# **10.** *New Organic Sulphur Vesicants. Part IV.* 1 : 2-*Di-*(2-*chloroethylthio*)*ethane and its Analogues.*

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The powerful vesicant 1 : 2-di-(2-chloroethylthio)ethane, the third member of the homologous series having the general formula (I), has been obtained in admixture with (II) by the action of hydrogen chloride on a mixture of thiodiglycol and 2-hydroxyethanethiol (III). With initial concentrations of (III) greater than 10%, condensation compounds of the general formula (IV) are obtained in addition.

Homologues (I; $n = 0, 1, 3, 4, 5, 6, 8, 9$ and 10) have also been synthesised, all of which, except the last three, are vesicant to man. 1 : 2-Di-(2-chloro-*n*-propylthio)ethane has also been prepared.

1 : 2-DI-(2-CHLOROETHYLTHIO)ETHANE (" sesqui-H "; Q) (I; $n = 2$), the third member of the homologous series having the general formula (I), has vesicant power approximately five times that of 2 : 2′-dichlorodiethyl sulphide (II) (mustard gas; H). It was first obtained by Bennett *et al.* (*J.*, 1921, **119**, 1860; 1922, **121**, 2146) by the action of thionyl chloride on the corresponding hydroxy-compound, prepared by interaction of ethylene dibromide and 2-hydroxyethanethiol (III) in alcoholic sodium ethoxide. Rosen and Reid (*J. Amer. Chem. Soc.*, 1922, **44**, 634) confirmed its structure by synthesis from ethane-1 : 2-dithiol and ethylene chlorohydrin.

$$\text{(I.)}\quad \mathrm{Cl{\cdot}C_2H_4{\cdot}S{\cdot}[CH_2]_{\mathit{n}}{\cdot}S{\cdot}C_2H_4Cl} \qquad\qquad \mathrm{Cl{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CH_2Cl}\quad \text{(II.)}$$

The compound (I; $n = 2$) has now been prepared, together with (II), by the action of hydrogen chloride on a mixture of (III) and 2 : 2′-dihydroxydiethyl sulphide (thiodiglycol) at 90°:

$$\mathrm{S(C_2H_4{\cdot}OH)_2} + \underset{\text{(III.)}}{\mathrm{HS{\cdot}C_2H_4{\cdot}OH}} \xrightarrow{\mathrm{HCl}} (\mathrm{I};\, n = 2) + \mathrm{3H_2O}$$

With less than 10% of (III) in the initial reaction mixture a product is obtained which, when freed from (II) by distillation under reduced pressure, is essentially pure (I; $n = 2$). With higher initial concentrations, further condensation occurs:

$$\mathrm{S(C_2H_4{\cdot}OH)_2} \longrightarrow \{\mathrm{HO{\cdot}[C_2H_4{\cdot}S]_{\mathit{n}}{\cdot}C_2H_4{\cdot}OH}\} \xrightarrow{\mathrm{HCl}\,+\,\text{(III)}} \mathrm{Cl{\cdot}[C_2H_4{\cdot}S]_{\mathit{n}}{\cdot}C_2H_4Cl} \qquad \text{(IV.)}$$

From the condensation products obtained, (IV; $n = 3$) and (IV; $n = 5$) have been isolated.

The preparations of (I; $n = 0$, 1, 3, and 4) have also been described previously, but as in some cases the purity of the compounds obtained was open to doubt, these preparations have been repeated. In addition, *compounds* (I), where $n = 5$, 6, 8, 9, and 10, have been prepared. With the exception of (I; $n = 0$), all nine compounds were obtained by the general reactions:

$$\mathrm{X{\cdot}[CH_2]_{\mathit{n}}{\cdot}X} \xrightarrow{\text{(III)}\,+\,\mathrm{NaOEt}} \mathrm{[CH_2]_{\mathit{n}}[S{\cdot}C_2H_4{\cdot}OH]_2} \xrightarrow{\mathrm{SOCl_2}} \mathrm{[CH_2]_{\mathit{n}}(S{\cdot}C_2H_4Cl)_2}$$

The hydroxy-precursor of the first compound of the series was obtained by oxidation of (III) with hydrogen peroxide.

The empirical vesicant powers of these compounds (compared with H = 100) were assessed by the Physiological Section, Chemical Defence Experimental Station, Porton. The method of expressing physiological activity is the same as in Part II. Table I gives details of the compounds prepared and tested.

TABLE I.

*M. p., b. p., and empirical vesicant powers of compounds of the series* $\mathrm{[CH_2]_{\mathit{n}}(S{\cdot}C_2H_4X)_2}$.

| | X = OH. | | X = Cl. | | Empirical vesicant power |
|---|---|---|---|---|---|
| *n*. | B. p. | M. p. | B. p. | M. p. | (H = 100). |
| 0 | 106°/0·015 mm. | 25—26° | 100°/0·5 mm.,<br>150/30 mm. (*a*) | −2° to 0° | 1 |
| 1 | 114—115/0·005 mm.,<br>200—203/17 mm. (*b*) | 18 | 80—81/0·03 mm. | 30·7, < −27 (*b*) | 200 |
| 2 | — | — | *ca.* 140/2 mm. | 57 | 500 |
| | | 64 (*c*) | | 54 (*c*) | |
| | | 117 (*d*) | | 64 (*d*) | |
| 3 | 200/4 mm.;<br>89—90/0·003 mm. | 18 | 86/0·04 mm. | 11·5 | 400—500 |
| | 230—233/17 mm. (*b*) | — | 200—204/17 mm. (*b*) | liquid (*b*) | |
| 4 | 207/3 mm. | 30 | 104/0·06 mm. | −1 | 400 |
| | | 27—29 (*e*) | | < −20 (*e*) | |
| 5 | 210/3 mm. | 30 | 104/0·003 mm. | −6 | 200 |
| 6 | *ca.* 130/0·02 mm. | 45 | 112/0·03 mm. | 14—15 | 50 |
| 8 | — | 60—61 (*f*) | 134/0·045 mm. | 21—22 | 1 |
| 9 | — | 63—64 (*f*) | — | 24 (*h*) | 1 |
| 10 | — | 70 (*g*) | — | 32 (*h*) | 1 |

(*a*) Bennett, *J.*, 1921, **119**, 424.
(*b*) Alexander, Ph.D. Thesis, 1933, Cambridge.
(*c*) Bennett and Whincop, *J.*, 1921, **119**, 1860.
(*d*) Rosen and Reid, *loc. cit.*
(*e*) Kent and McCombie; unpublished work.
(*f*) Crystallised from ethyl acetate–light petroleum.
(*g*) Crystallised from ethyl acetate.
(*h*) Crystallised from methanol–chloroform.

1 : 2-*Di*-(2-*hydroxy*-n-*propylthio*)*ethane* has been obtained by the interaction of (II) and 2-hydroxypropanethiol in alcoholic sodium ethoxide. The corresponding *chloro*-compound (empirical vesicant power = 50) is obtained by interaction with thionyl chloride.

## EXPERIMENTAL.

*Condensation of Thiodiglycol and 2-Hydroxyethanethiol.*—The thioglycols (100 g. total) were well mixed in the required proportion (see below) in a 2-l. round-bottomed flask and heated under reflux with concentrated hydrochloric acid (400 c.c.) for 75 minutes at 90°. After cooling of the reaction product, the lower non-aqueous layer was separated and the 2 : 2′-dichlorodiethyl sulphide (II) removed by distillation at 2·5 mm., leaving the crude substance (I; $n = 2$) as an undistillable residue. Mixed glycol and thiol in the following respective proportions by weight were condensed.

90 : 10. The product (122·5 g.) was a pale yellow liquid, s. p. 8°. On distillation it gave (II) (80·8%), m. p. 13·5°, as distillate and a residue of crude (I; $n = 2$) (19·2%), m. p. 51° after softening at 48—49°. Bennett and Whincop (*loc. cit.*) give m. p. 54° (Found : S, 29·6; Cl, 32·1. Calc. for $C_6H_{12}S_2Cl_2$ : S, 29·3; Cl, 32·4%).

80 : 20. The product (115 g.), m. p. 5°, on distillation gave (II) (69·0%), m. p. 13·6°, and a residue, m. p. 47°, finally clearing at 61° (Found : S, 30·9; Cl, 30·3%).

70 : 30. At room temperature the product (98·7 g.) deposited a white crystalline solid (40 g.). Distillation afforded (II) (54·6%), m. p. 13·3°, and the residue (45·4%) had m. p. 60—65° (Found : S, 33·7; Cl, 27·3%). This and the residue described above are presumably mixtures of (IV; $n = 2$ and 3) (Calc. for $C_8H_{16}S_3Cl_2$ : S, 34·4; Cl, 25·4%).

61 : 39 (equimolar). The non-aqueous layer (106 g.) was separated at 70°, below which temperature crystals began to separate. Distillation yielded (II) (46·0%), m. p. 12°, and a residue (54·0%) melting between 68° and 75°. This on fractional crystallisation from alcohol–chloroform gave crude (I; $n = 2$) (20·6 g.), m. p. 57—59°, a mixed fraction (12 g.), m. p. 45—51° (Found : S, 32·4; Cl, 23·8%), and 1 : 17-*dichloro*-3 : 6 : 9 : 12 : 15-*pentathiaheptadecane* (IV; $n = 5$), an amorphous solid, m. p. 100° (Found : S, 40·2; Cl, 17·5; *M*, cryoscopic in $CHBr_3$, 362. $C_{12}H_{24}S_5Cl_2$ requires S, 40·1; Cl, 17·8%; *M*, 399).

*Synthesis of Compounds of the Series* $[CH_2]_n(S{\cdot}C_2H_4X)_2$.—With the exception of the first compound ($n = 0$), the method described in Part II for the synthesis of 2 : 2′-di-(2-chloroethylthio)diethyl sulphide was employed throughout. In all cases purification was effected by distillation in a vacuum. The highest homologues and their hydroxy-precursors were also purified by crystallisation. The analytical data are given in Table II.

TABLE II.

| | X = OH. | | | X = Cl. | | | | |
|---|---|---|---|---|---|---|---|---|
| | | S, %. | | | Found, %. | | Calc., %. | |
| *n*. | Formula. | Found. | Calc. | Formula. | Cl. | S. | Cl. | S. |
| 0 | $C_4H_{10}O_2S_2$ | 41·6 | 41·6 | $C_4H_8Cl_2S_2$ | 35·3 (*a*) | 34·1 | 37·2 | 33·5 |
| 1 | — | — | — | $C_5H_{10}Cl_2S_2$ | 34·6 | 31·8 | 34·6 | 31·2 |
| 3 | $C_7H_{16}O_2S_2$ | 32·2 | 32·6 | $C_7H_{14}Cl_2S_2$ | 30·1 | — | 30·1 | — |
| 4 | $C_8H_{18}O_2S_2$ | 30·1 | 30·5 | $C_8H_{16}Cl_2S_2$ | 28·5 | — | 28·7 | — |
| 5 | $C_9H_{20}O_2S_2$ | 28·3 | 28·5 | $C_9H_{18}Cl_2S_2$ | 27·3 | — | 27·2 | — |
| 8 | $C_{12}H_{26}O_2S_2$ | 24·1 | 24·1 | $C_{12}H_{24}Cl_2S_2$ | 23·1 | 20·9 | 23·4 | 21·1 |
| 9 | $C_{13}H_{28}O_2S_2$ | 23·2 | 22·9 | $C_{13}H_{26}Cl_2S_2$ | 22·4 * | 21·7 * | 22·4 | 20·2 |
| 10 | $C_{14}H_{30}O_2S_2$ | 22·1 | 21·8 | $C_{14}H_{28}Cl_2S_2$ | 22·0 | 19·3 | 21·5 | 19·3 |

(*a*) Cf. Bennett (*loc. cit.*) for similar low Cl result.

Except with di-(2-chloroethylthio)methane, where methylene chloride was used, alkylene dibromides were employed as starting materials in each case. 1 : 6-Dibromohexane was obtained in 50% yield by refluxing hexane-1 : 6-diol (Muller and Sauerwald, *Monatsh.*, 1927, **48**, 521) with constant-boiling hydrobromic acid in the presence of a trace of concentrated sulphuric acid. The octane-, nonane-, and decane-diols were obtained from ethyl suberate (52% yield), azelate (64% yield), and sebacate (75% yield), respectively, by Bouveault–Blanc reduction and the technique of Bennett and Mosses (*J.*, 1931, 1697). Conversion into the αω-dibromides was effected by the action of dry gaseous hydrogen bromide on the molten diols at *ca.* 130° (cf. Carothers, *J. Amer. Chem. Soc.*, 1930, **52**, 5279). Yields obtained were : 1 : 8-dibromo-octane, b. p. 116°/3 mm., 86%; 1 : 9-dibromononane, b. p. 120°/3 mm., 80%; 1 : 10-dibromodecane, b. p. 138°/4 mm., m. p. 27°, 73%. 1 : 2-Di-(2-chloro-*n*-propylthio)ethane was similarly obtained from ethylene dibromide and 2-hydroxypropanethiol. The intermediate 1 : 2-*di*-(2-*hydroxy*-n-*propylthio*)*ethane* was obtained as a wax, b. p. 189—190°/5 mm., m. p. 28° (Found : S, 30·6; OH, 16·0. $C_8H_{18}O_2S_2$ requires S, 30·5; OH, 16·0%). The *chloro*-compound had b. p. 78—79°/0·005 mm., m. p. 14—15° (Found : Cl, 28·4. $C_8H_{16}Cl_2S_2$ requires Cl, 28·7%).

*Di-(2-chloroethyl) Disulphide.*—2-Hydroxyethanethiol (60 g.) was oxidised by careful addition of 30·5% w/v hydrogen peroxide (43 c.c.), the temperature being kept below 50°. After removal of the water under low pressure, a thick colourless syrup remained which could not be induced to crystallise, but could be distilled in small batches, if done quickly. The pure *dihydroxy-disulphide* was obtained as a white solid, b. p. 106°/0·015 mm., m. p. 25—26° (Found : S, 41·6. $C_4H_{10}O_2S_2$ requires S, 41·6%). Conversion into the chloro-compound by means of thionyl chloride was effected in the usual manner.

Microanalyses marked * were carried out by Mr. G. Ingram; other analyses were done by, or under the direction of, Mr. A. Wright.

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