

ADDITION REACTIONS OF THIAZOLIUM YLIDS WITH ARYLISOTHIOCYANATES
AND DI-P-TOLYL CARBODIIMIDE.

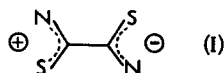
NOVEL ZWITTER-IONIC COMPOUNDS STABILIZED BY NITROGEN AND SULFUR*¹

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Our continued studies on the reactivities of thiazolium ylids related to thiamine (I) led to new findings that reactions of the thiazolium ylids with arylisothiocyanates gave resonance stabilized zwitter-ionic (1 : 1) adducts having a partial structure (I) and with di-p-tolylcarbodiimide gave (1:1) adducts as hydrogen halides which on alkaline treatment underwent facile ring expansion to 1,4-thiazine derivatives as follows.



Reaction of phenylisothiocyanate with the ylid IIa (R = H, resulting from 3,4-dimethyl-5 β -hydroxyethylthiazolium iodide and NEt₃ in DMF) gave a dipolar (1 : 1) adduct IIIa (R = X = H) [m.p. 135-136°, UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (log ϵ): 285 (3.95)] as brown crystals in ca. 30 % yield accompanied with a small amount of its O-thiocarbamoyl derivative (m.p. 175-176°). The NMR signals and molecular weight determination were agreeable with the proposed structure. By the action of EtOH-HCl, IIIa gave a hydrochloride V [m.p. 206-209°, IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 2720 (SH), UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (log ϵ): 305 (3.85), 339 (3.82), NMR (d₆-DMSO) τ : 5.99 (N-CH₃)] which was readily reconverted into IIIa by aqueous Na₂CO₃. IIIa and V were rapidly reduced by NaBH₄ to the same thiazolidine derivative VI [oil, NMR (CDCl₃) τ : 8.75 (doublet, J = 9 c.p.s., -CH-CH₃), 7.58 (N-CH₃), 5.30 (N-S⁺CH₃)]. The non polar structure such as VII or other alternatives should be excluded by the fact that IIIa is quite stable in refluxing EtOH or MeOH. Reactions of IIa, IIb (R = C₆H₅, resulting from 3-benzyl-4-methyl-5 β -hydroxyethylthiazolium bromide and NEt₃ in DMF) and IIc (R = 2-methyl-4-aminopyrimidin-5-yl, resulting from thiamine hydrochloride and NEt₃ in DMF) with

*¹ This paper constitutes Studies on Pyrimidine Derivatives and Related Compounds LVI.

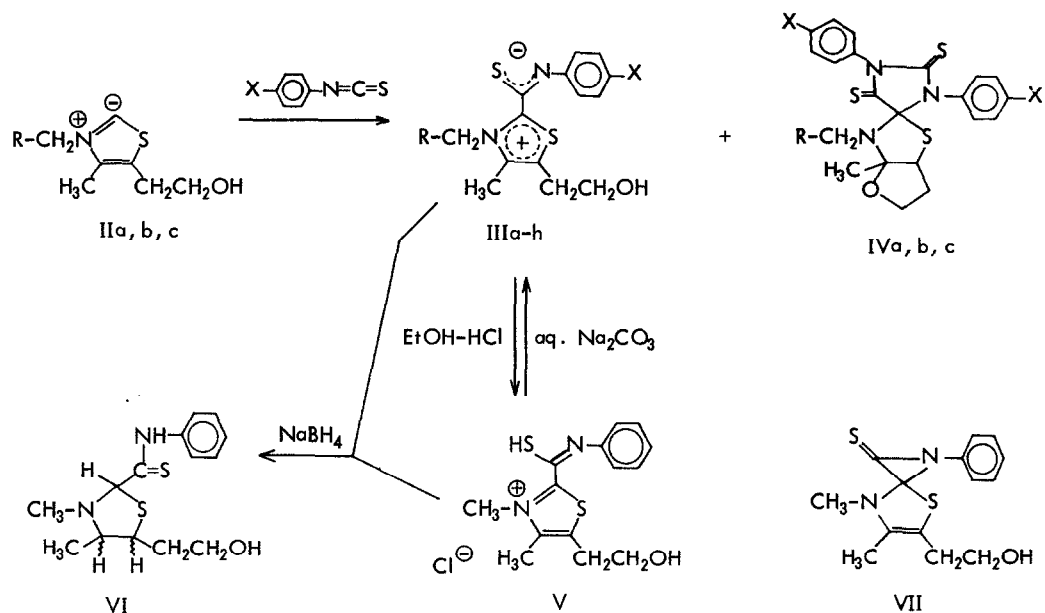


TABLE I. Physical Constants of the (1:1) Dipolar Adducts IIIa-h

III	R	X	m.p.	Chemical shifts (τ)	
				N-CH ₃	N-CH ₂
a	H	H	135-136°	5.84(CDCl ₃)	—
b	H	NO ₂	180-181°	5.77(d ₆ -DMSO)	—
c	H	Cl	168-169°	5.77(")	—
d	C ₆ H ₅	H	153-154°	—	3.63(CDCl ₃)
e	C ₆ H ₅	Cl	132-134°	—	3.82(d ₆ -DMSO)
f	Pym	H	144-145°(d.)	—	3.97(")
g	Pym	Cl	164-165°(d.)	—	4.03(")
h	Pym	NO ₂	130-131°(d.)	—	4.02(")

* Pym = 2-methyl-4-aminopyrimidin-5-yl.

some arylisothiocyanates were also shown to give corresponding (1:1) dipolar adducts IIIb-h in fair yields. By analogy with IIIa, structures of these (1:1) adducts were confirmed by the absence of NMR signal due to -CSNH- proton as well as the chemical shifts of N-methyl or N-methylene protons (TABLE I). In cases of the reactions of p-chlorophenylisothiocyanate with these ylids, however, corresponding (1:2) cycloadducts were obtained besides (1:1) dipolar adducts. Thus, IIa and IIc afforded IVa (R = H, X = Cl) m.p. 182-183°,

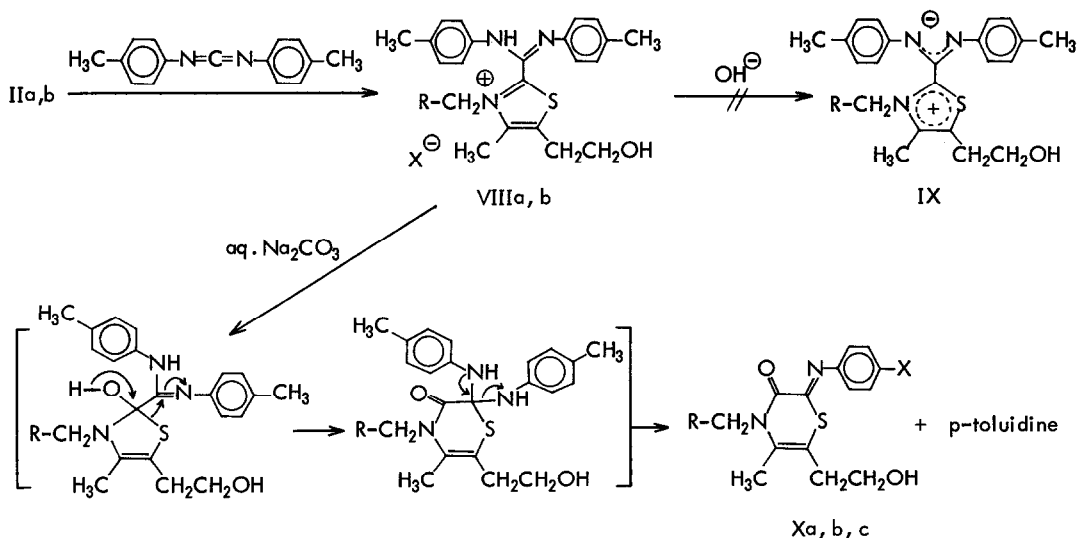


Chart - 2

$\text{UV } \lambda_{\text{max}}^{\text{EtOH}} \text{ m}\mu (\log \epsilon): 322 (4.18)$, NMR (CDCl_3) $\tau: 8.32 (\text{C}_4-\text{CH}_3)$, $7.47 (\text{N}-\text{CH}_3)$ (25%) and IVb (R = 2-methyl-4-aminopyrimidin-5-yl, X = Cl) [m.p. $210-212^\circ$ (decomp.)], $\text{UV } \lambda_{\text{max}}^{\text{EtOH}} \text{ m}\mu (\log \epsilon): 326 (4.18)$, NMR (d_6 -DMSO) $\tau: 9.08 (\text{C}_4-\text{CH}_3)$ (5%) respectively.*² Reaction of p-methylphenylisothiocyanate with IIa gave also the (1:2) cycloadduct IVc (R = H, X = CH₃) [m.p. $182-183^\circ$, $\text{UV } \lambda_{\text{max}}^{\text{EtOH}} \text{ m}\mu (\log \epsilon): 324 (4.16)$], in this case, however, the (1:1) dipolar adduct could not be obtained. These differences of the reactivity may be attributable to the decrease of resonance stabilization of the negative charge on the (1:1) adduct by p-methyl and p-chlorosubstituents.

Recently, Ramirez and co-workers (3) reported that hexaphenylcarbodiphosphorane gave stable (1:1) polar adducts by reactions with phenylisocyanate and di-p-tolylcarbodiimide. Reactions of our thiazolium ylids IIa and IIb with di-p-tolylcarbodiimide, however, did not afford the dipolar adducts IX, but their corresponding hydrogen halides VIIIa (R = H, X = I) [m.p. $194-196^\circ$, $\text{UV } \lambda_{\text{max}}^{\text{EtOH}} \text{ m}\mu (\log \epsilon): 281.5 (4.23)$, IR $\nu_{\text{max}}^{\text{Nujol}} \text{ cm}^{-1}: 1632 (\text{C}=\text{N})$, NMR (CDCl_3) $\tau: 7.77, 7.68$ (two tolyl methyls)] (57%) and VIIIb (R = C₆H₅, X = Br) [m.p. $193-194^\circ$, IR $\nu_{\text{max}}^{\text{Nujol}} \text{ cm}^{-1}: 1638 (\text{C}=\text{N})$, $\text{UV } \lambda_{\text{max}}^{\text{EtOH}} \text{ m}\mu (\log \epsilon): 283 (4.25)$]

*² Reactions of thiamine and related thiazolium ylids with alkylisothiocyanates were shown to afford in general the analogous (1:2) cycloadducts as stereoisomeric mixtures (2).

(43%) were obtained respectively (HX originates from the starting thiazolium halide). Various attempts to obtain the dipolar compound IX from these products failed, and by the action of aqueous Na_2CO_3 VIIIa and VIIIb were readily converted into Xa ($R = \text{H}$, $X = \text{CH}_3$) [m.p. 161–162°, IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1645 (C=O), 1635 (C=N), NMR (CDCl_3) τ : 6.56 (N- CH_3)] (79%) and Xb ($R = \text{C}_6\text{H}_5$, $X = \text{CH}_3$) [m.p. 164–165°, IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1650 (C=O), 1635 (C=N), NMR (CDCl_3) τ : 4.76 (N- CH_3)] (62%) respectively accompanied with p-toluidine involving ring expansion. The analogous ring expansion was also observed for the thiazolium ylid-arylisothiocyanate (1:1) adducts. For example, treatment of IIIa with aqueous NaOH afforded Xc ($R = X = \text{H}$) [oil, IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1650 (C=O), 1645 (C=N)].

The present and previously reported (2,4) results indicate that both N-aryl group and sulfur may significantly participate in the stabilization of the negative charge of the zwitter-ionic system (I).

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4. By the reaction of phenylisocyanate with thiamine ylid, the (1:2) cycloaddition proceeded preferentially and no (1:1) polar adduct was obtained. A Takamizawa, K. Hirai, S. Matsumoto, and T. Ishiba, Chem. Pharm. Bull. (Tokyo) in contribution.