27. *The Preparation of Some* N-*Substituted Derivatives of* p-*Toluenesulphonamide.*

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Derivatives of type p-$CH_3\cdot C_6H_4\cdot SO_2\cdot NH\cdot COR$ (R = aliphatic, aromatic, or mixed aliphatic aromatic) have been prepared.

Aroylation was achieved by three methods. Some new substituted benzamidines have been prepared from *p*-toluenesulphon-α-chlorobenzylideneamide, p-$CH_3\cdot C_6H_4\cdot SO_2\cdot N{:}CCl\cdot C_6H_5$, and the stability of the chlorine atom towards various reducing agents investigated.

The following series of reactions was attempted in the hope of obtaining a general method for the preparation of aldehydes :

$$p\text{-}CH_3\cdot C_6H_4\cdot SO_2\cdot NH_2 \xrightarrow{R\cdot CO\cdot Cl} p\text{-}CH_3\cdot C_6H_4\cdot SO_2\cdot NH\cdot COR \xrightarrow{PCl_5} p\text{-}CH_3\cdot C_6H_4\cdot SO_2\cdot N{:}CClR \xrightarrow{H_2}$$

$$p\text{-}CH_3\cdot C_6H_4\cdot SO_2\cdot N{:}CHR \xrightarrow{H_2O} p\text{-}CH_3\cdot C_6H_4\cdot SO_2\cdot NH_2 + R\cdot CHO$$

Using similar schemes both Sonn and Muller (*Ber.*, 1919, **52**, 1927) and Staudinger (*ibid.*, 1908, **41**, 2217) prepared benzaldehyde from benzanilide. In the present case ($R = C_6H_5$) the reduction of the iminochloride, *p*-toluenesulphon-α-chlorobenzylideneamide, has not so far been effected.

Benzanilide iminochloride is reduced quite readily by stannous chloride (Sonn and Muller, *loc. cit.*) to the corresponding azomethine, $C_6H_5\cdot CH{:}N\cdot C_6H_5$. One of us (Stephen, *J.*, 1925, 1874) in an aldehyde synthesis from cyanides has reduced similar iminochlorides by means of stannous chloride and hydrogen chloride. Neither this last method nor other reducing agents—*e.g.*, sodium in alcohol, tin and hydrochloric acid, zinc dust in alcohol, zinc dust in glacial acetic acid—had any effect, except that some hydrolysis always took place. Thus the introduction of the SO_2 group into the benzanilide iminochloride type of molecule seems to reduce the mobility of the halogen considerably.

Meanwhile, other *N*-aroyl and *N*-acyl derivatives of *p*-toluenesulphonamide have been prepared. Three methods of aroylation were used :

(i) Dry fusion of *p*-toluenesulphonamide and the acid chloride at temperatures under 150°, following the method of Gerhardt and Chiozza (*Annalen*, 1853, **87**, 299; Wallach, *ibid.*, 1882, **214**, 209; Wallach and Grossman, *Ber.*, 1878, **11**, 753).

The above authors mention the decomposition of *N*-acyl sulphonamides to cyanides and sulphonic acids at temperatures above 150°. We confirmed this for the reaction between α-naphthoyl chloride and *p*-toluenesulphonamide. At 180° α-naphthyl cyanide and *p*-toluenesulphonic acid were the only products obtained. No *p*-toluenesulphon-α-naphthamide was detected.

(ii) In pyridine solution (Northey *et al.*, *J. Amer. Chem. Soc.*, 1939, **61**, 2950; and many recent patents, *e.g.*, B.PP. 581,932; 581,934).

(iii) By a modification of the Schotten–Baumann method of benzoylation.

When *p*-toluenesulphonamide was benzoylated using the ordinary procedure, poor yields were obtained together with *p*-toluenesulphonamide. *N*-Acyl and *N*-aroyl derivatives of *p*-toluenesulphonamide are strong acids (Wolkowa, *Z. Chem.*, 1870, **6**, 577; Chaplin and

Hunter, *J.*, 1937, 1118; Oxley *et al.*, *J.*, 1946, 768). At the start of the reaction, the *p*-toluenesulphonamide was present as the sodium salt, which then reacts with the acid chloride to form the *N*-acyl or *N*-aroyl derivative. Since this is more acidic than the starting material its sodium salt is produced, and the liberated *p*-toluenesulphonamide is precipitated. If two moles of sodium hydroxide are used, both sodium hydroxide and the sodium salt of *p*-toluenesulphonamide are competing for the benzoyl chloride. We therefore used the sodium salt of *p*-toluenesulphonamide (2 moles) and acid chloride (1 mole), and obtained much improved yields (calculated on acid chloride).

N-Acyl derivatives of *p*-toluenesulphonamide were prepared from the acid anhydrides. Methods as given for the preparation of *N*-acetyl-*p*-toluenesulphonamide (D.R.-P. 466,519; Chaplin and Hunter, *loc. cit.*) were modified. The reaction was strongly exothermic, and long heating was not necessary; also only a few drops of sulphuric acid were required to catalyse the reaction.

A series of substituted benzamidines of type $p\text{-}CH_3{\cdot}C_6H_4{\cdot}SO_2{\cdot}N{:}C(NHR){\cdot}C_6H_5$ was prepared (Gerhardt, *Annalen*, 1858, **108**, 214; Wallach, *loc. cit.*; Geigy, B.P. 538,822). One of these ($R = C_6H_5$) was also prepared by the condensation of benzanilide iminochloride and *p*-toluenesulphonamide.

EXPERIMENTAL.

The Direct Heating Method.—Pure *p*-toluenesulphonamide (1 mole) and the corresponding acid chloride (1 mole or slightly more) were heated at 130—140° until evolution of hydrogen chloride had ceased. The crude product was then extracted with successive quantities of boiling water, dried, and crystallised from alcohol. Results are given below. In one run, using α-naphthoyl chloride, the temperature was maintained at 180°; α-naphthyl cyanide was isolated by steam distillation, m. p. 37—38° undepressed by admixture with an authentic specimen. *p*-Toluenesulphonic acid was identified by the production of *p*-cresol on potassium hydroxide fusion of the residue obtained after steam distillation.

p-Toluenesulphonamide.	*p*-Toluene-sulphonamide (g.).	Acid chloride (g.).	Yield (%).	M. p.
1. *N*-Benzoyl-	50	45	86	147°
2. N-o-*Toluoyl-*	11·5	11·5	*ca.* 5	112·5—113
3. N-m-*Toluoyl-*	5·1	5·1	2—4	132
4. N-3 : 4 : 5-*Trimethoxybenzoyl-*	16·1	21·75	54	168—169
5. N-*Phenoxyacetyl-*	20	20	49	139
6. N-β-*Naphthoyl-*	20	20	79	162·5—163
7. N-*Veratroyl-*	4·67 *	4·84	2—4	130—134 (decomp.)

* Sodium salt used.

Notes 1. Wolkowa (*loc. cit.*) gives m. p. 147—150° (Found: C, 61·1; H, 4·8. Calc. for $C_{14}H_{13}O_3NS$: C, 61·05; H, 4·8%).
2. (Found: C, 61·9; H, 5·2. $C_{15}H_{15}O_3NS$ requires C, 62·2; H, 5·2%.)
3. Mixed m. p. with *p*-toluenesulphonamide, 116—134° (Found: C, 62·1; H, 5·3. $C_{15}H_{15}O_3NS$ requires C, 62·2; H, 5·3%).
4. Mixed m. p. with 3 : 4 : 5-trimethoxybenzoic acid (m. p. 167—169°) 140—160° (Found: C, 55·8; H, 5·35. $C_{17}H_{19}O_6NS$ requires C, 55·9; H, 5·2%).
5. (Found: C, 58·9; H, 5·0. $C_{15}H_{15}O_4NS$ requires C, 59·0; H, 4·9%.)
6. (Found: C, 66·1; H, 4·8. $C_{18}H_{15}O_3NS$ requires C, 66·5; H, 4·6%.)
7. (Found: C, 54·5; H, 5·5. $C_{16}H_{17}O_5NS,H_2O$ requires C, 54·4; H, 5·4%.) In another experiment 2·0044 g. of *N*-veratroyl-*p*-toluenesulphonamide on drying for 3 hours at 140°/60 mm. lost 0·1129 g., *i.e.*, 1·1 moles of water per mole of derivative.

Aroylation in Pyridine.—A mixture of *p*-toluenesulphonamide (1 mole) dissolved in pyridine (2 moles) and the acid chloride (1 mole) was heated on the water-bath for 75 minutes, then poured into dilute hydrochloric acid. On cooling and stirring, the oil solidified, and the solid was extracted once or twice with boiling water, dried, and crystallised from alcohol. Results are given below.

p-Toluenesulphonamide.	*p*-Toluene-sulphonamide (g.).	Acid chloride (g.).	Yield (%).	M. p.
1. *N*-Benzoyl-	5	4·12	80	147°
2. N-p-*Toluoyl-*	5·7	5·1	78	138—139
3. N-*Phenylacetyl-*	5·13	4·64	0	—
4. *N*-Veratroyl-	5·13	6·02	3—5	132—134 (decomp.)
5. *N*-3 : 4 : 5-Trimethoxybenzoyl-	3·42	4·61	2—5	152—159

Notes 2. (Found: C, 61·6; H, 5·25. $C_{15}H_{15}O_3NS$ requires C, 62·2; H, 5·2%.)
5. A small amount of intractable material was obtained.

Modified Schotten–Baumann Method.—*p*-Toluenesulphonamide (2 moles) was dissolved in aqueous sodium hydroxide (2 moles of 5%), and the acid chloride (1 mole) was added in small quantities at a time, with shaking and cooling. When from 1/4 to 1/2 had been added, a precipitate of *p*-toluenesulphonamide began to form, increasing in amount as more acid chloride was added. When the addition was complete, the reaction mixture was left for 5 minutes, *p*-toluenesulphonamide collected, and the filtrate carefully acidified with concentrated hydrochloric acid. The precipitated derivative was digested several times with boiling water, then crystallised from alcohol or acetic acid. Results are given below.

p-Toluenesulphonamide.	*p*-Toluene-sulphonamide (g.).	Acid chloride (g.).	*p*-Toluene-sulphonamide recovered (g.).	Yield (%).	M. p.
1. *N*-Benzoyl-	17	7	8·3	76	147°
2. *N*-*o*-Toluoyl-	11·4	5·1	11·3	0	—
3. *N*-*m*-Toluoyl-	10·5	4·5	4·55	48	132—132·5
4. *N*-*p*-Toluoyl-	10·5	4·5	8·9	7	138—139
5. *N*-Phenylacetyl-	6·84	3·09	3·4	65	147·5—148·5

Note 5. (Found : C, 62·1; H, 5·3. $C_{15}H_{15}O_3NS$ requires C, 62·2; H, 5·2%.)

Formation of p-*Toluenesulphonyl*-N-*acylamides*.—*p*-Toluenesulphonamide (1 mole) was mixed with the acid anhydride (1 mole) and a few drops of concentrated sulphuric acid were added. The temperature rose rapidly, the reaction mixture becoming liquid (mixture was warmed gently, if necessary, to give a clear solution). When cold, the solid product was boiled with a little water, and the residue collected and dried. In two cases the compounds crystallised from hot water. Results are given below.

p-Toluenesulphonamide.	*p*-Toluene-sulphonamide (g.).	Acid anhydride (g.).	Yield (%).	M. p.
1. *N*-Acetyl-	5·13	3·06	90	137°
2. N-*Propionyl*-	5·13	3·9	85·6	111—112
3. N-*Butyryl*-	5·13	4·74	82	82—83

Notes 1. D.R.-P. 466,519 gives m. p. 139°; Chaplin and Hunter (*loc. cit.*) give m. p. 136—137°. We obtained the compound in needles from alcohol, mixed m. p. with *p*-toluenesulphonamide 103—116° (Found : C, 51·0; H, 5·2. Calc. for $C_9H_{11}O_3NS$: C, 50·7; H, 5·2%).

2. Needles from hot water (Found : C, 52·95; H, 5·8. $C_{10}H_{13}O_3NS$ requires C, 52·8; H, 5·8%).

3. Feathery needles from hot water (Found : C, 54·8; H, 6·3. $C_{11}H_{15}O_3NS$ requires C, 54·7; H, 6·3%).

p-*Toluenesulphon*-α-*chlorobenzylideneamide*.—This was prepared according to Wolkowa (*Ber.*, 1872, **5**, 140); m. p. 103° (Wolkowa gives m. p. 100°). Washings and crude product both smelled strongly of phenyl cyanide. Yield, 51% (Found : N, 4·7. Calc. for $C_{14}H_{12}O_2NClS$: N, 4·8%).

Substituted Benzamidines.—(*a*) *N*-*p*-Toluenesulphonylbenzamidine was prepared as follows. Dry ammonia gas was passed into a solution of *p*-toluenesulphon-α-chlorobenzylideneamide (0·5 g.), in dry ether (75 ml.), until saturated. The precipitate of ammonium chloride was removed, and from the filtrate a white solid (m. p. 146—147°) was obtained by evaporation; mixed m. p. with *N*-*p*-toluenesulphonylbenzamide 114—135°. Wolkowa (*Ber.*, 1872, **5**, 141) gives m. p. of *N*-*p*-toluenesulphonylbenzamidine as 114° (Found : N, 10·3. Calc. for $C_{14}H_{14}O_2N_2S$: N, 10·2%).

(*b*) The following method was used for the preparation of the other substituted benzamidines. *p*-Toluenesulphon-α-chlorobenzylideneamide (1·5 g.) was dissolved in dry ether (50 ml.), and the amine, in slight excess over the calculated quantity, added in solution in dry ether (25 ml.). The precipitate was left overnight, collected, washed with distilled water, and crystallised from alcohol. The following compounds were prepared by this method :

N′-p-*Toluenesulphonyl*-N-*phenylbenzamidine*, m. p. 146—147°. Yield, 86%. Also crystallises in a form, m. p. 151—152°. Mixed m. p. with *p*-toluenesulphonylbenzamide 115—145° (Found : N, 8·1. $C_{20}H_{18}O_2N_2S$ requires N, 8·0%).

The compound was also prepared from benzanilide iminochloride (10·9 g.) and *p*-toluenesulphonamide (8·7 g.) by heating for 1 hour at 100° and then for a further ½ hour at 140°. On cooling, the product solidified, and was obtained in crystals from alcohol, m. p. 127—138°. Further purification gave a product, m. p. 144—145°, undepressed by admixture with pure material prepared by the first method. Yield, 8 g. (crude).

N′-p-*Toluenesulphonyl*-N-o-*tolylbenzamidine*, m. p. 137—138°. Yield, 77%. Mixed m. p. with *p*-toluenesulphonamide 109—120° (Found : N, 7·9. $C_{21}H_{20}O_2N_2S$ requires N, 7·7%).

N′-p-*Toluenesulphonyl*-N-m-*tolylbenzamidine*, m. p. 156—157°. Yield, 84% (Found : N, 7·9%).

N′-p-*Toluenesulphonyl*-N-p-*tolylbenzamidine*, m. p. 167—168°. Yield, 89% (Found : N, 7·9%).

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