642. *Cytotoxic Compounds. Part V.*[1] *Derivatives of* p-(NN-*Di*-2-*chloroethyl- and of* p-(NN-*Di*-2-*bromoethyl-amino*)*benzenesulphonic Acid.*

By M. H. Benn, A. M. Creighton, B. J. Johnson, L. N. Owen, and G. R. White.

p-(*NN*-Di-2-chloroethylamino)benzenesulphonyl chloride and the di-2-bromoethyl analogue have been synthesised. These are useful reagents for the attachment of a " nitrogen mustard " to other compounds, and various types of sulphonamides, sulphonhydrazides, and sulphonic esters have been prepared from them.

Although " nitrogen mustards " in great variety have been synthesised in the search for an effective anti-tumour agent,[2] aromatic sulphonamides (I) or sulphonic esters (II) of the mustard type have not hitherto been described. The former class of derivative would be interesting in view of the well-known biological activity of certain sulphonamides, whilst the esters would contain an alkylating group additional to the pair possessed by the nitrogen-mustard function. The obvious source of such derivatives is the corresponding sulphonyl chloride, which moreover would be a useful reagent for the attachment of a nitrogen-mustard group to a wide range of other compounds. Thus by reaction with a substance involved in cell metabolism, such as a sugar or an amino-acid, the product might be biologically effective by means of an " active transport " mechanism through the cell wall.[3]

p-$(CH_2Cl\cdot CH_2)_2N\cdot C_6H_4\cdot SO_2\cdot NHX$ (I) *p*-$(CH_2Cl\cdot CH_2)_2N\cdot C_6H_4\cdot SO_3X$ (II)

[1] Part IV, Grice and Owen, *J.*, 1963, 1947.
[2] Ross, " Biological Alkylating Agents," Butterworths, London, 1962.
[3] Ref. 2, p. 132.

Reaction of *NN*-di-2′-chloroethylaniline with an excess of chlorosulphonic acid gave as the main product a crystalline sulphonyl chloride, which was proved to be the *p*-compound by reduction with lithium aluminium hydride to the known [4] *p*-(*NN*-di-2-chloroethylamino)thiophenol. The sulphonyl chloride reacted smoothly with ammonia, aniline, glycine ethyl ester, 2-aminopyridine, or 2-aminothiazole to give the sulphonamides (I; X = H, Ph, etc.), and with hydrazine it gave the sulphonhydrazide (I; X = NH_2). The yields were high, an indication that the chloroethyl groups were relatively unreactive —clearly a consequence of the powerful electron-withdrawing effect of the sulphonyl group. This was also demonstrated by the preparation of the sodium sulphonate (II; X = Na) by hydrolysis of the sulphonyl chloride and progressive neutralisation of the free acid so formed. Esters were obtained by reaction in pyridine with cholesterol, 1,2-*O*-isopropylideneglycerol, and 1,3-*O*-benzylideneglycerol (the last two being models for possible later applications to carbohydrate derivatives). 2,4-Dinitrophenol under similar conditions gave only the water-soluble quaternary pyridinium salt (II; X = *N*-2,4-dinitrophenylpyridinium), presumably because of the powerful alkylating properties of 2,4-dinitrophenyl arenesulphonates.[5] The ester, which was required not only for this reason but also because of the additional toxic properties which would be conferred on the compound by the 2,4-dinitrophenyl group itself, was eventually obtained by reaction of the sulphonyl chloride with sodium 2,4-dinitrophenate in acetone.

The deactivating effect of the sulphonyl group on the reactivity of the nitrogen-mustard portion was confirmed by the very low figures obtained for the degree of hydrolysis of these derivatives under the standard conditions used by Ross [6] (30 minutes in boiling 50% aqueous acetone; see Table). Furthermore, in biological tests * the compounds all showed very low toxicity and little or no anti-tumour action. It is known, however, that di-2-bromoethylamines are more reactive than the chloro-compounds, and, although more toxic, may be more effective biologically.[4,7] Attention was therefore turned to the di-2-bromoethyl analogues of (I) and (II). The necessary *p*-(*NN*-di-2-bromoethylamino)benzenesulphonyl chloride was prepared from *NN*-di-2′-bromoethylaniline and its structure established by reduction to the known [4] thiol. Even from this chloride it was possible to form esters, sulphonamides, and sulphonhydrazides without appreciable decomposition of the nitrogen-mustard portion, and the rates of hydrolysis of the derivatives, though in general greater than those of the di-2-chloroethyl analogues, were still quite small (see Table). Nevertheless, the sulphonamide (IC 56) and the sulphonhydrazide (IC 57), which happened to be amongst the earliest compounds tested, were strikingly effective against the Walker tumour in rats; an additional point of interest was that the sulphonamide showed an unusual form of delayed toxicity, the symptoms of which were not those of mustard poisoning, but of folic-acid deficiency.[8] For these reasons, derivatives of more diverse types were prepared. Those containing carboxyl groups were designed to be soluble (as sodium salts) in aqueous solution; some of these were made by interaction of the sulphonyl chloride with an amino-acid (IC 149, 150) or with *p*-carboxyphenylhydrazine (IC 154), but others were obtained indirectly. Two esters (IC 120 and 118) were made by reaction of methyl isocyanatoacetate [9] with the free sulphonamide and the free sulphonhydrazide, respectively. Selective hydrolysis of the first ester failed to give a pure product, but the second gave the corresponding carboxylic acid (IC 119). The normal reactivity of the free sulphonhydrazide towards carbonyl compounds provided a simple method for the preparation of the pyruvic-acid derivative (IC 121).

* These were carried out, on compounds described in this and the following Paper, by Professor J. F. Danielli, F.R.S., and will be reported in detail elsewhere.

[4] Benn, Owen, and Creighton, *J.*, 1958, 2800.
[5] Cf. Tipson, *J. Org. Chem.*, 1944, **9**, 235.
[6] Ross, *J.*, 1949, 183.
[7] Davis, Everett, and Ross, *J.*, 1950, 1331.
[8] Danielli, *Ann. Reports British Empire Cancer Campaign*, 1961, **39**, 574.
[9] Benn, Creighton, Owen, and White, *J.*, 1961, 2365.

Sulphonates, sulphonamides, and sulphonhydrazides.

R = *p*-$(CH_2Cl\cdot CH_2)_2N\cdot C_6H_4$; R′ = *p*-$(CH_2Br\cdot CH_2)_2N\cdot C_6H_4$

IC No.	Compound	Method [a]	Cryst.[b]	M. p.	Found (%) C	H	Hal	N	Formula	Requires (%) C	H	Hal	N	Hydrolysis (%) [c]
18	R·SO_3·CH_2·(2,2-dimethyl-1,3-dioxolan-4-yl)	(i)	M	96°	46·5	5·7	17·5		$C_{16}H_{23}Cl_2NO_5S$	46·6	5·6	17·2		2
92	R·SO_3·(2-phenyl-1,3-dioxan-5-yl)	(i)	E	117	52·3	5·25	15·3		$C_{20}H_{23}Cl_2NO_5S$	52·2	5·0	15·0		
19	R·SO_3·(cholest-5-en-3β-yl)	(i)	E	149	66·6	8·6	11·1		$C_{37}H_{57}Cl_2NO_3S$	66·6	8·6	10·65		2
179	R·SO_3·$C_6H_3(NO_2)_2$-2,4		A–E	92				9·0	$C_{16}H_{15}Cl_2N_3O_7S$				9·05	
20	R·SO_2·NH_2		B	91	40·6	4·9	24·7	9·1	$C_{10}H_{14}Cl_2N_2O_2S$	40·4	4·75	23·9	9·4	2
21	R·SO_2·NH·NH_2		E	125	38·5	4·8		13·2	$C_{10}H_{15}Cl_2N_3O_2S$	38·5	4·8		13·5	4
22	R·SO_2·NHPh	(i)	E	139	51·3	5·1		7·6	$C_{16}H_{18}Cl_2N_2O_2S$	51·5	4·9		7·5	4
23	R·SO_2·NH(2-pyridyl)	(i)	F	199	48·3	4·8		11·2	$C_{15}H_{17}Cl_2N_3O_2S$	48·1	4·6		11·2	3
24	R·SO_2·NH(2-thiazolyl)	(i)	E	155	41·3	4·1		10·9	$C_{13}H_{15}Cl_2N_3O_2S_2$	41·1	4·0		11·1	4
54	R·SO_2·NH·CH_2·CO_2Et	(ii)	E–L	105	44·2	5·3		7·1	$C_{14}H_{20}Cl_2N_2O_4S$	43·9	5·3		7·3	2
63	R′·SO_3Me		M	91	33·1	4·0			$C_{11}H_{15}Br_2NO_3S$	32·9	3·8			8
64	R′·SO_3Et		E	83	34·8	4·1		3·3	$C_{12}H_{17}Br_2NO_3S$	34·7	4·1		3·4	8
65	R′·SO_3·$C_6H_3(NO_2)_2$-2,4		A–I	107	(O, 20·4)			7·7	$C_{16}H_{15}Br_2N_3O_7S$	(O, 20·25)			7·6	
153	R′·SO_3·C_6H_4·NHAc-*p*	(i)	A	150			30·5	5·4	$C_{18}H_{20}Br_2N_2O_4S$			30·7	5·4	
56	R′·SO_2·NH_2		H	118	30·9	3·9	41·5		$C_{10}H_{14}Br_2N_2O_2S$	31·1	3·7	41·4		8
57	R′·SO_2·NH·NH_2		H	142	29·7	3·8		10·4	$C_{10}H_{15}Br_2N_3O_2S$	29·9	3·8		10·5	7
76	R′·SO_2·NHPr^i		G–L	84			37·6	6·5	$C_{13}H_{20}Br_2N_2O_2S$			37·3	6·5	9
72	R′·SO_2·NHPh	(i)	E–H	135			34·4	6·3	$C_{16}H_{18}Br_2N_2O_2S$			34·6	6·1	5
71	R′·SO_2·NH(2-pyridyl)	(i)	D	184				9·1	$C_{15}H_{17}Br_2N_3O_2S$				9·1	6
146	R′·SO_2·NH·C_6H_4·OH-*p*	(i)	A–C	161	40·2	3·8	33·4		$C_{16}H_{18}Br_2N_2O_3S$	40·8	4·3	33·6		5
147	R′·SO_2·NH·C_6H_4·SO_2·NH_2-*p*	(i)	A–C	196			29·3		$C_{16}H_{19}Br_2N_3O_4S_2$			29·4		4
149	R′·SO_2·NH·C_6H_4·CO_2H-*p*	(i)	H–L	216			31·2		$C_{17}H_{18}Br_2N_2O_4S$			31·5		
144	R′·SO_2·NH·C_6H_4·CO_2Me-*p*	(i)	M	172			29·6	5·7	$C_{18}H_{20}Br_2N_2O_4S$			30·7	5·4	
150	R′·SO_2·NH(5-carboxy-2-hydroxyphenyl)	(i)	A–C	232	39·7	4·0	30·5		$C_{17}H_{18}Br_2N_2O_5S$	39·1	3·5	30·6		
107	R′·SO_2·NH·CH_2·CO_2Me	(ii)	H	123	34·1	3·9		6·0	$C_{13}H_{18}Br_2N_2O_4S$	34·1	4·0		6·1	
61	R′·SO_2·NH·CH_2·CO_2Et	(ii)	H–L	107	35·7	4·6			$C_{14}H_{20}Br_2N_2O_4S$	35·6	4·3			7
108	R′·SO_2·NH·CH_2·CO_2H		B–L	133–135	34·9	4·0	34·9		$C_{12}H_{16}Br_2N_2O_4S$ + $\frac{1}{4}C_6H_6$	34·95	3·85	34·5		
120	R′·SO_2·NH·CO·NH·CH_2·CO_2Me		A–H	156	32·95	4·0			$C_{14}H_{19}Br_2N_3O_5S$	33·5	3·8			
170	R′·SO_2·NH·NH·$C_6H_3(NO_2)_2$-2,4	(i)	B	182	35·7	3·3	27·6		$C_{16}H_{17}Br_2N_5O_6S$ + $\frac{1}{4}C_6H_6$	35·7		3·5	27·3	
154	R′·SO_2·NH·NH·C_6H_4·CO_2H-*p*	(i)	B	194	41·8	4·0	29·5		$C_{17}H_{19}Br_2N_3O_4S$ + $\frac{1}{4}C_6H_6$	41·1		3·9	29·4	
118	R′·SO_2·NH·NH·CO·NH·CH_2·CO_2Me		A–H	154			30·9	11·1	$C_{14}H_{20}Br_2N_4O_5S$			31·0	10·9	
119	R′·SO_2·NH·NH·CO·NH·CH_2·CO_2H		N	191	31·05	4·1			$C_{13}H_{18}Br_2N_4O_5S$	31·1	3·6			
121	R′·SO_2·NH·N:CMe·CO_2H		G–L	197			32·8	8·8	$C_{13}H_{17}Br_2N_3O_4S$			33·1	8·9	
201	R′·SO_2·NH·NH·CO_2Me		M–L	168	(O, 14·2)		35·3		$C_{12}H_{17}Br_2N_3O_4S$	(O, 14·0)		34·8		

[a] For procedure, see Experimental section; (i) and (ii) refer to the general methods described therein. [b] Solvents: A, acetone; B, benzene; C, carbon tetrachloride; D, dioxan; E, ethanol; F, acetic acid; G, ethyl acetate; H, chloroform; I, propan-2-ol; L, light petroleum, b. p. 60—80°; M, methanol; N, nitromethane. [c] Extent of hydrolysis of the halogen after 30 min. in boiling 50% aqueous acetone, by titration of acid produced (indicator, methyl red); see ref. 6.

The methoxycarbonyl derivative (IC 201) was obtained by brief treatment of the free sulphonhydrazide with methyl chloroformate in the presence of one equivalent of pyridine; it is of special interest because it contains the urethane group, a feature which may make it susceptible to attack by adaptive enzymes.[8,9]

Although nitrogen mustards containing iodoethyl groups appear to be less reactive towards solvolysis than the bromo-compounds, and have seldom proved to have promising anti-tumour properties,[10] the sulphonamide (III) was prepared, for comparison, from the bromo-compound (IC 56) by reaction with sodium iodide. The hydrolysis rate in aqueous acetone was the same for both compounds.

The " reversed " sulphonamide (IV) was made by the interaction of *NN*-di-2′-chloroethyl-*p*-phenylenediamine and *p*-acetamidobenzenesulphonyl chloride. The " hydrolysis rate " (13%), as expected, was considerably greater than for the compounds of type (I).

p-$(CH_2I\cdot CH_2)_2N\cdot C_6H_4\cdot SO_2\cdot NH_2$ (III) p-$(CH_2Cl\cdot CH_2)_2N\cdot C_6H_4\cdot NH\cdot SO_2\cdot C_6H_4\cdot NHAc$-$p'$ (IV)

The non-mustard analogues of IC 56 and 57, *p-NN*-diethylaminobenzenesulphonamide and the hydrazide, were synthesised from *NN*-diethylaniline for biological comparison with the mustards, particularly with regard to the unusual toxicity of IC 56 (see above).

Experimental

Analyses and melting points are given below only for compounds not included in the Table. For other compounds, the IC number provides a cross-reference.

p-(NN-*Di*-2-*chloroethylamino*)*benzenesulphonyl Chloride*.—Chlorosulphonic acid (100 g.) was added slowly to molten *NN*-di-2′-chloroethylaniline [4] (50 g.), with occasional cooling to maintain the temperature at 50—60°. The mixture was heated on a steam-bath for 30 min., then cooled and poured on to crushed ice (1 kg.). The crude precipitate was taken up in chloroform, and the solution was washed with water, dried, and concentrated. Recrystallisation of the residue from benzene–light petroleum (b. p. 60—80°) (charcoal) gave pale yellow needles of the *sulphonyl chloride* (31 g.), m. p. 102° (Found: C, 38·1; H, 3·9; Cl, 34·1; S, 10·7. $C_{10}H_{12}Cl_3NO_2S$ requires C, 37·9; H, 3·8; Cl, 33·6; S, 10·1%).

Reaction of the chloride (5·0 g.) in acetone (20 c.c.) with aqueous ammonia (15 c.c., *d* 0·88) for 15 min., followed by dilution with water, gave the *sulphonamide* (IC 20) (4·0 g.). The *sulphonhydrazide* (IC 21) (2·5 g.) was prepared by addition of the chloride (3·0 g.) to a stirred solution of 90% hydrazine hydrate (8 c.c.) in ethanol (40 c.c.), and precipitation after 10 min. by addition of water.

Proof of structure. The chloride (7·0 g.) was reduced with lithium aluminium hydride (1·8 g.) in boiling ether (300 c.c.) for 1 hr. After addition of 2N-hydrochloric acid the ethereal layer was separated, washed with water, dried, and evaporated to give crude *p*-(*NN*-di-2-chloroethylamino)thiophenol (4·5 g.); this was characterised by reaction with chloro-2,4-dinitrobenzene to form *p*-(*NN*-di-2-chloroethylamino)phenyl 2,4-dinitrophenyl sulphide (70%), m. p. and mixed [4] m. p. 156—157°.

Sodium p-(NN-*Di*-2-*chloroethylamino*)*benzenesulphonate*.—A boiling solution of the acid chloride (3·0 g.) in ethanol (70 c.c.) was continuously titrated with 20% aqueous sodium hydroxide (phenolphthalein). When consumption had almost ceased (2 hr.) the solution was evaporated to dryness. The residue was first boiled with benzene (this extract being rejected) and then with ethanol (3 × 30 c.c.). The latter extracts were evaporated to a white powder, which still contained some sodium chloride. It was dissolved in hot isopropanol and fractionally precipitated with ether. The first fraction contained sodium chloride, but the remainder consisted of the pure *sodium sulphonate* (1·2 g.), m. p. 220—240° (decomp.) (Found: C, 37·7; H, 4·25; Na, 7·2. $C_{10}H_{12}Cl_2NNaO_3S$ requires C, 37·5; H, 3·8; Na, 7·2%); extent of hydrolysis, 6% (cf. Table).

The S-*benzylisothiouronium salt* of the sulphonic acid, prepared from the sodium salt, crystallised from ethanol in needles, m. p. 171° (Found: C, 46·9; H, 4·9; Cl, 15·5; N, 8·8. $C_{18}H_{23}Cl_2N_3O_3S_2$ requires C, 46·6; H, 5·0; Cl, 15·3; N, 9·05%).

[10] Ref. 2, p. 106.

p-(NN-*Di*-2-*bromoethylamino*)*benzenesulphonyl Chloride*.—Chlorosulphonic acid (100 g.) was added slowly to a stirred and cooled solution of *NN*-di-2′-bromoethylaniline [4] (55 g.) in carbon tetrachloride (20 c.c.). The mixture was then heated to 120° during 1 hr. (the carbon tetrachloride being allowed to escape) and kept at 120—130° for 4 hr. The product was isolated as described above for the dichloro-analogue, and on recrystallisation from chloroform–light petroleum (b. p. 60—80°) formed pale yellow prisms (48·3 g.) of the *sulphonyl chloride*, m. p. 106° (Found: C, 29·7; H, 3·0; S, 8·1. $C_{10}H_{12}Br_2ClNO_2S$ requires C, 29·6; H, 3·0; S, 7·9%).

Reduction of a portion with lithium aluminium hydride, as described above, gave the corresponding thiol, characterised by reaction with 2,4-dinitrobenzenesulphenyl chloride to form *p*-(*NN*-di-2-bromoethylamino)phenyl-2,4-dinitrophenyl disulphide, m. p. and mixed [4] m. p. 132—133°.

The *sulphonamide* (IC 56) and the *sulphonhydrazide* (IC 57) were prepared from the sulphonyl chloride as described for the dichloro analogues. The N-*isopropylsulphonamide* (IC 76) was obtained by reaction with isopropylamine in acetone.

General Methods.—(i) A solution of *p*-(*NN*-di-2-chloroethylamino)- or of *p*-(*NN*-di-2-bromoethylamino)-benzenesulphonyl chloride (0·025 mole) in pyridine (20 c.c.) was added to a stirred solution of the alcohol, phenol, amine, or hydrazine (0·025 mole) in pyridine (20 c.c., or more if necessary). The mixture was set aside overnight (but for 48 hr. for alcohols), then poured into 2N-hydrochloric or hydrobromic acid (500 c.c.) at 0°. The precipitate was washed with water, dried, and recrystallised. The crude products from some of the amines were dark in colour, and were given a preliminary purification by chromatography in chloroform on alumina.

(ii) A solution of the amino-ester hydrochloride (0·01 mole) in water (5 c.c.) was added to a stirred solution of the appropriate sulphonyl chloride (0·01 mole) in acetone (20 c.c.) containing a suspension of potassium carbonate (3 g.). Stirring was maintained for 30 min., and the mixture was then poured into water and the precipitate treated as described above.

Methyl and Ethyl p-(NN-*Di*-2-*bromoethylamino*)*benzenesulphonate*.—A mixture of *p*-(*NN*-di-2-bromoethylamino)benzenesulphonyl chloride (4·0 g.), calcium carbonate (1·0 g.), and methanol (25 c.c.) was boiled under reflux for 10 min., then cooled and poured into water to give the *methyl ester* (IC 63). The *ethyl ester* (IC 64) was prepared similarly.

2,4-*Dinitrophenylpyridinium* p-(NN-*Di*-2-*chloroethylamino*)*benzenesulphonate*.—*p*-(*NN*-Di-2-chloroethylamino)benzenesulphonyl chloride (3·5 g.) was added to a solution of 2,4-dinitrophenol (1·85 g.) in pyridine (25 c.c.) at −5°. The mixture was stirred until homogeneous, then kept for 1 hr. at 0° before being poured into water. No solid separated, but extraction with chloroform gave a red oil which crystallised from ethanol to give the 2,4-*dinitrophenylpyridinium salt* (0·7 g.), orange leaflets, m. p. 204—205° (Found: C, 46·7; H, 3·7; Cl, 12·5. $C_{21}H_{20}Cl_2N_4O_7S$ requires C, 46·6; H, 3·7; Cl, 13·05%).

2,4-*Dinitrophenyl* p-(NN-*Di*-2-*chloroethylamino*)*benzenesulphonate*.—The sulphonyl chloride (3·5 g.), sodium 2,4-dinitrophenate (2·1 g.), and dry acetone (50 c.c.) were boiled together under reflux for 30 min. The mixture was then poured into saturated aqueous sodium hydrogen carbonate and extracted with chloroform to give the *ester* (IC 38; 4·7 g.). When heated with pyridine in ethanol it was converted almost quantitatively into the quaternary pyridinium salt described above.

The corresponding *di*-2-*bromoethyl*-compound (IC 65) was prepared by interaction of *p*-(*NN*-di-2-bromoethylamino)benzenesulphonyl chloride (2·25 g.) and sodium 2,4-dinitrophenate (1·05 g.) in acetone (50 c.c.) at room temperature for 48 hr. (yield 2·1 g.).

p-(NN-*Di*-2-*bromoethylamino*)*benzenesulphonamidoacetic Acid*.—The corresponding methyl ester (IC 107; 9·3 g.) was boiled under reflux for 4 min. with acetic acid (20 c.c.) and concentrated hydrochloric acid (20 c.c.). The solution was then cooled and diluted with ice–water (100 c.c.). The precipitated oil crystallised on trituration with benzene, and on recrystallisation gave the *acid* (IC 108; 5·4 g.).

N-[p-(NN-*Di*-2-*bromoethylamino*)*benzenesulphonyl*]-N′-(*methoxycarbonylmethyl*)*urea*.—*p*-(*NN*-Di-2-bromoethylamino)benzenesulphonamide (IC 56; 0·36 g.) and methyl isocyanatoacetate [9] (0·11 g.) were heated together in a sealed tube at 100° for 5 hr. Recrystallisation of the product gave the *urea* (IC 120; 0·10 g.).

N-[p-(NN-*Di*-2-*bromoethylamino*)*benzenesulphonamido*]-N′-(*methoxycarbonylmethyl*)*urea*.—A solution of *p*-(*NN*-di-2-bromoethylamino)benzenesulphonhydrazide (IC 57; 4·0 g.) and methyl isocyanatoacetate (1·2 g.) in chloroform (300 c.c.) was boiled under reflux for 2 hr., then cooled

and diluted with light petroleum (b. p. 40—60°; 700 c.c.). The precipitate (4·6 g.) was collected and recrystallised to give the substituted *sulphonhydrazide* (IC 118).

N-[p-(NN-*Di*-2-*bromoethylamino*)*benzenesulphonamido*]-N′-(*carboxymethyl*)*urea*.—The preceding methyl ester (3·8 g.) was boiled under reflux with acetic acid (18 c.c.) and concentrated hydrochloric acid (18 c.c.) for 4 min. The *acid* (IC 119; 3·3 g.) was isolated by precipitation with water.

p-(NN-*Di*-2-*bromoethylamino*)*benzenesulphonhydrazone of Pyruvic Acid*.—A mixture of *p*-(*NN*-di-2-bromoethylamino)benzenesulphonhydrazide (1·2 g.), pyruvic acid (1·3 g.), and concentrated hydrochloric acid (0·1 c.c.) was heated at 110°/15 mm. under reflux for 7 hr. The solid product was boiled with chloroform–acetone (1 : 1, 50 c.c.) and the extract was washed with water, then dried and filtered through charcoal. Addition of light petroleum (b. p. 60—80°) precipitated the *hydrazone* (IC 121).

ω-N-*Methoxycarbonyl*-p-(NN-*di*-2-*bromoethylamino*)*benzenesulphonhydrazide*.—On the addition of pyridine (0·5 c.c.) to a suspension of *p*-(*NN*-di-2-bromoethylamino)benzenesulphonhydrazide (2·0 g.) in chloroform (50 c.c.), containing methyl chloroformate (0·4 c.c.), heat was evolved and a clear solution was obtained. After 5 min., this was washed with water, then dried and evaporated. The residual solid was dissolved in boiling methanol (30 c.c.). Light petroleum (b. p. 60—80°) (10 c.c.) was added, and the solution was nucleated and stored at 0°. Crystallisation occurred slowly to give hard prisms of the *derivative* (IC 201; 1·45 g.).

p-(NN-*Di*-2-*iodoethylamino*)*benzenesulphonamide*.—A solution of *p*-(*NN*-di-2-bromoethylamino)benzenesulphonamide (5·0 g.) and sodium iodide (20 g.) in isopropyl methyl ketone (250 c.c.) was boiled under reflux for 8 hr., then cooled, filtered, passed through a column of " Zeo-Karb 225 " (acid form) and concentrated to give the *di-iodo* compound (3·2 g.), m. p. 165° (from chloroform) (Found: C, 25·3; H, 2·9; I, 52·6; N, 5·85. $C_{10}H_{14}I_2N_2O_2S$ requires C, 25·0; H, 2·9; I, 52·8; N, 5·8%); hydrolysis rate, 8% (cf. Table).

p-NN-*Diethylaminobenzenesulphonyl Chloride*.—This was prepared by chlorosulphonation of *NN*-diethylaniline under the same conditions, and on the same scale, as described above for the di-2-bromoethyl analogue. The *product* (70%) after recrystallisation from benzene–light petroleum (b. p. 60—80°) had m. p. 86° (Found: C, 48·6; H, 5·8; N, 5·7. $C_{10}H_{14}ClNO_2S$ requires C, 48·5; H, 5·7; N, 5·7%). It was converted in the usual way into the *sulphonamide*, m. p. 141° (Found: C, 52·5; H, 7·0; N, 12·2. $C_{10}H_{16}N_2O_2S$ requires C, 52·6; H, 7·1; N, 12·3%); the *sulphonanilide*, m. p. 176° (Found: C, 63·05; H, 6·4; N, 9·0. $C_{10}H_{20}N_2O_2S$ requires C, 63·1; H, 6·6; N, 9·2%); and the *sulphonhydrazide*, m. p. 130° (Found: C, 49·8; H, 7·0; N, 17·5; S, 12·9. $C_{10}H_{17}N_3O_2S$ requires C, 49·4; H, 7·05; N, 17·3; S, 13·15%). Each derivative crystallised from benzene–light petroleum (b. p. 60—80°). Reaction of the sulphonhydrazide with acetone gave *acetone* p-NN-*diethylaminobenzenesulphonhydrazone*, m. p. 182° (from chloroform) (Found: C, 54·9; H, 7·6. $C_{13}H_{21}N_3O_2S$ requires C, 55·1; H, 7·5%).

p-(p-N-*Acetamidobenzenesulphonamido*)-NN-*di*-2-*chloroethylaniline*.—A solution of *p*-acetamidobenzenesulphonyl chloride (1·15 g.) in pyridine (10 c.c.) was added to *NN*-di-2-chloroethyl-*p*-phenylenediamine (from 1·32 g. of hydrochloride) in chloroform (50 c.c.). Next day the mixture was filtered, and the solution was washed with 2N-hydrochloric acid, then with water, and dried. Evaporation of the solvent gave a solid which on recrystallisation from acetone–benzene gave the *derivative* (0·6 g.), m. p. 202—204° (Found: C, 50·3; H, 5·0; Cl, 16·55. $C_{18}H_{21}Cl_2N_3O_3S$ requires C, 50·1; H, 5·1; Cl, 16·4%); hydrolysis rate, 13% (cf. Table).

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Department of Chemistry, Imperial College of Science and Technology,
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