

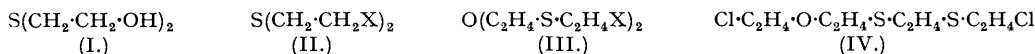
7. *New Organic Sulphur Vesicants. Part I. 2 : 2'-Di-(2-chloroethylthio)diethyl Ether.*

By F. N. WOODWARD.

Davies and Oxford (*J.*, 1931, 224) showed that, at 100°, thiodiglycol and hydrogen chloride reacted to produce a mixture of (II; X = Cl) and an undistillable chloro-sulphide. The reaction has now been studied in detail and under a variety of conditions and the undistillable compound characterised as (III; X = Cl) which has been found to be highly vesicant to man. Bromo-, iodo-, cyano-, and thiocyanato-analogues of (III) have been prepared, and the interaction of hydrogen chloride and bromide with (III; X = Cl) and (III; X = OH) studied.

THE conversion of thiodiglycol (I) into 2 : 2'-dichlorodiethyl sulphide (II; X = Cl) (mustard gas; H) by means of hot concentrated hydrochloric acid was first effected by Clarke (*J.*, 1912, 101, 1585), thus overcoming the difficulties associated with the use of phosphorus trichloride in Meyer's original method (*Ber.*, 1886, 19, 3259).

The process has since been the subject of many investigations as it was the sole method used by the Germans in the First World War for the manufacture of mustard gas. Davies and Oxford (*loc. cit.*) found that at 100° the reaction afforded a mixture of (II; X = Cl) and an undistillable oil, which they showed to be either (III; R = Cl), believed to be formed through the then



unknown 2-chloroethyl 2'-hydroxyethyl sulphide, or, less probably, the isomeric 2-(2-chloroethoxy)-2'-(2-chloroethylthio)diethyl sulphide (IV), possibly produced by the scission of an intermediate chlorosulphonium chloride.

The reaction was further studied in detail in these laboratories in 1932 when, although it was found impossible to repeat Davies and Oxford's findings in their entirety, it was proved that the main constituent of the undistillable oil was (III; X = Cl) and not (IV) and also that this compound had an empirical vesicant power of 325 compared with the arbitrary standard of 100 for (II; X = Cl) when tested in an inert solvent on the arms of 32 male volunteers.

Pure (III; X = Cl) has now been synthesised by the action of thionyl chloride in chloroform or dimethylaniline on (III; X = OH) obtained from dichlorodiethyl ether and the sodium salt of 2-hydroxyethanethiol. Its diphenoxy-derivative was found to be non-vesicant and identical with that obtained by Davies and Oxford, and further confirmation was obtained when Rosser (private communication) synthesised (IV) and found it to have properties unlike those of (III; X = Cl). The parent hydroxy-compound (III; X = OH) forms an oily *dimethiodide* and crystalline *bis- α -naphthyl-* and *-phenyl-urethanes*, whereas with concentrated hydrochloric acid at 100° a mixture of equal parts of (II; X = Cl) and (III; X = Cl) is obtained; similarly, excess 40% hydrobromic acid at 100° afforded a mixture of 75% of 2 : 2'-dibromodiethyl sulphide (II; X = Br) [*sulphilimine*, m. p. 161° (decomp.)] and 25% of crude 2 : 2'-di-(2-bromoethylthio)diethyl ether.

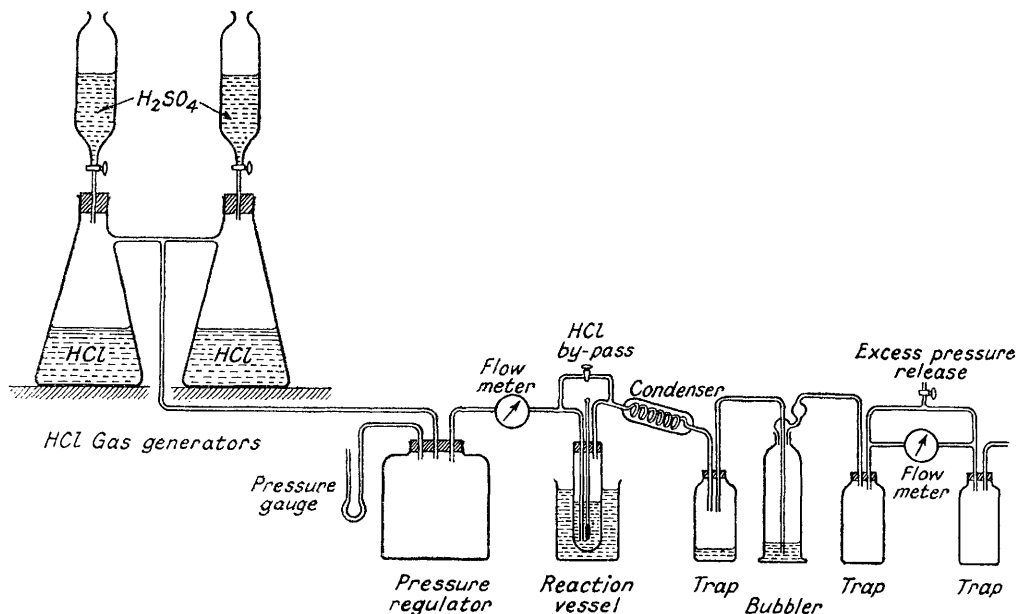
The *chloro-ether* (III; X = Cl) is a colourless liquid with a typical mustard odour, distilling with considerable decomposition at 174°/2 mm. but smoothly at 120°/0.001 mm. Its purification and physical properties will be described elsewhere. Unlike (III; X = OH) it does not react with alkyl iodides, chloramine-T, mercuric chloride or iodide, iodine, or bromine. It possesses the reactive chlorine atoms common to all β -chloroalkyl sulphides, and the *dicyano-*, *dithiocyanato-*, *di-s-tribromophenoxy-*, dipiperidino- (characterised as its *dipicrate*), and *di-iodo-*derivatives have been prepared by conventional methods; the first three on physiological examination were found to be non-vesicant. The chloro-compound (III; X = Cl) is practically unaffected by concentrated hydrochloric acid at 100°, although hydrogen chloride at elevated temperatures results in partial scission with formation of (II; X = Cl) and water. The controlled action of hydrogen bromide at 70° affords a mixture of (II; X = Br) and 2-chloro-2'-bromodiethyl sulphide, whilst excess results in complete conversion into (II;

X = Br). The interaction of hydrogen chloride or bromide and (III; X = OH) in its simplest form is therefore essentially a three-fold reaction, giving (II; X = Cl or Br) both directly and through the intermediate (III; X = Cl or Br).

A more complete study of the course of the reaction between hydrogen chloride and (I) and (III; X = OH) will be described elsewhere.

EXPERIMENTAL.

Action of Hydrogen Chloride on Thiodiglycol.—Davies and Oxford's method (*loc. cit.*) consisted in saturating thiodiglycol at 100–106° with hydrogen chloride; the lower, non-aqueous, layer was separated and distilled, yielding 56% of (II; X = Cl) and 44% of an undistillable chloro-sulphide. Repetitions of the preparation under conditions as nearly identical with their's as was possible from the short description given, afforded undistillable fractions differing materially in composition [Found (Oxford and Davies's results in parenthesis): Cl, 20.4, 20.6, 21.1, (23.7); S, 26.4, 26.9, 26.6, (25.7). Calc. for $C_8H_{16}OCl_2S_2$: Cl, 27.0; S, 24.3%] and yield [58, 60, 60 (44%)]. As the rate of passage of hydrogen chloride, quantity of thiodiglycol used, and time and temperature of reaction all affected the yield and quality of this product, the reaction was investigated under controlled conditions and with the standardised apparatus shown in the figure. The reaction was conducted in a 150-c.c. 1" boiling-tube immersed in an oil-bath, hydrogen chloride was obtained from a sulphuric-hydrochloric acid generator,



and all gas flow-rates were measured by conventional U-type flow-meters. In the first series of experiments, pure distilled thiodiglycol (80 g.) was heated to the required temperature in the reaction vessel, and hydrogen chloride (99% HCl) passed through at such a rate (3 l./hr.) that a constant exhaust was maintained throughout the 75 minutes required to complete the reaction. A reflux condenser fitted above the reaction vessel allowed the aqueous reaction products to reflux at temperatures above 110°. In the second series the conditions were identical, except that the reflux condenser was replaced by a still-head to allow the volatile products to be removed by distillation continuously throughout the reaction. At the end of the reaction period, the product was cooled, drawn into cold water, washed, separated, dried by heating at 100°/50 mm. for 30 minutes, and weighed. The content of (II; X = Cl) was then determined by quantitative distillation, and the m. p. of the distilled (II; X = Cl) and that of the residue determined by the conventional Beckmann-Holleman cooling-curve method. The residue was analysed but not the distilled (II; X = Cl) as its m. p. in most cases closely approximated to 14.2°, that of the pure substance.

2:2'-Di-(2-chloroethylthio)diethyl Ether (III; X = Cl).—Redistilled 2:2'-dichlorodiethyl ether (47.7 g.) was slowly added down a reflux condenser to a solution of sodium (15 g.) in absolute alcohol (250 c.c.) to which had been added 2-hydroxyethanethiol (52 g.). After subsidence of the vigorous reaction, the mixture was heated on the steam-bath for 15 minutes and freed from precipitated salt by filtration; after removal of the alcohol by distillation, the residual salt in solution was precipitated by addition of acetone (200 c.c.). The solution was filtered and freed from solvent, crude 2:2'-di-(2-hydroxyethylthio)diethyl ether (III; X = OH) remaining as a yellow oil. It was purified by distillation at 215°/2.5 mm. Crystallisation from ether gave a white wax-like solid, m. p. 32°. Determination of sulphur by the Carius method was not practicable, and use was made of the method of Rosser and Woodward (*J.*, 1932, 2357) (Found: S, 28.5, 28.3; OH, 15.2, 15.2. $C_8H_{18}O_3S_2$ requires S, 28.3; OH, 15.0%).

Distilled and undistillable products of the interaction of thiodiglycol and hydrogen chloride.

Reaction conditions.	Distilled (II; X = Cl):			Undistillable residue:		
	yield, %.	m. p.	yield, %.	m. p.	Cl.	S.
60°; refluxed	94.2	12.2°	5.8	—	24.8	27.6
70° "	95.0	13.0	5.0	—	27.3	26.6
80° "	90.9	14.2	9.1(a)	— 7.2°	27.1	26.6
90° "	87.6	14.1	12.4	— 6.8	27.8	27.3
100° "	84.9	14.2	15.1	— 11.7	26.9	26.2
110° "	—	—	—	— 16.6	25.1	27.2
115°; distilled	57.0*	10.7	43.0	— 19	24.3	25.3
120° "	49.3	10.6	50.7	— 20.1	23.6	24.3
120°; refluxed	57.8	13.5	42.2(a)	— 20.7	24.5	26.3
130° "	15.0	—	85.0	—	28.2	17.4
130°; distilled	41.9	8.8	58.1	— 19.9	23.1	27.0
140° "	23.0	5.2(b)	77.0	— 8.3(b)	18.0	26.6

(a) Diphenoxy-derivative, m. p. 60°, prepared.

(b) Contained dithian.

An oily *dimethiodide* was obtained by prolonged heating at 100° with excess of methyl iodide (Found: I, 51.8. C₁₆H₂₄O₂I₂S₂ requires I, 50.0%). *Bis- α -naphthylurethane*: pinkish-white ill-defined crystals, m. p. 81.5°, from alcohol (Found*: C, 63.7; H, 5.7; S, 11.2. C₃₀H₃₂O₆N₂S₂ requires C, 63.8; H, 5.7; S, 11.3%). *Bisphenylurethane*: felted mass of small white needles from alcohol (Found*: C, 56.5; H, 6.2; S, 13.6. C₂₂H₂₈O₂N₂S₂ requires C, 56.9; H, 6.2; S, 13.8%).

Conversion of the hydroxy-sulphide into the chloro-compound (III; X = Cl) was more difficult than is usual with β -hydroxy-sulphides, on account of the ease with which decomposition takes place in presence of thionyl chloride alone or in ether-pyridine, alcoholic hydrogen chloride, or phosphorus pentachloride. The best method was to add slowly twice-distilled thionyl chloride, b. p. 75–76°/765 mm. (22 c.c.), to a vigorously stirred solution of the hydroxy-sulphide (28 g.) in chloroform (100 c.c.) which had been freshly distilled over phosphoric oxide, keeping the temperature below 40° throughout. When the evolution of sulphur dioxide had abated, the mixture was heated under reflux on a steam-bath for 20 minutes, and the solvent and excess of thionyl chloride were removed by distillation, followed by the passage of a rapid stream of dry air through the liquid at 90–100° for 30 minutes. The residual 2:2'-*di-(2-chloroethylthio)diethyl ether* (III; X = Cl) distilled with considerable decomposition at 174°/2 mm. but smoothly at 120°/0.001 mm. (Found: Cl, 26.6; S, 24.5. C₆H₁₆OCl₂S₂ requires Cl, 26.9; S, 24.3%). Diphenoxy-derivative: long lustrous needles, m. p. 60°, from alcohol; mixed m. p. with Davies and Oxford's sample (m. p. 55–57°) 58° (Found*: C, 63.4; H, 6.5; S, 17.0. Calc. for C₂₀H₂₆O₂S₂: C, 63.5; H, 6.9; S, 16.9%). *Di-s-tribromophenoxy*-derivative: blunt white needles, m. p. 70–71°, from alcohol-chloroform (2:1) (Found*: C, 28.3; H, 2.5; Br, 56.1. C₂₀H₂₀O₂Br₂S₂ requires S, 28.2; H, 2.3; Br, 56.4%). *Dipiperidino-dipicrate*: yellow blunt needles, m. p. 137–139°, from glacial acetic acid (Found*: C, 43.8; H, 5.1. C₃₀H₄₂O₁₅N₆S₂ requires C, 44.0; H, 5.1%). Attempted conversion of the hydroxy-ether (III; X = OH) into the chloro-ether (III; X = Cl) by heating with excess of concentrated hydrochloric acid resulted in an oil, 50% of which distilled at 96°/10 mm., the remainder being undistillable at 160°/2 mm. The former was shown to be (II; X = Cl), as it had m. p. 13.5°, analysed correctly (Found: Cl, 42.4. Calc. for C₄H₈Cl₂S: Cl, 42.8%), and formed a sulphilimine, m. p. 144° (Mann and Pope, *J.*, 1922, **121**, 1053, give m. p. 144.5°), which did not depress the m. p. of an authentic specimen. The undistillable residue was (III; X = Cl) (Found: Cl, 26.7%), affording a diphenoxy-derivative, m. p. 60°, undepressed by an authentic specimen. Similarly, from a heated mixture of 2:2'-*di-(2-hydroxyethylthio)diethyl ether* (1 vol.) and 40% aqueous hydrobromic acid (10 vol.) a light brown oil separated, 75% of which distilled at 115°/6 mm. The residue was impure 2:2'-*di-(2-bromoethylthio)diethyl ether* (III; X = Br) (Found: Br, 47.6. C₆H₁₆OBr₂S₂ requires Br, 45.3%), whilst the distillate, which set to a lustrous crystalline mass, m. p. 31°, was 2:2'-*dibromodiethyl sulphide*.

2:2'-*Dibromodiethyl Sulphide*.—In view of the discrepancy between the observed and recorded values for the b. p. (Steinkopf, Herold, and Stohr, *Ber.*, 1920, **53**, 1007, give b. p. 115°/1 mm.), this compound, b. p. 115°/6 mm., m. p. 31°, was synthesised by heating thiodiglycol with excess of aqueous hydrobromic acid in a manner identical with that used by Clarke (*loc. cit.*) in the synthesis of the chloro-analogue (II; X = Cl) (Found: Br, 64.3. Calc. for C₄H₈Br₂S: 64.4%). Both the suspected and the authentic specimen afforded a *sulphilimine*, fine needles, m. p. 161° (decomp.), from alcohol (Found*: C, 31.8; H, 3.7; S, 15.3. C₁₁H₁₅O₂NBr₂S₂ requires C, 31.6; H, 3.6; S, 15.3%).

Scission of 2:2'-Di-(2-chloroethylthio)diethyl Ether.—Hydrogen bromide was bubbled through the chloro-sulphide (60 g.) for 150 minutes at 100°. After removal of dissolved acid and the water formed, the residual oil all distilled at 140–141°/18 mm. and solidified to a crystalline mass, m. p. 31°, identified as 2:2'-*dibromodiethyl sulphide* through its sulphilimine, m. p. 160° (decomp.). By limiting the passage of hydrogen bromide to 30 minutes at 70°, a mixture was obtained from which 8 g. distilled at 125–130°/18 mm. The residue was unreacted (III; X = Cl), whilst the distillate was 2-chloro-2'-*bromodiethyl sulphide* (Kretov, *J. Russ. Phys. Chem. Soc.*, 1929, **61**, 2345, gave b. p. 125–132°/18 mm.) (Found: 0.2194 g. gave 0.3520 g. AgCl + AgBr; S, 15.4. Calc. for C₄H₈ClBrS: AgCl + AgBr, 0.3570 g.; S, 15.7%).

2:2'-*Di-(2-cyanoethylthio)diethyl Ether*.—The chloro-sulphide (10 g.) was added to a saturated solution of sodium cyanide in methyl alcohol (100 c.c.) and refluxed for 6 hours. After cooling, water (70 c.c.) was added and the oil deposited taken up in ether and dried (Na₂CO₃). Removal of the solvent left the *cyano*-compound as a pale yellow liquid, *d*_D²⁰ 1.1283, which would neither distil nor crystallise (Found: S, 26.3. C₁₆H₁₆ON₂S₂ requires S, 26.2%).

2:2'-*Di-(2-thiocyanatoethylthio)diethyl Ether*.—By using a saturated methyl-alcoholic solution of

potassium thiocyanate in place of the sodium cyanide, the *thiocyanato-ether* was similarly obtained as a viscous liquid, d_4^{20} 1.2465, which could not be induced to crystallise (Found : S, 41.4. $C_{10}H_{16}ON_2S_4$ requires S, 41.5%).

2 : 2'-Di-(2-iodoethylthio)diethyl Ether.—By using an excess of an acetone solution of sodium iodide, the *iodo*-analogue was similarly obtained as an unstable oil, d_4^{20} 1.3372, decomposing on standing or attempted distillation (Found : I, 57.5. $C_8H_{16}OI_2S_2$ requires I, 57.0%).

Microanalyses marked * were carried out by Drs. Weiler and Strauss.

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