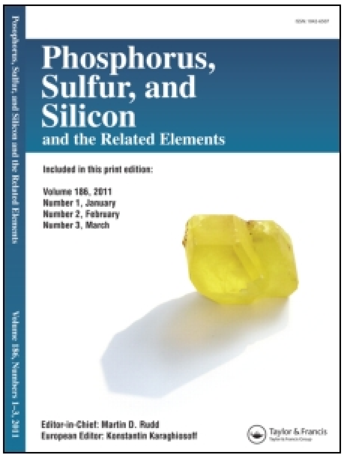

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FORMATION OF SULFOXIDE 'DIMERS' FROM HYDROGEN PEROXIDE OXIDATION OF 2-CHLOROETHYL METHYL SULFIDE AND 2-CHLOROETHYL ETHYL SULFIDE

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The oxidation of 2-chloroethyl methyl sulfide and 2-chloroethyl ethyl sulfide (analogs of sulfur mustard) by hydrogen peroxide have resulted in the isolation of the oxidation products in crystalline form. The IR spectra of these products showed the typical sulfoxide absorption in the 1070-1030 cm^{-1} region. However, MS and NMR spectroscopy indicated that oxidation of 2-chloroethyl sulfides resulted in a dimerization and elimination reaction, leading to the formation of sulfoxides having the structure $RSOCH_2CH_2SOCH_2CH_2Cl$, where R = $—CH_3$ or $—CH_2CH_3$. Similar dimers were not produced from thiodiglycol, which contains no beta chlorine. The structures of these dimeric sulfoxides were fully established by spectroscopic and elemental analyses.

Key words: Hydrogen peroxide oxidation; formation of atypical sulfoxide "dimers"; 2-chloroethyl ethyl sulfide; 2-chloroethyl methyl sulfide; thiodiglycol.

INTRODUCTION

Conversion of sulfide vesicants to the corresponding sulfoxides of substantially less toxicity can be achieved by oxidation with peroxides[1–3] or by catalytic oxidation with dihaloruthenium oxygen complexes,[4] Ce(IV),[5] iodine,[6] and peroxidases.[7] Although peroxides are excellent oxidizing agents for preparing sulfoxides, we had difficulty in obtaining sulfoxides from 2-chloroethyl ethyl sulfide (CEES) and 2-chloroethyl methyl sulfide (CEMS) by either the hydrogen peroxide or m-chloroperbenzoic acid method.[1–3] Subsequent investigation of the peroxide reactions, a quantitative yield of thiodiglycol (TDG) sulfoxide was obtained by direct interacting TDG with 30% H_2O_2 in the absence of any organic acid or solvent system. However, under similar reaction conditions used for TDG, hydrogen peroxide oxidation of CEMS and CEES resulted in the formation of atypical sulfoxides of unexpected chemical structures according to the reaction scheme shown below,[8] where R = $—CH_3$ or $—CH_2CH_3$.

$$2\ RSCH_2CH_2Cl + 2\ H_2O_2 \rightarrow RSOCH_2CH_2SOCH_2CH_2Cl + RCl + 2\ H_2O$$

The structures of these crystalline "dimeric" sulfoxides were established by IR, MS, NMR spectroscopy and elemental analysis. The possible mechanism involved in the dimerization and elimination reactions will be discussed.

RESULTS AND DISCUSSION

1. *Formation of $CH_3SOCH_2CH_2SOCH_2CH_2Cl$ from the Oxidation of CEMS*

By eliminating the need for an organic acid or a solvent system, a quantitative yield of TDG sulfoxide was obtained by slowly adding 30% H_2O_2 to pure TDG. The structure of the product was characterized by spectroscopy and elemental analysis. Under similar reaction conditions used for TDG, a crystalline product was also obtained from H_2O_2 oxidation of CEMS. The IR spectrum of the product showed the typical sulfoxide and aliphatic C—H stretching bands at 1045 and 3000 cm^{-1}, respectively. However, the MS spectrum showed significant mass peaks higher than that of the CEMS sulfoxide monomer (126). The peak 203 is believed to represent a protonated molecular ion of the "dimeric" sulfoxide as shown above. The formation of the sulfoxide dimer was further substantiated by the appearance of masses $CH_3SOCH_2CH_2SO^+$ (139), $CH_3SOCH_2CH_2^+$ (91), and a chloride isotope peak near 203. The mass spectrum of the new product is shown in Figure 1.

The ^{13}C chemical shifts of the sulfoxide dimer (lc) are listed in Table I together with the ^{13}C NMR parameters of the starting material (1a) and its corresponding sulfoxide monomer (lb). As can be seen, the chemical shifts of the α-carbons in 1b and 1c were shifted downfield about 17.5 to 21.6 ppm and those of the β-carbons experienced upfield shifts of about −6.0 ppm. The carbons in $—SOCH_2CH_2SO—$, on the other hand, experienced both shielding and deshielding effects from the two

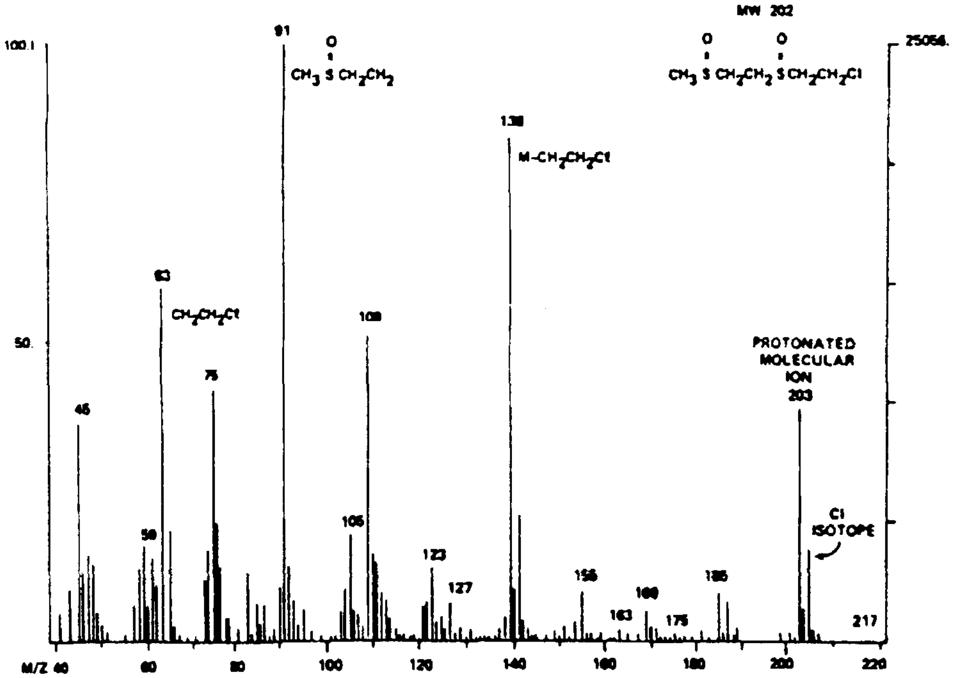


FIGURE 1 Mass spectrum of the crystalline product obtained from hydrogen peroxide oxidation of CEMS.

TABLE I
^{13}C NMR chemical shifts (ppm) of sulfides and sulfoxides

COMPOUND	CH_3S	CH_3CH_2S		$SOCH_2CH_2SO$		CH_2CH_2X	
1a. $CH_3SCH_2CH_2Cl$	15.5	—	—	—	—	36.2	43.1 (X = Cl)
1b. $CH_3SOCH_2CH_2Cl$	37.1	—	—	—	—	54.7	37.2
1c. $CH_3SOCH_2CH_2SOCH_2CH_2Cl$	36.9	—	—	45.3	43.6	53.7	37.07
2a. $CH_3CH_2SCH_2CH_2Cl$	—	15.1	26.2	—	—	33.9	43.4
2b. $CH_3CH_2SOCH_2CH_2Cl$	—	9.2	47.6	—	—	55.7	40.4
2c. $CH_3CH_2SOCH_2CH_2SOCH_2CH_2Cl$	—	6.0	44.9	42.8	43.8	53.7	37.0
3a. $HOCH_2CH_2SCH_2CH_2OH$						65.3	38.1
3b. $HOCH_2CH_2SOCH_2CH_2OH$						56.1	56.3 (X = OH)

^{13}C NMR of 1a and 2a were determined in $CDCl_3$ and the others in D_2O. 1c and 2c are the oxidation products obtained from CEMS and CEES and are named as 2-chloroethyl (methylethylsulfinyl) sulfoxide and 2-chloroethyl (ethylethyl sulfinyl) sulfoxide, respectively. ^{13}C shifts relative to external TSP.

flanking sulfoxide groups, resulting in the observed ^{13}C shifts of about 7–9 ppm smaller than those of the other carbons attached to the same sulfoxide groups. The observed shift differences, as relative to the δ values in the starting material (1a), agreed well with those reported in the literature.[9,10] These ^{13}C NMR data are consistent with the chemical structures of 1b and 1c. Furthermore, the ^{13}C NMR data indicated that the new product was a 5-carbon compound rather than the 3-carbon compound normally expected from CEMS. The structure of 1c was strongly supported by data obtained from ^1H NMR spectroscopy as to the total number of protons and their relative configuration in the molecule. The structure of 1c was fully established by elemental analysis.

2. *Formation of* $CH_3CH_2SOCH_2CH_2SOCH_2CH_2Cl$ *from the Oxidation of CEES*

Similarly, H_2O_2 oxidation of CEES in the absence of any organic acids or solvents resulted in the formation of solid product, for which the IR spectrum showed the typical sulfoxide and C—H stretching bands at 1030 and 2960 cm^{-1}, respectively. However, the mass spectrum (Figure 2) showed significant mass fragments higher than the base peak of the sulfoxide monomer (140). The mass 217 fits well with a protonated molecular ion of the chemical structure of 2c (Table I), which was supported by the appearance of fragments $CH_3CH_2SOCH_2CH_2SO^+$ (153), $CH_3CH_2SOCH_2CH_2^+$ (105), and a chlorine isotope peak close to 217.

Table I also lists the ^{13}C NMR shifts of the new product, 2c; the starting material, 2a; and the corresponding sulfoxide monomer, 2b. As expected, the effect of the sulfoxide groups on the chemical sifts of the α- and β-carbons resulted in the downfield ($\Delta\delta = 18.7 - 19.8$ ppm) and upfield ($\Delta\delta = -6.4$ to -9.1 ppm) shifts of the respective carbons.[9,10] As for 1c, the observed ^{13}C shifts of these carbons are consistent with the above structural assignment, i.e., the solid product was a 6-carbon compound rather than the 4-carbon compound normally expected for a

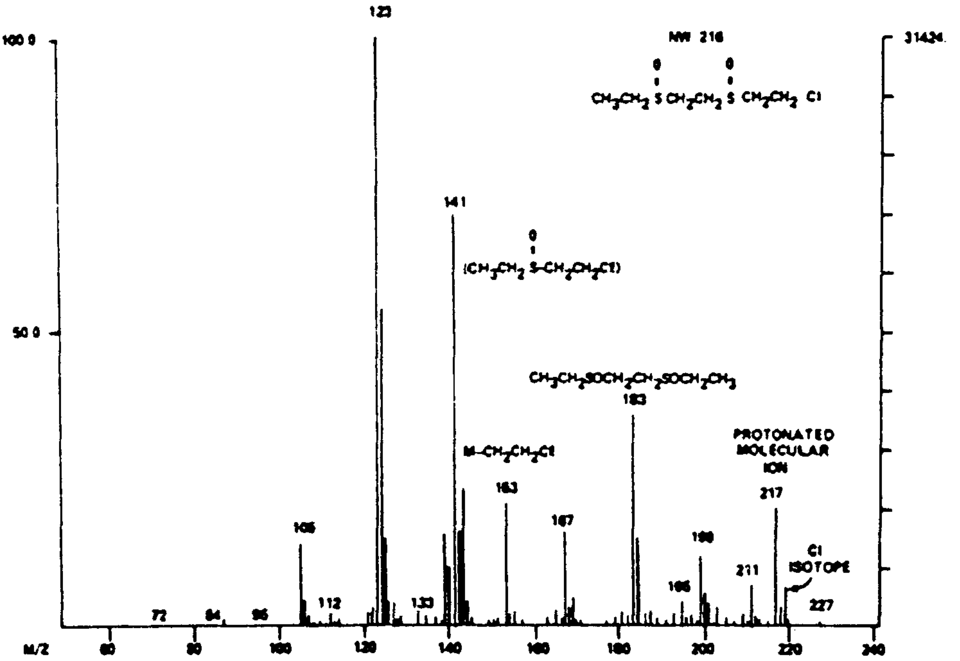
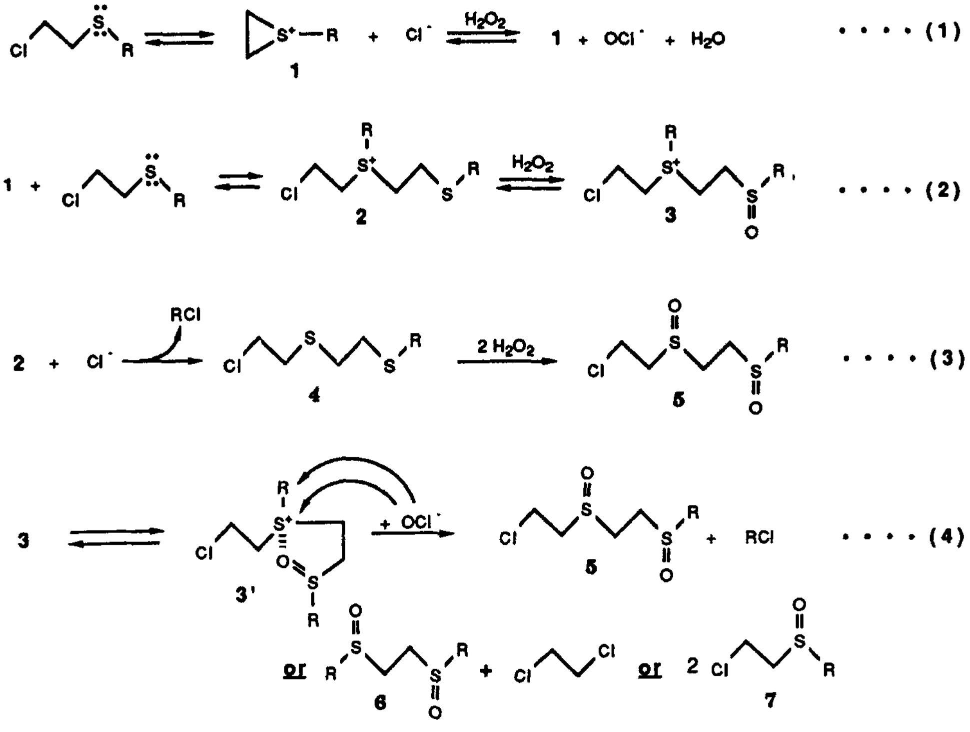


FIGURE 2 Mass spectrum of the crystalline product obtained from hydrogen peroxide oxidation of CEES.

sulfoxide produced from CEES. Furthermore, the structure of 2c was strongly supported by ^{1}H NMR spectroscopy as to the total number and the relative configuration of the protons in the molecule, and fully established by data obtained from the elemental analysis.

3. *Possible Reaction Mechanism for Forming the Sulfoxide Dimers*

Using the recent advent of high field FTNMR and GC/MS, 2-chloroethyl sulfides have been shown to give rise to sulfonium ion intermediates under a variety of conditions. The sulfonium ion intermediates exist primarily in dimeric form.[11-13] Thus the general mechanism for the dimerization and elimination reaction is believed to proceed via the formation of the dimeric sulfonium ion intermediates with the possible overall reaction mechanism depicted in Scheme I. The existence of the thiiranium ion 1 and the dimeric sulfonium ions 2 have been well documented.[13-17] Nucleophilic attack of 2 by Cl^- can lead to dealkylation of 2 to thiodiether 4, which can be subsequently oxidized to products 5 (1c and 2c). Indeed, up to 2% of 4 has been demonstrated to exist in aged 2-chloroethyl sulfides by Rohrbaugh, et al.[16] On the other hand, oxidation of 2 can lead to 3, which can be further oxidized to the potential products 5, 6 and 7, which were observable by GC/MS spectroscopy. The oxidation reaction, which resulted in the elimination of RCl as an electronically favored departing group and yielded sulfoxide 5 as the major product, indicates that 1 is extremely resistant to direct nucleophilic replacement,[14,15] and that the oxidation of Cl^- to ClO^- had greatly enhanced the nu-



SCHEME I

cleophilicity of the anion.[17] The fact that oxidation of TDG does not produce any dimeric sulfoxide substantiates the formation of 1 in the dimerization and elimination reaction. The possible involvement of the alkoxysulfonium ion 3′ is also suggested, since the 5-membered ring has been considered as a model reaction mechanism for demethylation of methionine to homocysteine.[18]

Furthermore, the possible existence of two diastereomers of the products 1c and 2c is recognized.† Although the products appear to be spectroscopically "pure" by NMR, spectral nonequivance may be shown in the presence of a chiral solvent or an achiral shift reagent. Further characterization of the absolute configuration of these products will be pursued.

EXPERIMENTAL

Redistilled TDG, CEMS, and CEES were obtained from Fairfield Chemical Co., Blythewood, SC. Reagent grade hydrogen peroxide (30%) was purchased from Aldrich Chemical Co., Milwaukee, WI.

A Varian XL-200 Superconducting FTNMR was used for measuring ^{13}C and ^{1}H spectra with external sodium 3-(trimethylsilyl) propionate-2,2′, 3,3′-4d (TSP) in D_2O as reference. Samples were also characterized on a Finnigan 5100 GC/MS using electron impact ionization. The instrument was equipped with a 15-m RSL-200 capillary column with a split ratio of 25:1. The injection port temperature was 200°C; the interface temperature was 230°C; and the oven temperature was programmed from 60 to 260°C/min. The mass range was scanned from 40 to 450 amu at 1 scan/s. Direct exposure probe (DEP) data were obtained by ramping the probe from 0 to 1 amp at 0.2 amp/s. Spectral identification was

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† We thank Dr. Slayton A. Evans, Jr., University of North Carolina, for this observation.

obtained by comparison with spectra either in the national Bureau of Standard (NBS) 39,000 compound library or in a user library generated in-house for mustard and related compounds in reference to spectra reported in the literature.[19]

IR spectra were run on a Perkin-Elmer 1420 Infrared Spectrophotometer in KBr or chloroform. Melting points were measured in a Mettler 61 Melting Point Apparatus.

1. Oxidation of TDG. About 0.8 ml of 30% H_2O_2 was added to 1.0 ml of redistilled TDG (9.7 mmoles) over 4 to 5 hrs (10μl/addition) with vigorous stirring. After complete addition of H_2O_2, the reaction mixtures were allowed to stand at room temperature for an additional 2 to 3 days or until white crystals formed. The mixtures were then dried in a desiccator over solid NaOH using a vacuum pump and yielded 1.3 gm of colorless needles of almost pure TDG sulfoxide (97%). Recrystallization from isopropanol produced 0.8 gm of TDG sulfoxide. MP 110.0°C (uncor.); IR (KBr): 1060 (S═O) and 3304 (C—H stretching) cm^{-1}; ^{13}C NMR: δ = 56.1, 56.3; ^1H NMR (D_2O): δ 3.13 (m) ($OSCH_2$) and 4.05 (m) (CH_2OH); MS: m/z = 138 (M^+). Found: C, 34.89; H, 7.69; S, 23.76%. Calc. for $C_4H_{10}O_3S$: C, 34.78; H, 7.29; S, 23.76%.

2. Oxidation of CEMS and CEES. About 2.5 ml of 30% H_2O_2 was added (20 μl/addition) to 3.0 ml of CEMS (30 mmoles) or CEES (28.8 mmoles) over 4 to 5 hrs with continual vigorous stirring. At the end of the peroxide addition, the cloudy tubid mixture became a clear solution. The reaction was allowed to continue for an additional 2 to 3 days at room temperature with continuous vigorous stirring. Unlike TDG, prolonged standing of the reaction mixtures at either room temperature or below did not result in any precipitate formations. The mixtures were first dried in a rotary evaporator at 40°C and then in a desiccator over solid NaOH under reduced pressure. Crystals formed in about 5 days and continued to grow for another week, yielding a total of about 1.0 gm of colorless needles (30%) in both cases.

The product from CEMS was recrystallized from ethyl acetate and produced about 200 mg of a colorless solid, mp 113.5°C (uncor.); IR (KBr): 1045 (S═O) and 3000 (C—H stretching) cm^{-1}; MS: m/z (Rel.%) = 203 (39%), 139 (82%), 91 (100%), 63 (60%), 109 (50%), 75 (41%); ^{13}C NMR (D_2O): δ = 36.97 (CH_3), 37.07 (CH_2C1), 45.3 and 43.6 ($OSCH_2CH_2SO$), and 53.7 ($OSCH_2CH_2C1$). ^1H NMR: 2.79 (s, 3H, CH_3), 3.20–3.49 (m, 6H, $OSCH_2CH_2SOCH_2$), 3.96–4.07 (m, 2H, CH_2Cl). Found: C, 29.37; H, 5.57; S, 31.23%. Calc. for $C_5H_{11}S_2O_2C1$: C, 29.60; H, 5.47; S, 31.64%.

The product isolated from CEES was recrystallized from amyl acetate and gave about 140 mg of colorless solid, mp 120°C (uncor.); IR ($CHCl_3$): 1030 (S═O) and 2960 (C—H stretching) cm^{-1}; MS: m/z (Rel.%) = 217 (20%), 183 (37%) (product 6 ?), 153 (21%), 141 (75%, monomer?), 123 (100%), 105 (15%); ^{13}C NMR: δ = 6.0 (CH_3), 37.0 (—CH_2C1), 42.8 and 43.8 ($OSCH_2CH_2SO$), 44.9 (CH_3CH_2SO), and 53.7 ($OSCH_2CH_2C1$). ^1H NMR: 1.33 (t, J = 7.5 Hz, 3H, CH_3), 2.91–3.07 (m, 2H, CH_3CH_2), 3.28–3.44 (m, 6H, $SOCH_2CH_2SOCH_2$), 3.98-4.07 (m, 2H, CH_2Cl). Found: C, 32.92; H. 6.76; S, 29.16%. Calc. for $C_6H_{13}S_2O_2C1$: C, 33.25; H, 6.05; S, 29.58%.

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