11. *Carboxylic Acid Derivatives of 4 : 4′-Diaminodiphenylsulphone.*

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The object of this work was the preparation of a series of carboxylic acid derivatives of 4 : 4′-diaminodiphenylsulphone by insertion of dicarboxylic acid side-chains into the amino-groups. Some of these retain the chemotherapeutic activity of the sulphone, and yield injectable soluble salts. The corresponding cyclic imides were also obtained, and yielded the carboxylic acids on mild hydrolysis.

The isolation of 4 : 4′-diaminodiphenylsulphone as a by-product in the modern process of manufacture of *p*-aminobenzenesulphonamide led to the observation that the sulphone is much the more effective of the two in experimental pneumococcus infections (Buttle, Stephenson, Smith, Dewing, and Foster, *Lancet*, 1937, i, 1331), but its rather marked toxicity, and its insolubility over the range of p_H permissible for injection, make it unsuitable for clinical use. Certain Schiff's bases have considerably lower toxicity and unimpaired curative action (Wellcome Foundation, Ltd., Henry, and Gray, B.P. 419,265); ready solubility is attained when the sulphone is converted into monoamides of dicarboxylic acids, which form salts of low toxicity and useful pharmacological activity.

Several methods were used in preparing these amides. Those of the higher aliphatic dibasic acids were not obtained by heating the acid and the sulphone together; mixtures of products resulted, which could not be separated. This is probably to be attributed to prior formation of the acid anhydrides, since it has been shown by Carothers and co-workers (*J. Amer. Chem. Soc.*, 1933, **55**, 5023) that adipic anhydride and higher homologues are polymers with molecular weights of 3000 to 5000, and react with bases to give mixtures of products. A similar difficulty was experienced when the anhydrides themselves were employed. At the temperatures here used, also, the mixtures may be complicated by the presence of the imides; from succinic anhydride, which is monomeric, a mixture of amide (I; $n = 2$) and imide (II) was formed.

(I.) $SO_2(C_6H_4\cdot NH\cdot CO\cdot[CH_2]_n\cdot CO_2H)_2$ $\qquad$ $SO_2\left(C_6H_4\cdot N<\begin{matrix}CO\text{—}CH_2\\CO\text{—}CH_2\end{matrix}\right)_2$ (II).

(III.) $C_6H_4<\begin{matrix}CO\\CO\end{matrix}>N\cdot C_6H_4\cdot SO_2\cdot C_6H_4\cdot NH_2$ $\qquad$ $SO_2\left(C_6H_4\cdot N<\begin{matrix}CO\\CO\end{matrix}>C_6H_4\right)_2$ (IV.)

(V.) $HO_2C\cdot C_6H_4\cdot CO\cdot NH\cdot C_6H_4\cdot SO_2\cdot C_6H_4\cdot NH_2$

(VI.) $SO_2(C_6H_4\cdot NH\cdot CO\cdot C_6H_4\cdot CO_2H)_2$ $\qquad$ $C_6H_4<\begin{matrix}CO\cdot NH\cdot C_6H_4\\CO\cdot NH\cdot C_6H_4\end{matrix}>SO_2$ (VII.)

From phthalic anhydride, the mono- and the bis-imide (III and IV) were obtained in good yield by heating the requisite molecular proportion with the sulphone. By hydrolysis with aqueous alkali one of

the imide rings is opened, and the other broken off to leave the original amino-group, so that the monoimide (III) and the bisimide (IV) under these conditions both yield the monoamide (V). By milder hydrolysis, (IV) gives the bisamide (VI). The imides were also obtained by heating the sulphone with acid or neutral phthalic esters. (III) gives a diazo-reaction and so cannot have the alternative structure (VII); it is precipitated unchanged from hydrochloric acid solution on dilution with water, showing that the amino-group does not arise through hydrolysis during the test.

Partial hydrolysis, on the same lines, of 4 : 4′-*biscarbethoxyformamidodiphenylsulphone*, made by heating with ethyl oxalate, gave the analogous mono- and bis-carboxyformamido-derivatives. Esters of the higher aliphatic dibasic acids, like the anhydrides, gave products difficult to purify, and their amides were best prepared by the action of the ester chlorides upon the sulphone in presence of acid-binding agents.

Camphoric anhydride reacted more slowly than phthalic anhydride; in this case the bisimide was isolated. Similar reactions appear to occur with pimelic, maleic, malic, mucic, glutamic, and quinolinic acids, and the products are being investigated.

The toxicity and protective action of the compounds have been tested on mice by Dr. Stephenson of the Wellcome Physiological Research Laboratories, and the results are shown in the table. In streptococcal infections the activity is expressed in terms of that of *p*-aminobenzenesulphonamide, or for Nos. 5 and 8 of disodium *p*-(γ-phenylpropylamino)benzenesulphonamide αγ-disulphonate; in pneumococcal and staphylococcal infections of 2-(*p*-aminobenzenesulphonamido)pyridine; Nos. 1—4 and 8—12 were administered in 100 mg. doses to uninfected mice and caused no toxic symptoms.

No.	Name.	Activity in infections due to Streptococci.	Pneumococci.	Staphylococci.
1	4-Amino-4′-carboxyformamidodiphenylsulphone	0·1	0·34	10 mg. inactive
2	4 : 4′-Biscarbethoxyformamidodiphenylsulphone	1·0	trace	trace
3	4 : 4′-Biscarboxyformamidodiphenylsulphone	1·0	1·0	10 mg. inactive
4	4 : 4′-Biscarboxyacetamidodiphenylsulphone	0·1	0·1	—
5	4 : 4′-Bis-β-carboxypropionamidodiphenylsulphone	1·0	—	—
6	4 : 4′-Bis-succinimidodiphenylsulphone	trace	—	—
7	4 : 4′-Bis-δ-carbethoxyvaleramidodiphenylsulphone	somewhat <1	—	—
8	Disodium bis-δ-carboxyvaleramidodiphenylsulphone	5·0	1·0	—
9	4-Amino-4′-phthalimidodiphenylsulphone	inactive	inactive	inactive
10	4 : 4′-Bisphthalimidodiphenylsulphone	,,	,,	,,
11	4-Amino-4′-*o*-carboxybenzamidodiphenylsulphone	1·0	0·1—0·3	0·1
12	4 : 4′-Bis-*o*-carboxybenzamidodiphenylsulphone	0·01	trace	10 mg. inactive

Experimental.

4-*Amino*-4′-*carboxyformamidodiphenylsulphone.*—4 : 4′-Biscarbethoxyformamidodiphenylsulphone (8·0 g.) was added to 2·5% sodium hydroxide solution (87 c.c.) and heated over a gauze. After 6 minutes, when solution was complete, water (300 c.c.) was added, and the whole immediately cooled, since heating for a longer time gave rise to a precipitate of 4 : 4′-diaminodiphenylsulphone. The solution, filtered from a trace of insoluble matter, was acidified with dilute hydrochloric acid; the precipitated solid was ground with 10% hydrochloric acid (100 c.c.), washed with water, dried, and twice crystallised from aqueous acetone, yielding the *amino-acid* (4 g.), which frothed at 195° (Found: C, 51·5; H, 3·7; N, 8·7; S, 10·1. $C_{14}H_{12}O_5N_2S$ requires C, 52·5; H, 3·8; N, 8·7; S, 10·0%).

4 : 4′-*Biscarbethoxyformamidodiphenylsulphone.*—4 : 4′-Diaminodiphenylsulphone (7·5 g.; 1 mol.) and ethyl oxalate (17·5 g.; 4 mols.) were refluxed for 1½ hours, by which time the whole was practically solid. The cooled mass was ground and washed successively with ether, 10% hydrochloric acid (60 c.c.), and water; the product (11·7 g.), thrice crystallised from aqueous dioxan, yielded the 4 : 4′-*bis-ethyl* ester, m. p. 257° (Found: C, 53·6; H, 4·7; N, 6·4; S, 6·8. $C_{20}H_{20}O_8N_2S$ requires C, 53·5; H, 4·5; N, 6·2; S, 7·1%).

4 : 4′-*Biscarboxyformamidodiphenylsulphone.*—4 : 4′-Biscarbethoxyformamidodiphenylsulphone (16·5 g.) was added to ethyl-alcoholic potassium hydroxide (1240 c.c. of 0·5%); the solid dissolved and a precipitate immediately appeared. To ensure complete reaction, the whole was heated for 15 minutes on the water-bath. After cooling, the precipitate was collected, washed with alcohol, and extracted with cold water (1250 c.c.). The filtered aqueous solution was acidified with dilute hydrochloric acid to yield a white precipitate, which, after two recrystallisations from 50% aqueous acetic acid, gave the pure *bis-acid* (7·6 g.). This frothed at 188° to a solid, m. p. 275° (approx.) (Found: C, 49·6; H, 3·5; N, 7·3; S, 7·8. $C_{16}H_{12}O_8N_2S$ requires C, 49·0; H, 3·1; N, 7·1; S, 8·1%).

4 : 4′-*Biscarboxyacetamidodiphenylsulphone.*—Crude malonyl chloride (25 g., from 40 g. of malonic acid), dissolved in cold dioxan (40 c.c.), was slowly run into a solution of 4 : 4′-diaminodiphenylsulphone (20 g.) in dioxan (250 c.c.) at 65°. A bulky yellow precipitate formed during the addition, which was completed in ½ hour. After standing overnight, the precipitate was collected, washed with cold water, triturated with 10% hydrochloric acid (100 c.c.), and finally washed with water. The crude product was extracted with boiling water (1 l.); the filtrate, on cooling, deposited colourless needles of the *bis-acid* containing one molecule of

water of crystallisation (4·6 g.) (Found : C, 50·1; H, 4·25; N, 6·8; S, 7·2; equiv., by titration with NaOH, 225. $C_{18}H_{16}O_8N_2S,H_2O$ requires C, 49·4; H, 4·1; N, 6·4; S, 7·3%; equiv., 219). The crystals frothed at 183° with evolution of carbon dioxide to give 4 : 4′-bisacetamidodiphenylsulphone, m. p. 278° (Fromm and Wittmann, *Ber.*, 1908, **41**, 2270, give m. p. 280°).

4 : 4′-*Bis*-β-*carboxypropionamidodiphenylsulphone.*—An intimate mixture of 4 : 4′-diaminodiphenylsulphone (1·24 g.; 1 mol.) and freshly crystallised succinic anhydride (1 g.; 2 mols.) was heated at 170° for 3 hours, and the product extracted with boiling alcohol. A small insoluble portion (0·07 g.), which proved to be the imide (see below), was removed. Yield 1·62 g., sparingly soluble in water or acetone, m. p. 227°, resolidifying and remelting at the m. p. of the imide (Found : C, 53·6; H, 4·6; N, 6·3; S, 7·5. $C_{20}H_{20}O_8N_2S$ requires C, 53·6; H, 4·5; N, 6·3; S, 7·15%).

4 : 4′-*Bis-succinimidodiphenylsulphone.*—4 : 4′-Diaminodiphenylsulphone (1·24 g.) and succinic anhydride (1 g.) were heated together at 225° for 2 hours. The product was finely ground and shaken with acetone until the m. p. became constant; yield 1·35 g., insoluble in water, chloroform, and cold dilute alkali, m. p. 343° (Found : C, 58·5; H, 4·0; N, 6·8; S, 7·8. $C_{20}H_{16}O_6N_2S$ requires, C 58·3; H, 3·9; N, 6·8; S, 7·8%).

4 : 4′-*Bis*-δ-*carbethoxyvaleramidodiphenylsulphone.*—δ-Carbethoxyvaleryl chloride (21 c.c.) was added gradually with continuous stirring to 4 : 4′-diaminodiphenylsulphone (13·6 g.) dissolved in acetone (70 c.c.) containing precipitated calcium carbonate (10·9 g.) in suspension, and the mixture heated on the water-bath under reflux for 1½ hours. The acetone was removed under diminished pressure, and the oily residue macerated with cold water until crisp and recrystallised from acetone; yield 10·1 g., m. p. 139° (Found : C, 60·0; H, 6·4; N, 5·2. $C_{28}H_{36}O_8N_2S$ requires C, 60·0; H, 6·5; N, 5·0%). This was hydrolysed to the sodium salt of the free acid, for pharmacological testing, in the same way as the azelayl derivative (below).

4 : 4′-*Bis*-η-*carbomethoxyoctamidodiphenylsulphone.*—4 : 4′-Diaminodiphenylsulphone (4·2 g.) dissolved in acetone (22 c.c.) containing calcium carbonate (3·4 g.) in suspension, was treated gradually with η-carbomethoxyoctoyl chloride (7·4 g.), and the mixture heated under reflux for 2 hours. It was worked up in the same way as the adipic derivative; yield of first crop, 3·7 g., m. p. 122° (Found : C, 62·2; H, 7·2; N, 5·1; S, 5·2. $C_{32}H_{44}O_8N_2S$ requires C, 62·3; H, 7·2; N, 4·5; S, 5·2%).

4 : 4′-*Bis*-η-*carboxyoctamidodiphenylsulphone.*—4 : 4′-Bis-η-carbomethoxyoctamidodiphenylsulphone (1 g.) was heated on the water-bath under reflux with N-sodium hydroxide (3·25 c.c.) for several hours. The solution was filtered from a trace of unchanged ester, cooled in ice, and acidified slightly with dilute hydrochloric acid. The precipitated *acid* (0·6 g.) was dissolved in alcohol, the solution cooled in ice, and water added gradually with continual stirring; yield 0·44 g., m. p. 134° (Found : C, 61·1; H, 6·9; N, 4·9; S, 5·5. $C_{30}H_{40}O_8N_2S$ requires C, 61·2; H, 6·9; N, 4·8; S, 5·5%).

4-*Amino*-4′-*phthalimidodiphenylsulphone.*—(*a*) Phthalic anhydride (4·5 g.; 1 mol.) was added to a solution of 4 : 4′-diaminodiphenylsulphone (7·5 g.; 1 mol.) in pyridine (5·0 g.). The whole, heated for 1½ hours on the water-bath, became solid. After cooling, the product was ground with 10% hydrochloric acid (100 c.c.), and the insoluble portion collected, washed with water, dried, and thrice crystallised from dioxan, giving a white product (7·4 g.), m. p. 256—258° (Found : C, 63·3; H, 3·9; N, 8·0; S, 8·5. $C_{20}H_{14}O_4N_2S$ requires C, 63·3; H, 3·7; N, 7·4; S, 8·5%).

(*b*) 4 : 4′-Diaminodiphenylsulphone (7·5 g.) and phthalic anhydride (4·5 g.; 1 mol.), finely ground and intimately mixed, were heated at 200° for several hours, 10·7 g. of the same imide being obtained almost pure, m. p. 258—261°; after one recrystallisation from dioxan it melted at 262°.

(*c*) 4 : 4′-Diaminodiphenylsulphone (2·5 g.; 1 mol.), methyl hydrogen phthalate (1·8 g.; 1 mol.), and anhydrous zinc chloride (0·3 g.) were heated on the water-bath for 4 hours. The cooled mass was treated as in (*a*) to yield the required product.

(*d*) 4 : 4′-Diaminodiphenylsulphone (2·5 g.; 1 mol.) was heated with methyl hydrogen phthalate (3·6 g.; 2 mols.) for 5 hours on the steam-bath, and the cooled product treated as in (*a*) to give the pure *mono-imide* (3·0 g.).

4 : 4′-*Bisphthalimidodiphenylsulphone.*—(*a*) 4 : 4′-Diaminodiphenylsulphone (7·6 g.; 1 mol.) was heated for 2 hours on the steam-bath with a solution of phthalic anhydride (9·0 g.; 2 mols.) in pyridine (6 g.). The cooled mass was treated as in (*a*) above and the *bis-imide* (3·7 g.), m. p. 310°, was obtained after crystallisation from ethylene chlorohydrin (Found : C, 66·1; H, 3·2; N, 5·4; S, 6·3. $C_{28}H_{16}O_6N_2S$ requires C, 66·1; H, 3·2; N, 5·5; S, 6·3%).

A better yield was obtained by heating 4 : 4′-diaminodiphenylsulphone (7·6 g.; 1 mol.), phthalic anhydride (9·0 g.; 2 mols.), and pyridine (21 g.) under reflux for 1 hour. The bis-imide (12·3 g.), m. p. 311—313°, was obtained by treating the product as above.

(*b*) 4 : 4′-Diaminodiphenylsulphone (1·2 g.; 1 mol.) was heated with methyl hydrogen phthalate (3·6 g.; 4 mols.) for 6½ hours at 100°, followed by 3 hours' heating at 190—205°. The cooled melt was ground with 10% hydrochloric acid (30 c.c.); the insoluble portion was washed, dried, and recrystallised from ethylene chlorohydrin to yield the bis-imide (1·5 g.), m. p. 313—315°.

Boiling 50% acetic acid or N/2-sodium acetate had no effect on the bis-imide.

(*c*) 4 : 4′-Diaminodiphenylsulphone (14·9 g.) and ethyl phthalate (23·6 c.c.; 2 mols.) were boiled for 5 hours, the alcohol formed being distilled off through a downward condenser. The solid product obtained was

extracted with boiling acetone–alcohol (1 : 1), and the insoluble portion crystallised from pyridine (55 c.c.) and then from ethylene chlorohydrin (140 c.c.); yield, 16·7 g. (Found : C 66·2; H, 3·4; N, 5·5; S, 6·1%).

4-Amino-4′-o-carboxybenzamidodiphenylsulphone.—(*a*) 4-Amino-4′-phthalimidodiphenylsulphone (4·6 g.) was heated for 25 minutes on the steam-bath with 5% aqueous sodium hydroxide (115 c.c.). The resultant clear solution was cooled, diluted with water (250 c.c.), and acidified with dilute hydrochloric acid. The precipitate was dissolved in 2% aqueous sodium hydroxide, decolourised with charcoal, and reprecipitated from the cold clear solution with dilute mineral acid. The dried precipitate was *4-amino-4′-o-carboxybenzamidodiphenylsulphone* (3·0 g.) (Found : C, 60·4; H, 4·0; N, 7·3; S, 7·7; equiv. by titration with NaOH, 391. $C_{20}H_{16}O_5N_2S$ requires C, 60·6; H, 4·1; N, 7·1; S, 8·1%; equiv., 396).

The solid frothed at 176° to a liquid, which on continued heating resolidified to give the monoimide. The latter is also obtained by prolonged treatment of the former with boiling water.

(*b*) 4 : 4′-Bisphthalimidodiphenylsulphone (0·5 g.) was boiled for 20 minutes with N/10-sodium hydroxide (60 c.c.); the resultant clear solution was, after cooling, acidified with dilute hydrochloric acid to yield the amino-acid (0·4 g.).

On very slow heating of 4-amino-4′-*o*-carboxybenzamidodiphenylsulphone, no frothing was observable and melting occurred at 248—250°, *i.e.*, at the m. p. of 4-amino-4′-phthalimidodiphenylsulphone.

4 : 4′-Bis-o-carboxybenzamidodiphenylsulphone.—4 : 4′-Bisphthalimidodiphenylsulphone (6·5 g.) was refluxed for ½ hour with 0·5% ethyl-alcoholic potassium hydroxide (570 c.c.). The resultant clear liquid was immediately diluted with water to 3000 c.c. and cooled. Acidification with dilute hydrochloric acid gave a white precipitate, which after one recrystallisation from aqueous acetone yielded the required product (5·6 g.) (Found : C, 61·6; H, 3·9; N, 5·3; S, 5·6. $C_{28}H_{20}O_8N_2S$ requires C, 61·7; H, 3·7; N, 5·1; S, 5·9%). This on moderately rapid heating melted at 182°, frothed, and gave a solid, m. p. 300°—this was 4 : 4′-bisphthalimidodiphenylsulphone. On very slow heating, no frothing was apparent, only a slight softening at approximately 185° with final melting at 304—307°.

4 : 4′-Biscamphorimidodiphenylsulphone.—4 : 4′-Diaminodiphenylsulphone (7·5 g.), camphoric anhydride (11·0 g.; 2 mols.), and pyridine (6 c.c.) were boiled together under reflux for 14 hours. When boiled for a shorter time (1 hour), little reaction took place. The thick syrup obtained was freed from pyridine by steam-distillation and then boiled with alcohol, which caused it to crystallise (1·2 g.). The solid was purified by solution in cold chloroform and gradual addition of alcohol; m. p. 375°. It formed short columns, almost insoluble in alcohol, acetone, dioxan or water, but readily soluble in chloroform or pyridine (Found : C, 65·5; H, 6·2; N, 4·7; S, 5·2. $C_{32}H_{36}O_6N_2S,\frac{1}{2}H_2O$ requires C, 65·6; H, 6·4; N, 4·8; S, 5·5%).

Malonyl Monochloride.—It was not found possible to prepare the acid chloride by Staudinger and Ott's method (*Ber.*, 1908, **41**, 2211). The following proved to be the best method: dry malonic acid (8 g.; 1 mol.) and pure thionyl chloride (9·7 c.c.; 1·5 mols.) were heated for 3—4 hours at 45—50°. The excess of thionyl chloride was removed from the brown mass in a vacuum at room temperature. The resultant greenish-brown solid was extracted three times with cold chloroform; addition of light petroleum precipitated crystals of the acid chloride (3 g.), m. p. 62—64° (decomp.).

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