

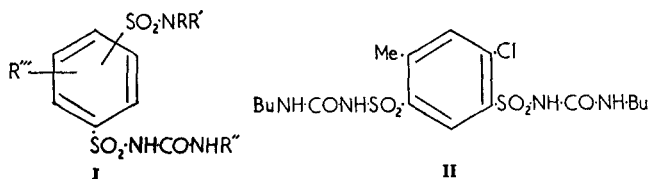
HYPOGLYCAEMIC AGENTS. PART II

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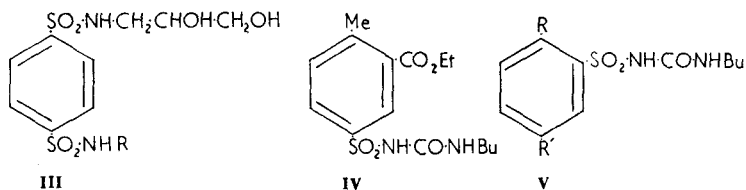
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Various derivatives of 1-benzenesulphonyl-3-butyl(or cyclohexyl)ureas substituted in the aryl nucleus are described.

SOME aromatic 1,3- and 1,4-disulphonamides containing one unsubstituted sulphamoyl residue were described by Petrow, Stephenson and Wild (1960). Several of them have now been converted into the corresponding sulphonylureas (cf. I, where $R = H$ or alkyl and $R' = \text{alkyl}$, or $\text{NRR}' = \text{heterocyclic nucleus}$; $R'' = \text{butyl or cyclohexyl}$ and $R''' = H, \text{Me}$ or Cl) by reaction with the appropriate isocyanate in aqueous acetone in the presence of one equivalent of sodium hydroxide. Additionally the bisulphonylurea (II) was obtained by reaction of 5-chlorotoluene 2,4-disulphonamide (Boggiano and others, 1960) with butyl isocyanate. A few related 1,4-bisulphonylureas were also prepared.



Most of the foregoing compounds were insoluble in water. A more soluble type was obtained by the reaction of *p*-(2,3-dihydroxypropylsulphamoyl)benzenesulphonamide (III a, $R = H$) with butyl isocyanate. The product so formed failed to crystallise and was assumed to be the *O*-carbamate ester. It was readily converted into the required product (IIIb, $R = \text{CONHBu}$) by hydrolysis with boiling aqueous sodium hydroxide.



Finally, ethyl 2-methyl-5-sulphamoylbenzoate, ethyl 4-chloro-3-sulphamoylbenzoate and methyl 4-methyl-3-sulphamoylphenyl sulphone (Jackman, Petrow, Stephenson and Wild, 1962) were condensed with butyl isocyanate to yield compounds IV, Va ($R = \text{Cl}$; $R' = \text{CO}_2\text{Et}$) Vb ($R = \text{Me}$; $R' = \text{SO}_2\text{Me}$) respectively.

TABLE I



I	Substituent at position			m.pt. °C.	Formula	Found			Required						
	2	3	4			5	C	H	Cl	N	S	C	H	Cl	N
R		SO ₂ NMe ₃													
R'		SO ₂ NMe ₃													
R'			NH ₂		138-140	C ₁₂ H ₁₂ N ₂ O ₂ S ₂	42.9	5.9	11.6	17.4	43.0	5.8	11.6	17.6	
R'			NHAc		166-168	C ₁₂ H ₁₂ N ₂ O ₂ S ₂	46.9	6.2	10.6	16.1	46.3	6.0	10.8	16.5	
R'					179-180	C ₁₂ H ₁₂ N ₂ O ₂ S ₂	52.6	6.1	14.5	11.0	52.5	6.4	14.1	10.8	
R'					206-207	C ₁₂ H ₁₂ N ₂ O ₂ S ₂	53.1	6.2	12.4	9.2	53.1	6.2	12.4	9.5	
R'			SO ₂ NHMe		189-191	C ₁₂ H ₁₂ N ₂ O ₂ S ₂	41.3	5.6	12.5	18.4	41.3	5.5	12.0	18.4	
R'			SO ₂ NHMe		199-200	C ₁₂ H ₁₂ N ₂ O ₂ S ₂	44.7	5.7	11.4	17.0	44.8	5.6	11.2	17.1	
R'			SO ₂ NHMe		177-179	C ₁₂ H ₁₂ N ₂ O ₂ S ₂	43.1	5.7	11.6	17.5	43.0	5.8	11.6	17.6	
R'			SO ₂ NMe ₃		168-170	C ₁₂ H ₁₂ N ₂ O ₂ S ₂	43.0	5.9	11.7	17.6	43.0	5.8	11.6	17.6	
R'			SO ₂ NMe ₃		196-197	C ₁₂ H ₁₂ N ₂ O ₂ S ₂	46.5	5.9	10.8	16.0	46.3	6.0	10.8	16.5	
R'			SO ₂ NHPh		186-188	C ₁₇ H ₂₁ N ₂ O ₂ S ₂	50.0	5.3	10.1	15.2	49.6	5.2	10.2	15.6	
R					146-147	C ₁₀ H ₁₂ N ₂ O ₂ S ₂	48.0	5.9	10.6	16.0	47.9	5.8	10.5	16.0	
R					165-167	C ₁₀ H ₁₂ N ₂ O ₂ S ₂	47.4	5.9	10.6	16.0	47.6	6.3	10.4	15.9	
R					177-179	C ₁₅ H ₁₈ N ₂ O ₄ S ₂	44.1	5.9	10.5	15.9	44.4	5.7	10.4	15.8	
R					161-162	C ₁₄ H ₁₆ N ₂ O ₂ S ₂	40.8	5.3	9.2	16.1	41.1	5.7	10.3	15.7	
R					14-142	C ₁₄ H ₁₆ N ₂ O ₂ S ₂	50.9	5.6	8.5	10.2	51.2	6.1	8.5	9.8	
R					218-220 (d)	C ₁₄ H ₁₆ N ₂ O ₂ S ₂	44.3	6.1	12.9	14.8	44.2	6.0	12.9	14.8	
R					212-214 (d)	C ₁₄ H ₁₆ N ₂ O ₂ S ₂	49.1	6.2	11.5	13.5	49.4	6.2	11.5	13.2	
Me	SO ₂ NHMe				130-132	C ₁₄ H ₁₆ N ₂ O ₂ S ₂	43.6	5.9	10.9	17.7	43.0	5.8	11.6	17.6	
Me	SO ₂ NMe ₃				136-138	C ₁₄ H ₁₆ N ₂ O ₂ S ₂	44.5	5.1	8.2	18.7	44.8	6.1	11.1	17.0	
Me	R				158-159	C ₁₄ H ₁₆ N ₂ O ₂ S ₂	44.7	6.0	7.4	17.1	44.1	5.9	7.5	17.1	
Me	R				191-192	C ₁₄ H ₁₆ N ₂ O ₂ S ₂	48.3	6.0	11.1	16.9	44.5	6.1	11.1	17.0	
Me	R				134-135	C ₁₄ H ₁₆ N ₂ O ₂ S ₂	44.4	6.1	11.1	16.9	44.5	6.1	11.1	17.0	
Me	R				151-152	C ₁₄ H ₁₆ N ₂ O ₂ S ₂	44.6	6.1	11.2	17.2	44.5	6.1	11.1	17.0	
Me	R				111-112	C ₁₄ H ₁₆ N ₂ O ₂ S ₂	52.5	6.2	7.8	9.1	52.6	6.5	8.2	9.4	
Me	R				164-166	C ₁₄ H ₁₆ N ₂ O ₂ S ₂	37.7	4.8	11.1	16.9	37.5	4.7	10.9	16.7	
Cl	SO ₂ NHMe				180-183	C ₁₄ H ₁₆ ClN ₂ O ₂ S ₂	41.6	5.2	8.9	10.3	41.0	4.9	8.7	10.3	
Cl	SO ₂ NHMe				153-155	C ₁₄ H ₁₆ ClN ₂ O ₂ S ₂	39.3	5.2	9.1	10.7	39.2	5.1	8.9	10.6	
Cl	SO ₂ NHMe				168-170	C ₁₄ H ₁₆ ClN ₂ O ₂ S ₂	41.3	5.0	9.1	10.6	41.0	4.9	8.7	10.3	
Cl	SO ₂ NHMe				190-162	C ₁₄ H ₁₆ ClN ₂ O ₂ S ₂ *	39.5	5.0	9.2	10.6	39.2	5.1	8.9	10.6	
Cl	SO ₂ NMe ₃				176-178	C ₁₄ H ₁₆ ClN ₂ O ₂ S ₂	40.9	5.6	7.8	12.1	41.0	5.4	8.9	10.6	
Cl	R				170-171	C ₁₄ H ₁₆ ClN ₂ O ₂ S ₂	46.5	5.1	8.9	7.7	46.3	5.3	8.8	7.7	
Cl	R				168-170	C ₁₄ H ₁₆ ClN ₂ O ₂ S ₂	38.8	4.8	9.0	10.6	39.2	5.1	8.4	9.9	
Cl	R				174-176	C ₁₄ H ₁₆ ClN ₂ O ₂ S ₂	43.0	5.6	8.3	15.4	42.5	5.2	8.4	15.1	
Cl	R				214 (d)	C ₁₇ H ₂₁ ClN ₂ O ₄ S ₂ †	42.4	5.5	7.5	11.6	42.3	5.6	7.3	11.6	

* Prepared by Mr. A. M. Wild. † Prepared by Dr. G. B. Jackman.

HYPOGLYCAEMIC AGENTS. PART II

The foregoing sulphonylureas were tested for oral hypoglycaemic activity by Dr. A. David and his colleagues but proved to be without interest.

Table I summarises analytical data for those compounds not described in detail in the Experimental Section.

EXPERIMENTAL

The intermediates employed below are described by Petrow, Stephenson and Wild (1960) and Jackman, Petrow, Stephenson and Wild (1962).

p-Sulphamoylbenzenesulphonethylamide. Sulphamoylbenzene-*p*-sulphonyl chloride (17 g.) was added in portions with stirring to 5 per cent aqueous ethylamine (240 ml.) previously cooled to 0°. After 2 hr., excess of ethylamine was boiled off and the residual liquid acidified with dilute hydrochloric acid. The product was collected and washed with cold water. It had m.p. 166–168° after crystallisation from water. Found: C, 36.4; H, 4.4; N, 10.8. C₈H₁₂N₂O₄S₂ requires C, 36.4; H, 4.6; N, 10.6 per cent.

p-(2,3-dihydroxypropylsulphamoyl)benzenesulphonamide was prepared by reaction of sulphamoylbenzene-*p*-sulphonyl chloride with 3-amino-propane-1,2-diol in aqueous solution at below 5°. It had m.p. 141–143° after crystallisation from a small amount of water. Found: C, 34.9; H, 4.2; N, 8.7; S, 20.3. C₉H₁₄N₂O₆S₂ requires C, 34.8; H, 4.5; N, 9.0; S, 20.7 per cent.

p-Sulphamoylbenzenesulphonanilide, had m.p. 230–231° after crystallisation from aqueous ethanol. Found: C, 46.4; H, 3.8; N, 9.0; S, 20.4. C₁₂H₁₂N₂O₄S₂ requires C, 46.1; H, 3.9; N, 9.0; S, 20.5 per cent.

N-(*p*-Sulphamoylbenzenesulphonyl)piperidine. A solution of sulphamoylbenzene-*p*-sulphonyl chloride (15.35 g.) in chloroform (60 ml.) was added with stirring to a solution of piperidine (15.3 g.) in water (100 ml.). After 30 min. excess of chloroform and piperidine were evaporated at reduced pressure. The residue was dissolved in water and acidified with hydrochloric acid to yield the product (15.3 g.), m.p. 220–221° (from aqueous ethanol). Found: C, 43.5; H, 5.1; N, 9.2; S, 21.0. C₁₁H₁₆N₂O₄S₂ requires C, 43.4; H, 5.3; N, 9.2; S, 21.1 per cent.

1,2,3,4-Tetrahydro-*N*-(*p*-sulphamoylbenzenesulphonyl)pyridine was prepared as above. It was obtained in 90 per cent yield, m.p. 181–182° (from aqueous ethanol). Found: C, 43.7; H, 4.6; N, 9.0; S, 21.1. C₁₁H₁₄N₂O₄S₂ requires C, 43.7; H, 4.7; N, 9.3; S, 21.2 per cent.

N-(*p*-Sulphamoylbenzenesulphonyl)morpholine had m.p. 191–192° (from aqueous ethanol). Found: C, 39.6; H, 4.7; N, 9.2; S, 20.6. C₁₀H₁₄N₂O₅S₂ requires C, 39.2; H, 4.6; N, 9.2; S, 20.9 per cent.

2-Chloro-5-sulphamoylbenzenesulphonethylamide was prepared by reaction of 2-chloro-5-sulphamoylbenzenesulphonyl chloride with 5 per cent aqueous ethylamine at below 10°. It had m.p. 144–145° (from water). Found: C, 32.5; H, 3.8; Cl, 11.5; N, 9.3; S, 21.5. C₈H₁₁ClN₂O₄S₂ requires C, 32.2; H, 3.7; Cl, 11.9 per cent; N, 9.4; S, 21.5.

2-Chloro-5-sulphamoylbenzenesulphondimethylamide had m.p. 146–147° (from aqueous ethanol). Found: C 32.6; H, 3.8; Cl, 11.7; N, 9.3; S, 21.5. $C_8H_{11}N_2O_4S_2Cl$ requires C, 32.2; H, 3.7; Cl, 11.9; N, 9.4; S, 21.5 per cent.

5-Nitrotoluene-2-sulphondimethylamide. A solution of 5-nitrotoluene-2-sulphonyl chloride in chloroform (100 ml.) was added over 20 min. with stirring to 25 per cent aqueous dimethylamine at room temperature. After 30 min., excess of amine and chloroform were boiled off and the residue was cooled and acidified with dilute hydrochloric acid. The product was collected and washed with cold water. It had m.p. 103–104° (from 95 per cent ethanol). Found: C, 44.3; H, 5.1; N, 11.2; S, 12.8. $C_9H_{12}N_2O_4S$ requires C, 44.3; H, 5.0; N, 11.5; S, 13.1 per cent.

5-Aminotoluene-2-sulphondimethylamide. A mixture of the foregoing nitro-compound (34.6 g.), iron powder (28.6 g.), acetic acid (1.7 ml.), water (220 ml.) and octanol (1 ml.) was heated under reflux with stirring for 6 hr. Ethanol (200 ml.) was then added and the mixture boiled with charcoal and filtered. The filtrate was cooled and saturated with hydrogen chloride to yield the product as the *hydrochloride* (28 g.), m.p. 172–174° (from ethanol-ether). Found: C, 43.4; H, 5.9; Cl, 14.0; N, 11.1; S, 12.7. $C_9H_{15}ClN_2O_2S$ requires C, 43.1; H, 6.0; Cl, 14.2; N, 11.2; S, 12.8 per cent.

5-Chlorosulphonyltoluene-2-sulphondimethylamide. A solution of the foregoing hydrochloride (28 g.) in 24 per cent hydrochloric acid was diazotised at 0° by the addition of sodium nitrite (8.36 g.) in water (20 ml.). The resultant solution was added with stirring to a saturated solution of sulphur dioxide in acetic acid (350 ml.) containing cuprous chloride dihydrate (7.7 g.) at 20–25°. After 30 min. the mixture was diluted with ice-water and the sulphonyl chloride collected and washed with cold water. It had m.p. 109–111° after crystallisation from 1,2-dichloroethane-light petroleum (b.p. 60–80°). Found: C, 36.6; H, 3.9; Cl, 12.0; N, 4.6; S, 21.5. $C_9H_{12}ClNO_4S_2$ requires C, 36.3; H, 4.1; Cl, 11.9; N, 4.7; S, 21.5 per cent.

5-Sulphamoyltoluene-2-sulphondimethylamide. A solution of the foregoing sulphonyl chloride (29.8 g., moist material) in chloroform (150 ml.) was added with stirring to ammonium hydroxide solution (300 ml., $d = 0.880$) at below 10°. After 1 hr. excess of ammonia and chloroform were boiled off, and the cooled residue was acidified with hydrochloric acid. The product (22.6 g.) was collected and washed with cold water. It had m.p. 149–151° (from ethanol). Found: C, 39.2; H, 4.8; N, 10.0; S, 23.3. $C_9H_{14}N_2O_4S_2$ requires C, 38.8; H, 5.1; N, 10.1; S, 23.0 per cent.

4-Chlorosulphonyl-2-methylbenzoic acid. A mixture of *o*-toluic acid (68 g.) and chlorosulphonic acid (200 ml.) was heated at 125° for 2½ hr. when it was cooled and poured on to ice. The product (101.5 g.) was collected and washed with ice-water. It had m.p. 154–155° after crystallisation from 1,2-dichloroethane-light petroleum (b.p. 60–80°). Found: C, 40.8; H, 2.7; Cl, 15.1; S, 13.4. $C_8H_7ClO_4S$ requires C, 41.0; H, 3.0; Cl, 15.1; S, 13.7 per cent.

HYPOGLYCAEMIC AGENTS. PART II

Ethyl 2-methyl-5-sulphamoyl benzoate, obtained by esterification of the carboxylic acid, had m.p. 146–147° (from aqueous ethanol). Found: C, 49.6; H, 5.0; N, 6.0; S, 13.0. $C_{10}H_{13}NO_4S$ requires C, 49.4; H, 5.4; N, 5.8; S, 13.2 per cent.

1-*Cyclohexyl-3-[p-(p-toluenesulphonamido)benzenesulphonyl]urea*. Toluene *p*-sulphonyl chloride (0.69 g.) was added in portions with cooling to a solution of 1-(*p*-aminobenzenesulphonyl)-3-cyclohexylurea (1.07 g.) in pyridine (1.5 g.). After 1 hr. the mixture was heated on the steam-bath for 30 min., cooled, diluted with water and acidified with hydrochloric acid. The *product* (1.1 g.) was collected and washed with water. It had m.p. 195° after crystallisation from aqueous ethanol. Found: C, 53.0; H, 5.4; N, 9.3; S, 14.0. $C_{20}H_{25}N_3O_5S_2$ requires C, 53.2; H, 5.6; N, 9.3; S, 14.2 per cent.

1-*Chloro-2,4-di(ethylcarbamoylsulphamoyl)benzene* (by Dr. G. B. Jackman). A solution of 4-chlorobenzene-1,3-disulphonamide (13.5 g.) in acetone (60 ml.) was treated with a solution of sodium hydroxide (4.0 g.) in water (40 ml.). The mixture was cooled below 10° and ethyl isocyanate (8.2 g.) added dropwise with stirring. After 1 hr. at room temperature the mixture was acidified to Congo red with concentrated hydrochloric acid and the solids collected and washed with water. Extraction with boiling ethyl acetate yielded the insoluble *product* (16 g.), m.p. 203° (decomp.). Found: C, 35.0; H, 3.9; Cl, 8.3; N, 14.0. $C_{12}H_{17}ClN_4O_6S_2$ requires C, 34.9; H, 4.2; Cl, 8.6; N, 13.6 per cent.

1-*Butyl-3-[p-(2,3-dihydroxypropylsulphamoyl)benzenesulphonyl]urea*. A solution of *p*-(2,3-dihydroxypropylsulphamoyl)benzenesulphonamide (12.4 g.) in acetone (100 ml.) was treated with a solution of sodium hydroxide (1.6 g.) in the minimum of water. The mixture was cooled to 0°, stirred and treated with butyl isocyanate (13.1 g.) added dropwise. After 30 min. the mixture was heated at 60° for 6 hr. when it was cooled, poured on to ice and acidified to pH 5 by the addition of hydrochloric acid. The resultant oil was extracted with ethyl acetate and the extract dried with anhydrous sodium sulphate. Removal of the solvent left an oil which failed to crystallise. The oil was heated at reflux temperature with 4*N* sodium hydroxide (100 ml.) for 30 min. when the solution was treated with charcoal and filtered. The filtrate was cooled and acidified to pH 5 with hydrochloric acid when the solid product (9 g.) separated. It had m.p. 161–162° after crystallisation from water.

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