CHEMOTHERAPY OF BACTERIAL INFECTIONS

XIII. Synthesis of Unsymmetrical Diphenylsulphones

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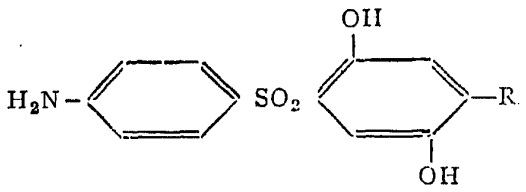
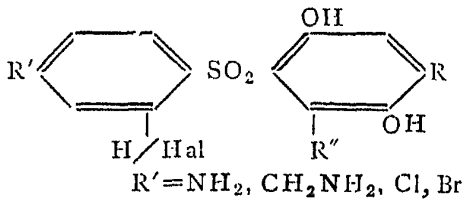
While investigating the chemotherapeutic agents in the sulphone group, Walker[1] synthesised 2:5-dihydroxy-4′-aminodiphenylsulphone (I, R = H) and derivatives and showed that the compound (I, R = H) approached sulphathiazole in its activity against *P. pestis* and *B. coli* and slightly better than sulphathiazole against the organisms belonging to the *Clostridia* group. When locally applied to mice infected with *Clostridium septicum*, it was reported to show marked effect and it had low chronic toxicity when fed to



(I)



$R' = NH_2, CH_2NH_2, Cl, Br$

(II)

mice. This shows that the substitution of the amino group in one benzene ring by the hydroxyl groups produced compounds of greater degree of activity, and in addition lower toxicity. So we decided to investigate compounds of general formulæ I and II. In introducing further substituents in one benzene ring, we selected the halogen atoms and the methylamino group because sulphanilamido derivatives with these substituents have been shown to be not reversed as far as their therapeutic activity is concerned by *para*-aminobenzoic acid.[2]

The requisite sulphone derivatives were prepared by the Hinsberg reaction[3] which consisted in reacting the sulphinic acids with benzoquinone derivatives. In this work, we selected *p*-acetaminobenzenesulphinic acid, *p*-acetaminomethylbenzenesulphinic acid, *p*-chlorobenzenesulphinic acid, *p*-bromobenzenesulphinic acid and benzenesulphinic acid as the representative sulphinic acids. Benzoquinone, 2-chlorobenzoquinone, 2-bromobenzoquinone, and 2:5-dichlorobenzoquinone were the representative quinones. The nineteen sulphones obtained are listed in the table.

The structure of the sulphones obtained from benzoquinone or the 2:5-dichlorobenzoquinone is unambiguous because of the symmetrical

TABLE I

Sl. No.	Name of Compound	Formula	M. P. °C.	Analysis %	
				Found	Require
1	2:5–Dihydroxy-3:6-dichloro-4′-acetaminodiphenylsulphone	$C_{14}H_{11}O_5NSCl_2$	246° dec.	Cl, 18·8 N, 3·5	18·9 3·7
2	2:5-Dihydroxy-3:6-dichloro-4′-aminodiphenylsulphone hydrochloride	$C_{12}H_{10}O_4NSCl_3$	200–02° dec.	Cl, 28·0	28·7
3	2:5-Dihydroxy-4(?)-bromo-4′-acetaminodiphenylsulphone	$C_{14}H_{12}O_5NSBr$	262° dec.	Br. 20·9	20·7
4	2:5-Dihydroxy-4(?)-bromo-4′-aminodiphenylsulphone	$C_{12}H_{10}O_4NSBr$	180–82°		
5	2:5-Dihydroxy-4′-acetamino-methyldiphenylsulphone	$C_{15}H_{15}O_5NS$	238°	N, 4·5	4·4
6	2:5-Dihydroxy-4′-aminomethyl-diphenylsulphone-hydrochloride	$C_{13}H_{14}O_4NSCl$	247–48° d.	Cl, 11·6	11·3
7	2:5-Dihydroxy-4′-aminomethyl-diphenylsulphone	$C_{13}H_{13}O_4NS$	172–74°	N, 4·8	5·0
8	2:5 Dihydroxy-4(?)-chloro-4′-acetaminomethyldiphenylsulphone	$C_{15}H_{14}O_5NSCl$	210–11°	Cl, 10·2	10·0
9	2:5-Dihydroxy-4(?)-chloro-4′-aminomethyldiphenylsulphone-hydrochloride	$C_{13}H_{13}O_4NSCl_2$	245° d.	Cl, 20·1	20·3
10	2:5-Dihydroxy-4(?)-chloro-4′-aminomethyldiphenylsulphone	$C_{13}H_{12}O_4NSCl$	230–31°	Cl, 11·0	11·3
11	2:5-Dihydroxy-3:6-dichloro-4′-acetaminomethyldiphenylsulphone	$C_{15}H_{13}O_5NSCl_2$	211–12° d.	Cl, 18·5	18·2
12	2:5-Dihydroxy-3:6-dichloro-4′-aminomethyl-diphenylsulphone hydrochloride	$C_{13}H_{12}O_4NSCl_3$	Decomposes above 235	Cl, 27·8	27·7
13	2:5-Dihydroxy-3:6-dichloro-4′-aminomethyldiphenylsulphone	$C_{13}H_{11}O_4NSCl_2$	Decomposes above 195	Cl, 20·0	20·4
14	2:5-Dihydroxy-2′:5′-dichlorodiphenylsulphone	$C_{12}H_8O_4SCl_2$	188–90°	Cl, 22·1	22·3
15	2:5-Dihydroxy-4(?)-chloro-2′:-5′-dichlorodiphenylsulphone	$C_{12}H_7O_4SCl_3$	135°	Cl, 30·3	30·1
16	2:5-Dihydroxy-3:6:2′:5′-tetrachlorodiphenylsulphone	$C_{12}H_6O_4SCl_4$	197–98°	Cl, 36·2	36·6
17	2:5-Dihydroxy-4(?) bromo-2′:5′-dichlorodiphenyl-sulphone	$C_{12}H_7O_4SCl_2Br$	128–30		
18	2:5-Dihydroxy-4′-chlorodiphenylsulphone	$C_{12}H_9O_4SCl$	205–06°	Cl, 12·4	12·5
19	2:5-Dihydroxy-4′-bromo-diphenylsulphone	$C_{12}H_9O_4SBr$	211–12°	Br. 24·4	24·3

distribution of the substituents in the ring. In the case of the sulphones prepared from monosubstituted benzoquinone however, there are three possibilities because the halogen atom can occupy three possible positions. Under the experimental conditions employed, we have isolated only one compound and for the compounds, we assign the structure (I) as the most probable.

A number of compounds from among those synthesised were tested for activity against *P. gallinaceum* in mosquitoes for the prophylactic activity and but they were found to be devoid of activity. The results of testing them in bacterial infections will be reported in due course.

Experimental

The sulphinic acids were prepared by the general method of Bere and Smiles[4] by the sulphite reduction of the sulphochlorides. The modification of the sulphite reduction by the use of sodium carbonate instead of sodium hydroxide as described by Short and Koebner[5] resulted in better yields and purer products. The alkali metal salts of the sulphinic acids were more stable than the free acids, this being particularly true of *p*-chloro and *p*-bromobenzene sulphinic acids. The decomposition of these acids was hastened by even traces of acids.

2: 5-*Dihydroxy*-3:6-*dichloro*-4'-*acetaminodiphenylsulphone.*—*p*-Acetaminobenzenesulphinic acid (5 g.) was suspended in a mixture of ethanol (50 c.c.) and water (5 c.c.) and cooled in an ice-bath. To the cooled suspension was added powdered 2: 5-dichlorobenzoquinone (4 g.) and the mixture vigorously shaken. Decolorisation took place with the suspended reactants going into a practically colourless solution and shortly thereafter white crystals began to separate. The contents were then heated on the steam-bath for about fifteen minutes, cooled and filtered. The solid was washed with dilute ethanol and dried (yield, 7·0 g., m.p. 246° dec.). On crystallisation from dilute ethanol, it had m.p. 246° (dec.).

2: 5-*Dihydroxy*-3:6-*dichloro*-4'-*aminodiphenylsulphone hydrochloride.*—The above described acetyl compound (4 g.) was suspended in a mixture of ethanol (20 c.c.), hydrochloric acid (20 c.c.) and water (20 c.c.) and the mixture refluxed for about six to seven hours when the solid went completely into solution. The solution was clarified (charcoal), filtered hot and kept in an ice-box. The crystals that had separated were filtered and dried (yield, 3·2 g., m.p. 190–93°). It was recrystallised from dilute ethanol.

The compounds listed in the table were prepared by the above described general method.

Summary

Nineteen diarylsulphones of general formulæ (I) and (II) listed in the table have been synthesised by the Hinsberg reaction, with a view to study them for their action against gram positive anaerobes.

References

1. Walker .. *J. Chem. Soc.*, 1945, 630.
2. Goetchius and Lawrence .. *J. Bact.*, 1945, **49**, 575.
3. Hinsberg .. *Ber.*, 1894, **27**, 3259.
4. Bere and Smiles .. *J. Chem. Soc.*, 1924, 2361.
5. Short and Koebner .. *C. A.*, 1947, **41**, 3818 (Brit. P., 584, 584).