The Formation of Methyl Methanethiolsulfonate, an Antibacterial Substance, from Dimethylsulfoxide

By Tsutomu TSUCHIYA, Setsuko IRIYAMA and Sumio UMEZAWA

(Received September 10, 1963)

When dimethylsulfoxide (DMSO) as a solvent is treated with an excess of hydrogen chloride and when the reaction product is subjected to paper bioautography, there is found an antibacterial spot which was presumed to be derived from DMSO; therefore, an attempt has been made to isolate the active substance from the reaction product of DMSO with hydrogen chloride. The purpose of this paper is to establish that the active substance is methyl methanethiolsulfonate.

Sulfoxides (I) are basic, as is indicated by their ability to form salts with strong acids, and it is known that sulfoxides are reduced by hydrogen halides to sulfides[1] (IV) via the diacid salts (III):

$$\begin{array}{ccccccc} R_2SO & \xrightarrow{HX} & R_2SO\cdot HX & \xrightarrow[-H_2O]{HX} & [R_2SX]^+X^- & \xrightarrow[-X_2]{} & R_2S \\ (I) & & (II) & & (III) & & (IV) \end{array}$$

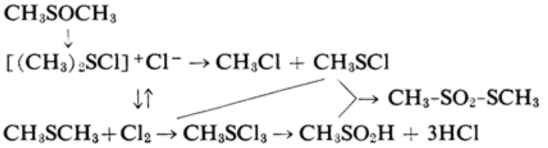
The reaction between DMSO and hydrogen chloride, however, is complicated and not fully understood.

When DMSO was caused to react with equimolecular hydrogen chloride under cooling, a semi-crystalline mush, which was presumably the monoacid salt (II, $R=CH_3$), was formed and there was no antibacterial activity against *Bacillus subtilis*. When DMSO was further treated with an excess of hydrogen chloride, however, a clear solution was obtained, and when the solution was allowed to stand, the temperature of the solution spontaneously rose to about 60°C and a considerable amount of gas was evolved. The low-boiling product collected was found to be mainly composed of hydrogen chloride and a water-insoluble component which was presumably dimethyl sulfide (IV, $R=CH_3$). The resulting solution was neutralized thoroughly with powdered sodium bicarbonate or pyridine and, as described in the experimental section, repeatedly treated with organic solvents to produce a crude product almost free from chlorine. This product was purified by vacuum-distillation to give methyl methanethiolsulfonate ($CH_3-SO_2-SCH_3$). The product purified gave analyses for methyl methanethiolsulfonate, and the boiling point and infrared absorption bands corresponded well with those reported for the compound prepared by a different method.[2]

Methyl methanethiolsulfonate has been found to have antibacterial and antifungal activities. This suggested that the methanethiolsulfonates have an antimicrobial interest. An antimicrobial test of a variety of methanethiolsulfonates is, therefore, under way.

Discussion

The inter-relationships of the products in the reaction of DMSO with hydrogen chloride may be represented by the accompanying diagram. All the inter-relationships except the formation of methanesulfenyl chloride ($CH_3\cdot SCl$) have been established.



$$\begin{array}{l} CH_3SOCH_3 \\ \downarrow \\ [(CH_3)_2SCl]^+Cl^- \rightarrow CH_3Cl + CH_3SCl \\ \qquad\qquad \downarrow\uparrow \qquad\qquad\qquad\qquad \rightarrow CH_3\text{-}SO_2\text{-}SCH_3 \\ CH_3SCH_3 + Cl_2 \rightarrow CH_3SCl_3 \rightarrow CH_3SO_2H + 3HCl \end{array}$$

The formation of methylsulfur trichloride (CH_3SCl_3) from methanesulfenyl chloride and chlorine was established by Douglass and coworkers.[3] The formation of methanesulfinic acid (CH_3SO_2H) by the hydrolysis of methylsulfur trichloride was found by Douglass and Farah.[2] The reaction of sulfenyl chloride with sulfinic acid was applied to the preparation of thiolsulfonate esters ($R-SO_2-SR$) by Stirling.[4] The formation of thiolsulfonate esters from sulfenyl chlorides and sulfinic acids was also concluded by Douglass and Farah[2] in the chlorination of alkyl disulfides.

Any mechanism which would account for the formation of methanesulfenyl chloride must involve the rupture of the sulfur-carbon bond,

---

[1] Recent applications of the reaction to the preparation of sulfides have been described in the following papers: B. Iselin, *Helv. Chim. Acta*, **44**, 61 (1961); E. N. Karaulova and G. D. Gal'pern, *Zhur. Obshchei Khm.*, **29**, 3033 (1959); *Chem. Abstr.*, **54**, 12096 (1960).

[2] I. B. Douglass and B. S. Farah, *J. Org. Chem.*, **24**, 973 (1959).

[3] K. R. Brower and I. B. Douglass, *J. Am. Chem. Soc.*, **73**, 5787 (1951); I. B. Douglass, K. R. Brower and F. T. Martin, ibid., **74**, 5770 (1952).

[4] C. J. M. Stirling, *J. Chem. Soc.*, **1957**, 3597.

and it seems reasonable to suppose that the diacid salt of DMSO decomposes into methanesulfenyl chloride and methyl chloride. This kind of decomposition is rather unusual and the major known product of the decomposition of the diacid salt of DMSO is dimethyl sulfide. Several instances of this kind of decomposition, however, have been found in the literature related to the chlorination of sulfides. An example is the formation⁵⁾ of 2-nitro-4-methylbenzenesulfenyl chloride from methyl 2-nitro-4-methylphenyl sulfide and chlorine. Moreover, Bordwell and Pitt⁶⁾ described that the presence of colored impurities in several of the products obtained by the chlorination of sulfides suggested contamination by sulfenyl chlorides.

Methanesulfenyl chloride probably was formed by the nucleophilic attack of chloride ions on the carbon in the chlorosulfonium ions.

Experimental

Methyl Methanethiolsulfonate.—DMSO was dried over potassium carbonate or potassium hydroxide and vacuum-distilled (b. p. 51°C/3.5 mmHg). DMSO (100 g.) was placed in a three-neck flask fitted with a sealed stirrer, a thermometer and a gas inlet tube. The flask and its contents were then cooled and a gentle stream of dry hydrogen chloride gas was admitted until about 60 g. hydrogen chloride had been absorbed. The temperature of the contents was not allowed to rise above 40°C. When about half of the hydrogen chloride had been absorbed, the contents crystallized. When the addition of hydrogen chloride was complete, however, a solution was obtained.

While the resulting solution was allowed to stand at room temperature, the temperature of the contents spontaneously rose to about 60°C and a considerable amount of gas evolved. The low-boiling product, collected in a bottle cooled in liquid air, mainly consisted of a water-insoluble liquid (about 15 g.) and hydrogen chloride. The water-insoluble liquid had a b. p. of about 37°C and was presumed to be dimethyl sulfide.

The solution left after the gas evolution was subjected to vacuum-distillation at about 50°C; when the vacuum reached 2 mmHg, the distillation was stopped. The viscous liquid (70 g.) left in the flask was thoroughly neutralized with sodium bicarbonate (about 50 g.) by mixing, and the mixture was allowed to stand at room temperature for 1 hr. The mixture was then extracted four times with 150 ml. portions of ethanol. The extracts were combined and allowed to stand for a while to give a small quantity of precipitate. After removal of the precipitate by filtration, the extract was distilled under reduced pressure to remove the solvent. The oily residue was again extracted with acetone (300 ml.), and the solvent was removed by distillation to give a yellowish, clear liquid (7.0 g.). The product was finally extracted three times with portions of 15 ml. of ether. The ether-insoluble part obtained was a viscous liquid and had a weak antibacterial activity against *Bacillue subtilis*.

The ethereal extract was distilled under reduced pressure to yield a colorless liquid of methyl methanethiolsulfonate, b. p. 82.5~83.5°C (2.5 mmHg)⁷⁾ at a bath-temperature of 100~120°C; yield, 3.5 g. The infrared spectrum showed strong absorptions at 1330, 1305, 1135, 958 and 750 cm^{-1}.

Found: C, 19.54; H, 4.99; S, 50.62. MW,* 117. Calcd. for $C_2H_6O_2S_2$: C, 19.04; H, 4.79; S, 50.81%. MW, 126.

The product inhibited the growth of *Trichophyton rubrum*, *Trichopyton asteroides*, *Bacillus subtilis* and *Escherichia coli* in the minimum concentrations of 15.6, 31.2, 125 and 125 mcg./ml. respectively. A detailed report on the antimicrobial spectrum and toxicity will be published elsewhere.

Summary

1) Methyl methanethiolsulfonate has been obtained from the reaction product of dimethyl sulfoxide with hydrogen chloride. Methyl methanethiolsulfonate has been found to have antifungal and antibacterial activities.

2) It has been suggested that methanesulfenyl chloride is formed from the diacid salt of DMSO and that it reacts with methanesulfinic acid to yield methyl methanethiolsulfonate.

The authors are indebted to Mr. Saburo Nakada for the microanalyses and to Mr. Hiroshi Saito for his assistance in the experimental work.

Department of Applied Chemistry
Faculty of Engineering
Keio University
Koganei-shi, Tokyo

---

5) T. Zincke and H. Röse, *Ann.*, **406**, 127 (1914).

6) F. G. Bordwell and B. M. Pitt, *J. Am. Chem. Soc.*, **77**, 573 (1955).

7) E. J. Baker, *Rec. trav. chim.*, **67**, 897 (1948); reported b. p. 84~85°C/2.5 mmHg.

* By the cryoscopic method with benzene.