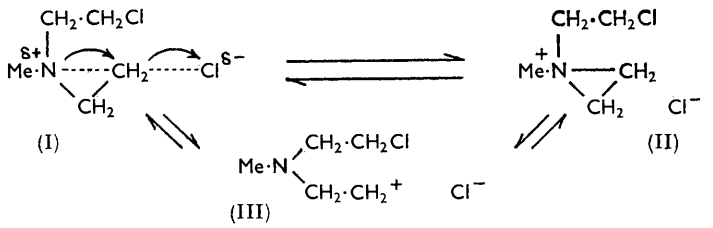
136. *The Reaction between* N-*Methyldi-(2-chloroethyl)amine and Thiosulphate.*

By E. Boyland and R. Nery.

N-Methyldi-(2-chloroethyl)amine reacts with an excess of thiosulphate in aqueous solution at physiological pH to yield the "Bunte" salt $[MeN(CH_2{\cdot}CH_2{\cdot}S{\cdot}SO_3Na)_2]$ which is converted into tetrahydro-5-methyl-1,2,5-dithiazepine and a polymeric disulphide in strongly alkaline media. Equimolar solutions of *N*-methyldi-(2-chloroethyl)amine and thiosulphate in water or 50% aqueous ethanol at pH 8 give perhydro-6-methyl-1,2,3,6-oxadithiazocine 2,2-dioxide in yields which appear to depend on the solubility of the product and on the dielectric constant of the reaction medium.

The rate of the unimolecular ionisation of *N*-methyldi-(2-chloroethyl)amine hydrochloride in aqueous sodium hydrogen carbonate is much greater than that of ethyl chloride in the same medium owing to the accelerating influence of the tertiary nitrogen atom. The formation of the 1,2′-chloroethyl-1-methylaziridinium ion (II) has been demonstrated from kinetic measurements by Hanby, Hartley, Powell, and Rydon.[1] Golumbic, Fruton, and Bergmann [2] showed that the reaction rapidly produced chloride ion without an equivalent

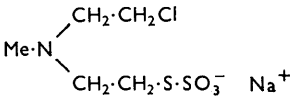


amount of hydrogen ion, and they isolated the picrylsulphonate salt corresponding to compound (II). Bartlett, Ross, and Swain [3] showed by kinetic measurements that reaction of the compound (II) with strong nucleophilic reagents ($S_2O_3^{2-}$, OH^-, Et_3N) is of first order with respect to the original tertiary base. Attack on the aziridinium ion (II) by a nucleophilic reagent weaker than the parent amine, *e.g.*, water, proceeds at a rate comparable with that of the initial ionisation; competitive attack by unchanged amine becomes evident and the kinetic course does not approximate to simple order. It is thus

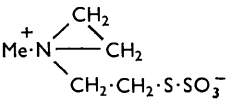
[1] Hanby, Hartley, Powell, and Rydon, *J.*, 1947, 519.
[2] Columbic, Fruton, and Bergman, *J. Org. Chem.*, 1946, **11**, 518.
[3] Bartlett, Ross, and Swain, *J. Amer. Chem. Soc.*, 1947, **69**, 2971.

evident that reaction of the tertiary base with thiosulphate in aqueous sodium hydrogen carbonate is an apparent S_N1 reaction, but that attack by weaker nucleophilic reagents may involve a bimolecular process. It is thus likely, by analogy with " mustard gas," that reaction of the tertiary base with biological materials (cf. the low competition factors [4] of phosphate, carboxylate, heterocyclic tertiary nitrogen, and amino-groups at physiological pH) proceeds largely by an S_N2 mechanism. The rate of nucleophilic substitution in acidic media is considerably reduced, since protonation reduces the acceleration by the tertiary nitrogen to a minimum.

Reaction of *N*-methyldi-(2-chloroethyl)amine with one equivalent of aqueous thiosulphate gives the sodium *S*-alkyl thiosulphate (IV). Here the $CH_2{\cdot}S{\cdot}SO_3^-$ group increases the rate of the ionisation of the second 2-chloroethyl group by increasing the nucleophilic character of the tertiary nitrogen, but at the same time hinders the approach of a new nucleophilic reagent (*e.g.*, a second $S_2O_3^{2-}$ ion) by exerting an electrostatic shielding effect on, and also by direct reaction with, the seat of substitution. Direct interaction between the two reactive centres of the dipolar ion (V), or replacement of chlorine by $\cdot S{\cdot}SO_3^-$ in compound (IV), would involve transition states typical of intramolecular S_N2 reactions having lower electrostatic potentials than the reactants; one characteristic of such reactions is that the rate increases if the dielectric constant of the solvents is decreased.[5] Thus, an equimolar aqueous solution of *N*-methyldi-(2-chloroethyl)amine and sodium thiosulphate at pH 8 yielded small amounts of perhydro-6-methyl-1,2,3,6-oxadithia-azocine 2,2-dioxide (VI), but in 50% aqueous ethanol an almost quantitative yield of this base was obtained. This may appear surprising in view of the low competition factor (see below) of a negatively charged oxygen anion for a 2-chloroethyl group; precipitation of the product from solution



(IV)



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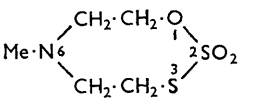
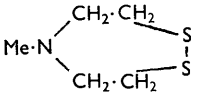


(VI)

probably accounts for the high yield. The following observations indicate that the structure assigned to compound (VI) is preferable to the alternative structures (V) and (VII) having the same empirical formula: (*a*) the substance is insoluble in cold water and in dilute alkali; (*b*) a saturated aqueous solution at 60° does not consume thiosulphate; and (*c*) high dilution has no appreciable effect on the yield. Facts (*a*) and (*b*) are incompatible with the ionic structure (V), and fact (*c*) with the polymeric structure (VII).

(VII)



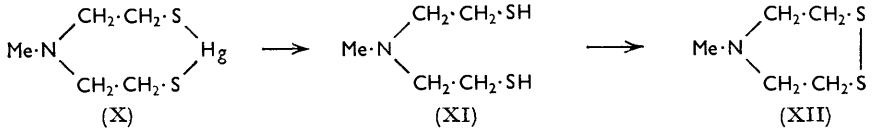
(VIII)

(IX)

In view of the low competition factor [4] of a negatively charged oxygen anion (SO_4^{2-}, $F = 4{\cdot}9$) compared with that of negatively charged sulphur in the thiosulphate anion ($F = 2{\cdot}7 \times 10^4$) for " mustard gas," it is unlikely that the reaction of di-(2-chloroethyl-amines with excess of aqueous thiosulphate is affected appreciably by competition involving the negatively charged oxygen of the thiosulphate ion. It is, however, significant that rather less than exactly two moles of thiosulphate are consumed per mole of tertiary base in 2 : 1 acetone–water solutions.[3]

[4] Ogston, *Trans. Faraday Soc.*, 1948, **44**, 45.
[5] Hughes, *Trans. Faraday Soc.*, 1941, **37**, 608.

The primary substitution products of alkyl halides and thiosulphate, the so-called " Bunte " salts, have been shown [6] to undergo intermolecular reaction in alkaline media to yield the corresponding disulphides. It is now reported that the " Bunte " salt from *N*-methyldi-(2-chloroethyl)amine, *i.e.*, $Me{\cdot}N(CH_2{\cdot}CH_2{\cdot}S{\cdot}SO_3^-Na^+)_2$, reacts further in strongly alkaline solution to yield a mixture of disulphides (VIII) and (IX), resulting from intramolecular and intermolecular interaction, respectively. A product analogous to (XII) has been prepared by reaction of di-(2-chloroethyl)amine with sodium disulphide.[7] The size of the polymer (IX) apparently varies with the concentration, basicity, and time and temperature of heating since the product varies from a viscous gum to a rubbery material.



(X) (XI) (XII)

These polymers are insoluble in water and alkali but dissolve in strong mineral acids. They are reduced by zinc and hydrochloric acid to products, probably thiols, that are converted to varying extents in alkaline solutions into tetrahydro-5-methyl-1,2,5-dithiazepine (VIII), a yellow oil characterised as its crystalline picrate and *N*-methiodide. It is reduced by zinc and acetic acid to a dithiol that has been isolated as its mercury derivative, probably (X). An aqueous suspension of compound (X), on treatment with hydrogen sulphide, yields the theoretical amount of mercuric sulphide; the liberated dithiol (XI) reverts to the cyclic disulphide (VIII) in alkaline solution.

Alkylating agents, including " nitrogen mustard," are known to react rapidly with thiosulphate to give non-toxic derivatives.[8] The present work developed out of an attempt to use the reaction of " nitrogen mustards " with sodium thiosulphate for the estimation of the former in biological fluids, but this was not pursued because the reaction with 4-4′-nitrobenzylpyridine [9] proved a more convenient method.

Experimental

Perhydro-6-methyl-1,2,3,6-oxadithiazocine 2,2-Dioxide (VI).—(a) *In 50% aqueous ethanol.* A solution of *N*-methyldi-(2-chloroethyl)amine hydrochloride (5·7 g., 0·03 mole) in ethanol (25 ml.) was added to one of sodium thiosulphate heptahydrate (7·5 g., 0·03 mole) in water (25 ml.) containing sodium hydrogen carbonate (5·0 g.). The mixture was kept at room temperature for 1 hr., then for 60 hr. at 0°. The precipitate (A) (3·0 g.), m. p. 216—220° (decomp.), was filtered off and the bulk of the alcohol was removed from the filtrate by azeotropic distillation. The residual liquid, on cooling, yielded a solid (2·5 g.), m. p. and mixed m. p. with solid (A), 216—220° (decomp.). The two solids were combined and recrystallised twice from water, to yield colourless prisms of the basic *sulphone* (VI) (5·0 g., 81%), m. p. 224° (decomp.) (Found: C 29·1; H, 5·6; N, 6·8; S, 31·2; H_2O, 4·2. $C_5H_{11}NO_3S_2,\frac{1}{2}H_2O$ requires C, 29·1; H, 5·9; N, 6·8; S, 31·1; H_2O, 4·3%).

(b) *In aqueous solution.* *N*-Methyl di-(2-chloroethyl)amine hydrochloride (5·7 g., 0·03 mole) was added to one of sodium thiosulphate heptahydrate (7·5 g., 0·03 mole) in water (50 ml.) containing sodium hydrogen carbonate (5 g.). The free tertiary base separated as an oil. The mixture was shaken rapidly at room temperature for 3 hr., giving a homogeneous solution, then kept at 0° overnight, and the precipitated solid (0·85 g.) was isolated and identified as the sulphone (VI), m. p. and mixed m. p. 224° (decomp.).

(c) *In dilute 50% aqueous ethanol.* *N*-Methyldi-(2-chloroethyl)amine hydrochloride (2·8 g.,

[6] Stutz and Shriner, *J. Amer. Chem. Soc.*, 1933, **55**, 1242; Schoberl and Bauer, *Angew. Chem.*, 1957, **69**, 478.
[7] Günther and Mautner, *J. Amer. Chem. Soc.*, 1960, **82**, 2762.
[8] Cf. Callaway and Pearce, *Brit. J. Pharmacol.*, 1958, **13**, 395.
[9] Epstein, Rosenthal, and Ess, *Analyt. Chem.*, 1955, **27**, 1435.

0·015 mole) was added to a solution of sodium thiosulphate hydrate (3·7 g., 0·015 mole) in 50% aqueous ethanol (500 ml.) containing sodium hydrogen carbonate (2·5 g.), and the whole was kept at room temperature for 1 hr. and at 0° for 16 hr. The solution was concentrated *in vacuo* to about 20 ml. and, on cooling, deposited a solid (2·6 g.) which after two crystallisations from water gave compound (VI) (2·4 g.), m. p. and mixed m. p. 224° (decomp.).

Tetrahydro-5-methyl-1,2,5-dithiazepine (VIII).—(a) *From the " Bunte " salt.* *N*-Methyldi-(2-chloroethyl)amine hydrochloride (1·9 g.) was shaken with a solution of sodium thiosulphate heptahydrate (5·0 g.) in water (50 ml.) containing sodium hydrogen carbonate (2 g.) and at room temperature for 8 hr. A small precipitate was formed. The mixture was filtered and the filtrate evaporated to dryness *in vacuo*. The residue was extracted with boiling absolute ethanol (2 × 30 ml.) and the combined ethanol extracts were reduced to 5 ml. on the steam-bath. On cooling, the solution deposited a solid (0·82 g.) which failed to melt below 350° and contained sodium, nitrogen, and sulphur. This was heated in 4N-potassium hydroxide (10 ml.) on the steam-bath for 40 min., a brown colour developing. The mixture was cooled and extracted with ether (3 × 15 ml.), and the combined extracts were washed with water (2 × 10 ml.), dried (Na_2SO_4), and evaporated at 40°. The residual brown liquid, on treatment with saturated aqueous picric acid (15 ml.), gave *tetrahydro-5-methyl-1,2,5-dithiazepinium picrate* which crystallised from ethanol as yellow needles (0·02 g.), m. p. 209° (Found: C, 34·8; H, 3·7. $C_{11}H_{14}N_4O_7S_2$ requires C, 34·9; H, 3·7%).

(b) *Directly from* N-*methyldi-(2-chloroethylamine hydrochloride and excess of thiosulphate.* A solution of *N*-methyldi-(2-chloroethyl)amine hydrochloride (6·0 g., 0·0314 mole) in ethanol (10 ml.) was treated with one of sodium thiosulphate hydrate (19·8 g., 0·08 mole) in water (40 ml.), and the mixture adjusted to pH 8 with 2N-potassium hydroxide and heated with stirring at 80° for 1 hr. Potassium hydroxide (10 g.) in water (30 ml.) was then added dropwise during 20 min. to the stirred mixture at 80°. After a further 30 min., during which the mixture became brown and an insoluble viscous polymer (2·4 g.) (IX) was formed, the mixture was cooled and extracted with ether (3 × 40 ml.). The combined ether extracts were washed with water (2 × 10 ml.) and dried (Na_2SO_4), and the solvent was removed through a 20″ fractionating column. The residual brown liquid (1·2 g.) gave the above picrate, m. p. and mixed m. p. 209°. A solution of the liquid (0·3 g.) in absolute ethanol (2 ml.) gave, on treatment with methyl iodide (1 ml.), *tetrahydro-5,5-dimethyl-1,2,5-dithiazepinium iodide*, rhombs (from methanol), m. p. 212° (decomp.) (Found: C, 25·1; H, 5·0; N, 4·8; S, 22·3; I, 43·6. $C_6H_{14}INS_2$ requires C, 24·9; H, 4·8; N, 4·8; S, 22·0; I, 43·6%).

A similar reaction but with 100 ml. of ethanol and 400 ml. of water gave 1·49 g. of the polymer and 1·82 g. of the methiodide.

The compound (VI) did not react with thiosulphate at 60° during 3 hr.

(c) *From* N-*methyldi-(2-chloroethyl)amine and sodium disulphide.* A mixture of sodium sulphide (9·6 g.) and sulphur (1·3 g.) was heated to form a clear red melt which, after cooling, was treated with a solution of sodium carbonate (6 g.) in ice-water (200 ml.). Methyldi-(2-chloroethyl)amine hydrochloride (6 g.) was added and the resulting pale green suspension containing droplets of the free base was shaken at room temperature for 4 hr. and kept at 0° overnight. A solution of potassium cyanide (0·1 g.) in 6N-sodium hydroxide (20 ml.) was added and the resulting mixture heated at 100° for 1 hr., cooled, and extracted with ether (4 × 50 ml.). The ether extracts were combined, washed with water (2 × 30 ml.), dried (Na_2SO_4), and evaporated *in vacuo* to yield a residual brown oil (1·2 g.). A methanolic solution of this oil, on treatment with methyl iodide, gave the above methiodide, m. p. and mixed m. p. 210—212° (decomp.).

Mercury Derivative (X) *of* N-*Methyldi-(2-mercaptoethyl)amine.*—A solution of the disulphide (VIII) (0·45 g.) in 50% acetic acid (15 ml.) was shaken with zinc powder (0·5 g.) at 65—70° for 1 hr., then cooled and filtered, and the filtrate was adjusted to pH 6 with 2N-potassium hydroxide. On addition of 4% mercuric acetate (1 ml.), the mercury derivative (X) was precipitated as colourless rhombs (Found: Hg, 56·5. $C_5H_{11}HgNS_2$ requires Hg, 57·4%).

Conversion of the Polymer (IX) *into Tetrahydro-5-methyl-1,2,5-dithiazepine* (VII).—A solution of the polymer (1·0 g.) in 2N-hydrochloric acid (10 ml.) was heated with zinc powder at 60° for 90 min., then cooled and filtered. The filtrate was treated with 4N-potassium hydroxide (6 ml.), heated on the steam-bath for 15 min., cooled, and extracted with ether (2 × 10 ml.). The combined ether extracts were washed, dried (Na_2SO_4), treated with methyl iodide (0·5 ml.), and stored overnight at 0°. Tetrahydro-5,5-dimethyl-1,2,5-dithiazepinium iodide, m. p. and mixed m. p. 210—213 (decomp.), was obtained.

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