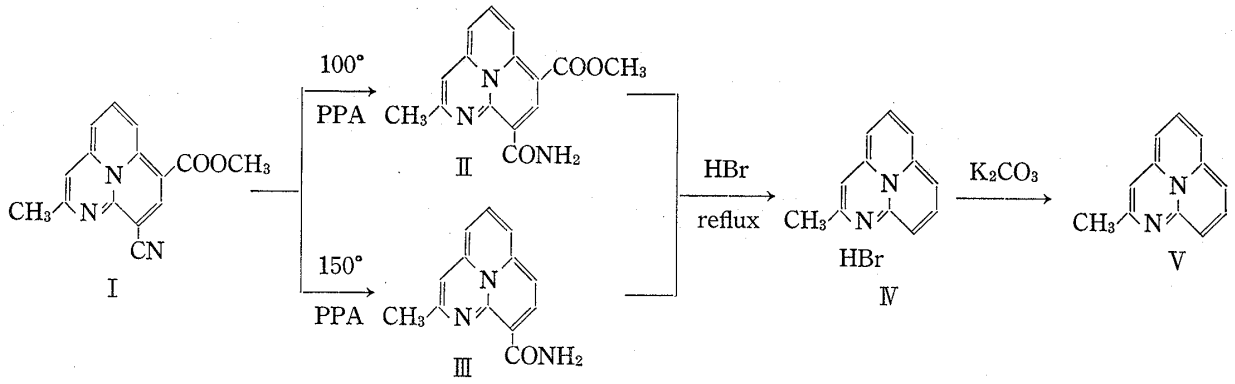

Chart 1

5.40 (1H, triplet), 4.54 (1H, doublet), 4.28 (1H, doublet), 4.24 (1H, doublet), 3.84 (1H, doublet), 3.71 (1H, singlet), 1.02 (3H, singlet), all coupling constants being *ca.* 8 Hz.

Recently, Ceder and co-worker[3] reported the synthesis of 2-methyl-1,3,6-triazacycl-[3,3,3]azine which possessed aromatic properties but we do not regard this low degree of deshielding as evidence of an aromatic property in a new [12] annulene heterocyclic ring system, azacyclazine (V).

The structures of the products (I, II, III, IV) are confirmed by satistactory elemental analyses, infrared and ultraviolet spectra. Further works on the purification of the free base (V) by sublimation and the synthesis of the parent compound are in progress.

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3) O. Ceder and J.E. Andersson, *Acta Chem. Scand.*, **26**, 596 (1972).

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Synthesis and Reactions of Thiamine Disulfide Sulfur Analogues

We have previously reported[1,2] the synthesis of thiamine sulfur analogues and methylsulfinylethylthiamine (MSIT, I) was found to be very effective against avian coccidiosis.[3] Here, we wish to report a ready transformation of MSIT into disulfides through intramolecular thiol-sulfoxide interaction.

An aqueous solution of MSIT was adjusted to pH 7—8 by the addition of sodium bicarbonate. A crystalline product separated which showed three spots on thin-layer chromato-

1) *a*) A. Takamizawa, K. Hirai, and T. Ishiba, *Tetrahedron Letters*, **1970**, 437, 441; *b*) A. Takamizawa, K. Hirai, and T. Ishiba, *Chem. Pharm. Bull.* (Tokyo), **19**, 1022, 2009 (1971).
2) A. Takamizawa, K. Hirai, and T. Ishiba, *Chem. Pharm. Bull.* (Tokyo), **19**, 2222, 2229 (1971).
3) H. Oikawa, H. Kawaguchi, E. Yoshida, and T. Minesita, *Shionogi Kenkyusho Nempo*, **21**, 32 (1971).

graphy (TLC) [Al_2O_3, AcOEt(2)–EtOH(1)], *Rf* values of 0.29, 0.45, and 0.63. From this crude product two compounds, II (mp 155.5—157°, *Rf* 0.29) and III (mp 165—166°, *Rf* 0.63), were isolated. For both compounds a thiochrome test was negative but became positive after treatment with cycteine or sodium thiosulfate, suggesting disulfide structures. The structures of II and III were deduced from their analytical and spectroscopic data [II: NMR (DMSO-d_6) δ 1.77, 2.07 (3H, d, CH_3–C=), 2.32 (3H, s, pyrimidine-2-CH_3), 2.57 (3H, s, CH_3–S=O), 2.5—2.8 (4H, m, $-CH_2CH_2-$), 4.40 (2H, broad s, N–CH_2–), 6.68 (2H, broad s, NH_2), 7.87 (2H, s, pyrimidine-6-H, N–CHO); IR (KBr) 3400 (NH_2), 1650 (C=O), 1050 (S=O) cm^{-1}; UV $\lambda_{max}^{0.01N\ HCl}$ 243 nm, $\lambda_{max}^{1\%\ NaHCO_3}$ 233, 279 nm. III: NMR (DMSO-d_6) δ 1.72, 2.00 (3H, d, CH_3–C=), 2.06 (3H, s, CH_3–S), 2.32 (3H, s, pyrimidine-2-CH_3), 2.48 (4H, broad s, $-CH_2CH_2-$), 4.38 (2H, broad s, N–CH_2–), 6.68 (2H, broad s, NH_2), 7.85 (2H, s, pyrimidine-6-H, N–CHO); UV $\lambda_{max}^{0.01N\ HCl}$ 243 nm, $\lambda_{max}^{1\%\ NaHCO_3}$ 233, 278 nm].

To confirm their structures, MSIT and MTET (methylthioethylthiamine, IV)[2] were converted into the corresponding disulfides, *via* the thiolates, by oxidation with iodine-potassium iodide or potassium ferricyanate in an alakaline solution (pH 11—12). They were identical with the samples obtained from MSIT in a neutral solution. Despite attempts to obtain a pure compound (V) corresponding to the spot of *Rf* 0.45 on the TLC of the crude product, isolation was unsuccessful and only a mixture containing three compounds, II, III, and V was obtained. This rapid disproportionation of V suggested it to be a mixed disulfide of MSIT and MTET.[4]

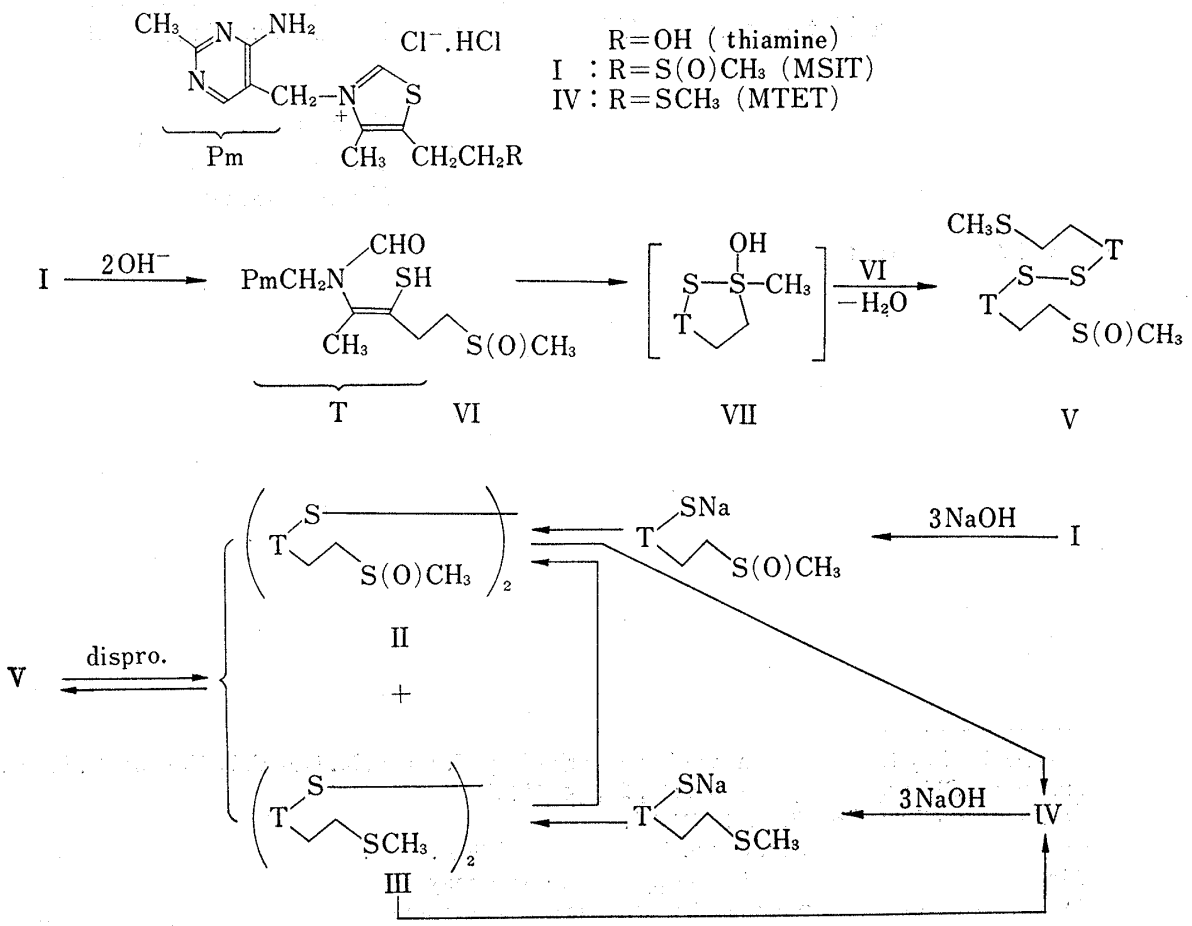

Chart 1

4) Disproportionation of thiamine disulfide monobenzoate into a mixture of thiamine disulfide and benzoylthiamine disulfide was reported by N. Yoneda, H. Yasuo, Y. Mushika, and K. Masukawa, *Vitamins* (Kyoto), **42**, 212 (1970).

In the range pH 6—8, the reaction rate increased with pH. In a 500 μg/ml buffered solution at pH 8, the initial rate of disappearance of MSIT[5] followed first-order kinetics with $k=2.53\times10^{-3}$ sec^{-1} at 60°. The temperature dependence of the reaction rate has been measured between 30 and 60° at pH 8, and the activation energy was found to be 23.8 kcal/mole. No difference was observed between the reaction rate in nitrogen and that in air. MTET and thiamine were stable under conditions where MSIT was destroyed. These facts indicated that the sulfoxide group in MSIT plays an important role in this reaction.

Thiols can be oxidized to their disulfides by sulfoxides, two moles of thiol reacting stoichiometrically with one mole of sulfoxide to produce one mole of disulfide and one mole of sulfide.[6] Sulfoxide-thiol adduct was posturated by Wallace and Mahon[7] as an unstable intermediate. To explain our observations, we propose a reaction route from MSIT to disulfides as outlined in Chart 1.

MSIT reacts with two moles of alkali to produce ring opened thiol (VI) and intramolecular thiol-sulfoxide interaction occurs to form an unstable thiol-sulfoxide adduct (VII) as an intermediate that is rapidly destroyed by reaction with another molecule of thiol (VI) to give an unsymmetrical disulfide (V). Disproportionation of V follows to afford a mixture of symmetric disulfides II and III. Of special interest is the fact that a weak acidic thiol VI is easily oxidized at pH 7—8. This will be accounted for by the favorable geometry of MSIT for the intramolecular thiol-sulfoxide interaction.[8]

II was also obtained from III by oxidation with hydrogen peroxide in acetic acid solution. On the other hand, on heating II or III with L-cysteine hydrochloride in aqueous suspension followed by hydrochloric acid treatment, MTET was obtained in an excellent yield.[9]

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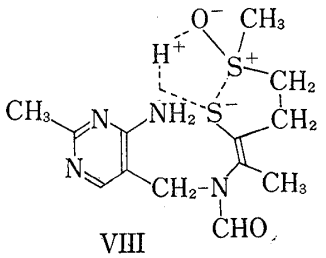
5) MSIT was determined by the thiochrome method described by K. Inazu, M. Mukai, E. Takebe, M. Inoue, and R. Yamamoto, *Shionogi Kenkyusho Nempo*, **21**, 54 (1971).
6) T.J. Wallace, *J. Am. Chem. Soc.*, **86**, 2018 (1964).
7) T.J. Wallace and J.J. Mahon, *J. Am. Chem. Soc.*, **86**, 4099 (1964).
8) As shown in VIII, the amino group in the pyrimidine ring may be involved in formation of a five membered ring intermediate causing increase in the ionic character of the sulfur-hydrogen bond in the transition state and thereby helping to accelerate the reaction rate. The catalytic effect of bases in the thiolsulfoxide reaction was reported by T.J. Wallace and J.J. Mahon, *J. Org. Chem.*, **30**, 1502 (1965).
9) Compounds (II and III) showed high anticoccidial activities against avian coccidiosis.



VIII