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REACTIONS OF THIAMINE ANHYDRIDE WITH THIOLS

Akira Takamizawa, Kentaro Hirai, and Teruyuki Ishiba

Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka, Japan

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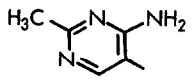
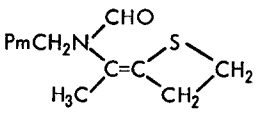
In a preceding communication (1), we described the first example of a reaction of thiamine anhydride (I). In this communication we report other examples of various types of reaction of I with thiols (2).

When I was allowed to react with thiophenol in DMF at room temperature, N-(1-methyl-2-phenyldithio-4-phenylthiobutyl)-N-[(2-methyl-4-amino-5-pyrimidinyl)methyl]formamide (IIb, R = H) (3) [mp 107-110°, $C_{24}H_{28}ON_4S_3$, UV $\lambda^{EtOH}_{shoulder}$ 237, 257, 280 mμ (log ε 4.26, 4.07, 3.85), NMR ($CDCl_3$) τ 8.83 (3H-doublet, J = 6.5 Hz, $\underline{CH_3}$-CH<), 7.7-8.5 (2H-multiplet, C_2-methylene), 6.2-7.3 (4H-multiplet, C_3-H, C_4-H, C_1-methylene), 7.53 (3H-singlet, pyrimidine C_2-CH_3), 6.15, 5.90, 5.60, 5.35 (2H-AB quartet, bridged methylene), 3.97 (deuterium exchangeable 2H-broad singlet, NH_2), 2.07, 2.00 (1-H singlets, pyrimidine C_6-H, N-CHO)] and 2,7-dimethyl-5,6-dihydro-6-formyl-8-(2-phenylthioethyl)-9H-pyrimido[4,5-e]1,4-diazepine (IIIb, R = H) (4) [mp 148-150° (decomp), $C_{18}H_{20}ON_4S$, UV λ^{EtOH}_{max} 245, 305 mμ (log ε 4.08, 3.97), NMR ($CDCl_3$) τ 7.45 (3H-singlet, 2-CH_3), 7.97 (3H-singlet, 7-CH_3), 7.37, 6.75 (2H-doublets, J = 7 Hz, 8-CH_2CH_2), 5.62 (2H-singlet, 5-methylene), 3.42 (deuterium exchangeable 1H-broad singlet, NH), 2.80 (5H-broad singlet, C_6H_5)] were obtained in 29 and 34% yields, respectively.

The reaction of I with p-thiocresol under the same conditions gave the dithio compound (IIa, R = CH_3), mp 83-83.5°, and the pyrimidodiazepine compound (IIIa, R = CH_3), mp 104-107°, in 35 and 27% yields, respectively. The reaction of I with p-bromothiophenol was also carried out, giving the pyrimidodiazepine compound (IIIc, R = Br), mp 146-148°, and p-bromophenylthioethyl-SB_1 (IVc, R = Br) [mp 165-167°, $C_{18}H_{19}N_4S_3Br$, UV λ^{EtOH}_{max} 230, 264, 326 mμ (log ε 4.27, 4.26, 4.17), NMR ($CDCl_3$) τ 7.92 (3H-singlet, thiazoline 4-CH_3), 7.53 (3H-singlet, pyrimidine 2-CH_3), 6.67-7.42 (4H-multiplet, thiazoline 5-CH_2CH_2), 4.63 (2H-singlet, bridged methylene), 3.70 (deuterium exchangeable 2H-broad singlet, NH_2), 2.50-2.92 (4H-multiplet, C_6H_4), 1.90 (1H-singlet, pyrimidine 6-H)] in 13 and 12% yields, respectively. Reaction of

Pm =





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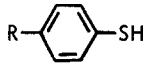
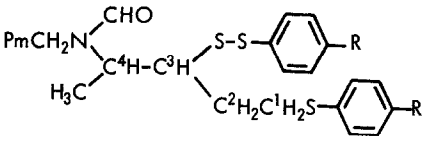


in DMF



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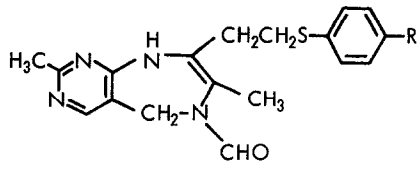

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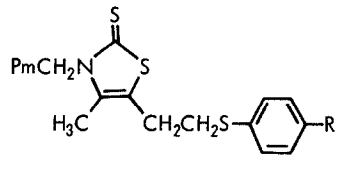


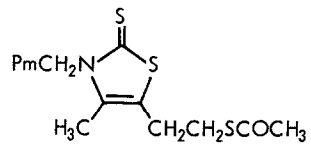
IV

TABLE I
pKa's of Thiols and Yields of Products

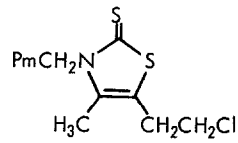
	R-⟨⟩-SH	pKa [5]	II (%)	III (%)	IV (%)
a	R = CH_3	8.03	35	27	-
b	R = H	7.76	29	34	-
c	R = Br	6.99	-	13	12
d	R = NO_2	5.11	-	-	61

I + AcSH

in DMF



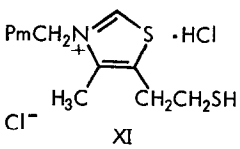
VIII



IX

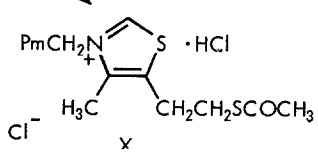
AcSH in DMF

1) H_2O_2
2) $BaCl_2$

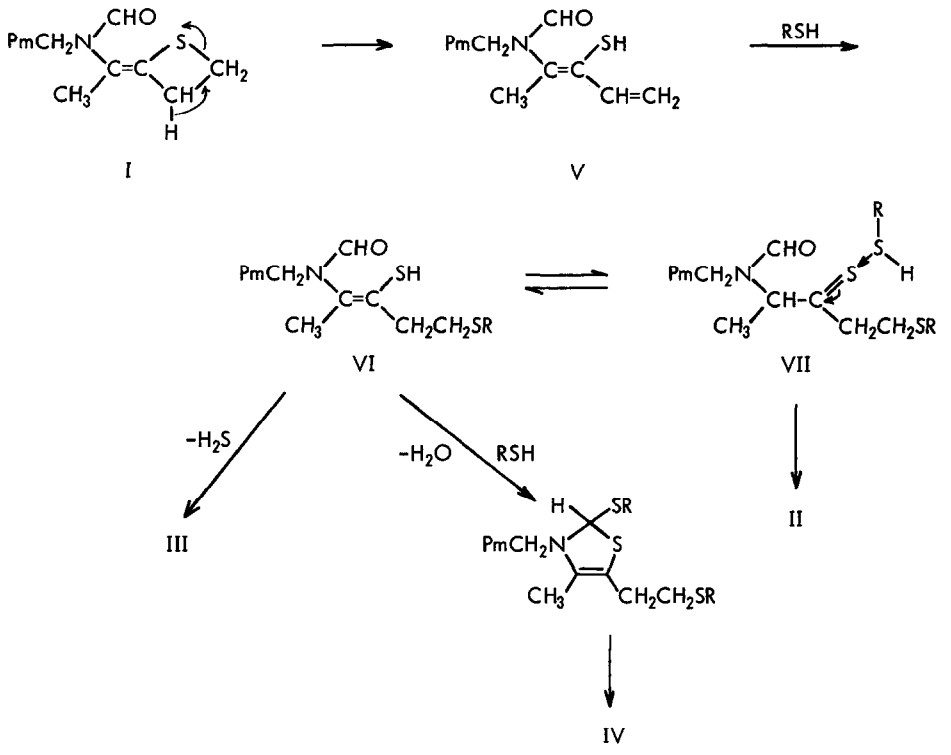


XI

HCl



X



p-nitrothiophenol with I in DMF afforded p-nitrophenylthioethyl SB_1 (IVd, R = NO_2), mp 217-220° (decomp), in 61% yield accompanied by p,p'-nitrophenyldisulfide and p,p'-nitrophenylsulfide.

Correlation of the pKa values of thiols used with product distribution (Table I) revealed that thiols having large pKa values give dithio compounds but more acidic thiols afford SB_1 type compounds preferentially, and pyrimidodiazepine compounds are yielded in a medium pKa.

A proposed mechanism involves the addition of thiol to the vinyl group giving VI, while attack of thiol to the tautomeric thioketone VII affords the dithio compound II. Removal of H_2S from VI gives the pyrimidodiazepine compound III and SB_1 compound IV is produced via the pseudo base. These reaction pathways are significantly dependent upon subtle pH differences of the reaction mixtures leading to the formation of three types of products.

Of particular interest is the fact that thiamine anhydride, which has been considered to be quite stable, displayes a very high reactivity, affording routes to new thiamine derivatives.

Thiolacetic acid reacted with I in DMF giving acetylthioethyl SB_1 (VIII), mp 149-151° (decomp), which

was identical with the product obtained from chloroethyl SB_1 (6) (IX) and thiolacetic acid. The action of hydrogen peroxide on VIII followed by treatment with $BaCl_2$ gave acetylthioethyl B_1 hydrochloride (X), mp 228-231° (decomp), which was hydrolized to mercaptoethyl B_1 hydrochloride (XI) (7), mp 207-210° (decomp), in high yield.

X and XI are interesting as B_1 S-analogs and showed marked anticoccidial activity for chickens.

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