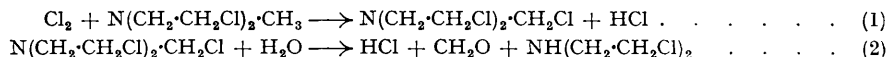


**179. The Chlorination of Methyl-di-2-(chloroethyl)amine and Related Compounds.**

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Chlorinations of the bases methyl-di-(2-chloroethyl)amine, ethyl-di-(2-chloroethyl)amine and tri-(2-chloroethyl)amine have been studied, using for this purpose (a) free chlorine, (b) *N*-chloroimides, and (c) aqueous bleaching powder. Each reaction leads to dealkylation, due to  $\alpha$ -chlorination, *e.g.* :



but  $\beta$ -chlorination always occurs concurrently.

Aldehydic products were characterised as 2 : 4-dinitrophenylhydrazones, whilst the secondary bases were characterised either as picrates or as *p*-nitrobenzoyl derivatives. When bleaching powder was used the secondary bases yielded, in part, oily *N*-chloroamines.

The salts of these tertiary bases are all highly resistant to chlorination.

IN view of the many similarities between the tertiary bases,  $\text{NR}(\text{CH}_2\cdot\text{CH}_2\text{Cl})_2$ , and 2 : 2'-dichlorodiethyl sulphide,  $\text{S}(\text{CH}_2\cdot\text{CH}_2\text{Cl})_2$ , it has been a matter of importance to compare the chemical reactions of substances of these types with chlorinating and oxidising agents. In contrast to the reactions of 2 : 2'-dichlorodiethyl sulphide, it has been found that any chlorinating agent must be used in a very large excess to effect complete reaction with a tertiary base, since the chemical changes proceed in successive stages, of which the first appears to be the most sluggish. Moreover, the reaction of an amine with chlorine yields hydrogen chloride, and unless this is neutralised immediately, there is formed an organic ammonium salt,  $(\text{R}_3\text{NH})^+\text{Cl}^-$ , which is resistant to chlorination.

Nevertheless, it has been possible to trace the systematic breakdown of these tertiary bases by successive chlorination of the attached alkyl groups. *N*-Chloroimides, which will chlorinate smoothly in organic solvents without the immediate production of hydrogen chloride, have been found to be valuable reagents in effecting this diagnosis. The study of the chlorination of methyl-di-(2-chloroethyl)amine has afforded the simplest results, in the light of which it has been possible to interpret the reactions of its analogues.

When methyl-di-(2-chloroethyl)amine, in cold carbon tetrachloride solution, is treated with chlorine, at least half of the base is precipitated as the hydrochloride, and the solution thereafter fumes in moist air, giving off hydrogen chloride and a little formaldehyde. The filtered carbon tetrachloride solution, after treatment with water, contains both formaldehyde and glyoxal. The main initial chlorination reaction is evidently (1), since when the *N*-chloroimide of 2 : 4 : 6-trichlorobenzanilide,  $\text{NCIBz}\cdot\text{C}_6\text{H}_3\text{Cl}_3$ , is used as the chlorinating agent in the same solvent 2 : 4 : 6-trichlorobenzanilide crystallises out almost quantitatively, and the filtrate, on treatment with water, gives hydrochloric acid and formaldehyde, together with the secondary base di-(2-chloroethyl)amine (reaction 2), which was characterised as its *p*-nitrobenzoyl derivative.

Simultaneously, however, there is some attack on the 2-chloroethyl group in both the 1 and the 2 position, since glyoxal, chloral, and methyl-2-chloroethylamine have all been identified as reaction products when the

*N*-chloroimide was used in excess (2—3 equivalents). Whilst chlorination in the 1-position leads to the production of aldehydes, the  $\beta$ -chlorination involves the liberation of some hydrogen chloride which, in a solvent such as carbon tetrachloride or chloroform, immediately precipitates some of the base as the inert hydrochloride.

The chlorination of ethyldi-(2-chloroethyl)amine proceeds similarly. With chlorine in carbon tetrachloride about 78% of the base is precipitated as the hydrochloride, the remainder being chlorinated, mainly at the ethyl group. When only one equivalent of *N*-chloroimide was used for chlorination, acetaldehyde could be isolated as a reaction product, but larger quantities of chlorinating agent led to the formation of glyoxal, chloral, and glyoxylic acid, together with di-(2-chloroethyl)amine. Triethylamine was shown to react in a similar manner, and much more rapidly than did the ethyldi-(2-chloroethyl)amine.

Chloroacetaldehyde could not be identified as an initial product of the reaction between *N*-chloroimides and tri-(2-chloroethyl)amine in carbon tetrachloride solution, though glyoxal and di-(2-chloroethyl)amine were regularly found. Chloroacetaldehyde was, however, characterised as a product of the reactions of free chlorine with aqueous solutions of the hydrochlorides of both methyldi-(2-chloroethyl)amine and tri-(2-chloroethyl)amine.

Since the  $\alpha$ -chlorination products of these tertiary amines are immediately decomposed by water, with liberation of hydrochloric acid, whereas  $\beta$ -chlorination products (*e.g.*, dichloroacetaldehyde, chloral) are only hydrolysed slowly, it was possible to estimate the relative percentages of  $\alpha$ - and  $\beta$ -chlorination effected by *N*-chloroimides. Typical results are given in the Table.

*Chlorination of N(CH<sub>2</sub>·CH<sub>2</sub>Cl)·CH<sub>3</sub> with NCIBz·C<sub>6</sub>H<sub>5</sub>Cl<sub>2</sub> in Carbon Tetrachloride Solution.*

Mols. of <i>N</i> -chloroimide taken per mol. of base.	Mols. of <i>N</i> -chloroimide used per mol. of base.	Mols. of HCl formed per mol. of base.	Mols. of active Cl not converted into HCl.	$\alpha$ -Chlorination (%)
(a) Reaction time 43 hours.				
1.028	0.995	0.427	0.568	42.9
1.028	0.993	0.430	0.563	43.3
2.054	2.044	0.834	1.190	40.8
2.054	2.043	0.854	1.189	41.8
3.083	2.734	1.116	1.618	40.8
(b) Reaction time 48 hours.				
2.585	2.473	0.978	1.494	39.6
2.585	2.473	0.973	1.500	39.3
3.440	3.080	1.188	1.892	38.6
3.440	3.100	1.277	1.873	39.6

*Chlorination of N(CH<sub>2</sub>·CH<sub>2</sub>Cl)<sub>3</sub> with NCIBz·C<sub>6</sub>H<sub>5</sub>Cl<sub>3</sub> in Carbon Tetrachloride Solution.*

0.931	0.903	0.293	0.611	32.4
1.863	1.806	0.624	1.184	34.5
2.794	2.555	0.875	1.680	34.2
3.725	2.474	0.889	1.585	35.9

These figures are sufficiently consistent and reproducible to indicate that the  $\alpha$ - and the  $\beta$ -chlorination processes must occur as simultaneous reactions, for even when excess of the chlorinating agent was used the percentage of  $\alpha$ -chlorinated product remained substantially constant. It will be noted that  $\beta$ -chlorination appears to occur slightly more easily than  $\alpha$ -chlorination.

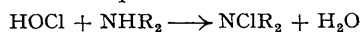
The action of aqueous calcium hypochlorite on these tertiary bases is similar to, but somewhat more complicated than, that of anhydrous chlorinating agents. When methyldi-(2-chloroethyl)amine is added to a freshly filtered solution of bleaching powder a vigorous reaction occurs and the mixture becomes hot. Calcium carbonate and calcium oxalate are both precipitated, but though the active chlorine soon disappears from the aqueous layer a noticeable amount of insoluble oil remains in the reaction mixture, unless a very large excess (over 10 mol. equivalents) of hypochlorite is used. This insoluble oil contains, besides unchanged base which can be washed out with cold dilute acid, an insoluble *N*-chloroamine, which liberates iodine from potassium iodide, and decomposes violently when heated. Analysis indicated that it is chiefly *N*-chlorodi-(2-chloroethyl)amine,  $\text{NCl}(\text{CH}_2\cdot\text{CH}_2\text{Cl})_2$ , a sample of which was prepared for comparison from di-(2-chloroethyl)amine.

Similar *N*-chloroamines were obtained from ethyldi-(2-chloroethyl)amine and tri-(2-chloroethyl)amine. On warming with dilute hydrochloric acid they decomposed, liberating chlorine, and yielding di-(2-chloroethyl)amine, which was identified as its *p*-nitrobenzoyl derivative. Triethylamine also gave an oil which, with acid, decomposed to diethylamine.

The aqueous filtrates from the above reactions of methyldi-(2-chloroethyl)amine invariably yielded both formaldehyde and glyoxal. When only one equivalent of hypochlorite had been used chloroacetaldehyde was also identified, together with the dimer of the original base, and also its chlorohydrin. Ethyldi-(2-chloroethyl)amine similarly yielded acetaldehyde, glyoxal, glycollic acid, and the dimer of the original base, whilst tri-(2-chloroethyl)amine gave glyoxal and chloral. From triethylamine the water-soluble reaction products were acetaldehyde, glycollic acid, and a little glyoxal; acetate could not be characterised.

It is thus evident that the action of aqueous hypochlorites on these tertiary bases is very similar to their

actions with free chlorine and subsequent hydrolysis, except that following the dealkylation there occurs a reaction between the secondary base and hypochlorite to form an *N*-chloroamine which, being non-basic and insoluble in water, is resistant to further decomposition.



Meisenheimer (*Ber.*, 1913, 46, 1148) has drawn similar conclusions from his studies of the reactions of trimethylamine and triethylamine with hypochlorites, and has stressed the point that the hypochlorite evidently attacks the alkyl group and does not form the amine oxide.

#### EXPERIMENTAL.

*The Reaction of Methyldi-(2-chloroethyl)amine with Chlorine.*—(a) The base (19.5 g.) in carbon tetrachloride (250 c.c.) was treated, with cooling, with a solution of chlorine (8.86 g.; 1 mol. equiv.) in carbon tetrachloride (100 c.c.). An immediate vigorous reaction took place, and solid separated rapidly, but after being left overnight the mixture still contained some free chlorine. The solid was then filtered off, washed, and dried (17.5 g.). It was identified as the hydrochloride of methyldi-(2-chloroethyl)amine by conversion into its picrate, m. p. and mixed m. p. 134° (from methanol). Free chlorine was removed from the filtrate by aspiration, and the carbon tetrachloride was then extracted with dilute hydrochloric acid. On concentration, under reduced pressure, the extract yielded a brown gum, but the acid distillate gave a precipitate on treatment with 2 : 4-dinitrophenylhydrazine in methanol-sulphuric acid. By extraction with alcohol this precipitate was separated into alcohol-soluble formaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 166°, and the insoluble orange bis-2 : 4-dinitrophenylhydrazone of glyoxal, which crystallised from *o*-dichlorobenzene in red needles, m. p. and mixed m. p. 323° (Found: C, 40.3; H, 2.83. Calc. for  $\text{C}_{14}\text{H}_{10}\text{O}_8\text{N}_8$ : C, 40.2; H, 2.4%). When only 0.75 equivalent of chlorine was used, formaldehyde was again detected, but not glyoxal.

(b) The hydrochloride of methyldi-(2-chloroethyl)amine (7.7 g.) dissolved in water (100 c.c.) was added to an ice-cold solution of chlorine (2.83 g.; 1 equiv.) in water (400 c.c.). After an hour the mixture became turbid. After 3 days the product, which still contained free chlorine, was concentrated, leaving a residue containing 5 g. of unchanged base hydrochloride, and giving a distillate which contained formaldehyde, identified as its dimedone derivative, m. p. 191°, and chloroacetaldehyde, identified as its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 155°.

The reaction of ethyldi-(2-chloroethyl)amine with chlorine in carbon tetrachloride proceeded similarly; 78% of the base was precipitated as the hydrochloride. The mixture of 2 : 4-dinitrophenylhydrazones was separated, by alcohol extraction, into the alcohol-soluble 2 : 4-dinitrophenylhydrazone of ethyl glyoxylate, m. p. 124° (Found: 42.4; H, 3.8; N, 19.6.  $\text{C}_{10}\text{H}_{10}\text{O}_8\text{N}_4$  requires C, 42.5; H, 3.6; N, 19.8%), and the alcohol-insoluble bis-2 : 4-dinitrophenylhydrazone of chloroglyoxal, m. p. 289° (Found: C, 37.3; H, 2.24; N, 24.9.  $\text{C}_{14}\text{H}_8\text{O}_8\text{N}_8\text{Cl}$  requires C, 37.1; H, 2.0; N, 24.8%). These two products were shown to be formed together from chloral and 2 : 4-dinitrophenylhydrazine by condensation under the conditions used (sulphuric acid in ethyl alcohol). Reaction in the cold was shown to yield the 2 : 4-dinitrophenylhydrazone of glyoxylic acid, m. p. 194° (from dilute acetic acid); reaction in hot ethyl alcohol-sulphuric acid yielded its ethyl ester (above); whilst reaction in hot methyl alcohol-sulphuric acid yielded the methyl ester, m. p. 146° (Found: C, 40.4; H, 3.17; N, 21.2.  $\text{C}_8\text{H}_8\text{O}_6\text{N}_4$  requires C, 40.3; H, 3.0; N, 20.9%). Reaction between chloral hydrate and 2 : 4-dinitrophenylhydrazine in hydrochloric acid yielded chloroglyoxal bis-2 : 4-dinitrophenylhydrazone (above) and chloral 2 : 4-dinitrophenylhydrazone, m. p. 152–153° (from acetic acid) (Found: C, 29.6; H, 1.72; N, 17.1; Cl, 31.8.  $\text{C}_8\text{H}_8\text{O}_4\text{N}_4\text{Cl}_2$  requires C, 29.3; H, 1.54; N, 17.1; Cl, 32.5%).

*The Reaction between Tri-(2-chloroethyl)amine Hydrochloride and Aqueous Chlorine.*—The hydrochloride (10 g.) was dissolved in water (400 c.c.), and the solution was saturated with chlorine. An oil gradually separated. After 6 days this was decanted, and the aqueous solution was distilled under reduced pressure. The distillate yielded the 2 : 4-dinitrophenylhydrazone of chloroacetaldehyde, m. p. 155°, but no glyoxal or chloral derivatives. The residual oil dissolved, with evolution of chlorine, when boiled with dilute hydrochloric acid, and the resulting solution contained di-(2-chloroethyl)amine, which was characterised as its *p*-nitrobenzoyl derivative, m. p. 98° (see below).

*The Reaction between Methyldi-(2-chloroethyl)amine and N-Chloro-2 : 4 : 6-trichlorobenzanilide.*—The base (30.8 g.) was added to the *N*-chloroimide (66.5 g.; 1 mol. equiv.) in carbon tetrachloride (500 c.c.). After an induction period of a few minutes the solution became cloudy, and the temperature rose appreciably as solid was deposited. Free formaldehyde could be smelt, and when the vapours from the reaction mixture were led into a 10% alcoholic solution of dimedone its formaldehyde derivative, m. p. 191°, was precipitated. After 24 hours the pasty reaction product was filtered. The crystalline precipitate, after being washed with carbon tetrachloride and water, proved to be pure trichlorobenzanilide (59.3 g.). The aqueous washings contained the hydrochloride of the original base, and gave 21.5 g. of picrate, corresponding to 8.7 g. of unchanged base. Less hydrochloride was formed when carefully dried carbon tetrachloride was used as the solvent.

The carbon tetrachloride solution was extracted with dilute hydrochloric acid, and the extract was concentrated under reduced pressure to a viscous semi-crystalline residue; the distillate gave the 2 : 4-dinitrophenylhydrazones of both formaldehyde and glyoxal. Portions of the residue (i) on treatment with picric acid gave a picrate, from which was crystallised the picrate of unchanged methyldi-(2-chloroethyl)amine, m. p. 133°; (ii) gave a carbylamine reaction with aniline and alcoholic sodium hydroxide, and a deep blue colour, indicative of chloral, with resorcinol-potassium bromide and concentrated sulphuric acid; (iii) on treatment with *p*-nitrobenzoyl chloride and sodium bicarbonate gave a white crystalline amide, m. p. 98°, which, on heating resolidified and then remelted at about 190°. The *p*-nitrobenzoyl derivative of di-(2-chloroethyl)amine was made for comparison (Found: C, 45.7; H, 4.45.  $\text{C}_{11}\text{H}_{12}\text{O}_3\text{N}_2\text{Cl}_2$  requires C, 45.4; H, 4.1%). It too had these same two m. p., as also did mixtures with the reaction product. It is probable that the resolidification may be due to dimerisation of the amide to a dipiperazinium salt.

A similar reaction was carried out between the base and excess of *N*-chloroimide. When 3 or 4 equivalents of the latter were used it was possible to isolate from the mixture of picrates [cf. (i) above] a little of the picrate of methyldi-(2-chloroethyl)amine, m. p. and mixed m. p. 103° (Found: C, 33.4; H, 3.34.  $\text{C}_9\text{H}_{11}\text{C}_7\text{N}_4\text{Cl}$  requires C, 33.3; H, 3.44%).

The *N*-chloroimide of 2 : 4-dichlorobenzanilide reacted with methyldi-(2-chloroethyl)amine in a similar manner. When 3 or more equivalents of *N*-chloroimide were used no unchanged base could be detected. The reaction was studied quantitatively (compare Table) as follows. Weighed quantities of base and *N*-chloroimide were allowed to react, in carbon tetrachloride solution, in stoppered flasks. After 48 hours, distilled water was added immediately the flasks were unstoppered; the products were transferred to a tap-funnel, the two liquid layers were separated, and the carbon tetrachloride layer was washed repeatedly with dilute nitric acid. Unchanged *N*-chloroimide was estimated iodometrically in the carbon tetrachloride layer, and ionised chloride was estimated by Volhard's method in the combined aqueous layers. Blank tests showed that the *N*-chloroimides used do not yield chloride ion by this treatment, and also that the 2-chloroethylamines used do not hydrolyse appreciably in the presence of an excess of cold dilute nitric acid. Reproducible results were obtained by using carbon tetrachloride as solvent, but not by using chloroform.

The reaction between ethyldi-(2-chloroethyl)amine and *N*-chloro-2 : 4 : 6-trichlorobenzanilide was carried out similarly. When 1 equivalent of *N*-chloroimide was used the vapours from the reaction mixture contained acetaldehyde. Other products (also identified when higher proportions of *N*-chloroimide were used) were glyoxal, chloral, and ethyl glyoxylate (as 2 : 4-dinitrophenylhydrazones) and di-(2-chloroethyl)amine (as *p*-nitrobenzoyl derivative). 4 Equivalents of *N*-chloroimide were needed to bring about the complete decomposition of the original base.

The reaction between tri-(2-chloroethyl)amine and *N*-chloro-2 : 4 : 6-trichlorobenzanilide yielded glyoxal and ethyl glyoxylate (as dinitrophenylhydrazones) and di-(2-chloroethyl)amine, isolated as the *p*-nitrobenzoyl derivative of m. p. 98° (remelts at 190°). 3 Equivalents of *N*-chloroimide effected the complete decomposition of the original base.

The reaction between triethylamine and *N*-chloro-2 : 4 : 6-trichlorobenzanilide (1 equiv. of each) in carbon tetrachloride took place immediately, with heat evolution. The reaction products were acetaldehyde and chloroglyoxal, which were identified as dinitrophenylhydrazones, and diethylamine, which was characterised as *p*-nitrobenz-diethylamide, m. p. and mixed m. p. 65—66°; 40% of the base remained unchanged. Glyoxal and diethylamine were identified as reaction products when 3 equivalents of *N*-chloroimide were used.

*The Reaction between Methyldi-(2-chloroethyl)amine and Calcium Hypochlorite Solution.*—Freshly distilled base (61.5 g.) was added to a freshly-filtered solution prepared from bleaching powder (100 g.) and water (450 c.c.) (2 mol. equivs. of hypochlorite by titration). After a time the mixture became hot and some insoluble calcium salts were deposited, whilst some carbon dioxide was evolved. When the solution had cooled it was found that practically all the hypochlorite had decomposed, though much oil still remained. Air was aspirated through the solution, and tests showed the presence of small quantities of both formaldehyde and glyoxal. From a similar reaction in which only one equivalent of hypochlorite was used chloroacetaldehyde was identified as its dinitrophenylhydrazone, m. p. 155°.

The solution was filtered, and the insoluble oil was extracted with light petroleum. Tests showed that the insoluble product was a mixture of calcium carbonate and calcium oxalate. The light petroleum solution was shaken with dilute acid, which removed unchanged base (identified as its picrate) and the remaining liquid was evaporated cautiously on the water-bath. There remained about 2 g. of an oil which liberated iodine from potassium iodide solution. Larger quantities of this product were obtained by controlling the initial reaction by external cooling. This oil decomposed on heating, and when kept deposited long colourless needles. It resembled *N*-chlorodi-(2-chloroethyl)amine, which was prepared for comparison by treating di-(2-chloroethyl)amine with excess of cold hypochlorite solution.

The aqueous solution from the reaction was concentrated, calcium was precipitated as the sulphate, and the picrates of the residual organic bases were fractionally crystallised. The main products were the picrates of methyldi-(2-chloroethyl)amine (m. p. 133°) and its dimer (m. p. 203—204°), the latter accounting for 50% of the original base. A trace of the picrate of the chlorohydrin of the original base was also obtained.

The reaction between ethyldi-(2-chloroethyl)amine and calcium hypochlorite solution proceeded similarly. When the vapours from the initial reaction were aspirated into 2 : 4-dinitrophenylhydrazine reagent the 2 : 4-dinitrophenylhydrazone of acetaldehyde was obtained. The light petroleum extract from the reaction with 3 equivalents of hypochlorite, after decomposition with dilute hydrochloric acid gave a mixture of bases, from which were isolated the picrates of the original base (m. p. 101°) and a dimer [m. p. 254° (decomp.)] (Found: C, 39.5; H, 3.85.  $C_{24}H_{30}O_{14}N_8Cl_2$  requires C, 39.7; H, 4.17%). The aqueous solution was shown to contain glyoxal, and gave a strong positive test for glycollic acid when treated with chromotropic and concentrated sulphuric acids. Tests for acetate and oxalate gave negative results. From the reaction with 4 equivalents of hypochlorite there was obtained a pale yellow oil, which gave the reactions of an *N*-chloroamine. After decomposition with hydrochloric acid this oil gave a mixture of the hydrochlorides of the original base (picrate, m. p. 100°) and di-(2-chloroethyl)amine (*p*-nitrobenzoyl derivative, m. p. 98°). 8 Equivalents of hypochlorite were needed to effect the complete destruction of the original base.

Analogous reactions of tri-(2-chloroethyl)amine yielded chloral, glyoxal, and *N*-chlorodi-(2-chloroethyl)amine, whilst triethylamine gave acetaldehyde, glyoxal, glycolate, and a small amount of an *N*-chloroamine, which after decomposition with hydrochloric acid was identified, by the formation of *p*-nitrobenzdiethylamide, m. p. and mixed m. p. 64—65°, as *N*-chlorodiethylamine.

The  $\beta$ -chlorinated tertiary amines all inflamed when treated, in bulk, with dry bleaching powder, and this was the most rapid way of effecting their destruction.

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