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The Reaction of Benzyl Phenylmethanethiosulfinate with Amines

Mitsuru Furukawa, Seishi Tsuiji, Yoko Kojima,
and Seigoro Hayashi

Faculty of Pharmaceutical Sciences, Kumamoto University[1]

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The reaction of benzyl phenylmethanethiosulfinate with morpholine was found to give dibenzyl trisulfide together with dibenzyl disulfide, benzaldehyde and N-thiobenzoylmorpholine and the reaction mechanism was discussed. In the reaction with other secondary amines instead of morpholine, dibenzyl trisulfide was also obtained.

It has been known that thiosulfonates react with amines to give the corresponding sulfenamides.[2] Recently we also reported that the reaction of benzyl benzenethiosulfonate with morpholine in ether at room temperature for 3 hours gave a 57% yield of N-(benzylthio)-morpholine, which was further converted into dibenzyl disulfide, N-thiobenzoylmorpholine and benzaldehyde.[3] Owing to the structural similarity, benzyl phenylmethanethiosulfinate might be expected to show some behaviors analogous to those of benzyl benzenethiosulfonate toward morpholine. This paper deals with the reaction of benzyl phenylmethanethiosulfinate with morpholine and other amines.

The reaction between benzyl phenylmethanethiosulfinate and morpholine was attempted under a few different reaction conditions. When benzyl phenylmethanethiosulfinate (I) was heated with an excess of morpholine in water under reflux for 5 hours, a 33% yield of dibenzyl disulfide (II) and a small amount of benzaldehyde (III) were obtained and the formation of N-thiobenzoylmorpholine (IV) was also observed by thin-layer chromatography (TLC). The same reaction in the presence of sulfur under the similar conditions gave II and IV in 4% and 38% yields, respectively, accompanying a small amount of III. On the other hand, when I was treated with an excess of morpholine in ether at room temperature for 10 hours, dibenzyl trisulfide (V) was unexpectedly found in a 30% yield, in addition to a 12% yield of II, a 5% yield of IV and a small amount of III. In the course of the reaction, the formation of N-(benzylthio)morpholine (VI) was also observed by TLC.

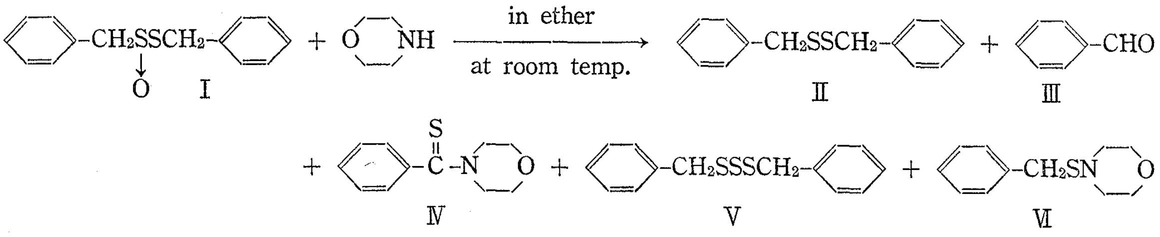

Chart 1

Regarding the formation of II, Backer[4] and Barnard[5] have reported that thiosulfinates were readily converted into thiosulfonates and disulfides by disproportionation. On the other hand, it is well known that sulfenamides are generally unstable and easily decomposed

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

[2] *a*) B.G. Boldyrev and S.A. Kolesnikova, *C.A.*, **62**, 13076e (1965); *b*) J.E. Dunbar and J.H. Rogers, *J. Org. Chem.*, **31**, 2842 (1966); *idem*, *Tetrahedron Letters*, **1965**, 4291.

[3] M. Furukawa, K. Shiraishi, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 2315 (1972).

[4] H.J. Backer and H. Kloosterziel, *Rec. Trav. Chim.*, **73**, 129 (1954).

[5] D. Barnard, *J. Chem. Soc.*, **1957**, 4675.

to disulfides on allowing to stand and more rapidly on heating or in the presence of acids and alkalis.[6] We have also found that N-(benzylthio)morpholine was readily converted with morpholine into dibenzyl disulfide and N-thiobenzoylmorpholine, accompanying the formation of benzaldehyde.[3]

The fact that the formation of VI was actually observed in the reaction between I and morpholine, though an effort for the isolation resulted in failure, suggests that the mechanism through the initial nucleophilic attack of morpholine to the sulfenyl sulfur atom of I might be involved in the reaction. Furthermore, it must be noted that all of the intermediates and products formed in the reaction coincided with those in the similar reaction between sodium benzylthiosulfate and morpholine, of which the mechanistic pathway[3] was substantially revealed by us. By this result, it is reasonable to conclude that these two reactions would proceed through the same mechanism. Namely, at the first step the nucleophilic attack of morpholine to the sulfenyl sulfur of I forms the intermediate VI followed by facile conversion into II. Although it has been revealed that the nucleophilic attack center in thiosulfinates is different depending upon the specific charactor of the nucleophilic reagents,[7] little has been reported relating to the reaction with amines. Abstraction of the methylene hydrogen of II with morpholine affords thiobenzaldehyde (VII), which may be also formed by prototropy due to the intramolecular abstraction of the methylene hydrogen of VI with the nitrogen atom of the morpholino group. Addition of morpholine to VII forms phenylmorpholino-

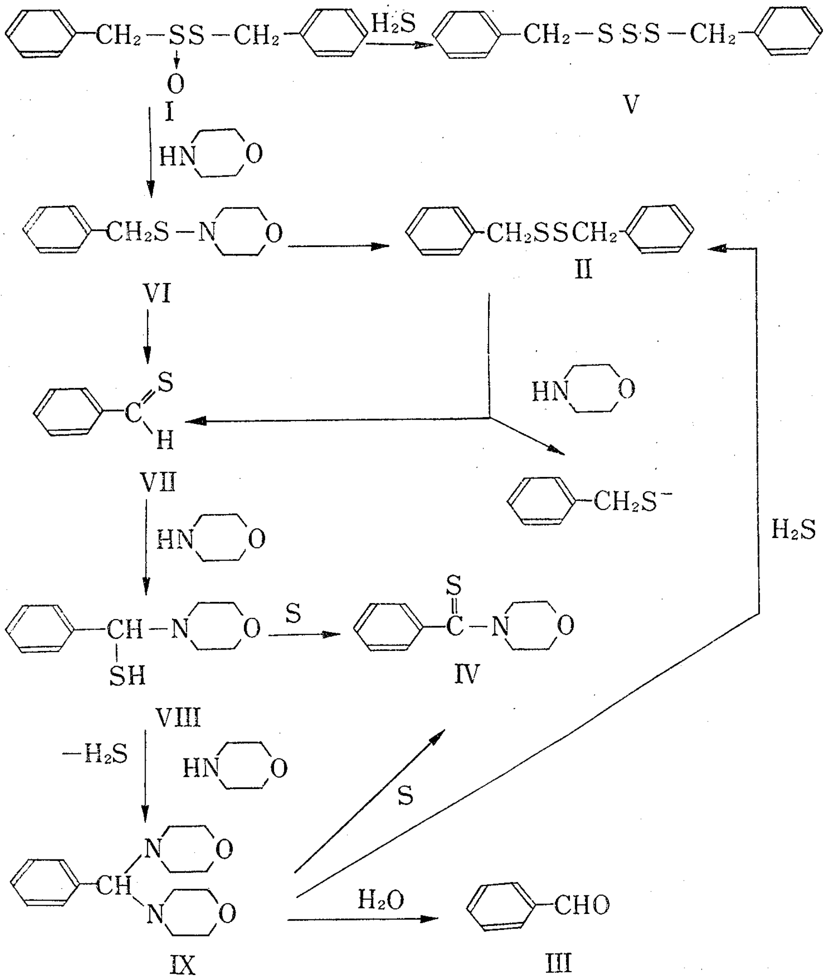

Chart 2

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6) E.L. Carr, G.E.P. Smith, and G. Alliger, *J. Org. Chem.*, **14**, 921 (1946).
7) S. Oae and G. Tsukamoto, *Kagaku* (Japan), **26**, 172 (1971).

methanethiol (VIII), which reacts with further morpholine to give phenyldimorpholinomethane (IX) accompanying the elimination of hydrogen sulfide. The liberation of hydrogen sulfide was actually confirmed by the positive lead acetate test in the course of the reaction of I with morpholine. At the final step VIII and IX provide IV by participation of sulfur probably formed in the course of the reaction.

The pathway through VIII to IV has been proved by Asinger[8] in the reaction of α-ketosulfenamide with amine. The pathway to IV from IX is supported by the fact that IX reacts with sulfur to give IV in an excellent yield.[9] IX is readily converted into III by hydrolysis and also forms II. The conversion of IX to II with hydrogen sulfide has been reported by Yugawa.[10]

Hydrogen sulfide liberated in the course of the reaction would react with I to give dibenzyl trisulfide (V). This assumption may be supported by the fact that the reaction of cystine S-monoxide with hydrogen sulfide gives dialanyl trisulfide.[11] To elucidate that the formation of V is due to the participation of hydrogen sulfide, the reaction of I with morpholine was carried out under introducing a stream of hydrogen sulfide. In the result, the evident increase of the yield of V was observed. The nucleophilic attack of hydrogen sulfide to the sulfenyl sulfur of I may form benzyl hydrodisulfide (X), accompanying the elimination of phenylmethanesulfinic acid.

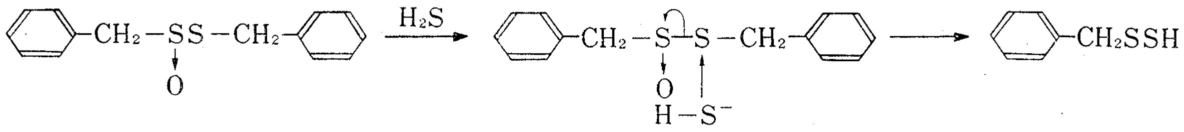

Chart 3

The formation of trisulfides from aralkyl hydrodisulfides with amines has been known by Tsurugi[12] and the mechanism has been also proposed. By analogy, X would react with morpholine to afford V as shown by the following steps.

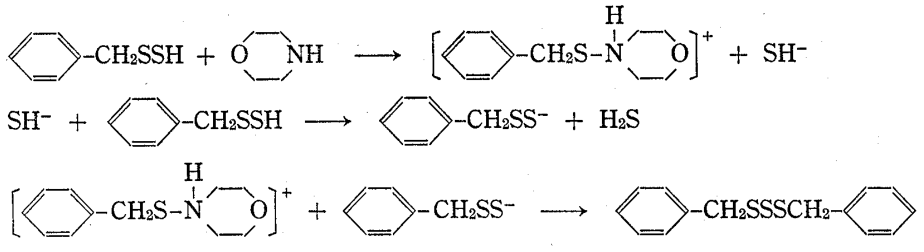

Chart 4

Another mechanism through the further nucleophilic attack of X to I may be also possible.

In order to elucidate the direct participation of I but not the intermediates for the formation of V, the intermediates VI and II were allowed to react with morpholine under the similar reaction conditions. Treatment of VI with morpholine in ether at room temperature for 20 hours gave a 16% yield of II as the only product, no trace of any other compounds anticipated being isolated. Heating of the both reactants in water under reflux for 5 hours afforded II and IV in 56% and 5% yields, respectively, accompanying a small amount of III. In both cases, no formation of V was observed in the pursuance by TLC. Analogously, the reaction of II with morpholine under the similar conditions gave no trace of V. These results suggest that I is the direct reactant essential for the formation of V.

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8) F. Asinger, W. Schäfer, K. Halcour, A. Saus, and H. Triem, *Angew. Chem.*, **75**, 1050 (1963).
9) F.H. McMillan and J.A. King, *J. Am. Chem. Soc.*, **70**, 4143 (1948).
10) Y. Yugawa, F. Tokuda, and S. Amano, *J. Chem. Soc. Japan*, **73**, 498 (1952).
11) W.E. Savige and J.A. Maclasen, "Organic Sulfur Compound," Vol. 2, 1966, Chap. 15.
12) J. Tsurugi, Y. Abe, T. Nakabayashi, and S. Kawamura, *J. Org. Chem.*, **35**, 3263 (1970).

The reaction of I with other several amines was also attempted. When treated with piperidine and diethanolamine in ether at room temperature for 10 hours, V was successfully obtained in 33% and 27% yields, respectively. Treatment with piperazine in methanol under the similar conditions analogously afforded V in a low yield, together with a 36% yield of II. The formation of III was also observed in all cases. However, in the reaction with ethylamine of a primary amine and triethylamine of a tertiary amine, no trace of any V was isolated, though II was formed in 42% and 35% yields, respectively, as the only product isolated.

Experimental

Benzyl Phenylmethanethiosulfinate——A suspension of 0.04 g of tungstic acid in 2 ml of H_2O was made at pH 11.3 with 50% NaOH solution and then at pH 5.6 with acetic acid. The suspension was added with stirring to a solution of 10 g of dibenzyl disulfide in 100 ml of EtOH. To the solution was added slowly with stirring 5 ml of 30% H_2O_2 solution keeping the temperature at 55—60° and the stirring was continued for additional 20 min. After cooling, the precipitates deposited were collected by filtration and recrystallized from ether to give 3—4 g (30—40%) of colorless plates melting at 83—85°. *Anal.* Calcd. for $C_{14}H_{14}OS_2$: C, 64.09; H, 5.38. Found: C, 63.95; H, 5.34. IR ν_{max}^{KBr} cm^{-1}: 1100 (SO).

Reaction of Benzyl Phenylmethanethiosulfinate with Morpholine——a) In Water: A mixture of 1.3 g (0.005 mole) of benzyl phenylmethanesulfinate, 1.6 g (0.02 mole) of morpholine and 50 ml of H_2O was heated for 5 hours under reflux. Liberation of hydrogen sulfide was confirmed by the positive lead acetate test. After cooling, the solution was neutralized with dil. HCl and extracted with benzene. The extract was washed with H_2O, dried over Na_2SO_4, concentrated and chromatographed on silica gel. Development with benzene gave 0.4 g (33%) of dibenzyl disulfide[13] melting at 70—71° after recrystallization from EtOH. The development with EtOH gave benzaldehyde, which was converted into the phenylhydrazone melting at 155—156°. The formation of N-thiobenzoylmorpholine was also observed by TLC.

When the same reaction was carried out in the presence of sulfur, dibenzyl disulfide and N-thiobenzoylmorpholine melting at 136—137° were obtained in 4% and 38% yields, respectively. Benzaldehyde was also confirmed by conversion into the phenylhydrazone.

The identification of crystalline products was carried out by mixed melting point determination and infrared (IR) comparison with authentic samples.

b) In Ether: A solution of 3.0 g (0.012 mole) of benzyl phenylmethanethiosulfinate in 100 ml of dry ether was treated with stirring with 3.8 g (0.048 mole) of morpholine at room temperature for 10 hours. The solution was washed with H_2O and concentrated. The precipitates deposited on cooling were collected and recrystallized from EtOH to give 1.0 g (30%) of dibenzyl trisulfide[14] melting at 48—49°. *Anal.* Calcd. for $C_{14}H_{14}S_3$: C, 60.43; H, 5.07. Found: C, 60.20; H, 4.92. Development of the filtrate with benzene gave 0.35 g (12%) of dibenzyl disulfide[13] melting at 70—71° after recrystallization from EtOH. Development with EtOH gave 0.15 g (5%) of N-thiobenzoylmorpholine melting at 136—137° after recrystallization from EtOH. Benzaldehyde was also confirmed by conversion into the phenylhydrazone. By pursuance with TLC, the formation of N-(benzylthio)morpholine was also confirmed.

When a solution of 3.0 g (0.012 mole) of benzyl phenylmethanethiosulfinate and 3.8 g (0.048 mole) of morpholine in 100 ml of dry ether was stirred at room temperature for 1 hour introducing a solw stream of hydrogen sulfide, dibenzyl trisulfide and dibenzyl disulfide were obtained in 57% and 16% yields, respectively.

Reaction of N-(Benzylthio)morpholine with Morpholine——a) A solution of 1.0 g (0.005 mole) of N-(benzylthio)morpholine in 50 ml of dry ether was treated with stirring with 1.8 g (0.02 mole) of morpholine at room temperature for 20 hours. The solution was concentrated and the precipitates deposited on cooling were collected by filtration to give 0.6 g (60%) of unchanged N-(benzylthio)morpholine. The filtrate was neutralized with dil. HCl and extracted with benzene. The extract was evaporated and the residue was recrystallized from EtOH to give 0.2 g (16%) of dibenzyl disulfide melting at 70—71°.

b) A solution of 1.0 g (0.005 mole) of N-(benzylthio)morpholine in 50 ml of dry ether was treated with stirring with 1.8 g (0.02 mole) of morpholine under introducing a slow stream of hydrogen sulfide at room temperature for 6 hours. The solution was then concentrated and 0.03 g of sulfur isolated was filtered off. The filtrate was neutralized with dil. HCl and extracted with benzene. After the extract was concentrated, the precipitates deposited on cooling were collected and recrystallized from EtOH to give 0.6 g (49%) of dibenzyl disulfide[13] melting at 70—71°. From the filtrate, benzaldehyde was isolated by conversion into the phenylhydrazone. The formation of N-thiobenzoylmorpholine was also observed by TLC.

Reaction of Benzyl Phenylmethanethiosulfinate with Diethanolamine——A solution of 4.2 g (0.016 mole) of benzyl phenylmethanethiosulfinate and 1.7 g (0.016 mole) of diethanolamine in 100 ml of dry ether

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13) C. Marcker, *Ann.*, **136**, 88 (1965).

14) B. Milligan, B. Saville, and J.M. Swan, *J. Chem. Soc.*, **1963**, 3608.

was stirred at room temperature for 10 hours. The solution was washed with H_2O and evaporated. The residue was allowed to stand overnight and the precipitates deposited were collected and recrystallized from EtOH to give 1.4 g (33%) of dibenzyl trisulfide[14) melting at 48—49°. By adding an ethanolic phenylhydrazine solution to the filtrate, benzaldehyde phenylhydrazone melting at 155—156° was obtained.

Reaction of Benzyl Phenylmethanethiosulfinate with Piperidine——A solution of 3.0 g (0.012 mole) of benzyl phenylmethanethiosulfinate and 1.0 g (0.012 mole) of piperidine in 100 ml of dry ether was stirred at room temperature for 8 hours. The solution was concentrated and the residue was allowed to stand overnight in a refrigerator. The precipitates deposited were collected and recrystallized from EtOH to give 0.8 g (27%) of dibenzyl trisulfide14) melting at 48—49°.

Reaction of Benzyl Phenylmethanethiosulfinate with Piperazine——A mixture of 5 g (0.02 mole) of benzyl phenylmethanethiosulfinate, 7.6 g (0.088 mole) of piperazine hexahydrate and 100 ml of dehyd. MeOH was stirred at room temperature for 8 hours. The mixture was then allowed to stand overnight in a refrigerator and the precipitates deposited were collected and recrystallized from EtOH to give 1.8 g (36%) of dibenzyl disulfide13) melting at 70—71°. On concentrating of the filtrate, a small amount of dibenzyl trisulfide14) melting at 48—49° was also obtained.

Reaction of Benzyl Phenylmethanethiosulfinate with Ethylamine——A mixture of 1.3 g (0.005 mole) of benzyl phenylmethanethiosulfinate, 0.63 g (0.02 mole) of 70% ethylamine solution and 50 ml of dry ether was stirred at room temperature for 20 hours. The mixture was evaporated and the precipitates deposited on cooling were collected. Recrystallization from EtOH gave 0.5 g (40%) of dibenzyl disulfide13) melting at 70—71°.

Reaction of Benzyl Phenylmethanesulfinate with Triethylamine——A solution of 1.3 g (0.005 mole) of benzyl phenylmethanethiosulfinate in 50 ml of dry ether was treated with stirring with 2.0 g (0.002 mole) of triethylamine at room temperature for 20 hours. The solution was evaporated and the residue was recrystallized from EtOH to give 0.3 g (35%) of dibenzyl disulfide13) melting at 70—71°.

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