724. *Some* NN-*Di*-2-*chloroalkyl Derivatives of Carboxyamides and Sulphonamides.*

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A number of *NN*-di-2-chloroalkyl-carboxyamides and -sulphonamides have been prepared for testing as cytotoxic agents. The mechanism of the acid-catalysed rearrangement of the carboxyamides to 2-acyloxyethyl-2′-chloroethylammonium chlorides is discussed.

In the search for chemotherapeutic agents which could be converted by enzymic action into more potent compounds [1] attention has recently turned towards di-2-chloroalkylamides which on hydrolysis of the amide linkage would be expected to give tumour-growth inhibitory di-2-chloroalkylamines.[2] A certain level of chemical reactivity of the chlorine atom is necessary for biological activity [3] and it is unlikely that this is reached in the parent amides. Friedman and Seligman [4] and Arnold *et al.*[5] have examined various halogenoalkylphosphoramides which are presumed to release active halogenoalkylamines *in vivo*. It is probable that certain cytotoxic *NN*-di-2-chloroalkylurethanes owe their activity [6] to

[1] Everett and Ross, *J.*, 1949, p. 1972; Danielli, *Nature*, 1952, **170**, 862; *idem*, "Ciba Foundation Symposium on Leukaemia Research," 1954, London, p. 263; Danielli and Hebborn, *Biochem. Pharm.*, 1958, **1**, 19; Ross, *Acta Unio Internat. contra Cancrum*, 1954, **10**, 159; Ross, Warwick, and Roberts, *J.*, 1955, p. 3110; Ross and Warwick, *J.*, 1956, p. 1364.

[2] Peczenik, *Brit. J. Cancer*, 1952, **6**, 262; Haddow, "British Empire Cancer Campaign Report," 1957, London, Pt. II, p. 41.

[3] Ross, *Adv. Cancer Res.*, 1953, **1**, 397.

[4] Friedman and Seligman, *J. Amer. Chem. Soc.*, 1954, **76**, 655, 658.

[5] Arnold, Bourseaux, and Brock, *Nature*, 1958, **181**, 931.

[6] Haddow (unpublished results), see also Skipper, Bryan, Riser, Welty, and Stelzenmuller, *J. Nat. Cancer Inst.*, 1948, **9**, 77.

the similar release of " nitrogen-mustard "-like compounds since tumour-inhibitory activity is observed in the di-2-chloroethyl derivative (I) but not in the monofunctional analogue (II) [7]—this requirement is characteristic of growth-retarding halogenoalkylamines.[8]

(I) $EtO{\cdot}CO{\cdot}N(CH_2{\cdot}CH_2Cl)_2$ $EtO{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2Cl$ (II)

The present paper describes the preparation and properties of some *NN*-di-2-chloroalkyl derivatives of aliphatic and aromatic carboxyamides and also of some sulphonamides.

Jones and Wilson [9] prepared *NN*-di-2-chloroethylbenzamide by the Schotten–Baumann technique and more recently Preussmann [10] has reported the preparation of compounds alleged to be *N*-formyl-, *N*-acetyl-, *N*-trichloroacetyl-, and *N*-benzoyl-di-2-chloroethylamine (but see below). The formyl derivative was obtained by the action of thionyl chloride on *NN*-di-2-hydroxyethylformamide whilst the other amides were prepared from di-2-chloroethylamine and the appropriate acid chloride in the presence of triethylamine in an inert solvent.

The latter method has proved satisfactory for the preparation of *NN*-2-chloroethylamides of *o*-, and *p*-nitrobenzoic acid, 3 : 5-dinitrobenzoic acid, and terephthalic acid. Attempts to prepare di-2-chloroethylbenzamide (III; R = Ph) gave 2-benzoyloxyethyl-2′-chloroethylammonium chloride (IV; R = Ph), which Jones and Wilson [9] had previously obtained in small amounts during the recrystallisation of the benzamide (III; R = Ph) and which Mann [11] had earlier obtained and described as di-2-chloroethylamine benzoate:

$$RCO{\cdot}N(CH_2{\cdot}CH_2Cl)_2 \xrightarrow{H_2O} RCO_2{\cdot}CH_2{\cdot}CH_2{\cdot}NH(HCl){\cdot}CH_2{\cdot}CH_2Cl \qquad HO_2C{\cdot}X{\cdot}CO{\cdot}N(CH_2{\cdot}CH_2Cl)_2$$
(III) (IV) (V)

The amide (III; R = Ph), which was readily obtained by the Schotten–Baumann technique, slowly rearranged in acetone–ether or acetone–light petroleum giving the benzoyloxyethyl derivative. Preussmann's product is clearly impure rearranged material (IV; R = Ph) and not the benzamide as claimed.

All attempts to obtain stable *NN*-di-2-chloroethyl-amides of *p*-anisic, *p*-toluic, *p*-chlorobenzoic, *p*-bromobenzoic, phenylacetic, and cinnamic acids were unsuccessful. On chromatographic purification of the products one obtained oils which slowly deposited the acyloxethylammonium chloride. Succinic anhydride, maleic anhydride, and phthalic anhydride with di-2-chloroethylamine gave the monoamides (V).

NN-Di-2-chloroethyl-amides of the aliphatic acids were oils which could be distilled under reduced pressure with only slight decomposition, with the exception of the acrylamide which polymerised. The distilled amides slowly rearranged giving acyloxyethyl derivatives of structure (IV). Preussmann [10] indicates that his acetamido-compound slowly crystallised—it is obvious that the crystals which separated must have been those of the rearranged product.

The rearrangement of all the *NN*-di-2-chloroethyl-amides could be accelerated by dissolution in acetone containing a few drops of concentrated hydrochloric acid. In most cases the hydrochloride of the acyloxyethyl derivative crystallised within 2—3 days.

Acylation of 2′-acyloxyethyl-2-chloroethylamines followed by acid-induced rearrangement of the products gave bis-2-acyloxyethylamines. In this way symmetrically acylated derivatives such as bis-2-acetoxy- (VI; R = Me), bis-2-benzoyloxy- (VI; R = Ph), and bis-2-*p*-methoxybenzoyloxyethylammonium (VI; R = *p*-$MeOC_6H_4$) chlorides and one unsymmetrical derivative, 2-*p*-bromobenzoyloxyethyl-2′-*p*-nitrobenzoylethylammonium chloride (VII) were obtained.

(VI) $(R{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2)_2NH{\cdot}HCl$ (VII) $BrC_6H_4{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2{\cdot}NH(HCl){\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CO{\cdot}C_6H_4{\cdot}NO_2$

[7] Bergel, Haddow, and Hopwood, personal communication.
[8] Haddow, Kon, and Ross, *Nature*, 1948, **162**, 824.
[9] Jones and Wilson, *J.*, 1949, p. 547.
[10] Preussmann, *Arzneimittelforschung*, 1958, **8**, 9.
[11] Mann, *J.*, 1934, p. 464.

TABLE 1. *Amides* $RCO\cdot N(CH_2\cdot CH_2Cl)_2$.

R	B. p. or M. p.	Form	Solvent [1]	Formula	Found (%) C	H	N	Required (%) C	H	N	Method	Yield (%)
Me	122—126°/1 mm.[2]	Oil		$C_6H_{11}ONCl_2$	39·1	6·0	7·6	39·4	5·4	7·4	i	73
CH_2Cl	148—149/0·8 mm.[3]	Oil		$C_6H_{10}ONCl_3$	33·0	4·6	6·4	32·2	4·7	6·3	i	57
CH_2F	137—140/1·2 mm.	Oil		$C_6H_{10}ONCl_2F$	36·0	5·3	6·7	35·6	5·0	6·9	i	77
CCl_3	146—148/0·01 mm.	Pale yellow oil		$C_6H_8ONCl_5$	25·0	2·8	4·9	25·7	3·0	4·9	i	87
CF_3	63/0·35 mm.	Oil		$C_6H_8ONCl_2F_3$	30·0	3·5	5·8	30·3	3·4	5·8	i	70
Ph	49	Needles	A	$C_{11}H_{13}ONCl_2$	53·7	5·3	5·7	53·7	5·3	5·7	ii	72
$2\text{-}NO_2\cdot C_6H_4$	62—64	Pale yellow prisms	A	$C_{11}H_{12}O_3N_2Cl_2$	45·2	4·4	9·5	45·4	4·1	9·6	*	38
$4\text{-}NO_2\cdot C_6H_4$	94—96	Pale yellow prisms	B–C	$C_{11}H_{12}O_3N_2Cl_2$	45·6	4·3	9·7	45·4	4·1	9·6	i	79
$3,5\text{-}(NO_2)_2C_6H_3$	116	Pale yellow prisms	B–C	$C_{11}H_{11}O_5N_3Cl_2$	39·4	3·6	12·3	39·3	3·3	12·5	i	78
$4\text{-}NO_2\cdot C_6H_4\cdot CH_2$	82—83	Yellow prisms	D–E	$C_{12}H_{14}O_3N_2Cl_2$	47·5	4·7	9·5	47·2	4·6	9·2	ii	20
$1,2\text{-}C_6H_4$	—	Viscous oil		$C_{16}H_{20}O_2N_2Cl_4$	46·5	4·9	6·6	46·4	4·8	6·8	i	90
$1,4\text{-}C_6H_4$ [4]	176—177	Prisms	B–E	$C_{16}H_{20}O_2N_2Cl_4$	46·6	5·1	6·7	46·4	4·8	6·8	i	66
$2\text{-}C_6H_4\cdot CO_2H$	141	Prisms	B–F	$C_{12}H_{13}O_3NCl_2$	49·8	4·6	4·9	49·7	4·5	4·8	*	78
$[CH_2]_2\cdot CO_2H$	77—78	Needles	D–F	$C_8H_{13}O_3NCl_2$	39·5	5·8	5·5	39·7	5·4	5·8	*	80
$CH{=}CH\cdot CO_2H$	102·5	Prisms	B	$C_8H_{11}O_3NCl_2$	39·8	4·9	5·9	40·0	4·6	5·8	*	85

[1] Solvents used for crystallisation are: A, light petroleum (b. p. 80—100°); B, chloroform; C, ether; D, benzene; E, light petroleum (b. p. 60—80°); F, light petroleum (b. p. 40—60°). [2] Childs *et al.* (ref. 19) give b. p. 130—135°/0·2 mm. and Preussmann (ref. 10), b. p. 134—138°/4 mm. [3] Childs *et al.* give b. p. 160—164°/0·2 mm. [4] This compound separated as crystals from the initial mixture. * See experimental section.

TABLE 2. *Amine hydrochlorides* $RCO_2\cdot CH_2\cdot CH_2\cdot NH\cdot CH_2\cdot CH_2Cl,HCl$ *and the corresponding picrates.*

R	M. p.	Form	Solvents [1]	Formula	Found (%) C	H	N	Cl	Required (%) C	H	N	Cl	Yield (%)
Me	100—101°	Plates	A–B	$C_6H_{13}O_2NCl_2$	35·8	6·4	7·0		35·6	6·4	6·9		25
CH_2Cl	93	Needles	A	$C_6H_{12}O_2NCl_3$	29·8	5·2	6·0		30·4	5·1	5·9		32
CH_2F	86—88	Plates	A	$C_6H_{12}O_2NCl_2F$	32·8	5·2	6·4		32·8	5·4	6·4		15
CH_2Ph	105—106	Plates	A	$C_{12}H_{17}O_2NCl_2$	51·8	6·2	5·1		51·8	6·1	5·2		70
$4\text{-}NO_2\cdot C_6H_4\cdot CH_2$	122—124	Needles	A	$C_{12}H_{16}O_4N_2Cl_2$	44·8	5·1	8·6		44·6	5·0	8·7		47
(picrate)	86—88	Plates	C–E	$C_{18}H_{18}O_{11}N_5Cl$			13·1	6·7			13·6	6·9	
Ph	129—131	Plates	A	$C_{11}H_{15}O_2NCl_2$	50·2	5·9	5·3		50·0	5·7	5·3		48
(picrate)	181·5	Needles	C	$C_{17}H_{17}O_9N_4Cl$			12·4	8·1			12·3	7·8	
$4\text{-}Me\cdot C_6H_4$	150	Needles	A	$C_{12}H_{17}O_2NCl_2$	52·1	6·4	5·2		51·8	6·1	5·2		66
(picrate)	174—176	Prisms	C	$C_{18}H_{19}O_9N_4Cl$			11·8	7·6			11·9	7·5	
$4\text{-}MeO\cdot C_6H_4$	126	Plates	A	$C_{12}H_{17}O_3NCl_2$	48·9	5·9	4·8		49·0	5·8	4·8		64
(picrate)	163	Prisms	C	$C_{18}H_{19}O_{10}N_4Cl$			11·2	6·9			11·5	7·3	
$4\text{-}Cl\cdot C_6H_4$	129—131	Needles	A	$C_{11}H_{14}O_2NCl_3$	44·3	4·6	4·6		44·2	4·7	4·7		43
(picrate)	168—169	Needles	C	$C_{17}H_{16}O_9N_4Cl_2$			11·4	14·2			11·4	14·5	
$4\text{-}Br\cdot C_6H_4$	151—153	Needles	A–D	$C_{11}H_{14}O_2NCl_2Br$	38·8	4·4	4·0		38·5	4·1	4·1		55
(picrate)	174	Prisms	C	$C_{17}H_{16}O_9N_4ClBr$			10·1	6·5			10·5	6·6	
$4\text{-}NO_2\cdot C_6H_4$	191—193	Yellow needles	A–D	$C_{11}H_{14}O_4N_2Cl_2$	42·8	4·7	9·2		42·7	4·7	9·4		80
(picrate)	171	Needles	C	$C_{17}H_{16}O_{11}N_5Cl$			13·7	6·8			13·9	7·1	
$3,5\text{-}(NO_2)_2C_6H_3$	170—171	Yellow needles	A	$C_{11}H_{13}O_6N_3Cl_2$	37·7	3·8	11·9		37·4	3·7	11·8		35
(picrate)	192—193	Needles	C	$C_{17}H_{15}O_{13}N_6Cl$			15·6	6·3			15·8	6·5	
$Ph\cdot CH{=}CH$	120	Needles	A	$C_{13}H_{17}O_2NCl_2$	54·0	6·0	4·8		53·8	5·9	4·8		21
(dipicrate)	147	Prisms	C	$C_{25}H_{22}O_{16}N_7Cl$			13·7	5·0			13·8	5·0	
$1,4\text{-}C_6H_4$	225	Prisms	A–D	$C_{16}H_{24}O_4N_2Cl_4$	42·8	5·4	6·4		42·7	5·3	6·2		92
(dipicrate)	174	Prisms	C	$C_{28}H_{28}O_{18}N_8Cl_2$			13·4	8·6			13·8	8·8	
$[CH_2]_2\cdot CO_2H$	104—105	Plates	A–D	$C_8H_{15}O_4NCl_2$	37·1	6·1	5·4		36·9	5·8	5·4		70
$CH{=}CH\cdot CO_2H$	141—143	Plates	D–F	$C_8H_{13}O_4NCl_2$	37·2	4·8	5·4		37·2	5·0	5·4		67

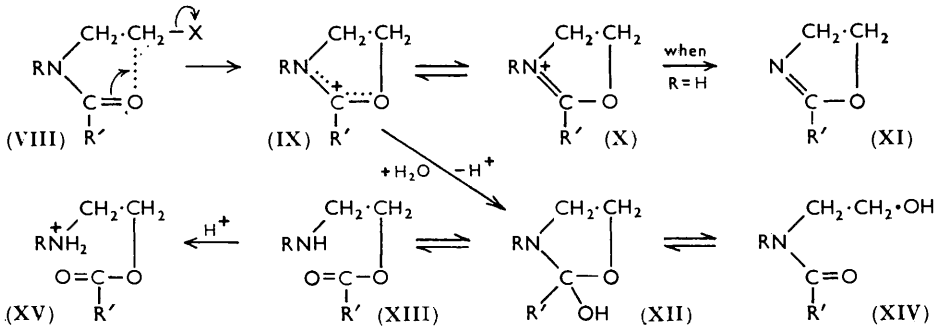
[1] Solvents used for crystallisation are: A, acetone; B, light petroleum (b. p. 60—80°); C, ethanol; D, methanol; E, water; F, ether.

The di-2-chloroethyl-amides now prepared are listed in Table 1 and the acyloxyethyl-chloroethylammonium chlorides in Table 2.

Dr. R. Wade drew our attention to the greater stability towards rearrangement of certain *NN*-di-2-chloropropyl-amides and accordingly *NN*-di-2-chloropropylbenzamide was examined. It was stable under conditions which converted the corresponding di-2-chloroethyl-amide into 2-benzoyloxyethyl-2′-chloroethylammonium chloride.

NN-Di-2-chloroethyl-amides of several sulphonic acids were readily obtained from the appropriate acid chloride and di-2-chloroethylamine in pyridine. These amides, which were quite stable and showed no tendency to undergo acid-catalysed rearrangement, are listed in Table 3.

The rearrangement of *NN*-di-2-chloroethyl-amides, which involves intramolecular acyl-group migration, can be depicted as below:



The acid-catalysed formation of the bridged cation (IX) which can be stabilised by resonance with the quaternary ion (X) is a special instance of the first stage suggested [12] for migrations in substituted ethane systems. The scheme is consistent with the formation of phenyloxazoline (XI; R′ = Ph) from *N*-2-bromoethylbenzamide (VIII; R = H, R′ = Ph, X = Br) which occurs [13] when the halide is rapidly dissolved in boiling water. In this

TABLE 3. *Sulphonamides* $RSO_2{\cdot}N(CH_2{\cdot}CH_2Cl)_2$.

R	M. p.	Form	Solvent [1]	Formula	Found (%) / Required (%) C	H	N	Yield (%)
Me	67° [2]	Needles	A	$C_5H_{11}O_2NCl_2S$	27·7	5·1	6·5	70
					27·3	5·0	6·4	
Ph	45—46	Prisms	A	$C_{10}H_{13}O_2NCl_2S$	42·6	4·8	4·6	62
					42·6	4·6	5·0	
4-Me·C_6H_4	46 [3]	Prisms	A	$C_{11}H_{15}O_2NCl_2S$	44·6	5·2	4·5	65
					44·7	5·1	4·7	
4-MeO·C_6H_4	76	Prisms	B	$C_{11}H_{15}O_3NCl_2S$	42·5	5·1	4·6	67
					42·3	4·8	4·5	
4-ClC_6H_4	91	Needles	B	$C_{10}H_{12}O_2NCl_3S$	37·7	4·0	4·6	76
					37·9	3·8	4·4	
4-Br·C_6H_4	81·5	Prisms	B	$C_{10}H_{12}O_2NBrCl_2S$	33·3	3·1	4·1	71
					33·2	3·3	3·9	
4-AcNH·C_6H_4	111 [3]	Needles	A–C	$C_{12}H_{16}O_3N_2Cl_2S$	42·2	4·8	8·2	15
					42·5	4·7	8·3	
4-$NO_2{\cdot}C_6H_4$	124	Prisms	B	$C_{10}H_{12}O_4N_2Cl_2S$	36·7	3·7	9·0	61
					36·7	3·7	8·6	

[1] Solvents used for crystallisation are: A, methanol; B, ethanol; C, water. [2] Preussmann (ref. 10) gives 76—78°. [3] These agree with Preussmann's values (ref. 10).

instance the cation (X) will lose a proton to give a weakly basic oxazoline, but with *N*-2-chloroethyl-*N*-methylbenzamide and the di-2-chloroethyl-amide (VIII; R = Me, R′ = Ph) such stabilisation is not possible.

[12] Cram, "Steric Effects in Organic Chemistry," ed. M. S. Newman, John Wiley and Sons, Ltd., New York, 1956, p. 290.

[13] Gabriel and Heymann, *Ber.*, 1890, **23**, 2497.

Markwald and Frobenius [14] have shown that the compound (VIII; R = Me, R′ = Ph, X = Cl) undergoes rearrangement similar to that now being discussed giving 2-methylaminoethyl benzoate.

Ortho-acid derivatives (XII) postulated in this scheme and also regarded [15] as intermediates in the N ⇌ O acyl-group migration (XIII ⇌ XIV) have been shown [16] to exist by the synthesis of the magnesium salt of *threo*-2-hydroxy-3,4-dimethyl-2,5-diphenyloxazolidine. The equilibrium (XIII ⇌ XII ⇌ XIV) is displaced to the left by acids and to the right by bases.[17] This is consistent with (XIV) being the most stable structure, the equilibrium only being displaced in favour of (XIII) when this is stabilised in acid solution by the addition of a proton giving (XV) from which (XII) cannot be derived. Only catalytic amounts of acid are required for complete rearrangement of compounds (VIII) since acid is produced as (XIII) is formed and the amount is sufficient to ensure complete conversion.

The greater stability of 2-chloroethyl-amides (VIII) when R′ is an electron-attracting group—as in the various nitrobenzoic acid derivatives—is expected if formation of the bridged cation (IX) is involved for in such compounds the mobility of electrons in the carbonyl bond in the direction indicated will be reduced thus hindering the depicted ring closure by O–C bond formation. Again the slower rate of rearrangement of 2-chloropropyl-amides would be due to the relative steric hindrance to the formation of this same O–C bond.

It was not possible to determine the hydrolysis rates of the chlorine atoms in the amides (VIII; R = $CH_2 \cdot CH_2Cl$, X = Cl) since under the conditions used for the measurement of these rates [18] the *NN*-di-2-chloroethyl-amides rapidly underwent prior rearrangement to the esters (XIII).

Most of the *NN*-di-2-chloroethyl-amides (III) and their rearrangement products (IV) have been tested for effect on the growth of the transplanted Walker rat carcinoma. The derivatives from succinic (XVI) and phthalic acid (XVII) showed activity of a low order but the remainder were inactive.

(XVI) $HO_2C \cdot CH_2 \cdot CH_2 \cdot CO \cdot N(CH_2 \cdot CH_2Cl)_2$ o-$HO_2C \cdot C_6H_4 \cdot CO \cdot N(CH_2 \cdot CH_2Cl)_2$ (XVII)

The original hope that di-2-chloroethylamine would be released by hydrolysis *in vivo* of the amide linkage now seems unlikely in view of the rearrangement to the ester (IV).

Experimental

Preparation of Di-2-chloroethyl-amides.—Method (i). The unpurified acid chloride [prepared by action of thionyl chloride on the acid (0·04 mol.)] in chloroform was added slowly to a stirred solution of di-2-chloroethylamine prepared from the hydrochloride (0·045 mol.) and triethylamine (0·045 mol.) in chloroform. Stirring was continued for 30 min. and the mixture was then washed with water, 2N-hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and finally again with water. Distillation of the solvent from the dried (magnesium or sodium sulphate) solution afforded thick oils which solidified on cooling in the case of *p*-nitro- and 3,5-dinitro-benzamide. The other amides prepared by this method were obtained as viscous oils which were rearranged to the ester hydrochlorides on storage or attempted crystallisation from hydroxylic solvents. In the attempted preparation of amides from *p*-nitrophenylacetic acid, *p*-anisic acid, and *p*-toluic acid, the acyloxyethylammonium chlorides separated from the chloroform solutions of the initial product. The tendency to rearrange was clearly enhanced by washing with dilute hydrochloric acid for when this step was omitted the separation of the crystalline hydrochloride was considerably delayed, or even prevented. The general method

[14] Markwald and Frobenius, *Ber.*, 1901, **34**, 3544.
[15] Phillips and Baltzly, *J. Amer. Chem. Soc.*, 1947, **69**, 200.
[16] Koczka and Fodor, *Acta Chim. Hung.*, 1957, **13**, 6.
[17] Reasenberg and Goldberg, *J. Amer. Chem. Soc.*, 1945, **67**, 933.
[18] Ross, *J.*, 1949, p. 183.

was satisfactory for the preparation of trichloro- and trifluoro-acetamide which showed no tendency to rearrange. Attempted distillation of the acrylamide derivative led to extensive polymerisation.

Childs *et al.*[19] have used a modification of this method in which the acid chloride dissolved in a small volume of chloroform was added simultaneously with alkali to a stirred aqueous suspension of di-2-chloroethylamine so that the mixture remained alkaline. Even when this method was used and the dried chloroform solution was distilled immediately, the amides of acetic, chloroacetic, and fluoroacetic acid were obtained as syrups from which the ester hydrochlorides slowly separated.

Method (ii). A solution of di-2-chloroethylammonium chloride (0·05 mol.) in water (25 ml.) was stirred at 0—5°, and the acid chloride (0·03 mol.) in dry acetone (10 ml.) and aqueous sodium hydroxide (50 ml.; N) were run in simultaneously during 20 min. The rates of addition were adjusted so that the solution remained slightly alkaline. Stirring was continued for a further hour and the product, if solid, was filtered off and washed with aqueous sodium hydrogen carbonate followed by light petroleum (b. p. 40—60°). When the product was an oil it was extracted into chloroform, and the extract washed with water and dried ($MgSO_4$). *NN*-Di-2-chloroethyl-benzamide and -p-nitrophenylacetamide were obtained crystalline by this modification of Jones and Wilson's method [9] whereas the derivatives of other aromatic acids examined were obtained as oils which were converted into the acyloxyethylammonium chlorides as described below.

NN-*Di*-2-*chloropropylbenzamide*.—This compound, prepared from di-2-chloropropylamine by method (ii) formed large prisms, m. p. 75—77°, from light petroleum (b. p. 60—80°) (Found: C, 56·6; H, 6·0; N, 5·1. $C_{13}H_{17}ONCl_2$ requires C, 56·9; H, 6·2; N, 5·1%). The amide was unchanged when a solution in acetone containing concentrated hydrochloric acid was kept for 1 week.

NN-*Di*-2-*chloroethyl*-o-*nitrobenzamide*.—*o*-Nitrobenzoyl chloride, prepared by the action of thionyl chloride (13·1 g.) on the acid (16·7 g.) in benzene solution, was added dropwise during 15 min. to a stirred solution of di-2-chloroethylamine [from the hydrochloride (18 g.) and triethylamine (14·2 ml.) in benzene (50 ml.)]. After being stirred for a further hour the mixture was washed with water, and the solvent removed under reduced pressure. A benzene solution of the residue was allowed to percolate through activated alumina which was washed with fresh benzene. Early eluates contained a yellow oil which slowly crystallised. Recrystallisation from a large volume of light petroleum (b. p. 80—100°) gave the amide as large yellow prisms (7·3 g.), m. p. 61—63°. More crude amide (3·8 g.), m. p. 58—61°, was present in the mother liquors. The analytical specimen had m. p. 62—64°.

NN-*Di*-2-*chloroethyl Derivatives of Phthalamic, Succinamic, and Maleamic Acids*.—The phthalamic and maleamic acid derivatives were obtained in excellent yield by mixing equimolecular amounts of the acid anhydride and di-2-chloroethylamine in dry chloroform; the products separated almost immediately as crystals. To prepare the succinamic acid derivative succinic anhydride was added to a benzene solution of the base at $<30°$. Subsequent addition of light petroleum (b. p. 60—80°) initiated crystallisation of product which was again obtained in good yield. The derivative could be recrystallised from benzene–light petroleum (b. p. 60—80°) but is was essential to keep the temperature below 40° to prevent separation of non-crystallisable oil.

Attempted Preparation of NN-*Di*-2-*chloroethyl*-p-*nitrophenylacetamide*.—Before this compound was successfully obtained by method (ii) an attempt was made to prepare it by adding dicyclohexylcarbodi-imide to equimolecular quantities of *p*-nitrophenylacetic acid and di-2-chloroethylamine in tetrahydrofuran; only a small amount of 2-*p*-nitrophenylacetoxyethyl-2′-chloroethylammonium chloride was obtained.

Acid-catalysed Rearrangement of NN-*Di*-2-*chloroethylamides*.—The compound was dissolved in acetone (about 10 ml. per g.) and a few drops of concentrated hydrochloric acid were added. The acyloxyethylchloroethylammonium chlorides began to crystallise from the solution after 1—5 days and were collected after 2 weeks. They were recrystallised from acetone and when possible were further characterised as the picrates. The rate of rearrangement was slowest when the group R in (II) carried electron-attracting substituents; for example, the 3,5-dinitrobenzoic acid derivative rearranged very slowly—36% being unchanged after 3 weeks. The

[19] Childs, Goldsworthy, Harding, King, Nineham, Norris, Plant, Selton, and Tompsett, *J.*, 1948, p. 2174.

trichloro- and trifluoro-acetamides and those of *o*-nitrobenzoic acid and phthalamic acid were not rearranged under the above conditions.

Di-2-acetoxyethylammonium Chloride.—To a well-stirred solution of 2-acetoxyethyl-2′-chloroethylammonium chloride (4·5 g.) and triethylamine (5 ml.) in chloroform (20 ml.), acetyl chloride (5 ml.) in chloroform (5 ml.) was added during 10 min. After being stirred for 1 hr. at room temperature the solution was washed with water, dried ($MgSO_4$), and concentrated. The product was dissolved in acetone (10 ml.) to which one drop of concentrated hydrochloric acid had been added. After 18 hr. the rearrangement product (1·2 g.) was collected and recrystallised from acetone. Di-2-acetoxyethylammonium chloride formed plates, m. p. 147—148° undepressed on admixture with an authentic specimen prepared by Mann's method;[11] he gives m. p. 147—149°.

Di-2-benzoyloxyethylammonium Chloride.—2-Benzoyloxyethyl-2′-chloroethylammonium chloride was converted into the oily benzamide by treatment with benzoyl chloride, method (i) or (ii) being used. *Di-2-benzoyloxyethylammonium chloride*, obtained by acid-catalysed rearrangement of the amide, formed small felted needles, m. p. 160° from acetone (Found: C, 62·2; H, 6·1; N, 4·0. $C_{18}H_{20}O_4NCl$ requires C, 61·8; H, 5·7; N, 4·0%). The *picrate* crystallised from ethanol as needles, m. p. 124—125° (Found: C, 52·8; H, 4·4; N, 10·2. $C_{24}H_{22}O_{11}N_4$ requires C, 53·1; H, 4·1; N, 10·3%).

Di-2-p-*methoxybenzoyloxyethylammonium Chloride.*—This compound was similarly prepared; it formed needles, m. p. 165°, from acetone–methanol (Found: C, 58·8; H, 6·2; N, 3·7. $C_{20}H_{24}O_6NCl$ requires C, 58·6; H, 5·9; N, 3·4%). The *picrate* formed golden blades, m. p. 145—147°, from ethanol (Found: C, 51·6; H, 4·7; N, 9·3. $C_{26}H_{26}O_{13}N_4$ requires C, 51·8; H, 4·3; N, 9·3%).

2-p-*Bromobenzoyloxyethyl*-2′-p-*nitrobenzoyloxyethylammonium Chloride.*—*p*-Nitrobenzoylation of 2-*p*-bromobenzoyloxyethyl-2′-chloroethylamine by method (i) gave a product which crystallised from ethanol without rearrangement. It formed prisms, m. p. 98° (Found: C, 47·6; H, 3·8; N, 6·0. $C_{18}H_{16}O_5N_2BrCl$ requires C, 47·4; H, 3·5; N, 6·1%). This amide (5 g.) was dissolved in acetone (20 ml.) containing two drops of concentrated hydrochloric acid, and the rearrangement *product* (2·6 g.) (VII) was collected at intervals during 3 weeks; it formed flattened needles, m. p. 182—183°, from methanol (Found: C, 45·6; H, 4·2; N, 6·4. $C_{18}H_{18}O_6N_2BrCl$ requires C, 45·6; H, 3·8; N, 5·9%). The N-*benzenesulphonyl derivative* was obtained as needles, m. p. 108°, from methanol (Found: C, 49·9; H, 3·7; N, 5·0; $C_{24}H_{21}O_8N_2BrS$ requires C, 49·9; H, 3·6; N, 4·9%).

NN-*Di*-2-*chloroethylsulphonamides.*—The sulphonyl chloride (0·025 mol.) was added to a solution of di-2-chloroethylammonium chloride (0·05 mol.) in pyridine (25 ml.), and the mixture was heated on a steam-bath for 1 hr. and then poured into water. The product was filtered off and washed with water. The sulphonamides were crystallised from ethanol or methanol (Table 3).

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