420. *Aryl-2-halogenoalkylamines. Part II.*

By J. L. Everett and W. C. J. Ross.

Ross (this vol., p. 183) described the preparation and some reactions of a series of aryl-2-halogenoethylamines. In view of the interesting biological activity of these compounds this work has now been extended. A further series of arylhalogenoethylamines and a number of arylhalogenopropylamines have been examined. The effect of structural modification on the reactivity of the halogen atoms (as measured by the rate of hydrolysis in aqueous acetone) is discussed.

Many aryldi-(2-halogenoethyl)amines, a number of which has recently been described (Ross, this vol., p. 183), show interesting biological properties, notably an inhibiting effect on the growth of certain transplantable rat tumours (*e.g.*, the Walker carcinoma : Haddow, Kon, and Ross, *Nature*, 1948, **162**, 824 ; British Empire Cancer Campaign Report for 1947). This work has now been extended.

The results so far obtained suggest that, in order to exhibit cytotoxic activity, the compound

must possess two reactive 2-halogenoalkyl groups attached to a nitrogen atom (though these need not necessarily be attached to the same nitrogen atom—see below), and that substitution in the aromatic nucleus tending to reduce the chemical reactivity of the halogen atoms (as measured by the rate of hydrolysis in aqueous acetone) also reduces the biological activity. Compounds with only one halogenoethylamino-group are inactive.

Most of the new *NN*-di-(2-halogenoethyl) compounds now described have been made by the general methods detailed in Part I; these derivatives are listed, together with related compounds, in Table I. For the preparation of aryl-di-(2-hydroxyethyl)amines the action of ethylene oxide on the amine is preferred since this leads to purer products: it has been found desirable to carry out the reaction at 150° with all amines as monosubstitution may occur at lower temperatures, particularly with the less basic amines.

The action of ethylene oxide on ethyl *p*-aminobenzoate yields the NN-*di*-(2-*hydroxyethyl*) derivative which has been converted into the corresponding *dichloro*-compound. This ester may be hydrolysed by use of concentrated hydrochloric acid to give the acid which was previously obtained by the oxidation of the aldehyde (Part I); esterification with diazomethane affords the *methyl* ester.

Benzenediazonium chloride couples with *NN*-di-(2-hydroxyethyl)aniline to form NN-*di*-(2-*hydroxyethyl*)-p-*aminoazobenzene* which may be converted into the *dichloro*-compound. This derivative may also be obtained by the direct coupling of benzenediazonium chloride with *NN*-di-(2-chloroethyl)aniline; p′-*nitro*-NN-*di*-(2-*chloroethyl*)-p-*aminoazobenzene* is similarly obtained from the amine and *p*-nitrobenzenediazonium chloride. These two azo-compounds were prepared with the intention of obtaining active coloured derivatives the location of which in the treated animal's tissue could be determined. The more intensely coloured *p*-nitro-compound was inactive but the other was effective, and it was considered possible that reduction of the azo-link might occur *in vivo*. It was therefore of interest to prepare and examine *NN*-di-(2-chloroethyl)-*p*-phenylenediamine.

Attempts to obtain this amine by the reduction of the azo-compound were unsuccessful owing to the difficulty of separating the two products which are formed. The desired *p*-amino-derivative was eventually obtained by the reduction of p-*nitroso*-NN-(2-*dichloroethyl*)*aniline* which could be prepared by direct nitrosation of the aniline in acid solution. *NN*-Di-(2-chloro-ethyl)-*p*-phenylenediamine was isolated as its *monohydrochloride*; this is a water-soluble substance of high toxicity and powerful vesicant action. *Acetyl* and *benzoyl* derivatives were prepared by the action of acetic anhydride and benzoyl chloride respectively on ice-cold aqueous suspensions of the free base.

It is known that, in the non-aromatic series of chloroethylamines, the two halogenoethylamino-groups essential for activity need not be situated on the same nitrogen atom, for example, *NN*′-di-(2-chloroethyl)piperazine is an effective compound. It was hoped to prepare derivatives of the phenylenediamines in which each nitrogen atom carried one chloroethyl group but this has not been possible on account of the unstable nature of the intermediate hydroxyethyl compounds which rapidly darken when exposed to air and which did not give homogeneous products when chlorinated. A compound of the desired structure was, however, obtained in the following way: *oo*′-dinitrodiphenyl was reduced with stannous chloride to give the diamine (an attempted reduction using a Raney nickel catalyst gave only benzcinnoline) which was converted successfully into the *bistoluene*-p-*sulphonamide*, the *dimethylbistoluene*-p-*sulphonamide*, and NN′-*dimethyl*-oo′-*diaminodiphenyl*. Chlorination of the NN′-*di*-(2-*hydroxyethyl*) derivative obtained by the action of ethylene oxide on this diamine afforded NN′-*dimethyl*-NN′-*di*-(2-*chloroethyl*)-oo′-*diaminodiphenyl*. This compound is not an effective tumour-growth inhibitor but it was later found that diphenyl derivatives as a class are not active, possibly on account of their very low water solubility, for example, NNN′N′-*tetra*-(2-*chloroethyl*)-oo′-*diaminodiphenyl* and -*pp*′-diaminodiphenyl (Part I) are also inactive.

It had previously been found that 2-aminofluorene reacts at 90° to give a monosubstituted product but when the reaction is carried out at a higher temperature NN-*di*-(2-*hydroxyethyl*)-2-*aminofluorene* is formed; this may be converted into the *dichloro*-derivative in the usual way.

The derivatives listed in Table I represent variations of the halogen in the side chain and also of the nature of the aromatic nucleus carrying this side chain. Attention has also been paid to varying the nature of the halogenoalkyl group. Table II shows a series of arylhalogenopropyl-amines and related compounds. 2-Halogeno-*n*-propyl derivatives were obtained by chlorinating the products of the reaction of arylamines with propylene oxide. It is known that in its reactions with amines propylene oxide undergoes ring opening almost exclusively in the direction leading to the formation of 2-hydroxy-*n*-propyl derivatives; in the case of disubstituted compounds

TABLE I.

Aryl-2-halogenoethylamines and related compounds.

Compound	M. p.	Crystal form	*S*	Formula	Found, % C	H	N	Required, % C	H	N
NN-*Di*-(2-*iodoethyl*)*aniline*	—	(Oil)	—	$C_{10}H_{13}NI_2$	(I = 62·8)			(I = 63·3)		
NN-*Di*-(2-*hydroxyethyl*)-p-tert.-*butylaniline* *	114—115°	Plates	C	$C_{14}H_{23}O_2N$	70·7	9·7	—	70·9	9·8	—
NN-*Di*-(2-*chloroethyl*)-p-tert.-*butylaniline* *	—	(Oil)	—	$C_{14}H_{21}NCl_2$	61·6	7·9	—	61·3	7·7	—
NN-*Di*-(2-*hydroxyethyl*)-vic.-m-*xylidine*	—	(Oil)	—	$C_{12}H_{19}O_2N$	68·9	9·2	—	69·0	9·2	—
NN-*Di*-(2-*chloroethyl*)-vic.-m-*xylidine*	32	Plates	D	$C_{12}H_{17}NCl_2$	58·8	6·9	—	58·5	7·0	—
p-*Nitroso*-NN-*di*-(2-*chloroethyl*)*aniline*	79—80	Deep green plates	F	$C_{10}H_{12}ON_2Cl_2$	48·8	5·1	11·6	48·6	4·9	11·3
NN-*Di*-(2-*chloroethyl*)-p-*phenylenediamine hydrochloride*	250—260 (decomp.)	Plates	A–F	$C_{10}H_{15}N_2Cl_3$	44·7	5·8	—	44·5	5·6	—
N′-*Acetyl*-NN-*di*-(2-*chloroethyl*)-p-*phenylenediamine*	124—126	Flattened needles	C–D	$C_{12}H_{16}ON_2Cl_2$	52·7	6·0	—	52·4	5·9	—
N′-*Benzoyl*-NN-*di*-(2-*chloroethyl*)-p-*phenylenediamine*	164—165	Fine needles	C	$C_{17}H_{18}ON_2Cl_2$	60·2	5·6	—	60·5	5·4	—
Methyl NN-*di*-(2-*chloroethyl*)-p-*aminobenzoate*	58	Plates	E	$C_{12}H_{15}O_2NCl_2$	52·2	5·7	—	52·2	5·5	—
Ethyl NN-*di*-(2-*hydroxyethyl*)-p-*aminobenzoate*	70	Small prisms	C	$C_{13}H_{19}O_4N$	61·7	7·2	—	61·6	7·6	—
Ethyl NN-*di*-(2-*chloroethyl*)-p-*aminobenzoate*	62	Flattened needles	G	$C_{13}H_{17}O_2NCl_2$	53·8	5·9	—	53·8	5·9	—
o-*Xenyldi*-(2-*hydroxyethyl*)*amine*	—	(Oil)	—	$C_{16}H_{19}O_2N$	74·7	7·5	—	74·7	7·4	—
o-*Xenyldi*-(2-*chloroethyl*)*amine*	61	Needles	D	$C_{16}H_{17}NCl_2$	65·0	5·9	4·7	65·3	5·8	4·8
o-*Xenyldi*-(2-*bromoethyl*)*amine*	81	Needles	E	$C_{16}H_{17}NBr_2$	50·5	4·7	—	50·2	4·5	—
o-*Xenyldi*-(2-*iodoethyl*)*amine*	112	Needles	H	$C_{16}H_{17}NI_2$	40·5	3·5	—	40·3	3·6	—
p-*Xenyldi*-(2-*bromoethyl*)*amine*	103	Plates	H	$C_{16}H_{17}NBr_2$	50·7	4·5	—	50·2	4·5	—
p-*Xenyldi*-(2-*iodoethyl*)*amine*	124	Plates	E	$C_{16}H_{17}NI_2$	41·0	3·7	—	40·3	3·6	—
NN′-*Dimethyl*-NN′-*di*-(2-*hydroxyethyl*)-oo′-*diaminodiphenyl*	75—76	Prisms	E	$C_{18}H_{24}O_2N_2$	71·6	8·1	—	71·9	8·1	—
NN′-*Dimethyl*-NN′-*di*-(2-*chloroethyl*)-oo′-*diaminodiphenyl*	41—43	Prisms	D	$C_{18}H_{22}N_2Cl_2$	64·3	6·4	—	64·1	6·6	—
NNN′N′-*Tetra*-(2-*chloroethyl*)-oo′-*diaminodiphenyl*	76—78	Prisms	A	$C_{20}H_{24}N_2Cl_4$	55·5	5·6	—	55·3	5·6	—
NN-*Di*-(2-*hydroxyethyl*)-p-*aminodiphenyl ether*	98	Plates	C	$C_{16}H_{19}O_3N$	70·0	7·2	—	70·3	7·0	—
NN-*Di*-(2-*chloroethyl*)-p-*aminodiphenyl ether*	—	(Oil)	—	$C_{16}H_{17}ONCl_2$	62·2	5·7	—	61·9	5·5	—
NN-*Di*-(2-*hydroxyethyl*)-p-*aminoazobenzene*	133—135	Deep orange plates	C	$C_{16}H_{19}O_2N_3$	67·9	6·5	—	67·4	6·7	—
NN-*Di*-(2-*chloroethyl*)-p-*aminoazobenzene*	73—75	Pale orange plates	D	$C_{16}H_{17}N_3Cl_2$	59·7	5·4	13·4	59·6	5·3	13·1
p′-*Nitro*-NN-*di*-(2-*chloroethyl*)-p-*aminoazobenzene*	166—167	Deep red plates	I	$C_{16}H_{16}O_2N_4Cl_2$	52·5	4·5	15·2	52·3	4·4	15·3
NN-*Di*-(2-*hydroxyethyl*)-m-*aminostilbene* *	100—101	Cream plates	C	$C_{18}H_{21}O_2N$	76·5	7·4	—	76·3	7·5	—
NN-*Di*-(2-*chloroethyl*)-m-*aminostilbene* *	64—65	Felted needles	D	$C_{18}H_{19}NCl_2$	67·8	5·6	—	67·5	6·0	—
NN-*Di*(-2-*bromoethyl*)-m-*aminostilbene*	67	Plates	D	$C_{18}H_{19}NBr_2$	53·2	4·7	—	52·9	4·7	—
NN-*Di*-(2-*iodoethyl*)-m-*aminostilbene*	95	Needles	E	$C_{18}H_{19}NI_2$	43·3	4·0	—	43·0	3·8	—
NNN′N′-*Tetra*-(2-*hydroxyethyl*)-pp′-*diaminostilbene* *	194—195	Pale yellow plates	B–J	$C_{22}H_{30}O_4N_2$	67·9	8·1	—	68·3	7·8	—
α-*Naphthyldi*-(2-*bromoethyl*)*amine*	43	Thick needles	G	$C_{14}H_{15}NBr_2$	47·4	4·4	—	47·1	4·2	—
α-*Naphthyldi*-(2-*iodoethyl*)*amine*	60	Needles	G	$C_{14}H_{15}NI_2$	37·8	3·6	—	37·3	3·4	—
β-*Naphthyldi*-(2-*bromoethyl*)*amine*	60—62	Plates	D	$C_{14}H_{15}NBr_2$	47·3	4·2	—	47·1	4·2	—
β-*Naphthyldi*-(2-*iodoethyl*)*amine*	73—75	Felted needles	D	$C_{14}H_{15}NI_2$	37·3	3·0	—	37·3	3·4	—
4-*Benzeneazo*-α-*naphthyl*-NN-*di*-(2-*chloroethyl*)*amine*	—	(Oil)	—	$C_{20}H_{19}N_3Cl_2$	64·7	5·5	—	64·5	5·2	—
NN-*Di*-(2-*hydroxyethyl*)-2-*aminofluorene*	137	Small plates	C	$C_{17}H_{19}O_2N$	76·2	7·2	—	75·8	7·1	—
NN-*Di*-(2-*chloroethyl*)-2-*aminofluorene*	138	Plates	C	$C_{17}H_{17}NCl_2$	66·7	5·5	—	66·7	5·6	—

Solvents (*S*) used for crystallisation are: A, methanol; B, ethanol; C, benzene; D, light petroleum (b. p. 40—60°); E, light petroleum (b. p. 60—80°); F, ether; G, pentane; H, *cyclo*hexane; I, acetone; J, water. Since decomposition usually occurs on distillation, no b. p.s are given for the oily materials; the preparations were deemed satisfactory if good analytical figures were obtained for the product.

* These compounds in Tables I and II were prepared by Mr. R. G. W. Spickett who also prepared *NN*-di-(2-chloro-1-*cyclo*hexyl)aniline and assisted in the preparation of the two β-naphthylchloropropylamines by method *b*.

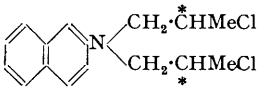
TABLE II.

Arylhalogenopropylamines and related compounds.

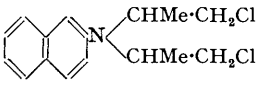
Compound	M. p.	Crystal form	*S*	Formula	Found, % C	Found, % H	Found, % N	Required, % C	Required, % H	Required, % N
N-*Ethyl*-N-(2-*hydroxy*-n-*propyl*)*aniline picrate*	124°	Flattened needles	A	$C_{17}H_{20}O_8N_4$	50·0	5·0	14·4	50·0	4·9	13·7
N-*Ethyl*-N-(2-*chloro*-n-*propyl*)*aniline picrate*	107—108	Needles	A	$C_{17}H_{19}O_7N_4Cl$	48·0	4·7	13·2	47·9	4·5	13·1
NN-*Di*-(2-*chloro*-n-*propyl*)*aniline*	62— 64	Prisms	D	$C_{12}H_{17}NCl_2$	58·8	6·8	—	58·5	7·0	—
p-*Chloro*-NN-*di*-(2-*hydroxy*-n-*propyl*)*aniline*	109—110	Flattened needles	C–E	$C_{12}H_{18}O_2NCl$	59·1	7·5	—	59·2	7·4	—
p-*Chloro*-NN-*di*-(2-*chloro*-n-*propyl*)*aniline*	109—110	Long needles	D	$C_{12}H_{16}NCl_3$	51·8	5·8	5·2	51·4	5·8	5·0
NN-*Di*-(2-*chloro*-n-*propyl*)-p-*anisidine*	68— 70	Thick plates	A	$C_{13}H_{19}ONCl_2$	56·5	7·0	—	56·5	6·9	—
p-*Xenyldi*-(2-*hydroxy*-n-*propyl*)*amine*	117—119	Small prisms	C–E	$C_{18}H_{23}O_2N$	76·0	8·0	—	75·8	8·1	—
p-*Xenyldi*-(2-*chloro*-n-*propyl*)*amine*	94— 97	Prisms	D	$C_{18}H_{21}NCl_2$	67·1	6·6	4·5	67·1	6·6	4·3
p-*Xenyldi*-(2-*bromo*-n-*propyl*)*amine*	84	Needles	D	$C_{18}H_{21}NBr_2$	52·7	5·2	—	52·6	5·2	—
NNN′N′-*Tetra*-(2-*chloro*-n-*propyl*)*benzidine*	112	Plates	E	$C_{24}H_{32}N_2Cl_4$	58·6	6·6	5·8	58·8	6·6	5·7
NN-*Di*-(2-*hydroxy*-n-*propyl*)-p-*aminostilbene*	132	Short needles	C	$C_{20}H_{25}O_2N$	77·2	7·9	—	77·1	8·1	—
NN-*Di*-2-(*chloro*-n-*propyl*)-p-*aminostilbene*	93	Short needles	E	$C_{20}H_{23}NCl_2$	67·2	6·6	—	67·0	6·5	—
α-*Naphthyldi*-(2-*hydroxy*-n-*propyl*)*amine*	134—136	Small prisms	C	$C_{16}H_{21}O_2N$	73·9	8·2	—	74·1	8·2	—
α-*Naphthyldi*-(2-*chloro*-n-*propyl*)*amine*	—	(Oil)	—	$C_{16}H_{19}NCl_2$	65·0	6·4	—	64·9	6·5	—
					(Cl = 23·8)			(Cl = 23·9)		
β-*Naphthyldi*-(2-*hydroxy*-n-*propyl*)*amine A* *	111	Plates	E	$C_{16}H_{21}O_2N$	74·5	8·3	—	74·1	8·2	—
Trinitrobenzene complex thereof *	154—155	Purple needles	C–E	$C_{22}H_{24}O_8N_4$	—	—	11·9	—	—	11·9
β-*Naphthyldi*-(2-*chloro*-n-*propyl*)*amine A*	102	Prisms	D	$C_{16}H_{19}NCl_2$	64·7	6·5	—	64·9	6·5	—
β-*Naphthyldi*-(2-*hydroxy*-n-*propyl*)*amine B* *	100—101	Plates	D	$C_{16}H_{21}O_2N$	73·9	8·3	—	74·1	8·2	—
β-*Naphthyldi*-(2-*chloro*-n-*propyl*)*amine B*	82	Prisms	D	$C_{16}H_{19}NCl_2$	64·6	6·3	—	64·9	6·5	—
NN-*Di*-(3-*hydroxy*-n-*propyl*)*aniline*	60	Plates	C	$C_{12}H_{19}O_2N$	69·0	9·1	—	68·9	9·2	—
NN-*Di*-(3-*chloro*-n-*propyl*)*aniline*	—	(Oil)	—	$C_{12}H_{17}NCl_2$	(Cl = 29·0)			(Cl = 28·8)		
Picrate thereof	129—130	Prisms	C	$C_{18}H_{20}O_7N_4Cl_2$	45·4	4·4	—	45·5	4·3	—
NN-*Di*-(3-*bromo*-n-*propyl*)*aniline*	—	(Oil)	—	$C_{12}H_{17}NBr_2$	(Br = 48·0)			(Br = 47·7)		
Picrate thereof	138	Prisms	C	$C_{18}H_{20}O_7N_4Br_2$	38·5	3·7	—	38·3	3·6	—
NN-*Di*-(3-*iodo*-n-*propyl*)*aniline*	48	Prisms	E	$C_{12}H_{17}NI_2$	33·6	3·9	—	33·6	4·0	—
					(I = 60·0)			(I = 59·2)		
NN-*Di*-(3-*chloro*-2-*hydroxy*-n-*propyl*)-p-*anisidine*	109—111	Prismatic needles	C	$C_{13}H_{19}O_3NCl_2$	51·1	6·2	—	50·7	6·2	—
NN-*Di*-(2 : 3-*dichloro*-n-*propyl*)-p-*anisidine*	—	(Oil)	—	$C_{13}H_{17}ONCl_4$	(Cl = 41·0)			(Cl = 41·1)		
NNN′N′-*Tetra*-(3-*chloro*-2-*hydroxy*-n-*propyl*)-p-*phenylenediamine*	130	Small needles	C	$C_{18}H_{28}O_4N_2Cl_4$	45·4	5·6	—	45·2	5·9	—

Solvents (*S*) as in Table I.

the molecule will contain two asymmetric carbon atoms and normally a mixture of products is to be expected. Generally the hydroxypropyl derivatives were not obtained in a solid form but it was usually possible to prepare crystalline chloro-compounds : many of these do not melt sharply and thus probably consist of a mixture of stereoisomers. In the case of the product derived from β-naphthylamine two compounds were separated—these are regarded as the racemic and the *meso*-form of β-*naphthyldi*-(2-*chloro*-n-*propyl*)*amine* (I). The possibility that one of these products might be a 1-chloro-2-propyl derivative (II) formed by a different direction of ring opening appears to be ruled out by the preparation of both isomers by chlorinating the hydroxypropyl derivatives obtained when 1-bromopropan-2-ol reacts with β-naphthylamine. Further evidence that both isomers are *n*-propyl derivatives is afforded by the hydrolysis reactions described below.



(I.)



(II.)

Attempts to prepare the 2-chloro*iso*propyl derivative (II) by condensing 2-chloro-1-acetoxypropane with β-naphthylamine have been unsuccessful. It is difficult to introduce two α-substituted alkyl groups on to the nitrogen atom of an arylamine, for example, whereas phenylglycine condenses with chloroacetic acid to give phenyliminodiacetic acid (Vorlander and Mumme, *Ber.*, 1901, **34**, 1647), *N*-β-naphthylalanine ethyl ester would not react with α-bromopropionic ester under any of the conditions tried—the product could have been reduced, either by means of sodium and alcohol or catalytically, to give the required *iso*propyl compound. The α-methyl group of the ethyl ester of β-naphthylalanine probably reduces the reactivity of the amino-nitrogen atom by a steric hindering effect; the ester could not be induced to react with ethylene oxide at a high temperature.

Aniline condenses with 3-chloropropan-1-ol to give a hydroxy-*n*-propyl derivative which on chlorination yields NN-*di*-(3-*chloro*-n-*propyl*)*aniline*. Epichlorohydrin condenses with the more basic aromatic amines affording disubstituted products; for example, Strukov (*Khim. Farm. Prom.*, 1934, No. 2, 11 ; *Chem. Abs.*, 1934, **28**, 5421) describes the reaction with *p*-phenetidine hydrochloride. Similarly *p*-anisidine yields NN-*di*-(3-*chloro*-2-*hydroxy*-n-*propyl*)-p-*anisidine* and this has now been converted into the corresponding 2 : 3-*dichloro*-n-*propyl* derivative. *p*-Phenylenediamine dihydrochloride reacts in aqueous solution to give NNN'N'-*tetra*-(3-*chloro*-2-*hydroxy*-n-*propyl*)-p-*phenylenediamine* which is very sensitive to oxidation ; for example, it gives a deep blue colour with a trace of nitrate ions; it has not been possible to convert this into the 2 : 3-dichloro-derivative.

Several unsuccessful attempts have been made to prepare *NN*-di-(4-chloro-*n*-butyl)aniline. The condensation of 4-chlorobutan-1-ol with aniline on one occasion gave 1-phenylpyrrolidine whilst another experiment gave mainly N-(4-*hydroxy*-n-*butyl*)*aniline*. When this monohydroxy-compound was treated with a further quantity of chlorobutanol in aqueous chalk suspension all the alcohol was converted into tetrahydrofuran and none reacted with the amine. When aniline reacted with 4-chloro-1-acetoxybutane the monohydroxybutyl derivative and acetanilide were the only identifiable products. On the other hand aniline condensed normally with 6-chlorohexan-1-ol and chlorination of the *di*(*hydroxy*-n-*hexyl*) derivative thus obtained afforded NN-*di*-(6-*chloro*-n-*hexyl*)*aniline*.

Contrary to the findings of Brunel (*Ann. Chim.*, 1905, **6**, 200), who stated that *cyclo*hexene oxide would only react with aniline to give a mono-substituted product whatever the proportions or the temperature, we have now obtained NN-*di*-(2-*hydroxy*-1-cyclo*hexyl*)*aniline*, chlorination of which yields the *di*-(2-*chloro*-1-cyclo*hexyl*) derivative.

Table III shows the extent of the hydrolysis of a selection of the new arylhalogenoalkylamines in unbuffered aqueous acetone solutions under the standard conditions already described (Part I). The more insoluble compounds had to be hydrolysed at higher dilutions than in the standard procedure and the figures are not strictly comparable though the deviation is relatively small and the effects of the various structural modifications are readily apparent.

The higher rate of hydrolysis of the chloroethyl groups in *NN'*-dimethyl-*NN'*-di-(2-chloroethyl)-*oo'*-diaminodiphenyl as compared with those in *NNN'N'*-tetra-(2-chloroethyl)-*oo'*-diaminodiphenyl confirms the finding that in *NN*-di-(2-chloroethyl) derivatives the mutual effect of the chlorine atoms is to decrease the negative charge on each. The ratio of the rates of hydrolysis for the diphenyl compounds (22 : 56) is almost identical with that previously found for the corresponding aniline derivatives (20 : 58).

TABLE III.

Compound (0·5 millimoles)	Vol. of acetone : water (ml.)	% Hydrolysis in 30 mins. at 66°
NN-Di-(2-chloroethyl)-*p*-*tert*.-butylaniline	25 : 25	29
Ethyl *NN*-di-(2-chloroethyl)-*p*-aminobenzoate	25 : 25	1·5
N'-Acetyl-*NN*-di-(2-chloroethyl)-*p*-phenylenediamine	25 : 25	41
p-Chloro-*NN*-di-(2-bromoethyl)aniline	25 : 25	66
o-Xenyldi-(2-chloroethyl)amine	50 : 50	31
o-Xenyldi-(2-bromomethyl)amine	50 : 50	94
p-Xenyldi-(2-chloroethyl)amine	50 : 50	12
p-Xenyldi-(2-bromoethyl)amine	50 : 50	70
NN'-Dimethyl-*NN'*-di-(2-chloroethyl)-*oo'*-diaminodiphenyl	35 : 35	56
NNN'N'-Tetra-(2-chloroethyl)-*oo'*-diaminodiphenyl	35 : 35	22
N-Ethyl-*N*-(2-chloro-*n*-propyl)aniline (as picrate)	60 : 60	99
NN-Di-(2-chloro-*n*-propyl)aniline	25 : 25	90
α-Naphthyldi-(2-chloro-*n*-propyl)amine	35 : 35	96
β-Naphthyldi-(2-chloro-*n*-propyl)amine A	35 : 35	82
β-Naphthyldi-(2-chloro-*n*-propyl)amine B	35 : 35	88
NN-Di-(2-chloro-*n*-propyl)-*p*-anisidine	25 : 25	100
p-Chloro-*NN*-di-(2-chloro-*n*-propyl)aniline	30 : 30	64
p-Xenyldi-(2-chloro-*n*-propyl)amine	50 : 50	85
p-Xenyldi-(2-bromo-*n*-propyl)amine	50 : 50	100
NN-Di-(3-chloro-2-hydroxy-*n*-propyl)-*p*-anisidine	25 : 25	4 (8 in 120 mins.)
NN-Di-(2 : 3-dichloro-*n*-propyl)-*p*-anisidine	25 : 25	34
NN-Di-(3-chloro-*n*-propyl)aniline	25 : 25	(1 in 60 mins.) (3 in 120 mins.) (16 in 360 mins.)
NN-Di-(3-bromo-*n*-propyl)aniline	40 : 40	9
NN-Di-(3-iodo-*n*-propyl)aniline	50 : 50	23

All the 2-chloro-*n*-propyl compounds hydrolyse much faster than the corresponding 2-chloroethyl derivatives. The effect of placing a methyl group on the 2-carbon atom, thus making the compounds secondary chloro-derivatives, has a far greater effect on the activity of the halogen atom than any substitution in the aromatic nucleus. Nevertheless the variation in velocity of reaction in the substituted *NN*-di-(2-chloro-*n*-propyl)anilines is still discernible as follows :

$$p\text{-MeO} > \text{H} > p\text{-Ph} > p\text{-Cl}$$

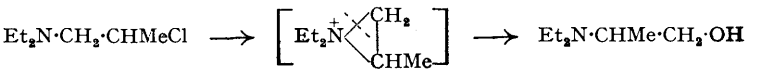
The two *NN*-di-(2-chloro-*n*-propyl)-β-naphthylamines have a similar high rate of hydrolysis; it is doubtful whether a 2-chloro*iso*propyl derivative, which does not contain a secondary chlorine atom, would hydrolyse at this greatly increased rate. This evidence would seem to confirm the formulation of both the naphthylamine compounds as (I).

Whilst the introduction of a 2-methyl group into *NN*-di-(2-chloroethyl)-*p*-anisidine (58% hydrolysed under the standard conditions) has the expected activating effect on the chlorine atoms, the introduction of a 2-chloromethyl group reduces the activity of the original halogen atom even though this atom is now secondary. This is another instance of the mutual effect of chlorine atoms reducing the negative charge on each other and hence their reactivity.

Increasing the distance of the chlorine atom from the nitrogen atom has the expected effect of reducing the rate of hydrolysis, thus the chlorine atoms in *NN*-di-(3-chloro-*n*-propyl)- and *NN*-di-(6-chloro-*n*-hexyl)-aniline are not appreciably hydrolysed under the standard conditions.

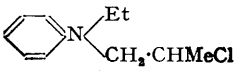
In Part I it was stated that the course of the hydrolysis of *NN*-di-(2-bromoethyl) and *NN*-di-(2-iodoethyl) compounds was complex and appeared to resemble that of the aliphatic " nitrogen-mustards." This conclusion was suggested by the fact that, during the hydrolysis, halide ions seemed to be liberated at a greater rate than hydrogen ions : this indicated the production of quaternary nitrogen atoms in the solution as is the case with the aliphatic compounds. It has since been established that the rate of elimination of halide ions and hydrogen ions is practically identical in the hydrolyses of the bromo- and iodo-derivatives. The higher values for the ionic halogen previously obtained were due to the fact that these compounds hydrolyse quite rapidly even in the cold in the presence of silver nitrate—it has now been established that the increased rate of hydrolysis is caused by the precipitation of halide ions which were previously able to convert some of the carbonium ion (see below) back into the alkyl halide. This effect is most marked in the case of the iodo-compounds but may also be discerned by a drifting end point in the titration of the more rapidly hydrolysed bromo-derivatives. Rapid titration of a well-cooled solution indicates that the halide and hydrogen ion titres are almost identical.

There is good evidence for the existence of ethyleneiminium ions in aqueous solution of the aliphatic chloroalkylamines (Golumbic, Fruton, and Bergmann, *J. Org. Chem.*, 1946, **11**, 518; Hanby, Hartley, Powell, and Rydon, *J.*, 1947, 519). Briefly the existence of these ions is based on (*a*) the rapid elimination, in such solutions, of one equivalent of chloride ion but only traces of hydrogen ion; (*b*) the rapid reaction of the solution with sodium thiosulphate—this reaction is considered to be due to the presence of an ethyleneiminium ion and the so-called instantaneous thiosulphate titre is used as a measure of the concentration of this ion; (*c*) the re-arrangement during hydrolysis of (III) to (V) which is readily interpreted if the ion (IV) is an intermediate and that subsequent re-opening of the ring occurs in a different direction from its formation (S. D. Ross, *J. Amer. Chem. Soc.*, 1947, **69**, 2982).

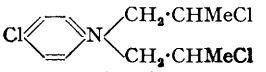


(III.) (IV.) (V.)

There is no such evidence for the existence of an ion of this type during the hydrolysis of the aromatic nitrogen mustards since (*a*) the rates of production of halide and of hydrogen ions are at all times equal; (*b*) the instantaneous thiosulphate titre is negligible; (*c*) compounds (VI) and (VII) have been shown to hydrolyse without change in structure.



(VI.)

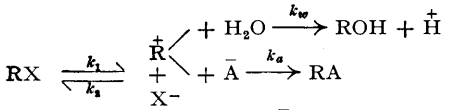


(VII.)

The formation of ethyleneiminium ions and cyclic dimers involves internal or mutual quaternisation. Such quaternisation would appear to be less likely in the case of the feebly basic aromatic derivatives and no dimers have been isolated as yet. It has also proved impossible to prepare quaternary salts by heating any arylhalogenoamine with methyl iodide.

It is fully realised that the evidence presented here only indicates that there can never be any appreciable concentration of an ethyleneimonium ion in aqueous acetone solutions but it does not entirely rule out the possibility of the transitory existence of such ions particularly in wholly aqueous solutions which cannot readily be studied on account of the low water solubility of the compounds.

The relative reactivity of arylhalogenoalkylamines with the various ions and groups likely to be encountered in cellular fluids is of considerable biological significance. The effect of adding salts of organic acids to hydrolysing solutions of the halides has been studied. It was shown in Part I that these hydrolyses proceed by an S_N1 mechanism, and in the presence of an added anion the course of the reaction can be represented as



(where RX = halide, $\bar{A}$ = anion).

The proportion of ROH and RA formed will depend on the magnitude of the rate constants k_w and k_a. The extent of the re-formation of RX (the arylhalogenoalkylamine) will not affect the ratio of the amounts of end products since the halide formed eventually re-ionises and is distributed between the added anion and water. In the earlier experiments on the hydrolysis of the halides in aqueous acetone the sodium hydroxide titre measured the extent of the reaction of $\overset{+}{R}$ with water and the silver nitrate titre measured the extent of the ionisation of the halide. The identity of these two values showed that all the $\overset{+}{R}$ reacted with water and none was involved in quaternary-salt formation. In the presence of added anions these two values will no longer be identical since the reaction of $\overset{+}{R}$ with the anion no longer leads to the production of titratable acid. It can be seen that the extent of the formation of ROH is still measured by the sodium hydroxide titre and the extent of the formation of RA by the difference in the sodium hydroxide and silver nitrate titres. The results obtained in some preliminary experiments made by adding sodium acetate to solutions in which β-naphthyldi-(2-chloroethyl)amine was hydrolysing are shown in Table IV. The ratio of the amounts of ROAc and ROH formed in this experiment

TABLE IV.

Hydrolysis of β-naphthyldi-(2-chloroethyl)amine at 66°.

A, 2 Millimols of amine dissolved in 100 c.c. each of acetone and water (c = 0·01M.). *B*, As *A* with the addition of 40 millimols of sodium acetate (c = 0·20M.).

	*A.**		*B.**		
Time, hours	$\overset{+}{H}$, %	$\overset{-}{Cl}$, %	$\overset{+}{H}$, %	$\overset{-}{Cl}$, %	$\overset{-}{Cl}$, % − $\overset{+}{H}$, %
½	13	13·25	1·3	13	11·7
1	20·75	21·0	2·2	23·3	21·1
4	49·7	49·7	6·5	65·3	58·8

* Based on the replacement of two chlorine atoms.

are: after ½ hour, 9·0; after 1 hour 9·6; after 4 hours 9·1. If this ratio is divided by the concentration of the acetate one obtains a figure which is practically identical with the "competition factor" described by Ogston (*Biochem. Soc. Symposium* No. 2, p. 2). This factor is such that its reciprocal gives the concentration at which the anion must be present—in our experiments in a mixture of equal volumes of acetone and water—so that half of the halide shall react with the anion. From Table IV it can be deduced that at a concentration of 0·2M. the competition factor of the acetate ion is 45·5 (based on the 4-hour titration figures which can be measured with greater accuracy). It is intended to compile a table of competition factors for the arylhalogenoalkylamines similar to that given by Ogston (*loc. cit.*) for di-(2-chloroethyl) sulphide. It will be necessary to examine the effect of varying the pH on the rate of hydrolysis of these halides since acid is produced and salts of different anions will buffer the solutions to different extents. It is, however, possible at the moment to compare the competition factors of different halides with a single anion; a few values for the acetate ion are given in Table V.

TABLE V.

Compound	Competition factor for acetate ions ([NaOAc] = 0·2M. in 1 : 1 acetone–water)	% Hydrolysis in ½ hr. at 66° in acetone–water (Part I)
β-Naphthyldi-(2-chloroethyl)amine	47	15
β-Naphthyldi-(2-bromoethyl)amine	50	80
NN-Di-(2-chloroethyl)-*p*-toluidine	52	38
NN-Di-(2-chloroethyl)-*p*-anisidine	57	58
N-Ethyl-*N*-2-chloroethylaniline	57	58
β-Naphthyldi-(2-chloro-*n*-propyl)amine A	14	82
β-Naphthyldi-(2-chloro-*n*-propyl)amine B	14	88
NN-Di(2-chloro-*n*-propyl)aniline	13	90
NN-Di-(2-chloro-*n*-propyl)-*p*-anisidine	15	100

The values of the competition factor of a chloroethylamine do not vary a great deal from compound to compound even though the rates of hydrolysis of the derivatives vary considerably. It is particularly interesting to note that in the case of the two β-naphthyl-halogenoethylamines the factor is almost the same for the chloro- and bromo-compounds; this is to be expected if an S_N1 mechanism is operating, for the ratio of the end products will depend on the carbonium ion and should be independent of the halogen (compare Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 1005). The fact that the aniline derivative which contains a single chloroethyl group has practically the same factor as the disubstituted compounds, supports the view that each chloroethyl group can react independently. The dependence of biological activity on the presence of two halogenoalkyl groups would not appear to be connected with any mutual effect on their ability to react with organic anions.

The substitution of the 2-carbon atom in the halogenoethyl compounds with a methyl group, besides having a large effect on the rate of hydrolysis of the derivative, also greatly influences the competition factor, for under comparable conditions the chloro-*n*-propylamines will react with about one-quarter to one-third as much acetate ion as the chloroethylamines. Further, the two isomeric β-naphthyl(chloro-*n*-propyl)amines have identical factors—another indication that they are stereoisomers and not structural isomers.

There is a further difference between the aliphatic and the aromatic chloroethylamines, namely, in their hydrolyses in the presence of acetate ions. Fruton, Stein, and Bergmann (*J. Org. Chem.*, 1946, **11**, 567) state that there is no evidence of ester formation when methyl- or ethyl-di-(2-chloroethyl)amine hydrolyses in the presence of sodium acetate. This they

ascribe to the rapid hydrolysis of any ester that might be formed. It has been established that β-*naphthyldi-*(2-*acetoxyethyl*)*amine* is not hydrolysed under the conditions of the determination of the competition factor. This difference between the chloroalkylamines suggests that the aromatic derivatives would form more stable products when they interact with carboxyl groups in biological material.

The structural requirements for activity in the halogenoalkylamines—two reactive groups in the molecule—suggested that other compounds containing two groupings capable of reacting with functional centres of biological systems might be effective as cytotoxic agents. It is well known that iodoacetyl groups react with thiols even more readily than the sulphur and nitrogen mustards and so it was considered of interest to prepare and examine NN′-*di*(*iodoacetyl*)-o-*phenylenediamine*. Although this compound does not appreciably inhibit the growth of the transplanted Walker tumour under our conditions of test it does produce similar effects on chromosomes (*e.g.*, breakage and anaphase bridging in epithelial cells of the newt, *Triturus palmatus*) to those obtained with the nitrogen-mustards (private communication from Mr. A. Loveless of this Institute). This result suggests that it would be desirable to test other compounds containing two reactive groups in the molecule : this line of approach is now being pursued.

Experimental.

Preparation of Arylhalogenoethylamines.—For the preparation of the hydroxyethyl compounds it has been found preferable to use Method A (Part I), heating the sealed tubes to 150° in all cases. Conversion into the halogeno-derivatives was carried out as before; the yield of chloro-compound was generally about 50%, and lower yields of bromo- and iodo-compounds were obtained. During the bromination of the hydroxy-compounds with phosphorus tribromide an orange complex has been encountered on several occasions and unless this is decomposed by shaking it with a solution of sodium hydrogen carbonate low yields of the bromoethyl derivatives are obtained. It is not possible to prepare the iodo-compounds by heating the chloroalkylamines with sodium iodide in acetone solution since the reaction is so slow that some hydrolysis of the iodide occurs during the preparation. Even when the bromo-derivatives are converted into iodides it is advisable to dry the sodium iodide and the acetone used in order to minimise the loss of the readily hydrolysed iodo-compounds.

NN-*Di*-(2-*chloroethyl*)-p-*aminobenzoic Acid.*—Ethyl *NN*-di-(2-chloroethyl)-*p*-aminobenzoate (1 g., prepared by chlorinating the product obtained by the action of ethylene oxide on ethyl *p*-aminobenzoate) was heated under reflux with concentrated hydrochloric acid for 15 minutes. Gradually the acid separated in a crystalline form, which gave needles, m. p. 171·5°, undepressed by admixture with a specimen prepared as described by Ross (*loc. cit.*), when crystallised from aqueous methanol. The *methyl* ester, formed by the action of ethereal diazomethane on the acid, melted at 58° (plates from light petroleum, b. p. 60—80°).

NN-*Di*-(2-*hydroxyethyl*)-p-*aminoazobenzene.*—A solution of the diazonium salt prepared from aniline (1·8 c.c.), concentrated hydrochloric acid (6 c.c.), water (20 c.c.), and sodium nitrite (1·4 g.) was added to a cooled solution of *NN*-di-(2-hydroxyethyl)aniline (3·6 g.) in methanol (10 c.c.). After ½ hour the deep red solution was basified with ammonium hydroxide and extracted with ether. Concentration of the dried extract by evaporation gave the *azo*-compound which crystallised from benzene in deep-orange plates, m. p. 133—135°.

NN-*Di*-(2-*chloroethyl*)-p-*aminoazobenzene.*—(*a*) A solution of benzenediazonium chloride, prepared as above, was added to a solution of *NN*-di-(2-chloroethyl)aniline (4·4 g.) in ethanol (100 c.c.). The mixture was shaken for ½ hour and then diluted with water (200 c.c.). The oily precipitate gradually solidified and was dissolved in benzene and the solution was passed down a column of activated alumina which was then washed with fresh benzene. Evaporation of the orange eluates afforded the *chloro*-compound, m. p. 73—75°, which formed large thin orange plates from light petroleum (b. p. 40—60°) in which it is very soluble.

(*b*) The hydroxy-azo-derivative (2 g.), phosphorus oxychloride (5 c.c.), and benzene (30 c.c.) were heated under reflux for ½ hour. The cooled mixture was poured on to ice and the benzene layer was dried and passed through a column of alumina. The product had m. p. 72—74°, not depressed by material prepared by method (*a*). The azo-compound yields a light orange solution in alcohol the colour of which changes to a deep crimson when concentrated hydrochloric acid is added.

p′-*Nitro*-NN-*di*-(2-*chloroethyl*)-p-*aminoazobenzene.*—A solution of the diazonium salt prepared from *p*-nitroaniline (7 g.), concentrated hydrochloric acid (10 c.c.), water (150 c.c.), and sodium nitrite (3·5 g.) was added to a solution of *NN*-di-(2-chloroethyl)aniline (11 g.) in ethanol (250 c.c.). The red precipitate was collected, dried, and crystallised from acetone; it formed large, deep red glistening plates, m. p. 166—167°. The orange-red alcoholic solution of the azo-compound assumes an intense crimson colour when an excess of concentrated hydrochloric acid is added.

NN-*Di*-(2-*chloroethyl*)-p-*nitrosoaniline.*—*NN*-Di-(2-chloroethyl)aniline (54 g.) was dissolved in a warm mixture of concentrated hydrochloric acid (105 c.c.) and water (100 c.c.). After being cooled to 5° the solution was vigorously stirred and a solution of sodium nitrite (18 g.) in water (50 c.c.) was added at such a rate that the temperature remained at 5—7°. After the addition, which took one hour, the mixture was stirred for a further 20 minutes and then ether (1 l.) and water (1 l.) were added. The aqueous layer was separated and re-extracted twice with ether (1 l.). The dried extracts deposited the *nitroso*-derivative as deep green plates (49 g.), m. p. 79—80°, when evaporated.

NN-*Di*-(2-*chloroethyl*)-p-*phenylenediamine.*—The nitrosoamine (2·0 g.) was dissolved in concentrated hydrochloric acid (40 c.c.) and stannous chloride crystals (3 g.) were gradually added with constant shaking and cooling. The stannichloride of the amine separated in the form of a buff granular precipitate;

this was collected by filtration and washed with a little concentrated hydrochloric acid. The product was dissolved in water, treated with a slight excess of N-sodium hydroxide, and rapidly extracted with ether. Hydrogen chloride was passed into the dried ethereal solution until plates of the *monohydrochloride* of the amine separated. The amount of gas passed into the solution must be only slightly in excess of the theoretical quantity or the base is thrown out as an oil which is probably the dihydrochloride. The monohydrochloride was dissolved in a small amount of methanol and, on the addition of ether to the filtered solution, the salt was obtained as large colourless plates, m. p. 250—260° (decomp.). The monohydrochloride is water soluble (20 mg. per 1 c.c. at 20°). One drop of this solution placed on the skin will produce a blister of approximately one inch in diameter after 24 hours. As in the case of the aliphatic nitrogen-mustards such blisters are slow to heal.

Esters of NN-*Di*-(2-*chloroethyl*)-p-*phenylenediamine*.—(*a*) The monohydrochloride (1 g.) was dissolved in water (10 c.c.) and the solution was saturated with sodium acetate. A slight excess of acetic anhydride was added dropwise to the well-cooled and shaken solution. The solid *acetyl* derivative which separated was collected and dissolved in benzene. On the addition of light petroleum (b. p. 60—80°) to the concentrated solution flattened needles, m. p. 124—126°, were deposited.

(*b*) A slight excess of benzoyl chloride was added to a cooled, stirred mixture of the monohydrochloride (1 g.) in water (50 c.c.) containing sodium carbonate (5 g.). When all the benzoyl chloride had reacted the product was extracted with benzene, and the dried extract was allowed to percolate through a short column of alumina. The *benzoyl* derivative was obtained as fine colourless needles, m. p. 164—165°, on concentrating the eluates.

Reduction of oo′-*Dinitrodiphenyl*.—(*a*) *oo*′-Dinitrodiphenyl (6·1 g., prepared by the method of Shaw and Turner, *J.*, 1933, 139), Raney nickel catalyst (2 g.), and ethanol (100 c.c.) were shaken in an atmosphere of hydrogen until the uptake of gas ceased (8 hours). When half of the theoretical amount of hydrogen had been absorbed a mass of fine white needles separated but these re-dissolved as more gas was taken up. On concentrating the filtered solution yellow prisms of benzcinnoline, m. p. 156—158°, were deposited (Found : C, 80·2; H, 4·6. Calc. for $C_{12}H_8N_2$: C, 80·0; H, 4·5%).

(*b*) Dinitrodiphenyl (43 g.), stannous chloride crystals (240 g.), concentrated hydrochloric acid (210 c.c.), and ethanol (100 c.c.) were heated on a steam-bath until a vigorous reaction occurred. This was controlled by cooling, and when all the material had dissolved the mixture was heated on steam for a further ½ hour. An excess of sodium hydroxide was then added and the product extracted with ether. The diamine formed prisms, m. p. 77—78°, from benzene–light petroleum (b. p. 60—80°) (Found : C, 78·0; H, 6·6. Calc. for $C_{12}H_{12}N_2$: C, 78·2; H, 6·6%).

oo′-*Di*-(N-*methyltoluene*-p-*sulphonamido*)*diphenyl*.—Toluene-*p*-sulphonyl chloride (40 g.) was gradually added to a solution of diaminodiphenyl (18·4 g.) in dry pyridine (40 c.c.). After the initial reaction had moderated the mixture was heated for one hour on a steam-bath. The *bistoluene*-p-*sulphonamide* was precipitated by the addition of water; after crystallisation from methanol it melted at 147—149° (Found : C, 63·6; H, 4·8. $C_{26}H_{24}O_4N_2S_2$ requires C, 63·4; H, 4·9%). A solution of the sulphonamide (18 g.) in water (65 c.c.) and N-sodium hydroxide (65 c.c.) was treated with dimethyl sulphate (3·1 c.c.). After ½ hour's stirring N-sodium hydroxide (50 c.c.) and dimethyl sulphate (2·5 c.c.) were added and the reaction was allowed to continue until the resinous precipitate of oo′-*di*-(N-*methyltoluene*-p-*sulphonamido*)*diphenyl* solidified. After several crystallisations from acetone, large prisms, m. p. 192—193°, were obtained (Found : C, 64·5; H, 5·4. $C_{28}H_{28}O_4N_2S_2$ requires C, 64·6; H, 5·4%).

NN′-*Dimethyl*-oo′-*diaminodiphenyl*.—The sulphonamide (45 g.) was heated at 160° for 5 minutes with sulphuric acid (150 c.c. of 80% acid, prepared by mixing 3 vols. of acid with 1 vol. of water). After cooling, the solution was poured into water, basified with sodium hydroxide, and the *diamine* which separated was crystallised from acetone–methanol. It formed prismatic needles, m. p. 154—156° (Found : C, 78·7; H, 7·6. $C_{14}H_{16}N_2$ requires C, 79·2; H, 7·6%). The diamine was converted successively into the *di*-(2-*hydroxyethyl*) and the *di*-(2-*chloroethyl*) derivative. The latter is very soluble in light petroleum (b. p. 40—60°) and solutions have to be cooled in a freezing mixture in order to obtain reasonable yields on recrystallisation.

Preparation of 2-*Chloro*-n-*propylamines*.—The arylamine (0·1 mol.) and propylene oxide (0·22 mol.; 15 c.c.) were heated in a sealed tube at 150° for 16 hours. When ethylene oxide is used it is very necessary to use exactly theoretical quantities of reactants to prevent side reactions but it is possible to use an excess of propylene oxide (compare Hanby and Rydon, *J.*, 1947, 514). Whenever possible the reaction product was crystallised from benzene or light petroleum (b. p. 60—80°). If any difficulty was encountered, the crude hydroxypropyl compound was chlorinated as described in Part I (preparation of chloroethylamines; Method B). Better results have generally been obtained when the hydroxy-derivative was first dissolved in an amount of dry benzene equal in volume to that of the phosphorus oxychloride used. The 2-chloropropylamines were usually submitted to a chromatographic purification and crystallised from light petroleum (b. p. 40—60°).

β-*Naphthyldi*-(2-*chloro*-n-*propyl*)*amine* A *and* B.—(*a*) A mixture of the chloropropylamines was prepared from β-naphthylamine exactly as described above; the crude material melted at 84—90°. Repeated crystallisation from light petroleum (b. p. 40—60°) eventually gave the less soluble derivative designated β-*naphthyldi*(*chloropropyl*)*amine* A, m. p. 102°; the more soluble *compound* B, m. p. 82°, was obtained by fractional crystallisation of the mother liquors.

(*b*) β-Naphthylamine (14·3 g.), 1-bromopropan-2-ol (41·7 g.), calcium carbonate (15 g.), and water (20 c.c.) were heated under reflux for 24 hours. The cooled, filtered solution was extracted with benzene and the dried extract was passed through a column of alumina. This column was washed with fresh benzene until all the unchanged naphthylamine had been removed and the eluates were colourless. Further elution of the column with chloroform gave a dark oil (5 g.) which was chlorinated and the product was crystallised from light petroleum. Isomer *A*, m. p. 102°, was readily obtained in low yield but in order to obtain the lower-melting isomer the mother liquors were passed through a column of alumina. The first eluates yielded solid, m. p. 82°, unchanged by crystallisation. It is not possible to identify the isomers by a mixed melting point test since one isomer barely depresses the melting point of the other—most mixtures melt at intermediate temperatures.

Hydrolysis of the Naphthylchloropropylamines.—The chloro-compound (1 g.) and acetone (200 c.c.) containing sodium hydroxide (3·4 c.c. of 2N.) were heated under reflux for 3 hours. After removal of the acetone under reduced pressure the solution was saturated with sodium chloride and extracted several times with ether. The dried ethereal extracts were evaporated and the residue crystallised from light petroleum. The characteristics of the hydroxy-compounds are given in Table II.

Hydrolysis of N-*Ethyl*-N-(2-*chloro*-n-*propyl*)*aniline Picrate.*—The picrate (432 mg.) was dissolved in acetone (60 c.c.) and the solution was titrated with N/10-sodium hydroxide using phenolphthalein as indicator : 10·1 c.c. of alkali were required. Water (50 c.c.) was added and the mixture was heated under reflux for 30 minutes. Titration with alkali indicated that hydrolysis was complete. The hydroxy-compound was isolated as above and converted into the picrate, m. p. 123—124°, undepressed by admixture with picrate of the compound obtained by the reaction of ethylaniline with propylene oxide.

Hydrolysis of p-*Chloro*-NN-*di*-(2-*chloro*-n-*propyl*)*aniline.*—The chloropropylamine (280 mg.) was heated under reflux for ½ hour in water (70 c.c.) and acetone (70 c.c.). Titration of the acidity produced indicated that 65% of the halide had hydrolysed. The hydroxy-compound was isolated as before and crystallised from light petroleum (b. p. 60—80°). It melted at 104—106° and was identical with the product originally obtained by the action of propylene oxide on *p*-chloroaniline.

Attempted Reaction of N-*β-Naphthylalanine Ethyl Ester.*—(a) *With α-bromopropionic ester.* *N*-*β*-Naphthylalanine ethyl ester (0·1 mol.), ethyl *α*-bromopropionate (0·1 mol.), and anhydrous sodium acetate (0·15 mol.) were heated for 5 hours at 180—200°. Only unchanged material could be isolated from the reaction mixture.

(b) *With ethylene oxide.* The alanine derivative (0·1 mol.) was heated with ethylene oxide (0·1 mol.; 5 c.c.) in a sealed tube at 160° for 12 hours. Again, only unchanged ester could be isolated.

NN-*Di*-(3-*hydroxy*-n-*propyl*)- *and* NN-*Di*-(6-*hydroxy*-n-*hexyl*)-*aniline.*—These hydroxyalkyl derivatives were obtained by heating aniline (0·5 mol.), 3-chloropropan-1-ol or 6-chlorohexan-1-ol (1·5 mols.), calcium carbonate (0·5 mol.), and water (500 c.c.) under reflux with vigorous stirring until all the chalk had dissolved (30 hours). The *hydroxyhexyl* derivative was obtained as an oil which distilled at about 200°/0·01 mm. (oil-bath temperature—some decomposition occurred and a higher-boiling fraction was left in the flask) (Found : C, 73·3; H, 10·7. $C_{18}H_{31}O_2N$ requires C, 73·7; H, 10·6%); it formed a *bis*-3 : 5-*dinitrobenzoate*, m. p. 112°, crimson needles from ethyl acetate–ethanol (Found : C, 56·5; H, 5·4. $C_{32}H_{35}O_{12}N_5$ requires C, 56·4; H, 5·2%).

NN-*Di*-(6-*chloro*-n-*hexyl*)*aniline* was obtained as a colourless oil (Found : C, 65·6; H, 8·7. $C_{18}H_{29}NCl_2$ requires C, 65·4; H, 8·9%).

The Condensation of 4-*Chlorobutan*-1-*ol with Aniline.*—Aniline (18·6 g.), 4-chlorobutan-1-ol (65 g.), calcium carbonate (80 g.), and water (100 c.c.) were heated under reflux with vigorous stirring. When an oil was observed to be condensing the water in the condenser was stopped and the oil was collected at 64—66° and was shown to be tetrahydrofuran. More chlorobutanol (30 c.c.) was added and the heating was continued for 6 hours. Altogether 25 g. of tetrahydrofuran were collected. The cooled mixture was extracted with ether and the dried extract was distilled.

N-(4-*Hydroxy*-n-*butyl*)*aniline* was collected at 125—135°/1 mm. (Found : C, 72·5; H, 8·6. $C_{10}H_{15}ON$ requires C, 72·7; H, 9·1%). The *trinitrobenzene* complex formed reddish-brown needles, m. p. 73—74°, from benzene–*cyclo*hexane (Found : N, 14·6. $C_{16}H_{18}O_7N_4$ requires N, 14·8%).

Hydroxybutylaniline (7·3 g.), 4-chlorobutan-1-ol (14·4 g.), calcium carbonate (15 g.), and water (20 c.c.) were heated with stirring for four hours. During this time tetrahydrofuran was evolved. Only unchanged monohydroxybutylaniline could be isolated from the reaction mixture.

NN-*Di*-(2 : 3-*dichloro*-n-*propyl*)-p-*anisidine.*—*p*-Anisidine (6·15 g.) and epichlorohydrin (8 c.c.) were warmed together until solution was complete and then kept at room temperature for 2 days. The solid *product* crystallised from benzene as prismatic needles, m. p. 109—111°. Chlorination of the hydroxy-derivative with phosphorus oxychloride afforded a yellow oil which gave good analytical figures after a chromatographic purification.

NNN′N′-*Tetra*-(3-*chloro*-2-*hydroxy*-n-*propyl*)-p-*phenylenediamine.*—*p*-Phenylenediamine (5·4 g.), epichlorohydrin (16 c.c.), concentrated hydrochloric acid (10 c.c.), and water (40 c.c.) were shaken at room temperature for 30 hours. The purple solid which separated was dried and crystallised twice from benzene as small bluish needles, m. p. 130°. The blue colour is probably due to the presence of an oxidation product for when a solution of the hydroxy-compound is treated with traces of oxidant (*e.g.* nitrates, ferric chloride, or hydrogen peroxide) an intense blue colour develops. All attempts to chlorinate this substance gave only dark resins.

NN-*Di*-(2-*hydroxy*-1-*cyclohexyl*)*aniline.*—Aniline (9·3 g.), *cyclo*hexene oxide (19·6 g.), and benzene (10 c.c.) were heated in a sealed tube at 185° for 24 hours. After the excess of *cyclo*hexene oxide and benzene had been removed by evaporation NN-*di*-(2-*hydroxy*-1-*cyclohexyl*)*aniline* was crystallised from benzene as felted needles (3·5 g.), m. p. 175—177° (Found : C, 74·8; H, 9·3; N, 4·7. $C_{18}H_{27}O_2N$ requires C, 74·7; H, 9·4; N, 4·8%).

NN-*Di*-(2-*chloro*-1-*cyclohexyl*)*aniline.*—The above hydroxy-compound (1 g.), phosphorus oxychloride (1 c.c.), and benzene (10 c.c.) were heated under reflux for 2 hours. The mixture was poured on to ice, the dried benzene layer was evaporated, and the residue dissolved in light petroleum (b. p. 60—80°). This solution was shaken with a little activated alumina, filtered, and evaporated. The *chloro*-compound thus obtained crystallised from pentane as small prisms, m. p. 97—99° (Found : C, 66·2; H, 7·7; N, 4·6. $C_{18}H_{25}NCl_2$ requires C, 66·2; H, 7·7; N, 4·3%).

NN′-*Di*-(*chloroacetyl*)- *and* -(*iodoacetyl*)-o-*phenylenediamine.*—Finely powdered *o*-phenylenediamine (10·8 g.) was suspended in water (100 c.c.) and the mixture was cooled and stirred whilst chloroacetyl chloride (14 c.c.) was added dropwise. After being kept for ½ hour the dark product was collected and dried, then mixed with charcoal and extracted with acetone in a Soxhlet apparatus. The pink extract was recrystallised from acetone giving colourless flattened needles of the *chloroacetyl* compound, m. p. 204° (Found : C, 45·7; H, 3·9. $C_{10}H_{10}O_2N_2Cl_2$ requires C, 46·0; H, 3·9%). The bischloroacetamide (1 g.), anhydrous sodium iodide (2 g.), and dry acetone (25 c.c.) were heated on a steam-bath for ½ hour. Water was added to dissolve the sodium chloride which had rapidly separated from the solution and, on cooling,

the *iodoacetyl* derivative was deposited. Recrystallisation from methanol gave long felted needles, m. p. 201—202° (Found : C, 26·8, 27·3; H, 2·3, 2·4. $C_{10}H_{10}O_2N_2I_2$ requires C, 27·1; H, 2·3%).

Both halogenoacetyl compounds react with thiophenol in methanol to give a *disulphide*, m. p. 143—144°, needles from aqueous methanol (Found : C, 65·1; H, 5·1. $C_{22}H_{20}O_2N_2S_2$ requires C, 64·7; H, 4·9%).

Attempted Formation of Quaternary Salts.—(*a*) *NN*-Di-(2-hydroxyethyl)aniline was recovered unchanged after being heated under reflux with a large excess of methyl iodide for 8 hours.

(*b*) *NN*-Di-(2-chloroethyl)aniline was also unaffected when heated for 24 hours with an excess of methyl iodide or ethylene dibromide.

Rates of Hydrolysis of Arylhalogenoamines.—(*a*) *In unbuffered solutions.* The rates of hydrolysis at 66° in 1 : 1-acetone–water solutions were determined exactly as in Part I. In the case of the more rapidly hydrolysed halides, particularly the iodo- and bromo-derivatives, it was necessary to cool the solutions in ice before titrating in order to obtain clear end-points in the titration with silver nitrate.

(*b*) *In the presence of sodium acetate* (*determination of competition factor*). Water (100 c.c.) and acetone (100 c.c.) containing sodium acetate (40 millimoles, giving a 0·2M-solution) was neutralised with N/10-sodium hydroxide (phenolphthalein) and heated to boiling point. The arylhalogenoalkylamine (2 millimoles) was then added, and the solution was heated under reflux for the required time. The well cooled solution was titrated first with N/10-alkali and then with N/10-silver nitrate (dichlorofluorescein).

Preparation and Attempted Hydrolysis of β-Naphthyldi-(2-acetoxyethyl)amine.—β-Naphthyldi-(2-hydroxyethyl)amine (2 g.), acetic anhydride (2 c.c.), and benzene (10 c.c.) were heated on a steam-bath for one hour. After removal of the solvents a solution of the residue in benzene was passed through a column of alumina and the early eluates were concentrated giving the *acetoxy*-compound as a colourless oil (215 mg. of this oil required 13·7 c.c. of N/10-alkali for complete hydrolysis; theory for $C_{18}H_{21}O_4N$ = 13·7 c.c.).

312 Mg. of the compound were heated under reflux with acetone and water (50 c.c. of each) for 3 hours. Approximately 0·2 c.c. of N/10-alkali was required to titrate the acidity produced. Thus the acetate is stable to hot neutral aqueous solutions.

308 Mg. of the acetoxy-derivative were heated under reflux for 3 hours with acetone and water (50 c.c. of each) containing acetic acid (20 c.c.; N/10—this is a considerably higher proportion of acid than is likely to be encountered in the determination of the competition factor). No extra acidity was developed during this heating thus indicating that the acetate is stable under these conditions.

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