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Studies on Antitumor Substances. X.[1] Reactions of Thiosulfonates with Some Nucleophilic Compounds

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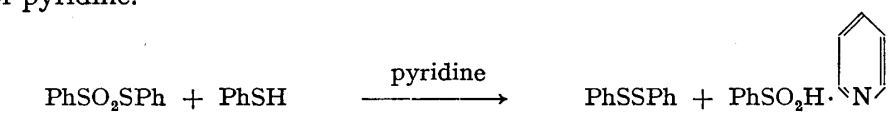
Reactivities of mono and difunctional thiosulfonates toward several nucleophilic compounds, such as thiols, amines and the related compounds, were examined. In the result, some chemical behaviors unexpected were found in addition to the reactivity anticipated. Namely, in the reaction with piperazine, aralkyl thiosulfonate afforded aralkyltrisulfide in about 20% yield, without any formation of sulfenamide. Moreover, aromatic thiosulfonate gave a comparable good yield of 1-phenyl-2-arylsulfonylhydrazine in the reaction with phenylhydrazine, in addition to the formation of phenylhydrazinium salt of aromatic sulfinic acid.

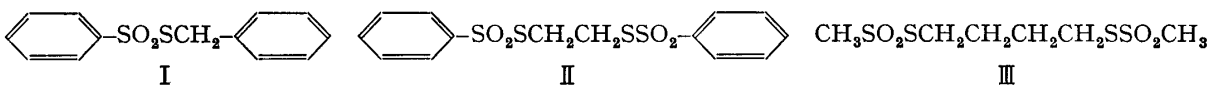
From the chemical behaviors, Hayashi, *et al.*[3] has suggested that the mechanism of the antitumor action of bismethanesulfonylthioalkane was different from that of Myleran,[4] bismethanesulfonyloxybutane, well known to be antitumor substance. By the additional investigation regarding to the chemical behaviors, we have attempted to elucidate the mechanism of the antitumor action of bismethanesulfonylthioalkane. This paper deals with the reaction between thiosulfonates and some nucleophilic compounds, such as thiol, amine and hydrazine.

Reaction of Thiosulfonate with Thiol

It has been reported by Parsons, *et al.*[5] that the equimolar reaction of phenyl benzenethiosulfonate with thiophenol afforded diphenyldisulfide in the presence of an equimolar amount of pyridine.



In order to extend this reaction, the reaction of thiosulfonates, such as benzyl benzenethiosulfonate (I),[3,6] 1,2-bis(benzenesulfonylthio)ethane (II)[6,7] and 1,4-bis(methanesulfonyl-

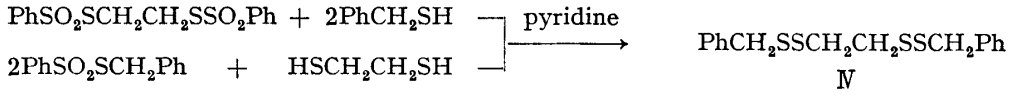


I II III

thio)butane (III),[6,7] with several thiols, such as thiophenol, phenylmethanethiol and butanethiol, was attempted under the similar condition. In the result, benzyl benzenethiosulfonate

1) Part IX: S. Hayashi, M. Furukawa, Y. Fujino, and S. Yoshimatsu, *Chem. Pharm. Bull.* (Tokyo), **17**, 329 (1969).
2) Location: *a*) *Oehoncho, Kumamoto*; *b*) *Tsukamotocho, Higashiyodogawa, Osaka.*
3) S. Hayashi, M. Furukawa, J. Yamamoto, and K. Niigata, *Chem. Pharm. Bull.* (Tokyo), **15**, 1188 (1967).
4) G.M. Timmis and R.F. Hudson, *Ann. N.Y. Acad. Sci.*, **68**, 727 (1958).
5) T.F. Parsons, J.D. Buckman, D.E. Pearson, and L. Field, *J. Org. Chem.*, **30**, 1923 (1965).
6) R. Otto, *Ber.*, **15**, 129 (1882).
7) S. Hayashi, H. Ueki, S. Harano, J. Komiya, S. Iyama, K. Harano, K. Miyata, K. Niigata, and Y. Yonemura, *Chem. Pharm. Bull.* (Tokyo), **12**, 1271 (1964).

(I) was allowed to react with all of these thiols to give the corresponding disulfide as expected. 1,2-Bis(benzenesulfonylthio)ethane (II) and 1,4-bis(methanesulfonylthio)butane (III) were respectively allowed to react with two molar amount of thiophenol and phenylmethanethiol in the presence of four molar amount of pyridine to give the corresponding bifunctional disulfide, while with ethanethiol and butanethiol to afford diethyldisulfide and dibutyldisulfide, respectively, probably formed by the atmospheric oxidation of these thiols themselves, without any formation of the anticipated bifunctional disulfide. The product obtained by the reaction of 1,2-bis(benzenesulfonylthio)ethane (II) with phenylmethanethiol was confirmed to be identical with 1,2-bis(benzyldithio)ethane (IV) prepared by treating benzyl benzenethiosulfonate (I) with 1,2-ethylenedithiol under the similar condition. The compounds obtained in these



reactions were shown in Table I.

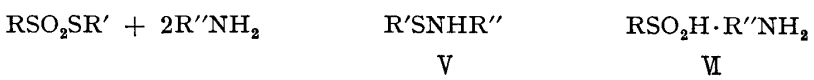
Table I. Disulfide

RSSR′

R	R′	Yield %	mp or bp °C	°C/mm	Formula	Analysis % Calcd. C	Calcd. H	Found C	Found H
$PhCH_2$	Ph	30	130—132	2	$C_{13}H_{12}S_2$	67.19	5.20	67.28	5.10
$PhCH_2$	CH_2Ph	72	71—72		$C_{14}H_{14}S_2$	68.25	5.73	68.22	5.15
$PhCH_2$	$(CH_2)_3CH_3$	39	93—94	2	$C_{11}H_{16}S_2$	62.21	7.59	62.47	7.69
$PhCH_2$	$(CH_2)_2SSCH_2Ph$	88	109—110		$C_{14}H_{14}S_4$	54.15	4.55	54.36	4.76
$PhCH_2$	$(CH_2)_4SSCH_2Ph$	32	72—73		$C_{16}H_{18}S_4$	58.96	6.05	58.87	5.95
Ph	$(CH_2)_2SSPh$	57	48—49		$C_{18}H_{22}S_4$	56.75	5.36	56.52	5.29

Reaction of Thiosulfonate with Amine and the Related Compound

Bolyrev[8] and Dunbar[9] have independently reported that thiosulfonate reacted with amine to afforde the corresponding sulfenamide.



In order to expand this reaction, benzyl benzenethiosulfonate (I), *o*-nitrophenyl benzenethiosulfonate, 1,2-bis(benzenesulfonylthio)ethane (II) and 1,4-bis(methanesulfonylthio)butane (III) were attempted to react with amine, hydrazine and amino acid, respectively. All of these thiosulfonates failed to react with aromatic amines to recover any product. In the reaction between benzyl benzenethiosulfonate (I) and some aliphatic amines, such as phenethylamine, benzylamine and piperazine, no corresponding sulfenamides anticipated were isolated, though corresponding amine salts of benzenesulfinic acid (VI) were obtainable in all cases. However, when morpholine, diethanolamine and ethylenediamine were employed in the reaction, some thiosulfonates were allowed to react to yield the corresponding sulfenamides (V) as expected. The sulfenamides (V) obtained were as follows: N,N-(3-oxapentamethylene)-phenylmethanesulfenamide (Va)[8] and bis[N,N-(3-oxapentamethylene)]-1,4-butanedisulfenamide (Vb), by the reaction of benzyl benzenethiosulfonate and 1,4-bis(methanesulfonylthio)-

8) B.G. Boldyrev and S.A. Kolesnikova, *Zh. Obsch. Khim.*, **35**, 198 (1965) [*C.A.*, **62**, 13076*e* (1965)].
9) J.E. Dunbar and J.H. Rogers, *J. Org. Chem.*, **31**, 2842 (1965); *idem*, *Tetrahedron Letters*, **1965**, 4291.

butane with morpholine, respectively. 1,2-Ethylene-bis(*o*-nitrobenzenesulfenamide) (Vc), N, N-bis(2-hydroxyethyl)-*o*-nitrobenzenesulfenamide (Vd), N-carboethoxymethyl-*o*-nitrobenzenesulfenamide (Ve), by the reaction of *o*-nitrophenyl benzenethiosulfonate with ethylenediamine, diethanolamine and ethyl glycinate, respectively. These compounds obtained were summarized in Table II. These results suggested that the possible isolation of sulfenamides was

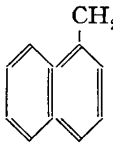
Table II. Substituted Sulfenamide

Structure	Yield %	mp °C	Formula	Analysis % Calcd. C	H	N	Found C	H	N
$C_6H_5CH_2SN$⟨morpholino⟩O	52	74—75	$C_{11}H_{15}ONS$	63.11	7.21	6.69	63.12	7.18	6.85
$(o\text{-}NO_2C_6H_4SNHCH_2\text{–})_2$	25	172—174	$C_{10}H_{14}O_4N_4S$	45.89	3.86	15.30	46.00	3.77	15.21
$o\text{-}NO_2C_6H_4SN(CH_2CH_2OH)_2$	65	82	$C_{10}H_{14}O_4N_2S$	46.31	5.47	10.85	46.69	5.44	10.69
$o\text{-}NO_2C_6H_4SNHCH_2COOEt$	18	79—80	$C_{10}H_{12}O_4N_2S$	46.85	4.73	10.93	46.87	4.60	10.89
O⟨morpholino⟩$NS(CH_2)_4SN$⟨morpholino⟩O	43	72—74	$C_{12}H_{24}O_2N_2S_2$	49.28	8.27	9.57	49.14	8.56	9.04

dependent on their stability. As shown in the Table II, it might be assumed that the existence of *o*-nitrophenyl and morpholino groups should extremely contributed to the stability of the sulfenamides.

Different from these amines employed, piperazine was found to show interesting unique chemical behavior toward thiosulfonate. Namely, thiosulfonates, such as benzyl benzenethiosulfonate (I), benzyl *p*-toluenethiosulfonate, *p*-xylyl methanethiosulfonate and 1-naphthylmethyl benzenethiosulfonate gave the corresponding trisulfides (VII) and piperazine salts of the sulfinic acids in the reaction with piperazine under the similar condition. These trisulfides were confirmed to be identical with those prepared from Bunte salts and sodium sulfide. If the reaction was carried out in the absence of piperazine, trisulfides were not obtainable at any rate. Therefore, it might be evident that piperazine should participate in the reaction.

$$RSO_2SR' \xrightarrow{\text{piperazine}} \underset{\text{VII}}{R'SSSR'} + (RSO_2H)_2HN\langle\text{piperazine}\rangle NH$$

R=Ph, *p*-$CH_3C_6H_4$, CH_3 R′=$PhCH_2$, *p*-$CH_3C_6H_4CH_2$, 

However, the reaction mechanism remains unsolved at present. On the other hand, alkyl benzenethiosulfonate failed to react with piperazine to give any alkyltrisulfide under the similar condition.

In the reaction of benzyl benzenethiosulfonate (I) with hydrazine hydrate, dibenzyldisulfide was unexpectedly yielded, without any product corresponding to sulfenehydrazide. On the other hand, the reaction of the same thiosulfonate with phenylhydrazine was found to afford 1-phenyl-2-benzenesulfonylhydrazine (VIII) in 67% yield, in addition to the forma-

$$RSO_2SR + PhNHNH_2 \longrightarrow \underset{\text{VIII}}{RSO_2NHMHPh} + \underset{\text{IX}}{RSO_2H\cdot NH_2NHPh}$$

R=Ph, *p*-$CH_3C_6H_4$ R′=Ph, $PhCH_2$

10) B. Milligan, B. Saville, and J.M. Swan, *J. Chem. Soc.*, **1961**, 4850.

tion of phenylhydrazinium salt of benzenesulfinic acid (IX). The infrared (IR) spectrum of the former showed an absorption assigned to sulfonyl group at 1320 cm^{-1} and 1150 cm^{-1}, and to amino group at 3300 cm^{-1} and 1605 cm^{-1}. The same compound was also yielded by the reaction of phenyl benzenethiosulfonate with phenylhydrazine. Similarly, 1-phenyl-2-*p*-toluenesulfonylhydrazine was obtained from benzyl *p*-toluenethiosulfonate and phenylhydrazine.

Experimental

Reaction between Thiosulfonate and Thiol——1) General Procedure: To a solution of 0.02 mole of thiol and 0.02 mole of thiosulfonate in 60 ml of abs. ether, 0.02 mole of pyridine was added and the solution was warmed with stirring at 35—40° for 5 hr. After completion of the reaction, 40 ml of H_2O was added and the etheral layer was dried over Na_2SO_4. The oily or crystalline residue obtained by the removal of ether was purified by distillation under reduced pressure or recrystallization. When a bifunctional thiosulfonate was used, 0.04 mole of pyridine was required. Disulfides thus obtained were summarized in the Table I.

2) 1,2-Bis (benzyldithio)ethane (IV) from Benzyl Benzenethiosulfonate and 1,2-Ethylenedithiol: A mixture of 11.2 g (0.02 mole) of benzyl benzenethiosulfonate, 2 g (0.02 mole) of 1,2-ethylenedithiol and 6.3 g (0.08 mole) of pyridine in 70 ml of abs. ether was refluxed with stirring for 5 hr under nitrogen atmospher. The precipitates gradually separated from the mixture were collected by suction, washed with ether and recrystallized from EtOH–benzene to give 5 g (69%) of 1,2-bis (benzyldithio)ethane (IV).

Reaction between Thiosulfonate and Amine——1) N,N-(3-Oxapentamethylene)phenylmethanesulfenamide (Va): A mixture of 5.3 g (0.02 mole) of benzyl benzenethiosulfonate and 7.0 g (0.08 mole) of morpholine in 70 ml of ether was stirred at room temperature for 3 hr. Deposited morpholinium benzenesulfinate was removed by suction, and the filtrate was washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from EtOH.

2) Bis[N,N-(3-oxapentamethylene)]-1,4-butanedisulfenamide (Vb): A mixture of 5.6 g (0.02 mole) of 1,4-bis(methanesulfonylthio)butane and 7.0 g (0.08 mole) of morpholine in 70 ml of ether was stirred at room temperature for 3 hr. The morpholinium salt of the sulfinic acid deposited was filtered off, and the filtrate was washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from EtOH.

3) 1,2-Ethylene-bis(*o*-nitrobenzenesulfenamide) (Vc): A mixture of 5 g (0.07 mole) of *o*-nitrophenyl benzenethiosulfonate and 2.03 g (0.03 mole) of ethylenediamine in 70 ml of ether was stirred for 5 hr at room temperature. Then ether was removed by evaporation and the residue was washed with H_2O and recrystallized from benzene–acetone.

4) N,N,-Bis(2-hydroxyethyl)-*o*-nitrobenzenesulfenamide (Vd): A mixture of 3 g (0.01 mole) of *o*-nitrophenyl benzenethiosulfonate and 2.4 g (0.023 mole) of diethanolamine in 70 ml of EtOH was stirred for 5 hr at room temperature and then EtOH was removed by evaporation *in vacuo*. The residue was washed with H_2O and recrystallized from benzine–benzene. The insoluble parts were recrystallized from acetone to give di-*o*-nitrophenyldisulfide melting at 195.

5) N-Carboethoxymethyl-*o*-nitrobenzenesulfenamide (Ve): A suspension of 7 g (0.05 mole) of ethyl glycinate hydrochloride in a suitable amount of abs. ether was stirred with 8 g (0.035 mole) of Ag_2O at room temperature for 2.5 hr and the precipitates were filtered off. To the filtrate, 5 g (0.017 mole) of *o*-nitrophenyl benzenethiosulfonate was added and the mixture was stirred for 5 hr at room temperature. After completion of the reaction, 60 ml of H_2O was added to the reaction mixture and the etheral layer was separated and dried over Na_2SO_4. The residue obtained by evaporation of ether was extracted with EtOH and the extract was cooled to give N-carboethoxymethyl-*o*-nitrobenzenesulfenamide (Ve), which was repeatedly recrystallized from dilute EtOH. The insoluble parts in EtOH were recrystallized from acetone to give

Table III. Trisulfide

RSSSR

R	Yield %	mp °C	Formula	Analysis % Calcd. C	Calcd. H	Found C	Found H
$PhCH_2$	22	46	$C_{14}H_{14}S_3$	60.39	5.07	60.55	5.09
p-$CH_3C_6H_4CH_2$	25	66—67	$C_{16}H_{18}S_3$	62.69	5.92	62.60	5.82
$C_{10}H_7CH_2$	25	146	$C_{22}H_{18}S_3$	69.80	4.79	69.65	4.70

di-*o*-nitrophenyldisulfide. The compounds obtained by the methods described above were summarized in the Table II.

Reaction of Thiosulfonate in the Presence of Piperazine (VII)——A mixture of 0.02 mole of thiosulfonate and 0.03 mole of piperazine hexahydrate in benzene was heated for 6 hr under reflux. Then 50 ml of H_2O was added to the reaction mixture and the benzene layer was separated and dried over Na_2SO_4. Evaporation of the benzene *in vacuo* gave needless of trisulfide, which was recrystallized from EtOH. These trisulfides were shown in the following Table.

Reaction between Thiosulfonate and Phenylhydrazine——A mixture of 0.02 mole of thiosulfonate and 0.04 mole of phenylhydrazine was stirred in 80 ml of ether at room temperature. Phenylhydrazinium salt of sulfinic acid gradually separated from the reaction mixture was removed by filtration. The filtrate was washed with H_2O, dried over Na_2SO_4 and evaporated under reduced pressure. The resulted oily residue was recrystallized from ligroin–EtOH. 1-Phenyl-2-benzenesulfonylhydrazine (VIII); yield, 67%. mp, 153—154°. *Anal.* Calcd. for $C_{12}H_{12}O_2N_2S$: C, 58.11; H, 4.88; N, 11.30. Found: C, 58.19; H, 4.81; N, 11.32. 1-Phenyl-2-*p*-toluenesulfonylhydrazine; yield, 29%. mp, 155°. *Anal.* Calcd. for $C_{13}H_{14}O_2N_2S$: C, 53.05; H, 4.80; N, 9.51. Found: C, 53.00; H, 4.85; N, 9.61.

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