221. *Cyanamides. Part I. The Synthesis of Substituted Arylsulphonylcyanamides.*

By Frederick Kurzer.

The interaction of aromatic sulphonyl chlorides with arylureas in pyridine at low temperatures has been found to result in the formation of arylsulphonylcyanamides of the type $R \cdot SO_2 \cdot NR' \cdot CN$. The reaction is favoured by the presence of a large excess of sulphonyl chloride, nearly theoretical yields of the products then being obtained. A number of arylsulphonylcyanamides has been prepared by this new method and their structure confirmed by an alternative synthesis.

The action of arylsulphonyl chlorides on urea, first studied by Elander (*Bull. Soc. chim.*, 1880, **34**, 207), was investigated in some detail by Remsen and Garner (*Amer. Chem. J.*, 1901, **25**, 175), who found that benzenesulphonyl chloride and urea, when heated to 100°, react violently to form dicyandiamide benzenesulphonate. The interaction of sulphonyl chlorides with ethyl*iso*urea produces sulphonylethyl*iso*ureas, $Ar \cdot SO_2 \cdot N{:}C(OEt) \cdot NH_2$, converted by hydrolysis into sulphonylureas, $Ar \cdot SO_2 \cdot NH \cdot CO \cdot NH_2$ [Cox and Raymond, *J. Amer. Chem. Soc.*, 1941, **63**, 300; Cox, *J. Org. Chem.*, 1942, **7**, 307 (available in this country in abstract only)]. Unsuccessful attempts to obtain arylsulphonylureas directly from sulphonyl chlorides and urea were reported by Haak (G.P. 741,533, 1943) in connection with work on sulphonamides of chemotherapeutic value. Passing mention was made of the formation of sulphonic acids, together with products derived from urea by dehydration and polymerization, such as dicyandiamide, but no details were given. In marked contrast, arylsulphonylguanidines can be synthesized readily from the appropriate sulphonyl chloride and guanidine under various conditions (Marshall *et al.*, *Johns Hopkins Hosp. Bull.*, 1940, **67**, 163; Backer and Moed, *Rec. Trav. chim.*, 1947, **66**, 335).

The present investigation has shown that sulphonyl chlorides react with arylureas at low temperatures to produce substituted sulphonylcyanamides of general formula (IV). The reaction is best carried out by treating 1 mol. of the arylurea, dissolved or suspended in pyridine, with 3 mols. of the sulphonyl chloride, the temperature being kept below 30°. With the excess of sulphonyl chloride employed, the arylurea usually undergoes complete reaction. In this way phenyl-, *p*-tolyl-, *p*-methoxyphenyl-, and 1-*naphthyl-benzenesulphonylcyanamide, phenyl-,* p-*tolyl-,* p-*methoxyphenyl-,* and 1-*naphthyl-toluene*-p-*sulphonylcyanamide,* and *phenyl-,* and 1-*naphthyl*-p-*nitrobenzenesulphonylcyanamide* were obtained. Owing to the ease with which the reaction takes place, the presence of groups such as hydroxyl which normally interact with acid halides does not interfere with its general course. Thus, *p*-hydroxyphenylurea when treated with toluene-*p*-sulphonyl chloride for longer periods reacted with simultaneous esterification of the phenolic hydroxyl, giving *toluene*-p-*sulphonyltoluene*-p-*sulphonyloxyphenylcyanamide.* Benzenesulphonylcyanamides have previously been prepared by the action of cyanogen bromide on a number of benzenesulphonanilides (II) in the presence of sodium ethoxide (vön Braun, *Ber.*, 1904, **37**, 2809). The substances synthesized by the present method were identical in all respects with specimens prepared by von Braun's procedure, and the structure of the products was further established by a second independent synthesis: phenylcyanamide (III) reacted, in pyridine solution, with benzene-, *p*-toluene- and *p*-nitrobenzenesulphonyl chlorides, to yield benzenesulphonyl-, toluene-*p*-sulphonyl-, and *p*-nitrobenzenesulphonyl-phenylcyanamide, respectively, which proved identical with the compounds obtained from phenylurea.

$$\mathrm{Ph{\cdot}SO_2{\cdot}NHR'\ (II.)} \longrightarrow \mathrm{Ph{\cdot}SO_2{\cdot}NNaR'} + \mathrm{CN{\cdot}Br} \longrightarrow \mathrm{Ph{\cdot}SO_2{\cdot}NR'{\cdot}CN\ (IV.)} + \mathrm{NaBr}$$

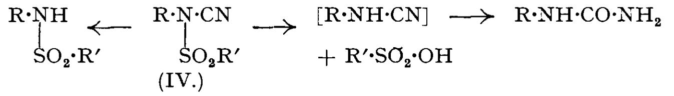
$$\mathrm{R{\cdot}SO_2Cl} + \mathrm{NHPh{\cdot}CN\ (III.)} \longrightarrow \mathrm{R{\cdot}SO_2{\cdot}NPh{\cdot}CN\ (IV.)} + \mathrm{HCl}$$

The mechanism of the synthesis of sulphonylcyanamides from arylureas and sulphonyl chlorides involves probably the intermediate formation of arylsulphonylureas (I), which are immediately dehydrated by the excess of sulphonyl chloride and rearrange to form substituted sulphonylcyanamides (IV). The sulphonyl chloride acting as dehydrating agent is itself converted into the corresponding sulphonic acid, the presence of which may be demonstrated by cooling the reaction mixture to 0°, whereupon direct crystallization of a pyridinesulphonic acid salt occurs. The yields of sulphonylcyanamide increase regularly with the use of greater molecular proportions of sulphonyl chloride (cf. table, p. 1036) because increasingly larger quantities of the reagent are made available for the purpose of dehydrating the intermediate.

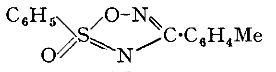
$$\mathrm{R{\cdot}SO_2Cl} + \overset{2}{\mathrm{N}}\mathrm{H_2{\cdot}CO{\cdot}}\overset{1}{\mathrm{N}}\mathrm{HR'} \longrightarrow \underset{\text{(I.)}}{\mathrm{R{\cdot}SO_2{\cdot}NH{\cdot}CO{\cdot}NHR'}} \xrightarrow{\mathrm{R{\cdot}SO_2Cl}} \underset{\text{(IV.)}}{\mathrm{R{\cdot}SO_2{\cdot}NR'{\cdot}CN}} + \mathrm{R{\cdot}SO_2{\cdot}OH} + \mathrm{HCl}$$

The expectation that arylsulphonylureas, synthesized by alternative methods, might be dehydrated readily by arylsulphonyl chlorides under the mild conditions described has so far not been realized. The ease with which water is eliminated from the intermediate compound in the present synthesis may therefore be restricted to the instant of its formation. Alternatively, the sulphonyl chloride may indeed substitute the hydrogen atom attached to the nitrogen N^1, forming an intermediate $\mathrm{R{\cdot}SO_2{\cdot}}\overset{1}{\mathrm{N}}\mathrm{R'{\cdot}CO{\cdot}}\overset{2}{\mathrm{N}}\mathrm{H_2}$, from which the sulphonylcyanamide could be formed directly, and in which case a rearrangement need not be postulated. Backer and Moed (*loc. cit.*), however, have recently shown that arylsulphonyl chlorides, although reacting readily with *p*-nitrobenzenesulphonylguanidine, fail to do so with the corresponding N^2-dimethyl derivative, $\mathrm{NO_2{\cdot}C_6H_4{\cdot}SO_2{\cdot}NH{\cdot}C(\dot{:}NH){\cdot}NMe_2}$, and this observation makes the latter view less probable. Further work on the dehydration of arylsulphonylureas is in progress.

The hydrolytic fission of sulphonylcyanamides proceeds in the expected manner. Treatment with ammonia in the cold results in their conversion into the corresponding substituted sulphonamide, and hydrolysis under more severe condition produces, in addition, the appropriate sulphonic acids and arylureas. For example, toluene-*p*-sulphonylphenylcyanamide gave toluene-*p*-sulphonanilide, m. p. 103°, together with varying quantities of phenylurea and diphenylurea, according to the conditions of the reaction. Hydrolytic conversion into urea is well known in the case of cyanamide itself, and is no doubt preceded, in the present case, by intermediate hydrolysis to phenylcyanamide:



$$\underset{\mathrm{SO_2{\cdot}R'}}{\mathrm{R{\cdot}NH}} \longleftarrow \underset{\text{(IV.)}}{\underset{\mathrm{SO_2R'}}{\mathrm{R{\cdot}N{\cdot}CN}}} \longrightarrow \underset{+\ \mathrm{R'{\cdot}SO_2{\cdot}OH}}{[\mathrm{R{\cdot}NH{\cdot}CN}]} \longrightarrow \mathrm{R{\cdot}NH{\cdot}CO{\cdot}NH_2}$$



(V.)

The synthesis of sulphonylcyanamides by the present method has occasioned the re-examination of the action of benzenesulphonyl chloride upon *p*-toluamidoxime, $CH_3\cdot C_6H_4\cdot C(:NH)\cdot NH\cdot OH$. Pinnow (*Ber.*, 1891, **24**, 4167, 4173), when treating a chloroform suspension of this amidoxime with benzenesulphonyl chloride in the presence of alkali, obtained *p*-tolylurea, together with a compound $C_{14}H_{12}O_2N_2S$ [" anhydro-(*p*-toluene amidoxime)-benzenesulphonate "] to which structure (V) was assigned. Its reported physical constants, and the simultaneous formation of *p*-tolylurea, suggested that the product was in fact benzenesulphonyl-*p*-tolylcyanamide. Repetition of Pinnow's work gave small yields of a substance, $C_{14}H_{12}O_2N_2S$, m. p. 91—92°, which showed no depression of the melting point in admixture with benzenesulphonyl-*p*-tolylcyanamide prepared by the above method. The formation of this compound from *p*-toluamidoxime involves presumably a preliminary isomerization to *p*-tolylurea, as shown by its isolation from the reaction mixture, followed by interaction with the excess of sulphonyl chloride in the manner shown above.

The scope and limitations of the present synthesis are being further investigated, particularly with regard to its applicability to *ortho*-substituted derivatives which v. Braun failed to prepare by the cyanogen bromide method. Work on the interaction of sulphinyl chlorides and aliphatic sulphonyl chlorides with arylureas is also in progress.

EXPERIMENTAL.

(Melting points are uncorrected. Analyses by Drs. Weiler and Strauss, Oxford.)

Benzenesulphonylphenylcyanamide.—(a) *From phenylurea.* To a solution of phenylurea (13·6 g.; 0·1 mol.) in pyridine (50 ml.), benzenesulphonyl chloride (35 g., *i.e.*, 28 c.c., 0·2 mol.) was added within 3 minutes with external cooling, the temperature of the mixture being kept below 30°. After 10 minutes' standing, the liquid was poured into ice-water (400 ml.), and the separated oil solidified on stirring. Small quantities of unchanged phenylurea were removed by heating the mechanically stirred mixture to 60°, allowing it to cool spontaneously to 40°, and filtering it (filtrate A). The insoluble crude material (12—14 g., 40—54%) was crystallized by treating its boiling ethanolic solution (80 ml.) with charcoal, filtering, and diluting the nearly colourless filtrate with water (20 ml.). On cooling, large colourless lustrous plates of benzenesulphonylphenylcyanamide separated, m. p. 64—66° [Found: C, 60·2, 60·2; H, 4·2, 4·1; N, 11·0, 10·9; S, 11·9, 11·8; *M* (Rast), 256, 266. Calc. for $C_{13}H_{10}O_2N_2S$: C, 60·5; H, 3·9; N, 10·85; S, 12·4%; *M*, 258], not depressed in admixture with material prepared according to v. Braun's method (*loc. cit.*). Varying quantities of sodium benzenesulphonate were isolated from filtrate A after removal of the pyridine by ether-extraction, addition of alkali, and evaporation to small bulk.

(b) *From phenylcyanamide.* A solution of phenylcyanamide (5·5 g.; 0·05 mol.) in pyridine (40 ml.) was treated with benzenesulphonyl chloride (17·6 g.; 14 c.c., 0·1 mol.), heated on the steam-bath for 1 hour, and poured into ice-water (250 ml.); the separated brown oil solidified on standing and gave, on purification with carbon and crystallization from ethanol-water, benzenesulphonylphenylcyanamide (7·8 g., 60%), m. p. 64—66° (Found: C, 60·1; H, 4·1%). Mixed m. p. with material prepared by method (a): 63—66°.

Benzenesulphonylphenylcyanamide and all substituted sulphonylcyanamides subsequently described are highly soluble in cold chloroform, benzene, and acetic anhydride, hot ethanol and acetone; soluble in hot, and sparingly soluble in cold ether and light petroleum; and insoluble in alkalis and water.

*Toluene-*p*-sulphonylphenylcyanamide.*—(a) *From phenylurea.* Phenylurea (27·2 g.; 0·2 mol.), when dissolved in pyridine (100 ml.) and treated with toluene-*p*-sulphonyl chloride (57 g.; 0·3 mol.) as described above, gave a product (22 g.; 40%), which on recrystallization from aqueous ethanol gave lustrous platelets of *toluene-*p*-sulphonylphenylcyanamide*, m. p. 85—87° [Found: C, 61·5, 61·9; H, 4·5, 4·2; N, 10·5, 10·1; S, 11·4, 11·3; *M* (Rast), 260, 268. $C_{14}H_{12}O_2N_2S$ requires C, 61·8; H, 4·4; N, 10·3; S, 11·8%; *M*, 272]. The yield can be raised by the use of a greater excess of sulphonyl chloride (see table). Interaction of the specified quantities of reactants for 6, 3, and 1 hour at room temperature, and 1 hour at 100°, resulted in the formation of 6, 12, 15, and 1% of the theoretical yield, respectively, accompanied by varying quantities of uncrystallizable oily products in the last case.

Mols. of $C_6H_4Me\cdot SO_2Cl$ per mol. of arylurea ...		½	1	2	3	4	5	6
Yield of sulphonyl-cyanamide, %	from phenylurea	5	24	41	52	74	90	95
	from *p*-tolylurea	6	22	50	72	86	92	93

(b) *From phenylcyanamide.* Phenylcyanamide (5·5 g.; 0·05 mol.), dissolved in pyridine (50 ml.), was heated with toluene-*p*-sulphonyl chloride (19·0 g.; 0·1 mol.) to 100° for 1 hour. When the mixture was poured into ice-water (300 ml.) the crude product separated and gave, after purification and crystallization from aqueous ethanol, toluene-*p*-sulphonylphenylcyanamide, m. p. 85—87° (Found: C, 61·8; H, 4·3%). Mixed m. p. with material prepared by method (a): 84—87°.

Toluene-*p*-sulphonylphenylcyanamide (1 g.), dissolved in pyridine (12 ml.) and heated to 100° for 2 hours, was recovered quantitatively.

Hydrolysis to Substituted Sulphonamides.—Into a solution of toluene-*p*-sulphonylphenylcyanamide (5 g.) in ethanol (100 ml.)–benzene (10 ml.), ammonia was passed until the concentration in the liquid corresponded to 3% of ammonium hydroxide (w/v, determined acidimetrically). The clear solution was allowed to stand at room temperature for 24 hours, and evaporated to 15 ml. On neutralization with a few drops of hydrochloric acid and further standing, a white solid separated out which gave, on crystallization from ethanol–light petroleum (b. p. 60—80°), a crystalline mass of toluene-*p*-sulphonamide,

m. p. 137—138°, undepressed in admixture with authentic material From the mother-liquors toluene-*p*-sulphonanilide, m. p. 102—103°, was isolated.

Hydrolysis to Substituted Ureas.—(a) *In alkaline medium.* A solution of toluene-*p*-sulphonylphenylcyanamide (13·6 g.; 0·05 mol.) in alcoholic potassium hydroxide [from 11·2 g. (0·2 mol.) of alkali in 10 ml. of water and 120 ml. of ethanol] was heated under reflux on the steam-bath for 2 hours. The solution, which remained colourless and water-clear during the heating, was nearly neutralized by the addition of concentrated hydrochloric acid (25 ml.) and concentrated to approx. 40 ml. under reduced pressure. On treatment of the residue with water (200 ml.) an oil separated which failed to solidify on standing at 0° for 48 hours. The reaction mixture, again made strongly alkaline (30 ml. of 35% potassium hydroxide), was exhaustively extracted with hot ether (aqueous phase : A), the ethereal extract washed till nearly neutral with water, evaporated in a vacuum, and the oily residue taken up in ethanol. On prolonged standing at 0°, large lustrous prisms of phenylurea crystallized; m. p. 144—147° (3·4 g.; 50%) (Found : C, 61·5; H, 5·7. Calc. for $C_7H_8ON_2$: C, 61·8; H, 5·9%), undepressed in admixture with authentic material. The mother-liquors gave an uncrystallizable oil (1 g.) which was not identified. The aqueous phase A was concentrated to 100 ml., and just neutralized with concentrated hydrochloric acid. On standing, white needles (1·05 g.) separated and gave, on crystallization from ethanol–light petroleum (b. p. 60—80°), toluene-*p*-sulphonanilide, m. p. 102—103° (8·5% of theoretical) (Found : C, 63·4; H, 5·3. Calc. for $C_{13}H_{13}O_2NS$: C, 63·2; H, 5·3%), undepressed in admixture with authentic material. Further evaporation of the aqueous phase A gave varying quantities of sodium toluene-*p*-sulphonate.

(b) *In acid medium.* Toluene-*p*-sulphonylphenylcyanamide, when heated with acetic anhydride or acetic anhydride–pyridine at 100° for 3 hours, was recovered unchanged. A solution of the cyanamide (5·4 g.) in acetic anhydride (40 ml.) was heated under reflux for 5 hours, and the resulting colourless liquid cooled and slowly stirred into ice-water (200 ml.). The separated oil solidified when the whole mixture was shaken with ether (20 ml.), and was filtered off (filtrate : A). The solid (1·9 g.; melting between 130° and 200°) gave toluene-*p*-sulphonanilide, m. p. 101—102°, by extraction with sodium hydroxide solution and reprecipitation with acid. The alkali-insoluble portion was diphenylurea, m. p. 236—238° (Found : C, 73·7; H, 5·4. Calc. for $C_{13}H_{12}ON_2$: C, 73·6; H, 5·7%). The filtrate A contained a small quantity of oil in suspension, which proved to be unchanged starting material.

p-*Nitrobenzenesulphonylphenylcyanamide.*—To a solution of phenylurea (2·8 g.; 0·02 mol.) in pyridine (30 ml.), *p*-nitrobenzenesulphonyl chloride (8·8 g.; 0·04 mol.) was added in one portion, and the temperature kept below 35° by external cooling. Isolation as previously described, and two crystallizations from acetone–ethanol (15 and 25 ml., respectively), gave long, pale yellow needles (4 g.; 66%) of the *cyanamide*, m. p. 147—149° (Found : C, 51·2; H, 3·25; N, 13·4. $C_{13}H_9O_4N_3S$ requires C, 51·5; H, 3·0; N, 13·9%). In a separate experiment the above quantities of reactants were allowed to interact in the smallest possible volume of solvent (12 ml.) (maximum temperature reached : 45°) and the resulting viscous yellow liquid was cooled to 0° for ½ hour. The separated pyridinium *p*-nitrobenzenesulphonate which was highly soluble in water, was filtered off (filtrate A), and identified by conversion (*via* the sulphonyl chloride) into *p*-nitrobenzenesulphonamide, m. p. 178—179°. Filtrate A was worked up as above and gave a 25% yield of *p*-nitrobenzenesulphonylphenylcyanamide, m. p. 147—148°.

Benzenesulphonyl-p-*tolylcyanamide.*—This cyanamide, obtained by addition of benzenesulphonyl chloride (26·4 g.; 20 ml., 0·15 mol.) to a solution of *p*-tolylurea (7·5 g.; 0·05 mol.) in pyridine (50 ml.) in 72% yield, formed large lustrous needles, m. p. 91—93°, from ethanol (Found : C, 61·5; H, 4·75. Calc. for $C_{14}H_{12}O_2N_2S$: C, 61·8; H, 4·4%); not depressed on admixture with material (m. p. 89—91°) prepared according to v. Braun (*loc. cit.*), who reports m. p. 88°.

Toluene-p-*sulphonyl*-p-*tolylcyanamide* resulted in 75% yield from toluene-*p*-sulphonyl chloride (28·5 g.; 0·15 mol.) and *p*-tolylurea (7·5 g.; 0·05 mol.); it formed flat plates, m. p. 124—126°, from ethanol (Found : C, 62·5; H, 5·1. $C_{15}H_{14}O_2N_2S$ requires C, 62·9; H, 4·9%).

Benzenesulphonyl-*p*-methoxyphenylcyanamide was prepared by the interaction of *p*-methoxyphenylurea (8·3 g.; 0·05 mol.) and benzenesulphonyl chloride (17·5 g.; 0·1 mol.) in pyridine (40 ml.). Isolation of the crude material as previously described, and crystallization from aqueous ethanol, gave long colourless lustrous needles, m. p. 102—103° (Found : C, 58·25, 58·1; H, 4·1, 4·1. Calc. for $C_{14}H_{12}O_3N_2S$: C, 58·3; H, 4·2%).

Toluene-p-*sulphonyl*-p-*methoxyphenylcyanamide* resulted from the interaction of *p*-methoxyphenylurea (8·3 g.; 0·05 mol.) and toluene-*p*-sulphonyl chloride (19 g.; 0·1 mol.) in pyridine (40 ml.) and formed colourless lustrous platelets, m. p. 117—118° [Found : C, 59·75; H, 4·65; N, 8·95; S, 10·0; *M* (Rast), 300. $C_{15}H_{14}O_3N_2S$ requires C, 59·6; H, 4·6; N, 9·3; S, 10·6%; *M*, 302].

Toluene-p-*sulphonyltoluene*-p-*sulphonyloxyphenylcyanamide.*—A solution of *p*-hydroxyphenylurea (3 g.; 0·02 mol.) in pyridine (50 ml.) was treated with toluene-*p*-sulphonyl chloride (11·4 g.; 0·06 mol.) with external cooling, and the mixture was kept at 30° for 6 hours. On pouring into ice-water (350 ml.), the oily product first separating out solidified (5·9 g.; 67%) and gave, on four crystallizations from acetone–ethanol–water (3 : 5 : 1), lustrous needles of the *cyanamide*, m. p. 171—173° (Found : C, 57·0; H, 4·2; N, 6·4. $C_{21}H_{18}O_5N_2S_2$ requires C, 57·0; H, 4·1; N, 6·3%).

Benzenesulphonyl-1-*naphthylcyanamide.*—A suspension of 1-naphthylurea (9·3 g.; 0·05 mol.) in pyridine (60 ml.) was treated with benzenesulphonyl chloride (17·6 g.; 14 ml.; 0·1 mol.) below 30°. After 15 minutes' standing, the clear yellow liquid was poured into ice-water, and the oily product solidified on short standing. The mechanically stirred mixture was heated to 60°, and the crude product filtered off. From the filtrate unchanged 1-naphthylurea (1·3 g.; m. p. 224—225°) separated overnight. Two crystallizations of the crude *cyanamide* (8 g.; 52%) from acetone–ethanol (20 and 50 ml., respectively) gave colourless minute needles, m. p. 144—146° (Found : C, 66·3; H, 3·9. $C_{17}H_{12}O_2N_2S$ requires C, 66·2; H, 3·9%).

Toluene-p-*sulphonyl*-1-*naphthylcyanamide* was similarly prepared from 1-naphthylurea (9·3 g.; 0·05 mol.) and toluene-*p*-sulphonyl chloride (19 g.; 0·1 mol.) in 56% yield, and crystallized in lustrous needles, m. p. 156—157° (Found : C, 67·1; H, 4·0. $C_{18}H_{14}O_2N_2S$ requires C, 67·1; H, 4·35%).

p-*Nitrobenzenesulphonyl*-1-*naphthylcyanamide* resulted from the interaction of 1-naphthylurea (4·7 g.; 0·025 mol.) and *p*-nitrobenzenesulphonyl chloride (11·1 g.; 0·05 mol.) and formed pale yellow needles, m. p. 177—178°, from acetone–ethanol (Found: C, 57·6; H, 3·3. $C_{17}H_{11}O_4N_3S$ requires C, 57·8; H, 3·1%).

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KING'S COLLEGE OF HOUSEHOLD AND SOCIAL SCIENCE,
(UNIVERSITY OF LONDON), W. 8.

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