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# Studies on Pyrimidine Derivatives and Related Compounds. LXX.[1] A Novel Reaction of Thiamine Anhydride[2]

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Reaction of thiamine Na salt with COS gave the compound having 1,2-dithiolane ring (IV). This compound was readily obtained from the reaction of thiamine anhydride (I) and $H_2S$ in DMF solution. Reaction of I with $D_2S$ gave deuterium incorporated derivatives and the mechanism for the formation of IV was suggested.

Although thiamine anhydride (I) is well known as a product resulting from thiamine and its derivatives by various reactions,[4] no reports have yet appeared regarding its reactivity. Reported here is the first example of a reaction of I, ring expansion by hydrogene sulfide to give 1,2-dithiolane derivatives (IV).

In a previous communication,[5] it was shown that thiamine sodium salt (II) reacted with carbon disulfide followed by the action of alkyl halide to give dithioalkoxycarbonyl thiamine (III). Here, carbon oxysulfide instead of carbon disulfide was allowed to react with II in dimethyl formamide (DMF) and the compound IV was isolated in 22% yield. Compound IV, mp 144—147°, has the molecular formula $C_{12}H_{18}ON_4S_2$, *i.e.*, $H_2S$ more than I. Therefore, I was allowed to react with hydrogen sulfide in DMF for 5 days at room temperature and the same product, IV, was obtained in 91% yield. This reaction proceeded in the dark and no effect on the reaction rate was observed by light or addition of benzoylperoxide, indicating that the reaction proceeds by an ionic process. Next, a 0.2 equimolar amount of piperidine was added in this reaction mixture and the reaction period was found to be shortened. When DMSO, instead of DMF, was used as a solvent, sulfur separated from the reaction mixture and the yield of IV was as low as 27%. Addition of *p*-toluenesulfonic acid in DMF solution also inhibited the reaction. In contrast, when isomeric thiamine anhydride (I')[6-8] was treated with hydrogen sulfide in DMF, no reaction occurred and the starting material was recovered.

The ultraviolet (UV) spectrum of IV in EtOH gives absorption bands at 237, 278, and 330 mμ (log ε 3.92, 3.69, 2.55). The nuclear magnetic resonance (NMR) spectrum[9] of IV (Fig. 1)

1) Part LXIX: A. Takamizawa, K. Hirai, T. Ishiba, and I. Makino, *Chem. Pharm. Bull.* (Tokyo), **19**, 759 (1971).
2) A part of this work has appeared in a preliminary form: A. Takamizawa, K. Hirai, and T. Ishiba, *Tetrahedron Letters*, **1970**, 441.
3) Location: *Fukushima-ku, Osaka.*
4) H. Yonemoto, *Yakugaku Zasshi*, **77**, 1128 (1957); C. Kawasaki, I. Tomita, and T. Motoyama, *Vitamins* (Kyoto), **13**, 57 (1957); C. Kawasaki and I. Tomita, *Yakugaku Zasshi*, **78**, 1160, 1163 (1958); **79**, 295 (1959).
5) A. Takamizawa, K. Hirai, and T. Ishiba, *Chem. Pharm. Bull.* (Tokyo), **17**, 2299 (1969).
6) A. Takamizawa and S. Sakai, *Vitamins* (Kyoto), **38**, 222 (1968).
7) Y. Koyama, H. Nakai, A. Takamizawa, and K. Hirai, The 23rd Annual Meeting of Chemical Society of Japan, Tokyo, April 1970.
8) K. Kamitani, K. Wada, M. Nishikawa, H. Asakawa, and H. Hirano, *Takeda Kenkyusho Nempo*, **29**, 394 (1970).
9) NMR spectra were taken with a Varian A-60 spectrometer in $CDCl_3$ containing TMS as an internal reference. Chemical shifts are given as τ values.

suggests the presence of a $CH_3$-CH< system ($\tau$ 8.63, 3H-doublet, $J$=6.5 Hz) and a 1,2-dithiolane ring, showing a similar pattern to lipoic acid which has 1,2-dithiolane ring; in addition to the (4-amino-2-methyl-5-pyrimidinyl) methyl group (pyrimidine 2-$CH_3$,$\tau$ 7.53,3H-singlet; bridged methylene, $\tau$ 5.17, 5.42, 5.70, 5.95, AB quartet; amino, $\tau$ 3.90, deuterium exchangeable 2H-broad singlet; N-CHO, pyrimidine $C_6$-H, $\tau$ 1.98, 1.70, 1H-singlets).

The mass spectrum[10] of IV (Fig. 2) exhibits significant peaks at $m/e$ values of 105, 122, 132, and 193 in addition to the molecular ion peak (298). $NaBH_4$ reduction of IV followed by the action of benzyl chloride afforded S,S'-dibenzyl sulfide (V) as an oil (NMR: 2X $PhC\underline{H}_2$: $\tau$ 6.42, 6.35, 2H-singlets; $C_{26}H_{32}ON_4S_2$; $m/e$ ($M^+$) 480).

The above observations suggest the structure N-[4-amino-2-methyl-5-pyrimidinyl)methyl]-N-[1-(1,2-dithiolan-3-yl)ethyl] formamide for the compound IV. In an attempt to clarify the reaction mechanism, reaction of I in DMF was carried out with deuterium sulfide, instead of hydrogen sulfide. The compound VI, mp 138—139°, was obtained in a good yield and a comparison of the NMR spectra of IV and VI exhibited the following differences (Fig. 1): the 3H-doublet at $\tau$ 8.63 changed into a 3H-singlet at $\tau$ 8.67, indicating a $CH_3$-CD system; the 2H-multiplet around $\tau$ 8.0, due to C-2 methylene, disappeared; the 2H-multiplet centered at $\tau$ 6.82, due to C-1 methylene, changed into a broad 2H singlet at $\tau$ 6.87; and the 2H-multiplet centered at $\tau$ 6.35, due to C-3 and C-4 methines, changed into a broad 0.5H-singlet at $\tau$ 6.35. These facts suggest that the hydrogens at C-2 and C-4 positions were exchanged by

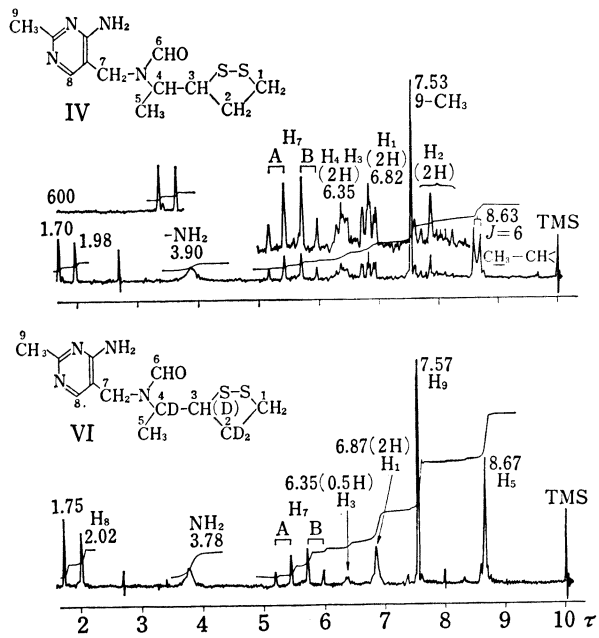


Fig. 1. NMR Spectra of IV and VI in $CDCl_3$

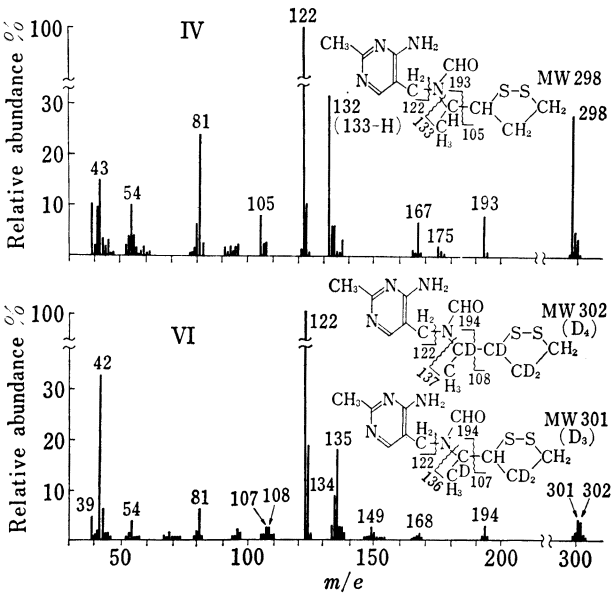


Fig. 2. Mass Spectra of IV and VI

10) Mass spectra were taken with a Hitachi RMU-6E mass spectrometer using direct inlet system with the ionizing energy at 70 eV and the ionizing current at 80 $\mu$A.

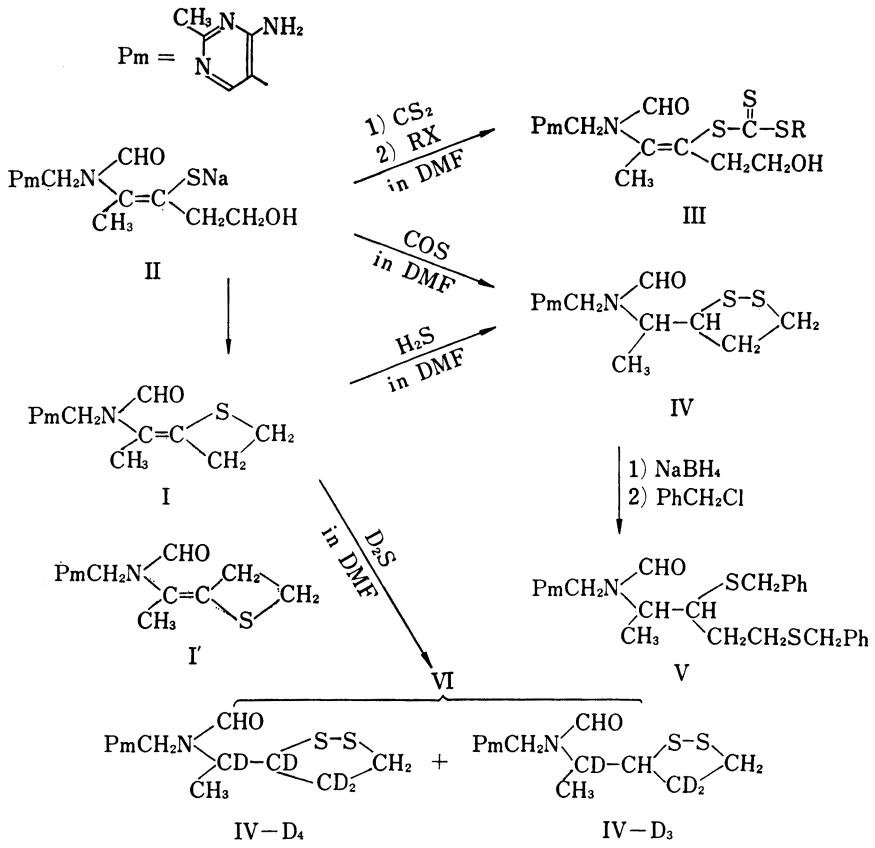


Chart 1

deuterium and that the hydrogen at C-3 positjon was half deuterated. Thus, compound VI was a 1:1 mixture of IV-$D_3$ (three deuteriums incorporated) and IV-$D_4$ (four deuteriums incorporated). The mass spectrum of VI (Fig. 2) strongly supports the structure. Molecular ion peaks appeared at *m/e* values of 301 and 302 corresponding to IV-$D_3$ and IV-$D_4$ in about 1:1 ratio. Formation of other fragments at *m/e* values of 194, 135, 122, 108, and 107 can be rationalized as indicated at Fig. 2.

Previously, Yurugi, *et al.*[11] reported the formafon of a 5-membered ring disulfide from the thiethane ring by heating with sulfur in the synthesis of lipoic acid. However, our reaction proceeded smoothly at a room temperature and a reasonable mechanism that accounts for all the above data is proposed as a base induced elimination-addifon reaction, as shown in Chart 2. Deuterium sulfide adds to the vinyl group in VII which was derived by the proton abstraction. Repeated elimination and addition reaction gives the compound deuterated at $C_2$-methylene in deuteromercapto ethyl group (VIII). Tautomerism of thiol-thioketone allows attack by a mercapto group to the sulfur atom of the thioketone giving the 1,2-dithiolane compound IV. Following Opitz's consideration[12] that a thioketone has a polarizing direction as $>\overset{\delta-}{C}—\overset{\delta+}{S}$, a mercaptan sulfur (soft base)[13] bonds with the sulfur of a thioketone (soft acid)[13] giving the disulfide linkage.

11) S. Yurugi, H. Yonemitsu, T. Fushimi, and M. Numata, *Yakugaku Zasshi*, **80**, 1691 (1960).
12) G. Opitz, *Angew. Chem. Intern. Ed. Engl.*, **6**, 107 (1967).
13) B. Saville, *Angew. Chem. Intern. Ed. Engl.*, **6**, 928 (1967).

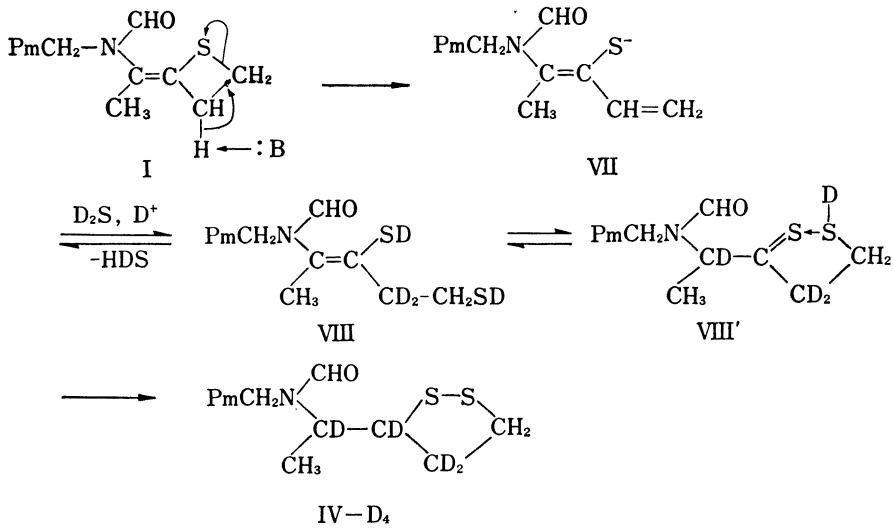

Chart 2

Half deuteration of C-3-H might be due to half hydrogen exchange at the acidic C-3 position on $H_2O$ treatment after the deuteration reaction. Of particular interest is the fact that thiamine anhydride, which has been considered to be quite stable, displayed a very high reactivity. Our recent inspection of the structure of thiamine anhydride (I) and its isomer (I') by X-ray crystallographic analyses[7] well explains its reactivity. The thietanylidene ring in I is distored suggesting that ring opening would release the strain. On the other hand, the thietanylidene ring in isomeric I' is not distored being almost complete plane.[7,8] Thus, I' is quite stable compared with I.

The fact that the reaction of thiamine sodium salt (II) with carbon oxysulfide also gave the same product IV suggests that thiamine anhydride is initially formed by a route such as that shown in Chart 3, this then follows the sequence in Chart 2 to yield IV.

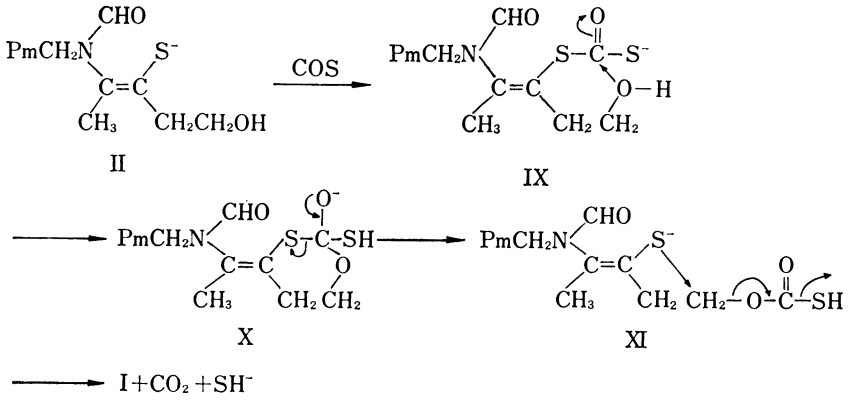

Chart 3

**Experimental**[14]

**N-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-N-[1-(1,2-dithiolan-3-yl)ethyl]formamide (IV)**——a) To a solution of 4.5 g of II in 40 ml of DMF, 2.2 g of COS was added in ice-cooling. After stirring for 3 hr under ice-

14) All melting points are uncorrected.

cooling, allowed to stand overnight at room temp. The reaction mixture was evaporated *in vacuo*, the residue was extracted with $CHCl_3$, the $CHCl_3$ extract was washed with $H_2O$, dried over anhyd. $Na_2SO_4$, evaporated, and chromatographed on neutral $Al_2O_3$ with AcOEt to give 0.55 g of crystals. Recrystallization from AcOEt gave pale yellow prisms, mp 144—147°. *Anal.* Calcd. for $C_{12}H_{18}ON_4S_2$: C, 48.31; H, 6.08; O, 5.36; N, 18.78; S, 21.46. mol. wt., 298.3. Found: C, 48.00; H, 6.12; O, 5.36; N, 18.42; S, 21.33. Mol. wt., 290 ($CHCl_3$). Mass Spectrum *m/e*: 298 ($M^+$), 193 ($M^+-105$), 132, 122 (base), 105. UV $\lambda_{max}^{EtOH}$ m$\mu$ (log $\varepsilon$): 237, 278, 330 (3.92, 3.69, 2.55). NMR $\tau$: 8.63 (3H, d, $J$=6.5 Hz, $CH_3$–CH$\langle$), 7.53 (3H, s, Pm–2–$CH_3$), 5.95, 5.70, 5.42, 5.17 (2H, AB q, Pm–$CH_2$–N), 3.90 (2H, b, $NH_2$), 1.98 (1H, s), 1.70 (1H, s, Pm-6-H, CHO).

b) To a solution of 1.41 g of I in 10 ml of DMF was saturated with $H_2S$ under ice–cooling. After standing at room temp. for 5 days in a sealed tube, reaction mixture was concentrated *in vacuo*. The residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed wih $H_2O$, dried over anhyd. $Na_2SO_4$, evaporated, and the residue was treated with ether–AcOEt to give 1.21 g (91%) of IV.

c) To a solution of 1.5 g of I and 0.1 g of piperidine in 10 ml of DMF was saturated with $H_2S$ under ice–cooling. After standing at room temp. for 17 hr in a sealed tube, treated as above a) to give 1.15 g (77%) of IV.

d) To a solution of 1.5 g of I in 10 ml of DMSO was saturated with $H_2S$ under ice–cooling. After standing at room temp., separated sulfur (0.25 g) was removed. The filtrate was concentrated *in vacuo*, and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with $H_2O$, dried over anhyd. $Na_2SO_4$, and evaporated. The residue was chromatographed on silica gel with acetone to give 0.4 g (27%) of IV.

**Reaction of I with $H_2S$ in the Presence of *p*-Toluenesulfonic Acid**——To a solution of 1.5 g of I and 0.19 g of *p*-toluenesulfonic acid in 15 ml of DMF was saturated with $H_2S$ under ice–cooling. After standing for 5 days at room temp., the reaction mixture was concentrated *in vacuo*, and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with $H_2O$, dried over anhyd. $Na_2SO_4$, and evaporated to recover 1.3 g of I.

**Reaction of Isothiamine Anhydride (I′) with $H_2S$**——To a solution of 0.2 g of I′ in 8 ml of DMF was saturated with $H_2S$ under ice–cooling. After standing for 5 days at room temp., the reaction mixture was concentrated *in vacuo*, and the residue was washed with ether to recover 0.16 g of I′.

**N-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-N-[1-(1,3-dibenzylthiopropan-1-yl)ethyl]formamide (V)**—— To a solution of 1.0 g of IV in 20 ml of MeOH was added dropwise a solution of 1.0 g of $NaBH_4$ in 10 ml of EtOH under ice–cooling. After stirring for 30 min, 8 g of $PhCH_2Cl$ was added dropwise, and refluxed for 1 hr. The reaction mixture was concentrated *in vacuo*, and the residue was chromatographed on silica gel with acetone to give 1.05 g of oil. *Anal.* Calcd. for $C_{26}H_{32}ON_4S_2$: C, 64.98; H, 6.71; N, 11.66; S, 13.32. Found: C, 64.69; H, 6.84; N, 11.14; S. 12.89. UV $\lambda_{max}^{EtOH}$ m$\mu$ (log $\varepsilon$): 234, 276.5 (4.01, 3.70). Mass Spectrum *m/e*: 480 ($M^+$). NMR $\tau$: 8.88 (3H, d, $J$=7 Hz, $CH_3$–CH$\langle$), 7.55 (3H, s, Pm–2–$CH_3$), 6.42 (2H, s, Ph$CH_2$–), 6.35 (2H, s, Ph$CH_2$), 6.12, 5.92, 5.80, 5.55 (2H, AB q, Pm–$CH_2$–N), 3.80 (2H, b, $NH_2$), 2.23 (1H, s, CHO), 1.88 (1H, s, Pm–6–H).

**Reaction of I with $D_2S$**——To a solution of 1.32 g of I in 15 ml of DMF was added $D_2S$ prepared from 6.5 g of $P_4S_{10}$ and 4.2 g of $D_2O$ under ice–cooling. After standing for 6 days at room temp., treated as the case of $H_2S$ to give 1.06 g of crystals of mp 138—139°. Mass Spectrum *m/e*: 302, 301 ($M^+$), 194, 135, 134, 122 (base peak), 108, 107. NMR $\tau$: 8.67 (3H, s, $CH_3$–CD$\langle$), 7.57 (3H, s, Pm–2–$CH_3$), 6.87 (2H, s, S–$CH_2$–$CD_2$), 6.35 (0.5H, b), 6.00, 5.73, 5.47, 5.22 (2H, AB q, Pm–$CH_2$N), 3.78 (2H, b, $NH_2$), 2.02 (1H, s), 1.75 (1H, s, CHO, pm–6–H).

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