[Chem. Pharm. Bull. 22(2) 293—298 (1974)]

UDC 547.789.04 : 547.491.3.04

Studies on Pyrimidine Derivatives and Related Compounds. LXXXI.[1] Reactions of Aryl Isothiocyanates with Thiamine and Related Thiazolium Ylides[2]

Akira Takamizawa, Saichi Matsumoto, and Shoji Sakai

Shionogi Research Laboratory, Shionogi & Co., Ltd.[3]

(Received March 30, 1973)

Reactions of thiamine and related thiazolium ylides with aryl isothiocyanates afforded zwitterionic adducts (Va—j) or cycloadducts (VIa—c). An electron attracting substituent in the aryl group favored the zwitterion formation, while an electron donating substituent favored the cycloadduct formation. A ring expansion reaction of 2-thiocarbamoylated thiazolium ring giving 1,4-thiazine derivative was also described.

In connection with the studies of nucleophilic reactivities of thiazolium C-2 position of thiamine, we have previously reported that the reactions of alkyl isothiocyanates with thiazolium ylides (I) gave the (1: 2) cycloadduct (II) having a fused spiro ring system.[4] This reaction can be envisaged as involving (1: 1) adduct followed by cycloaddition of another molecule of RNCS with the 1,3-dipolar intermediate. Such type of the 1,3-dipolar species

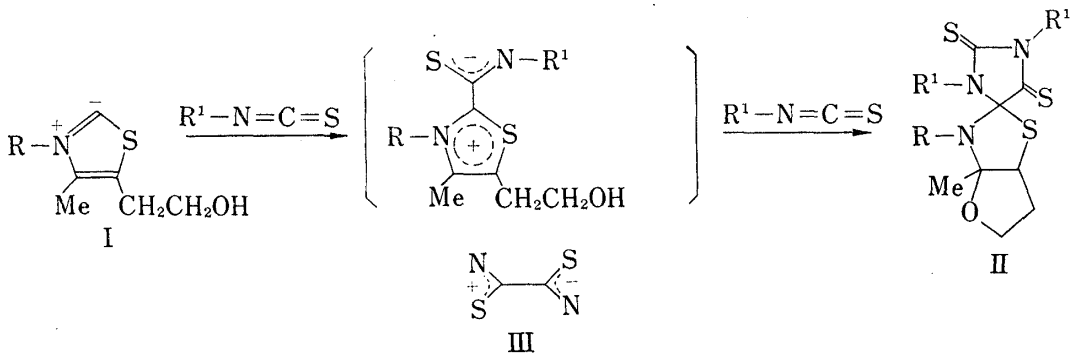

Chart 1

have been isolated in the reactions of aryl isothiocyanates with imidazolium ylide[5] or with tetraaminoethylene derivatives.[6] We have now studied the addition reactions of aryl isothiocyanates with thiazolium ylides including thiamine, and found that the stable (1: 1) adduct having a novel zwitterionic system (III) could be isolated and that the product distribution between the (1: 1) adduct and the (1: 2) cycloadduct depended largely on the nature of the substituent in aryl isothiocyanate.

Reaction of 3,4-dimethyl-5-(2-hydroxyethyl)thiazolium iodide (IVa) with an excess amount of phenyl isothiocyanate in the presence of triethylamine (NEt_3) in N,N-dimethylformamide (DMF) afforded (1: 1) adduct Va ($C_{14}H_{16}ON_2S_2$, mp 135—136°) as a major product

1) Part LXXX: A. Takamizawa, T. Makino, and Y. Yonezawa, *Chem. Pharm. Bull.* (Tokyo), **22**, 286 (1974).
2) A part of this work was reported preliminarily in *Tetrahedron Letters*, **1968**, 4027.
3) Location: *Fukushima-ku, Osaka, 553, Japan.*
4) A. Takamizawa, K. Hirai, S. Matsumoto, S. Sakai, and Y. Nakagawa, *Chem. Pharm. Bull.* (Tokyo), **17**, 910 (1969).
5) H.-T. Schönherr and H.-W. Wanzlick, *Chem. Ber.*, **103**, 1037 (1970).
6) H.E. Winberg and D.D. Coffman, *J. Am. Chem. Soc.*, **87**, 2776 (1965); M. Regitz, J. Hocker, W. Schössler, B. Weber, and A. Liedhegener, *Ann. Chem.*, **748**, 1 (1971).

accompanied by a small amount of (1:2) adduct Vb ($C_{21}H_{21}ON_3S_3$, mp 175—176°). Both products were obtained as stable brown crystals. On the treatment with EtOH–HCl, Va gave a hydrochloride VIII, mp 206—209°, which was reconverted into Va by the action of aq. Na_2CO_3. Both Va and VIII were readily reduced by $NaBH_4$ to give a same tetrahydro derivative IX. The nuclear magnetic resonance (NMR) spectrum of Va showed, in addition to a phenyl and -CH_2CH_2OH signals, two singlets at τ 5.84 and τ 7.75 corresponding to the thiazolium N-CH_3 and C_4-CH_3 protons respectively, while the tetrahydro derivative IX showed a singlet at τ 7.58 (N-CH_3), a doublet (J=7 Hz) at τ 8.75 (C_4-CH_3) and a singlet at τ 5.30 ($^{N}_{S}\times^{H}$). These NMR data showed that Va should have a 2-substituted thiazolium structure which was reduced by $NaBH_4$ to a thiazolidine ring. Thus the structure of Va was assigned as 3,4-dimethyl-5-(2-hydroxyethyl)thiazolium-2-N-phenylthiocarbamoylide. The ultraviolet (UV) spectrum of Va had a maximum at 285 mμ (log ε=3.95), while its hydrochloride VIII showed maxima at 305 mμ (log ε=3.85) and 339 mμ (log ε=3.82). Combined with the fact that VIII had an infrared (IR) absorption band at 2720 cm^{-1} corresponding to SH group, the marked UV red shift indicated that the protonation occurred at the sulfur of the thiocarbamoylide moiety in Va. The structure of the minor product Vb was assigned as O-phenylthiocarbamate of Va rather than the (1:2) cycloadduct because it showed no UV absorption due to dithiohydantoin chromophore[4] and its NMR spectrum exhibited singlets at τ 5.77 (N-CH_3) and τ 7.65 (C_4-CH_3) besides a pair of triplet at τ 5.30 and τ 6.67 (-CH_2CH_2O-), a broad singlet at τ −1.10 (NH) and a multiplet due to two phenyl groups. Reaction of 3-benzyl-4-methyl-5-(2-hydroxyethyl)thiazolium bromide (IVb) with phenyl isothiocyanate

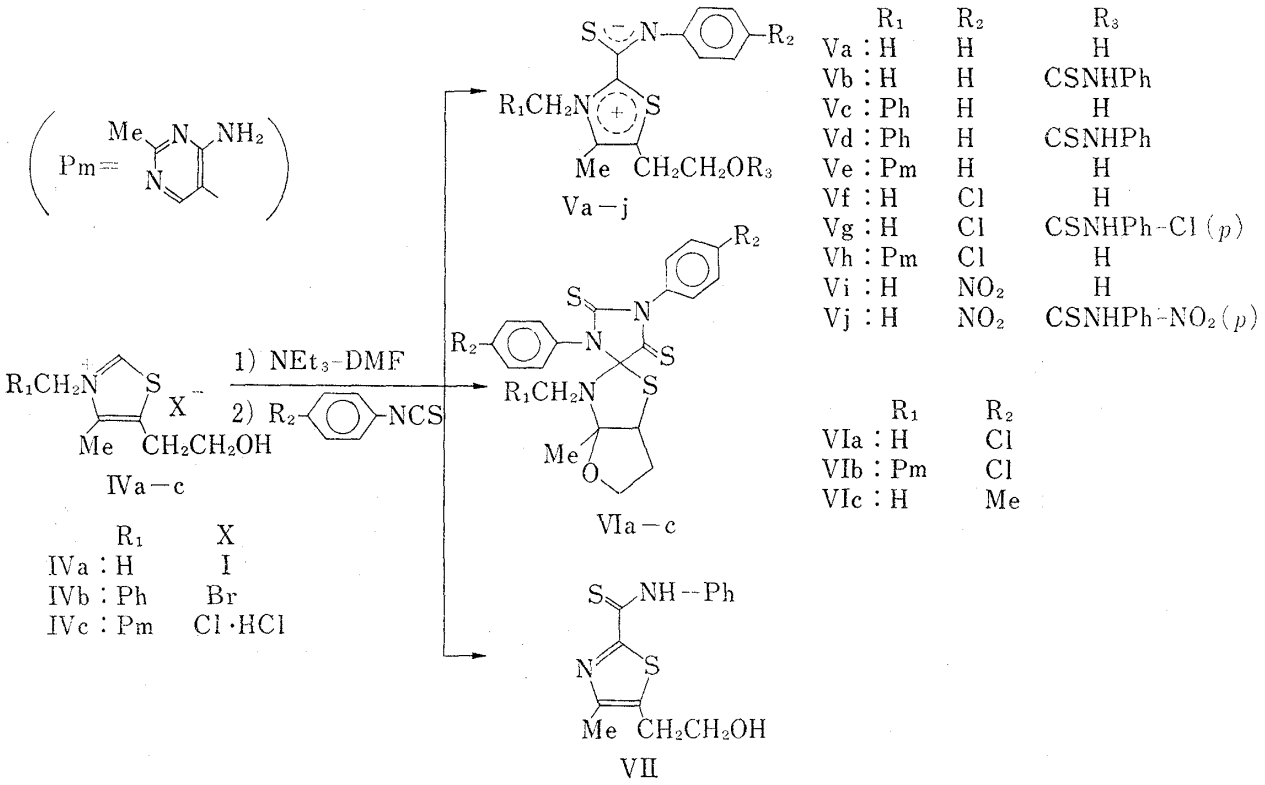

Chart 2

also gave the zwitterionic (1:1) adduct Vc, mp 153—154°, and its O-phenylthiocarbamate Vd, mp 144—145°, whose structures were confirmed by the complete similarity of their spectral data to those of Va and Ve respectively (see Experimental). In the case of the reaction of thiamine hydrochloride (IVc) with phenyl isothiocyanate gave a complex mixture from which

the (1:1) adduct Ve, mp 144—145° (decomp.), and a yellow crystalline product VII, mp 113—114°, were isolated in a poor yield respectively. The latter product was analyzed as $C_{13}H_{14}ON_2S_2$ indicating that this compound was arisen by the loss of pyrimidylmethyl moiety from Ve, and its structure was assigned as 2-N-phenylthiocarbamoyl-4-methyl-5-(2-hydroxyethyl)thiazole on the basis of NMR data [broad singlets at τ −0.67 (NH) and τ 8.18 (OH), multiplets at τ 1.9—2.8 (phenyl), a pair of triplet at τ 6.13 and τ 7.00 (CH_2CH_2O-), and a singlet at τ 7.60 (C_4-CH_3)]. This compound is considered to be produced by a hydrolytic fission of the C-N bond between the quaternary nitrogen and methylene carbon in Ve, however, the possible counter part could not be isolated from the reaction mixture. Similar C-N bond fission has been observed in the addition reactions of thiamine with aromatic aldehydes[7] or thiamine analogues with diethyl benzoylphosphonate,[8] although mechanistically differed from each other.

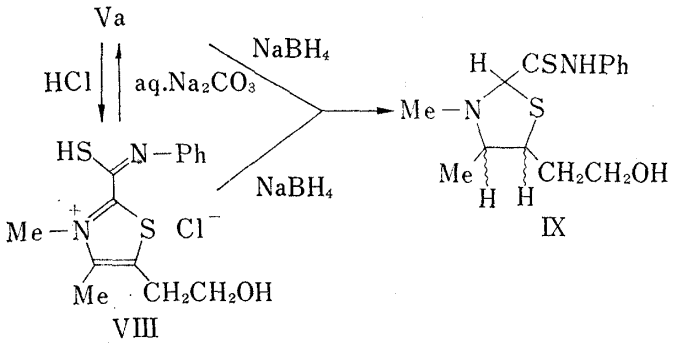

Chart 3

Table I. The Effect of Substituent on the Product Distribution in the Reaction of 3,4-Dimethyl-5-(2-hydroxyethyl)-thiazolium Iodide (IVa) with R-NCS

R	Yield of adduct	
	Zwitterions (%)	(1:2) Cycloadduct %
$-CH_3$ [a]	0	43 [a]
$-C_6H_4-CH_3$ (*p*)	0 (7) [b]	4
$-C_6H_4-Cl$ (*p*)	34	25
$-C_6H_5$	34	0
$-C_6H_4-NO_2$ (*p*)	20	0

a) ref. 4)
b) yield of the hydroiodide (X)

Reaction of *p*-chlorophenyl isothiocyanate with IVa afforded two zwitterionic (1:1) adduct Vf, mp 168—170°, and (1:2) adduct Vg, mp 175—176°, and in this case (1:2) cycloadduct VIa, mp 182—183°, was also obtained in a considerable yield. The structure of the cycloadduct was confirmed by the characteristic spectral data as follows. VIa showed a UV absorption maximum at 322 mμ (log ε=4.18) attributable to dithiohydantoin ring[4] and the NMR spectrum exhibited an N-CH_3 signal at τ 7.47 and a C-CH_3 signal at τ 8.32 besides a complex multiplet due to -$\dot{C}HCH_2CH_2O$- system in the region τ 6.1—8.0.

Reaction of thiamine with *p*-chlorophenyl isothiocyanate also afforded the corresponding (1:2) cycloadduct VIb, mp 210—212° (decomp.), and the zwitterionic (1:1) adduct Vh mp 164—165° (decomp.). To investigate in more detail the effect of the isothiocyanate substituent upon the product distribution between the zwitterionic adduct and (1:2) cycloadduct, reactions of IVa with *p*-tolyl and *p*-nitrophenyl isothiocyanates were carried out. The results are summerized in Table I in which the yield of zwitterions shows the sum of the yield of (1:1) adduct and its O-thiocarbamate. For comparison, a previously reported result for methyl isothiocyanate is also listed in the table. *p*-Nitrophenyl isothiocyanate gave only the zwitterionic adducts Vi, mp 180—181°, and Vj, mp 187—187.5°, while *p*-tolyl isothiocyanate gave the (1:2) cycloadduct VIc, mp 182—183°. In the latter case, the (1:1) adduct was obtained as a hydrogen iodide X, mp 141—143°, instead of the zwitterionic form, which indicates that the basicity of the zwitterion is considerably increased by the *p*-methyl substituent. The compound (X) was recovered unchanged on treatment with aq. Na_2CO_3,

7) Y. Oka, S. Kishimoto, and H. Hirano, *Chem. Pharm. Bull.* (Tokyo), **18**, 536 (1970).
8) A. Takamizawa and H. Harada, *Chem. Pharm. Bull.* (Tokyo), **21**, 770 (1973).

whereas the action of aq. NaOH resulted in the formation of iodine free compound (XIa), mp 161—162°, which was analyzed as $C_{15}H_{18}O_2N_2S$. XIa showed IR bands due to C=O (1645 cm^{-1}) and C=N (1635 cm^{-1}), and its NMR spectrum exhibited three sharp singlets at τ 6.56 (N-CH_3) and τ 7.65, 7.83 (C-CH_3 and/or Ph-CH_3) besides the signals due to -CH_2CH_2OH and four aromatic protons. From these evidences the structure of XIa was established as 2-*p*-tolylimino-4,5-dimethyl-6-(2-hydroxyethyl)-2,3-dihydro-1,4-thiazin-3-one. Action of aq. NaOH upon Va also afforded the corresponding 1,4-thiazine derivative XIb. These 1,4-

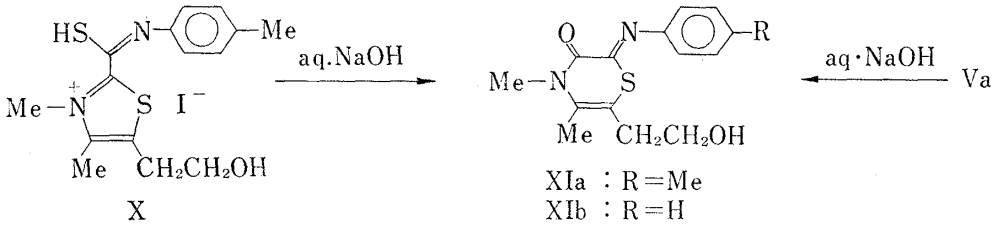

Chart 4

thiazine derivatives might be produced by the same mechanism as known for the ring expansion of 2-substituted thiazolium salts.[9]

From the table it is evident that an electron donating substituent in phenyl isothiocyanate relatively favors the formation of (1 : 2) cycloadduct, whereas an electron attracting substituent favors the formation of zwitterionic adduct. This indicates that destabilization of negative charge in the zwitterionic system leads to the increase of its nucleophilic reactivity as a 1,3-dipole, while stabilization of the negative charge by delocalization decreases its 1,3-dipolar reactivity.

Experimental

All melting points were determined in capillaries and uncorrected. NMR spectra were taken on a Varian Associates A-60 spectrometer in $CDCl_3$ or d_6-DMSO solution with tetramethylsilane as an internal standard. UV spectra were taken on a Hitachi EPS-3 spectrophotometer in 99% EtOH. IR spectra were taken in nujol mull on a Japan Spectroscopic Company IR-S spectrophotometer using a NaCl prism unless otherwise indicated. Column chromatographies were carried out by using SiO_2 (Davision, grade 950) or Al_2O_3 (Woelm, neutral, grade 1).

Reaction of 3,4-Dimethyl-5-(2-hydroxyethyl)thiazolium Iodide (IVa) with Aryl Isothiocyanate——General Procedure: 2.85 g (0.01 mole) of IVa was dissolved in 30 ml of DMF, then 1.5 g (0.015 mole) of NEt_3 was added to the solution and the mixture was stirred for 30 min at room temperature. To the reaction mixture, approximately two equimolar amounts of aryl isothiocyanate was added and stirred for 4 hr at 50°. The reaction mixture was concentrated *in vacuo*, and the resulting residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over abs. Na_2SO_4 and concentrated *in vacuo* to leave a residue which was chromatographed with SiO_2 column using AcOEt or acetone as an eluant.

Phenyl Isothiocyanate: 2.7 g of PhNCS was allowed to react with IVa according to the general procedure. The reaction mixture was chromatographed first with AcOEt. The AcOEt fraction gave first N,N'-diphenylthiourea (140 mg), and, secondly, 3,4-dimethyl 5-[2-(N-phenylthiocarbamoyloxy)ethyl]thiazolium-2-N-phenylthiocarbamoylide (Vb) (158 mg, 3.7%) which was recrystallized from acetone to give brown prisms, mp 175—176°. *Anal.* Calcd. for $C_{21}H_{21}ON_3S_3$: C, 59.01; H, 4.95; N, 9.83; S, 22.46. Found: C, 58.78; H, 5.12; N, 9.61; S, 22.31. NMR (d_6-DMSO, τ): −1.10 (1H, broad, NH), 2.4—2.8 (10H, m, 2×Ph), 5.30 and 6.67 (each 2H, t, -CH_2CH_2O-), 5.77 (3H, s, N-CH_3), 7.65 (3H, s, C_4-CH_3). Then elution with the mixture of AcOEt (10) and MeOH (1) gave 3,4-dimethyl-5-(2-hydroxyethyl)thiazolium-2-N-phenylthiocarbamoylide (Va) (875 mg, 30%) which was recrystallized from MeOH to give brown prisms, mp 135—136°. *Anal.* Calcd. for $C_{14}H_{16}ON_2S_2$: C, 57.49; H, 5.51; N, 9.58; S, 21.93; mol. wt., 292.41. Found: C, 57.77; H, 5.38; N, 10.05; S, 22.21; mol. wt., 308 (vapor pressure osmometry). NMR ($CDCl_3$, τ): 2.68 (5H, m, Ph), 5.84 (3H, s, N-CH_3), 6.11 (1H, broad, OH), 6.33 and 7.17 (each 2H, t, -CH_2CH_2O-), 7.75 (3H, s, C_4-CH_3). UV λ_{max} mμ (log ε): 285 (3.95).

9) A. Takamizawa, Y. Hamashima, and H. Satoh, *J. Org. Chem.*, 33, 4038 (1968).

p-Chlorophenyl Isothiocyanate: 2.4 g of *p*-chlorophenyl isothiocyanate was allowed to react according to the general procedure. The (1:2) cycloadduct (VIa) crystallized from the crude reaction mixture after concentration, and collected to give yellow prisms, mp 182—183° (1.24 g, 25%). *Anal.* Calcd. for $C_{21}H_{19}ON_3S_3Cl_2$: C, 50.80; H, 3.86; N, 8.47; S, 19.37; Cl, 14.29. Found: C, 50.80; H, 3.94; N, 8.73; S, 19.51; Cl, 14.12. UV λ_{max} mμ (log ε): 322 (4.18). NMR ($CDCl_3$, τ): 6.1—8.0 (5H, m, $-\dot{C}HCH_2CH_2O-$), 7.47 (3H, s, $N-CH_3$), 8.32 (3H, s, $C-CH_3$). The mother liquor was chromatographed first with AcOEt to give Vg (1.63 g, 32.5%) which was recrystallized from acetone giving brown prisms, mp 175—176°. *Anal.* Calcd. for $C_{21}H_{19}ON_3S_3Cl_2$: C, 50.80; H, 3.86; N, 8.47; S, 19.37; Cl, 14.29. Found: C, 50.84; H, 4.00; N, 8.68; S, 19.14; Cl, 14.29. NMR (d_6-DMSO, τ): −1.40 (1H, broad, NH), 5.77 (3H, s, $N-CH_3$), 7.61 (3H, s, C_4-CH_3). Finally, elution with acetone gave the (1:1) adduct (Vf) (39 mg, 1.2%) which was recrystallized from acetone giving brown prisms, mp 168—170°. *Anal.* Calcd. for $C_{14}H_{15}ON_2S_2Cl$: C, 51.42; H, 4.62; N, 8.57; S, 19.61; Cl, 10.84. Found: C, 50.96; H, 4.63; N, 8.45; S, 19.98; Cl, 10.33. NMR (d_6-DMSO, τ): 5.77 (3H, s, $N-CH_3$), 7.60 (3H, s, C_4-CH_3).

p-Nitrophenyl Isothiocyanate: 3.6 g of *p*-nitrophenyl isothiocyanate was allowed to react with IVa according to the general procedure, and the reaction mixture was chromatographed with acetone. The first fraction gave Vj (232 mg, 4.5%) as dark red crystals, mp 187—187.5°. *Anal.* Calcd. for $C_{21}H_{19}O_5N_5S_3$: C, 48.73; H, 3.70; N, 13.53; O, 15.45; S, 18.59. Found: C, 49.01; H, 3.80; N, 13.23; O, 15.07; S, 18.46. NMR (d_6-DMSO, τ): 5.73 (3H, s, $N-CH_3$), 7.56 (3H, s, C_4-CH_3). The second fraction gave Vi (520 mg, 15.4%) as red crystals, mp 180—181°. *Anal.* Calcd. for $C_{14}H_{15}O_3N_3S_2$: C, 49.82; H, 4.48; N, 12.45; O, 14.22; S, 19.00. Found: C, 49.40; H, 4.49; N, 12.15; O, 14.48; S, 19.15. NMR (d_6-DMSO, τ): 5.77 (3H, s, $N-CH_3$), 7.59 (3H, s, C_4-CH_3).

p-Tolyl Isothiocyanate: 3.0 g of *p*-tolyl isothiocyanate was allowed to react with IVa according to the general procedure and the reaction mixture was chromatographed with AcOEt. The first fraction gave the (1:2) cycloadduct (IVc) (185 mg, 4%) which was recrystallized from acetone to give yellow prisms, mp 182—183°. *Anal.* Calcd. for $C_{23}H_{25}ON_3S_3$: C, 60.64; H, 5.53; N, 9.23; S, 21.12. Found: C, 59.94; H, 5.47; N, 9.13; S, 20.71. UV λ_{max} mμ (log ε): 324 (4.01). NMR ($CDCl_3$, τ): 7.47 (3H, s, $N-CH_3$), 8.31 (3H, s, $C-CH_3$). The second fraction, which was eluted with acetone, gave X (322 mg, 7%) as yellow crystals, mp 141—143°. *Anal.* Calcd. for $C_{15}H_{18}ON_2S_2 \cdot HI$: C, 41.46; H, 4.44; N, 6.45; I, 29.22. Found: C, 41.62; H, 4.38; N, 6.44; I, 29.52. UV λ_{max} mμ: 309, 345. NMR ($CDCl_3$, τ): 6.03 (3H, s, $N-CH_3$), 7.49 and 7.63 (each 3H, s, C_4-CH_3 and/or $Ph-CH_3$).

Treatment of Va with EtOH-HCl——150 mg of Va was dissolved in 10 ml of 30% HCl-EtOH, then EtOH was evaporated *in vacuo* to give yellow crystalline residue which was recrystallized from EtOH to give hydrochloride (VIII) as pale yellow prisms (125 mg), mp 206—209°. *Anal.* Calcd. for $C_{14}H_{16}ON_2S_2 \cdot HCl$: C, 51.11; H, 5.21; N, 8.52; S, 19.49; Cl, 10.78. Found: C, 50.93; H, 5.20; N, 8.63; S, 19.23; Cl, 11.29. IR ν_{max}^{Nujol} cm^{-1}: 2720 (SH). UV λ_{max} (log ε): 305 (3.85), 339 (3.82). To the aq. solution of VIII (100 mg in 5 ml H_2O), 10% aq. Na_2CO_3 solution was added with stirring in an ice bath to make alkaline, then the deposited brown crystals were collected to give 82 mg of Va.

$NaBH_4$ Reduction of Va and VIII——a) To the suspension of Va (50 mg) in MeOH (15 ml), 70 mg of $NaBH_4$ was added with stirring in an ice bath. After stirring for 20 min, the reaction mixture was concentrated *in vacuo*, and the resulting residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over abs. $MgSO_4$ and concentrated *in vacuo* to give an oily residue which was chromatographed over SiO_2 column with AcOEt. The AcOEt eluate afforded IX as a pale yellow oil, 43 mg (84%). *Anal.* Calcd. for $C_{14}H_{20}ON_2S_2$: C, 56.70; H, 6.80; N, 9.44; S, 21.63. Found: C, 56.48; H, 6.71; N, 9.34; S, 21.52. NMR ($CDCl_3$, τ): 3.30 (1H, broad, NH), 5.30 (1H, s, $\overset{N}{S}\times\overset{H}{}$), 7.58 (3H, s, $N-CH_3$), 8.75 (3H, d, $J=7$ Hz, C_4-CH_3).

b) 50 mg of VIII was reduced by 70 mg of $NaBH_4$ in MeOH (15 ml), and the reaction mixture was treated quite similarly as employed for the reduction of Va to give 38 mg (79%) of IX.

Reaction of 3-Benzyl-4-methyl-5-(2-hydroxylethyl)thiazolium Bromide (IVb) with Phenyl Isothiocyanate——3.14 g of IVb was dissolved in 30 ml of DMF, then 1.5 g of NEt_3 was added to the solution. After stirring for 30 min at room temperature, 5.28 g of PhNCS was added and the reaction mixture was stirred for 6 hr at 40—45°. After evaporation of DMF *in vacuo*, the resulting residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over abs. Na_2SO_4, and concentrated *in vacuo* to give brown oil which was chromatographed over Al_2O_3 column with AcOEt. The first fraction gave N,N'-diphenylthiourea (90 mg), and the second fraction gave 3-benzyl-4-methyl-5-[2-(N-phenylthiocarbamoyloxy)ethyl]-thiazolium-2-N-phenylthiocarbamoylide (Vd) (320 mg, 6.4%) which was recrystallized from acetone to give brown prisms, mp 144—145°. *Anal.* Calcd. for $C_{27}H_{25}ON_3S_3$: C, 64.40; H, 5.01; N, 8.35; S, 19.06. Found: C, 64.43; H, 4.83; N, 8.63; S, 18.09. NMR ($CDCl_3$, τ): 1.05 (1H, broad, NH), 2.74 (15H, m, $3\times Ph$), 3.70 (2H, s, $Ph\underline{CH_2}$), 5.35 and 6.97 (each 2H, t, $-CH_2CH_2O-$), 7.96 (3H, s, C_4-CH_3). The third fraction gave 3-benzyl-4-methyl-5 (2-hydroxyethyl)thiazolium-2-N-phenylthiocarbamoylide (Vc) (530 mg, 14.4%) which was recrystallized from acetone to give brown prisms, mp 153—154°. *Anal.* Calcd. for $C_{20}H_{20}ON_2S_2$: C, 65.21; H, 5.47; N, 7.61; O, 4.34. Found: C, 64.51; H, 5.37; N, 8.18; O, 4.99. NMR (d_6-DMSO, τ): 2.6—3.1 (10H, m, $2\times Ph$), 3.67 (2H, s, $Ph\underline{CH_2}$), 6.29 and 7.10 (each 2H, t, $-CH_2CH_2O-$), 7.75 (3H, s, C_4-CH_3).

Reaction of Thiamine Hydrochloride (IVc) with Phenyl Isothiocyanate——To a suspension of IVc (10.11 g) in DMF (80 ml) was added NEt_3 (9.11 g) and the mixture was stirred for 30 min at room temperature. Then PhNCS (12.23 g) was added and stirred for 6 hr at 40—45°. After standing overnight at room temperature, the reaction mixture was concentrated *in vacuo* to give a brown residue which was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over abs. Na_2SO_4 and evaporated *in vacuo*. The resulting residue was chromatographed over SiO_2 column which was first eluted with acetone. The first eluate gave N,N'-diphenyl thiourea (240 mg), and the second fraction gave 2-N-phenylthiocarbamoyl-4-methyl-5-(2-hydroxyethyl)thiazole (VII) (130 mg) which was recrystallized from acetone-ether mixture to give yellow prisms, mp 113—114°. *Anal.* Calcd. for $C_{13}H_{14}ON_2S_2$: C, 56.11; H, 5.07; N, 10.07; S, 23.00. Found: C, 56.28; H, 5.19; N, 10.37; S, 22.98. NMR ($CDCl_3$, τ): −0.67 (1H, broad, NH), 1.9—2.8 (5H, m, Ph), 6.13 and 7.00 (each 2H, t, $-CH_2CH_2O-$), 7.60 (3H, s, C_4-CH_3), 8.18 (1H, broad, OH). Then the column was eluted with the mixture of acetone (10) and MeOH (1) to give 3-(2-methyl-4-amino-5-pyrimidinyl)methyl-4-methyl-5-(2-hydroxyethyl)thiazolium-2-N-phenylthiocarbamoylide (Ve) (124 mg) which was recrystallized from EtOH to give brown prisms, mp 144—145° (decomp.). *Anal.* Calcd. for $C_{19}H_{21}ON_5S_2 \cdot 1/2H_2O$: C, 55.90; H, 5.43; N, 16.17; S, 15.13. Found: C, 55.50; H, 5.50; N, 15.73; S, 16.04. NMR (d_6-DMSO, τ): 2.70 (5H, m, Ph), 3.97 (2H, broad, $Pm-CH_2$), 7.68 and 7.73 (each 3H, s, C_4-CH_3 and/or $Pm-CH_3$). Further elution with acetone (10)–MeOH (1) mixture gave an uncharacterizable mixture consisting of more than three components (TLC).

Reaction of Thiamine Hydrochloride (IVc) with *p*-Chlorophenyl Isothiocyanate——To a suspension of IVc (5.0 g) in DMF (60 ml) was added NEt_3 (5 g), and the mixture was stirred for 30 min at room temperature. Then *p*-chlorophenyl isothiocyanate (4.0 g) was added to the reaction mixture and stirred for 6 hr at 40—45°. After evaporation of DMF *in vacuo*, the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over abs. Na_2SO_4 and concentrated *in vacuo* to give a brown residue which was chromatographed over SiO_2 column and eluted with acetone. The first eluate gave N,N'-di-(*p*-chlorophenyl)thiourea (1.3 g), and the second fraction gave the (1: 2) cycloadduct (VIb) (150 mg, 4%) which was recrystallized from MeOH to give yellow prisms, mp 210—212° (decomp.). *Anal.* Calcd. for $C_{26}H_{24}ON_6S_3Cl_2$: C, 51.73; H, 3.98; N, 13.92; S, 15.94; Cl, 11.75. Found: C, 51.44; H, 4.04; N, 13.60; S, 16.11; Cl, 11.34. UV λ_{max} mμ (log ε): 326 (4.18). NMR (d_6-DMSO, τ): 6.05 (2H, s, $Pm-\underline{CH_2}$), 7.71 (3H, s, $Pm-\underline{CH_3}$), 9.08 (3H, s, $C-CH_3$). The second eluate gave a mixture as a brown gum which contains at least two compounds (TLC), but they could not be separated. Finally elution with the mixture of acetone (10) and MeOH (1) gave the (1: 1) adduct Vh (32 mg) as a brown crystals, mp 164—165° (decomp.). *Anal.* Calcd. for $C_{19}H_{20}ON_5S_2Cl$: C, 52.60; H, 4.65; N, 16.14; S, 14.78; Cl, 8.17. Found: C, 52.81; H, 4.87; N, 15.79; S, 14.86; Cl, 8.01. NMR (d_6-DMSO, τ): 2.70 (4H, s, Ph), 4.03 (2H, broad, $Pm-CH_2$), 7.70 and 7.75 (each 3H, s, $Pm-CH_2$ and/or C_4-CH_3).

NaOH Treatment of X——To the solution of X (217 mg) in EtOH (20 ml) was added 10% aq. NaOH (1 ml), and the mixture was stirred for 1 hr at room temperature. After addition of saturated aq. NH_4Cl solution (5 ml), EtOH was removed by evaporation *in vacuo* and the resulting aq. layer was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over abs. Na_2SO_4 and concentrated to leave an oil which crystallized by addition of acetone. The crystals were collected and recrystallized from MeOH to give 2-*p*-tolylimino-4,5-dimethyl-6-(2-hydroxyethyl)-2,3-dihydro-1,4-thiazin-3-one (XIa) (650 mg, 45%) as yellow prisms, mp 161—162°. *Anal.* Calcd. for $C_{15}H_{18}O_2N_2S$: C, 62.01; H, 6.25; O, 11.02; N, 9.64; S, 11.05. Found: C, 62.13; H, 6.29; O, 11.12; N, 9.56; S, 11.59. IR ν_{max}: 1645 (C=O), 1635 (C=N). NMR ($CDCl_3$, τ): 2.80 and 3.21 (each 2H, ABq, aromatic protons), 6.40 and 7.52 (each 2H, t, $-CH_2CH_2O-$), 6.56 (3H, s, $N-CH_3$), 7.65 and 7.83 (each 3H, s, $Ph-CH_3$ and/or C_6-CH_3).

NaOH Treatment of Va——To the solution of Va (50 mg) in EtOH (5 ml) was added 10% aq. NaOH solution (1 ml), and the mixture was stirred for 1 hr at room temperature. After addition of saturated aq. NH_4Cl solution (2 ml), EtOH was removed by evaporation *in vacuo* and the resulting aq. layer was extracted with $CHCl_3$. The $CHCl_3$ extract was concentrated to give an oily residue from which 12 mg of crude XIb was isolated by a preparative thin layer chromatography using SiO_2–AcOEt system.

The crude XIb was obtained as a yellow powder. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650 (C=O), 1645 (C=N). Mass Spectrum (Hitachi RMU-7 mass spectrometer) *m/e*; 276 (M^+).