

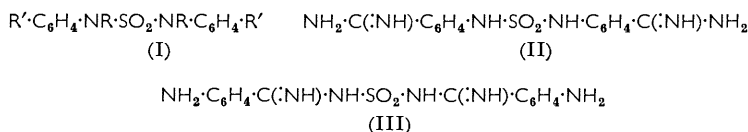
847. Some Substituted Sulphanilides.

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Some 3,3'- and 4,4'-substituted sulphanilides (I) are described. The compounds had no significant activity against a range of bacteria, protozoa, and helminths.

SULPHANILIDE was first synthesised by Traube¹ from phenylsulphamyl chloride and aniline. An obvious preparative method, the reaction between sulphuryl chloride and aromatic amines, was investigated earlier by Wenghoffer² and Behrend,³ who obtained only oxidation and chlorination products. Subsequently, Wohl and Koch⁴ showed that the reaction between an excess of aniline in ether and sulphuryl chloride gave a good yield of sulphanilide and a small amount of azobenzene; with some substituted anilines only complex oxidations occurred. Sulphanilide has also been prepared by several other workers.⁵

Some substituted sulphanilides were needed for chemotherapeutic investigation. The direct reaction of the appropriately substituted aniline with sulphuryl chloride appeared to be the most convenient method of preparation, but in view of the earlier results,^{3,4} modifications of the conditions seemed necessary. I find that a good yield of the required sulphanilide could usually be obtained if the reaction was carried out at 0° in dry pyridine.



When this method gave a poor yield, as for example with *p*-chloroaniline, the use of one mole of pyridine in chloroform at a low temperature gave a much improved yield. The sulphanilides so prepared were often unstable towards hydroxylic solvents. They were best obtained pure by precipitation from solution in dilute alkali with acetic acid. 4,4'-Dinitro-, 3,3'-dinitro-, 4,4'-dicyano-, and 3,3'-dicyano-sulphanilide readily gave *NN'*-dimethyl derivatives which were stable, crystalline solids.

The dicyano-compounds were converted into the stable diamidines by Pinner's method. The diamidine (II), prepared from 4,4'-dicyanosulphanilide, was insoluble in aqueous sodium hydroxide and could not be diazotised. When its preparation was attempted from *p*-aminobenzamidine monohydrochloride and sulphuryl chloride, the product had the correct analysis, but it was soluble in dilute alkali and after diazotisation it coupled with alkaline β -naphthol. This evidence and the fact that amidines are known to be acylated in the presence of bases and to undergo the closely related reaction with carbonyl chloride⁶ led to the formulation of this substance as (III).

Attempted reduction of 4,4'-dinitrosulphanilide with iron and acetic acid led to fission of the molecule and formation of *p*-phenylenediamine. The required 4,4'-diamino-sulphanilide was obtained by catalytic reduction of the dinitro-compound.

When 4,4'-dinitrosulphanilide was treated with acetic anhydride in pyridine at room temperature, fission again occurred and only *p*-nitroacetanilide was isolated.

¹ Traube, *Ber.*, 1891, **24**, 362.

² Wenghoffer, *Ber.*, 1876, **10**, 441.

³ Behrend, *Annalen*, 1884, **222**, 116.

⁴ Wohl and Koch, *Ber.*, 1910, **43**, 3295.

⁵ Battagay, French Patent, 735,765; Battagay and Maybeck, *Compt. rend.*, 1932, **194**, 186; Maybeck, *Ann. Chim.*, 1932, **17**, 129; Paquin, *Angew. Chem.*, 1948, *A*, **60**, 316.

⁶ Shriner and Neumann, *Chem. Rev.*, 1944, **35**, 390.

EXPERIMENTAL

4,4'-Dinitrosulphanilide. Method A.—Sulphuryl chloride (40 ml.) was added dropwise during 1 hr. to a vigorously stirred solution of *p*-nitroaniline (100 g.) in dry pyridine (300 ml.) maintained at -5° to 0° . After being kept at room temperature overnight the solution was added gradually to rapidly stirred, concentrated hydrochloric acid (300 ml.) and water (1,500 ml.). The gum was filtered off and extracted with cold *n*-sodium hydroxide (500 ml.). The alkaline extract was added to 2*N*-acetic acid (300 ml.) in water (700 ml.); the product, a granular solid, was purified similarly to give *4,4'*-dinitrosulphanilide (69 g., 56%), m. p. 195—197° (decomp.).

TABLE 1. *Sulphanilides* $R \cdot C_6H_4 \cdot NH \cdot SO_2 \cdot NH \cdot C_6H_4 \cdot R$.

R	Yield (%)	Cryst. solvent	M. p.	Formula	Found (%)				Required (%)			
					C	H	N	S	C	H	N	S
4-NO ₂ ^a ...	56	— ^c	195—197 ^{e,f}	C ₁₂ H ₁₀ N ₄ O ₆ S	42.4	2.8	16.65	9.2	42.6	3.0	16.6	9.4
3-NO ₂ ^a ...	63	— ^c	205 ^f	C ₁₂ H ₁₀ N ₄ O ₆ S	42.1	3.0	16.55	9.2	42.6	3.0	16.6	9.4
4-CN ^a ...	66	— ^c	168—170 ^f	C ₁₄ H ₁₆ N ₄ O ₂ S	56.35	3.6	18.7	10.6	56.4	3.35	18.8	10.7
3-CN ^a ...	95	MeNO ₂	165—170 ^{e,f}	C ₁₄ H ₁₀ N ₄ O ₂ S	55.9	3.6	18.9	10.4	56.4	3.35	18.8	10.7
4-MeSO ₂ ^a	83	— ^c	232—234 ^f	C ₁₄ H ₁₆ N ₂ O ₆ S ₃	41.9	3.9	6.7	23.2	41.6	4.0	7.0	23.7
4-Cl ^b ...	68	Petrol ^d	120—121	C ₁₂ H ₁₀ Cl ₂ N ₂ O ₂ S ^g	45.6	3.4	8.8	10.4	45.4	3.2	8.8	10.1
3-Cl ^a ...	34	EtOH ^d	156—158 ^f	C ₁₂ H ₁₀ Cl ₂ N ₂ O ₂ S ^h	45.5	3.2	8.8	10.5	45.4	3.2	8.8	10.1

^a Compound prepared by method A. ^b Compound prepared by method B. ^c The product was purified by precipitation from alkali with acetic acid. ^d Light petroleum (b. p. 100—120°). ^e The m. p. varies greatly with the rate of heating. ^f (Decomp.). ^g Found: Cl, 22.2. Required: Cl, 22.4%. ^h Found: Cl, 22.4. Required: Cl, 22.4%.

TABLE 2. *NN'*-Dimethylsulphanilides $R \cdot C_6H_4 \cdot NMe \cdot SO_2 \cdot NMe \cdot C_6H_4 \cdot R$.

R	Yield (%)	Cryst. solvent	M. p.	Formula	Found (%)				Required (%)			
					C	H	N	S	C	H	N	S
4-NO ₂ ...	64	A	142—143°	C ₁₄ H ₁₄ N ₄ O ₆ S	45.8	3.9	15.4	9.0	45.9	3.8	15.3	8.7
3-NO ₂ ...	85	A	103—104	C ₁₄ H ₁₄ N ₄ O ₆ S	45.7	3.9	15.4	8.7	45.9	3.8	15.3	8.7
4-CN...	67	A	151—153	C ₁₆ H ₁₄ N ₄ O ₂ S	58.9	4.4	17.2	9.7	58.9	4.3	17.2	9.8
3-CN...	75	B	142—143	C ₁₆ H ₁₄ N ₄ O ₂ S	58.5	4.3	17.0	10.1	58.9	4.3	17.2	9.8

A = 2-Ethoxyethanol. B = Ethanol.

TABLE 3. *Amidine salts* $NH_2 \cdot C(:NH) \cdot C_6H_4 \cdot NR \cdot SO_2 \cdot NR \cdot C_6H_4 \cdot C(:NH) \cdot NH_2 \cdot 2HX$

No.	Position of amidine groups	R	X	Solvent used to prepare imido-ester	Yield (%)	Cryst. solvent	M. p.	Found (%)				Required (%)				
								C	H	N	Cl	S	C	H	N	Cl
1	4	H	Cl	A	— ^a	D	284—286 ^b									
2	4	Me	MeSO ₃ ^c	B	73	E	289—290 ^b									
3	3	H	Cl	C	63	F	158									
4	3	Me	Cl	C	63	G	275 ^b									

A = 2-Ethoxyethanol alone. B = EtOH (2 mol.)—CHCl₃. C = EtOH. D = 2*N*-HCl. E = COMe₂—H₂O. F = 3*N*-HCl. G = MeOH—COMe₂.

^a Compound was very difficult to obtain pure and the yield was poor. ^b (Decomp.). ^c The methanesulphonate was prepared in methanol from the base isolated by addition of 50% aqueous sodium hydroxide to an aqueous solution of the dihydrochloride.

4,4'-Dichlorosulphanilide. Method B.—Sulphuryl chloride (31.8 ml.) was added dropwise during 1½ hr. to a stirred, fine suspension of *p*-chloroaniline (100 g.) in dry chloroform (500 ml.) containing dry pyridine (63.6 ml.) at -20° to -30° . The black solution was kept at room temperature overnight and then poured into 2*N*-acetic acid (1200 ml.). Extraction of the chloroform layer with *n*-sodium hydroxide (3 × 200 ml.) and acidification of the combined alkaline extracts with dilute acetic acid gave a gum which soon crystallised. The crude

sulphanilide (84 g., 68%) had m. p. 118—121°. The disubstituted sulphanilides in Table 1 were prepared similarly.

N,N-Dimethyl-4,4'-dinitrosulphanilide.—4,4'-Dinitrosulphanilide (25 g.), dissolved in 2*N*-sodium hydroxide (100 ml.), was treated with one portion of methyl sulphate (17.0 ml.). After $\frac{1}{2}$ hr. 2*N*-sodium hydroxide (10 ml.) and methyl sulphate (5 ml.) were added and after a further $\frac{1}{4}$ hr. this addition was repeated. After being stirred for another $\frac{1}{4}$ hr. the crude product (21.0 g., 78%), m. p. 138—140°, was crystallised from 2-ethoxyethanol; it formed prisms, m. p. 142—143°. The compounds in Table 2 were prepared similarly.

Amidinosulphanilides.—The imido-ester hydrochlorides were prepared from the finely powdered dinitrile suspended or dissolved in the solvent indicated in Table 3. The corresponding diamidines, prepared by the standard method, are described in the same Table.

Reduction of 4,4'-Dinitrosulphanilide with Iron in Acetic Acid.—Iron powder (1.0 g.) was added portionwise during 5 min. to a boiling solution of 4,4'-dinitrosulphanilide (1.0 g.) in acetic acid (5.0 ml.) and water (1.0 ml.). The mixture was diluted with water (5.0 ml.), boiled again, and then filtered. Methanesulphonic acid (5.0 ml.) was added to the filtrate. The salt (0.7 g.) which crystallised on cooling was dissolved in water, and the solution basified with 50% aqueous sodium hydroxide. The base had m. p. 139—142°, undepressed on admixture with *p*-phenylenediamine.

4,4'-Diaminosulphanilide.—4,4'-Dinitrosulphanilide (50 g.) suspended in warm ethanol (500 ml.) with Adams catalyst (5.0 g.) was reduced with hydrogen at atmospheric pressure. The theoretical uptake of hydrogen occurred in 0.75 hr. The cooled mixture was filtered and the solid extracted with *N*-hydrochloric acid (*ca.* 200 ml.). The mixture was filtered and the filtrate treated with sodium hydrogen carbonate to precipitate the pure base (28.5 g., 69%), m. p. 175° (decomp.) (Found: N, 19.9; S, 11.35. $C_{12}H_{14}N_4O_2S$ requires N, 20.2; S, 11.5%). The *bis*-toluene-*p*-sulphonate crystallised from ethanol-ether as minute needles, m. p. 212° (decomp.) (Found: C, 50.7; H, 5.0; N, 8.75; S, 15.2. $C_{12}H_{14}N_4O_2S_2 \cdot 2C_7H_8O_3S$ requires C, 50.2; H, 4.8; N, 9.0; S, 15.4%).

Reaction of p-Aminobenzamidine with Sulphuryl Chloride.—Sulphuryl chloride (1.6 ml.) was added dropwise to a stirred suspension of *p*-aminobenzamidine monohydrochloride (5 g.) in dry pyridine (15 ml.) at 3—5° during 0.3 hr. The gummy mixture was kept overnight then poured into water. The solution was basified (aqueous ammonia) and concentrated *in vacuo*. The residue solidified when triturated with water, giving a solid (1.3 g.), m. p. 215° (decomp.). This base was dissolved in warm methanolic methanesulphonic acid, the solution filtered (charcoal), and ether added to the filtrate which on cooling deposited the crystalline salt (0.7 g.), m. p. 225° (decomp.) (Found: C, 36.8; H, 4.4; N, 15.4; S, 17.9. $C_{16}H_{24}N_6O_8S_3 \cdot 2CH_4O_3S$ requires C, 36.7; H, 4.6; N, 16.0; S, 18.3%). The base, regenerated from the salt, was soluble in 2*N*-sodium hydroxide.

Reaction of 4,4'-Dinitrosulphanilide with Acetic Anhydride.—4,4'-Dinitrosulphanilide (10 g.) in dry pyridine (30 ml.) at 0—5° was treated with acetic anhydride (6.2 ml.). The mixture was stirred overnight, then poured into 2*N*-hydrochloric acid. The resultant solid crystallised from ethyl acetate in needles (3.8 g.), m. p. 214—215°. It did not depress the m. p. of authentic *p*-nitroacetanilide.

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