STUDIES IN THE FIELD OF DIURETIC AGENTS. PART VI
SOME SULPHAMOYLBENZOIC ACIDS

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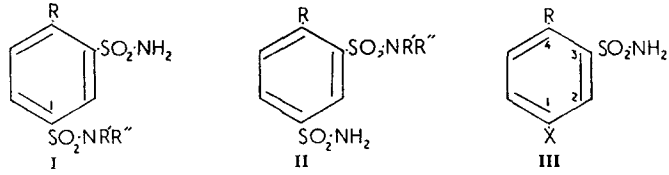
The requirements for diuretic activity in the sulphamoylbenzoic acid series have been studied. Optimal activity is shown by 4-halogeno-3-sulphamoylbenzoic acids.

IN Part V (Petrow, Stephenson and Wild, 1960) we studied the relationship between structure and diuretic activity in *N*-alkyl- and *NN*-dialkylbenzene-1,3-disulphonamides of types (I) and (II). Our results showed clearly the outstanding superiority of structure (I) over its isomer (II). In extending these observations we decided initially to retain intact the substituents present in positions 3 and 4 in (I) and to vary the electronegative group (X) at position 1 as in (III).



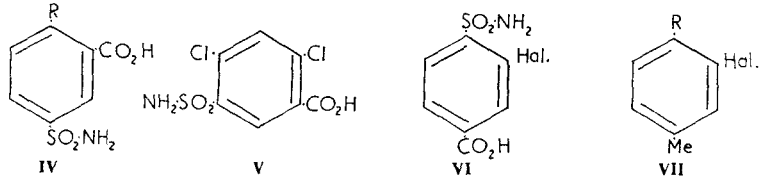
4-Nitrotoluene-2-sulphonamide (III; R = Me, X = NO_2) and 2-chloro-5-nitrobenzenesulphonamide (III; R = Cl, X = NO_2) (Petrow, Stephenson and Wild, 1960), though unlikely to be of any clinical interest, were tested biologically and found to possess some oral diuretic activity, albeit only at doses of 90 mg./kg. (in the saline-loaded rat). Methyl 4-methyl(or chloro)-3-sulphamoylphenyl sulphones (III; R = Me or Cl, X = SO_2Me), prepared directly from the appropriate sulphones, were active oral diuretics at the 30 mg./kg. dose level. The trifluoromethyl analogue (III; R = Cl, X = CF_3) was found to be inactive at this dosage.

Attention was next directed to substituted *m*-sulphamoylbenzoic acids (III; X = CO_2H), a class of readily available compounds which has been virtually neglected hitherto.

m-Sulphamoylbenzoic acid (Smiles and Stewart, 1921) and its methyl ester were both devoid of oral diuretic activity. This was expected since we had already shown (Petrow, Stephenson and Wild, 1960) that disulphamoyl compounds of type (I; R = H) were inactive or possessed only low activity. The corresponding toluic acid derivative (III; R = Me, X = CO_2H) was of some interest and although only a very weak inhibitor of carbonic anhydrase (*ca.* 1/250th of acetazolamide), it proved to be an effective oral diuretic at doses of 8 mg./kg. in the saline-loaded rat. This compound, prepared previously by the oxidation of *p*-xylenesulphonamide (Iles and Remsen, 1878) or of cymene-2-sulphonamide (Hall and Remsen,

1879) with chromic acid, was more readily obtained by us by direct chlorosulphonation of *p*-toluic acid followed by reaction of the sulphonyl chloride with ammonia. Its methyl, ethyl and butyl esters were all less effective than the parent acid, a fact which again emphasised the lack of a direct relation between diuretic potency and carbonic anhydrase inhibitory activity, since the butyl ester was twenty times as active as the acid as an inhibitor of the enzyme.

Inter alia we examined the isomeric 2-methyl-5-sulphamoylbenzoic acid (IV; R = Me). This compound was prepared originally (Jacobsen, 1881) by oxidation of *o*-xylenesulphonamide and fractional crystallisation of the resultant mixed product. It was obtained by us directly from *o*-toluic acid, and proved to be without diuretic activity. Its methyl ester was also inactive.



IV V VI VII

Attention was next directed to the halogenated analogues of the potent 4-methyl-3-sulphamoylbenzoic acid. Three 4-halogeno-3-sulphamoylbenzoic acids (III; R = F, Cl or Br; X = CO_2H) were prepared by direct chlorosulphonation of the appropriate halogenobenzoic acid followed by reaction of the resultant sulphonyl chlorides with ammonia. The diuretic activity of these acids increased in the order—bromo>chloro>fluoro, the bromo-compound being approximately eight times as active as 4-methyl-3-sulphamoylbenzoic acid. On the other hand, the carbonic anhydrase inhibitory activity of the acids was chloro (0:1), fluoro and bromo (<0·01) (compared with acetazolamide = 1·0), so that there was again no direct correlation between the two parameters.

One isomeric acid, 2-chloro-5-sulphamoylbenzoic acid (IV; R = Cl), prepared earlier (Basu and Das Gupta, 1939) by oxidation of the corresponding toluene derivative and obtained by us *via* direct chlorosulphonation of *o*-chlorobenzoic acid, resembled the corresponding *o*-toluic acid derivatives in being devoid of diuretic activity. Introduction of a halogen substituent into 4-chloro-3-sulphamoylbenzoic acid (III; R = Cl, X = CO_2H) to give 2,4-dichloro-5-sulphamoylbenzoic acid (V) (prepared from 2,4-dichlorobenzoic acid), was likewise accompanied by loss of biological potency.

In further attempts to define the structural requirements necessary for diuretic activity in the sulphamoylbenzoic acids series, the preparation was undertaken of the isomeric 3-bromo- and 3-chloro-4-sulphamoylbenzoic acids (VI) in which the halogen-group and sulphamoyl group of 4-bromo- or 4-chloro-3-sulphamoylbenzoic acid (III; R = Br or Cl, X = CO_2H) are interchanged. These compounds were obtained *via* the 4-amino-3-halogenotoluenes (VII; R = NH_2) which were converted

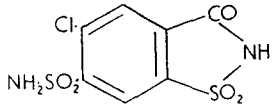
into the sulphonyl chlorides (VII; R = SO_3Cl) by diazotisation and reaction of the diazonium chloride with a saturated solution of sulphur dioxide in acetic acid in the presence of cuprous salts (cf. Petrow and others, 1960). The sulphonamides (VII; R = SO_2NH_2) were obtained in the normal way and furnished the required products (VI) by oxidation with aqueous potassium permanganate.

The compounds (VI; Hal = Cl or Br) had no diuretic activity at doses of 10 mg./kg. in saline-loaded rats.

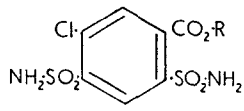
Finally, we examined the oxidation of 4-methyl-3-sulphamoylbenzoic acid, 5-chlorotoluene-2,4-disulphonamide (disulphamide) and 2-chlorotoluene-3,5-disulphonamide. The latter two compounds described earlier (Boggiano and others, 1960) had both been found to possess noteworthy diuretic activity.

Oxidation of the first compound with potassium permanganate in aqueous alkaline solution yielded a crude mixture of acid (III; R = X = CO_2H) and the derived saccharin, which, without separation, was converted directly into methyl 2-sulphamoylterephthalate (III; R = X = CO_2Me) by heating with methanolic hydrogen chloride.

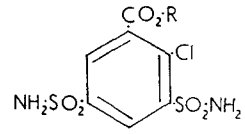
Oxidation of disulphamide with aqueous alkaline potassium permanganate below 40° yielded a mixture of the saccharin (VIII) (de Stevens, Halamandaris, Ricca and Werner, 1959) and the acid (IX; R = H) which were readily separated by graded acidification of the reaction mixture. Both compounds retained some diuretic activity,



VIII



IX



X

though neither was superior to the original disulphamide. The derived methyl (IX; R = Me) and butyl (IX; R = Bu) esters were prepared, most conveniently from crude mixtures of acid and saccharin. The latter ester had almost the same diuretic potency as disulphamide and more than five times the carbonic anhydrase inhibitory activity of acetazolamide (cf. Beasley, Overell, Petrow and Stephenson, 1958).

Similar oxidation of 2-chlorotoluene-3,5-disulphonamide yielded the acid (X; R = H), which was converted into the butyl ester (X; R = Bu), but both compounds were markedly inferior to the original disulphonamide as diuretic agents.

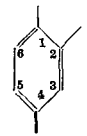
Experimental

The early experiments illustrate the methods used for the preparation of compounds listed in Table I, which also contains the analyses.

Methyl 4-methyl-3-sulphamoylphenyl sulphone. Methyl *p*-tolyl sulphone (30 g.) was dissolved in chlorosulphonic acid (120 g.) and the mixture heated on the steam bath for 1 hr. It was then cooled, poured on to ice, the solids collected and washed with cold water. Crystallisation from

TABLE I

SULPHAMOYLBENZOIC ACIDS



Substituent at position			m.p. °C.	Formula	Found					Required				
1	2	4			C	H	Cl	N	S	C	H	Cl	N	S
H	SO_2NH_2	CO_2H	246	$C_7H_7NO_4S$										
H	SO_2NH_2	CO_2Me	131–133	$C_8H_9NO_4S$	44·5	4·2		6·2		44·7	4·2		6·5	
Me	SO_2NH_2	CO_2H	267–269	$C_8H_9NO_4S$	44·7	4·5		6·3		44·7	4·2		6·5	
Me	SO_2NH_2	CO_2Me	119–120	$C_9H_{11}NO_4S$	47·4	4·8		6·0	14·1	47·1	4·8		6·1	14·0
Me	SO_2NH_2	CO_2Et	106–107	$C_{10}H_{13}NO_4S$	49·3	5·3		5·8	13·0	49·4	5·4		5·8	13·2
Me	SO_2NH_2	CO_2Bu	96–98	$C_{12}H_{17}NO_4S$	53·1	6·1		5·0	12·0	53·1	6·3		5·2	11·8
Me	SO_2NHMe	CO_2H	210–212	$C_9H_{11}NO_4S$	47·3	4·8		6·1	13·6	47·1	4·8		6·1	14·0
Me	CO_2H	SO_2NH_2	250	$C_8H_9NO_4S$	44·4	4·1		6·6	14·7	44·7	4·2		6·5	14·9
Me	CO_2Me	SO_2NH_2	148–149	$C_9H_{11}NO_4S$	46·8	4·5		6·5		47·1	4·8		6·1	
Me	SO_2NH_2	SO_2Me	202–204	$C_9H_{11}NO_4S_2$	38·5	4·3		5·8	25·7	38·6	4·5		5·6	25·7
F	SO_2NH_2	CO_2H	239–241	$C_7H_6FNO_4S$	38·7	3·0		6·0		38·4	2·8		6·4	
F	CO_2H	CO_2H	297–298	$C_8H_5FO_4$	52·6	2·6				52·2	2·7			
Cl	SO_2NH_2	CO_2H	258–260	$C_7H_6ClNO_4S$	36·0	2·6	14·9	6·3	13·5	35·7	2·6	15·0	5·9	13·6
Cl	SO_2NH_2	CO_2Me	124–125	$C_8H_8ClNO_4S$	38·3	3·1	14·4	5·5		38·5	3·2	14·2	5·6	
Cl	SO_2NH_2	CO_2Et	139–140	$C_9H_{10}ClNO_4S$	41·1	3·9	13·6	5·5		41·0	3·8	13·5	5·3	
Cl	SO_2NHMe	CO_2H	236–238	$C_8H_8ClNO_4S$	38·7	3·0		5·6		38·5	3·2		5·6	
Cl	SO_2NMe_2	CO_2H	247–248	$C_9H_{10}ClNO_4S$	41·5	4·0	13·4	5·4	12·0	41·0	3·8	13·5	5·3	12·2
Cl	SO_2NH_2	CF_3	161–163	$C_7H_5ClF_3NO_2S$	32·7	2·3		5·1		32·4	1·9		5·4	
Cl	CO_2H	SO_2NH_2	220–222	$C_7H_6ClNO_4S$	35·8	2·2	15·2	5·9	13·9	35·7	2·6	15·0	5·9	13·6
Cl	CO_2Et	SO_2NH_2	128–130	$C_9H_{10}ClNO_4S$	41·3	3·7	13·5	5·8	12·4	41·0	3·8	13·5	5·3	12·2
Cl	SO_2NH_2	SO_2Me	227–229	$C_7H_6ClNO_4S_2$	31·4	3·3	13·1	5·1	23·9	31·2	3·0	13·1	5·2	23·8
Br	SO_2NH_2	CO_2H	273–275	$C_7H_6BrNO_4S$	30·0	2·4	28·5*	5·1	11·5	30·0	2·2	28·5*	5·0	11·4
CO_2Me	SO_2NH_2	CO_2Me	172–173	$C_{10}H_{11}NO_6S$	43·9	4·1		5·1	11·3	43·9	4·1		5·1	11·7
SO_2NH_2	Cl	CO_2H	235–237	$C_7H_6ClNO_4S$	35·8	2·7	15·3	6·0	13·6	35·7	2·6	15·1	5·9	13·6
SO_2NH_2	Br	CO_2H	259–260	$C_7H_6BrNO_4S$	30·0	2·0	29·0*	5·2		30·0	2·2	28·5*	5·0	
SO_2NH_2	Br	CO_2Me	154–155	$C_8H_8BrNO_4S$	32·7	2·6	27·4*	4·9		32·7	2·7	27·2*	4·8	

* Bromine

1,2-dichloroethane-light petroleum (b.p. 60–80°) furnished *3-chlorosulphonyl-4-methylphenylmethyl sulphone*, m.p. 145–147°. Found: C, 35·6; H, 3·3; S, 23·8; Cl, 13·4. $C_8H_9ClO_4S_2$ requires C, 35·8; H, 3·4; S, 23·9; Cl, 13·2 per cent. The sulphonyl chloride was added with stirring at room temperature to a mixture of aqueous ammonia (500 ml.; d = 0·880) and chloroform (200 ml.). Stirring was continued for 30 min. when excess of ammonia and chloroform were boiled off. The residual liquid was cooled and acidified with hydrochloric acid to yield the *product*, which had m.p. 202–204° after crystallisation from ethanol.

4-Chloro-3-sulphamoylphenylmethyl sulphone. The preparation of *4-chloro-3-chlorosulphonylphenylmethyl sulphone* from *p*-chlorophenyl methyl sulphone was carried out as described in the preceding experiment. It had m.p. 145–147° after crystallisation from 1,2-dichloroethane. Found: C, 29·1; H, 2·3; S, 22·4; Cl, 24·2. $C_7H_6Cl_2O_4S_2$ requires C, 29·1; H, 2·1; S, 22·2; Cl, 24·5 per cent. It reacted with aqueous ammonia-chloroform to yield the *product*, m.p. 227–229° (from ethanol).

4-Methyl-3-sulphamoylbenzoic acid. *p*-Toluic acid (34 g.) was added in portions with stirring and cooling below 20° to chlorosulphonic acid (100 ml.) when the mixture was heated to 120° for 7 hr. It was cooled, poured on to ice and the crude sulphonyl chloride extracted with chloroform. The extract was washed with ice-water, dried with anhydrous sodium sulphate and concentrated to *ca* 300 ml. *3-Chlorosulphonyl-4-methylbenzoic acid* separated and had m.p. 173° after crystallisation from chloroform. Found: C, 41·4; H, 3·0; S, 13·4. $C_8H_7ClO_4S$ requires C, 41·0; H, 3·0; S, 13·7 per cent. The sulphonyl chloride (23·5 g.) was added in portions with stirring to liquid ammonia (200 ml.) and the ammonia was then allowed to evaporate. The residue was dissolved in water and acidified with hydrochloric acid to yield the *product* which had m.p. 267–269° after crystallisation from water.

Butyl 4-methyl-3-sulphamoylbenzoate. A solution of the foregoing acid (12·8 g.) in butanol (120 ml.) containing hydrogen chloride (2 g.) was heated under reflux for 4 hr. when excess of solvent was distilled off at reduced pressure. Crystallisation of the residue from ether-light petroleum (b.p. 40–60°) furnished the *product*, m.p. 96–98°. It was occasionally obtained in a metastable form, m.p. 69–71°.

4-Chloro-3-sulphamoylbenzoic acid. A mixture of *p*-chlorobenzoic acid (410 g.), chlorosulphonic acid (1232 g.) and pentachloroethane (315 ml.) was heated at reflux temperature (125–140°) for 3 hr. The *sulphonyl chloride*, isolated in the usual manner, had m.p. 168–170° after crystallisation from 1,2-dichloroethane. Found: C, 33·2; H, 1·6; S, 12·4; Cl, 28·0. $C_7H_4Cl_2O_4S$ requires C, 33·0; H, 1·6; S, 12·6; Cl, 27·8 per cent. Reaction with liquid ammonia as described earlier yielded the *product* which had m.p. 258–260° after crystallisation from aqueous ethanol.

4-Fluoro-3-sulphamoylbenzoic acid. The *sulphonyl chloride* prepared by heating *p*-fluorobenzoic acid (30 g.) with chlorosulphonic acid (70 ml.) at 120° for 8 hr. had m.p. 147–148° after crystallisation from 1,2-dichloroethane-light petroleum (b.p. 60–80°). Found: C, 34·7; H, 1·7; S, 13·1;

Cl, 14·9. $C_7H_4ClFO_4S$ requires C, 35·2; H, 1·7; S, 13·4; Cl, 14·9 per cent. Reaction of the sulphonyl chloride with liquid ammonia furnished the *product* which had m.p. 239–241° after crystallisation from water.

4-*Bromo*-3-*chlorosulphonylbenzoic acid*, prepared as described for the 4-chloro analogue, had m.p. 203–205° after crystallisation from 1,2-dichloroethane. Found: C, 28·3; H, 1·5; S, 10·9. $C_7H_4BrClO_4S$ requires C, 27·9; H, 1·3; S, 10·6 per cent.

2,4-*Dichloro*-5-*sulphamoylbenzoic acid* was prepared by chlorosulphonation of 2,4-dichlorobenzoic acid at 140° for 8 hr. followed by reaction of the resultant sulphonyl chloride with liquid ammonia. It had m.p. 235–236° after crystallisation from aqueous ethanol. Found: C, 31·2; H, 2·1; N, 5·3; S, 12·0; Cl, 25·9. $C_7H_5Cl_2NO_4S$ requires C, 31·1; H, 1·9; N, 5·2; S, 11·9; Cl, 26·3 per cent.

3-*Bromo*-4-*sulphamoylbenzoic acid.* (*a*) 3-*Bromo*-4-*chlorosulphonyltoluene.* 4-Amino-3-bromotoluene (37·2 g.) was added with stirring to 24 per cent hydrochloric acid and the mixture diazotised at 0–5° by the slow addition of a solution of sodium nitrite (15·2 g.) in water (30 ml.). The diazo-solution was added over 5 min. with stirring to a saturated solution of sulphur dioxide in acetic acid (320 ml.) containing cuprous chloride dihydrate (14 g.) in water (10 ml.) at 15°. The temperature of the mixture rose to 27° and reaction was completed by heating to 40°. The mixture was cooled and crushed ice added to complete precipitation of the sulphonyl chloride. The crude product was used for the next stage in the reaction. A portion, crystallised from light petroleum (b.p. 60–80°) had m.p. 70–71°. Found: C, 31·5; H, 2·3; S, 12·2; total halogen 43·2. $C_7H_6BrClO_2S$ requires C, 31·2; H, 2·2; S, 11·9; total halogen, 42·8 per cent.

(*b*) 3-*Bromotoluene*-4-*sulphonamide.* A solution of the foregoing sulphonyl chloride in chloroform (150 ml.) was added with stirring to aqueous ammonia prepared from ammonia solution (150 ml., d = 0·880) and water (150 ml.). Stirring was continued for 1 hr. The solids (35·4 g., m.p. 188–190°) were collected. Concentration of the filtrate followed by acidification with hydrochloric acid furnished a second crop of material (8·5 g., m.p. 186–188°). A portion of the product had m.p. 188–190° after crystallisation from aqueous ethanol. Found: C, 33·9; H, 3·2; N, 5·4; S, 12·5. $C_7H_8BrNO_2S$ requires C, 33·6; H, 3·2; N, 5·6; S, 12·8 per cent.

(*c*) 3-*Bromo*-4-*sulphamoylbenzoic acid.* A solution of the foregoing sulphonamide (10 g.) in water (60 ml.) containing sodium hydroxide (1·6 g.) was heated on the steam bath to about 60° and treated in portions with a slurry of potassium permanganate (12·7 g.) in water (50 ml.). When the reaction was complete the mixture was decolourised with sulphur dioxide and the *product* collected, washed with water and dried (yield = 10·0 g.). A portion, crystallised from aqueous methanol had m.p. 259–260°.

3-*Chloro*-4-*sulphamoylbenzoic acid.* (*a*) 3-*Chlorotoluene*-4-*sulphonamide* was prepared from 4-amino-3-chlorotoluene as described for the preceding bromo-analogue. The sulphonyl chloride, obtained as an

oil from the diazo-reaction was dissolved in chloroform and condensed directly with ammonia solution (d = 0·880). The *product* had m.p. 184–186° after crystallisation from aqueous ethanol. Found: C, 40·8; H, 4·1; N, 6·8; S, 15·3; Cl, 17·3. Calc. for $C_7H_8ClNO_2S$: C, 40·9; H, 3·9; N, 6·8; S, 15·6; Cl, 17·2 per cent.

(*b*) 3-*Chloro*-4-*sulphamoylbenzoic acid* was prepared by oxidation of the foregoing sulphonamide with alkaline permanganate solution at 40–45° and finally at 60–70°. It had m.p. 235–237° after crystallisation from water.

Methyl 2-*sulphamoylterephthalate*. A solution of 4-methyl-3-sulphamoylbenzoic acid in water (500 ml.) containing anhydrous sodium carbonate (10·6 g.) was stirred and treated with powdered potassium permanganate (63·2 g.) added over 20 hr. at 45°. The precipitated manganese dioxide was filtered off and washed with hot water (100 ml.). The filtrate and washings were concentrated to half bulk and neutralised with hydrochloric acid. The solids (10·6 g.) which separated (unchanged starting material), were filtered off. The filtrate, acidified to pH 4 with hydrochloric acid furnished solids (19·2 g.) m.p. 312–314° (decomp.) after crystallisation from water. These were suspended in methanol (180 ml.) and hydrogen chloride (8 g.) was passed into the mixture which was heated under reflux for 6 hr. Slight dilution with water furnished the *dimethyl ester* (10 g.) which had m.p. 172–173° after crystallisation from methanol.

Oxidation of 5-*chlorotoluene*-2,4-*disulphonamide* (with Dr. B. G. Boggiano). A solution of disulphamide (56·8 g.) in water (800 ml.) containing sodium hydroxide (12 g.) was heated at 40–45° with stirring and treated with powdered potassium permanganate (63·2 g.) added in portions over 6 hr. When reaction was complete the mixture was filtered hot and the filtrate concentrated to 300 ml. at reduced pressure. The solution was cooled and the pH adjusted to 7·5 when unchanged disulphamide (13·8 g.) separated out and was collected. Acidification of the filtrate to pH 6 furnished 5-*chloro*-6-*sulphamoylsaccharin* (11 g.) which had m.p. 276–278° after crystallisation from water. Found: C, 28·2; H, 2·1; N, 9·6; S, 21·6; Cl, 11·5. $C_7H_5ClN_2O_5S_2$ requires C, 28·3; H, 1·7; N, 9·4; S, 21·6; Cl, 12·0 per cent. Strong acidification of the filtrate with concentrated hydrochloric acid yielded 5-*chloro*-2,4-*disulphamoylbenzoic acid* m.p. 333° (decomp.). Found: C, 27·2; H, 1·5; N, 9·1; S, 20·8; Cl, 11·5. $C_7H_7ClN_2O_6S_2$ requires C, 26·7; H, 2·2; N, 8·9; S, 20·4; Cl, 11·3 per cent. A solution of the saccharin (3 g.) in butanol (40 ml.) containing hydrogen chloride (0·5 g.) was heated under reflux for 2 hr. Concentration of the solution followed by crystallisation from water yielded *butyl* 5-*chloro*-2,4-*disulphamoylbenzoate*, m.p. 159°. Found: C, 35·7; H, 4·0; N, 7·7; Cl, 9·9. $C_{11}H_{15}ClN_2O_6S_2$ requires C, 35·6; H, 4·1; N, 7·6; Cl, 9·6 per cent.

Methyl 5-*chloro*-2,4-*disulphamoylbenzoate* had m.p. 218–219° after crystallisation from aqueous methanol. Found: C, 29·5; H, 2·7; N, 8·6; Cl, 10·5. $C_8H_9ClN_2O_6S_2$ requires C, 29·2; H, 2·8; N, 8·5; Cl, 10·8 per cent.

2-Chloro-3,5-disulphamoylbenzoic acid was prepared by the oxidation of 2-chlorotoluene-3,5-disulphonamide (28·5 g.) with potassium permanganate (47 g.) in water (500 ml.) containing sodium hydroxide (5 g.) at 55–75°. It had m.p. 260–262° after crystallisation from water. Found: C, 27·2; H, 2·6; N, 9·1; Cl, 11·0. $C_7H_7ClN_2O_6S_2$ requires C, 26·7; H, 2·3; N, 8·9; Cl, 11·3 per cent. The *butyl ester* had m.p. 151–153° after crystallisation from water. Found: C, 35·8; H, 4·2; N, 7·3. $C_{11}H_{15}N_2O_6S_2$ requires C, 35·6; H, 4·1; N, 7·6 per cent.

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References

Basu, U. P. and Das Gupta, S. J. (1939). *J. Indian chem. Soc.*, **16**, 100–106.
Beasley, Y. M., Overell, B. G., Petrow, V. and Stephenson, O. (1958). *J. Pharm. Pharmacol.*, **10**, 696–705.
Boggiano, B. G., Condon, S., Davies, M. T., Jackman, G. B., Overell, B. G., Petrow, V., Stephenson, O. and Wild, A. M. (1960). *Ibid.*, **12**, 419–425.
De Stevens, G., Halamandaris, A., Ricca, S. and Werner, L. H. (1959). *J. med. pharm. Chem.*, **1**, 565–576.
Hall, L. B. and Remsen, I. (1879). *Ber.*, **12**, 1432–1436.
Iles, M. W. and Remsen, I. (1878). *Ibid.*, **11**, 229–232.
Jacobsen, O. (1881). *Ibid.*, **14**, 38–43.
Petrow, V., Stephenson, O. and Wild, A. M. (1960). *J. Pharm. Pharmacol.*, **12**, 705–719.
Smiles, S. and Stewart, J. (1921). *J. chem. Soc.*, **119**, 1792–1798.