## 43. *Aryl-2-halogenoalkylamines. Part I.*

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The preparation of a number of aryl-2-halogenoethylamines is described. A study has been made of the hydrolysis of these amines in aqueous acetone.

IN view of the cytotoxic action of aliphatic 2-chloroethylamines particularly towards those tissues that are in a state of active proliferation (summaries of this work are to be found in " Approaches to Tumour Chemotherapy ", Washington, 1947, and in an article by Haddow, *Brit. Med. Bull.*, 1947, **4**, 422) it was considered desirable to prepare and examine a series of 2-halogenoethyl derivatives of aromatic amines. It has been shown that in the aliphatic series of compounds two 2-chloroethyl substituents are essential for activity and this now appears to be the case for the aromatic series, hence this paper deals mainly with the preparation of aryldi-(2-chloroethyl)amines.

The are a number of methods available for the preparation of *N*-2-hydroxyethyl derivatives of aromatic amines. *NN*-Di-(2-hydroxyethyl)aniline has been prepared by the successive replacement of the hydrogen atoms in the amino-group of aniline using ethylene chlorohydrin (Knorr, *Ber.*, 1889, **22**, 2093) and also by the action of two equivalents of ethylene oxide on aniline (Gabel, *Ber.*, 1925, **58**, 577). Anker, Cook, and Heilbron (*J.*, 1945, 917) have prepared *NN*-di-(2-hydroxyethyl)-*p*-anisidine by the action of ethylene chlorohydrin on *p*-anisidine without the use of a solvent and there are examples in the patent literature (for instance, U.S.P. 2,044,045) of the production of dihydroxy-compounds by the condensation of aromatic amines with ethylene chlorohydrin in aqueous suspensions of calcium carbonate. 2 : 4-Dinitro-*NN*-di-(2-hydroxyethyl)aniline has been obtained by heating 1-chloro-2 : 4-dinitrobenzene with diethanolamine (Waldkötter, *Rec. Trav. chim.*, 1939, **58**, 132).

The 2-hydroxyethyl compounds described in the present paper have been prepared from the aromatic amine by the action of ethylene chlorohydrin in aqueous solution or of ethylene oxide in sealed tubes. The various amines studied vary in their reactivity towards ethylene oxide for whilst aniline, *o*-, *m*-, and *p*-toluidine, *o*- and *p*-anisidine, α- and β-naphthylamine, and *p*-xenylamine react at 90° to give disubstituted products, 2-aminofluorene and *p*-aminostilbene afford monosubstituted derivatives at this temperature. At 150° *p*-aminostilbene gives the disubstituted compound as does *p*-chloroaniline while *o*-xenylamine yields a monosubstituted product and *o*- and *m*-chloroaniline, 2 : 5-dichloroaniline, and *o*- and *p*-nitroaniline do not react at this temperature. *p*-Phenylenediamine reacts very vigorously with ethylene oxide at 90° and benzidine, *o*-tolidine, and *o*-dianisidine react at 150° to give *NNN'N'*-tetra-(2-hydroxyethyl) compounds. In general the most basic arylamines react the most readily with ethylene oxide.

Robinson and Watt (*J.*, 1934, 1536) first prepared *NN*-di-(2-chloroethyl)aniline and Anker, Cook, and Heilbron (*loc. cit.*) obtained the corresponding *p*-anisidine derivative : the remaining arylhalogenoethylamines now described do not appear to have been prepared before.* It has been found that the best yields in the chlorination of the hydroxy-compounds are obtained when phosphorus oxychloride is used; lower yields result when phosphorus pentachloride or thionyl chloride is employed. The 2-chloroethyl derivatives are weak bases and are not extracted from organic solvents by dilute mineral acids whereas the parent hydroxy-compounds can be so extracted. A preliminary purification of the product of chlorination is thus obtained when the reaction mixture is shaken with water and benzene for the chloro-compounds pass into the benzene layer whilst any unchanged material remains in the aqueous layer which contains acid arising from the hydrolysis of the excess of chlorinating agent.

NN-*Di-(2-chloroethyl)-p-aminostilbene* has been prepared by two methods : first by the chlorination of the di-(2-hydroxyethyl) compound, and secondly by Professor Kon and Mr. Everett (personal communication) by the action of benzylmagnesium chloride on *NN*-di-(2-chloroethyl)-*p*-aminobenzaldehyde (Anker and Cook, *J.*, 1944, 489)—the carbinol first formed dehydrates during the working up affording the required stilbene derivative. Oxidation of the above aldehyde by potassium permanganate in acetone solution gives NN-*di-(2-chloroethyl)-p-aminobenzoic acid*.

The bromoethyl derivatives have been prepared by the action of phosphorus tribromide on

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* *Added September 13th,* 1948.—Cerkovnikov and Stern (*Archiv Kem.*, 1946, **18**, 12; *Chem. Abs.*, 1948, 1938) have described the preparation of di-(2-bromoethyl)aniline, m. p. 52—53°, by the action of hydrogen bromide on phenylmorpholine.

TABLE I.

*Aryl-2-hydroxy- and -halogeno-ethylamines.*

| Compound. | M.p. | Crystal form. | S. | Formula. | Found, % C | H | N | Required, % C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| NN-Di-(2-hydroxyethyl)aniline[1] | 55° | Prisms | D | — | — | — | — | — | — | — |
| NN-Di-(2-chloroethyl)aniline[2] | 45 | Prisms | D | — | — | — | — | — | — | — |
| NN-Di-(2-chloroethyl)aniline picrate[3] | 81—82 | Plates | B | $C_{16}H_{16}O_7N_4Cl$ | 46·5 | 4·3 | 16·4 | 46·6 | 4·2 | 16·2 |
| N-Ethyl-N-2-chloroethylaniline picrate[3] | 110 | Prisms | B | $C_{16}H_{17}O_7N_4Cl$ | 39·3 | 4·2 | 13·8 | 39·1 | 4·3 | 13·6 |
| NN-Di-(2-bromoethyl)aniline | 53—55 | Pyramids | D | $C_{10}H_{13}NBr_2$ | — | — | — | — | — | — |
| NN-Di-(2-hydroxyethyl)-o-toluidine picrate | 110 | Prisms | B | $C_{17}H_{20}O_9N_4$ | 48·1 | 4·8 | 13·2 | 48·1 | 4·8 | 13·2 |
| NN-Di-(2-chloroethyl)-o-toluidine picrate | 92 | Prismatic needles | C | $C_{17}H_{18}O_7N_4Cl_2$ | 44·7 | 4·1 | 12·3 | 44·3 | 3·9 | 12·1 |
| NN-Di-(2-hydroxyethyl)-m-toluidine | 72—73 | Prisms | B | $C_{11}H_{17}O_2N$ | 68·1 | 8·9 | — | 67·7 | 8·8 | — |
| NN-Di-(2-chloroethyl)-m-toluidine | 33 | Prisms | A | $C_{11}H_{15}NCl_2$ | 56·9 | 6·5 | — | 56·9 | 6·5 | — |
| NN-Di-(2-chloroethyl)-m-toluidine picrate | 113 | Prisms | D | $C_{17}H_{18}O_7N_4Cl_2$ | 44·6 | 3·9 | 12·3 | 44·3 | 3·9 | 12·1 |
| NN-Di-(2-bromoethyl)-m-toluidine | 42 | Plates | C | $C_{11}H_{15}NBr_2$ | 41·1 | 4·7 | — | 41·3 | 4·7 | — |
| NN-Di-(2-iodoethyl)-m-toluidine | 61—62 | Prismatic needles | B | $C_{11}H_{15}NI_2$ | 31·9 | 3·7 | — | 31·8 | 3·6 | — |
| NN-Di-(2-hydroxyethyl)-p-toluidine | 53—54 | Prisms | D | $C_{11}H_{17}O_2N$ | 67·7 | 8·8 | — | 67·7 | 8·8 | — |
| NN-Di-(2-chloroethyl)-p-toluidine | 43—45 | Flattened rhombs | C | $C_{11}H_{15}NCl_2$ | 57·3 | 6·6 | — | 56·9 | 6·5 | — |
| NN-Di-(2-chloroethyl)-p-toluidine picrate | 72—73 | Plates | B | $C_{17}H_{18}O_7N_4Cl_2$ | — | — | 12·6 | — | — | 12·7 |
| NN-Di-(2-bromoethyl)-p-toluidine | 62—63 | Thick plates | D | $C_{11}H_{15}NBr_2$ | 41·2 | 4·7 | — | 41·3 | 4·7 | — |
| NN-Di-(2-iodoethyl)-p-toluidine | 69 | Needles | B | $C_{11}H_{15}NI_2$ | 31·9 | 3·3 | — | 31·8 | 3·6 | — |
| NN-Di-(2-hydroxyethyl)-o-anisidine picrate | 140—141 | Prismatic needles | B | $C_{17}H_{20}O_{10}N_4$ | 46·7 | 4·5 | — | 46·4 | 4·6 | — |
| NN-Di-(2-chloroethyl)-o-anisidine picrate | 98—99 | Plates | B | $C_{17}H_{18}O_8N_4Cl_2$ | 42·8 | 4·0 | — | 42·8 | 3·8 | — |
| NN-Di-(2-hydroxyethyl)-p-anisidine | 70—71 | Prisms | C | $C_{11}H_{17}O_2N$ | 62·6 | 8·5 | 6·9 | 62·5 | 8·1 | 6·6 |
| NN-Di-(2-hydroxyethyl)-p-anisidine picrate | 113—114 | Prisms | B | $C_{17}H_{20}O_{10}N_4$ | 46·1 | 4·5 | 12·8 | 46·4 | 4·6 | 12·7 |
| NN-Di-(2-chloroethyl)-p-anisidine picrate | 52 | Plates | E-A | $C_{11}H_{15}ONCl_2$ | 52·9 | 6·1 | 5·8 | 53·2 | 6·1 | 5·6 |
| NN-Di-(2-bromoethyl)-p-anisidine picrate | 104 | Prismatic needles | A | $C_{17}H_{18}O_9N_4Cl_2$ | — | — | 11·7 | — | — | 11·7 |
| NN-Di-(2-bromoethyl)-p-anisidine | 47—49 | Prismatic needles | A | $C_{11}H_{15}ONBr_2$ | 39·2 | 4·3 | — | 39·2 | 4·5 | — |
| NN-Di-(2-iodoethyl)-p-anisidine | 40 | Prismatic needles | D | $C_{11}H_{15}ONI_2$ | 31·0 | 3·6 | — | 30·6 | 3·5 | — |
| p-Chloro-NN-di-(2-hydroxyethyl)aniline | 95—96 | Thick plates | C | $C_{10}H_{14}O_2NCl$ | 55·6 | 6·4 | — | 55·7 | 6·5 | — |
| p-Chloro-NN-di-(2-hydroxyethyl)aniline picrate | 122—123 | Plates | B | $C_{16}H_{15}O_8N_4Cl$ | 43·2 | 4·1 | 12·7 | 43·3 | 3·9 | 12·6 |
| p-Chloro-NN-di-(2-chloroethyl)aniline | 74—75 | Prismatic needles | D | $C_{10}H_{12}NCl_3$ | 47·7 | 4·9 | — | 47·5 | 4·8 | — |
| p-Chloro-NN-di-(2-chloroethyl)aniline picrate | 147—149 | Plates | B | $C_{16}H_{15}O_8N_4Cl_3$ | — | — | 11·9 | — | — | 11·8 |
| p-Chloro-NN-di-(2-bromoethyl)aniline | 67—68 | Prismatic needles | B | $C_{10}H_{12}NClBr_2$ | 35·2 | 3·6 | — | 35·2 | 3·5 | — |
| p-Chloro-NN-di-(2-iodoethyl)aniline | 106 | Plates | A | $C_{10}H_{12}NClI_2$ | 27·3 | 2·7 | — | 27·6 | 2·8 | — |
| o-Xenyl-2-hydroxyethylamine picrate[4] | 155—156 | Prisms | A | $C_{20}H_{18}O_8N_4$ | 54·5 | 4·3 | 13·0 | 54·3 | 4·1 | 12·7 |
| p-Xenyldi-(2-hydroxyethyl)amine | 149—151 | Plates | B | $C_{16}H_{19}O_2N$ | 74·8 | 7·4 | — | 74·7 | 7·4 | — |
| p-Xenyldi-(2-chloroethyl)amine | 106—107 | Yellow needles | D | $C_{16}H_{17}NCl_2$ | 65·3 | 5·9 | — | 65·3 | 5·8 | — |
| 2:4-Dinitro-NN-di-(2-chloroethyl)aniline[5] | 98 | Yellow plates | A | $C_{10}H_{11}O_4N_3Cl_2$ | 39·2 | 3·8 | — | 39·0 | 3·6 | — |
| α-Naphthyldi-(2-hydroxyethyl)amine | 116—118 | Yellow needles | F | $C_{20}H_{20}O_9N_4$ | 52·4 | 4·4 | — | 52·2 | 4·4 | — |
| α-Naphthyldi-(2-chloroethyl)amine[6] | 161—163 | (Oil) | C-D | $C_{14}H_{15}NCl_2$ | 62·4 | 5·4 | — | 62·7 | 5·6 | — |
| β-Naphthyldi-(2-hydroxyethyl)amine | 96—98 | Plates | C-D | $C_{14}H_{17}O_2N$ | 72·8 | 7·5 | — | 72·7 | 7·4 | — |
| β-Naphthyldi-(2-hydroxyethyl)amine picrate | 134—136 | Needles | B | $C_{20}H_{20}O_9N_4$ | 52·3 | 4·4 | — | 52·2 | 4·4 | — |

| Compound. | M. p. | Crystal form. | S. | Formula. | Found, %. C. | H. | N. | Required, %. C. | H. | N. |
|---|---|---|---|---|---|---|---|---|---|---|
| β-Naphthyldi-(2-chloroethyl)amine | 52—55° | Plates | D | $C_{14}H_{15}NCl_2$ | 62·3 | 5·5 | — | 62·7 | 5·6 | — |
| β-Naphthyldi-(2-chloroethyl)amine picrate | 102 | Purple needles | A | $C_{20}H_{18}O_7N_4Cl_2$ | 48·3 | 3·7 | — | 48·3 | 3·7 | — |
| NN-Di-(2-chloroethyl)-p-aminobenzaldehyde [7] | 87—88 | Flattened needles | B | — | — | — | — | — | — | — |
| NN-Di-(2-chloroethyl)-p-aminobenzoic acid | 168—169 | Needles | A | $C_{11}H_{13}O_2NCl_2$ | 50·3 | 5·1 | — | 50·4 | 5·0 | — |
| N-2-Hydroxyethyl-p-aminostilbene | 158—159 | Plates | C | $C_{16}H_{17}ON$ | 80·6 | 7·5 | — | 80·4 | 7·2 | — |
| N-2-Chloroethyl-p-aminostilbene | 135 | Plates | C | $C_{16}H_{16}NCl$ | 74·4 | 6·4 | — | 74·6 | 6·3 | — |
| NN-Di-(2-hydroxyethyl)-p-aminostilbene | 150—152 | Plates | F | $C_{18}H_{21}O_2N$ | 76·6 | 7·5 | — | 76·3 | 7·5 | — |
| NN-Di-(2-chloroethyl)-p-aminostilbene | 126 | Needles | B | $C_{18}H_{19}NO$ | 67·5 | 6·1 | — | 67·5 | 6·5 | — |
| N-2-Hydroxyethyl-2-aminofluorene | 144—146 | Plates | C | $C_{15}H_{14}NCl$ | 79·9 | 6·6 | — | 80·0 | 6·7 | — |
| N-2-Chloroethyl-2-aminofluorene | 127—129 | Prisms | D | $C_{15}H_{14}NCl$ | 74·1 | 5·8 | — | 74·0 | 5·8 | — |
| p-Phenylenetetra-(2-chloroethyl)diamine [8] | 79—80 | Needles | D | $C_{14}H_{20}N_2Cl_2$ | 47·1 | 5·6 | — | 47·0 | 5·6 | — |
| NNN'N'-Tetra-(2-hydroxyethyl)benzidine | 174—176 | Plates | A | $C_{20}H_{28}O_4N_2$ | 66·7 | 7·8 | — | 66·6 | 7·8 | — |
| NNN'N'-Tetra-(2-chloroethyl)benzidine | 125—126 | Thick plates | C | $C_{20}H_{24}N_2Cl_4$ | 55·6 | 5·7 | — | 55·3 | 5·6 | — |
| NNN'N'-Tetra-2-(bromoethyl)benzidine | 145 | Plates | G–A | $C_{20}H_{24}N_2Br_4$ | 39·0 | 4·2 | — | 39·3 | 4·0 | — |
| NNN'N'-Tetra-(2-hydroxyethyl)-o-tolidine dipicrate | 202 (d) | Flattened needles | A | $C_{34}H_{38}O_{18}N_8$ | 48·2 | 4·8 | 13·5 | 48·3 | 4·5 | 13·2 |
| NNN'N'-Tetra-(2-chloroethyl)-o-tolidine | 72—73 | Needles | E–A | $C_{22}H_{28}N_2Cl_4$ | 57·2 | 6·1 | — | 57·2 | 6·1 | — |
| NNN'N'-Tetra-(2-hydroxyethyl)-o-dianisidine dipicrate | 195 (d) | Prismatic needles | B | $C_{34}H_{38}O_{20}N_8$ | 46·3 | 4·5 | 13·0 | 46·5 | 4·4 | 12·8 |
| NNN'N'-Tetra-(2-chloroethyl)-o-dianisidine | 81—82 | Felted needles | E–A | $C_{22}H_{28}O_2N_2Cl_4$ | 53·6 | 5·8 | — | 53·5 | 5·7 | — |

Solvents (S) used for crystallisation are indicated: A, methanol; B, ethanol; C, benzene; D, light petroleum (b. p. 40—60°); E, ether; F, acetone; G, chloroform.

[1] Gabel (loc. cit.) gives m. p. 58°.
[2] Robinson and Watt (loc. cit.) give m. p. 45°.
[3] The free base, which was an oil, was prepared from N-ethyl-N-2-hydroxyethylaniline as described in the patent literature (I.G. Farbenind. A.-G. D.R.-P. 650,259, September 18th, 1937).
[4] An attempt to chlorinate the hydroxyethylamine did not yield a recognisable product.
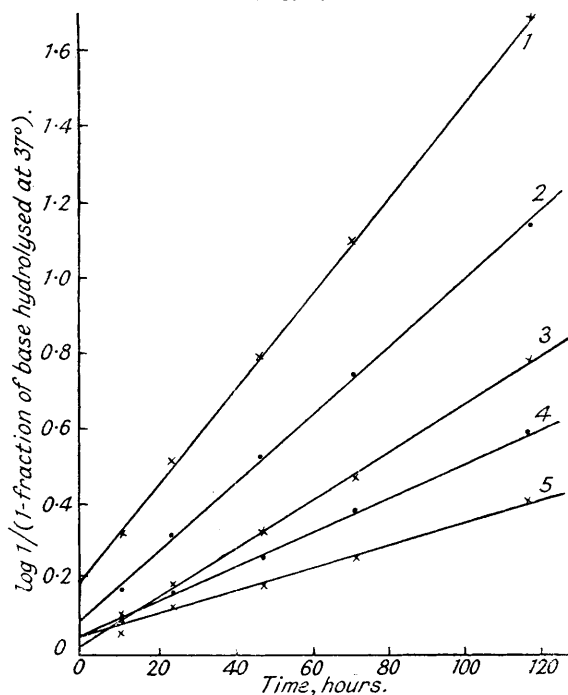[5] Waldkötter (loc. cit.) gives m. p. 99°.
[6] No crystalline picrate could be obtained from this compound but on mixing solutions of the amine and picric acid a purple colour developed.
[7] Anker and Cook (loc. cit.) give m. p. 88·5°.
[8] The parent tetrahydroxy-compound was very unstable and its solutions darkened rapidly in air; alcoholic solutions of the tetrachloro-compound rapidly developed a deep blue colour but a solution in light petroleum was stable in air.

the hydroxy-compounds and the iodoethyl derivatives have been obtained by heating these bromo-compounds with sodium iodide in dry acetone solution. A list of the compounds prepared in this work is given in Table I.

A number of the halogen compounds now described exhibit a remarkably strong photo-luminescence. This is particularly noticeable in the case of *NN*-di-(2-chloroethyl)-*p*-anisidine, *p*-chloro-*NN*-di-(2-chloroethyl)aniline, and *p*-chloro-*NN*-di-(2-bromoethyl)aniline and to a lesser extent in the chloroethyl derivatives of aniline and *p*-toluidine. When these substances are exposed to the light from a mercury arc which has passed through Wood's glass they momentarily fluoresce a dull blue colour and this soon gives rise to an intense yellow-green luminescence which persists for at least five seconds after switching off the light source. The photo-luminescence is only observed in the crystalline form and so, as in the case of inorganic phosphors, the effect is probably due to small amounts of impurities in the crystal lattice—these may be phosphorus compounds which are formed during the chlorination. In support of this view is the fact that the intensity of luminescence gradually diminishes when the compound is purified by recrystallisation or by chromatography. Tetraphenylmethane was prepared for comparison with the above phosphors (see Clapp, *J. Amer. Chem. Soc.*, 1939, **61**, 527) : our compounds showed a much greater intensity of luminescence. The only organic compound of the many examined in these laboratories which showed a photoluminescence comparable to that of the arylhalogenoethylamines was triphenylene which exhibits a beautiful red afterglow of at least ten seconds' duration.

Most of the hydroxyethyl and halogenoethyl compounds described are light-sensitive and develop deep colours on exposure to air especially in dilute solutions.

Table II shows the rate of hydrolysis of several of the chloroethylamines in 1 : 1 acetone–water at 37°. This temperature was chosen because of the interest in the biological activity of

TABLE II.

Concentration of reactants : 5 Millimols. of amine in 250 c.c. each of acetone and water. Temperature : 37°.

A. *NN*-Di-(2-chloroethyl)aniline.      B. *NN*-Di-(2-chloroethyl)-*m*-toluidine.
C. *NN*-Di-(2-chloroethyl)-*p*-toluidine.      D. *NN*-Di-(2-chloroethyl)-*p*-anisidine.
E. *β*-Naphthyldi-(2-chloroethyl)amine.

| Time, hours. | A. H, %.* | A. Cl, %.* | B. H, %. | B. Cl, %. | C. H, %. | C. Cl, %. | D. H, %. | D. Cl, %. | E.† H, %. | E.† Cl, %. |
|---|---|---|---|---|---|---|---|---|---|---|
| 10 | 18 | 17 | 18 | 18 | 31 | 31 | 51 | 51 | 10 | 10 |
| 24 | 31 | 30 | 34 | 35 | 51 | 51 | 71 | 71 | 25 | 24 |
| 48 | 47 | 45 | 53 | 52·5 | 70 | 70 | 85 | 84 | 38 | 35 |
| 72 | 60 | 58 | 66 | 66 | 83 | 81·5 | 92·5 | 92 | 53 | 50 |
| 120 | 74 | 71 | 85 | 84 | 96 | 93 | 100 | 98 | 65 | 61 |

\* These figures are based on complete hydrolysis to the di-(2-hydroxyethyl) compound.

† This compound is rather less soluble and was dissolved in 350 c.c. each of acetone and water : during its hydrolysis a brown colour developed in the solution.   .

these substances and aqueous acetone was used as solvent because of the low water solubility of the compounds—for example, *NN*-di-(2-chloroethyl)aniline has a solubility of approximately 20 mg. per litre of water. The rates of hydrolysis of the compounds as measured by the liberation of hydrogen or chloride ions are practically unimolecular with respect to the amine (Fig. 1). Since this hydrolysis occurs in the presence of a large excess of water the kinetic order of the reaction does not indicate its mechanism. The hydrolysis of the chloroethylamines involves a number of consecutive steps :

$$R \cdot N \begin{array}{l} CH_2 \cdot CH_2Cl \\ CH_2 \cdot CH_2Cl \end{array} \rightleftharpoons R \cdot N \begin{array}{l} CH_2 \cdot \overset{+}{C}H_2 + \bar{C}l \\ CH_2 \cdot CH_2Cl \end{array} \xrightarrow{H_2O} R \cdot N \begin{array}{l} CH_2 \cdot CH_2 \cdot OH \\ CH_2 \cdot CH_2Cl \end{array} + \overset{+}{H} \rightleftharpoons$$

(I.)        (II.)        (III.)

$$\text{(IV.)} \quad R \cdot N \begin{array}{l} CH_2 \cdot CH_2 \cdot OH \\ CH_2 \cdot \overset{+}{C}H_2 + \bar{C}l \end{array} \xrightarrow{H_2O} R \cdot N \begin{array}{l} CH_2 \cdot CH_2 \cdot OH \\ CH_2 \cdot CH_2 \cdot OH \end{array} + \overset{+}{H} \quad \text{(V.)}$$

If, as seems likely from the experience with the aliphatic chloroethylamines (Hanby, Hartley, Powell, and Rydon, *J.*, 1947, 520), the rate of hydrolysis of the chlorohydrin (III) is considerably greater than that of the original amine (I) then the rate of production of hydrogen and chloride

ions will be controlled by the rate of hydrolysis of (I). There is evidence that the reaction is of the $S_N1$ type and that the rate-determining step is the initial ionisation of (I). The slowing up of the rate of hydrolysis by the addition of chloride ions supports this mechanism (Table III).

FIG. 1.



1. NN-*Di*-(2-*chloroethyl*)-p-*anisidine.*
2. NN-*Di*-(2-*chloroethyl*)-p-*toluidine.*
3. NN-*Di*-(2-*chloroethyl*)-m-*toluidine.*
4. NN-*Di*-(2-*chloroethyl*)*aniline.*
5. β-*Naphthyldi*-(2-*chloroethyl*)*amine.*

TABLE III.

Hydrolysis of *NN*-di-(2-chloroethyl)aniline at 37°.

A–D, 5 Millimols. of amine dissolved in 250 c.c. each of acetone and water : A plus 10 millimols. of sodium hydrogen carbonate; B plus 86 millimols. of sodium chloride; C plus 10 millimols. of sodium thiosulphate; D plus 10 millimols. of sodium thiosulphate and 86 millimols. of sodium chloride; E, 5 Millimols. of amine dissolved in 250 c.c. each of ethanol and water.

| Time, hours. | A. | | B. | | C. % consumption of thiosulphate.* | D. % consumption of thiosulphate. | E. | |
|---|---|---|---|---|---|---|---|---|
| | H, %. | Cl, %. | H, %. | Cl, %. | | | H, %. | Cl, %. |
| 10 | 20 | 20 | 2·5 | — | 20 | 20 | 31 | 31 |
| 24 | 38 | 39 | 5 | — | 44 | 44 | 54 | 54 |
| 48 | 58 | 59 | 9 | — | 74 | 72 | 75 | 77 |
| 72 | 69 | 70 | 12·5 | — | 91 | 89 | 87 | 89 |

\* Based on the replacement of both chlorine atoms.

During the hydrolysis of the chloroethylamines in the absence of added ions the chloride-ion concentration will be continuously increasing and eventually the back reaction by which (I) is re-formed from (II) will become an important factor and the overall rate of hydrolysis will decrease. If an ion which has a very high competition factor for (II) as compared with the chloride ion is present in the solution (compare Price and Wakefield, *J. Org. Chem.*, 1947, **12**, 232) then the back reaction referred to will not be important and the rate of disappearance of the amine (I) will not be slowed up by the increasing chloride-ion concentration. The thiosulphate ion is known to have a very high competition factor for the ions derived from aliphatic chloroethylamines, and Table III shows that the rate of disappearance of the original amine is greater in the presence of thiosulphate; even when the chloride-ion concentration is

raised to 0·086M by the addition of sodium chloride, there is no slowing up of the rate of reaction in the presence of thiosulphate.

The effect of substituents in the aromatic ring of the arylchloroethylamines on the rates of hydrolysis also supports an $S_N1$ mechanism. Table IV shows that the variation in velocity of reaction in aqueous acetone at 66°—this temperature, which is the b. p. of the mixture, was chosen so that a more rapid comparison of the rates could be made—for substituted $NN$-di-(2-chloroethyl)anilines is in the order : $o$-MeO > $o$-Me > $p$-MeO > $p$-Me > $m$-Me > H > $p$-Ph > $p$-Cl > $p$-CHO, $p$-CO$_2$H, and 2 : 4-(NO$_2$)$_2$. Table IV also shows the rates of hydrolysis of some

TABLE IV.

| Compound. | Volume acetone : water (0·5 mM. amine). | % Hydrolysis in 30 mins. at 66°. | $pK_a$ of parent amine. |
|---|---|---|---|
| $NN$-Di-(2-chloroethyl)- | | | |
| aniline | 25 : 25 | 20 | 4·58 |
| $o$-toluidine | 25 : 25 | 83 | 4·39 |
| $m$-toluidine | 25 : 25 | 21 | 4·67 |
| $p$-toluidine | 25 : 25 | 38 | 5·07 |
| $o$-anisidine | 25 : 25 | 89 | 4·49 |
| $p$-anisidine | 25 : 25 | 58 | 5·29 |
| $p$-chloroaniline | 30 : 30 | 9 | — |
| $p$-xenylamine | 60 : 60 | 12 | 4·27 |
| 2 : 4-dinitroaniline | 25 : 25 | <1 | — |
| $\alpha$-naphthylamine | 30 : 30 | 50 | 3·92 |
| $\beta$-naphthylamine | 25 : 25 | 15 | 4·11 |
| $p$-aminobenzaldehyde | 25 : 25 | <1 | — |
| $p$-aminobenzoic acid | 25 : 25 | <1 | — |
| $p$-aminobenzoic acid (Na salt, see p. 191) | 25 : 25 | 11 | — |
| $p$-aminostilbene | 150 : 150 | 18 | — |
| $NNN'N'$-Tetra-(2-chloroethyl)- | | | |
| benzidine | 70 : 70 | 22 | — |
| $o$-tolidine | 70 : 70 | 86 | — |
| $NN$-Di-(2-bromoethyl)- | | | |
| aniline | 25 : 25 | 79 | — |
| $\beta$-naphthylamine | 55 : 55 | 80 | — |
| $p$-anisidine | 25 : 25 | 98 | — |
| $N$-Ethyl-$N$-(2-chloroethyl)aniline | 25 : 25 | 58 | — |

other less soluble chloroethylamines at various concentrations : Fig. 2 shows the variation in the amount of hydrolysis with dilution for the derivative of $p$-anisidine. The retarding effect of the increasing chloride-ion concentration becomes less important at higher dilutions and the rate of hydrolysis approaches a constant value.

FIG. 2.



c.c. each of acetone and water per 0·5 mM. of amine.
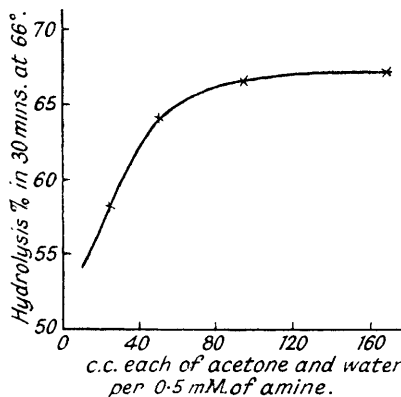
It will be observed that with two exceptions which will be discussed later the order of the rates of hydrolysis of the chloroethylamines of the type (VI) is the same as the order of basicities of the parent arylamines of general formula (VII). This basicity is dependent on the relative availability of the lone pair of electrons on the nitrogen atom. Substituent groups which cause

a displacement of electrons towards the nitrogen atom will clearly increase the basicity of the amine. These same groups will increase the ease with which the chlorine atom will ionise
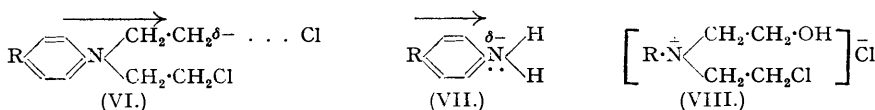


away from the rest of the molecule, and from what has already been said this will lead to an increased rate of reaction. If the hydrolysis were of the $S_N2$ type the effects of the substituents on basicities and rates of hydrolysis would be in opposite directions (compare Baddiley and Bennett, *J.*, 1933, 261).

The exceptions mentioned above are the compounds derived from *o*-anisidine and *o*-toluidine and with these can be grouped the derivative of α-naphthylamine which also hydrolyses at a much greater rate than would be expected from the basicity of the parent amine. The basic strength of these *o*-substituted amines is considerably lower than would be expected from their structures if one considers only the electron displacements caused by the substituents. Hall and Sprinkle (*J. Amer. Chem. Soc.*, 1932, **54**, 3469) give figures for the $pK_a$ values of alkylated amines which help to explain this abnormality—the figures relevant to the present problem are given in Table V. It will be seen from these that while monoalkylation of *o*-toluidine causes a

TABLE V.

| Amine. | $pK_a$-NH$_2$. | $pK_a$-NHMe. | $pK_a$-NMe$_2$. | $pK_a$-NHEt. | $pK_a$-NEt$_2$. |
|---|---|---|---|---|---|
| Aniline | 4·58 | 4·85 | 5·06 | 5·11 | 6·56 |
| *o*-Toluidine | 4·39 | 4·59 | 5·86 | 4·92 | 7·18 |
| *m*-Toluidine | 4·69 | 4·94 | 5·24 | — | — |
| *p*-Toluidine | 5·07 | 5·33 | 5·50 | 5·67 | 7·09 |
| α-Naphthylamine | 3·92 | 3·70 | 4·88 | — | — |

normal increment in basicity, dialkylation produces an abnormally large increase; the same is true in the case of α-naphthylamine and almost certainly so in the case of *o*-anisidine, though no figures are given by Hall and Sprinkle. It would appear that the *o*-substituted arylamines have unusually low basicities because of an interaction between the hydrogen atom of the amino-group and the substituting group. The compounds described in the present paper are of course dialkylated derivatives and hence the rates of hydrolysis will be a more accurate measure of the electron-repelling power of the substituting group. This partially explains the high rate of reaction of the *o*-substituted compounds and of the derivative of α-naphthylamine though it must be admitted that the observed rates are still considerably higher than would be expected even from a comparison of the basicities of the dialkylated amines.

The rate of hydrolysis of *NN*-di-(2-chloroethyl)aniline is considerably less than that of *N*-ethyl-*N*-2-chloroethylaniline and this is probably due to the electron-attracting capacity of the second chlorine atom. In the disubstituted compound the mutual effect of the chlorine atoms will be to decrease the negative charge on each. The electron-attracting capacity of the chlorine atoms is shown in the low basicities of the two compounds mentioned above. In preliminary measurements at 25° using 50% aqueous alcohol Mr. Goss of this Institute finds $pK_a = 2·2$ for the dichloro-compound and $pK_a = 3·5$ for the monochloro-compound as compared with diethylaniline, $pK_a = 5·84$.

The hydrolysis of the arylchloroethylamines in aqueous solutions was expected to follow the same pattern as that observed for the corresponding aliphatic series (Golumbic, Fruton, and Bergman, *J. Org. Chem.*, 1946, **11**, 518; Hanby *et al.*, *loc. cit.*; Bartlett, Davis, Ross, and Swain *J. Amer. Chem. Soc.*, 1947, **69**, 2977) except that the rates of hydrolysis would be slower owing to the lower basicities of the compounds. It is now apparent that there are important differences between the two series. In unbuffered solution the aliphatic compounds rapidly liberate one equivalent of chloride ion and more slowly liberate one equivalent of hydrogen ion —the reaction stops without the release of the second chlorine atom. In aqueous acetone solutions methyldi-(2-chloroethyl)amine is rapidly converted into a cyclic dimer and less than 10% of hydrolysis occurs; on the other hand the ethyl homologue undergoes a far greater proportion of hydrolysis with less dimerisation (Bartlett *et al.*, *loc. cit.*). The aromatic derivatives react with aqueous acetone giving continuous replacement of the chlorine atoms, and there is no dimerisation and no indication of the existence of appreciable amounts of quaternary nitrogen compounds in the solution as shown by the fact that the liberation of chloride ion is always accompanied by an equivalent amount of hydrogen ion. In the case of aliphatic compounds

the liberation of chloride ion probably stops when 50% reaction has occurred because the chlorohydrin is stabilised by salt formation giving (VIII).

The positive charge on the nitrogen atom will oppose the ionisation of the second chlorine atom and hydrolysis will be arrested. As the aromatic derivatives are much weaker bases the amount of salt formation under the conditions of the hydrolysis will be small and most of the intermediate chlorohydrin will be present as the free base and will be able to hydrolyse further. It has already been suggested that the chlorohydrin will hydrolyse more readily than the original di-(2-chloroethyl)amine—an attempt to make this compound by the action of ethylene dichloride on *N*-2-hydroxyethylaniline gave *N*-phenylmorpholine; if it hydrolyses at a very much slower rate one would expect to be able to isolate it from the reaction mixture as is the case with the aliphatic compounds. From a solution of the *p*-anisidine derivative which had reached 50% elimination of chloride ion only *NN*-di-(2-chloroethyl)- and *NN*-di-(2-hydroxyethyl)-*p*-anisidine could be isolated in amounts which accounted for the whole of the amine originally present. Only the pure di-(2-hydroxyethyl) compound is present in solutions in which 100% elimination of chloride ion has occurred. This is an additional proof that no dimerisation occurs in the case of the aromatic compounds.

The hydrolysis of the di-(2-bromoethyl)amines examined proceeds at a considerably faster rate than that of the corresponding chloro-compounds and the iodo-derivatives are decomposed at an even greater rate, but in the last case the reaction is more complex and appears to be more closely related to that of the aliphatic " nitrogen-mustards ". A more detailed study of the reactions of the bromo- and iodo-compounds is now being undertaken.

A number of the aryldi-(2-halogenoethyl)amines now described shows a marked cytotoxic effect on tumours which will be discussed elsewhere. The more rapidly hydrolysed compounds exert a vesicant action on the human skin.

### EXPERIMENTAL.

*Preparation of Arylhydroxyethylamines.—Method A.* The arylamine (0·1 mol.) was introduced into a Carius tube which was constricted and then cooled in ice. After the introduction of ethylene oxide (0·2 mol.) the tube was sealed. When only small amounts of the amine were available the ethylene oxide was diluted with its own volume of dry benzene to aid its introduction into the tube. The tube was heated at 90° or 150° (see p. 183) for 16 hours. The contents were extracted with alcohol and crystallised from aqueous alcohol or benzene. In the few cases where the hydroxyethyl compound did not crystallise the product was characterised by the preparation of a picrate. The picrates are formed slowly and are often very soluble in alcohol.

*Method B.* The arylamine (0·5 mol.), ethylene chlorohydrin (2·5 mols.), water (500 c.c.), and calcium carbonate (0·7 mol.) were heated under reflux with very vigorous stirring. The more basic amines reacted almost completely in 7 hours but the less basic amines, such as the naphthylamines, required heating for 30 hours. The mixture was filtered hot and the unreacted chalk was washed with hot water. The filtrate was saturated with sodium chloride, cooled, and then extracted with the ether which had previously been used to extract the chalk. The dried ether solution was evaporated and the residue was purified by fractional distillation, in the case of the aniline derivatives, or by crystallisation. Appreciable amounts of the monosubstituted derivatives are formed in this reaction; for example in one run with aniline (320 g.) *N*-2-hydroxyethylaniline (120 g.), b. p. 130—135°/3 mm., and *NN*-di-(2-hydroxyethyl)aniline (330 g.), b. p. 175—180°/3 mm., were formed.

When an attempt was made to prepare *NN*-di-(2-hydroxyethyl)-*p*-anisidine by heating *p*-anisidine (1 mol.) with ethylene chlorohydrin (1 mol.) (Anker, Cook, and Heilbron, *loc. cit.*) only N-(2-*hydroxyethyl*)-p-*anisidine* (needles, m. p. 44—45°, from methanol) (Found : C, 65·3; H, 7·9. $C_9H_{13}O_2N$ requires C, 64·8; H, 7·9%) could be isolated. A similar experiment with aniline gave mainly *NN*-di-phenylpiperazine, m. p. 164—165°.

*Preparation of Arylchloroethylamines.—Method A.* The arylhydroxyethylamine (1 mol.) was gradually added to a suspension of powdered phosphorus pentachloride (1·2 mols.) in dry chloroform (1 l.) with cooling. After heating under reflux for one hour the mixture was cooled and poured on ice. The dried chloroform layer was evaporated and the product was dissolved in benzene and passed through a short column of activated alumina. Evaporation of the eluates gave the required chloro-compound which was crystallised from light petroleum (b. p. 40—60°) or anhydrous methanol; considerable hydrolysis occurred if aqueous methanol was used. Generally, distillation of the chloro-compounds was impracticable since decomposition occurred even at low pressures.

*Method B.* The amine (1 mol.) was slowly added to phosphorus oxychloride (2 mol.) and the mixture was heated on a steam-bath until a clear liquid was obtained and evolution of gas had ceased (about ½ hour). Benzene and crushed ice were added and the mixture was vigorously shaken. The dried benzene layer was worked up as under method A.

*Preparation of Arylbromoethylamines.—*The arylhydroxyethylamine (1 mol.) was gradually added to phosphorus tribromide (3 mol.) and the mixture was heated on a steam-bath until the reaction slackened. Crushed ice and benzene were then added and the product was isolated as in method B above.

*Preparation of Aryliodoethylamines.—*A solution of the bromo-compound (1 mol.) in dry acetone (1 l.) containing sodium iodide (2 mols.) was heated under reflux for 2 hours. The precipitated sodium bromide was removed and the solution was evaporated. The residue was dissolved in light petroleum

(b. p. 60—80°) and percolated through a short column of activated alumina. The eluted iodo-compound was crystallised from light petroleum (b. p. 40—60°) or anhydrous methanol.

*Alternative Preparation of* NN-*Di-*(2-*chloroethyl*)-p-*aminostilbene.*—12·3 G. of *NN*-di-(2-chloroethyl)-*p*-aminobenzaldehyde dissolved in benzene (50 c.c.) were added to the Grignard reagent formed from benzyl chloride (6·3 g.), magnesium (1·2 g.), and ether (20 c.c.). After being heated for 30 mins. on a steam-bath the mixture was shaken with dilute ammonium chloride solution and the ether–benzene layer was dried and evaporated. The stilbene *derivative* formed colourless felted needles, m. p. 126°, from methanol : there was no depression on admixture with a specimen prepared by the first method from *p*-aminostilbene.

NN-*Di-*(2-*chloroethyl*)-p-*aminobenzoic Acid.*—*NN*-Di-(2-chloroethyl)-*p*-aminobenzaldehyde (1 g.) was dissolved in acetone and an excess of powdered potassium permanganate was added. The mixture warmed to 30° during the addition and eventually set solid owing to the precipitation of manganese dioxide. After dilution with water a stream of sulphur dioxide was passed through until the dioxide dissolved. The ether extract of the mixture was shaken with dilute sodium carbonate solution and the acid product was liberated by the addition of dilute hydrochloric acid and crystallised from aqueous methanol forming needles, m. p. 168—169°.

*Rates of Hydrolysis at* 37° *in* 1 : 1 *Acetone–Water.*—The chloroethylamine (5 millimols.) was dissolved in acetone (250 ml.), water (250 ml.) was then added and the solution was rapidly heated to 37° and transferred to the thermostat. 50 Ml. of the solution were removed at appropriate times and titrated first with N/10-sodium hydroxide (phenolphthalein indicator) and then, after the addition of one drop of N/10-acetic acid, with N/10-silver nitrate (dichlorofluorescein indicator). The results are shown in Table II.

Control experiments had shown that, in aqueous acetone, hydrochloric acid could be titrated quantitatively using phenolphthalein as indicator in the presence of dimethylaniline—a stronger base than any likely to be encountered in these experiments. There is a contraction on mixing equal volumes of water and acetone but the expansion on warming to 37° practically compensates for this and so no volume correction has been made. Since the hydrolysis is a relatively slow process it was not necessary to arrest the reaction by acidification before the titrations.

*Isolation of Products from the Hydrolysis of* NN-*Di-*(2-*chloroethyl*)-p-*anisidine.*—A 24 hour-old solution of the amine prepared as above in which 50% hydrolysis had occurred—as measured by the liberation of chloride and hydrogen ion—was rapidly evaporated under reduced pressure at 37° until all the acetone had been removed. The cooled solution deposited the di-(2-chloroethyl) compound (46% of the original amine), m. p. 50° (undepressed by admixture with an authentic specimen). An ether extract of the filtrate which had been neutralised with sodium hydroxide and saturated with sodium chloride yielded the di-(2-hydroxyethyl) compound (48%), m. p. and mixed m. p. 71°.

When a 120 hour-old solution was neutralised with sodium hydroxide and saturated with sodium chloride and then extracted with ether the di-(2-hydroxyethyl) compound (98%), m. p. 72°, was obtained.

*The Effect of added Reagents on the Rate of Hydrolysis of* NN-*Di-*(2-*chloroethyl*)*aniline.*—The experiment was started as above except that the added reagent was dissolved in the water before the solutions were mixed. The liberation of hydrogen ion in experiment A (Table III) was measured by the acidification of a 50 ml. aliquot with standard sulphuric acid and the removal of carbon dioxide by evacuation, followed by back titration with N/10-sodium hydroxide. The liberated chloride ion could be titrated in this same aliquot or in a fresh sample without neutralisation : the same result was obtained by both methods.

The thiosulphate consumption in experiments C and D was followed by titration with N/10-iodine using starch as indicator ; the end-point was indistinct unless the 50 ml. aliquot was diluted with water (100 ml.)—under these conditions the blank due to the reaction between acetone and iodine was negligible.

*Hydrolysis of Chloroethylamines at* 66° *in* 1 : 1 *Acetone–Water.*—The amine (0·5 millimol.) was dissolved in acetone and water (25 ml. of each)—or in the least volume of 1 : 1 acetone–water which would effect solution when heated—and the solution was heated under reflux. A thermometer in the boiling liquid registered 66°. After ½ hour the mixture was rapidly cooled and the liberated chloride and hydrogen ion were determined as before. Since unsatisfactory end-points were obtained with the bromo-derivatives using an eosin indicator 5 ml. of N/10-sodium chloride were added after hydrolysis and dichlorofluorescein was used and the bromide ion value obtained by difference.

The rate of hydrolysis of *NN*-di-(2-chloroethyl)-*p*-aminobenzoic acid was measured as above and after a preliminary titration of the carboxyl group with N/10-sodium hydroxide (5 ml. of alkali being required for 0·5 millimol. of acid). It was only possible to measure the liberated hydrogen ion in this experiment since the amino-acid interfered with the chloride end-point.