

451. Some Derivatives of Ethane-1:2-dithiol and 2-Mercaptoethyl Sulphoxides.

By A. H. FORD-MOORE.

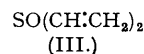
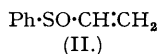
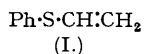
The preparation of certain derivatives of phenyl vinyl sulphide, phenyl vinyl sulphoxide, and divinyl sulphoxide is described.

Iodosobenzene forms a useful reagent for the oxidation of sulphides to sulphoxides.

It was shown (Ford-Moore, Peters, and Wakelin, this vol., p. 1754) that the reaction $R'SO_2 \cdot CH_2 \cdot CH_2 + SHR'' \longrightarrow R'SO_2 \cdot CH_2 \cdot CH_2 \cdot SR''$ was reversible under conditions approaching the biological. It seemed of interest, therefore, to see whether corresponding sulphides and sulphoxides, $R'S \cdot CH_2 \cdot CH_2 \cdot SR''$ and $R'SO \cdot CH_2 \cdot CH_2 \cdot SR''$, would also respond to a similar type of fission. This paper describes the preparation of certain compounds of these two types.

(A) *Dithio-derivatives*.—Phenyl vinyl sulphide (I) is not nearly so reactive as the corresponding sulphone (*idem, ibid.*) and disulphides cannot as a rule be prepared by the direct addition of a thiol to it. In this case, phenyl 2-chloroethyl sulphide is used as the starting material and the desired substance is prepared by allowing it to react with the appropriate thiol in the presence of ethanolic potassium hydroxide.

(B) *Thionyl Sulphides*.—Two series of compounds in this group were examined, the first being derived from phenyl vinyl sulphoxide (II) and the second from divinyl sulphoxide (III).



When 2:2'-dichlorodiethyl sulphide ("mustard gas") is oxidised with 30% hydrogen peroxide in acetic acid, excellent yields of the corresponding sulphoxide and sulphone can be obtained. The nature of the oxidation product depends on the proportion of peroxide to sulphide. Similar oxidations of phenyl 2-chloroethyl sulphide, phenyl 2-hydroxyethyl sulphide and phenyl 2-*p*-nitrobenzoyloxyethyl sulphide to their corresponding sulphones have been described (*idem, ibid.*). In the oxidation of the first of these, if the amount of peroxide corresponding to oxidation to the sulphoxide stage is taken, the product consists mainly of sulphone and unreacted sulphide. A very convenient reagent for converting sulphides into sulphoxides (when the hydrogen peroxide-acetic acid method fails) has been found in iodosobenzene, the reaction proceeding as follows: $\text{PhIO} + R'S \cdot R'' \longrightarrow \text{PhI} + R'SO \cdot R''$. Thiodiglycol (2:2'-dihydroxydiethyl sulphide) can be oxidised to 2:2'-dihydroxydiethyl sulphoxide by treatment with this reagent, though the oxidation can be carried out equally successfully with aqueous hydrogen peroxide. Iodosobenzene was therefore used to prepare (II) from phenyl 2-chloroethyl sulphide *via* phenyl 2-chloroethyl sulphoxide. The latter substance can be converted into (II) by warming it with aqueous potassium hydroxide. If ethanolic potassium hydroxide is used, a considerable amount of phenyl 2-ethoxyethyl sulphoxide is formed simultaneously.

Phenyl vinyl sulphoxide (II) lies between the sulphone and (I) in reactivity but more nearly approaches the former. It reacted with thiophenol in the presence of a trace of triethylamine with considerable evolution of heat but the product could not be induced to crystallise. It condensed with 2-mercaptobenzoic acid and with cysteine in the presence of aqueous sodium hydrogen carbonate or triethylamine to give the expected products.

The sulphoxide (III) resembles (II) in reactivity. Its preparation was described by Alexander and McCombie (*J.*, 1931, 1913) who obtained it by the action of triethylamine on 2:2'-di-iododiethyl sulphoxide, the corresponding 2:2'-dichloro-compound failing to react with this reagent. Levin (*J. pr. Chem.*, 1930, 127, 77) also prepared it by the oxidation of divinyl sulphide (Bales and Nickelson, *J.*, 1922, 121, 2137) with benzoyl hydroperoxide. A more convenient method, which does not involve the preparation of the di-iodo-compound, consists in boiling dichlorodiethyl sulphoxide with a slight excess of aqueous sodium carbonate and extracting the product with chloroform. It cannot be obtained by the oxidation of divinyl sulphide with hydrogen peroxide in acetic acid or acetone. It reacts with mercaptobenzoic acid and with cysteine to give the expected products.

EXPERIMENTAL.

2-Phenylthioethylthioacetic Acid, $\text{Ph} \cdot \text{S} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{S} \cdot \text{CH}_2 \cdot \text{CO}_2\text{H}$.—Thioglycollic acid (3.9 g.) was dissolved in 2*N*-ethanolic potassium hydroxide (42 c.c.), and phenyl 2-chloroethyl sulphide (6.4 g.) added.

After being heated under reflux for 1 hour on a steam-bath, the mixture was cooled and filtered, and most of the ethanol distilled from the filtrate. Water was added to the residue, and after the removal of a small amount of oily impurity, it was acidified with hydrochloric acid. The resulting acid was twice recrystallised from benzene-light petroleum (b. p. 40—60°) and then melted at 50—51° (Found : C, 52.7; H, 5.3. $C_{10}H_{12}O_2S_2$ requires C, 52.6; H, 5.3).

β -(2-Phenylthioethylthio)propionic Acid, $Ph \cdot S \cdot CH_2 \cdot CH_2 \cdot S \cdot CH_2 \cdot CH_2 \cdot CO_2H$.—2-Phenylthioethanethiol, $Ph \cdot S \cdot CH_2 \cdot CH_2 \cdot SH$, was prepared by dissolving sodium (4.6 g.) in ethanol (200 c.c.), saturating the solution with hydrogen sulphide, adding a solution of phenyl 2-chloroethyl sulphide (34.5 g.) in ethanol (60 c.c.), and heating the mixture under reflux for 1 hour. The mixture was filtered hot, and the filtrate, on cooling, deposited crystals of di-(2-phenylthioethyl) sulphide, $S(CH_2 \cdot CH_2 \cdot SPh)_2$ (14 g.), m. p. 56—57° not altered on admixture with an authentic specimen from sodium thiophenoxide and 2 : 2'-dichlorodiethyl sulphide. The filtrate from these crystals was evaporated to dryness and extracted with 10% aqueous sodium hydroxide to remove a further small amount of trisulphide. The alkaline extract was acidified and extracted with chloroform, and the product isolated by distillation under reduced pressure after removal of the chloroform. The yield of material, b. p. 134°/11 mm., was 6.3 g.

A mixture of 2-chloropropionic acid (4.2 g.) and water (40 c.c.) was neutralised by addition of anhydrous sodium carbonate (2.1 g.), and a solution of 2-phenylthioethanethiol (6.2 g.) in 10% aqueous sodium hydroxide (15 c.c.) added. The mixture was heated to boiling, cooled, and acidified, giving 8.0 g. of crude product. This was crystallised first from benzene-light petroleum and then from carbon tetrachloride, and then melted at 78—79° (Found : C, 54.7; H, 5.7. $C_{11}H_{14}O_2S_2$ requires C, 54.5; H, 5.8%).

S-2-Phenylthioethylcysteine, $Ph \cdot S \cdot CH_2 \cdot CH_2 \cdot S \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$.—Cysteine hydrochloride (3.2 g.) and sodium hydrogen carbonate (1.8 g.) were dissolved in water (5 c.c.) and treated with a solution of phenyl 2-chloroethyl sulphide (3.5 g.) in ethanol (20 c.c.). The mixture was heated on a steam-bath, and 2*N*-ethanolic potassium hydroxide (10 c.c.) added dropwise during 0.5 hour. Heating was continued for a further 2 hours, at the end of which the mixture was cooled and filtered. The residue was dissolved in hot dilute hydrochloric acid, and the solution treated with sodium acetate till no longer acid to Congo-red. The product was filtered off, washed with cold distilled water, and dried *in vacuo*; m. p. 208° (decomp.) (Found : C, 51.45; H, 6.2; N, 5.4. $C_{11}H_{15}O_2NS_2$ requires C, 51.5; H, 5.9; N, 5.4%).

Divinyl Sulphoxide (III).—2'-Dichlorodiethyl sulphoxide (100 g.), hydrated sodium carbonate (172 g.), and water (200 c.c.) were heated to boiling in a 700-c.c. flask fitted with an efficient reflux condenser. When a vigorous reaction set in, the source of heat was withdrawn till it had moderated, and heat was again applied for a further hour. After cooling, the mixture was made just acid to Congo-red by the cautious addition of hydrochloric acid (*d* 1.18) and extracted with three 100-c.c. portions of chloroform. The extracts were separated and dried ($MgSO_4$), and the solvent removed. The residue was fractionated under reduced pressure and collected at 72—74°/8 mm. (Alexander and McCombie, *loc. cit.*, give b. p. 86—87°/18 mm.; Levin, *loc. cit.*, gives b. p. 58—59°/3.5 mm., 67—68°/5—6 mm.); yield, 44—47 g. (76—81%).

Di-[2-(2'-amino-2'-carboxyethylthio)ethyl] Sulphoxide, $SO[CH_2 \cdot CH_2 \cdot S \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H]_2$.—Sodium hydrogen carbonate (7.5 g.), dissolved in water (70 c.c.), was saturated with carbon dioxide, and cysteine (7.1 g.) and divinyl sulphoxide (2.8 g.) were added. The mixture was warmed to 50° for 10 minutes and kept at room temperature overnight. It was made just acid to litmus by cautious addition of 25% acetic acid, and evaporated to dryness under reduced pressure, the residue being extracted twice with hot ethanol to remove sodium acetate. The residue after this extraction was dissolved in a little boiling water containing a few drops of acetic acid (charcoal) and filtered, and ethanol was added to the hot filtrate to turbidity. The product that separated on cooling was filtered off and suspended in boiling ethanol, and water added dropwise till dissolution just took place. The pure compound separated on cooling; m. p. 226—227° (decomp.) (Found : C, 34.7; H, 5.8; N, 8.0; S, 27.7. $C_{10}H_{20}O_6N_2S_4$ requires C, 34.9; H, 5.85; N, 8.1; S, 27.9).

2 : 2'-Di-(o-carboxyphenylthio)diethyl Sulphoxide, $SO(CH_2 \cdot CH_2 \cdot S \cdot C_6H_4 \cdot CO_2H)_2$.—o-Mercaptobenzoic acid (7.5 g.), sodium hydrogen carbonate (7.5 g.), divinyl sulphoxide (2.0 g.), and water (60 c.c.) were warmed on a water-bath for 10 minutes. After 1 hour at room temperature, the mixture was acidified with hydrochloric acid. The product separated in a sticky condition but rapidly crystallised when washed with cold water. It was sparingly soluble in hot ethanol, methyl ethyl ketone, ethyl acetate, or benzene, and was crystallised from acetic acid; m. p. 202° (decomp.) (Found : C, 52.4; H, 4.4. $C_{18}H_{18}O_6S_3$ requires C, 52.7; H, 4.4%).

2 : 2'-Dihydroxydiethyl Sulphoxide.—Thiodiglycol (12 g.) in water (50 c.c.) was heated on a steam-bath, and iodobenzene (25 g.) added. The reaction appeared to be complete in about 15 minutes. The mixture was cooled and filtered, and the residue washed with water (10 c.c.). The iodobenzene in the filtrate (13 g.) was separated from the aqueous portion, and the latter taken to dryness *in vacuo* on a steam-bath. The residue when cold was treated with acetone and filtered, giving 13 g. of crude product. This was crystallised from ethanol, from which 11 g. of pure sulphoxide separated in large needles, m. p. 111° (Levin, *loc. cit.*, gives 111—112°), unaltered on admixture with a specimen prepared from thiodiglycol by oxidation with aqueous hydrogen peroxide.

Phenyl Vinyl Sulphoxide (II).—Iodobenzene (13 g.), dried *in vacuo* over sulphuric acid, phenyl 2-chloroethyl sulphide, and benzene (40 c.c.) were heated under reflux on a steam-bath till all the iodobenzene had disappeared (9.5 hours). The mixture was filtered from a little solid impurity, and the benzene distilled from the filtrate. The iodobenzene formed in the reaction was next removed under reduced pressure below 100°, leaving a residue of crude phenyl 2-chloroethyl sulphoxide that could not be made to solidify and decomposed on attempted distillation under reduced pressure.

This was heated under reflux for 1.5 hours with a solution of potassium hydroxide (3 g.) in water (30 c.c.) and cooled, and the product extracted with chloroform. After removal of solvent, the residue was distilled under reduced pressure and collected at 98—105°/0.5 mm. On redistillation, it boiled at 93—95°/0.2 mm.; yield 4.8 g. (53%, based on the phenyl 2-chloroethyl sulphide) (Found : C, 62.8; H, 5.3. C_8H_8OS requires C, 63.15; H, 5.3%).

When ethanolic potassium hydroxide was used in place of the aqueous solution, a considerable

amount of somewhat impure *phenyl 2-ethoxyethyl sulphoxide*, b. p. 128—136°/0.3 mm., was formed (Found : C, 60.15; H, 7.8. $C_{10}H_{14}O_2S$ requires C, 60.6; H, 7.1%).

Phenyl 2-(o-Carboxyphenylthio)ethyl Sulphoxide, $Ph \cdot SO \cdot CH_2 \cdot CH_2 \cdot S \cdot C_6H_4 \cdot CO_2H$.—*o*-Mercaptobenzoic acid (1.5 g.) was dissolved in water (20 c.c.) containing sodium hydrogen carbonate (2.0 g.). Phenyl vinyl sulphoxide (1.5 g.) was added, and the mixture warmed on a steam-bath with occasional shaking. The sulphoxide dissolved in about 0.5 hour. After a further 0.5 hour's heating, the mixture was cooled and acidified. The water was decanted from the sticky precipitate, which rapidly crystallised on treatment with hot benzene. It was sparingly soluble in hot benzene, readily so in cold methanol, and was recrystallised from ethyl acetate containing a little methanol; m. p. 154° (Found : C, 58.3; H, 4.7. $C_{15}H_{14}O_3S_2$ requires C, 58.8; H, 4.6%).

S-2-Phenylsulphinylethylcysteine, $Ph \cdot SO \cdot CH_2 \cdot CH_2 \cdot S \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$.—Phenyl vinyl sulphoxide (3.0 g.) was added to a mixture of cysteine (2.4 g.), water (30 c.c.), and triethylamine (0.1 g.). The reaction started in the cold, the temperature rising about 10° and the sulphoxide dissolving in ca. 15 minutes. After being kept overnight, the water was removed under reduced pressure and the residue treated with ethanol. After being filtered off, the *product* was recrystallised by boiling with ethanol and adding water dropwise till dissolution just took place. It was then obtained pure and decomposed without melting at 181—182° (Found : C, 47.95; H, 5.45; N, 5.3; S, 23.3. $C_{11}H_{15}O_3NS_2$ requires C, 48.3; H, 5.5; N, 5.1; S, 23.5%).

2-Phenylsulphinylethylthioacetic Acid, $Ph \cdot SO \cdot CH_2 \cdot CH_2 \cdot S \cdot CH_2 \cdot CO_2H$.—Phenyl vinyl sulphoxide and thioglycollic acid readily combine in the presence of aqueous sodium hydrogen carbonate but the free acid on liberation tends to dissociate rather rapidly into the starting materials. It can be isolated as its *barium* salt as follows. The sulphoxide (1.8 g.), thioglycollic acid (1.1 g.), and saturated aqueous baryta (32 c.c.) were kept at room temperature for 1 hour. The mixture was then saturated with carbon dioxide and filtered, and the filtrate concentrated under reduced pressure. When kept for several days *in vacuo* over sulphuric acid, the salt crystallised (Found : C, 39.05; H, 3.7; S, 20.3; Ba, 22.8. $C_{20}H_{22}O_6S_4Ba$ requires C, 39.5; H, 3.6; S, 20.55; Ba, 22.2%).

The microanalyses were carried out by Messrs. Weiler and Strauss and by Mr. G. Ingram.

This work, part of which was carried out while the author was a member of Sir Robert Robinson's team at the Dyson Perrins Laboratory, Oxford, is published by permission of the Chief Scientist, Ministry of Supply.

CHEMICAL DEFENCE EXPERIMENTAL ESTABLISHMENT,
PORTON, WILTS.

[Received, January 18th, 1949.]