[Chem. Pharm. Bull. 15(9)1310~1314(1967)]

UDC 615.771.7 : 547.269.3.07

164. Seigoro Hayashi, Mitsuru Furukawa, Junko Yamamoto,[*1] and Kimio Hamamura[*2] : Studies on Antitumor Substances. Ⅵ.[*3] Chemical Behaviors of Thiosulfonates, Disulfonyl Sulfides, and Related Compounds.

(*Faculty of Pharmaceutical Sciences, Kumamoto University*[*1] *and Research Laboratories, Eisai, Co., Ltd.*[*2])

1. A general method for the preparation of symmetrical and unsymmetrical disulfonyl sulfides was established starting from sodium alkanethiosulfonates and alkanesulfonyl chlorides.

2. Thiosulfonates and disulfonyl sulfides were found to be reduced to the corresponding disulfides and trisulfides respectively. These results suggest that the unsymmetrical disulfides and trisulfides might be prepared generally by this method.

3. Trisulfides were found to be desulfurizated to the corresponding sulfides *via* disulfides.

4. Oxidation of alkylaryldisulfides occurred preferentially on the farthest sulfur atom from the electron releasing alkyl group.

(Received Septenmber 26, 1966)

As described in the previous paper,[*3] in order to elucidate the mechanism of the action of thiosulfonates[1,2] having the antitumor and antienzyme activities, their chemical behaviors between active methylene compounds were studied by Hayashi, *et al.* In the result, it was found that the mercapto groups were introduced in the active methylene compounds.

In continuation of this work, the reactivities of thiosulfonates, disulfonyl sulfides, and related compounds for a reducing agent or oxidizing agent such as triphenylphosphine or hydrogen peroxide respectively were investigated by the present authors.

I. Reduction of Thiosulfonates and Disulfonyl Sulfides with Triphenylphosphine

It was reported[3] that the thiosulfonates were reduced with lithium aluminum hydride to result the corresponding thiols by the reductive fission of SO_2-S linkages. In order to reduce thiosulfonates to the corresponding disulfides, triphenylphosphine was used successfully as the reducing agent.

The materials we used were as follows : *n*-butyl phenylmethanethiosulfonate, benzyl butanethiosulfonate, benzyl benzenethiosulfonate, ethylene 1,2-bisphenylmethanethiosulfonate and dibenzyl 1,2-bisethanethiosulfonate.

This method was found to be convenient to prepare unsymmetrical disulfides which are otherwise difficult to obtain.

Thiosulfinates were found to be the intermediate of this reduction by the fact that the infrared (IR) absorption assigned to a SO_2 group was wholly disappeared and a strong band assigned to a SO group was appeared at $1050\,cm^{-1}$.

The reaction was assumed to occur by the nucleophilic attack of triphenylphosphine to either the SO_2 group or the S group in thiosulfonates resulting thiosulfinates and triphenylphosphine oxide, as shown in Chart 1.

[*1] Kuhonji Oe-machi, Kumamoto (林 清五郎, 古川 潮, 山本順子).

[*2] Koishikawa, Bunkyo-ku, Tokyo (浜村吉三郎).

[*3] Part Ⅴ : This Bulletin, **15**, 1188 (1967).

1) S. Hayashi, H. Ueki, S. Harano, J. Komiya, S. Iyama, K. Harano, K. Miyata, K. Niigata, Y. Yonemura : This Bulletin, **12**, 1271 (1964).

2) S. Hayashi, H. Ueki, J. Komiya : Gann, **55**, 1, 289 (1964).

3) J. Starting : Rec. trav. chim., **69**, 638 (1950).

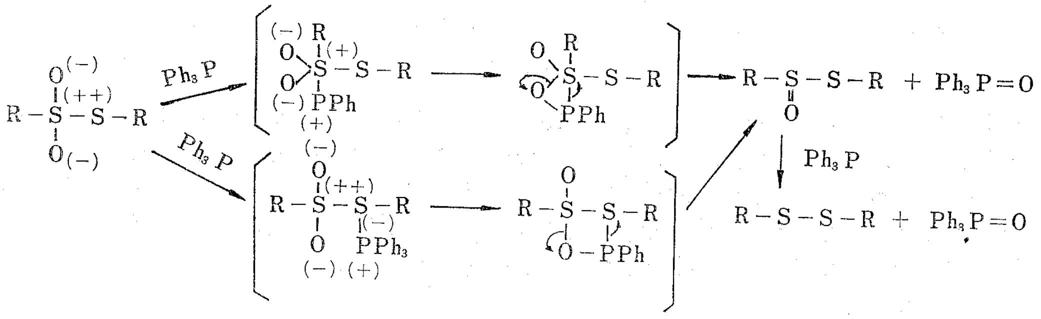

Chart 1.

Of these two assumptions, the latter four membered ring structure may be preferably considerable to exist as a transition state from the fact that active methylene compounds were converted to their mercapto derivatives by the nucleophilic attack to the S group but not to the SO_2 group in thiosulfonates, because of the fielding effect and the steric hindrance of the SO_2 group, as shown in Chart 2. The thiosulfinates would be converted to the corresponding disulfides by the same mechanism.

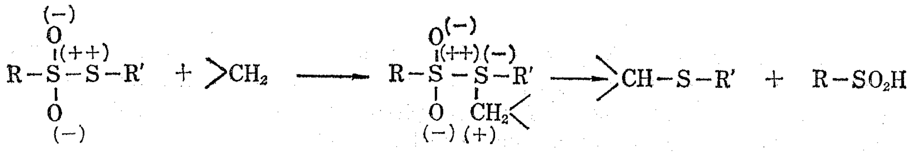

Chart 2.

Several disulfonyl sulfides were also reduced to the corresponding trisulfides by this reagent, as shown in Chart 3, offering a new method to prepare both of symmetrical and unsymmetrical trisulfides.

$$R\text{-}SO_2\text{-}S\text{-}SO_2\text{-}R' \longrightarrow R\text{-}S\text{-}S\text{-}S\text{-}R'$$

Chart 3.

II. Desulfurization of Trisulfides with Triphenylphosphine

Dibenzyl trisulfides obtained by the reduction of the corresponding dibenzylsulfonyl sulfides were desulfurizated to dibenzyl disulfides in about 60% yield by treating with one mole of triphenylphosphine. The disulfides were more desulfurizated to afford the dibenzyl sulfides in about 50% yield by the same treatment as shown in Chart 4.

$$Ph\text{-}CH_2\text{-}S\text{-}S\text{-}S\text{-}CH_2\text{-}Ph \xrightarrow{Ph_3P} Ph\text{-}CH_2\text{-}S\text{-}S\text{-}CH_2\text{-}Ph \xrightarrow{Ph_3P} Ph\text{-}CH_2\text{-}S\text{-}CH_2\text{-}Ph$$

Chart 4.

The same results were obtained with di-*p*-tolyltrisulfide and phenylbenzyltrisulfide resulting di-*p*-tolylsulfide and phenylbenzylsulfide in about 30% yield respectively. In these reactions, triphenylphosphine sulfide was isolated from the reaction mixture. Therefore, these reactions were considered to initiate by the nucleophilic attack of phosphine to the sulfur of trisulfides.

III. Oxidation of Unsymmetrical Disulfides

Although there exist only a kind of reaction product in the oxidation of symmetrical disulfides, two isomers should be afforded in the oxidation of unsymmetrical disulfides as shown in Chart 5.

$$\text{R-S-S-R}' \xrightarrow{H_2O_2} \text{R-SO}_2\text{-S-R}' \quad \text{or} \quad \text{R-S-SO}_2\text{-R}'$$

Chart 5.

Leandri, *et al.*[4] found that the oxidation of unsymmetrical diaryldisulfides occurred preferentially on the farthest sulfur atom from electron releasing substituents. Namely, *p*-tolyl *p*-nitrobenzenethiosulfonate and *p*-tolyl 2,4-dibromobenzenethiosulfonate were obtained by the oxidation of 4-methyl-4-nitrodiphenyldisulfide and 2,4-dibromo-4-methyldiphenyldisulfide respectively. However, nothing was known concerning the oxidation of alkylaryldisulfides.

In this respect, it was found to be similar to the oxidation of diaryldisulfides from the fact *n*-butyl phenylmethanethiosulfonate and ethylene 1,2-bisphenylmethanethiosulfonate were obtained by the oxidation of *n*-butylbenzyldisulfide and ethylene bisdibenzyldisulfide in 62% and 54% yield respectively. The oxidation was carried out with the usual method for the preparation of dibenzylsulfone from dibenzylsulfide using tungstic acid as a catalyst. The products were identified by the mixed melting point method and the comparison of their infrared spectra with the authentic samples prepared by the other method described.

Experimental

Preparation of Thiosulfonates——A mixture of 0.1 mole of anhyd. sodium alkanethiosulfonates and 0.1 mole of alkyl halides in 250 ml. of abs. EtOH was refluxed for 10~15 hr. on water bath. The hot mixture was then filtered and the colorless crystals precipitated on cooling were collected by suction, washed with a large amount of H_2O and recrystallized from EtOH or AcOEt.

Thiosulfonates prepared by this method were shown in Table I.

Table I.

R	R′	m.p. (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	Found C	H
				R-SO₂-S-R′				
$PhCH_2$	n-C_3H_7	88	38	$C_{10}H_{14}O_2S_2$	52.14	6.13	51.86	6.25
$PhCH_2$	n-C_4H_9	94	43	$C_{11}H_{16}O_2S_2$	54.06	6.60	54.22	6.65
$PhCH_2$	n-C_5H_{11}	101	35	$C_{12}H_{18}O_2S_2$	55.77	7.02	55.90	6.88
$PhCH_2$	$PhCH_2$	106	52	$C_{14}H_{14}O_2S_2$	60.40	5.07	60.68	5.15
n-C_4H_9	$PhCH_2$	85	23	$C_{11}H_{16}O_2S_2$	54.06	6.60	54.29	6.53
Ph	$PhCH_2$	43	56	$C_{13}H_{12}O_2S_2$	59.06	4.57	59.27	4.59
p-CH_3Ph	$PhCH_2$	60	52	$C_{14}H_{14}O_2S_2$	60.40	5.07	60.58	5.21
				R-SO₂-S-(CH₂)₂-S-SO₂-R				
Ph		85	34	$C_{14}H_{14}O_4S_4$	—	—	—	—
$PhCH_2$		174	32	$C_{16}H_{18}O_4S_4$	47.73	4.50	48.00	4.62
p-CH_3Ph		76	29	$C_{16}H_{18}O_4S_4$	—	—	—	—
				R-S-SO₂-(CH₂)₂-SO₂-S-R				
$PhCH_2$		183	22	$C_{16}H_{18}O_4S_4$	47.73	4.50	47.57	4.41

Preparation of Disulfonyl Sulfides——A solution of 0.1 mole of powdered anhyd. sodium alkanethiosulfonates and 0.1 mole of alkanesulfonyl chlorides in 300 ml. of abs. EtOH was refluxed for 10~12 hr. on water bath. The hot mixture was then filtered and the white crystals precipitated on cooling were corrected by suction, washed with a large amount of H_2O and recrystallized from benzene or AcOEt. These compounds are soluble in almost all organic solvents and insoluble in H_2O.

Disulfonyl sulfides prepared by this method are shown in Table II.

---

4) G. Leandri, A. Tundo: Ann. Chim. (Rome), **44**, 74 (1954).

TABLE II.

R	R′	m.p. (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	Found C	H
				$R-SO_2-S-SO_2-R'$				
Ph	Ph	133	26	$C_{12}H_{10}O_4S_3$	—	—	—	—
Ph	$\mathrm{PhCH_2}$	139	30	$C_{13}H_{12}O_4S_3$	47.53	3.69	47.80	3.76
Ph	*p*-$\mathrm{CH_3Ph}$	135	28	$C_{13}H_{12}O_4S_3$	47.53	3.69	47.41	3.72
$\mathrm{PhCH_2}$	*p*-$\mathrm{CH_3Ph}$	158	32	$C_{14}H_{14}O_4S_3$	49.09	4.12	49.32	4.20
$\mathrm{PhCH_2}$	$\mathrm{PhCH_2}$	171	38	$C_{14}H_{14}O_4S_3$	49.09	4.12	48.77	4.15
p-$\mathrm{CH_3Ph}$	*p*-$\mathrm{CH_3Ph}$	131	25	$C_{14}H_{14}O_4S_3$	—	—	—	—
				$R-SO_2-S-SO_2-(CH_2)_2-SO_2-S-SO_2-R$				
Ph		112	26	$C_{14}H_{14}O_8S_6$	33.45	2.81	33.68	2.86
$\mathrm{PhCH_2}$		193	33	$C_{16}H_{18}O_8S_6$	36.21	3.42	36.01	3.50
p-$\mathrm{CH_3Ph}$		102	25	$C_{16}H_{18}O_8S_6$	36.21	3.42	35.94	3.52

Reduction of Thiosulfonates and Disulfonyl Sulfides——To a solution of 0.01 mole of thiosulfonates or 0.005 mole of disulfonyl sulfides in 80 ml. of anhyd. ether or benzene, a solution of 0.02 mole of triphenylphosphine in 50 ml. of anhyd. ether or benzene was added dropwise wtih stirring during 1.5 hr. in a stream of nitrogen under anhydrous condition. The mixture was then refluxed with stirring for $7\sim12$ hr. After completion of the reaction, the mixture was allowed to stand for 1.5 hr. at room temperature. Resulting triphenylphosphine oxide deposited was filtered off and the filtrate was concentrated to dryness. The residual white solid was recrystallized from EtOH or AcOEt. Disulfides and trisulfides obtained by this reduction are listed in Table III.

TABLE III.

R	R′	m.p. (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	Found C	H
				$R-S-S-R'$				
$\mathrm{PhCH_2}$	*n*-$\mathrm{C_4H_9}$	80	64	$C_{11}H_{16}S_2$	62.21	7.59	61.94	7.67
Ph	$\mathrm{PhCH_2}$	58	55	$C_{13}H_{12}S_2$	67.19	5.20	67.22	5.21
$\mathrm{PhCH_2}$	$\mathrm{PhCH_2}$	71	50	$C_{14}H_{14}S_2$	—	—	—	—
n-$\mathrm{C_4H_9}$	$\mathrm{PhCH_2}$	80	61	$C_{11}H_{16}S_2$	62.21	7.59	62.39	7.57
p-$\mathrm{CH_3Ph}$	$\mathrm{PhCH_2}$	60	46	$C_{14}H_{14}S_2$	68.25	5.73	68.02	5.79
p-$\mathrm{CH_3Ph}$	*p*-$\mathrm{CH_3Ph}$	47	52	$C_{14}H_{14}S_2$	—	—	—	—
				$R-S-S-(CH_2)_2-S-S-R$				
Ph		40	37	$C_{14}H_{14}S_4$	54.15	4.55	54.38	4.57
$\mathrm{PhCH_2}$		66	48	$C_{16}H_{18}S_4$	56.75	5.36	56.87	5.31
p-$\mathrm{CH_3Ph}$		38	40	$C_{16}H_{18}S_4$	56.75	5.36	56.44	5.33
				$R-S-S-S-R'$				
Ph	$\mathrm{PhCH_2}$	42	37	$C_{13}H_{12}S_3$	59.04	4.57	59.12	4.55
Ph	*p*-$\mathrm{CH_3Ph}$	54	30	$C_{13}H_{12}S_3$	59.04	4.57	59.37	4.59
$\mathrm{PhCH_2}$	$\mathrm{PhCH_2}$	49	45	$C_{14}H_{14}S_3$	—	—	—	—
$\mathrm{PhCH_2}$	*p*-$\mathrm{CH_3Ph}$	61	32	$C_{14}H_{14}S_3$	60.38	5.07	60.53	5.14
p-$\mathrm{CH_3Ph}$	*p*-$\mathrm{CH_3Ph}$	76	38	$C_{14}H_{14}S_3$	—	—	—	—
				$R-S-S-S-(CH_2)_2-S-S-S-R$				
Ph		57	21	$C_{14}H_{14}S_6$	44.88	3.76	44.99	3.75
$\mathrm{PhCH_2}$		75	27	$C_{16}H_{18}S_6$	47.71	4.50	47.58	4.54

Reduction of Thiosulfonates to Thiosulfinates——Thiosulfonates were converted to thiosulfinates with the equivalent amount of triphenylphosphine by the same procedure as described above. The compounds obtained are shown in Table Ⅳ.

TABLE Ⅳ.

R	R′	m.p. (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Found C	Found H
				R-SO-S-R′				
Ph	$PhCH_2$	62	35	$C_{13}H_{12}OS_2$	62.86	4.87	63.03	4.90
$PhCH_2$	$PhCH_2$	130	40	$C_{14}H_{14}OS_2$	64.08	5.38	64.32	5.36
$PhCH_2$	n-C_4H_9	50	37	$C_{11}H_{16}OS_2$	54.05	6.60	54.20	6.61

Thiosulfinates were also reduced to disulfides with the equivalent amount of triphenylphosphine by the same method.

Reduction of Sulfones to Sulfoxides——The reduction of sulfones to sulfoxides was carried out by the same procedure for the reduction of thiosulfonates to thiosulfinates. Benzylphenylsulfoxide; m.p. 125°. Yield 46%. Dibenzylsulfoxide; m.p. 132°. Yield 41%. The melting points of these compounds were in accord with those of the same compounds described in literature.[5,6]

Reduction of Sulfoxides to Sulfides——The reduction of sulfoxides to sulfides was carried out by the same procedure described above. Benzylphenylsulfide; m.p. 44°. Yield 31%. Dibenzylsulfide; m.p. 49°. Yield 28%. These compounds did not show depression of melting point on admixture with authentic samples prepared by desulfurization of the corresponding disulfides described below.

Desulfurization of Trisulfides——A solution of 0.0025 mole of triphenylphosphine in 50 ml. of anhyd. ether was added dropwise during 1.5 hr. to a stirred solution of 0.0025 mole of trisulfides in 80 ml. of anhyd. ether in a stream of nitrogen under anhydrous condition. The reaction mixture was then heated with stirring under reflux for 7 hr. Triphenylphosphine sulfide deposited on cooling was removed by suction and the filtrate was concentrated to dryness. The resulting residue was recrystallized from ether or AcOEt. By this method, benzylphenyldisulfide and dibenzyldisulfide were obtained from the corresponding trisulfides in 50% and 45% yield respectively. These compounds did not show depression of melting point on admixture with authentic samples obtained by the reduction of the corresponding thiosulfonates. Disulfide were also desulfurizated to sulfides by the same method. The yields of benzylphenylsulfide, dibenzylsulfide and di-*p*-tolylsulfide thus obtained were in 34%, 44% and 34% respectively. These compounds did not depress on admixture with authentic samples obtained by the reduction of the corresponding sulfoxides described above.

Oxidation of Alkylaryldisulfides——To a solution of 0.003 mole of disulfides in 20 ml. of EtOH involving a tungustic acid catalyst,[7] a solution of 0.006 mole of 30% aqueous hydrogen peroxide in 10 ml. of H_2O was added dropwise with stirring and heating at 60∼65°, during about 30 min. After additional 10 min., a starch-iodide test was negative. A slight excess of hydrogen peroxide was then added dropwise very slowly with a slight heating, while testing with a starch-iodide paper. A trace of excess hydrogen peroxide was destroyed with 0.2 g. of sodium bisulfite. The hot mixture was filtered and white crystallines precipitated on cooling were collected by filtration, washed with a small amount of ether and dried in vacuum. The crude product was recrystallized from EtOH as colorless needles. By this method, *n*-butyl phenylmethanethiosulfonate and 1,2-diphenylmethanesulfonylthioethane were obtained from the corresponding disulfides in 62% and 54% yield respectively. These compounds were confirmed to be identical with the authentic samples synthesized with the method described above by the mixed melting point method and the comparison of their infrared spectra.

The authors wish to thank to Mrs. Y. Tanaka for infrared analyses and Miss K. Ogata for the elemental analyses.

---

5) Pummerer: Ber., **43**, 1406 (1910).
6) Smythe: J. Chem. Soc., **95**, 349 (1909).
7) T. Wood: J. Am. Chem. Soc., **50**, 1226 (1928).