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SULFONES. I. THE ISOMERIC X,X'-DIAMINODIPHENYL SULFONES

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In order to determine the relationship of the structure to chemotherapeutic activity in 4,4'-diaminodiphenyl sulfone, the effect of the positions of the amino groups on activity was undertaken. There are six possible isomers of diaminodiphenyl sulfone having one amino group in each ring. Of these, three have been described in the literature, namely, 2,4'-diaminodiphenyl sulfone (1), 3,3'-diaminodiphenyl sulfone (2) and, of course, 4,4'-diaminodiphenyl sulfone. Two of the remaining three isomers have one amino group in the 3-position. The easiest method of introducing an amino group in this position appeared to be by nitration of the proper sulfone, a *meta*-directing group (3), followed by reduction. Thus, nitration of 4-nitrodiphenyl sulfone and 2-nitrodiphenyl sulfone would be expected to lead to 3,4'-dinitro- and 2,3'-dinitro-diphenyl sulfone, respectively. Reduction with stannous chloride in hydrochloric acid gave the corresponding diamines. The last isomer, 2,2'-diaminodiphenyl sulfone was obtained by simultaneous reduction and hydrolysis of the known 2-acetamino-2'-nitrodiphenyl sulfone (4).

Of the six isomers only 4,4'-diaminodiphenyl sulfone showed chemotherapeutic activity.[1]

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EXPERIMENTAL

2,3'-Dinitrodiphenyl sulfone. 2-Nitrodiphenyl sulfone was obtained in 78% yield, m.p. 138–141°, by the condensation of sodium benzenesulfinate and *o*-chloronitrobenzene in a mixture of ethylene glycol and Carbitol at 160° for fifteen hours.

Ullmann and Pasdermadjian (5) have recorded a yield of 88% of product, m.p. 147.5°, when the reaction was carried out in alcohol in a sealed tube at 160°.

To a mixture of 23 g. of 2-nitrodiphenyl sulfone and 80 cc. of concentrated sulfuric acid was added dropwise over a period of ten minutes 40 cc. of nitric acid ($d = 1.42$). The temperature was maintained at 55–60° by occasional cooling. After being stirred at 55–60° for fifteen minutes more, the mixture was poured on ice. The product was washed thoroughly with water, and heated to boiling with alcohol, then cooled, to remove impurities; yield, 24.1 g. (90%), m.p. 168–171°. Recrystallization from acetic acid gave cream-colored crystals, m.p. 173–175°.

Anal. Calc'd for $C_{12}H_8N_2O_6S$: C, 46.6; H, 2.6; N, 9.1.
Found: C; 46.7; H, 2.9; N, 9.6.

3,4'-Dinitrodiphenyl sulfone. 4-Nitrodiphenyl sulfone was obtained in 46% yield, m.p. 140–142°, by the condensation of sodium benzenesulfinate and *p*-chloronitrobenzene in boiling Carbitol (six hours) containing a little sodium iodide. Ullmann and Pasdermadjian (5) have recorded a m.p. of 143° when the reaction was run in alcohol at 160° in a sealed tube.

[1] The biological studies will be reported elsewhere.

Nitration in the same manner as described for 2,3′-dinitrodiphenyl sulfone resulted in a 96% yield of product, m.p. 174–179°. Recrystallization from acetic acid gave orange crystals, m.p. 182–184°.

Anal. Calc'd for $C_{12}H_8N_2O_6S$: C, 46.6; H, 2.6; N, 9.1.
Found: C, 46.8; H, 3.6; N, 9.2.

3,4′-Diaminodiphenyl sulfone. To a solution of 156 g. of stannous chloride dihydrate in 156 cc. of concentrated hydrochloric acid was added 24.3 g. of 3,4′-dinitrodiphenyl sulfone. The mixture was warmed gently on the steam-bath to initiate the reaction which was then controlled by cooling in an ice-bath. In about two minutes the reaction had subsided and most of the nitro sulfone had dissolved. After being heated on the steam-bath for two hours, the solution was poured into 170 g. of sodium hydroxide in 170 cc. of water diluted with excess ice. The solid was collected on a sintered-glass funnel. An ethyl acetate solution of the solid was clarified with Norit, diluted with an equal volume of benzene, and petroleum ether was added to incipient crystallization; yield, 14.1 g. (72%) of white crystals, m.p. 129–131°. Recrystallization from the same solvents raised the m.p. to 131.5–133°.

Anal. Calc'd for $C_{12}H_{12}N_2O_2$: C, 58.1; H, 4.8; N, 11.3.
Found: C, 58.5; H, 5.2; N, 11.4.

2,3′-Diaminodiphenyl sulfone. Reduction of 2,3′-dinitrodiphenyl sulfone was carried out the same as in the preceding experiment in 67% yield, m.p. 118–120°. Recrystallization from benzene gave white crystals, m.p. 124–126°.

Anal. Calc'd for $C_{12}H_{12}N_2O_2S$: C, 58.1; H, 4.8; N, 11.3.
Found: C, 57.7; H, 5.0; N, 11.7.

3,3′-Diaminodiphenyl sulfone was prepared in the same way from 3,3′-dinitrodiphenyl sulfone (6) in 40% yield, m.p. 168–170°. Catalytic reduction in acetic acid with Adams' catalyst gave a 36% yield, m.p. 158–163°.

Marchak, *et al.* (2) record a yield of 70% and m.p. 168–169°, using ammonium sulfide as the reducing agent.

2,2′-Diaminodiphenyl sulfone. 2-Nitro-2-aminodiphenyl sulfide was prepared from *o*-chloronitrobenzene and sodium sulfide in 50% yield according to Lantz (7). The amine was acetylated, then oxidized with hydrogen peroxide to 2-acetamino-2′-nitrodiphenyl sulfone in 64% yield essentially according to the method of Evans and Smiles (4). From 24.6 g. of the sulfone, 78 g. of stannous chloride dihydrate, and 78 cc. of conc'd hydrochloric acid was obtained 17.1 g. (90%) of 2,2′-diaminodiphenyl sulfone, m.p. 143–145°, in the same way as described for 3,4′-diaminodiphenyl sulfone except that the crude product was purified by recrystallization from alcohol-water. The analytical sample formed white crystals, m.p. 146–147°.

Anal. Calc'd for $C_{12}H_{12}N_2O_2S$: C, 58.1; H, 4.8; N, 11.3.
Found: C, 57.8; H, 5.2; N, 11.1.

SUMMARY

Syntheses of three unknown isomers of 4,4′-diaminodiphenyl sulfone have been described.

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