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Formation of Trisulfide from Thiosulfonate with Amine Catalyst

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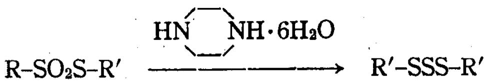
Benzyl *p*-toluenethiosulfonate was found to form dibenzyltrisulfide with amine catalyst in the presence of water. On the other hand, α-benzylmercaptobenzyl *p*-toluenethiosulfonate was formed with amine catalyst in the presence of sulfur in 15% yield, without any dibenzyltrisulfide was obtained. The treatment with sodium hydroxide solution also gave benzylmercaptobenzyl *p*-toluenethiosulfonate in 49% yield. The mechanism of these reaction was presumed.

It has been known by Boldylev[2] and Dunbar[3] that thiosulfonate reacted with amine to give the corresponding sulfenamide. On the other hand, Hayashi, *et .al.*[4] found that the reaction of alkyl thiosulfonate with piperazine hexahydrate formed exclusively alkyltrisulfide under the similar reaction condition, without formation of any sulfenamide. When the reaction was carried out in the absence of piperazine hexahydrate, no trisulfide was obtained at all. Moreover, it should be emphasized that the reaction with another amines have never formed any trisulfide, though, in some cases, the corresponding sulfenamides were obtained. Therefore, it is evident that piperazine hexahydrate participates indirectly in the formation of trisulfide, though the reaction mechanism remains unsolved. In order to find out another direct factors essential to the formation of the trisulfide and elucidate the reaction mechanism, attempts were made in this paper.



First, benzyl *p*-toluenethiosulfonate (I)[5] was allowed to react with piperazine hexahydrate in the presence of sulfur to examine the participation of sulfur which is predictable to form in the course of the reaction. In the absence of sulfur, heating of (I) with piperazine hexahydrate in benzene gave dibenzyltrisulfide (II) from the benzene layer in 14% yield. However, in the presence of sulfur, no trace of any dibenzyltrisulfide was isolated, though α-benzylmercaptobenzyl *p*-toluenethiosulfonate (III) was obtained from the benzene layer in 15% yield and dibenzyldisulfide (IV), piperazinium mono-*p*-toluenesulfinate (V) and piperazinium di-*p*-toluenesulfinate (VI) were isolated from the aqueous layer in 6%, 10% and 7% yields, respectively.

(III) exhibited the infrared (IR) absorption assignable to the sulfonyl group at 1317 cm^{-1} and 1143 cm^{-1}, and was confirmed to be identical with the authentic material prepared by self-condensation of benzyl *p*-toluenethiosulfonate with sodium ethoxide catalyst.

The mechanism of the reaction is proposed as follow.

The formation of the carbonium anion in the methylene group adjacent to the sulfur atom in benzyl *p*-toluenethiosulfonate with amine catalyst would be enhanced by the interaction of

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[1] Location: *Oe-moto-machi, Kumamoto.*

[2] B.G. Boldyrev and S.A. Kolesnikova, *Zh. Obsch. Khim.*, **35**, 198 (1965) [*C. A.*, **62**, 13076e (1965)].

[3] J.E. Dunbar and J.H. Rogers, *J. Org. Chem.*, 31, 2842 (1966); *idem*, *Tetrahedron Letters*, **1965**, 4291.

[4] S. Hayashi, M. Furukawa, Y. Fujino and H. Matsukura, *Chem. Pharm. Bull.* (Tokyo), **17**, 954 (1969).

[5] S. Hayashi, M. Furukawa, J. Yamamoto, and K. Niigata, *Chem. Pharm. Bull.*, (Tokyo)., **15**, 1188 (1967).

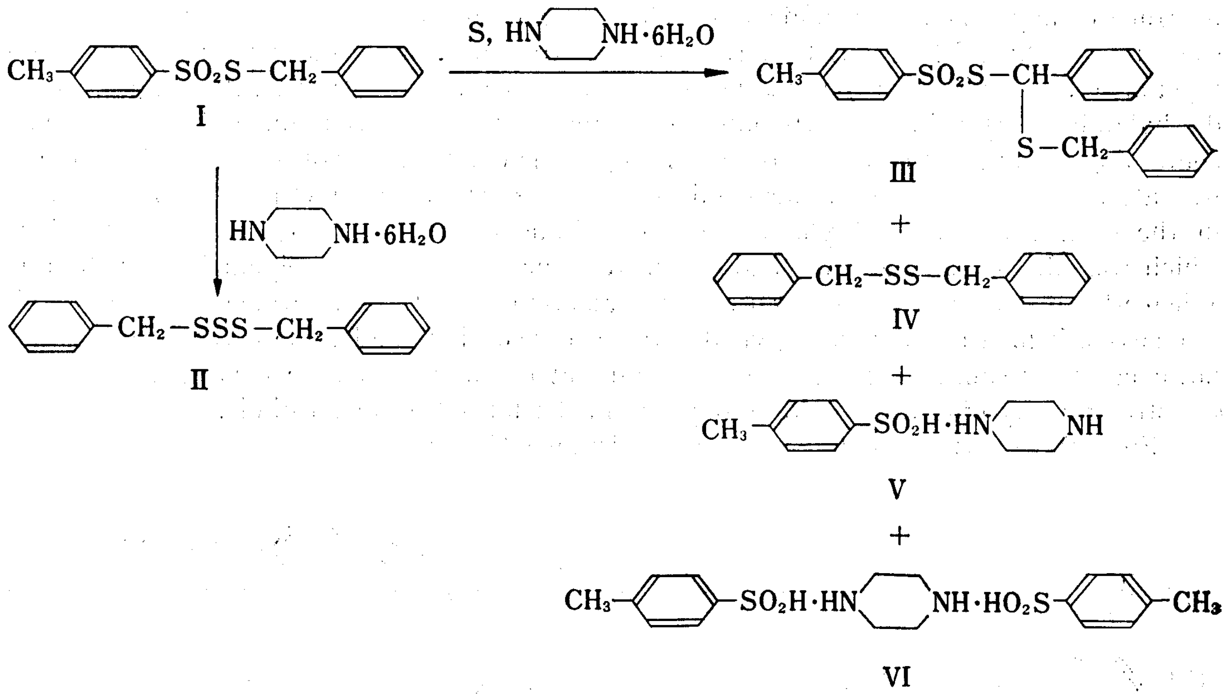

Chart 1

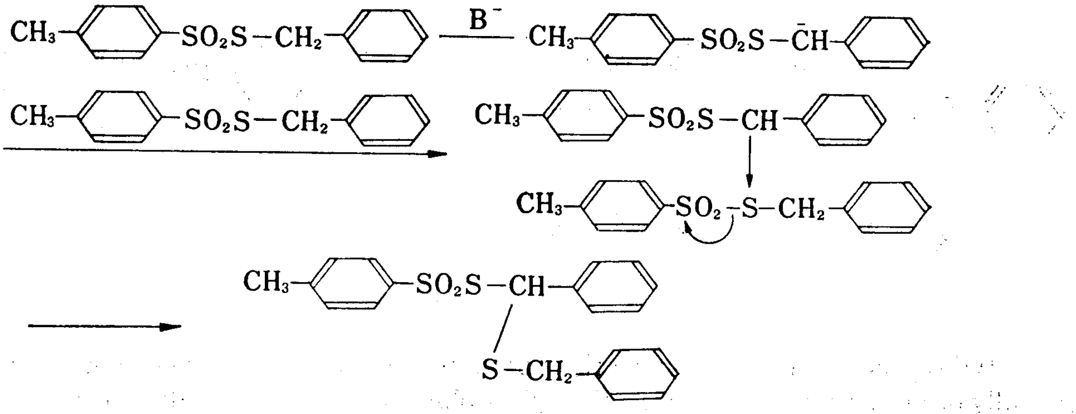

Chart 2

the amine with sulfur added and the resulting carbonium anion would attack the positive charge on the sulfur atom in the unchanged molecule to give α-benzylmercaptobenzyl *p*-toluenethiosulfonate.

V was confirmed by the elementary analysis and IR spectrum which exhibited absorptions due to the free amino group at 3260 cm^{-1}, assignable to the amine salt at near 3000 cm^{-1} and attributed to the sulfinic acid group at 1213 cm^{-1} and 1053 cm^{-1}. VI was also confirmed by the elementary analysis and IR spectrum which exhibited the abosrption pattern analogous to that of piperazinium mono-*p*-toluenesulfinate, though the absorption of the free amino group disappeared. The broad band assignable to the amine salt at near 3000 cm^{-1} and absorptions due to the sulfinic acid group at 1155 cm^{-1}, 1098 cm^{-1} and 1038 cm^{-1} were observed.

Next, I was allowed to react with piperazine hexahydrate in the presence of dibenzyldisulfide which would be probably formed in the course of the reaction. If dibenzyldisulfide participates in the reaction, the yield of trisulfide will be increased. However, the increase of the yield was not observed.

Then, in order to examine the participation of the crystal water of piperazine hexahydrate, I was allowed to react with piperazine anhydrate under the similar condition. In the result, no trace of any dibenzyltrisulfide was isolated. This result suggests that water should be essential and trisulfide might be formed by the treatment with another amines instead of piperazine hexahydrate in the presence of water. Therefore, heating I with amines, such as diethylamine, piperidine, morpholine, diethanolamine and triethanolamine, in benzene containing the amount of water corresponding to the crystal water of piperazine hexahydrate was attempted under the similar condition. As expected, dibenzyltrisulfide was obtained in the treatment with diethylamine and piperidine in 15% and 13% yields, respectively, which was almost same as the yield obtained in the treatment with piperazine hexahydrate. When ether instead of benzene was used as the reaction solvent, the treatment with morpholine also gave dibenzyltrisulfide in 8% yield. In the case of diethanolamine and triethanolamine, however, the trisulfide was not obtained at all and the materials were recovered. Probably the strong basity of amine would be required in the formation of trisulfide.

From these results, the following mechanism would be proposed.

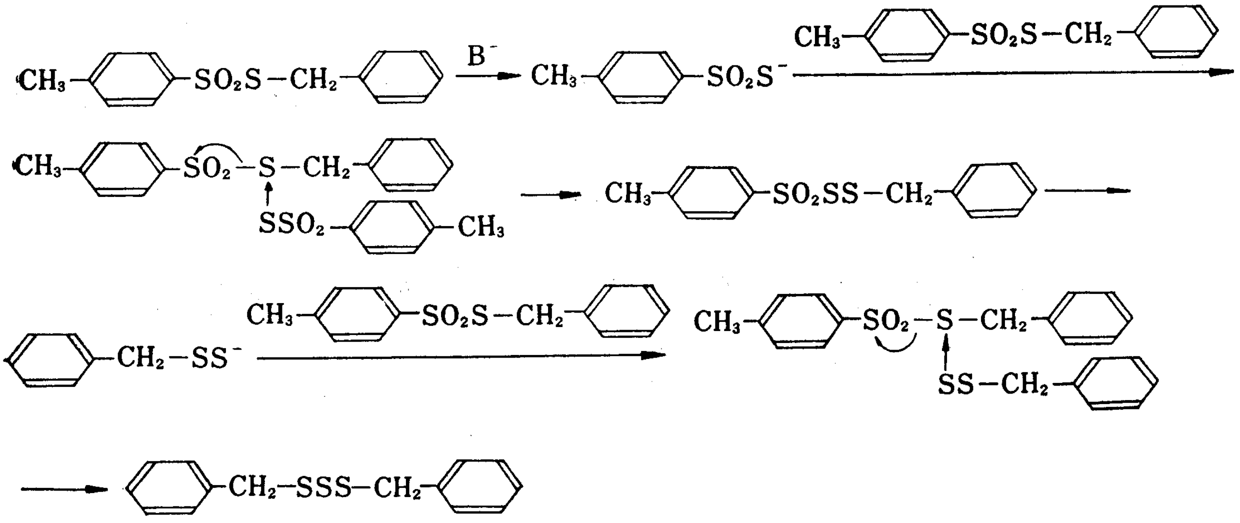

Chart 3

Hydrolysis of bezyl *p*-toluenethiosulfonate to form *p*-toluenesulfonylthio anion must initially occur in this mechanism. Benzyl *p*-toluenethiosulfonate will be partly polarized with a positive charge on the sulfur atom. *p*-Toluenesulfonylthio anion formed would attack the positive charge on the sulfur atom to form benzyl *p*-toluenesulfonyldisulfide, which is hydrolyzed to form benzyldithio anion, followed by the nucleophilic attack to the positive charge on the sulfur atom in unchanged benzyl *p*-toluenethiosulfonate to form dibenzyltrisulfide.

To promote the hydrolysis of benzyl *p*-toluenethiosulfonate, the use of sodium hydroxide as a catalyst was unsuccessful and α-benzylmercaptobenzyl *p*-toluenethiosulfonate was obtained in 49% yield. Probably, the formation of the carbonium anion on the methylene group would occure in preference of the hydrolysis to *p*-toluenesulfonylthio anion.

Experimental

Reaction of Benzyl *p*-Toluenethiosulfonate with Piperazine Hexahydrate——a) A solution of 5.56 g (0.02 mole) of benzyl *p*-toluenethiosulfonate and 5.83 g (0.03 mole) of piperazine hexahydrate in 100 ml of benzene was heated with stirring for 6 hr under reflux. After cooling, the solution was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from EtOH to give 0.8 g (14%) of dibenzyltrisulfide melting at 49°. This compound was confirmed to be identical with the authentic sample prepared by another method.[6]

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[6] B. Milligan, B. Saville, and J.M. Swan, *J. Chem. Soc.*, **1963**, 3608.

b) A mixture of 5.56 g (0.02 mole) of benzyl *p*-toluenethiosulfonate, 5.83 g (0.03 mole) of piperazine hexahydrate and 0.64 g (0.02 mole) of sulfur in 100 ml of benzene was heated with stirring for 6 hr under reflux. After cooling, the solution was extracted with 50 ml of H_2O and the benzene layer was dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from EtOH to give 1.2 g (15%) of colorless plates melting at 143—144°. This product was identical with the authentic sample of α-benzylmercaptobenzyl *p*-toluenethiosulfonate prepared by another method.[5] IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1325, 1140 (SO_2). *Anal.* Calcd. for $C_{21}H_{20}O_2S_2$: C, 62.97; H, 5.04. Found: C, 63.11; H, 4.95.

The aqueous layer was evaporated to dryness under reduced pressure. The residue was extracted with EtOH and the extract was concentrated. The precipitates deposited on cooling were recrystallized from EtOH to give 0.48 g (10 %) of piperazinium mono-*p*-toluenesulfinate melting at 206—210° (decomp.). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3260 (NH); 3000 (N^+H_2, broad); 1213, 1050 (SO_2H). *Anal.* Calcd. for $C_{11}H_{18}O_2N_2S$: C, 54.53; H, 7.49; N, 11.56. Found: C, 54.19; H, 7.60; N, 11.21. The insoluble solid was extracted with EtOH–MeOH. The extract was concentrated and the precipitates deposited on cooling were recrystallized from EtOH–MeOH to give 0.28 g (7 %) of piperazinium di-*p*-toluenesulfinate melting at 227—230° (decomp.). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3000 (N^+H_2, broad); 1155, 1098, 1038 (SO_2H). *Anal.* Calcd. for $C_{18}H_{26}O_4N_2S_2$: C, 54.24; H, 6.57; N, 7.03. Found: C, 54.16; H, 6.61; N, 6.98. The insoluble solid in EtOH–MeOH was recrystallized from MeOH to give 0.15 g (6 %) of dibenzyldisulfide melting at 71°. This compound was confirmed to be identical with the authentic sample prepared by another method.

Reaction of Benzyl *p*-Toluenethiosulfonate with Amine Containing Water——a) With Diethylamine: A mixture of 5.56 g (0.02 mole) of benzyl *p*-toluenethiosulfonate, 2.1 g (0.03 mole) of diethylamine and 2.5 ml of H_2O in 100 ml of benzene was heated with stirring for 6 hr under reflux. After cooling, the solution was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from EtOH to give 0.9 g (15 %) of dibenzyltrisulfide melting at 49°.

b) With piperidine: A mixture of 5.56 g (0.02 mole) of benzyl *p*-toluenethiosulfonate, 2.55 g (0.03 mole) of piperidine and 4 ml of H_2O was treated as described above. Recrystallization from EtOH gave 0.7 g (13%) of dibenzyltrisulfide melting at 49°.

c) With Morpholine: A mixture of 5.56 g (0.02 mole) of benzyl *p*-toluenethiosulfonate, 2.6 g (0.03 mole) of morpholine and 3.4 ml of H_2O in 100 ml of ether was refluxed with stirring for 6 hr. After cooling, the solution was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from EtOH to give 0.45 g (8%) of dibenzyltrisulfide melting at 49°.

Reaction of Benzyl *p*-Toluenethiosulfonate with Sodium Hydroxide——A mixture of 5.56 g (0.02 mole) of benzyl *p*-toluenethiosulfonate and 3.3 ml of an aqueous sodium hydroxide (0.64 g) solution in benzene was heated with stirring for 6 hr under reflux. After cooling, the solution was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was recrystallized from EtOH to give 3.92 g (49%) of colorless plates melting at 143—144°. This product was identical with the authentic sample of α-benzylmercaptobenzyl *p*-toluenethiosulfonate prepared by another method. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1325, 1140 (SO_2).

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