598. *Aryl-2-halogenoalkylamines. Part VIII. A Comparison of the Stability of Esters derived from Some Aryl-2-halogenoalkylamines with those obtained from Other Radiomimetic Compounds.*

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The rates of hydrolysis of esters derived from certain aryl-2-halogenoalkylamines have been measured and compared with those of esters derived from radiomimetic sulphur and aliphatic nitrogen " mustards " and also from some epoxides. The relative alkali-lability of all these esters suggests that acid groups in biological systems which were esterified by these various agents would be only temporarily blocked.

It has been shown in Part III (*J.*, 1949, 2589) that aryl-2-halogenoalkylamines react under mild conditions with anions of organic and inorganic acids to form esters. A consideration of the reactivity, at physiological pH, of the various groups present in mixed biological systems towards carbonium ions derived from halogenoalkylamines has led to the view that combination with acidic groups in proteins and nucleic acids is specially favoured (*J.*, 1950, 815). The esterification of carboxyl groups in proteins by compounds of the mustard gas type has been demonstrated; the evidence is drawn mainly from the effects of treatment on the titration curves of the material and from the formation of alkali-labile linkages (Herriott, Anson, and Northrup, *J. Gen. Physiol.*, 1946, **30**, 185; Banks, Boursnell, Francis, Hopwood, and Wormall, *Biochem. J.*, 1946, **40**, 745; Carpenter, Wood, Stevens, and du Vigneaud, *J. Amer. Chem. Soc.*, 1948, **70**, 2551; Ormsbee, Henriques, and Ball, *Arch. Biochem.*, 1949, **21**, 301). Fruton, Stein, Stahmann, and Golumbic (*J. Org. Chem.*, 1946, **11**, 571) have shown that the phosphate groups of nucleotides are esterified by methyldi-2-chloroethylamine, and the formation of alkali-labile linkages by the action of butyl 2-chloroethyl sulphide on the nucleic acid moiety of tobacco mosaic virus has been established by Carpenter *et al.* (*loc. cit.*).

Fruton, Stein, and Bergmann (*J. Org. Chem.*, 1946, **11**, 567) failed to obtain an ester when methyldi-2-chloroethylamine was allowed to react in aqueous sodium acetate solutions whereas stable esters can be obtained in similar manner form several aryl-2-halogenoalkylamines (Part III). These results indicated a difference in the stability of esters derived from the two series of compounds. Since some of the biological effects of the mustard-gas type of compound could be interpreted if acidic groups were only temporarily blocked by the agents and subsequently regenerated by the hydrolysis of the esters formed (compare Peters, *Nature*, 1947, **159**, 149; also Boursnell, Cohen, Dixon, Francis, Greville, Needham, and Wormall, *Biochem. J.*, 1946, **40**, 756, who showed that much of the mustard gas fixed in tissues had disappeared twelve hours after treatment), it was of interest to prepare ester derivatives of various " radiomimetic " agents (Boyland, *Biochem. Symposia*, 1948, No. 2, p. 67) and to measure their relative stabilities. It was hoped that a correlation of ester stability with the degree and duration of the cytotoxic effect might be achieved.

In the present study acetates and benzoates derived from the following compounds have been examined: dimethyl-2-chloroethylamine, methyldi-2-chloroethylamine, ethyl 2-chloroethyl sulphide, di-2-chloroethyl sulphide, *N*-ethyl-*N*-2-chloroethylaniline, *NN*-di-2-chloroethylaniline, *NN*-di-2-chloroethyl-*p*-anisidine, 2-naphthyldi-2′-chloroethylamine, 2-naphthyldi-2′-chloro-*n*-propylamine, and 1 : 2-3 : 4-diepoxybutane. The monochloroethyl compounds were included because, although they have not been shown to exhibit cytotoxic activity as judged against the growth of the transplanted Walker rat carcinoma, the aliphatic derivatives will induce chromosomal abnormalities in the growing root tips of *Vicia faba* (unpublished work by Mr. A. Loveless).

Materials.

Dimethyl-2-acetoxyethylamine was prepared and converted into acetylcholine iodide as described by Jones and Major (*J. Amer. Chem. Soc.*, 1930, **52**, 307). The hydrochloride of the corresponding benzoate was obtained by the action of benzoyl chloride on dimethylaminoethanol, and the free base was converted into benzoylcholine iodide (cf. Gulland, Partridge, and Randall, *J.*, 1940, 419). Acetylation of methyldi-2-hydroxyethylamine with acetic anhydride and sodium acetate afforded the acetyl derivative, and treatment of the hydroxy-amine with benzoyl chloride at room temperature yielded the hydrochloride of the benzoate. The free benzoyloxyethylamine was obtained by Pyman (*J.*, 1908, **93**, 1796) by the action of benzoyl chloride on the amine in alkaline solution. The acetate and benzoate of methyldi-2-hydroxyethylamine were converted into methiodides by reaction with methyl iodide in acetone solution.

Ethyl 2-acetoxyethyl sulphide was obtained by the action of acetic anhydride on the alcohol, and ethyl 2-benzoyloxyethyl sulphide was formed when ethyl 2-chloroethyl sulphide reacted in an aqueous acetone solution of sodium benzoate. Di-2-acetoxyethyl sulphide (Helfrich and Reid, *J. Amer. Chem. Soc.*, 1920, **42**, 1228; Clayton and Reid, *ibid.*, 1942, **64**, 908) and di-2-benzoyloxyethyl sulphide (Fromm and Kohn, *Ber.*, 1921, **54**, 320) have already been described.

Acetylation of *N*-ethyl-*N*-2-hydroxyethylaniline yielded the acetyl derivative, whilst the corresponding benzoate was prepared by allowing *N*-ethyl-*N*-2-chloroethylaniline to react in an aqueous acetone solution of sodium benzoate. Acylation of *NN*-di-2-hydroxyethylaniline by acetic anhydride or benzoyl chloride in pyridine afforded *NN*-di-2-acetoxy- and *NN*-di-2-benzoyloxy-ethylaniline respectively. The preparation of the acetyl and benzoyl derivatives of *NN*-di-2-hydroxyethyl-*p*-anisidine and 2-naphthyldi-2′-hydroxyethylamine has been described (Ross, *J.*, 1949, 2589) and similar methods have now been used to prepare esters from the isomeric mixture of 2-naphthyldi-2′-hydroxy-*n*-propylamines (Everett and Ross, *J.*, 1949, 1972).

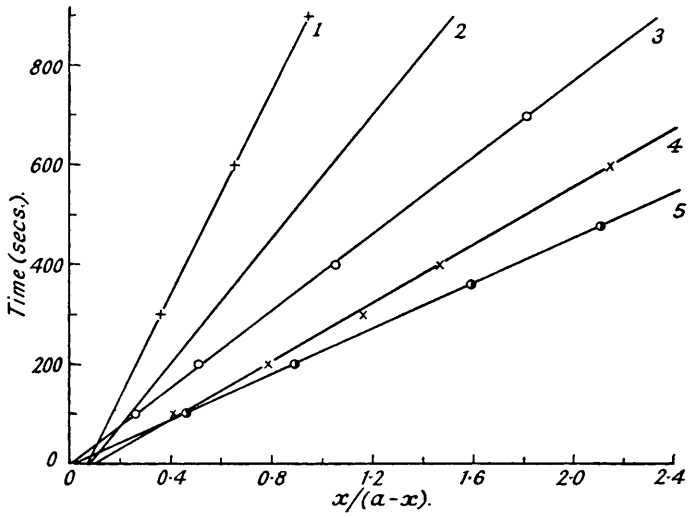
When 1 : 2-3 : 4-diepoxybutane reacts in an aqueous solution of sodium benzoate which is continuously titrated with benzoic acid a mixture of the isomeric 1 : 4-dibenzoates of erythritol is formed (Ross, *J.*, 1950, 2257) from which pure *meso*erythritol 1 : 4-dibenzoate can be isolated; a mixture of the isomeric 1 : 4-diacetates has now been prepared. A similar method has been used to prepare ethylene glycol monoacetate—previously obtained by heating ethylene glycol and acetic acid with anhydrous copper sulphate (Drushel and Bancroft, *Amer. J. Sci.*, 1917, **44**, 373)—and the monobenzoate—first prepared by the action of sodium benzoate on ethylene chlorohydrin in diethylamine solution (Cretcher and Pittinger, *J. Amer. Chem. Soc.*, 1925, **47**, 2561). Glycerol α-monobenzoate was obtained by heating α-monochlorohydrin with potassium benzoate (Krafft, *Ber.*, 1903, **36**, 4339).

Methods.

Skrabal (*Monatsh.*, 1926, **47**, 17; see also Hammett, " Physical Organic Chemistry," New York, 1940, p. 211) has shown that variation in the alcohol component of an ester has a much greater effect on the rate of alkaline hydrolysis than on the rate of acid hydrolysis. Since we were especially interested in differences in ester stability we have so far confined our studies to the alkaline hydrolysis of the esters. The aromatic derivatives prepared in this work are sparingly soluble in water and since it was desired to determine the rates of hydrolysis of all esters under exactly comparable conditions the measurements have been made in 80% aqueous acetone at 50°.

Equivalent amounts of ester and sodium hydroxide were used in each experiment so that, on a bimolecular reaction mechanism, $k' = x/ta(a - x)$, where the symbols have their usual significance. Since k' and a are constant for any given set of determinations a plot of t against $x/(a - x)$ will give a

straight line if the reaction is truly bimolecular. The figure shows the results of plotting these values for several of the esters now examined, and Table II shows the details of the hydrolysis of *NN*-di-2-acetoxyethylaniline. The slope of the line in the figure will be $1/k'a$, from which k' can be calculated since a is known. The bimolecular constant k given in Table I was calculated by dividing k' by N/v, where N is the normality of the standard solutions used and v is the volume of the solution in which the hydrolysis was carried out; the units in which k is expressed being g.-mols. $l.^{-1}$ $sec.^{-1}$.



	10^2k.		10^2k.
1. *Ethyl acetate*	19	4. *Methyldi-2-acetoxyethylamine*	68
2. N-*Ethyl*-N-2-*acetoxyethylaniline*	34	5. *Dimethyl-2-acetoxyethylamine*	88
3. NN-*Di*-2-*acetoxyethylaniline*	52		

Discussion.

Table I shows that there is a considerable difference between the rates of alkaline hydrolysis of esters of ethyl or *iso*propyl alcohol and those of comparable structure derived from alcohols related to the sulphur and " nitrogen-mustard " type of compound. The presence of the sulphur atom or the substituted nitrogen atom in the esters clearly has the effect of increasing the alkali-lability of the ester group. There is much less difference in the relative rates of hydrolysis of the acetates and benzoates derived from the various " mustards " than in the rates of hydrolysis of the parent halides (see Parts I and II). Except in the case of the acetates of dimethyl-2-hydroxyethylamine and methyldi-2-hydroxyethylamine the diesters hydrolyse somewhat faster than the corresponding monoesters. It was at first thought that this difference might be caused by the presence in the hydrolysing solution of a greater proportion of the cationic form of the more strongly basic monoester (see below). However, the pK_a—in 80%

Table I.

Second-order velocity constants for the alkaline hydrolysis of the esters.

Radiomimetic agent.	Acetate.	10^2k.	Benzoate.	10^2k.
	$CH_3\cdot CH_2\cdot OAc$	19	$CH_3\cdot CH_2\cdot OBz$	3·1
	$(CH_3)_2CH\cdot OAc$	3·5	$(CH_3)_2CH\cdot OBz$	0·4
$(CH_3)_2N\cdot CH_2\cdot CH_2Cl$	$(CH_3)_2N\cdot CH_2\cdot CH_2\cdot OAc$	84	$(CH_3)_2N\cdot CH_2\cdot CH_2\cdot OBz$	9
$CH_3\cdot N(CH_2\cdot CH_2Cl)_2$	$CH_3\cdot N(CH_2\cdot CH_2\cdot OAc)_2$	64	$CH_3\cdot N(CH_2\cdot CH_2\cdot OBz)_2$	10
$CH_3\cdot CH_2\cdot S\cdot CH_2\cdot CH_2Cl$	$CH_3\cdot CH_2\cdot S\cdot CH_2\cdot CH_2\cdot OAc$	58	$CH_3\cdot CH_2\cdot S\cdot CH_2\cdot CH_2\cdot OBz$	8
$S(CH_2\cdot CH_2Cl)_2$	$S(CH_2\cdot CH_2\cdot OAc)$	81	$S(CH_2\cdot CH_2\cdot OBz)_2$	12
$Ph\cdot N(CH_2\cdot CH_3)\cdot CH_2\cdot CH_2Cl$	$Ph\cdot N(CH_2\cdot CH_3)\cdot CH_2\cdot CH_2\cdot OAc$	34	$Ph\cdot N(CH_2CH_3)\cdot CH_2\cdot CH_2\cdot OBz$	5
$Ph\cdot N(CH_2\cdot CH_2Cl)_2$	$Ph\cdot N(CH_2\cdot CH_2\cdot OAc)_2$	52	$Ph\cdot N(CH_2\cdot CH_2\cdot OBz)_2$	7
$p\text{-}CH_3O\cdot C_6H_4\cdot N(CH_2\cdot CH_2Cl)_2$	$p\text{-}CH_3O\cdot C_6H_4\cdot N(CH_2\cdot CH_2\cdot OAc)_2$	46	$p\text{-}CH_3O\cdot C_6H_4\cdot N(CH_2\cdot CH_2\cdot OBz)_2$	6
$2\text{-}C_{10}H_7\cdot N(CH_2\cdot CH_2Cl)_2$	$2\text{-}C_{10}H_7\cdot N(CH_2\cdot CH_2\cdot OAc)_2$	48	$2\text{-}C_{10}H_7\cdot N(CH_2\cdot CH_2\cdot OBz)_2$	7
$2\text{-}C_{10}H_7\cdot N(CH_2\cdot CHMeCl)_2$	$2\text{-}C_{10}H_7\cdot N(CH_2\cdot CHMe\cdot OAc)_2$	8	$2\text{-}C_{10}H_7\cdot N(CH_2\cdot CHMe\cdot OBz)_2$	1
$[CH_2]_2>O$	$HO\cdot CH_2\cdot CH_2\cdot OAc$	192	$HO\cdot CH_2\cdot CH_2\cdot OBz$	30
Epichlorohydrin	—	—	$HO\cdot CH_2\cdot CH(OH)\cdot CH_2\cdot OBz$	79
1 : 2-3 : 4-Diepoxybutane	$[\cdot CH(OH)\cdot CH_2\cdot OAc]_2$	506	$[\cdot CH(OH)\cdot CH_2\cdot OBz]_2$	114
	$[(CH_3)_3N^+\cdot CH_2\cdot CH_2\cdot OAc]I^-$	2700	$[(CH_3)_3N^+\cdot CH_2\cdot CH_2\cdot OBz]I^-$	1300
	$[(CH_3)_2N^+(\cdot CH_2\cdot CH_2\cdot OAc)_2]I^-$	3350	$[(CH_3)_2N^+(\cdot CH_2\cdot CH_2\cdot OBz)_2]I^-$	1780

TABLE II.

Hydrolysis of NN-*di*-2-*acetoxyethylaniline in* 80% *aqueous acetone.*

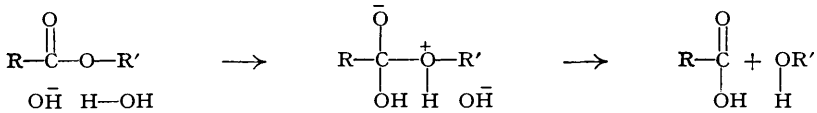
Weight of ester taken for each determination, 139·7 mg. Vol. of 0·025N-sodium hydroxide used in each run (*a*), 39·6 ml. Total volume of reaction solution (*v*), 200 ml. Temp., 50°.

Time (secs.).	0·025N-Hydrochloric acid added to arrest hydrolysis (ml.).	0·025N-Alkali required to back-titrate (ml.).	0·025N-Alkali consumed (x) (ml.).	$x/(a-x)$.
100	38·0	6·6	8·2	0·26
200	33·0	6·8	13·4	0·51
400	26·0	6·7	20·3	1·05
700	21·0	6·9	25·5	1·81

From the graph (figure) the slope of the line $1/k'a = 900/2·32$.
Hence $k = k'v/N = 2·32v/900aN = 0·52$ g.-mol. l.$^{-1}$ sec.$^{-1}$, since $a = 39·6$, $v = 200$, and $N = 0·025$.

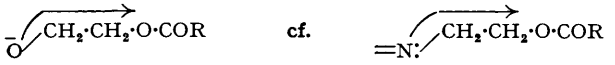
acetone—of the monoester was found to be 7·3 and of the diester 5·6, while the pH of the alkaline solution was 11·5; thus negligible amounts of either ester were in the cationic form under the conditions employed. There is not the considerable variation between the rates of hydrolysis of esters derived from mono- and di-hydroxyethyl compounds that is encountered with corresponding mono- and di-halides. These differences are not unexpected since the halides are known to hydrolyse by an S_N1 mechanism whereas the esters of the organic acids have now been shown to hydrolyse by a bimolecular mechanism; this is confirmed by the linear plot of the points in the figure. It has been found that even in the case of the diesters the plot of $x/(a-x)$ is still linear up to 80% reaction, suggesting that the ester groups are hydrolysed at the same rates. The α-hydroxy-esters derived from 1 : 2-epoxides are much more labile under the conditions used in this work than are esters derived from the mustard-gas type of compound. It would also appear that the rate of hydrolysis of such esters depends on the number of hydroxyl groups in the molecule.

The Lowry mechanism for the alkaline hydrolysis of an ester (*J.*, 1927, 2558) is as follows:



The formation of the intermediate complex involves an attack (*a*) by the hydroxyl ion and (*b*) by the water molecule resulting in proton transfer. Stage (*a*) will be accelerated by electron-attracting substituents in R which will facilitate the attack by the negatively charged hydroxyl ion; this effect has been amply confirmed by measurements on the rate of hydrolysis of substituted benzoic esters. On the other hand, stage (*b*) should be aided by electron-repelling groups in R′. The electron-repelling character of the nitrogen or sulphur atom attached to halogenoethyl side chains is well established and accounts for the ease of hydrolysis of such halides. It is now suggested that this same electron repelling character is responsible for the increased rate of hydrolysis of esters derived from the radiomimetic agents listed in Table I because of the effect on the proton-transfer reaction proposed in the Lowry mechanism. The effect of the nitrogen or sulphur atom will not extend to the carboxyl-carbon atom of the ester group; compare the absence of an effect on the reactivity of the halogen atoms in 3-chloro-*n*-propylamines. At first sight it would appear that esters of *iso*propyl alcohol should hydrolyse faster than those of ethyl alcohol since a methyl group is electron-repelling as compared with a hydrogen atom but the approach of a water molecule to the oxygen atom (stage *b*) would be hindered and the steric effect must outweigh the effect on increased electron availability. In the esters derived from the mustard-gas types we have the electron-displacement effect uncomplicated by the steric effect.

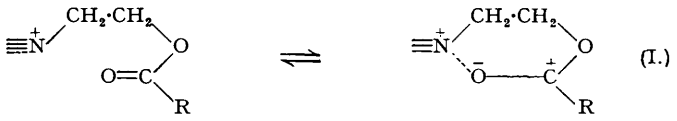
The increased rates of hydrolysis of the mono-esters of glycols could be similarly accounted for by a tendency of the hydroxyl group to assume the ionic form in alkaline solution:



the electron displacement then induced is similar to that in the other esters.

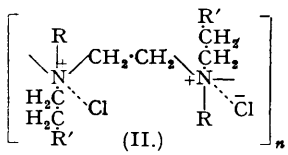
It was originally thought that if the nitrogen atom were quaternised the activating effect on the rate of hydrolysis should be either lost or reversed. However, esters containing quaternary nitrogen atoms were very rapidly hydrolysed under the conditions now employed; this alkalilability of choline esters is, in fact, well-known. It seems possible that the enhancing effect of

the positively charged nitrogen atom is caused by the relative stabilisation of a cyclic structure such as (I) in which the attack of the hydroxyl ion on the carboxyl-carbon atom would be greatly facilitated, with a corresponding effect on the overall hydrolysis rate.



(I.)

The lability of esters containing quaternary nitrogen atoms is of interest in connection with Rose, Hendry, and Walpole's suggestion concerning the mode of action of radiomimetic compounds (*Nature*, 1950, **165**, 993). It was considered that these agents form polymers with reactive side chains and which in the case of the " nitrogen mustards " would have the structure (II; R = Cl). Whilst polymers of this type could be formed from the aliphatic series (cf. Langman, McKay, and Wright, *J. Org. Chem.*, 1949, **14**, 550) it is rather unlikely that such a polymer could be formed from an aromatic " nitrogen mustard " in view of the known difficulty of obtaining quaternary derivatives from these compounds (Everett and Ross, *J.*, 1949, 1972), and the polymer, even if formed, would have unreactive halogen atoms since the activating effect of the uncharged nitrogen atom would have been lost. An alternative suggestion seems more feasible; this is that one side chain of a dihalogenoalkylamine reacts with, say, an organic acid group to give a chloro-ester which subsequently polymerises to give a compound of type (II; R = –O·COR''). However produced, such linkages would be more labile than those formed by the reaction of the dihalide to give a simple diester.



(II.)

It is realised that the values in Table I do not necessarily bear a direct relationship to the rate of hydrolysis of the ester groups at physiological pH in purely aqueous solutions; for example, about 20% of the ester derived from methyldi-2-chloroethylamine (which has pK_a in water = 6·8) will be present in the cationic form at pH 7·4 and hence will be more labile under these conditions than esters derived from sulphur or aromatic nitrogen " mustards." This would explain the observations of Cohen and van Artsdalen (cited by Fruton, Stein, and Bergmann, *J. Org. Chem.*, 1946, **11**, 559) that esters of methyldi-2-hydroxyethylamine are hydrolysed at pH 7·4 with great rapidity. The environment of the acid group which is esterified will also have a profound effect on the stability of the ester link formed; for example, Blackburn, Carter, and Phillips (*Biochem. J.*, 1941, **35**, 627) have shown that methyl esters of wool proteins are unexpectedly labile at pH 9·5, and Alexander (*Biochem. J.*, in the press) has also found that esters produced by the action of epoxides on wool are readily hydrolysed.

The limited evidence so far available seems to support the suggestion made in the introduction that acidic groups would be only temporarily blocked by the various radiomimetic agents.

Experimental.

Dimethyl-2-benzoyloxyethylamine.—Dimethylaminoethanol (44·5 g., 0·5 mol.) was cooled to 0° and benzoyl chloride (77 g., 0·55 mol.) was slowly added with stirring. After being kept at room temperature overnight the solid mass was ground under cold acetone and the hydrochloride was collected and recrystallised from acetone, giving prismatic needles, m. p. 148° (Found: C, 57·5; H, 7·3. Calc. for $C_{11}H_{15}O_2N,HCl$: C, 57·5; H, 7·0%). Gulland *et al.* (*loc. cit.*) give m. p. 151°.

An aqueous solution of the hydrochloride was treated with an excess of potassium carbonate and the liberated base was extracted with benzene. The material obtained on evaporation of the dried extract was was dissolved in warm acetone, and a slight excess of methyl iodide was added. The methiodide separated as glistening plates, m. p. 244° (decomp.) (Gulland *et al.*, *loc. cit.*, give m. p. 243—244°), unchanged after further crystallisation from acetone–methanol (Found: C, 42·9; H, 5·8; I', by titration with 0·1N-silver nitrate using eosin as indicator, 37·8%; equiv., 333. Calc. for $C_{12}H_{18}O_2NI$: C, 42·9; H, 5·4; I', 37·9%; equiv., 335).

Methyldi-2-acetoxyethylamine.—Methyldi-2-hydroxyethylamine (16·1 g.) (prepared by methylating di-2-hydroxyethylamine with formaldehyde and formic acid; Hanby and Rydon, *J.*, 1947, 513), acetic anhydride (45 ml.), and anhydrous sodium acetate (200 mg.) were heated under reflux for 1 hour and then distilled. The fraction of b. p. 110°/4 mm. was *methyldi-2-acetoxyethylamine* (Found: equiv., 101. $C_9H_{17}O_4N$ requires equiv., 101·5).

The *methiodide*, plates (from acetone), m. p. 117—118°, was prepared as described above (Found: C, 34·4; H, 5·9; I', 37·3%; equiv., 173. $C_{10}H_{20}O_4NI$ requires C, 34·8; H, 5·8; I', 36·8%; equiv., 172·6).

Methyldi-2-benzoyloxyethylamine.—(*a*) Methyldi-2-hydroxyethylamine (6·45 g., 0·05 mol.) and benzoyl chloride (7·7 g., 0·055 mol.) were mixed with cooling and left at room temperature. Next day the semi-solid product was extracted with cold acetone and then with ether. The hydrochloride formed diamond-

shaped prisms, m. p. 133—134°, from acetone (Found : C, 62·6, 63·1; H, 6·0, 6·5. Calc. for $C_{19}H_{24}O_4N,HCl$: C, 62·8; H, 6·1%). Pyman (*loc. cit.*) gives m. p. 132—133°.

(*b*) Methyldi-2-chloroethylamine hydrochloride (20 g.) was added to a solution of sodium benzoate (100 g.) in water (250 ml.), and the mixture was heated for ½ hour on a steam-bath. The cooled solution was extracted with ether and the dried extract was saturated with hydrogen chloride. The oil which separated became solid when kept, and formed prisms, m. p. 133° [undepressed on admixture with material obtained by method (*a*)], when crystallised from acetone.

The free base was liberated and treated with methyl iodide as previously described; the *methiodide* formed large plates, m. p. 181—182°, from acetone (Found : C, 51·3; H, 5·3; I′, 26·8%; equiv., 233. $C_{20}H_{24}O_4NI$ requires C, 51·2; H, 5·2; I′, 27·1%; equiv., 234·7).

Ethyl 2-Acetoxyethyl Sulphide.—Ethyl 2-hydroxyethyl sulphide (10 g.) and acetic anhydride (50 ml.) were heated under reflux for 4 hours. The solution was concentrated under reduced pressure and then extracted with benzene. Distillation of the washed and dried extract yielded *ethyl 2-acetoxyethyl sulphide* as a sweet smelling oil, b. p. 90°/4 mm. (Found : equiv., 151. $C_6H_{12}O_2S$ requires equiv., 148).

Ethyl 2-Benzoyloxyethyl Sulphide.—Ethyl 2-chloroethyl sulphide (5 g.), dissolved in a saturated solution of sodium benzoate in 50% aqueous acetone (100 ml.), was heated under reflux for 3 hours. The colourless oil which separated after removal of the acetone was dissolved in light petroleum (b. p. 60—80°) and the dried solution was passed through a column of activated alumina. Concentration of the eluates gave the *benzoate* as a colourless oil (Found : equiv., 214. $C_{11}H_{14}O_2S$ requires equiv., 210).

Di-2-benzoyloxyethyl Sulphide.—Benzoyl chloride (125 ml.) was slowly added to an ice-cooled solution of di-(2-hydroxyethyl) sulphide (25 g.) in pyridine (250 ml.), and then the mixture was heated for 3 hours on a steam-bath. Next day the solution was washed twice with water (400 ml.), and the dried non-aqueous layer yielded two fractions, b. p. 168°/2 mm. and 240°/1 mm., respectively. The latter fraction solidified on cooling, and after one crystallisation from benzene and then from methanol the benzoyl derivative was obtained as rectangular prisms, m. p. 68° (Found : C, 65·5; H, 5·5%; equiv., 171. Calc. for $C_{18}H_{18}O_4S$: C, 65·4; H, 5·5%; equiv., 165). Fromm and Kohn (*loc. cit.*) give m. p. 65°.

N-*Ethyl*-N-2-*acetoxyethylaniline.*—*N*-Ethyl-*N*-2-hydroxyethylaniline (15 ml.), acetic anhydride (50 ml.), and anhydrous sodium acetate (1 g.) were heated under reflux for 5 hours in an oil-bath at 150—160°. Next day the mixture was concentrated under reduced pressure and the residue dissolved in benzene, washed with water, dried, and allowed to percolate through a short column of activated alumina. The eluates yielded the *acetate* as a light yellow oil (Found : equiv., 209. $C_{12}H_{17}O_2N$ requires equiv., 207).

N-*Ethyl*-N-2-*benzoyloxyethylaniline.*—*N*-Ethyl-*N*-2-chloroethylaniline (3·4 g.), dissolved in a solution of sodium benzoate (15 g.) in 50% aqueous acetone (400 ml.), was refluxed for 2 hours. The product was isolated and submitted to a chromatographic purification as already described. The *benzoate*, obtained as a colourless oil (Found : equiv., 268. $C_{17}H_{19}O_2N$ requires equiv., 269), forms a *picrate*, m. p. 153—154°, prisms from acetone–methanol (Found : C, 55·3; H, 4·7. $C_{23}H_{22}O_9N_4$ requires C, 55·4; H, 4·5%).

NN-*Di*-2-*acetoxyethylaniline.*—*NN*-Di-2-hydroxyethylaniline was acetylated in the same manner as the monohydroxy-compound. The *acetate* was obtained as a yellow oil (Found : equiv., 137. $C_{14}H_{19}O_4N$ requires equiv., 133).

NN-*Di*-2-*Benzoyloxyethylaniline.*—Benzoyl chloride (50 ml.) was slowly added to an ice-cooled solution of *NN*-di-2-hydroxyethylaniline (15 g.) in dry pyridine (100 ml.), and then the mixture was heated for 5 hours on a steam-bath. The mixture was poured into water (200 ml.) and left for 2 hours, and then the oily product was shaken with dilute ammonia solution, after which a solid mass was obtained. NN-*Di*-2-*benzoyloxyethylaniline* was obtained as flattened prisms, m. p. 76°, from methanol (Found : C, 73·8; H, 6·4%; equiv., 196. $C_{24}H_{23}O_4N$ requires C, 74·0; H, 6·0%; equiv., 195).

Esters of 2-*Naphthyldi*-2′-*hydroxy*-n-*propylamine.*—The *acetate* (Found : equiv., 168. $C_{20}H_{25}O_4N$ requires equiv., 171·7) and the *benzoate* (Found : equiv., 226. $C_{30}H_{29}O_4N$ requires equiv., 233·8) were obtained as faintly fluorescent viscous oils from the chloropropylamines as described in Part III.

Esters of Ethylene Glycol.—A stream of ethylene oxide was passed for 8 hours through a saturated solution of sodium acetate in 25% aqueous acetone maintained at 80°. The mixture was kept just acidic by the addition, as required, of glacial acetic acid, phenolphthalein being used as an internal indicator. After removal of the acetone under reduced pressure the aqueous solution was extracted with ether (4 × 500 ml.), and the dried extracts were distilled. The acetate had b. p. 187°/761 mm. (Found : equiv., 107. Calc. for $C_4H_8O_3$: equiv., 104); Drushel and Bancroft (*loc. cit.*) give b. p. 187—189° at atmospheric pressure.

Ethylene glycol monobenzoate similarly prepared had b. p. 170—170·5°/2 mm. (Found : equiv., 168. Calc. for $C_9H_{10}O_3$: equiv., 166); Cretcher and Pittenger (*loc. cit.*) give b. p. 173°/21 mm.

When 1 : 2-3 : 4-diepoxybutane was allowed to react with sodium acetate under similar conditions a *diacetate* was formed (Found : equiv., 101. $C_8H_{14}O_6$ requires equiv., 103).

Velocity of the Alkaline Hydrolysis of the Esters.—The ester (0·01 mol. for a monoester or 0·005 mol. for a diester)was dissolved in AnalaR acetone, and the solution made up to 100 ml. To a 10-ml. aliquot of this solution were added 60 ml. of 0·025N-sodium hydroxide, and the mixture was heated under reflux for 3 hours. A blank determination on 10 ml. of AnalaR acetone was carried out at the same time. The excess of alkali present in the cooled solution was determined by titration with 0·025N-hydrochloric acid, with bromothymol-blue as indicator. The infinity value (*a*) (see Table II) was thus obtained and this value was used in subsequent calculations of the velocity constant.

In order to measure the rate of hydrolysis of the ester a 10-ml. aliquot was transferred to a three-necked 700-ml. flask, carrying a reflux condenser and an electrically driven stirrer, and diluted with 150 ml. of acetone. The flask was then kept in a thermostat at 50°. A volume of 0·025N-sodium hydroxide exactly equivalent to the ester contained in the 10-ml. aliquot (40 ml. for monoesters of 100% purity) was measured into a 50-ml. conical flask and kept in the thermostat. While the alkali was warming up to 50° a suitable volume of 0·025N-hydrochloric acid containing bromothymol-blue was placed in a similar 50-ml. flask, and a 10-ml. burette containing 0·025N-sodium hydroxide was fitted so that it could be quickly inserted into the centre neck of the reaction-flask. When the solutions had reached 50° the alkali in the flask was quickly poured into the vigorously stirred ester solution, giving a concentration (c) = 0·005N. in volume (v) = 200 ml., and the stopwatch was started. After the required time the standard acid was rapidly added, the burette inserted, and the excess of acid back-titrated. This procedure was repeated for a series of times, the excess of acid added to arrest the hydrolysis being adjusted in each case so that the back-titration required about 7 ml. of standard alkali. By ensuring that the two 50-ml. flasks were completely free from grease by cleaning them with chromic–sulphuric acid and then carefully rinsing and drying them, it was found that the drainage error in the two additions cancelled out and was in any case less than 0·1 ml. The hydrolyses of all the esters recorded in Table I were carried out by this procedure, except that, for the less soluble hydrochloride of methyldi-2-benzoyloxyethylamine, (c) = 0·0033N. and (v) = 300 ml., and, for the hydrochloride of dimethyl-2-benzoyloxyethylamine, (c) = 0·0025N. and (v) = 400 ml., and, for the four methiodides, (c) = 0·0005N. and (v) = 400 ml. In the case of the four methiodides the measurements were made at higher dilution because of the extreme rapidity of the hydrolyses at the usual concentration. k in Table I is, nevertheless, expressed in the same units in all cases. Phenolphthalein was used as indicator in the hydrolyses of the esters of dimethyl-2-hydroxyethylamine since this amine is sufficiently basic to interfere with the end-point when bromothymol-blue is used.

*p*K$_a$ *Values for Acetates of Methyldi-2-hydroxyethylamine and Dimethyl-2-hydroxyethylamine.*—These values were determined by titrating an M/20-solution of the ester in either water or 80% aqueous acetone with N-hydrochloric acid and measuring the pH of the solution, after each addition, with a glass-electrode system. The values: methyldi-2-acetoxyethylamine, pK_a in water 6·8, in 80% acetone 5·7, and dimethyl-2-acetoxyethylamine, pK_a in water 8·3, in 80% acetone 7·3, were calculated from the titration curves.

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