270. *Aryl-2-halogenoalkylamines. Part VII. Some Derivatives of 2-Naphthyldi-2′-halogenoalkylamines.*

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

The preparation of certain derivatives of 2-naphthyldi-2′-halogenoalkylamines is described. The reactivity of the halogen atoms in these compounds—as measured by the rate of hydrolysis in aqueous acetone—is discussed.

The preparation of a number of aryldi-2-halogenoalkylamines has already been described (Parts I and II, *J.*, 1949, 183, 1972). Many of these compounds have the property of inhibiting the growth of various animal tumours and of spontaneous and transmitted leukæmia in the Furth AK 1 pure line (Haddow, Kon, and Ross, *Nature*, 1948, **162**, 824). One of the compounds examined, 2-naphthyldi-2′-chloroethylamine, has been used clinically for the treatment of various lymphadenopathies in human patients with encouraging results. The present communication deals mainly with compounds related to this effective compound.

The compounds now described include the di-2′-chloroethyl derivatives of 6- and 8-methyl-, 8-ethyl-, 8-acetyl-, 1 : 2 : 3 : 4-tetrahydro-, and 5 : 6 : 7 : 8-tetrahydro-2-naphthylamine, and also of 2- and 3-aminophenanthrene which can be regarded as 5 : 6- and 7 : 8-benz-derivatives of 2-naphthylamine. Aryldi-2′-halogenoethylamines were prepared from the parent aromatic amines exactly as described in Part I.

6-Methyl-2-naphthylamine was obtained by the Bucherer reaction on the naphthol, which was prepared from the sulphonation product of 2-methylnaphthalene (Dziewonski, Schoenówna, and Waldmann, *Ber.*, 1925, **58**, 1212). 1-Keto-7-methoxy-1 : 2 : 3 : 4-tetrahydronaphthalene was converted into 8-methyl-2-naphthylamine as described by Haworth and Sheldrick (*J.*, 1934, 1950). Brown, Jacobs, Winsten, Levy, Moss, and Ott (*J. Org. Chem.*, 1946, **11**, 163) obtained an acetyl-2-naphthylamine, by a Friedel–Crafts reaction on 2-acetnaphthalide, which they regarded as 1-acetyl-2-naphthylamine but it was later shown to be the 8-acetyl derivative (Leonard and Hyson, *J. Org. Chem.*, 1948, **13**, 164). Reduction of 8-acetyl-2-naphthylamine by Huang-Minlon's modified Kishner–Wolff procedure (*J. Amer. Chem. Soc.*, 1946, **68**, 2487) afforded 8-ethyl-2-naphthylamine which was characterised by the preparation of the *acetyl* derivative. A mixture of 5- and 6-nitro-1 : 2 : 3 : 4-tetrahydronaphthalene is obtained by the nitration of 1 : 2 : 3 : 4-tetrahydronaphthalene (Schroeter, *Annalen*, 1922, **426**, 39); this was readily resolved by a fractional distillation through an electrically heated column. Catalytic reduction of the nitro-compounds by using Raney nickel yielded the required 5 : 6 : 7 : 8-tetrahydronaphthylamines. 1 : 2 : 3 : 4-Tetrahydro-2-naphthylamine (*Org. Synth.*, Coll. Vol. I, p. 499) and 1 : 2 : 3 : 4-tetrahydro-1-naphthylamine, prepared by the reduction of 1-keto-1 : 2 : 3 : 4-tetrahydronaphthalene oxime with sodium and ethanol (compare von Braun, *Ber.*, 1922, **55**, 3648), were converted into the di-2-hydroxyethyl derivatives in the usual manner but it was found preferable to use thionyl chloride in chloroform solution for the chlorination stage. On one occasion the reaction between ethylene oxide and 1 : 2 : 3 : 4-tetrahydro-2-naphthylamine afforded a mixture of mono- and di-2′-hydroxyethyl derivatives which was resolved after conversion into the chloroethylamine hydrochlorides.

Bachmann and Boatner's method (*J. Amer. Chem. Soc.*, 1936, **58**, 2097) was used to prepare 2- and 3-aminophenanthrene.

For further confirmation of the finding that it is necessary to have two reactive groups in the molecule for growth-inhibitory activity *N*-2-naphthyl-*N*-methyl-2′-chloroethylamine and *N*-2-naphthyl-*N*-methyl-2′-chloro-*n*-propylamine were prepared. Both these compounds were inactive.

N′-Acetyl- and *N*′-benzoyl-*NN*-di-2-chloroethyl-*p*-phenylenediamine were described in

TABLE I.

Aryl-2-hydroxy- and -halogeno-alkylamines.

Compound.	M. p.	Crystal form.	S.	Formula.	Found, %. C.	Found, %. H.	Required, %. C.	Required, %. H.
2-*Methyl*-1-*naphthyldi*-2′-*chloroethylamine*	(Oil)	—	—	$C_{15}H_{17}NCl_2$	(Cl, 25·0)		(Cl, 25·1)	
1 : 2 : 3 : 4-*Tetrahydro*-1-*naphthyldi*-2′-*hydroxyethylamine*	89°	Prismatic needles	C–E	$C_{14}H_{21}O_2N$	71·5	9·2	71·5	9·0
1 : 2 : 3 : 4-*Tetrahydro*-1-*naphthyldi*-2′-*hydroxyethylamine picrate*	140	Sword-shaped	A	$C_{20}H_{24}O_9N_4$	51·8	5·4	51·7	5·2
1 : 2 : 3 : 4-*Tetrahydro*-1-*naphthyldi*-2′-*chloroethylamine hydrochloride*	158	Prismatic needles	B	$C_{14}H_{20}NCl_3$	54·3	6·5	54·5	6·5
5 : 6 : 7 : 8-*Tetrahydro*-1-*naphthyldi*-2′-*hydroxyethylamine picrate*	199 (decomp.)	Needles	A	$C_{20}H_{24}O_9N_4$	51·3	4·8	51·7	5·2
5 : 6 : 7 : 8-*Tetrahydro*-1-*naphthyldi*-2′-*chloroethylamine*	(Oil)	—	—	$C_{14}H_{19}NCl_2$	(Cl, 26·0)		(Cl, 26·1)	
5 : 6 : 7 : 8-*Tetrahydro*-1-*naphthyldi*-2′-*chloroethylamine picrate*	121	Plates	A	$C_{20}H_{22}O_7N_4Cl_2$	47·7	4·7	47·9	4·4
N-2-*Naphthyl*-N-*methyl*-2′-*hydroxyethylamine picrate*	160	Needles	B	$C_{19}H_{18}O_8N_4$	53·3	4·1	53·0	4·2
N-2-*Naphthyl*-N-*methyl*-2′-*chloroethylamine*	52·5	Needles	D	$C_{13}H_{14}NCl$	71·2	6·4	71·1	6·4
N-2-*Naphthyl*-N-*methyl*-2′-*hydroxy*-n-*propylamine picrate*	154	Needles	B	$C_{20}H_{20}O_8N_4$	54·0	4·5	54·1	4·5
N-2-*Naphthyl*-N-*methyl*-2′-*chloro*-n-*propylamine*	64	Needles	D	$C_{14}H_{16}NCl$	71·8	6·9	71·9	6·9
6-*Methyl*-2-*naphthyldi*-2′-*hydroxyethylamine*	94	Fine needles	C	$C_{15}H_{19}O_2N$	73·3	7·9	73·4	7·8
6-*Methyl*-2-*naphthyldi*-2′-*chloroethylamine*	65	Needles	D	$C_{15}H_{17}NCl_2$	63·8	6·0	63·9	6·1
6-*Methyl*-2-*naphthyldi*-2′-*bromoethylamine*	88	Rhombs	E	$C_{15}H_{17}NBr_2$	48·3	4·5	48·5	4·6
6-*Methyl*-2-*naphthyldi*-2′-*iodoethylamine*	100—101	Flattened needles	E	$C_{15}H_{17}NI_2$	39·3 (I, 55·0)	4·0	38·8 (I, 54·6)	3·7
8-*Methyl*-2-*naphthyldi*-2′-*chloroethylamine*	63	Prisms	D	$C_{15}H_{17}NCl_2$	63·9	6·2	63·9	6·1
8-*Ethyl*-2-*naphthyldi*-2′-*chloroethylamine*	48	Prismatic needles	D	$C_{16}H_{19}NCl_2$	65·1	6·7	64·9	6·5
8-*Ethyl*-2-*naphthyldi*-2′-*bromoethylamine*	57	Flattened rhombs	E	$C_{16}H_{19}NBr_2$	49·9	5·1	49·9	5·0
8-*Ethyl*-2-*naphthyldi*-2′-*iodoethylamine*	85	Prisms	D	$C_{16}H_{19}NI_2$	40·0 (I, 53·2)	3·8	40·1 (I, 53·0)	4·0
8-*Acetyl*-2-*naphthyldi*-2′-*hydroxyethylamine*	113	Yellow needles	C	$C_{16}H_{19}O_3N$	70·6	7·1	70·3	7·0
8-*Acetyl*-2-*naphthyldi*-2′-*chloroethylamine* [1]	84	Yellow needles	E	$C_{16}H_{17}ONCl_2$	62·2	5·4	61·9	5·5
8-*Acetyl*-2-*naphthyldi*-2′-*bromoethylamine* [1]	94·5	Yellow needles	E	$C_{16}H_{17}ONBr_2$	48·4	4·3	48·2	4·3
1 : 2 : 3 : 4-*Tetrahydro*-2-*naphthyl*-2′-*chloroethylamine hydrochloride*	215	Felted needles	A	$C_{12}H_{17}NCl_2$	58·1	7·1	58·5	6·9
1 : 2 : 3 : 4-*Tetrahydro*-2-*naphthyl*-2′-*chloroethylamine picrate*	197	Prismatic needles	B–F	$C_{18}H_{19}O_7N_4Cl$	49·3	4·1	49·3	4·3
1 : 2 : 3 : 4-Tetrahydro-2-naphthyldi-2′-hydroxyethylamine picrate [2]	142	Felted needles	A	$C_{20}H_{24}O_9N_4$	51·6	5·4	51·7	5·2
1 : 2 : 3 : 4-*Tetrahydro*-2-*naphthyldi*-2′-*chloroethylamine hydrochloride*	164	Small prisms	B	$C_{14}H_{20}NCl_3$	(Cl, 34·2)		(Cl, 34·5)	
1 : 2 : 3 : 4-*Tetrahydro*-2-*naphthyldi*-2′-*bromoethylamine hydrobromide*	229	Fine needles	B	$C_{14}H_{20}NBr_3$	(Br, 54·5)		(Br, 54·3)	
5 : 6 : 7 : 8-*Tetrahydro*-2-*naphthyldi*-2′-*hydroxyethylamine*	57	Needles	G	$C_{14}H_{21}O_2N$	71·5	9·0	71·5	9·0
5 : 6 : 7 : 8-*Tetrahydro*-2-*naphthyldi*-2′-*chloroethylamine* [3]	65	Prismatic needles	D	$C_{14}H_{19}NCl_2$	61·5	7·0	61·8	7·0
2-*Phenanthryldi*-2′-*hydroxyethylamine*	155	Plates	C–B	$C_{18}H_{19}O_2N$	77·1	6·9	76·8	6·8
2-*Phenanthryldi*-2′-*chloroethylamine*	91—92	Needles	E	$C_{18}H_{17}NCl_2$	67·7	5·5	67·9	5·4
2-*Phenanthryldi*-2′-*bromoethylamine*	111—112	Needles	E	$C_{18}H_{17}NBr_2$	53·3	4·4	53·1	4·2
2-*Phenanthryldi*-2′-*iodoethylamine*	117	Needles	E	$C_{18}H_{17}NI_2$	42·7	3·5	43·1	3·4
3-*Phenanthryldi*-2′-*hydroxyethylamine*	109—110	Plates	C	$C_{18}H_{19}O_2N$	76·9	6·9	76·8	6·8
3-*Phenanthryldi*-2′-*chloroethylamine*	73	Rhombs	E	$C_{18}H_{17}NCl_2$	68·1	5·4	67·9	5·4
3-*Phenanthryldi*-2′-*bromoethylamine*	98	Needles	E	$C_{18}H_{17}NBr_2$	52·7	3·9	53·1	4·2
3-*Phenanthryldi*-2′-*iodoethylamine*	125	Needles	E	$C_{18}H_{17}NI_2$	43·7	3·7	43·1	3·4
N-2′-Hydroxyethyl-2-aminofluorene [4]	150	Yellow plates	C	$C_{15}H_{15}ON$	79·8	6·7	80·0	6·7

TABLE I (*continued*).

Compound.	M. p.	Crystal form.	S.	Formula.	Found, %. C.	Found, %. H.	Required %. C.	Required %. H.
NN-*Di*-2′-*bromoethyl*-2-*aminofluorene*	137	Prismatic needles	C–E	$C_{17}H_{17}NBr_2$	52·0	4·5	51·7	4·3
N′-*Propionyl*-NN-*di*-2-*chloroethyl*-p-*phenylenediamine*	101—103	Prisms	E	$C_{13}H_{18}ON_2Cl_2$	53·9	6·4	54·0	6·3
NN-*Di*-2-*chloropropyl*-p-*aminobenzoic acid* [5]	165—166	Stout needles	A–H	$C_{13}H_{17}O_2NCl_2$	54·0	6·0	53·8	5·9
Methyl NN-*di*-2-*chloropropyl*-p-*aminobenzoate*	61	Needles	E	$C_{14}H_{19}O_2NCl_2$	55·6	6·2	55·3	6·3

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, acetone; G, *cyclo*hexane; and H, water.

[1] Solutions of these compounds exhibit an intense yellow-green fluorescence. [2] Matskevich (*J. Gen. Chem. Russia*, 1941, **11**, 1023) reported m. p. 140°. [3] This compound is photoluminescent (cf. Part I). [4] In Part I the m. p. was given as 144—146°. [5] This acid was prepared by hydrolysing the product of the reaction between propylene oxide and ethyl *p*-aminobenzoate with concentrated hydrochloric acid (cf. Part II).

Part II; only the acetyl derivative was active. The active substance is probably the amine derived by hydrolysis of the acyl group and it would be expected that such hydrolysis would be more difficult in the case of the benzoate. Another derivative, N′-*propionyl*-NN-*di*-2-*chloroethyl*-p-*phenylenediamine*, has been prepared; this is also a very effective compound.

The reactivity of the halogen atoms in *NN*-di-2-chloroethyl-*p*-aminobenzoic acid is not of a high order (Part I) and so to obtain a more reactive acidic compound the corresponding *di*-2-*chloro*-n-*propyl* derivative and its methyl ester have been prepared. For the same reason the *bromo*-compound corresponding to the feebly active *NN*-di-2′-chloroethyl-2-aminofluorene was examined.

The preparation of *N*-2′-chloroethyl-2-aminofluorene (cf. Part I) has been re-examined. *N*-2′-Hydroxyethyl-2-aminofluorene, prepared as previously described, was obtained in purer form after a chromatographic purification of the reaction product. Chlorination of this hydroxy-compound presented difficulties on a larger scale but a satisfactory method using phosphorus pentachloride in chloroform solution at low temperature was eventually evolved.

Peters and Wakelin (*Biochem. J.*, 1947, **41**, 545) have shown that the potentiating action of sodium diethyldithiocarbamate on the action of di-2-chloroethyl sulphide is due to the formation of an ester derivative. When *NN*-di-2-chloroethyl-*p*-anisidine was allowed to react in a solution containing sodium diethyldithiocarbamate NN-*di*-2-(*diethyldithiocarbamatoethyl*)-p-*anisidine* was formed; the chloroethyl(diethyldithiocarbamatoethyl) derivative was not isolated. The disubstituted compound, like the corresponding derivative of " mustard gas," was less toxic than the parent halide, no doubt owing to the fact that it no longer possesses an active halogen atom. The increased toxicity of the monosubstituted product obtained by Peters and Wakelin is almost certainly due to the increased reactivity of the remaining halogen atom which would be expected if one chlorine atom was replaced by a sulphur-containing group. Such an increase in the reactivity of the second halogen atom is indicated in Ogston's experiments (*Trans. Faraday Soc.*, 1948, **44**, 45) in which mustard gas reacts with various thio-esters.

A consideration of the reactions of aryldi-2-halogenoalkylamines suggested that when they reacted with naturally occurring substances under mild conditions, they could be regarded as difunctional electrophilic reagents. Under similar conditions epoxides may be regarded as electrophilic reagents (Hammett, " Physical Organic Chemistry," New York, 1940, p. 301) and it therefore seemed of interest to examine a number of diepoxides. The first compound of this type to be tested, NN-*di*-(2 : 3-*epoxypropyl*)-p-*anisidine*, was prepared by the action of sodium hydroxide on *NN*-di-(3-chloro-2-hydroxy-*n*-propyl)-*p*-anisidine (Part II). Whilst this substance was not effective, a number of more reactive diepoxides including 1 : 2-3 : 4-diepoxybutane, 1 : 2-5 : 6-diepoxyhexane, di-2 : 3-epoxypropyl ether, and 1 : 4-di-(2′ : 3′-epoxypropoxy)-benzene do induce the formation of chromosome abnormalities and inhibit the growth of transplanted tumours in a manner indistinguishable from that characteristic of the " mustards." Monoepoxides, for example, propylene oxide, epichlorohydrin, and *cyclo*hexene oxide, appear to be inactive as tumour-growth inhibitors.

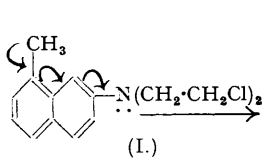
A list of the compounds prepared in this work is given in Table I.

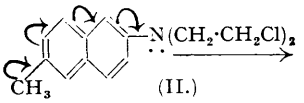
Table II shows the rate of hydrolysis of a number of the halogenoalkylamines in unbuffered 50% aqueous acetone at 66°. Many of the compounds now prepared are less soluble than those

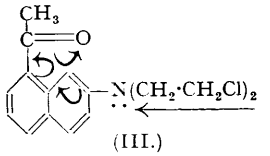
examined in Parts I and II and had to be hydrolysed at higher dilutions than in the standard procedure. Since the hydrolysis proceeds by an S_N1 mechanism the effect of dilution is merely to reduce the extent of the bimolecular back reaction with halide ions and so the values obtained in more dilute solutions are relatively higher (see below).

The influence of dilution on the rate of hydrolysis of *NN*-di-2-chloroethyl-*p*-anisidine was shown in Part I. 58% Hydrolysis occurred at 66° when 0·5 millimol. of amine was dissolved in 50 ml. of 50% aqueous acetone; 64% when the volume was 100 ml.; and 67% in 320 ml. The effect is most marked at higher concentrations and it is not serious when 0·5 millimol. of the amine is dissolved in 100 ml. or more of 50% aqueous acetone. Since most of the hydrolysis rates given in Table II had to be measured at higher dilutions no great error is made in comparing the values as in the discussion below.

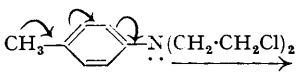
A 2-methyl substituent in the 1-naphthylamine derivative causes an appreciable increase in the reactivity of the chlorine atom. The substitution of the hydrogen atoms in the 6- and 8-positions of the 2-naphthylamine nucleus by methyl groups results in a significantly higher rate of hydrolysis of the di-2′-chloroethyl derivatives whereas an 8-ethyl substituent has little effect on the reactivity of the halogen in the dichloro-, dibromo-, or di-iodo-ethylamine. The effect of the 6- and 8-methyl groups would have been expected since they could increase the electron availability on the nitrogen atom which in turn would activate the halogen atoms (I—II):

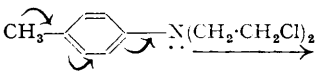

(I.)


(II.)


(III.)

The bond structure of the naphthalene nucleus shown in (I), (II), and (III) is only one of the possible forms and it is interesting to note that the effect of the methyl group is greater in the aniline derivative (Part I) where the two predominating possible structures (IV) and (V) both permit activation of the halogen atom:


(IV.)


(V.)

The hydrolysis rate of the *p*-toluidine derivative is 38% and that of the aniline derivative 20%.

The electron-release effect of the ethyl group is less than that of the methyl group in a system such as that under consideration [compare the relative basicities of *NN*-dimethyl-*p*-toluidine (pK_a 4·77) and *NN*-dimethyl-*p*-ethylaniline (pK_a 4·69); Davies, *J.*, 1938, 1865]; this is reflected in the negligible effect of the 8-ethyl substituent.

An 8-acetyl substituent has an appreciable deactivating effect on the halogen in both the 2′-chloro- and the 2′-bromo-ethylamines; this would be expected in view of the electron-attracting capacity of the acetyl group as demonstrated in (III).

5 : 6 : 7 : 8-Tetrahydro-2-naphthyldi-2′-chloroethylamine can be regarded as the aniline compound with alkyl substituents in the *m*- and *p*-positions. A *m*-methyl group has little effect on the activity of the halogen atom in the aniline derivative (hydrolysis rates: *NN*-di-2-chloroethylaniline, 20%; *NN*-di-2-chloroethyl-*m*-toluidine, 21%; *NN*-di-2-chloroethyl-*p*-toluidine, 38%), but a *p*-methyl group causes a considerable increase. This is quite comparable to the effect of fusing the alicyclic ring as in this tetrahydro-compound. In 5 : 6 : 7 : 8-tetrahydro-1-naphthyldi-2′-chloroethylamine the alicyclic ring can be likened to *o*- and *m*-substituents and again the effect is comparable for *NN*-di-2-chloroethyl-*o*-toluidine has a hydrolysis rate of 83%.

The fusion of an aromatic ring system to the 3 : 4-position of the aniline nucleus—giving the 2-naphthyl derivative—causes a decrease in the reactivity of the halogen atom. For the chloro-compounds the decrease is from 20% to 15% hydrolysis and whilst the bromo-derivatives hydrolyse at about the same rate (80%) the value for the 2-naphthyl compound was determined at a higher dilution and is therefore relatively high. A similar decrease in the reactivity of the halogens is produced when benzene rings are fused on to the 5 : 6- or 7 : 8-positions of the 2-naphthyl nucleus. In the case of each of the halogenoethyl derivatives of the phenanthrylamines the hydrolysis rates had to be determined at higher dilutions but this only serves to

emphasise the effect of the substituent for had the rates been measured at the same dilution the depression of the reactivity of the halogen atom must have been more marked.

TABLE II.

Compound (0·5 millimoles).	Volume of acetone : water (ml.).	% Hydrolysis in 30 mins. at 66°.
1-Naphthyldi-2′-chloroethylamine	30 : 30	50
2-Methyl-1-naphthyldi-2′-chloroethylamine	50 : 50	75
2-Naphthyldi-2′-chloroethylamine	25 : 25	15
2-Naphthyldi-2′-bromoethylamine	55 : 55	80
2-Naphthyldi-2′-iodoethylamine	70 : 70	64
2-Naphthyldi-2′-chloro-*n*-propylamine	35 : 35	86
N-2-Naphthyl-*N*-methyl-2′-chloroethylamine	25 : 25	25
N-2-Naphthyl-*N*-methyl-2′-chloro-*n*-propylamine	25 : 25	87
6-Methyl-2-naphthyldi-2′-chloroethylamine	50 : 50	24
6-Methyl-2-naphthyldi-2′-bromoethylamine	50 : 50	85
6-Methyl-2-naphthyldi-2′-iodoethylamine	70 : 70	74
8-Methyl-2-naphthyldi-2′-chloroethylamine	50 : 50	21
8-Ethyl-2-naphthyldi-2′-chloroethylamine	50 : 50	14
8-Ethyl-2-naphthyldi-2′-bromoethylamine	70 : 70	84
8-Ethyl-2-naphthyldi-2′-iodoethylamine	75 : 75	66
8-Acetyl-2-naphthyldi-2′-chloroethylamine	50 : 50	4
8-Acetyl-2-naphthyldi-2′-bromoethylamine	50 : 50	45
5 : 6 : 7 : 8-Tetrahydro-2-naphthyldi-2′-chloroethylamine	50 : 50	44
5 : 6 : 7 : 8-Tetrahydro-1-naphthyldi-2′-chloroethylamine	60 : 60	86
2-Phenanthryldi-2′-chloroethylamine	75 : 75	9
2-Phenanthryldi-2′-bromoethylamine	100 : 100	79
2-Phenanthryldi-2′-iodoethylamine	300 : 300	52
3-Phenanthryldi-2′-chloroethylamine	75 : 75	11
3-Phenanthryldi-2′-bromoethylamine	75 : 75	76
3-Phenanthryldi-2′-iodoethylamine	300 : 300	54
NN-Di-2′-chloroethyl-2-aminofluorene	100 : 100	26
NN-Di-2′-bromoethyl-2-aminofluorene	100 : 100	90

		H, %.	Cl, %.[b]
1 : 2 : 3 : 4-Tetrahydro-1-naphthyldi-2′-chloroethylamine	50 : 50	89	98
1 : 2 : 3 : 4-Tetrahydro-2-naphthyldi-2′-chloroethylamine	50 : 50	70	83
1 : 2 : 3 : 4-Tetrahydro-2-naphthyldi-2′-bromoethylamine	85 : 85	—	100
Methyldi-2-chloroethylamine	25 : 25	44	54
Dimethyl-2-chloroethylamine	25 : 25	11	97
Di-2-chloroethyl sulphide	25 : 25	100	100
Ethyl 2-chloroethyl sulphide	25 : 25	89	100

In the first series of derivatives of aromatic amines the chloride and the hydrogen-ion titre after hydrolysis were identical. [b] In the second series of derivatives of aliphatic amines the two titres sometimes differed (see discussion). The figures are based on complete hydrolysis.

TABLE III.

Hydrolysis of 2-naphthyldi-2′-halogenoethylamines in 66% acetone (*a*) alone and (*b*) in the presence of sodium thiosulphate (0·0066M.). Concn. of amine, 0·00166M.; Temp., 37°; Time, 2 hours.

Compound.	(*a*) % Hydrolysis.	(*b*) % consumption of thiosulphate.
2-Naphthyldi-2′-chloroethylamine	2	4
2-Naphthyldi-2′-bromoethylamine	18	44
2-Naphthyldi-2′-iodoethylamine	9	65

(*a*) and (*b*) are based on the complete reaction of the halides.

Table II shows four complete series of chloro-, bromo-, and iodo-ethylamines—those of 2-naphthylamine, 6-methyl-2-naphthylamine, and 2- and 3-phenanthrylamines. In each instance there is the expected increase in the rate of hydrolysis on passing from the chlorides to the bromides but then a somewhat surprising decrease for the iodides. It would be expected that the extent of ionisation of the iodide ion from the 2′-carbon atom would be greater than that of the bromide ion. Since it is known that the competition factor of the iodide ion for the carbonium ion is much higher than that of either the chloride or bromide ion (Part III, *J.*, 1949, 2589, and Ogston, *loc. cit.*) it was thought possible that the apparently slower rate of hydrolysis of the iodides might be due to a relatively faster bimolecular, back reaction whereby halide is re-formed, rather than to a slower rate of ionisation. If the hydrolyses are carried out in the presence of an excess of sodium thiosulphate the rate of consumption of thiosulphate can be reagarded as a measure of the rate of formation of carbonium ion (Part III). When 8-ethyl-2-naphthyldi-2′-halogenoethylamines are hydrolysed as recorded in Table II but with the

addition of thiosulphate, the extent of carbonium-ion formation is found to be: chloro-compound, 17%; bromo-compound, 100%; and iodo-compound, 100%. It is therefore clear that the differences in the values for the bromo- and iodo-derivatives given in Table II must be due to a difference in the degree of the back reaction. A further series of experiments in which 2-naphthyldi-2′-halogenoethylamines were hydrolysed in 66% aqueous acetone at 37° showed that, under these conditions, the iodo-compound does actually ionise faster than the corresponding bromo-compound (Table III).

The second section of Table II gives the rate of production of hydrogen and chloride ions from tetrahydronaphthyldi-2′-halogenoethylamines, which may be regarded as derivatives of aliphatic amines. As with the simple aliphatic " nitrogen mustards " the rate of production of the two ions is not identical and the difference in the values can be ascribed to the formation of quaternary nitrogen compounds—either an ethyleneimonium ion or a piperazine dimer (Golumbic, Fruton, and Bergmann, *J. Org. Chem.*, 1946, **11**, 518; Hanby, Hartley, Powell, and Rydon, *J.*, 1947, 520).

When methyldi-2-chloroethylamine (pK_a 6·45) is hydrolysed under the standard conditions the reaction stops when about one-half of the halogen has been eliminated; this is probably due to the fact that the pH change caused by the elimination of one equivalent of hydrochloric acid leads to the stabilisation of the chlorohydrin (pK_a 7·5) by salt formation. Dimethyl-2-chloroethylamine (pK_a 8·6) gives an almost total elimination of chloride ion but only about 10% of the theoretical acidity is developed. This means that only one-tenth of the carbonium ion formed reacts with water. These results can be interpreted if it is assumed that the base competes with water for reaction with the carbonium ion. Since a stronger base will compete more efficiently, more quaternary salt is formed in the case of the dimethylamine derivative. The tetrahydronaphthylamine derivatives being weaker bases compete less effectively and only about 10% of quaternary salt is formed. There is no indication of sulphonium-salt formation in the hydrolysis of di-2-chloroethyl sulphide in aqueous acetone, but about 10% of sulphonium salt is formed in the case of ethyl chloroethyl sulphide. At physiological pH (about 7·5) approximately 90% of dimethyl-2-chloroethylamine will be in the form of an ammonium cation which cannot yield a carbonium ion, and of the molecules yielding such an ion a high proportion will not be available for reaction with functional centres in the biological systems because of quaternary-salt formation. This should be borne in mind when conclusions are drawn from the fact that this compound is biologically inactive whereas the corresponding difunctional compound, which will be more reactive towards external centres, is effective. These objections would not appear to apply to the derivatives of aromatic amines which are much weaker bases (for example, *NN*-di-2-chloroethylaniline, pK_a 2·2; *N*-ethyl-*N*-2-chloroethylaniline, pK_a 3·5) or to the chloroethyl sulphides.

Experimental.

8-Ethyl-2-naphthylamine.—8-Acetyl-2-naphthylamine (Brown *et al.*, *loc. cit.*) (16 g.) was added to a cooled solution of sodium hydroxide (11·2 g.) and hydrazine hydrate (18·4 ml.; 50% solution) in diethylene glycol (175 ml.) contained in a flask carrying a short air condenser. The mixture was gradually heated to 195°. After 3 hours at this temperature the solution was cooled and extracted with ether. 8-Ethyl-2-naphthylamine (14·5 g.) was obtained as a brown oil when the dried extract was distilled. When a benzene solution of the amine was warmed with a slight excess of acetic anhydride the *acetyl* derivative, m. p. 167°, was formed (Found: C, 79·1; H, 7·2. $C_{14}H_{15}ON$ requires C, 78·8; H, 7·1%).

5- and 6-Nitro-1 : 2 : 3 : 4-tetrahydronaphthalene. 1 : 2 : 3 : 4-Tetrahydronaphthalene (264 g.) was nitrated as described by Schroeter (*loc. cit.*). The cooled nitration mixture was extracted with benzene (1500 ml.), and the washed and dried extract was allowed to percolate through a long column of activated alumina. Evaporation of the eluates gave a pale brown oil which was distilled (under reduced pressure) and the fraction, b. p. 140—180°/15 mm., was redistilled in a Towers fractional distillation unit, incorporating an electrically heated column and a variable take-off head. Three sharply separated fractions were obtained: (*a*) unchanged tetrahydronaphthalene, b. p. 90°/3 mm.; (*b*) 5-nitro-1 : 2 : 3 : 4-tetrahydronaphthalene, b. p. 154°/7 mm. (60 g.; m. p. 33°) (Schroeter gives m. p. 34°); and (*c*) 6-nitro-1 : 2 : 3 : 4-tetrahydronaphthalene, b. p. 158°/7 mm. (45 g.; m. p. 31·5°) (Schroeter gives m. p. 31·4°).

5 : 6 : 7 : 8-Tetrahydro-1- and -2-naphthylamine.—The nitro-compound (50 g.) dissolved in ethanol (200 ml.) containing Raney nickel catalyst (10 g.) was shaken in an atmosphere of hydrogen, at a pressure slightly greater than atmospheric, until the theoretical volume of gas was absorbed. After the addition of a slight excess of concentrated hydrochloric acid to the filtered solution it was concentrated under reduced pressure. The colourless plates of the hydrochloride which separated were dissolved in water and the base, liberated by addition of 2N-sodium hydroxide, was extracted with ether. After being dried over potassium hydroxide the amine was distilled; in this way 5 : 6 : 7 : 8-tetrahydro-1-naphthylamine (30 g.), b. p. 114°/3 mm., and 5 : 6 : 7 : 8-tetrahydro-2-naphthylamine (33 g.), b. p. 115°/4 mm., were obtained from the corresponding nitrotetrahydronaphthalenes.

1 : 2 : 3 : 4-Tetrahydro-1-naphthylamine.—Sodium (63 g. in small pieces) was added to a solution of 1-keto-1 : 2 : 3 : 4-tetrahydronaphthalene oxime (38 g.) in ethanol (500 ml.) at such a rate that the

mixture was kept refluxing gently. After the addition of water (600 ml.) the mixture was steam-distilled, the distillate being collected in a receiver containing hydrochloric acid (80 ml.; 5N.). When this solution was concentrated and cooled crystals of the amine hydrochloride separated; these were dissolved in water and the base was liberated by adding potassium hydroxide. The tetrahydronaphthylamine was obtained as a colourless viscous liquid when distilled in an atmosphere of hydrogen; it had b. p. 114°/10 mm. (Bamberger and Bammann, *Ber.*, 1889, **22**, 951, give b. p. 246·5°/714 mm.).

Halogenation of ac-*Tetrahydronaphthyldi-2-hydroxyethylamines.*—The hydroxyethyl compound (0·1 mole) dissolved in chloroform (50 ml.) was added to a solution of thionyl chloride (or bromide) (0·2 mole) in chloroform (50 ml.) and the mixture was heated under reflux for one hour. The residue obtained after removal of the solvent under reduced pressure was crystallised from ethanol (charcoal) and gave the hydrochloride or hydrobromide of the chloroethylamine.

N-2′-*Chloroethyl-2-aminofluorene.*—2-Aminofluorene (11·1 g.), ethylene oxide (3·1 ml.), and benzene (10 ml.) were heated in a sealed tube at 90° for 8 hours. The product was diluted with benzene and the solution allowed to percolate down a long column of activated alumina. The early eluates contained unchanged amine but on developing the chromatogram with fresh benzene *N*-2′-hydroxyethyl-2-aminofluorene was obtained. The hydroxy-compound (5 g.) was dissolved in chloroform [150 ml.; dried ($CaCl_2$)] and to the ice-cooled solution phosphorus pentachloride (10 g.) was added slowly with shaking. After being kept in the ice-chest overnight the clear solution was poured on crushed ice, and the residue obtained by evaporating the dried chloroform layer was dissolved in benzene and allowed to percolate through a short column of alumina. The eluates contained the chloro-compound which formed prisms, m. p. 127°, from light petroleum (b. p. 60—80°).

NN-*Di*-2-(*diethyldithiocarbamatoethyl*)-p-*anisidine.*—*NN*-Di-2-chloroethyl-*p*-anisidine (2·5 g.) dissolved in 50% aqueous acetone (200 ml.) containing sodium diethyldithiocarbamate (3·4 g.) was heated under reflux for 2 hours. The oil which separated after removal of the acetone under reduced pressure was dissolved in benzene and purified chromatographically. NN-*Di*-2-*diethyldithiocarbamatoethyl*-p-*anisidine* formed thick prismatic needles, m. p. 85—86°, from ether or light petroleum (b. p. 40—60°) (Found: C, 53·6; H, 7·5. $C_{21}H_{35}ON_3S_4$ requires C, 53·3; H, 7·4%).

NN-*Di*-2 : 3-*epoxypropyl*-p-*anisidine.*—*NN*-Di-3-chloro-2-hydroxy-*n*-propyl-*p*-anisidine (40 g.) was suspended in dry ether (500 ml.) and the mixture gently refluxed whilst finely powdered potassium hydroxide (40 g.) was slowly added. After one hour all the amine had dissolved; the solution was filtered and evaporated, and the residue dissolved in benzene and then shaken with activated alumina (20 g.). The *anisidine* distilled as a yellow oil, b. p. 228—229°/9 mm. (Found: C, 66·7; H, 7·3. $C_{13}H_{17}O_2N$ requires C, 66·3; H, 7·3%).

Hydrolysis of Chloroethylamines.—The hydrolysis rates given in Table II were determined exactly as described in Part I and reactions in the presence of sodium thiosulphate were carried out by adding the required amount of the salt to the water before mixing with acetone; otherwise the conditions were the same. The thiosulphate consumption was followed by titration of an aliquot, diluted with twice its volume of water, with 0·1N-iodine solution (starch indicator).

This investigation has been supported by grants made to the Royal Cancer Hospital by the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, the Anna Fuller Fund, and the Division of Research Grants of the U.S. Public Health Service, and was carried out during the tenure by one of the authors (W. C. J. R.) of a Sir Halley Stewart Fellowship. The authors thank Professor G. A. R. Kon, F.R.S., for his interest in this work and Miss K. Chilton and Miss J. Ross for carrying out the semi-microanalyses.

THE CHESTER BEATTY RESEARCH INSTITUTE, THE ROYAL CANCER HOSPITAL,
FULHAM ROAD, LONDON, S.W.3. [*Received, February 9th*, 1950.]