 g) and β-naphthylglyoxal (4 g) were allowed to react in 100 ml of EtOH according to the general procedure to give crude Vf as an amorphous powder. Yield 2.2 g (46%). UV λ_{max}^{EtOH} mμ: 434. The crude Vf (1.3 g) was dissolved in 10 ml of (1:1) aqueous pyridine and benzoyl chloride (*ca.* 1 g) was added dropwise with stirring in an ice bath. After stirring for 30 min at room temperature, the resulting crystalline yellow deposits were collected and recrystallized from EtOH to give yellow prisms, mp 171—174° (decomp.). Yield 1.1 g. *Anal.* Calcd. for $C_{31}H_{28}N_4O_4S \cdot 5/2H_2O$: C, 62.31; H, 5.56; N, 9.38; S, 5.36. Found: C, 62.50; H, 4.77; N, 8.84; S, 5.53. IR ν_{max}^{Nujol} cm^{-1}: 1740 (C=O), 1665 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 216 (4.62), 231 (4.31), 264 (3.92), 402 (4.39).

2-*t*-Butyloxalylthiamine (Vg) and Diacetate (XIn)——III (6.2 g) and *t*-butylglyoxal (3.9 g) were allowed to react according to the general procedure to give crude Vg as pale yellow powder, mp 157—160° (decomp.). Yield 2.3 g (30%). IR ν_{max}^{Nujol} cm^{-1}: 1670 (C=O). UV λ_{max}^{EtOH} mμ: 235, 272, 384. Column chromatography of the mother liquor of Vg gave thiamine thiazolone (VI) (630 mg). Vg (490 mg) was dissolved in 5 ml of pyridine and 2 ml of Ac_2O was added and stirred for 4 hr at room temperature under N_2 stream. After evaporation of the reaction mixture under reduced pressure, the resulting residue was extracted with $CHCl_3$, then the $CHCl_3$ layer was washed, dried and concentrated to give gummy residue which was crystallized by the addition of acetone, collected and recrystallized to give XIn as pale yellow prisms, mp 179—183° (decomp.). Yield 32 mg. *Anal.* Calcd, for $C_{22}H_{30}N_4O_5S \cdot 1/2H_2O$: C, 56.06; H, 6.62; N, 11.89; S, 6.79. Found: C, 56.57; H, 6.39; N, 11.73; S, 7.09. IR ν_{max}^{Nujol} cm^{-1}: 1779 (C=O), 1742 (C=O), 1670 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 233 (4.30), 274 (4.07), 363 (4.42). NMR ($CDCl_3$) τ: 2.27 (1H, s, pym-H), 4.90 (2H, broad, NH_2), 5.12 (2H, broad s, pym-CH_2), 5.84 and 7.20 (each 2H, t, =C-CH_2CH_2O-), 7.52 (3H, s, pym-CH_3), 7.98 (6H, s, =C-CH_3 and Ac), 8.02 (3H, s, Ac), 8.87 (9H, s, $C(CH_3)_3$).

2-Isopropyloxalylthiamine (Vh) and Diacetate (XIo)——III (9 g) and isopropylglyoxal (4 g) were allowed to react according to the general procedure to give crude Vh as pale yellow crystalline powder, mp 162—169° (decomp.). Yield 2.5 g (23%). IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O). UV λ_{max}^{EtOH} mμ: 235, 272, 384. Vh (600 mg) was dissolved in 5 ml of pyridine, and Ac_2O (2 ml) was added with stirring in an ice bath, then the reaction mixture was stirred for 4 hr at room temperature. After concentration under reduced pressure, the reaction mixture was extracted with $CHCl_3$ and the $CHCl_3$ extract was washed, dried and concentrated to leave an oily residue which was subjected to column chromatography to give XIo. Recrystallization of XIo from acetone gave pale yellow prisms, mp 178—180° (decomp.). Yield 250 mg. *Anal.* Calcd. for $C_{21}H_{28}N_4O_5S$: C, 56.24; H, 6.29; N, 12.49; S, 7.14. Found: C, 55.96; H, 6.18; N, 12.26; S, 7.65. IR ν_{max}^{Nujol} cm^{-1}: 1780 (C=O), 1750 (C=O), 1675 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 232.5 (4.31), 273 (3.92), 362 (4.41). NMR ($CDCl_3$) τ: 2.40 (1H, s, pym-H), 4.55 (2H, broad, NH_2), 5.05 (2H, broad s, pym-CH_2), 5.83 and 7.19 (each 2H, t, =C-CH_2CH_2O-), 7.50 and 7.96 (each 3H, s, pym-CH_3 and =C-CH_3 respectively), 8.00 and 8.11 (each 3H, s, 2XAc), 8.98 (6H, d, J=7 cps, -CH$\langle^{CH_3}_{CH_3}$).

2-Isobutyloxalylthiamine (Vi) and Diacetate (XIp)——III (4.8 g) and isobutylglyoxal (2.56 g) were allowed to react according to the general procedure to give crude Vi as pale yellow amorphous powder. Yield 300 mg (7%). IR ν_{max}^{Nujol} cm^{-1}: 1650 (C=O). UV λ_{max}^{EtOH} mμ: 235, 271, 385. To a solution of Vi (200 mg) in pyridine (4 ml), Ac_2O (1 ml) was added dropwise with stirring in an ice bath and the reaction mixture was stirred for 4 hr at room temperature. After addition of H_2O (30 ml), the reaction mixture was extracted with $CHCl_3$ and the $CHCl_3$ extract was washed, dried and concentrated to leave an oily residue which was subjected to column chromatography to give crude XIp. Recrystallization of the crude XIp from acetone–ether (1:1) gave pale yellow prisms, mp 169—170° (decomp.). Yield 98 mg. *Anal.* Calcd. for $C_{22}H_{30}N_4O_5S$: C, 57.12; H, 6.54; N, 12.11. Found: C, 57.02; H, 6.51; N, 11.98. IR ν_{max}^{Nujol} cm^{-1}: 1770 (C=O), 1730 (C=O), 1665 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 232 (4.24), 273 (3.90), 373 (4.42). NMR ($CDCl_3$) τ: 2.44 (1H, s, pym-H), 4.50 (2H, broad, NH_2), 5.05 (2H, broad s, pym-CH_2), 5.84 and 7.21 (each 2H, t, =C-CH_2CH_2O-), 7.52 and 7.95 (each 3H, s, pym-CH_3 and =C-CH_3 respectively), 7.97 and 8.11 (each 3H, s, 2XAc), 9.15 (6H, d, J=5 cps, -CH$\langle^{CH_3}_{CH_3}$), 7.89 (2H, d, J=6 cps, -CO-CH_2-).

2-*sec*-Butyloxalylthiamine (Vj) and Diacetate (XIq)——III (12.7 g) and *sec*-butylglyoxal (6.5 g) were allowed to react in 100 ml of EtOH according to the general procedure to give Vj as pale yellow crystalline powder, mp 168—170° (decomp.). Yield 3.9 g (34%). IR ν_{max}^{Nujol} cm^{-1}: 1650 (C=O). UV λ_{max}^{EtOH} mμ: 236, 271, 385. To a solution of Vj (1.0 g) in pyridine (10 ml), Ac_2O (4 ml) was added with stirring in an ice bath, then the reaction mixture was stirred for 4 hr at room temperature. After addition of H_2O (100 ml), the reaction mixture was extracted with $CHCl_3$, and the $CHCl_3$ extract was washed, dried and concentrated to leave an oily residue which was subjected to column chromatography to give XIq. Recrystallization of XIq from acetone–ether (1:1) gave pale yellow prisms, mp 180—181° (decomp.). Yield 320 mg. *Anal.* Calcd. for $C_{22}H_{30}N_4O_5S$: C, 57.12; H, 6.54; N, 12.11. Found: C, 57.07; H, 6.50; N, 11.86. IR ν_{max}^{Nujol} cm^{-1}: 1780 (C=O), 1750 (C=O), 1674 (C=O). NMR ($CDCl_3$) τ: 2.41 (1H, s, pym-H), 4.57 (2H, broad, NH_2), 5.05 (2H, broad, pym-CH_2), 5.84 and 7.20 (each 2H, t, =C–CH_2CH_2O–), 7.51 and 7.99 (each 3H, s, pym-CH_3 and =C–CH_3), 7.97, 8.11 (each 3H, s, 2XAc), 8.59 (1H, sext, CO–CH–), 9.01 (3H, d, J=6 cps, –CH–$\underline{CH_3}$), 9.23 (3H, t, $-CH_2-\underline{CH_3}$).

***trans*-Cinnamylglyoxal**——SeO_2 (11.1 g) was dissolved in 60 ml of refluxing tetrahydrofuran (THF) containing 2 ml of H_2O, and to the solution, *trans*-benzalacetone (14.6 g) was added and refluxed for 3.5 hr. After cooling the reaction mixture, the deposited Se was removed by filtration, and the filtrate was concentrated under reduced pressure to give brown oily residue which was subjected to vacuum distillation and the fraction of bp 95—96° (2.5 mmHg) was collected to give pure *trans*-cinnamylglyoxal as yellow crystals, mp 49—50°. Yield 9.3 g (58%). *Anal.* Calcd. for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 75.83; H, 5.33. IR ν_{max}^{Nujol} cm^{-1}: 1690 (C=O), 1670 (C=O). NMR ($CDCl_3$) τ: 0.6 (1H, s, –CHO), 2.02 and 2.77 (each 2H, d, J=16.5 cps, $_{H}\!>\!C\!=\!C\!<^{H}$), 1.1—1.9 (5H, m, phenyl). In the similar procedure, *trans-p*-chlorobenzalacetone (7 g) and SeO_2 (4.3 g) in THF (23.4 ml) and H_2O (0.8 ml) afforded crude *trans-p*-chlorocinnamylglyoxal as unstable yellow oil. Yield 6.2 g. It gave a crystalline hydrate as colorless prisms, mp 110—112°. IR ν_{max}^{Nujol} cm^{-1}: 3320 (OH), 1705 (C=O).

2-*trans*-Cinnamyloxalylthiamine (Vk) and Diacetate (XIr)——III (9.0 g) and *trans*-cinnamylglyoxal (6.6 g) were allowed to react according to the general procedure to give Vk as deep red crystalline powder, mp 120—125° (decomp.). Yield 3.7 g (41%). IR ν_{max}^{Nujol} cm^{-1}: 1640 (C=O). UV λ_{max}^{EtOH} mμ: 215, 221.6, 233, 275, 468. To a stirred solution of Vk (1.0 g) in pyridine (10 ml), Ac_2O (4 ml) was added dropwise while cooling in an ice bath, then the reaction mixture was stirred for 3 hr at room temperature. After addition of H_2O (50 ml), the reaction mixture was extracted with $CHCl_3$ and the $CHCl_3$ extract was washed, dried and evaporated under reduced pressure to leave a crystalline residue which was recrystallized from acetone–ether (1:1) to give XIr as deep red prisms, mp 178—179° (decomp.). Yield 700 mg. *Anal.* Calcd. for $C_{26}H_{28}O_5N_4S$: C, 61.40; H, 5.55; N, 11.02; S, 6.30. Found: C, 61.18; H, 5.40; N, 10.88; S, 6.40. IR ν_{max}^{Nujol} cm^{-1}: 1770 (C=O), 1750 (C=O), 1630 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 229 (4.31), 290 (4.18), 307 (4.08), 438 (4.40). NMR ($CDCl_3$) τ: 2.47 (1H, s, pym-H), 2.40 and 3.23 (each 1H, d, J=16.5 cps, $_{H}\!>\!C\!=\!C\!<^{H}$), 2.6—2.95 (5H, m, phenyl), 4.43 (2H, broad, NH_2), 5.12 (2H, broad, pym-CH_2), 5.83 and 7.18 (each 2H, t, =C–CH_2CH_2O–), 7.51 and 8.05 (each 3H, s, pym-CH_3 and =C–CH_3), 7.96 and 8.20 (each 3H, s, 2XAc).

2-(*trans-p*-Chlorocinnamyl)oxalylthiamine (Vl)——Reaction of III (1.35 g) with *trans-p*-chlorocinnamylglyoxal (600 mg) in 20 ml of EtOH according to the general procedure gave Vl as deep red crystalline powder, mp 110—115° (decomp.). Yield 1.0 g (68%). IR ν_{max}^{Nujol} cm^{-1}: 1650 (C=O). UV λ_{max}^{EtOH} mμ: 226, 279, 466. Acetylation of Vl with Ac_2O in pyridine gave thiamine thiazolone (VI) and a gummyl substance which was not fully characterized.

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