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Studies on Heterocyclic Ketenethioacetal Derivatives. VII.[1] Reactions of 3-Ethyl-5-bis(methylthio)methylene-2-thioxothiazol-4(5H)-one

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3-Ethyl-5-bis(methylthio)methylene-2-thioxothiazol-4(5H)one (**2**), which was prepared by the reaction of 3-ethylrhodanine with carbon disulfide in the presence of sodium hydroxide in dimethyl sulfoxide, reacted with nucleophilic reagents such as amines or active methylenes to give the corresponding replacement products of one or two methylthio groups in good yield.

In our previous paper, we have reported the synthesis and the reaction of 3-bis(methylthio)methylenoxindole,[3] 9-methyl-4-bis(methylthio)methylene-1,3-dioxo-1,2,3,4-tetrahydro-β-carboline,[4] 4-bis(methylthio)methylene-1,3-dioxo-1,2,3,4-tetrahydroisoquinolines,[5] 3-bis(methylthio)methylene-1,4-dioxo-1,2,3,4-tetrahydroisoquinolines,[6] and 2-bis(methylthio)-methylenebenzothiophen-3(2H)-one.[1] It was found that the methylthio group of these bis(methylthio)methylene derivatives was substituted with strong nucleophilic reagents such as amines, active methylenes, and cyano anion to give the corresponding substituted products.[7] These bis(methylthio) methylene derivatives as electrophiles would be very substantial intermediate compounds.

In the present paper, we report that the synthesis and the reaction of 3-ethyl-5-bis(methylthio)methylene-2-thioxothiazol-4(5H)-one (**2**). It is well known that active methylene compounds react with carbon disulfide in the presence of some base.[8] In a similar, it was found that carbon disulfide react also with active methylene of heterocyclic compounds.[9] Edwards reported the synthesis of 2-thioxo-3-methyl-5-bis(methylthio)methylenethiazol-4(5H)-one by the reaction of 3-methylrhodanine with carbon disulfide in the presence of metallic sodium as base in ether, followed by the treatment with methyl iodide, but he did not examine a reactivity of the methylthio group.[9a] We have reported the available synthetic methods of bis(methylthio)methylene derivatives as followed: the reaction of heterocyclic compounds with carbon disulfide and followed by the treatment with dimethyl sulfate in the presence of sodium hydroxide in dimethyl sulfoxide gave heterocyclic ketenethioacetal derivatives with good results. This method gave also the best results in the case of 3-ethylrhodanine. Namely,

1) Part VI: Y. Tominaga, Y. Morita, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **23**, 2390 (1975).
2) Location: *1-14 Bunkyo-machi, Nagasaki, 852, Japan.*
3) G. Kobayashi, S. Furukawa, and Y. Matsuda, *Yakugaku Zasshi*, **86**, 1152 (1966).
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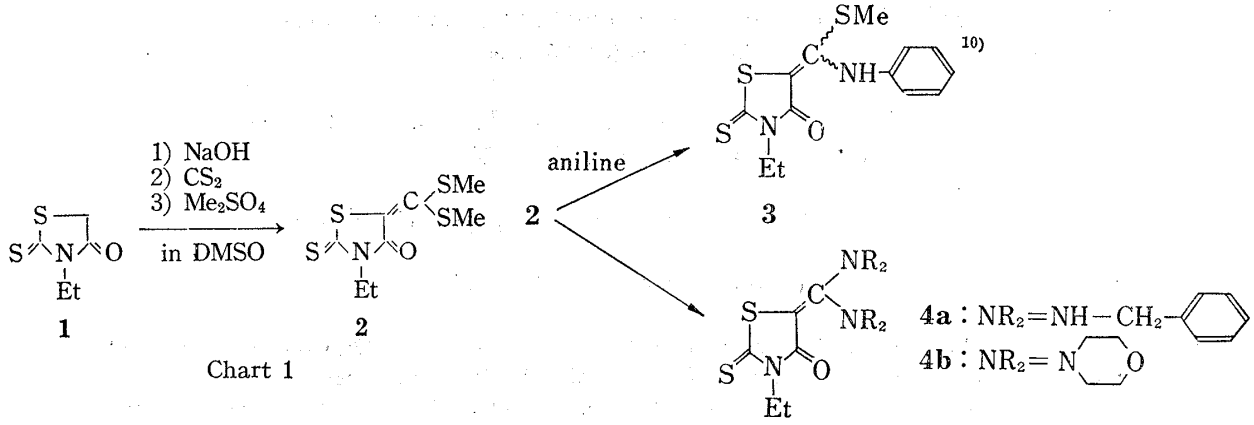
9) *a*) H.D. Edwards and J.D. Kendall, *Chem. Abst.*, **45**, 4052h (1951): *b*) P. Papini and M. Ridi, *Gazz. Chem. Ital.*, **89**, 526 (1959): *c*) P. Papini and G. Auzzi, *Gazz. Chem. Ital.*, **96**, 125, 430 (1966): *d*) P. Rioult and J. Vialle, *Bull. Soc. Chim. France*, **1965**, 3315: *e*) R. Philipe and V. Jean, *Bull. Soc. Chim. France*, **1965**, 3312: *f*) G. Matolcsy, P. Sohar, and B. Bordas, *Chem. Ber.*, **104**, 1155 (1971).

the reaction 3-ethylrhodanine with carbon disulfide in the presence of sodium hydroxide in dimethyl sulfoxide gave 3-ethyl-5-bis(methylthio)methylene-2-thioxothiazol-4(5H)-one (**2**) as yellow needles of mp 109° in 85% yield.



1 **2** **3** **4a,b**

Chart 1 Chart 2

The active ketenethioacetals react easily with amines under the refluxing or the stirring at room temperature in methanol or ethanol to form the corresponding amine derivatives with good results. However, **2** did not react with 1 mole amine (aniline, benzylamine, morpholine) under the refluxing in ethanol. When a mixture of **2** and amine (aniline, benzylamine, morpholine) was heated at 150° for 1 hr, substitution reactions occurred between methylthio group in this ketenethioacetal and those amines to give mono- and di-amine derivatives (**3**, **4a**, **b**).

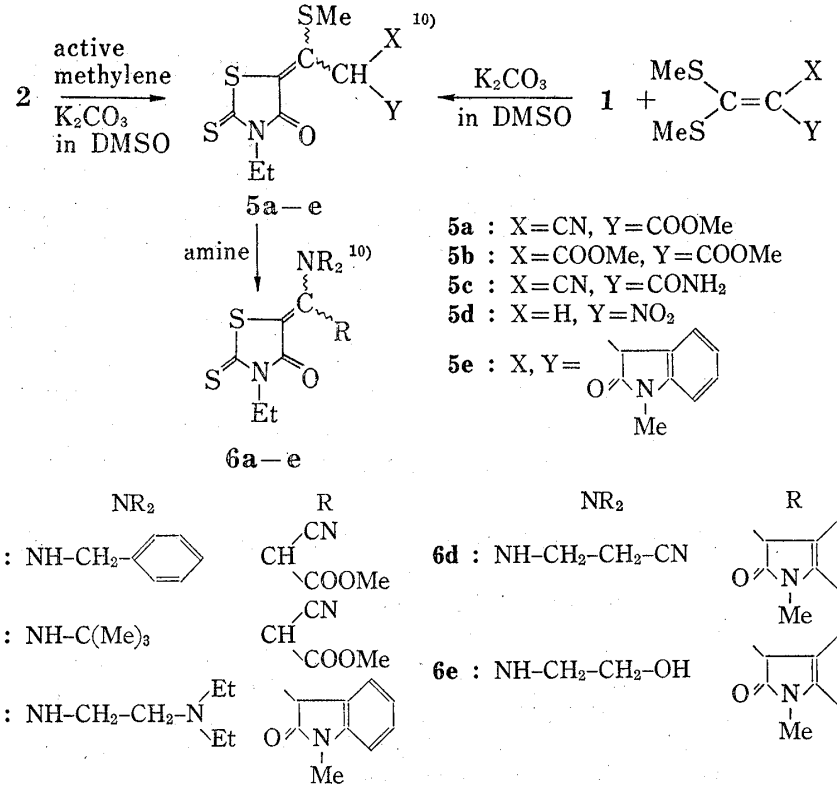


Chart 3

10) Configuration of geometrical isomers of **3**, **5**, and **6** in Chart 2 and 3 were not elucidated.

Next, the reaction of **2** with active methylene compound (methyl cyanoacetate, dimethyl malonate, cyanoacetamide, nitromethane, 1-methyloxindole) in the presence of potassium carbonate in dimethyl sulfoxide at room temperature afforded the corresponding replaced products of one methylthio group of **2** in good yields. These substituted products of methylthio group with active methylenes were also obtained by the reaction between **1** and ketenethioacetal (methyl 2-cyano-3,3-bis(methylthio)acrylate, methyl 2-methoxycarbonyl-3,3-bis(methylthio)acrylate, 2-cyano-3,3-bis(methylthio)acrylamide, 1-nitro-2,2-bis(methylthio)ethylene, 1-methyl-3-bis(methylthio)methylenoxindole). Since, **5a**—**e** have an active methylthio group, these compounds are useful synthetic intermediate of rhodanine derivatives. For example, the reaction of **5a** and **e** with amine (benzylamine, *t*-butylamine, diethylaminoethylamine, *β*-aminopropionitrile, ethanolamine) afforded the amine deirvatives, **6a**—**e** which were replaced products of methylthio group of compound **5**.

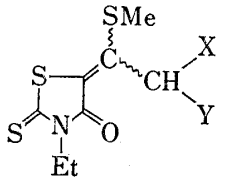
Experimental

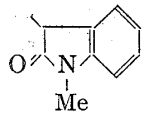
All melting points were determined in a capillary and are uncorrected. The infrared (IR) spectra were recorded in KBr-pellets on a Nippon-bunko IRA-2 spectrometer. The ultraviolet (UV) absorption spectra were determined on a Hitachi EPS-2 spectrometer in 95% EtOH. The nuclear magnetic resonance (NMR) spectra were obtained using a JNM-PS-100 (100 Mcps) spectrometer with tetramethylsilane as an internal standard unless otherwise indicated.

3-Ethyl-5-bis(methylthio)methylene-2-thioxothiazol-4(5H)-one (**2**)——To a solution of 16.1 g of **1** in 100 ml of Me_2SO, conc. NaOH aquation (10 g of NaOH in 30 ml of H_2O) was added under stirring and 7.6 g of CS_2 was then added slowly dropwise under stirring over a period of 30 min while the temperature of the mixture was maintained at 5—10°. The reaction mixture was stirred for 1 hr and 35 g of Me_2SO_4 was added dropwise with cooling over a period of 20 min. The mixture was stirred for 2 hr and poured into ice-water. The precipitate was collected by filtration, washed with 5% NaOH and with H_2O, and recrystallized from benzene to give **2** as yellow needles of mp 109° in 85% yield. *Anal.* Calcd. for $C_8H_{11}ONS_4$: C, 36.20; H, 4.18; N, 5.28; S, 48.32. Found: C, 36.15; H, 4.17; N, 5.23; S, 48.45. IR (KBr): 1680 cm^{-1} (C=O). UV λ_{max}^{EtOH} nm (log ε): 290 (3.98), 320 (3.86), 420 (4.42). NMR (in $CDCl_3$) ppm: 2.58, 2.68 (SCH_3).

Reaction of 2 with Aniline——A mixture of 1.3 g of **2** and 2 g of aniline was heated at 150° for 30 min. After cooling, the mixture was washed with petroleum benzine and the residue was recrystallized from MeOH

TABLE I.



	X	Y	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	UV λ_{max}^{EtOH} nm (log ε)	IR(KBr) cm^{-1}
5a	CN	COOMe	80	112	$C_{11}H_{12}O_3N_2S_3$	41.75 (41.62)	3.82 (3.81)	8.85 (8.79)	242(4.52) 282(4.17) 315(4.12) 475(4.36)	ν_{CN} 2220 $\nu_{C=O}$ 1740 1680
5b	COOMe	COOMe	50	110	$C_{12}H_{15}O_5NS_3$	41.24 (41.56)	4.33 (4.22)	4.01 (4.35)	294(3.90) 384(4.34)	$\nu_{C=O}$ 1762 1690
5c	CN	$CONH_2$	62	188	$C_{10}H_{11}O_2N_3S_3$	39.85 (39.82)	3.68 (3.64)	13.94 (14.21)	292(3.95) 384(4.10) 479(4.29)	ν_{CN} 2250 $\nu_{C=O}$ 1675
5d	H	NO_2	85	132	$C_8H_{10}O_3N_2S_3$	34.54 (34.62)	3.62 (3.58)	10.07 (10.02)	387(4.46)	$\nu_{C=O}$ 1685 ν_{NO_2} 1540
5e			70	136	$C_{16}H_{16}O_2N_2S_3$	52.72 (52.18)	4.42 (4.50)	7.69 (7.20)	258(4.14) 289(4.09) 386(4.33) 525(3.74)	$\nu_{C=O}$ 1685 1705

to give mono amine derivative, **3**, as yellow needles of mp 109° in 53% yield. *Anal.* Calcd. for $C_{12}H_{14}ON_2S_3$: C, 48.29; H, 4.73; N, 9.39. Found: C, 48.01, H, 4.82; N, 9.21. IR (KBr): 1640 cm^{-1} (C=O). UV λ_{max}^{EtOH} nm (log ε): 248 (3.93), 288 (4.01), 422 (4.62).

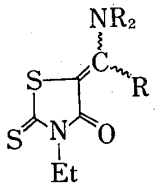
5-Diaminomethylene-3-ethyl-2-thioxothiazol-4(5H)-one (4a, b)——A mixture of 0.01 mol of **2** and 0.04—0.05 mol of amine (benzylamine, morpholine) was heated at 150° for 30 min. After cooling, the mixture was washed with petroleum benzine and the residue was recrystallized from MeOH to give diamine derivatives (**4a, b**) in 87%, 57% yield, respectively. **4a**: 5-Dibenzylaminomethylene-3-ethyl-2-thioxothiazol-4(5H)-one, mp 148—149°. *Anal.* Calcd. for $C_{20}H_{21}ON_3S_2$: C, 62.63; H, 5.52; N, 10.96. Found: C, 62.93; H, 5.43; N, 11.10. IR (KBr): 3370 cm^{-1} (NH), 1595 cm^{-1} (C=O). UV λ_{max}^{EtOH} nm (log ε): 262 (4.04), 380 (4.37). **4b**: 3-Ethyl-5-dimorpholinomethylene-2-thioxothiazol-4(5H)-one, mp 259°. Yellow needles. *Anal.* Calcd. for $C_{13}H_{21}O_3N_3S_2$: C, 47.10; H, 6.39, N, 12.68. Found: C, 47.21, H, 6.35, N, 12.64. IR (KBr): 1640 cm^{-1} (C=O). UV λ_{max}^{EtOH} nm (log ε): 277 (4.21), 405 (4.57).

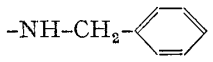
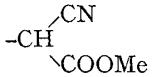
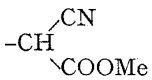
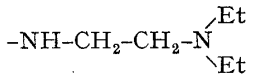
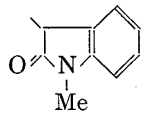
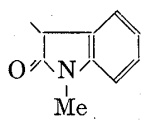
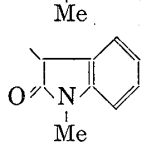
Reaction of 2 with Active Methylene Compounds——To a solution of 0.012 mol of active methylene (methyl cyanoacetate, dimethyl malonate, cyanoacetamide, nitromethane, 1-methyloxindole) and 0.03 mol of K_2CO_3 in 30 ml of Me_2SO, 0.01 mol of **2** was added with stirring at room temperature for 3 hr. The color of the reaction mixture turned reddish brown. The mixture was poured into ice-water and acidified with 10% HCl solution. The precipitate was collected by filtration, washed with water, and recrystallized from MeOH to give **5a—e**. These results are shown in Table I.

Reaction of 1 with Ketenethioacetals——To a solution of 0.01 mol of **1** and 0.03 mol of K_2CO_3 in 30 ml of Me_2SO, 0.01 mol of ketenethioacetal derivative (methyl 2-cyano-3,3-bis(methylthio)acrylate, methyl 2-methoxycarbonyl-3,3-bis(methylthio)acrylate, 2-cyano-3,3-bis(methylthio)acrylamide, 1-nitro-2,2-bis(methylthio)ethylene, 1-methyl-3-bis(methylthio)methylenoxindole) was added with stirring at room temperature. The mixture was stirred at room temperature for 3 hr, by which the mixture turned reddish brown. The mixture was poured into ice-water, acidified with 10% HCl solution, the precipitate was collected by filtration, washed with water, and recrystallized from MeOH to give mono substitute of methylthio group of ketenethioacetal in a high yield such as 70—80% yield.

Reaction of 5a and 5e with Amines——A mixture of 0.01 mol of **5a** or **5e** and 0.02 mol of amine (benzylamine, *t*-butylamine, diethylaminoethylamine, β-aminopropionitrile, ethanolamine) in 30 ml of MeOH was refluxed

TABLE II.



	NR_2	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR(KBr) cm^{-1}	
6a			75	156	$C_{17}H_{17}O_3N_3S_2$	54.40 (54.23)	4.57 (4.61)	11.20 (11.04)	ν_{NH} ν_{CN} $\nu_{C=O}$	3300 2210 1725 1657
6b	$-NH-C(Me)_3$		50	195	$C_{14}H_{19}O_3N_3S_2 \cdot H_2O$	46.79 (46.26)	5.89 (5.79)	11.70 (11.30)	ν_{CN} $\nu_{C=O}$	2180 1640
6c			70	160	$C_{21}H_{28}O_2N_4S_2$	58.32 (58.26)	6.53 (6.57)	12.96 (12.75)	ν_{NH} $\nu_{C=O}$	3530 1630
6d	$NH-CH_2-CH_2-CN$		83	180	$C_{13}H_{13}O_2N_4S_2$	55.95 (55.57)	4.70 (4.79)	14.50 (14.24)	ν_{CN} $\nu_{C=O}$	2230 1705 1630
6e	$NH-CH_2-CH_2-OH$		80	190	$C_{17}H_{19}O_3N_3S_2$	54.11 (53.51)	5.08 (5.06)	11.14 (10.70)	ν_{NH} $\nu_{C=O}$	3470 1705 1633

on a boiling water bath for 1 hr. The solvent was evaporated and the residue was washed by 5% HCl solution. The precipitate was collected by filtration, washed with water, and recrystallized from MeOH to give amine derivatives (**6a—e**).

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Some Properties of Sulfanilamide Monohydrate

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The crystalline form taken by sulfanilamide monohydrate depends on the concentration of sulfanilamide in the aqueous solution from which it is crystallized. Apparent heats of solution are reported for the four (anhydrous) polymorphic forms of sulfanilamide.

Theoretical

The phenomena of polymorphism and hydrate formation in sulfanilamide have attracted considerable attention recently.[2-7)] We would like to contribute some additional observations.

In contrast to previous investigators, we have found that the form taken by sulfanilamide monohydrate depends on the conditions of its crystallization. In addition, we have observed that the various polymorphs of sulfanilamide are not inevitably converted to the more stable β form when in contact with water at temperatures above the temperature at which transition from the monohydrate to the anhydrous form occurs.

Slow cooling of hot, aqueous sulfanilamide solutions containing 15%, 8%, and 5% of the solute usually produces crystals which, on filtration and storage in a vacuum desiccator over diluted sulfuric acid (density, 1.08g/ml, 96% relative humidity) exhibit differential thermal analysis (DTA) thermograms of the type represented in Figure 1 as α', β', and δ', respectively. While the DTA thermograms of these hydrated species appear to be quite similar, exhibiting peaks near 40° corresponding to the breaking of interactions between water molecules and the crystal lattice, and near 100°, corresponding to the vaporization of water from the sample tube, the DTA thermograms obtained following exposure of these crystals to the atmosphere are quite different. Exposure of the hydrates to air causes the crystals to lose moisture rapidly, and after a few days of such exposure, it is found that the α' crystals on dehydration exhibit an endothermic peak at 110°, characteristic of the α form of sulfanilamide, and an infrared spectrum which is also characteristic of this form.[3)]

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