281. *Cyanamides. Part V.* N-*Aryl*-N′-*arylsulphonylureas.*

By FREDERICK KURZER.

N-Aryl-*N*′-arylsulphonylureas, R′·NH·CO·NH·SO$_2$R, have been prepared by two methods, and some aspects of their chemical behaviour have been examined.

INTERACTION of arylureas and aromatic sulphonyl chlorides has recently been shown to occur with simultaneous dehydration to yield *N*-aryl-*N*-arylsulphonylcyanamides R′·SO$_2$·NR·CN (Part I, *J.*, 1949, 1034). This probably involves the intermediate formation of the highly unstable *iso*urea sulphonates of the type R′·SO$_2$·O·C(:NH)·NHR (Oxley, Partridge, Peak, and Short, *Chem. and Ind.*, 1949, 419; Kurzer, *ibid.*, p. 522), several observations having provided indirect evidence in support (Parts III and IV, *J.*, 1949, 3033; 1950, 3269). An alternative mechanism, *viz.*, the intermediate formation of *N*-aryl-*N*′-arylsulphonylureas, followed by dehydration and rearrangement if necessary, had been tentatively considered (cf. Part I, *loc. cit.*); it was pointed out at the same time, however, that such compounds, synthesised by independent methods, were not dehydrated under the conditions of the urea–sulphonyl chloride reaction, and all subsequent observations have supported the mechanism involving *iso*urea sulphonates. Some new observations on the synthesis and properties of *N*-aryl-*N*′-arylsulphonylureas are now recorded.

Before 1940 only two methods for the preparation of sulphonylureas had been reported. Cleve (*Ber.*, 1888, **21**, 3266, 3273) had obtained two apparently impure sulphonylurea derivatives by the action of potassium cyanate on sulphonamides of the naphthalene series, and Billeter (*Ber.*, 1904, **37**, 690) synthesised several benzenesulphonylureas by interaction of amines with the difficultly accessible benzenesulphonyl *iso*cyanate. During recent years interest in certain substituted sulphonylureas was aroused because of their close structural relation to chemotherapeutically valuable sulphonamides. Thus, *p*-aminobenzenesulphonylurea and related compounds were prepared by suitable variations of the numerous conventional urea syntheses (see references 3—9, Table 1).

The only two routes explored for the preparation of *N*-aryl-*N*′-arylsulphonylureas are Billeter's method which afforded *N*-benzenesulphonyl-*N*′-phenylurea (equation 1, p. 1259), and the interaction of a sulphonamide with an aryl *iso*cyanate (Haak, U.S.P. 2,385,571; Geigy, B.P. 538,884) (equation 2).

In the present investigation three possible methods of preparing such urea derivatives were examined. Interaction of sulphonamides and arylureas in alkaline media (equation 3) gave *N*-phenyl-*N*′-toluene-*p*-sulphonylurea and the *N*-*p*-methoxyphenyl analogue, but not the corresponding benzenesulphonylphenylurea. Although various conditions were employed, the yield did not exceed 10—15%. A further disadvantage was the necessity of removing unchanged sulphonamide and *s*-diarylurea, formed as by-product during the prolonged heating.

More favourable results were obtained in the interaction of aromatic sulphonamides and *iso*cyanates (equation 2). Haak (*loc. cit.*) had condensed the reactants in the absence of solvents, and Geigy (*loc. cit.*) had used nitrobenzene as medium. Preliminary experiments in various solvents gave moderate yields, which were greatly improved by the presence of triethylamine. Thus, in anhydrous toluene 25—30% yields of the sulphonylurea were obtained, and *s*-diphenylurea was formed as by-product; the addition of triethylamine, particularly in relatively large quantities (approximately 0·25 mole), accelerated the condensation considerably and gave up to 90% yields. The use of tertiary amines for catalysing the reaction between *iso*cyanates and hydroxyl-containing compounds is well known (Tarbell, Mallat, and Wilson, *J. Amer. Chem. Soc.*, 1942, **64**, 2229) and has recently been studied in detail by Baker and Gaunt (*J.*, 1949, 9). The interaction of *iso*cyanates and amines, on the other hand, proceeds normally so readily that no attempts to employ tertiary amines as catalysts appear to be on record (cf. Saunders and Slocombe, *Chem. Reviews*, 1948, **43**, 203). It may be pointed out that in the latter reaction the amine may be responsible for autocatalytic effects. When replaced, in the present reaction, by a sulphonamide, of essentially acidic character, the addition of a tertiary base becomes significant. The difference in the velocity with which amino- and sulphonamido-groups react with *iso*cyanic esters is clearly illustrated by Roth and Degering's observation (*J. Amer. Chem. Soc.*, 1945, **67**, 126) that approximately equimolecular proportions of *p*-aminobenzenesulphonamide and *iso*cyanates react to form *N*-aryl-*N*′-*p*-sulphonamidophenylureas: the *iso*cyanate is consumed preferentially by the primary amino-group of the molecule, and the sulphonamido-grouping remains unaffected. Analogous results have also been obtained in the thiourea series (Dyson, B.P. 517, 682).

$$R'{\cdot}SO_2{\cdot}NCO + R{\cdot}NH_2 \longrightarrow R'{\cdot}SO_2{\cdot}NH{\cdot}CO{\cdot}NHR \quad . \; . \; . \; . \; . \; (1)$$

$$R'{\cdot}SO_2{\cdot}NH_2 + R{\cdot}NCO \longrightarrow R'{\cdot}SO_2{\cdot}NH{\cdot}CO{\cdot}NHR \quad . \; . \; . \; . \; . \; (2)$$

$$R'{\cdot}SO_2{\cdot}NH_2 + R{\cdot}NH{\cdot}CO{\cdot}NH_2 \longrightarrow R'{\cdot}SO_2{\cdot}NH{\cdot}CO{\cdot}NHR + NH_3 \quad . \; . \; . \; (3)$$

$$R'{\cdot}SO_2Cl + R{\cdot}NH{\cdot}CO{\cdot}NH_2 \longrightarrow R'{\cdot}SO_2{\cdot}NH{\cdot}CO{\cdot}NHR + HCl \quad . \; . \; . \; (4)$$

It has been claimed (Geigy, B.P. 538,884; U.S.P. 2,371,178; Swiss P., 224,070) that melting *p*-nitrobenzenesulphonyl chloride with urea, first at 100—120° and later at 140°, gave *p*-nitrobenzenesulphonylurea (equation 4). However, the constants quoted for this compound, and for the *p*-amino-derivative obtained therefrom by reduction, are anomalous (see Table). Remsen and Garner (*Amer. Chem. J.*, 1901, **25**, 175) have shown that aromatic sulphonyl chlorides and urea at *ca.* 100° yield sulphonates of amidinourea, $NH_2{\cdot}CO{\cdot}NH{\cdot}C(\colon NH){\cdot}NH_2$. Repetition of Remsen's work, under Geigy's conditions, gave no evidence of sulphonylurea formation.

In this connexion the behaviour of an aromatic urea on fusion with a sulphonyl chloride was also examined. Phenylurea and toluene-*p*-sulphonyl chloride formed a homogeneous melt and interacted slowly at 100°, yielding toluene-*p*-sulphonanilide. Above 140—150°, vigorous evolution of hydrogen chloride occurred, but decomposition resulted, producing the sulphonanilide, ammonium toluene-*p*-sulphonate, and *s*-diphenylurea. Since a blank experiment established that *N*-phenyl-*N*-toluene-*p*-sulphonylcyanamide does not yield toluene-*p*-sulphonanilide on prolonged fusion with toluene-*p*-sulphonyl chloride—although it does afford the latter product in acid media under certain conditions (cf. Part II, *J.*, 1949, 3029)—the sulphonylcyanamide does not appear to be an intermediate in the arylurea–sulphonyl chloride fusion. The reaction products are therefore probably formed directly by the union of the sulphonyl chloride with the decomposition products of the aromatic urea.

A second synthesis of sulphonylureas and sulphonylthioureas from sulphonyl halides and substituted ureas, using a modified Schotten–Baumann technique, has been claimed (Migliardi and Tappi, *Arch. Sci. biol.*, 1941, **27**, 164). Here again the results were not confirmed and have been discussed elsewhere (Leitch *et al.*, *Canad. J. Res.*, 1945, **23**, *B*, 139; Kurzer, *J. Appl. Chem.*, 1951, **1**, 80).

	Method.	$NO_2{\cdot}C_6H_4{\cdot}SO_2{\cdot}NH{\cdot}CO{\cdot}NH_2$. M. p.	$NH_2{\cdot}C_6H_4{\cdot}SO_2{\cdot}NH{\cdot}CO{\cdot}NH_2$. M. p.
I.	$R{\cdot}SO_2Cl + NH_2{\cdot}CO{\cdot}NH_2$ ...	190° (decomp.) [1]	320° (subl.) [1]; 303° (decomp.) [2];
II.	$R{\cdot}SO_2{\cdot}NH_2 + H{\cdot}NCO$	—	149—154° [3]; 158—160° [4];
III.	$R{\cdot}SO_2{\cdot}NH{\cdot}CN + H{\cdot}OH$	178—180° [5]	143—147° [6]; 140° [7];
IV.	$R{\cdot}SO_2Cl + NH_2{\cdot}C(OMe)\colon NH$ [8]	—	140° [7]; 140—146° [9]

[1] Geigy, *loc. cit.* [2] Migliardi and Tappi, *loc. cit.* [3] Haak, *loc. cit.* [4] Martin *et al.*, U.S.P. 2,411,661. [5] Backer and Moed, *Rec. Trav. chim.*, 1947, **66**, 335. [6] Leitch *et al.*, *loc. cit.* [7] Winnek *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 1682. [8] Followed by hydrolysis. [9] Cox, *ibid.*, p. 2225; see also Haak, G.P. 741,533.

The persistent failure of urea and its *N*-substituted derivatives to afford *N*-sulphonylureas by interaction with sulphonyl chlorides (equation 4) under all conditions so far examined is in marked contrast to the behaviour of *O*-substituted ureas, which yield *N*-sulphonyl derivatives without difficulty (Cox and Raymond, *J. Amer. Chem. Soc.*, 1941, **63**, 300) (equation 5). This is accounted for satisfactorily if sulphonyl halides will be substituted at the nitrogen atom only if the enolic hydroxyl group is already effectively blocked by a substituent. In the absence of such substituents the formation of highly unstable intermediate *O*-sulphonyl*iso*ureas, $R{\cdot}NH{\cdot}C(O{\cdot}SO_2R'){:}NH$, may be assumed. Their immediate decomposition to cyanamides and arylsulphonic acids, followed by further changes, explains the production of amidinourea from urea (cf. Oxley, Partridge, Peak, and Short, *loc. cit.*) and of sulphonylcyanamides from *N*-arylureas (this series, Parts II—IV, *locc. cit.*). Intermediate *O*-sulphonyl esters cannot, of course, arise from *O*-substituted *iso*ureas, which react therefore simply to yield *N*-sulphonyl*iso*ureas (equation 5) in aqueous media in the presence of sodium hydroxide, *i.e.*, under conditions where ureas fail to react at all.

$$R'{\cdot}SO_2Cl + NH_2{\cdot}C(OMe){:}NH \longrightarrow R'{\cdot}SO_2{\cdot}NH{\cdot}C(OMe){:}NH \quad . \; . \; . \; . \quad (5)$$

Sulphonylureas decompose on melting. Arylsulphonylureas, for example, resolidified immediately after melting and then decomposed at a higher temperature. Backer and Moed (*Rec. Trav. chim.*, 1947, **66**, 689; *Bull. Soc. chim. Belg.*, 1948, **57**, 211) have shown that certain *p*-nitroarylsulphonyl-guanidines and -ureas decomposed in alkaline media, and sometimes on prolonged fusion, with elimination of sulphur dioxide (equation 6). It has now been found that, in general, sulphonylureas decompose fairly rapidly above their melting points to yield the corresponding sulphonamide and *iso*cyanate (equation 7):

$$NO_2{\cdot}C_6H_4{\cdot}SO_2{\cdot}NH{\cdot}C({:}NPh){\cdot}NHPh \longrightarrow NO_2{\cdot}C_6H_4{\cdot}NH{\cdot}C({:}NPh){\cdot}NHPh + SO_2 \quad . \quad (6)$$

$$R'{\cdot}SO_2{\cdot}NH{\cdot}CO{\cdot}NHR \longrightarrow R'{\cdot}SO_2{\cdot}NH_2 + R{\cdot}NCO \quad . \; . \; . \; . \; . \quad (7)$$

Toluene-*p*-sulphonylurea, for example, when kept above 220° for 30 minutes decomposed completely to yield toluene-*p*-sulphonamide and cyanuric acid (probably by polymerisation of the intermediate *iso*cyanic acid). The formation of cyanuric acid accounts for the resolidification, after fusion, of arylsulphonylureas and for the resumed decomposition at higher temperatures. Urea derivatives bearing substituents on both nitrogen atoms decomposed analogously: *N*-phenyl-*N'*-toluene-*p*-sulphonylurea evolved phenyl *iso*cyanate and gave a residue of the sulphonamide and small quantities of *s*-diphenylurea.

The action of certain dehydrating agents on *N*-aryl-*N'*-arylsulphonylureas has also been examined. Thionyl chloride, phosphorus oxychloride, and toluene-*p*-sulphonyl chloride, which are generally employed in the conversion of amides into nitriles, failed to remove the elements of water from sulphonylureas under the conditions used. Under restrained conditions (*e.g.*, short action of thionyl chloride at room temperature; heating with toluene-*p*-sulphonyl chloride in pyridine) the sulphonylurea was unaffected while more vigorous action resulted in fission: *N*-phenyl-*N'*-toluene-*p*-sulphonylurea, for example, gave toluene-*p*-sulphonyl chloride and aniline on brief boiling with phosphorus oxychloride. Heating the sulphonylurea with thionyl chloride or phosphorus oxychloride in pyridine gave intractable oils. These results show that *N*-aryl-*N'*-arylsulphonylureas do not undergo dehydration under the conditions of the synthesis of *N*-aryl-*N*-arylsulphonylcyanamides from aromatic ureas (cf. Part I, *loc. cit.*). Their intermediate formation in the latter reaction is therefore ruled out, which provides further indirect support for the alternative mechanism involving *O*-sulphonylureas.

EXPERIMENTAL.

M. p.s are uncorrected. Analyses by Drs. Weiler and Strauss, Oxford.

N-*Phenyl*-N'-*toluene*-p-*sulphonylurea*.—(a) *From phenylurea.* A solution of toluene-*p*-sulphonamide (17·1 g., 0·1 mol.), phenylurea (15 g.; 0·11 mol.), and sodium carbonate (7·2 g., 0·14 equiv.) in water (180 ml.) was refluxed for 12 hours. A white crystalline deposit collected gradually in the condenser, ammonia was slowly given off, and small quantities (2—4 g.) of *s*-diphenylurea appeared in suspension and were quickly filtered off with suction when refluxing was complete. The filtrate was diluted with water (300 ml.), made strongly alkaline with sodium hydroxide solution (20% w/w; 50 ml.), and cooled; a small deposit of unchanged phenylurea (1—2 g.; m. p. 145—148°) separating overnight was removed by filtration. On acidification of the filtrate to Congo-red with concentrated hydrochloric acid (50 ml.) in the cold, unchanged toluene-*p*-sulphonamide and the reaction product were precipitated. When the mechanically stirred mixture was slowly heated to 95°, the former product dissolved; the crude sulphonylurea was quickly filtered off (filtrate A) and washed by twice heating it nearly to boiling with water (2 × 100 ml.). Crystallisation of the dried material (4—5 g.; m. p. 169—173°) by dissolution in acetone (10 ml.)–benzene (30 ml.), treatment with charcoal, and addition of light petroleum (b. p. 60—80°; 35 ml.) gave white needles of N-*phenyl*-N'-*toluene*-p-*sulphonylurea*, m. p. 172—174° (3—4 g., 10—14%) (Found: C, 57·95; H, 5·0. $C_{14}H_{14}O_3N_2S$ requires C, 57·9; H, 4·8%), soluble in acetone, ethanol, benzene, or sodium hydroxide solution, sparingly soluble in light petroleum or chloroform, and insoluble in water. From filtrate A, unchanged toluene-*p*-sulphonamide (10 g., 60%) separated overnight.

When the sodium carbonate was substituted by equivalent quantities of sodium or potassium hydroxide, or when the time of reaction was prolonged, no significant increases of the yields were observed. Addition of various proportions of ethanol to the solvent did not accelerate the reaction, nor were yields improved.

The method failed to afford *N*-benzenesulphonyl-*N′*-phenylurea from benzenesulphonamide and phenylurea in alkaline media.

(b) *From phenyl* iso*cyanate*. To a suspension of toluene-*p*-sulphonamide (43 g., 0·25 mol.) in phenyl *iso*cyanate (40 g., 0·33 mol.), triethylamine (6 ml.) was added and the mixture, the temperature of which rose spontaneously, was heated on the steam-bath for 6 hours. The orange-yellow viscous liquid, which began to solidify after 3 hours and set to a hard crystalline mass on cooling, was broken into lumps while still warm, powdered, and dissolved by stirring with successive portions of sodium hydroxide solution at 60° (total 1200 ml.; 4% w/w). The residual insoluble white powder was filtered off and gave, after further extraction with alkali (200 ml.; 4% w/w) and washing with hot water, small quantities of *s*-diphenylurea, m. p. 242° (6—8 g.). The combined alkaline extracts were stirred with charcoal at 30° for 15 minutes and filtered. The clear colourless filtrate was cooled to 0° and slowly added with stirring to excess of ice-cold acetic acid (1 l.; 30%), the crude sulphonylurea separating as a white flocculent precipitate. (Precipitation by the addition of acid to the alkaline liquid at room temperature yielded a yellow oil that solidified slowly and was purified with difficulty.) After being set aside at 0° for several hours, the material was filtered off, washed with water (dry wt., 60—65 g., 83—90%; m. p. 152—156°) and crystallised from ethanol–water (120 ml. and 40 ml. respectively), giving colourless, glass-like, large needles (32—35 g., 44—48%) of *N*-phenyl-*N′*-toluene-*p*-sulphonylurea, m. p. 172—174° (Found: C, 58·0; H, 4·9%). It was difficult to isolate further pure material from the sticky filtrate, which tended to yield oils. After removal of the solvent, further small quantities (6—10 g.) of the product, m. p. 170—171°, could be obtained by reprecipitation from alkaline solution as described above. [N.B. Material purified by two reprecipitations instead of crystallisation, although having a lower m. p. (160—164°), gave excellent analytical results (C, 57·9; H, 4·9%) and was suitable for use in further experiments.]

Interaction of the reagents in toluene (1 l.) for 20 hours, in the absence of the tertiary base as catalyst, gave 25—30% yields. (See also below, N-benzenesulphonyl-*N′*-phenylurea).

N-*Benzenesulphonyl*-N′-*phenylurea*.—A solution of benzenesulphonamide (15·7 g., 0·1 mol.) and phenyl *iso*cyanate (35·7 g., 0·3 mol.) in anhydrous toluene (400 ml.) was refluxed for 18 hours. After removal of the solvent on the steam-bath under reduced pressure, the viscous oily residue was twice extracted with hot sodium hydroxide solution (2 × 250 ml.; 4% w/w), the granular *s*-diphenylurea (8 g.) filtered with suction, and the cooled filtrate slowly added to excess of ice-cold acetic acid, the product separating as a white precipitate (18·5 g.; m. p. 164—166°). Crystallisation from ethanol–water (30 : 20 ml.) gave *N*-benzenesulphonyl-*N′*-phenylurea (9·2 g., 33%), m. p. 166—167°, in small needles (Found: C, 56·75; H, 4·5. Calc. for $C_{13}H_{12}O_3N_2S$: C, 56·5; H, 4·35%). Base-catalysed interaction of the reactants in the absence of solvent (as described for *N*-phenyl-*N′*-toluene-*p*-sulphonylurea) gave improved yields (60—70%).

N-p-*Methoxyphenyl*-N′-*toluene*-p-*sulphonylurea*.—A hot solution of toluene-*p*-sulphonamide (8·6 g., 0·05 mol.) and *p*-methoxyphenylurea (10·0 g., 0·06 mol.) in ethanol (40 ml.)–water (40 ml.) was treated with sodium carbonate (5·3 g., 0·1 equiv.) in water (60 ml.) and refluxed for 15 hours. After removal of most of the ethanol by distillation and addition of sodium hydroxide solution (100 ml.; 5% w/w), the purple liquid deposited unchanged *p*-methoxyphenylurea (5 g.) on cooling. The filtrate was made acid to Congo-red with concentrated hydrochloric acid. On dilution to 200 ml. and heating to 80°, the unchanged toluene-*p*-sulphonamide (4·3 g., 50%) dissolved and was quickly decanted from the purple oil, which gave, on repeated crystallisation from benzene–light petroleum and finally benzene, large elongated lustrous prisms of N-p-*methoxyphenyl*-N′-*toluene*-p-*sulphonylurea*, initially separating with benzene of crystallisation and having an indefinite m. p. (Yield, 2·2 g., 15%) (Found: C, 63·8; H, 5·2. $C_{15}H_{16}O_4N_2S,C_6H_6$ requires C, 63·3; H, 5·5%). Short drying at 80—100° yielded the compound as a microcrystalline powder, m. p. 160—162° (Found: C, 56·1; H, 5·3; N, 9·0; S, 9·75. $C_{15}H_{16}O_4N_2S$ requires C, 56·25; H, 5·0; N, 8·75; S, 10·0%).

Toluene-p-*sulphonylurea* (cf. Haak, U.S.P. 2,385,571).—A solution of toluene-*p*-sulphonamide (57 g., 0·33 mol.) in ethanol, to which sodium cyanate (32 g., 0·5 mol.) dissolved in water (100 ml.) was added, was boiled under reflux for 8 hours. The suspended cyanate dissolved gradually (3—4 hours). After removal of about two-thirds of the ethanol in a vacuum, the residual solution was diluted with water (400 ml.) and filtered, and deposited overnight small quantities of the starting material. The filtrate therefrom gave, on acidification with acetic acid, a white precipitate (48 g., 68%) of toluene-*p*-sulphonylurea. Crystallisation from boiling water (80 ml. per g.) gave minute lustrous needles, m. p. 200—202° (followed by rapid resolidification; subsequent decomposition at >320°) (Found: N, 12·8. Calc. for $C_8H_{10}O_3N_2S$: N, 13·1%). Haak (*loc. cit.*) gives m. p. 184—188°.

Thermal Decomposition of Toluene-p-*sulphonylurea*.—Toluene-*p*-sulphonylurea (10·7 g., 0·05 mol.) was inserted in a metal-bath at 230°. After fusing completely within a few minutes, the material began to resolidify to a yellowish-white paste while slight loss of *iso*cyanic acid occurred. Heating at 220—210° was continued for ½ hour, the cooled product boiled with three successive portions of ethanol (25, 12, and 12 ml.), and the residual white powder filtered off (filtrate A). The residue (1·6 g., 75%) was recrystallised from boiling water (40 ml.), giving prismatic crystals of cyanuric acid [Found: C, 28·2; H, 2·5; N, 33·0; *M* (volumetrically; cf. Hantzsch, *Ber.*, 1906, **39**, 139), 132, 136. Calc. for $C_3H_3O_3N_3$: C, 27·9; H, 2·3; N, 32·6%; *M*, 129]. It was identified by conversion into the *p*-nitrobenzyl derivative,

m. p. 278° (Found : N, 21·4. Calc. for $C_{10}H_8O_5N_4$: N, 21·2%), the m. p. being undepressed on admixture with a specimen prepared from authentic cyanuric acid (cf. Lyons and Reid, *J. Amer. Chem. Soc.*, 1917, **39**, 1727).

The ethanolic filtrates (A) were evaporated to smaller volume (20 ml.) and filtered from a further trace of granular solid, and then deposited toluene-*p*-sulphonamide, m. p. 136—137° (undepressed by authentic material) (total, 7·2 g., 84%).

Thermal Decomposition of N-*Phenyl*-N'-*toluene*-p-*sulphonylurea*.—This urea (2·9 g., 0·01 mol.), when heated at 210—200° for ½ hour, gave a clear melt, from which phenyl *iso*cyanate was evolved. The cooled material was boiled with successive portions of water (20, 5, and 5 ml.). The small insoluble residue (0·4 g.) was *s*-diphenylurea, m. p. 237—238° (Found : N, 13·1. Calc. for $C_{13}H_{12}ON_2$: N, 13·2%). From the aqueous extracts toluene-*p*-sulphonamide (1·2 g., 70%) was isolated.

Interaction of Phenylurea and Toluene-p-*sulphonyl chloride*.—(a) *Vigorous conditions*. An intimate mixture of powdered phenylurea (6·8 g., 0·05 mol.) and toluene-*p*-sulphonyl chloride (19·0 g., 0·1 mol.) was inserted into an oil-bath at 160° and kept at 155—165° for 15 minutes. Reaction set in vigorously as soon as the melt reached a temperature of 145—150° and hydrogen chloride was evolved. The effervescence slackened after 12—15 minutes; when reaction ceased the dark-brown reaction mixture was allowed to cool to 50°. The solidified cake was heated with chloroform (100 ml.), giving a purple solution, from which a white crystalline solid was filtered off. Crystallisation of this material (4·2—4·5 g.) from ethanol (50 ml.) gave lustrous white blades of ammonium toluene-*p*-sulphonate, m. p. 339—340° (decomp.) [Found : C, 44·3; H, 5·95; N, 7·4; S, 16·85%; *M*, 195 (volumetric). Calc. for $C_7H_{11}O_3NS$: C, 44·4; H, 5·8; N, 7·4; S, 16·9%; *M*, 189].

The chloroform filtrate A was exhaustively extracted with sodium hydroxide solution (3 × 60 ml.; 3% w/w) (extracted chloroform layer = B). The collected extracts, when filtered with carbon, and slowly acidified to Congo-red at 0°, gave a white crystalline precipitate of toluene-*p*-sulphonanilide, m. p. 101—103° (4·6 g.). The residual chloroform extracts B were washed until neutral and quickly evaporated in a vacuum. The residue was taken up in ethanol (25 ml.) and deposited white needles of *s*-diphenylurea, m. p. 235—236° (1·2 g.). The filtrate therefrom contained small quantities of unchanged toluene-*p*-sulphonyl chloride (m. p. 69—72°), identified by conversion into the amide (m. p. 136°).

(b) *Moderate conditions*. A mixture of phenylurea (6·8 g., 0·05 mol.) and toluene-*p*-sulphonyl chloride (14·3 g., 0·075 mol.) was carefully melted and stirred mechanically at 100° for 2 hours. The melt was dissolved in sodium hydroxide solution (10%; 60 ml.) at 70°, filtered from a small quantity of insoluble material (0·3 g.), cooled to 0°, and slowly addded to acetic acid (50% w/w; 40 ml.) at 0°. The white flocculent material which separated coagulated to a viscous oil, and solidified to a wax-like solid on storage. Since crystallisation proved difficult, the whole acid-insoluble fraction (4·2 g.) was methylated by dissolving it in sodium hydroxide (100 ml.; 10% w/w) and adding dimethyl sulphate (20 g.) in 4 portions at 70°. The separated product (3·2 g.) was methyltoluene-*p*-sulphonanilide, m. p. 94—95° (from ethanol). The alkaline filtrate therefrom was acidified and deposited a small quantity (0·3 g.) of white product of indefinite m. p. (150—180°).

Control experiments showed that *N*-phenyl-*N'*-toluene-*p*-sulphonylurea is neither methylated by methyl sulphate nor affected by 10% sodium hydroxide solution under the above conditions, and if formed should therefore be contained in the alkaline filtrate from the methylation.

Action of Dehydrating Agents.—(*a*) When solutions of *N*-phenyl-*N'*-toluene-*p*-sulphonylurea (1·45 g., 0·005 mol.) in pyridine (10 ml.) were treated with toluene-*p*-sulphonyl chloride (3·8 g., 0·02 mol.) and kept at room temperature, or at 60—80°, for 15 minutes, the sulphonylurea was recovered unchanged.

(*b*) The sulphonylurea was not affected when its solution in thionyl chloride was set aside at room temperature for 1 hour. Interaction with thionyl chloride or phosphorus oxychloride in pyridine at 100° gave intractable orange oils.

(*c*) A solution of *N*-phenyl-*N'*-toluene-*p*-sulphonylurea (1·45 g., 0·005 mol.) in excess of phosphorus oxychloride (10 ml.) was boiled under reflux until it separated into two phases (12—15 minutes; more prolonged refluxing caused partial decomposition). The cooled reaction mixture was slowly added to ice-water (100 ml.); on continued stirring, the excess of phosphorus oxychloride decomposed, leaving a white crystalline residue of toluene-*p*-sulphonyl chloride, (0·78 g., 82%), m. p. (after crystallisation) 69—70°, identified by conversion into the amide, m. p. 136—137°. The aqueous filtrate from the acid chloride contained aniline.

The writer gratefully acknowledges the advice and support given by Dr. A. Lawson and thanks Dr. J. W. Baker, of Leeds University, for a valuable discussion. Thanks are due to the Chemical Society for a grant from the Research Fund.

ROYAL FREE HOSPITAL SCHOOL OF MEDICINE
(UNIVERSITY OF LONDON), W.C.1.

[*Received, February 5th*, 1951.]