62. *Preparation and Properties of Sulphonacetamides: A Method for the Separation of Sulphonamides from N-Alkylsulphonamides.*

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A number of sulphonacetamides and *N*-alkylsulphonacetamides have been prepared. The determination of the titration equivalent of a sulphonacetamide gives a convenient method for the characterisation of the corresponding sulphonamide. A mixture of a sulphonamide and a *N*-alkylsulphonamide can be separated by acetylation and treatment of the resulting mixture with sodium bicarbonate solution, in which sulphonacetamides, but not *N*-alkylsulphonacetamides, are soluble. The acetyl groups can be removed subsequently by hydrolysis.

Aromatic hydrocarbons and ethers, aryl chlorides and bromides are frequently identified by chlorosulphonation and subsequent conversion of the sulphonyl chloride into the corresponding sulphonamide (Huntress and Carten, *J. Amer. Chem. Soc.*, 1940, **62**, 511, 603; Huntress and Autenrieth, *ibid.*, 1941, **63**, 3446). A convenient and accurate method for the characterisation of sulphonamides and the estimation of their molecular weight has now been developed.

The small number of sulphonacetamides described in the literature were mostly prepared by boiling the corresponding sulphonamide with acetic anhydride for prolonged periods [D.R.-P. 466,519 (1929); Chaplin and Hunter, J., 1937, 1114; Jensen and Lundquist, *Dansk. Tids. Farm.*, 1940, **14**, 129; Kostsova, *J. Gen. Chem. Russia*, 1941, **11**, 63]. *o*-Nitrobenzenesulphonacetamide was obtained from the parent sulphonamide by the action of acetic anhydride and pyridine (Tozer and Smiles, J., 1938, 2052). Noelting (*Ber.*, 1875, **8**, 598) converted *p*-bromobenzenesulphonamide into its *N*-acetyl derivative by heating with acetyl chloride. The last method has the advantage of being very rapid and generally applicable. By this method seventeen sulphonacetamides have been prepared (Table I); of these, five have been previously described.

Chaplin and Hunter (*loc. cit.*) showed that toluene-*p*-sulphonacetamide decomposes carbonates and behaves as a monobasic acid when titrated against alkali with phenolphthalein as indicator. We likewise find that the sulphonacetamides shown in Table I are fairly strong acids (for toluene-*p*-sulphonacetamide, pK = 4·8 at 22·5°), and can readily be purified, since they are freely soluble in sodium bicarbonate solution. Furthermore they can be titrated against standard alkali with phenolphthalein as indicator. The observed and the calculated equivalents are shown in Table I.

The acidic properties of sulphonacetamides can be used to effect a separation of a sulphonamide from a *N*-alkylsulphonamide. Acetylation of such a mixture gives one of a sulphonacetamide and a *N*-alkylsulphonacetamide, of which only the former component is soluble in sodium bicarbonate solution. Sulphonacetamides and *N*-alkylsulphonacetamides are readily hydrolysed in alkaline solution, giving the corresponding sulphonamides and *N*-alkylsulphonamides respectively. A number of separations of this type have been effected. Of the *N*-alkylsulphonacetamides prepared by us, those which have not been described previously are listed in Table II.

* (*Note added in proof.*) A mixture of this with a sample of *iso*caffeine, m. p. 284—286°, kindly supplied by Professor J. M. Gulland, F.R.S., had m. p. 284—286°.

TABLE I.

Sulphonacetamides, Ar·SO_2·NHAc.

	Crystal form from aqueous alcohol.	M. p.	Formula.	N, %. Found.	N, %. Calc.	Equivalent. Found.	Equivalent. Calc.
Benzene-	Prismatic needles	124–125°	$C_8H_9O_3NS$	6·9	7·0	198; 198	199
Toluene-*p*-	Flattened needles	137 [1]	$C_9H_{11}O_3NS$	—	—	214; 213; 213	213
Toluene-α-	Needles	130 [2]	$C_9H_{11}O_3NS$	6·5	6·6	211; 213	213
p-Ethylbenzene-	Microcryst.	97	$C_{10}H_{13}O_3NS$	5·9	6·2	230	227
2 : 4 : 5-Trimethylbenzene-	Prisms	155	$C_{11}H_{15}O_3NS$	5·8	5·8	241	241
2 : 4 : 6-Trimethylbenzene-	Prismatic needles	165·5	$C_{11}H_{15}O_3NS$	5·9	5·8	241; 240	241
Naphthalene-1-	Large prisms	185	$C_{12}H_{11}O_3NS$	5·6	5·6	249; 248; 250	249
Naphthalene-2-	Small plates	145—146	$C_{12}H_{11}O_3NS$	5·6	5·6	249; 249	249
Tetralin-6-	Fine needles	138 [3]	$C_{12}H_{15}O_3NS$	5·3	5·5	255; 255	253
p-Cymene-?-	Laminæ	149	$C_{13}H_{17}O_3NS$	5·7	5·5	256; 256	255
p-Methoxybenzene-	Prisms	140	$C_9H_{11}O_4NS$	6·0	6·1	228; 230; 231	229
p-Ethoxybenzene-	Prismatic needles	151·5 [4]	$C_{10}H_{13}O_4NS$	5·7	5·8	244; 244	243
m-Nitrobenzene-	Small leaflets	189 [5]	$C_8H_8O_5N_2S$	11·6	11·5	244; 243	244
p-Nitrobenzene-	Prismatic needles	192 [6]	$C_8H_8O_5N_2S$	11·2	11·5	247; 244	244
p-Bromobenzene-	Leaflets	202—203 [7]	$C_8H_8O_3NBrS$	5·3	5·0	277; 278; 276	278
2 : 5-Dichlorobenzene-	Needles	214	$C_8H_7O_3NCl_2S$	5·2	5·2	270·5; 271	268
2 : 5-Dibromobenzene-	Prisms	228	$C_8H_7O_3NBr_2S$	3·7	3·9	354	357

[1] D.R.-P. 466,519 gives m. p. 139°. Hug, *Bull. Soc. chim.*, 1934, **1**, 990, gives m. p. 139; Chaplin and Hunter (*loc. cit.*) give m. p. 136—137°.
[2] Kostsova (*loc. cit.*) gives m. p. 129°.
[3] A mixture with the parent sulphonamide (m. p. 135°) melted at 117—119°.
[4] A mixture with the parent sulphonamide (m. p. 150°) melted at 132°.
[5] Jensen and Lundquist (*loc. cit.*) give m. p. 190—191°.
[6] Jensen and Lundquist (*loc. cit.*) give m. p. 192—193°.
[7] Noelting (*loc. cit.*) gives m.p. 202—203°.

TABLE II.

N-*Alkylsulphonacetamides*, Ar·SO_2·NR·COMe.

Ar.	R.	Crystal form from aqueous alcohol.	M. p.	Formula.	N, %. Found.	N, %. Calc.
C_6H_5	C_6H_5·CH_2	Prisms	76°	$C_{15}H_{15}O_3NS$	5·05	4·85
p-CH_3·C_6H_4	C_6H_5·CH_2	Laminæ	98	$C_{16}H_{17}O_3NS$	4·6	4·6
p-C_6H_4·Br	CH_3	Flattened needles	94	$C_9H_{10}O_3NBrS$	4·9	4·8
p-C_6H_4·Br	C_2H_5	Prisms	88·5—89·5	$C_{10}H_{12}O_3NBrS$	4·45	4·6
p-C_6H_4·Br	C_6H_5·CH_2	Small needles	88—89	$C_{15}H_{14}O_3NBrS$	3·9	3·8
m-NO_2·C_6H_4	CH_3	Plates	132	$C_9H_{10}O_5N_2S$	10·9	10·85
m-NO_2·C_6H_4	C_2H_5	Prismatic needles	89	$C_{10}H_{12}O_5N_2S$	10·65	10·3
β-$C_{10}H_7$	CH_3	Fine needles	82	$C_{13}H_{13}O_3NS$	5·5	5·3
β-$C_{10}H_7$	C_2H_5	Needles	76	$C_{14}H_{15}O_3NS$	5·2	5·05
β-$C_{10}H_7$	C_6H_5·CH_2	Plates	168·5—169	$C_{19}H_{17}O_3NS$	3·9	4·1

Sulphonacetamides can be methylated by means of diazomethane to give the corresponding *N*-methylsulphonacetamide identical with that prepared by acetylation of the *N*-methylsulphonamide.

EXPERIMENTAL.

Sulphonacetamides.—The sulphonamide (1 part) was refluxed for 30 minutes with acetyl chloride (2½ parts): if solution was not complete in 5 minutes, glacial acetic acid (up to 2½ parts) was added. After removal of the excess of acetyl chloride, the cold reaction mixture was added to water, and the product collected, washed with water, and dissolved in warm sodium bicarbonate solution. The filtered solution was acidified with glacial acetic acid, and the sulphonacetamide crystallised from aqueous alcohol. The equivalent was determined by weighing accurately approximately 0·3 g. of the acetyl derivative, dissolving it in alcohol (50 c.c.; 50%), and titrating the solution against N/10-sodium hydroxide with phenolphthalein as indicator.

The dissociation constant of toluene-*p*-sulphonacetamide was estimated as follows: The amide (0·0020 mole) was dissolved in aqueous caustic soda (20·0 ml. of N/10, diluted to 50 ml.) by gentle warming, and the resulting solution cooled to room temperature (22·5°) and subjected to electrometric titration with N/10-hydrochloric acid, a "Cambridge" pH meter and a glass electrode being used. When 10·0 ml. of acid had been added, the solution had pH 4·79. The dissociation constant is thus approximately $1·6 \times 10^{-5}$ at 22·5°.

N-*Alkylsulphonacetamides.*—The *N*-alkylsulphonamide was acetylated as described above. The reaction mixture was poured into water, and the product crystallised from aqueous alcohol. Separation of mixtures of a sulphonamide and a *N*-alkylsulphonamide was achieved as follows: The mixture was acetylated as described above. The cold reaction mixture was poured into water, and the product collected, washed with water, and digested with warm sodium bicarbonate solution. The insoluble *N*-alkylsulphonacetamide was collected and crystallised from aqueous alcohol. The alkaline filtrate was acidified with acetic acid, and the sulphonacetamide collected and crystallised from aqueous alcohol.

Hydrolysis of Toluene-p-*sulphonacetamide.*—The sulphonacetamide (2 g.) was refluxed with aqueous potassium hydroxide (5%; *ca.* 60 c.c.) for 1 hour. The cold solution was acidified with dilute hydrochloric acid, and the solid collected. A dried specimen had m. p. 135—136°. It was insoluble in sodium bicarbonate solution, and was undepressed in m. p. when mixed with authentic toluene-*p*-sulphonamide. The hydrolysis was also complete when the reaction period was reduced to 45 minutes, but when the reflux period was 30 minutes, 0·4 g. of unchanged toluene-*p*-sulphonacetamide (soluble in sodium bicarbonate) was recovered. Similar conditions led to the hydrolysis of naphthalene-1-sulphonacetamide.

N-Methyl-*p*-bromobenzenesulphonacetamide and *N*-methylnaphthalene-2-sulphonacetamide were hydrolysed by refluxing with 5% aqueous-alcoholic potassium hydroxide for 1 hour.

N-*Methyl*-p-*bromobenzenesulphonacetamide*.—A solution of *p*-bromobenzenesulphonacetamide (0·5 g.) in ether (60 c.c.) and methyl alcohol (10 c.c.) was treated with an ethereal solution of diazomethane. Reaction was instantaneous. The addition of the reagent was continued until the solution acquired a permanent yellow colour. After 1 hour the solution was evaporated to dryness, and the residue warmed with saturated sodium bicarbonate solution. The insoluble oil was separated; it solidified on trituration with cold water. Crystallisation from aqueous alcohol gave *N*-methyl-*p*-bromobenzenesulphonacetamide as sword-like needles, m. p. 94°, undepressed when mixed with a specimen prepared by acetylation of *N*-methyl-*p*-bromobenzenesulphonamide. Similar treatment of naphthalene-2-sulphonacetamide and of toluene-*p*-sulphonacetamide gave respectively *N*-methylnaphthalene-2-sulphonacetamide (needles from aqueous alcohol, m. p. 82°, undepressed when mixed with a specimen prepared by acetylation of *N*-methylnaphthalene-2-sulphonamide) and *N*-methyltoluene-*p*-sulphonacetamide [prisms from aqueous alcohol, m. p. 59°, undepressed when mixed with the specimen obtained by acetylation of *N*-methyltoluene-*p*-sulphonamide (Chaplin and Hunter, *loc. cit.*)].

Our thanks are due to Misses Audrey Barlow, Jean Caley, and Sonia Dunstan, Messrs. F. Brown, E. F. Chandley, N. C. George, T. G. Halsall, G. A. Lombard, F. Long, G. W. Loynd, and S. W. Milne for very considerable assistance in carrying out these experiments.

THE UNIVERSITY, MANCHESTER. [*Received, November 28th*, 1944.]