41. *Compounds Related to 4 : 4′-Diaminodiphenyl Sulphone. p-Arylsulphonylphenylethylamines and Related Compounds.*

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Various *p*-arylsulphonylphenylalanines and related acids have been synthesised, but they could not be decarboxylated satisfactorily. 1-*p*-Arylsulphonylphenylethylamines and related amines were best obtained from the corresponding ketones by the Leuckart reaction, whilst the 2-substituted ethylamines were prepared from the appropriate arylpropionic acids by the Curtius azide rearrangement.

In continuation of previous work (*J.*, 1945, **14**, 468; 1947, **52**; 1948, **525**, 528) on the synthesis of compounds related to 4 : 4′-diaminodiphenyl sulphone, we decided to investigate typical diaryl and aryl alkyl sulphones containing an aminoalkyl group. Apart from isolated examples, for instance, 1- and 2-*p*-methylsulphonylphenylethylamines (Fuller, Tonkin, and Walker, *J.*, 1945, 633), few of these compounds have been investigated.

Our first exploratory route was to convert the previously described (*J.*, 1948, 601) *p*-arylsulphonylbenzaldehydes through the corresponding *azlactones* into the p-*arylsulphonylphenylalanines*. We could not, however, decarboxylate the amino-acids at all satisfactorily. The 2-*p*-arylsulphonylethylamines were finally prepared by the route : benzaldehyde ⟶ cinnamic acid ⟶ arylpropionic acid ⟶ ethylamine, using the Curtius azide rearrangement for the final step. The method was very successful in spite of the many intermediate stages involved.

1-*p*-Arylsulphonylethylamines and related amines were prepared in good yield from the appropriate ketones by Leuckart's method (*Ber.*, 1885, **18**, 2341), as modified by Ingersoll (*J. Amer. Chem. Soc.*, 1936, **58**, 1808).

Minor differences in technique were often employed, especially when substituents present were known to be sensitive towards the reagents generally used; these differences are detailed in the experimental section.

We were particularly interested in p-*sulphamylphenylalanine*,

$$p\text{-}NH_2\cdot SO_2\cdot C_6H_4\cdot CH_2\cdot CH(NH_2)\cdot CO_2H$$

and the related amines, since Schaffer (*Proc. Soc. Exp. Biol. Med.*, 1938, **37**, 648) had reported that the above amino-acid had a greater antistreptococcal activity than sulphanilamide. We were unable to find any description of the compound in the literature and we accordingly synthesised the amino-acid and the related 1- and 2-p-*sulphamylphenylethylamines*. It was surprising to find that the amino-acid and both these amines had little or no activity against *Strep. hæmolyticus in vitro*, *i.e.*, no growth inhibition at a dilution of 1 : 1000. Another noteworthy result was that 4-p-*aminophenylsulphonylphenylalanine*, $p\text{-}NH_2\cdot C_6H_4\cdot SO_2\cdot C_6H_4\cdot CH_2\cdot CH(NH_2)\cdot CO_2H\text{-}p$, was similarly inactive.

Experimental.

4-p-*Nitrophenylsulphonylbenzaldehyde*.—4-Nitro-4′-methyldiphenyl sulphone, m. p. 170—171°, prepared by oxidation of the sulphide with 30% hydrogen peroxide in acetic acid at 100°, was oxidised with chromic oxide in acetic acid–acetic anhydride–sulphuric acid as described previously (Burton and Hu, *J.*, 1948, 602). The intermediate 4-p-*nitrophenylsulphonylbenzylidene diacetate*, colourless prisms from 95% alcohol, m. p. 150—151° (Found : S, 7·5. $C_{17}H_{15}O_8NS$ requires S, 8·1%), was hydrolysed to the free *aldehyde* (74% yield), colourless prisms from 80% acetic acid, m. p. 214—215° (Found : C, 53·0; H, 3·3; N, 4·5; S, 10·9. $C_{13}H_9O_5NS$ requires C, 53·6; H, 3·1; N, 4·8; S, 11·0%).

4-2′ : 5′-*Dihydroxyphenylsulphonylbenzaldehyde*.—Finely powdered 2 : 5-dihydroxy-4′-cyanodiphenyl

sulphone (6 g.), prepared from *p*-benzoquinone and *p*-cyanobenzenesulphinic acid, was added to a Stephen's reagent from 9 g. of anhydrous stannous chloride in 130 c.c. of ether. The mixture was shaken mechanically for 7 hours, kept overnight, and the insoluble product decomposed with hot dilute hydrochloric acid. Crystalline material separated from the cooled solution; recrystallisation from dilute alcohol gave the *aldehyde* (5 g.), m. p. 200—201°, in nearly colourless prisms (Found : C, 55·8; H, 3·8. $C_{13}H_{10}O_5S$ requires C, 56·1; H, 3·6%).

5-Keto-2-phenyl-4-p-methylsulphonylbenzylidene-4 : 5-dihydro-oxazole.—*p*-Methylsulphonylbenzaldehyde (6 g.; 0·033 mol.), hippuric acid (7 g.; 0·033 mol.), fused sodium acetate (8 g.), and acetic anhydride (30 c.c.) were heated on the steam-bath, with frequent shaking, for 1 hour. The mixture was then decomposed with hot water, filtered hot, and the residual crystalline material washed repeatedly with boiling water. As partial hydrolysis appeared to occur, the *product* (5 g.) was crystallised from acetic anhydride; it separated in yellow prisms, m. p. 186—187° (Found : C, 62·0; H, 4·0; N, 4·0. $C_{17}H_{13}O_4NS$ requires C, 62·4; H, 4·0; N, 4·3%).

Hydrolysis with warm dilute sodium hydroxide afforded *α-benzamido-*p*-methylsulphonylcinnamic acid*, m. p. 245—246° (decomp.), when crystallised from acetic acid (Found : C, 59·5; H, 4·5. $C_{17}H_{15}O_5NS$ requires C, 59·1; H, 4·3%).

The following were similarly prepared. *5-Keto-2-phenyl-4-*p*-phenylsulphonylbenzylidene-4 : 5-dihydro-oxazole* (73% yield), yellow prisms from acetic anhydride, m. p. 222—223° (Found : N, 3·4. $C_{22}H_{15}O_4NS$ requires N, 3·6%); *α-benzamido-*p*-phenylsulphonylcinnamic acid*, m. p. 226—227° from dilute acetic acid (Found : C, 64·6; H, 4·3. $C_{22}H_{17}O_5NS$ requires C, 64·9; H, 4·2%); *5-keto-2-phenyl-4-4′-p-chlorophenylsulphonylbenzylidene-4 : 5-dihydro-oxazole* (60% yield), m. p. 212—213°, orange-red prisms from benzene (Found : C, 62·5; H, 3·4. $C_{22}H_{14}O_4NClS$ requires C, 62·3; H, 3·3%); *5-keto-2-phenyl-4-4′-*p*-methoxyphenylsulphonylbenzylidene-4 : 5-dihydro-oxazole* (90% yield), yellow prisms from acetic anhydride, m. p. 196—197° (Found : C, 65·3; H, 4·1. $C_{23}H_{17}O_5NS$ requires C, 65·9; H, 4·1%); *5-keto-2-phenyl-4-4′-*p*-nitrophenylsulphonylbenzylidene-4 : 5-dihydro-oxazole* (58%), m. p. 270—272° (Found : C, 60·8; H, 3·4; N, 6·6; S, 7·4. $C_{22}H_{14}O_6N_2S$ requires C, 60·8; H, 3·2; N, 6·4; S, 7·3%); *5-keto-2-phenyl-4-*p*-N-acetylsulphamylbenzylidene-4 : 5-dihydro-oxazole* (62% from *p*-sulphamylbenzaldehyde), orange-red prisms from acetic anhydride, m. p. 240—241° (decomp.) (Found : C, 58·2; H, 4·1; S, 8·5. $C_{18}H_{14}O_5N_2S$ requires C, 58·4; H, 3·8; S, 8·6%).

p-Methylsulphonylphenylalanine.—5-Keto-2-phenyl-4-*p*-methylsulphonylbenzylidene-4 : 5-dihydro-oxazole (9 g.) was reduced with red phosphorus (5·6 g.) and hydriodic acid (*d*, 1·56; 35 c.c.) in acetic anhydride (35 c.c.) as described by Gillespie and Snyder (*Org. Synth.*, Coll. Vol. II, 1943, 489). The *amino-acid* (5·5 g.) crystallised from water in nearly colourless prisms, m. p. 270° (decomp.) (Found : C, 49·5; H, 5·1; N, 5·6. $C_{10}H_{13}O_4NS$ requires C, 49·4; H, 5·4; N, 5·7%).

The following were similarly prepared. p-*Phenylsulphonylphenylalanine* (70%), m. p. 252° (decomp.) after crystallisation from dilute alcohol (Found : C, 58·9; H, 4·9. $C_{15}H_{15}O_4NS$ requires C, 59·0; H, 4·9%); 4-p-*chlorophenylsulphonylphenylalanine* (73%), micro-crystalline powder from 95% alcohol, m. p. 259° (decomp.) (Found : C, 52·8; H, 4·0. $C_{15}H_{14}O_4NClS$ requires C, 53·0; H, 4·1%); 4-p-*hydroxyphenylsulphonylphenylalanine* (62% from the methoxy-compound), micro-crystalline powder from 30% alcohol, m. p. 265° (decomp.), which appeared to contain 1 molecule of water of crystallisation (Found : C, 53·1; H, 5·0; N, 4·3. $C_{15}H_{15}O_5NS,H_2O$ requires C, 53·1; H, 5·0; N, 4·1%); 4-p-*aminophenylsulphonylphenylalanine* (40%), yellowish prisms from water, m. p. 195° (decomp.) (Found : C, 56·5; H, 5·4; N, 8·4. $C_{15}H_{16}O_4N_2S$ requires C, 56·2; H, 5·0; N, 8·8%).

p-*Sulphamylphenylalanine.*—5-Keto-2-phenyl-4-*p*-*N*-acetylsulphamylbenzylidene-4 : 5-dihydro-oxazole (5 g.), suspended in 95% alcohol (60 c.c.), was heated at 75° (bath temp.) under reflux and stirred mechanically. 3% Sodium amalgam (26 g.) was added, and after 1½ hours a further 26 g.; heating and stirring were then continued for a further 2½ hours. The hot alcoholic filtrate was evaporated, and the residue dissolved in water (15 c.c.) and acidified (concentrated hydrochloric acid). The gummy product which separated solidified on keeping and crystallisation from alcohol gave colourless leaflets of *α-benzamido-β-*p*-sulphamylphenylpropionic acid*, m. p. 176—178° (Found : C, 55·3; H, 4·8. $C_{16}H_{16}O_5N_2S$ requires C, 55·2; 4·6%). Hydrolysis of the crude product with boiling 10% hydrochloric acid (20 c.c.) for 3 hours, and repeated extraction with ether to remove benzoic acid, left a solution which was evaporated under reduced pressure; the resulting solid residue crystallised from absolute alcohol in colourless prisms (2·0 g.), m. p. 237° (decomp.), and was p-*sulphamylphenylalanine hydrochloride* (Found : C, 38·6; H, 4·6; Cl, 12·6. $C_9H_{13}O_4N_2ClS$ requires C, 38·5; H, 4·6; Cl, 12·65%).

Attempted Decarboxylation of the Amino-acids.—The amino-acids were heated alone in a high vacuum, and in various solvents such as glycerol, diphenylamine, or high-boiling paraffin. In some cases traces of impure crystalline material were obtained.

Substituted Cinnamic Acids.—The appropriate aldehyde was heated at 100° (bath temp.) with malonic acid in pyridine containing a little piperidine until effervescence ceased, and then treated with excess of 6N-hydrochloric acid. Recrystallisation (from 2-ethoxyethanol except where stated otherwise) gave the cinnamic acids in 67—87% yield. The following were prepared. *p*-Methylsulphonylcinnamic acid, m. p. 288°; p-*phenylsulphonylcinnamic acid*, m. p. 298° (Found : C, 62·3; H, 4·5; S, 11·1. $C_{15}H_{12}O_4S$ requires C, 62·5; H, 4·2; S, 11·1%); 4-p-*chlorophenylsulphonylcinnamic acid*, m. p. 282° (Found : C, 55·4; H, 3·6; Cl, 10·9. $C_{15}H_{11}O_4ClS$ requires C, 55·8; H, 3·4; Cl, 11·0%); 4-p-*methoxyphenylsulphonylcinnamic acid*, m. p. 259—261° (decomp.) (Found : C, 59·6; H, 4·7; S, 10·5. $C_{16}H_{14}O_5S$ requires C, 60·4; H, 4·4; S, 10·1%); 4-2′ : 5′-*dihydroxyphenylsulphonylcinnamic acid*, prisms from 50% acetic acid, m. p. 262° (Found : C, 55·4; H, 4·0. $C_{15}H_{12}O_6S$ requires C, 56·0; H, 3·8%); 4-p-*nitrophenylsulphonylcinnamic acid*, m. p. 273—275° (Found : C, 53·4; H, 3·2; N, 4·4. $C_{15}H_{11}O_6NS$ requires C, 54·0; H, 3·3; N, 4·2%); p-*sulphamylcinnamic acid*, prisms from acetic acid, m. p. 276° (decomp.) (Found : C, 47·5; H, 4·3; S, 14·0. $C_9H_9O_4NS$ requires C, 47·6; H, 4·0; S, 14·1%).

Substituted Phenylpropionic Acids.—Except for the above nitro- and sulphamyl-acids, the cinnamic acids (as sodium salts in water) were reduced with hydrogen in presence of Raney nickel at ordinary temperature and pressure. The following were prepared in 77—90% yields. *β-p*-Methylsulphonyl-

phenylpropionic acid, m. p. 171°, prisms from 95% alcohol; *β*-p-*phenylsulphonylphenylpropionic acid*, m. p. 173—174°, plates from 30% alcohol (Found: C, 61·9; H, 4·9; S, 11·2. $C_{15}H_{14}O_4S$ requires C, 62·1; H, 4·8; S, 11·0%); *β*-4-p-*chlorophenylsulphonylphenylpropionic acid*, m. p. 194—195° from 95% alcohol (Found: C, 55·8; H, 4·2; Cl, 10·9. $C_{15}H_{13}O_4ClS$ requires C, 55·5; H, 4·0; Cl, 10·9%); *β*-4-p-*methoxyphenylsulphonylphenylpropionic acid*, plates from 95% alcohol, m. p. 168° (Found: C, 59·7; H, 5·0. $C_{16}H_{16}O_5S$ requires C, 60·0; H, 5·0%); *β*-4-2′ : 5′-*dihydroxyphenylsulphonylphenylpropionic acid*, prisms from 50% alcohol, m. p. 180° (Found: C, 55·7; H, 4·3; S, 10·1. $C_{15}H_{14}O_6S$ requires C, 55·9; H, 4·3; S, 9·9%).

The nitro-acid (above) could be reduced catalytically to *β*-4-*p*-aminophenylsulphonylphenylpropionic acid, the *hydrochloride* of which separated from 2N-hydrochloric acid in colourless prisms, m. p. 209° (decomp.) (Found: C, 53·1; H, 4·7. $C_{15}H_{16}O_4NClS$ requires C, 52·8; H, 4·7%), and the *acetyl* derivative of which crystallised from 50% alcohol in not very well defined form, m. p. 215°, which appeared to be a monohydrate (Found: C, 56·1; H, 4·8; N, 3·7; S, 8·5. $C_{17}H_{17}O_5NS,H_2O$ requires C, 56·0; H, 5·2; N, 3·8; S, 8·7%). Owing to solubility difficulties it was found better to reduce the nitro-acid (3 g.) with iron powder (3 g.) in alcohol (37 c.c.) containing water (10 c.c.) and concentrated hydrochloric acid (0·5 c.c.). The crude 4-*p*-aminophenylsulphonylcinnamic acid thus formed was acetylated, and the resulting *acetyl* derivative, m. p. 237° after crystallisation from 50% alcohol (Found: C, 56·6; H, 4·4; N, 3·6; S, 8·4. $C_{17}H_{15}O_5NS,H_2O$ requires C, 56·2; H, 4·7; N, 3·8; S, 8·8%), reduced catalytically as the sodium salt to *β*-4-*p*-acetamidophenylsulphonylphenylpropionic acid, m. p. and mixed m. p. 215°.

p-Sulphamylcinnamic acid (3 g.) was reduced with 3% sodium amalgam (70 g.) in dilute sodium hydroxide (20 c.c.) during 3—4 hours. The resulting *β*-p-*sulphamylphenylpropionic acid* (2·5 g.) crystallised from water in colourless small plates, m. p. 148—150° (Found: S, 14·4. $C_9H_{11}O_4NS$ requires S, 14·0%).

2-*Substituted Ethylamines.*—The substituted phenylpropionic acid was refluxed with a slight excess of thionyl chloride and 1 drop of pyridine in dry chloroform for ½ hour, and the volatile products removed by distillation under reduced pressure. The acid chloride, usually a syrup, was then dissolved in acetone and stirred vigorously during the addition of the requisite amount of 25% aqueous sodium azide. The mixture was stirred for a further 10 minutes at 0°; cold water was added to precipitate the azide, which was then collected and dried in a vacuum desiccator. The dry azide was warmed cautiously in dry benzene and finally boiled for 5 minutes; 2N-hydrochloric acid was then added, the benzene removed by distillation, and the resulting acidic solution filtered (if necessary) whilst still hot from any tar. The filtrate was evaporated to dryness and the resulting amine hydrochloride crystallised. The following were prepared in yields of 40—60%. 2-*p*-Methylsulphonylphenylethylamine hydrochloride, colourless prisms from absolute alcohol, m. p. 204° (Found: N, 5·8; Cl, 15·2. Calc. for $C_9H_{14}O_2NClS$: N, 5·9; Cl, 15·1%); 2-p-*phenylsulphonylphenylethylamine hydrochloride*, colourless long needles from water, m. p. 184—185° (Found: C, 56·0; H, 5·5; Cl, 11·6. $C_{14}H_{16}O_2NClS$ requires C, 56·5; H, 5·4; Cl, 11·9%); 2-4′-p-*chlorophenylsulphonylphenylethylamine hydrochloride*, small plates from absolute alcohol, m. p. 251° (Found: C, 50·5; H, 4·4. $C_{14}H_{15}O_2NCl_2S$ requires C, 50·4; H, 4·8%); 2-4′-p-*methoxyphenylsulphonylphenylethylamine hydrochloride*, needles from 2N-hydrochloric acid, m. p. 170° (Found: C, 54·6; H, 5·3; Cl, 11·3. $C_{15}H_{18}O_2NClS$ requires Cl, 11·4%); 2-4′-2″ : 5″-*dihydroxyphenylsulphonylphenylethylamine hydrochloride*, prisms from 2N-hydrochloric acid, m. p. 197° (Found: N, 4·0; S, 9·7. $C_{14}H_{16}O_4NClS$ requires N, 4·3; S, 9·7%). 2-4′-p-*Aminophenylsulphonylphenylethylamine* was best isolated as the free base, m. p. 129° after crystallisation from alcohol (Found: C, 61·1; H, 5·6. $C_{14}H_{16}O_2N_2S$ requires C, 60·9; H, 5·8%), as was 2-p-*sulphamylphenylethylamine*, m. p. 149° after crystallisation from alcohol (Found: C, 48·0; H, 6·1. $C_8H_{12}O_2N_2S$ requires C, 48·0; H, 6·0%).

1-*Substituted Ethylamines.*—The appropriate ketone (1 mol.) and ammonium formate (4 mols.) were heated gradually to 180—185° and kept at this temperature for 3 hours. The cooled product was extracted with a little cold water, and the insoluble material hydrolysed with boiling concentrated hydrochloric acid. The following were prepared in yields of 50—66%. 1-*p*-Methylsulphonylphenylethylamine hydrochloride, m. p. 278° (Fuller, Tonkin, and Walker, *loc. cit.*, give m. p. 274°) (Found: Cl, 15·2. Calc. for $C_9H_{14}O_2NClS$: Cl, 15·1%); 1-p-*phenylsulphonylphenylethylamine*, prisms from dilute alcohol, m. p. 85° (Found: N, 5·0. $C_{14}H_{15}O_2NS$ requires N, 5·4%), and its *hydrochloride*, m. p. 218—219° after crystallisation from alcohol (Found: C, 56·7; H, 5·3. $C_{14}H_{16}O_2NClS$ requires C, 56·5; H, 5·4%); 1-p-*sulphamylphenylethylamine*, colourless prisms from water, m. p. 172° (Found: C, 48·3; H, 6·3; N, 14·4; S, 16·2. $C_8H_{12}O_2N_2S$ requires C, 48·0; H, 6·0; N, 14·0; S, 16·0%).

p-*Methylsulphonyldiphenylmethylamine*, *p*-$Me{\cdot}SO_2{\cdot}C_6H_4{\cdot}CHPh{\cdot}NH_2$.—*p*-Methylsulphonylbenzophenone was treated with ammonium formate as described above. The *amine* (yield, 62%) crystallised from benzene–light petroleum in colourless plates, m. p. 92—93° (Found: C, 63·7; H, 5·7; N, 5·5. $C_{14}H_{15}O_2NS$ requires C, 64·4; H, 5·8; N, 5·4%).

p-*Phenylsulphonyldiphenylmethylamine*, *p*-$Ph{\cdot}SO_2{\cdot}C_6H_4{\cdot}CHPh{\cdot}NH_2$.—Similar condensation of *p*-phenylsulphonylbenzophenone with ammonium formate gave the above *amine* (80%), m. p. 154—155° after crystallisation from 30% alcohol (Found: C, 70·6; H, 5·4; N, 3·9. $C_{19}H_{17}O_2NS$ requires C, 70·6; H, 5·3; N, 4·2%).

p-*Sulphamylacetophenone*, *p*-$NH_2{\cdot}SO_2{\cdot}C_6H_4{\cdot}COMe$.—*p*-Aminoacetophenone (6 g.) in 2N-hydrochloric acid (60 c.c.) was diazotised with sodium nitrite (4·2 g. in 15 c.c. of water) and then treated with sodium acetate trihydrate (12 g.). This solution was then added gradually with vigorous stirring to potassium ethyl xanthate (17 g.) in water (30 c.c.) at 70—80° and kept at this temperature for 1 hour. The oily product was extracted with ether and then refluxed with alcohol (40 c.c.) containing potassium hydroxide (2·3 g.) and glucose (2·3 g.) for 3 hours. The alcohol was removed by distillation, the aqueous residue acidified with dilute sulphuric acid, and the free thiol removed by steam-distillation. The ether-soluble material from the steam-distillate was oxidised by excess of anhydrous ferric chloride in acetic acid, giving impure 4 : 4′-*diacetyldiphenyl disulphide* (20%), which crystallised from light petroleum in colourless plates, m. p. 92—93° (Found: S, 23·0. $C_{16}H_{14}O_2S_2$ requires S, 21·2%). The crude disulphide (2·4 g.) in cold 80% acetic acid (60 c.c.) was treated with a solution of chlorine (3·2 g.) in 80% acetic acid

(60 c.c.), the mixture being shaken vigorously for 10 minutes. Dilution with water precipitated the sulphonyl chloride which was filtered off, and while still moist was treated with solid ammonium carbonate (4 g.) and chloroform (20 c.c.). The mixture was evaporated to dryness on the steam-bath, and the crystalline residue washed repeatedly with cold water; the resultant p-*sulphamylacetophenone* (1·0 g.) crystallised from water in colourless prisms, m. p. 178—179° (Found: C, 48·6; H, 4·5. $C_8H_9O_3NS$ requires C, 48·2; H, 4·5%).

An attempted preparation of the above disulphide from diazotised *p*-aminoacetophenone (4·5 g.) and sodium disulphide (0·037 mol.) in water (10 c.c.) first at below 5° and then at room temperature for 2 hours gave 4 : 4′-*diacetyldiphenyl sulphide* (2·5 g.), almost colourless plates from light petroleum, m. p. 88° (Found: S, 12·1. $C_{16}H_{14}O_2S$ requires S, 11·85%). Oxidation with 30% hydrogen peroxide in acetic acid at 100° gave 4 : 4′-*diacetyldiphenyl sulphone*, prisms, m. p. 209° (Found: C, 63·1; H, 4·8; S, 10·4. $C_{16}H_{14}O_4S$ requires C, 63·6; H, 4·6; S, 10·6%).

We thank the British Council for a scholarship, and the Universities China Committee for financial assistance, to one of us (P. F. H.). We are indebted to Messrs. Imperial Chemicals (Pharmaceuticals) Ltd., Manchester, for the antibacterial tests.

THE UNIVERSITY, LEEDS, 2. [*Received, April 28th,* 1948.]