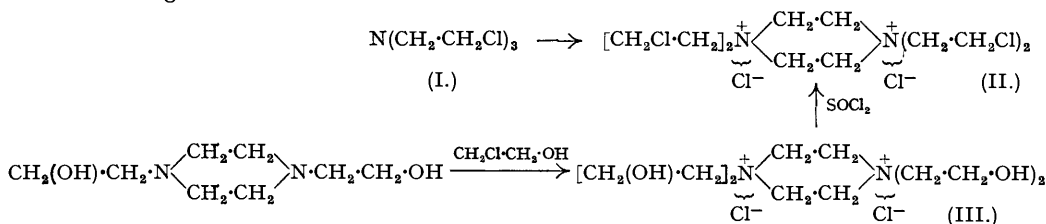


100. *The Chemistry of 2-Chloroalkylamines. Part III. The Dimerisation and Hydrolysis of 2 : 2' : 2''-Trichlorotriethylamine.*

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The solid deposited by dry 2 : 2' : 2''-trichlorotriethylamine on being kept or heated has been identified as the dimer, NNN'N'-*tetra*-(2-chloroethyl)piperazinium dichloride (II), by comparison with a synthetic specimen. In contrast to the alkyldi-(2-chloroethyl)amines (Part I, this vol., p. 513) the main action of methyl alcohol on 2 : 2' : 2''-trichlorotriethylamine is not dimerisation but substitution. The action of water on 2 : 2' : 2''-trichlorotriethylamine is shown to yield a little dimer, much 2-chloroethyldi-(2-hydroxyethyl)amine and some 2 : 2' : 2''-trihydroxytriethylamine.

MASON and GASCH (*J. Amer. Chem. Soc.*, 1938, **60**, 2816) noted that, on long keeping, 2 : 2' : 2''-trichlorotriethylamine (I) deposited a solid which they did not attempt to identify. Work on the dimerisation of alkyldi-(2-chloroethyl)amines (Part I, *loc. cit.*) made it very probable that this solid was the dimer, NNN'N'-tetra-(2-chloroethyl)piperazinium dichloride (II); this conclusion has been verified by comparison with material synthesised as outlined in the following scheme :

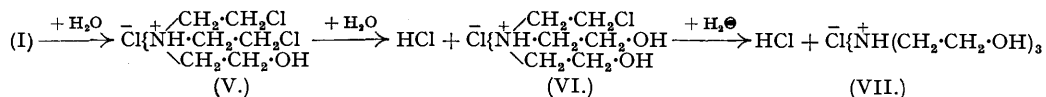


The dimerisation of dry 2 : 2' : 2''-trichlorotriethylamine on keeping or heating is a much slower process than that of methyl-di-(2-chloroethyl)amine, and the dimer (II) is most readily obtained by heating the amine (I) with 98% formic acid. The foregoing observations apply to the dimerisation of dry material; the presence of water leads to hydrolysis with the liberation of hydrochloric acid and the deposition, in crystalline form, of 2 : 2' : 2''-trichlorotriethylamine hydrochloride, and it is possible that the crystalline solid obtained by Mason and Gasch (*loc. cit.*) was really this hydrochloride. In this connexion it is noteworthy that McCombie and Purdie (*J.*, 1935, 1217) observed the formation of the hydrochloride during the distillation of 2 : 2' : 2''-trichlorotriethylamine; we have always observed this in the distillation of all but the driest samples of the amine.

Unlike methyl-di-(2-chloroethyl)amine, 2 : 2' : 2''-trichlorotriethylamine undergoes only a little dimerisation in methyl alcohol solution, the main reaction being substitution leading to the formation of *di*-(2-chloroethyl)-2-methoxyethylamine (IV). This tendency towards substitution rather than dimerisation is probably to be ascribed to the comparative weakness of 2 : 2' : 2''-trichlorotriethylamine as a base [$pK_a = 3.0$ as compared with $pK_a = 6.1$ for methyl-di-(2-chloroethyl)amine] and the consequent relative reluctance of the nitrogen atom to take part in ammonium salt formation. This view is strengthened by the observation that the methanolysis product (IV), which is a stronger base ($pK_a = ca. 5.5$), differs from 2 : 2' : 2''-trichlorotriethylamine in readily dimerising in methyl alcohol to yield NN'-*di*-(2-chloroethyl)-NN'-*di*-(2-methoxyethyl)piperazinium dichloride.

Owing to the relative insolubility of 2 : 2' : 2''-trichlorotriethylamine in water we were unable to carry out so complete a study of the reaction with water as was possible with the alkyldi-(2-chloroethyl)amines (Part II, preceding paper). However, such results as could be obtained indicated that, in an eventually 1% solution, only about 4% of the dimer (II) was formed; otherwise the reaction appeared to be, formally at least, a simple hydrolysis. We were unable to determine whether or not an ethyleneimonium salt intervened in the early stages. The first equivalent of hydrochloric acid was liberated in about 20 hours, during much of which time two phases were present, and was followed by a slower further liberation of acid, which was still proceeding after 240 hours at 25° when nearly 1.5 equivalents of hydrochloric acid had been liberated.

Of the three expected hydrolysis products, (V), (VI), and (VII), two, *viz.*, 2-chloroethyl-di-(2-hydroxyethyl)ammonium chloride (VI) and 2 : 2' : 2''-trihydroxytriethylamine hydrochloride (VII) were isolated, the former as its *picrate*, from the hydrolysis products. The free base



derived from (VI) resembles the methanolysis product (IV) in rapidly dimerising in alcoholic solution to yield NNN'N'-tetra-(2-hydroxyethyl)piperazinium dichloride (III) which was identified by comparison with the synthetic product; this identity serves also to confirm the structure assigned to (VI). A number of unsuccessful attempts were made to synthesise (V) and (VI); in the course of this work 2-acetoxyethylamine and *phthal*-2-acetoxyethylamide were prepared, and the preparation of 2 : 2'-diacetoxydiethylamine hydrochloride was improved.

EXPERIMENTAL.

Dimerisation of 2 : 2' : 2''-Trichlorotriethylamine.—The amine (10 g.) was heated on the water-bath for 5½ hours with 98% formic acid (2.3 g.). The brown sticky product was rubbed with acetone and filtered; two precipitations from water with acetone yielded NNN'N'-tetra-(2-chloroethyl)piperazinium dichloride (II), m. p. 331° (decomp.) not depressed on admixture with the synthetic product (below) (Found: C, 35.3; H, 5.75. C₁₂H₂₄N₂Cl₆ requires C, 35.2; H, 5.9%). The identity was further confirmed by conversion into the *dipicrate*, orange-yellow prisms from dilute acetone, m. p. 222° (decomp.) not depressed on admixture with the synthetic product (Found: C, 36.8; H, 3.3; N, 14.0. C₂₄H₂₈O₁₄N₈Cl₄ requires C, 36.3; H, 3.5; N, 14.1%).

The same product was obtained by heating 2 : 2' : 2''-trichlorotriethylamine in a sealed tube at 100° for 20 days.

Synthesis of NNN'N'-Tetra-(2-chloroethyl)piperazinium Dichloride.—NN'-Di-(2-hydroxyethyl)-piperazine (2.6 g.; Adelson, MacDowell, and Pollard, *J. Amer. Chem. Soc.*, 1935, **57**, 1988) was heated on the water-bath for 33 hours with ethylene chlorohydrin (7.2 g.). The cooled mixture was treated with acetone and the precipitated, very deliquescent, piperazinium salt (III) (300 mg.), m. p. 220—221°, characterised as its picrate, NNN'N'-tetra-(2-hydroxyethyl)piperazinium *dipicrate*, yellow needles from water, m. p. 215—216° (Found: C, 39.9; H, 4.7. C₂₄H₃₂N₈O₁₈ requires C, 40.0; H, 4.45%).

The dichloride (III) (250 mg.) was heated under reflux on the water-bath for 7 hours with thionyl chloride (5 c.c.); after removal of excess of thionyl chloride under reduced pressure, the product was dissolved in water and precipitated with acetone. NNN'N'-tetra-(2-chloroethyl)piperazinium dichloride (II), m. p. 330° (decomp.), crystallised from dilute acetone in micro-crystals (Found: C, 34.8; H, 6.4; N, 6.3. C₁₂H₂₄N₂Cl₆ requires C, 35.2; H, 5.9; N, 6.85%); the *dipicrate* crystallised from water in orange-yellow prisms, m. p. 224° (decomp.) (Found: C, 37.0; H, 3.5; N, 13.75. C₂₄H₂₈O₁₄N₈Cl₄ requires C, 36.3; H, 3.5; N, 14.1%).

Action of Methanol on 2 : 2' : 2''-Trichlorotriethylamine.—2 : 2' : 2''-Trichlorotriethylamine (27 g.) was refluxed on the water-bath for 30 hours with methanol (75 c.c.). After evaporation under reduced pressure, treatment of the product with acetone gave 1.5 g. (5%) of the dimer (II), m. p. 330—331° after recrystallisation from aqueous acetone; evaporation of the acetone mother-liquor and crystallisation of the residue from benzene yielded 25.5 g. (82%) of *di-(2-chloroethyl)-2-methoxyethylammonium chloride*, leaflets m. p. 133—134° (Found: C, 36.2; H, 6.6; N, 5.8; Cl, 45.0. C₇H₁₆ONCl₂ requires C, 35.5; H, 6.8; N, 5.9; Cl, 45.0%). This was dissolved in water and basified; the liberated base was extracted with benzene, dried, and distilled, yielding 15.6 g. (72%) of *di-(2-chloroethyl)-2-methoxyethylamine* (IV) as a colourless oil, b. p. 103—104°/4 mm. (Found: Cl, 35.0. C₇H₁₅ONCl₂ requires Cl, 35.5%); the *picrate* crystallised from dilute acetone in yellow needles, m. p. 109—110° (Found: C, 36.4; H, 4.5. C₁₃H₁₆O₈N₂Cl₂ requires C, 36.4; H, 4.2%). Kept overnight in methanol (5 vols.), the free base yielded NN'-*di-(2-chloroethyl)-NN'-di-(2-methoxyethyl)piperazinium dichloride*, m. p. 258° (decomp.) from dilute acetone (Found: C, 41.9; H, 7.2; N, 6.7. C₁₄H₃₀O₂N₂Cl₄ requires C, 42.0; H, 7.55; N, 7.0%); the *dipicrate* crystallised from dilute acetone in needles, m. p. 179—180° (Found: C, 40.2; H, 4.7. C₂₈H₃₅O₁₆N₈Cl₂ requires C, 39.7; H, 4.45%).

Action of Water on 2 : 2' : 2''-Trichlorotriethylamine.—(a) *Kinetic measurements.* The freshly distilled amine (5.000 g.) was made up to 500 c.c. with water and the mixture shaken mechanically at room temperature until solution was complete (several hours). The solution was then kept at 25° while samples were withdrawn at intervals and analysed for ionic chlorine (electrometric titration with silver nitrate) and hydrochloric acid (titration with barium hydroxide using alizarin yellow). The following values are interpolated from a curve constructed from the experimental results (31 double determinations):

Time (hrs.)	20	30	40	50	70	90	140	160	190	210	240
Equiv. per mol. of (I) $\left\{ \begin{array}{l} \text{Cl}^- \\ \text{HCl} \end{array} \right.$	1.04	1.14	1.19	1.22	1.26	1.29	1.35	1.38	1.40	1.42	1.43
	1.00	1.10	1.15	1.18	1.22	1.25	1.31	1.34	1.36	1.37	1.39

(b) *Isolation of products.* The amine was dissolved in water (100 parts by weight) by mechanical shaking for 20 hours; the resulting solution was kept at room temperature for 3 days and then treated with 0.5N-calcium picrate (582 c.c.). Several crops of picrate, some heavily contaminated with picric acid, were isolated by filtration, at once and after successive concentrations under reduced pressure, and were subjected to systematic fractional crystallisation. In this way a little of the dimer *dipicrate*, m. p. and mixed m. p. 222° (decomp.), was isolated from a less soluble fraction, while acidification of the combined mother liquors from the picrate of (VI), followed by removal of picric acid and evaporation, yielded 2 : 2 : 2''-trihydroxytriethylamine hydrochloride, m. p. and mixed m. p. 179—180° after crystallisation from 80% alcohol.

The only new picrate isolated was 2-chloroethyl*di-(2-hydroxyethyl)ammonium picrate*, which crystallised from ethyl acetate-alcohol in large orange rhombs, m. p. 119° (Found: C, 36.3; H, 4.3; N, 13.7; Cl, 9.3. C₁₂H₁₇O₉N₄Cl requires C, 36.3; H, 4.3; N, 14.1; Cl, 9.0%). This picrate was dissolved in water and the solution treated with excess of hydrochloric acid; after removal of picric acid by filtration, and extraction with benzene, the solution was evaporated to dryness under reduced pressure. Two crystallisations of the solid residue from anhydrous alcohol-ether yielded 2-chloroethyl*di-(2-hydroxyethyl)ammonium chloride* (VI), m. p. 93—94° (Found: C, 35.2; H, 7.1; Cl, 35.4. C₆H₁₅O₂NCl₂ requires C, 35.3; H, 7.35; Cl, 34.8%); heating with thionyl chloride yielded 2 : 2' : 2''-trichlorotriethylamine hydrochloride, m. p. and mixed m. p. 134—135°. The hydrochloride (VI) (7.306 g.), dissolved in absolute alcohol, was treated with 0.385N-alcoholic sodium ethoxide (93 c.c.); the precipitated sodium chloride was filtered off and the filtrate evaporated to dryness under reduced pressure at room temperature. The solid residue, twice crystallised from 80% alcohol, yielded NNN'N'-tetra-(2-hydroxyethyl)piperazinium dichloride (III), m. p. 230—231° (decomp.) (Found: C, 43.0; H, 8.2; N, 8.3. C₁₂H₂₈O₄N₂Cl₂ requires C, 43.0; H, 8.4; N, 8.4%), identified by conversion into its picrate, m. p. and mixed m. p. with a

synthetic specimen 215—216° (Found : C, 40·3; H, 4·6; N, 15·7. Calc. for $C_{24}H_{32}O_{18}N_8$: C, 40·0; H, 4·45; N, 15·6%).

Miscellaneous Preparations.—*2-Acetoxyethylamine.* A mixture of 2-hydroxyethylamine (122 g.) and acetic acid (132 g.) was saturated with dry hydrogen chloride at 0° and the mixture kept at room temperature overnight. Next day excess hydrogen chloride was removed in a current of dry air and the desired hydrochloride (210 g.; 75%) precipitated with dry acetone. *2-Acetoxyethylammonium chloride* crystallises from acetone in stout needles, m. p. 130° (Found : C, 34·9; H, 6·9; N, 9·55. $C_4H_{10}O_2NCl$ requires C, 34·4; H, 7·2; N, 10·0%). This hydrochloride (98 g.) was dissolved in absolute alcohol and treated, with cooling and shaking, with sodium ethoxide from sodium (17·8 g.) and absolute alcohol (300 c.c.). Distillation of the filtrate from the precipitated sodium chloride yielded *2-acetoxyethylamine* (35·9 g.; 50%) as a viscous oil, b. p. 160—161°/4 mm., n_D^{20} 1·4716 (Found : C, 46·7; H, 8·7; N, 13·55. $C_4H_9O_2N$ requires C, 46·6; H, 8·7; N, 13·6%). No well-defined products were obtained on condensing this base with ethylene oxide or ethylene chlorohydrin.

Phthalo-2-acetoxyethylimide. Phthalo-2-hydroxyethylimide (50 g.; Wenker, *J. Amer. Chem. Soc.*, 1937, **59**, 422) was refluxed for 2 hours with acetic anhydride (30 g.); the product was poured into water and collected after for some hours. Crystallisation from dilute alcohol yielded the *acetate* (40 g.; 63%) in flattened needles, m. p. 89—90° (Found : C, 61·7; H, 4·8; N, 5·8. $C_{12}H_{11}O_4N$ requires C, 61·8; H, 4·7; N, 6·0%). The method of Ing and Manske (*J.*, 1926, 2348) was not successful in bringing about the fission of this compound.

2:2'-Diacetoxydiethylammonium chloride. The following procedure is simpler than that described by Mann (*J.*, 1934, 461). Diethanolamine was dissolved in acetic acid (2 equivs.) with cooling, and the solution was saturated with dry hydrogen chloride at 0°. Next day most of the excess of hydrogen chloride was removed under reduced pressure and the remainder by aspirating dry air through a suspension of the reaction product in dry chloroform. Filtration, followed by washing with acetone and ether, yielded the desired hydrochloride which crystallised from alcohol in large glistening plates, m. p. 146—148° (Found : C, 42·7; H, 6·8; N, 6·0. Calc. for $C_8H_{16}O_4NCl$: C, 42·6; H, 7·1; N, 6·2%). We were unable to distil the free base liberated from this hydrochloride, and no definite product could be isolated from the reaction product of the crude base and ethylene oxide.

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