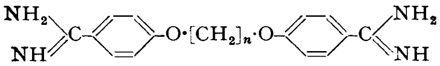
423. *Nuclear-substituted Derivatives of* 4 : 4′-*Diaminodiphenyl Sulphone.*

By S. S. Berg.

4 : 4′-Diaminodiphenyl sulphone has been substituted in the *ortho*-positions to the sulphone bridge with halogen and hydroxyl groups.

Introduction of nuclear halogen and hydroxyl groups into symmetrical diamidines of the types



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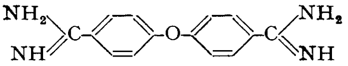
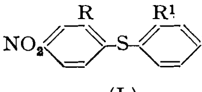


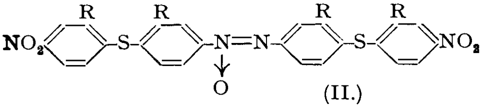
has been shown to yield products of enhanced bactericidal activity (Berg and Newbery, this vol., p. 642). The therapeutic effect of 4 : 4-diaminodiphenyl sulphone on infections caused by bacilli pathogenic to man prompted an investigation into the effects of similar substituents in the *ortho*-position to the sulphone linkage.

On account of their extreme insolubility, and ease of hydrolysis of their salts in aqueous solution, the halogen derivatives were tested orally *in vivo* against *Staph. aureus* and *Strep. pyogenes* in mice. A decrease in toxicity in the order Cl $<$ Br $<$ I, together with corresponding decrease in activity, was observed. These results were almost certainly due to the poor absorption of the products. Whilst this work was in progress Youmans and Doub (*Amer. Rev. Tuberc.*, 1946, **54**, 287) and Youmans, Feldman, and Doub (*ibid.*, p. 295) reported that 2-chloro- and 2-hydroxy-4 : 4′-diaminodiphenyl sulphone were less active than 4 : 4′-diaminodiphenyl sulphone for the virulent *Mycobacterium tuberculosis*, human type, *in vitro*, and that the 2-chloro-derivative was inactive *in vivo*. In view of these results further work in this series was not undertaken, but the chemical work is now published because of the appearance of a paper by Hodgson, Dodgson, and Smith (*J.*, 1948, 1104) in which two of the intermediates prepared during the course of this work are described. Although 2-chloro- and 2-hydroxy-4 : 4′-diaminodiphenyl sulphone are listed by Wiselogle in his " Survey of Antimalarials," the preparation and properties of the former had not been described, but the latter compound, now prepared by an unambiguous route, was identical with that described by Burton and Hoggarth (*J.*, 1945, 469), so its structure is now established.

The mono- and di-substituted halogen derivatives were obtained by the oxidation of 2- and 2 : 2′-halogenated 4 : 4′-dinitrodiphenyl sulphide (I), followed by reduction of the nitro-groups. Oxidation was effected with potassium permanganate; use of hydrogen peroxide gave products contaminated with the corresponding sulphoxide. The condensation of sodium *p*-nitrothiophenoxide with the appropriate 1-chloro-2-halogeno-4-nitrobenzene gave (I; R′ = H). When R = R′ = Cl or I, condensation of the appropriate 1-chloro-2-halogeno-4-nitrobenzene with sodium sulphide gave the required sulphide in poor yield. The latter reaction gave also an appreciable amount of a highly coloured, non-basic compound probably, (II), obtained by reduction of (I).



(I.)



(II.)

4 : 4′-*Diamino*-2-*hydroxydiphenyl sulphone* was obtained by the reduction of 4 : 4′-*dinitro*-2-*hydroxydiphenyl sulphone*, prepared as its *acetate* by the oxidation of 4 : 4′-*dinitro*-2-*acetoxydiphenyl sulphide*. Condensation of *p*-nitrobenzenethiol with 2-*bromo*-5-*nitrophenyl acetate* in acetone–potassium carbonate yielded the required sulphide.

Experimental.

1-*Chloro*-2-*bromo*-4-*nitrobenzene*.—A suspension of 2-bromo-4-nitroaniline (Rowe, Jambuserwal, and Partridge, *J.*, 1935, 1135) (18·5 g.) in hydrochloric acid (*d* 1·16; 75 c.c.) was added to ice (100 g.) and sodium nitrite (7·5 g.). The solution was added dropwise (during 30 minutes) to cuprous chloride (12·5 g.) in hydrochloric acid (*d* 1·16; 50 c.c.) at 20—25°. Nitrogen was evolved, and after an hour's heating at 90°, an oil separated which solidified on cooling. The solid was collected, washed successively with water, dilute sodium hydroxide, and water, and then dried. The *product* (12·5 g.) distilled as a yellow oil, b. p. 100°/0·1 mm., which crystallised in white fluffy needles, m. p. 61°, from light petroleum (b. p. 40—60°) (Found : C, 30·5; H, 1·4; N, 5·9. $C_6H_3O_2NClBr$ requires C, 30·4; H, 1·3; N, 6·0%).

2-*Chloro*-4 : 4′-*dinitrodiphenyl Sulphide*.—*p*-Nitrobenzenethiol (Mayer, *Ber.*, 1909, **42**, 3050) (1·55 g.) and sodium hydroxide (0·4 g.) in ethanol (20 c.c.) were added to a boiling solution of 3 : 4-dichloronitrobenzene (1·9 g.) in ethanol (10 c.c.). A solid was precipitated after 10 minutes, and after being heated under reflux for 2 hours the mixture was cooled, and the solid collected. The *sulphide* (1·3 g.) crystallised from acetic acid in yellow prisms, m. p. 144° (Found : N, 9·0; Cl, 11·6. $C_{12}H_7O_4N_2ClS$ requires N, 9·0; Cl, 11·5%).

2-*Bromo*-4 : 4′-*dinitrodiphenyl sulphide*, yellow prismatic needles (from acetic acid), m. p. 159° (Found : N, 8·0; Br, 22·6. $C_{12}H_7O_4N_2BrS$ requires N, 7·9; Br, 22·5%), and 2-*iodo*-4 : 4′-*dinitrodiphenyl sulphide*, yellow prisms (from acetic acid), m. p. 168° (Found : N, 6·9; I, 31·1; S, 8·0. $C_{12}H_7O_4N_2IS$ requires N, 7·0; I, 31·6; S, 8·0%), were prepared similarly from 1-chloro-2-bromo- and 2-iodo-4-nitrobenzene (Willgerodt and Arnold, *Ber.*, 1901, **34**, 3344), respectively.

2 : 2′-*Dichloro*-4 : 4′-*dinitrodiphenyl Sulphide*.—A stirred, boiling solution of 3 : 4-dichloronitrobenzene (15 g.) in ethanol (60 c.c.) was treated, during 5 minutes, with sodium sulphide nonahydrate (10 g.) in 25% aqueous ethanol (40 c.c.). After being heated under reflux for 6 hours, the mixture was cooled, and the solid collected and washed with hot water, dilute hydrochloric acid, ethanol, and ether. The solid was then extracted with boiling 95% acetic acid; the sulphide (7·2 g.) separated in yellow prisms, m. p. 163° (Found : N, 8·2; Cl, 21·0; S, 9·4. Calc. for $C_{12}H_6O_4N_2Cl_2S$: N, 8·2; Cl, 20·7; S, 9·3%). Hodgson *et al.* (*loc. cit.*) describe the product as crystallising in yellow needles, m. p. 166°. The solid (3 g.) which was insoluble in 95% acetic acid crystallised from benzene, and then from acetic acid, in large red prisms, m. p. 195° (Found : C, 45·0; H, 2·2; N, 8·5; Cl, 22·0; S, 10·25. $C_{24}H_{12}O_5N_4Cl_4S_2$ requires C, 45·0; H, 1·9; N, 8·7; Cl, 22·1; S, 10·0%).

2 : 2′-*Di-iodo*-4 : 4′-*dinitrodiphenyl sulphide*, pale red rhombs (from 90% aqueous acetic acid), m. p. 186° (Found : N, 5·2; I, 47·8. $C_{12}H_6O_4N_2I_2S$ requires N, 5·3; I, 48·1%), was prepared similarly.

2-*Bromo*-5-*nitrophenyl Acetate*.—Treatment of 2-bromo-4-nitrophenol (Henley and Turner, *J.*, 1930, 938) with acetic anhydride gave the *acetate*, which formed pale yellow needles, m. p. 86°, from ethanol (Found : N, 5·3; Br, 30·6. $C_8H_6O_4NBr$ requires N, 5·4; Br, 30·8%).

4 : 4′-*Dinitro*-2-*acetoxydiphenyl Sulphide*.—2-Bromo-5-nitrophenyl acetate (13 g.), *p*-nitrobenzenethiol (7·8 g.), fused potassium carbonate (3·5 g.), and acetone (100 c.c.) were heated under reflux for 2 hours. After filtration, the filtrate yielded the *sulphide* (6·0 g.), which crystallised in yellow prisms, m. p. 100°, from ethanol (Found : C, 50·1; H, 3·1; N, 8·2. $C_{14}H_{10}O_6N_2S$ requires C, 50·3; H, 3·0; N, 8·4%).

2-*Chloro*-4 : 4′-*dinitrodiphenyl Sulphone*.—Potassium permanganate (7·5 g.) in hot water (50 c.c.) was added dropwise, with stirring, to 2-chloro-4 : 4′-dinitrodiphenyl sulphide (10 g.) in boiling acetic acid (150 c.c.). After addition was complete, water (150 c.c.) was added, and the cooled mixture decolorised with sulphur dioxide. The *sulphone* (8·0 g.) was collected, and crystallised from 70% aqueous acetic acid in long white needles, m. p. 182—183° (Found : N, 8·2; Cl, 10·6. $C_{12}H_7O_6N_2ClS$ requires N, 8·2; Cl, 10·4%).

The following were obtained similarly : 2-*bromo*-4 : 4′-*dinitrodiphenyl sulphone*, white needles, m. p. 162°, from 70% aqueous acetic acid (Found : N, 7·0; Br, 20·8. $C_{12}H_7O_6N_2BrS$ requires N, 7·2; Br, 20·7%); 2-*iodo*-4 : 4′-*dinitrodiphenyl sulphone*, pale yellow needles, m. p. 165°, from 70% aqueous acetic acid (Found : N, 6·4; I, 29·0; S, 7·6. $C_{12}H_7O_6N_2IS$ requires N, 6·4; I, 29·3; S, 7·4%); 2 : 2′-dichloro-4 : 4′-dinitrodiphenyl sulphone, orange plates, m. p. 218°, from acetic acid (Found : N, 7·5; Cl, 18·7; S, 8·6. Calc. for $C_{12}H_6O_6N_2Cl_2S$: N, 7·5; Cl, 18·8; S, 8·5%) (Hodgson *et al.*, *loc. cit.*, describe the same compound as crystallising in colourless needles, m. p. 169°); and 2 : 2′-*di-iodo*-4 : 4′-*dinitrodiphenyl sulphone*, yellow prisms, m. p. 260°, from acetic acid (Found : N, 5·2; I, 45·1. $C_{12}H_6O_6N_2I_2S$ requires N, 5·0; I, 45·4%).

4 : 4′-*Dinitro-2-hydroxydiphenyl Sulphone*.—4 : 4′-Dinitro-2-acetoxydiphenyl sulphide was oxidised with potassium permanganate in boiling aqueous acetic acid, and the solid, collected after decolorisation with sulphur dioxide, was readily hydrolysed with boiling aqueous sodium carbonate. The *sulphone*

separated in yellow prismatic needles, m. p. 216°, from acetic acid (Found : C, 44·2; H, 2·4; N, 8·6. $C_{12}H_8O_7N_2S$ requires C, 44·2; H, 2·5; N, 8·6%).

2-*Chloro*-4 : 4′-*diaminodiphenyl Sulphone*.—Reduced iron (10 g.) was added slowly to a boiling solution of 2-chloro-4 : 4′-dinitrodiphenyl sulphone (5 g.) in 60% aqueous acetic acid (200 c.c.). After being heated at 90° for 10 minutes, the mixture was filtered, and the filtrate diluted with water (600 c.c.). The solid was collected, washed with water, and dissolved in warm 2N-hydrochloric acid (50 c.c.). The solution was basified with 2N-sodium hydroxide, and the *sulphone* (3·0 g.) collected. It separated in pale yellow prismatic needles, m. p. 114°, from dilute acetic acid (Found: N, 9·9; Cl, 12·7. $C_{12}H_{11}O_2N_2ClS$ requires N, 9·9; Cl, 12·6%). The following were prepared similarly : 2-*bromo*-4 : 4′-*diaminodiphenyl sulphone*, yellow needles, m. p. 157°, from dilute acetic acid (Found : N, 8·7; Br, 24·5; S, 10·1. $C_{12}H_{11}O_2N_2BrS$ requires N, 8·6; Br, 24·4; S, 9·8%); 2-*iodo*-4 : 4′-*diaminodiphenyl sulphone*, buff needles, m. p. 207°, from aqueous acetic acid (Found : N, 7·4; I, 33·5. $C_{12}H_{11}O_2N_2IS$ requires N, 7·5; I, 34·0%); 2 : 2′-*dichloro*-4 : 4′-*diaminodiphenyl sulphone*, orange needles, m. p. 263°, from aqueous acetic acid (Found : N, 9·0; Cl, 22·6; S, 10·1. $C_{12}H_{10}O_2N_2Cl_2S$ requires N, 8·9; Cl, 22·4; S, 10·0%); and 2 : 2′-*di-iodo*-4 : 4′-*diaminodiphenyl sulphone*, white prismatic needles, m. p. 280°, from aqueous acetic acid (Found : N, 5·7; I, 50·6. $C_{12}H_{10}O_2N_2I_2S$ requires N, 5·6; I, 50·8%).

4 : 4′-*Diamino*-2-*hydroxydiphenyl Sulphone*.—4 : 4′-Dinitro-2-hydroxydiphenyl sulphone (10 g.) in boiling 90% aqueous acetic acid (150 c.c.) was treated with iron powder (10 g.). The mixture was filtered, and the filtrate evaporated to dryness. Treatment with 3N-sulphuric acid yielded the *sulphate* (10 g.) of the diamino-sulphone, which crystallised in white prismatic needles, m. p. 208° (decomp.), from 2N-sulphuric acid (Found : C, 31·4; H, 3·3; N, 6·2. $C_{12}H_{12}O_3N_2S,2H_2SO_4$ requires C, 31·3; H, 3·5; N, 6·1%). Neutralisation of the hot aqueous solution of the sulphate with sodium acetate yielded the base as white needles, m. p. 134—135°, from water. This was identical with the compound described by Burton and Hoggarth (*loc. cit.*).

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