150. *Synthesis of Amino-sulphones.**

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A general method for the synthesis of *p*-aminobenzenesulphonylalkylcarboxylic acids has been evolved, and a series of these compounds prepared for examination as bacterial inhibitors. Observations have been made on the stability of α-sulphonyl carboxylic acids and 1 : 3-sulphone ketones, and two new syntheses of *p*-aminophenylmethylsulphone by the hydrolytic scission of such compounds have been recorded.

The high antibacterial activity of 4 : 4′-diaminodiphenylsulphone and allied compounds has led to the belief that the molecular grouping essential for activity is the $NH_2 \cdot C_6H_4 \cdot S$ complex (Green and Bielschowsky, *Brit. J. Exp. Path.*, 1942, **23**, 13; also compare Fourneau *et al.*, *Compt. rend. Soc. Biol.*, 1938, **127**, 393). Because of the high toxicity of 4 : 4′-diaminodiphenylsulphone it was thought desirable to examine a series of *p*-aminobenzenesulphonylalkylcarboxylic acids, since these would be expected to be less toxic.

Two general methods appeared suitable for the preparation of these acids, *viz.*, (i) the condensation of *p*-acetamidobenzenesulphonyl chloride with the sodio-derivatives of ethyl acetoacetate or ethyl malonate, followed by " acid " hydrolysis of the product, and (ii) the condensation of alkali *p*-acetamidobenzenesulphinates with halogenoalkylcarboxylic acids or their functional derivatives. Toluene-*p*-sulphonylacetic acid has been obtained by both methods (Kohler and Macdonald, *Amer. Chem. J.*, 1899, **22**, 234; cf. also Ashley and Schriner, *J. Amer. Chem. Soc.*, 1932, **54**, 4410).

Interaction of *p*-acetamidobenzenesulphonyl chloride with ethyl sodio-malonate in alcohol or benzene gave a condensate which, although insoluble in the usual solvents, was instantly soluble in dilute cold aqueous alkalis; hydrolysis with hot aqueous alkalis yielded sulphanilic acid. By the action of sodium *p*-acetamidobenzenesulphinate upon ethyl bromomalonate a condensate was obtained possessing the same properties. The solubility in alkali together with the apparent identity of the two products would suggest that in both cases ethyl *p*-acetamidobenzenesulphonylmalonate is produced and that hydrolysis effects rupture of the carbon–sulphur bond, with formation of sulphanilic acid. Exactly comparable results were obtained by condensation of *p*-acetamidobenzenesulphonyl chloride with ethyl sodio-acetoacetate and of sodium *p*-acetamidobenzenesulphinate with ethyl acetochloroacetate; in both instances sodium halide was eliminated, with production of a condensate which yielded sulphanilic acid upon alkaline hydrolysis. These observations may be correlated with those of Kohler and Macdonald (*loc. cit.*) upon the formation of sodium *p*-toluenesulphonate by the interaction of sodium *p*-toluenesulphinate and ethyl acetochloroacetate.

Condensation of sodium *p*-acetamidobenzenesulphinate with ethyl chloroacetate in boiling amyl alcohol or toluene gave *ethyl* p-*acetamidobenzenesulphonylacetate* in good yield. Anhydrous ethyl-alcoholic hydrogen chloride effected deacetylation to *ethyl* p-*aminobenzenesulphonylacetate*, but hydrolysis with aqueous hydrochloric acid yielded p-*aminobenzenesulphonylacetic acid*. Alkaline hydrolysis of the ethyl *p*-acetamidobenzenesulphonylacetate was unsuitable owing to partial decarboxylation (see below). The method would appear to be of general application, since sodium *p*-acetamidobenzenesulphinate has been condensed with ethyl α-bromopropionate, α-bromobutyrate, and β-chloropropionate, and in all cases the yields of the ethyl *p*-acetamidobenzenesulphonylalkylcarboxylate, ethyl *p*-aminobenzenesulphonylalkylcarboxylate and *p*-aminobenzenesulphonylalkylcarboxylic acid were high.

In boiling aqueous solution sodium *p*-acetamidobenzenesulphinate condenses readily with sodium chloroacetate but the product depends upon the duration of the reaction. In 2—4 hours a high yield of p-*acetamidobenzenesulphonylacetic acid* is obtained, but longer reaction causes simultaneous decarboxylation, with formation

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of p-*acetamidophenylmethylsulphone*. The proportions of sulphonylcarboxylic acid and neutral sulphone produced after 7 and 20 hours are of the order of 60 : 40 and 15 : 85, respectively; they may be separated by evaporation of the reaction solution to dryness and extraction of the neutral sulphone with hot acetone, in which the sodium salt of the sulphonyl-carboxylic acid is insoluble. After 30 hours' interaction at the boiling point the decarboxylation is complete but is accompanied by partial deacetylation; by hydrolysis of the product with dilute acid or alkali very high yields of p-*aminophenylmethylsulphone* are obtained. Decarboxylation of α-sulphonyl-carboxylic acids by aqueous alkali has been previously observed by Tröger and Uhde (*J. pr. Chem.*, 1899, **59**, 334), Kohler and Rainer (*Amer. Chem. J.*, 1904, **31**, 176), and also in U.S.P. 1,939,416, B.P. 404,794, and F.P. 746,410, but decarboxylation in neutral aqueous solution has not previously been reported. *p*-Aminobenzenesulphonylacetic acid is stable on long boiling in 5N-hydrochloric acid and also in aqueous solution at the pH *ca.* 3·5 which the amino-acid itself develops; the boiling aqueous solution of the sodium salt (pH 7·2) slowly loses carbon dioxide, the decarboxylation being complete in 30—35 hours.

p-Aminobenzenesulphonylacetic acid possesses a lower *in vivo* activity against *Streptococcus* Aronson infections in mice than sulphanilamide; the median lethal dosage (LD 50), however, is of the order of 12·0 g./kg., as compared with 2·0 g./kg. for sulphanilamide. In rabbits, *p*-aminobenzenesulphonylacetic acid effects potentiation of insulin hypoglycæmia (Goldberg and Jefferies, in the press).

Sodium *p*-acetamidobenzenesulphinate rapidly condenses with sodium dichloroacetate in hot aqueous solution to yield p-*acetamidophenyl(chloromethyl)sulphone*, which on hydrolysis gives p-*aminophenyl(chloromethyl)sulphone*. The failure to isolate the intermediately formed *p*-acetamidobenzenechloroacetic acid may be compared with the observations of Michael and Adair (*Ber.*, 1877, **10**, 583). Otto (*J. pr. Chem.*, 1889, **40**, 527), Otto (*Ber.*, 1886, **19**, 1835), Ranberg (*Z. physiol. Chem.*, 1900, **34**, 586), and Fonque and La Croix (*Bull. Soc. chim.*, 1923, **33**, 180) upon the spontaneous decomposition of intermediately formed α-chloro-α-sulphonylcarboxylic acids at room temperature. Interaction of 2 mols. of the sodium sulphinate with 1 mol. of sodium dichloroacetate also gave *p*-acetamidophenyl(chloromethyl)sulphone. The halogen substituent in the latter completely resists replacement; the compound fails to react with ammonia at 100°, or with *cyclo*hexylamine or aniline at temperatures above 120° even in the presence of a copper catalyst. The deactivation of a halogen substituent for metathesis by an α-sulphonyl group has been observed by Zeigler and Connor (*J. Amer. Chem. Soc.*, 1940, **62**, 2596), Kostova (*J. Gen. Chem. Russia*, 1941, **11**, 63), Johnson and Douglas (*J. Amer. Chem. Soc.*, 1941, **63**, 1571), and Schriner and Land (*J. Org. Chem.*, 1941, **6**, 888), and it may be contrasted with the high reactivity of the halogen in β-halogenosulphonyl compounds (Alexander and McCombie, J., 1931, 1913; Goldberg, this vol., p. 464).

Sodium *p*-acetamidobenzenesulphinate and chloroacetonitrile gave p-*acetamidobenzenesulphonylacetonitrile*, which was deacetylated by boiling 3·3N-hydrochloric acid to p-*aminobenzenesulphonylacetonitrile*; this was converted by the normal routes into p-*aminobenzenesulphonyl-thioacetamide*, *-acetamidoxime*, and -acetamidine (as *hydrochloride*). None of these compounds possesses any observable activity against *Tr. equiperdum* infections in mice.

Sodium *p*-acetamidobenzenesulphinate reacted readily with phenacyl bromide in boiling amyl alcohol solution to give p-*acetamidophenylphenacylsulphone*. The compound is stable towards boiling dilute mineral acid as far as the 1 : 3-sulphone ketone complex is concerned and gives p-*aminophenylphenacylsulphone* in good yield. With 2·5N-aqueous alkalis, however, hydrolytic scission of the sulphur–carbon bond takes place with production of *p*-aminophenylmethylsulphone and benzoic acid; since the hydrolysis is quantitative, this constitutes an alternative facile route to this sulphone. p-*Acetamidophenyl*-p′-*bromophenacylsulphone* behaves in the same manner and gives quantitative yields of the same sulphone and *p*-bromobenzoic acid. Similar hydrolytic cleavage of 1 : 3-sulphone ketones by means of *concentrated* alkali has been observed by Otto (*J. pr. Chem.*, 1887, **36**, 427) and Tröger *et al.* (*ibid.*, 1897, **55**, 411; 1923, **105**, 208; 1926, **112**, 221).

Ethylation of *p*-acetamidophenylphenacylsulphone with alcoholic sodium ethoxide and ethyl iodide afforded the C-*ethyl* derivative, which on alkaline hydrolysis yielded p-*aminophenyl*-n-*propylsulphone* and benzoic acid. Since the overall yield of this sulphone from sodium *p*-acetamidobenzenesulphinate was *ca.* 25%, this method is a useful route to sulphones not obtainable from the direct interaction of the sodium sulphinate and an alkyl halide.

Experimental.

Ethyl p-*Acetamidobenzenesulphonylacetate*.—Anhydrous sodium *p*-acetamidobenzenesulphinate (44·2 g.) was refluxed with a solution of ethyl chloroacetate (24·4 g.) in xylene (300 c.c.) containing a trace of copper powder for 5 hours, an almost clear solution being then obtained. The xylene was removed by distillation in steam, and the residual oil, which solidified on cooling, was collected and recrystallised from the minimal quantity of 90% alcohol, the *ethyl* ester being obtained (40 g.) in long white needles, m. p. 120—122°. For analysis it was recrystallised from ethanol–benzene–ligroin and obtained in white needles, m. p. 122—124° (Found: N, 5·1; S, 11·4. $C_{12}H_{15}O_5NS$ requires N, 4·9; S 11·2%).

Ethyl p-*Aminobenzenesulphonylacetate*.—A solution of the foregoing ester (20 g.) in a saturated anhydrous alcoholic solution of hydrogen chloride (200 c.c.) was refluxed on the water-bath for 1½ hours. A white crystalline precipitate was rapidly formed, and the contents of the flask finally set to a semi-solid white crystalline mass. The *ethyl* p-*aminobenzenesulphonylacetate hydrochloride* was collected and, after being washed with ether and dried at 90°/10 mm., had m. p. 198—200° (18·5 g.) (Found: N, 5·3; Cl, 12·4; S, 11·6; *M*, by titration, 279. $C_{10}H_{14}O_4NClS$ requires N, 5·0; Cl, 12·7; S, 11·4%; *M*, 279·5).

This hydrochloride (15 g.) was dissolved in the minimum amount of boiling water, and the amino-ester precipitated by addition of the theoretical quantity of sodium bicarbonate in concentrated aqueous solution. After cooling on ice, the solid was collected and recrystallised from dilute alcohol, *ethyl* p-*aminobenzenesulphonylacetate* being obtained in glittering white leaves (11 g.), m. p. 112—114° (Found: N, 6·0; S, 13·0. $C_{10}H_{13}O_4NS$ requires N, 5·8; S, 13·1%).

p-*Aminobenzenesulphonylacetamide.*—Ethyl *p*-aminobenzenesulphonylacetate hydrochloride (5 g.) and aqueous ammonia (20 c.c.; *d* 0·880) were shaken in a closed bottle with glass beads for 3 hours. The insoluble *amide* was collected and recrystallised from 50% methyl alcohol, and obtained as heavy white prisms (4 g.), m. p. 220—222° (Found : N, 13·3; S, 14·8. $C_8H_{10}O_3N_2S$ requires N, 13·1; S, 14·9%), soluble in boiling water. p-*Acetamidobenzenesulphonylacetamide* was obtained in the same manner from ethyl *p*-acetamidobenzenesulphonylacetate in almost theoretical yield; it crystallised from 90% methyl alcohol in white tablets, m. p. 194—196° (Found : N, 11·1; S, 12·3. $C_{10}H_{12}O_4N_2S$ requires N, 10·9; S, 12·5%).

p-*Aminobenzenesulphonylacetic Acid.*—A suspension of ethyl *p*-acetamidobenzenesulphonylacetate (57 g.) in 5N-hydrochloric acid (320 c.c.) was refluxed for 75 minutes, and the clear solution thus obtained was filtered (charcoal) and evaporated in a vacuum on the water-bath to very small volume. After standing on ice the p-*aminobenzenesulphonylacetic acid hydrochloride* separated as a mass of fine needles, which were drained at the pump and washed with a little alcohol–ether; yield 41 g.; m. p. 214—216° (decomp.) (Found : Cl, 14·2; *M*, by titration as a dibasic acid, 253. $C_8H_{10}O_4NClS$ requires Cl, 14·1%; *M*, 251·5).

The hydrochloride (40 g.) was dissolved in boiling water (38 c.c.) and the theoretical amount of 5N-sodium hydroxide (31 c.c.) slowly added with rapid stirring; after standing for several hours in the ice-chest, the thick precipitate of the free *acid* was well drained at the pump and dried (32 g.; m. p. 158—162°). Recrystallisation from the minimum amount of boiling water (*ca.* 95 c.c.) containing hydrochloric acid (3 c.c.) gave the pure compound in stellate clusters of stout white prisms, m. p. 162—164° (26 g.) (Found : N, 6·6; S, 15·0; *M*, by titration, 215. $C_8H_9O_4NS$ requires N, 6·5; S, 14·9%; *M*, 215).

p-*Acetamidobenzenesulphonylacetic Acid.*—*p*-Acetamidobenzenesulphinic acid (199 g.) and chloroacetic acid (95 g.) were dissolved in water (500 c.c.) and 5N-sodium hydroxide (400 c.c.), and the solution adjusted to pH 7·0—7·2 by addition of traces of the sulphinic acid or sodium hydroxide solution. The clear solution was refluxed over a flame for 2½ hrs. and then evaporated in a vacuum on the water-bath during a further 2½ hrs. The volume was made up to 580 c.c. by addition of water and then, with rapid stirring, hydrochloric acid (150 c.c.) was slowly added. After standing on ice for several hours the thick white precipitate was collected, drained at the pump, and recrystallised from the minimum amount of boiling water (1150 c.c.), p-*acetamidobenzenesulphonylacetic acid* being obtained in stout white needles (135 g.), m. p. 196—198° (Found : *M*, 266). Recrystallisation of a sample from water gave the pure compound in white needles, m. p. 206—208° (decomp.) (Found : N, 5·7; S, 12·6; *M*, by titration, 258. $C_{10}H_{11}O_5NS$ requires N, 5·5; S, 12·5%; *M*, 257).

p-*Aminobenzenesulphonylacetic Acid.*—A solution of the last acid (120 g.) in 5N-hydrochloric acid (600 c.c.) was refluxed over a flame for 1½ hours and then concentrated to small volume at reduced pressure on the water-bath with occasional addition of acetone to assist evaporation. The residual semi-solid mass was kept on ice, drained at the pump, and the crystalline residue of p-*aminobenzenesulphonylacetic acid hydrochloride* washed with acetone–ether and dried; yield 102 g.; m. p. 206—208° (decomp.) (Found : *M*, by titration, 260. $C_8H_9O_4N,HCl$ requires *M*, 251·5). This was dissolved in boiling water (80 c.c.), the theoretical amount of 5N-sodium hydroxide (80 c.c.) added with vigorous stirring, the semi-solid mass chilled, and the *p*-aminobenzenesulphonylacetic acid collected (86 g.), m. p. 158—160° (Found : *M*, 220); recrystallisation from boiling water (220 c.c.) containing hydrochloric acid (10 c.c.) gave the pure acid as stout white needles (70 g.), m. p. 162—164° (Found : N, 6·7; S, 15·0; *M*, by titration, 215. Calc. : N, 6·5; S, 14·9%; *M*, 215).

Stability in aqueous solutions at various pH values. (i) A solution of *p*-aminobenzenesulphonylacetic acid (5 g.) in 5N-hydrochloric acid (15 c.c.) was heated at 100° (immersion) for 20 hours. 5N-Sodium hydroxide (15 c.c.) was added and, after standing on ice for 12 hours, the precipitate was collected, drained, and dried (5·2 g.). This was recrystallised from the minimum amount of boiling water containing two drops of hydrochloric acid, and 3·7 g. of the acid were recovered; m. p. 162—164° (Found : *M*, 215).

(ii) A solution of the acid (5 g.) in water (15 c.c.) was heated to 100° for 20 hours; the pH value (3·2—3·4) was that developed by the amino-acid itself. On cooling, an oily solid was obtained which, after drying, had m. p. 150—158° (4·5 g.). Recrystallisation from acidulated water gave 3·2 g. of unchanged acid, m. p. 158—160° (Found : *M*, 226).

(iii) The acid (5 g.) was dissolved in water, the solution adjusted to pH 7·4 by addition of 5N-sodium hydroxide (final volume, 15 c.c.), heated to 100° for 20 hours, and chilled, and *p*-aminophenylmethylsulphone filtered off (1·9 g.; m. p. 134—136°). The filtrate was adjusted to pH 3·0—3·5 with hydrochloric acid and kept on ice overnight; impure *p*-aminobenzenesulphonylacetic acid (2·3 g.) was recovered; m. p. 148—156° (Found : *M*, 242).

p-*Acetamidophenylmethylsulphone.*—(I) *p*-Acetamidobenzenesulphinic acid (39·8 g.; 0·2 mol.) and chloroacetic acid (18·9 g.; 0·2 mol.) were dissolved in water (100 c.c.) and 5N-sodium hydroxide (80 c.c.; 0·4 mol.), the solution adjusted to pH 7·0—7·2, refluxed for 2 hours, and then evaporated to dryness on the water-bath at reduced pressure during a further 2 hours. The finely ground residue was extracted twice with boiling acetone (2 × 250 c.c.), the insoluble residue dissolved in boiling water (90 c.c.), the cold filtered solution acidified with hydrochloric acid (30 c.c.), and the precipitated *p*-acetamidobenzenesulphonylacetic acid collected and drained. After drying, this weighed 36 g. and had m. p. 206—210°; recrystallisation from the minimum amount of boiling water (280 c.c.) gave 28 g. of the pure acid, m. p. 210—212° (Found : *M*, by titration, 258). The acetone extract was evaporated to dryness, and the *sulphone* remained (8 g.) as a white powder, m. p. 176—184°. Recrystallisation from water gave the pure compound in lustrous white prisms, m. p. 186—188° (Found : N, 6·8; S, 15·2. $C_9H_{11}O_3NS$ requires N, 6·6; S, 15·0%).

(II) The above procedure was repeated except that the solution was refluxed for 5 hours and then evaporated to dryness over a further 2 hours. The acetone-insoluble material yielded 22 g. of pure *p*-acetamidobenzenesulphonylacetic acid; the acetone extract gave, on evaporation, 14 g. of a mixture of *p*-acetamido- and *p*-amino-phenylmethylsulphone.

(III) The procedure was repeated with a reflux period of 18 hours, followed by evaporation as before. The acetone-insoluble portion yielded only 4 g. of crude *p*-acetamidobenzenesulphonylacetic acid (m. p. 200—204°) and the acetone extract on evaporation gave a mixture, m. p. 130—165°, of *p*-acetamido- and *p*-amino-phenylmethylsulphone. Four recrystallisations of this from water gave 16 g. of pure *p*-acetamido-sulphone, m. p. 180—184°; the mother-liquors of these crystallisations were evaporated, rendered strongly alkaline with sodium hydroxide solution, refluxed for 1 hour, and cooled, 7 g. of the *p*-amino-sulphone crystallising in lustrous flakes (m. p. 126—128°).

(IV) The following was the best method for obtaining *p*-aminophenylmethylsulphone. The foregoing procedure was repeated, but with a reflux period of 30 hours. The resulting solution was evaporated to dryness on the water-bath, and the residue boiled with acetone (600 c.c.), whereupon most of it dissolved. The filtered acetone solution was evaporated to dryness, the residue (34 g.) refluxed for 1½ hours with 5N-hydrochloric acid (175 c.c.), and the clear solution kept on ice, p-*aminophenylmethylsulphone hydrochloride* separating as small glittering tablets. After collection and washing with ether and drying, these weighed 29 g. and had m. p. 240—246° (Found : *M*, 209). The compound was insoluble in absolute alcohol but very soluble in boiling 95% alcohol; recrystallisation of a sample from this medium containing a few drops of hydrochloric acid gave the substance in long white needles, m. p. 242—246° (softening at 230°) (Found, by titration, *M*, 207. $C_7H_{10}O_2NClS$ requires *M*, 207·5). The hydrochloride was dissolved in the minimum volume of boiling

water, and a slight excess of sodium carbonate added; on cooling, the *sulphone* base separated in mother-of-pearl flakes (23 g.), m. p. 134—136° (Found : N, 8·4; S, 18·9. $C_7H_9O_2NS$ requires N, 8·2; S, 18·7%), very soluble in boiling, and almost insoluble in cold water. Median lethal dose : 1·5 g./kg.

p-*Acetamidophenyl(chloromethyl)sulphone.*—*p*-Acetamidobenzenesulphinic acid (39·8 g.; 0·2 mol.) and dichloroacetic acid (26 g.; 0·2 mol.) were dissolved in water (100 c.c.) and 5N-sodium hydroxide (80 c.c.; 0·4 mol.), and the solution, after adjustment to pH 7·2, refluxed over a flame for 6 hours. A crystalline precipitate rapidly appeared, and the liquid finally set to a semi-solid, crystalline mass. The *sulphone* (30 g.; m. p. 202—204°) was collected and a further crop (5 g.) obtained by refluxing the filtrate for a further 8 hours. A sample recrystallised from dilute alcohol in the form of long white prisms, m. p. 204—206° (Found : N, 5·9; Cl, 14·3; S, 12·8. $C_9H_{10}O_3NClS$ requires N, 5·7; Cl, 14·3; S, 12·9%). The same compound was obtained when 2 mols. of the sulphinic acid and 1 mol. of dichloroacetic acid were refluxed together in aqueous solution at pH 7·2.

p-*Aminophenyl(chloromethyl)sulphone.*—The foregoing sulphone (11 g.) was refluxed with 5N-hydrochloric acid (200 c.c.) for 1½ hours, and the clear solution evaporated to dryness under reduced pressure; the amino-sulphone *hydrochloride* remained as a white crystalline powder. A sample recrystallised from absolute alcohol containing anhydrous hydrogen chloride was obtained in pearly flakes, m. p. 198—200° (Found : *M*, by titration, 244. $C_7H_9O_2NCl_2S$ requires *M*, 242). The main portion was dissolved in water and basified with dilute sodium hydroxide; an oil was precipitated and rapidly solidified. Collection and recrystallisation from 50% alcohol gave p-*aminophenyl(chloromethyl)sulphone* (8 g.) as glistening white plates, m. p. 96—98° (Found : Cl, 17·4; S, 15·8. $C_7H_8O_2NClS$ requires Cl, 17·3; S, 15·6%). The same product was obtained in good yield by refluxing a solution of *p*-acetamidophenyl(chloromethyl)sulphone (5 g.) in ethyl alcohol (50 c.c.) and 5N-sodium hydroxide (50 c.c.) for 2 hours.

p-*Aminobenzenesulphonylacetonitrile.*—Anhydrous potassium *p*-acetamidobenzenesulphinate (23·7 g.) was heated with a solution of chloroacetonitrile (8 c.c.) in amyl alcohol (100 c.c.) containing a trace of copper powder for 3 hours with frequent shaking (oil-bath temp. 120°). The amyl alcohol was removed by distillation in steam, the residual solid collected (20 g.; m. p. 248—254°) and recrystallised from aqueous acetone–alcohol. p-*Acetamidobenzenesulphonylacetonitrile* (14 g.) was thus obtained in the form of white needles, m. p. 260—262° (Found : N, 12·0; S. 13·5. $C_{10}H_{10}O_3N_2S$ requires N, 11·8; S, 13·4%).

The foregoing acetyl compound (10 g.) was refluxed with 3·3N-hydrochloric acid (60 c.c.) for 45 minutes, a clear solution then being obtained. This was filtered (charcoal) and kept on ice for several hours; p-*aminobenzenesulphonylacetonitrile hydrochloride* separated in long white needles (7 g.), m. p. 206—208° (Found : Cl, 15·0; S, 13·8; *M*, by titration, 233. $C_8H_9O_2N_2ClS$ requires Cl, 15·2; S, 13·7; *M*, 232·5%). This hydrochloride was dissolved in boiling water and the solution adjusted to pH 7·2 with ammonia; sufficient alcohol was added to dissolve the precipitated oil at the b. p. and the filtered solution (charcoal) allowed to cool slowly; the free *nitrile* separated in glistening white leaves, m. p. 122—124° (Found : N, 14·5; S, 16·0. $C_8H_8O_2N_2S$ requires N, 14·3; S, 16·3%).

p-*Aminobenzenesulphonylacetamidoxime.*—The foregoing nitrile hydrochloride (6·96 g.). hydroxylamine hydrochloride (4·2 g.), and anhydrous sodium carbonate (4·8 g.) were suspended in alcohol (90 c.c.) and water (12 c.c.), shaken in a closed bottle with glass beads for 48 hours at 30—35°, and the crystalline insoluble material collected. Recrystallisation from dilute alcohol gave the *acetamidoxime* (5·1 g.) in stout white prisms, m. p. 216—218° (decomp.) (Found : N, 18·3; S, 13·7. $C_8H_{11}O_3N_3S$ requires N, 18·3; S, 13·95%).

p-*Aminobenzenesulphonylacetamidine.*—A solution of *p*-aminobenzenesulphonylacetonitrile (4·9 g.) in anhydrous dioxan (100 c.c.) and anhydrous ethyl alcohol (9·4 c.c.) was saturated at 5° with dry hydrogen chloride and the resulting suspension shaken as above for 20 days at room temperature. The bulk of the dioxan and excess of hydrogen chloride were pumped off below 35°, the residue dissolved in anhydrous alcohol (125 c.c.) previously saturated with dry ammonia at 0°, and the solution heated in a closed vessel at 45—50° for 72 hours. The solution was evaporated to dryness at 50°/10 mm., the crystalline residue dissolved in cold water and 5N-sodium hydroxide, and the clear solution adjusted to pH 7·2 with hydrochloric acid. After chilling, the *acetamidine hydrochloride* (3·5 g.) was collected and recrystallised from 90% alcohol, being obtained in heavy white prisms, m. p. >300° (3·0 g.) (Found, in salt dehydrated at 110°/2 mm. : N, 17·0; Cl, 13·9. $C_8H_{12}O_2N_3ClS$ requires N, 16·8; Cl, 14·2%), soluble in water but precipitated on addition of hydrochloric acid.

p-*Aminobenzenesulphonylthioacetamide.*—The above nitrile hydrochloride (5 g.) was dissolved in 4N-alcoholic ammonia (50 c.c.) and water (5 c.c.), the solution saturated with hydrogen sulphide, and kept with frequent shaking in a closed vessel at 35° for 24 hours, more hydrogen sulphide being passed in from time to time. After chilling, the yellow solid was collected and washed with water; recrystallisation from dilute alcohol (250 c.c.) gave the *thioacetamide* as long pale yellow needles (3 g.), m. p. 212—214° (decomp.) (Found : N, 12·6; S, 27·7. $C_8H_{10}O_2N_2S_2$ requires N, 12·2; S, 27·8%).

Ethyl α-(p-*Acetamidobenzenesulphonyl)propionate.*—*p*-Acetamidobenzenesulphinic acid (40 g.) and ethyl α-bromopropionate (36 g.) were dissolved in alcohol (225 c.c.), water (150 c.c.) and 5N-potassium hydroxide (40 c.c.), the solution adjusted to pH 7·0—7·2 and refluxed for 6 hours on the water bath in the presence of a trace of copper powder. After filtration (charcoal) the solution was evaporated until it became cloudy, and then allowed slowly to cool; the *ethyl* ester was precipitated in long white needles (52 g.), m. p. 114—118°. A sample recrystallised from dilute alcohol had m. p. 118—120° (Found : N, 4·7; S, 10·6. $C_{13}H_{17}O_5NS$ requires N, 4·7; S, 10·7%).

Ethyl α-(p-*Aminobenzenesulphonyl)propionate.*—A solution of the foregoing acetyl compound (20 g.) in saturated anhydrous alcoholic hydrogen chloride (250 c.c.) was refluxed for 2 hours. The liquid was evaporated to dryness under reduced pressure, and water (100 c.c.) and sodium bicarbonate (6 g.) added to the oily residue of the hydrochloride. The mixture was heated on the water-bath, and sufficient alcohol added to effect solution; after several days' standing, the filtered solution deposited the *propionate* (14 g.) as a mass of white needles, m. p. 68—70°, raised by recrystallisation from dilute alcohol to 72—74° (Found : N, 5·7; S, 12·5. $C_{11}H_{15}O_4NS$ requires N, 5·5; S, 12·5%).

α-(p-*Aminobenzenesulphonyl)propionic Acid.*—The acetamido-ester (20 g.) was refluxed with 5N-hydrochloric acid (200 c.c.), and 50 c.c. of liquid were allowed to distil off during the first hour. More 5N-hydrochloric acid (50 c.c.) was added, and the refluxing continued for a further 3 hours. The solution was evaporated to dryness under reduced pressure, acetone being added from time to time to assist evaporation; the residual glutinous hydrochloride became friable on trituration with ether. The solid was collected, dissolved in the minimum amount of boiling water, the theoretical amount of 5N-sodium hydroxide added, and the solution kept on ice overnight. The crystalline mass of the *acid* was collected, and a further crop obtained by evaporation of the mother-liquors. The combined material (14 g.; m. p. 156—158°) was recrystallised from boiling water (40 c.c.), the pure compound (9 g.) being obtained in small white leaves, m. p. 168—170° (Found : N, 6·0; S, 13·9; *M*, by titration, 230. $C_9H_{11}O_4NS$ requires N, 6·1; S, 14·0%; *M*, 229).

α-(p-*Aminobenzenesulphonyl*)-n-*butyric Acid.*—Potassium *p*-acetamidobenzenesulphinate (23·8 g.), ethyl α-bromo-*n*-butyrate (19·5 g.), and a trace of copper powder were refluxed in amyl alcohol (150 c.c.) for 7 hours. *Ethyl* α-(p-*acetamidobenzenesulphonyl*)-n-*butyrate*, isolated in the usual manner, recrystallised from dilute alcohol as lustrous white cubes (23 g.), m. p. 140—142° (Found : N, 4·8; S, 10·3. $C_{14}H_{19}O_5NS$ requires N, 4·45; S, 10·1%). It was also obtained, but in lower yield, when the reaction was carried out in aqueous ethyl alcohol.

The foregoing ester (22 g.) was refluxed with saturated ethyl-alcoholic hydrochloric acid (200 c.c.) for 2 hours.

Removal of the alcohol under reduced pressure, and addition of ether, precipitated *ethyl* α-(p-*aminobenzenesulphonyl*)-n-*butyrate hydrochloride* as small white prisms (16 g.). These were dried at 50°/2 mm. over charcoal and phosphoric oxide and then had m. p. 164—166° (Found: *M*, by titration, 308. $C_{12}H_{18}O_4NClS$ requires *M*, 307·5). This was converted in the usual manner into the free *ethyl* ester (11 g.), which crystallised from dilute alcohol in hard white cubes, m. p. 94—96° (Found: N, 5·4. $C_{12}H_{17}O_4NS$ requires N, 5·2%).

Ethyl α-(*p*-acetamidobenzenesulphonyl)-*n*-butyrate (13 g.) was refluxed with 5N-hydrochloric acid (125 c.c.) for 2 hours, 25 c.c. of liquid being allowed to distil over. The solution was evaporated to dryness under reduced pressure, and the residual hydrochloride recrystallised from the minimum amount of boiling water containing the theoretical amount of sodium bicarbonate. α-(p-*Aminobenzenesulphonyl*)-n-*butyric acid* (8 g.) was obtained in small white leaves, m. p. 162—164° (Found: N, 6·0; S, 12·9; *M*, by titration, 243. $C_{10}H_{13}O_4NS$ requires N, 5·8; S, 13·1%; *M*, 243). This acid was also obtained by refluxing the acetamido-ester (15 g.) with 2N-sodium hydroxide (150 c.c.) for 2 hours. The solution was adjusted to pH 7·0, evaporated to dryness, the finely divided residue extracted with boiling acetone, and the insoluble residue boiled with water (30 c.c.) and filtered. The filtrate was adjusted to pH 3·0 with hydrochloric acid, and the amino-acid separated as an oily solid. Recrystallisation from water gave 6 g. of the pure amino-acid, m. p. 162—164° (Found: *M*, 244).

Ethyl β-(p-*Acetamidobenzenesulphonyl*)*propionate*.—Potassium *p*-acetamidobenzenesulphinate (23·8 g.) was refluxed with a solution of ethyl β-chloropropionate (13·6 g.) in amyl alcohol (150 c.c.) and a trace of copper powder for 6 hours. Isolation in the usual manner and recrystallisation from dilute alcohol gave the *ethyl* ester (19 g.) in long white needles, m. p. 132—134° (Found: N, 4·9; S, 10·9. $C_{13}H_{17}O_5NS$ requires N, 4·7; S, 10·7%).

Ethyl β-(p-*Aminobenzenesulphonyl*)*propionate*.—A solution of the foregoing ester (18 g.) in saturated alcoholic hydrogen chloride (200 c.c.) was refluxed for 2 hours. After a short time iridescent leaves of *ethyl* β-(p-*aminobenzenesulphonyl*)-*propionate hydrochloride* began to separate, and finally the liquid was full of crystals. These were collected, and washed with ligroin (b. p. 40—60°); m. p. 200—202° with previous softening (15 g.) (Found: *M*, by titration, 292. $C_{11}H_{16}O_4NClS$ requires *M*, 293·5). The hydrochloride (15 g.) was dissolved in boiling water (70 c.c.) containing the theoretical amount of sodium bicarbonate. After chilling, the oily crystals were collected and recrystallised from dilute alcohol, the free *ethyl* ester being obtained (11 g.) in stout white prisms, m. p. 102—104° (Found: N, 5·7; S, 12·6. $C_{11}H_{15}O_4NS$ requires N, 5·45; S, 12·4%).

β-(p-*Aminobenzenesulphonyl*)*propionic Acid*.—The acetamido-ester (10 g.) was refluxed with 5N-hydrochloric acid (150 c.c.), and during the first hour 50 c.c. of liquid were allowed to distil off; 5N-hydrochloric acid (50 c.c.) was added, and the refluxing continued for a further 4 hours. After evaporation to dryness, 8·5 g. of the *acid hydrochloride* remained as small white cubes, m. p. 238—240° (Found: *M* by titration, 264. $C_9H_{12}O_4NClS$ requires *M*, 265·5). The hydrochloride was dissolved in boiling water (30 c.c.) and the theoretical amount of sodium bicarbonate added; on cooling, the free *acid* separated in white leaves (6 g.), m. p. 158—160° (Found: N, 6·3; S, 13·9; *M*, 230. $C_9H_{11}O_4NS$ requires N, 6·1; S, 13·95%; *M*, 229).

p-*Aminophenylcetylsulphone*.—Anhydrous sodium *p*-acetamidobenzenesulphinate (22·1 g.) and cetyl iodide (35·2 g.) were refluxed in amyl alcohol (100 c.c.) with a trace of copper powder for 4 hours. After removal of the amyl alcohol by steam distillation, the residual oil slowly solidified; this was recrystallised from 90% alcohol and gave the *acetamidosulphone* as white sebaceous needles (30 g.), m. p. 92—94° (Found: S, 7·5. $C_{24}H_{41}O_3NS$ requires S, 7·3%).

This sulphone (20 g.) was dissolved in alcohol (100 c.c.) and 10N-hydrochloric acid (100 c.c.), and the solution refluxed on the water-bath for 2 hours. The solid precipitate of hydrochloride was collected, triturated with dilute aqueous ammonia, drained, washed with water, dried in a vacuum, redissolved in alcohol, and the hydrochloride reprecipitated by the passage of dry hydrogen chloride. The hydrochloride, which is insoluble in alcohol and water, was collected, converted into the free amine with aqueous ammonia, and recrystallised from alcohol, p-*aminophenylcetylsulphone* being obtained as white needles, m. p. 110—112° (Found: N, 3·7; S, 7·9. $C_{23}H_{39}O_2NS$ requires N, 3·6; S, 8·15%).

p-*Aminophenylbenzylsulphone*.—Sodium *p*-acetamidobenzenesulphinate (22·1 g.) was refluxed with a solution of benzyl bromide (17·1 g.) in amyl alcohol (100 c.c.) and a trace of copper powder for 4 hours. The acetyl sulphone was isolated in the usual manner (30 g.), dissolved in alcohol (100 c.c.) and 10N-hydrochloric acid (100 c.c.), and the solution refluxed for 1½ hours. The crystalline precipitate of the hydrochloride was collected, ground with dilute aqueous ammonia, drained, and recrystallised from dilute alcohol; p-*aminophenylbenzylsulphone* was obtained (21 g.) in long white needles, m. p. 218—220° (Found: N, 5·8; S, 13·0. $C_{13}H_{13}O_2NS$ requires N, 5·7; S, 12·95%).

1 : 3-*Sulphone Ketones*.—p-*Aminophenylphenacylsulphone*. Sodium *p*-acetamidobenzenesulphinate (44·2 g.) and phenacyl bromide (40 g.) were refluxed with xylene (300 c.c.) with frequent shaking in the presence of a trace of copper powder for 7 hours. After removal of the xylene, the residual insoluble solid was dried and extracted with a small amount of benzene–ligroin to remove unchanged phenacyl bromide. The residue, recrystallised from a boiling mixture of acetic acid (200 c.c.) and water (400 c.c.), gave p-*acetamidophenylphenacylsulphone* in lustrous white tablets, m. p. 176—178° (48 g.) (Found: N, 4·7; S, 10·1. $C_{16}H_{15}O_4NS$ requires N, 4·4; S, 10·1%).

The foregoing acetyl compound (20 g.) was dissolved in *iso*propyl alcohol (120 c.c.), water (60 c.c.), and 10N-hydrochloric acid (120 c.c.), and the solution refluxed for 1½ hours. On cooling, *p*-aminophenylphenacylsulphone hydrochloride separated in iridescent yellow leaves, m. p. 206—210° (18 g.). This was suspended in water (120 c.c.), the calculated amount of sodium bicarbonate added, and the mixture warmed on the water-bath for 10 minutes. The insoluble material was collected and recrystallised from 80% alcohol, p-*aminophenylphenacylsulphone* being obtained (13 g.) in orange-yellow needles, m. p. 160—162° (mixed m. p. with foregoing acetyl derivative, 136—140°), soluble in dilute mineral acids and in dilute aqueous alkalis (Found: N, 5·2; S, 11·8. $C_{14}H_{13}O_3NS$ requires N, 5·1; S, 11·6%).

p-*Acetamidophenyl*-p′-*bromophenacylsulphone*. This was obtained in the same manner as the foregoing in almost theoretical yield from the sodium sulphinate and *p*-bromophenacyl bromide. The crude product, after being washed with alcohol, had m. p. 200—204°; a sample recrystallised from acetic acid formed hard white cubes, m. p. 202—204° (Found: N, 3·7; Br, 20·2. $C_{16}H_{14}O_4NBrS$ requires N, 3·5; Br, 20·2%). It is insoluble in alcohol and so could not be hydrolysed with aqueous-alcoholic hydrochloric acid.

Alkaline Hydrolysis of the 1 : 3-*Sulphone Ketones*.—(i) A solution of *p*-acetamidophenylphenacylsulphone (10 g.) in alcohol (40 c.c.) and 5N-sodium hydroxide (40 c.c.) was refluxed for 1¼ hours. The solution was adjusted to pH 8·5—9·0 with hydrochloric acid, the alcohol removed on the water-bath under reduced pressure, and the volume made up to 100 c.c. with water. Hydrochloric acid (20 c.c.) was then added and, after standing on ice for several hours, the precipitated benzoic acid was collected and washed into the filtrate with a little cold water. The amount of benzoic acid was 3·7 g., m. p. 116—118°; recrystallisation from water gave 3·1 g. of pure acid, m. p. and mixed m. p. 120° (Found: *M*, 122. Calc.: *M*, 122). The filtrate was made just alkaline to phenolphthalein and evaporated to small volume; on standing on ice, *p*-aminophenylmethylsulphone (5·2 g.) crystallised in characteristic mother-of-pearl flakes, m. p. 130—132°. Recrystallisation from boiling water gave 4·7 g., m. p. 134—136° (Found: S, 18·9. Calc.: S, 18·7%).

(ii) Hydrolysis of *p*-acetamidophenyl-*p*′-bromophenacylsulphone (10 g.) in the same manner yielded 4·6 g. of *p*-bromobenzoic acid, m. p. 252—254° (Found: *M*, 201. Calc.: *M*, 201), and 4·0 g. of *p*-aminophenylmethylsulphone, m. p. 134—136°.

Ethylation of p-*Acetamidophenylphenacylsulphone*: *Preparation of* p-*Aminophenyl*-n-*propylsulphone.*—*p*-Acetamidophenylphenacylsulphone (31·7 g.) was added to a solution of sodium (2·3 g.) in anhydrous ethyl alcohol (200 c.c.), and the solution refluxed for 20 minutes. Ethyl iodide (34 g.) was added, and the solution refluxed for 5 hours and set aside overnight. A portion of the alcohol (*ca.* 100 c.c.) was distilled off, and the residue diluted with water; the precipitated oil rapidly solidified, and was collected and recrystallised from 50% acetic acid (260 c.c.); the C-*ethyl* derivative crystallised in white tablets (23 g.), m. p. 184—186°. A sample recrystallised from the same solvent had m. p. 188—190° (mixed m. p. with parent sulphone-ketone, 158—162°) (Found: N, 4·3; S, 9·1. $C_{18}H_{19}O_4NS$ requires N, 4·1; S, 9·3%).

A solution of the foregoing *C*-ethyl compound (24 g.) in alcohol (120 c.c.) and 5N-sodium hydroxide (120 c.c) was refluxed for 1¼ hours, cooled, and adjusted to pH 9 by addition of hydrochloric acid. The bulk of the alcohol was distilled off, the volume made up to 450 c.c. with water, and the precipitated oil, which rapidly solidified, collected (12 g.; m. p. 96—98°). Recrystallisation from dilute alcohol containing a trace of 5N-sodium hydroxide gave p-*aminophenyl*-n-*propylsulphone* as white leaves (9·6 g.), m. p. 98—100° (Found: N, 7·3; S, 16·0. $C_9H_{13}O_2NS$ requires N, 7·05; S, 16·1%). The aqueous alkaline mother-liquors (450 c.c.) were acidified with hydrochloric acid and the precipitated benzoic acid collected (7·5 g., m. p. 120—122°. Found: *M*, 120. Calc.: *M*, 122).

Addition of p-*Acetamidobenzenesulphinic Acid to Cinnamic Acid.*—The sulphinic acid (40 g.) and cinnamic acid (29 g.) were boiled with water (200 c.c.) until all the oil had solidified (*ca.* 4 hours). The mixture was chilled, the solid collected and recrystallised from acetic acid, β-(p-*acetamidobenzenesulphonyl*)-β-*phenylpropionic acid* being obtained (27 g.) in white prisms. m. p. 228—230° (Found: S, 9·5; *M*, 348. $C_{17}H_{17}O_5NS$ requires S, 9·2%; *M*, 347). This acid (24 g.) was refluxed with 5N-hydrochloric acid (250 c.c.) for ¾ hour. The clear solution was cooled, the crystalline precipitate collected, and recrystallised from acetic acid and then from alcohol; β-(p-*aminobenzenesulphonyl*)-β-*phenylpropionic acid* (14 g.) was obtained, m. p. 258—260° (Found, in recrystallised acid: S, 10·3; *M*, 303. $C_{15}H_{15}O_4NS$ requires S, 10·5%; *M*, 305).

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