120. *Synthesis of Derivatives of Taurinamide.*

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A general method for the synthesis of *NN'*-disubstituted taurinamides has been evolved, and a series of β-*p*-aminobenzenesulphonamidoethanesulphonamides prepared for examination as bacterial inhibitors.

Homologues of sulphanilamide containing a methylene group or groups between the aryl nucleus and the amino- and sulphonamido-residues respectively have been synthesised and reported to possess high antibacterial activity (Miller, Sprague, Kissinger, and McBurney, *J. Amer. Chem. Soc.*, 1940, **62**, 2100; G.P. 726,386). It was of interest to prepare derivatives of sulphanilamide in which the N_1 position was substituted by an alkylenesulphonamido-chain; these compounds, which have the structure $NH_2 \cdot C_6H_4 \cdot SO_2 \cdot NH \cdot C_2H_4 \cdot SO_2 \cdot NHR$, are derivatives both of sulphanilamide and of taurinamide and it would accordingly be expected that their toxicities would be of a low order (Goldberg, J., 1943, 4).

In the course of synthesising compounds of this nature a general method has been evolved for preparing *NN'*-disubstituted taurinamides of the type $R_1 \cdot NH \cdot C_2H_4 \cdot SO_2 \cdot NHR_2$. The method employed was the interaction of β-chloroethanesulphonyl chloride with amines at low temperature, followed by condensation of the *N*-substituted ethylenesulphonamide thus produced with an amine or sodio-sulphonamide at high temperature in the presence of a copper catalyst. Non-activated arylamines such as aniline, toluidine or anisidine react with β-chloroethanesulphonyl chloride in cold acetone solution with production of the ethylenesulphonarylamide in substantial yield. With alkylamines, however, it was impossible to obtain the desired ethylenesulphonalkylamide, since, even under the most favourable conditions for the production of the latter, only the β-alkylaminoethanesulphonalkylamide could be isolated. For example, when 1 mol. of *cyclo*hexylamine is added to a solution of 1 mol. of β-chloroethanesulphonyl chloride at 0° in the presence of calcium carbonate as acid acceptor, only β-*cyclo*hexylaminoethanesulphon*cyclo*hexylamide and unchanged initial materials could be isolated; similar results were obtained with activated arylamines such as *p*-nitroaniline.

The high reactivity of the alkyl halogen in β-chloroethanesulphonyl chloride was first observed by Leymann (*Ber.*, 1885, **18**, 870), who found that the compound (1 mol.) reacts with aniline (3 mols.) in dry ethereal solution with production of β-phenylaminoethanesulphonanilide together with a small amount of " phenylanhydrotaurine." Later, Autenreith and Rudolph (*Ber.*, 1901, **34**, 3470) identified Leymann's " phenylanhydrotaurine " as ethylenesulphonanilide and stated, without giving details, that it is formed by the interaction of β-chloroethanesulphonyl chloride with aniline in cold benzene solution.

Leymann (*loc. cit.*) also presumed without proof the presence of β-chloroethanesulphonanilide in the oily residues. In order to attempt to obtain β-chloroethanesulphonanilide, a solution of aniline (2 mols.) was added to β-chloroethanesulphonyl chloride (1 mol.) in acetone at 8—10°; treatment of the product without the use of alkali, however (*v.i.*), yielded only ethylenesulphonanilide together with a small amount of phenylaminoethanesulphonanilide. It would appear, therefore, that when β-chloroethanesulphonyl chloride is treated with amines, three reactions are involved, (i) the normal formation of sulphonamide, (ii) dehydrohalogenation, and (iii) addition of the amine to the double bond of the ethylenesulphonamide thus produced. Results of the present work indicate the rates of reactions (i) and (ii) to be of the same high order and this would explain the failure to obtain the β-chloroethanesulphonamides. With alkylamines the rate of reaction (iii) is of a high order and in consequence only the alkylaminoethanesulphonalkylamide is produced; while with arylamines, where the rate of reaction (iii) is low, it is possible to isolate the ethylenesulphonarylamide in substantial yield. This explanation accords with the facile dehydrohalogenation of sodium β-chloroethanesulphonate effected by dilute aqueous alkali carbonates (G.P. 678,730) and also with the work of Bruylants (*Bull. Soc. chim. Belg.*, 1923, **32**, 256) on the addition of amines to vinylacetonitrile and with that of Korner and Menozzi (*Gazzetta*, 1887, **17**, 226), Wender (*ibid.*, 1889, **19**, 437) and Autenreith and Pretzell (*Ber.*, 1903, **36**, 1262) on the addition of amines to unsaturated carboxylic acids.

The reaction of arylamines on β-chloroethanesulphonyl chloride is a more direct route to the ethylenesulphonarylamides than that from ethane-αβ-disulphonyl chloride described by Kohler (*Amer. Chem. J.*, 1897, **19**, 728), Autenreith and Rudolph (*loc. cit.*), Autenreith and Koburger (*Ber.*, 1903, **36**, 3626), and Cohen and Clutterbuck (J., 1922, **121**, 120). The lability of the β-halogen in β-chloroethanesulphonyl chloride may be contrasted with the low reactivity of the α-halogen in α-chloroethanesulphonyl chloride (Kostova, *J. Gen. Chem. Russ.*, 1941, **11**, 63; Johnson and Douglas, *J. Amer. Chem. Soc.*, 1941, **63**, 1571; Schriner and Land, *J. Org. Chem.*, 1941, **6**, 888).

The ethylenesulphonarylamides react easily with arylamines or alkylamines in boiling xylene or amyl alcohol solution, preferably in the presence of copper, with production of the *alkyl-* and *aryl-aminoethanesulphonarylamides* in good yield. In addition, the ethylenesulphonarylamides condense readily with the sodium derivative of N_4-acetylsulphanilamide with formation of the *acetylsulphanilamidoethanesulphonarylamides*, which are hydrolysed on heating with dilute acids with production of the *sulphanilamidoethanesulphonarylamides*; the latter may, however, be more readily obtained by the direct condensation of sodium sulphanilamide with the ethylenesulphonarylamide.

For the preparation of symmetrical *NN'*-disubstituted taurinamides it is more convenient to add the chloroethanesulphonyl chloride to an excess of the alkylamine or arylamine in xylene or amyl alcohol and then to reflux the mixture in the presence of copper powder.

The ethylenesulphonarylamides are low-melting solids almost insoluble in water but easily soluble in dilute alkali hydroxide provided that a high concentration of strong electrolytes is absent. They are soluble in ether and in benzene and this property may be utilised to separate them from aryl- and alkyl-aminoethanesulphonarylamides, the hydrochlorides of which are insoluble in these media. The alkyl- and aryl-aminoethanesulphonarylamides and the sulphanilamidoethanesulphonarylamides are insoluble in water but dissolve easily in dilute alkali hydroxides and also in dilute mineral acids, although frequently a large volume of the latter must be used. The isoelectric point varies with the nature of the substituents but provided a suitable indicator is employed the *hydrochlorides* may be titrated without interference from the acidic and basic sources of the parent amino-sulphonamide to give the correct molecular weight.

In general the alkyl- and aryl-aminoethanesulphonamides possess only very slight *in vitro* anti-bacterial activity; the sulphanilamidoethanesulphonarylamides, however, possess considerable *in vitro* and *in vivo* activity and toxicities of a very low order.

Experimental.

β-Chloroethanesulphonyl Chloride (compare Rumpf, *Bull. Soc. chim.*, 1938, **5**, 877).—Powdered phosphorus pentachloride (400 g.) was cautiously added to sodium isethionate (118 g.; Goldberg, J., 1942, 716), which had previously been dehydrated at 130°/5 mm. for 4 hours, and the mixture, which developed much heat and rapidly became liquid, heated with frequent shaking in an oil-bath at 120—125° for 4 hours. The liquid product was cooled, poured on ice (*ca.* 2 kg.), and the heavy oil which separated stirred in the ice-water until all the phosphoryl chloride contained in it had reacted with the water (*ca.* 2 hours). The oil was separated, taken up in benzene, and dried over calcium chloride, the benzene removed, and the residual β-chloroethanesulphonyl chloride distilled; the whole came over at 77—79°/4 mm. or 66—68°/2 mm. as a heavy colourless oil (80 g.) (Found: Cl, 43·8. Calc.: Cl, 43·6%).

In the same manner potassium isethionate (215 g.) and phosphorus pentachloride (750 g.) gave 140 g. of distilled product (66% of the theoretical yield).

Ethylenesulphonanilide.—A solution of aniline (93 g.; 1 mol.) in acetone (200 c.c.) was added to a stirred ice-cooled solution of β-chloroethanesulphonyl chloride (48·6 g.; 31·8 c.c.; 0·33 mol.) in acetone (200 c.c.) at such a rate that during the addition (*ca.* ¾ hour) the temperature was maintained at 10—12°. Stirring at room temperature was continued for a further 2 hours, 5N-hydrochloric acid (100 c.c.) added to fix any excess of aniline as the hydrochloride, and the bulk of the acetone removed in a vacuum at a temperature not exceeding 60°. 2N-Hydrochloric acid (600 c.c.) was then added, the liquor kept on ice for several hours, and the heavy oil separated. This was dissolved in warm water (200 c.c.) and 5N-sodium hydroxide (60 c.c.), the solution filtered (charcoal), and an excess of hydrochloric acid added. After standing, the heavy oil was collected and heated on the water-bath with benzene (450 c.c.), and the insoluble β-phenylaminoethanesulphonanilide hydrochloride (8 g.) filtered off. The filtrate was washed with dilute hydrochloric acid and then with water, dried over sodium sulphate, and the benzene removed in a vacuum on the water-bath; ethylenesulphonanilide remained as a heavy golden oil (44 g.; 72%) which slowly solidified in the ice-chest to a mass of soft needles, m. p. 42—46°; this was sufficiently pure for further use (Found in crude oil: Cl, 0·7%). For purification the crude material was dissolved in ether, the ethereal solution washed several times with 2N-hydrochloric acid and dried over sodium sulphate, and the ether removed. The oil thus obtained solidified overnight in the ice-chest to a hard crystalline mass, which was pressed on a pre-cooled tile and washed with ligroin (b. p. 30—40°). After draining and standing in a vacuum over charcoal the m. p. was 62—64°; recrystallisation from strongly diluted alcohol gave the ethylenesulphonanilide as white nacreous flakes, m. p. 68° (Found: no halogen; N, 7·9; S, 17·6. Calc. for $C_8H_9O_2NS$: N, 7·7; S, 17·5%).

Modified Procedure: Attempted Preparation of β-Chloroethanesulphonanilide.—The solution of aniline (61 g.; 0·66 mol.) in acetone (200 c.c.) was added during ½ hour with rapid stirring to the solution of the β-chloroethanesulphonyl chloride (48·6 g.; 0·33 mol.) in acetone (200 c.c.), the temperature being maintained at 8—10°. Stirring at 8—10° was continued for a further ½ hour, the aniline hydrochloride filtered off, 5N-hydrochloric acid (80 c.c.) added to the filtrate, and the acetone distilled off in a vacuum at 50°. 5N-Hydrochloric acid (500 c.c.) was added to the residue and, after standing overnight, the precipitated oil collected, dissolved in ether, and washed three times with 2N-hydrochloric acid. After drying over sodium sulphate, the ether was removed; the residual oil, when chilled, crystallised (26 g.; 43%). The crystals were drained on a porous tile and dissolved in dry ether, and the ether allowed to evaporate in a stream of filtered air; the ethylenesulphonanilide then separated as a mass of hard white cubes, m. p. 68° (Found: no chlorine; C, 52·6; H, 5·0; N, 8·0; S, 17·7. Calc. for $C_8H_9O_2NS$: C, 52·4; H, 4·9; N, 7·7; S, 17·5%). From the hydrochloric acid washings of the ethereal solution, 5 g. of β-phenylaminoethanesulphonanilide hydrochloride, m. p. 170—172°, separated on long standing.

*Ethylenesulphon-*p*-toluidide.*—This was obtained by the first method in 64% yield as a thick oil which slowly crystallised (Found: S, 15·3%). Recrystallisation of a sample from strongly diluted alcohol gave the pure compound in white needles, m. p. 74° (Found: N, 7·3; S, 16·3. Calc. for $C_9H_{11}O_2NS$: N, 7·1; S, 16·2%).

Ethylenesulphon-p-*phenetidide.*—This was obtained in the same manner from β-chloroethanesulphonyl chloride (1 mol.) and *p*-phenetidine (2·75 mols.), by the first procedure, as a pale golden oil which slowly solidified in the ice-chest to a crystalline mass, m. p. 72—74° (yield 70%). Recrystallisation from strongly diluted alcohol gave the compound in clusters of long white needles, m. p. 86—88° [Found: *M* (Rast), 224; C, 52·9; H, 5·9; N, 6·1; S, 14·2. Calc. for $C_{10}H_{13}O_3NS$: *M*, 227; C, 52·9; H, 5·7; N, 6·2; S, 14·1%].

Ethylenesulphon-p-*anisidide.*—This was obtained in approximately the same yield as the foregoing compound as a viscous amber oil which would not crystallise (Found: S, 14·1. Calc.: S, 15·0%).

β-p-*Phenetidinoethanesulphonanilide.*—A solution of ethylenesulphonanilide (11 g.; 0·05 mol.) and *p*-phenetidine (20·5 g.; 0·15 mol.) in xylene (100 c.c.) containing a trace of copper powder was refluxed in an oil-bath at 140° for 4 hours. Sodium carbonate (20 g.) was added, the xylene removed by distillation in steam, and the residual oil collected, taken up in N-sodium hydroxide (250 c.c.), and the solution filtered hot (charcoal). The filtrate was made strongly acid with hydrochloric acid and heated on the water-bath with shaking for ½ hour to dissolve any phenetidine present. On cooling, the insoluble oil crystallised; this was collected, redissolved in N-sodium hydroxide (300 c.c.), filtered (charcoal), and reprecipitated by an excess of hydrochloric acid. The precipitated oil, which rapidly became solid and friable, was dissolved in boiling N-hydrochloric acid (800 c.c.) and filtered (charcoal); the clear filtrate, on standing in the ice-chest for several days, gave p-*phenetidinoethanesulphonanilide hydrochloride* as a mass of long white needles (9 g.), m. p. 162—164° [Found: *M* (titration), 357: Cl, 10·0; N, 7·9; S, 8·8. $C_{16}H_{20}O_3N_2S$,HCl requires *M*, 356·5; Cl, 10·0; N, 7·9; S, 9·0%]. The hydrochloride was insoluble in absolute ethyl alcohol but very soluble in 95% alcohol, from which it crystallised in stout white needles.

β-p-*Anisidinoethanesulphon*-p-*phenetidide.*—This was obtained in the same manner as the foregoing compound from ethylenesulphon-*p*-phenetidide (10·9 g.) and *p*-anisidine (20 g.). The crude product was extracted with two successive quantities of N-hydrochloric acid (800 c.c. each), and the combined solutions filtered (charcoal) and kept on ice for 6 days; β-p-*anisidinoethanesulphon*-p-*phenetidide hydrochloride* was then obtained as a mass of long white needles (9 g.), m. p. 188—190°. On recrystallisation from boiling 96% alcohol these were obtained in stout white needles, m. p. 192—194° [Found: *M* (titration), 386; Cl, 9·0; N, 7·8; S, 8·2. $C_{17}H_{22}O_4N_2S$,HCl requires *M*, 386·5; Cl, 9·2; N, 7·3; S, 8·3%].

β-*Phenylaminoethanesulphon*-p-*toluidide.*—This was prepared in the same manner as the foregoing compound from aniline and ethylenesulphon-*p*-toluidide. The crude product was extracted four times with boiling N-hydrochloric acid, and the combined extracts filtered (charcoal) and adjusted to pH 7·0. The precipitate was collected after 12 hours and recrystallised from 95% alcohol, β-*phenylaminoethanesulphon*-p-*toluidide* being obtained in stout white needles, m. p. 78—80° (Found: N, 9·6; S, 10·9. $C_{15}H_{18}O_2N_2S$ requires N, 9·7; S, 11·0%). The *hydrochloride* crystallised from a large excess of dilute hydrochloric acid in white leaves, m. p. 158—160° (Found: *M*, 329. $C_{15}H_{18}O_2N_2S$,HCl requires *M*, 326·5).

β-*Diethylaminoethanesulphonanilide.*—A solution of ethylenesulphonanilide (10·9 g.) and diethylamine (11 g.) in xylene (50 c.c.) containing a trace of copper powder was heated in a sealed vessel at 100° for 15 hours. Sodium carbonate (15 g.) was added, and the xylene and excess of diethylamine removed by distillation in steam; the residual oil was dissolved in N-sodium hydroxide (250 c.c.), filtered, made strongly acid with hydrochloric acid, and filtered again. Sodium hydroxide was added until the pH value was exactly 7 and, after standing, the precipitated oil was collected and dissolved in benzene. This solution was dried over sodium sulphate, and the benzene removed in a vacuum; β-*diethylaminoethanesulphonanilide* was then obtained (8·5 g.) as a heavy golden oil. All attempts to obtain a crystalline hydrochloride failed (Found: N, 11·3; S, 12·9. $C_{12}H_{20}O_2N_2S$ requires N, 10·9; S, 12·5%). The compound was almost insoluble in water but easily soluble in dilute acid or alkali.

β-cyclo*Hexylaminoethanesulphonanilide.*—A solution of *cyclo*hexylamine (30 g.) and ethylenesulphonanilide (21·9 g.) in xylene (100 c.c.) was refluxed with a trace of copper powder for 4 hours. After steam distillation in the usual manner in the presence of sodium carbonate the crude oil obtained was separated, dissolved in N-sodium hydroxide (200 c.c.), filtered, and hydrochloric acid added until the pH value was 7·5—8·0; an oil was then precipitated which slowly solidified. The solid was dried on the water-bath, dissolved in acetone, a small amount of hydrochloric acid added, and the liquor evaporated nearly to dryness; β-cyclo*hexylaminoethanesulphonanilide hydrochloride* (13 g.) was then obtained as a white crystal mass. Recrystallisation from boiling dilute alcohol gave the pure compound in long white needles (10 g.), m. p. 220—222° (Found: Cl, 10·8; N, 8·8; S, 10·1. $C_{14}H_{22}O_2N_2S$,HCl requires Cl, 11·1; N, 8·75; S, 10·05%).

β-*Piperidinoethanesulphonanilide.*—This was obtained in the same way as the foregoing compound from piperidine (15 g.), ethylenesulphonanilide (10·9 g.), xylene (100 c.c.), and a trace of copper. The crude product was dissolved in acetone and treated with dry hydrogen chloride; on evaporation of the acetone β-*piperidinoethanesulphonanilide hydrochloride* was obtained as a mass of crystals. Recrystallisation from 96% alcohol gave the compound in long white needles (9 g.), m. p. 174—176° [Found: *M* (titration), 304; Cl, 11·7; N, 9·4; S, 10·5. $C_{13}H_{20}O_2N_2S$,HCl requires *M*, 304·5; Cl, 11·65; N, 9·2; S, 10·5%].

N-(*Phenylaminoethanesulphonyl*)*anthranilic Acid.*—To a stirred ice-cold solution of anthranilic acid (27·4 g.; 0·2 mol.) in water (80 c.c.), acetone (40 c.c.), and 5N-sodium hydroxide (40 c.c.) were simultaneously added 5N-sodium hydroxide (80 c.c.) and a solution of β-chloroethanesulphonyl chloride (32·4 g.; 21·2 c.c.; 0·2 mol.) in acetone (40 c.c.) at such a rate that the pH of the reacting mixture was maintained at 7·5—8·5 during the addition (¾ hour). After a further ½ hour's stirring, the acetone was removed on the water-bath under reduced pressure, and 5N-hydrochloric acid (120 c.c.) added; the oil then precipitated rapidly solidified. This was collected and ground with warm 2N-hydrochloric acid (200 c.c.) to dissolve unchanged anthranilic acid; the insoluble residue was collected and dissolved in alcohol, and the filtered solution (charcoal) evaporated to very small volume, 2-(*ethylenesulphonamido*)*benzoic acid* being obtained as a micro-crystalline powder (23 g.) pure enough for further use. It was very soluble in alcohol and acetone and insoluble in benzene and was obtained pure with great difficulty (Found: S, 13·3. $C_9H_9O_4NS$ requires S, 14·1%). The foregoing crude compound (12 g.), aniline (25 c.c.), amyl alcohol (50 c.c.), and xylene (100 c.c.) were refluxed with a trace of copper for 6 hours. After distillation of the solvents in steam the residual solid was extracted several times with boiling N-hydrochloric acid (300 c.c. each time), and the combined filtered solutions adjusted to pH 5—6; an oily solid was then precipitated which rapidly became friable. This was dissolved in dilute sodium hydroxide solution, filtered (charcoal), and reprecipitated at pH 5—6 with dilute hydrochloric acid. The collected solid was ground up with a little 5N-hydrochloric acid in order to form the hydrochloride, the suspension drained (pump), and the solid recrystallised from boiling ethyl alcohol containing a few drops of hydrochloric acid, β-*phenylaminoethanesulphonylanthranilic acid hydrochloride* being obtained (7 g.) in pearly plates, m. p. 216—218° (Found: N, 7·8; S, 8·9. $C_{15}H_{16}O_4N_2S$,HCl requires N, 7·9; S, 9·0%). This hydrochloride was very difficultly soluble in water; at pH 5 the free phenylaminoethanesulphonylanthranilic acid was precipitated, which dissolved as the sodium salt at pH 7·0.

β-cyclo*Hexylaminoethanesulphon*cyclo*hexylamide.*—*cyclo*Hexylamine (20 g.) was added to a solution of β-chloroethanesulphonyl chloride (8·1 g.) in xylene (100 c.c.) containing a trace of copper powder, and the whole refluxed (oil-bath) at 140° for 4 hours. The xylene and excess of *cyclo*hexylamine were removed by distillation in steam in presence of sodium carbonate (20 g.), and the solid residue in the flask collected (13 g.) and recrystallised twice from alcohol

(charcoal), cyclo*hexylaminoethanesulphon*cyclo*hexylamide* (8 g.) being obtained in long white needles, m. p. 250—252° (Found: N, 9·5; S, 11·0, 11·1. $C_{14}H_{28}O_2N_2S$ requires N, 9·7; S, 11·1%), insoluble in water but soluble in dilute sodium hydroxide solution and in a large volume of dilute hydrochloric acid.

β-Piperidinoethanesulphonpiperidide.—Piperidine (30 g.) was slowly added to a cooled solution of β-chloroethanesulphonyl chloride (12·2 g.) in xylene (70 c.c.), and the resulting liquid heated at 100° for 9 hours. Sodium carbonate (20 g.) and water were added, the xylene removed by distillation in steam, and the residual liquor, containing a thick black oil, kept in the ice-chest for 2 days; the oil then solidified. This solid (20 g.) was dissolved in methyl alcohol (40 c.c.) and a small amount of hydrochloric acid and filtered (charcoal); *piperidinoethanesulphonpiperidide hydrochloride* slowly crystallised in clusters of hard white needles (12 g.), m. p. 202—204°. For analysis it was recrystallised from ethyl alcohol containing a few drops of hydrochloric acid; it then had m. p. 204—206° [Found: *M* (titration), 298; Cl, 11·9; N, 9·8; S, 10·9. $C_{12}H_{24}O_2N_2S$,HCl requires *M*, 296·5; Cl, 12·0; N, 9·5; S, 10·8%]. On neutralisation of the aqueous solution the parent compound was precipitated at pH 6—7 as a heavy oil; this did not redissolve on addition of sodium hydroxide, since the compound does not contain an acidic hydrogen atom.

*β-*p*-Ethoxyphenylaminoethanesulphon-*p*-ethoxyanilide.*—A solution of *p*-phenetidine (42 g.) and β-chloroethanesulphonyl chloride (12·1 g.) in xylene (150 c.c.) was refluxed with copper powder for 4 hours. After the steam distillation the thick residual oil was shaken with warm water (400 c.c.) and hydrochloric acid (25 c.c.) in order to extract unchanged phenetidine; the undissolved portion was removed, dissolved in N-sodium hydroxide (400 c.c.), filtered (charcoal), and reprecipitated in the cold by addition of a large excess of hydrochloric acid. The precipitate was extracted with five successive quantities of boiling N-hydrochloric acid (600 c.c. each time), and the combined filtered (charcoal) extracts kept on ice for several days; *p-ethoxyphenylaminoethanesulphon-*p*-ethoxyanilide hydrochloride* (10·5 g.) then came down in white needles, m. p. 188—190°. On recrystallisation from 95% alcohol (60 c.c.) it was obtained in clusters of white leaves, m. p. 190—192° (Found: Cl, 9·1; N, 7·4; S, 7·7. $C_{18}H_{24}O_4N_2S$,HCl requires Cl, 8·9; N, 7·0; S, 8·0%).

*β-*p*-Toluidinoethanesulphon-*p*-toluidide.*—This was obtained in the same way from *p*-toluidine (38 g.), β-chloroethanesulphonyl chloride (12·2 g.), and xylene (130 c.c.) in the presence of copper. The crude product was separated, washed, dissolved in dilute sodium hydroxide solution, filtered (charcoal), and the pH value adjusted to 7·0 by the addition of hydrochloric acid. The glutinous precipitate (24 g.) became solid on standing and was recrystallised three times from boiling dilute alcohol, *β-*p*-toluidinoethanesulphon-*p*-toluidide* being then obtained in stellate clusters of white needles, m. p. 98—100° (Found: N, 9·1; S, 10·2. $C_{16}H_{20}O_2N_2S$ requires N, 9·2; S, 10·5%). It was very soluble in dilute sodium hydroxide solution in the absence of electrolytes and in a large excess of boiling dilute hydrochloric acid; from this solution the *hydrochloride* came down in white feathers, m. p. 162—164° [Found: *M* (titration), 345. $C_{16}H_{20}O_2N_2S$,HCl requires *M*, 340·5].

β-Phenylaminoethanesulphonanilide.—This was obtained in the same manner from aniline (48 g.), β-chloroethanesulphonyl chloride (13 g.), xylene (50 c.c.), and a trace of copper. The product crystallised from dilute methyl alcohol in pearly scales (16 g.), m. p. 72—74° (Found: N, 11·3. Calc.: N, 11·5%), insoluble in water but readily soluble in cold dilute sodium hydroxide solution and in a large volume of hot dilute hydrochloric acid. The hydrochloride was obtained in white needles, m. p. 172—174°, from dilute alcoholic hydrochloric acid (Lellman, *loc. cit.*, gives m. p. 169°).

Acetylsulphanilamidoethanesulphonanilide.—Anhydrous sodium N_4-acetylsulphanilamide (23·6 g.; 0·1 mol.) and a trace of copper powder were refluxed with a solution of ethylenesulphonanilide (21·9 g.; 0·1 mol.) in amyl alcohol (150 c.c.) for 4½ hours, giving a clear solution. The amyl alcohol was removed by distillation in steam, and the solid residue dissolved in warm *ca.* 0·5N-sodium hydroxide; when the solution was filtered (charcoal) and made acid to litmus, the *acetylsulphanilamidoethanesulphonanilide* was precipitated as an oil which rapidly solidified (30 g.). This, recrystallised twice from alcohol–benzene–ligroin, formed stellate clusters of white needles (21 g.), m. p. 184—186° (Found: N, 10·7; S, 16·2. $C_{16}H_{19}O_5N_3S_2$ requires N, 10·6; S, 16·1%), very soluble in alcohol, less so in benzene and insoluble in ligroin.

β-Sulphanilamidoethanesulphonanilide.—(i) The foregoing (crude) compound (15 g.) was dissolved in 2·5N-sodium hydroxide (75 c.c.), and the solution boiled for 1½ hours. Hydrochloric acid was added until the pH value was 7·0; a heavy oil was then precipitated which rapidly became solid; this was dissolved in hot 2·5N-hydrochloric acid (300 c.c.), and the solution filtered (charcoal) and adjusted to pH 7·0 with dilute aqueous sodium hydroxide; the *sulphanilamidoethanesulphonanilide* then came down as a white flocculent precipitate (9 g.), m. p. 146—150°. On recrystallisation from dilute ethyl alcohol it was obtained in stout white needles (8 g.), m. p. 160—162° (Found: N, 11·6; S, 18·2. $C_{14}H_{17}O_4N_3S_2$ requires N, 11·8; S, 18·0%).

(ii) Anhydrous sodium sulphanilamide (19·4 g.) was refluxed with a solution of ethylenesulphonanilide (21·9 g.) in amyl alcohol (200 c.c.) containing a trace of copper, until a clear solution was obtained (5 hours). The amyl alcohol was removed, and the crude residue collected and extracted with 2·5N-hydrochloric acid (300 c.c.); when the solution thus obtained was filtered (charcoal) and adjusted to pH 7, sulphanilamidoethanesulphonanilide was precipitated as a white flocculent powder; recrystallisation from dilute alcohol yielded 19 g. of the pure compound, m. p. (and mixed m. p. with the above) 160—162° (Found: N, 11·7; S, 18·1%). It was very soluble in an aqueous medium below pH 3·0 and above pH 9·5 but insoluble between these two values.

*β-Sulphanilamidoethanesulphon-*p*-phenetidide.*—This was obtained in the same manner as described under (ii) above from sodium sulphanilamide (9·7 g.) and ethylenesulphon-*p*-phenetidide (13·2 g.). Recrystallisation from dilute alcohol gave 9 g. in small white needles, m. p. 136—138° (Found: N, 10·7; S, 16·1. $C_{16}H_{21}O_5N_3S_2$ requires N, 10·5; S, 16·05%).

*β-Sulphanilamidoethanesulphon-*p*-anisidide*, obtained in like manner from sodium sulphanilamide and ethylenesulphon-*p*-anisidide and recrystallised from dilute alcohol, formed stout white needles, m. p. 134—136° (Found: N, 11·1; S, 16·7. $C_{15}H_{19}O_5N_3S_2$ requires N, 10·9; S, 16·6%).

N-(*Sulphanilamidoethanesulphonyl*)*anthranilic Acid.*—A suspension of crude 2-(ethylenesulphonamido)benzoic acid (13·2 g.), anhydrous sodium sulphanilamide (9·7 g.), and potassium carbonate (4·0 g.) in amyl alcohol (100 c.c.) was refluxed with stirring for 4½ hours. The amyl alcohol was removed by distillation in steam, and the residual solid collected and dissolved in N-sodium hydroxide (200 c.c.); N-hydrochloric acid was added to the cold filtered solution until the pH value was 8·5—9·0 and, after several hours, the small amount of precipitated sulphanilamide removed. The filtrate was adjusted to pH 6·5 and, after standing, the flocculent precipitate collected; this was dissolved in hot 0·1N-hydrochloric acid, filtered (charcoal), the pH value adjusted to 6·5, and the white flocculent precipitate filtered off and recrystallised from dilute alcohol, N-(*sulphanilamidoethanesulphonyl*)*anthranilic acid* being obtained in white needles, m. p. 178—180° (Found: N, 10·2; S, 16·1. $C_{15}H_{17}O_6N_3S_2$ requires N, 10·5; S, 16·0%). This compound was very soluble in dilute alcohol and benzene and insoluble in ligroin.

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