Aryl-2-halogenoalkylamines. Part XV. Some Cationic and Basically Substituted Aryl Compounds.*

By F. Bergel, J. L. Everett, J. J. Roberts, and W. C. J. Ross.

[Reprint Order No. 6415.]

The preparation of some *p*-di-(2-chloroethyl)aminobenzene derivatives with side chains carrying basic and cationic groups is described.

In continuation of work described in Part XII (*J.*, 1953, 2386) which aimed at obtaining aryl-2-halogenoalkylamines of more selective action on neoplasms by incorporating into the molecule substituents which would modify the physical properties, a series of compounds possessing basic and cationic side-chains has now been prepared. The first group of compounds has the general formula (I) whilst the cationic derivatives are trimethylammonium iodides of general formula (II).

(I) $(Cl\cdot CH_2\cdot CH_2)_2N\cdot C_6H_4\cdot[CH_2]_n\cdot NR'R$ $(Cl\cdot CH_2\cdot CH_2)_2N\cdot C_6H_4\cdot[CH_2]_n\cdot NMe_3^+\}I^-$ (II)

The *p*-phenylenediamine derivative (I; $n = 0$, $R = R' = H$) was described in Part II (*J.*, 1949, 1972); the preparation of its *NN*-dimethyl derivative (I; $n = 0$, $R = R' = Me$) and the related trimethylammonium iodide (II; $n = 0$) is here reported.

p-Di-(2-chloroethyl)aminobenzylamine (I; $n = 1$, $R = R' = H$) was obtained by hydrogenation of the oxime of *p*-di-(2-chloroethyl)aminobenzaldehyde over a platinum catalyst; it was characterised as the monohydrochloride. Catalytic hydrogenation over Raney nickel of the Schiff's base obtained by condensing *p*-di-(2-chloroethyl)aminobenzaldehyde with methylamine afforded *p*-di-(2-chloroethyl)aminobenzylmethylamine (I; $n = 1$, $R = Me$, $R' = H$) and this on treatment with methyl iodide yielded the quaternary iodide (II; $n = 1$).

Nitration of *N*-phenethylsuccinimide gave the *p*-nitro-derivative which on hydrogenation over palladium–calcium carbonate afforded *N*-*p*-aminophenethylsuccinimide. This was converted into the di-(2-hydroxyethyl)amino- and di-(2-chloroethyl)amino-derivatives by the usual methods. Hydrolysis of the last compound by hot concentrated hydrochloric acid gave *p*-di-(2-chloroethyl)aminophenethylamine (I; $n = 2$, $R = R' = H$) which was isolated as the dihydrochloride monohydrate. The dichloroethyl derivative (I; $n = 2$, $R = R' = H$) was also prepared by an alternative route whereby *N*-*p*-nitrophenethylphthalimide formed the starting material and the aliphatic amino-group was throughout protected by the phthaloyl group. Somewhat better yields were obtained by this method.

On treatment of *N*-benzylidene-*p*-nitrophenethylamine with methyl iodide at 100°, a product was obtained which with hot acetic anhydride afforded *N*-acetyl-*N*-*p*-nitrophenethylmethylamine. This nitro-compound was hydrogenated over Raney nickel and the resultant *p*-amino-amide was converted into the di-(2-chloroethyl)amino-derivative in the usual manner. Removal of the acetyl group by acid gave *N*-[*p*-di-(2-chloroethyl)-aminophenethyl]methylamine (I; $n = 2$, $R = Me$, $R' = H$) which was characterised as the dihydrochloride.

p-Nitrophenethylamine yielded the *NN*-dimethyl derivative when treated with formaldehyde and formic acid. The *p*-amino-compound obtained by hydrogenation of this was converted successively into the *p*-di-(2-hydroxyethyl)amino- and the *p*-di-(2-chloroethyl)amino-compound (I; $n = 2$, $R = R' = Me$). The latter yielded the trimethylammonium iodide (II; $n = 2$).

Model experiments established that 2-*p*-acetamidophenoxyethyl bromide (III; R = NHAc) readily combined with trimethylamine, under conditions too mild for the reaction of a chloroethylarylamino-group, giving the quaternary salt (IV; R = NHAc). 2-*p*-Di-(2-hydroxyethyl)aminophenoxyethyl bromide [III; $R = N(CH_2\cdot CH_2\cdot OH)_2$]

* Part XIV, *J.*, 1955, 3110.

similarly gave *N*-[2-*p*-di-(2-hydroxyethyl)aminophenoxyethyl]trimethylammonium bromide [IV; R = $N(CH_2 \cdot CH_2 \cdot OH)_2$]. *N*-[2-*p*-Di-(2-chloroethyl)aminophenoxyethyl]-trimethylammonium bromide [IV; R = $N(CH_2 \cdot CH_2Cl)_2$] was not obtained by the action of phosphoryl chloride on the di(hydroxyethyl)amino-salt [IV; R = $N(CH_2 \cdot CH_2 \cdot OH)_2$] but was readily prepared from 2-*p*-di-(2-chloroethyl)aminophenoxyethyl bromide [III;

$R \cdot C_6H_4 \cdot O \cdot CH_2 \cdot CH_2Br$ (III) $\quad R \cdot C_6H_4 \cdot O \cdot CH_2 \cdot CH_2 \cdot NMe_3^+\}Br^-$ (IV) $\quad (X \cdot CH_2 \cdot CH_2)_2N \cdot C_6H_4 \cdot O \cdot CH_2 \cdot CH_2 \cdot NEt_2$ (V)

R = $N(CH_2 \cdot CH_2Cl)_2$] which was in turn derived from the di(hydroxyethyl) analogue [III; R = $N(CH_2 \cdot CH_2 \cdot OH)_2$]. The quaternary iodide was similarly prepared from the phenoxyethyl iodide. *NN*-Diethyl-*N*-[2-*p*-di-(2-hydroxyethyl)aminophenoxyethyl]-amine (V; X = OH), obtained by the action of diethylamine on the phenoxyethyl bromide, was readily converted into the di-(2-chloroethyl)amino-derivative (V; X = Cl).

Preliminary biological results indicate that whereas the primary amines (I; $n = 0$ and 2, R = R′ = H) are effective tumour-growth inhibitors, the tertiary amine (I; $n = 2$, R = R′ = Me) and the quaternary salts (II; $n = 2$) and [IV; R = $N(CH_2 \cdot CH_2Cl)_2$] are ineffective at the dose levels so far employed. This suggests that the un-ionised form of the amines is the active species but that conclusion is not supported by the dissociation constants of the series (I; $n = 2$). The pK_a's of the primary, secondary, and tertiary amines in this series (determined by potentiometric titration in water) are 9·7, 9·9, and 8·9 respectively. This indicates that a higher proportion of the active primary amine than of the inactive tertiary amine is in the cationic form at physiological pH.

It has not been possible to obtain rates of hydrolysis of the new compounds which can be directly compared with rates given in earlier Parts of this series, owing, in the case of the amines, to the instability (probably polymerisation) of the free bases when liberated from the hydrochlorides in aqueous solutions. The hydrolysis rates of the quarternary salts will be greatly influenced by the initial presence of the halide ions (cf. Part III, *J.*, 1949, 2589). The bromide [IV; R = $N(CH_2 \cdot CH_2Cl)_2$] and the corresponding iodide are hydrolysed to the extent of 35% and 30% respectively in 30 minutes under standard conditions.

A more complete account of the biological activity of the new compounds together with further physical measurements will be given elsewhere.

Experimental

NN-*Dimethyl*-p-*di*-(2-*chloroethyl*)*aminoaniline Dihydrochloride*.—A solution of *p*-di-(2-chloroethyl)aminoaniline hydrochloride (1·7 g.) and formaldehyde (5 ml. of 36% solution) in ethanol (40 ml.) containing platinum oxide (50 mg.) was shaken in an atmosphere of hydrogen for 12 hr. The filtered solution was saturated with anhydrous hydrogen chloride and then evaporated under reduced pressure. The *dihydrochloride* thus obtained formed prisms, m. p. 186—188°, from ether–ethanol (Found : C, 43·1; H, 6·2; N, 8·5. $C_{12}H_{18}N_2Cl_2$,2HCl requires C, 43·1; H, 6·0; N, 8·4%).

NNN-*Trimethyl*-p-*di*-(2-*chloroethyl*)*aminoanilinium Iodide*.—*p*-Di-(2-chloroethyl)aminoaniline hydrochloride (7 g.), methyl iodide (12 ml.), and sodium carbonate (6 g.) in ethanol (60 ml.) were heated on a steam-bath for 2 hr. The quaternary *iodide* which separated when the filtered solution was cooled formed plates, m. p. 145—146°, from ethanol (Found : C, 38·9; H, 5·5; N, 7·0. $C_{13}H_{21}N_2Cl_2I$ requires C, 38·7; H, 5·2; N, 7·0%).

p-*Di*-(2-*chloroethyl*)*aminobenzylamine Hydrochloride*.—Hydroxylamine hydrochloride (14·3 g.) and sodium acetate (16·6 g.) in water (50 ml.) were added to *p*-di-(2-chloroethyl)aminobenzaldehyde (Anker and Cook, *J.*, 1944, 489) (25 g.) in methanol (300 ml.). p-*Di*-(2-*chloroethyl*)-*aminobenzaldoxime* which separated overnight formed prisms, m. p. 104—106°, from benzene–light petroleum (b. p. 40—60°) (Found : C, 50·5; H, 5·6; N, 10·5. $C_{11}H_{14}ON_2Cl_2$ requires C, 50·6; H, 5·4; N, 10·7%). A solution of the oxime (1·9 g.) in methanol (50 ml.) was shaken in hydrogen over a platinum catalyst. The filtered solution was saturated with dry hydrogen chloride and diluted with dry ether. The p-*di*-(2-*chloroethyl*)*aminobenzylamine hydrochloride* (1·2 g.) thus obtained formed prisms, m. p. 218—221°, from ether–methanol (Found : C, 46·7; H, 6·0; N, 9·6. $C_{11}H_{17}N_2Cl_3$ requires C, 46·6; H, 6·0; N, 9·9%).

N-p-*Di*-(2-*chloroethyl*)*aminobenzylmethylamine Dihydrochloride*.—A mixture of ethanolic methylamine (1·2 ml.; 33% w/v) and *p*-di-(2-chloroethyl)aminobenzaldehyde (2·5 g.) in ethanol (30 ml.) was shaken at room temperature for 4 hr. Next day the filtered solution was evaporated under reduced pressure and the residual *N*-*p*-di-(2-chloroethyl)aminobenzylidenemethylamine was characterised by the preparation of its *picrate*, prisms, m. p. 164° (after sintering at 147°) (from ethanol) (Found: C, 44·6; H, 4·1; N, 14·0. $C_{18}H_{19}O_7N_5Cl_2$ requires C, 44·3; H, 3·9; N, 14·3%). The Schiff's base (1·8 g.), without further purification, was hydrogenated in ethanol (50 ml.) over Raney nickel. Dry hydrogen chloride was passed into the filtered solution which on dilution with dry ether afforded N-p-*di*-(2-*chloroethyl*)*aminobenzylmethylamine dihydrochloride* (0·7 g.), prisms, m. p. 165—170° (decomp.) (from ether–ethanol) (Found: C, 43·2; H, 6·5; N, 8·2. $C_{12}H_{18}N_2Cl_2$,2HCl requires C, 43·1; H, 6·1; N, 8·4%).

N-p-*Di*-(2-*chloroethyl*)*aminobenzyltrimethylammonium Iodide*.—A mixture of the above product (0·17 g.), methyl iodide (2 ml.), and sodium carbonate (0·5 g.) in ethanol (10 ml.) was kept at room temperature for 48 hr. On dilution of the filtered solution with ether the quaternary *salt*, which formed prisms, m. p. 164—167°, from methanol, was obtained (Found: C, 40·5; H, 5·9; H, 6·4. $C_{14}H_{23}N_2Cl_2I$ requires C, 40·3; H, 5·6; N, 6·7%).

N-p-*Aminophenethylsuccinimide*.—*N*-Phenethylsuccinimide (20 g.) was added to concentrated nitric acid (100 ml.), and the stirred mixture was kept at 20° for 5 hr. The solid which separated when the mixture was poured on crushed ice was extracted with *cyclo*hexane, and the residue was crystallised from benzene. The p-*nitro*-derivative formed prisms, m. p. 125—126° (Found: C, 58·1; H, 4·9; N, 11·5. $C_{12}H_{12}O_4N_2$ requires C, 58·1; H, 4·8; N, 11·3%). The p-*amino*-derivative obtained by hydrogenation of the nitro-compound over palladium–calcium carbonate in ethanol–ethyl acetate formed plates, m. p. 198°, from ethyl acetate (Found: C, 65·7; H, 6·6; N, 12·8. $C_{12}H_{14}O_2N_2$ requires C, 65·9; H, 6·5; N, 12·8%).

p-*Di*-(2-*chloroethyl*)*aminophenethylamine*.—Ethylene oxide (5 ml.) was added to *N*-*p*-aminophenethylsuccinimide (2 g.) dissolved in dilute acetic acid (20 ml., 50% v/v), and the mixture was stirred at 20°. After 18 hr. the product was isolated in the usual manner. N-p-*Di*-(2-*hydroxyethyl*)*aminophenethylsuccinimide* (yield, 0·7 g.) formed plates, m. p. 161—162°, from benzene (Found: C, 62·4; H, 7·3; N, 8·9. $C_{16}H_{22}O_4N_2$ requires C, 62·7; H, 7·2; N, 9·1%).

On treatment with phosphorus oxychloride in benzene solution this compound was converted into the *di*-(2-*chloroethyl*)*amino*-derivative, which formed platelets, m. p. 77°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 56·0; H, 6·0; N, 8·4; Cl, 20·5. $C_{16}H_{20}O_2N_2Cl_2$ requires C, 56·0; H, 5·9; N, 8·2; Cl, 20·7%). The di-(2-chloroethyl)amino-derivative (0·7 g.) was heated for 2 hr. with concentrated hydrochloric acid (4 ml.), and then the solution was evaporated to dryness under reduced pressure. The solid residue, crystallised from methanol–ethyl acetate, gave p-*di*-(2-*chloroethyl*)*aminophenethylamine dihydrochloride monohydrate*, m. p. 163° (Found: C, 40·9; H, 6·3; N, 8·0; Cl, 40·1. $C_{12}H_{18}N_2Cl_2$,2HCl,H_2O requires C, 40·9; H, 6·3; N, 8·0; Cl, 40·3%).

N-p-*Aminophenethylphthalimide*.—Phthalic anhydride (14 g.) was added to 2-*p*-nitrophenethylamine (16 g.) dissolved in benzene (30 ml.) and the mixture was shaken at room temperature for 2 hr. The solid which separated was crystallised from pentyl alcohol, giving N-p-*nitrophenethylphthalimide* (14 g.), as plates, m. p. 205—206° (Found: C, 64·7; H, 4·3; $C_{16}H_{12}O_4N_2$ requires C, 64·8; H, 4·1%).

Hydrogenation of the *p*-nitro-compound over palladium–calcium carbonate in methanol afforded N-p-*aminophenethylphthalimide* (9·0 g.), which formed cream-coloured needles, m. p. 162°, from benzene (Found: C, 72·2; H, 5·3. $C_{16}H_{14}O_2N_2$ requires C, 72·1; H, 5·4%).

N-p-*Di*-(2-*chloroethyl*)*aminophenethylphthalimide*.—The *p*-amino-compound (2·0 g.) was hydroxyethylated in the usual manner, giving the *di*-(2-*hydroxyethyl*)*amino*-derivative (1·1 g.), yellow needles, m. p. 140° (from benzene) (Found: 67·8; H, 6·4. $C_{20}H_{22}O_4N_2$ requires C, 67·8; H, 6·3%). This was converted into the corresponding *di*-(2-*chloroethyl*)*amino*-derivative (0·5 g.), which formed needles, m. p. 107—109°, from pentane (Found: C, 61·5; H, 5·3. $C_{20}H_{20}O_2N_2Cl_2$ requires C, 61·4; H, 5·2%). The *N*-*p*-di-(2-chloroethyl)aminophenethyl)-phthalimide (400 mg.) was heated under reflux for 3 hr. with concentrated hydrochloric acid (20 ml.). After removal of the phthalic acid which separated from the cooled solution the filtrate was evaporated under reduced pressure, the dihydrochloride monohydrate, m. p. 163° (230 mg.), described above, being obtained.

N-*Acetyl*-N-p-*nitrophenethylmethylamine*.—N-*Benzylidene*-p-*nitrophenethylamine* (23·2 g.), prepared by mixing *p*-nitrophenethylamine (16·8 g.) and benzaldehyde (10·6 g.), formed needles, m. p. 77°, from light petroleum (b. p. 60—80°) (Found: C, 70·8; H, 5·6; N, 11·5. $C_{15}H_{14}O_2N_2$ requires C, 70·8; H, 5·5; N, 11·0%). This derivative (5·8 g.) and methyl iodide

(2·8 g.) were heated together in a sealed tube at 100° for 5 hr. The product was dissolved in hot aqueous ethanol (95%; 20 ml.) and on the addition of ether (200 ml.) a hydriodide (5·2 g.), m. p. 145°, was precipitated. Heating the free base (obtained by treating the hydriodide with 2N-sodium carbonate) with acetic anhydride (4 vols.) gave N-*acetyl*-N-*nitrophenethylmethylamine*, m. p. 101°, needles (from *cyclo*hexane) (Found: C, 59·7; H, 6·4; N, 13·0. $C_{11}H_{14}O_3N_2$ requires C, 59·5; H, 6·4; N, 12·6%).

N-*Acetyl*-N-p-*aminophenethylmethylamine*.—The nitro-compound was hydrogenated in methanol over palladium–calcium carbonate. The *p*-amino-compound thus obtained formed a *hydrochloride*, m. p. 184°, plates from ether–methanol (Found: C, 50·1; H, 7·0; Cl, 26·0. $C_{11}H_{16}ON_2,2HCl$ requires C, 49·8; H, 6·8; Cl, 26·7%).

N-*Acetyl*-N-[p-*di*-(2-*chloroethyl*)*aminophenethyl*]*methylamine*.—The above amine (10 g.) was dissolved in 2N-acetic acid (100 ml.) containing ethylene oxide (10 ml.) and kept at room temperature overnight. The excess of ethylene oxide was then removed under reduced pressure and the product was extracted from the aqueous solution with ether after neutralisation with aqueous ammonia. The non-crystalline *N*-acetyl-*N*-[*p*-di-(2-hydroxyethyl)aminophenethyl]-methylamine (5 g.), dissolved in dry benzene (50 ml.), was heated under reflux with phosphorus oxychloride (10 ml.) for 30 min., after which the mixture was evaporated under reduced pressure. Concentrated hydrochloric acid (20 ml.) was added, the mixture was heated for 30 min. and then cooled, and the pH adjusted to 7 by the addition of aqueous 2N-ammonia. The liberated N-*acetyl*-N-[p-*di*-(2-*chloroethyl*)*aminophenethyl*]*methylamine* formed plates, m. p. 111°, from light petroleum (b. p. 60—80°) (Found: C, 56·9; H, 7·2. $C_{15}H_{22}ON_2Cl_2$ requires C, 56·8; H, 7·0%).

N-[p-*Di*-(2-*chloroethyl*)*aminophenethyl*]*methylamine*.—The preceding *N*-acetyl compound was (0·5 g.) heated under reflux with concentrated hydrochloric acid (10 ml.) for 3 hr. and then the solution was evaporated to dryness under reduced pressure (0·7 g.). Crystallising the residue from ether–ethanol gave the N-[p-*di*-(2-*chloroethyl*)*aminophenethyl*]*methylamine dihydrochloride* as plates, m. p. 196° (Found: C, 45·0; H, 6·6; N, 8·0; Cl, 39·3. $C_{13}H_{20}N_2Cl_2,2HCl$ requires C, 44·8; H, 6·4; N, 8·1; Cl, 40·7%).

N-p-*Aminophenethyldimethylamine*.—A mixture of *p*-nitrophenethylamine (8 g.), 90% formic acid (12 g.), and 35% formaldehyde (12 ml.) was kept at 40° until evolution of gas began and then left at room temperature for 24 hr. After addition of concentrated hydrochloric acid (60 ml.) the mixture was steam-distilled in order to remove formic acid and formaldehyde. Excess of sodium hydroxide was then added and the mixture again steam-distilled. The distillate, after addition of solid potassium hydroxide, was extracted with ether, and after evaporation of the ether the residue was passed in pentane down a short column of alumina. The oily main product (3 g.) on elution with pentane formed a picrate, m. p. 162° (prisms from benzene). The picrate of *p*-nitrophenethyldimethylamine prepared by Goss, Hanhart, and Ingold (*J.*, 1926, 256) by nitration of phenethyldimethylamine had the same m. p.

Catalytic hydrogenation of the *p*-nitro-compound (3 g.) over palladium–calcium carbonate in methanol gave 2-*p*-aminophenethyldimethylamine (2·5 g.), as an oil which formed a *picrate*, m. p. 150° (prisms from ethanol–benzene) (Found: C, 49·0; H, 4·8; N, 17·7. $C_{16}H_{19}O_7N_5$ requires C, 48·9; H, 4·8; N, 17·8%).

N-[p-*Di*-(2-*chloroethyl*)*aminophenethyl*]*dimethylamine*.—The di-(2-hydroxyethyl)amino-derivative (1·5 g.) obtained by treating the above *p*-amino-compound with ethylene oxide in the usual manner was heated with thionyl chloride (2 ml.) in benzene (20 ml.) for 1 hr. The solid which separated was collected and dissolved in water. Ammonia was added and the mixture was extracted with ether–benzene. The dried extract was evaporated and the residue was dissolved in pentane and passed down a short column of activated alumina. The eluates afforded the *di*-(2-*chloroethyl*)*amino*-compound as a light yellow oil (Found: C, 58·1; H, 7·5. $C_{14}H_{22}N_2Cl_2$ requires C, 58·2; H, 7·3%).

Heating this with an equal weight of methyl iodide in benzene for 5 min. gave the corresponding *trimethylammonium iodide*, m. p. 148—149° (from water) (Found: N, 6·3; total halogen, 45·3. $C_{15}H_{25}N_2Cl_2I$ requires N, 6·5; total halogen, 45·9%).

N-(2-p-*Acetamidophenoxyethyl*)*trimethylammonium Bromide*.—2-*p*-Acetamidophenoxyethyl bromide (200 mg.) and trimethylamine (2 ml.) in methanol (15 ml.) were heated in a sealed tube at 100° for 1 hr. On cooling to −10° the solution deposited a solid which was collected and washed with ether. The quaternary *bromide* had m. p. 235°, when precipitated from methanol by ether (Found: 48·8; H, 6·7; N, 8·8. $C_{13}H_{21}O_2N_2Br$ requires C, 49·2; H, 6·7; N, 8·8%).

N-[2-p-*Di*-(2-*hydroxyethyl*)*aminophenoxyethyl*]*trimethylammonium Bromide*.—A solution of 2-*p*-di-(2-hydroxyethyl)aminophenoxyethyl bromide (500 mg.) in methanol (6 ml.) containing

trimethylamine (3 ml.) was kept at room temperature for 48 hr. The oil which separated on addition of ether yielded a solid when rubbed with acetone. The quaternary *bromide* thus obtained formed small prisms, m. p. 112—113°, from ether–methanol (Found : C, 49·6; H, 7·6; N, 7·6. $C_{15}H_{27}O_3N_2Br$ requires C, 49·6; H, 7·5; N, 7·7%).

2-*Di*-(2-*chloroethyl*)*aminophenoxyethyl Bromide and Iodide*.—*p*-Di-(2-hydroxyethyl)aminophenoxyethyl bromide (5 g.) was heated for 2 hr. with phosphorus oxychloride (5 ml.) in dry benzene (20 ml.). The cooled solution was poured on ice, and the dried benzene layer was passed through activated alumina. The eluates contained 2-p-*di*-(2-*chloroethyl*)*aminophenoxyethyl bromide* (2·6 g.) which formed prisms, m. p. 79—80°, from light petroleum (b. p. 40—60°) (Found : C, 42·5; H, 4·9; N, 4·2. $C_{12}H_{16}ONCl_2Br$ requires C, 42·3; H, 4·7; N, 4·1%).

The bromide (340 mg.) was heated for 2 hr. in a solution of sodium iodide (200 mg.) in acetone (5 ml.). The *iodide* thus obtained formed needles, m. p. 75°, from light petroleum (b. p. 40—60°) (Found : C, 37·5; H, 4·4. $C_{12}H_{16}ONCl_2I$ requires C, 37·1; H, 4·2%).

N-[2-p-*Di*-(2-*chloroethyl*)*aminophenoxyethyl*]*trimethylammonium bromide* which formed plates, m. p. 114—116°, from methanol (Found : C, 44·8; H, 6·4; N, 6·9. $C_{15}H_{25}ON_2Cl_2Br$ requires C, 45·0; H, 6·3; N, 7·0%) and the corresponding *iodide*, needles, m. p. 139°, from ether–methanol (Found : C, 39·8; H, 6·1; N, 6·0. $C_{15}H_{25}ON_2Cl_2I$ requires C, 40·3; H, 5·6; N, 6·3%) were similarly prepared from the appropriate halides which are described above.

N-[2-p-*Di*-(2-*hydroxyethyl*)*aminophenoxyethyl*]*diethylamine*.—2-*p*-Di-(2-hydroxyethyl)aminophenoxyethyl bromide (5 g.) and diethylamine (5 ml.) in benzene (50 ml.) were heated under reflux for 17 hr. The solution was then washed with 2N-ammonia and water, dried, and evaporated. The oily diamine formed a *dipicrate*, m. p. 159—160°, as prisms from benzene–methanol (Found : C, 45·1; H, 5·0; N, 14·8. $C_{28}H_{34}O_{17}N_8$ requires C, 44·6; H, 4·5; N, 14·8%).

N-[2-p-*Di*-(2-*chloroethyl*)*aminophenoxyethyl*]*diethylamine*.—The above diamine (5 g.) was heated for 1 hr. in a solution of phosphorus oxychloride (5 ml.) in benzene (15 ml.). The solution was then evaporated under reduced pressure and this process was repeated twice after the addition of dry benzene (25 ml.). The residue was heated for 20 min. with concentrated hydrochloric acid (20 ml.), and the cooled solution was saturated with sodium acetate. The solution was extracted with chloroform and the aqueous layer was neutralised with sodium carbonate and again extracted. The combined chloroform extracts were dried and evaporated and a solution of the residue in light petroleum (b. p. 60—80°) was passed through alumina. The *di*-(2-*chloroethyl*)*amino*-compound was obtained as a straw-coloured oil (Found : N, 8·5; Cl, 21·6. $C_{16}H_{26}ON_2Cl_2$ requires N, 8·4; Cl, 21·2%). The diamine formed a *dihydrochloride*, prisms, m. p. 162—163°, from methanol–ether (Found : C, 46·9; H, 6·7; N, 7·1. $C_{16}H_{26}ON_2Cl_2$,2HCl requires C, 47·3; H, 6·9; N, 6·9%) and a *dipicrate*, prisms, m. p. 119—121°, from benzene (Found : N, 14·2. $C_{28}H_{32}O_{15}N_8Cl_2$ requires N, 14·2%).

Potentiometric titration of the diamine indicated that the pK_a of the basic groups were 3·1 and 8·2.

This investigation was supported by grants to this Institute from the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, the Anna Fuller Fund, and the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service. The authors thank Professor A. Haddow for permission to quote the results of tumour-inhibition studies.

THE CHESTER BEATTY RESEARCH INSTITUTE,
INSTITUTE OF CANCER RESEARCH : ROYAL CANCER HOSPITAL,
FULHAM ROAD, LONDON, S.W.3. [*Received, May 11th*, 1955.]