117. *The Preparation of Some Chloroalkylamino-compounds.*

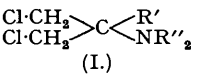
By E. R. H. Jones and Walter Wilson.

Several new aliphatic amines, with two or three chlorine atoms in the β- or γ-positions and a number of *N*-substituted β-chloro-amines, including nitroso-compounds and chloroacetamides, have been prepared. The formation and rearrangement of *benzodi-(2-chloroethyl)amide* are discussed.

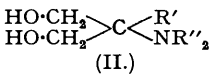
The vesicant properties of tri-(2-chloroethyl)amine, $N(CH_2 \cdot CH_2Cl)_3$ (Ward, *J. Amer. Chem. Soc.*, 1935, **57**, 914; McCombie and Purdie, *J.*, 1935, 1217) and methyldi-(2-chloroethyl)amine, $NMe(CH_2 \cdot CH_2Cl)_2$ (Eisleb, *Ber.*, 1941, **74**, 1433; Jensen and Lundquist, *Dansk Tidsskr. Farm.*,

1941, **15**, 201) are well known and these two compounds are often termed " nitrogen mustards " in view of their relationship, both structurally and in physiological properties, to mustard gas, $S(CH_2 \cdot CH_2Cl)_2$. The nitrogen mustards have been intensively studied in recent years and biological investigations have indicated that these compounds may have therapeutic applications (Gilman and Philips, *Science*, 1946, **103**, 409; Boyland, *Brit. J. Pharmacol.*, 1946, **1**, 247; Rhoads, *J. Amer. Med. Assoc.*, 1946, **131**, 656; Karnofsky, Burchenal, Ormsbee, Cornman, and Rhoads, *Cancer Research*, 1947, **7**, 50; Haddow, *Brit. Med. Bull.*, 1947, **4**, 422). Syntheses of series of chloroalkylamines have been published recently (Ford-Moore, Lidstone, and Waters, *J.*, 1946, 819; Hanby and Rydon, *J.*, 1947, 513) and their reactions have also been studied (Crane, Stephenson, Forrest, and Waters, *J.*, 1946, 827; Golumbic, Fruton, and Bergmann, *J. Org. Chem.*, 1946, **11**, 518; Hanby, Hartley, Powell, and Rydon, *J.*, 1947, 519; Crane and Rydon, *J.*, 1947, 527; Price, Pohland, and Velzen, *J. Org. Chem.*, 1947, **12**, 308).

A number of chloroalkylamines and related compounds were prepared in these laboratories during the war. The halogenated amines, which contained two or three chlorine atoms, are enumerated in the experimental section. They were made from appropriate hydroxy-compounds by treatment with thionyl chloride in chloroform (cf. Hanby and Rydon, *loc. cit.*). Interesting results were obtained during attempts to prepare branched chain amines of type (I). *Diethyl*



(I.)



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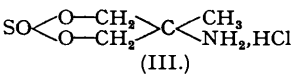
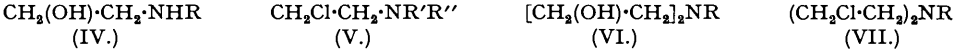


(III.)

dimethylaminomalonate was readily obtained from dimethylamine and bromomalonic ester, but none of the required amino-glycol (II; R′ = R″ = H) was formed on reduction by the Bouveault–Blanc method. An homologous amino-glycol (II; R′ = Me; R″ = H) was fortunately available. With thionyl chloride in chloroform, however, this did not yield the expected chloro-amine, but a *cyclic sulphite hydrochloride* (III). Similar cyclic sulphites have been obtained from other 1 : 3-glycols, *e.g.*, pentaerythritol (Govaert, Hansens, and Beyeart, *Versl. Ned. Akad. Wetensch. Afd. Natuurk.*, 1943, **52**, 135). The glycol was readily methylated to *2-dimethylamino-2-methylpropane*-1 : 3-*diol* (II; R′ = R″ = Me), which reacted normally with thionyl chloride giving the branched chain dichloro-amine, 1 : 3-*dichloro*-2-*dimethylamino*-2-*methylpropane* (I; R′ = R″ = Me).

2-Hydroxyethylaminomethyl cyanide (IV; R = $CH_2 \cdot CN$) was obtained from 2-hydroxyethylamine and hydroxymethyl cyanide, and converted into *ethyl 2-chloroethylaminoacetate* (V; R′ = H; R″ = $CH_2 \cdot CO_2Et$) by successive reaction with alcoholic hydrogen chloride and thionyl chloride.



(IV.) (V.) (VI.) (VII.)

Unsuccessful attempts were made to isolate di-(2-hydroxyethyl)hydrazines (VI; R = NH_2 or NMe_2), from which it was hoped to prepare the di-(2-chloroethyl) compounds. Distillation of the product obtained by condensing *as*-dimethylhydrazine with ethylene oxide was not possible without decomposition into di-(2-hydroxyethyl)amine. Reduction (zinc dust and acetic acid) of *di-(2-hydroxyethyl)nitrosoamine* (VI; R = NO) likewise gave only di-(2-hydroxyethyl)amine. Previous workers have commented on the instability of 2-hydroxyalkylhydrazines (Knorr and Brownsden, *Ber.*, 1902, **35**, 4474; Plisov, *Ukraine Chem. J.*, 1928, **3**, 125).

2-Hydroxyethylhydroxylamines have been described and appear to be stable (Jones and Burns, *J. Amer. Chem. Soc.*, 1925, **47**, 2966; Jones and Major, *ibid.*, 1927, **49**, 1538). Ethylene oxide condensed smoothly with *O*-methylhydroxylamine and the resulting O-*methyldi-(2-hydroxyethyl)hydroxylamine* (VI; R = OMe) was converted by thionyl chloride into O-*methyl-di-(2-chloroethyl)hydroxylamine* (VII; R = OMe). The dichloro-compound was notable for its weakly basic properties; unlike the parent dihydroxy-compound, it did not form a picrate. It was soluble in strong (>6N) hydrochloric acid, but was re-precipitated on dilution with water.

Di-(2-chloroethyl)nitrosoamine (VII; R = NO) and *methyl-2-chloroethylnitrosoamine* (V; R′ = Me; R″ = NO) were obtained from the requisite secondary amine hydrochlorides and sodium nitrite. The urethanes, N-*carbethoxydi-(2-chloroethyl)amine* (VII; R = CO_2Et) and N-*carbomethoxy*-2-*chloro*-n-*propylamine*, were prepared by the usual methods. Carbonyl chloride reacted with methyl-2-chloroethylamine in benzene in the presence of aqueous sodium hydrogen carbonate yielding N-*chlorocarbonyl*-N-*methyl*-2-*chloroethylamine* (V; R′ = Me; R″ = COCl) and not the substituted urea.

Some simple chloroaceto-2-chloroethylamides were prepared. Thus *chloroaceto*-2-*chloro*-

ethylamide (V; R′ = H; R″ = CO·CH_2Cl) was obtained from chloroaceto-2-hydroxyethylamide and thionyl chloride, or, more conveniently, from chloroacetyl chloride and 2-chloroethylamine. *Chloroacetomethyl-2-chloroethylamide* (V; R′ = Me; R″ = CO·CH_2Cl) and *chloroacetodi-(2-chloroethyl)amide* (VII.; R = CO·CH_2Cl) were also prepared by the chloroacetylation method. Reaction of dichloroacetyl chloride with 2-hydroxyethylamine and 2-chloroethylamine gave *dichloroaceto-2-hydroxyethylamide* (IV; R = CO·$CHCl_2$) and *dichloroaceto-2-chloroethylamide* (V; R′ = H; R″ = CO·$CHCl_2$) respectively. The latter was also obtained from the former and thionyl chloride, or unexpectedly (15% yield) by heating with phosphorus pentasulphide. This reaction was expected to yield a thiazoline (cf. Wenker, *J. Amer. Chem. Soc.*, 1935, **57**, 1079). Attempts to obtain an oxazoline by heating dichloroacetic acid with 2-hydroxyethylamine (cf. Wenker, *loc. cit.*) were also unsuccessful, and the only product isolated was dichloroaceto-2-chloroethylamide. It may be noted that trichloroaceto-2-chloroethylamide (V; R′ = H; R″ = CO·CCl_3) has been used in Germany as an insect repellent (C.I.O.S. Report, XXVI—73; XXIII—20).

Benzoylation (Schotten–Baumann) of di-(2-chloroethyl)amine, with suitable precautions, yielded *benzodi-(2-chloroethyl)amide* (VIII) During the purification of this a small amount of *2-chloroethyl-2′-benzoyloxyethylamine hydrochloride* (IX), m p. 132—134°, was isolated. Mann (*J.*, 1934, 464) had previously obtained the crude amide (VIII) but on attempted crystallisation from alcohol it changed into a salt-like compound $C_{11}H_{15}O_2NCl_2$, m. p. 135—136°. The above hydrochloride (IX) is probably identical with Mann's compound, and its formation is almost certainly due to a hydrolytic rearrangement of the amide :

$$\text{(VIII.)}\ \begin{matrix}CH_2Cl\cdot CH_2\\CH_2Cl\cdot CH_2\end{matrix}\!\!>\!N\cdot CO\cdot Ph + H_2O \longrightarrow \begin{matrix}Ph\cdot CO_2\cdot CH_2\cdot CH_2\\CH_2Cl\cdot CH_2\end{matrix}\!\!>\!NH,HCl\ \text{(IX.)}$$

Such reactions have been described for benzo-2-bromoethylamide (Gabriel and Heymann, *Ber.*, 1890, **23**, 2497) and benzomethyl-2-chloroethylamide (Marckwald and Frobenius, *Ber.*, 1901, **34**, 3550), and are closely related to the acid catalysed rearrangements studied by Horenstein and Pählicke (*Ber.*, 1938, **71**, 1644) and by Reasenberg and Goldberg (*J. Amer. Chem. Soc.*, 1945, **67**, 933). To minimise the formation of this by-product and obtain pure benzodi-(2-chloroethyl)amide, experimental conditions were used in which acidity was not permitted to develop, and the product was crystallised from a dry non-hydroxylic solvent.

Experimental.

*Methyl-2-hydroxyethyl-3-hydroxy-*n*-propylamine.*—Methyl-2-hydroxyethylamine (30 g.; Knorr and Matthes, *Ber.*, 1898, **31**, 1069), 3-chloropropanol (19 g.; Hultmann, Davies, and Clarke, *J. Amer. Chem. Soc.*, 1921, **43**, 369), and water (30 c.c.) were heated at 100° for 4 hours. Potassium hydroxide (13 g.) was added and the *amine* (20 g.), b. p. 154—155°/20 mm.; 135—137°/0·8 mm.; $n_D^{20°}$ 1·4660 (Found : C, 53·1; H, 11·1. $C_6H_{15}O_2N$ requires C, 54·1; H, 11·3%), was isolated by extraction with acetone. *Picrate*, m. p. 101·5°, orange-yellow crystals from ethyl acetate (Found : N, 15·7. $C_{12}H_{18}O_9N_4$ requires N, 15·5%).

*Methyl-2-chloroethyl-3-chloro-*n*-propylamine.*—Thionyl chloride (45 g.) in chloroform (50 c.c.) was added to a mixture of the above hydroxy-amine (15 g.) and chloroform (25 c.c.). After boiling for 30 minutes, the chloroform was distilled off, and the residue dissolved in cold water. Basification and extraction with ether yielded the *base* (14 g.), b. p. 104—106°/23 mm.; $n_D^{22°}$ 1·4640 (Found : C, 42·2; H, 7·4. $C_6H_{13}NCl_2$ requires C, 42·3; H, 7·6%). The *methiodide* formed needles (ethanol), m. p. 182° (decomp.) (Found : C, 26·4; H, 5·3. $C_7H_{16}NCl_2I$ requires C, 26·9; H, 5·1%). A picrate, m. p. 75°, was also obtained, but not analysed.

*Methyl-2-hydroxyethyl-2-hydroxy-*n*-propylamine.*—Methyl-2-hydroxyethylamine (30 g.), 1-chloropropan-2-ol (19 g.; Dewael, *Bull. Soc. chim. Belg.*, 1930, **39**, 87), and water (30 c.c.) were heated at 100° for 24 hours. Potassium hydroxide (13 g.) was added, and the *hydroxy-amine*, b. p. 127°/16 mm., $n_D^{21·5°}$ 1·4522, was isolated by extraction with acetone (Found : C, 53·9; H, 10·9. $C_6H_{15}O_2N$ requires C, 54·1; H, 11·3%). The *picrate* formed yellow clusters, m. p. 71—72°, from ethyl acetate (Found : N, 15·0. $C_{12}H_{18}O_9N_4$ requires N, 15·5%).

*Methyl-2-chloroethyl-2-chloro-*n*-propylamine.*—The hydroxy-amine (15 g.) was treated with thionyl chloride in chloroform as in the previous example. The *chloro-amine* (15 g.), b. p. 94—94·5°/21 mm.; $n_D^{17°}$ 1·4622 (Found : C, 42·4; H, 7·8. $C_6H_{13}NCl_2$ requires C, 42·3; H, 7·6%), formed a *picrate*, glistening yellow plates, m. p. 122—123°, from ethyl acetate (Found : N, 13·7. $C_{12}H_{16}O_7N_4Cl_2$ requires N, 14·0%).

*Methyldi-(2-hydroxy-*n*-propyl)amine.*—This base, b. p. 137°/23 mm.; $n_D^{19°}$ 1·4470, was obtained from propylene oxide and methylamine. The picrate formed yellow needles, m. p. 111—112°, from ethyl acetate (Found : C, 42·0; H, 5·4. Calc. for $C_{13}H_{20}O_9N_4$: C, 41·5; H, 5·3%). (Hanby and Rydon, *J.*, 1947, 513, describe the amine, and give m. p. 88° for the picrate.)

*Methyldi-(2-chloro-*n*-propyl)amine.*—This base, b. p. 96—97°/19 mm.; $n_D^{19°}$ 1·4585, was made from the hydroxyamine and thionyl chloride. The chloro-amine is mentioned without details in B.P. 501,135, and since our work was completed has been described by Hanby and Rydon (*loc. cit.*).

*Di-(2-hydroxyethyl)-2-hydroxy-*n*-propylamine.*—Di-(2-hydroxyethyl)amine (42 g.), 1-chloropropan-2-ol (17 g.), and water (50 c.c.) were heated at 100° for 12 hours. After the addition of potassium hydroxide (13 g.), extraction with alcohol yielded the *triol* (20 g.), b. p. 145°/0·6 mm.; $n_D^{19°}$ 1·4770 (Found : C, 51·3;

H, 10·4. $C_7H_{17}O_3N$ requires C, 51·5; H, 10·4%). A picrate, m. p. 99°, was obtained but not purified. The hydrochloride has recently been described (Ford-Moore, Lidstone, and Waters, *loc. cit.*), and converted into the trichloro-amine.

*Di-(2-hydroxyethyl)-3-hydroxy-*n*-propylamine.*—Di-(2-hydroxyethyl)amine (31·5 g.), 3-chloropropanol (14·3 g.), and water (50 c.c.) were heated at 100° and worked up as before, giving the *triol* (17·6 g.), b. p. 167—169°/0·8 mm.; $n_D^{19°}$ 1·4870 (Found: C, 52·0; H, 10·8. $C_7H_{17}O_3N$ requires C, 51·5; H, 10·4%). A picrate, m. p. 82°, was not purified.

*Di-(2-chloroethyl)-3-chloro-*n*-propylamine.*—The above triol (17 g.) was converted into the hydrochloride and treated with thionyl chloride (40 g.) in chloroform (40 c.c.). The *trichloro-amine* (11 g.) was a colourless oil, b. p. 116°/1·3 mm.; $n_D^{17°}$ 1·4936 (Found: C, 38·6; H, 6·5; Cl, 49·1. $C_7H_{14}NCl_3$ requires C, 38·4; H, 6·4; Cl, 48·5%). The *picrate* formed glistening crystals, m. p. 93—94°, from ethyl acetate (Found: Cl, 23·7. $C_{13}H_{17}O_7N_4Cl_3$ requires Cl, 23·8%).

Diethyl Dimethylaminomalonate.—A solution of dimethylamine (18 g.) in ethanol (50 c.c.) was added slowly to a mixture of ethyl bromomalonate (47·6 g.; Palmer and McWherter, *Org. Synth.*, 1941, Coll. Vol. I, 245) and ethanol (40 c.c.). The reaction was completed by heating at 60° for one hour. Ether (50 c.c.) was added, and the dimethylammonium bromide (32 g.) filtered off. Distillation of the filtrate gave *diethyl dimethylaminomalonate* (30 g.), b. p. 113—117°/15 mm.; $n_D^{19°}$ 1·4320 (Found: N, 6·6. $C_9H_{17}O_4N$ requires N, 6·9%). The ester (2·5 g.) boiled for 2 hours with 6N-hydrochloric acid (20 c.c.) yielded dimethylglycine hydrochloride (1·4 g.), m. p. 188°, not depressed on mixing with an authentic specimen.

*2-Amino-2-methylpropane-*1 : 3*-diol* (II; R′ = Me; R″ = H).—The commercial material was redistilled, b. p. 130°/2 mm.; m. p. 104—106°. The *picrate* crystallised from ethyl acetate in orange tablets, m. p. 131—132° (Found: N, 16·5. $C_{10}H_{14}O_9N_4$ requires N, 16·8%).

*Reaction of 2-Amino-2-methylpropane-*1 : 3*-diol with Thionyl Chloride.*—The diol (21 g.), chloroform (50 c.c.), and thionyl chloride (70 g.) were boiled together for 3 hours. The impure *2-amino-2-methylpropane-*1 : 3*-diol sulphite hydrochloride* (III) was filtered off and washed with hot ethanol; m. p. 179—181° (decomp.) (Found: Cl, 18·7. $C_4H_{10}O_3NClS$ requires Cl, 18·9%). The hydrochloride was soluble in water; addition of alkali liberated an ether-soluble oil, reconverted by hydrogen chloride in dry ether into the original hydrochloride, m. p. 179—181° (decomp.).

*2-Dimethylamino-2-methylpropane-*1 : 3*-diol* (II; R′ = R″ = Me).—2-Amino-2-methylpropane-1 : 3-diol (42 g.), methyl iodide (120 g.), and ethanol (120 c.c.) were heated under reflux for two days. Potassium hydroxide (46 g.) was added and heating continued for one day. The potassium iodide was filtered off and washed with hot alcohol. Distillation gave *2-dimethylamino-2-methylpropane-*1 : 3*-diol* (18 g.), b. p. 96°/1 mm., solidifying to waxy crystals, m. p. 40—50° (Found: C, 53·9; H, 11·8. $C_6H_{15}O_2N$ requires C, 54·1; H, 11·3%); *picrate*, yellow tablets, m. p. 222° (decomp.), from methanol (Found: N, 14·9. $C_{12}H_{18}O_9N_4$ requires N, 15·5%).

1 : 3-Dichloro-2-dimethylamino-2-methylpropane (I; R′ = R″ = Me).—This was obtained from the above glycol (16 g.) and thionyl chloride (50 c.c.) in chloroform (30 c.c.). The *dichloro-amine* (7 g.) was a colourless mobile liquid, b. p. 52—53°/2·3 mm.; $n_D^{20°}$ 1·4560 (Found: C, 43·0; H, 7·6. $C_6H_{13}NCl_2$ requires C, 42·4; H, 7·7%). The *picrate* formed feathery crystals, m. p. 158°, from ethyl acetate, (Found: N, 14·4. $C_{12}H_{16}O_7N_4Cl_2$ requires N, 14·0%).

2-Hydroxyethylaminomethyl Cyanide (IV; R = CH_2·CN).—A mixture of 2-hydroxyethylamine (30·5 g.) and hydroxymethyl cyanide (28·5 g.) (Polstorff and Meyer, *Ber.*, 1912, **45**, 1911; Yarnall and Wallis, *J. Org. Chem.*, 1939, **4**, 287) was left for 12 hours, then dehydrated at 90° in a vacuum. The solid obtained on cooling was recrystallised from acetone. *2-Hydroxyethylaminomethyl cyanide* (18·5 g.) formed needles, m. p. 55—56° (Found: C, 47·9; H, 7·5. $C_4H_8ON_2$ requires C, 48·0; H, 8·0%). A picrate, m. p. 114—115°, was obtained, but the analysis was unsatisfactory.

Ethyl 2-Chloroethylaminoacetate (V; R′ = H; R″ = CH_2·CO_2Et).—The above cyanide (10 g.) was boiled for 2 hours with ethanol (50 c.c.) containing hydrogen chloride (20 g.). The ammonium chloride was filtered off, and the alcohol removed by distillation. The residual syrup was dissolved in chloroform (15 c.c.) and boiled with thionyl chloride (20 c.c.) for 2 hours. Removal of the chloroform and crystallisation from ethanol–ethyl acetate gave needles of *ethyl 2-chloroethylaminoacetate hydrochloride* (13 g.), m. p. 152° (Found: C, 36·1; H, 6·4; Cl, 34·6. $C_6H_{13}O_2NCl_2$ requires C, 35·6; H, 6·4; Cl, 35·1%). Cold alkali liberated *ethyl 2-chloroethylaminoacetate*, b. p. 108—109°/15 mm.; $n_D^{17°}$ 1·4518 (Found: N, 8·4. $C_6H_{12}O_2NCl$ requires N, 8·5%).

Di-(2-hydroxyethyl)nitrosoamine (VI; R = NO).—Sodium nitrite (27 g.) dissolved in water (30 c.c.) was slowly added (30—35°; stirring) to a solution of di-(2-hydroxyethyl)amine (35 g.) in water (25 c.c.), which had been previously neutralised with 2N-hydrochloric acid. After 1½ hours, the water was removed at 80° in a vacuum. Extraction with ethanol yielded *di-(2-hydroxyethyl)nitrosoamine* (35 g.), b. p. 100—120°/2·6 × 10^{-5} mm.; $n_D^{20°}$ 1·4849 (Found: N, 21·0. $C_4H_{10}O_3N_2$ requires N, 20·9%).

O-Methyldi-(2-hydroxyethyl)hydroxylamine (VI; R = OMe).—Ethylene oxide (35 g.) was passed into a solution of *O*-methylhydroxylamine (16·3 g.) in water (30 c.c.) at 5°. After 12 hours at 0°, water was distilled off in a vacuum, and the residue distilled yielding *O-methyldi-(2-hydroxyethyl)hydroxylamine* (25 g.), b. p. 114°/1·5 mm.; $n_D^{20°}$ 1·4540 (Found: C, 44·2; H, 9·9. $C_5H_{13}O_3N$ requires C, 44·4; H, 9·65%). The *picrate* was obtained in yellow prisms, m. p. 113°, from methanol (Found: C, 36·6; H, 4·5. $C_{11}H_{16}O_{10}N_4$ requires C, 36·3; H, 4·4%).

O-Methyldi-(2-chloroethyl)hydroxylamine (VII; R = OMe).—The hydroxy-compound (14 g.) was dissolved in chloroform (20 c.c.) and saturated with dry hydrogen chloride. Thionyl chloride (35 c.c.) in chloroform (40 c.c.) was added, and the mixture boiled for one hour. Chloroform was removed in a vacuum and water (100 c.c.) added. The heavy oil was isolated by means of ether; no more was obtained on basifying the aqueous layer.

O-Methyldi-(2-chloroethyl)hydroxylamine (10·5 g.) was a colourless, mobile liquid, b. p. 92—95°/18 mm.; $n_D^{22°}$ 1·4580 (Found: C, 35·2; H, 6·5; Cl, 41·0. $C_5H_{11}ONCl_2$ requires C, 34·9; H, 6·4; Cl, 41·2%). It did not form a picrate, but dissolved in 6N-hydrochloric acid, and was reprecipitated on diluting with water.

Methyl-2-chloroethylnitrosoamine (V; R′ = Me; R″ = NO).—Methyl-2-chloroethylamine hydrochloride (13 g.) (I.G. Farbenindustrie, F.P., 802,416) was dissolved in water (10 c.c.) and a solution of sodium nitrite (6·9 g.) in water (10 c.c.) added. No reaction took place until acetic acid (2 c.c.) was added. The *methyl-2-chloroethylnitrosoamine* (8 g.), b. p. 62—65°/0·3 mm.; $n_D^{22°}$ 1·4762 (Found: C, 29·5; H, 6·05; N, 22·3. $C_3H_7ON_2Cl$ requires C, 29·4; H, 5·7; N, 22·9%), was isolated by extraction with chloroform.

Di-(2-chloroethyl)nitrosoamine (VII; R = NO).—Di-(2-chloroethyl)amine hydrochloride (18·9 g.) (Mann, *J.*, 1934, 464) in water (50 c.c.) was treated with sodium nitrite (6·9 g.) dissolved in water (50 c.c.). After stirring for one hour at 15°, extraction with ether yielded *di-(2-chloroethyl)nitrosoamine* (15 g.); $n_D^{15°}$ 1·5022 (Found: N, 16·1. $C_4H_8ON_2Cl_2$ requires N, 16·3%). It was a viscous pale yellow oil which distilled at 75°/3 × 10^{-4} mm. with some decomposition.

2-*Chloro*-n-*propylamine Hydrochloride*.—2-Hydroxy-*n*-propylamine (10 g.) was neutralised with hydrochloric acid and the water removed in a vacuum. The product was suspended in chloroform (10 c.c.) and a mixture of thionyl chloride (25 g.) and chloroform (20 c.c.) added. After boiling for 3 hours, the chloroform was distilled off, and the 2-chloro-*n*-propylamine hydrochloride (12 g.), m. p. 179—180°, recrystallised from ethanol–ether (Smith and Platton, *J. Amer. Chem. Soc.*, 1922, **55**, 3143, give m. p. 179°).

N-*Carbomethoxy-2-chloro*-n-*propylamine*.—A mixture of 2-chloro-*n*-propylamine hydrochloride (11·4 g.), water (10 c.c.), and ether (10 c.c.) was stirred whilst methyl chloroformate (9·0 g.), and potassium hydroxide (6·8 g.) in water (40 c.c) were dropped in simultaneously. After one hour, ether extraction yielded N-*carbomethoxy-2-chloro*-n-*propylamine* (6·8 g.), b. p. 76°/1 mm.; $n_D^{18°}$ 1·4564 (Found: C, 39·9; H, 6·7. $C_5H_{10}O_2NCl$ requires C, 40·1; H, 6·7%).

N-*Carbethoxydi-(2-chloroethyl)amine* (VII; R = CO_2Et).—Ethyl chloroformate (55 g.) and 2N-sodium hydroxide (500 c.c.) were simultaneously dropped into a stirred solution of di-(2-chloroethyl)amine hydrochloride (90 g.) in water (75 c.c.). The rates of addition were adjusted to maintain the alkalinity of the solution, which was cooled to 7—10°. N-*Carbethoxydi-(2-chloroethyl)amine* (90 g.), b. p. 112—116°/3 mm. (Found: N, 6·95. $C_7H_{13}O_2NCl_2$ requires N, 6·55%), was isolated by means of ether.

N-*Chlorocarbonyl*-N-*methyl-2-chloroethylamine* (V; R′ = Me; R″ = COCl).—Methyl-2-chloroethylamine hydrochloride (5·2 g.) was dissolved in water (20 c.c.), and added to a mixture of benzene (50 c.c.), water (20 c.c.), and sodium hydrogen carbonate (8·4 g.) at 5—10°. Carbonyl chloride was bubbled through the mixture for one hour at 10°. The benzene layer was separated, dried, and distilled, yielding N-*chlorocarbonyl*-N-*methyl-2-chloroethylamine* (2·7 g.), b. p. 98°/10 mm.; $n_D^{18°}$ 1·4850 (Found: C, 30·9; H, 4·5; Cl, 45·9. $C_4H_7ONCl_2$ requires C, 30·8; H, 4·5; Cl, 45·5%).

Chloroaceto-2-chloroethylamide (V; R′ = H; R″ = $CO{\cdot}CH_2Cl$).—(*a*) Thionyl chloride (16 g.) in chloroform (25 c.c.) was run into a solution of chloroaceto-2-hydroxyethylamide (14 g.) (Jacobs and Heidelberger, *J. Biol. Chem.*, 1915, **21**, 407) in chloroform (25 c.c.) at 40°. Distillation gave *chloroaceto-2-chloroethylamide*, b. p. 95°/0·2 mm., solidifying to a waxy solid, m. p. 51—53°. Recrystallisation from petroleum (b. p. 60—80°) gave needles, m. p. 57—57·5° (Found: N, 9·0; 9·3; Cl, 45·8. $C_4H_7ONCl_2$ requires N, 9·0; Cl, 45·5%).

(*b*) 2-Chloroethylamine hydrochloride (12 g.) (Ward, *J. Amer. Chem. Soc.*, 1935, **57**, 914) was added to 2N-sodium hydroxide (52 c.c.) at −10°. Chloroacetyl chloride (17·4 g.) and 2N-sodium hydroxide (147 c.c.) were dropped in with stirring and cooling to −7°. The solid (13·3 g.), m. p. 57—58°, was recrystallised from petroleum (b. p. 60—80°) giving the pure amide in needles, m. p 58°, undepressed on mixing with the specimen from (*a*).

Chloroacetomethyl-2-chloroethylamide (V; R′ = Me; R″ = $CO{\cdot}CH_2Cl$).—Methyl-2-chloroethylamine hydrochloride (12·9 g.) in water (25 c.c.) was added to a suspension of sodium hydrogen carbonate (50 g.) in water (100 c.c.) at 15°. Chloroacetyl chloride (16·9 g.) was then slowly dropped in with stirring. *Chloroacetomethyl-2-chloroethylamide* (6 g.), b. p. 110—112°/0·8 mm.; $n_D^{18°}$ 1·5010 (Found: C, 35·3; H, 5·1. $C_5H_9ONCl_2$ requires C, 35·3; H, 5·3%), was isolated by extraction with ether.

Chloroacetodi-(2-chloroethyl)amide (VII; R = $CO{\cdot}CH_2Cl$).—Di-(2-chloroethyl)amine hydrochloride (35 g.) was added to a solution of sodium hydroxide (16 g.) in water (200 c.c.) at 0°. Chloroacetyl chloride (22·5 g.) was dropped in with efficient stirring. The crude product was isolated by extraction with ether. Trituration with benzene removed a small amount of an insoluble *compound*, m. p. 97—99° (Found: N, 6·1; Cl, 45·2. $C_6H_{12}O_2NCl_3$ requires N, 5·9; Cl, 45·0%). Distillation of the benzene filtrate gave *chloroacetodi-(2-chloroethyl)amide* as a colourless, viscous oil, b. p. 140—144°/0·05 mm.; $n_D^{17°}$ 1·5198 (Found: N, 6·2; Cl, 48·6. $C_6H_{10}ONCl_3$ requires N, 6·4; Cl, 48·7%).

Dichloroaceto-(2-hydroxyethyl)amide (IV; R = $CO{\cdot}CHCl_2$).—Dichloroacetyl chloride (37 g.) (Brown, *J. Amer. Chem. Soc.*, 1938, **60**, 1325) was dropped into a stirred mixture of 2-hydroxyethylamine (30 g.), ethyl acetate (100 c.c.), and chloroform (40 c.c.). The 2-hydroxyethylamine hydrochloride (29 g.) was filtered off and washed with ethyl acetate. The filtrate was evaporated, and the residue recrystallised from ethyl acetate–light petroleum (b. p. 60—80°), yielding *dichloroaceto-(2-hydroxyethyl)amide* (36·5 g.), needles, m. p. 85—86° (Found: C, 28·1; H, 4·05; N, 8·2. $C_4H_7O_2NCl_2$ requires C, 27·9; H, 4·05; N, 8·15%).

Dichloroaceto-(2-chloroethyl)amide (V; R′ = H; R″ = $CO{\cdot}CHCl_2$).—(a) *From 2-hydroxyethylamine and dichloroacetic acid*. The amine (6 g.) and dichloroacetic acid (13 g.) were cautiously mixed. The mixture was heated to 160°, and the temperature increased to 185° during 45 minutes. Distillation gave a pale yellow oil (3·9 g.), b. p. 108—110°/1 mm., which solidified. This was recrystallised from ethyl acetate–light petroleum (b. p. 40—60°) giving *dichloroaceto-(2-chloroethyl)amide*, needles, m. p. 65·5—66·5° (Found: C, 25·2; H, 3·1; N, 7·7; Cl, 55·4. $C_4H_6ONCl_3$ requires C, 25·2; H, 3·15; N, 7·35; Cl, 55·9%).

(b) *From the hydroxyethylamide and thionyl chloride*. Dichloroaceto-(2-hydroxyethyl)amide (3·4 g.), chloroform (10 c.c.), and thionyl chloride (5 c.c.) were boiled for 10 minutes. Evaporation and recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave needles (1·6 g.; 42%) of the 2-chloroethylamide, m. p. 64—65°.

(c) *From 2-chloroethylamine*. 2-Chloroethylamine hydrochloride (4·6 g.) dissolved in 1·2N-sodium

hydroxide (25 c.c.) was treated at 0° with dichloroacetyl chloride (6·0 g.) and 2N-sodium hydroxide (25 c.c.). The product (1·0 g.; 21%; m. p. 65—66°) was extracted with ether and purified as in (b).

(d) *From the hydroxyethylamide and phosphorus pentasulphide.* Dichloroaceto-2-hydroxyethylamide (4·3 g.), phosphorus pentasulphide (1·5 g.), and toluene (10 c.c.) were boiled for 4 hours; some hydrogen chloride was evolved. The black tar was extracted with boiling ethyl acetate, giving the amide (0·76 g.; 15%), m. p. 65—66°.

Benzoylation of Di-(2-chloroethyl)amine.—Di-(2-chloroethyl)amine hydrochloride (17·9 g.) in water (50 c.c.) was stirred at 0—5° and benzoyl chloride (16·8 g.) and 3N-sodium hydroxide (100 c.c.) were run in simultaneously during 45 minutes. The rates of addition were controlled so that the solution was slightly alkaline throughout. The mixture was stirred for 1¾ hours and the granular solid filtered off, powdered, and washed successively with 6% sodium hydrogen carbonate solution, water, and light petroleum (b. p. 40—60°). After drying in a vacuum, the product (20·5 g.; m. p. 48—48·5°) was recrystallised from petroleum (b. p. 80—100°), yielding *benzodi-(2-chloroethyl)amide* (VIII), needles, m. p. 50·5—52° (Found: C, 53·8; H, 5·2; N, 5·9; Cl, 27·7. $C_{11}H_{13}ONCl_2$ requires C, 53·65; H, 5·3; N, 5·7; Cl, 28·9%). During the recrystallisation a small amount of an insoluble solid was obtained. This was crystallised from alcohol, and finally from acetone–ether, giving *2-benzoyloxyethyl-2′-chloroethylamine hydrochloride* (IX), m. p. 132—134° (Found: C, 50·0; H, 5·7; N, 5·35; Cl, 25·6. $C_{11}H_{15}O_2NCl_2$ requires C, 49·95; H, 5·7; N, 5·3; Cl, 26·9%). The compound was easily soluble in water (solution contained chloride ions) and sodium hydroxide precipitated an oil. This was isolated by means of ether, and treated with picric acid, giving *2-benzoyloxyethyl-2′-chloroethylamine picrate*, yellow needles, m. p. 188—189°, from acetone (Found: N, 12·55; Cl, 7·9. $C_{17}H_{17}O_9N_4Cl$ requires N, 12·25; Cl, 7·75%).

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
LONDON, S.W.7.

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