[1949] Ross: Aryl-2-halogenoalkylamines. Part III. 2589

547. Aryl-2-halogenoalkylamines. Part III. The Reactions of NN-Di-2-chloroethyl-p-anisidine and β-Naphthyldi-2-chloroethylamine in Aqueous-acetone Salt Solutions.

By W. C. J. Ross.

The reactions of NN-di-2-chloroethyl-p-anisidine and β -naphthyl-di-2-chloroethylamine in aqueous acetone solutions of various salts have been studied. These arylhalogenoalkylamines react under mild conditions with anions of organic and inorganic acids to form esters; the characterisation of a number of these esters is described.

MANY of the aryldi-2-halogenoalkylamines described in Parts I and II (this vol., pp. 183, 1972) show a considerable cytotoxic activity as judged against the growth of various animal tumours

Ross : Aryl-2-halogenoalkylamines. Part III.

(Haddow, Kon, and Ross, *Nature*, 1948, **162**, 824), and more recently tumour induction has been achieved with these "aromatic nitrogen mustards" (Haddow, Horning, and Koller, in the press). The reactions of these compounds under mild conditions approximating to those found in biological systems are therefore being studied. In this paper it is shown that aryldi-2-halogenoalkylamines react in aqueous-acetone solutions of a number of salts with the formation of stable esters.

In Part II it was suggested that the reaction of the halides in the presence of anions could be represented :

$$RX \stackrel{k_1}{\underset{k_1}{\overset{k_1}{\underset{k_1}{\overset{k_1}{\overset{k_1}{\overset{k_2}{\overset{k_1}{\overset{k_2}{\overset{k_1}{\overset{k_2}{\overset{k_1}{\overset{k_2}{\overset{k_2}{\overset{k_2}{\overset{k_1}{\overset{k_2}}{\overset{k_2}}{\overset{k_2}{\overset{k_2}{\overset{k_2}{\overset{k_2}{\overset{k}}{\overset{k_2}}{\overset{k}}{\overset{k_2}}{\overset{k}}{\overset{k_2}}{\overset{k}}{\overset{k}}{\overset{k}}{\overset{k}}{\overset{k}}{\overset{k}}{\overset{k}}{\overset{k}}{\overset{k}}{\overset{k}}{\overset{k}}{\overset{k}}{\overset{k}}{\overset{k}}{\overset{k}}}{\overset{k}}}{\overset$$

(where RX is the halide and A^- the anion).

From this scheme, which is recognised as a simplification of the actual process, it can be deduced that :

$$\frac{\text{Rate of formation of ROH}}{\text{Rate of formation of RA}} = \frac{k_w[R^+][H_2O]}{k_s[R^+][A^-]} = \frac{x_H}{x_{CI} - x_H} \quad . \quad . \quad . \quad (1)$$

(where $x_{\rm H}$ and $x_{\rm cl}$ are the percentage liberation of hydrogen and chloride ions, respectively, in the presence of an anion under standard conditions).

Ogston (*Trans. Faraday Soc.*, 1948, 44, 45) in his study of mustard gas has defined the competition factor (F) as $k_a/(k_w[H_2O])$, and from equation (1)

In the present experiments the competition factor has been calculated by using expression (2). Ogston used a somewhat different method : he had shown that

$$\frac{\text{Rate of liberation of hydrogen ion in the presence of an anion}}{\text{Rate of liberation of hydrogen ion in the absence of an anion}} = y H = 1/(1 + F[A^-]). \quad (3)$$
and hence:
$$F = (y_{\rm H} - x_{\rm H})/x_{\rm H}[A^-]. \quad (4)$$

(where $y_{\rm H}$ —which in the case of the arylhalogenoalkylamines has been shown to equal $y_{\rm CI}$ —is the percentage liberation of hydrogen ions in standard time when no anion is present). The two expressions (2) and (4) become identical if $y_{\rm H}$ (and therefore $y_{\rm CI}$) = $x_{\rm CI}$.

Since the hydrolysis of these halides proceeds by an S_N mechanism the rate-determining step is the preliminary ionisation of the halide. If the salt concentration is not sufficiently high to affect the rate of ionisation of the halide, then y_{cl} should be identical with x_{cl} since the production of chloride ions depends on the rate of ionisation and is independent of the fate of the carbonium ion. Another factor must, however, be taken into account, namely the back reaction whereby the halide is re-formed, for y_{cl} measures, not the rate of ionisation of the halide, but this rate less the rate of re-formation of the halide by the bimolecular back reaction. In the presence of an added anion the carbonium ion is no longer distributed between water and the chloride ion alone since a proportion will now react with the anion. The effect will be to reduce the extent of the back reaction because the ester (RA) which is formed will not re-ionise. Clearly the higher the competition from the anion the less chance there will be of re-forming the halide. x_{cl} will therefore exceed y_{cl} by an amount depending on the proportion of ester formed -this effect has been observed (see below). In Ogston's experiments with mustard gas the discrepancy between x_{cl} and y_{cl} would not have been so large as in the present case because of the lower competition factor of the chloride ion under the conditions of his hydrolyses. He found $F_{cl} = 21$, whereas we find $F_{cl} =$ approximately 250 under our conditions: this will mean that in the experiments with mustard gas the back reaction was relatively less important and no serious error was introduced by equating x_{cl} to y_{cl} and hence to y_{H} .

If an S_{N1} mechanism is operating there will be a limiting value for x_{CD} , for the rate of production of chloride ions can never exceed the rate of ionisation of the halide (see below).

It was realised that before an extended series of competition factors could be determined the effect of variations in the pH of the solution on the rate of ionisation of the halides would have to be studied. In view of the difficulty of determining the pH of acetone-water mixtures the problem was tackled by adding varying amounts of acid to the solutions in which the halide was hydrolysing. Table I shows the effect of adding nitric, sulphuric, hydrochloric, and acetic

or

Ross: Aryl-2-halogenoalkylamines. Part III.

TABLE I.*

Reaction of β-naphthyldi-2-chloroethylamine in 1:1 acetone-water solutions of acids and salts. Concn. of amine, 0.0066M. Temp., 37°. Time, 24 hours.

Added reagent.	н. %.	Cl. %.	% ester formed.
0:01N-HNO.	23.0	23.0	
0.02 N-H _s SO ₄	22.7	22.3	
0.02N-H ₂ SO ₄ + 0.02 N-Na ₂ SO ₄	19.0	26.0	7
0.02N-Na ₂ SO ₄	10.5	24.5	14
0.01N-AcÕH [*]	21.5	21.5	
0.01n-AcOH + 0.01 n-NaOAc	10.0	$22 \cdot 3$	12.7
0.01N-NaOAc	11.0	23.7	12.7
0.01N-HCl	9.0	8.5	(12.5)
0.01n-NaCl	7.5	7.5	(14.0)
Nil	21.5	21.5	

* In all the tables these figures are based on the replacement of both chlorine atoms.

acids on the rate of hydrolysis of β -naphthyldi-2-chloroethylamine. It will be seen that, except in the case of hydrochloric acid, the effect of the added acid is not very appreciable and, if the experiments in which the competition factor is determined are designed so that the concentration of free acid never exceeds 0.01N., then the effect of the acidity which is developed during the hydrolysis can be neglected. In the standard experiment for determining the factor the acidity never exceeds 0.005N. and is usually much less. The abnormal effect of hydrochloric acid is due to the addition of chloride ions and not to the acidity, since the same concentration of sodium chloride has a similar effect on the rate.

TABLE II.

Reaction of β-naphthyldi-2-chloroethylamine in 1:1 acetone-water solutions of sodium acetate. Concn. of amine: 0.0066M. Temp., 37°. Time, 24 hours.

Sodium acetate	н %	Cl %	Cl, %	F	Sodium acetate	H. %.	C1 %	Cl, %.	F.
0.2N.	2.5	26.0	(25.7)	47	0.01N.	11.0	23.7	(23.8)	116
0.1N.	3.25	25.8	(25.5)	69	0.005n.	14.5	$23 \cdot 2$	(23.0)	121
0.05n.	4.75	25.0	$(25 \cdot 3)$	85	0.0025n.	17.5	22.7	$(22 \cdot 4)$	120
0·02n.	8.0	24.5	(24.5)	103					

Table II shows the effect of varying concentration on the competition factor of the acetate ion; the factor is not as constant as that found by Ogston (*loc. cit.*) in his studies on mustard gas in almost completely aqueous solutions. At higher concentrations the salt will be less completely ionised, and this will lower the anion concentration and hence the competition factor.

In view of this variation at higher concentrations it was decided to estimate the competition factors of a range of anions at a concentration of 0.02N, that is, a concentration of 0.02M for the sodium salts of monobasic acids and of 0.01M. for the salts of dibasic acids. The reactions were carried out at 37° in aqueous acetone (50% by volume) since it was desired to demonstrate that the halogenoalkylamines could form esters under mild conditions. It has not yet been possible to study the reactions in completely aqueous solutions because of the very low solubility of the compounds in water. The total amount of halide reacting in these experiments does not exceed 26%, and thus the extent of reaction is similar to that in Ogston's studies.

Table III shows the results obtained. The total amount of halide reacting is calculated from the chloride ion titre (x_{cl}) and the amount of ester formed from the difference between the chloride and hydrogen ion titres $(x_{cl} - x_{fl})$. The expected increase in x_{cl} as more ester is formed is shown in Tables II and III. The expression

$$x_{\rm Cl} = y_{\rm Cl} + 0.18 (x_{\rm Cl} - x_{\rm H})$$

$$x_{\rm Cl} = (y_{\rm Cl} - 0.18x_{\rm H})/0.82 \dots (5)$$

gives reasonable agreement with observed values (see Table II). This expression has been used to calculate the amount of halide reacting in those cases where the chloride ion titration cannot be performed owing to the interference of the anion (e.g., for tartrate, succinate, oxalate, etc.); figures obtained in this way are shown in parentheses in Table III. If the anion has a very high competition factor, then $x_{\rm H}$ will approach 0 and $x_{\rm cl}$ will approach $y_{\rm cl}/0.82 = 21.5/0.82 = 26.2\%$;

TABLE III.

Reaction of β -naphthyldi-2-chloroethylamine in 1:1 acetone-water solutions of various sodium salts. Concn. of amine: 0.0066M. Concn. of salt: 0.02N. Temp., 37°. Time, 24 hours.

			Ester formed	(H-Cl), %	0
Anion.	Н, %.	Cl, %.	(H-Cl), %.	$\frac{-1}{Cl}$ $%$	$F \times 10^{-2}$.
Thiosulphate	0.75	(26.0)	25.25	96	16.8
Iodide	1.6	$(25 \cdot 8)$	$24 \cdot 2$	94	7.6
Chloride	4.25	$25 \cdot 2^{\prime}$	21.0	83	2.5
Phenylacetate	5.5	25.5	20.0	78	1.8
Adipate	5.75	(25.0)	19.25	77	1.7
Succinate	6.6	(24.8)	18.2	74	1.4
Oxalate	6.6	(24.8)	18.2	74	1.4
Mandelate	6.75	25.2	18.5	73.5	1.4
Crotonate	6.75	25.0	18.25	73	1.35
Fumarate	6.75	(24.7)	18.0	73	1.35
Bromide	7.0	(24.6)	17.6	71.5	1.25
Malonate	$7 \cdot 0$	(24.6)	17.6	71.5	1.25
Benzoate	7.25	25.0	17.7	71	$1 \cdot 2$
Malate	7.75	(24.5)	16.75	68.5	1.1
Maleate	8.0	$(24 \cdot 4)$	16.4	67	1.0
Acetate	8.0	24.5	16.5	67	1.0
Tartrate	8.75	$(24 \cdot 3)$	15.5	64	0.9
Sulphate	10.5	24.5	14.0	57.5	0.7
Formate	10.5	$24 \cdot 2$	13.8	57	0.65
Hippurate	10.5	(23.9)	13.4	56	0.65
Lactate	11.0	24.5	13.5	55	0.6
Glycollate	11.25	24.5	13.2	54	0.6
Chloroacetate	13.0	23.8	10.7	45	0.4
Fluoride	18.75	22.5	3.8	17	0.2
Nitrate	20.25	22.0	1.8	8	0.04
Nil	21.5	21.5	0		

this means that $26\cdot2\%$ of the halide is ionised under the standard conditions. In confirmation of this is the fact that, when thiosulphate is present, almost all the carbonium ions react with this anion—because of its high competition factor—and the thiosulphate consumed indicates that $26\cdot5\%$ of the carbonium ions are actually formed in the 24-hour period.

No great accuracy is claimed for the values of the competition factors, particularly those of thiosulphate and iodide, the purpose of this work being first to show that aryldi-2-halogenoalkylamines will react in solutions containing ions to form esters, and secondly to demonstrate that there is a difference in the reactivity of various anions. An alternative method of expressing the reactivity of an anion is given in Table III in the column which shows the percentage of halide which reacts with the anion; *e.g.*, in a 0.02N-solution of sodium acetate, 67% of the reacting β -naphthyldi-2-chloroethylamine forms the diacetate. The value of the competition factor for the chloride ion has been calculated in the same manner as for any other anion using the expression (5) to give x_{Cl} ; this treatment makes the value somewhat hypothetical since in reality $x_{Cl} = x_{H}$. The general order of the competition factors of the various anions is the same as that found for the same anions in their reactions with mustard gas (Ogston, *loc. cit.*; Linstead and Doering, O.S.R.D. Report No. 1094, Dec. 9th).

The formation of esters under the conditions of the determination of the competition factor has been verified by the isolation and characterisation of a number of the derivatives. The *diformate, diacetate, di(chloroacetate), di(phenylacetate), dibenzoate,* and *dimandelate* of NN-di-2-hydroxyethyl-2-*p*-anisidine, and the *diacetate* and *dibenzoate* of β -naphthyldi-2-hydroxyethylamine have been obtained.

It was stated in Part I that iodoethylamines could not be obtained in reasonable yield from the corresponding chloroethylamines by the action of sodium iodide in acetone solution because of the slow rate of the bimolecular reaction. It is, however, quite feasible to prepare these compounds by allowing the chloroethylamine to react with an aqueous acetone solution of sodium iodide. The iodide ion has a high competition factor for the carbonium ion derived from the chloroethylamine with the result that most of the chloro-compound is eventually converted into the iodoethylamine at a rate dependent on the rate of ionisation of the chloride. NN-Di-2-iodoethyl-p-anisidine and β -naphthyldi-2-iodoethylamine have been prepared by this method. When sodium iodide is added to a saturated solution of NN-di-2-chloroethyl-panisidine in 50% acetone at 37°, N-2-chloroethyl-N-2-iodoethyl-p-anisidine separates as an oil after several hours; its formation involves the preliminary ionisation of one chlorine atom, followed by the combination of the carbonium ion thus formed with the highly competing

[1949] Ross: Aryl-2-halogenoalkylamines. Part III. 2593

iodide ion. The chloroiodo-compound being less soluble than the original dichloride separates from the solution, and no further action is possible. The formation of fluoroethylamines by this method is unfortunately not possible because of the low competition factor of the fluoride ion.

The figures in Table I indicate that there is no appreciable production of esters when β naphthyldi-2-chloroethylamine reacts in solutions containing 0.02N-sulphuric or 0.01N-acetic acid, whereas in the presence of 0.01 n-hydrochloric acid almost as much ester is formed as in the presence of 0.01n-sodium chloride. The reason for the non-formation of esters is suggested by experiments in which both acid and salt are added to the solution. When sodium acetate and acetic acid are both added, the amount of ester formed is practically identical with that when sodium acetate alone is present, but when sodium sulphate and sulphuric acid are both added there is less ester formed than in the presence of sodium sulphate alone. Acetic acid, being a weak acid, will be but slightly ionised in 50% acetone and the non-formation of ester in this case will be due to the absence of anions---the carbonium ion will not react with an undissociated carboxyl group. In the case of sulphuric acid it is clear that there is reduced ester formation even when the concentration of sulphate ions is appreciable. It is probable that the rate of hydrolysis of the alkyl sulphate formed is increased in the presence of free acid and that this will account for the reduced ester formation. Alkyl chlorides are known to be more resistant to hydrolysis than alkyl sulphates, thus accounting for the considerable proportion of ester formed in the presence of hydrochloric acid.

In the method for determining competition factors it is assumed that, during the period of the experiment, the reaction of the halide follows a unimolecular course. Since there are two chlorine atoms being successively replaced the overall reaction will only follow a unimolecular course if both atoms are replaced at a comparable rate. In order to obtain information concerning the relative rates of reaction of the two chlorine atoms a fuller study of the hydrolyses of NN-di-2-chloroethyl-*p*-anisidine and β -naphthyldi-2-chloroethylamine was made. Table IV shows that the rate constants based on a unimolecular reaction become progressively smaller. This in itself cannot be taken to indicate that the chlorine atom in the chlorohydroxy-compound is ionised at a slower rate than the chlorine atom in the dichloro-compound because of the increasing importance of the bimolecular back reaction whereby the halide is re-formed from the carbonium ion and the chloride ion.

It was thought that if the hydrolyses were carried out in the presence of silver nitrate the effect of this back reaction could be eliminated as the chloride ion would be removed as fast as it was formed. The nitrate ion has a low competition factor and thus would not seriously affect the course of the reaction. Actually the rate of the reaction of the halide in the presence of silver nitrate was considerably faster than would have been expected simply by the suppression of the back reaction. The reaction of the halide in solutions containing silver nitrate is more complex than in the presence of sodium salts; *e.g.*, whereas it can be seen from Table II that when the concentration of sodium acetate is increased the extent of the reaction of the halide increases in proportion to this concentration (Table V). The results indicate a bimolecular reaction between the silver nitrate or the silver cation and the halogenoethylamine superimposed upon the normal hydrolysis. The small differences in the percentages of hydrogen and chloride ions liberated at higher silver nitrate concentrations (Table V) are, of course, due to the small amount of competition from the nitrate ion.

	Т	ABLE	IV.	
--	---	------	-----	--

Hydrolysis of (A) NN-di-2-chloroethyl-p-anisidine and (B) β-naphthyl-di-2-chloroethylamine in 1: 1 acetone-water. Concn. of amine, 0.0066M. Temp., 37°.

А.			B.			
Time, hrs.	Н, %.	Cl, %.	k, hr1.	H, %.	Cl, %.	k, hr1.
3	32	31	0.124			
61	46	48	0.100			
24^{-}	83	83	0.074	22	23	0.0109
48	100	97	(0.073)	39	37	0.0096
72	100	98	· /	52	49	0.0093
96				61	56	0.0086
168				85	73	0.0078
216				102	82	0.0079

The values of k are calculated from the chloride values because there is a small increase in acidity, particularly in series (B), which seems to be associated with the darkening of the solution; it is probably connected with the light-catalysed decomposition of the amines (compare Part I).

2594

Ross: Aryl-2-halogenoalkylamines. Part III.

TABLE V.

Reaction of β-naphthyldi-2-chloroethylamine in 1:1 acetone-water in the presence of silver nitrate. Concn. of amine, 0.0066M. Time, 24 hours. Temp., 37°.

Concn. of AgNO ₃	0	0.0083n.	0·0133n.	0·02n.	0.0266n.
н, %	21.5	44.8	58.3	67.5	87.8
Cl, %	21.5	45.0	58.3	70.0	90.5

TABLE VI.

Hydrolysis of β-naphthyldi-2-chloroethylamine in 1:1 acetone-water containing sodium hydroxide. Concn. of amine, 0.0066M. Temp., 37°. Time, 24 hours.

Concn. of NaOH, N	0	0.005n.	0.01N.	0.02n.	0·03n.	0.04n
Cl, %	21.5	25.5	$32 \cdot 2$	3 6·0	40.0	43 ·0

TABLE VII.

Hydrolysis of β-naphthyldi-2-chloroethylamine in 1:1 acetone-water containing (a) 0.04n-sodium hydroxide and (b) 0.04n-sodium hydroxide plus 0.02n-sodium chloride. Concn. of amine, 0.0066m. Temp., 37°.

Time, hrs.	((a).	(b).		
	Čl, %.	$k, hr.^{-1}$.	Ćl, %.	k, hr1.	
24	43	0.023	37	0.019	
48	67	0.023	61	0.020	
72	79.5	0.022	75.5	0.019	
120	95	0.025	92	0.021	
143	97		94		
170	98		98		

TABLE VIII.

Reaction of (A) NN-di-2-chloroethyl-p-anisidine and (B) β-naphthyldi-2-chloroethylamine in 1:1 acetone-water in the presence of 0.02N-sodium benzoate. Concn. of amine, 0.0066M. Temp., 37°.

	(A).			(B).				
Time, hrs.	н , %.	Cl, %.	$k, hr.^{-1}$.	H, %.	Cl, %.	k, hr1.		
3	15	41	0.176	_				
61	19.5	64	0.157					
24	30	97.5	0.153	7.25	25	0.0120		
48	33	101		13.2	45	0.0125		
72	34	101		17.5	59.5	0.0125		
96	33	101		22	66	0.0113		
168				27.4	82	0.0104		
216	_	_		31.6	89	0.0102		

Another method by which the effect of the back reaction could be eliminated, suggested by Bartlett, Davis, Ross, and Swain (J. Amer. Chem. Soc., 1947, 69, 2977), involves carrying out the hydrolysis in the presence of an excess of hydroxyl ions which have a much higher competition factor for the carbonium ion than have chloride ions. Table VI shows the effect of adding varying amounts of sodium hydroxide to solutions in which β -naphthyldi-2-chloroethylamine is being hydrolysed. As in the case of silver nitrate the amount of halide reacting increases in proportion to the concentration of sodium hydroxide, suggesting some direct reaction between the hydroxyl ions and the halide since the rate of elimination of chloride ions exceeds the postulated rate of ionisation of the halide. Table VII shows the course of the complete hydrolysis of the β -naphthyl derivative in the presence of 0.04N-sodium hydroxide alone and with the addition of sodium chloride-the relatively small effect of increasing the chloride ion concentration to 0.02 n. confirms the high competition factor of the hydroxyl ion. When 50% acetone solutions containing sodium hydroxide are kept at 37° there is a small consumption of alkali and, for this reason, only the amount of chloride ion liberated can be measured with accuracy. It is obviously impossible to use either of these suggested methods for the elimination of the back reaction with chloride ions.

The course of the reaction of NN-di-2-chloroethyl-*p*-anisidine and β -naphthyl-di-2-chloroethylamine in the presence of benzoate ions is shown in Table VIII. As has already been indicated the back reaction with chloride ions is reduced in the presence of competing anions. This can readily be observed by comparing the figures in Tables IV and VIII. It is also of

[1949] Ross: Aryl-2-halogenoalkylamines. Part III. 2595

interest to note that the unimolecular rate constant for the disappearance of halide—based on the chloride-ion values—does not fall so much in the presence of benzoate ions; this is also due to the suppression of the back reaction. The unimolecular rate constant for the initial stage of the reaction of β -naphthyldi-2-chloroethylamine based on the rate of production of the carbonium ion (p. 2592) is 0.0127 hr.⁻¹.

It is not possible to deduce the rate constant for the reaction of the chloride atom in the chlorohydrin (I) from any of the above experiments, firstly because of the appreciable back reaction when no added anions are present, and secondly because when an anion such as the benzoate ion is added to diminish the effect of this back reaction the second stage of the process involves, not the chlorohydrin (I), but mainly the chlorobenzoate (II).

$$\begin{array}{ccc} 2\text{-}C_{10}\text{H}_{7}\text{\cdot}\text{N} \underbrace{\begin{matrix} \text{CH}_{2}\text{\cdot}\text{CH}_{2}\text{C}\text{H}_{2}\text{C}\text{H}_{2}\text{\cdot}\text{OH} \\ \text{(I.)} \end{matrix} \\ \begin{array}{c} 2\text{-}C_{10}\text{H}_{7}\text{\cdot}\text{N} \underbrace{\begin{matrix} \text{CH}_{2}\text{\cdot}\text{CH}_{2}\text{C}\text{H}_{2}\text{OBz} \\ \text{CH}_{2}\text{\cdot}\text{CH}_{2}\text{C}\text{H}_$$

The rate of reaction of the second chlorine atom will depend on the nature of the substituent Y in (III). It was shown in Part I that the chlorine atom is replaced more readily when Y = H than when Y = Cl. Generally the reactivity will depend on the electron displacement caused by the substituent Y. An approximate guide to the effect of a substituent is obtained from the dissociation constant of the acid HY, for a strong electron-attracting group will give rise to a strong acid. Possible substituents can be arranged in the following order of electron-attracting power, X > OBz > OH > NHR, so that a halogen atom (X) would be expected to produce the maximum reduction of activity in the second chlorine atom. The compound (III; Y = NHR) should have a more reactive chlorine atom than the chlorohydrin (I) and in consequence the rate of elimination of chloride ions from an arylhalogenoalkylamine should be faster in the presence of an amine. This has been observed in the reactions of β -naphthyldi-2-chloroethylamine in the presence of aromatic amines, and this work, which is being extended, will form the subject of a later communication.

The results now presented confirm the view put forward in Part II that, when they react with ionised carboxyl groups in biological material, the aromatic nitrogen mustards would form more stable products than would their aliphatic analogues (compare Fruton, Stein, and Bergmann, J. Org. Chem., 1946, 11, 567).

EXPERIMENTAL.

Reaction of β -naphthyldi-2-chloroethylamine in 1 : 1 Acetone-Water at 37°.—(a) In the presence of acids. β -Naphthyldi-2-chloroethylamine (536 mg.) was dissolved in AnalaR acetone (150 ml.), water (150 ml.) containing the required amount of acid was added, and the mixture was rapidly heated to 37°. The stoppered vessel was then transferred to a thermostat. After 24 hours the mixture was rapidly cooled and titrated first with 0-1N-solium hydroxide (phenolphthalein) and then with 0-1N-silver nitrate (dichlorofluorescein). The results were expressed as the percentage elimination of hydrogen and chloride ions based on the complete reaction of the halide (Table I).

(highly block of the complete reaction of the halide (Table I). (b) In the presence of salts. The conditions were exactly as above except that the sodium salts were dissolved in the water before mixing. Just before heating to 37° the mixtures were rendered faintly alkaline to phenolphthalein with 0·1N-sodium hydroxide (acetone always contains some titratable acid). Allowance was made for this acidity in calculating the results of experiment (a). After 24 hours the mixtures were titrated as before; in some cases separation of the ester occurred on cooling the mixture, and the presence of this interfered with the chloride end-point. Sharp end-points were obtained if acetone sufficient to dissolve the ester was added after completing the titration of the acid.

(c) In the presence of silver mitrate. The experiments were carried out exactly as in (b) except that after 24 hours sufficient 0.1N-sodium chloride was added to precipitate all the silver which had originally been added, before proceeding with the two titrations.

been added, before proceeding with the two titrations. (d) In the presence of sodium thiosulphate. The amount of thiosulphate consumed by interaction with the carbonium ion was determined by titration of an aliquot with 0.1N-iodine at the start of the experiment and after 24 hours. In order to obtain a sharp end-point to the titration using starch as indicator it was necessary to dilute the aliquot with twice its volume of water.

Solution and and the first of the location of solution to be point point of the form of

started as before. At appropriate intervals aliquots (100 ml.) were removed and titrated in the usual manner. During the course of the longer hydrolyses some evaporation occurred, and allowance had to be made for this. The results are presented in Tables IV and VIII. *Isolation of the Esters.*—In a typical experiment NN-di-2-chloroethyl-p-anisidine (1 g.) and sodium benzoate (5 g.) were dissolved in 1 : 1 acetone-water (200 ml.), and the solution was kept at 37° until 100% elimination of chloride ion had occurred. The acetone was then removed under reduced pressure, and the residue was extracted with benzene. After passage of the dried extract through a column of activated alumina, the solution was evaporated, giving the *dibenzoate* which crystallised from methanol in long flattened needles, m. p. 63—64° (Found : C, 71·3; H, 6·1. C₂₅H₂₅O₅N requires C, 71·6; H,

Barton and Brooks: The Application of the Method of 2596

6.0%). It afforded a *picrate* which crystallised from methanol as felted needles, m. p. 113—115° (Found : C, 57·1; H, 4·4. C₃₁H₂₈O₁₂N₄ requires C, 57·4; H, 4·4%). The following esters were made by similar methods. NN-Di-(2-formoxyethyl)-p-anisidine (Found : equiv., 134. C₁₃H₁₇O₅N requires equiv., 134), which gave a *picrate*, prisms (from benzene-methanol), m. p. 63—65° (Found : C, 45·6, H, 4·8. C₁₉H₂₀O₁₂N₄, CH₃·OH requires C, 45·5 : H, 4·6%). The picrate would not crystallise in the absence of methanol and the solvent of crystallisation was removed only after 4 hours at 40°(0:001 mm (Found : C 46.2 : H 4·4 C H O. N requires C, 46:0 : H picrate would not crystallise in the absence of methanol and the solvent of crystallisation was removed only after 4 hours at 40°/0.001 mm. (Found : C, 46.2; H, 4.4. $C_{19}H_{20}O_{13}N_4$ requires C, 46.0; H, 4.1%). NN-Di-2-acetoxyethyl- (Found : equiv., 148. $C_{15}H_{21}O_5N$ requires equiv., 148), NN-di-2-chloroacetoxyethyl- (Found : equiv., 180. $C_{15}H_{19}O_5NCl_2$ requires equiv., 182), NN-di-2-phenylacetoxy-ethyl- (Found : equiv; 224. $C_{27}H_{29}O_5N$ requires equiv., 224), and NN-di-2-phenylacetoxy-ethyl- (Found : equiv., 240). β -Naphthyldi-2-acetoxyethylamine (Found : equiv., 156. $C_{18}H_{21}O_4N$ requires equiv., 158). β -Naphthyldi-2-benzoyloxyethylamine, felted needles (from methanol), m. p. 92° (Found : C, 76.5; H, 5.9. $C_{28}H_{25}O_4N$ requires C, 76.5 : H, 5.7%), yields a picrate, prisms (from methanol), m. p. 128° (Found : C, 60.9 : H, 4.0. $C_{34}H_{25}O_{11}N_4$ requires C, 61.1; H, 4.2%). Where no m. p. is given the ester was obtained as a colourless oil. Formation of Iodoethylamines.—(a) NN-Di-2-chloroethyl-p-anisidine (1 g.) was dissolved in 1 : 1 acetone-water (600 ml.) containing sodium iodide (5 g.), and the solution was kept at 37°. After 48

acetone-water (600 ml.) containing sodium iodide (5 g.), and the solution was kept at 37°. After 48 hours the product was isolated and submitted to a chromatographic purification as already described. NN-Di-2-iodoethyl-p-anisidine, m. p. 38° (undepressed by a specimen, m. p. 40°, obtained by the method given in Part I), was obtained. β -Naphthyldi-2-iodoethylamine, m. p. 73°, was similarly prepared from the corresponding chloroethylamine.

the corresponding chloroethylamine. (b) NN-Di-2-chloroethyl-p-anisidine (1 g.) was dissolved in 1:1 acetone-water (200 ml.) containing sodium iodide (5 g.). After the solution had been kept at 37° for 4 hours a turbity developed, and after 10 hours a large drop of oil had separated. This was removed and dissolved in light petroleum (b. p. $40-60^{\circ}$), and the dried solution was passed through a short column of alumina. When the eluates were concentrated and then cooled to 0°, flattened needles, m. p. 28-31°, of N-chloroethyl-N-iodoethyl-p-amisidime were obtained (after complete hydrolysis in aqueous acetone solution 178 mg. of the iodo-chloride required 10.6 ml. of 0·1N-sodium hydroxide to neutralise the acidity and 10.7 ml. of 0·1N-silver nitrate to titrate the halogen ions liberated; $C_{11}H_{15}$ ONCII requires 10.5 ml. of each). The compound gives a *picrate*, which forms prisms, m. p. 114-115° (Found : C, 35.8; H, 3.2; N, 9.7. $C_{17}H_{18}O_8N_4$ CII requires C, 35.9; H, 3.2; N, 9.9%), from methanol. The di-iodo-compound was isolated from the adueous phase. aqueous phase.

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 conducted during the tenure by the author of a Sir Halley Stewart Fellowship. The author thanks Professor G. A. R. Kon, F.R.S., for his interest in this work.

CHESTER BEATTY RESEARCH INSTITUTE, FULHAM ROAD, LONDON, S.W.3.

[Received, April 29th, 1949.]