STUDIES IN SULPHONAMIDES

Benzene 1, 4-Disulphonamides*

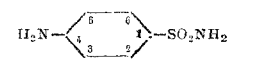
BY M. RAGHAVAN, B. H. IYER AND P. C. GUHA

(Department of Organic Chemistry, Indian Institute of Science, Bangalore-3)

SUMMARY

The preparation and properties of twenty-four benzene-1 : 4-disulphonamides are described in this paper.

Compounds of the sulphanilamide (I) group evolved so far has provided medical science with some of the most potent weapons for the effective conquest of many diseases of bacterial origin.



Out of the large number of sulphanilamide compounds prepared so far, only a few have justified their introduction into extensive clinical use. These are azo-sulphamide (neoprontosil), sulphanilamide, sulphapyridine, sulphathiazole, sulphadiazine, sulphamerazine, sulphamethazine, sulphacetamide, sulphaguanidine and succinyl sulphathiazole. Most of these compounds contain a heterocyclic ring in the N^1-position.

A careful survey of literature in the field of sulphonamides as chemotherapeutic agents would reveal that a lot of attention has been bestowed in modifying the sulphanilamide molecule (I) by the introduction of suitable substituents in the N^1- and N^4-positions so as to render it specific against certain types of bacteria and to eliminate some of its undesirable reactions.

Correlating structure and activity, Fourneau and co-workers[1] claimed that the structural unit essential for sulphanilamide type activity is $=N\langle\rangle S-$. But the absolute need of both sulphur and nitrogen has been called in question by the finding of moderate activity for such compounds as *p*-nitrobenzoic acid,[2,3] 4, 4'-dihydroxy diphenyl sulphone,[4] aniline 3, 5-disulphonamide,[5] and 3, 5-dibromobenzene sulphonanilide.[6]

The synthesis and pharmacological testing of di- or poly-sulphonamides have not received much attention. As such it was decided to prepare a

* A preliminary note on this work appeared in *Curr. Sci.*, 1947, **16**, 344-45.

series of benzene 1 : 4-disulphonamides with or without basic substituents in the nucleus as potential antibacterial substances. Accordingly the synthesis of a series of disulphonamides of the general formula, 1 : 4-$C_6H_4(SO_2NHR)_2$ where R is alkyl, aryl or heterocyclic residue was undertaken. This paper deals with the preparation and properties of twenty-four disulphonamides obtained by the action of benzene 1 : 4-disulphonyl chloride on various amines, some of which are themselves of therapeutic interest.

Benzene 1 : 4-disulphonyl chloride required for this work was prepared in an unambiguous way starting from sulphanilic acid according to the method of Leuckart.[7] The disulphonamides that have been synthesised are listed in Tables I and II.

The disulphonamides derived from monoamines are very crystalline in nature and have sharp melting points. They could be crystallised from such solvents as alcohol, acetone or water. The disulphonamides obtained from diamines melt at high temperature with decomposition. They could not be crystallised from the common organic solvents.

EXPERIMENTAL

Preparation of benzene 1 : 4-*di-(potassium sulphonate).*—Sulphanilic acid (105 g.) was diazotised and the diazo-compound was added in small portions to a concentrated solution of potassium xanthate in a shallow basin. After the addition of the diazo-compound, the mixture was heated on a water-bath for one hour at 67–70° C. The reaction mixture was evaporated to a small bulk on the steam-bath when the 4 : 4'-dipotassium sulphonate of diphenyl disulphide (KO_3S-C_6H_4-S-S-C_6H_4-SO_3K) was formed. The disulphide was oxidised with potassium permanganate (about 160 g.) to *p*-benzene di-(potassium sulphonate). A sixty-two per cent. yield of the disulphonate was obtained from sulphanilic acid by the xanthate process. The salt was purified by crystallisation from water. Yield, 85 g.

Preparation of benzene 1 : 4-*disulphonyl chlordie.*—Potassium benzene 1 : 4-disulphonate (85 g.) was dried in a nickel basin at 200–220° C. in an air oven to remove the water of crystallisation. The dry salt was transferred to a three-necked flask protected with a calcium chloride tube and fitted with a stirrer. An equivalent amount of phosphorus pentachloride was added and the mixture well stirred. The contents were warmed over a water-bath for two hours. The hydrochloric acid evolved was led to a gas trap. The cold reaction mixture was treated with cold water to remove sodium chloride. The water-insoluble diacid chloride was filtered, dried in a desiccator and purified by crystallisation from ether. Yield, 60 g., m.p. 131° C., m.p. of the disulphonamide, 288° C.

TABLE I

No.	R	Amine used	Molecular formula of the compound	Nitrogen %		Sulphur %		Melting point °C.
				Found	Required	Found	Required	
1	CH_3—	Methyl amine	$C_8H_{12}O_4N_2S_2$	10·3	10·6	24·6	24·2	219—220
2	C_2H_5—	Ethyl amine	$C_{10}H_{16}O_4N_2S_2$	9·4	9·6	22·1	21·9	172—173
3	$CH_3—CH_2—CH_2—CH(CH_3)$—	2-Aminopentane	$C_{14}H_{24}O_4N_2S_2$	7·5	7·4	17·3	17·0	123
4	$(CH_3)_2CH—CH_2—CH(CH_3)$—	2-Amino 4, 4-di-methyl-butane	$C_{18}H_{32}O_4N_2S_2$	6·8	6·9	16	15·8	174—175
5	o-C_6H_4—(CH_3)—	o-Toluidine	$C_{20}H_{20}O_4N_2S_2$	6·9	6·7	15·6	15·4	253—255
6	p-C_6H_4—(CH_3)—	p-Toluidine	$C_{20}H_{20}O_4N_2S_2$	6·8	6·7	15·5	15·4	273—274
7	2, 3—$(CH_3)_2$—C_6H_3—	o-Xylidine ($-NH_2$, CH_3-CH_3)(1, 2, 3)	$C_{22}H_{24}O_4N_2S_2$	6·2	6·3	14·7	14·4	251—252
8	2, 4—$(CH_3)_2$—C_6H_3—	m-Xylidine ($-NH_2$-CH_3-CH_3)(1, 2, 4)	$C_{22}H_{24}O_4N_2S_2$	6·4	6·3	14·6	14·4	244—246
9	2, 5—$(CH_3)_2$—C_6H_3—	p-Xylidine ($-NH_2$-CH_3-CH_3) (1, 2, 5)	$C_{22}H_{24}O_4N_2S_2$	6·4	6·3	14·8	14·4	234—235
10	p-$(CH_3O—)$—C_6H_4—	p-Anisidine	$C_{20}H_{20}O_6N_2S_2$	6·6	6·3	14·6	14·3	233—235
11	p-(C_2H_5O)—C_6H_4—	p-Phenetidine	$C_{22}H_{24}O_6N_2S_2$	5·9	5·9	13·6	13·4	252—254
12	o-Cl—C_6H_4—	o-Chloroaniline	$C_{18}H_{12}O_4N_2Cl_2S_2$	6·4	6·1	14·2	14	275—276
13	p-Cl—C_6H_4—	p-Chloroaniline	$C_{18}H_{12}O_4N_2Cl_2S_2$	6·3	6·1	14·3	14	291—292
14	m-BrC_6H_3—	m-Bromoaniline	$C_{18}H_{12}O_4N_2Br_2S_2$	5	5·1	11·5	11·7	240—260
15	p-H_2NO_2S—C_6H_4—	Sulphanilamide	$C_{18}H_{18}O_8N_4S_4$	10	10·3	23·6	23·4	297—299
16	C_6H_5—NH—	Phenylhydrazine	$C_{18}H_{18}O_4N_4S_2$	13·2	13·4	15·1	15·3	169—170
17	α-$C_{10}H_7$—	α-Naphthylamine	$C_{30}H_{28}O_4N_2S_2$	5·9	5·7	13·3	13·1	285—287
18	β-$C_{10}H_7$—	β-Naphthylamine	$C_{30}H_{28}O_4N_2S_2$	5·6	5·7	13·4	13·1	263—265
19	α-C_5H_4N—	α-Aminopyridine	$C_{16}H_{14}O_4N_4S_2$	14·2	14·4	16·2	16·4	279—281

TABLE II

1, 4—C_6H_4<$SO_2—NH$ / $SO_2—NH$>R′

No.	R′	Amine used	Molecular formula of the compound	Nitrogen %		Sulphur %		Melting point °C.
				Found	Required	Found	Required	
20	1, 4-C_6H_4=	*p*-Phenylene-diamine	$C_{16}H_{16}O_4N_2S_2$	8·9	9	20·8	20·6	340 (*a*)
21	—C_6H_4·C_6H_4—	Benzidine	$C_{22}H_{18}O_4N_2S_2$	7·5	7·3	16·7	16·6	300 (*a*)
22	—$(CH_3)C_6H_2$—$C_6H_2(CH_3)$—	*o*-Tolidine	$C_{26}H_{26}O_4N_2S_2$	6·6	6·8	15·8	15·5	310 (*a*)
23	—C_6H_4—S—C_6H_4—	4, 4′—Diamino-diphenylsulphide	$C_{18}H_{14}O_4N_2S_3$	6·8	6·7	22·8	22·9	316 (*a*)
24	—C_6H_4—SO_2—C_6H_4—	4, 4′—Diamino-diphenylsulphone	$C_{18}H_{14}O_6N_2S_3$	6·4	6·2	21·2	21·3	285 (*a*)

Preparation of the disulphonamides (Table I).—Benzene 1 : 4-disulphonyl chloride (·01 M) was refluxed with the mono-amine (·04 M) in benzene solution for nearly an hour. A few drops of pyridine were added during the course of the reaction. The mixture of the amine hydrochloride and the disulphonamide was filtered. An aqueous solution of the sodium salt of the sulphonamide was made by stirring the solid mixture with sodium hydroxide solution (5%). The amine was ether extracted and the disulphonamide was reprecipitated by neutralising the aqueous alkaline solution with dilute acetic acid. The disulphonamide was filtered, washed with water and dried. The disulphonamides derived from monoamines (Table I) were crystallised from alcohol, acetone or water. They are insoluble in benzene and ether.

The disulphonamides obtained from aromatic diamino compounds (Table II) could not be crystallised from the common organic solvents. They were purified by a repeated procedure of dissolving in dilute sodium hydroxide solution (5%), and reprecipitating by dilute acetic acid. They melt at very high temperature with decomposition. The disulphonamides from the monoamines have sharp melting points and are crystalline in nature.

Twenty-four disulphonamides thus prepared are listed in Tables I and II.

REFERENCES

1. Fourneau, *et al.* .. *Compt. rend. soc. biol.*, 1936, **122**, 258 ; 1938, **127**, 393 ; .. *Bull. acad. Med.*, 1937, **118**, 210.
2. Mayer and Oechslin .. *Compt. rend. soc. biol.*, 1939, **130**, 311.
3. Rosenthal and Bauer .. *Public Health Reports, U.S. Treasury Dept.*, 1939, **54**, 1317.
4. Levadite, *et al.* .. *Compt. rend. soc. biol.*, 1938, **127**, 19.
5. Northey .. *Chemical Reviews*, 1940, **27**, 92.
6. Kaplan and Lenbaner .. *J. Amer. Chem. Soc.*, 1945, **67**, 1076.
7. Leuckart .. *J. pr. Chem.*, 1890, **41**, 179.