36. *The Action of Chlorine on Aqueous Solutions of Ammonium Sulphinates.*

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The action of chlorine or sodium hypochlorite on solutions of the ammonium salts of *p*-acetamidobenzenesulphinic acid, *p*-nitrobenzenesulphinic acid and ω-acetamido-*p*-toluenesulphinic acid gives the corresponding sulphonamides. Application of the reaction to the salts of these sulphinic acids with heterocyclic primary amines is less successful owing to side reactions, although 2-(*p*-acetamidobenzenesulphonamido)pyridine and 2-(*p*-nitrobenzenesulphonamido)pyridine are obtained in low yield from the action of chlorine on solutions of the salts of 2-aminopyridine with the appropriate sulphinic acid.

Therapeutically valuable sulphonamides have been prepared by the oxidation of sulphenamides (B.P. 550,446, 551,205, 551,206, 551,207, 557,055 and 559,384), and sulphinamides (Morren and Lehmann, *J. Pharm. Belg.*, 1942, **1**, 127). It has been reported in D.R.-P. 122,567 (Basler Chemische Fabrik) that certain aromatic sulphonamides can be obtained by passing chlorine into an aqueous alcoholic ammoniacal solution of the sulphinic acid in presence of excess of ammonia or sodium carbonate. No attempts appear to have been made to apply this reaction to the preparation of therapeutically useful sulphonamides.

p-Acetamidobenzenesulphinic, *p*-nitrobenzenesulphinic, and ω-acetamido-*p*-toluenesulphinic acid were prepared from the corresponding sulphonyl chlorides and aqueous sodium sulphite, and it is now shown that the action of chlorine or sodium hypochlorite on the ammonium salts of these acids in aqueous alcohol at 35—40° gives the corresponding sulphonamides, namely, *p*-acetamidobenzenesulphonamide, *p*-nitrobenzenesulphonamide, which was reduced to *p*-aminobenzenesulphonamide, and ω-acetamido-*p*-toluenesulphonamide respectively. Application of the reaction to salts of sulphinic acids with heterocyclic primary amines gave less satisfactory results. Treatment of 2-aminopyridine *p*-acetamidobenzenesulphinate with chlorine, under the conditions used successfully with the above ammonium sulphinates, gave in low yield 2-(*p*-acetamidobenzenesulphonamido)pyridine, which was hydrolysed to 2-(*p*-aminobenzenesulphonamido)pyridine, the main product being acetanilide-*p*-disulphone. Various modifications in the experimental conditions, as described in the experimental section, led to an increase in the yield of the sulphonamidopyridine from 5 to 18%. In similar manner the action of chlorine on the salt of *p*-nitrobenzenesulphinic acid with 2-aminopyridine gave 2-(*p*-nitrobenzenesulphonamido)pyridine. Subsequent experiments with the sulphinic acid salts of other heterocyclic primary amines, *e.g.*, 2-aminothiazole, 2-aminopyrimidine, and 2-amino-4 : 6-dimethylpyrimidine, failed to yield the corresponding sulphonamides but gave mainly water-soluble products, which probably consisted of salts of the corresponding sulphonic acids, and in some cases the disulphone.

According to Otto and Ostrop (*Annalen*, 1867, **141**, 372) arylsulphinic acids are converted into the corresponding sulphonyl chlorides or bromides by warming with aqueous chlorine or bromine. It is considered possible that the action of chlorine on the ammonium sulphinates gives the corresponding sulphonyl chlorides, but a direct oxidation mechanism is also possible, especially since the disulphone, which is formed as a by-product in some cases, is known to be obtained when sulphinic acids are oxidised in acetic acid solution with potassium permanganate (Child and Smiles, *J.*, 1926, 2696). On the other hand, the same disulphone may result from the interaction of the sulphonyl chloride with the sulphinic acid as represented below (reaction *b*, iii). The active agent is almost certainly hypochlorous acid since the reaction does not proceed under anhydrous conditions, and aqueous sodium hypochlorite can replace aqueous chlorine in these reactions. The overall reaction may be represented by the following equations in which the formation of the sulphonamide is but one of three simultaneous reactions :

$$(a) \quad R{\cdot}SO_2H + HOCl \longrightarrow R{\cdot}SO_2Cl + H_2O$$

$$(b)\ (i) \quad R{\cdot}SO_2Cl + H_2O \longrightarrow R{\cdot}SO_2{\cdot}OH + HCl$$

$$(ii) \quad R{\cdot}SO_2Cl + R'{\cdot}NH_2 \longrightarrow R{\cdot}SO_2{\cdot}NHR' + HCl$$

$$(iii) \quad R{\cdot}SO_2Cl + R{\cdot}SO_2H \longrightarrow R{\cdot}SO_2{\cdot}SO_2R + HCl$$

Experimental.

p-Acetamidobenzenesulphinic acid, m. p. 155° (decomp.), was prepared in 60% yield from *p*-acetamidobenzenesulphonyl chloride and sodium sulphite as described by Smiles and Bere (*Org. Synth.*, Coll. Vol. I, 7).

p-Nitrobenzenesulphinic acid was prepared in 50% yield from diazotised *p*-nitroaniline and sulphur dioxide in presence of copper, according to the general procedure of Hanke (*J. Amer. Chem. Soc.*, 1923, **45**, 1325) for the preparation of *p*-chlorobenzenesulphinic acid. The acid separated from water in pale yellow needles which sintered at 136° and had m. p. 160° (decomp.), in agreement with Zincke and Lenhardt (*Annalen*, 1913, **400**, 15). *p*-Nitrobenzenesulphinic acid was also prepared in 55% yield from *p*-nitrobenzenesulphonyl chloride and sodium sulphite by the same procedure as used for the preparation of *p*-acetamidobenzenesulphinic acid. The *p*-nitrobenzenesulphonyl chloride was prepared by the method of Bell (*J.*, 1928, 2776).

ω-Acetamido-p-toluenesulphinic Acid.—Crude ω-acetamido-*p*-toluenesulphonyl chloride, prepared from acetbenzylamide (20 g.) as described by Bergeim and Braker (*J. Amer. Chem. Soc.*, 1944, **66**, 1459), was shaken for 2 hours with a cold solution of crystalline sodium sulphite (67·2 g.) in water (135 c.c.) with the periodical addition of small quantities of 50% aqueous sodium hydroxide to keep the mixture just alkaline. The cold filtered solution was carefully acidified with an ice-cold solution of sulphuric acid (40 g.) in water (40 c.c.) and the precipitated sulphinic acid collected at the pump, washed with ice–water, and placed in a vacuum desiccator over potassium hydroxide. The crude product containing sodium sulphate was recrystallised from pre-heated water (200 c.c.) and ω-acetamido-*p*-toluenesulphinic acid (6·9 g.) separated in colourless plates, m. p. 138° (Found : C, 50·6; H, 5·3. Calc. for $C_9H_{11}O_3NS$: C, 50·7; H, 5·2%). Subsequent to the completion of this work this acid has been described by Jensen and Schmith (*Z. physiol. Chem.*, 1944, **280**, 35) and by Dewing (*J.*, 1946, 467), who give m. p. 137—138° and 148° respectively. More recently it has also been described by Boots Pure Drug Co., Koebner and Short (B.P. 584,584), who record m. p. 139—140°.

Action of Chlorine on Ammonium p-*Acetamidobenzenesulphinate.*—Chlorine (450 c.c.) was passed from a graduated aspirator into a clear warm solution of *p*-acetamidobenzenesulphinic acid (4 g.) in aqueous ammonia (*d* 0·88, 4 c.c.), water (4 c.c.), and ethyl alcohol (6 c.c.) at a slow rate such that the temperature

was maintained at 35—40°. Towards the end of the reaction a mass of colourless needles separated. The mixture was cooled in ice and the crystalline deposit collected at the pump and air-dried at 50° (2·75 g., m. p. 207°). Recrystallisation from water gave *p*-acetamidobenzenesulphonamide (2·5 g.) in colourless needles, m. p. 219°, alone or on admixture with an authentic specimen prepared by the method of Gelmo (*J. pr. Chem.*, 1908, **77**, 371).

Action of Sodium Hypochlorite on Ammonium p-*Acetamidobenzenesulphinate.*—A 12% aqueous solution of sodium hypochlorite (7·8 c.c.) was added slowly to a solution of *p*-acetamidobenzenesulphinic acid (2·5 g.) and aqueous ammonia (*d* 0·88, 1·5 c.c.) in water (5 c.c.) at 35—40°. Neutralisation with hydrochloric acid gave *p*-acetamidobenzenesulphonamide (1·9 g.), m. p. and mixed m. p. 219°.

Action of Chlorine on Ammonium p-*Nitrobenzenesulphinate.*—Chlorine (225 c.c.) was passed slowly into a solution of *p*-nitrobenzenesulphinic acid (1·87 g.) in water (3 c.c.), aqueous ammonia (*d* 0·88, 2 c.c.), and alcohol (3 c.c.) at 35—40°. Pale yellow needles (1·02 g.) separated on cooling. Recrystallisation from water gave *p*-nitrobenzenesulphonamide in pale yellow needles, m. p. and mixed m. p. with an authentic specimen 177°, in agreement with Blanksma (*Rec. Trav. chim.*, 1901, **20**, 129).

Action of Sodium Hypochlorite on Ammonium p-*Nitrobenzenesulphinate.*—Aqueous sodium hypochlorite (9·4%, 4 c.c.) was added slowly to a solution of *p*-nitrobenzenesulphinic acid (0·93 g.) in water (2 c.c.), aqueous ammonia (*d* 0·88, 0·75 c.c.), and alcohol (3 c.c.). The solution was neutralised with hydrochloric acid and the precipitated sulphonamide (0·4 g.) crystallised from water. The *p*-nitrobenzenesulphonamide, which was obtained in pale yellow needles, m. p. and mixed m. p. 177°, was boiled with stirring under reflux with iron filings (1·5 g.) and methylated spirit (25 c.c.) containing water (0·25 c.c.) and concentrated hydrochloric acid (0·1 c.c.). After 12 hours a further portion (0·1 c.c.) of concentrated hydrochloric acid was added and boiling was continued for a further 12 hours. The mixture was filtered hot and the filtrate made alkaline with 40% aqueous sodium hydroxide. The precipitated iron hydroxide was removed by filtration with the aid of charcoal, and the filtrate, after neutralisation with hydrochloric acid, was evaporated to dryness. Extraction of the residue with absolute alcohol gave *p*-aminobenzenesulphonamide (0·2 g.) in colourless prisms, m. p. 163°, alone or on admixture with an authentic specimen.

*Action of Chlorine on Ammonium ω-Acetamido-*p-*toluenesulphinate.*—Chlorine (225 c.c.) was passed into a solution of ω-acetamido-*p*-toluenesulphinic acid (2·13 g.) in water (5 c.c.) containing ammonia (*d* 0·88, 2 c.c.) and alcohol (5 c.c.) at 35—40°. The crystalline deposit which separated overnight was collected at the pump, washed with a little water, and air-dried at 50°. Recrystallisation from alcohol gave ω-acetamido-*p*-toluenesulphonamide (1·23 g.) in colourless needles, m. p. 173°, alone or on admixture with an authentic specimen prepared from ω-acetamido-*p*-toluenesulphonyl chloride and ammonia, as described by Bergeim and Braker (*loc. cit.*) (cf. Miller, Sprague, Kissinger, and McBurney, *J. Amer. Chem. Soc.*, 1940, **62**, 2102).

Action of Chlorine on 2-Aminopyridine p-*Acetamidobenzenesulphinate.*—Chlorine (225 c.c.) was passed into a solution of *p*-acetamidobenzenesulphinic acid (2 g.) and 2-aminopyridine (2·8 g.) in water (50 c.c.) at 0° during 10 minutes. The white solid which had separated during the reaction was filtered off, washed successively with water, alcohol, and ether, and dried [0·13 g., m. p. 247° (decomp.)]. This insoluble product was regarded as acetanilide-*p*-disulphone (Found : N, 7·2. Calc. for $C_{16}H_{16}O_6N_2S_2$: N, 7·1%), previously prepared by Child and Smiles (*loc. cit.*) from *p*-acetamidobenzenesulphinic acid and potassium permanganate in glacial acetic acid solution. The filtrate was left for 2 days at room temperature, during which time crude 2-(*p*-acetamidobenzenesulphonamido)pyridine separated; crystallisation of this from 70% alcohol gave 0·52 g., m. p. 225°, alone or on admixture with an authentic specimen prepared from *p*-acetamidobenzenesulphonyl chloride and 2-aminopyridine (Crossley, Northey, and Hultquist, *J. Amer. Chem. Soc.*, 1940, **62**, 372). Hydrolysis by boiling under reflux for 2 hours with 2N-sodium hydroxide followed by addition of hydrochloric acid to pH 6 precipitated 2-(*p*-aminobenzenesulphonamido)pyridine, which separated from alcohol in prisms, m. p. 190°, alone or on admixture with an authentic specimen. When the chlorination was carried out at 35—40° the yield of the disulphone was increased at the expense of the sulphonamide. The reaction did not take place when water was replaced by dioxan or alcohol as solvent. Part of the excess of 2-aminopyridine could be replaced by sodium carbonate.

Action of Chlorine on 2-Aminopyridine p-*Nitrobenzenesulphinate.*—Chlorine (225 c.c.) was passed into a solution of *p*-nitrobenzenesulphinic acid (1·87 g.), 2-aminopyridine (1·88 g.), and anhydrous sodium carbonate (1·06 g.) in water (50 c.c.) with shaking and ice-cooling during 10 minutes. After several days the crystalline deposit was collected; recrystallisation from 50% acetic acid gave 2-(*p*-nitrobenzenesulphonamido)pyridine (0·24 g.) in pale yellow needles, m. p. 180°, alone or an admixture with an authentic specimen prepared from *p*-nitrobenzenesulphonyl chloride and 2-aminopyridine (Ewins and Phillips, B.P. 512,145; cf. Barber, B.P. 550,446).

The action of chlorine, in similar manner, on the salts of *p*-acetamidobenzenesulphinic acid and of *p*-nitrobenzenesulphinic acid with 2-aminothiazole, 2-aminopyrimidine, and 2-amino-4 : 6-dimethylpyrimidine, did not yield the corresponding sulphonamides. In most cases the only products isolated were acetanilide-*p*-disulphone or nitrobenzene-*p*-disulphone and sulphonic acids.

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