101. *Some Dichloroamine Derivatives.*

By L. J. Lermit and (the late) R. C. G. Moggridge.

The dihydroxyamines (I), (II), and (III) have been prepared by the action of di- (or tri-) ethylene chlorohydrin on the appropriate amines; they have been converted by the action of thionyl chloride into the corresponding dichloroamines (V), (VI), and (VII). These compounds undergo spontaneous ring-closure to give quaternary ammonium compounds; (VI) gives a piperazinium (X) and (VII) gives a morpholinium derivative (XII), while (V) gives one of two compounds (IX or XI) according to the conditions used.

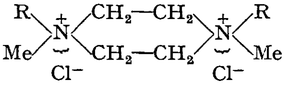
In connection with work on methyl-2 : 2′-dichlorodiethylamine (IV) (Eisleb, *Ber.*, 1941, **74**, *B*, 1433) it was desired to have specimens of the related dichloroamines (V—VII), and the corresponding diols (I—III). In this paper the preparation and characterisation of these compounds are described.

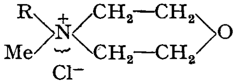
$$CHRR'{\cdot}CH_2{\cdot}NMe{\cdot}CH_2{\cdot}CH_2R''$$

I; $R = O{\cdot}CH_2{\cdot}CH_2{\cdot}OH$, $R' = H$, $R'' = OH$.
II; $R = O{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}OH$, $R' = H$, $R'' = OH$.
III; $R = R'' = O{\cdot}CH_2{\cdot}CH_2{\cdot}OH$, $R' = H$.
IV; $R = R'' = Cl$, $R' = H$.
V; $R = O{\cdot}CH_2{\cdot}CH_2Cl$, $R' = H$, $R'' = Cl$.
VI; $R = O{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2Cl$, $R' = H$, $R'' = Cl$.
VII; $R = R'' = O{\cdot}CH_2{\cdot}CH_2Cl$, $R' = H$.

The *diols* (I—III) were prepared without difficulty by the interaction of di-(or tri-) ethylene chlorohydrin with the appropriate amine [methylamine for (III), methyl-2-hydroxyethylamine for (I) and (II)]; these reactions were carried out in the presence of either sodium carbonate or excess of amine. The products were colourless oils, miscible with water; many derivatives crystallised only with difficulty. Derivatives suitable for characterisation were the *picrolonates* (m. p. 116°, 98°, and 75° respectively) and the *picrates* of the bis-*p*-nitrobenzoates (m. p. 124°, 128°, and 109·5° respectively).

The *dichlorides* (V—VII) were prepared without difficulty by the action of thionyl chloride on the corresponding diols. All the products were colourless oils which could be identified by their *picrolonates*; their most characteristic property, however, was that of undergoing ring-closure to give the quaternary ammonium derivatives. Similar behaviour is shown by (IV) (Eisleb, *loc. cit.*), the product in this case being the piperazinium derivative (VIII) (Hanby and Rydon, this vol., p. **513** *). The behaviour of (V) is of special interest, since it might form either the *piperazinium* derivative (IX) or the *morpholinium* derivative (XI).





VIII; R = $CH_2{\cdot}CH_2Cl$.
IX; R = $CH_2{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2Cl$.
X; R = $CH_2{\cdot}CH_2{\cdot}[O{\cdot}CH_2{\cdot}CH_2]_2{\cdot}Cl$.

XI; R = $CH_2{\cdot}CH_2Cl$.
XII; R = $CH_2{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2Cl$.
XIII; R = $CH_2{\cdot}CH_2{\cdot}OH$.

Hanby and Rydon (*loc. cit.*) have in fact shown that both these compounds (IX and XI) can be formed from (V), the nature of the product depending on the conditions. Our results are essentially similar, (IX) being formed if (V) is heated alone, (XI) if (V) is dissolved in alcohol and left, either in the hot or in the cold. On leaving (V) alone at room temperature we have consistently obtained (XI), though Hanby and Rydon under these conditions obtained (IX). The two changes clearly occur with nearly equal ease, and this discrepancy is probably to be attributed to some minor difference of conditions. Hanby and Rydon have proved the structure of (XI) by synthesis from *N*-2-chloroethylmorpholine; the opportunity is taken here to describe two additional syntheses. In the first, *N*-methylmorpholine was treated directly with ethylene chloride; in the second, (XIII) was first prepared by the action of ethylene chlorohydrin on *N*-methylmorpholine, and then converted into (XI) by the action of thionyl chloride.

There is no ambiguity about the nature of the products of ring-closure of (VI) and (VII), since (VI) cannot give a morpholinium, nor (VII) a piperazinium, derivative. The products are therefore considered to be (X) and (XII) respectively; this is confirmed by the analysis of (X), and of the *picrates* and *styphnates* of both (X) and (XII). The ring-closures of the chloro-compounds (V), (VI), and (VII) proceed with considerable ease; the percentage reaction of the pure compounds after 18—19 hours at room temperature was about 14, 28, and 74% respectively.

EXPERIMENTAL.

The equivalents quoted were obtained by titration against N/10-sulphuric acid using methyl-red as indicator. Picrate, styphnate, and picrolonate figures were obtained by means of the " Nitron " reagent.

Methyl-2-hydroxyethyl-2-(2-hydroxyethoxy)ethylamine (I).—2-(2-Hydroxyethoxy)ethyl chloride (25 g.; Fourneau and Ribas, *Bull. Soc. chim.*, 1927, **41**, 1046) and methyl-2-hydroxyethylamine (75 g.; Knorr and Mathes, *Ber.*, 1898, **31**, 1069) were heated to 90°; reaction then took place with evolution of heat. The mixture was kept at 95—100° for 1 hour, the excess of methyl-2-hydroxyethylamine removed under reduced pressure, and the residue treated with excess of concentrated aqueous sodium hydroxide. The mixture was extracted by chloroform, the extracts were dried and concentrated, and the residue was distilled to give the required *diol* (I); 25 g., b. p. 126°/2 mm. (Found : equiv., 164. $C_7H_{17}O_3N$ requires equiv., 163). If the above reaction were carried out using sodium hydroxide solution instead of excess of amine very poor yields were obtained. The *picrolonate* had m. p. 116° after recrystallisation from alcohol–ethyl acetate (Found : picrolonic acid, 62·0. $C_{17}H_{25}O_8N_5$ requires picrolonic acid, 61·8%). The *styphnate* had m. p. 77° after recrystallisation from alcohol–ethyl acetate (Found : C, 38·4; H, 5·1; N, 13·8; styphnic acid, 60·2. $C_{13}H_{20}O_{11}N_4$ requires C, 38·2; H, 4·9; N, 13·7; styphnic acid, 60·0%).

The bis-*p*-nitrobenzoate, prepared from the diol (I) and *p*-nitrobenzoyl chloride in pyridine, was first obtained with m. p. 75°; the material changed spontaneously, however, either on standing or during recrystallisation from alcohol, into another form, m. p. 114°. That these were two forms of the same compound was shown by the fact that both gave the same *picrate*, m. p. 124° after recrystallisation from alcohol–acetone (Found : picric acid, 33·1. $C_{27}H_{26}O_{16}N_6$ requires picric acid, 33·1%).

With benzyl iodide in acetone the diol (I) gave a quaternary *iodide*; recrystallised from alcohol–ether, m. p. 82—83° (Found : I, 32·8. $C_{14}H_{24}O_3NI$ requires I, 33·3%).

With 3 : 5-dinitrobenzoyl chloride, triphenylmethyl chloride, methyl iodide, methyl-*p*-toluenesulphonate, α-naphthyl *iso*cyanate, or picric acid, the diol (I) gave compounds that did not crystallise.

Methyl-2-hydroxyethyl-2-{2-(2-hydroxyethoxy)ethoxy}ethylamine (II).—The fraction, b. p. 110—150°/15 mm., obtained in the preparation of 2-(2-hydroxyethoxy)ethyl chloride on redistillation yielded 2-{2-(2-hydroxyethoxy)ethoxy}ethyl chloride, b. p. 113—114°/2 mm. (Lourenco, *Ann. Chim.*, 1863, **67**, 290, gives b. p. 222—232°) (Found : Cl, 20·5. Calc. for $C_6H_{13}O_3Cl$: Cl, 21·1%). This compound (85 g.), methyl-2-hydroxyethylamine (38 g.), sodium carbonate (35 g.), and water (150 c.c.) were refluxed for 8 hours. The mixture was then cooled, and solid sodium hydroxide (*ca.* 100 g.) added gradually with cooling until sodium salts began to crystallise. The solution was then extracted with chloroform, the extract dried and concentrated, and the residue distilled to give the required *diol* (II) in 68% yield, b. p. 165—167°/2 mm. (Found : equiv., 206. $C_9H_{21}O_4N$ requires equiv., 207). Substitution of sodium hydroxide for sodium carbonate in the above reaction resulted in very low yields. The chlorohydrin and methyl-2-hydroxyethylamine reacted in the absence of solvent at 125°, but the yield of the diol (II) was only 36%. The *picrolonate* of (II), recrystallised from alcohol–ethyl acetate, had m. p. 98° (Found : picrolonic acid, 56·2. $C_{19}H_{29}O_9N_5$ requires picrolonic acid, 56·1%).

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* The results of Hanby and Rydon became available to the authors at a late stage of this work. The authors wish to express their appreciation of the courtesy shown to them in this matter by Dr. Rydon.

The bis-*p*-nitrobenzoate, prepared from (II) and *p*-nitrobenzoyl chloride in pyridine, was an oil; with picric acid in acetone it gave a *picrate*, recrystallised from alcohol–acetone, m. p. 128° (Found: picric acid, 31·1. $C_{29}H_{30}O_{17}N_6$ requires picric acid, 31·0%).

With picric and styphnic acids, triphenylmethyl chloride, and benzyl and *p*-nitrobenzyl iodides, the diol (II) gave compounds which did not crystallise.

Methyldi-2-(2-*hydroxyethoxy*)*ethylamine* (III) *and Methyl*-2-(2-*hydroxyethoxy*)*ethylamine*.—2-(2-Hydroxyethoxy)ethyl chloride (62 g.) and methylamine (46 c.c. of a 35% aqueous solution) were put in a pressure bottle and heated for 8 hours; during the first 6 hours the temperature was slowly raised from 55° to 75°, during the last 2 hours from 75° to 100°. The solution was then cooled, the bottle opened, and the reaction products isolated as in the case of the diol (II). Two well-defined fractions were obtained on distillation, *viz.*: (*a*) *methyl*-2-(2-*hydroxyethoxy*)*ethylamine*, b. p. 90—91°/4·5 mm., 11% yield (Found: equiv., 121. $C_5H_{13}O_2N$ requires equiv., 119); *picrate*, m. p. 103° after recrystallisation from alcohol (Found: picric acid, 65·8. $C_{11}H_{16}O_9N_4$ requires picric acid, 65·8%). (*b*) The *diol* (III), b. p. 165°/2 mm., 55% yield (Found: equiv., 207·5. $C_9H_{21}O_4N$ requires equiv., 207). The *picrolonate*, recrystallised from ethyl acetate, had m. p. 75° (Found: picrolonic acid, 56·0. $C_{19}H_{29}O_9N_5$ requires picrolonic acid, 56·1%). The oily bis-*p*-nitrobenzoate gave a *picrate*, m. p. 109·5° after recrystallisation from alcohol–acetone (Found: picric acid, 31·0. $C_{29}H_{30}O_{17}N_6$ requires picric acid, 31·0%).

Preparation of the Dichlorides (V—VII).—The diol (I, II, or III, 0·1 g.-mol.) in dry trichloroethylene (40 c.c.) was saturated with dry hydrogen chloride; the diol hydrochloride then separated as an oil. The mixture was refluxed on the water-bath while thionyl chloride (8 c.c.) was added gradually; the mixture was then boiled till the evolution of sulphur dioxide and hydrogen chloride had almost ceased. The mixture was then cooled and extracted with water, and the extracts were treated with excess of aqueous sodium carbonate. The oily product was separated and dried (Na_2SO_4). The dichlorides (V—VII) were all unstable, and were therefore not analysed; nor were they normally distilled. In order approximately to determine their b. ps., however, small amounts were distilled in a vacuum from a flask with a short distillation passage, the flask being immersed in an oil-bath preheated to about 20° above the boiling point.

Methyl-2-*chloroethyl*-2-(2-*chloroethoxy*)*ethylamine* (V). This was prepared as above in 65% yield; b. p. 96—98°/3·5 mm. The *picrate*, crystallised from ethyl acetate, had m. p. 59° (Found: picric acid, 53·3. $C_{13}H_{18}O_8N_4Cl_2$ requires picric acid, 53·4%). The *picrolonate*, crystallised from ethyl acetate, had m. p. 114—115° (Found: picrolonic acid, 56·8. $C_{17}H_{23}O_6N_5Cl_2$ requires picrolonic acid, 56·9%). With benzyl iodide in acetone a quaternary *iodide* was formed; this, after recrystallisation from acetone–ether, had m. p. 96—98° (Found: I, 30·0. $C_{14}H_{22}ONCl_2I$ requires I, 30·4%).

The dichloride (V) was a colourless oil which when kept at room temperature deposited colourless crystals. An approximate idea of the rate of this change was obtained by keeping a sample in a sealed tube for 19 hours and then estimating the ionic chlorine formed. 7% of the total chlorine had become ionic, corresponding to 14% change. The nature of the crystalline product obtained from (V) depended on the conditions used, *viz.*: (*a*) NN′-*Dimethyl*-NN′-*di*-2-(2-*chloroethoxy*)*ethylpiperazinium dichloride* (IX; cf. Hanby and Rydon, *loc. cit.*) was obtained if (V) were kept at room temperature, alone or in alcoholic solution; if it were warmed in alcoholic solution, the ring-closure occurred with considerable evolution of heat. The compound (IX) was obtained as plates from methanol or from aqueous alcohol; it was not deliquescent, and was not molten by 240° (Found: Cl′, 17·6. $C_{14}H_{30}O_2N_2Cl_4$ requires Cl′, 17·75%). The *dipicrate*, needles from aqueous acetone, had m. p. 191° (Found: Cl, 8·93; picric acid, 58·0. $C_{26}H_{34}O_{16}N_8Cl_2$ requires Cl, 9·05; picric acid, 58·1%). On two occasions a labile form of the dipicrate was obtained, separating in needles from aqueous acetic acid, m. p. 160°; this changed spontaneously during further recrystallisation to the form, m. p. 191°. The *distyphnate*, recrystallised from aqueous acetone, had m. p. 190—195° (decomp.) (Found: styphnic acid, 59·5. $C_{26}H_{34}O_{18}N_8Cl_2$ requires styphnic acid, 59·7%).

(*b*) N-*Methyl*-N-2-*chloroethylmorpholinium chloride* (XI) was formed on warming (V) alone in the absence of solvent; deliquescent needles from alcohol or alcohol–ether, m. p. 175—180° (decomp.) (Found: Cl, 36·1; N, 7·4; Cl′, 17·8. $C_7H_{15}ONCl_2$ requires Cl, 35·5; N, 7·0; Cl, 17·75%). The *picrate*, recrystallised from aqueous acetone, had m. p. 170—171° (Found: picric acid, 58·0. $C_{13}H_{17}O_8N_4Cl$ requires picric acid, 58·1%). The *styphnate*, needles from alcohol–acetic acid, had m. p. 117° (Found: styphnic acid, 59·7. $C_{13}H_{17}O_9N_4Cl$ requires styphnic acid, 59·7%).

The picrate of (XI) was also synthesised as follows: (i) *N*-Methylmorpholine (1 c.c.), ethylene chlorohydrin (0·585 c.c.) and water (100 c.c.) were mixed and kept at room temperature for 5 hours; they were then heated to 100° for 1 hour, and the solution then concentrated to dryness under reduced pressure. The residual syrup was refluxed for 2 hours with dry chloroform and thionyl chloride (5 c.c.). The crystalline solid which separated was collected, dissolved in alcohol, reprecipitated by the addition of ethyl acetate, dissolved in water, and treated with aqueous picric acid. The picrate deposited had m. p. 170° after recrystallisation from aqueous acetone. (ii) *N*-Methylmorpholine (1 c.c.) in water and ethylene dichloride (0·725 c.c.) in chloroform were mixed and refluxed for 2 hours. The solvents were removed under reduced pressure, the residual syrup dissolved in water, and aqueous picric acid added. The resulting picrate had m. p. 169°. The products of both these syntheses were shown by mixed m. p. to be identical with the picrate of (XI) as prepared from the dichloride (V).

Methyl-2-*chloroethyl*-2-{2-(2-*chloroethoxy*)*ethoxy*}*ethylamine* (VI).—This, prepared from the diol (II) as above in 55% yield, had b. p. *ca.* 130°/2 mm. The *picrolonate*, from ethyl acetate–petrol, had m. p. 95—96° (Found: picrolonic acid, 48·0. $C_{19}H_{27}O_7N_5Cl_2$ requires picrolonic acid, 48·0%). With styphnic acid, flavianic acid, benzyl and *p*-nitrobenzyl iodides, and sodium tribromophenoxide the dichloride (VI) gave products which did not crystallise.

The dichloride (VI) changed on standing to the piperazinium *derivative* (X). The rate of change (estimated by formation of ionic chlorine) was *ca.* 28% in 19 hours at room temperature. The compound (X) was conveniently prepared by warming an alcoholic solution of (VI); it was recrystallised from absolute alcohol; m. p. 227° (decomp.) (Found: Cl, 29·3; N, 6·1; Cl′, 14·6. $C_{18}H_{38}O_4N_2Cl_4$ requires

Cl, 29·1; N, 5·75; Cl′, 14·55%). The *dipicrate*, from aqueous acetone, had m. p. 141—143° (Found: picric acid, 51·8. $C_{30}H_{42}O_{18}N_8Cl_2$ requires picric acid, 52·2%). The *distyphnate*, from aqueous acetone, had m. p. 169° (decomp.) (Found: styphnic acid, 53·8. $C_{30}H_{42}O_{20}N_8Cl_2$ requires styphnic acid, 53·9%).

Methyldi-2-(2-*chloroethoxy*)*ethylamine* (VII).—This, prepared from the diol (III) as above in 75% yield, had b. p. *ca.* 130°/2 mm. The *picrolonate*, from ethyl acetate–light petroleum, had m. p. 90° (Found: picrolonic acid, 48·0. $C_{19}H_{27}O_7N_5Cl_2$ requires picrolonic acid, 48·0%). This compound was even more unstable than (V) and (VI), undergoing *ca.* 74% change (judging by formation of ionic chlorine) in 18 hours at room temperature. The morpholinium compound (XII) formed was a colourless viscous liquid and was not obtained crystalline; its aqueous solution readily gave a *picrate* which, after recrystallisation from aqueous acetone, had m. p. 130—131° (Found: picric acid, 52·0. $C_{15}H_{21}O_9N_4Cl$ requires picric acid, 52·2%), and a *styphnate* which, after recrystallisation from ethyl acetate–acetic acid, had m. p. 125—127° (decomp.) (Found: styphnic acid, 54·0. $C_{15}H_{21}O_{10}N_4Cl$ requires styphnic acid, 53·9%).

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