Ambident Neighbouring Groups. Part V.[1] Mechanism of Cyclization of 2-Halogenoethylsulphonamides to Aziridines

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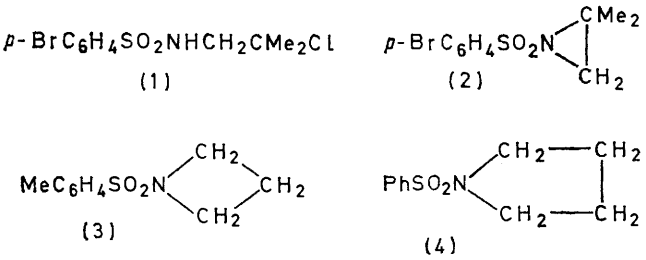
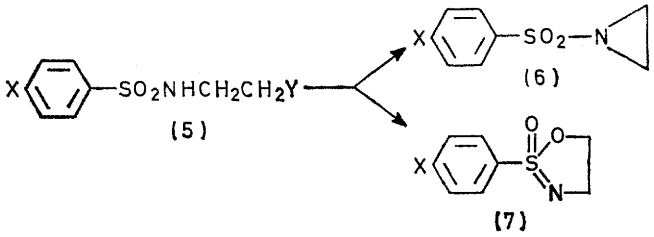
N-(2-Bromo- and 2-chloroethyl)sulphonamides are smoothly cyclized in basic solution to *N*-(arylsulphonyl)-aziridines. Kinetic studies [in water at 25°, μ = 1·0 (KCl)] imply that the sulphonamidate anion is the reactive species. Electron-withdrawing substituents in the aryl ring aid formation of the anion (ρ = +0·94, pK_a^0 = 10·59), while retarding the rate of cyclization of the anion (ρ = −0·58, log k_0 = −1·30), with Br^- as leaving group. The chlorides behave similarly, but are *ca.* 50-fold less reactive than the corresponding bromides. In ethanol containing an excess of ethoxide ion, particularly at higher substrate concentrations, other products including *N*-2-(ethoxyethyl)arylsulphonamides and dimeric materials such as piperazines are also formed. In aqueous solution the *N*-arylsulphonylaziridines undergo slow ring cleavage [to give *N*-(2-hydroxyethyl)arylsulphonamides], but only in strongly acidic or basic media.

It has been well established that amino-substituted alkyl halides can undergo cyclization, with the free amine acting as a neighbouring group to give three-, four-, five-, and six-membered nitrogen heterocycles.[2-4] There have also been several reports of the isolation of cyclic products on the reaction of the related sulphonamido-halides which provides suggestive evidence for the existence of a neighbouring group effect by the sulphonamido-group. Thus Adams and Cairns [2] have reported the formation of the *N*-sulphonylaziridine (2) (in 50% yield) on treatment of the substituted sulphonamide (1) with hydroxide ion at 100° for 15 min. This represents an [N^-–3] cyclization.[3] Vaughan and his co-workers [4] obtained the four-membered heterocycle (3) from the reaction of 3-(*p*-tolylsulphonamido)propyl toluene-*p*-sulphonate in refluxing ethanol containing ethoxide ion. Brown and Van Gulick,[5] on applying the



Hinsberg test to 4-bromobutylamine found that 1-phenylsulphonylpyrrolidine (4) was formed. This reaction possibly involves an intermediate *N*-(4-bromobutyl)benzenesulphonamide which cyclizes rapidly under the reaction conditions. An example of [N^-–6] cyclization comes from the work of Stirling; [6] sulphonylpiperazines were obtained in quantitative yield on the cyclization of the corresponding tosylates. From the severity of the conditions used to effect cyclization in the synthetic studies it appears that the ease of cyclization varies with the size of the heterocycle formed in the following order five > six > three ≫ four.

We have examined the rates of hydrogen halide elimination from the *N*-(2-halogenoethyl)arenesulphonamides (5). Under neutral conditions, these compounds might exhibit anchimerism *via* nitrogen or oxygen attack, as outlined in Scheme 1. Halide loss under



Scheme 1

these conditions is however very slow. We have examined the rate of solvolysis of *N*-(2-bromoethyl)-benzenesulphonamide (5; X = H, Y = Br) in 4 : 1 (v/v) ethanol–water at 100°. Under these conditions the rate constant for the loss of bromide ion was 5×10^{-6} s^{-1}. This compares with a rate of solvolysis of ethyl bromide in the same solvent but at 55° of $1{\cdot}4 \times 10^{-6}$ s^{-1}.[7] Thus the sulphonamido-function, far from exhibiting anchimerism, actually retards solvolysis. This is in contrast to the neutral amino-group which increases the rate of solvolysis of β-chloroalkanes by a factor of 100.[8]

Anchimerism is exhibited in the presence of base, however. The reaction of *N*-(2-bromoethyl)benzenesulphonamide (5; X = H, Y = Br) with sodium ethoxide in ethanol at 25° is complete within 1 min. We have studied the reaction of the corresponding chlorides (5; Y = Cl), which react more slowly, in absolute ethanol containing (at a minimum) a two molar excess of sodium ethoxide. The rates of reaction in this instance were followed by means of acid titration and also by measuring the rate of appearance of halide ion by the Volhard method. Under these conditions the reaction

[1] Part IV, F. L. Scott and C. V. Murphy, *Tetrahedron Letters*, 1970, 1731.

[2] (*a*) R. Adams and T. L. Cairns, *J. Amer. Chem. Soc.*, 1939, **61**, 2464; (*b*) M. S. Kharasch and H. M. Priestley, *ibid.*, 1939, **61**, 3425; (*c*) W. J. Geurber, *ibid.*, 1948, **70**, 1843.

[3] F. L. Scott, R. Glick, and S. Winstein, *Experientia*, 1957, **13**, 183.

[4] W. E. Vaughan, R. S. Klanowski, R. S. McElhinney, and B. B. Millward, *J. Org. Chem.*, 1961, **26**, 138.

[5] R. F. Brown and N. M. Van Gulick, *J. Amer. Chem. Soc.*, 1955, **77**, 1079.

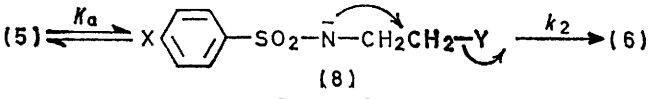
[6] C. J. M. Stirling, *J. Chem. Soc.*, 1962, 3676.

[7] L. C. Bateman, K. A. Cooper, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 1940, 925.

[8] H. Freundlich and G. Salaman, *Ber.*, 1933, **66**, 355.

was shown [9] to follow first-order kinetics and a ρ value of 0·93 was obtained for the influence of substituent X on the rate of halide ion loss (25°; ethanol). Under these conditions, because of the necessarily high substrate concentrations used, the products were complex (see below) although the aziridine (6) was always the major product. Also the bromides (5; X = Br) reacted too rapidly to permit measurement using this technique.

Because of the complex products obtained in the ethanol–ethoxide ion system, we have examined the rates of cyclization of both bromides and chlorides (5) in a purely aqueous system [H_2O; 25°; μ = 1·0 (KCl)]. The course of the reaction was followed spectrophotometrically at low substrate concentrations. Under these conditions the aziridines (6) were the sole products formed.



SCHEME 2

In each case the rate of cyclization of (5) rose rapidly as the pH was increased in the region 9—10; above pH *ca.* 12, the rate of cyclization was independent of pH. The observed rate constants (k_{obs}) at any pH were correlated by equation (1), which is derived from Scheme 2. Values of k_2, the specific rate constant for cyclization of the anion (8), and K_a, the acidity constant for ionization of the sulphonamide (5) were calculated from the best fit to the observed rate constants which were obtained at a minimum of eight pH values (see Figure 1 for a typical example). The values of k_2 and K_a thus obtained are summarized in Tables 1 and 2.

$$k_{obs} = k_2K_a/(K_a + a_H) \quad (1)$$

It is seen that the rates of cyclization (k_2) are not greatly influenced by substituents in the aryl ring. Electron-donating groups increase the rate of reaction and electron-withdrawing groups decrease the rate, a Hammett plot of the data in Table 1 giving ρ −0·58

TABLE 1

Rate constants for the cyclization of the anions (8) of *N*-(2-halogenoethyl)arenesulphonamides (5) to aziridines (6) at 25° in water [μ = 1·0 (KCl)]

X	Y	$10^2k_2/s^{-1}$
H	Br	4·84
4-Me	Br	6·50
4-Br	Br	3·56
3-NO_2	Br	2·14
4-NO_2	Br	1·66
H	Cl	0·086

(*r* 0·994) using the σ values of McDaniel and Brown [10] (see Figure 2). The substituent effect on k_2 in aqueous solution or in ethanol containing an excess of ethoxide ion is exercised directly on the nucleophilicity of the anion (8), and the less electron donating the nitrogen of this amide the lower the rate of cyclization to the aziridine, giving rise to a negative value of ρ.

TABLE 2

pK_a Values for *N*-2-bromoethylarenesulphonamides (5; Y = Br) and *N*-2-chloroethylbenzenesulphonamide (5; X = H, Y = Cl), measured in aqueous solution at 25° [μ 1·0 (KCl)]

X	Y	pK_a
H	Br	10·59
4-Me	Br	10·64
4-Br	Br	10·04
3-NO_2	Br	9·80
4-NO_2	Br	9·74
H	Cl	10·55

The pK_a values determined from the kinetic data for the *N*-2-bromoethylarenesulphonamides (5; Y = Br) and *N*-2-chloroethylbenzenesulphonamide (5; X = H,

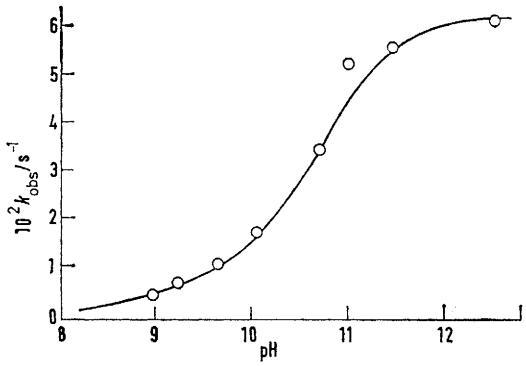


FIGURE 1 Plot of the observed rate constants *vs.* pH for the cyclization of *N*-(2-bromoethyl)toluene-*p*-sulphonamide (5; X = Me) to *N*-(*p*-tolylsulphonyl)aziridine (6; X = Me) at 25° in water [μ = 1·0 (KCl)]. The curve is theoretical using equation (1) with $k_2 = 6·5 \times 10^{-2}$ s^{-1} and pK_a = 10·64

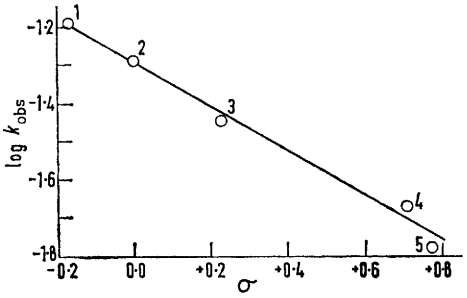


FIGURE 2 Plot of the observed plateau rate constants at high pH (k_2/s^{-1}) *vs.* σ for the cyclization of the anions of *N*-(2-bromoethyl)arenesulphonamides (5) at 25° in water [μ = 1·0 (KCl)]: 1, X = *p*-Me; 2, H; 3, *p*-Br; 4, *m*-NO_2; 5, *p*-NO_2

Y = Cl) are listed in Table 2. The values obtained fall between pK_a values reported for unsubstituted and *N*-methyl-substituted arenesulphonamides.[11] A Hammett plot using the results in Table 2 and the σ values of McDaniel and Brown [10] gives a value of ρ for the acidic dissociation of 0·94 (*r* 0·961). Dauphin and Kergomard [11] obtained ρ 0·883 for the acidic dissociation of arene-

[9] The observed rate constants in ethanol at 25° are given in the preliminary communication, F. L. Scott and E. Flynn, *Tetrahedron Letters*, 1965, 1675; see also K. G. Kleb, E. Siegel, and K. Sasse, *Angew. Chem.*, 1964, 408.

[10] D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 420.

[11] C. Dauphin and A. Kergomard, *Bull. Soc. chim. France*, 1961, 486.

sulphonamides ($ArSO_2NH_2$) in aqueous solution and ρ 1·44 for the acidic dissociation of *N*-methylarenesulphonamides under the same conditions. The higher ρ value obtained for the *N*-methylarenesulphonamides was explained by the inductive effect of the methyl group. As the inductive effect of a bromoethyl group is quite small [12] and positive, the closer correspondence of the ρ for the acidic dissociation of the *N*-2-bromoethylarenesulphonamides to the value for unsubstituted arenesulphonamides is understandable.

In ethanol in the presence of sodium ethoxide, good first-order plots were obtained for the reaction of (5; Y = Cl) when the base concentration was greater than

TABLE 3

Products of reaction of *N*-(2-bromoethyl)arenesulphonamide (5; Y = Br) in sodium ethoxide–ethanol at 25° ([substrate] = [ethoxide] = 10^{-2}M)

X	Aziridine (6) (%)	Piperazine (11) (%)
H	97	
4-Me	97	
4-MeO	98	
4-F	100	
4-NO_2	97	3
3-NO_2	94	3

that of the substrate.[9] These observations suggest that the substrate (5; Y = Cl) is converted essentially quantitatively to its conjugate base (8; Y = Cl) by one equivalent of ethoxide ion. This may be expected in view of the relative acidities of the substrate (5) and the solvent ethanol (pK_a *ca.* 17). Similar data, involving higher negative ρ value obtained in this instance is consistent with the change in the reaction medium from water to ethanol.

The products obtained from the eliminations studied in aqueous solution under the conditions used to study the kinetics were the corresponding aziridines (6). This was shown both by isolation of the aziridine when the reaction was carried out on a larger scale and by the identity of the spectra of the product obtained on completion of a reaction with those of an authentic sample of the aziridine. Product runs on the *N*-2-bromoethylarenesulphonamides (5; Y = Br) in ethanolic solution containing sodium ethoxide yielded exclusively the expected aziridines except in the case of the *meta*- and *para*-nitro derivatives (5; X = 3- or 4-NO_2, Y = Br) which gave 3% yields of the substituted piperazines (11; X = 3- or 4-NO_2), (Table 3). However, in the case of the *N*-2-chloroethylarenesulphonamides (5; Y = Cl), reaction with sodium ethoxide in ethanol yielded materials obtained from base-induced aziridine ring cleavage, such as the *N*-2-ethoxyethylarenesulphonamides (9) and higher derivatives thereof (10), in addition to the expected aziridines (see Table 4). Reasonable yields of piperazines (11) were obtained in some of these latter cases, amounting to 23% in the case of the 4-nitro-compound (5; X = 4-NO_2, Y = Cl) and 14% in that of the 3-nitro-compound (5; X = 3-NO_2, Y = Cl). Heine *et al.*[14] have shown that sulphonylaziridines can be isomerized to piperazines by treatment with iodide ion. There exists the possibility of such a

TABLE 4

Product analysis of reaction of compounds (5; Y = Cl) with sodium ethoxide in dry ethanol

Substrate	Method [a]	Sulphonamide : base ratio	Yields (%) Compound (6)	Compound (9)	Compound (11)	Compound (10)	Resin
(5; X = H)	(1)	1	94		2		
	(2)	1	60	15	2		13
	(3)	0·5	8	64	2		16
(5; X = Me)	(1)	1	94		2		
	(2)	1	65	20	2		8
	(3)	0·5	10	60	2		20
(5; X = MeO)	(1)	1	92		0		
	(2)	1	55	20	1		5
	(3)	0·5	10	56	1		14
(5; X = F)	(1)	1	92		3		
	(2)	1	55	24	3		13
	(3)	0·5	10	60	2		14
(5; X = 4-NO_2)	(1)	1	75		23		
	(2)	1		20	28	41	
	(3)	0·5		60	9	21	
5; X = 3-NO_2)	(1)	1	81		13		
	(2)	1		36	14	38	
	(3)	0·5		70	6	8	

[a] See Experimental section.

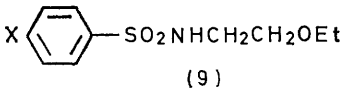
first-order kinetics have been reported by Baird and Winstein [13] in a neighbouring group study on substituted phenols, which are comparable in acidity to the sulphonamides (5). The sequence of steps involved in the reaction is therefore also shown in Scheme 2 except that ethoxide ion acts to remove the NH proton. The reaction occurring with bromide ion liberated under the reaction conditions. However, on treatment of *N*-*p*-nitrophenylsulphonylaziridine (6; X = 4-NO_2) with sodium bromide in ethanolic solution at 25°, substituted aziridine was recovered in 94% yield after 15 h. Treatment of the same aziridine with sodium ethoxide under

[12] H. C. Brown, D. H. MacDaniel, and O. Hafinger, in E. A. Braude and F. C. Nachod, 'Determination of Organic Structures by Physical Methods,' Academic Press, New York, 1955, vol. I, pp. 575—582.

[13] R. Baird and S. Winstein, *J. Amer. Chem. Soc.*, 1962, **84**, 788; 1963, **85**, 567.

[14] H. W. Heine, W. G. Kenyan, and E. M. Johnson, *J. Amer. Chem. Soc.*, 1961, **83**, 2570.

similar conditions gave *N*-(2-ethoxyethyl)-*p*-nitrobenzenesulphonamide (9; X = 4-NO_2) in 90% yield together with the higher derivative (10; X = 4-NO_2).



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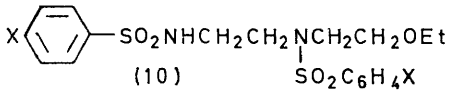

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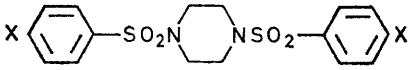
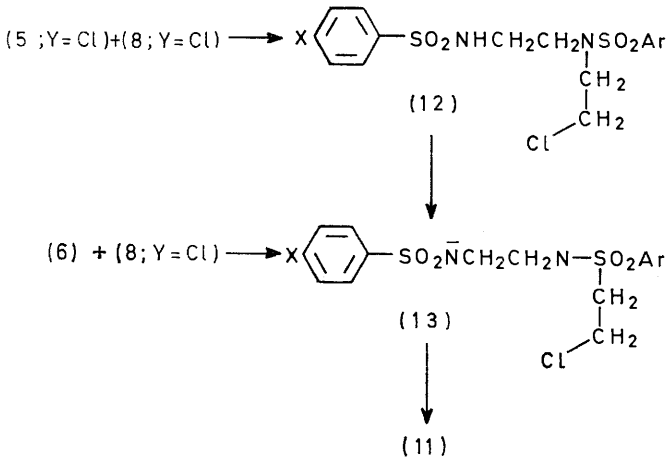


(11)

Similar results were obtained for *N*-*p*-tolylsulphonylaziridine. The above data suggest the sequences outlined in Scheme 3 as being the most likely routes to substituted piperazines. The sulphonamidate anion (8; Y = Cl) attacks starting material to form compounds of type (12) which react *via* the anion (13) to form the piperazine (11). Stirling has shown that compounds of type (12) readily convert to substituted piperazines.[6]

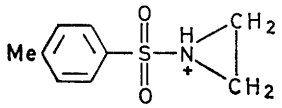


SCHEME 3

Since the *N*-(2-chloroethyl)sulphonamides are converted to the anions in the presence of an equivalent of sodium ethoxide, the more likely pathway to the piperazine involves the aziridine. We have demonstrated that an aziridine can be trapped by a sulphonamidate anion by reacting *N*-*p*-nitrophenylsulphonylaziridine (6) with the *N*-(2-ethoxyethyl)-*p*-nitrobenzenesulphonamide (9; X = 4-NO_2) in the presence of sodium ethoxide in ethanol to give the derivative (10; X = 4-NO_2) in 50% yield.

All the compounds described have been unambiguously synthesized and compared with the products isolated to establish correct identity. As these further reactions are found only for the *N*-2-chloroethylarenesulphonamides (and at higher concentrations) in ethanol with sodium ethoxide they may be ascribed to the lower rate of cyclization of these compounds which give time for reactions other than cyclization to become apparent.

The rate of hydrolysis of *N*-*p*-tolylsulphonylaziridine (6; X = Me) in acidic and basic solution was also studied. In strong acid solution the compound presumably exists in the protonated form (14). No pK_a value for this compound can be found above 0 (*i.e.* k_{obs} was proportional to [H^+] in the region pH 2—0; at pH 0, $k_{obs} = 4 \times 10^{-3}$ s^{-1}). This is not unexpected as studies on the protonation of aromatic sulphonamides in sulphuric acid–water mixtures at 25° have shown [15] the pK_a of *NN*-diethylbenzenesulphonamide to be −6·80 and that of *NN*-dimethyltoluene-*p*-sulphonamide to be



(14)

−6·19. A possible mechanism of ring opening therefore involves water attack on the protonated form (14).

Because of the extremely low basicity of the aziridines (6) the normal mechanism of hydrolysis of aziridines,[16] which involves hydroxide (or water) attack on the protonated species, does not occur to any appreciable extent. Thus the aziridine (6; X = Me) was stable in neutral solution at 25°. In basic solution (pH 13—14) slow further hydrolysis of the aziridine took place with the formation of *N*-(2-hydroxyethyl)toluene-*p*-sulphonamide (k_{obs} at [HO^-] = 1·0M is *ca.* $1{\cdot}0 \times 10^{-4}$ s^{-1}). This most likely results from a direct hydroxide ion attack on the neutral aziridine (6) since the rate of ring opening was proportional to hydroxide ion at high pH. Since the ring opening of the aziridines by HO^- was much slower than cyclization of the sulphonamides (5) at all pH values, the subsequent reaction did not interfere with measurements on the kinetics of cyclization.

EXPERIMENTAL

All inorganic materials used were AnalaR grade. The solvent used for the kinetic experiments was water which had been passed through a mixed cation–anion exchange resin and then distilled twice from alkaline permanganate. The ionic strength, μ, was maintained constant at 1·0 by the addition of potassium chloride. 2-Bromoethylamine hydrobromide was obtained commercially. 2-Chloroethylamine hydrochloride was synthesized by the method of Raiziss and Clemence.[17] All the benzenesulphonyl chlorides were obtained commercially. Aziridine was synthesized by the method of Wenker.[18]

Preparation of Substrates.—The *N*-(2-halogenoethyl)arenesulphonamides were synthesized by one of three general methods.

Method A. The 2-halogenoethylamine hydrohalide (0·05

[15] P. Virtanen, I. Olavi, and K. Heinamaki, *Suomen Kem.*, 1969, **42**, 142.

[16] G. A. Cockayne and P. J. Taylor, *J.C.S. Perkin II*, 1972, 2173.

[17] G. W. Raiziss and L. W. Clemence, *J. Amer. Chem. Soc.*, 1941, **63**, 3124.

[18] H. Wenker, *J. Amer. Chem. Soc.*, 1955, **57**, 2328.

mol) was dissolved in pyridine (15 ml). Heat was evolved during the addition. The appropriate benzenesulphonyl chloride (0·055 mol) was added with stirring and the mixture was heated for 1 h on a steam-bath, allowed to cool, and distributed between diethyl ether (25 ml) and water (25 ml). The aqueous layer was washed twice with diethyl ether (25 ml). The combined ether extracts were washed with 0·1M-hydrochloric acid (20 ml) followed by water (20 ml), dried (Na_2SO_4), and evaporated to give the crude product which was recrystallized from aqueous alcohol.

Method B. The method of Rajagopalan was employed.[19]

Method C. The method of Goldberg and Kelly was employed.[20]

The following *N*-(2-halogenoethyl)arenesulphonamides were synthesized by method A: *N*-2-(chloroethyl)benzenesulphonamide, yield 72%, m.p. 71—72° (lit.,[21] 64—66°), δ ($CDCl_3$) 8·10—7·35 (5H, m, ArH), 6·00—5·50 (1H, t, NH), and 3·78—3·06 (4H, m, NCH_2CH_2Cl); *N*-(2-chloroethyl)-*p*-methoxybenzenesulphonamide, 50%, 73—74° (Found: C, 43·8; H, 4·8. $C_9H_{12}ClNO_3S$ requires C, 43·7; H, 4·6%); *N*-(2-chloroethyl)-*p*-fluorobenzenesulphonamide, 40%, 66—67° (Found: C, 40·6; H, 4·0. $C_8H_9ClFNO_2S$ requires C, 40·4; H, 3·8%). *N*-(2-chloroethyl)-*p*-nitrobenzenesulphonamide, 50%, 123—125° (Found: C, 36·4; H, 3·4; Cl, 13·3; N, 10·1. $C_8H_9ClN_2O_4S$ requires C, 36·3; H, 3·4; Cl, 13·4; N, 10·6%); *N*-(2-chloroethyl)-*m*-nitrobenzenesulphonamide, 55%, 83—85° (lit.,[21] 74—75°).

The following *N*-(2-halogenoethyl)arenesulphonamides were prepared by method B: *N*-(2-chloroethyl)toluene-*p*-sulphonamide, yield 70%, m.p. 77—78° (lit.,[22] 79°); *N*-(2-bromoethyl)-*p*-methoxybenzenesulphonamide, 45%, 66—68° (Found: C, 37·7; H, 4·3; Br, 26·5. $C_9H_{12}BrNO_3S$ requires C, 36·8; H, 4·1; Br, 27·2%); *N*-(2-bromoethyl)-*p*-fluorobenzenesulphonamide, 45%, 63—65° (Found: C, 34·8; H, 2·9; F, 6·8; N, 5·2; S, 11·8. $C_8H_9BrFNO_2S$ requires C, 33·9; H, 3·2; F, 6·8; N, 5·0; S, 11·3%).

The following *N*-(2-halogenoethyl)arenesulphonamides were prepared by method C: *N*-(2-bromoethyl)benzenesulphonamide, yield 60%, m.p. 57—58° (lit.,[19] 58°), δ ($CDCl_3$) 8·06—7·42 (5H, m, ArH), 5·50—4·31 (1H, s, NH), and 3·39 (4H, s, NCH_2CH_2Br); *N*-(2-bromoethyl)-*p*-nitrobenzenesulphonamide, 50%, 116—118° (lit.,[23] 119·5—120°), δ ($CDCl_3$) 8·51—8·01 (4H, q, ArH), 5·00—5·33 (1H, s, NH), and 3·60—3·40 (4H, d, NCH_2CH_2Br); *N*-(2-bromoethyl)-*m*-nitrobenzenesulphonamide, 45%, 82·5°, δ ($CDCl_3$) 8·78—7·65 (4H, m, ArH), 6·53—5·89 (1H, s, NH), and 3·44 (4H, s, NCH_2CH_2Br) (Found: C, 31·3; H, 2·8; Br, 25·6; N, 9·1; S, 10·2. $C_8H_9BrN_2O_4S$ requires C, 31·1; H, 2·9; Br, 25·8; N, 9·1; S, 10·4%); *N*-(2-bromoethyl)toluene-*p*-sulphonamide, 55%, 89—91° (lit.,[22] 89—90°), δ ($CDCl_3$) 7·89—7·28 (4H, q, ArH), 5·00—5·44 (1H, s, NH), 3·48—3·32 (4H, m, NCH_2CH_2Br), and 2·47 (3H, s, ArMe); *N*-(2-bromoethyl)-*p*-bromobenzenesulphonamide, 50%, 70°, δ ($CDCl_3$) 7·91—7·53 (4H, m, ArH), 5·37—5·04 (1H, s, NH), and 3·46—3·35 (4H, m, NCH_2CH_2Br) (Found: C, 27·45; H, 2·4; N, 3·9; S, 9·7. $C_8H_9Br_2NO_2S$ requires C, 27·8; H, 2·7; N, 4·1; S, 9·3%).

Unambiguous Synthesis of Products.—The *N*-sulphonylaziridines were synthesized by the method of Howard and Marckwald:[24] *N*-(phenylsulphonyl)aziridine, yield 64%; *N*-(*p*-tolylsulphonyl)aziridine, 75%, m.p. 51—52° (lit.,[24] 52° and [25] 64·2—64·4°); *N*-(*p*-methoxyphenylsulphonyl)aziridine, 70%, 46—47° (Found: C, 51·2; H, 5·2; N, 6·7; S, 15·3. $C_9H_{11}NO_3S$ requires C, 50·7; H, 5·2; N, 6·6; S, 15·1%); *N*-(*p*-fluorophenylsulphonyl)-aziridine, 60%, 58—59° (Found: C, 47·8; H, 4·3; F, 9·2; N, 7·1; S, 16·3. $C_8H_8FNO_2S$ requires C, 47·8; H, 4·0; F, 9·4; N, 7·0; S, 16·0%); *N*-(*p*-nitrophenylsulphonyl)-aziridine, 65%), 132—135° (lit.,[23] 137°); *N*-(*m*-nitrophenylsulphonyl)aziridine, 57%, 101—103° (lit.,[14] 103—104°).

The n.m.r. spectra of the *N*-*p*-tolylsulphonyl- and *N*-*p*-nitrophenylsulphonyl-aziridines gave rise to a singlet for the ring methylene protons in deuteriochloroform at room temperature. Although the inversion rate of the amine nitrogen atom is comparatively slow the result confirms similar spectra obtained by Traylor.[25] The ethyl group in the *N*-2-bromoethylarenesulphonamides provides a good example of an A_2B_2 system, with a small $\Delta\nu/J$ ratio giving rise to degenerate or partially degenerate spectra. Indeed the four ethyl protons in *N*-2-bromoethylbenzenesulphonamide resonate as an apparent singlet (δ 3·40). A similar example is reported for benzylacetone.[26]

The 1,4-bisarylsulphonylpiperazines were prepared by the following general method.

The appropriate benzenesulphonyl chloride (2—6 mmol), piperazine hexahydrate (5·2 mmol), and sodium hydroxide (5 mmol) were stirred in water (40 ml) for 2 h. The insoluble sulphonylpiperazine was collected, dried, and recrystallized from dimethylformamide, to give the piperazines as follows: *NN*-(bisphenylsulphonyl)piperazine, yield 53%, m.p. 287—289° (lit.,[27] 291·3—291·7°); *NN*-(bis-*p*-tolylsulphonyl)piperazine, 66%, 296—298° (lit.,[27] 298·4—298·6°); *NN*-(bis-*p*-methoxyphenylsulphonyl)piperazine, 50%, 231—233° (Found: C, 51·3; H, 5·2; N, 7·0; S, 15·2. $C_{18}H_{22}N_2O_6S_2$ requires C, 50·7; H, 5·2; N, 6·6; S, 15·1%); *NN*-(bis-*p*-fluorophenylsulphonyl)piperazine, 61%, 291—293° (Found: C, 47·9; H, 4·0; F, 9·4; N, 7·0; S, 16·0. $C_{16}H_{16}F_2N_2O_4S_2$ requires C, 47·8; H, 4·0; F, 9·4; N, 7·0; S, 16·0%); *NN*-(bis-*p*-nitrophenylsulphonyl)-piperazine, 58%, 350° (decomp.) (Found: C, 42·3; H, 3·5; N, 11·8; S, 14·5. $C_{16}H_{16}N_4O_8S_2$ requires C, 42·1; H, 3·5; N, 12·3; S, 14·0%); *NN*-(bis-*m*-nitrophenylsulphonyl)-piperazine, 53%, 264—266° (lit.,[27] 262—264°).

The *N*-2-ethoxyethylarenesulphonamides were prepared by the following general method. The appropriate benzenesulphonyl chloride (2·6 mmol), 2-aminoethyl ethyl ether (3 mmol), and sodium hydroxide (6 mmol) were vigorously stirred in water (25 ml) for 1 h. On cooling in ice the solid which precipitated was collected and washed with water. [In some cases an oil was obtained on cooling. This was extracted with ether, dried (Na_2SO_4), and purified by chromatography.] The material was dried and recrystallized from benzene–pentane. This method yielded the following 2-ethoxysulphonamides: *N*-(2-ethoxyethyl)-benzenesulphonamide, yield 55%, a light oil (Found: C, 51·7; H, 6·5; N, 6·2; S, 14·4. $C_{10}H_{15}NO_3S$ requires C, 52·4; H, 6·6; N, 6·1; S, 14·0%); *N*-(2-ethoxyethyl)-toluene-*p*-sulphonamide, 50%, m.p. 35—37° (Found: C, 54·3; H, 6·9; N, 5·9; S, 13·3. $C_{11}H_{17}NO_3S$ requires C,

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54·3; H, 7·0; N, 5·8; S, 13·2%); *N*-(2-ethoxyethyl)-*p*-methoxybenzenesulphonamide, 45%, a light oil (Found: C, 50·8; H, 6·7; N, 5·5; S, 11·7. $C_{11}H_{17}NO_4S$ requires C, 50·8; H, 7·0; N, 5·4; S, 12·3%); *N*-(2-ethoxyethyl)-*p*-fluorobenzenesulphonamide, 52%, a light oil (Found: C, 47·8; H, 5·5; F, 7·4; N, 6·0; S, 12·7. $C_{10}H_{14}FNO_3S$ *requires* C, 48·6; H, 5·7; F, 7·7; N, 5·7; S, 13·0%); *N*-2-ethoxyethyl-*p*-nitrobenzenesulphonamide, 40%, 97—98° (Found: C, 44·0; H, 5·2; N, 9·7; S, 11·5. $C_{10}H_{14}N_2O_5S$ requires C, 43·8; H, 5·1; N, 10·2; S, 11·7%); *N*-2-ethoxyethyl-*m*-nitrobenzenesulphonamide, 43%, a light oil (Found: C, 44·2; H, 5·2; N, 10·3; S, 11·8. $C_{10}H_{14}N_2O_5S$ requires C, 43·8; H, 5·1; N, 10·2; S, 11·7%).

Kinetic Measurements.—The rates of aziridine formation from the *N*-2-bromoethylbenzenesulphonamides were studied in aqueous solution at 25°, with $\mu = 1{\cdot}0$ (KCl). The rate of hydrolysis of *N*-*p*-tolylsulphonylaziridine (6; X = Me) was studied under similar conditions. In both cases the rates were measured spectrophotometrically at suitable wavelengths in the u.v. region, using a Unicam SP 800 spectrometer. The solutions were buffered with either sodium acetate, borax, or mixed phosphate buffers depending on the pH region under examination. Separate experiments at various buffer concentrations at constant pH indicated the absence of significant buffer catalysis. The pH values quoted are the indicated pH values of the solutions using a glass electrode (Metrohm type EA 125 U) which had previously been standardized in aqueous buffers. A Radiometer pH meter model PHM 26 was used for all pH measurements.

The substrates were made up in concentrated solution (10^{-2}M) in dioxan and reaction was initiated by addition of 3—6 drops of this stock solution to the aqueous solution in the u.v. cell. All rate constants reported are first-order and were determined graphically. On completion of reaction of *N*-(2-bromoethyl)toluene-*p*-sulphonamide (5; X = Me, Y = Br) the resulting u.v. spectrum was the same as that of a synthetic solution of the corresponding aziridine (6; X = Me) under the same conditions.

The rates of solvolysis of the *N*-2-chloroethylarenesulphonamides were studied in ethanol at 25°. Commercial absolute ethanol was dried by the method of Smith,[28] and distilled before use. Solutions of nitric acid and sodium hydroxide were standardized with sodium carbonate, using Methyl Red as indicator. Solutions of sodium ethoxide were standardized against nitric acid, using Methyl Red as indicator. The kinetic procedure for these reactions was as follows. The required amount of sulphonamido-halide was weighed and transferred to a calibrated volumetric flask (50 ml). Dry ethanol (40 ml) was added, and the flask and contents were equilibrated at 25°. Standard sodium ethoxide in ethanol (5 ml) was then added and the flask was made up to the mark with dry ethanol. A further 2—5 min were allowed for equilibration. Aliquot portions (5 ml) were removed from the flask using an automatic calibrated pipette and the reaction was quenched by running the sample into an excess of nitric acid. The reaction was followed by two methods: (i) the disappearance of base was estimated using an acid titrant; (ii) the appearance of halide ion was estimated using the Volhard technique. Control experiments showed that unchanged starting material affected neither method.

Product Analyses.—Repetition of the reaction of the *N*-(2-bromoethyl)benzenesulphonamides (5; X = Me, Y = Br) and (5; X = 4-NO_2, Y = Br) in aqueous solution for five half-lives yielded the corresponding *N*-sulphonylaziridines as the sole products at pH 11·03. The products were identified by comparison with authentic samples and the absence of significant amounts of other materials was indicated by t.l.c.

The products of ethoxide ion induced reactions of the *N*-2-bromo- and *N*-2-chloro-ethylbenzenesulphonamides are listed in Table 3. Three differing sets of conditions were used in the product analyses. (1) The substrate (5; Y = Cl) ($0{\cdot}575 \times 10^{-3}$M) was dissolved in dry ethanol in a volumetric flask (50 ml) and standard ethanolic sodium ethoxide (5 ml) was added. The flask was then filled to the mark with dry ethanol [28] to give a final concentration of sulphonamide and ethoxide of $1{\cdot}15 \times 10^{-2}$M. The reactants were maintained at 25° for five half-lives. The solution was cooled in ice and a precipitate formed which was removed by suction. This was found to be almost pure piperazine (11). The filtrate was evaporated to dryness at 25° and extracted with ether to remove any sodium chloride. The ether was further extracted with ice cold sodium hydroxide (1·0M) to remove any alkali-soluble materials such as starting material and the appropriate *N*-2-ethoxyethylarenesulphonamide (9). Evaporation of the dried ether layer yielded the aziridine (6). The acidic substances were recovered from the alkali solution by acidification and ether extraction. (2) The procedure used was the same as for (1) but the reaction time was increased to 15 h. In this case *N*-2-ethoxyethyl-*N*-2-arylsulphonamidoethylarenesulphonamide (10) was isolated with any piperazine formed. These were separated by recrystallization from boiling ethanol in which the piperazine was insoluble. (3) This was identical to method (2) in all respects other than that the final concentration of base ($4{\cdot}0 \times 10^{-2}$M) was double that of sulphonamide ($2{\cdot}0 \times 10^{-2}$M).

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