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Mechanism for the Reaction of Sodium Benzylthiosulfate with Morpholine

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The reaction of sodium benzylthiosulfate with morpholine was investigated and found to proceed through the intermediate of phenylmethanesulfenylmorpholide and then of dibenzyl disulfide. Whole reaction mechanism was also presumed by the several results obtained.

Milligan[2] has shown that heating of sodium benzylthiosulfate with morpholine for five minutes gave dibenzyl disulfide and the same reaction in the presence of sulfur afforded benzothiomorpholide. However, the reaction mechanism has been remained unsolved. The purpose of this paper is to clarify the mechanism of the reaction of sodium benzylthiosulfate with morpholine.

Reaction of Sodium Benzylthiosulfate and Phenylmethanesulfenmorpholide with Morpholine

We found that prolonged heating of sodium benzylthiosulfate[2,3] with morpholine gave a 53% yield of benzothiomorpholide even in the absence of sulfur, accompanying dibenzyl disulfide and benzaldehyde as by-products. The reaction of benzyl benzenethiosulfonate, in which a functional group similar to that of sodium benzylthiosulfate is involved, with morpholine was also attempted. In the previous paper, Hayashi[4] has reported that benzyl benzenethiosulfonate reacted with morpholine in ether at room temperature to give phenylmethanesulfenmorpholide in 52% yield. In the similar conditions, we obtained not only phenylmethanesulfenmorpholide but also dibenzyl disulfide in 57% and 16% yields. By the pursuance of the reaction with thin-layer chromatograph (TLC), it was observed that phenylmethanesulfenmorpholide formed was converted into dibenzyl disulfide gradually.

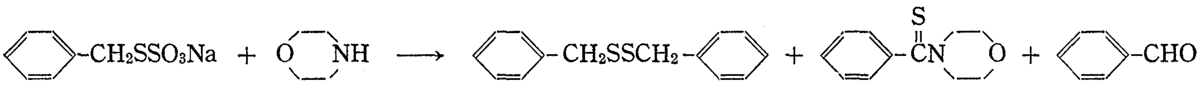

Chart 1

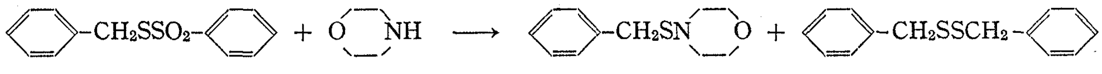

Chart 2

These results suggest that the reaction of sodium benzylthiosulfate with morpholine would proceed through the intermediate formation of phenylmethanesulfenmorpholide to give dibenzyl disulfide, benzothiomorpholide and benzaldehyde. In order to confirm this assumption, phenylmethanesulfenmorpholide[4] was allowed to react with morpholine under the conditions similar to that of the reaction of sodium benzylthiosulfate with morpholine. As the result, dibenzyl disulfide and benzothiomorpholide were obtained in 49% and 39% yields,

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[1] Location: *a) Oe-moto-machi, Kumamoto*; *b) Dosho-machi, Osaka.*
[2] B. Milligan and J.M. Swan, *J. Chem. Soc.*, **1969**, 2969; **1961**, 1194.
[3] H.E. Westlake and G. Dougherty, *J. Am. Chem. Soc.*, **63**, 658 (1941).
[4] S. Hayashi, M. Furukawa, Y. Fujino, and H. Matsukura, *Chem. Pharm. Bull.* (Tokyo), **17**, 954 (1969).

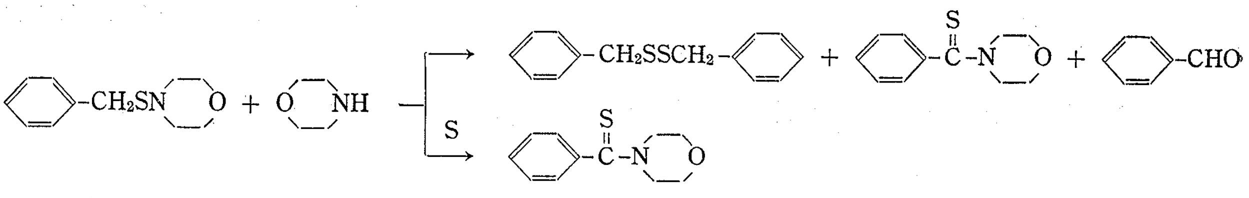

Chart 3

respectively and a small amount of benzaldehyde was also isolated. The same reaction in the presence of sulfur gave benzothiomorpholide in excellent yield, no trace of any dibenzyl disulfide being isolated. These results were parallel to those of the reaction of sodium benzylthiosulfate with morpholine. Therefore, it is presumed that the reaction between sodium benzylthiosulfate and morpholine would proceed through the intermediate formation of phenylmethanesulfenmorpholide, though only trace of phenylmethanesulfenmorpholide was detected in the course of the reaction.

Reaction of Dibenzyl Disulfide with Morpholine

By the pursuance of the time course in the reaction between sodium benzylthiosulfate and morpholine by TLC, dibenzyl disulfide formed in the course of the reaction was observed to disappear gradually and completely after five hours to result in the increased concentration of benzothiomorpholide. This suggests that benzothiomorpholide would be formed through dibenzyl disulfide. In order to reveal this presumption, the reaction of dibenzyl disulfide with morpholine under the similar conditions was attempted.

Heating of dibenzyl disulfide[5] with morpholine for five hours in the absence and presence of sulfur gave 5% and 63% yields of benzothiomorpholide and the small amount of benzaldehyde. When heated with aqueous morpholine for five hours in the presence of sulfur, the 53% yield of benzothiomorpholide and the small amount of benzaldehyde were obtained. While, in the absence of sulfur, no traces of any benzothiomorpholide and benzaldehyde were isolated and dibenzyl disulfide was recovered unchanged.

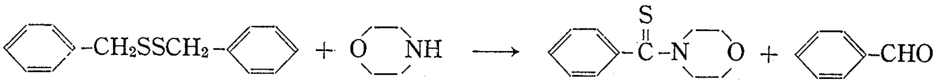

Chart 4

By these results, it is reasonable to consider that the reaction of sodium benzylthiosulfate with morpholine would proceed through the intermediate formation of dibenzyl disulfide to give benzothiomorpholide and benzaldehyde, and sulfur would participate in this reaction. Moreover, different from the case of dibenzyl disulfide, the fact that the reaction between sodium benzylthiosulfate with morpholine in the absence of sulfur gave benzothiomorpholide in comparatively good yield suggests that sulfur would be formed in the course of the reaction, which promotes the reaction toward the formation of benzothiomorpholide. Such a sulfur formation is suggested by Milligan[2] in the reaction of carbamoylmethylthiosulfate with amine. By the similar mechanism, sulfur would be formed from hydrogen sulfide and sulfite ion liberated in the course of the reaction. In fact, the liberation of hydrogen sulfide was observed, though no formation of sulfur could be confirmed.

Discussion of the Reaction Mechanism

Danehy[6] has reported that the conversion of dibenzyl disulfide with hydroxide ion into benzoic acid and phenylmethanethiol is clearly initiated by the elimination of the methylene hydrogen of dibenzyl disulfide to give thiobenzaldehyde and benzylsulfen anion, followed

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5) G.G. Stomer and G. Dougherty, *J. Am. Chem. Soc.*, **63**, 987 (1941).
6) J.P. Danehy and K.N. Parameswaran, *J. Org. Chem.*, **33**, 568 (1968).

by the conversion of thiobenzaldehyde into benzaldehyde and then Cannizaro reaction. The formation of thiobenzaldehyde from dibenzyl disulfide would be also analogously achieved with morpholine and more promptly with morpholinosulfen anion.[7]

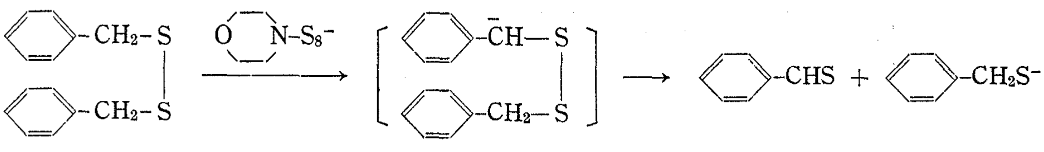
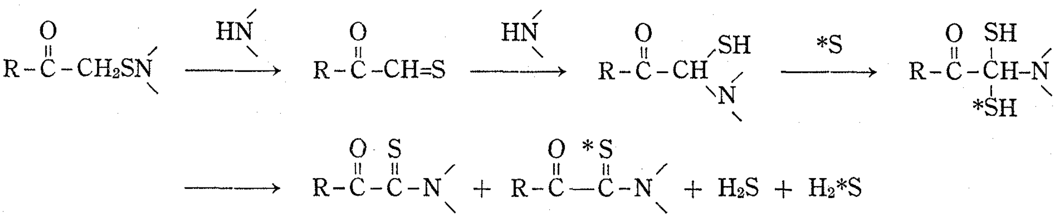


Chart 5

Milligan[8] has reported that heating of a mixture of phenyldimorpholinomethane and sulfur gave benzothiomorpholide in an excellent yield. Yugawa[9] has shown that thiobenzaldehyde was converted into benzothiomorpholide with morpholine and hydrogen sulfide in the presence of sulfur and that phenyldimorpholinomethane reacted with hydrogen sulfide in morpholine to give dibenzyl disulfide and in alcohol to yield thiobenzaldehyde polymer. On the other hand, we found that all of sodium benzylthiosulfate, phenylmethanesulfenmorpholide and dibenzyl disulfide reacted with morpholine to give benzaldehyde together with benzothiomorpholide and dibenzyl disulfide, as described above. Therefore, it is presumed that these reactions would involve the intermediate formation of phenyldimorpholinomethane, which is readily converted into benzaldehyde, because the formation of benzaldehyde is the most likely to explain by such a mechanism.

In the formation of benzothiomorpholide from phenyldimorpholinomethane, it is suggested that the presence of sulfur is essentially required. However, direct formation which has no need of sulfur and probably proceeds through phenylmorpholinomethanethiol should be also considered, because the reactions of sodium benzylthiosulfate and phenylmethanesulfenmorpholide with morpholine were readily achieved in the absence of sulfur to give benzothiomorpholide. Asinger[10] has proved that, by using sulfur isotope, the reaction of α-ketosulfenamide with amine proceeded through the unstable intermediate of α-ketoaminodithiol to give α-ketothioamide. Therefore, it is presumed that benzothiomorpholide is also formed through phenylmorpholinomethanedithiol from phenylmorpholinomethanethiol, though no evidence was provided.



By these facts and results obtained, the following mechanism would be proposed for the reaction of sodium benzylthiosulfate with morpholine.

At the first step the nucleophilic attack[11] of morpholine to the sulfenyl sulfur in sodium benzylthiosulfate (I) forms sulfite ion and phenylmethanesulfenmorpholide (II), followed by the conversion into dibenzyl disulfide (III),[12] which affords thiobenzaldehyde (IV) by abstraction of the methylene hydrogen with morpholine. Thiobenzaldehyde (IV) may be

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[7] R.E. Davis and H.F. Nakshbendi, *J. Am. Chem. Soc.*, **84**, 2085 (1962).

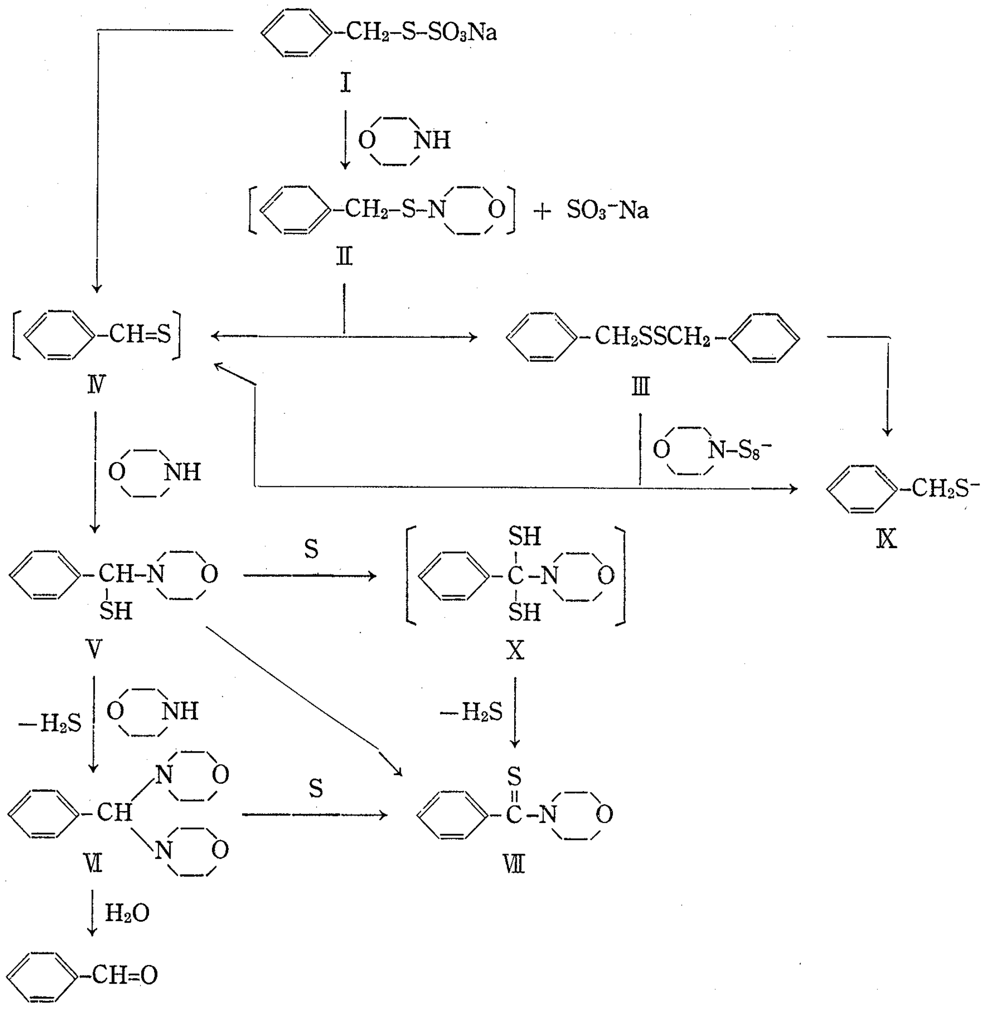
[8] F.H. McMillan and J.A. King, *J. Am. Chem. Soc.*, **70**, 4143 (1948).

[9] Y. Yugawa, F. Tokuda, and S. Amano, *J. Chem. Soc. Japan*, **73**, 498 (1952).

[10] F. Asinger, W. Schafer, K. Halcour, A. Saus, and H. Triem, *Angew. Chem.*, **75**, 1050 (1963).

[11] S. Hayashi, M. Furukawa, Y. Fujino, T. Nakao, and S. Inoue, *Chem. Pharm. Bull.* (Tokyo), **19**, 1557 (1971).

[12] S. One, G. Tsukamoto, and T. Kurisu, *Chemistry* (Japan), **26**, 1066 (1971).



$2H_2S + SO_3^{2-} \longrightarrow 3S + H_2O + 2OH^-$

Chart 6

also provided by the prototropy due to the intramolecular abstraction of the methylene hydrogen with the nitrogen atom of the morpholino group. Addition of morpholine to the thiobenzaldehyde (IV) forms phenylmorpholinomethanethiol (V), which reacts with further morpholine to give phenyldimorpholinomethane (VI), eliminating hydrogen sulfide. The hydrogen sulfide liberated reacts with sulfite ion to form sulfur, which reacts with phenyldimorpholinomethane (VI) to afford the final product of benzothiomorpholide (VII). While, hydrolysis of phenyldimorpholinomethane (VI) forms benzaldehyde (VIII). Sulfur reacts with morpholine to form morpholinosulfen anion[7] and promotes the abstraction of methylene hydrogens in phenylmethanesulfenmorpholide (II), dibenzyl disulfide (III) and probably sodium benzylthiosulfate (I) to form directly thiobenzaldehyde (V). Benzylsulfen anion (IX) which is formed by cleavage of the S-S group in dibenzyl disulfide (III) affords again dibenzyl disulfide (III) by spontaneous oxidation.

Experimental

Reaction of Sodium Benzylthiosulfate with Morpholine——a) In Morpholine: A suspension of 2.3 g of sodium benzylthiosulfate in 10 ml of morpholine was heated for 5 hr under reflux. Evolution of hydrogen sulfide was confirmed with mercuric chloride positive test. After cooling, the solution was neutralized with dil. HCl and extracted with ether. The extracts were washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from EtOH to give 1.1 g (53%) of yellow needles of benzothiomorpholide melting at 137°, which was identified with the authentic sample by IR and mixed melting point determination. *Anal.* Calcd. for $C_{11}H_{13}ONS$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.93;

H, 6.17; N, 7.17. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1030 (C=S). To the recrystallization filtrate was added with stirring phenylhydrazine and the precipitates deposited were recrystallized from EtOH to give colorless needles of benzaldehyde–phenylhydrazone, which was identified with the authentic sample by IR and mixed melting point determination.

b) In Water: A solution of 2.3 g of sodium benzylthiosulfate and 2.6 g morpholine in 30 ml of H_2O was heated for 5 hr under reflux. After cooling, the solution was neutralized with dil. HCl and extracted with ether. The extracts were washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. The residue was taken up with benzene and the extracts were concentrated to charge on a column of silica gel. Development with benzene gave 1.3 g (24%) of dibenzyl disulfide melting at 70—71°. It was identified with the authentic sample by IR and mixed melting point determination. Development with EtOH gave 0.1 g (5%) of benzothiomorpholide melting at 137°. Addition of phenylhydrazine to the EtOH fraction separated benzaldehyde as the phenylhydrazone.

Reaction of Dibenzyl Disulfide with Morpholine——a) In Morpholine: A solution of 1.2 g of dibenzyl disulfide in 10 ml of morpholine was heated for 5 hr under reflux. After cooling, the solution was neutralized with dil. HCl and extracted with benzene. The extracts was washed with H_2O, dried over Na_2SO_4, concentrated and chromatographed on silica gel. Development with benzene and then EtOH gave 0.9 g (75%) of unchanged dibenzyl disulfide and 0.1 g (10%) of benzothiomorpholide, respectively. From the EtOH fraction, benzaldehyde was detected as phenylhydrazone.

In the presence of 0.16 g of sulfur, the treatment of 1.2 g of dibenzyl disulfide with 10 ml of morpholine under the similar condition gave 0.2 g (17%) of dibenzyl disulfide, 1.3 g (63%) of benzothiomorpholide and benzaldehyde.

b) In Water: A mixture of 1.2 g of dibenzyl disulfide and 1.3 g of morpholine in 20 ml of H_2O was heated for 5 hr under reflux. In the result, dibenzyl disulfide was recovered unchanged, no trace of any expected compounds being isolated.

In the presence of 0.16 g of sulfur, a solution of 1.2 g of dibenzyl disulfide and 1.3 g of morpholine in 20 ml of H_2O was heated for 5 hr under reflux. After cooling, the solution was neutralized with dil. HCl and taken up with benzene. The extracts were washed with H_2O, dried over Na_2SO_4, concentrated and chromatographed on silica gel. Development with benzene and EtOH gave 0.3 g (25%) of dibenzyldisulfide and 1.1 g (53%) of benzothiomorpholide. From the EtOH fraction, benzaldehyde was also separated as the phenylhydrazone.

Reaction of Benzyl Benzenethiosulfonate with Morpholine——A solution of 2.1 g of benzyl benzenethiosulfonate and 3.5 g of morpholine in 50 ml of ether was stirred for 3 hr at room temperature and the precipitates deposited were filtered off. The filtrate was evaporated to dryness and the residue was extracted with benzene. The extracts were washed with H_2O, dried over Na_2SO_4, concentrated and chromatographed on silica gel. Development with benzene gave 0.2 g (16%) of dibenzyl disulfide and 1.2 g (57%) of phenylmethanesulfenylmorpholide melting at 74—75°, which was identified with the authentic sample by IR and mixed melting point determination. *Anal.* Calcd. for $C_{11}H_{15}ONS$: C, 63.11; H, 7.21; N, 6.69. Found: C, 63.18; H, 7.27; N, 6.76.

Reaction of Phenylmethanesulfenylmorpholide with Morpholine——a) In Morpholine: A solution of 1.0 g of phenylmethanesulfenylmorpholide in 10 ml of morpholine was heated for 5 hr under reflux. After cooling, the solution was neutralized with dil. HCl and extracted with benzene. The extracts were washed with H_2O, dried over Na_2SO_4, concentrated and chromatographed on silica gel. Development with benzene and then EtOH gave 0.3 g (49%) of dibenzyl disulfide and 0.4 g (39%) of benzothiomorpholide, respectively. From the EtOH fraction, benzaldehyde was detected as the phenylhydrazone.

In the presence of 0.16 g of sulfur, a solution of 1.0 g of phenylmethanesulfenylmorpholide in 10 ml of morpholine was heated for 30 min under reflux. After cooling, the solution was poured into H_2O and the precipitates deposited were collected by filtration. Recrystallization from EtOH gave 0.9 g (87%) of benzothiomorpholide.

b) In Water: A mixture of 1.0 g of phenylmethanesulfenylmorpholide and 1.3 g of morpholine in 20 ml of H_2O was heated for 5 hr under reflux. After cooling, the solution was neutralized with dil. HCl and extracted with benzene. The extracts were washed with H_2O, dried over Na_2SO_4, concentrated and chromatographed on silica gel. Development with benzene and then EtOH gave 0.4 g (65%) of dibenzyl disulfide and a small amount of benzothiomorpholide. From the EtOH fraction, benzaldehyde was also detected.

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