ON THE REACTION OF AZOLIUM YLIDES WITH DIALKYL ACYLPHOSPHONATE; A NEW SYNTHESIS FOR HETEROCYCLIC COMPOUNDS

Akira Takamizawa*, Hiroshi Harada, Hisao Sato and Yoshio Hamashima

Shionogi Research Laboratory, Shionogi & Co., Ltd.,

Fukushima-ku, Osaka, 553 Japan

Azolium ylides react with dialkyl acylphosphonate to form generally six membered azine derivatives by ring expansion of the azolium heterocycle. This article gives a survey of the reaction with thiazolium, thiadiazolium, oxazolium, oxadiazolium, and imidazolium, and also discusses the relationship of the nature of 4'-substituents to the stability and reactivity of thiamine and its analogues in this novel reaction.

Many reports have been published on the mechanism of decarboxylation of pyruvate by the enzyme pyruvate decarboxylase, and since the thiazolium ylide hypothesis was proposed by Breslow[1] interest has especially centred on the formation of 2-substituted thiazolium compounds by the reaction of thiamine and the related thiazolium salts with various electrophiles. The authors themselves have tried the reaction with aldehydes,[2] α-ketoaldehydes,[3] isocyanates,[4] isothiocyanates,[5] and carbodiimides[6];

chemical model experiments for the first step of the decarboxylation reaction. Compared with these electrophiles, dialkyl acylphosphonates react with thiamine and related thiazolium salts in better yields, giving the 3-oxo-2,3-dihydro-4H-thiazine ring system.

When applied to other azolium salts, the acylphosphonate reaction proceeds in almost the same way as with thiazolium, though some differences are observed depending on the character of the azolium salt used. These differences are mostly attributed to the character of heteroatom involved. In this paper we wish to give an outline of our studies on the acylphosphonate reaction with thiazolium, thiadiazolium, oxazolium, oxadiazolium, and imidazolium salts, as the results seem to be interesting for understanding the nature of azolium heterocycles.

I. Thiamine[7-12]

This reaction is carried out under basic conditions as it involves a thiazolium ylide as an intermediate. Our experimental conditions were as follows: to an ice-cooled suspension of thiamine hydrochloride in dry dimethylformamide, three molar amounts of triethylamine and an equimolar amount of dialkyl acylphosphonate were added and the mixture was allowed to stand overnight at room temperature under nitrogen atmosphere. Evaporation of the dimethylformamide, extraction with chloroform, washing the chloroform extract with aqueous sodium bicarbonate solution and evaporation of chloroform left yellow crystals of 1-phenyl-3(2-hydroxyethyl)-4,9-dimethyl-1,6-dihydropyrimido[4',5'-4,5]pyrimido[2,3-c][1,4]thiazine (III) in 87% yield. With ordinary azolium salts which have no amino group participating in the reaction center,

Chart 1

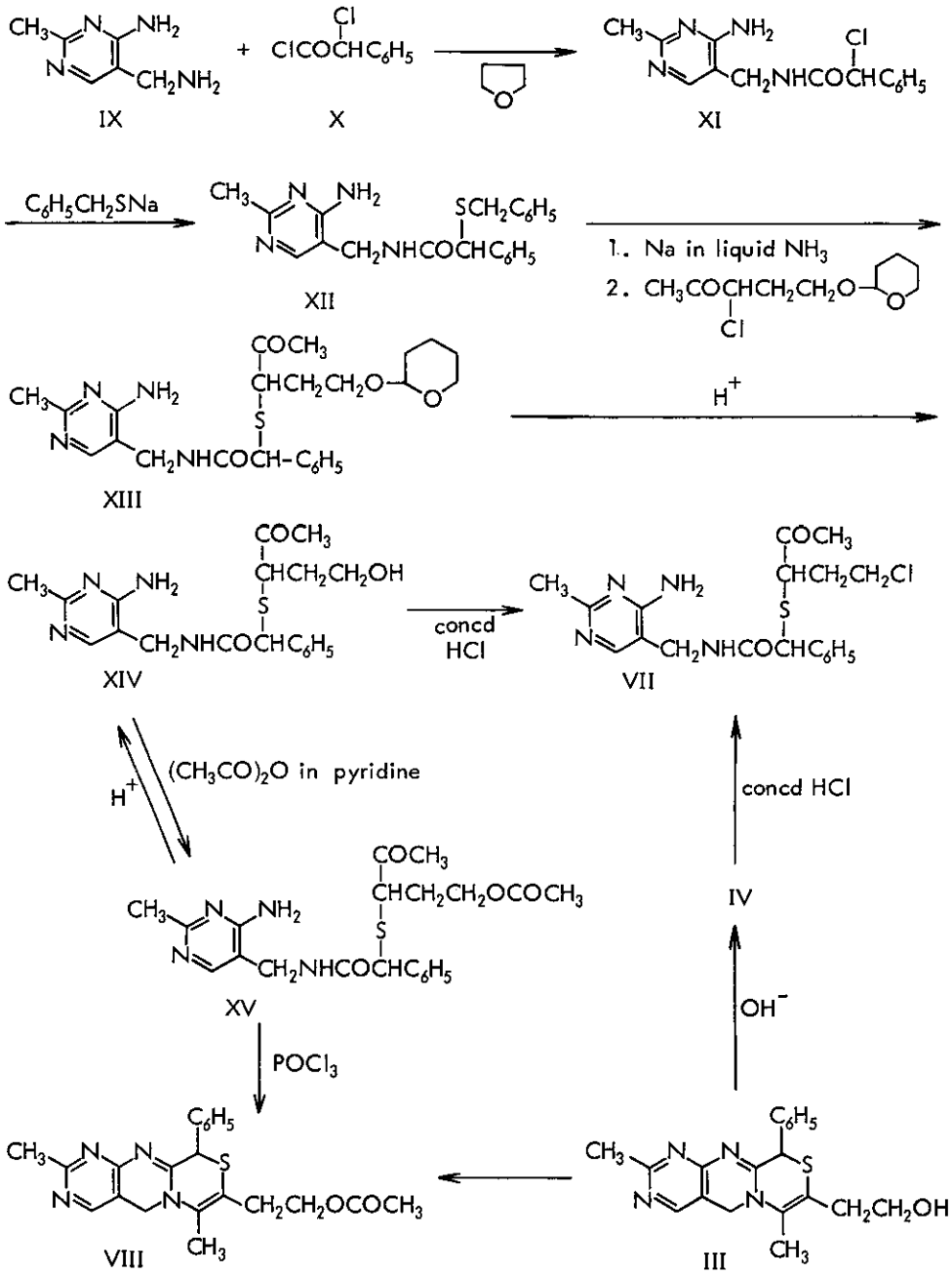
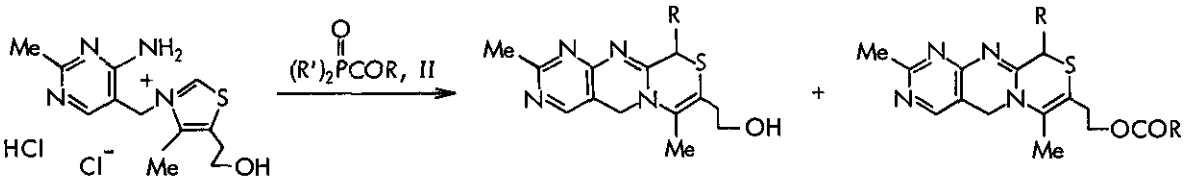

IX
X
XI
XII
XIII
XIV
VII
XV
IV
III
VIII
concd HCl
H+
(CH3CO)2O in pyridine
POCl3
OH−
1. Na in liquid NH3
2. CH3COCHCH2CH2O
Cl

Chart 2

Table 1



I IIIa IIIb

Conditions	R'	R	IIIa (%)	IIIb (%)	Total (%)
4M·Et_3N, 2M·II	MeO	Me	21	19	40
	EtO	Me	24	30	54
	n-PrO	Me	25	30	55
	n-BuO	Me	23	27	50
3M·Et_3N, 1M·II	Ph, MeO	Me	54	-	54
3M·Et_3N, 1M·II	MeO	Ph	78	-	78
	EtO	Ph	86	-	86
	n-PrO	Ph	82	-	82
	n-BuO	Ph	83	-	83
	Ph, MeO	Ph	64	-	64
4M·Et_3N, 2M·II	Ph, MeO	Ph	60	27	87

it was necessary to treat the reaction mixture with alkali after evaporation of dimethylformamide.

Compound (III) produced aminolactam (IV) by alkaline hydrolysis, and oxidation of the product (IV) with hydrogen peroxide formed V, which was rearranged to VI by acyloin type rearrangement. This compound (VI) regenerated thiamine (I) and benzoic acid by the action of hydrogen chloride (Chart 1). Hydrolysis of the aminolactam (IV) with conc. hydrogen chloride gave VII which was identified with an authentic sample, and the acetate (VIII) of the reaction product (III) itself was synthesized by the route shown in Chart 2. Thus, it was shown that this phosphonate reaction is a unique reaction involving ring expansion of the thiazolium ring to a 3-oxo-2,3-dihydro-4H-1,4-thiazine ring system.

This reaction proceeds not only with dialkyl acylphosphonates, but also with methyl phenylbenzoylphosphinate. Different phosphonates and phosphinates used, quantities, and products are shown in Table 1.

II. Mechanism[13]

The mechanism of this novel reaction was elucidated using 3-benzyl-4-methyl-5-(2-benzoyloxyethyl)thiazolium halide (XVI) as starting material. Reaction of the thiazolium salt (XVI) with diethyl benzoylphosphonate in triethylamine-dimethylformamide and evaporation of the solvent left an intermediate whose structure was determined as a 1 : 1 adduct of thiazolium and benzoylphosphonate, 2-(1-diethylphosphoroyl)benzyl-3-benzyl-4-methyl-5-(2-benzoyloxyethyl)thiazolium halide (XXI). Alkaline treatment of this adduct (XXI) effected ready rearrangement to the final product, 2-phenyl-3-oxo-4-benzyl-5-methyl-6-(2-benzoyloxyethyl)-2,3-di-

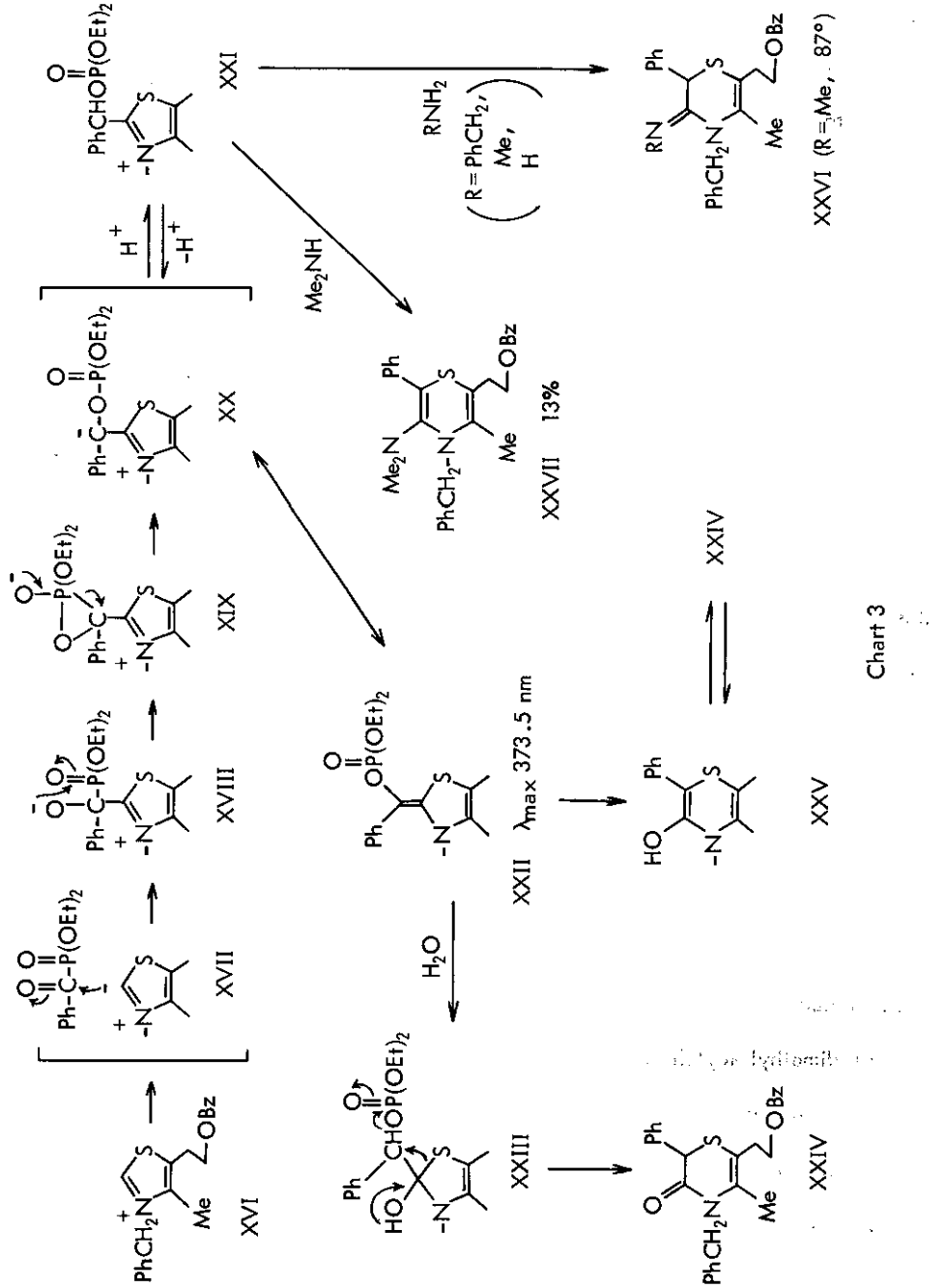


Chart 3

hydro-4H-1,4-thiazine (XXIV), while action of amines on the intermediate (XXI) gave imino derivatives (XXVI, XXVII) corresponding to XXIV (Chart 3).

From this data it can be suggested that the reaction proceeds as follows: thiazolium ylide (XVII) formed by triethylamine treatment reacts with the carbonyl carbon of acylphosphonate to give betaine XVIII, the anion of which attacks the pentavalent phosphorus atom to form a cyclic oxyphosphorane XIX, which easily rearranges to the intermediate betaine (XX).

On alkaline treatment the absorption maxima at 229 and 276 nm of XXI immediately disappear and a strong maximum at 373.5 nm simultaneously appears. The intensity of the new band decreases gradually and the final spectrum shows the same pattern as XXIV. The rate of decrease showed pseudo first order kinetics. In view of this spectral consideration, XXI might rearrange to the final product (XXIV) via XXII, formed by deprotonation of the active methine proton of XXI.

The evidence for rearrangement in the conversion of XVIII to XXI might also be of value for elucidation of the mechanism of the Perkow reaction.

III. Thiazolium[14-16]

The acylphosphonate reaction observed with thiamine is also applicable to general 2-unsubstituted thiazolium salts, 3-oxo-2,3-dihydro-4H-1,4-thiazine derivatives being obtained by treating the reaction mixture with aqueous alkali.

With dimethyl acylphosphonates the intermediates were obtained as O-methyl-O-1-(2-thiazolium)ethylphosphoric acid betaine (XXXI) (Chart 4). Results and yields of 4-methylthiazolium and benzothiazolium salts are shown on the Tables 2 and 3.

Concerning the substituent effect at the 4 and 5 positions of thiazolium bearing a

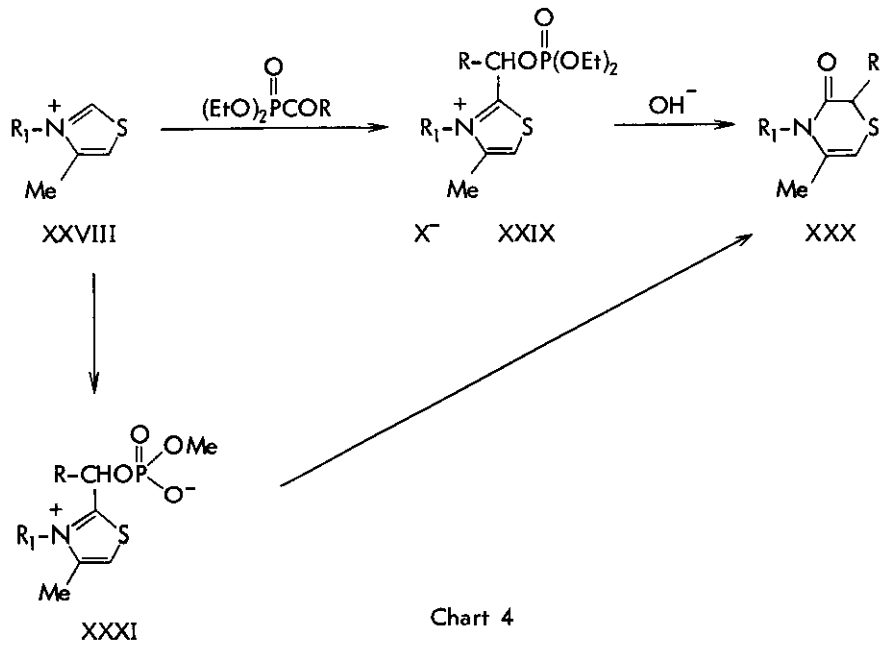


Chart 4

Table 2

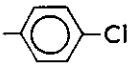
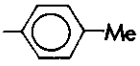
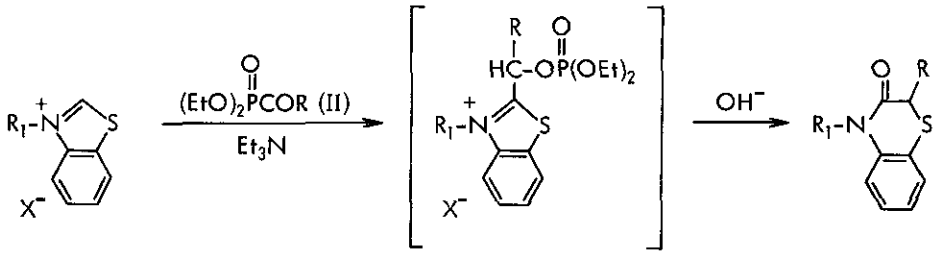
R_1	R	XXX (%)
$PhCH_2$		55
$PhCH_2$		59
$PhCH_2$		52
Me	CH_2Ph	28
Me	Ph	50
Me	Me	52

Table 3



XXXII XXXIII

Compd. No.	Substituents R_1	R	mp (C°)	Yield (%)
XXXIIIa	$PhCH_2$	Ph	126-131	73
XXXIIIb	Me	Ph	153-156	37
XXXIIIc	$PhCH_2$	Me	oil	48
XXXIIId	$PhCH_2$	$PhCH_2$	oil	73
XXXIIIe	$PhCH_2$	p-Me-Ph	137-141	21
XXXIIIf	$PhCH_2$	p-Cl-Ph	153-155	53
XXXIIIg	p-NO_2-$PhCH_2$	Ph	oil	85

(2-methyl-4-amino-5-pyrimidinyl)methyl group at the 3 position, we found that the compound reacted with dialkyl acylphosphonate in the presence of triethylamine to give corresponding 1,4-thiazine derivatives XXXVa,b in about 80% yield when the 5-substituent was β-hydroxyethyl or unsubstituted (R = CH_2CH_2OH or H, XXXIVa,b), while with XXXIVc (R = COOEt) or benzothiazolium (XXXIVd), the yield of 1,4-thiazine product (27-28%) decreased markedly evenwhen triethylamine was added to the suspension of dialkyl acylphosphonate and thiazolium. Reversing the order of addition of triethylamine and acylphosphonate to the thiazolium salts gave only

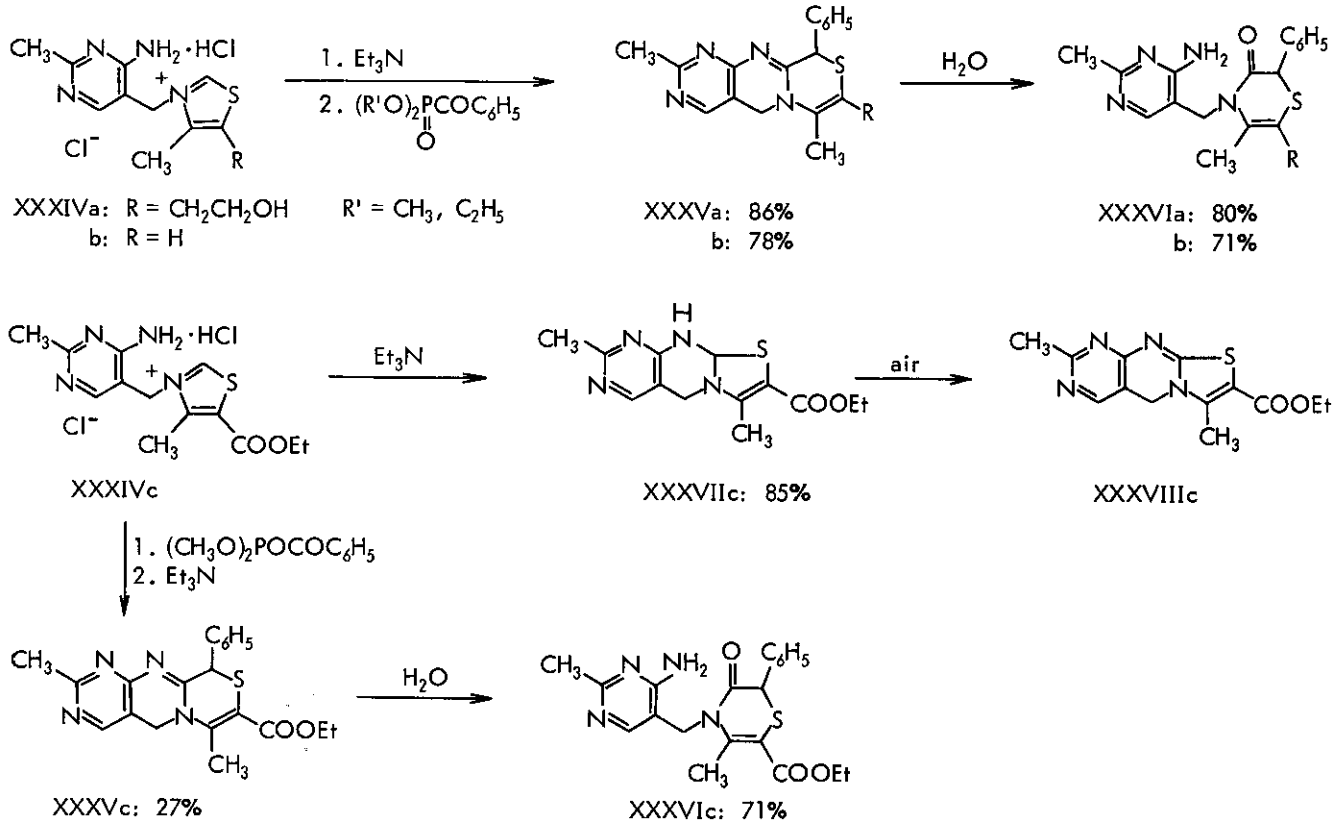

1. Et3N
2. (R'O)2PCOC6H5
H2O
XXXIVa: R = CH2CH2OH
b: R = H
R' = CH3, C2H5
XXXVa: 86%
b: 78%
XXXVIa: 80%
b: 71%
Et3N
air
XXXIVc
XXXVIIc: 85%
XXXVIIIc
1. (CH3O)2POCOC6H5
2. Et3N
H2O
XXXVc: 27%
XXXVIc: 71%

Chart 5

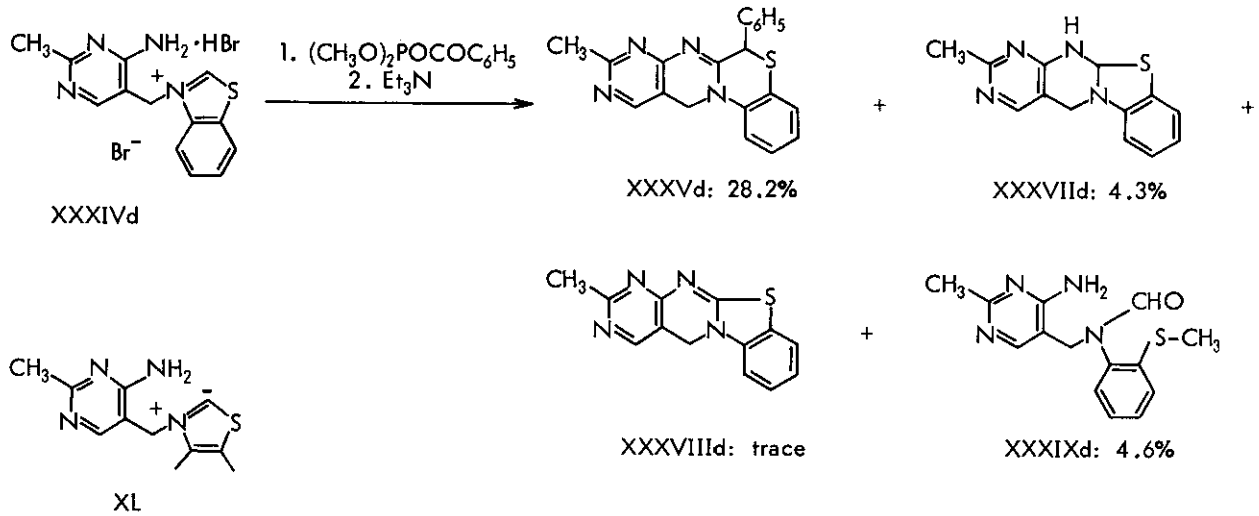


Chart 5 (continued)

tricyclic dihydrothiochrome derivatives (XXXVIIc,d), formed by nucleophilic addition of 4'-amino group to the thiazolium 2 position (Chart 5). These differences according to substituents are attributed to the stability of the thiazolium ylide (XL) formed by the action of triethylamine: unsubstituted ylides or those bearing a 5-alkyl group (XXXIVa,b) are comparatively stable and the 2-carbanion attacks the acyl carbon of acylphosphonate; however, in the case of XXXIVc,d, quasi-aromatic resonance stabilization by π electron participation is inhibited by 4,5 substituents, and the 2 position of thiazolium is attacked by the 4'-amino group as an electrophilic reaction center, resulting in formation of dihydrothiochrome derivatives (XXXVII) via an intramolecular cyclization (Chart 5).

IV. Thiadiazolium

From the observation that the 2 hydrogen of 3-substituted 1,3,4-thiadiazolium exchanges about 3000 times faster than the 2 hydrogen of thiazolium,[17] it is concluded that thiadiazolium has both higher nucleophilic and electrophilic character than thiazolium, a result of introduction of the electronegative nitrogen atom into the nucleus.

The acylphosphonate reaction with simple thiadiazolium salts proceeded in the same way as that with thiazolium compounds. However, the reaction with 3-(2-methyl-4-amino-5-pyrimidinyl)methyl-1,3,4-thiadiazolium salts and 3-methyl-4-(2-methyl-4-amino-5-pyrimidinyl)methyl-1,2,4-thiadiazolium salts, which have an amino group located in a position where it can easily participate at the reaction center, showed some differences in reaction behaviour.

i) 1,2,4-Thiadiazolium.[18] Reaction of 3-methyl-4-benzyl-1,2,4-thiadiazolium bromide with diethyl acetylphosphonate and benzoylphosphonate gave the

ring expanded products 4-benzyl-5,6-dihydro-3,6-dimethyl(and 3-methyl-6-phenyl)-5-oxo-4H-1,2,4-thiadiazine in 10 and 7% yields respectively. It may be supposed that these low yields are due to instability of 1,2,4-thiadiazolium. On the other hand, the action of dialkyl benzoylphosphonate on 3-methyl-4-(2-methyl-4-amino-5-pyrimidinyl)methyl-1,2,4-thiadiazolium bromide (XLI) under moist conditions yielded 10a-(1-dialkylphosphoroylbenzyl)4,5,10,10a-tetrahydro-3,8-dimethyl-1,2,4-thiadiazolo[4',5'-1,2]pyrimido[4,5-d]pyrimidine (XLII), formed by nucleophilic addition of the 4' amino group to the 5 position of the intermediate (XLIV), and the ring expanded product 4-(2-methyl-4-amino-5-pyrimidinyl)methyl-3-methyl-6-phenyl-4H-1,2,4-thiadiazin-5(6H)-one (XLIII). The intermediate (XLIV) was obtained by the acid treatment of XLII, and alkaline treatment of the intermediate (XLIV) effected rearrangement to XLII and XLIII. The same treatment of the N-carbamate (XLVI) of XLIV yielded the 1,2,4-thiadiazine derivative (XLVII) only (Chart 6).

ii) 1,3,4-Thiadiazolium.[19] Reaction of simple 1,3,4-thiadiazolium salts with dialkyl acylphosphonate gave 5,6-dihydro-5-oxo-4H-1,3,4-thiadiazines in about 60% yield as shown in Table 4. The same reaction with 3-(2-methyl-4-amino-5-pyrimidinyl)methyl-1,3,4-thiadiazolium bromide (L), however, yielded 10a-(1-dimethylphosphoroylbenzyl)-10,10a-dihydro-8-methyl-5H-pyrimido[4,5-d]-1,3,4-thiadiazolo-[3,2-a]pyrimidine (R_1 = H, LI) similarly as found with 1,2,4-thiadiazolium derivatives. Hydrolysis of LI with water caused rearrangement to aminolactam (LIII), while treatment with aqueous sodium bicarbonate-sodium carbonate solution gave 4,10-dihydro-7-methyl-4-phenylpyrimido[4',5'-4,5]pyrimido[1,2-d]1,3,4-thiadiazine (R_1 = H, R = Ph, LII), which was transformed to 5,10-dihydro-2-methyl-9-phenylpyrazolo[1,5-a]pyrimido[4,5-d]pyrimidine (R_1 = H, R = Ph, LIV) by desulfurization

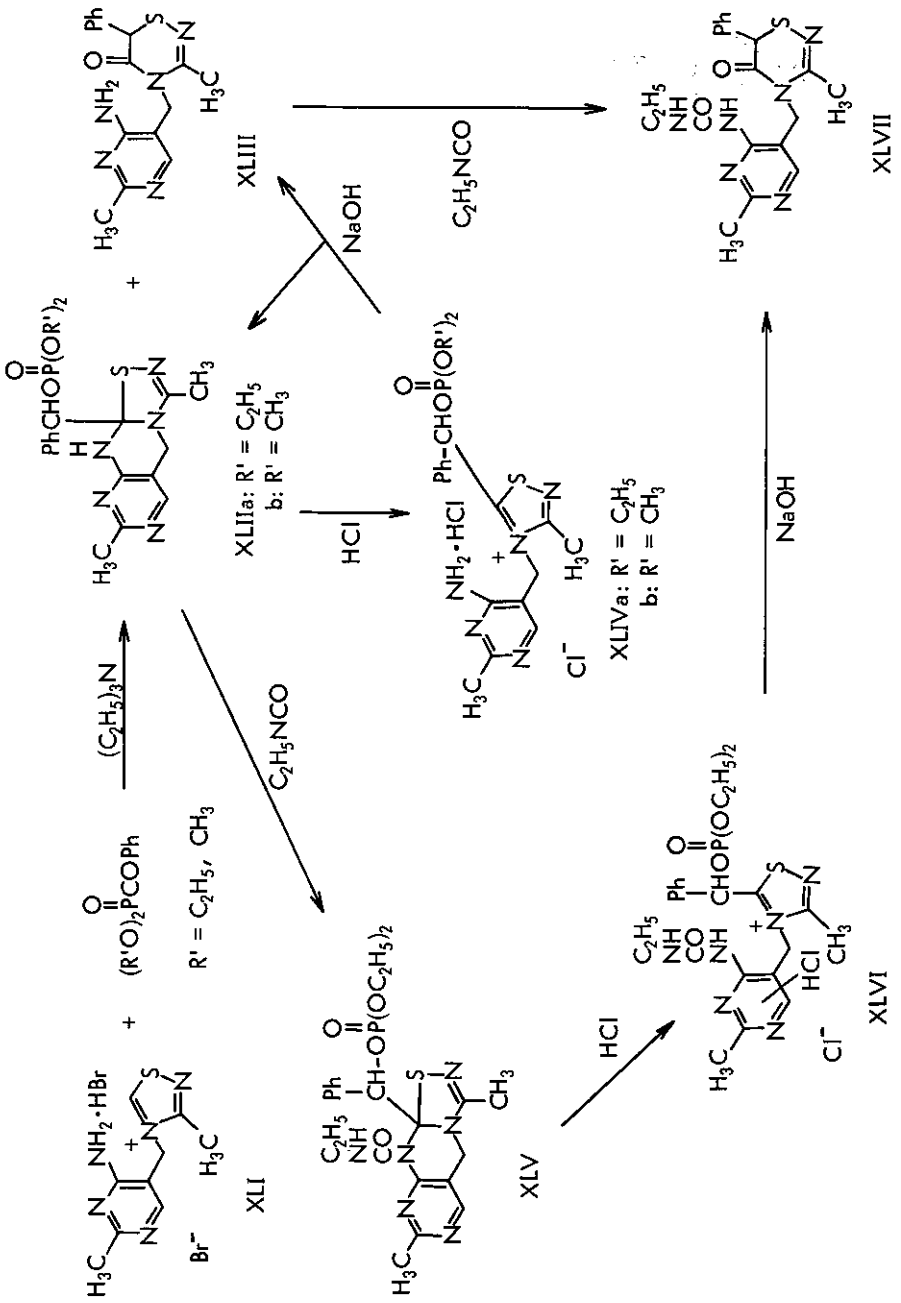


Chart 6

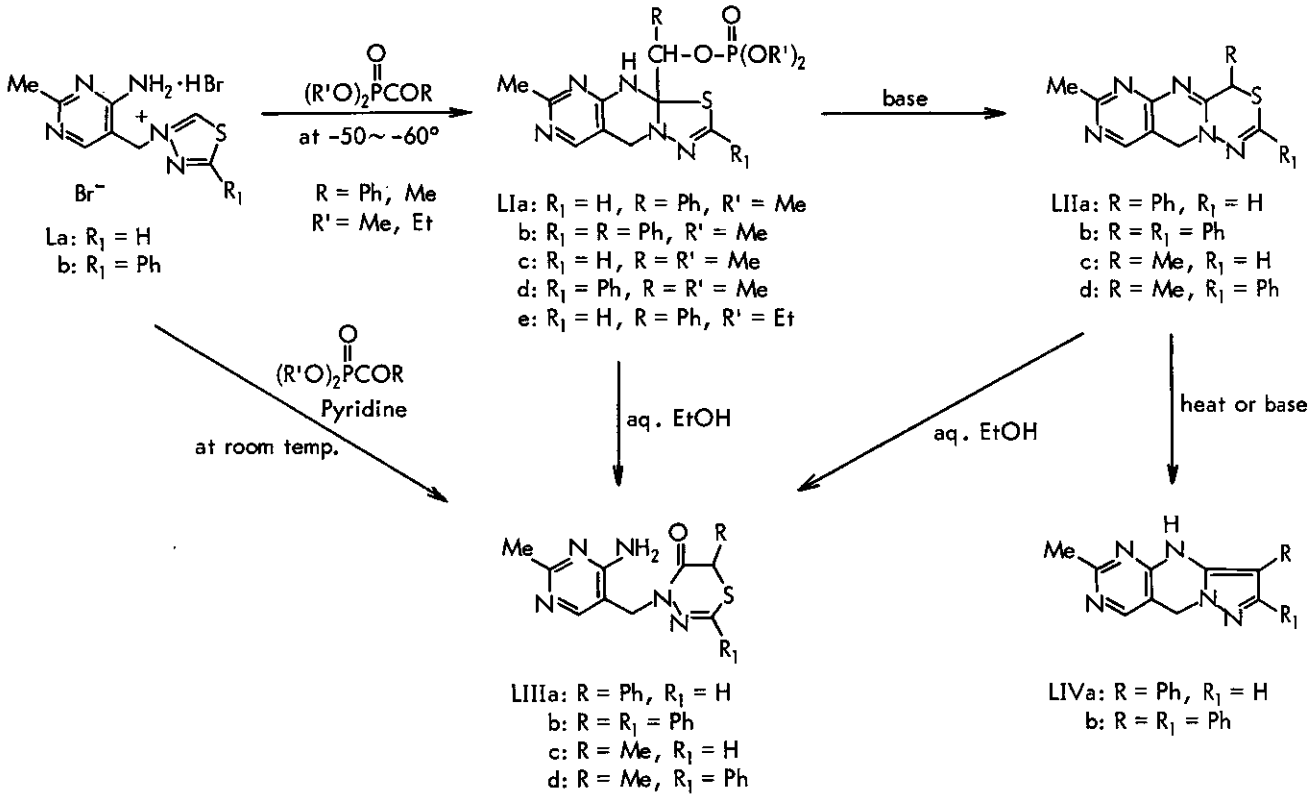
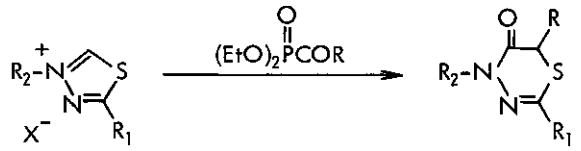

Me
NH2·HBr
Br⁻
La: R1 = H
b: R1 = Ph
(R'O)2PCOR
at -50~-60°
R = Ph, Me
R' = Me, Et
R
O
H
CH-O-P(OR')2
LIa: R1 = H, R = Ph, R' = Me
b: R1 = R = Ph, R' = Me
c: R1 = H, R = R' = Me
d: R1 = Ph, R = R' = Me
e: R1 = H, R = Ph, R' = Et
base
LIIa: R = Ph, R1 = H
b: R = R1 = Ph
c: R = Me, R1 = H
d: R = Me, R1 = Ph
(R'O)2PCOR
Pyridine
at room temp.
aq. EtOH
aq. EtOH
heat or base
NH2
LIIIa: R = Ph, R1 = H
b: R = R1 = Ph
c: R = Me, R1 = H
d: R = Me, R1 = Ph
LIVa: R = Ph, R1 = H
b: R = R1 = Ph

Chart 7

Table 4



XLVIII XLIX

R_1	R_2	R	mp (°C) [bp °C/mmHg]	Yield (%)
Ph	Me	Ph	137-138	63.2
Ph	Me	Me	oil	
Ph	$PhCH_2$	Ph	115-120	62.5
H	$PhCH_2$	Ph	[140-150/0.15]	
Ph	$PhCH_2$	Me	oil	

under alkaline conditions (Chart 7).

V. Oxazolium[20]

In the phosphonate reaction with oxazolium salts, O-[1-phenyl-2-oxo-2-(N-phenacylbenzylamino)ethyl]O,O-dimethyl phosphate (LVI), having a ring-opened phosphate structure, was obtained as intermediate. The formation of LVI may be explained by the difference in nucleophilic and tautomeric character of the enolate and thiolate anions in the hydrolyzed form. Enolate anion formed by hydrolysis of the first intermediate, 2-(1-phosphoroylbenzyl)oxazolium salt, tautomerizes to carbonyl, and as the nucleophilicity of the latter is low, no rearrangement to 1,4-oxazine derivatives occurs; hydrolysis of the thiazolium intermediate, however, gives a thiolate anion having high nucleophilicity, and this immediately rearranges to the final 1,4-thiazine

derivative.

Action of strong base on LVI resulted in 3-oxo-2,3-dihydro-4H-1,4-oxazine (LVII), analogues of the products in the thiazolium-phosphate reaction, and 2-oxoazetidine derivatives (LVIII) which were formed by the nucleophilic attack of carbanion at the 4-position of the oxazolium salt, promoted by deprotonation of the active methylene group (Chart 8).

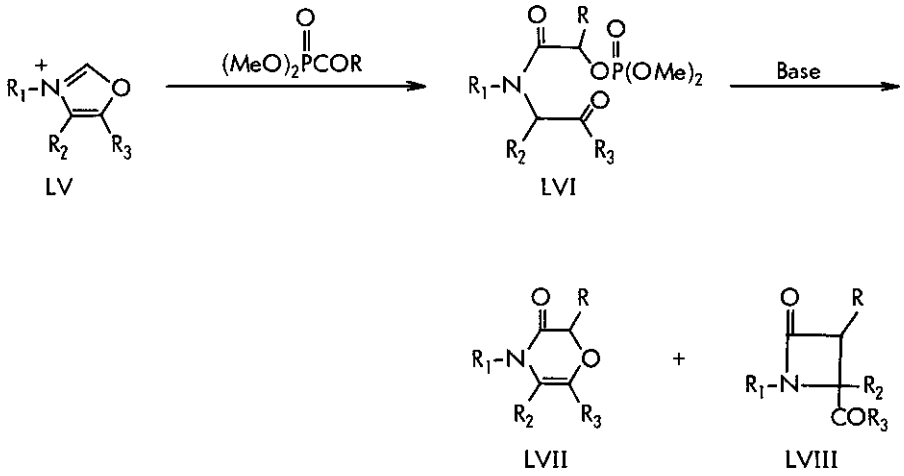


Chart 8

The ratio of products LVII/LVIII was clearly influenced by the types of substituents R and R_2, as shown in Table 5. In particular, no 1,4-oxazine derivative was obtained when R = R_2 = Ph, but the ratio of trans/cis product in LVIII became about 1 when R_2 = Me (Table 6). It might be thought that the stereospecific cyclization proceeds by charge-transfer interaction between R = Ph and R_2 = Ph groups in the transition state in S_N2 substitution reaction.

Table 5

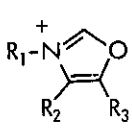
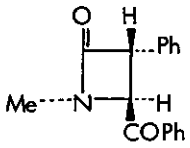
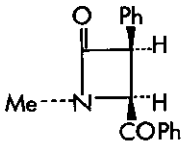
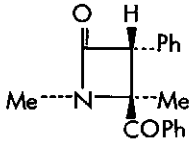
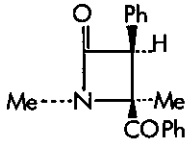
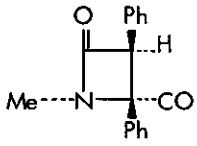
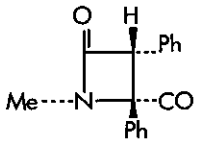
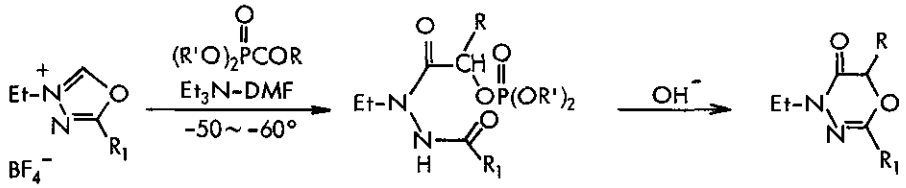
	R_1	$PhCH_2$	$PhCH_2$	$PhCH_2$	Me	Me	Me	Me	Me	Me	Me	Me	Me	Me	Me
	R_2	H	H	H	H	Me	Me	Me	Ph	Ph	Ph	Ph	Ph	Ph	Ph
	R_3	Ph	Ph	Ph	Ph	Ph	Ph	Ph	Ph	Me	Ph	Ph	Me	Me	Ph
$(MeO)_2PCOR$	R	Me	$PhCH_2$	Ph	Ph	Me	CH_2Ph	Ph	Me	Me	CH_2Ph	CH_2Ph	Ph	Ph	
LVII (%)		5	8	26	18	13	17	0.5	13	4	5	1	-	-	
LVIII (%)		-	-	14	10	-	-	12	3	0.5	-	-	16	22	

Table 6

	Ph/COPh-trans in LVIII		Ph/COPh-cis in LVIII	
R_2 = H	dl	 7.6%	dl	 2.7%
R_2 = Me	dl	 6.2%	dl	 5.6%
R_2 = Ph	dl	 21.1%	dl	 0.8%

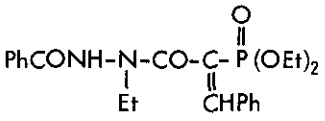
VI. Oxadiazolium[21]

1,3,4-Oxadiazolium salts show the same reaction behaviour as oxazolium salts. Ring-opened intermediate LX was isolated, and this rearranged to 5-oxo-5,6-dihydro-4H-1,3,4-oxadiazine derivative (LXI) on alkali treatment as shown in Chart 9.



LIX Chart 9 LX 55-65% LXI

Kinds of acylphosphonates, products, and yields are shown in Table 7. In the reaction of 3-ethyl-5-phenyl-1,3,4-oxadiazolium with diethyl phenylacetylphosphonate, a side reaction forming LXII by deprotonation of the active benzylic position was observed.



LXII

Table 7

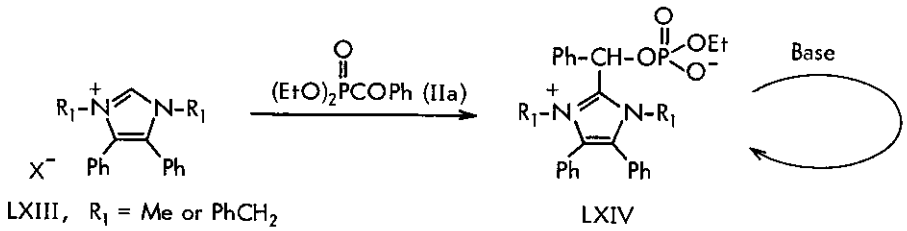
BF_4^- R_1	$(R'O)_2PCOR$ R	R'	LX (%)	LXI (%)
Ph	Ph	Et	63	66
Ph	Ph	Me	65	60
Ph	Me	Me	not isolated	12
Ph	CH_2Ph	Et	not isolated	3
Ph	$C_6H_4Cl(p)$	Et	55	37
Ph	$C_6H_4Br(p)$	Et	61	47
Ph	$C_6H_4Me(p)$	Et	61	65
Ph	$C_6H_4OMe(p)$	Et	25	54
$C_6H_4Cl(p)$	Ph	Et	58	27
$C_6H_4OMe(o)$	Ph	Et	62	24

VII. Imidazolium[22]

Reaction of N,N-disubstituted imidazolium and benzimidazolium salts with dialkyl acylphosphonate is somewhat different from the corresponding reaction with thiazolium salts. The imidazolium salts reacted with acylphosphonate to form 1 : 1 adducts, 1,3-dialkyl-2-(dialkylphosphoroylbenzyl)imidazolium halide (LXIV, LXVI) or O-alkyl-O-1-(1,3-dialkyl-2-imidazolium)benzylphosphoric acid betaine (LXXII) in high yields, but the anticipated 1,4-diazine or quinoxaline derivatives (LXXIII) were not obtained on alkaline treatment of these intermediates, only the hydrolyzed products (LXV-LXXI) being obtained as shown in Chart 10. Changes in the substituents on the nitrogen atoms at position 1 and 3 in the benzimidazolium salts (LXVb-d) also failed to affect the course of the reaction and did not result in quinoxaline derivative formation. In the case of 1,3-dimethyl-5-nitrobenzimidazolium iodide, however, the ring-opened product (LXXVI) was readily obtained on alkaline treatment, but ring closure to a quinoxaline derivative could not be effected. The only case in which a quinoxaline derivative was formed was in the treatment of LXXV with dimethyl sulfoxide under neutral conditions, 1,4-dimethyl-3-hydroxy-3-phenyl-7-nitro-1,2,3,4-tetrahydro-2-oxo-quinoxaline (LXXVIII) being obtained in moderate yield together with LXXVIa and LXXVII (Chart 11). Chart 12 outlines a possible mechanism for this reaction in dimethyl sulfoxide.

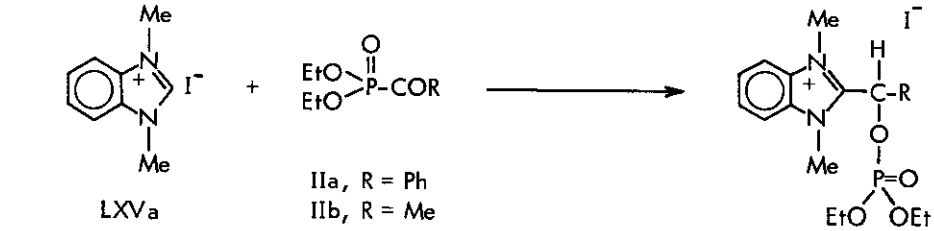
The differences in the behaviour of thiazolium and imidazolium adducts mentioned above are attributed to the enhanced stability of the imidazolium ring system toward alkali and lower nucleophilicity of nitrogen compared to sulfur.

VIII. Relationship of the type 4'-Substituent to the Stability and the Reactivity of Thiamine and Its Analogues.[23,24]



LXIII, R_1 = Me or $PhCH_2$

LXIV



LXVa

IIa, R = Ph
IIb, R = Me

LXVIa: R = Ph
b: R = Me

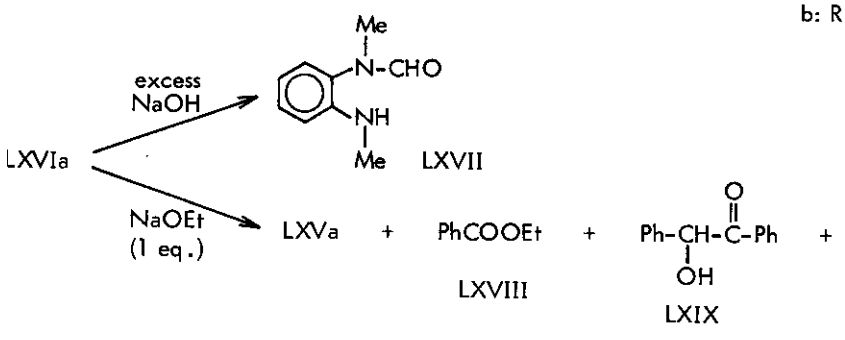
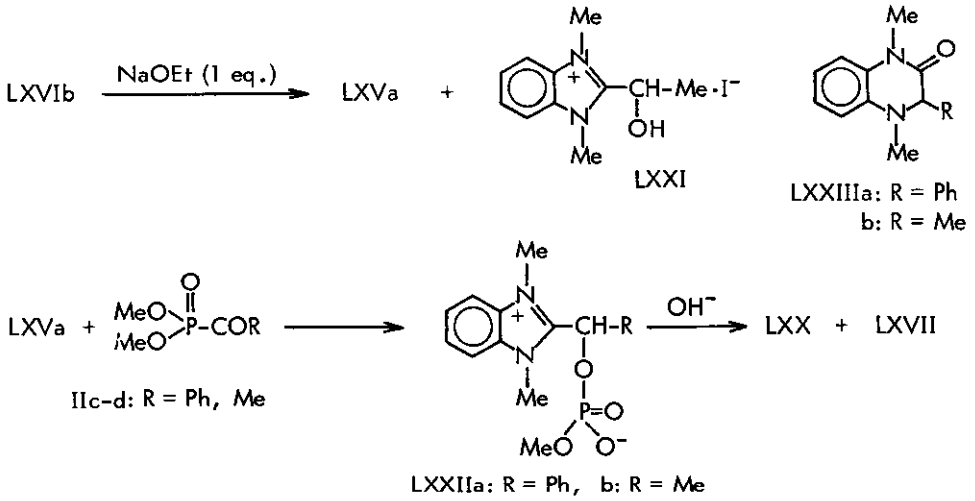


Chart 10



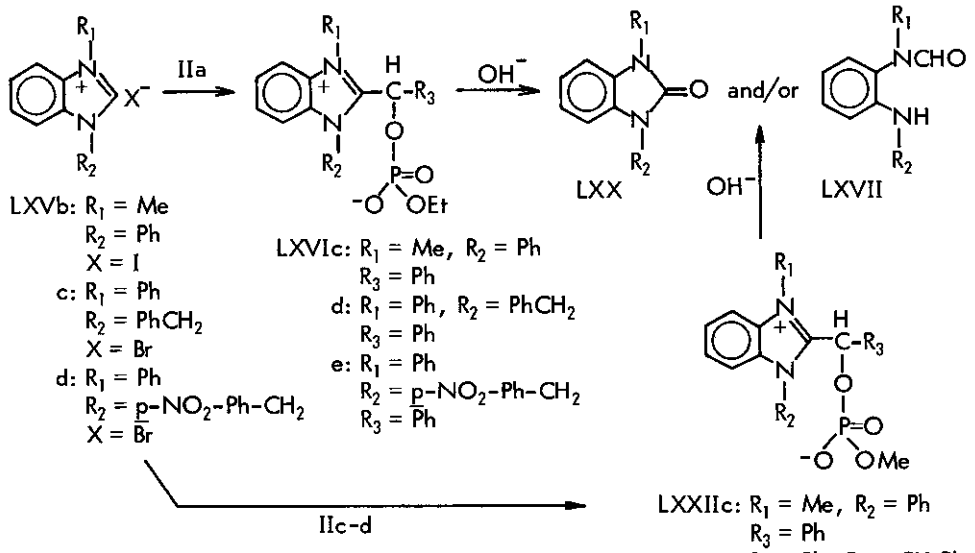


Chart 10 (continued)

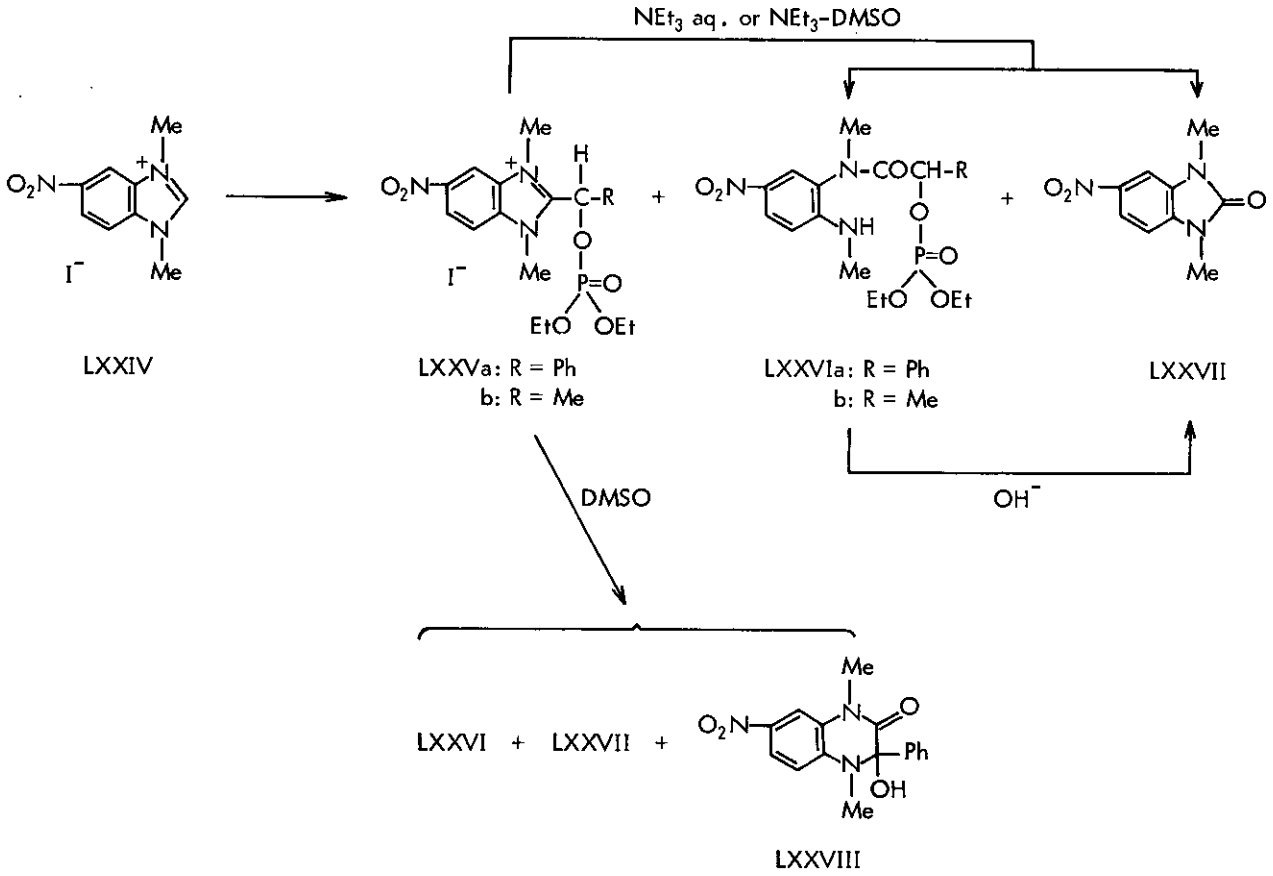

NEt3 aq. or NEt3-DMSO
LXXIV
LXXVa: R = Ph
b: R = Me
LXXVIa: R = Ph
b: R = Me
LXXVII
DMSO
OH⁻
LXXVI + LXXVII +
LXXVIII

Chart 11

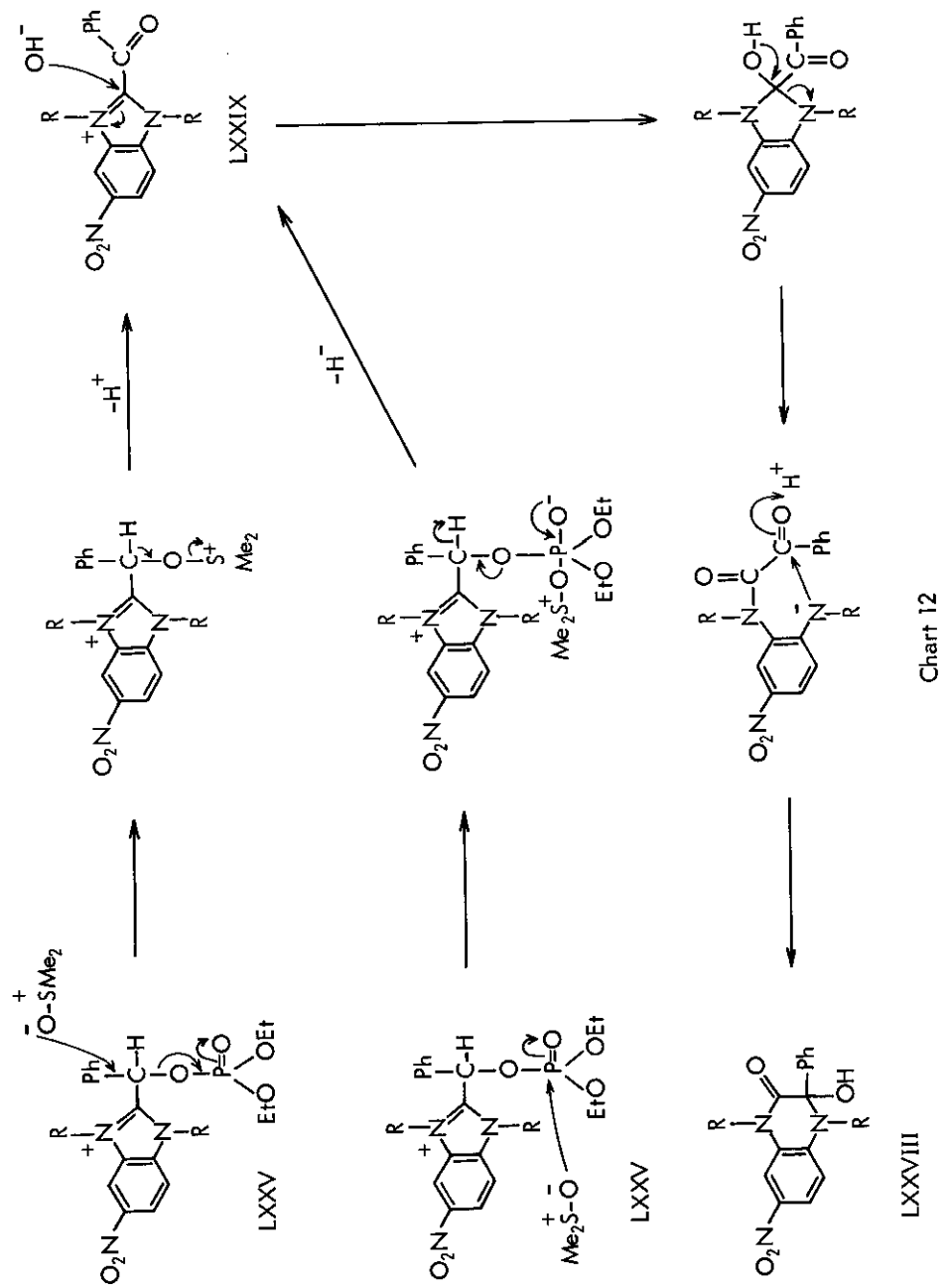


Chart 12

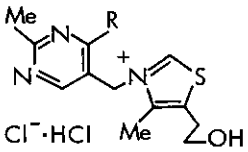
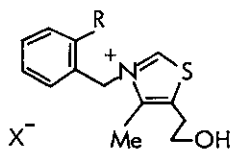
We have previously reported the reaction of thiamine with various electrophiles such as aldehydes,[2] glyoxals,[3] isocyanates,[4] isothiocyanates,[5] and carbodiimides[6] as chemical model experiments for the first step of the decarboxylation. Compared with these electrophiles, dialkyl acylphosphonates react with thiamine and other thiazolium salts in better yields, giving 1,4-thiazine derivatives as final products by the ring expansion of thiazolium. On the influence exerted by 4'-substituents on the co-carboxylase activity of thiamine analogues, Sykes et al.[25] reported that there is no relationship between the pKa value of a thiamine analogue and its ability to catalyse acetoin formation. However, there are large differences between these chemical model experiments and actual enzymatic conditions.[26] Now we have used this reagent to investigate the reactivity of thiamine analogues, especially that at the thiazolium 2-position, by studying the reaction of diethyl benzoylphosphonate with 4'-substituted thiamine analogues (LXXX), 3-(2-methyl-4-substituted-5-pyrimidinyl)-methyl-4-methyl- (LXXXI) and 3-(2-substituted benzyl)-4-methyl-5-(2-hydroxyethyl)-thiazolium salts (LXXXII). Comparison of reactivities of the analogues in aprotic solvents is of particular interest, considering the hypothesis of Lienhard and Crosby[27] that catalysis in thiamine pyrophosphate dependent enzymatic reactions may be due in large part to binding of the thiazolium nucleus to a hydrophobic region of the enzymes.

Prior to a study of reaction with acylphosphonate, the reactivity of the C 2 position in substituted thiazolium salts was examined by the technique of hydrogen-deuterium exchange rate determination; also, the stability of thiazolium molecules under the reaction conditions was determined by measurement of the formation of the thiazole moiety (LXXXIII).

The hydrogen-deuterium exchange rates ($k_{obs.}/[OD^-]$) of substituted thiazolium

salts in an acetate buffer did not vary significantly either on replacement of the pyrimidine nuclei by other rings or by change of substituents in the respective rings, as shown in Table 8. This suggests that nucleophilic attack of the thiazolium ylide carbanion to pyruvate in water in the initial step of the decarboxylation is not affected in vitro by the nature of the 4'-substituent nor by that of the ring, as was indicated in model experiments on the acetoin formation.

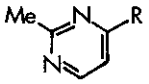
Table 8. Rate Constants for Exchange of the 2-Hydrogen of Thiamine Analogues and N-Substituted Thiazolium Salts in an Acetate Buffer

Compounds	Temp. (°C)	pD	$10^9 \cdot [OD^-]$ M	$10^3 \cdot k_{obs.}$ sec^{-1}	10^{-6} $(k_{obs.}/[OD^-])$ $M^{-1} \cdot sec^{-1}$
 $Cl^- \cdot HCl$					
R = NH_2 (LXXXb)	43	5.78	1.74	7.25	4.17
R = NHMe (LXXXc)	43	5.85	2.04	5.38	2.86
R = OH (LXXXf)	43	5.68	1.38	2.22	1.61
 X^-					
R = H (LXXXIIb) X = Br^-	40.5	6.00	2.89	3.86	1.34
R = NH_2 (LXXXIId) X = $Cl^- \cdot HCl$	40.5	5.55	1.02	1.53	1.55

Regarding the stability of the substituted thiazolium salts under the same conditions as those obtaining in the phosphonate reaction, triethylamine treatment of the thiazolium salts in N,N-dimethylformamide solution or suspension gave rise to the thiazole moiety (LXXXIII) by cleavage of the bond between the pyrimidinylmethyl carbon and the thiazolium nitrogen. From the results shown in Table 9, it is seen that the hydroxy compound in each series shows very high ability to form the thiazole moiety (LXXXIII), while in contrast the unsubstituted and the amino derivatives in the pyrimidine series are considerably more stable under these reaction conditions. Thus, the 4'-amino group of thiamine must make some contribution not only to stability, but also to the enzymatic activity, since there is little difference between

Table 9. Yields (%) of 4-Methyl-5-(2-hydroxyethyl)thiazole (LXXXIII) from Treatment of Thiazolium Salts (LXXX and LXXXII) with Base

LXXXIII

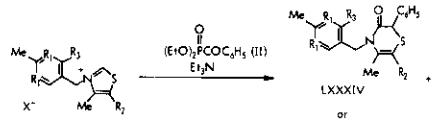
G		
R	LXXX	LXXXII
Cl		8
H	trace	7
OMe		5
NH_2	trace	14
NHMe	trace	
NMe_2	9	6
OH	63	60

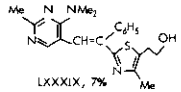
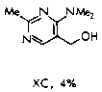
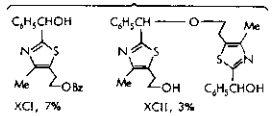
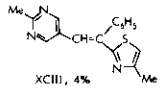
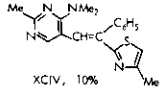
the formation of thiazole from thiamine and from the 4'-H analogue (deamino-thiamine, LXXXa). The reactions with acylphosphonate were then carried out in the light of this preliminary knowledge.

Reaction of these thiazolium salts with diethyl benzoylphosphonate was carried out in N,N-dimethylformamide solution or suspension using triethylamine as a base. The reaction mixtures were kept at room temperature overnight, then solvent was removed in vacuo. Except where the compounds had an amino substituent (LXXXb and LXXXIId), the residues were treated with aqueous ethanolic sodium hydroxide for 30 min at 60°. The reaction mixtures were extracted with chloroform and separated using preparative layer chromatography. Products and yields are listed in Table 10.

It is seen in Table 10 that there are large differences in reactivity in the thiamine analogues (LXXX) depending on the substituent (R_3); this in spite of the fact that significant differences were not recognized in the hydrogen-deuterium exchange rates in water. Thus, though 1,4-thiazine derivatives were obtained in good yields when R_3 = H or NH_2, the yields of 1,4-thiazine derivatives and 2-substituted thiazoles decreased markedly when the substituent R_3 was NHMe or NMe_2. In thiamine analogues (LXXX) and the 3-(2-methyl-4-substituted-5-pyrimidinyl)methyl-4-methyl-thiazolium salts (LXXXI), the order of the yields of normal ring expanded products obtained in the acylphosphonate reaction was almost comparable with the order of magnitude of the stabilities of the C-N bonds. On the contrary, products in 3-(2-substituted benzyl)-4-methyl-5-(2-hydroxyethyl)thiazolium salts (LXXXII) were little affected by the substituent R_3. The large dependence of the reactivity in this reaction on the nature of the nucleus and the substituent R_3 is in interesting contrast to

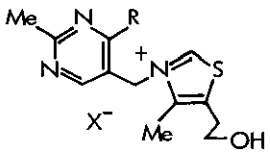
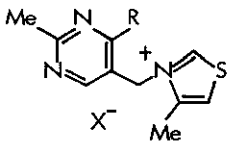
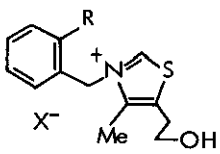
Table 10. Products and Yields in the Reaction of Thiamine Analogues (LXXX, LXXXI, LXXXII) with Diethyl Benzoylphosphonate (II)



Compd. No.	R_1	R_2	R_3	X	LXXXIV or LXXXV	LXXXIII	LXXXVI	LXXXVII	LXXXVIII	Other thiazole derivs.	Pyrimidine derivs.
LXXXa	N	$(CH_2)_2OH$	H	ClO_4^-	93% (LXXXIVa)						
LXXXb	N	$(CH_2)_2OH$	NH_2	Cl^-·HCl	96.6 (LXXXVb)						
LXXXc	N	$(CH_2)_2OH$	NHMe	Cl^-·HCl	28.5% (LXXXIVc)						
LXXXd	N	$(CH_2)_2OH$	NMe_2	Cl^-·HCl				4%		 LXXXIX, 7%	 XC, 4%
LXXXe	N	$(CH_2)_2OH$	OMe	Cl^-·HCl	12.5% (LXXXIVd)						
LXXXf	N	$(CH_2)_2OH$	OH	Cl^-·HCl		1.3%	1%	23%		 XCI, 7% XCII, 3%	
LXXXIa	N	H	H	Cl^-·HCl	51% (LXXXIVe)					 XCIII, 4%	
LXXXIb	N	H	NH_2	Br^-·HBr	67% (LXXXIVf)						
LXXXIc	N	H	NHMe	Cl^-·HCl	16% (LXXXIVg)			8%	24%		
LXXXId	N	H	NMe_2	Cl^-·HCl				14%	20%	 XCIV, 10%	XC, 12%
LXXXIe	N	H	OMe	Cl^-	71% (LXXXIVh)						
LXXXIIa	CH	$(CH_2)_2OH$	Cl	Cl^-	57% (LXXXIVi)						
LXXXIIb	CH	$(CH_2)_2OH$	H	Br^-	60% (LXXXIVj)						
LXXXIIc	CH	$(CH_2)_2OH$	OMe	Cl^-	62.5% (LXXXIVk)						
LXXXIId	CH	$(CH_2)_2OH$	NH_2	Cl^-·HCl	77% (LXXXIVl)						
LXXXIIe	CH	$(CH_2)_2OH$	NMe_2	Cl^-·HCl	88% (LXXXIVm)						
LXXXIIf	CH	$(CH_2)_2OH$	OH	Cl^-				1.2%			

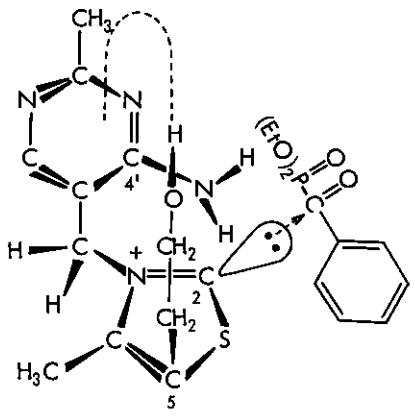
the acetoin formation experiments in water where such dependence was not observed. The total yields of products substituted at the thiazolium 2 position are shown in Table 11. In addition to the above, comparison of each series shows that the presence of both substituents, the pyrimidine nucleus and the hydroxyethyl group at the 5 position, is necessary for appearance of the substituent effect of 4'-substituents.

Table 11. Total Yields (%) of the Products which was Substituted at 2 Position of Thiazolium in the Benzoylphosphonate Reaction

Compds.			
R	LXXX	LXXXI	LXXXII
H	93	55	60
NH_2	90	67	77
NHMe	29	48	
NMe_2	11	44	88
OMe	13	71	63

Consideration of the roles of both substituents suggests the possibility of direct or indirect mutual intramolecular interaction between these substituents, such that the pyrimidine and thiazolium rings are fixed in a constant conformation and the 4'-substituent R_3 and the 2 position of the thiazolium ring are in proximity to each other, the yields of products substituted at the 2 position in thiamine analogues (LXXX) consequently being decrease by steric repulsion between 4'-substituents and the entering electrophile to an extent proportional to the bulkiness of 4'-substituent, as shown in

XCV. If we compare the conformation of thiamine (LXXXb) mentioned above to that presented by Schellenberger,[26] we see that the 4'-substituent is close to the thiazolium 2 position, and the 4'-amino group is located in a position where it can easily act to release an aldehyde molecule as intramolecular catalysis, thus our proposed conformation furnishes support for Schellenberger's[26] hypothesis. In the coenzyme, however, the hydroxyethyl substituent exists as pyrophosphate ester. The role of this pyrophosphate group is thought to be as a binding site for apoprotein, but it may have the additional role of fixing the coenzyme molecule in a constant conformation by interaction with the pyrimidine nucleus. On this point, work is now in progress to see whether these substituent effects found in thiamine analogues apply to their pyrophosphate esters too.



XCV

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