[Chem. Pharm. Bull. 21(4) 770—784 (1973)]

UDC 547.853.3'789.04 : 547.559.04

Studies on Pyrimidine Derivatives and Related Compounds. LXXVII.[1] Reaction of Thiamine Analogues with Diethyl Benzoylphosphonate

Akira Takamizawa and Hiroshi Harada

Shionogi Research Laboratory, Shionogi & Co., Ltd.[2]

(Received August 3, 1972)

Reaction of thiamine analogues (**8**, **14**, and **17**) with diethyl benzoylphosphonate (**20**) was carried out and an interesting difference in reactivity in aprotic solvent according to substituents and nuclei was observed.

It has been shown by Breslow[3] that the initial step of the decarboxylation of pyruvic acid by coenzyme thiamine pyrophosphate is the nucleophilic addition of thiazolium ylide carbanion to the carbonyl carbon of pyruvate.

We have previously reported the reaction of thiamine with various electrophiles such as aldehydes,[4] glyoxals,[5] isocyanates,[6] isothiocyanates,[7] and carbodiimides[8] as chemical model experiments of the first step of the decarboxylation. Compared with these electrophiles, dialkyl acylphosphonate, which was developed as an electrophile by our group,[9] reacts with thiamine and other thiazolium salts in better yields, giving 1,4-thiazine derivatives as final products by the ring expansion of thiazolium. In the present work 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 3-(2-methyl-4-substituted-5-pyrimidinyl)methyl(**8**), 3-(6-methyl-2-substituted-3-pyridinyl)methyl(**14**) and 3-(2-substitutedbenzyl)-4-methyl-5-(2-hydroxyethyl)thiazolium salts (**17**). Comparison of reactivities of the analogues in aprotic solvents was particularly interesting on the basis of the reports of Lienhard and Crosby.[10]

As the 4'-substituted thiamine analogues (**8**) used for model experiments, 4'-unsubstituted (**8d**), 4'-methylamino (**8a**), dimethylamino (**8b**) and methoxy (**8c**) thiamine analogues were synthesized by the route shown in Chart 1 using N-(2-methyl-4-amino-5-pyrimidinylmethyl)

1) Part LXXVI: A. Takamizawa and S. Matsumoto, *J. Vitaminology*, **17**, 175 (1971).
2) Location: *Fukushima-ku, Osaka, 553, Japan.*
3) R. Breslow, *Ann. N.Y. Acad. Sci.*, **98**, 445 (1962); *idem*, *Chem. Ind.* (London), **1957**, 893; *idem*, *J. Am. Chem. Soc.*, **80**, 3719 (1958).
4) A. Takamizawa, K. Hirai, Y. Hamashima, and S. Matsumoto, *Tetrahedron Letters*, **1967**, 5071; *idem*, *Chem. Pharm. Bull.* (Tokyo), **16**, 1210 (1968).
5) A. Takamizawa, S. Matsumoto, and S. Sakai, *Tetrahedron Letters*, **1968**, 2189; *idem*, *Chem. Pharm. Bull.* (Tokyo), **17**, 128 (1969).
6) A. Takamizawa, K. Hirai, S. Matsumoto, and T. Ishiba, *Chem. Pharm. Bull.* (Tokyo), **16**, 2130 (1968); *idem*, *ibid.*, **17**, 462 (1969).
7) A. Takamizawa, K. Hirai, S. Matsumoto, T. Ishiba, and Y. Nakagawa, *Chem. Pharm. Bull.* (Tokyo), **17**, 910 (1969).
8) A. Takamizawa, K. Hirai, and S. Matsumoto, *Tetrahedron Letters*, **1968**, 4027.
9) A. Takamizawa, K. Hirai, Y. Sato, H. Sato, S. Tanaka, H. Ito, and Y. Mori, *J. Org. Chem.*, **31**, 2951 (1966); A. Takamizawa and Y. Sato, *Chem. Pharm. Bull.* (Tokyo), **14**, 742 (1966); A. Takamizawa, Y. Hamashima, and H. Sato, *J. Org. Chem.*, **33**, 4038 (1968); A. Takamizawa, Y. Hamashima, H. Sato, and S. Sakai, *Chem. Pharm. Bull.* (Tokyo), **17**, 1356 (1969); A. Takamizawa and H. Sato, *ibid.*, **18**, 1201 (1970); A. Takamizawa and H. Harada, *ibid.*, **18**, 1402 (1970); A. Takamizawa, Y. Hamashima, H. Sato, and Y. Matsumoto, *ibid.*, **18**, 1576 (1970); A. Takamizawa and H. Sato, *Yakugaku Zasshi*, **92**, 27 (1972).
10) J. Crosby and G. E. Lienhard, *J. Am. Chem. Soc.*, **92**, 5707 (1970); J. Crosby, R. Stone, and G.E. Lienhard, *ibid.*, **92**, 2891 (1970).

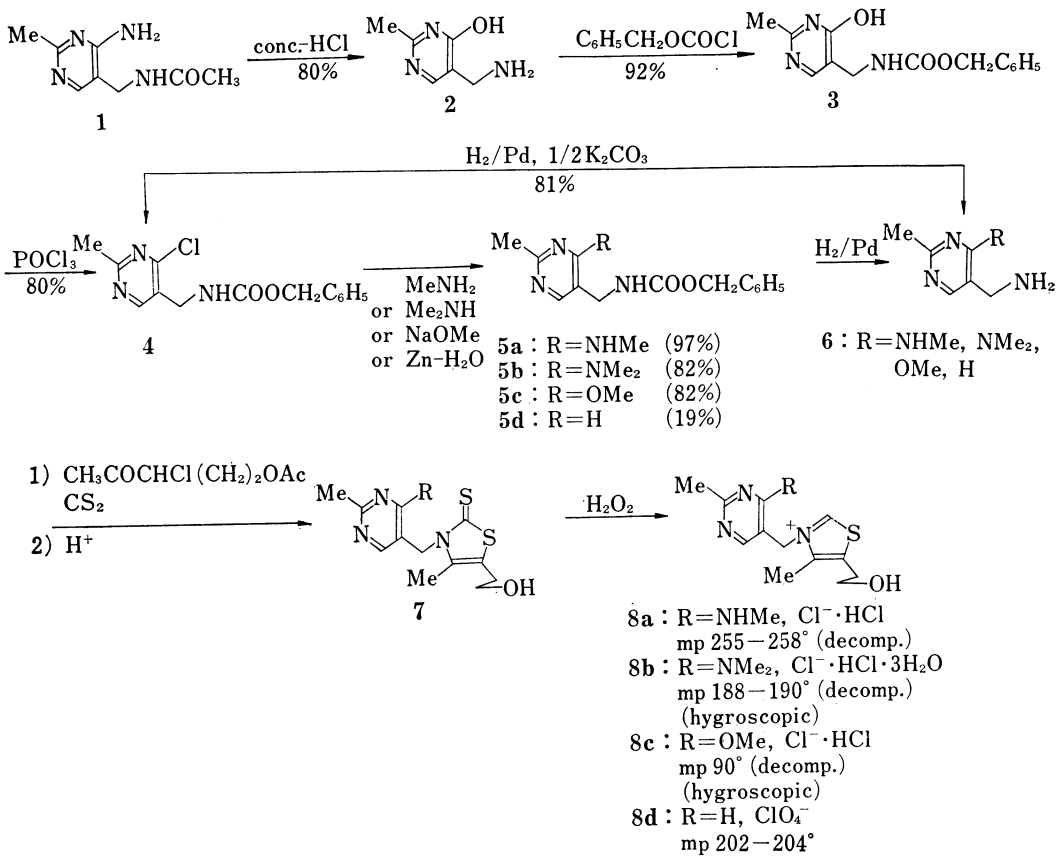


Chart 1

acetamide (**1**)[11] as starting material. Deaminothiamine (**8d**) was obtained rather simply and in better yield by this route than by others found in literature.[12]

Substituted pyridinylmethylthiazolium salts (**14**) were obtained by the method of Matsukawa and Matsuno[13] shown in Chart 2, starting from 3-cyano-6-methyl-2-pyridone (**9**).

Substituted benzylthiazolium salts (R=NO_2, Cl, OMe, H) (**17a—d**) were made by quaternizing 4-methyl-5-(2-hydroxyethyl)thiazole (**16**) with the corresponding benzyl halides, and 2′-dimethylamino (**17f**) and 2′-hydroxy (**17g**) derivatives were synthesized from N,N-dimethylanthranilamide (**18a**) and salicylamide (**18b**) as shown in Chart 3.

Prior to reaction with acylphosphonate, the reactivities of the C 2 position in the substituted thiazolium salts were examined by the technique of hydrogen-deuterium exchange rate determination; also, the stability of the thiazolium molecules under the reaction conditions was determined by measurement of the formation of the thiazole moiety (**16**).

The hydrogen-deuterium exchange rates ($k_{obs.}/[OD^-]$) of the 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 I. This suggests that the nucleophilic attack of the thiazolium ylide carbanion to pyruvate in

11) A. Takamizawa, K. Ikawa, and K. Tori, *Yakugaku Zasshi*, **78**, 647 (1958).
12) A. Schellenberger, W. Rödel, and H. Rödel, *Z. Physiol. Chem.*, **339**, 122 (1964); H. Nakao, M. Ito, and S. Muramatsu, *Ann. Sankyo Res. Lab.*, **18**, 33 (1966).
13) T. Matsukawa and T. Matsuno, *Yakugaku Zasshi*, **64**, 145 (1944).

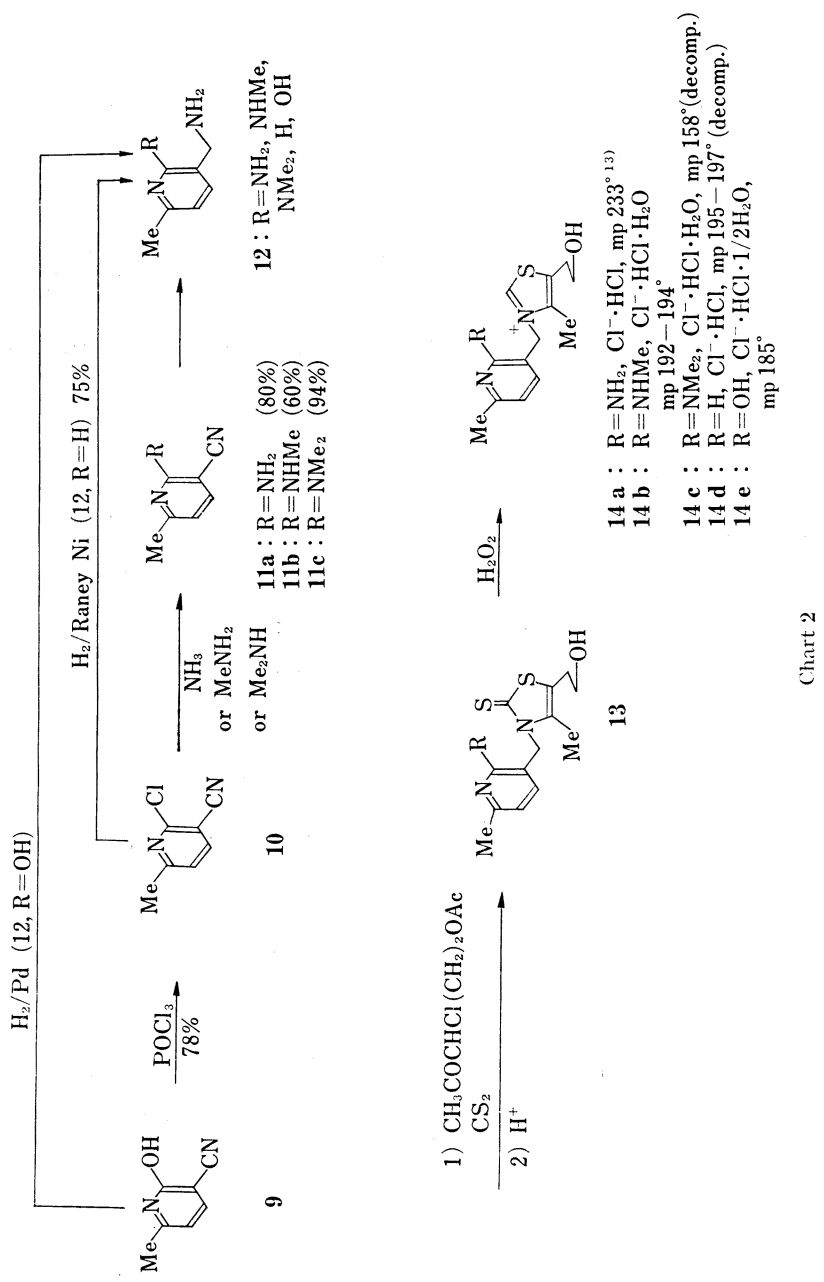


Chart 2

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 the model experiments on the acetoin formation.[14]

Regarding the stability of the substituted thiazolium salts under the same conditions as those obtaining the phosphonate reaction, triethylamine treatment of the thiazolium salts in N,N-dimethylformamide solution or suspension gave rise to the thiazole moiety (**16**) by

14) C.D. May and P. Sykes, *J. Chem. Soc.* (*C*), **1966**. 649,

cleavage of the bond between the pyrimidinylmethyl or pyridinylmethyl carbon and the thiazolium nitrogen. We allowed suspensions of the thiazolium salts in the solvent (Et_3N-1% aq-DMF) to stand for a week at room temperature, then extracted them with chloroform. The quantity of the thiazole moiety formed was determined by gas chromatography, but the chloroform extract was washed with a little water to remove quaternary salt prior to the

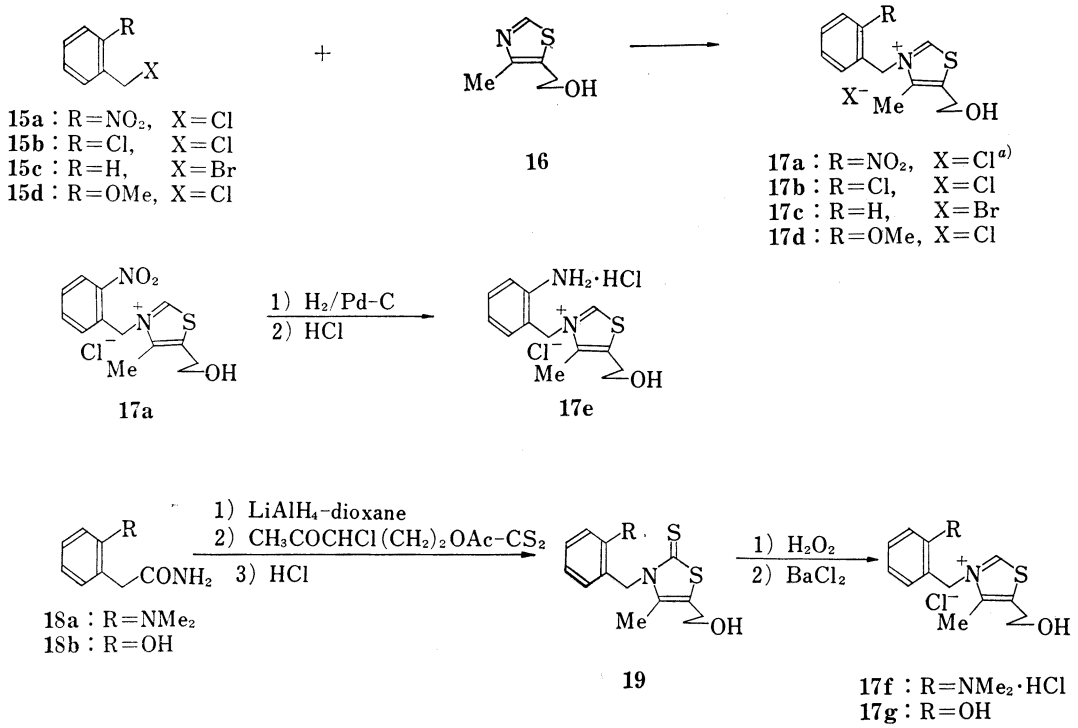
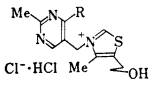
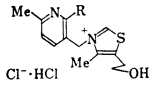
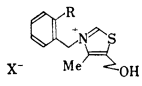


Chart 3

a) T. Matsukawa and S. Yurugi, *Yakugaku Zasshi*, **72**, 990(1952).

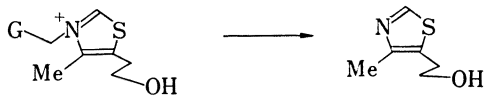
TABLE I. Rate Constants for Exchange of the 2-Hydrogen of Thiamine Analogues and N-Substituted Thiazolium Salts in an Acetate Buffer

Compounds		Temp. (°C)	pD[a]	$10^9 \cdot [OD^-]$ M[b]	$10^3 \cdot k_{obs.}$ sec^{-1}	$10^{-6}(k_{obs}/[OD^-])$ $M^{-1} \cdot sec^{-1}$
	R=NH_2 (**8e**)	43	5.78	1.74	7.25	4.17
	R=NHMe (**8a**)	43	5.85	2.04	5.38	2.86
	R=OH (**8f**)	43	5.68	1.38	2.22	1.61
	R=H (**14d**)	35	5.58	1.10	4.17	3.79
	R=NH_2 (**14a**)	35	5.78	1.74	7.24	4.16
	R=H (**17c**) X⁻=Br^-	40.5	6.00	2.89	3.86	1.34
	R=NH_2 (**17e**) X⁻=Cl^-·HCl	40.5	5.55	1.02	1.53	1.55
	R=NO_2 (**17a**) X⁻=Cl^-	39	5.99	2.82	4.37	1.55

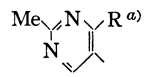
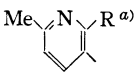
a) pD=pH+0.40, P.K. Glasoe and F.A. Long, *J. Phys. Chem.*, **64**, 188 (1960). pH values were measured on a Metrohm Potentiograph Model E 336 after the exchange had finished.
b) Using pK_c (D_2O)=14.54, A.K. Covington, R.A. Robinson and R.G. Bates, *J. Phys. Chem.*, **70**, 3820(1966).

determination because direct analysis of the reaction mixture by gas chromatography resulted in thermal decomposition of the quaternary salts. From the results shown in Table II, it is seen that the hydroxy compound in each series shows very high ability to form the thiazole moiety, while in contrast, the unsubstituted and the amino derivatives in pyrimidine series are considerably stable under these reaction conditions. The abnormally high formation of the thiazole moiety from 3-(2-methylamino-6-methyl-3-pyridinyl)methylthiazolium salt (**14b**) might be due to contaminants having the same retention time as the thiazole derivative in the gas chromatographic analysis. In similar experiment carried out on oxythiamine (**8f**), 3-(2-hydroxy-6-methyl-3-pyridinyl)methyl- (**14e**), and 3-(2-hydroxybenzyl)-4-methyl-5-(2-hydroxyethyl)thiazolium chloride (**17g**), 4-methyl-5-(2-hydroxyethyl)thiazole (**16**) was isolated in 39, 41 and 65% yields respectively. For the hydroxy compound, the cleavage reaction may proceed by an E_2-like mechanism initiated by proton abstraction of the hydroxy group or the N-H group of the tautomeric form. The reactions with acylphosphonate were then carried out in the light of this preliminary knowledge.

Table II. Yields (%) of 4-Methyl-5(2-hydroxyethyl)thiazole (**16**) from Treatment of Thiazolium Salts (**8**, **14**, **17**) with Base



8, **14**, **17** **16**

R	G  **8**	 **14**	 **17**
NO_2	—	—	4
Cl	—	—	8
H	trace	1.3	7
OMe	—	—	5
NH_2	trace	5	14
NHMe	trace	33	—
NMe_2	9	9	6
OH	63	63	60

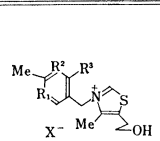
a) 2-Aminothiazole was used as an internal standard.

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 (**8e**, **14a** and **17e**), 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 III.

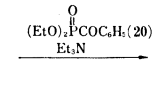
The structures of ring expanded products, 1,4-thiazine derivatives, were elucidated by comparing their physico-chemical data with those for analogous compounds which had been obtained by this procedure as reported previously.[9] One of the products, 2-hydroxybenzyl-4-methyl-5-(2-hydroxyethyl)thiazole (**24**) was identified with the product obtained by the alternative synthetic procedure shown in Chart 4.

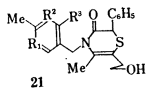
In the reaction of oxythiamine (**8f**), a dimeric thiazole (**28**) was obtained in which two unequivalent benzylic protons, τ 4.05 and 4.50 were observed. Acetylation of the dimer (**28**) in acetic anhydride-pyridine gave the diacetate in which the original signal at τ 4.05 was shifted to a lower field at τ 3.01, while at the same time two of the 4 methylene protons

TABLE III. Products and Yields in the Reaction of Thiamine Analogues (**8**, **14**, **17**) with Diethyl Benzoylphosphonate (**20**)



8, 14, 17





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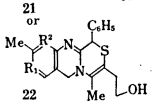

22

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16

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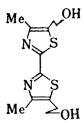

23

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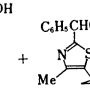

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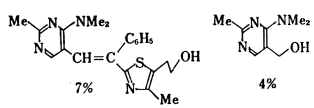
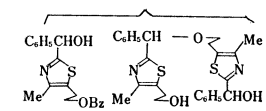
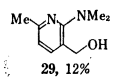
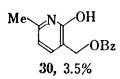
Compd. No.	R_1	R_2	R_3	X^-	21 or 22	16	23	24	+ Other thiazole derivs.	+ Pyridine or pyrimidine derivs.
8 d	N	N	H	ClO_4^-	93 % (oil) (**21a**)					
8 e	N	N	NH_2	$Cl^-\cdot HCl$	90 % (**22a**)					
8 a	N	N	NHMe	$Cl^-\cdot HCl$	28.5% (**21b**)					
8 b	N	N	NMe_2	$Cl^-\cdot HCl$				4 % .	 7% **25** 4% **26**	
8 c	N	N	OMe	$Cl^-\cdot HCl$	12.5% (**21c**)					
8 f	N	N	OH	$Cl^-\cdot HCl$		1.3%	1 %	23 %	 **27**, 7% **28**, 3%	
14 d	CH	N	H	$Cl^-\cdot HCl$	70 % (**21d**)					
14 a	CH	N	NH_2	$Cl^-\cdot HCl$	32 % (**22b**)					
14 b	CH	N	NHMe	$Cl^-\cdot HCl$	6 % (**21e**)			9.3%		
14 c	CH	N	NMe_2	$Cl^-\cdot HCl$		3 %	6.5%	8 %	 **29**, 12%	
14 e	CH	N	OH	Cl^-				9.3%	 **30**, 3.5%	
17 a	CH	CH	NO_2	Cl^-	26.5% (**21f**)					
17 b	CH	CH	Cl	Cl^-	57 % (**21g**)					
17 c	CH	CH	H	Br^-	60 % (**21h**)					
17 d	CH	CH	OMe	Cl^-	62.5% (**21i**)					
17 e	CH	CH	NH_2	$Cl^-\cdot HCl$	77 % (**22c**)					
17 f	CH	CH	NMe_2	$Cl^-\cdot HCl$	88 % (**21j**)					
17 g	CH	CH	OH	Cl^-				1.2%		

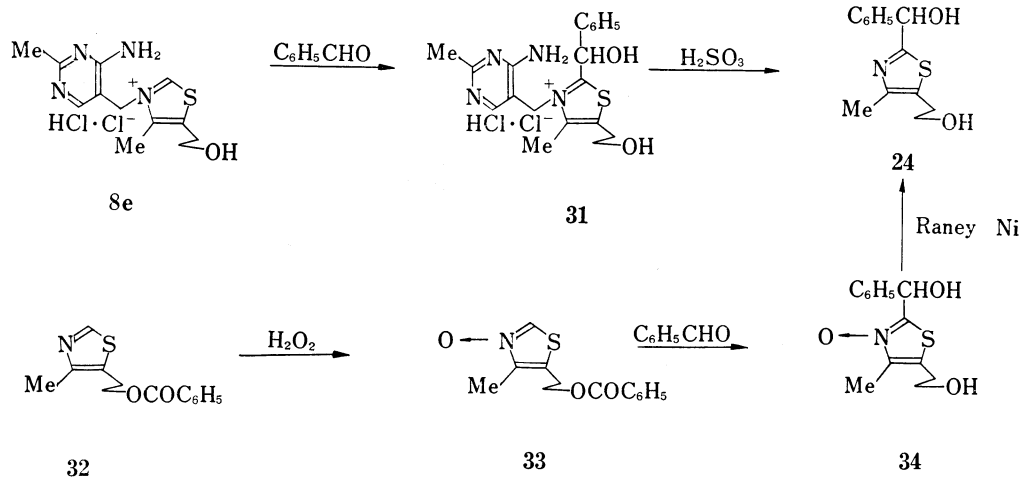


Chart 4

(2×-OCH_2-) of the alcoholic dimer (**28**) were shifted from τ 6.33 to τ 5.83. Thus, the dimeric thiazole must have the unsymmetrical structure (**28**).

The dimethylamino thiamine analogue (**8b**) afforded a rearranged product whose structure was elucidated as **25** from the lack of N-methylene protons in its nuclear magnetic resonance (NMR) spectrum and by comparison of its ultraviolet (UV) spectra with that of the amino analogue (**37**)[15] obtained by dehydration of a reaction product (**36**) given by treatment of thiamine analogue (**8g**) with benzaldehyde (Chart 5). Compound (**25**) showed maxima at 255, 289, and 354 mμ, while **37** was reported to have maximum at 351 mμ in the UV spectra. The estimated structure was finally confirmed by conversion to known 2-benzoyl-4-methyl-5-(hydroxyethyl)thiazole (**35b**) by ozonolysis. The mechanism of the rearrangement may be as shown in **38**, subsequent dehydration of the tertiary alcohol yielding **25**.

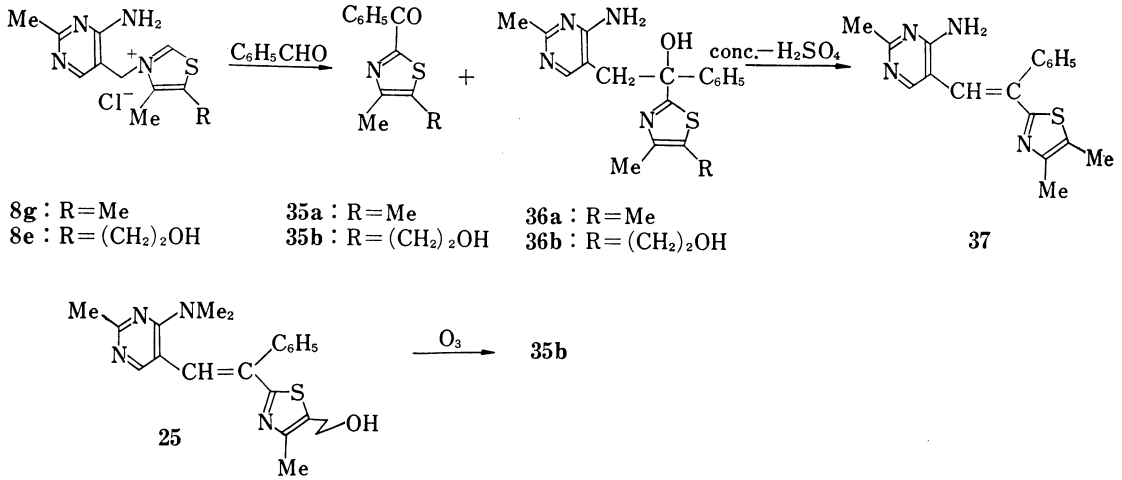
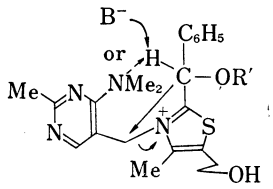


Chart 5

15) H. Hirano and Y. Oka, Presented at the Annual Meeting of the Pharmaceutical Society of Japan at Nagoya, April 1969.



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It is seen in Table III that there are large differences in reactivity in the pyrimidine and pyridine series 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=H or NH_2; the yields of 1,4-thiazine derivatives and 2-substituted thiazoles decreased markably when the substituent R was NHMe or NMe_2. In both the pyrimidine and pyridine series, the order of the yields of normal ring expanded products obtained in the acylphosphonate reaction is almost comparable with the order of magnitude of the stabilities of the C-N bonds. On the contrary, products in the benzyl series were little affected by the substituent (R_3); an exception being the reaction of the nitro derivative, where reactivity of the nitro group probably led to side reactions. 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 the acetoin formation experiments in water where such dependence was not observed. Further study is now in progress on this dependence of reactivity and stability toward base on the substituents and the nuclei. Cleavage of the quaternary nitrogen-methylene carbon bond occurred with the hydroxy derivatives of the pyrimidine and pyridine series both in the phosphonate reaction and in the reaction with base. Cleavage in both reactions was similarly observed, though to a lesser extent, with the dimethylamino derivatives in the two series.

Experimental[16]

2-Methyl-4-hydroxy-5-aminomethylpyrimidine Hydrochloride (2)——A solution of **1** (20 g) in conc. HCl was refluxed for 6 hr. The solution was then concentrated and neutralized to pH 5 with 20% NaOH and the crystals which precipitated were collected by filtration. Recrystallization from aqueous MeOH gave colorless needles (16 g), mp 310°. *Anal.* Calcd. for $C_6H_{10}ON_3Cl$: C, 41.04; H, 5.74; N, 23.93; Cl, 20.19. Found: C, 41.04; H, 5.31; N, 24.53; Cl, 20.08.

Benzyl N-(2-Methyl-4-hydroxy-5-pyrimidinylmethyl)-carbamate (3)——To an ice-cooled solution of **2** (53 g) in 10% NaOH (160 ml) was added benzyloxycarbonyl chloride (55 g) with stirring, then 40% NaOH (55 ml) was added dropwise. The reaction mixture was diluted with water to give a clear solution and stirring was continued for 3 hr at room temperature. The solution was washed with $CHCl_3$ then neutralized with acetic acid; the precipitate which formed was collected by filtration (76 g, 92%). Recrystallization from acetone gave colorless needles, mp 215—217°. *Anal.* Calcd. for $C_{14}H_{15}O_3N_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.85; H, 5.32; N, 15.69.

Benzyl N-(2-Methyl-4-chloro-5-pyrimidinylmethyl)-carbamate (4)——A solution of **3** (30 g) in phosphorus oxychloride (90 ml) and N,N-dimethylaniline (150 ml) was warmed at 80° for 1.5 hr. The mixture was poured slowly onto ice (500 g) with vigorous stirring. Stirring under ice-cooling was continued for 2 hr then the precipitate was collected by filtration and washed twice with water. Recrystallization from *n*-hexane–acetone gave colorless needles (23 g, 75%), mp 51—53°. *Anal.* Calcd. for $C_{14}H_{14}O_2N_3Cl \cdot 1/2H_2O$: C, 55.91; H, 5.03; N, 13.97; Cl, 11.79. Found: C, 56.02; H, 5.37; N, 13.88; Cl, 12.47.

Benzyl N-(2-Methyl-4-methylamino-5-pyrimidinylmethyl)-carbamate (5a)——To an ice-cooled solution of **4** (7.9 g) in EtOH (70 ml) in a sealed tube was added 30% ethanolic methylamine (27 ml) and the mixture was allowed to stand overnight at room temperature. The mixture was evaporated *in vacuo*, the residue dissolved in $CHCl_3$, and the chloroform solution was washed with water. Evaporation of $CHCl_3$ left a yellow oil which was crystallized from ether. Recrystallization from ethyl acetate gave colorless needles (7.5 g, 95%), mp 121°. *Anal.* Calcd. for $C_{15}H_{18}O_2N_4$: C, 62.92; H, 6.34; N, 19.57. Found: C, 63.19; H, 6.41; N, 18.90.

Benzyl N-(2-methyl-4-dimethylamino-5-pyrimidinylmethyl)-carbamate (**5b**) was obtained as colorless needles (from ether) by a similar method to that for **5a**: mp 101°; yield, 82%. *Anal.* Calcd. for $C_{16}H_{20}O_2N_4$: C, 63.93; H, 6.71; N, 18.65. Found: C, 63.98; H, 6.69; N, 18.83.

16) All melting points are uncorrected. All NMR spectra were taken with a Varian A-60 Spectrometer on solutions in deuterochloroform or deuterodimethylsulfoxide containing tetramethylsilane as internal reference. Chemical shifts are expressed in τ values and coupling constants in Hz. Multiplicities of signals are represented as a s(singlet), d(doublet), t(triplet), q(quartet), b(broad), and m(multiplet).

Benzyl N-(2-Methyl-4-methoxy-5-pyrimidinylmethyl)-carbamate (5c)——To a stirred solution of **4** (2.9 g) in abs. MeOH (6 ml) was added an equivalent amount of methanolic sodium methoxide and stirring was continued for 4 hr, after which the mixture was allowed to stand overnight at room temperature. After removal of MeOH *in vacuo*, the residue was dissolved in $CHCl_3$ and washed with water. Evaporation of $CHCl_3$ and recrystallization from ethyl acetate gave colorless flakes (2.4 g, 82%), mp 92—93°. *Anal.* Calcd. for $C_{15}H_{17}O_3N_3$: C, 62.71; H, 5.96; N, 14.62. Found: C, 62.72; H, 5.74; N, 14.91.

Benzyl N-(2-Methyl-5-pyrimidinylmethyl)-carbamate (5d)——A suspension of **4** (20 g) and zinc powder (40 g) in water (600 ml) was refluxed for 2 hr, the reaction mixture was extracted with $CHCl_3$, and the $CHCl_3$ solution was dried and evaporated. The residual oil was dissolved in ether and treated with decolorizing charcoal, and the solvent was removed *in vacuo*. Recrystallization from ether–*n*-hexane gave colorless needles (3.35 g, 19%), mp 60°. *Anal.* Calcd. for $C_{14}H_{15}O_2N_3$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.10; H, 5.84; N, 16.57.

Catalytic Reduction of 5d——A solution of **5d** (2.57 g) and $Ba(OH)_2 \cdot 8H_2O$ (3.15 g) in MeOH (30 ml) and water (50 ml) was hydrogenated over palladium-black catalyst. After absorption of the theoretical amount of hydrogen, carbon dioxide was bubbled into the reaction mixture, then catalyst was removed by filtration and the filtrate evaporated *in vacuo*. The residual oil was dissolved in ethyl acetate and the solution dried over anhyd. K_2CO_3. After evaporation of ethyl acetate, the residue was extracted with ether and the ethereal solution treated with decolorizing charcoal. Evaporation of the solvent gave pale-yellow oily product, the NMR spectrum of which was almost identical with that of 2-methyl-5-aminomethylpyrimidine (**6d**) obtained as below except for some signals arising from a small amount of impurity.

3-(2-Methyl-5-pyrimidinyl)methyl-4-methyl-5-(2-hydroxyethyl)-thiazolin-2-thione (7d)——To a solution of **4** (14.8 g) in dioxane (100 ml) was added a solution of aqueous K_2CO_3 solution (K_2CO_3 3.5 g, 45 ml) and the mixture was hydrogenated at atmospheric pressure and room temperature over palladium-black catalyst. The absorption vessel contained soda lime in oder to take up carbon dioxide evolved. After absorption of 2 moles of hydrogen, catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was dissolved in $CHCl_3$ and dried over anhyd. K_2CO_3. Filtration and evaporation left hygroscopic colorless crystals (5.05 g, 81%), (**6d**). The crystals were dissolved in a mixture of 3-chloro-5-acetoxy-2-pentanone (10 g), water (10 ml), conc. NH_4OH (6 ml), and EtOH (30 ml). Carbon disulfide (7.5 ml) was added dropwise to the solution and stirring was continued for 3 hr at room temperature. After overnight standing, the solvent was evaporated *in vacuo* and the residual oil was hydrolyzed with 10% HCl (50 ml) at 60° for 30 min. The mixture was washed with $CHCl_3$ and the aqueous layer neutralized with 40% NaOH. Collection by filtration and recrystallization from EtOH using decolorizing charcoal gave pale-yellow prisms (4.90 g, 38%), mp 147°. *Anal.* Calcd. for $C_{12}H_{15}ON_3S_2$: C, 51.22; H, 5.37; N, 14.93; S, 22.79. Found: C, 51.47; H, 5.21; N, 14.92; S, 23.07.

3-(2-Methyl-4-methylamino-5-pyrimidinyl)methyl-4-methyl-5-(2-hydroxyethyl)thiazolin-2-thione (7a)——**5a** (7.5 g) was dissolved in MeOH (100 ml) and acetic acid (10 g) and hydrogenated over 5% palladium carbon using the same equipment as mentioned above. When an equimolar amount of hydrogen had been absorbed, the catalyst was filtered off and the filtrate was evaporated *in vacuo*. The residue was dissolved in a mixture of 3-chloro-5-acetoxy-2-pentanone (9 g), water (30 ml), conc. NH_4OH (30 ml), and EtOH (30 ml). Carbon disulfide (10 ml) was added dropwise to the solution and stirring was continued for 3 hr at room temperature. Treatment as for **7d** above gave 3.2 g (40%) of pale-yellow crystals (from MeOH), mp 237—239°. *Anal.* Calcd. for $C_{13}H_{18}ON_4S_2$: C, 50.30; H, 5.84; N, 18.05; S, 20.66. Found: C, 50.34; H, 5.94; N, 17.86; S, 20.48.

3-(2-Methyl-4-dimethylamino-5-pyrimidinyl)methyl-4-methyl-5-(2-hydroxyethyl)thiazolin-2-thione (**7b**) was obtained as colorless crystals (8.0 g), mp 180—182°, by a work-up similar to that used for **5b**. Yield, 28%. *Anal.* Calcd. for $C_{14}H_{20}ON_4S_2$: C, 51.82; H, 6.21; N, 17.27; S, 19.76. Found: C, 52.23; H, 6.14; N, 16.98; S, 19.23.

3-(2-Methyl-4-methoxy-5-pyrimidinyl)methyl-4-methyl-5-(2-hydroxyethyl)thiazolin-2-thione (**7c**) was obtained as colorless needles (8.36 g), mp 160°, by a work-up similar to that used for **5c**. Yield, 60%. *Anal.* Calcd. for $C_{13}H_{17}O_2N_3S_2$: C, 50.14; H, 5.50; N, 13.49; S, 20.59. Found: C, 49.89; H, 5.59; N, 13.38; S, 20.35.

3-(2-Methyl-5-pyrimidinyl)methyl-4-methyl-5-(2-hydroxyethyl)thiazolium Perchlorate (8d)——**7d** (0.35 g) was suspended in water (5 ml) containing 30% hydrogen peroxide (0.35 g) and stirred until a clear solution was obtained. Barium hydroxide solution ($Ba(OH)_2 \cdot 8H_2O$, 0.18 g) and decolorizing charcoal were added and the mixture was filtered by suction. The filtrate was washed with $CHCl_3$ and repeatedly passed through a column of Amberlite IRA400 (ClO_4^- form). The eluate was neutralized to pH 6 with sodium bicarbonate solution then water was removed *in vacuo*. The crystalline residue was recrystallized from MeOH to give colorless needles (40 mg), mp 202°. *Anal.* Calcd. for $C_{12}H_{16}ON_3S \cdot ClO_4$: C, 41.23; H, 4.61; N, 12.01; Cl, 10.14. Found: C, 40.94; H 4.60; N, 11.71; Cl, 10.28.

3-(2-Methyl-4-methylamino-5-pyrimidinyl)methyl-4-methyl-5-(2-hydroxyethyl)thiazolium Chloride Hydrochloride (8a)——**7a** (0.31 g) was suspended in water (10 ml) containing 30% hydrogen peroxide (0.50 ml) and stirred for 2 hr at room temperature. Barium chloride solution ($BaCl_2 \cdot 2H_2O$ 0.24 g) was added and precipitate was removed by filtration. Evaporation of the filtrate and recrystallization from EtOH gave colorless needles (0.22 g), mp 255—258° (decomp.) which were identified with a standard by infrared comparison.

3-(2-Methyl-4-dimethylamino-5-pyrimidinyl)methyl-4-methyl-5-(2-hydroxyethyl)thiazolium Chloride Hydrochloride (8b)——According to the above procedure. highly hygroscopic crystals (1.04 g) of mp 188—190° were obtained from a reaction mixture of **7b** (1.07 g), 30% hydrogen peroxide (1.3 ml) and $BaCl_2 \cdot 2H_2O$ (0.81 g). *Anal.* Calcd. for $C_{14}H_{22}ON_4SCl_2 \cdot 3H_2O$: C, 40.10; H, 6.73; N, 13.36; S, 7.65. Found: C, 40.12; H, 5.67; N, 13.06; S, 7.68.

3-(2-Methyl-4-methoxy-5-pyrimidinyl)methyl-4-methyl-5-(2-hydroxyethyl)thiazolium Chloride Hydrochloride (8c)——**7c** (1.94 g) was suspended in water (60 ml) containing 30% hydrogen peroxide (2.9 ml) and stirred for 4 hr. Barium chloride ($BaCl_2 \cdot 2H_2O$, 0.77 g) and barium hydroxide ($Ba(OH)_2 \cdot 8H_2O$, 0.99 g) solutions were added and the precipitate which formed was removed by filtration. The filtrate was evaporated to dryness and recrystallization of the residue from EtOH–acetone gave highly hygroscopic colorless crystals (0.85 g), mp 90°. *Anal.* Calcd. for $C_{13}H_{19}O_2N_3SCl_2$: C, 44.32; H, 5.44; N, 11.93; S, 9.10; Cl, 20.13. Found: C, 44.72; H, 5.62; N, 11.97; S, 9.40; Cl, 20.36.

2-Methylamino-3-cyano-6-methylpyridine (11b)——A mixture of 2-chloro-3-cyano-6-methylpyridine[13] (**10**) (3.0 g), EtOH (30 ml) and 30% ethanolic methylamine (30 ml) was allowed to stand overnight at room temperature and then refluxed for 3 hr. The residue obtained on evaporation of EtOH, was dissolved in $CHCl_3$ and washed with water. Removal of solvent and recrystallization from ethyl acetate gave colorless plates (1.7 g, 60%), mp 108°. *Anal.* Calcd. for $C_8H_9N_3$: C, 65.28; H, 6.16; N, 28.55. Found: C, 65.46; H, 6.26; N, 28.44.

2-Dimethylamino-3-cyano-6-methylpyridine (11c)——A mixture of **10** (6.0 g), EtOH (30 ml) and 18% ethanolic dimethylamine (30 ml) was refluxed for 2 hr. The residue obtained on evaporation of EtOH was dissolved in $CHCl_3$ and washed with water. Removal of solvent and distillation gave an oily product (5.9 g), bp_{12} 128°. *Anal.* Calcd. for $C_9H_{11}N_3$: C, 67.05; H, 6.88; N, 26.07. Found: C, 67.23; H, 6.96; N, 25.89.

3-(2-Methylamino-6-methyl-3-pyridinyl)methyl-4-methyl-5-(2-hydroxyethyl)thiazolin-2-thione (13b)——A solution of **11b** (1.47 g) in acetic acid (25 ml) and 4% HCl–acetic acid (25 ml) was hydrogenated at atmospheric pressure and room temperature over 5% palladium–carbon catalyst. After absorption of the theoretical amount of hydrogen, catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in a mixture of 3-chloro-5-acetoxy-2-pentanone (1.7 g), water (3 ml), conc. NH_4OH (2 ml), and EtOH (10 ml), and carbon disulfide (1.5 ml) was added dropwise to the solution with stirring. The mixture was stirred for 3 hr then allowed to stand overnight at room temperature. After evaporation *in vacuo*, 10% HCl (20 ml) was added to the residue and the solution was warmed at 60° for 30 min. Neutralization with K_2CO_3 gave a crystalline mass which was recrystallized from MeOH to give pale-yellow prisms (1.8 g, 58%), mp 188°. *Anal.* Calcd. for $C_{14}H_{19}ON_3S_2$: C, 54.34; H, 6.19; N, 13.58; S, 20.72. Found: C, 54.64; H, 6.30; N, 13.34; S, 20.68.

3-(2-Dimethylamino-6-methyl-3-pyridinyl)methyl-4-methyl-5-(2-hydroxyethyl)thiazolin-2-thione (13c)——To an ice-cooled solution of **11c** (6.4 g) in abs. ether (30 ml) was added a solution of $LiAlH_4$ (3.04 g) in abs. ether (30 ml) with stirring. Stirring was continued for an hour at room temperature, then the reactant was decomposed with water. Filtration and evaporation left a yellow oil (5.0 g). The residual oil was dissolved in mixture of 3-chloro-5-acetoxy-2-pentanone (7.5 g), water (15 ml), conc. NH_4OH (5 ml), and EtOH (30 ml) and carbon disulfide (3.5 ml) was added with stirring. Treatment according to the above procedure and neutralization with K_2CO_3 and 10% NaOH gave pale-yellow prisms (5.4 g, 42%), mp 124° (from EtOH). *Anal.* Calcd. for $C_{15}H_{21}ON_3S_2$: C, 55.70; H, 6.54; N, 12.99; S, 19.82. Found: C, 55.77; H, 6.66; N, 12.70; S, 19.87.

3-(2-Hydroxy-6-methyl-3-pyridinyl)methyl-4-methyl-5-(2-hydroxyethyl)thiazolin-2-thione (13e)——A solution of **9** (1.18 g) in 4% HCl–acetic acid (25 ml) and acetic acid (50 ml) was hydrogenated over 5% palladium carbon catalyst at room temperature. When 2 moles of hydrogen had been absorbed, catalyst was removed by filtration and the filtrate was evaporated under reduced pressure. The residue (1.18 g) was dissolved in a mixture of 3-chloro-5-acetoxy-2-pentanone (1.2 g), water (2.5 ml), conc. NH_4OH (1.3 ml), and EtOH (11 ml) and carbon disulfide (1.3 ml) was added to the solution with stirring. Subsequent treatment as described above and neutralization with K_2CO_3 gave pale-yellow prisms (0.6 g, 22%), mp 217°. *Anal.* Calcd. for $C_{13}H_{16}O_2N_2S_2$: C, 52.68; H, 5.44; N, 9.45; S, 21.63. Found: C, 52.61; H, 5.36; N, 9.45; S, 21.90.

3-(6-Methyl-3-pyridinyl)methyl-4-methyl-5-(2-hydroxyethyl)thiazolin-2-thione (13d)——A solution of **10** (15.25 g) in MeOH (200 ml) and 16% methanolic ammonia (70 ml) was hydrogenated over Raney Ni (W-2) catalyst at room temperature. Reaction ceased after absorption of 5.7 l of hydrogen (85% of the theoretical amount). Filtration and evaporation gave a crystalline residue. The residue was dissolved in $CHCl_3$ and washed with 10% NaOH twice, then the organic layer was dried and evaporated to give crude crystals of 3-aminomethyl-6-methylpyridine (15.2 g). The crude crystals were dissolved in a mixture of 3-chloro-5-acetoxy-2-pentanone (26.7 g), water (30 ml), conc. NH_4OH (20 ml), and EtOH (50 ml) and carbon disulfide was added dropwise to the solution with stirring. Subsequent treatment as described above gave pale-yellow prisms (14.7 g, 48%), mp 144°. *Anal.* Calcd. for $C_{13}H_{16}ON_2S_2$: C, 55.68; H, 5.75; N, 9.99; S, 22.87. Found: C, 55.85; H, 5.70; N, 9.71; S, 23.10.

3-(2-Methylamino-6-methyl-3-pyridinyl)methyl-4-methyl-5-(2-hydroxyethyl)thiazolium Chloride Hydrochloride (14b)——**13b** (3.09 g) was suspended in water (30 ml) containing 30% hydrogen peroxide (3.5 ml)

and stirred for 3 hr. Barium chloride solution ($BaCl_2 \cdot 2H_2O$, 2.44 g) was added, then precipitate was removed by filtration and the filtrate was evaporated to dryness. Recrystallization from EtOH gave colorless crystals (2.40 g, 65%), mp 192—194°. *Anal.* Calcd. for $C_{14}H_{21}ON_3SCl_2 \cdot H_2O$: C, 45.65; H, 6.29; N, 11.41; S, 8.71. Found: C, 45.72; H, 5.84; N, 11.36; S, 8.55.

3-(2-Dimethylamino-6-methyl-3-pyridinyl)methyl-4-methyl-5-(2-hydroxyethyl)thiazolium Chloride Hydrochloride (14c)——By the procedure used for **14b, 13c** (3.23 g) and 30% hydrogen peroxide (3.5 ml) gave hygroscopic colorless crystals (2.75 g, 71%), mp 158° (decomp.). *Anal.* Calcd. for $C_{15}H_{23}ON_3SCl_2 \cdot H_2O$: C, 47.12; H, 6.59; N, 10.99; S, 8.39; Cl, 18.54. Found: C, 47.42; H, 6.56; N, 10.78; S, 7.98; Cl, 18.31.

3-(2-Hydroxy-6-methyl-3-pyridinyl)methyl-4-methyl-5-(2-hydroxyethyl)thiazolium Chloride (14e)——By the procedure used for **14b, 13e** (2.96 g) and 30% hydrogen peroxide (3.0 ml) gave hygroscopic colorless crystals (1.2 g, 40%), mp 185° (decomp.). *Anal.* Calcd. for $C_{13}H_{17}O_2N_2SCl \cdot 1/2H_2O$: C, 50.40; H, 5.53; N, 9.04; S, 10.35. Found: C, 50.29; H, 5.64; N, 8.86; S, 10.81.

3-(6-Methyl-3-pyridinyl)methyl-4-methyl-5-(2-hydroxyethyl)thiazolium Chloride Hydrochloride (14d)——By the procedure used for **14b, 13d** (2.80 g) and 30% hydrogen peroxide (3.0 ml) gave hygroscopic colorless crystals (2.56 g, 80%), mp 195—197° (decomp.). *Anal.* Calcd. for $C_{13}H_{18}ON_2SCl_2$: C, 48.60; H, 5.65; N, 8.72; S, 9.98; Cl, 22.07. Found: C, 48.34; H, 5.70; N, 8.56; S, 10.04; Cl, 22.12.

3-(2-Chlorobenzyl)-4-methyl-5-(2-hydroxylethyl)thiazolium Chloride (17b)——A mixture of *o*-chlorobenzylchloride (16.1 g) and 4-methyl-5-(2-hydroxyethyl)thiazole (**16**) (14.2 g) was warmed at 80° for 20 hr. Recrystallization from EtOH gave colorless crystals (23.8 g, 78%), mp 184—185°. *Anal.* Calcd. for $C_{13}H_{15}ONSCl_2$: C, 51.32; H, 4.97; N, 4.60; S, 10.54; Cl, 23.31. Found: C, 51.50; H, 5.24; N, 4.78; S, 10.75; Cl, 23.13.

3-(2-Aminobenzyl)-4-methyl-5-(2-hydroxyethyl)thiazolium Chloride Hydrochloride (17e)——A solution of 2-nitrobenzyl thiazolium salt (**17a**) (22 g) in 15% aqueous hydrogen chloride (20 ml) and EtOH (500 ml) was hydrogenated over palladium carbon catalyst. After absorption of the theoretical amount of hydrogen, catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. Recrystallization from EtOH gave pale-yellow crystals (13 g, 58%), mp 140—143°. *Anal.* Calcd. for $C_{13}H_{18}ON_2SCl_2$: C, 48.60; H, 5.65; N, 8.72; S, 9.98; Cl, 22.07. Found: C, 48.67; H, 5.73; N, 8.63; S, 10.08; Cl, 21.54.

3-(2-Methoxybenzyl)-4-methyl-5-(2-hydroxyethyl)thiazolium Chloride (17c)——A mixture of *o*-chloromethyl anisol[17] (1.20 g) and 4-methyl-5-(2-hydroxyethyl)thiazole (**16**) (1.09 g) was heated at 100° for 7 hr. Recrystallization from EtOH–acetone gave colorless crystals (2.05 g, 89%), mp 161°. *Anal.* Calcd. for $C_{14}H_{18}O_2NSCl$: C, 56.09; H, 6.05; N, 4.67; S, 10.69; Cl, 11.82. Found: C, 56.07; H, 6.04; N, 4.93; S, 10.45; Cl, 11.65.

3-(2-Dimethylaminobenzyl)-4-methyl-5-(2-hydroxyethyl)thiazolin-2-thione (19f)——To a stirred solution of 2-dimethylaminobenzyl-carboxamide (**18a**) (10.4 g) in dry dioxane (170 ml) was added slowly solid $LiAlH_4$ (4 g) and the mixture was heated gradually to reflux. The reaction occurred suddenly at about 100°. Reflux was continued for 45 min then the mixture was cooled with ice–water and decomposed with water. After filtration, the aluminum hydroxide-lithium hydroxide residue was washed with $CHCl_3$ and the filtrate and the washing was mixed and evaporated. The residue was dissolved in $CHCl_3$ and extracted with 5%; HCl; the aqueous layer was then neutralized with conc. NH_4OH and the oil which separated extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated. The residue (10.6 g) was dissolved in a mixture of 3-chloro-5-acetoxy-2-pentanone (15 g), conc. NH_4OH (10 ml), and EtOH (50 ml) and carbon disulfide (10 ml) was added to the solution with stirring. Stirring was continued for 7 hr at room temperature then the mixture was allowed to stand overnight and evaporated. The residue was dissolved in 20% HCl (100 ml) and warmed at 60° for 30 min. The solution was washed with $CHCl_3$ and the aqueous layer, after neutralization with 10% NaOH, was extracted with $CHCl_3$ and the organic layer was dried over anhyd. K_2CO_3, then evaporated under reduced pressure. The residue, after treatment with decolorizing charcoal in acetone, was crystallized from ethyl acetate. Recrystallization from ethyl acetate gave pale-yellow crystals (7.6 g, 24%), mp 107°. *Anal.* Calcd. for $C_{15}H_{20}ON_2S_2$: C, 58.41; H, 6.54; N, 9.08; S, 20.79. Found: C, 58.60; H, 6.45; N, 9.16; S, 20.65.

3-(2-Hydroxybenzyl)-4-methyl-5-(2-hydroxyethyl)thiazolin-2-thione (19b)——To a stirred solution of salicylamide (**18b**) (25.6 g) in dry dioxane (250 ml) was added solid $LiAlH_4$ (10 g) and the mixture was heated gradually to reflux. The reaction occurred suddenly at about 100° (bath temperature). Reflux was continued for an hour then the reaction mixture was cooled in ice-water and decomposed with water. After dilution with ether and filtration, the residue containing aluminum hydroxide and lithium hydroxide was dissolved in conc. HCl and the acidic solution was neutralized with K_2CO_3 to pH 7—8. To the neutralized solution was added a mixture of 3-chloro-5-acetoxy-2-pentanone (50 g) and carbon disulfide (100 ml) with stirring. Stirring was continued for 3 days then the solution was acidified with 20% HCl and warmed at 80° for an hour. The acidic solution was extracted with $CHCl_3$ and phenolic compounds were extracted with 10% NaOH from the $CHCl_3$ solution. Acidification of the alkaline solution, collection by filtration and recrystallization from acetone gave pale-yellow crystals (15.7 g, 30%), mp 163°. *Anal.* Calcd. for $C_{13}H_{15}O_2NS_2$: C, 55.49; H, 5.37; N, 4.98; S, 22.79. Found: C, 55.73; H, 5.35; N, 5.05; S, 22.76.

17) R. Pschorr, D. Wolfes, and W. Buckow, *Chem. Ber.*, 33, 165 (1900).

3-(2-Dimethylaminobenzyl)-4-methyl-5-(2-hydroxyethyl)thiazolium Chloride Hydrochloride (17f)——19f (3.08 g) was suspended in 40 ml of aqueous ethanol (H_2O: EtOH, 3: 1) containing 30% hydrogen peroxide (3.2 ml) and stirred for 30 min at 80°. Barium chloride solution ($BaCl_2 \cdot 2H_2O$, 2.44 g) and decolorizing charcoal were added, then precipitate was removed by filtration and the filtrate was evaporated to dryness. Recrystallization from EtOH–acetone gave hygroscopic colorless crystals (2.6 g, 72%), mp 163° (decomp.). *Anal.* Calcd. for $C_{15}H_{22}ON_2SCl_2 \cdot 1/2H_2O$: C, 50.28; H, 6.47; N, 7.82; S, 8.95; Cl, 19.79. Found: C, 50.17; H, 6.43; N, 7.81; S, 8.60; Cl, 20.40.

3-(2-Hydroxybenzyl)-4-methyl-5-(2-hydroxyethyl)thiazolium Chloride (17 g)——19 g (2.80 g) was suspended in 30 ml of aqueous ethanol (H_2O: EtOH, 2: 1) containing 30% hydrogen peroxide (3.2 ml) and stirred for 5 hr at room temperature. Barium chloride solution ($BaCl_2 \cdot 2H_2O$, 2.44 g) and decolorizing charcoal was added. Filtration and evaporation of the filtrate *in vacuo* left a brown residue. The residue, after the decolorizing treatment in EtOH, gave a hygroscopic yellow oil (2.1 g, 71%). *Anal.* Calcd. for $C_{13}H_{16}O_2NSCl \cdot 1/2H_2O$: C, 52.97; H, 5.81; N, 4.75; Cl, 12.03. Found: C, 53.08; H, 5.77; N, 4.75; Cl, 12.16.

Measurement of Rates of Hydrogen Exchange——Solutions of the salts studied were prepared by dissolving 0.25 mmol of a salt in 0.5 ml of buffered solution (D_2O, 7.5 ml; CD_3COOD, 2.4 g; *ca.* 40% NaOD–D_2O, 2.0 ml; pD=5.93) at room temperature. The solution was transfered to an NMR tube and placed in the probe of the spectrometer; the integrated area measured for the 2-hydrogen signal was compared to that for the N_3-methylene signal (the exchange of N_3-methylene protons did not occur under the conditions used) as a function of time. Pseudo first order rate constants were observed. pH values were measured after the exchange had finished and the probe temperature was measured after each kinetic run from the chemical shift of ethylene glycol.

Treatment of Thiazolium Salts with Base——A suspension of the thiazolium salt (0.5 mmol) in a mixture of DMF–Et_3N–H_2O (92: 7: 1) (5 ml) was allowed to stand for a week under nitrogen atmosphere at room temperature with occasional shaking, then evaporated *in vacuo* (60°). The residue was dissolved in $CHCl_3$ (10 ml) and the solution was washed with satd. NaCl solution (2 ml), dried over anhyd. Na_2SO_4 (1.5 g), and evaporated *in vacuo*. In the experiments with thiazolium salts having pyrimidine or pyridine rings, the residue was dissolved in 0.40% 2-aminothiazole-DMF solution (5 ml, internal standard) and the quantity of thiazole (**16**) was measured by comparing the ratio of the areas of the thiazole peaks (2-aminothiazole/thiazole (**16**)) on the gas chromatogram with a standard line for the ratios obtained from known mixtures of 2-aminothiazole/thiazole (**16**). For benzylthiazolium salts, the residue was dissolved in 0.10% 2-aminothiazole-$CHCl_3$ solution (5 ml) and the area of the thiazole (**16**) gas chromatogram peak per 1.0 μl of the solution was compared with that of a standard solution of thiazole (**16**). This was because in benzyl series a decrease of the aminothiazole peak was found in some instances.

Table IV. Elemental Analysis of the Products obtained in the Phosphonate Reaction

Compound No.	mp (°C)	Formula	Calcd.				Found			
			C	H	N	S	C	H	N	S
21a	oil	$C_{19}H_{21}N_3O_2S \cdot 1/2H_2O$	62.79	6.05	11.55	8.80	62.76	6.11	11.54	8.92
21b	amorph.	$C_{20}H_{24}N_4O_2S \cdot 1/2H_2O$	61.05	6.40	14.24	8.15	60.84	6.66	13.38	8.16
21c	oil	$C_{20}H_{23}N_3O_3S \cdot 1/2H_2O$	60.89	6.13	10.65	8.13	60.73	6.34	9.87	7.90
21d	162	$C_{20}H_{22}N_2O_2S$	67.77	6.26	7.90	9.05	67.48	6.23	7.60	9.07
22b	175	$C_{20}H_{21}N_3OS$	68.36	6.02	11.96		68.47	5.79	11.78	
21e	146—147	$C_{21}H_{25}N_3O_2S$	65.77	6.57	10.96		65.36	6.41	10.76	
21f	amorph.	$C_{20}H_{20}N_2O_4 \cdot 3/2H_2O$	63.31	6.11	7.38		63.04	5.73	7.11	
21g	122	$C_{20}H_{20}NO_2SCl$	64.25	5.39	3.75	8.58	64.51	5.39	3.92	8.80
				Cl, 9.48				Cl, 9.76		
21i	oil	$C_{21}H_{23}NO_3S$	68.27	6.27	3.79	8.68	68.13	6.48	3.79	8.42
22c	amorph.	$C_{20}H_{20}N_2OS$	71.39	5.99	8.33		71.69	5.89	8.09	
21j	oil	$C_{22}H_{26}N_2O_2S$	69.08	6.85	7.32	8.38	69.09	7.00	7.29	8.02
23	189—190	$C_{12}H_{16}N_2O_2S_2$	50.70	5.67	9.86	22.53	50.58	5.82	9.50	22.74
24	102	$C_{13}H_{15}NO_2S$	62.62	6.06	5.62	12.86	62.67	6.21	5.58	12.73
25	181—183	$C_{21}H_{24}N_4OS$	66.29	6.36	14.72	8.43	65.92	6.57	15.03	9.20
26	125	$C_8H_{13}N_3O$	57.46	7.84	25.13		57.43	7.77	24.97	
27	oil	$C_{20}H_{19}NO_3S \cdot 1/2H_2O$	66.28	5.56	3.86	8.85	66.49	5.42	3.59	8.89
28	oil	$C_{26}H_{28}N_2O_3S_2 \cdot 1/2H_2O$	63.78	5.97	5.72	13.10	63.76	6.05	5.82	12.65
				M.W., 480.64				M.W., 509		
29	oil	$C_9H_{14}N_2O$	65.03	8.49	16.85		64.23	8.57	16.33	
30	207	$C_{14}H_{13}NO_3 \cdot H_2O$	64.36	5.79	5.36		64.97	4.89	5.00	

Treatment of Hydroxy Thiazolium Salts (8f, 14e, and 17 g) with Base——A suspension of a hydroxy thiazolium salt (**8f, 14,** and **17 g**) (1 mmol) in a mixture of DMF (5 ml), Et_3N (0.7 ml) and water (2 drops) was stirred under nitrogen atmosphere for 3 hr and the reaction mixture was allowed to stand for a week with occasional shaking, then evaporated *in vacuo* (60°). The residue was dissolved in $CHCl_3$ (30 ml) and the solution was washed with water (5 ml), dried and evaporated. PLC separation (Kieselgel GF_{254} nach Stahl, E. Merck) of the residual oil gave a pale-yellow oily product which was identical with **16** by infrared (IR) comparison.

General Procedure for the Phosphonate Reaction——To an ice-cooled suspension of thiazolium halide (1 mmol) and diethyl benzoylphosphonate (1.2 mmol) in dry dimethylformamide (5 ml) was added triethylamine (0.7 ml) with stirring in a nitrogen atmosphere. Stirring and ice-cooling were continued for 3 hr, then the mixture was allowed to stand overnight at room temperature. After evaporation of the dimethylformamide *in vacuo* at 60°, the resulting oil was dissolved in a mixture of EtOH (6 ml) and 10% NaOH (6 ml), warmed at 60° for 30 min, and the EtOH evaporated under reduced pressure. This alkaline treatment was omitted in the reaction in which the starting thiazolium halide had an amino substituent. The residue was dissolved in $CHCl_3$ and washed with water. Then $CHCl_3$ extract, after drying and evaporation, was separated using preparative layer chromatography (Kiesegel GF_{254} nach Stahl, E. Merck, developed with 8% MeOH–$CHCl_3$). The elemental analyses and NMR spectra of the reaction products are listed in Tables III, IV, and V.

TABLE V. NMR Spectra of the Products obtained in the Phosphonate Reaction

Compd. No.	Solv.	NMR (τ)
21a	$CDCl_3$	8.07(3H, s, Me), 7.82(1H, bs, OH), 7.63(2H, t, J=6.5Hz, -CH_2-), 7.30(3H, s, Me), 6.57(2H, t, J=6.5Hz, -CH_2O-), 5.41(1H, s, -CH$\langle^{Ph}_{S}$), 5.28, 4.68(2H, ABq, J=16.3Hz, Pm-CH_2N), 2.72(5H, s, Ph), 1.48(2H, s, Pm-4,6H)
21b	$CDCl_3$	7.98(3H, s, Me), 7.73(2H, m, -CH_2-), 7.51(3H, s, Me), 7.33(1H, s, OH), 6.99(3H, d, J=4.5Hz, NHMe), 6.59(2H, t, J=6.5Hz, -CH_2O), 5.45(1H, s, -CH$\langle^{Ph}_{S}$), 5.43, 4.86 (2H,ABq, J=15.5Hz, Pm-CH_2-N), 3.40(1H, m, NH), 2.70(5H, s, Ph), 2.11(1H, s, Pm-6H)
21c	$CDCl_3$	8.10(3H, s, Me), 7.69(2H, m, -CH_2-), 7.42(4H, s, Me, OH), 6.55(2H, t, J=7.0Hz, -CH_2O), 5.99(3H, s, OMe), 5.41(1H, s, -CH$\langle^{Ph}_{S}$), 5.32, 4.72(2H, ABq, J=17.0Hz, Pm-CH_2-N), 2.69(5H, s, Ph), 1.87(1H, s, Pm-6H)
21d	$CDCl_3$	8.55(1H, s, OH), 8.10(3H, s, Me), 8.1—7.5(2H, m, -CH_2-), 7.48(3H, s, Me), 6.60(2H, t, J=6.2Hz, -CH_2O), 5.40(1H, s, -CH$\langle^{Ph}_{S}$), 5.30, 4.58(2H, ABq, J=16.0Hz, Py-CH_2-N), 2.90(1H, d, J=8.0Hz, Py-5H), 2.68(5H, s, Ph), 2.52(1H, q, J=8.0, 2.4Hz, Py-4H), 1.65(1H, d, J=2.4Hz, Py-2H)
22b	$CDCl_3$	8.00(3H, s, Me), 7.53(3H, s, Me), 7.38(2H, m, -CH_2-), 6.60(2H, m, -CH_2O), 5.12(1H, s, -CH$\langle^{Ph}_{S}$), 5.25, 4.88(2H, ABq, J=14.0Hz, Py-CH_2-N), 3.16 (1H, d, J=7.0Hz, Py-H), 2.9—2.5(6H, m, Ph,Py-H)
21e	$CDCl_3$	8.07(3H, s, Me), 7.63(3H, s, Me), 7.9—7.5(2H, m, -CH_2-), 7.00(3H, bs, NHMe), 6.62 (2H, t, J=6.0Hz, -CH_2O), 5.42(1H, s, -CH$\langle^{Ph}_{S}$), 5.44, 4.79 (2H, ABq, J=16.0Hz, Py-CH_2-N), 3.67, 2.91(2H, ABq, J=7.8Hz, Py-4,5H), 2.71(5H, s, Ph)
21f	$CDCl_3$	8.40(1H, bs, OH), 8.13(3H, s, Me), 7.9—7.2(2H, m, -CH_2-), 6.55(2H, t, J=6.0Hz, -CH_2O), 5.35(1H, s, -CH$\langle^{Ph}_{S}$), 4.82, 4.22(2H, ABq, J=18.5Hz, Ph-CH_2-N), 2.67 (5H, s, Ph), 2.7—1.8(4H, m, Ph)
21g	$CDCl_3$	8.12(3H, s, Me), 7.85—7.15(2H, m, -CH_2-), 6.57 (2H, bt, -CH_2O), 5.33(1H, s, -CH$\langle^{Ph}_{S}$), 5.08, 4.46(2H, ABq, J=17.5Hz, Ph-CH_2-N-), 2.9—2.6(4H, m, Ph), 2.65 (5H, s, Ph)
22c	$CDCl_3$	8.00(3H, s, Me), 8.0—7.1(2H, m, -CH_2-), 7.05(1H, s, OH), 6.8—6.5(2H, m, -CH_2O), 5.10(1H, s, CH$\langle^{Ph}_{S}$), 5.29, 4.92(2H, ABq, J=14.0Hz, Ph-CH_2-N), 3.1—2.4(9H, m, Ph)
21i	$CDCl_3$	8.15(3H, s, Me), 8.0—7.2(2H, m, -CH_2-), 6.61(2H, t, J=6.3Hz, -CH_2O), 6.18(3H, s, OMe), 5.38(1H, s, -CH$\langle^{Ph}_{S}$), 5.16, 4.59(2H, ABq, J=17.0Hz, Ph-CH_2-N), 3.3—2.7(4H, m, Ph), 2.70(5H, s, Ph)

Compd. No.	Solv.	NMR (τ)
21j	$CDCl_3$	8.75(1H, s, OH), 8.28(3H, s, Me), 8.2—7.2(2H, m, -CH_2-), 7.31(6H, s, NMe_2), 6.65 (2H, t, J=6.0Hz, -CH_2O), 5.35(1H, s, $CH\langle^{Ph}_{S}$), 5.03, 4.52(2H, ABq, J=16.2 Hz, Ph-CH_2-N), 3.1—2.5(9H, m, Ph)
23	DMSO-d_6	7.68(6H, s, 2xMe), 7.11(4H, t, J=6.0 Hz, 2x-CH_2-), 6.38(4H, q, J=5.5Hz, 2x-CH_2O), 5.17(2H, t, J=5.0Hz, 2xOH)
24	$CDCl_3$	7.73(3H, s, Me), 7.15(2H, t, J=6.0Hz, -CH_2-), 6.32(2H, t, J=6.0Hz, -CH_2O), 4.17 (1H, s, -$CH\langle^{Ph}_{O}$), 2.67(5H, m, Ph)
25	$CDCl_3$	7.62(3H, s, Me), 7.60(3H, s, Me), 7.11 (2H, t, J=6.5Hz, -CH_2-), 6.89(6H, s, NMe_2), 6.78(1H, s, OH), 6.30(2H, t, J=6.5 Hz, -CH_2O), 2.70(5H, s, Ph), 2.47, 2.37(2H, 2xs Pm-6H, C=C$\langle_{H}$)
26	$CDCl_3$	7.56(3H, s, Me), 6.77(6H, s, NMe_2), 6.37(1H, bs, -OH), 5.45(2H, s, Pm-CH_2-O), 2.11(1H, bs, Pm-6H)
27	$CDCl_3$	7.67(3H, s, Me), 6.88(2H, t, J=7.0Hz, -CH_2-), 5.58(2H, t, J=7.0Hz, -CH_2O), 4.07 (1H, s, -$CH\langle^{Ph}_{O}$), 2.8—1.85(10H, 2xPh)
28	$CDCl_3$	7.77(6H, s, 2xMe), 7.17, 7.05(4H, 2xt, J=7.0Hz, 2x-CH_2-), 6.33(4H, t, J=7.0Hz, 2x-CH_2O), 4.50(1H, s, -$CH\langle^{Ph}_{O}$), 4.05(1H, bs, -$CH\langle^{Ph}_{O}$), 2.70(10H, m, 2xPh)
29	$CDCl_3$	7.58(3H, s, Me), 7.20(6H, s, NMe_2), 6.26(1H, bs, OH), 5.35(2H, s, Py-CH_2-O), 3.27, 2.58(2H, ABq, J=8.0Hz, Py-4,5H)
30	$CDCl_3$	7.60(3H, s, Me), 4.70(2H, s, Py-CH_2-O), 2.7—1.8(7H, m, Py-4.5H, Ph)

Ph=phenyl, Py=pyridine

2-Hydroxybenzyl-4-methyl-5-(2-hydroxyethyl)thiazole (**24**)——a) A solution of 2-hydroxybenzylthiamine chloride hydrochloride (29 mg)[4] in a mixture of 5.3% H_2SO_3 (2 ml) and pyridine (1 ml) was allowed to stand for 2 days at room temperature. Extraction with $CHCl_3$ and recrystallization from ethyl acetate gave colorless crystals (10 mg), mp 102°, which were shown to be identical with the product of the phosphonate reaction by mixed mp and IR comparison.

b) A solution of 2-hydroxybenzyl-4-methyl-5-(2-hydroxyethyl)thiazole-N-oxide (**34**) (see below) (25 mg) in MeOH (2.5 ml) was hydrogenated over Raney Ni (W-2) catalyst (*ca.* 240 mg). When 3 ml of hydrogen had been absorbed, catalyst was removed by filtration and the filtrate was evaporated. Recrystallization from ethyl acetate gave colorless needles (20 .5mg), mp 102°, which were identified with **24** obtained above by IR comparison.

4-Methyl-5-(2-benzoyloxyethyl)thiazole N-Oxide (**33**)——Thiazole (**32**) 20 g was dissolved in acetic acid (200 ml) containing 30% hydrogen peroxide (60 ml) and the mixture was allowed to stand for a week at room temperature. After decomposition of hydrogen peroxide with saturated sodium bisulfite solution, acetic acid was evaporated *in vacuo*. The residue was dissolved in EtOH and the white solid formed removed by filtration. The filtrate was evaporated and dissolved in $CHCl_3$, and the solution was washed with saturated potassium carbonate solution, dried, and evaporated. Recrystallization from acetone gave colorless crystals (5.11 g, 25%), mp 117—119°. *Anal.* Calcd. for $C_{13}H_{13}O_3NS$: C, 59.31; H, 4.98; N, 5.32; S, 12.18. Found: C, 59.38; H, 4.94; N, 4.70; S, 12.32.

2-Hydroxybenzyl-4-methyl-5-(2-hydroxyethyl)thiazole N-Oxide (**34**)——To a solution of **33** (526 mg) in MeOH (6 ml) was added benzaldehyde (270 mg) and sodium methoxide (500 mg) at room temperature and the mixture was stirred for a day. MeOH was evaporated *in vacuo*, the residue dissolved in $CHCl_3$, and the solution dried over $MgSO_4$ and evaporated. The residue was washed with ether and resultant solid recrystallized from acetone to give colorless crystals (66 mg, 12.5%), mp 161°. *Anal.* Calcd. for $C_{13}H_{15}O_3NS$: C, 58.84; H, 5.70; N, 5.28; S, 12.09. Found: C, 58.71; H, 5.68; N, 5.13; S, 11.56.

Acetylation of Dimeric Thiazole (**28**)——To a solution of **28** (27 mg) in pyridine (1 ml) was added acetic anhydride (0.5 ml) and the mixture was allowed to stand overnight at room temperature. The solution was evaporated *in vacuo* and the residual oil dissolved in $CHCl_3$. Washing with water, drying, and removal of the solvent gave a yellow oil (31 mg). TLC separation (Kieselgel GF_{254} nach Stahl, E. Merck) gave a light-yellow oily product (25 mg). *Anal.* Calcd. for $C_{30}H_{32}O_5N_2S_2 \cdot H_2O$: C, 61.83; H, 5.88; N, 4.81; S, 11.00; mol. wt. 564.7. Found: C, 62.31; H, 5.77; N, 4.72; S, 10.42; mol. wt. 538 ($CHCl_3$ sol.).

Ozonolysis of 25——A stream of ozone in oxygen (O_3, 1.8 mg) was passed through a solution of **25** (6 mg) in $CHCl_3$ (20 ml) for one minute at room temperature. The solution was allowed to stand for 3 min then

concentrated to 1 ml *in vacuo*. 5% sodium bisulfite solution (5 drops) was added to the concentrated solution, which was then dried over anhyd. Na_2SO_4 and evaporated *in vacuo*. TLC separation using Kieselgel GF_{254} nach Stahl (E. Merck)-4% MeOH–$CHCl_3$ and Aluminium Oxide GF_{254} (E. Merck)-benzene gave an oily product (0.5 mg) which was identified by IR comparison ($CHCl_3$ sol.) with 2-benzoyl-4-methyl-5-(2-hydroxyethyl)thiazole (**35b**) obtained by the action of benzaldehyde on thiamine chloride hydrochloride according to the procedure of Hirano and Oka,[15] mp 84°.