

## 98. The Chemistry of 2-Chloroalkylamines. Part I. Preparation and General Reactions.

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The preparation and properties of a number of *alkyl-di-(2-chloroethyl)amines* are described. The dimers formed from these substances on keeping or heating, alone or in methyl alcohol solution, have been shown to be diquaternary piperazinium salts. *Methyl-2-chloroethyl-2-(2-chloroethoxy)ethylamine*, a by-product in one method of preparation of methyl-di-(2-chloroethyl)amine, undergoes two types of cyclisation, depending on the reaction conditions, leading to either an isomeric quaternary morpholinium salt or a dimeric quaternary piperazinium salt. From old aqueous solutions of methyl-di-(2-chloroethyl)amine there have been isolated, as picrates, the piperazinium dimer, the original base, and the half-hydrolysis product, *methyl-2-chloroethyl-2-hydroxyethylamine*, which has also been synthesised.

A number of workers (Ward, *J. Amer. Chem. Soc.*, 1935, **57**, 914; McCombie and Purdie, *J.*, 1935, 1217; Mason and Gasch, *J. Amer. Chem. Soc.*, 1938, **60**, 2816) have prepared 2 : 2' : 2''-trichlorotriethylamine,  $N(\text{CH}_2\text{CH}_2\text{Cl})_3$ , and commented on its vesicant properties, while more recently attention has been drawn (Jensen and Lundquist, *Dansk Tidsskr. Farm.*, 1941, **15**, 201; Eisleb, *Ber.*, 1941, **74**, 1433) to the vesicant properties of methyl-di-(2-chloroethyl)amine,  $\text{NMe}(\text{CH}_2\text{CH}_2\text{Cl})_2$ , the hydrochloride of which was first prepared by Prelog and Stepán (*Coll. Czech. Chem. Comm.*, 1935, **7**, 93). The present series of papers describes work carried out with the object of adding to our knowledge of the chemistry of this type of vesicant, which differs from 2 : 2'-dichlorodiethyl sulphide ("mustard gas") only in the replacement of the thio-ether group by an alkylimino-group.

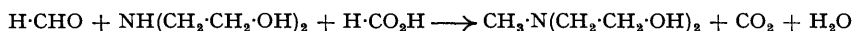
We have prepared eight representatives of this class of compound; all are basic liquids with vesicant properties which call for suitable precautions in manipulation. Some of their properties, and those of some derivatives, are collected in the Table.

## Properties of some 2-chloroalkylamines, NR'R''R'''.

Com- pound.	R'.	R''.	R'''	B. p.	pK <sub>a</sub> .	M. p. of hydro- chloride.	M. p. of picrate.
(I)	Me	CH <sub>2</sub> ·CH <sub>2</sub> Cl	CH <sub>2</sub> ·CH <sub>2</sub> Cl	64°/5 mm.	6.1	110°	133°
(II)	Et	CH <sub>2</sub> ·CH <sub>2</sub> Cl	CH <sub>2</sub> ·CH <sub>2</sub> Cl	73/4.5 mm.	6.3	141	100
(III)	Pr <sup>α</sup>	CH <sub>2</sub> ·CH <sub>2</sub> Cl	CH <sub>2</sub> ·CH <sub>2</sub> Cl	88—89/5.5 mm.	5.4	—	99
(IV)	Pr <sup>β</sup>	CH <sub>2</sub> ·CH <sub>2</sub> Cl	CH <sub>2</sub> ·CH <sub>2</sub> Cl	90/8 mm.	5.7	216	75
(V)	Me	CH <sub>2</sub> ·CHMeCl	CH <sub>2</sub> ·CHMeCl	82/9 mm.	—	—	110
(VI)	Me	CH <sub>2</sub> ·CH <sub>2</sub> Cl	CH <sub>2</sub> ·CH <sub>2</sub> ·O·CH <sub>2</sub> ·CH <sub>2</sub> Cl	—	7.1	66	59
(VII)	Me	CH <sub>2</sub> ·CH <sub>2</sub> Cl	CH <sub>2</sub> ·CH <sub>2</sub> ·OAc	78—80/1.5 mm.	—	—	85
(VIII)	Me	CH <sub>2</sub> ·CH <sub>2</sub> Cl	CH <sub>2</sub> ·CH <sub>2</sub> OH	—	—	54	76—78

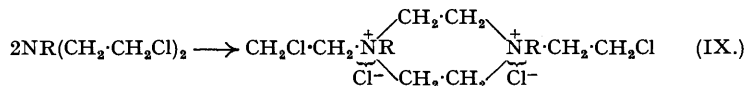
With the exception of (I), none of these compounds had previously been described; (IV) was prepared independently of our work, and some months earlier, by Prof. G. H. Coleman of Iowa State University.

Compounds (I) to (IV) were prepared from the corresponding alkyl-di-(2-hydroxyethyl)-amines, NR(CH<sub>2</sub>·CH<sub>2</sub>·OH)<sub>2</sub>. This reaction was fully investigated in the case of methyl-di-(2-chloroethyl)amine (I), and the best preparative procedure was found to be the use of thionyl chloride in boiling benzene, other chlorinating agents tried (sulphuryl chloride, sulphur monochloride, phosphorus trichloride) giving lower yields; the alkyl-di-(2-chloroethyl)amines can be isolated from the reaction product either in the free state, by basification, or as their hydrochlorides, which crystallise from the reaction mixture on cooling. Ethyl- and isopropyl-di-(2-hydroxyethyl)amines, required for (II) and (IV), were prepared by the action of ethylene oxide on the appropriate alkylamines in aqueous solution (cf. Knorr and Schmidt, *Ber.*, 1898, 31, 1074). It was, however, found preferable to prepare methyl-di-(2-hydroxyethyl)amine by methylation of di-(2-hydroxyethyl)amine with formaldehyde in the presence of formic acid as hydrogen donor, thus:



This method, which had previously been applied to the methylation of other secondary amines (cf. Clarke, Gillespie, and Weiss Haus, *J. Amer. Chem. Soc.*, 1933, 55, 4571; Forsee and Pollard, *ibid.*, 1935, 57, 1788), is preferable to the route from methylamine and ethylene oxide (Knorr and Matthes, *Ber.*, 1898, 31, 1071) since it avoids the formation of undesirable by-products arising from the reaction of more than two mols. of ethylene oxide with the amine. *n*-Propyl-di-(2-hydroxyethyl)amine (Matthes, *Annalen*, 1901, 315, 127) was prepared by the direct alkylation of di-(2-hydroxyethyl)amine with *n*-propyl bromide, and methyl-di-(2-hydroxy-*n*-propyl)amine, required for the preparation of (V), by treatment of aqueous methylamine with propylene oxide (it is noteworthy that propylene oxide, unlike ethylene oxide, shows little tendency to react with amines in a molar ratio of more than 2 : 1).

The alkyl-di-(2-chloroethyl)amines are all somewhat unstable, depositing solids on keeping at room temperature; the same solid products, which analysis shows to be quaternary ammonium salts with the same empirical formulæ as the parent amines, are formed more rapidly in methyl alcoholic solution. The reaction of the methyl compound (I) in methyl alcohol solution is markedly exothermic and may proceed almost explosively if the quantities of material involved are large. Similar products have been obtained from 2-chloroethylamines by other workers (Knorr, *Ber.*, 1905, 38, 3135; 1906, 39, 1420; Mason and Block, *J. Amer. Chem. Soc.*, 1940, 62, 1443) who concluded, on the basis of degradative evidence, that they were dimers with the piperazinium dichloride structure [as (IX)]. Comparison of the dimer obtained from methyl-di-(2-chloroethyl)amine (I) with synthetic *NN'*-dimethyl-*NN'*-di-(2-chloroethyl)-piperazinium dichloride (IX; R = Me) (Hanby and Rydon, *J.*, 1945, 835) shows the two substances to be identical; clearly the dimerisation process is



The stereoisomerism of compounds of type (IX) has already been discussed (Hanby and Rydon, *loc. cit.*); in the case of methyl-di-(2-chloroethyl)amine, which has been most fully studied, the *cis*-form of the dimer (IX; R = Me) predominates although some of the *trans*-isomer can also be isolated from the reaction product. Comparative studies of the rate of dimerisation of the compounds (I), (II), (III), and (IV) show that the rate falls off very markedly in the order Me > Et > Pr<sup>α</sup> > Pr<sup>β</sup>, the relative rates in unevacuated tubes at 100° being in the ratio



The results of several fractional crystallisation experiments indicate that a 48-hour old 1% solution of methyl-di-(2-chloroethyl)amine contains about 25 equiv. % of the dimer (IX; R = Me), 33% of the half-hydrolysis product (VIII), and 20% of the hydrochloride of the original amine (I); it will be shown in the following paper that the remaining 20 equiv. % must be methyl-di-(2-hydroxyethyl)amine. In more concentrated solutions there is less hydrolysis (B) and more dimerisation (A); thus a 79% yield of the picrate of the dimer (X; R = Me) was isolated from an 11% aqueous solution of (I) kept at room temperature for 10 days. The dimer produced by the reaction with water is mainly the *cis*-stereoisomeride, but a much smaller amount of the *trans*-compound is also present.

## EXPERIMENTAL.

*Preparation of 2-Chloro-alkylamines.*—*Methyl-di-(2-chloroethyl)amine* (I). Methyl-di-(2-hydroxyethyl)amine was most conveniently prepared as follows. Di-(2-hydroxyethyl)amine (1050 g.; 10 mols.) was mixed with 37.5% w/v formaldehyde (800 c.c.; 10 mols.); to the stirred solution 90% formic acid (425 c.c.; 10 mols.) was added dropwise over 2½ hours, the vigour of the reaction being conveniently regulated by varying the rate of addition. After being heated for 3 hours on the water-bath, the product was distilled, yielding 971 g. (81.5%) of methyl-di-(2-hydroxyethyl)amine, b. p. 123–125°/4 mm.,  $n_D^{20}$  1.4642 (Found: C, 50.5; H, 10.7; N, 11.25. Calc. for  $C_8H_{13}O_2N$ : C, 50.4; H, 10.9; N, 11.75%), characterised as its *di-p-nitrobenzoate*, rosettes of pale yellow prisms from alcohol, m. p. 112–113° (Found: C, 54.8; H, 4.6; N, 10.4.  $C_{18}H_{19}O_8N_3$  requires C, 54.7; H, 4.5; N, 10.1%), and picrate, and yellow needles from ethyl acetate, m. p. 95–96°.

Methyl-di-(2-hydroxyethyl)amine can also be prepared from ethylene oxide and methylamine (cf. Knorr and Matthes, *Ber.*, 1898, **31**, 1071). A 33% w/v aqueous solution of methylamine (300 c.c.; 3.23 mols.) was cooled in a freezing mixture in a flask fitted with a glass-spiral reflux condenser cooled with circulating ice-water. Ethylene oxide was passed in until the rate of absorption slackened notably (6½ hours), 255 g. (5.8 mols.) having then been taken up. After being kept overnight, the reaction mixture was distilled, yielding 235 g. (62%) of methyl-di-(2-hydroxyethyl)amine.

The following is the most satisfactory of many procedures tried for the conversion of methyl-di-(2-hydroxyethyl)amine into methyl-di-(2-chloroethyl)amine. Methyl-di-(2-hydroxyethyl)amine (120 g.; 1 mol.), in benzene (120 c.c.), was added dropwise, under reflux, during 1 hour, to a mixture of thionyl chloride (252 g.; 2.1 mols.) and benzene (120 c.c.); the mixture was then refluxed on the water-bath for 2 hours. Water (120 c.c.) was added to the cooled mixture, which was then basified with 40% sodium hydroxide solution (120 c.c.) and shaken; the aqueous layer was then run off and extracted once more with benzene (50 c.c.). The combined benzene solutions were dried ( $Na_2SO_4$ ) and distilled, yielding 132 g. (84%) of methyl-di-(2-chloroethyl)amine, (I), a mobile colourless liquid with a faint, but characteristic, odour and marked vesicant properties, b. p. 59°/2 mm., 64°/5 mm., 75°/10 mm. (Found: C, 38.6; H, 7.2; N, 9.2; Cl, 45.8. Calc. for  $C_8H_{11}NCl_2$ : C, 38.5; H, 7.05; N, 9.0; Cl, 45.5%). The hydrochloride, isolated from the cooled reaction mixture by filtration, crystallises from acetone or chloroform in leaflets, m. p. 110°; the picrate forms needles from benzene, m. p. 133°; the *mercuri-chloride*, prepared by shaking the free base with ice-cold 4% mercuric chloride solution, crystallises from water in needles, m. p. 187–188° (Found: Hg, 35.2.  $2C_8H_{11}NCl_2 \cdot HgCl_2$  requires Hg, 34.9%).

*Ethyl-di-(2-chloroethyl)amine* (II). Ethylene oxide was passed into ice-cooled 33% w/v ethylamine solution (53 c.c.) until the gain in weight was 35 g. (90 minutes); after 3 hours the product was distilled, yielding 33.8 g. (65%) of ethyl-di-(2-hydroxyethyl)amine, b. p. 117–118°/3 mm.,  $n_D^{18}$  1.4670. 86 G. of this intermediate, in chloroform (60 c.c.), were added dropwise over 45 minutes to thionyl chloride (170 g.) in chloroform (80 c.c.); after 1 hour's heating on the water-bath the semi-solid product was cooled and treated with a slight excess of sodium hydroxide solution. The mixture was shaken and separated, and the aqueous layer extracted twice more with chloroform; distillation of the combined dried ( $Na_2SO_4$ ) extracts yielded the amine (II) (87 g.; 79%), as a colourless, mobile, vesicant liquid, b. p. 66°/3 mm., 73°/4.5 mm. (Found: C, 42.9; H, 7.7; N, 8.3; Cl, 42.4.  $C_6H_{13}NCl_2$  requires C, 42.4; H, 7.7; N, 8.2; Cl, 41.7%). The hydrochloride, isolated in 72.5% yield by adding ether to the reaction product without basifying, crystallised from acetone in rosettes of acicular prisms, m. p. 141° (Found: N, 7.0; Cl, 51.1.  $C_6H_{13}NCl_3$  requires N, 6.8; Cl, 51.6%); the picrate crystallised from water in feathery clusters of phototropic (yellow to orange) prisms, m. p. 100° (Found: N, 14.3.  $C_{12}H_{16}O_7N_4Cl_2$  requires N, 14.0%).

*Di-(2-chloroethyl)-n-propylamine* (III). *n*-Propyl bromide (32.5 g.) was added, under reflux, with shaking, to a mixture of di-(2-hydroxyethyl)amine (27.5 g.) and anhydrous sodium carbonate (27.5 g.); after 1 hour at room temperature the mixture was refluxed on the water-bath for 4 hours. Alcohol was then added, sodium chloride filtered off, and the filtrate distilled, yielding 20 g. (52%) of di-(2-hydroxyethyl)-*n*-propylamine, b. p. 122–123°/3.5 mm.,  $n_D^{18}$  1.4638. Treatment with thionyl chloride, as described for the ethyl compound, gave a 75% yield of the *dichloro*-compound (III), a colourless vesicant liquid, b. p. 88–89°/5.5 mm. (Found: C, 45.8; H, 8.0; N, 7.9; Cl, 38.4.  $C_8H_{15}NCl_2$  requires C, 45.65; H, 8.2; N, 7.6; Cl, 38.6%); the picrate crystallised from benzene in thin, phototropic (yellow to orange) needles, m. p. 99° (Found: N, 13.9.  $C_{13}H_{18}O_7N_4Cl_2$  requires N, 13.55%).

*Di-(2-chloroethyl)isopropylamine* (IV). Ethylene oxide (14.4 g.) was passed into an ice-cooled solution of isopropylamine (9.6 g.) in water (60 c.c.) during 1 hour. The product was kept at room temperature overnight and then distilled, yielding 17.1 g. (72%) of di-(2-hydroxyethyl)isopropylamine, b. p. 129–131°/6 mm.,  $n_D^{21}$  1.4472; the picrate crystallised from alcohol in laths, m. p. 139–140° (Found: N, 14.75.  $C_{13}H_{19}O_8N_4$  requires N, 14.9%), and the *di-p-nitrobenzoate* from alcohol in rosettes of small prismatic needles, m. p. 129–130° (Found: C, 56.8; H, 5.1.  $C_{21}H_{23}O_8N_3$  requires C, 56.6; H, 5.2%). Treatment with thionyl chloride, as described for the ethyl compound, gave a 98% yield of *di-(2-chloroethyl)isopropylammonium chloride*, which crystallised from aqueous alcohol in prisms, m. p. 216° (Found:

C, 38.6; H, 6.8.  $C_7H_{16}NCl_3$  requires C, 38.1; H, 7.3%. The free base (IV) is a colourless vesicant liquid, b. p.  $90^{\circ}/8$  mm.; the *picrate* crystallises from aqueous alcohol in leaflets, m. p.  $75^{\circ}$  (Found: C, 37.5; H, 4.5.  $C_{13}H_{18}O_7N_4Cl_2$  requires C, 37.8; H, 4.4%).

*Methyl-di-(2-chloro-n-propyl)amine* (V). Propylene oxide was added to an aqueous solution (28%) of methylamine (58 g.; 1 mol.) cooled in a freezing mixture. After the initial vigorous reaction had abated the product was kept at room temperature, with occasional ice-cooling in the early stages, for 16 hours and then heated on the water-bath for 3 hours. Distillation yielded 62.7 g. (85%) of *methyl-di-(2-hydroxy-n-propyl)amine*, a viscous colourless oil, b. p.  $103-104^{\circ}/6$  mm.,  $n_D^{20}$  1.4472 (Found: C, 56.95; H, 11.5.  $C_7H_{17}O_2N$  requires C, 57.1; H, 11.5%); the *picrate* crystallised from ethyl acetate-benzene in hygroscopic orange-yellow prismatic needles, m. p.  $88^{\circ}$  (Found: C, 41.95; H, 5.8.  $C_{13}H_{20}O_9N_4$  requires C, 41.5; H, 5.3%). The amine (61 g.) was treated, as usual, with thionyl chloride in benzene, yielding the *dichloroamine* (V) (63.7 g.; 83.5%), b. p.  $82^{\circ}/9$  mm. (Found: C, 45.2; H, 8.7; Cl, 39.2.  $C_7H_{15}NCl_2$  requires C, 45.6; H, 8.2; Cl, 38.6%); the *picrate* crystallised from benzene in rectangular laths, m. p.  $110^{\circ}$  (Found: C, 38.2; H, 4.7.  $C_{13}H_{18}O_7N_4Cl_2$  requires C, 37.8; H, 4.35%).

*Methyl-2-chloroethyl-2-(2-chloroethoxy)ethylamine* (VI). Ethylene oxide (80 g.) was passed into a mixture of methyl-di-(2-hydroxyethyl)amine (240 g.) and water (250 c.c.), the reaction vessel being cooled with running water. Distillation and redistillation yielded methyl-2-hydroxyethyl-2-(2-hydroxyethoxy)ethylamine (75 g.; 23%), b. p.  $138^{\circ}/4$  mm.,  $n_D^{20}$  1.4675, characterised as its *di-p-nitrobenzoate*, m. p.  $116^{\circ}$  (Found: C, 54.2; H, 4.9.  $C_{21}H_{23}O_9N_3$  requires C, 54.7; H, 5.0%). This dihydroxy-amine (50 g.), in chloroform (50 c.c.), was added dropwise over 30 minutes to thionyl chloride (81 g.) in chloroform (100 c.c.); the reaction was completed by refluxing on the water-bath for 3 hours. Solvents, etc., were removed by distillation and by keeping the residue in a vacuum desiccator over sodium hydroxide; solution in absolute alcohol (100 c.c.) followed by precipitation with dry ether (500 c.c.) yielded *methyl-2-chloroethyl-2-(2-chloroethoxy)ethylammonium chloride* (56 g.; 77%), m. p.  $66^{\circ}$  (Found: C, 35.3; H, 6.6; Cl, 15.0.  $C_7H_{15}ONCl_2.HCl$  requires C, 35.5; H, 6.8; Cl, 15.0%); the *picrate* crystallised from alcohol in flattened needles, m. p.  $59^{\circ}$  (Found: C, 36.4; H, 4.4.  $C_{13}H_{18}O_8N_4Cl_2$  requires C, 36.4; H, 4.2%). The hydrochloride (12 g.) was dissolved in water (30 c.c.), covered with benzene (20 c.c.), and treated, with shaking and cooling, with sodium hydroxide (2 g.) dissolved in a little water; evaporation of the dried benzene solution under reduced pressure at room temperature yielded the free base (VI) as an unstable oil which could be kept for a few days at  $0^{\circ}$  (Found: equiv. by titration, 218.5.  $C_7H_{15}ONCl_2$  requires equiv., 200.0).

*Methyl-2-chloroethyl-2-hydroxyethylamine* (VIII). Methyl-2-hydroxyethylamine was prepared by the following modification of the method of Schotte, Priewe, and Roeschens (*Z. physiol. Chem.*, 1928, 174, 119; cf. D.R.-P. 442,413; Pierce and Adams, *J. Amer. Chem. Soc.*, 1923, 45, 790; Pierce, *ibid.*, 1928, 50, 241). 2-Chloroethyl chloroformate (98 g.) was added in small portions over 15 minutes, with stirring and ice-cooling, to 33% w/v methylamine solution (80 c.c.) containing sodium carbonate (39 g.). After a further 2 hours' stirring the 2-chloroethyl methylcarbamate was extracted with ether, washed with dilute hydrochloric acid and water, dried, and distilled; b. p.  $100^{\circ}/6$  mm., 65 g. (69%). This carbamate (120 g.) was added to a solution of potassium hydroxide (195 g.) in 90% alcohol (300 c.c.). After the vigorous reaction had abated the mixture was distilled and redistilled through a long column, yielding 47 g. (72%) of methyl-2-hydroxyethylamine, b. p.  $52^{\circ}/6$  mm.

Methyl-2-hydroxyethylamine (47 g.) was heated on the water-bath for 30 minutes with 2-chloroethyl acetate (76 g.) and anhydrous potassium carbonate (43 g.); potassium chloride was filtered from the cooled product and washed with chloroform. Two distillations of the filtrate and washings yielded impure *methyl-2-hydroxyethyl-2-acetoxyethylamine*, b. p.  $81-83^{\circ}/1$  mm. (30 g.; 30%) (Found: C, 49.1; H, 8.2; OH, 10.4.  $C_7H_{15}O_3N$  requires C, 52.2; H, 9.3; OH, 10.55%). This compound was treated with thionyl chloride in benzene, yielding 6.2 g. (27%) of *methyl-2-chloroethyl-2-acetoxyethylamine* (VII), b. p.  $78-80^{\circ}/1.5$  mm. (Found: C, 46.7; H, 7.5; N, 8.05.  $C_{17}H_{14}O_2NCl$  requires C, 46.75; H, 7.8; N, 7.8%), characterised as its *picrate*, yellow prisms from benzene, m. p.  $85^{\circ}$  (Found: C, 38.7; H, 4.4; Cl, 8.65.  $C_{13}H_{17}O_9N_4Cl$  requires C, 38.2; H, 4.2; Cl, 8.7%), and *methiodide*, needles from alcohol, m. p.  $150^{\circ}$  (decomp.) (Found: C, 30.2; H, 5.5; N, 4.35.  $C_6H_{11}O_2NCl$  requires C, 29.9; H, 5.3; N, 4.35%); the structure of (VII) was confirmed by its conversion, on being kept overnight with an equal volume of alcohol, into *cis-NN'*-dimethyl-*NN'*-di-(2-acetoxyethyl)piperazinium dichloride (Hanby and Rydon, *J.*, 1945, 833), m. p. and mixed m. p.  $228^{\circ}$  (*picrate*, m. p. and mixed m. p.  $188^{\circ}$ ). The chloro-acetoxy-compound (VII) (5 g.) was hydrolysed by refluxing for 9 hours with concentrated hydrochloric acid (9 c.c.) and water (4.5 c.c.); the resulting solution was evaporated to dryness under reduced pressure and the residue treated with 0.5N-calcium *picrate*. The crude *picrate* so precipitated (3.9 g.; 38%) had m. p.  $63-65^{\circ}$  and crystallised from benzene-ethyl acetate in orange-yellow prisms, m. p.  $72-74^{\circ}$ , raised to  $73-75^{\circ}$  on admixture with the *picrate* isolated from an old aqueous solution of methyl-di-(2-chloroethyl)amine (see p. 519).

*Dimerisation of 2-Chloroethylamines.*—(a) Methyl-di-(2-chloroethyl)amine (12.5 g.) was kept in methyl alcohol (25 c.c.) for 40 hours at room temperature. The semi-solid product was filtered off, washed with methyl alcohol, and purified by repeated precipitation from water with acetone; the product, m. p.  $329^{\circ}$  (decomp.) (Found: C, 37.4; H, 7.3; N, 8.9; Cl, 44.15; loss of weight on drying under reduced pressure over phosphoric oxide at  $100^{\circ}$ , 2.4, 3.1. Found, on material so dried: C, 38.25; H, 7.0; Cl, 45.7. Calc. for  $C_{10}H_{22}N_2Cl_4 \cdot \frac{1}{2}H_2O$ : C, 37.4; H, 7.2; N, 8.7; Cl, 44.3;  $H_2O$ , 2.8. Calc. for  $C_{10}H_{22}N_2Cl_4$ : C, 38.5; H, 7.05; Cl, 45.5%), was identified as *cis-NN'*-dimethyl-*NN'*-di-(2-chloroethyl)piperazinium dichloride (IX; R = Me) by mixed m. p. with a synthetic specimen (Hanby and Rydon, *J.*, 1945, 833) and by mixed m. p. of the derived *dipicrate*, leaflets or needles from water, m. p.  $208^{\circ}$  (decomp.). The same dimer is deposited by methyl-di-(2-chloroethyl)amine slowly at room temperature and more rapidly on heating.

(b) Ethyl-di-(2-chloroethyl)amine similarly yielded *NN'*-diethyl-*NN'*-di-(2-chloroethyl)piperazinium dichloride (IX; R = Et), m. p.  $312^{\circ}$  (decomp.) after crystallisation from acetone-methanol (Found: C, 42.2; H, 7.9; N, 8.4.  $C_{12}H_{26}N_2Cl_4$  requires C, 42.4; H, 7.7; N, 8.2%), characterised as its *dipicrate*, leaflets from water, m. p.  $232^{\circ}$  (Found: C, 39.5; H, 4.2.  $C_{24}H_{30}O_{14}N_8Cl_2$  requires C, 39.8; H, 4.1%).

(c) Di-(2-chloroethyl)-*n*-propylamine similarly yielded NN'-di-(2-chloroethyl)-NN'-di-*n*-propylpiperazinium dichloride (IX; R = Pr<sup>a</sup>), needles from methanol, m. p. 315° (decomp.) (Found: C, 45.4; H, 8.3; N, 7.5. C<sub>14</sub>H<sub>30</sub>N<sub>2</sub>Cl<sub>4</sub> requires C, 45.65; H, 8.15; N, 7.6%), and the *picrate*, small leaflets from water, m. p. 235° (Found: C, 41.6; H, 4.7. C<sub>28</sub>H<sub>34</sub>O<sub>14</sub>N<sub>8</sub>Cl<sub>2</sub> requires C, 41.4; H, 4.5%).

*Cyclisation Products of Methyl-2-chloroethyl-2-(2-chloroethoxy)ethylamine.*—(a) *N*-Methyl-*N*-2-chloroethylmorpholinium chloride (XI). Methyl iodide (8.0 g.) was added gradually, with ice-cooling, to *N*-2-chloroethylmorpholine (6.0 g.; Mason and Block, *J. Amer. Chem. Soc.*, 1940, **62**, 1443), and the mixture was kept overnight at room temperature; the semi-solid product was then rubbed with ether and the solid portion (9.6 g.; 82%) filtered off and dried at 100°. *N*-Methyl-*N*-2-chloroethylmorpholinium iodide crystallised from acetone containing a little water in acicular prisms, m. p. 156—157° (Found: C, 28.8; H, 5.1. C<sub>7</sub>H<sub>15</sub>ONClI requires C, 28.8; H, 5.15%), and was characterised as the *picrate*, long rectangular prisms, aggregating into leaflets, from water, m. p. 171—172° (Found: C, 40.4; H, 4.4; Cl, 8.8. C<sub>15</sub>H<sub>17</sub>O<sub>8</sub>N<sub>4</sub>ClI requires C, 39.75; H, 4.3; Cl, 9.05%). The iodide (2.9 g.), dissolved in water (25 c.c.), was shaken at room temperature for 24 hours with two equivs. of freshly precipitated silver chloride. Evaporation of the filtered solution and crystallisation of the residue from alcohol-ether yielded the *chloride* (XI) as deliquescent prisms, m. p. 169° (decomp.) (Found: C, 42.1; H, 7.5; Cl, 35.6. C<sub>7</sub>H<sub>15</sub>ONCl<sub>2</sub> requires C, 42.0; H, 7.5; Cl, 35.5%).

Methyl-2-chloroethyl-2-(2-chloroethoxy)ethylamine (VI) solidified completely after heating on the water-bath for 20 minutes. The product was identified as the morpholinium chloride (XI) by crystallisation from alcohol-ether to give a product, in 75% yield, having m. p. 171°, not depressed on admixture with the synthetic product; the identity was further confirmed by conversion into the *picrate*, m. p. and mixed m. p. 171—172°. The same morpholinium salt was formed, more slowly, when the dichloro-amine (VI) was kept at room temperature.

(b) NN'-Dimethyl-NN'-di-2-(2-chloroethoxy)ethylpiperazinium dichlorides (X). NN'-Dimethylpiperazine (3.5 g.) was heated on the water-bath for 24 hours with 2:2'-dichlorodiethyl ether (18 c.c.). The solid product (8.0 g.; 65%; m. p. 330—350°) was collected by filtration, washed with ether, and dried at 100°. Crystallisation from methanol-acetone yielded trans(?) -NN'-dimethyl-NN'-di-2-(2-chloroethoxy)ethylpiperazinium dichloride (X) as a micro-crystalline powder, decomp. 365° (Found: C, 41.8; H, 7.25. C<sub>14</sub>H<sub>30</sub>O<sub>2</sub>N<sub>2</sub>Cl<sub>4</sub> requires C, 42.0; H, 7.5%). Treatment of an aqueous solution with saturated potassium iodide solution and crystallisation of the precipitate from 95% alcohol yielded the corresponding *di-iodide* as a micro-crystalline powder, m. p. 303° (decomp.) (Found: C, 29.3; H, 5.1. C<sub>14</sub>H<sub>30</sub>O<sub>2</sub>N<sub>2</sub>Cl<sub>2</sub>I<sub>2</sub> requires C, 28.8; H, 5.15%).

Methyl-2-chloroethyl-2-(2-chloroethoxy)ethylamine (VI) (2 g.) was kept at room temperature overnight with methanol (5 c.c.); next day much ether was added and the solution filtered. The solid (1.4 g.) was extracted with warm alcohol to remove any morpholinium salt and then crystallised from methanol, yielding *cis*(?) -NN'-dimethyl-NN'-di-2-(2-chloroethoxy)ethylpiperazinium dichloride (X), decomp. 365° (Found: C, 42.2; H, 7.0; N, 6.5. C<sub>14</sub>H<sub>30</sub>O<sub>2</sub>N<sub>2</sub>Cl<sub>4</sub> requires C, 42.0; H, 7.5; N, 7.0%); the *di-iodide* crystallised from water in small leaflets, m. p. 289° (decomp.). A mixture of the *cis*- and *trans*-dichlorides melted at 310° but the di-iodides showed no depression of m. p. on admixture.

*Action of Water on Methyl-di-(2-chloroethyl)amine.*—(a) *Isolation of reaction products.* Methyl-di-(2-chloroethyl)amine (I) (11.5 g.) was shaken with water (1000 c.c.) until solution was complete (a few minutes); the solution was then kept at room temperature for 48 hours. To the solution (2.46 mg. Cl<sup>-</sup>/c.c.) was added 0.5*n*-calcium *picrate* (138 c.c.); fractional crystallisation from water of the immediate precipitate (11.1 g.; m. p. 175—185°) yielded the *picrate* of the dimer (IX; R = Me) (6.9 g.; 27%; m. p. 193—196°) and a rather impure specimen of the *picrate* of (I) (3.2 g.; 12%; m. p. 110—113°), which gave the pure *picrate*, m. p. 127—129°, on further recrystallisation. Three further crops (8.2 g., m. p. 72—74°; 2.9 g., m. p. 68—70°; 1.0 g., m. p. 65—66°) were obtained by concentration of the mother-liquor; these were combined and crystallised from ethyl acetate-benzene, yielding the typical orange prisms of the *picrate* of methyl-2-chloroethyl-2-hydroxyethylamine (VIII) (9.2 g.; 35%; m. p. 75—77°).

A similar experiment in which 0.1*N*-sodium *picrate* was used gave 3.2 g. (24%) of the *picrate* of the dimer (IX; R = Me) and 1.9 g. (12.5%) of the *picrate* of (I); it was not possible to isolate the *picrate* of (VIII) in good yield owing to contamination with sodium *picrate*.

In another experiment a solution of (I) (113.8 g.) in water (to 1000 c.c.) was kept at room temperature for 10 days and then treated with 0.1*N*-sodium *picrate* (720 c.c.); the precipitated *picrate* (20.1 g.; 79%) gave, on fractional crystallisation from water, only the *picrate* of the dimer (IX; R = Me), of which 18.4 g. were isolated in five crops (m. p. 202—203°, 203—205°, 201—202°, 199—200°, 198—200°).

(b) *Isolation of stereoisomerides of the dimer* (IX; R = Me). A solution of methyl-di-(2-chloroethyl)amine (226 g.) in water (20 l.) was kept at room temperature for 48 hours, after which time it was evaporated under reduced pressure to 500 c.c. The solid which crystallised on being kept for some time at room temperature was collected, and dried at 100°; this material (8.0 g.; 3.5%; m. p. 328—330°) was identified as the *trans*-dimer (IX; R = Me) by conversion into the *picrate*, orange needles from water, m. p. and mixed m. p. 225°. To the mother liquor, acetone (5000 c.c.) and water (200 c.c.) were added in several portions; the precipitated solid (59.2 g.; 26.3%; m. p. 328°) was identified as the *cis*-dimer (IX; R = Me) by conversion into the *picrate*, golden leaflets from water, m. p. and mixed m. p. 203°.

(c) *Preparation of stereoisomerides of the dimer* (IX; R = Me). (i) *Trans*. Methyl-di-(2-chloroethyl)amine was kept overnight with an equal volume of methanol; the precipitated dimer was filtered off and washed with acetone. The product was dissolved in the minimum quantity of water at 50—60° and the solution treated with an equal volume of acetone; on cooling, the filtered solution deposited the pure *trans*-dimer (IX; R = Me), identified by conversion into the *picrate*, m. p. 221° (crude), which crystallised from water in needles, m. p. 225°.

(ii) *Cis*. Methyl-di-(2-chloroethyl)amine (30 g.) was kept overnight with methanol (25 c.c.); the precipitated dimer (30 g.) was filtered off, washed with acetone, and dried at 100°. The finely powdered product was shaken vigorously with cold water (75 c.c.); the undissolved portions was shown, by

conversion into the picrate and fractional crystallisation, to contain about 75% of the *trans*- and 25% of the *cis*-dimer. Careful addition of acetone (250 c.c. in all) in three portions to the cold water solution yielded successive crops (0.5 g. + 5.1 g. + 8.0 g. = 13.6 g.) which were all identified as the *cis*-dimer by conversion into the picrate, golden leaflets from water, m. p. and mixed m. p. 206°.

(d) *Preparation of methyl-2-chloroethyl-2-hydroxyethylamine* (VIII). A 48 hour old 1% solution of methyl-di-(2-chloroethyl)amine (I) in water (10 l.) was treated with 0.5N-calcium picrate (1304 c.c.). The initial precipitate was filtered off and discarded and the filtrate concentrated under reduced pressure to 2500 c.c. On being kept overnight this solution deposited an initial crop (20.2 g.) of the crude picrate of (I); the mother liquor, on seeding, yielded 80 g. of the practically pure picrate of (VIII), m. p. 72—73°; a further crop (18.5 g.; m. p. 72—73°) was obtained by concentrating the mother liquor to 1000 c.c. *Methyl-2-chloroethyl-2-hydroxyethylammonium picrate* crystallises from ethyl acetate-benzene or water in large orange prisms, m. p. 76—78° (Found: C, 36.4; H, 3.8; N, 15.4.  $C_{11}H_{15}O_8N_4Cl$  requires C, 36.0; H, 4.1; N, 15.3%).

The combined crops of picrate (98.5 g.; 41%) were dissolved in hot water and treated with excess hydrochloric acid; the precipitated picric acid was removed by filtration and the remainder by repeated extraction with benzene. Evaporation of the residual solution under reduced pressure yielded methyl-2-chloroethyl-2-hydroxyethylammonium chloride as a thick oil which solidified on long keeping in a vacuum desiccator; the semi-solid product was filtered off and washed with a mixture of equal volumes of *isopropyl* alcohol and dry ether, yielding the very deliquescent *hydrochloride*, m. p. 54° (Found: C, 34.4; H, 7.7; Cl, 20.8.  $C_8H_{12}ONCl, HCl$  requires C, 34.5; H, 7.5; Cl, 20.4%). The *mercurichloride*, prepared in theoretical yield by treating an aqueous solution of the hydrochloride with aqueous mercuric chloride, crystallised from water in transparent prisms, m. p. 198° (decomp.) (Found: Hg, 45.8.  $C_8H_{12}ONCl, HCl, HgCl_2$  requires Hg, 45.0%). Basification of an aqueous solution of the hydrochloride, followed by extraction with chloroform, yielded the free base (VIII), which was, however, extremely unstable. On attempted vacuum distillation the crude product was rapidly converted into a white solid which was identified as a mixture of the stereoisomerides of *NN'*-dimethyl-*NN'*-di-(2-hydroxyethyl)piperazinium dichloride by conversion into the picrate; fractional crystallisation yielded both the *cis*- (m. p. 219—220°) and *trans*- (m. p. 250°) picrates, neither of which showed any depression of m. p. on admixture with synthetic specimens (Hanby and Rydon, *J.*, 1945, 835).

The crude hydrochloride (600 mg.) was refluxed for an hour with thionyl chloride (3 c.c.). Excess of thionyl chloride was removed under reduced pressure, and the residue dissolved in a little water and treated with 0.5N-calcium picrate (8 c.c.). Crystallisation of the precipitate from water yielded the picrate of methyl-di-(2-chloroethyl)amine in needles, m. p. 130—131°, mixed m. p. 131—132°.

The crude hydrochloride was similarly treated with acetyl chloride (5 c.c.) and then calcium picrate. Crystallisation of the crude picrate from benzene gave methyl-2-chloroethyl-2-acetoxyethylammonium picrate in lemon-yellow prisms, m. p. 83—84°, unchanged on admixture with the synthetic material (p. 517).

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