23. *Chemotherapeutic Diamidines. The Sulphur Analogue of 4 : 4'-Diamidinostilbene.*

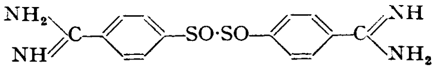
By LUDWIG BAUER and J. CYMERMAN.

Preparation of di-*p*-cyanophenyl disulphoxide (III) is described. Attempts to synthesise di-*p*-amidinophenyl disulphoxide (I), a sulphur analogue of 4 : 4'-diamidinostilbene, by interaction of (III) with ammonium thiocyanate, ammonium benzenesulphonate, and ammonium benzenesulphonate and ammonia gave, in every case, di-*p*-amidinophenyl disulphide, which has been prepared also by interaction of di-*p*-cyanophenyl disulphide with ammonium thiocyanate and by the Pinner method by way of the 4 : *4'-di(carboxyimino ethyl ether) dihydrochloride.* Application of the Pinner method to (III) gave its 4 : *4'-di(carboxyimino ethyl ether)* but alcoholic ammonia yielded only the disulphide diamidine. Reaction mechanisms are discussed. Heating the di-imino diethyl ether dihydrochlorides afforded the corresponding diamides; 4 : *4'-di-*(p-N-*phenylamidinophenyl) disulphide dibenzenesulphonate* was prepared, but attempted preparation of the disulphoxide analogue from (III) gave a deep-blue compound of unknown structure. Ultra-violet absorption spectra of aromatic disulphides and disulphoxides have been determined.

THE chemotherapeutic properties of diamidines are well known (Lourie and Yorke, *Ann. Trop. Med. Parasit.*, 1937, **31**, 435; 1939, **33**, 289; King, Lourie, and Yorke, *Lancet*, 1937, **233**, 136), the aromatic diamidines, in particular, showing pronounced antibacterial activity (Ashley, Barber, Ewins, Newbery and Self, *J.*, 1942, 103; Wien, *Brit. J. Pharmacol.*, 1948, **3**, 211). Replacement of carbon by sulphur in many organic compounds of biological interest has yielded sulphur analogues of lower toxicity and equal or increased activity (Steinkopf and Ohse, *Annalen*, 1924, **437**, 14; 1926, **448**, 205; Warren, Marsh, Thompson, Shelton, and Becker, *J. Pharm. Exp. Therap.*, 1943, **79**, 187; Dann and Moller, *Ber.*, 1947, **80**, 23) and it was thus of interest to attempt the synthesis of di-*p*-amidinophenyl disulphoxide (I), a sulphur analogue of 4 : 4'-diamidinostilbene (II) which has outstanding trypanocidal activity (Ashley *et al.*, *loc. cit.*).

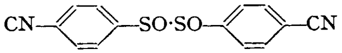
The required starting material, di-*p*-cyanophenyl disulphoxide (III), was obtained by Cymerman, Koebner, and Short (*J.*, 1948, 381) in low yield as a by-product in the preparation of *p*-cyanobenzenesulphinic acid. Its attempted preparation from the sulphinic acid at 80—90° in the presence of hydriodic acid and sulphur dioxide (Otto, *Ber.*, 1882, **15**, 121; Smiles and Gibson, *J.*, 1924, 180; von Braun and Weissbach, *Ber.*, 1930, **63**, 2836; Hilditch, *J.*, 1910, 1096) gave only an acidic hydrolysis product, presumably di-*p*-carboxyphenyl disulphoxide, in 90% yield, while the action of concentrated hydrochloric acid on the sulphinic acid at 25° for 3 days yielded the disulphoxide (55%) accompanied by the corresponding diamide. However, hydrochloric acid at 0° during 2—3 days readily afforded 70% of pure (III); the mother-liquors contained *p*-cyanobenzenesulphonic acid, isolated as the p-*toluidine* salt in 45% yield, in agreement with the accepted mechanism (1) for the formation of disulphoxides from the sulphinic acids (Otto, *Ber.*, 1876, **9**, 1639; Pauly and Otto, *ibid.*, 1877, **10**, 2181; 1878, **11**, 2070, 2073; von Braun and Weissbach, *loc. cit.*).

Synthetic methods available for the preparation of the required diamidine included the well-known Pinner synthesis (Pinner, *Ber.*, 1877, **10**, 1889; cf. Derby, *Amer. Chem. J.*, 1908, **39**, 437) through the imino-ether, and the recently-developed fusion methods using ammonium salts such as the benzenesulphonate (Oxley and Short, *J.*, 1946, 147) and thiocyanate (Partridge and Short, *J.*, 1947, 390).



(I.)

(II.)



(III.)

$$3R{\cdot}SO_2H \longrightarrow R{\cdot}SO_2{\cdot}SR + R{\cdot}SO_2{\cdot}OH + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Interaction of the disulphoxide (III) with ammonium thiocyanate at 180° (method *A*) gave a solid diamidine showing an intense colour in the Fuller reaction (Fuller, *Nature*, 1944, **154**, 773), and affording an 82·5% yield of a *dihydrochloride hemihydrate* (m. p. 316°) and from this an anhydrous *salt* (m. p. 310—311°) which gave analytical figures corresponding to di-*p*-amidinophenyl disulphide dihydrochloride. Further confirmation of the nature of the product was afforded by the preparation of the *dibenzenesulphonate, dipicrate*, and *dibenzoate dihydrate*.

This diamidine has been reported by Ashley *et al.* (*loc. cit.*) who obtained it by the Pinner synthesis from di-*p*-cyanophenyl disulphide and report m. p. >300° for the dihydrochloride dihydrate. In our hands the action of alcoholic hydrogen chloride on di-*p*-cyanophenyl disulphide (Bauer and Cymerman, *J.*, in the press) gave (method *D*) (*diphenyl disulphide*)-4 : 4′-*di*(*carboxyimino ethyl ether*) *dihydrochloride* in quantitative yield, and dry alcoholic ammonia converted this into the diamidine which gave a dibenzenesulphonate (53% yield) and dihydrochloride identical with those obtained from method *A*.

In order to examine the validity of the ammonium thiocyanate method in this case, interaction of di-*p*-cyanophenyl disulphide with this reagent was investigated (method *E*) and found to give the expected dibenzenesulphonate (35% yield), identical with that obtained from method *A*.

Attention was then turned to the alternative method of preparation using ammonium benzenesulphonate in the presence of ammonia gas (Oxley, Partridge, and Short, *J.*, 1948, 303). By this method the disulphoxide (III) at 180° (method *B*) afforded 51% of the dihydrochloride obtained in method *A*.

Finally, fusion of the disulphoxide (III) with ammonium benzenesulphonate alone at 250—255° (method *C*) yielded 81% of the dibenzenesulphonate identical with that obtained by method *A*. The aqueous mother-liquors afforded benzamidine-*p*-sulphonic acid (m. p. >360°) giving an intense amidine test (Fuller), completely soluble in sodium hydroxide solution (20%), and precipitated from this solution by hydrochloric acid (cf. Remsen and Muckenfuss, *Amer. Chem. J.*, 1896, **18**, 354). Disulphoxides are often regarded as reacting as the " thiolsulphonates " $R{\cdot}SO_2{\cdot}S{\cdot}R$ rather than as the symmetrical disulphoxides $R{\cdot}SO{\cdot}SO{\cdot}R$ (Gibson, Miller, and Smiles, *J.*, 1925, 1821; Gilman, Smith, and Parker, *J. Amer. Chem. Soc.*, 1925, **47**, 851; cf. however Fromm and Palma, *Ber.*, 1906, **39**, 3308; Hinsberg, *Ber.*, 1908, **41**, 2836, 4294; 1909, **42**, 1278). They are hydrolysed by alkali to a mixture of the disulphide and sulphinic acid (cf., *inter alia*, Pauly and Otto, *loc. cit.*; Bulmer and Mann, *J.*, 1945, 683); this has been variously postulated to proceed through the thiol (Otto and Rossing, *loc. cit.*), by hydrolytic fission (Zincke and Farr, *Annalen*, 1912, **391**, 58), through the sulphenic acid (Fromm, *loc. cit.*; Zincke, *Annalen*, 1914, **406**, 103), or by an oxidation–reduction mechanism (Zincke and Farr, *loc. cit.*), the overall reaction in every case being :

$$3R{\cdot}SO_2{\cdot}SR + 2H_2O \longrightarrow 4R{\cdot}SO_2H + RS{\cdot}SR \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The yields of di-*p*-amidinophenyl disulphide obtained by methods *A*, *B*, and *C*, however, all greatly exceed the theoretical figure calculated from reaction (2). It was shown by Halssig (*J. pr. Chem.*, 1897, **56**, 213) that the formation of disulphide and sulphonic acid from a sulphinic acid takes place, not only in an acidic environment, but also readily on warming the mixture in the presence of ammonia or by the action of heat on an ammonium sulphinate, according to reaction (1). Under the experimental conditions used, reactions (1) and (2) are thus consecutive and complementary, the net equation being (3) :

$$5R{\cdot}SO_2{\cdot}SR + 2H_2O \longrightarrow 3RS{\cdot}SR + 4R{\cdot}SO_2{\cdot}OH \quad . \quad . \quad . \quad . \quad . \quad (3)$$

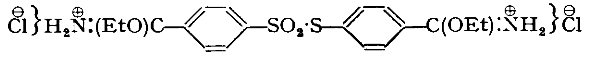
The expression (3) accounts satisfactorily for both the nature and the quantities of the two products obtained in methods *B* and *C*. The yields of diamidine obtained by method *A*, however, still exceed the theoretical amounts calculated from equation (3).

Disulphoxides are readily reduced to the corresponding disulphides by a variety of mild reducing agents (Hinsberg, *loc. cit.*; Smiles and Gibson, *loc. cit.*; Miller and Smiles, *J.*, 1925, 224) according to reaction (4); since ammonium thiocyanate, which at the reaction temperature (180°) exists as a mixture of thiourea, ammonia, hydrogen sulphide, and thiocyanic acid (Reynolds and Werner, *J.*, 1903, 1; Atkins and Werner, *J.*, 1912, 1172; Krall, *J.*, 1913, 1379), would be expected to possess reducing properties, direct reduction to the disulphide probably occurs during the reaction in method (*A*), the net reaction (5) being, in this case, a summation of (3) and (4). Calculation on this basis shows excellent agreement between the theoretical and experimental yields in method *A*.

$$2R{\cdot}SO_2{\cdot}SR + H_2 \longrightarrow 2R{\cdot}SO_2H + RS{\cdot}SR \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$4R{\cdot}SO_2{\cdot}SR + 3H_2 \longrightarrow 3RS{\cdot}SR + 2R{\cdot}SO_2{\cdot}OH + 2H_2O \quad . \quad . \quad . \quad . \quad (5)$$

Since it had so far proved impossible to obtain the desired compound (I), the Pinner method was next applied to di-*p*-cyanophenyl disulphoxide (method *F*). Reaction with alcoholic hydrogen chloride readily afforded a theoretical yield of (*diphenyl disulphoxide*)-4 : 4′-*di*(*carboxyimino ethyl ether*) *dihydrochloride* (V) and from this the crystalline *hemihydrate* of the free base. With ethanolic ammonia the imino-ether hydrochloride gave quantitatively the diamidine dihydrochloride obtained by method *A*. The extremely ready conversion of disulphoxides in alkaline solution into the disulphides and sulphinic acids (equation 1) has been noted by many workers (cf. Kharasch, Potempa, and Wehrmeister, *Chem. Reviews*, 1946, **39**, 328; Otto and Rossing, *loc. cit.*), as has their contrasting stability in acid (Zincke and Eismayer, *Ber.*, 1918, **51**, 751). After treatment with dry ammonia in ethanol at room temperature the disulphoxide (III) was recovered quantitatively even after two weeks, but interaction in ethylene glycol at 180° afforded, as sole product, 56% (calculated from equation 3) of di-*p*-cyanophenyl disulphide. The ready conversion of the imino-ether hydrochloride (IV) into the disulphide is thus surprising and must be occasioned by the labilising effect of the cationic iminium group on the thiolsulphinate system in (IV), especially in view of the weak donor ability of sulphur compared with oxygen (Gordy and Stanford, *J. Amer. Chem. Soc.*, 1940, **62**, 498; Copley, Marvel, and Ginsberg, *ibid.*, 1939, **61**, 3161).


(IV.)

The melting point of (diphenyl disulphide)-4 : 4'(-dicarboxyimino ethyl ether) dihydrochloride (268—270°) lies very close to that of the corresponding diamide (278°), and it was found that the action of heat (180°) on the former gave an excellent yield of the latter. By this reaction (diphenyl disulphoxide)-4 : 4'-di(carboxyimino ethyl ether) dihydrochloride afforded quantitatively *di*-p-*carbamylphenyl disulphoxide*. This decomposition (reaction 6) by heat or storage is mentioned by Pinner (*loc. cit.*; cf. Shriner and Neumann, *Chem. Reviews*, 1944, **35**, 357), and Derby (*loc. cit.*) describes the isolation of benzamide from benzimino ethyl ether hydrochloride.

$$\mathrm{R{\cdot}C(OEt){:}\overset{\oplus}{N}H_2}\}\overset{\ominus}{\mathrm{Cl}} \longrightarrow \mathrm{R{\cdot}CO{\cdot}NH_2 + EtCl} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Benzenesulphonates of imino-ethers appear not to have been described. Although *benzimino ethyl ether benzenesulphonate* was obtained in excellent yield as a crystalline solid, application of the same method to (IV) gave an uncrystallisable oil.

Ammonolysis of *N*-arylamidines to give the unsubstituted amidines according to equation (7) has been described by Pinner (*loc. cit.*; cf. Shriner and Neumann, *loc. cit.*) and by Oxley and Short (this vol., p. 449) and, since it occurs at a temperature lower than that required for the formation of an unsubstituted amidine from the corresponding cyanide, the possibility of obtaining (I) by this route, through the corresponding di-*N*-phenylamidino-compound was examined. Di-*p*-cyanophenyl disulphoxide and aniline benzenesulphonate (2 mols.) at 180° afforded a quantitative yield of a magnificent dark blue solid, which gave analytical figures for *di*-(p-N-*phenylamidinophenyl*) *disulphoxide dibenzenesulphonate* and showed solubilities in agreement with this structure. The material, softening at 100°, gave a blue solution in alcohol or acetone, from which it was reprecipitated unchanged by ether. Attempted preparation of the base by aqueous or alcoholic alkali was unsuccessful even after long refluxing. Ammonolysis of the blue material by gaseous ammonia, without a solvent or in ethylene glycol, at 180° for 6 hours gave only unchanged material.

$$\mathrm{R{\cdot}C({:}\overset{\oplus}{N}H_2){\cdot}NHR' + NH_3} \rightleftharpoons \mathrm{R{\cdot}C({:}\overset{\oplus}{N}H_2){\cdot}NH_2 + NH_2R'} \quad . \quad . \quad . \quad . \quad (7)$$

That the blue compound was not the corresponding disulphide derivative was shown by synthesis of the latter. Reaction of di-*p*-cyanophenyl disulphide and aniline benzenesulphonate at 220° gave *di*-(p-N-*phenylamidinophenyl*) *disulphide dibenzenesulphonate* as a white crystalline solid, m. p. 108°. Halssig (*loc. cit.*) reports that at 160—200° aniline toluene-*p*-sulphinate afforded a magnificent dark blue material which was physically and chemically similar to the blue product described above. Moreover, Halssig states that action of heat on the *p*-toluidine and *o*-toluidine salts of the same acid gave, respectively, a reddish-violet and a bluish-violet dye of very similar nature.

Heating a mixture of di-*p*-cyanophenyl disulphoxide and aniline did not give the blue dye, which was however obtained immediately by the addition of aniline benzenesulphonate to the melt. A mixture of diphenyl disulphoxide and aniline benzenesulphonate, when heated, also gave a deep-blue dye, and it was then found that a blue dye could also be produced from aniline benzenesulphonate alone by heating this to a higher temperature (250—300°) for a longer time. The nature of the blue dye was not further investigated.

In view of the ready conversion of disulphoxides into the corresponding disulphides and the resulting dependence on accurate analytical data, the ultra-violet absorption spectra of the compounds described above were determined (in alcohol) in order to investigate whether a generalisation capable of distinguishing between the two structures could be discovered.

Aromatic disulphides $(p\text{-R}\cdot C_6H_4\cdot S)_2$ (Table) have $\lambda_{max.}$ at 2410 A. when R = H or Me (cf. also Fox and Pope, *J.*, 1913, 1263; Lyons, *Nature*, 1948, **162**, 1004; Koch, this vol., p. 394), and the introduction of an unsaturated bond into the group R causes a bathochromic and hyperchromic displacement of +300—400 A. (Fig. 1).

FIG. 1.

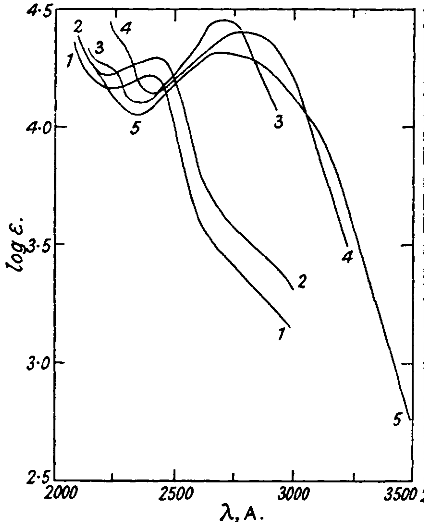


FIG. 2.

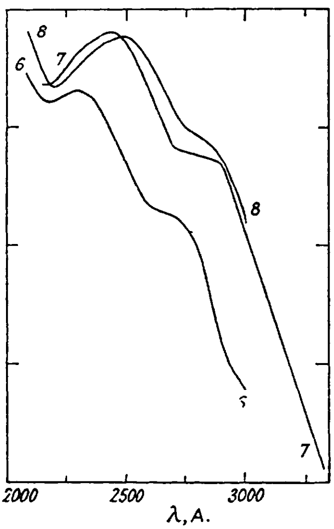
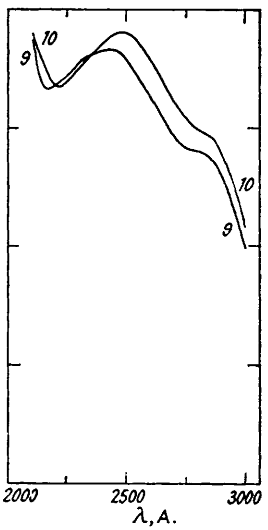


FIG. 3.



1. *Diphenyl disulphide.*—2. *Di-*p*-tolyl disulphide.*—3. *Di-*p*-cyanophenyl disulphide.*—4. *Di-*p*-amidinophenyl disulphide dibenzenesulphonate.*—5. (*Diphenyl disulphide*)*-4 : 4′-di*(*carboxyimino ethyl ether*) *dihydrochloride.*—6. *Diphenyl disulphoxide.*—7. *Di-*p*-cyanophenyl disulphoxide.*—8. (*Diphenyl disulphoxide*)*-4 : 4′-di*(*carboxyimino ethyl ether*) *hydrochloride.*—9. *Di-*p*-carbamylphenyl disulphoxide.*—10. *Diphenyl disulphoxide di*(*imino ethyl ether*).

The corresponding disulphoxides $p\text{-R}\cdot C_6H_4\cdot SO_2\cdot S\cdot C_6H_4\cdot \text{R-}p$ (Table), in which one sulphur atom is devoid of unshared electrons, have $\lambda_{max.}$ at 2300 A. when R = H, while the bathochromic and hyperchromic displacement caused by the introduction of an unsaturated centre into the group R of the disulphoxides is much smaller (+150 to 200 A.) than it is for the corresponding disulphides. The disulphoxides examined show a characteristic marked inflexion at 2720—2900 A. (Figs. 2 and 3).

Absorption spectra of disulphides, $(p\text{-R}\cdot C_6H_4\cdot S)_2$, *and disulphoxides,* $p\text{-R}\cdot C_6H_4\cdot SO_2\cdot S\cdot C_6H_4\cdot \text{R-}p$.

	Disulphide.		Disulphoxide.	
R =	$\lambda_{max.}$, A.	log $\varepsilon_{max.}$.	$\lambda_{max.}$, A.	log $\varepsilon_{max.}$.
H	2410	4·22	2300—2310 2720 *	4·15 3·60
Me	2420	4·29	—	—
NH_2,HCl	2540—2560 2900	4·21 3·91	—	—
CN	2670—2730	4·41	2430—2440 2910 *	4·40 3·85
$C{<}\substack{OEt\\NH}$	—	—	2490—2500 2830 *	4·40 3·99
$C{<}\substack{OEt\\NH_2Cl}$	2710—2750	4·31	2460—2480 2830 *	4·39 3·96
$C{<}\substack{NH_2\\NH_2Cl}$	2800—2840	4·38	—	—
$C{<}\substack{NH_2\\NH_2X}$ †	2800—2850	4·39	—	—
$CO\cdot NH_2$	—	—	2400—2440 2830 *	4·34 3·88

* Inflexion. † $X = C_6H_5\cdot SO_3$.

Examination of the ultra-violet absorption spectra thus not only affords valuable confirmatory evidence of the structure of (IV) but also makes it possible to distinguish readily between aromatic disulphides and disulphoxides.

EXPERIMENTAL.

*Di-*p*-cyanophenyl Disulphoxide.*—A solution of sodium *p*-cyanobenzenesulphinate (18·9 g., 0·1 mol.) in water (135 c.c.) was cooled to 0° and acidified strongly with concentrated hydrochloric acid (250 c.c.). The solution was set aside at 0° for 2 days, saturated with salt, and extracted with chloroform. Removal of solvent from the washed and dried (Na_2SO_4) chloroform extracts and crystallisation of the residue from alcohol gave white needles (7 g., 70%) of di-*p*-cyanophenyl disulphoxide, m. p. 158—159° (Cymerman, Koebner, and Short, *loc. cit.*, give m. p. 158—159°).

The original aqueous mother-liquors after extraction with chloroform were evaporated to half-bulk *in vacuo* and filtered, and the filtrate was treated with a solution of *p*-toluidine (7 g.) in hot dilute hydrochloric acid (5N.; 100 c.c.). Cooling to 0° gave white plates (4 g., 45%) of p*-toluidine* p*-cyanobenzenesulphonate* (Found : N, 9·55. $C_{14}H_{14}O_3N_2S$ requires N, 9·65%), m. p. 241°, undepressed on admixture with an authentic specimen (m. p. 241°) prepared from *p*-cyanobenzenesulphonyl chloride.

*Di-*p*-amidinophenyl Disulphide.*—*Method* A. (*a*) A mixture of di-*p*-cyanophenyl disulphoxide (4·5 g.) and ammonium thiocyanate (11 g., 10 mols.) was heated at 180° (bath temperature) for 3 hours with stirring. The cooled melt was then extracted with boiling water (300 c.c.) and filtered, and the filtrate basified at 0° (ice) with sodium hydroxide solution (10N.). The precipitated diamidine was collected on a funnel, washed with ice-water, and dissolved in the minimum amount of boiling hydrochloric acid (5N.). Cooling afforded white needles of *di-*p*-amidinophenyl disulphide dihydrochloride hemihydrate* (3·5 g., 82·5%), m. p. 316° (Found : N, 14·6; H_2O, 2·1. $C_{14}H_{16}N_4Cl_2S_2,\frac{1}{2}H_2O$ requires N, 14·6; H_2O, 2·35%). Drying at 120° gave the anhydrous *salt* (Found : C, 45·1; H, 4·35; N, 14·8, 14·75. $C_{14}H_{16}N_4Cl_2S_2$ requires C, 44·8; H, 4·3; N, 14·9%), m. p. 310—311°.

(*b*) The base precipitated from a fusion identical with that of (*a*) was dissolved in the minimum of hot aqueous benzenesulphonic acid. On cooling, *di-*p*-amidinophenyl disulphide dibenzenesulphonate* separated (6·75 g., 97%) as white needles, m. p. 253—254° (Found : C, 50·3; H, 4·2; N, 8·95. $C_{26}H_{26}O_6N_4S_4$ requires C, 50·5; H, 4·2; N, 9·05%).

(*c*) Equivalent quantities of the diamidine dihydrochloride and sodium picrate in the minimum of hot water were mixed and the quantitatively-formed yellow precipitate was recrystallised from aqueous 2-ethoxyethanol, giving the *dipicrate* as yellow needles, m. p. 257° (decomp). (Found : N, 18·35. $C_{26}H_{20}O_{14}N_{10}S_2$ requires N, 18·4%).

(*d*) Addition of excess of sodium benzoate solution to a solution of the diamidine dihydrochloride and recrystallisation of the white precipitate from methanol–ether afforded white crystals of the *dibenzoate dihydrate*, m. p. 250° (decomp.) (Found : C, 58·05, 58·1; H, 4·85, 5·05; N, 9·65, 9·5. $C_{28}H_{26}O_4N_4S_2,2H_2O$ requires C, 57·75; H, 5·15; N, 9·6%).

Method B. (*a*) A mixture of di-*p*-cyanophenyl disulphoxide (6 g.) and ammonium benzenesulphonate (7 g., 2 mols.) was stirred at 180° (bath) in an atmosphere of ammonia for 7 hours, the mixture becoming mobile after 2—3 hours. It was extracted with boiling water (400 c.c.), the filtrate basified at 0° (ice) with sodium hydroxide solution (10N.) and the base washed with ice-water on the filter. Dissolved in the minimum of hot dilute hydrochloric acid (5N.), it gave on cooling white needles of di-*p*-amidinophenyl disulphide dihydrochloride (2·3 g., 51%), m. p. 310—311° (decomp.), undepressed on admixture with the substance (m. p. 310—311°) from method *A* (Found : C, 44·8, 44·5, 45·1; H, 4·2, 4·05, 4·5; N, 14·35, 14·35%).

(*b*) An identical fusion, followed by dissolution of the base obtained in benzenesulphonic acid afforded the dibenzenesulphonate, m. p. 253—255° (4·8 g., 65%), as white needles (Found : C, 49·7; H, 4·7; N, 8·65%). It did not depress the m. p. of a sample (m. p. 253—254°) from method *A*.

(*c*) The dipicrate was obtained as very small yellow crystals (from 2-ethoxyethanol), m. p. 259° (decomp.) (Found : N, 17·75%), undepressed on admixture with the substance (m. p. 257°) from method *A*.

(*d*) The dibenzoate dihydrate was obtained as white crystals, m. p. 249° (decomp.) (Found : C, 58·1; H, 4·75; N, 9·33%). A mixed m. p. with the material (m. p. 250°) from method *A* was undepressed.

Method C. A mixture of di-*p*-cyanophenyl disulphoxide (6 g.) and ammonium benzenesulphonate (14 g., 4 mols.) was heated at 250—255° for 2 hours. The reaction mixture was extracted with boiling water, and the filtrate on cooling deposited white needles (6 g., 81%) of the dibenzenesulphonate, m. p. 250—254° (Found : C, 50·15; H, 4·4; N, 8·95%), undepressed on admixture with a sample (m. p. 253—254°) from method *A*. The aqueous mother-liquors on evaporation to dryness *in vacuo* left a solid residue (12 g.) from which ammonium benzenesulphonate was removed by extraction with cold water, leaving a white solid (2 g., 62·5%) crystallising from hot water in needles, m. p. >360°, of benzamidine-*p*-sulphonic acid (Found : N, 13·85. Calc. for $C_7H_8O_3N_2S$: N, 14·0%). Remsen and Muckenfuss (*Amer. Chem. J.*, 1896, **18**, 353) give m. p. >360°.

Method D. A solution of di-*p*-cyanophenyl disulphide (0·9 g.) in dry chloroform (20 c.c.) and dry alcohol (10 c.c.) was saturated with hydrogen chloride at 0° and set aside at room temperature for 8 days. Addition of dry ether gave (*diphenyl disulphide*)*-4 : 4'-di*(*carboxyimino ethyl ether*) *dihydrochloride* (1·4 g., 96%) as a white microcrystalline solid, m. p. (sealed tube) 268—270° (decomp.) after foaming at 120° (Found : N, 6·5. $C_{18}H_{22}O_2N_2Cl_2S_2$ requires N, 6·5%).

The dihydrochloride (1 g.) was suspended in dry alcohol (20 c.c.) saturated with ammonia at 0°, and set aside for 10 days. The alcoholic solution was poured into dry ether, the precipitate dissolved in dilute hydrochloric acid, and converted, *via* the base, into the diamidine dibenzenesulphonate (0·75 g., 53%), m. p. 252—255° (Found : N, 8·95%), which did not depress the m. p. of a sample (m. p. 253—254°) prepared by method *A*. This was converted, *via* the base, into the dihydrochloride, m. p. 310—311°

(Ashley, Barber, Ewins, Newbery, and Self, *loc. cit.*, give m. p. >300°), which did not depress the m. p. of the material (m. p. 310—311°) obtained by method *A*.

Method E. A mixture of di-*p*-cyanophenyl disulphide (2 g.) and ammonium thiocyanate (6 g.) was heated at 180° (bath) for 3 hours with stirring. Working-up as described above (method *A*) afforded white needles (1·6 g., 35%) of the dibenzenesulphonate, m. p. 253—255°, undepressed on admixture with a sample (m. p. 253—254°) prepared by method *A* (Found : N, 8·6, 8·5%).

The picrate crystallised from acetone–light petroleum (b. p. 40—60°) in yellow needles, m. p. 255° (decomp.) (Found : N, 18·1%), which showed no depression when mixed with the substance (m. p. 257°) from method *A*.

Method F. (*a*) A solution of di-*p*-cyanophenyl disulphoxide (6 g.) in chloroform (70 c.c.) and absolute alcohol (40 c.c.) was treated with dry hydrogen chloride at 0°, set aside at room temperature for 5 days, and then shaken for 6 hours. Addition of dry ether afforded (*diphenyl disulphoxide*) 4 : 4′-*di*(*imino diethyl ether*) *dihydrochloride* (9·2 g., 100%) as a white solid, m. p. (sealed tube) 225—230° (decomp.) after foaming at 120°, and forming a meniscus at 275—280° (Found: C, 45·9; H, 4·9; N, 6·25. $C_{18}H_{22}O_4N_2Cl_2S_2$ requires C, 46·5; H, 4·7; N, 6·0%).

(*b*) A mixture of this dihydrochloride (0·5 g.), anhydrous potassium carbonate (0·5 g.), and chloroform (50 c.c.) was shaken with water (25 c.c.), and the chloroform layer separated. The aqueous phase was extracted with chloroform, and the combined extracts dried (Na_2SO_4). Removal of solvent to small bulk and addition of light petroleum (b. p. 40—60°) afforded white cubes of (*diphenyl disulphoxide*)-4 : 4′-*di*(*carboxyimino ethyl ether*) *hemihydrate*, m. p. 220° (decomp.) (Found : C, 53·9; H, 5·6; N, 6·75, 6·55. $C_{18}H_{20}O_4N_2S_2,\frac{1}{2}H_2O$ requires C, 53·9; H, 5·3; N, 7·0%).

(*c*) A solution of the dihydrochloride obtained in (*a*) above (4·5 g.) in absolute alcohol (50 c.c.) saturated with ammonia at 0° was allowed to stand for 6 days. Addition of ether gave the crude diamidine dihydrochloride (4·0 g., 100%) which after purification *via* the base had m. p. 310—311°, undepressed on admixture with the compound (m. p. 310—311°) from method *A*. This was converted into the dibenzenesulphonate, m. p. 253—254° (Found : C, 50·1; H, 4·6; N, 8·95%) which showed no depression with the compound (m. p. 253—254°) from method *A*.

Di-p-*carbamylphenyl Disulphide*.—A small quantity of diphenyl disulphide 4 : 4′-di-imino diethyl ether dihydrochloride was heated at 180° (bath) for 1 hour. The residue, crystallised from acetic acid, gave white needles of di-*p*-carbamylphenyl disulphide, m. p. 276—277°. A mixed m. p. with an authentic specimen (McClelland and Warren, *J.*, 1930, 1102; m. p. 278°) gave no depression.

Di-p-*carbamylphenyl Disulphoxide*.—Heated at 180° (bath) for 1 hour, the disulphoxide di-iminoether dihydrochloride (0·5 g.) afforded 0·48 g. (100%) of *di*-p-*carbamylphenyl disulphoxide* as a white microcrystalline solid, m. p. 225—230° (decomp.), forming a meniscus at 275—280° (Found : N, 8·35. $C_{14}H_{12}O_4N_2S_2$ requires N, 8·35%).

Action of Ammonia on Di-p-*cyanophenyl Disulphoxide*.—A solution of di-*p*-cyanophenyl disulphoxide (0·5 g.) in ethylene glycol (10 c.c.) was kept at 180° for 2 hours in an atmosphere of ammonia. The solution was cooled, poured into water, and extracted with chloroform. Removal of solvent from the dried chloroform extracts afforded a residue (0·15 g.) which when purified by sublimation (0·01 mm.) and crystallisation from chloroform–light petroleum (b. p. 40—60°) had m. p. 165—168°, undepressed on admixture with di-*p*-cyanophenyl disulphide (m. p. 172—173°). A mixture with the starting material (m. p. 157—158°) gave a 30° depression in m. p.

Di-(p-N-*phenylamidinophenyl*) *Disulphoxide Dibenzenesulphonate*.—A mixture of di-*p*-cyanophenyl disulphoxide (6 g.) and aniline benzenesulphonate (10 g., 2 mols.) was heated at 180° (bath) for 2 hours, the mixture becoming mobile after 0·5 hour and then viscous after 1·4 hours. The cooled reaction mixture, recrystallised from alcohol–ether, gave a deep-blue *salt* (16 g., 100%), softening at 100° (Found : N, 7·0. $C_{38}H_{34}O_8N_4S_4$ requires N, 7·0%). It was soluble in methanol or acetone, moderately soluble in alcohol, sparingly soluble in *iso*propanol or water, and insoluble in ether.

Di-(p-N-*phenylamidinophenyl*) *Disulphide Dibenzenesulphonate*.—A mixture of di-*p*-cyanophenyl disulphide (0·1 g.) and aniline benzenesulphonate (0·38 g.) was heated at 220° (bath) for 2 hours. Extraction with boiling water afforded, on cooling, white prisms of the *dibenzenesulphonate*, m. p. 108° (Found : N, 6·85, 6·85. $C_{38}H_{34}O_6N_4S_4$ requires N, 7·25%).

Benzimino Ethyl Ether Benzenesulphonate.—Equivalent quantities of the benzimino-ether hydrochloride and potassium carbonate in the minimum amount of water were mixed and the free base was at once extracted with ether. The dried (Na_2SO_4) ethereal solution was added to a solution of benzenesulphonic acid in methanol. Cooling gave colourless needles, m. p. 137°, of *benzimino ethyl ether benzenesulphonate* (Found : N, 4·6. $C_{15}H_{17}O_4NS$ requires N, 4·55%).

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