594. *Aryl-2-halogenoalkylamines. Part IV. The Reactions of* NN-*Di-2-chloroethyl-*p-*anisidine and* β-*Naphthyldi-2-chloroethylamine in Aqueous Acetone Solutions of Amines.*

By W. C. J. Ross.

The reactions of *NN*-di-2-chloroethyl-*p*-anisidine and β-naphthyldi-2-chloroethylamine in aqueous solutions containing primary, secondary, and tertiary amines have been studied. It is shown that these arylhalogenoalkylamines readily react as bifunctional alkylating agents under mild conditions. The effect of the replacement of one chlorine atom on the reactivity of the second is discussed.

In Part III (this vol., p. 2589) it was shown that esters are formed when arylhalogenoalkylamines react in aqueous solutions of various salts and it was postulated that the reaction proceeded by an S_N1 mechanism, the carbonium ion derived from the halide being assumed to combine directly with the anion. The present communication describes the reactions of these so-called " aromatic nitrogen mustards " with amines under similar conditions. The result sobtained are consistent with the assumption that the first stage in the reactions is the ionisation of the halogenoalkylamine.

The rate of reaction of β-naphthyldi-2-chloroethylamine in unbuffered 50% acetone solutions with and without the addition of aniline and also with varying amounts of *p*-toluidine is shown in Tables I and II. The rate of reaction of the halide—measured by the rate of appearance of chloride ions—is considerably greater when the amine is present. The increased rate is, however, probably not connected with a bimolecular reaction between the amine and the halide because, as can be seen from Table II, the rate of reaction is practically independent of the amine concentration. The small increase observed is almost certainly caused by the decreased probability of the back reaction with chloride ions (compare Part I).

The expression k_{Cl}, which is a measure of the rate of appearance of chloride ions from the dihalide, is increased in the presence of aniline. In contrast, the value of k_{Cl} for the reaction

of β-naphthyl-2-chloroethylamine, also shown in Table I, is only slightly affected by the addition of amine.

TABLE I.

Reaction of (a) *β-naphthyldi-2-chloroethylamine and* (b) *β-naphthyl-2-chloroethylamine in* 50% *acetone solution. Concn. of halide,* (a) 0·0066M., (b) 0·0132M., *with and without the addition of aniline. Temp.,* 37°.

(a).							(b).						
Amine added.	Nil.			0·02M-Aniline.				Nil.			0·02M-Aniline.		
Time in hours.	H, %.*	Cl, %.	k_{Cl}, hr.$^{-1}$.	H, %.	Cl, %.	k_{Cl}, hr.$^{-1}$.	Time in hours.	H, %.	Cl, %.	k_{Cl}, hr.$^{-1}$.	H, %.	Cl, %.	k_{Cl}, hr.$^{-1}$.
24	22	23	0·0109	35	36	0·0186	3	7·5	9	0·031	9	10	0·035
48	39	37	0·0096	55	56	0·0171	6	13·2	15	0·027	17	18	0·033
72	52	49	0·0093	67	68	0·0158	24	34	36	0·019	46	47	0·026
96	61	56	0·0086	75	76	0·0149	48	47	52	0·015	65	64	0·021
168	85	73	0·0078										
216	102	82	0·0079										

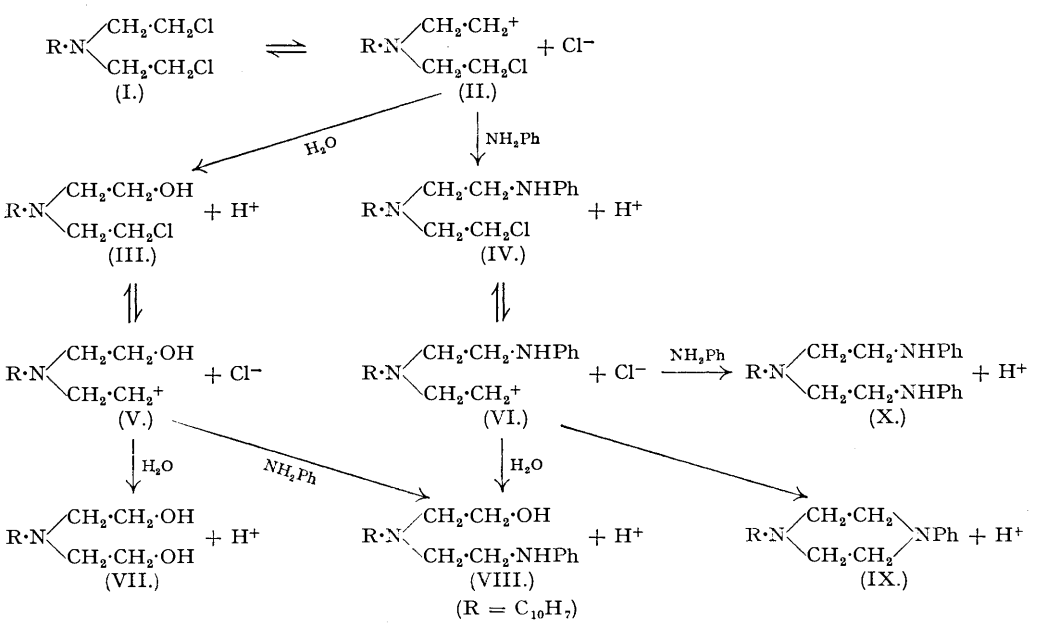
* The extra acidity developed in this experiment is apparently connected with the darkening of the solution (see Part III). In (*a*) the H and Cl titres are based on the reaction of both chlorine atoms. k_{Cl} has been calculated from the chlorine titres using the expression : $k_{Cl} = (2{\cdot}303/t) \log 100/(100 - \%\ Cl)$.

TABLE II.

Reaction of β-naphthyldi-2-chloroethylamine in 50% *acetone solution containing* p-*toluidine. Concn. of halide,* 0·0066M. *Temp.* 37°. *Time,* 24 *hours.*

	Concn. of *p*-toluidine.	H, %.	Cl, %.		Concn. of *p*-toluidine.	H, %.	Cl, %.
A	0·02M.	37	37	*C*	0·06M.	38·5	38·5
B	0·04M.	38	38				

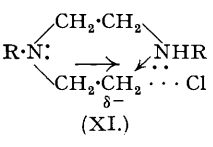
The sequence of reactions taking place when the dihalide reacts in the presence of aniline is as follows :



This scheme shows all the products that are theoretically possible; (VII) and (IX) have been isolated from the reaction mixture but (VIII) and (X) do not appear to be produced in significant quantities.

The rate-determining steps in the reaction will be the ionisation of the chlorine atoms in (I)

and (III) or (IV). As has already been pointed out in Part III, (IV) is expected to ionise more readily than (III) and hence the rate of reaction of the dihalide should be increased in the presence of a primary amine. This interpretation of the increased reaction rate is supported by the relative independence of the rate on the concentration of amine and by the non-existence of the effect in the case of the monohalide. In the latter case the small increase in the rate is merely due to a suppression of the back-reaction with chloride ions (II) ⟶ (I). The value of k_{Cl} (Table I) does diminish as reaction proceeds owing to the fact that this back-reaction becomes important when the concentration of chloride ions increases. The reactivity of the aromatic chloroethylamines is mainly due to the electron displacement induced by the lone pair of electrons on the nitrogen atom which facilitates the elimination of a chloride ion. The effect of the second nitrogen atom in (XI) will be to reinforce this electron displacement and an even greater rate of ionisation will result.



(XI.)

Besides a general displacement of charge along the chain of atoms there will probably also be an effect across space since the second nitrogen atom can approach close to the chlorine atom as shown by the fact that the main product of the reaction is a piperazine—the reaction does, in fact, provide a very convenient method for the synthesis of piperazines (Davis and Ross, following paper). The formation of (IX) from (IV) is greatly favoured on steric grounds and it is, no doubt, for this reason that little or no (X) is produced.

The possibility that a piperazine is formed from (IV) by an internal bimolecular-type reaction and that this is responsible for the increased rate of elimination of chloride ion appears to be unlikely for a number of reasons. First, when *NN*-di-2-chloroethyl-*p*-anisidine is heated with aniline or *p*-anisidine in dry acetone for two hours no significant amount of piperazine is formed, showing that the rate of bimolecular reaction between an amine and a chloroethylamine must be slow—this was to be expected in view of the very slow rate of replacement of the chlorine atom by iodine when the compound is heated with sodium iodide in dry acetone (another typical S_N2 type reaction; Part III). Again it has been pointed out above that the rate of reaction of β-naphthyl-2-chloroethylamine with aniline in aqueous acetone is no faster than the initial rate of ionisation of the halide. Lastly there is the fact that the rate of reaction of β-naphthyldi-2-chloroethylamine with *p*-toluidine is practically independent of the concentration of primary amine.

Ogston (*Trans. Faraday Soc.*, 1948, **44**, 45) has used a method for the determination of competition factors of substances which react with mustard gas in aqueous solution to give acidity. Briefly, the method consists in first allowing the halide to hydrolyse in the presence of an anion which reduces the amount of acidity developed and then allowing the hydrolysis to take place in the presence of the anion and the substance being examined; the increase in the amount of acidity developed is a measure of the reaction with the compound under test. It is not possible to obtain accurate values for the competition factors of amines by this method because of the increase in the rate of reaction of the halide when amines are added; the method of determining competition factors is based on the assumption that the halide is reacting at nearly the same rate throughout the experiment. Nevertheless this method can be used to assess the relative reactivity of a series of aromatic amines in competition with the acetate ion (Table III). The extent to which the amine reacts is proportional to its basicity, *p*-anisidine reacting more completely than *p*-chloroaniline. The percentage of chloride formed is a measure of the amount of arylhalogenoalkylamine reacting and it will be noted that more reacts in the presence of stronger bases—this is in agreement with the suggested mechanism for the activation of the second chlorine atom.

When glycine, alanine, or phenylalanine is present in unbuffered solutions in which *NN*-di-2-chloroethyl-*p*-anisidine is hydrolysing no reaction with the amino-acid takes place and only the di(hydroxyethyl)amine can be isolated, but when the ethyl ester of glycine is present 1-p-*methoxyphenyl*-4-*carbethoxymethylpiperazine* is formed.

TABLE III.

Reaction of β-naphthyldi-2-chloroethylamine in 50% acetone solution containing sodium acetate and various amines. Concn. of halide, 0·0066M. *Concn. of sodium acetate,* 0·02M. *Concn. of amines,* 0·02M. *Temp.,* 37°. *Time,* 24 *hours.*

Amine.	H, %.	Cl, %.	Amine.	H, %.	Cl, %.
p-Anisidine	30·0	34·5	β-Naphthylamine	21·3	31·0
p-Toluidine	29·0	34·0	*p*-Chloroaniline	11·5	25·2
Aniline	25·9	32·5	Nil	8·0	24·6

TABLE IV.

Reaction of β-naphthyldi-2-chloroethylamine in 50% acetone solution containing nitric acid and/or aniline. Concn. of halide, 0·0066M. Temp., 37°. Time, 24 hours.

Reagents added.	H, %.	Cl, %.	Reagents added.	H, %.	Cl, %.
Nil	21·5	21·5	0·02M-NH_2Ph	35	36
0·02M-HNO_3	24·5	24·5	0·02M-HNO_3 and 0·02M-NH_2Ph	25·0	25·2

It was shown in Part III and now confirmed, that when β-naphthyldi-2-chloroethylamine is hydrolysed in aqueous acetone containing a small amount of nitric acid there is a slight increase in the hydrolysis rate. If the solution is made 0·02M. with respect to aniline there is also an increase in the amount of halide reacting. If the solution contains aniline and nitric acid (0·02M. of each) no increase beyond that which would have been produced by the acid alone is observed (Table IV). This indicates that the carbonium ion derived from the halide does not react with the amine in the presence of acid. In other words, as would be expected, only the free amino-group can react whereas the ammonium cation $(RNH_3)^+$ cannot. This is important, for many of the basic groups present in biological systems will be highly dissociated at physiological pH and the amino-groups in amino-acids will be unreactive because of internal salt formation.

If the chromosome abnormalities induced by the di(chloroethyl)amines are due to a cross-linkage reaction (Goldacre, Loveless, and Ross, *Nature*, 1949, **163**, 667) it would seem improbable, in view of what has been said above, that this involves interaction with primary amino-groups. Since it is also known that di(chloroethyl) sulphide, which resembles chloroethylamines in many of its reactions, combines but slowly with thiol groups under physiological conditions (Dixon and Needham, *Nature*, 1946, **158**, 432), the centres most likely to react are ionised acidic groups (*e.g.*, carboxyl groups of proteins or secondary phosphoryl groups of nucleic acids).

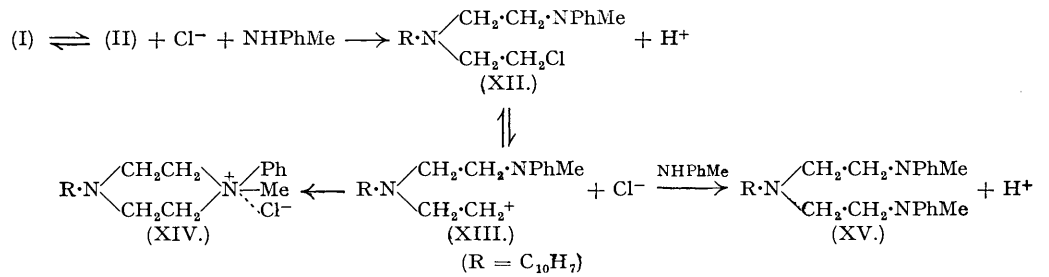
The rate of liberation of hydrogen and chloride ions when β-naphthyldi-2-chloroethylamine is allowed to hydrolyse in the presence of methylaniline is shown in Table V*a*. It will be seen that the total rate of reaction of the halide is about the same as in the presence of aniline but that the amount of hydrogen ion produced is much less. The reason for this result becomes clear when the sequence of reactions which occurs in the presence of secondary amine is considered.

TABLE V.

Reactions of β-naphthyldi-2-chloroethylamine in 50% acetone solution containing (a) 0·02M-*methylaniline and* (b) 0·02M-*dimethylaniline. Concn. of halide,* 0·0066M. *Temp.*, 37°.

	(*a*).				(*b*).			
Time in hours.	H, %.	Cl, %.	k_H, hr.$^{-1}$.	k_{Cl}, hr.$^{-1}$.	H, %.	Cl, %.	k_{Cl}, hr.$^{-1}$.	% reacting with water
24	23	36	0·0109	0·0186	5·5	23	0·0109	24
48	38	56	0·0100	0·0171	8·5	36	0·0093	23·6
72	48	73	0·0091	0·0181	11	50	0·0096	22
96	53	79	0·0079	0·0163	13	52	0·0077	25
117	—	—	—	—	15·5	54	0·0067	29
168	61	92	0·0056	0·0151	18·5	61	0·0056	30·5
216	66	100	0·0050	—	22·4	65	0·0049	34·5
275	—	—	—	—	29·5	71	0·0045	41·5

The early stages of the reaction (I) ⟶ (II) ⟶ (XII) are similar to those with a primary amine, but the carbonium ion (XIII) has been shown to react in two ways, giving either the

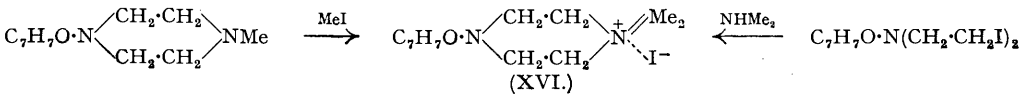


piperazinium chloride (XIV) by an internal quaternisation or (XV) by reacting with a further molecule of secondary amine. The isolation of NN-*di*-(2-N′-*methylanilinoethyl*)-p-*anisidine* and

the *picrate* corresponding to 4-phenyl-1-*p*-methoxyphenyl-4-methylpiperazinium chloride from solutions in which *NN*-di-2-chloroethyl-*p*-anisidine is hydrolysing in the presence of methylaniline confirms the proposed series of reactions. Stage (*a*), (I) ⟶ (II) ⟶ (XII), involves the formation of hydrogen and chlorine ions in equal amounts, as does stage (*b*), (XII) ⟶ (XIII) ⟶ (XV); but in stage (*c*), (XII) ⟶ (XIII) ⟶ (XIV), no hydrogen ions are formed. The difference in the amounts of hydrogen and chloride ions formed is, in fact, a measure of the extent of reaction (*c*) in which quaternary nitrogen is produced. The figures in Table V*a* indicate that 34% of the total reaction involves the formation of quaternary nitrogen, that is, that 68% of the chloroethylamine is transformed into the piperazinium salt. The total amount of methylaniline reacting cannot be deduced from the hydrogen-ion values because some simple hydrolysis to di(hydroxyethyl)amine always occurs. The figures in Table V*a* indicate that the increase in the rate of ionisation of the second chlorine atom is about the same in the presence of methylaniline and of aniline. This is to be expected on the explanation given above since the two aromatic bases have similar pK_a values (aniline, 4·58; methylaniline, 4·85).

The possibility that (XIV) might be formed first and then reconverted into (XIII)—in the same way that the ethyleneimonium ion derived from aliphatic chloroethylamines can be reconverted into the halide—was considered. However, Table VI*a* shows that during the hydrolysis of *NN*-di-2-chloroethyl-*p*-anisidine in the presence of methylaniline there is no increase in the hydrogen-ion value after all the chloroethylamine has reacted, thus indicating that there is no reconversion of (XIV) into (XIII); for if this occurred the whole of the halide would eventually be transformed into (XV) and the hydrogen and chlorine titres would become identical.

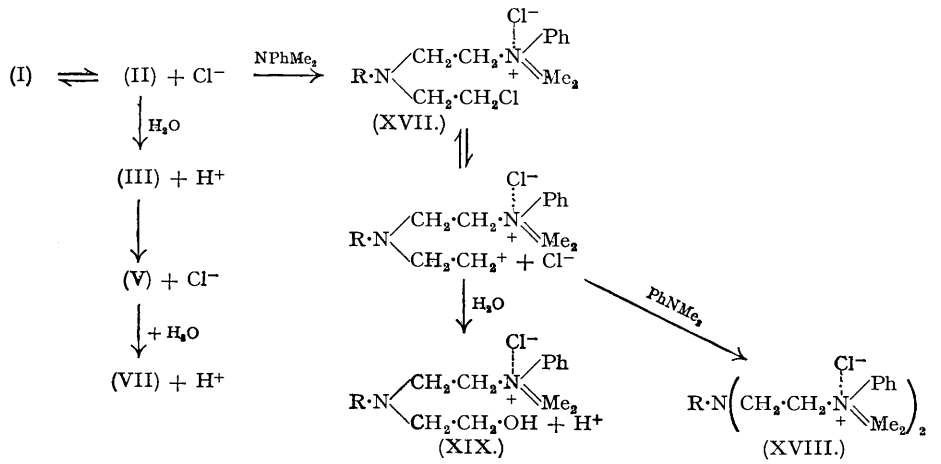
An attempt was made to prepare a piperazinium halide of type (XIV) by allowing methyl iodide to react with 1 : 4-diphenylpiperazine but no action took place after heating the reactants in benzene for 24 hours. No identifiable product was obtained by heating the piperazine in a sealed tube at 100° with methyl iodide, a method which has been described as giving the monomethiodide (Hofmann, *Jahresber.*, 1858, 353). It was, however, possible to prepare 1-p-*methoxyphenyl*-4 : 4-*dimethylpiperazinium iodide* (XVI) by two methods: (*a*) by the action of methyl iodide on 1-*p*-methoxyphenyl-4-methylpiperazine, and (*b*) by allowing *NN*-di-2-iodoethyl-*p*-anisidine to react with an aqueous acetone solution of dimethylamine.



(XVI.)

The piperazinium iodide was heated in aqueous acetone solution with or without an excess of aniline for 5 hours; no acidity developed and the unchanged halide was isolated from the solution. This again indicates that the quaternary salt is quite stable and no ring opening occurs.

When β-naphthyldi-2-chloroethylamine is allowed to react in 50% acetone containing dimethylaniline, the initial rate of elimination of chloride ions is the same as in aqueous acetone alone but the rate slows up considerably towards the end of the reaction (Table V*b*). The rate of liberation of hydrogen ions is very much reduced by the presence of the secondary amine. The sequence of reactions in this case is probably:



The dihydroxyethyl derivative (VII) and the *picrate* of the double quaternary salt (XVIII) have been isolated from the products of this reaction.

The intermediate (XVII) has a positively charged nitrogen atom on one ethyl side-chain and this will considerably reduce the rate of ionisation of the second chlorine atom. In the early stages of the reaction chloride ions are derived from the original dihalide, but later these ions come from (XVII) and hence their rate of production falls. That the presence of the quaternary nitrogen atom on one side chain of the compound does not completely suppress the ionisation of the second chlorine atom is shown by the fact that the amount of liberated chloride ion reaches 71% of the calculated value in 275 hours in the case of β-naphthyldi-2-chloroethylamine at 37° and practically 100% in 24 hours in the case of *NN*-di-2-chloroethyl-*p*-anisidine at 66° (Tables V*b* and VI*b*). If the second chlorine atom did not ionise the value could never exceed 50%.

The chloride-ion titres measure the rate of production of carbonium ion by all routes, and the hydrogen-ion titres measure the extent to which these carbonium ions react with water, so that an estimate can be made of the proportion of these ions that react with water. The percentage reaction with water at various stages of the process is shown in the final column of Tables V and VI. The value rises in each case towards the end of the reaction; this is because the amount of dimethylaniline available for reaction gradually decreases owing to quaternary-salt formation with carbonium ions and to hydrochloride formation with the acid formed in the hydrolysis. It was considered possible that the carbonium ion (XVII) might not be able to react so readily with a second molecule of dimethylaniline for steric reasons and that this might account for the relatively higher proportion of the reaction with water. However, Table VI*b* shows that of the last 30% of the dihalide reacting approximately one-half forms quaternary salt, indicating that the ion (XVII) can still react with a tertiary amine.

TABLE VI.

Reaction of NN-*di*-2-*chloroethyl*-p-*anisidine in* 50% *acetone solution containing* (a) 0·03M-*methylaniline*, (b) 0·03M-*dimethylaniline*. *Concn. of halide*, 0·01M. *Temp.* 66°.

	(*a*).		(*b*).		
Time in hours.	H, %.	Cl, %.	H, %.	Cl, %.	% reacting with water.
1	78	93	—	—	—
1½	—	—	26·5	70·5	37·6
2½	79·5	97·5	—	—	—
4	—	—	30·5	78·5	39
5½	80	99	—	—	—
24	80	100	42·5	99·5	43

No identifiable product other than the di(hydroxyethyl) derivatives was isolated when *NN*-di-2-chloroethyl-*p*-anisidine or β-naphthyldi-2-chloroethylamine was hydrolysed in the presence of phenol or thiophenol, but when sodium hydroxide equivalent to the phenol was added good yields of *di-2-phenoxyethyl-* and *di-2-phenylthioethyl-amine* were obtained. It would therefore appear that the carbonium ions derived from halogenoalkylamines will react with phenoxide ions and ionised thiol groups but not with the un-ionised forms. This is analogous to the reaction of the halides with carboxyl groups (compare the reactivity towards acetic acid and acetate ions, Part III).

EXPERIMENTAL.

Since it had been established that only a free amino-group would react with the carbonium ion derived from a halogenoalkylamine, most of the work described in the present paper deals with the reactions with aromatic amines which exist largely in the non-ionic form under the conditions chosen. There is also the added advantage that these amines are relatively weak bases and do not interfere with the volumetric determination of the hydrogen and chloride ions which are formed in the reactions.

Reaction of β-Naphthyldi-2-chloroethylamine in 50% *Acetone at* 37°.—(a) *In the presence of aniline* (*Table* I*a*), *methylaniline* (*Table* V*a*), *and dimethylaniline* (*Table* V*b*). β-Naphthyldi-2-chloroethylamine (1·072 g.) was dissolved in a mixture of AnalaR acetone (300 ml.) and water (300 ml.); aniline (1·11 g.), methylaniline (1·28 g.), or dimethylaniline (1·45 g.) was added and the mixture was rapidly heated to 37° and transferred to a thermostat. At appropriate intervals, aliquots (100 ml.) were removed and titrated first with 0·1N-sodium hydroxide (phenolphthalein) and secondly 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. During the reaction with aniline and methylaniline the solution developed a brown colour but this was not so pronounced in the presence of dimethylaniline. After 24 hours crystals of the piperazine derivative separated from the mixture containing aniline.

The reactions with β-naphthyl-2-chloroethylamine were carried out in a similar manner (Table I*b*).

(b) *In the presence of varying amounts of* p-*toluidine*. The conditions were exactly as above except

that in the first experiment (*A*) (Table II) 1·284 g. of *p*-toluidine were added, and in (*B*) 2·568 g. and (*C*) 3·852 g. of amine were present. The solutions were titrated after 24 hours and in each case the piperazine derivative had crystallised out. In order to estimate the amount of piperazine formed parallel experiments were carried out and the cooled solutions were filtered. The crystals were washed with a little methanol and ether and then weighed. The yields of piperazine were (*A*) 69%, (*B*) 70%, and (*C*) 72% (based on the amount of halide reacting). This method of isolation is only roughly quantitative so that these figures represent minimum yields showing that by far the greater amount of halide is converted into the piperazine.

(c) *In the presence of various amines and sodium acetate.* β-Naphthyldi-2-chloroethylamine (0·536 g.) was dissolved in acetone (150 ml.) and water (150 ml.) containing sodium acetate (0·816 g.). The required amount of amine was added, the reaction started as before, and after 24 hours the mixture was titrated in the usual manner (Table III).

(d) *In the presence of aniline and nitric acid.* The reaction was carried out exactly as under (*a*) except that where required 120 ml. of 0·1N-nitric acid were added to the water before mixing (Table IV).

Reaction of NN-*Di*-2-*chloroethyl*-p-*anisidine in* 50% *Acetone at* 66° *in the Presence of Methylaniline* (*Table* VI*a*) *and Dimethylaniline* (*Table* VI*b*).—*NN*-Di-2-chloroethyl-*p*-anisidine (0·500 g.) was dissolved in 50% acetone (200 ml.), and methylaniline (0·64 g.) or dimethylaniline (0·73 g.) was added. The mixture was heated rapidly to the b. p. (66°). At appropriate intervals the mixture was rapidly cooled and 50-ml. samples were removed for titration, the remainder being quickly reheated.

Various Reactions of NN-*Di*-2-*chloroethyl*-p-*anisidine.*—(a) *Amino-acids in unbuffered solution.* *NN*-Di-2-chloroethyl-*p*-anisidine (20 millimols.) and glycine, alanine, or phenylalanine (20 millimols.), dissolved in 1 l. of 50% acetone, were heated under reflux for 5 hours. After removal of the acetone under reduced pressure, the cooled mixture was extracted with ether—this extract contained a trace of resinous material. The aqueous solution was evaporated to a syrup, neutralised with sodium hydroxide, re-acidified with acetic acid, and then extracted with ether. This extract gave a solid which after crystallisation from benzene had m. p. 72—73°, undepressed by admixture with a specimen of *NN*-di-2-hydroxyethyl-*p*-anisidine, m. p. 73°. This was the only identifiable product in all three experiments.

(b) *Glycine ethyl ester.* The chloroethylamine (1 g.) and glycine ester hydrochloride (2 g.) were dissolved in 50% acetone (200 ml.), and sufficient N-sodium hydroxide to render the mixture alkaline to phenolphthalein was added. After the mixture had been heated under reflux for 4 hours the acetone was removed and the mixture extracted with benzene. The dried extract was allowed to percolate through a column of activated alumina. The early eluates contained the *piperazine* derivative, which formed large plates, m. p. 41—42°, from light petroleum (b. p. 40—60°) (Found : C, 64·8; H, 8·0. $C_{15}H_{22}O_3N_2$ requires C, 64·7; H, 8·0%).

(c) p-*Anisidine in dry acetone.* The chloroethylamine (1 g.) and *p*-anisidine (1 g.) were dissolved in acetone (20 ml.) and heated by steam for 3 hours. No 1 : 4-di-*p*-methoxyphenylpiperazine, which is sparingly soluble in acetone, separated during this time and none could be isolated from the mixture.

Isolation of the Products of the Reaction of NN-*Di*-2-*chloroethyl*-p-*anisidine with Aniline, etc.*—(a) *Aniline.* *NN*-Di-2-chloroethyl-*p*-anisidine (2·5 g.) and aniline (1·86 g.), dissolved in 50% acetone (500 ml.), were heated under reflux for 5 hours. During this period crystals separated from the solution. After cooling, the piperazine was collected by filtration and crystallised from acetone forming large plates, m. p. 168° (Found : C, 76·0; H, 7·6. Calc. for $C_{17}H_{20}ON_2$: C, 76·2; H, 7·5%). After removal of the acetone the solution was basified with sodium hydroxide, saturated with sodium chloride, and then extracted with ether. The extract contained a small amount of *NN*-di-2-hydroxyethyl-*p*-anisidine, m. p. 71°.

(b) *Methylaniline.* The reaction was carried out as under (*a*) but using methylaniline (2·20 g.). The cooled solution deposited plates, m. p. 108—110°, which were collected, and the mother-liquor was evaporated to a syrup, an ether extract of which contained more of the *di*-N-*methylanilinoethylamine*, m. p. 108°. The combined material crystallised from light petroleum (b. p. 60—80°) as prisms (1·1 g.), m. p. 109—111° (Found : C, 77·3; H, 8·1. $C_{25}H_{31}ON_3$ requires C, 77·1; H, 8·0%). An excess of aqueous ammonia was added to the syrup, and the liberated methylaniline was extracted with ether. After the ether had been boiled off, a saturated aqueous solution of sodium picrate was added. The red gum which separated solidified on storage and when crystallised from methanol afforded orange-brown prismatic needles of the *picrate*, m. p. 155—156°, of the piperazinium salt (Found : C, 56·4; H, 4·9. $C_{24}H_{25}O_8N_5$ requires C, 56·3; H, 5·0%).

(c) *Dimethylaniline.* The reaction was carried out as before, but using methylaniline (2·42 g.). After addition of an excess of aqueous ammonia the mixture was steam-distilled to remove acetone and dimethylaniline. The residual solution was evaporated to a low bulk and extracted with benzene. This extract contained the di(hydroxyethyl) derivative, m. p. 70°. Addition of sodium picrate solution to the aqueous layer caused the separation of an orange gum which was repeatedly crystallised from ethyl acetate. After a final crystallisation from methanol the *dipicrate* formed large orange plates, m. p. 140—141° (Found : C, 53·4; H, 4·8. $C_{39}H_{41}O_{15}N_9$ requires C, 53·5; H, 4·7%).

Attempted Preparation of a Methiodide of 1 : 4-*Diphenylpiperazine.*—(*a*) 1 : 4-Diphenylpiperazine (1·0 g.) was heated under reflux for 24 hours in a solution of methyl iodide (0·25 g.) in benzene (7·5 ml.). The piperazine was recovered unchanged.

(*b*) The piperazine (2 g.) was heated in a sealed tube for 3 hours at 100° with methyl iodide (10 ml.). The product was resinous.

Preparation of 1-p-*Methoxyphenyl*-4-*dimethylpiperazinium Iodide.*—(*a*) 1-*p*-Methoxyphenyl-4-methylpiperazine (Davis and Ross, following paper) (367 mg.) was warmed with a solution of methyl iodide (0·11 ml.) in benzene (5 ml.). The crystalline precipitate was filtered off, washed with ether, and crystallised from methanol. The *methiodide* formed small plates, m. p. 219—220° [Found : C, 44·6; H, 6·1. $C_{13}H_{21}ON_2I$ requires C, 44·8; H, 6·1%. 4·0 Ml. of 0·1N-silver nitrate were required to titrate the ionic iodine in 140 mg. of the methiodide (the titration was carried out in 50% acetone using di-iododimethylfluorescein as indicator). Calc. : 4·04 ml.].

(*b*) *NN*-Di-2-iodethyl-*p*-anisidine (Ross, this vol., p. 183) (200 mg.) was heated for ½ hour with a solution

of an excess of dimethylamine in 50% acetone (40 ml.). The mixture was then evaporated to dryness and the residue crystallised from methanol. Small plates of the methiodide, m. p. 219° [undepressed by admixture with a specimen prepared by method (*a*)], were obtained.

No acidity was developed when a solution of the methiodide (100 mg.) in 50% acetone (20 ml.) alone or containing an excess of aniline was heated under reflux for 5 hours.

Reaction of NN-*Di*-2-*chloroethyl*-p-*anisidine with Phenol or Thiophenol.*—(a) *Phenol.* The chloroethylamine (2·5 g.), phenol (1·88 g.), and 50% acetone (150 ml.) containing sodium hydroxide (10 ml.; 2N.) were heated under reflux for 3 hours. The oil which separated solidified when the mixture cooled. It was crystallised from light petroleum (b. p. 40—60°), forming long flattened needles of the *phenoxy*-derivative, m. p. 59—60° (Found: C, 76·3; H, 6·9. $C_{23}H_{25}O_3N$ requires C, 76·0; H, 6·9%). Similarly β-naphthyldi-2-chloroethylamine yielded a phenoxy-compound which formed a deep-purple *picrate*, m. p. 127° (Found: C, 63·4; H, 4·4. $C_{32}H_{28}O_9N_4$ requires C, 63·7; H, 4·7%).

(b) *Thiophenol.* *NN*-Di-2-chloroethyl-*p*-anisidine (1·25 g.), thiophenol (0·9 g.), and 50% acetone (150 ml.) containing sodium hydroxide (5 ml.; 2N.) were heated under reflux for 2 hours. The *product* which separated on cooling was crystallised from light petroleum (b. p. 60—80°) forming small prisms, m. p. 77—78° (Found: C, 69·9; H, 6·5. $C_{23}H_{25}ONS_2$ requires C, 69·9; H, 6·4%).

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