[Chem. Pharm. Bull. 26(12)3675—3681(1978)]

UDC 547.853.3'789.1.04 : 615.283.921.011.5.076.7

Synthesis and Reactions of Thiaminedisulfide Sulfur Derivatives[1)]

KENTARO HIRAI, TERUYUKI ISHIBA, HIROHIKO SUGIMOTO,
TETSUYA TAKAHASHI, and KUNIHEI INAZU

Shionogi Research Laboratory, Shionogi and Co., Ltd.[2)]

(Received May 1, 1978)

Methylsulfinylethylthiamine (MSIT) (I) was found to be converted readily into a mixture of disulfides in aqueous solution at pH 7—8. Disulfides II and III were isolated and their structures were confirmed to be MSIT-disulfide and MTETDS (methylthioethylthiaminedisulfide), respectively. Disulfide IV could not be isolated in a pure state, but rapid disproportionation into a mixture of II and III suggested that IV is a mixed disulfide of MSIT and MTET. In buffer solution at pH 8, the disappearance of MSIT followed first-order kinetics with $2.53 \times 10^{-3}\,\mathrm{sec}^{-1}$ at 60°, and the activation energy was found to be 23.8 kcal/mol.

Clearly, the sulfoxide group in MSIT plays an important role in this transformation reaction. In the proposed reaction route, MSIT reacts with two mol of alkali to produce ring opened thiol and intramolecular thiol-sulfoxide interaction occurs to form an unstable thiol-sulfoxide adduct that is rapidly destroyed by reaction with another molecule of thiol to give an unsymmetrical disulfide (IV). Disproportionation of IV follows to afford a mixture of symmetrical disulfides II and III. Independent synthesis of II and III was also achieved *via* halogeno-SB_1. Compounds II and III show high anticoccidial activities against avian coccidiosis.

Keywords——methylsulfinylethylthiamine (MSIT); intramolecular thiol-sulfoxide interaction; kinetics; unsymmetrical disulfide; disproportionation; reduction with cysteine; SB_1; anticoccidial activity

Continuing our studies on the chemistry of thiamine derivatives, we previously reported on the reaction of thiamine anhydride with various kinds of thiols which afford a variety of thiamine sulfur derivatives,[3)] Since the thiamine sulfur analogue is interesting from chemical and biological points of view, we prepared a number of new thiamine sulfur derivatives.[4)] Among these compounds, methylsulfinylethylamine (MSIT, I) was found to be very effective against avian coccidiosis,[5)] though it was relatively unstable in an admixture with chicken feed.

We attempted to clarify the reason for this instability, and to obtain more stable and effective compounds. As chicken feed is weekly alkaline, the following conditions were chosen for model experiments. Sufficient MSIT was mixed at 1% with a diluent, a mixture of lactose, wheat starch, and sodium bicarbonate, and stored for 3 days under 75% relative humidity at 37°. Extraction of this admixture with methanol or chloroform gave two compounds, II (mp 155.5—157°) and III (mp 165—166°). Both compounds gave a negative thiochrome test which was positive after treatment with cysteine or sodium thiosulfate, suggesting disulfide

---

1) A part of this work has appeared in a preliminary form: *Chem. Pharm. Bull.* (Tokyo), **22**, 1940 (1974). Presented in part at the 4th International Symposium on Medicinal Chemistry, Noordwijkerhaut, The Netherlands, Sept. 1974, and at the 3rd Symposium on Organic Sulfur and Phosphorus Compounds, Suita, Japan, Feb. 1975.

2) Location: *Fukushima-ku, Osaka 553, Japan.*

3) A. Takamizawa, K. Hirai, and T. Ishiba, *Tetrahedron Lett.*, **1970**, 437, 441; *idem, Chem. Pharm. Bull.* (Tokyo), **19**, 1022, 2010 (1971).

4) A. Takamizawa, K. Hirai, and T. Ishiba, *Chem. Pharm. Bull.* (Tokyo), **19**, 2222, 2229 (1971).

5) H. Oikawa, H. Harumoto, K. Kawaguchi, E. Yoshida, A. Takamizawa, K. Hirai, T. Ishiba, and T. Minesita, *Shionogi Kenkyusho Nempo*, **21**, 27 (1971); H. Oikawa, H. Kawaguchi, E. Yoshida, and T. Minesita, *ibid.*, **21**, 32 (1971).

Table I. Spectroscopic Data for II and III

Compd.	UV $\lambda_{\max}^{0.01N\ HCl}$ nm	$\lambda_{\max}^{1\%\ NaHCO_3}$ nm	IR $\nu_{\max}^{KBr}$ cm^{-1}	NMR (DMSO-d_6, δ)
II	243 (369)	233 (377) 279 (166)	3400 (NH_2) 1650 (C=O) 1050 (S=O)	1.77 and 2.07 (3H, 2×S, 3:8, CH_3–C=),[a) 2.32 (3H, s, pyrimidine-2-CH_3), 2.57 (3H, s, CH_3–S=O), 2.5—2.8 (4H, m, –CH_2-CH_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)
III	243 (406)	233 (402) 278 (178)	3400 (NH_2) 1650 (C=O)	1.72 and 2.00 (3H, 2×S, 1:3, CH_3–C=),[a) 2.06 (3H, s, CH_3S–), 2.32 (3H, s, pyrimidine-2-CH_3), 2.48 (4H, broad s, –CH_2-CH_2–), 4.38 (2H, broad s, NCH_2–), 6.68 (2H, broad s, NH_2), 7.85 (2H, s, pyrimidine-6-H, N–CHO)

a) Ref. 3.

Table II. Solubility of II and III

Solvent	II (% w/w)	III (% w/w)
Purified water	2.76	0.012
99% ethanol	2.95	6.29
Methanol	25.9	3.46
Ethyl acetate	0.00752	0.682
Acetone	0.0324	2.97
Chloroform	0.112	15.0
Benzene	0.00092	0.421
Carbon tetrachloride	0.00104	0.0131
Cyclohexane	0	0.0010

structures. The structures of II and III were deduced from their analytical and spectroscopic data as shown in Table I. The ultraviolet (UV) spectra of II and III showed the characteristic absorption bands due to the aminopyrimidine structure at 233 and 279 nm in aqueous sodium bicarbonate solution and at 243 nm in aqueous hydrochloric acid solution. The infrared (IR) spectra of II and III showed the characteristic amino (3400 cm^{-1}) and amide (1650 cm^{-1}) bands. Further, II exhibited the band indicative of the sulfoxide group at 1050 cm^{-1}, but III none at all. The significant difference of the nuclear magnetic resonance (NMR) spectra between II and III can be seen in the chemical shifts of the signals due to the sulfinylmethyl group in II (δ 2.57) and the thiomethyl group in III (δ 2.06).

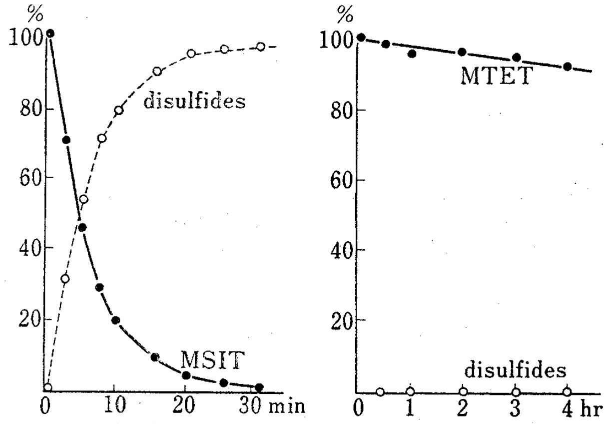

Fig. 1. Changes in Contents of MSIT and MTET in pH 8 Solution (500 μg/ml) under N_2 at 60°

Solubility tests (Table II) showed that II is more polar than III suggesting the presence of the sulfoxide group in the structure of II. These observations support the structure bis{2-[N-(2-methyl-4-aminopyrimidin-5-ylmethyl) formamido]-1-(2-methylsulfinylethyl)-1-propenyl}disulfide (MSIT-disulfide, MSITDS) for compound II, and the structure bis{2-[N-(2-methyl-4-aminopyrimidin-5-ylmethyl) formamido]-1-(2-methylthioethyl)-1-propenyl}disulfide (MTET-disulfide, MTETDS) for compound III.

This ready tranformation of MSIT into the disulfide derivatives prompted us to investigate the chemical change of MSIT in aqueous solution. As shown in Fig. 1, MSIT gradually disappeared in a buffered solution at pH 8, while there was an increase in the content of the disulfides which showed a negative thiochrome test then a positive one after treatment with cysteine. No difference was found between the total amount of MSIT and disulfides at the initial and final measurements. Therefore, the reaction to decrease MSIT content can be regarded as that which produces the disulfides. Also no difference was observed between the reaction rates in nitrogen atmosphere and air. Methylthioethylthiamine (MTET) (V) and thiamine, which have no sulfoxide group in their structure, were stable under the conditions where MSIT disappeared. These facts clearly indicate that the sulfoxide group in MSIT plays an important role in this reaction.

Disappearance rate constants of MSIT were obtained by the thiochrome method[6] in acetate and phosphate buffer solution (pH 4—8). The pH-rate profile is depicted in Fig. 2. The slope of the plot in Fig. 2 is near 1, and the slight difference from unity probably being due to dissociation of the intermediate species. However, the good linear relationship between log *k* and pH shows that the rate-determining step of the disappearance is that in which MSIT reacts with two mol of hydroxide anion, one is neutralization of the salt and the other for nucleophilic attack of the thiazolium ring, to produce the thiol-type intermediate. Good Arrhenius plots were also obtained as shown in Fig. 3, and the calculated activation energy was 23.8 kcal/mol. When 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 TLC [Al_2O_3, AcOEt (2)-EtOH (1)] with *Rf* values of 0.29, 0.45, and 0.63. From this crude product, two compounds, II (*Rf* 0.29) and III (*Rf* 0 63), were isolated.

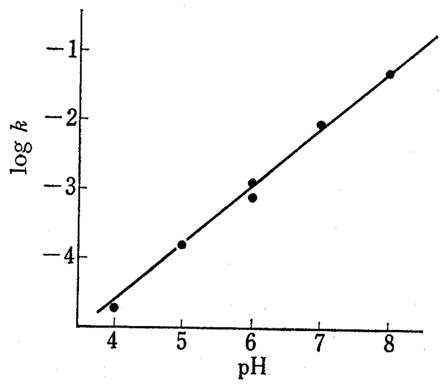

Fig. 2. The pH-rate Profile for the Disappearance of MSIT

The *k*'s values were extrapolated to zero buffer concentration (*k*, min^{-1}).

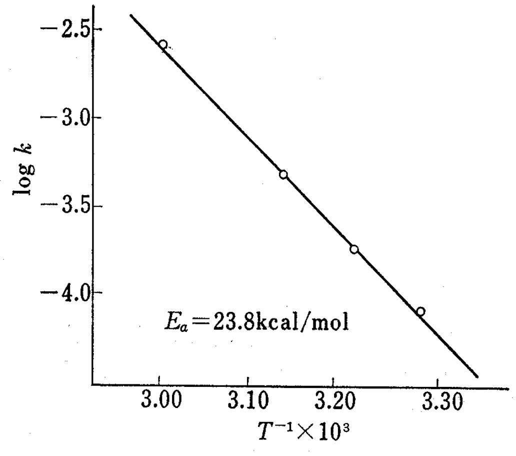

Fig. 3. Activation Energy Plots for the Disappearance of MSIT in pH 8 Solution between 30° and 60° (*k*, sec^{-1})

In spite of our efforts to obtain a pure compound IV corresponding to the spot of *Rf* 0.45 on the TLC of the crude product, isolation was unsuccessful and only a mixture containing II, III, and IV was obtained. This rapid disproportionation of IV suggested that it is a mixed disulfide of MSIT and MTET. Disproportionation of thiamine disulfide monobenzoate into a mixture of the symmetrical disulfides was reported by Yoneda.[7]

The results of our kinetic data indicate that the second order reaction of MSIT with OH^- is the rate determining step. In other words, the formation of the thiol-type MSIT determines the overall rate. Kinetic studies on the reaction between thiamine and propyl

---

6) I. Utsumi, K. Harada, Y. Kondo, and H. Hirao, *Vitamins* (Kyoto), **25**, 74 (1962).
7) N. Yoneda, H. Yasuo, Y. Mushika, and K. Masukawa, *Vitamins* (Kyoto), **42**, 212 (1970).

propanethiolsulfinate or thiolsulfonate to produce thiamine propyl disulfide have been reported by Nogami *et al.*,[8] and the rate limiting step was also found to be the rate of conversion to the thiol-type thiamine.

Furthermore, it is well established that thiols can be oxidized to their disulfides by sulfoxides, with two mol of thiol reacting stoichiometrically with one mol of sulfoxide.[9] The sulfoxide-thiol adduct was postulated as being an unstable intermediate by Wallace and Mahon.[10] The reactive species is not a thiolate anion but thiol. From these facts, our reaction can be best explained by the Wallace type intramolecular addition of the thiol which was formed by the reaction of MSIT with OH^-. The reaction route was outlined in Chart 1,

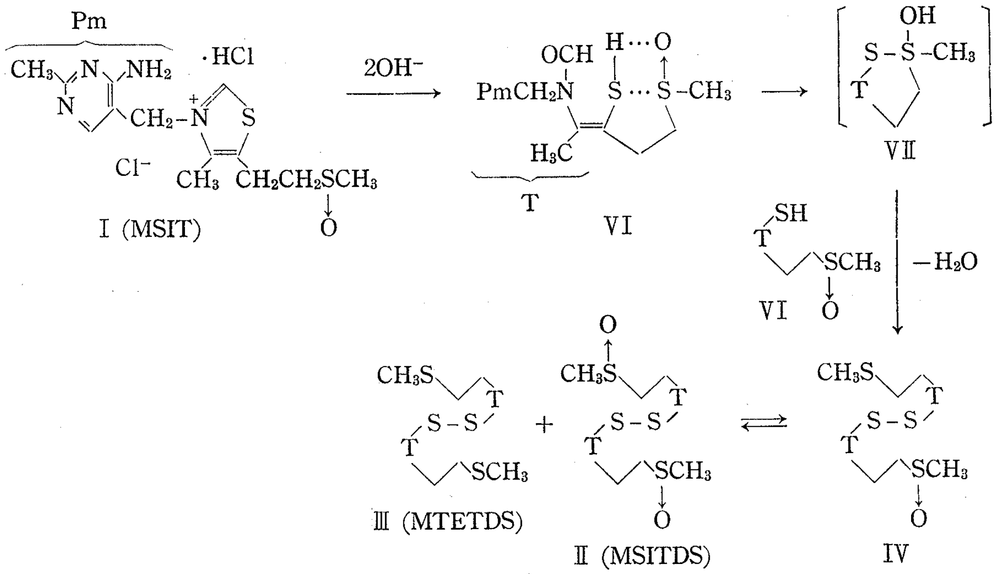

Chart 1

MSIT reacts with two mol of alkali to produce ring opened thiol (VI) and intramolecular thiol-sulfoxide interaction occurs to form an unstable thiol-sulfoxide adduct (VII) as the intermediate that is rapidly destroyed by reaction with another molecule of thiol (VI) to give an unsymmetrical disulfide (IV).

Reaction of MTETDS (III) with hydrogen peroxide in acetic acid solution gave MSITDS (II). But it is difficult to obtain MTETDS from MSITDS directly by selective reduction of the sulfoxide group of MSITDS. However, when an aqueous suspension of MSITDS was heated with cysteine hydrochloride for 2 hr, cystine and crude MTET were obtained. This crude MTET showed the contamination with MSIT on PPC.[11] This indicates that both sulfoxide and disulfide groups were reduced. The presence of MSIT suggests that the disulfide group was reduced prior to the sulfoxide group. Therefore, MSITDS was heated with cysteine hydrochloride at 90° for 3 hr giving highly pure MTET in almost quantitative yield. On heating MSIT with cysteine hydrochloride in aqueous solution at pH 5, MTET was also obtained in almost quantitative yield. MTET has been prepared[4] by condensation of bromomethylpyrimidine with S-methylthiazole. During this condensation reaction, cleavage of the S–Me bond by hydrogen bromide occurred and the yield of MTET was low (20%). On the

---

[8] H. Nogami, J. Hasegawa, M. Hanano, and K. Aoki, *Chem. Pharm. Bull.* (Tokyo), **19**, 2448 (1971); and the references therein.

[9] T.J. Wallace, *J. Am. Chem. Soc.*, **86**, 2018 (1964).

[10] *a*) T.J. Wallace and J.J. Mahon, *J. Am. Chem. Soc.*, **86**, 4099 (1964); *b*) *Idem*, *J. Org. Chem.*, **30**, 1502 (1965).

[11] Paper partition chromatography: AcOH, *n*-BuOH, H_2O (1: 4: 5), ascending method, Toyo Roshi #50.

other hand, the reaction using cysteine proceeded smoothly giving highly pure MTET in high yield.

MSIT and MTET were converted into the corresponding disulfide (II, III) *via* the thiolates (VIII, IX) by oxidation with iodine-potassium iodide, potassium ferricyanide, or hydrogen peroxide in an alkaline solution at pH 11—12.

Independent synthesis of MSITDS and MTETDS was also investigated starting from 3-(2-methyl-4-aminopyrimidin-5-yl)methyl-4-methyl-5-β-hydroxyethylthiazoline-2-thione (SB_1) (X).

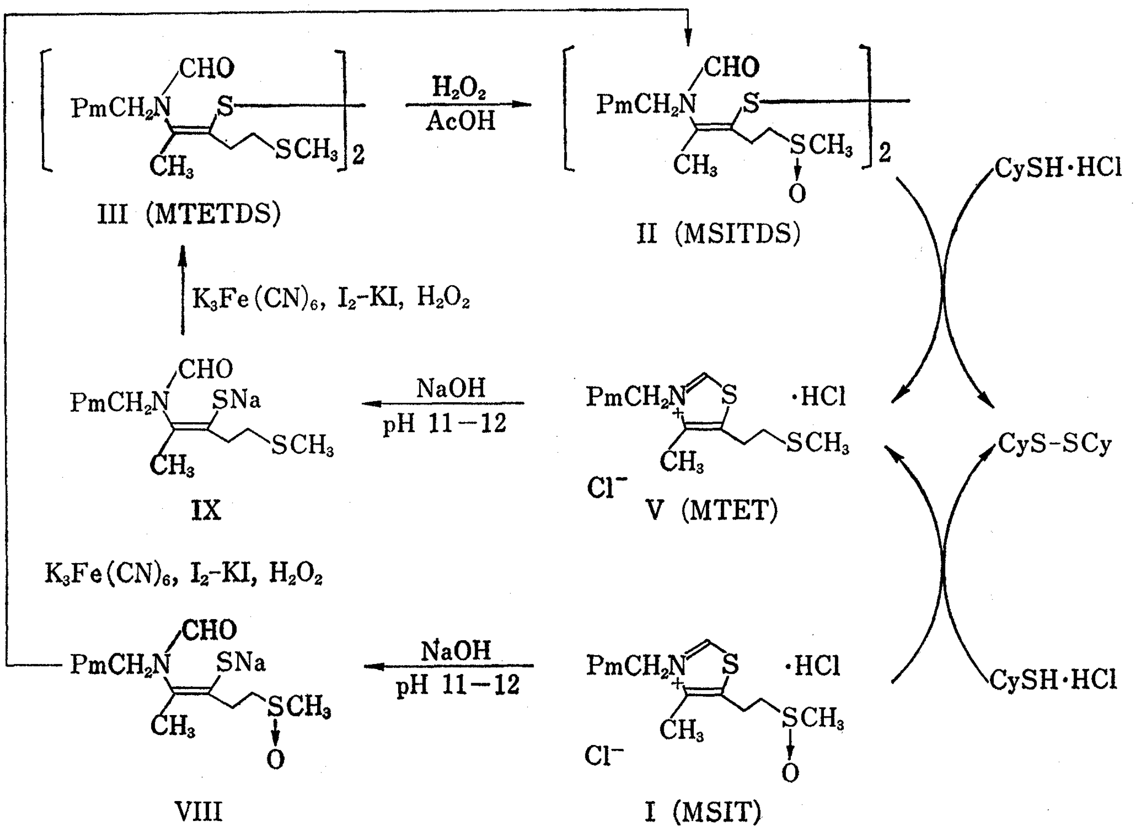

Chart 2

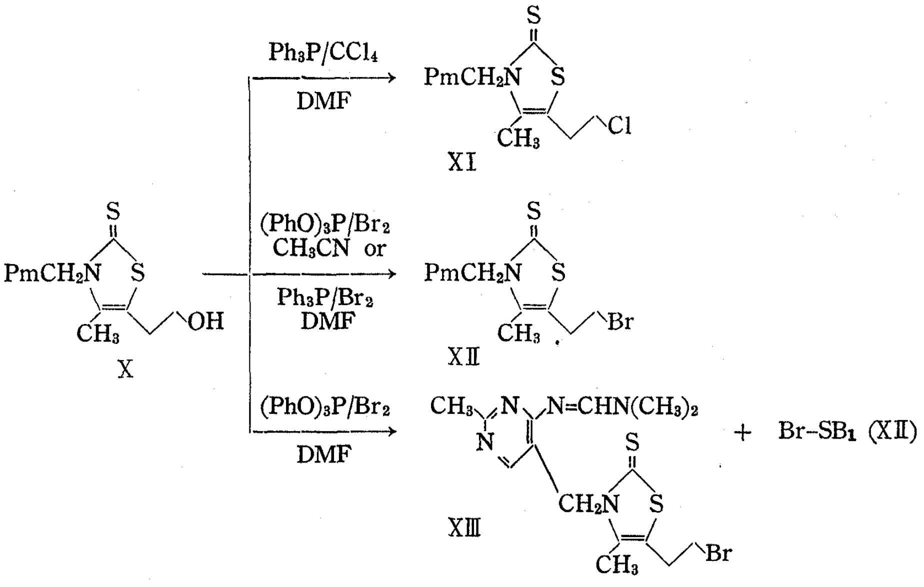

Chart 3

Reactions of SB_1 with $POCl_3$ or $SOCl_2$ gave complex products and the yield of chloroethyl-SB_1 (XI)[12] was low. However, treatment of SB_1 with triphenylphosphine and carbon tetrachloride[13] in dimethylformamide solution gave chloroethyl-SB_1 (XI) in 72% yield. On treatment of SB_1 with triphenyl phosphite and bromine in acetonitrile solution, bromoethyl SB_1 (XII) was obtained in 94% yield. These reactions proceeded smoothly under mild conditions giving haloethyl-SB_1 in high yield. But use of dimethylformamide as a solvent in this reaction gave the amidino compound (XIII).

Reaction of haloethyl-SB_1 (XI, XII) with sodium methylmercaptide was carried out in various solvents. In acetonitrile or dioxane, the starting material was recovered. In methanol, an elimination reaction occurred to give vinyl-SB_1 (XIV).[12] However, in dimethylformamide solution SCH_3–SB_1 (XV) was obtained in excellent yield.[4] XV was converted into MSIT by the action of 4 mol of hydrogen peroxide.[4] Since MSIT can be converted into MSITDS or MTETDS as mentioned before, these reactions are convenient route for obtaining MSITDS or MTETDS from SB_1.

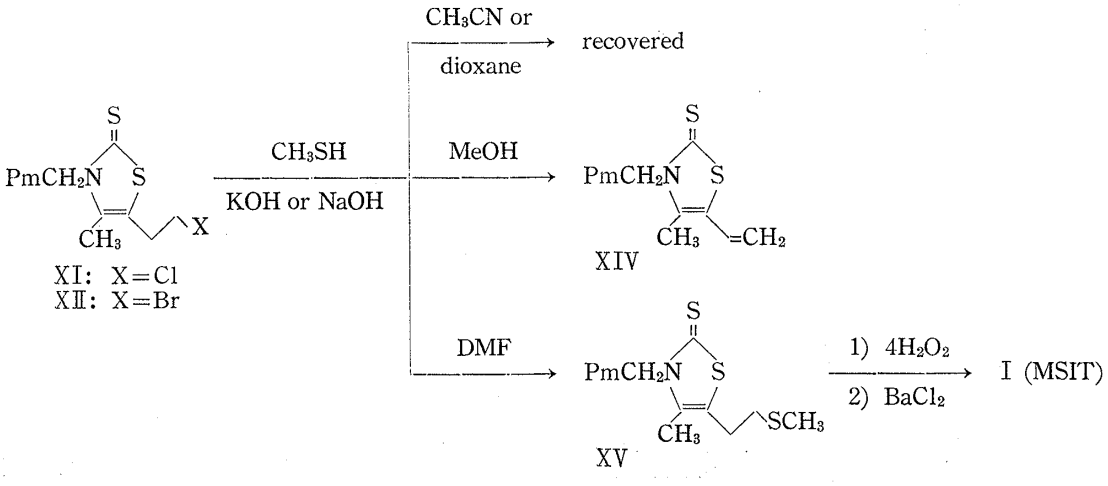

Chart 4

MSITDS and MTETDS are stable enough for pharmaceutical preparation[14] and show anticoccidial activities.[15]

Experimental

Melting points are uncorrected. The UV spectra were measured with a Hitachi EPS-2 spectrometer, IR spectra in KBr with a JASCO DS-403G spectrometer, NMR spectra on a Varian A-60 instrument with TMS as an internal standard.

Kinetics——The thiochrome method was described by I. Utsumi.[6] The details for the determination of MSITDS and MTETDS were reported by K. Inazu.[14]

Bis-{2-[N-(2-methyl-4-aminopyrimidin-5-ylmethyl)formamido]-1-(2-methylthioethyl)-1-propenyl} disulfide (MTETDS, III) and Bis-{2-[N-(2-methyl-4-aminopyrimidin-5-ylmethyl)formamido]-1-(2-methylsulfinylethyl)-1-propenyl}disulfide (MSITDS, II)——a) 3-(2-methyl-4-aminopyrimidin-5-ylmethyl)-4-methyl-5-(2-methylsulfinylethyl)thiazolium chloride hydrochloride (MSIT, I) (210 g) was dissolved in H_2O (420 ml), and 10% aqueous NaOH solution (400 g) was added thereto. The resultant solution was hetaed at 50°; and kept at pH 7.1 with 10% aqueous $NaHCO_3$ solution. The precipitates were collected and recrystallized from aqueous EtOH to give III tetrahydrate as colorless needles, which began to melt at about 85° and complete melting at about 130° to give yellowish white fused liquid. *Anal.* Calcd. for $C_{26}H_{38}N_8O_2S_4 \cdot 4H_2O$: C, 44.92; H, 6.67; N, 16.12; S, 18.51; H_2O, 10.36. Found: C, 44.99; H, 6.76; N, 15.89; S, 18.56; H_2O, 10.91.

Tetrahydrate was recrystallized from AcOEt to give the anhydrous colorless prisms of mp 164—165°.

---

12) S. Yoshida and M. Unoki, *Yakugaku Zasshi*, 72, 1431 (1952).
13) R.S. Monson, "Advanced Organic Synthesis," Academic Press, New York and London, 1971, p. 45.
14) K. Inazu, M. Iwakura, E. Takebe, and T. Takahashi, *Shionogi Kenkyusho Nempo*, **24**, 32 (1974).
15) H. Oikawa, H. Kawaguchi, R. Okuzawa, and K. Hirai, *Shionogi Kenkyusho Nempo*, **24**, 6 (1974).

Anal. Calcd. for $C_{26}H_{38}N_8O_2S_4$: C, 50.20; H, 6.16; N, 18.02; S, 20.62; MW, 622. Found: C, 49.82; H, 6.41; N, 17.78; S, 20.24; MW, 619.

The filtrate was extracted with *n*-BuOH. The extract was concentrated under reduced pressure and the residue was triturated with ether. Recrystallization from EtOH gave II·$1.5H_2O$ (23.3 g) as colorless prisms of mp 168—170° (dec.). *Anal.* Calcd. for $C_{26}H_{38}N_8O_4S_4 \cdot 1.5H_2O$: C, 45.79; H, 6.06; N, 16.43; S, 18.81. Found: C, 45.32; H, 6.30; N, 16.10; S, 18.50.

b) I (8.2 g) was dissolved in 1 N NaOH solution (60 ml) under ice-cooling, and the solution was allowed to stand for 0.5 hr. A solution of iodine (2.6 g) and KI (6 g) in H_2O (200 ml) was added dropwise in 1 hr below 10° thereto, and the resultant mixture was stirred for 0.5 hr. The reaction mixture was concentrated under reduced pressure, and the residue was extracted with *n*-BuOH. The *n*-BuOH extract was concentrated under reduced pressure, and the residue was crystallized from ether. The crystals were chromatographed on a column of alumina/EtOH to give II (2 g) as colorless prisms of mp 168—170° (dec.).

c) I (16.8 g) was added to a solution of NaOH (4.8 g) in H_2O (40 ml) under ice-cooling and the mixture was stirred for 15 min at 10°. A solution of $K_3Fe(CN)_6$ (13.2 g) in H_2O (70 ml) was added dropwise below 10° in 15 min thereto. The resultant mixture was adjusted to pH 11.5 with 10% aqueous NaOH solution and stirred at room temperature for 1.5 hr. The reaction mixture was extracted with *n*-BuOH. The organic layer was washed with H_2O, dried, and concentrated under reduced pressure to give II (12.7 g). This substance was recrystallized from EtOH to give colorless prisms of mp 168—170° (dec.).

d) 3-(2-Methyl-4-aminopyrimidin-5-ylmethyl)-4-methyl-5-(2-methylthioethyl)thiazolium chloride hydrochloride hydrate (MTET, V) (1.6 g) was dissolved in a solution of NaOH (0.36 g) in H_2O (6 ml) under ice-cooling, and the solution was allowed to stand for 0.5 hr. A solution of $K_3Fe(CN)$ (1.0 g) in H_2O (4 ml) was added dropwise thereto, and the mixture was adjusted to pH 11.5—11.8 with 10% NaOH solution. The resultant mixture was kept for 1.5 hr at 15° with stirring, and the precipitates were collected, washed with H_2O, and dried to give III tetrahydrate (0.87 g).

e) V (1.16 g) was dissolved in a solution of NaOH (0.36 g) in H_2O (6 ml) under ice-cooling, and the solution was allowed to stand for 0.5 hr at room temperature. A solution of iodine (0.38 g) and KI (0.9 g) in H_2O was added dropwise in 0.5 hr, and the resultant mixture was stirred for 0.5 hr. The precipitates were collected, washed with H_2O, and dried to give III tetrahydrate (0.72 g).

f) V (1.16 g) was dissolved in a solution of NaOH (0.36 g) in H_2O (6 ml) under ice-cooling, and the solution was allowed to stand for 0.5 hr at room temperature. A 30% H_2O_2 solution (0.68 g) was added dropwise thereto. The resultant mixture was kept at pH 11.8 and stirred under ice-cooling for 2 hr. The precipitates were collected, washed with H_2O, and dried to give III tetrahydrate (0.50 g).

3-(2-Methyl-4-aminopyrimidin-5-yl)methyl-4-methyl-5-(2-bromoethyl)thiazoline-2-thione (XII) and Amidine (XIII)——a) To a suspension of 3-(2-methyl-4-aminopyrimidin-5-yl)methyl-4-methyl-5-(2-hydroxyethyl)thiazoline-2-thione (SB_1, X) (15 g) and triphenylphosphine (21 g) in DMF (50 ml), bromine (12 g) was added dropwise below 40°. The reaction mixture was stirred for 1 hr at room temperature and then H_2O (1 l) was added. Separated oil was extracted with AcOEt to remove triphenylphosphine-oxide (24 g). The aqueous layer was neutralized with $NaHCO_3$ and the separated crystals were washed with acetone to give XII (13 g). Recrystallization from MeOH gave colorless prisms of mp 150—158° (dec.). *Anal.* Calcd. for $C_{12}H_{15}BrN_4S_2$: C, 40.11; H, 4.21; Br, 22.24; N, 15.59; S, 17.85. Found: C, 40.80; H, 4.31; Br, 22.35; N, 15.97; S, 18.08. NMR (DMSO-d_6) δ: 2.18 (3H, s, Pm–CH_3), 2.35 (3H, s, Th–CH_3), 3.22 (2H, t, J=6.0 Hz, $\underline{CH_2}CH_2$-Br), 3.69 (2H, t, J=6.0 Hz, $CH_2\underline{CH_2}Br$), 5.30 (2H, s, Pm–CH_2–Th), 6.95 (2H, s, NH_2), 7.43 (1H, s, Pm-6-H). UV λ_{max}^{EtOH} 233, 279, 324.5 nm (log ε 4.13, 3.81, 4.18).

b) To a suspension of X (2.96 g) and triphenylphosphite (4 g) in CH_3CN (15 ml), bromine (1.92 g) was added dropwise below 10°. The reaction mixture was stirred for 2 hr at 5°, and CH_3CN was removed under reduced pressure. The residue was washed with ether, suspended in H_2O, and neutralized with $NaHCO_3$. The separated oil was extracted with $CHCl_3$. The $CHCl_3$ extract was dried and concentrated under reduced pressure. The residue was washed with ether and acetone to give XII (3.15 g).

c) To a suspension of X (2.96 g) and triphenylphosphite (4 g) in DMF (10 ml), bromine (1.92 g) was added dropwise below 10°. The reaction mixture was stirred for 1 hr at 5° and ether was added. The separated crystals were collected, suspended in H_2O, and neutralized with $NaHCO_3$. The separated oil was extracted with $CHCl_3$. The $CHCl_3$ extract was dried and concentrated under reduced pressure. The residue was washed with acetone to give XII (1.8 g). The acetone washing was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give 0.3 g of XII and 0.25 g of amidine XIII. Recrystallization of XIII from acetone gave colorless crystals of mp 140—141°. *Anal.* Calcd. for $C_{15}H_{20}$ Br N_5S_2: C, 43.47; H, 4.86; Br, 19.28; N, 16.90; S, 15.48. Found: C, 44.07; H, 4.94; Br, 19.12; N, 16.87. S, 15.50. NMR (DMSO-d_6) δ: 2.13 (3H, s, Th–CH_3), 2.43 (3H, s, Ph–CH_3), 3.19, 3.12 (2×3H, 2×S, $N(CH_3)_2$), 3.65 (2H, t, J=6.0 Hz, $CH_2\underline{CH_2}Br$), 5.43 (2H, s, Pm–CH_2–Th), 8.72 (1H, s, N=CH–N). UV λ_{max}^{EtOH} 269.318 nm (log ε 4.13, 4.52).

3-(2-Methyl-4-aminopyrimidin-5-yl)methyl-4-methyl-5-(2-chloroethyl)thiazoline-2-thione (XI)——A suspension of X (2.96 g) and triphenylphosphine (3.9 g) in CCl_4 (10 ml) and DMF (10 ml) was stirred for 30 min at 80°. The reaction mixture was concentrated under reduced pressure and the residue was added H_2O. The separated oil was crystallized from AcOEt to give XI (2.25 g) mp 177°.