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Studies on Pyrimidine Derivatives and Related Compounds. LXII.[1] Cycloadditions of Alkyl Isothiocyanates with Thiamine and Related Thiazolium Ylids and Facile Conversions of the Adducts to Dihydroimidazo[4,5-*d*]thiazole Derivatives

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Thiamine and related thiazolium ylids react with alkyl isothiocyanates to give spiro-(perhydrofuro[2,3-*d*]thiazole-2,4′-imidazolidine)derivatives (IIa—i) involving two step cycloaddition. Confirmation of the structures is provided by chemical degradations and by infrared, ultraviolet, nuclear magnetic resonance spectroscopic evidences as well as by characteristic mass spectral fragmentations. On heating in acetic acid, some of these (1:2) adducts are readily converted to dihydroimidazo[4,5-*d*]thiazole derivatives (XIa—d) involving a novel intramolecular cyclization.

Our previous reports showed that the reactions of thiamine ylid with isocyanates afforded (1:2) adducts involving a novel two step cycloaddition.[3] The present paper deals with the further studies on the reactions of thiamine and related thiazolium ylids with alkyl isothiocyanates.

As a model compound for thiamine, 3-benzyl-4-methyl-5β-hydroxyethylthiazolium bromide (Ia) (R=C_6H_5, X=Br) was allowed to react with an excess amounts of methyl isothiocyanate in the presence of triethylamine in N,N-dimethylformamide (DMF) for 6 hours at 40—45° to afford a (1:2) cycloadduct IIa, $C_{17}H_{21}ON_3S_3$, mp 132—133°, as yellow crystals in *ca.* 50% yield. The structure of the product IIa was determined to be spiro {3-benzyl-3a-methylperhydrofuro[2,3-*d*]thiazole-2,4′-(1′,3′-dimethylimidazolidine-2′,5′-dithione)} on the bases of spectral data and chemical degradations. Infrared (IR) spectrum of IIa showed no signal due to OH, NH and C=N double bond, whereas a strong absorption band due to $\nu_{C=S}$ was observed at 1300 cm^{-1}. Its ultraviolet (UV) spectrum showed an absorption maximum at 322 mμ (log ε=4.19) due to dithiohydantoin ring. Sodium borohydride reduction of IIa afforded an oily product III which showed NMR signal due to a secondary methyl group at 8.79 τ (3H, doublet, J=6 cps) and an UV absorption maximum at 322 mμ (log ε=4.20) indicating that the reduction occurred only at C_4 position of thiazolidine ring involving hydrogenolysis of the tetrahydrofuran ring. Hydrogen peroxide oxidation of IIa in acetic acid yielded 1,3-dimethylparabanic acid (IV), whereas on catalytic hydrogenation with palladium charcoal in ethanol IIa afforded 1,3-dimethyl-2-thiohydantoin (V) accompanying benzylamine. These facts clearly confirmed the structure IIa for the cycloadduct and a possible alternative structure IX was excluded by the fact that the UV spectral pattern was found to be quite different from that of N,N′-dimethylpseudodithiohydantoin (VIII) which was obtained from 2-methylimino-3-methylthiazolidine-4-thione (VII) by the treatment with phosphorous pentasulfide in pyridine (see experimental section). Nuclear magnetic resonance (NMR) spectrum of IIa (Fig. 1) showed signals corresponding to two N-methyl groups

1) Part LXI: A. Takamizawa, K. Hirai, S. Matsumoto, and T. Ishiba, *Chem. Pharm. Bull.* (Tokyo), **17**, 462 (1969).
2) Location: *Fukushima-ku, Osaka.*
3) A. Takamizawa, K. Hirai, S. Matsumoto and T. Ishiba, *Chem. Pharm. Bull.* (Tokyo), **16**, 2130 (1968).

at 7.10 τ and 6.65 τ and a tertiary methyl group at 8.17 τ besides complex multiplets around 6.0 τ and 7.8 τ due to the protons of >CH–CH_2–CH_2–O system, which were in good agreement with the proposed structure, however it revealed that IIa contains a small quantity of stereoisomer presumably arisen by the different configuration at the spiro carbon in the ratio of *ca.* 5:1.

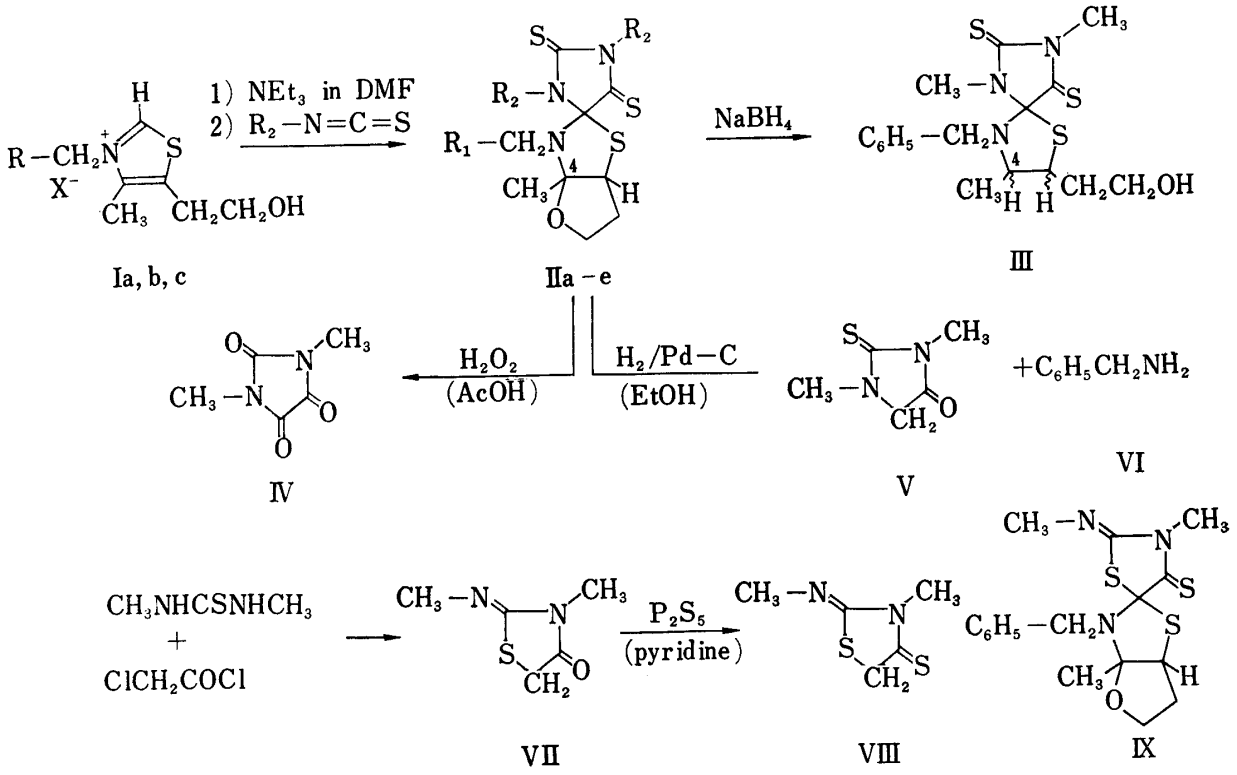


Chart 1

Similarly, reaction of 3,4-dimethyl-5β-hydroxyethylthiazolium iodide (Ib) (R=H, X=I) with methyl isothiocyanate in the presence of triethylamine in DMF afforded spiro{3,3a-dimethylperhydrofuro[2,3-*d*]thiazole-2,4'-(1',3'-dimethylimidazolidine-2',5'-dithione)} (IIb) as crystalline stereoisomeric mixture (4:1) whose spectral properties were quite analogous to those of IIa. Ia, Ib and 3-*p*-nitrobenzyl-4-methyl-5β-hydroxyethylthiazolium bromide (Ic) (R=*p*-nitrophenyl, X=Br) were also found to react with methyl isothiocyanate or with ethyl isothiocyanate to give corresponding (1:2) cycloadducts IIc—e analogously.

Application of this reaction to thiamine led to same result. Thus, the reactions of methyl, ethyl, allyl, and benzyl isothiocyanates with thiamine in the presence of triethylamine in DMF afforded the analogous (1:2) cycloadducts IIf—i respectively, although their yields were less satisfactory probably owing to the accompanying formation of thiothiamine (S–B_1) (X) in considerable quantities. These results are summarized in Table I. In Fig. 1, NMR spectra of IIa and IIg are shown. Mass spectrometry of these (1:2) cycloadducts shows many common

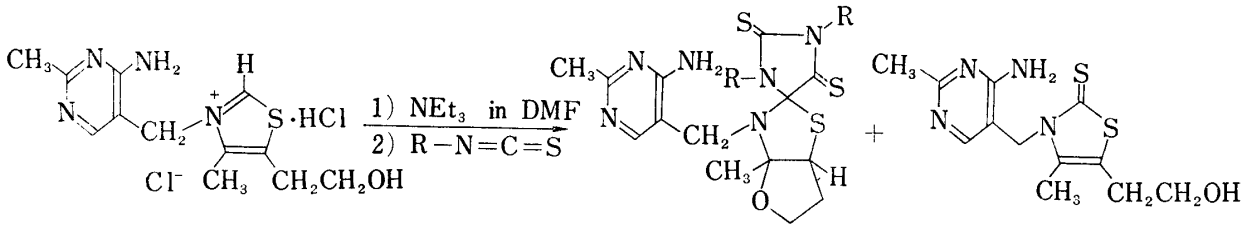


Chart 2

Table I. Spiro(perhydrofuro[2,3-*d*]thiazole-2,4′-imidazolidine) Derivatives (IIa—i)

II	R_1	R_2	mp (°C)	Yield (%)	UV λ_{max}^{EtOH} mμ (log ε)	Chemical shift[a] C_4–CH_3 (τ)
a	C_6H_5	CH_3	132—133	48	322 (4.19)	8.17
b	H	CH_3	82— 83	43	321 (4.22)	8.32
c	C_6H_4–NO_2(p)	CH_3	152—154	10	321 (4.18)	8.23
d	C_6H_5	C_2H_5	oil	23	325 (4.17)	8.21
e	H	C_2H_5	oil	11	323 (4.16)	8.30
f	pym[b]	CH_3	209—210(d)[c]	2.5	325 (4.18)	8.13
g	pym	C_2H_5	218—219(d)	2.5	325 (4.16)	8.12
h	pym	$CH_2CH{=}CH_2$	210—212(d)	6.0	325 (4.19)	8.14
i	pym	$CH_2C_6H_5$	oil	5.6	321 (4.16)	8.25

a) Signals due to the predominating stereoisomer are shown.
b) pym=2-methyl-4-aminopyrimidin-5-yl
c) d=decomposition

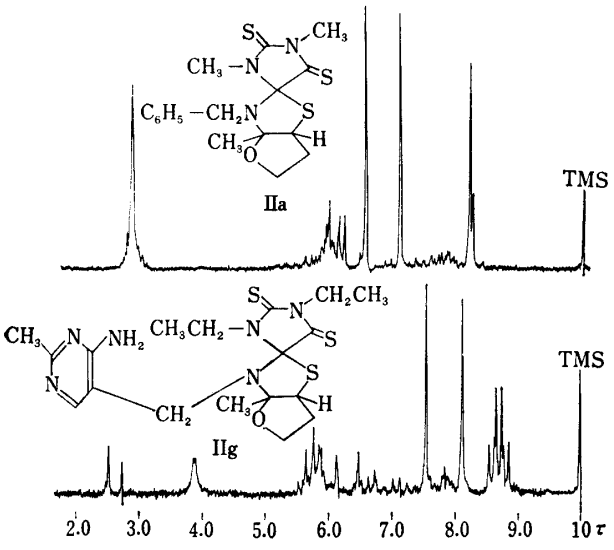


Fig. 1. NMR Spectra of IIa and IIg in $CDCl_3$ Solution

fragmentations typical of the ring system, which may be readily used to identify such compounds. The adduct IIa exhibited a molecular ion peak at *m/e* 379 (M^+) and prominent fragment ions at *m/e* 315 ($M-S_2$), 274, 264 ($M-C_5H_7OS$, base peak), 106, 91, 84, 43, whereas its monodeuterio derivative IIa′ (X=D) (D>75%) which was easily obtained by the reaction of Ia with methyl isothiocyanate in the presence of triethylamine in DMF containing deuterium oxide exhibited a molecular ion peak at *m/e* 380 (M^+) and fragment ions at *m/e* 316 ($M-S_2$), 275, 265 ($M-C_5H_7OS$), 107, 91, 85, 43. These data will be rationalized by the fragmentation paths (b), (c), (d), (e), (f), (g) and (h) illustrated in the Chart 3. Peak measurements of the high-resolution mass spectrum of IIa provided confirmatory support for these paths (Table III). Mass spectra of IIb, IIf, IIg, and IIh also showed common ions arising by the fragmentations (b), (c), (d), (e), (f), (g) and (h), respectively, which are summarized in Table II.

In attempts of chemical degradations of the spiro (perhydrofuro[2,3-*d*]thiazole-2,4′-imidazolidine) derivatives, we observed an interesting intramolecular cyclization reaction accompanied by dehydrogenation. The compound IIa, when heated at 100° for 8 hours in glacial acetic acid containing a trace quantity of water, was smoothly converted into a new compound XIa ($R_1=C_6H_5$, $R_2=CH_3$), $C_{12}H_{11}N_3S_2$, mp 201—202°, in 63% yield. UV spectrum of the new compound XIa showed maxima at 249 mμ (log ε=4.07), 280 mμ (log ε=4.15) and 375 mμ (log ε=4.32). In particular, NMR spectrum of XIa (Fig. 2) exhibited simple signal patterns of two N-methyl groups (6.16 τ and 6.23 τ) and of five aromatic protons (2.0—2.8 τ). On heating in hydrochloric acid, XIa was converted into XII, mp 101—102°, accompanied with benzoic acid and ammonium chloride, and the compound XII was reconvertible into XIa by the action of thiophosgene. On hydrogen peroxide oxidation in acetic acid, XIa afforded a quarternary salt XIII, as dihydrate, $C_{12}H_{13}O_4N_3S_2\cdot 2H_2O$, mp 258—256°, which showed a new NMR signal at 1.33 τ (1H, singlet) attributable to a proton locating on the imidazolium 2-position, and an alkaline treatment of XIII resulted XIV and XV as crystalline

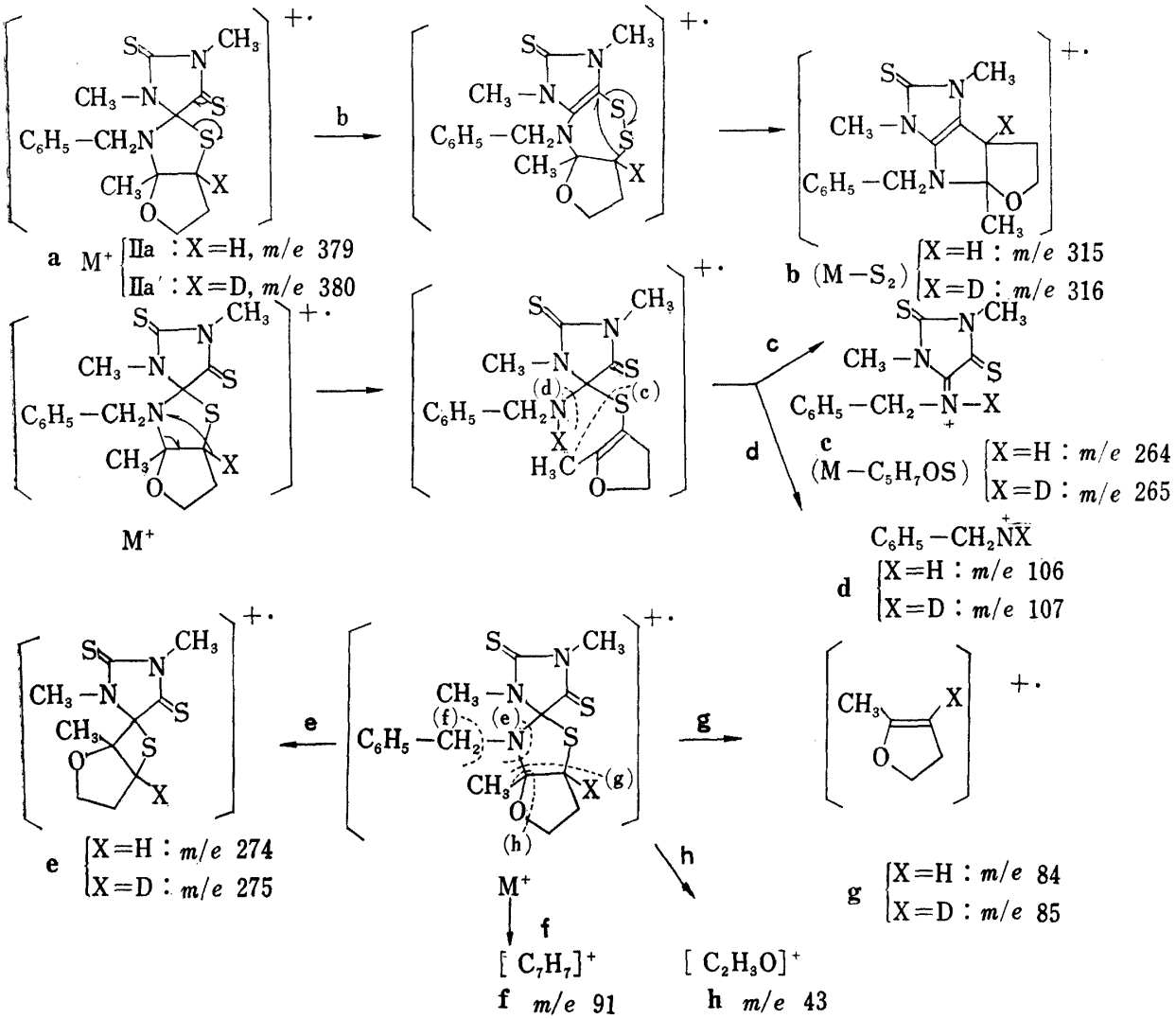


Chart 3

TABLE II. Characteristic Mass Spectral Peaks of Spiro(perhydrofuro-[2,3-*d*]thiazole-2,4′-imidazolidine] Derivatives

Compds.	Formula	Ions *m/e* (relative abundance %)							
		a(M)	b(M-S_2)	c(M-C_5H_7OS)	d	e	f	g	h
IIa	$C_{17}H_{21}ON_3S_3$	379 (25)	315 (20)	264 (100)	106 (38)	274 (13)	91 (74)	84 (47)	43 (25)
IIa′	$C_{17}H_{20}DON_3S_3$	380 (12)	316 (25)	265 (100)	107 (48)	275 (12)	91 (168)	85 (48)	43 (60)
IIb	$C_{11}H_{17}ON_3S_3$	303 (28)	239 (25)	188 (100)	—	274 (1)	—	84 (34)	43 (24)
IIf	$C_{16}H_{22}ON_6S_3$	410 (30)	346 (4)	295 (27)	137 (52)	274 (9)	122 (100)	84 (87)	43 (42)
IIg	$C_{18}H_{26}ON_6S_3$	438 (34)	374 (7)	323 (47)	137 (27)	302 (9)	122 (100)	84 (41)	43 (30)
IIh	$C_{20}H_{26}ON_6S_3$	462 (51)	398 (1)	347 (11)	137 (15)	326 (3)	122 (100)	84 (24)	43 (32)

isomeric mixture (1:1) (see experimental section). The structure of the new compound XIa was therefore assigned as 2-phenyl-4,6-dimethyldihydroimidazo[4,5-*d*]thiazole-5-thione. The same compound was also found to be obtainable from IIa by the action of sodium ethoxide in ethanol. Similarly, on heating in glacial acetic acid, the (1:2) cycloadduct IIc was converted into 2-*p*-nitrophenyl-4,6-dimethyldihydroimidazo[4,5-*d*]thiazole-5-thione (XIb), mp> 270°, in 42% yield. The (1:2) cycloadducts of thiamine with alkyl isothiocyanates IIf, IIh

Table III. High-Resolution Mass Spectrum of Spiro {3-benzyl-3a-methylperhydrofuro[2,3-*d*]thiazole-2,4'-(1',3'-dimethylimidazolidine-2,'5'-dithione)} (IIa)

Ions	Compositions	*m/e* calcd.	*m/e* found
a (M)	$C_{17}H_{21}ON_3S_3$	379.0847	379.084
b (M-S_2)	$C_{17}H_{21}ON_3S$	315.1405	315.140
c (M-C_5H_7OS)	$C_{12}H_{14}N_3S_2$	264.0629	264.064
d	C_7H_8N	106.0657	106.063
e	$C_{10}H_{14}ON_2S_3$	274.0268	274.024
f	C_7H_7	91.0548	91.0548[a]
g	C_5H_8O	84.0575	84.057
h	C_2H_3O	43.0184	43.018

a) This peak was overlapped by the reference ion $C_7H_7^+$ arising from toluene.

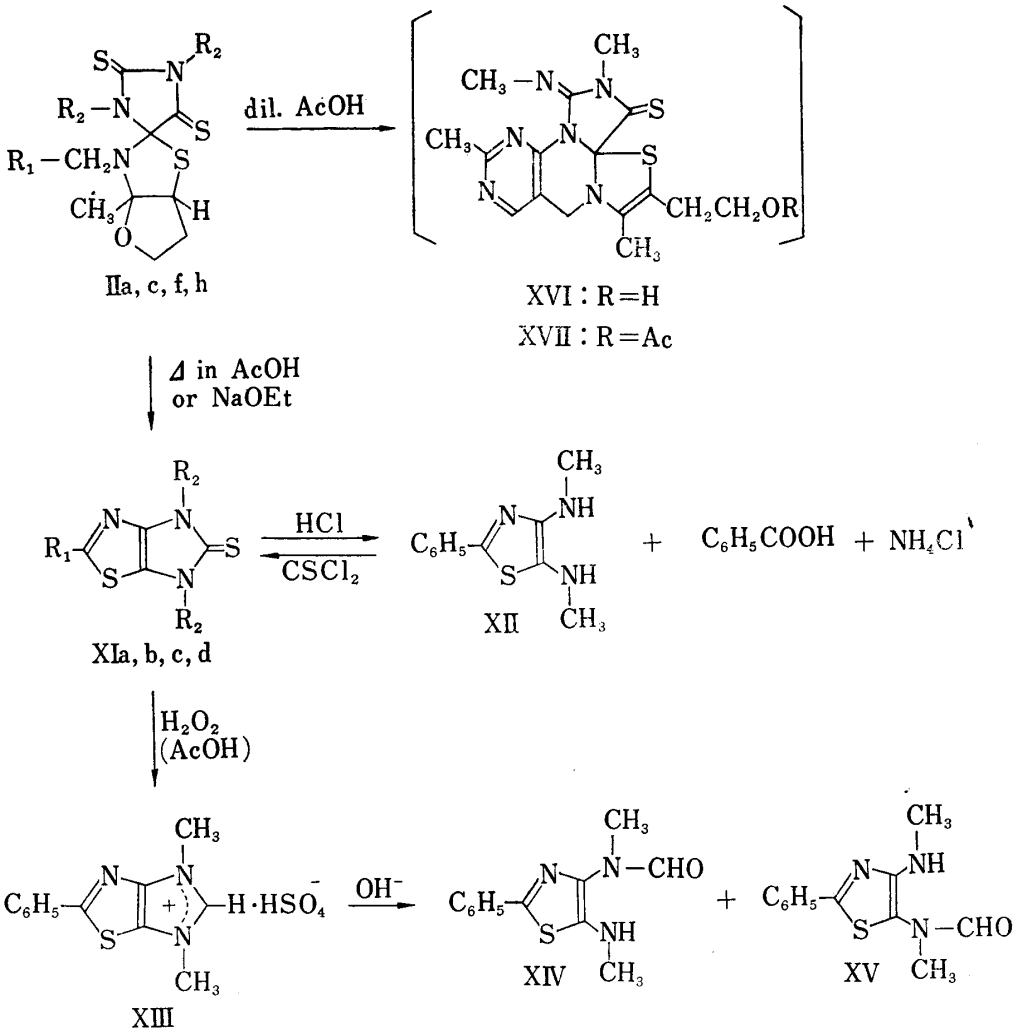


Chart 4

were similarly found to undergo analogous reaction on heating in acetic acid providing XIc (R_1=2-methyl-4-aminopyrimidin-5-yl, R_2=CH_3) and XId (R_1=2-methyl-4-aminopyrimidin-5-yl, R_2=allyl) in 50% yield respectively. These results are summarized in Table IV, and NMR spectra of the compounds XIa and XIc are shown in Fig. 2. On milder reaction condition however the (1:2) cycloadduct IIf was found to afford a different product. Thus, on the action of diluted acetic acid in chloroform at room temperature for 96 hours, compound

Table IV. Dihydroimidazo[4,5-*d*]thiazole Derivatives (XIa—d)

XI	R_1	R_2	mp (°C)	Yield (%)	UV λ_{max}^{EtOH} mμ (log ε)
a	C_6H_5	CH_3	201—202	63	249 (4.07), 280 (4.15), 375 (4.32)
b	C_6H_4-NO_2(*p*)	CH_3	>270	42	282.5 (4.17), 442 (4.26),
c	pym[a]	CH_3	>270	50	225 (4.11), 283 (4.15), 400 (4.31)
d	pym	$CH_2CH{=}CH_2$	259—260	50	225 (4.09), 287 (4.08), 399 (4.25)

a) pym=2-methyl-4-aminopyrimidin-5-yl

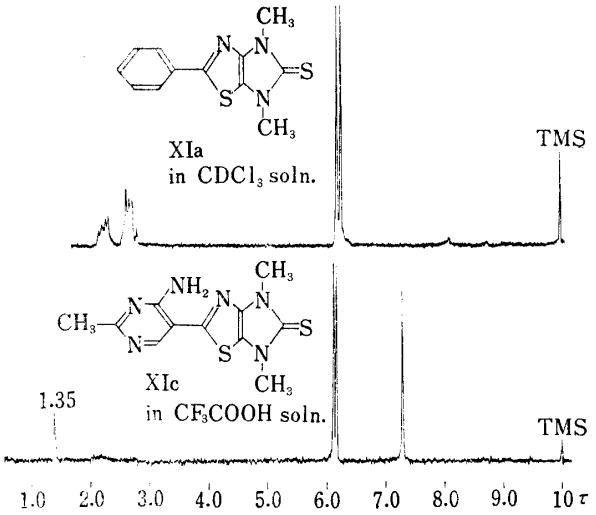


Fig. 2. NMR Spectra of XIa and XIc

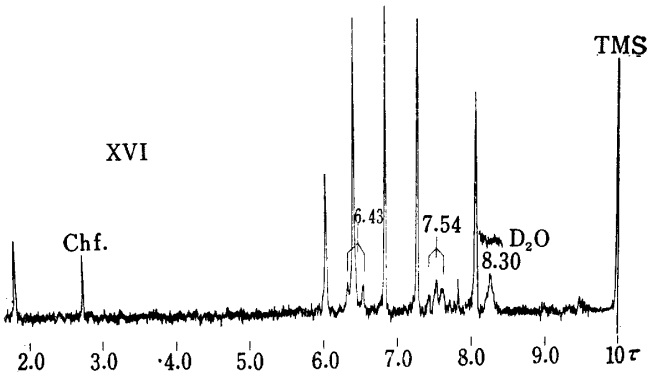


Fig. 3. NMR Spectrum of XVI in $CDCl_3$ Solution

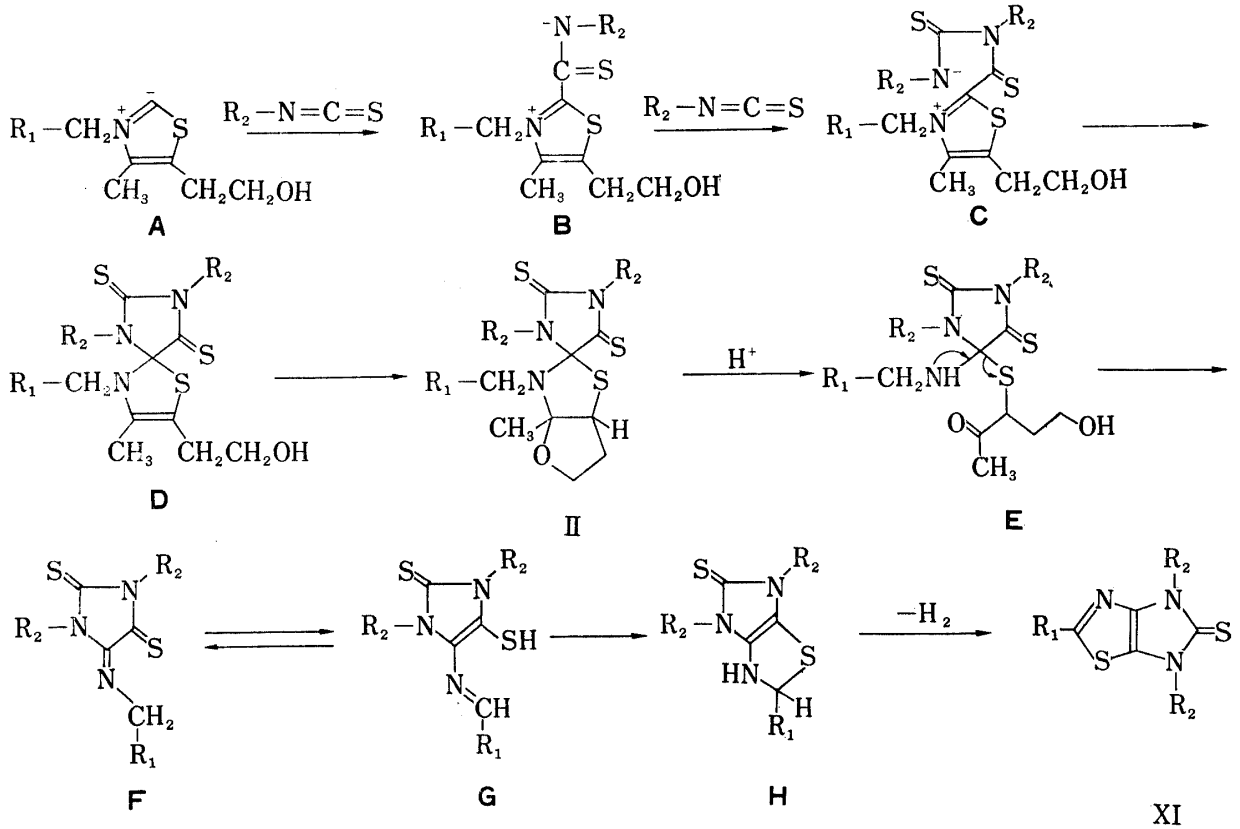


Chart 5

IIf was converted into a new compound XVI, $C_{16}H_{20}ON_6S$, mp 240—241° (decomp.) in 35% yield. Elementary analysis of XVI indicates elimination of one molecule of hydrogen sulfide from the starting material. Its IR and NMR spectrum (Fig. 3) showed the absence of NH_2 group, on the other hand, the presence of $=\overset{|}{C}-CH_2CH_2OH$ system was indicated by the IR absorptions at 3220 cm^{-1} and 1060 cm^{-1} as well as by the NMR signals of a pair of triplets at 6.43 τ and 7.54 τ. UV spectrum of the new compound showed absorption maxima at 224, 280 and 317 mμ. On the basis of these spectral data, the structure of the new compound will most possibly be represented by the formula XVI. Acetylation of XVI with acetic anhydride in pyridine afforded a monoacetate XVII, which provided an additional support for the structure.

Formations of spiro(perhydrofuro[2,3-*d*]thiazole-2,4'-imidazolidine)derivatives from thiazolium salts and alkyl isothiocyanates will be rationalized by the two step cycloaddition of alkyl isothiocyanates to the thiazolium ylid (**A**) *via* the dipolar (1:1) adduct (**B**) followed by cyclization of hydroxyethyl side chain. The intermediate (**B**) could not be isolated in the present reactions, however in cases of aromatic isothiocyanates, it has been shown to be isolable in stable crystalline state.[4] On the other hand, formations of dihydroimidazo[4,5-*d*]-thiazole derivatives (XI) from the (1:2) cycloadducts (II) will be explained by the following scheme. Initial cleavage of the thiazolidine ring will result (**E**) and subsequent elimination of thioether group will lead to (**G**) *via* the iminothione (**F**), then cyclization followed by dehydrogenation will lead to the final product (XI).

Experimental

All melting points were determined in capillaries and uncorrectegd. All NMR spectra were taken on a Varian-Associates A-60 recording spectrometer in $CDCl_3$ or d_6-DMSO solution with tetramethylsilane (TMS) as an internal standard unless otherwise indicated. Following abbreviations are used for the representation of NMR data: s=singlet, d=doublet, t=triplet, q=quartet, d.d=double doublet, m=multiplet, and pym =pyrimidine. For the compounds containing stereoisomer, the chemical shifts of the signals due to predominanting isomer are shown. UV spectra were taken on a Hitachi EPS-3 recording spectrophotometer in 99% EtOH, and IR spectra were taken in nujol mull on a Japan Spectroscopic Company IR-S infrared spectrophotometer using a NaCl prism. Silicagel (Davision, Grade 950) was used for column chromatography unless otherwise indicated. All low-resolution mass spectra were measured with a Hitachi RMU-6E mass spectrometer using direct inlet system with the ionizing energy at 70 eV and the ionizing current at 80 μA. High resolution mass spectrum was determined with a Hitachi RMU-7 mass spectrometer.

Spiro{3-benzyl-3a-methylperhydrofuro[2,3-*d*]thiazole-2,4'-(1',3'-dimethylimidazolidine-2',5'-dithione)} (IIa)——To a solution of 3-benzyl-4-methyl-5β-hydroxyethylthiazolium bromide (Ia) (3.1 g) in DMF (20 ml) was added NEt_3 (1.5 g) with stirring at room temperature, then methyl isothiocyanate (6.0 g) was added to the solution. After having been stirred for 8 hr at 45—50°, the solvent was evaporated under reduced pressure and the resulting residue was extracted with $CHCl_3$. The $CHCl_3$ extract, after washing, drying and concentration gave a crystalline residue which was recrystallized from MeOH to give IIa as yellow prisms, mp 132—133°. Yield 1.65 g (48%). *Anal.* Calcd. for $C_{17}H_{21}ON_3S_3$: C, 53.82; H, 5.58; N, 11.08; S, 25.30. Found: C, 54.06; H, 5.46; N, 11.10; S, 25.41. UV λ_{max}^{EtOH} mμ (log ε): 322 (4.19). NMR ($CDCl_3$) τ: 2.83 (5H, difused s, phenyl), 6.65 and 7.10 (each 3H, s, 2×N-CH_3), 7.6 (2H, m, -$\overset{|}{C}H$-$\underline{CH_2}$-), 8.17 (3H, s, C_4-CH_3). MS *m/e* (%): 379 (M^+, 25), 315 (20), 264 (100), 106 (38), 274 (13), 91 (74), 84 (47), 43 (25). Monodeuterio derivative IIa' was obtained quite similarly by reacting Ia (3.14 g) with methyl isothiocyanate (4.38 g) in the presence of NEt_3 (1.5 g) in DMF (30 ml) containing D_2O (1 g) in 55% yield. IR and UV spectra of IIa' were identical with those of IIa. In the mass spectrum, IIa' exhibited ions at *m/e* 380 and *m/e* 379, the latter corresponds to the molecular ion of the non deuterated product, in the ratio of *ca.* 4:1, respectively. The fragment ions are shown in Table II.

Spiro{3,3a-dimethylperhydrofuro[2,3-*d*]thiazole-2,4'-(1',3'-dimethylimidazolidine-2',5'-dithione)} (IIb)—— To a solution of 3,4-dimethyl-5β-hydroxyethylthiazolium iodide (Ib) (2.85 g) in DMF (30 ml) was added NEt_3 (1.5 g) with stirring at room temperature, then methyl isothiocyanate (3.2 g) was added. After having been stirred for 8 hr at 40—45°, the reaction mixture was concentrated to dryness under reduced pressure and the resulting residue was extracted with $CHCl_3$. The $CHCl_3$ extract after washing, drying and concentration was subjected to column chromatography to afford crude IIb which was recrystallized from MeOH to give

4) A. Takamizawa, K. Hirai and S. Matsumoto, *Tetrahedron Letters*, **1968**, 4027.

yellow prisms, mp 82—83°. Yield 1.3 g (43%). *Anal.* Calcd. for $C_{11}H_{17}ON_3S_3$: C, 43.57; H, 5.66; N, 13.86; S, 31.73. Found: C, 43.58; H, 5.65; N, 14.27; S, 31.59. UV λ_{max}^{EtOH} mμ (log ε): 321 (4.22). NMR ($CDCl_3$) τ: 6.40, 6.73 and 7.85 (each 3H, s, 3×N–CH_3), 8.32 (3H, s, C_4–CH_3). MS *m/e* (%): 303 (M^+, 28) 239 (M–S_2, 25), 188 (100), 274 (1), 84 (34), 43 (24).

Sprio{3-(4-nitrophenyl)methyl-3a-methylperhydrofuro[2,3-*d*]thiazole-2,4′-(1′,3′-dimethylimidazolidine-2′,5′-dithione)} (IIc)——To a solution of 3-(4-nitrophenyl)methyl-4-methyl-5β-hydroxyethylthiazolium bromide (Ic) (3.79 g) in DMF (40 ml) was added NEt_3 (1.5 g) with stirring at room temperature. To the reaction mixture, methyl isothiocyanate (4.5 g) was added and stirred for 8 hr at 40—45°. After concentration of the reaction mixture under reduced pressure, the resulting residue was extracted with $CHCl_3$ and the $CHCl_3$ extract was washed, dried and concentrated to leave a brown gum which was subjected to column chromatography over neutral Al_2O_3 and eluted with AcOEt to give IIc. Recrystallization of IIc from MeOH–acetone (2:1) gave yellow prisms, mp 152—154°. Yield 470 mg (10%). *Anal.* Calcd. for $C_{17}H_{20}O_3N_4S_3$: C, 48.11; H, 4.75; N, 13.20; S, 22.61. Found: C, 48.22; H, 4.73; N, 13.49; S, 21.68. UV λ_{max}^{EtOH} mμ (log ε): 321 (4.18). NMR ($CDCl_3$) τ: 6.52, 7.07 (each 3H, s, 2×N–CH_3), 8.23 (3H, s, C4–CH_3).

Spiro{3-benzyl-3a-methylperhydrofuro[2,3-*d*]thiazole-2,4′-(1′,3′-diethylimidazolidine-2′,5′-dithione)} (IId)——To a solution of Ia (3.14 g) in DMF (20 ml) was added NEt_3 (1.5 g) with stirring at room temperature, then ethyl isothiocyanate (5.2 g) was added to the reaction mixture. After having been stirred for 8 hr at 40—45°, the reaction mixture was concentrated under reduced pressure and the resulting residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed, dried and concentrated to leave a brown oil which was subjected to column chromatography over neutral Al_2O_3 and eluted with AcOEt to give IId as a pale yellow oil. Yield 980 mg (23%). UV λ_{max}^{EtOH} mμ (log ε): 325 (4.17). NMR ($CDCl_3$) τ: 2.83 (5H, m, phenyl), 8.21 (3H, s, C_4–CH_3), 8.66 and 8.79 (each 3H, t, 2×–$CH_2\underline{CH_3}$).

Spiro{3,3a-dimethylperhydrofuro[2,3-*d*]thiazole-2,4′-(1′,3′-diethylimidazolidine-2′,5′-dithione)} (IIe)——To a suspension of Ib (3.2 g) in CH_3CN (40 ml) was added NEt_3 (2.5 g) with stirring at room temperature, then ethyl isothiocyanate (6.9 g) was added to the reaction mixture. After having been stirred for 4 hr at 40—45°, the reaction mixture was concentrated and the resulting residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed, dried and evaporated to leave a brown oil which was subjected to column chromatography and from the $CHCl_3$ eluate IIe was obtained as a pale yellow oil. Yield 407 mg (11%). UV λ_{max}^{EtOH} mμ (log ε): 323 (4.16). NMR ($CDCl_3$) τ: 7.86 (3H, s, N–CH_3), 8.30 (3H, s, C_4–CH_3), 8.58, 8.75 (each 3H, t, 2×–$CH_2\underline{CH_3}$).

Spiro{3-(2-methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-*d*]thiazole-2,4′-(1′,3′-dimethylimidazolidine-2′,5′-dithione)} (IIf)——To a suspension of thiamine hydrochloride (Id) (6.7 g) in DMF (50 ml) was added NEt_3 (6 g) with stirring at room temperature, then methyl isothiocyanate (8.76 g) was added to the reaction mixture. After having been stirred for 8 hr at 50°, the reaction mixture was allowed to stand overnight at room temperature. The reaction mixture after concentration under reduced pressure was extracted with $CHCl_3$ and the $CHCl_3$ extract was washed, dried and concentrated to give an oily mixture which was subjected to column chromatography. The first acetone eluate gave unidentified oily substance and the second eluate gave IIf which on recrystallization from $CHCl_3$ furnished yellow prisms. mp 209—210° (decomp.). Yield 185 mg (2.5%). *Anal.* Calcd. for $C_{16}H_{22}ON_6S_3$: C, 46.82; H, 4.40; N, 20.48; S, 23.50. Found: C, 46.91; H, 5.31; N, 20.45; S, 22.41. UV λ_{max}^{EtOH} mμ (log ε): 325 (4.18). NMR ($CDCl_3$) τ: 2.53 (1H, s, pym-H), 3.92 (2H, broad, NH_2), 6.39, 6.68 (each 3H, s, 2×N–CH_3), 7.55 (3H, s, pym-CH_3), 8.13 (3H, s, C_4–CH_3). MS *m/e* (%): 410 (M^+, 30), 346 (M-S_2, 4), 295 (27), 137 (52), 274 (9), 122 (100), 84 (87), 43 (42). The third fraction gave thiothiamine (S-B_1) (X) (320 mg).

Spiro{3-(2-methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-*d*]thiazole-2,4′-(1′,3′-diethylimidazolidine-2′,5′-dithione)} (IIg)——To a suspension of thiamine hydrochloride (Id) (5.85 g) in DMF (50 ml) was added NEt_3 (5.25 g) with stirring at room temperature, then ethyl isothiocyanate (7.6 g) was added to the reaction mixture. After having been stirred for 10 hr at 50°, the reaction mixture was allowed to stand overnight at room temperature, and concentrated under reduced pressure to give a brown residue which was extracted with $CHCl_3$. The $CHCl_3$ extract was washed, dried and evaporated to leave an oil which was subjected to column chromatography. The first acetone eluate gave unidentified oily mixture and the second fraction gave IIg which on recrystallization from $CHCl_3$ afforded yellow prisms, mp 218—219° (decomp.). Yield 170 mg (2.5%). *Anal.* Calcd. for $C_{18}H_{26}ON_6S_3$: C, 49.24; H, 5.97; N, 19.15; S, 21.91. Found: C, 49.21; H, 6.09; N, 19.03; S, 21.62. UV λ_{max}^{EtOH} mμ (log ε): 325 (4.16). NMR ($CDCl_3$) τ: 2.50 (1H, s, pym-H), 3.85 (2H, broad, NH_2), 7.55 (3H, s, pym-CH_3), 8.12 (3H, s, C_4–CH_3), 8.67 and 8.77 (each 3H, t, 2×–$CH_2\underline{CH_3}$). MS *m/e* (%): 438 (M^+, 34), 374 (M-S_2, 7), 323 (47), 137 (27), 302 (9), 122 (100), 84 (41), 43 (30).

Spiro{3-(2-methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-*d*]thiazole-2,4′-(1′,3′-diallylimidazolidine-2′,5′-dithione)} (IIh)——To a stirred suspension of thiamine hydrochloride (Id) (6.7 g) in DMF (60 ml) was added NEt_3 (6.6 g) at room temperature, then allyl isothiocyanate (10 g) was added to the mixture. After having been stirred for 12 hr at 45—50°, the reaction mixture was allowed to stand overnight at room temperature and concentrated under reduced pressure. The resulting residue was extracted with $CHCl_3$, and the $CHCl_3$ extract was washed, dried and evaporated to leave a crystalline residue

which was recrystallized from acetone to give IIh as yellow prisms, mp 210—212° (decomp.). Yield 540 mg (6%). *Anal.* Calcd. for $C_{20}H_{26}ON_6S_3$: C, 51.94; H, 5.67; N, 18.17; S, 19.76. Found: C, 51.87; H, 5.65; N, 18.18; S, 19.57. UV λ_{max}^{EtOH} mμ (log ε): 325 (4.19). NMR ($CDCl_3$) τ: 2.49 (1H, s, pym-H), 3.90 (2H, broad, NH_2), 7.54 (3H, s, pym-CH_3), 8.14 (3H, s, C_4–CH_3). MS *m/e* (%): 438 (M^+, 34), 398 (M-S_2, 1), 347 (11), 137 (15), 326 (3), 122 (100), 84 (24), 43 (32).

Spiro{3-(2-methyl-4-aminopyrimidin-5-yl)methyl-3a-methyl-perhydrofuro[2,3-*d*]thiazole-2,4′-(1′,3′-dibenzylimidazolidine-2′,5′-dithione)} (IIi)——To a stirred suspension of thiamine hydrochloride (Id) (6.7 g) in DMF (50 ml) was added NEt_3 (6.0 g) at room temperature, then benzyl isothiocyanate (10 g) was added to the mixture. After having been stirred for 12 hr at 40—45°, the reaction mixture was concentrated under reduced pressure to give a brown residue which was extracted with $CHCl_3$ and the $CHCl_3$ extract was washed, dried and evaporated to leave an oily residue which was subjected to column chromatography. The first acetone eluate gave an unidentified oily mixture and the second fraction gave IIi as a pale yellow oil. Yield 620 mg (5.6%). UV λ_{max}^{EtOH} mμ (log ε): 321 (4.16). NMR ($CDCl_3$) τ: 7.54 (3H, s, pym-CH_3), 8.25 (3H, s, C_4–CH_3).

$NaBH_4$ Reduction of IIa——To a stirred suspension of IIa (400 mg) in MeOH (20 ml) was added $NaBH_4$ (200 mg) while cooling in an ice bath, then the mixture was stirred for 5 hr at room temperature. After evaporation of the reaction mixture under reduced pressure, the resulting residue was extracted with $CHCl_3$ and the $CHCl_3$ extract was washed, dried and concentrated to leave an oily residue which was subjected to column chromatography over neutral Al_2O_3 and eluted with $CHCl_3$. The first eluate gave recovered IIa (159 mg) and the second fraction gave III as pale yellow oil. Yield 59 mg. IR ν_{max}^{film} cm^{-1}: 3325 (OH), 1300 (C=S). UV λ_{max}^{EtOH} mμ: 322 (4.20). NMR ($CDCl_3$) τ: 6.44, 7.02 (each 3H, s, 2×N–CH_3), 8.79 (3H, d, J=6 cps, –CH–CH_3).

Hydrogen Peroxide Oxidation of IIa——IIa (980 mg) was dissolved in the mixture of $CHCl_3$ (10 ml) and AcOH (10 ml) and 35% H_2O_2 (2 ml) was added dropwise to the solution while cooling in an ice bath, then the reaction mixture was stirred for 4 hr at room temperature. After evaporation of the solvents under reduced pressure, the resulting crystalline residue was washed with cold MeOH and recrystallized from MeOH to give colorless plates, mp 150—151° (25 mg), which was identified as 1,3-dimethylparabanic acid by mixed mp and IR comparison with the authentic sample.

Catalytic Hydrogenation of IIa——IIa (400 mg) was hydrogenated with 2 ml of $PdCl_2$ (50 mg Pd/ml) and charcoal (200 mg) in EtOH (10 ml) for 8 hr at room temperature (28 ml of H_2 was absorbed). After filtration, the reaction mixture was concentrated under reduced pressure to leave a brown oily residue which was extracted with $CHCl_3$. From the $CHCl_3$ insoluble part, after concentration to dryness, benzylamine hydrochloride was obtained (21 mg). The $CHCl_3$ extract was washed, dried and concentrated to give a brown oil which was subjected to column chromatography over neutral Al_2O_3 and eluted with $CHCl_3$. The first eluate gave an unidentified oily substance and the second fraction gave V which was recrystallized from *n*-hexane to give colorless needles, mp 95—96°. Yield 63 mg. *Anal.* Calcd. for $C_5H_8ON_2S$: C, 41.66; H, 5.59; N, 19.44; S, 22.20. Found: C, 41.37; H, 5.60; N, 19.26; S, 22.42. V was identified as 1,3-dimethyl-2-thiohydantoin by IR comparison with the authentic sample.

N,N′-Dimethylpseudodithiohydantoin (VIII)——To a solution of 2-methylimino-3-methylthiazolidine-4-one (VII) (mp 67—68°, IR ν_{max}^{Nujol} cm^{-1}: 1722 (C=O), 1657 (C=N), obtained from N,N′-dimethylthiourea and chloroacetyl chloride in the presence of NaOH) (120 mg) in abs. pyridine (10 ml) was added P_2S_5 (200 mg) and refluxed for 6 hr. After evaporation of the reaction mixture under reduced pressure, the residue was subjected to column chromatography and eluted with AcOEt. From the first eluate VIII was obtained as brown crystalline powder, mp 105—106°. Yield 41 mg (30%). *Anal.* Calcd. for $C_5H_8N_2S_2$: C, 37.50; H, 5.04; N, 17.50; S, 39.97. Found: C, 37.43; H, 4.96; N, 17.57; S, 38.64. IR ν_{max}^{Nujol} cm^{-1}: 1650 (C=N), 1292 (C=S). UV λ_{max}^{EtOH} mμ (log ε): 290.5 (4.16). NMR ($CDCl_3$) τ: 5.67 (2H, s, –S–CH_2–CS–), 6.47, 6.75 (each, 3H, s, 2×N–CH_3).

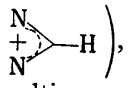
2-Phenyl-4,6-dimethyldihydroimidazo[4,5-*d*]thiazole-5-thione (XIa)——IIa (250 mg) was dissolved in AcOH (5 ml) and the solution was heated for 8 hr at 100°, then it was allowed to stand overnight at room temperature. After evaporation of the reaction mixture under reduced pressure, the crystalline residue was washed with MeOH and recrystallized from hot MeOH to give XIa as brown-yellow prisms, mp 201—202°. Yield 108 mg (63%). *Anal.* Calcd. for $C_{12}H_{11}N_3S_2$: C, 55.17; H, 4.24; N, 16.09; S, 24.50. Found: C, 55.08; H, 4.35; N, 16.13; S, 24.25. UV λ_{max}^{EtOH} mμ (log ε): 249 (4.07), 280 (4.15), 375 (4.32). NMR ($CDCl_3$) τ: 6.16, 6.23 (each 3H, s, 2×N–CH_3).

2-(4-Nitrophenyl)-4,6-dimethyldihydroimidazo[4,5-*d*]thiazole-5-thione (XIb)——IIc (200 mg) was dissolved in AcOH (5 ml) and the solution was heated for 6 hr at 90—100°, then the reaction mixture was allowed to stand overnight at room temperature. After evaporation of AcOH under reduced pressure, the residue was subjected to column chromatography over neutral Al_2O_3 and eluted with C_6H_6 to give XIb which was recrystallized from EtOH as red prisms, mp>270°. Yield 62 mg (42%). *Anal.* Calcd. for $C_{12}H_{10}O_2N_4S_2$: C, 47.06; H, 3.29; N, 18.30; S, 20.09. Found: C, 47.05; H, 3.79; N, 17.84; S, 19.87. UV λ_{max}^{EtOH} mμ (log ε): 282.5 (4.17), 442 (4.26). NMR ($CDCl_3$) τ: 6.12, 6.17 (each 3H, s, 2×N–CH_3).

2-(2-Methyl-4-aminopyrimidin-5-yl)-4,6-dimethyldihydroimidazo[4,5-*d*]thiazole-5-thione (XIc)——IIf (250 mg) was dissolved in AcOH (10 ml) and the solution was heated for 4 hr at 90—95°. After standing for two days at room temperature, the reaction mixture was concentrated under reduced pressure and the resulting crystalline residue was washed with acetone, collected and recrystallized from MeOH–AcOH (1:1) to give XIc as yellow prisms, mp >270°. Yield 90 mg (50%). *Anal.* Calcd. for $C_{11}H_{12}N_6S_2 \cdot 1/3H_2O$: C, 44.02; H, 4.84; N, 28.01; S, 21.33. Found: C, 43.95; H, 4.00; N, 27.54; S, 21.87. UV λ_{max}^{EtOH} mμ (log ε): 225 (4.11), 283 (4.15), 400 (4.31). NMR (CF_3COOH) τ: 1.35 (1H, s, pym-H), 6.05, 6.15 (each 3H, s, 2×N–CH_3), 7.28 (3H, s, pym-CH_3).

2-(2-Methyl-4-aminopyrimidin-5-yl)-4,6-diallyldihydroimidazo[4,5-*d*]thiazole-5-thione (XId)——IIh (250 mg) was dissolved in AcOH (10 ml) and the solution was heated for 8 hr at 90—100°, then it was allowed to stand overnight at room temperature. After evaporation of AcOH, the resulting crystalline residue was washed with MeOH and collected to give XId as yellow crystals, mp 259—260°. Yield 93 mg (50%). *Anal.* Calcd. for $C_{15}H_{16}N_6S_2$: C, 52.32; H, 4.68; N, 24.41; S, 18.59. Found: C, 52.22; H, 4.80; N, 24.06; S, 18.35. UV λ_{max}^{EtOH} mμ (log ε): 225 (4.09), 287 (4.08), 399 (4.25). NMR ($CDCl_3$) τ: 1.45 (1H, s, pym-H), 3.05 (2H, broad, NH_2), 7.45 (3H, s, pym-CH_3).

Treatment of XIa with Hydrochloric Acid——XIa (780 mg) was refluxed in 20% HCl (15 ml) for 3 days, then the resulting insoluble substance was filtered. The filtrate was extracted with $CHCl_3$, and from the $CHCl_3$ extract after washing, drying and evaporating benzoic acid (20 mg) was obtained. The acid layer was then concentrated under reduced pressure to leave a crystalline residue which was dissolved in MeOH and insoluble NH_4Cl was removed by filtration. The MeOH part after evaporation was dissolved in H_2O and alkalized by 10% NaOH then extracted with $CHCl_3$. The $CHCl_3$ extract was washed, dried and evaporated to leave a crystalline residue which was recrystallized from *n*-hexane to give crude XII (12 mg) as colorless prisms, mp 101—102°. (Further purification of XII was not attempted owing to insufficient quantity). IR ν_{max}^{Nujol} cm^{-1}: 3290 (NH). To a solution of crude XII (7 mg) in $CHCl_3$ (3 ml) was added two drops of $CSCl_2$, and the solution was allowed to stand overnight at room temperature. On the TLC (silica-gel) plate, the reaction mixture showed a spot which exhibited a pink–red coloring characteristic of XIa with Dragendorff's reagent. By the preparative TLC method, a trace quantity of the product was isolated and identified with XIa by the comparison of UV spectra.

Hydrogen Peroxide Oxidation of XIa——To a solution of XIa (150 mg) in AcOH (10 ml), few drops of 35% H_2O_2 was added with stirring in an ice bath, then the mixture was stirred for 20 min at room temperature. After evaporation of AcOH under reduced pressure, the resulting crystalline residue was washed with MeOH containing ether and collected to give XIII as colorless crystalline powder, mp 215—220°. Yield 92 mg (49%). *Anal.* Calcd. for $C_{12}H_{13}O_4N_3S_2 \cdot 2H_2O$: C, 39.67; H, 4.72; N, 11.57; S, 17.62. Found: C, 39.25; H, 3.92; N, 11.50; S, 17.73. UV λ_{max}^{EtOH} mμ (log ε): 227 (3.93), 240 (3.88), 308 (4.37). NMR (D_2O) τ: 1.33 (1H, s, ), 6.01 (6H, s, 2×N–CH_3). To a solution of XIII (50 mg) in H_2O (5 ml), 10% NaOH was added and resulting precipitates were extracted with $CHCl_3$. The $CHCl_3$ extract after washing, drying and evaporating gave a crystalline residue which was recrystallized from *n*-hexane–ether (1:1) to give pale yellow prisms, mp 258—260° (decomp.). Yield 32 mg. *Anal.* Calcd. for $C_{12}H_{13}ON_3S$: C, 58.29; H, 5.30; N, 17.00; S, 12.93. Found: C, 58.04; H, 5.18; N, 17.10; S, 12.11. IR ν_{max}^{Nujol} cm^{-1}: 3380 (NH), 1668 (CO). The NMR spectrum ($CDCl_3$) of the product showed two N–CHO and two N–CH_3 signals at 1.75, 1.90 τ and 6.53, 6.78 τ in equal intensities respectively, and a broad signal at 7.05 τ corresponding to two $NHCH_3$ groups. These data indicate that the product is the isomeric mixture of XIV and XV in the ratio of *ca.* 1:1.

Mild Treatment of IIf with AcOH——To a solution of IIf (154 mg) in $CHCl_3$ (10 ml), AcOH (two drops) was added and the solution was allowed to stand for 96 hr at room temperature. After evaporation of the reaction mixture under reduced pressure, the residue was subjected to column chromatography over neutral Al_2O_3 and eluted with AcOEt. From the first eluate IIf (50 mg) was recovered, and from the second eluate XVI was obtained. Recrystallization of XVI affored pale yellow prisms, mp 240—241° (decomp.). Yield 50 mg (35.4%). *Anal.* Calcd. for $C_{16}H_{20}ON_6S_2$: C, 51.06; H, 5.36; N, 22.33; S, 17.00. Found: C, 50.36; H, 5.29; N, 22.07; S, 16.76. IR ν_{max}^{Nujol} cm^{-1}: 3220 (OH), 1060 (C–O). UV λ_{max}^{EtOH} mμ :224, 280, 317, NMR ($CDCl_3$) τ: 1.78 (1H, s, pym-H), 6.02 (2H, s, pym-CH_2), 6.43 and 7.54 (each 2H, t, =C–CH_2CH_2–O), 6.41 and 6.85 (each 3H, s, 2×N–CH_3), 7.29 (3H, s, pym-CH_3), 8.07 (3H, s, =C–CH_3), 8.30 (1H, broad, OH). XVI (16 mg) was acetylated in pyridine (5 ml) containing Ac_2O (3 ml) at room temperature for 3 hr. After evaporation under reduced pressure, the reaction mixture was extracted with $CHCl_3$, and the $CHCl_3$ extract was washed, dried and evaporated to leave XVII as a pale yellow oil. Yield 15 mg (84.3%). IR ν_{max}^{film} cm^{-1}: 1740, 1230 ($OCOCH_3$). UV λ_{max}^{EtOH} mμ: 224, 280, 317. NMR ($CDCl_3$) τ: 1.82 (1H, s, pym-H), 6.03 (2H, s, pym-CH_2), 6.05 and 7.43 (each, 2H, t, =C–CH_2CH_2–OCO), 6.43 and 6.90 (each 3H, s, 2×N–CH_3), 7.30 (3H, s, pym-CH_3), 8.02 (3H, s, $OCOCH_3$), 8.10 (3H, s, =C–CH_3).

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