201. *Some Compounds related to the Aromatic "Nitrogen Mustards."*

By George A. R. Kon and John J. Roberts.

The preparation of certain compounds related to the cytotoxic "nitrogen mustards" is described.

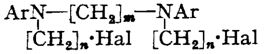
Numerous di(halogenoalkyl)arylamines, of which di-(2-chloroethyl)aniline $Ph{\cdot}N(CH_2{\cdot}CH_2Cl)_2$ is typical, have been found to have a powerful cytotoxic activity and to inhibit the growth of transplanted tumours in rats (Haddow, Kon, and Ross, *Nature*, 1948, **162**, 824). A number of such compounds has been described (Ross, *J.*, 1949, 183; Everett and Ross, *ibid.*, p. 1972) and certain generalisations have been made in relating the structure of the compounds to their biological activity. Thus, it appears essential that two halogenoalkyl chains should be present and that the halogen atoms should not be separated from the nitrogen by more than two carbon atoms; the activity of these compounds could be satisfactorily related to the ease of hydrolysis of the halogen atoms in aqueous acetone.

It appeared of interest to test these conclusions by examining related compounds possessing two side chains of unequal length, and also compounds with side chains longer than the optimum but with additional substituents conferring the requisite reactivity on the halogen atoms.

For this purpose a series of anilino-alcohols was prepared. These call for little comment, except that 4-anilinobutanol, which had already been obtained (Ross and Everett, *loc. cit.*), has now been prepared more easily in a pure state by condensing aniline with 4-chlorobutyl acetate to give the crystalline 4-*anilinobutyl acetate*, which was then hydrolysed. The latter acetate could also be condensed with a second molecule of chlorobutyl acetate to give *di*-(4-*acetoxybutyl*)-*aniline*, and the parent compound was obtained in a pure state by alkaline hydrolysis; however, all attempts to prepare the corresponding chloro-derivative failed.

Condensation of the anilino-alcohols with ethylene chlorohydrin afforded compounds of the type $Ph{\cdot}N(CH_2{\cdot}CH_2{\cdot}OH){\cdot}[CH_2]_n{\cdot}OH$, where n was 2, 3, 4, and 5, and the products were then converted into the chlorides. Attempts to prepare the same compounds with the aid of ethylene oxide were not successful. Similar compounds were obtained when using 3-chloropropyl alcohol in place of ethylene chlorohydrin, but the series was not extended further because compounds with longer side chains were invariably inactive, in agreement with their low rate of hydrolysis in aqueous acetone.

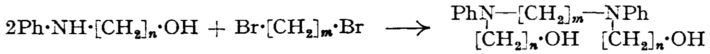
This inactivity was not due purely to steric factors such as the separation of the reacting groups in space owing to lengthening of the side chain; this was strikingly borne out by an examination of a series of compounds of the general type (I), in which the terminal halogen atoms can be more widely separated, for reactivity depends on their position with reference to the activating group, namely nitrogen.



$$\underset{[CH_2]_n\cdot Hal}{ArN}-[CH_2]_m-\underset{[CH_2]_n\cdot Hal}{NAr}$$

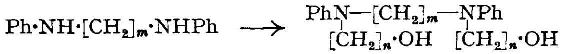
(I.)

For the preparation of compounds in which the nitrogen atoms are separated by two or more carbon atoms two methods are available and both have been used : in one of these two molecules of the anilino-alcohol are condensed with one of the appropriate alkylene dibromide, a method already much used by von Braun in analogous cases (*Ber.*, 1908, **41**, 2156) :



$$2Ph\cdot NH\cdot [CH_2]_n\cdot OH + Br\cdot [CH_2]_m\cdot Br \longrightarrow \underset{[CH_2]_n\cdot OH}{PhN}-[CH_2]_m-\underset{[CH_2]_n\cdot OH}{NPh}$$

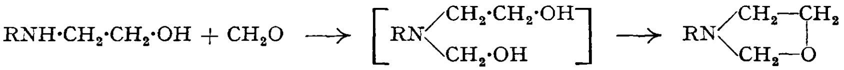
alternatively, an αω-dianilinoalkane is condensed with ethylene oxide or a chlorohydrin :



$$Ph\cdot NH\cdot [CH_2]_m\cdot NHPh \longrightarrow \underset{[CH_2]_n\cdot OH}{PhN}-[CH_2]_m-\underset{[CH_2]_n\cdot OH}{NPh}$$

Chlorination of the hydroxyl groups then affords the appropriate chloro-compound. The second method appeared to be especially promising as a route to compounds in which $m = 1$, since Eibner has described the preparation of di-(*o*-tolyl)methane and other similar compounds (*Annalen*, 1898, **302**, 349). This compound was condensed with ethylene chlorohydrin to give a product which appeared to be mainly the desired dihydroxyethyl derivative, but it could not be completely purified and gave no definite compound on chlorination.

It was hoped to obtain similar compounds by a variant of the first method, namely by condensing anilino-alcohols with formaldehyde. The condensation of some ethanolamines with formaldehyde, acetaldehyde, and benzaldehyde has been studied by Knorr and Matthes (*Ber.*, 1901, **34**, 3484), who showed that the intermediate compounds lose water and cyclise to oxazolidines :



Bergmann, Ulpts, and Camacho (*ibid.*, 1922, **55**, 2796) found that phenetidinoethanol behaved similarly. We have prepared a number of *N*-aryloxazolidines in the same way. 3-Anilinopropanol also condensed readily with formaldehyde to afford 3-*phenyl*-1 : 3-*oxazine*. 4-Anilinobutanol gave under similar conditions what appeared to be the intermediate hydroxymethyl compound, which was unstable and lost water on distillation to pass into the cyclic compound, 3-*phenyl*-1 : 3-*pentoxazoline* (3-*phenyl*-1-*oxa*-3-*aza*cyclo*heptane*). 5-*Anilinopentanol* and 6-*anilinohexanol* appeared to react with formaldehyde, but on distillation the products decomposed and the starting materials were the only products isolated. All efforts to condense esters of anilino-alcohols with formaldehyde and so avoid cyclisation were fruitless.

The preparation of compounds in which the nitrogen atoms are more widely separated did not present much difficulty; the compounds of type (I) in which $n = m = 2$ were some of the most active compounds yet tested and this has prompted the preparation of several analogues, in which the group Ar and the side-chain were varied. It may be noted that aliphatic analogues of these, such as *NN'*-diethyl-*NN'*-di-(2-chloroethyl)ethylenediamine, have proved to be active cytotoxic agents (SK 882, Abstract of Final Report to the Chemical Corps, March 14th, 1948).

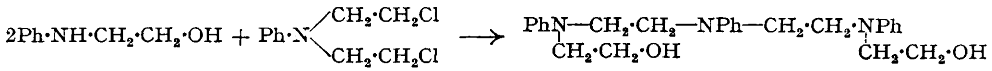
Biological activity is maintained in derivatives of propylenediamine and gradually falls off as the distance between the nitrogen atoms is increased. Lengthening of the halogenoalkyl side chains, on the other hand, leads to complete loss of activity, in agreement with the theoretical views developed above. Thus, already the di-3-chloropropyl derivative of *NN'*-diphenylethylenediamine is inactive.

To afford a comparison with the compounds already described by Ross (*loc. cit.*) a few representative compounds of type (I) have been hydrolysed in boiling 50% acetone–water for ½ hour and the following values obtained :

Ar.	*m.*	*n.*	% Hydrolysed.	Ar.	*m.*	*n.*	% Hydrolysed.
Ph	2	2	33	1-$C_{10}H_7$	2	2	67
Ph	3	2	40	2-$C_{10}H_7$	2	2	18
Ph	4	2	45	*p*-OMe·C_6H_4 ...	2	2	55
Ph	5	2	44	Ph	2	3	<1
Ph	6	2	54	Ph	2	*	83

* Side chain = ·CH_2·CHMeCl.

Interesting analogues of these compounds should be formed by the condensation of 2 moles of anilinoethanol with one of a di(halogenoalkyl)aniline :



$$2\mathrm{Ph{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}OH} + \mathrm{Ph{\cdot}N}\left\langle\begin{matrix}\mathrm{CH_2{\cdot}CH_2Cl}\\ \mathrm{CH_2{\cdot}CH_2Cl}\end{matrix}\right. \longrightarrow \underset{\mathrm{CH_2{\cdot}CH_2{\cdot}OH}}{\mathrm{PhN}}\mathrm{{-}CH_2{\cdot}CH_2{-}NPh{-}CH_2{\cdot}CH_2{\cdot}}\underset{\mathrm{CH_2{\cdot}CH_2{\cdot}OH}}{\mathrm{NPh}}$$

Unfortunately all attempts to prepare such compounds led to diarylpiperazines (cf. Davis and Ross, *J.*, 1949, 2831).

Experimental.

(M. p.s are uncorrected.)

Arylamino-alcohols.—2-Anilinoethanol was prepared as described by Schorygin and Smirnov (*J. Gen. Chem. Russia*, 1934, **4**, 830). 3-Anilinopropanol, which had previously been obtained in 29% yield by condensing allyl alcohol with aniline (Hromatka, *Ber.*, 1942, **75**, 379), has now been obtained in 70% yield from trimethylene chlorohydrin and aniline by Schorygin and Smirnov's procedure, namely by dropping the chlorohydrin (1 mol.) during ½ hour into aniline (2 mols.) and water (1 mol.) kept at about 140° and then gently boiling the mixture for 1 hour; alkali was added to the cooled product and the anilino-alcohol extracted with ether and purified by distillation. 2-Anilinopropanol (Dains, Joss, and Stubbs, *Univ. Kansas Sci. Bull.*, 1931, **20**, 161) was conveniently prepared by heating equimolecular quantities of aniline and propylene oxide to 150° for 15 hours and then working up the product as above (yield 70%). 4-Chlorobutyl acetate (Cloke and Pilgrim, *J. Amer. Chem. Soc.*, 1939, **61**, 2667) (0·1 mol.) was boiled under reflux with aniline (0·1 mol.), calcium carbonate (0·05 mol.), and water (50 c.c.) for 10 hours, with vigorous stirring; the product, isolated by means of ether, gave on distillation 25% of a fraction, b. p. 150—155°/1·8 mm., which solidified and then crystallised from pentane in plates, m. p. 33—34°, consisting of 4-*anilinobutyl acetate* (Found : C, 69·8; H, 8·7. $C_{12}H_{17}O_2N$ requires C, 69·5; H, 8·5%). The alcohol was obtained from the acetate by hydrolysis with cold methanolic potassium hydroxide and boiled at 138—140°/1 mm. (Found : C, 72·5; H, 9·2. Calc. for $C_{10}H_{15}ON$: C, 72·7; H, 9·2%). Pentamethylene chlorohydrin (Bennett and Heathcote, *J.*, 1929, 268) was boiled with 2 moles of aniline for 6 hours; excess of aqueous potassium hydroxide was added to the cooled product, which was extracted with ether, giving 45% of 5-*anilinopentanol*, b. p. 164°/1·4 mm. (Found : C, 73·7; H, 9·7. $C_{11}H_{17}ON$ requires C, 73·7; H, 9·6%). Hexamethylene chlorohydrin (Müller and Vanc, *Monatsh.*, 1947, **77**, 259) gave on similar treatment a 74% yield of 6-*anilinohexanol*, b. p. 138°/0·05 mm., crystallising as stout needles, m. p. 42°, from benzene–light petroleum (Found : C, 74·5; H, 10·0. $C_{12}H_{19}ON$ requires C, 74·5; H, 9·9%). When 2-naphthylamine was heated with ethylene chlorohydrin with or without the addition of chalk and water, 2-*naphthylaminoethanol* could not be isolated from the product; it was, however, formed together with the *NN*-bishydroxyethyl compound (Ross, *loc cit.*) on heating naphthylamine with one mole of ethylene oxide to 100° for 6 hours; the crude reaction product was freed from unchanged naphthylamine and some dinaphthylamine by chromatography in benzene solution on Spence type H alumina; the hydroxylated compounds were recovered by stripping the column with methanol; they were treated with formaldehyde (see below), and the *oxazolidine* formed was separated by chromatography in ethereal solution and recovered from the first runnings; it formed plates, m. p. 91—92°, from methanol (Found : C, 78·3; H, 6·6. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·6%). The oxazolidine (5 g.) was dissolved in the minimum amount of alcohol, and 10 c.c. of hydrochloric acid were added, causing a deep red colour to develop. The solution was heated to the b. p., rapidly cooled, diluted, basified, and extracted with ether. The ethereal extract gave a good yield of 2-naphthylaminoethanol, b. p. ~180°/0·7 mm., m. p. 49—50° (crystallised after being rubbed with light petroleum) (Found : C, 76·5; H, 7·0%. $C_{12}H_{13}ON$ requires C, 77·0; H, 7·0%). The compound rapidly darkens on exposure to light and air and is therefore difficult to crystallise although a small amount of prisms has been obtained by slow evaporation of a benzene–light petroleum solution.

N-2-*Hydroxyethyl*-N-3′-*hydroxypropylaniline*, obtained from 3-anilinopropanol and ethylene chlorohydrin in 75% yield as described for anilinobutyl acetate, had b. p. 180—190°/0·3 mm. (Found : C, 67·7; H, 8·8. $C_{11}H_{17}O_2N$ requires C, 67·7; H, 8·8%).

N-2-Chloroethyl-*N*-3′-chloropropylaniline was prepared from the preceding compound by the general method given by Everett and Ross (*loc. cit.*) and was a pale yellow oil, which was analysed in the form of its *picrate*, yellow plates, m. p. 91° (Found : N, 12·7. $C_{17}H_{18}O_7N_4Cl_2$ requires N, 12·3%). The yield was 50%; the same method of chlorination was used throughout this work and gave yields varying from 40 to 60%.

N-2-*Hydroxyethyl*-N-4′-*hydroxybutylaniline*, obtained from anilinobutanol in 76% yield as described for the previous compound, had b. p. 180—190°/0·4 mm. (Found : C, 69·1; H, 9·5. $C_{12}H_{19}O_2N$ requires C, 68·9; H, 9·2%).

N-2-Chloroethyl-*N*-4′-chlorobutylaniline was an oil which was analysed in the form of its *picrate*, yellow plates, m. p. 103—104° (Found : C, 45·9; H, 4·5. $C_{18}H_{20}O_7N_4Cl_2$ requires C, 45·5; H, 4·2%). When kept, the chloro-compound gradually deposited a solid, m. p. 174°. Titration with silver nitrate and dichlorofluorescein suggested that one chlorine had become ionic and the compound was probably *N*-phenyl-*N*-2-chloroethylpyrrolidinium chloride.

NN-*Di*-(4-*hydroxybutyl*)*aniline*. Equimolecular quantities of 4-anilinobutyl acetate and 4-chlorobutyl acetate were condensed as described under the preparation of the former compound (20 hours). The fraction, b. p. 190—210°/0·5 mm. (20% yield), was the *diacetate* (Found : C, 67·2; H, 8·3. $C_{18}H_{27}O_4N$ requires C, 67·3; H, 8·5%) from which the required alcohol was obtained on hydrolysis with cold methanolic potassium hydroxide; the *diol* had b. p. 190°/0·3 mm. (Found C, 70·7; H, 9·7. $C_{14}H_{23}O_2N$ requires C, 70·9; H, 9·8%). All attempts to prepare a dichloro-compound were unsuccessful.

Oxazolidines.—The appropriate anilino-alcohol (5 g.) was rubbed with excess of 40% formaldehyde solution, whereupon (in most cases) a clear solution formed in 1—2 minutes. This then became cloudy and a heavy colourless oil (or solid) separated, which could be isolated by extraction with ether and purified by distillation or crystallisation; the yields were quantitative. The following were obtained :

		Found,			Required,	
Compound.	M. p. or b. p. (solvent).	C, %.	H, %.	Formula.	C, %.	H,
3-*Phenyloxazolidine*	B. p. 94°/1·5 mm., m. p. 28° (pentane)	70·8	7·3	$C_9H_{11}ON$	70·6	7·3
3-p-*Methoxyphenyloxazolidine*	Plates, m. p. 88° (light petroleum)	67·0	7·5	$C_{10}H_{13}O_2N$	67·0	7·5
3-*Phenyl-5-methyloxazolidine* *	B. p. 120°/6 mm., m. p. 37—38° (pentane)	73·2	8·0	$C_{10}H_{13}ON$	73·6	8·0
3-*Phenyl*-1 : 3-*oxazine* *	B. p. 94°/0·4 mm.	73·7	7·8	$C_{10}H_{13}ON$	73·6	8·0
3-*Phenylpentoxazolidine* (3-*phenyl*-1-*oxa*-3-*aza*cyclo*heptane*)	B. p. 115°/0·4 mm.	74·6	8·7	$C_{11}H_{15}ON$	74·7	8·7
2 : 3-*Diphenyloxazolidine* †	Needles, m. p. 84—85° (methanol)	80·0	7·1	$C_{15}H_{15}ON$	80·0	6·7

* Purified by chromatography. † Benzaldehyde used in place of formaldehyde.

Diamines.—NN′-*Diphenyl*-NN′-*di*-(2-*hydroxyethyl*)*ethylenediamine*. 2-Anilinoethanol (0·2 mol.), ethylene dibromide (0·1 mol.), chalk (0·15 mol.), and water (100 c.c.) were boiled under reflux with mechanical stirring for 10 hours. The product was extracted with benzene, evaporated, and distilled; the fraction, b. p. 220—230°/0·7 mm., obtained in 74% yield, solidified and crystallised from benzene–light petroleum (b. p. 60—80°) in plates, m. p. 89—90° (Found : C, 72·2; H, 8·0. $C_{18}H_{24}O_2N_2$ requires C, 72·0; H, 8·1%).

NN′-*Diphenyl*-NN′-*di*-(2-*chloroethyl*)*ethylenediamine* formed stout needles, m. p. 81—82°, from light petroleum (b. p. 40—60°) (Found : C, 64·0; H, 6·5. $C_{18}H_{22}N_2Cl_2$ requires C, 64·1; H, 6·6%).

The following compounds were prepared by exactly similar methods unless otherwise stated :

NN′-*Diphenyl*-NN′-*di*-(2-*hydroxyethyl*)*trimethylenediamine*, b. p. 210—222°/0·6 mm., flattened needles (from benzene–light petroleum), m. p. 112—113° (75%) (Found : C, 72·8; H, 8·6. $C_{19}H_{26}O_2N_2$ requires C, 72·6; H, 8·3%).

NN′-*Diphenyl*-NN′-*di*-(2-*chloroethyl*)*trimethylenediamine*, an oil (Found : C, 65·1; H, 7·1. $C_{19}H_{24}N_2Cl_2$ requires C, 64·9; H, 6·9%).

NN′-*Diphenyl*-NN′-*di*-(2-*hydroxyethyl*)*tetramethylenediamine*. In the preparation of this compound and its pentamethylene analogue no chalk or water was used, the components being heated on the steam-bath for 6 hours, and the cooled mixture then treated with an excess of 2N-sodium hydroxide. The fraction, b. p. 200—220°/0·5 mm. (18% yield), solidified and was rubbed with ether, and then crystallised from benzene–light petroleum, forming plates, m. p. 79—80° (Found : C, 73·3; H, 8·5. $C_{20}H_{28}O_2N_2$ requires C, 73·2; H, 8·6%).

NN′-*Diphenyl*-NN′-*di*-(2-*chloroethyl*)*tetramethylenediamine* crystallised from pentane in prisms, m. p. 65° (Found : C, 65·4; H, 7·0. $C_{20}H_{26}N_2Cl_2$ requires C, 65·7; H, 7·2%).

NN′-*Diphenyl*-NN′-*di*-(2-*hydroxyethyl*)*pentamethylenediamine* was obtained exactly like the tetramethylene compound (yield 22%); the crude fraction, b. p. 200—210°/0·4 mm., was analysed (Found : C, 72·6; H, 8·6. $C_{21}H_{30}O_2N_2$ requires C, 73·7; H, 8·8%).

NN′-*Diphenyl*-NN′-*di*-(2-*chloroethyl*)*pentamethylenediamine* was a colourless oil, b. p. 170°/0·2 mm. (Found : C, 66·4; H, 7·6. $C_{21}H_{28}N_2Cl_2$ requires C, 66·5; H, 7·4%).

NN′-*Diphenyl*-NN′-*di*-(2-*hydroxyethyl*)*hexamethylenediamine*, obtained in 66% yield from *NN*′-diphenylhexamethylenediamine (von Braun, *Ber.*, 1910, **43**, 2859) and ethylene chlorohydrin by the chalk and water process, had b. p. 280°/2 mm. (Found : C, 74·0; H, 9·1. $C_{22}H_{32}O_2N_2$ requires C, 74·1; H, 9·1%).

NN′-*Diphenyl*-NN′-*di*-(2-*chloroethyl*)*hexamethylenediamine* was crystallised successively from light petroleum (b. p. 40—60°), alcohol, and again light petroleum, forming prisms, m. p. 66° (Found : C, 67·1; H, 8·0. $C_{22}H_{30}N_2Cl_2$ requires C, 67·2; H, 7·7%).

NN′-*Diphenyl*-NN′-*di*-(2-*hydroxypropyl*)*ethylenediamine* was produced in 61% yield from 2-anilinopropanol and ethylene dibromide. It was also formed on heating *NN*′-diphenylethylenediamine with an excess of propylene oxide in a sealed tube to 160° for 15 hours and was an oil, b. p. ~220°/0·1 mm. (Found : C, 73·2; H, 8·6. $C_{20}H_{28}O_2N_2$ requires C, 73·2; H, 8·6%). In the latter preparation there was formed a by-product boiling some 10° lower and forming plates (from methanol), m. p. 166—167°, probably 2-*ethyl*-1 : 3-*diphenyltetrahydroglyoxaline* (Found : C, 80·5; H, 8·3. $C_{17}H_{20}N_2$ requires C, 80·9; H, 8·0%). The formation of this compound presupposes the rearrangement of propylene oxide to propaldehyde which is known to occur at high temperature (Ipatiew and Leontowitsch, *Ber.*, 1903, **36**, 2017). When the reaction with propylene oxide was interrupted after 10 hours, the product was a solid, prisms (from benzene–light petroleum), m. p. 92°, consisting of NN′-*diphenyl*-N-(2-*hydroxypropyl*)-*ethylenediamine* (Found : C, 75·4; H, 8·0. $C_{17}H_{22}ON_2$ requires C, 75·5; H, 8·2%). The *picrate* had m. p. 142° (Found : N, 14·4. $C_{23}H_{25}O_8N_5$ requires N, 14·0%).

NN′-*Diphenyl*-NN′-*di*-(2-*chloropropyl*)*ethylenediamine* was an oil (Found : C, 65·5; H, 7·3. $C_{20}H_{26}N_2Cl_2$ requires C, 65·7; H, 7·2%).

NN′-*Diphenyl*-NN′-*di*-(3-*hydroxypropyl*)*ethylenediamine* (66% yield from 3-anilinopropanol) had m. p. 75° after crystallisation from benzene–light petroleum (b. p. 60—80°) (Found : C, 72·9; H, 8·8. $C_{20}H_{28}O_2N_2$ requires C, 73·2; H, 8·6%).

NN′-*Diphenyl*-NN′-*di*-(3-*chloropropyl*)*ethylenediamine* formed small prisms, m. p. 53·5—54°, after two crystallisations from pentane (Found : C, 66·1; H, 7·2. $C_{20}H_{26}N_2Cl_2$ requires C, 65·7; H, 7·2%).

NN′-*Diphenyl*-NN′-*di*-(4-*hydroxybutyl*)*ethylenediamine* (54% yield from 4-anilinobutanol) boiled at 220—240°/0·5 mm. and formed needles, m. p. 81°, from benzene–light petroleum (b. p. 60—80°) (Found : C, 74·1; H, 9·1. $C_{22}H_{32}O_2N_2$ requires C, 74·1; H, 9·1%).

NN'-*Diphenyl*-NN'-*di*-(4-*chlorobutyl*)*ethylenediamine* formed plates, m. p. 61°, from pentane (Found : C, 67·2; H, 8·1. $C_{22}H_{30}N_2Cl_2$ requires C, 67·2; H, 7·7%).

NN'-*Di*-(p-*methoxyphenyl*)-NN'-*di*-(2-*hydroxyethyl*)*ethylenediamine*, obtained in 62% yield from *N*-(2-hydroxyethyl)-*p*-anisidine (Ross, *J.*, 1949, 183), crystallised from benzene–light petroleum (b. p. 60—80°) in fine needles, m. p. 92—93° (Found : C, 66·2; H, 8·2. $C_{20}H_{28}O_4N_2$ requires C, 66·6; H, 7·8%).

NN'-*Di*-(p-*methoxyphenyl*)-NN'-*di*-(2-*chloroethyl*)*ethylenediamine* formed lustrous plates, m. p. 63—64° after crystallisation from light petroleum (b. p. 60—80°) (Found : C, 60·6; H, 6·4. $C_{20}H_{26}O_2N_2Cl_2$ requires C, 60·5; H, 6·6%).

NN'-*Di*-2-*naphthyl*-NN'-*di*-(2-*hydroxyethyl*)*ethylenediamine*. *NN'*-Di-2-naphthylethylenediamine (Bischoff and Hausdorfer, *Ber.*, 1890, **23**, 1985) (15 g.) was heated in a sealed tube with 5·5 c.c. of ethylene oxide and 5 c.c. of benzene for 12 hours at 160°. The residue obtained after evaporation of the solvent solidified and crystallised from benzene–light petroleum (b. p. 60—80°) in pearly plates, m. p. 96—97° (80%) (Found : C, 78·0; H, 7·1. $C_{26}H_{28}O_2N_2$ requires C, 78·0; H, 7·1%).

NN'-*Di*-2-*naphthyl*-NN'-*di*-(2-*chloroethyl*)*ethylenediamine* crystallised from benzene–light petroleum (b. p. 40—60°) in plates, m. p. 124—125° (Found : C, 71·5; H, 6·1. $C_{26}H_{26}N_2Cl_2$ requires C, 71·5; H, 6·0%).

NN'-*Di*-1-*naphthyl*-NN'-*di*-(2-*hydroxyethyl*)*ethylenediamine*, obtained in the same way as the 2-naphthyl derivative, formed plates, m. p. 92—93°, from benzene–light petroleum (Found : C, 78·1; H, 7·2. $C_{26}H_{28}O_2N_2$ requires C, 78·0; H, 7·1%). The *dipicrate* had m. p. 125° (Found : C, 53·3; H, 3·9. $C_{38}H_{64}O_{16}N_8$ requires C, 53·1; H, 4·0%).

NN'-*Di*-1-*naphthyl*-NN'-*di*-(2-*chloroethyl*)*ethylenediamine* crystallised from light petroleum (b. p. 60—80°) in stout prisms, m. p. 111° (Found : C, 71·6; H, 6·2. $C_{26}H_{26}N_2Cl_2$ requires C, 71·5; H, 6·0%).

The authors thank Miss K. Chilton and Miss J. Ross for the analyses. The investigation has been supported by grants from the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, the Anna Fuller Fund, and the Division of Research Grants and the U.S. Public Health Service.

THE CHESTER BEATTY RESEARCH INSTITUTE,
THE ROYAL CANCER HOSPITAL, FULHAM ROAD,
LONDON, S.W.3.

[*Received, January* 6*th*, 1950.]