156. *Amidines. Part II. Preparation of Cyanides, Amides, and Amidines from Carboxylic Acids.*

By P. Oxley, M. W. Partridge, T. D. Robson, and W. F. Short.

Evidence is advanced to show that five intermediate stages may be distinguished in the production of amidine sulphonates from carboxylic acids and sulphonamides. The conditions of the reaction can be modified so that cyanides and, in some cases, amides may be obtained in good yield.

Hartman (Diss., Johns Hopkins Univ., 1894; Remsen, Hartman, and Muckenfuss, *Amer. Chem. J.*, 1896, **18**, 150) showed that *p*-sulphonamidobenzoic acid afforded a monoammonium salt of *p*-sulphobenzoic acid when heated at its melting point, whereas at a higher temperature phenyl cyanide was obtained. Muckenfuss (*ibid.*, p. 349) found that if the acid is kept at 220° for a considerable time one of the products (" infusible diamide ") is a stable, neutral compound isomeric with *p*-sulphonamidobenzamide. Nakaseko (1899) suggested that this compound is benzamidine-*p*-sulphonic acid, and this was confirmed by Rouiller (*ibid.*, 1912, **47**, 475), who showed that a number of carboxylic acids were converted into amidine benzenesulphonates when heated in sealed tubes at 225° for 5 hours with benzenesulphonamide (2 mols.). Rouiller concluded that the reaction may be represented by the equation

$$\mathrm{R{\cdot}CO_2H + 2Ph{\cdot}SO_2{\cdot}NH_2 \longrightarrow R{\cdot}C({:}NH){\cdot}NH_2,Ph{\cdot}SO_3H + Ph{\cdot}SO_3H}$$

which in the case of benzoic acid was expanded to

$$\mathrm{Ph{\cdot}CO_2H + Ph{\cdot}SO_2{\cdot}NH_2 \longrightarrow Ph{\cdot}CO{\cdot}NH_2 + Ph{\cdot}SO_3H}$$
$$\mathrm{Ph{\cdot}CO{\cdot}NH_2 + Ph{\cdot}SO_2{\cdot}NH_2 \longrightarrow Ph{\cdot}C({:}NH){\cdot}NH_2,Ph{\cdot}SO_3H}$$

although it was shown that benzamide and benzenesulphonamide did not in fact yield benzamidine benzenesulphonate at 220° unless free benzenesulphonic acid (1 mol.) was also present. He also observed that phenyl cyanide (19·4%) is produced as a by-product in the reaction between benzoic acid and benzenesulphonamide at 225°, and at higher temperatures (300°) sufficient is produced to form a layer above the solidified reaction product. Amidines were also obtained from acetic acid, *m*-nitrobenzoic acid (15·5%), *p*-nitrobenzoic acid (31%, and 27% of cyanide), *m*-bromobenzoic acid (18·3%), phenylacetic acid (42·6%), and terephthalic acid, which also gave *p*-phenylene dicyanide (48%) and *p*-cyanobenzoic acid (3·4%). Phthalic acid gave a quantitative yield of phthalimide, and *iso*phthalic acid afforded the corresponding dicyanide (46·7%) and *m*-cyanobenzoic acid (6·8%). Neither amidines nor cyanides were obtained from chloroacetic, oxalic, malonic, tartaric, salicylic, *o*-anisic, *p*-hydroxy-, *o*-nitro-, and *o*- and *p*-amino-benzoic acids.

As the result of a detailed study of the reactions between carboxylic acids and sulphonamides we suggest that the production of amidine sulphonates may be represented as follows

$$\mathrm{R{\cdot}CO_2H + R'{\cdot}SO_2{\cdot}NH_2 \longleftrightarrow R{\cdot}CO{\cdot}NH_2 + R'{\cdot}SO_2{\cdot}OH} \quad \mathrm{(I)}$$
$$\mathrm{R{\cdot}CO{\cdot}NH_2 + R'{\cdot}SO_2{\cdot}NH_2 + R'{\cdot}SO_2{\cdot}OH \longrightarrow R{\cdot}CO{\cdot}NH{\cdot}SO_2R' + R'{\cdot}SO_2{\cdot}ONH_4} \quad \mathrm{(II)}$$
$$\mathrm{R{\cdot}CO{\cdot}NH{\cdot}SO_2R' \longleftrightarrow R{\cdot}C({:}NH){\cdot}O{\cdot}SO_2R'} \quad \mathrm{(III)}$$
$$\mathrm{R{\cdot}C({:}NH){\cdot}O{\cdot}SO_2R' \longrightarrow R{\cdot}CN + R'{\cdot}SO_2{\cdot}OH} \quad \mathrm{(IV)}$$
$$\mathrm{R{\cdot}CN + R'{\cdot}SO_2{\cdot}ONH_4 \longleftrightarrow R{\cdot}C({:}NH){\cdot}NH_2,R'{\cdot}SO_2{\cdot}OH} \quad \mathrm{(V)}$$

The evidence for the five stages postulated will be discussed in turn. Indirect evidence for the exchange of functions between the carboxylic acid and the sulphonamide is provided by the observation that benzoic acid and benzenesulphondimethylamide (1 mol.) react exothermically at 230° to yield benzdimethylamide (83%) and benzenesulphonic acid. Similarly, nicotinodiethylamide (nikethamide) is obtained in 81% yield by heating *nicotinic acid benzenesulphonate* and benzenesulphondiethylamide at 220°.* In these examples the reaction cannot proceed beyond Stage I, and more direct evidence for the functional exchange is provided by the observation that the reaction between a carboxylic acid and an unsubstituted sulphonamide can be arrested at this stage. If the reaction between a carbonamide and a sulphonamide is correctly represented by (II), the sulphonic acid (or its anion) acting as an indispensable neutralising agent, then it should be possible to arrest the reaction at Stage I by arranging the experimental conditions so that the acid produced at this stage is neutralised immediately. In agreement with this deduction, *nicotinamide benzenesulphonate* is produced when nicotinic acid and benzenesulphonamide (2 mols.) are heated at 225°. On the other hand, nicotinic acid benzenesulphonate and benzenesulphonamide (2·4 mols.) afford 3-*cyanopyridine benzenesulphonate* (75%) when heated at 230° for 40 minutes. When the carboxylic acid contains no basic group the reaction may be arrested at Stage I by mean of an added base. Thus, *p*-carboxyphenyl methyl sulphone, benzenesulphonamide (1·02 mols.), and pyridine (1·0 mol.) afford *p*-carbamylphenyl methyl sulphone, $\mathrm{Me{\cdot}SO_2{\cdot}C_6H_4{\cdot}CO{\cdot}NH_2}$, in 34% yield when heated under reflux. Pyridine and quinoline almost completely inhibit the reaction between benzoic acid and benzenesulphonamide at 230—250°, and it seems that the sulphonamide–carboxylic acid exchange is catalysed by acids; for instance, addition of a small amount of sulphonic acid reduces or eliminates the period of induction sometimes observed in the reaction between a sulphonamide and a weak carboxylic acid and shortens the duration of the first weakly exothermic phase in the reaction between benzenesulphonamide and *p*-nitrobenzoic acid

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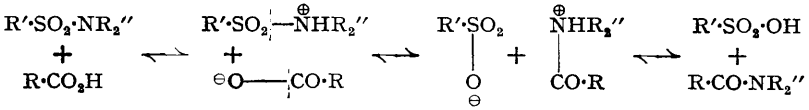
* See Boots Pure Drug Co., Oxley and Short, B.P. Appln., 1429/17.1.45.

(see Fig.). It is improbable that an intermediate of the type $R{\cdot}C(OH)_2{\cdot}NH{\cdot}SO_2R'$ intervenes in the sulphonamide–acid exchange, since it should spontaneously lose water to give $R{\cdot}CO{\cdot}NH{\cdot}SO_2R'$ which is known to decompose rapidly to cyanide (III and IV) at the temperature employed for the production of carbonamides. Moreover, the liberation of steam has not been observed, and the yields of cyanides are frequently so high that very little hydrolysis could occur during the course of the reaction. The production of an addition compound would be impossible when a dialkylsulphonamide is involved and the following mechanism is suggested

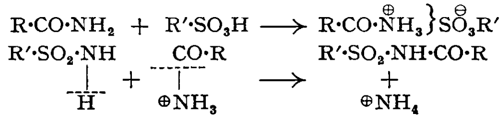


$$\begin{array}{ccccccc} R'{\cdot}SO_2{\cdot}NR_2'' & & R'{\cdot}SO_2\text{—}\overset{\oplus}{N}HR_2'' & & R'{\cdot}SO_2 \quad \overset{\oplus}{N}HR_2'' & & R'{\cdot}SO_2{\cdot}OH \\ + & \rightleftharpoons & + & \rightleftharpoons & |\quad + \quad | & \rightleftharpoons & + \\ R{\cdot}CO_2H & & {}^{\ominus}O\text{——}CO{\cdot}R & & \underset{\ominus}{O} \qquad CO{\cdot}R & & R{\cdot}CO{\cdot}NR_2'' \end{array}$$

(The dotted lines indicate the fate of the electron pairs originally forming the covalent bonds which are broken.)

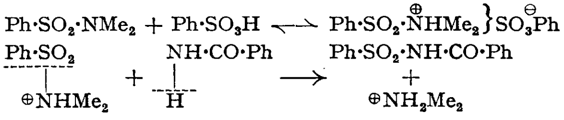
Fission of the kation $R'{\cdot}SO_2{\cdot}\overset{\oplus}{N}HR_2''$ is doubtless promoted by repulsion between the integral charge on the nitrogen atom and the fractional charge on the sulphur atom of the SO_2 double dipole. The stages in the interaction between the kation and the anion are regarded as simultaneous and not successive, so that the amine is never kinetically free. The catalytic effect of added sulphonic acid on the amide exchange may be due to an increase in the concentration of the kation $R'{\cdot}SO_2{\cdot}\overset{\oplus}{N}HR''_2$.

Rouiller (*loc. cit.*) found that the presence of benzenesulphonic acid (the monohydrate was used) is essential for the production of benzamidine benzenesulphonate by heating benzamide and benzenesulphonamide in a sealed tube at 220°, and we find that addition of *ca.* 0·5 mol. of benzenesulphonic acid is necessary to produce the maximum yields of phenyl cyanide and of ammonium benzenesulphonate when the reactants are heated at 235° for 20 minutes in an open vessel. The assumption that phenyl cyanide is produced by simple dehydration of benzamide, the water formed being utilised in the hydrolysis of the benzenesulphonamide under the catalytic influence of the sulphonic acid, is at variance with the stability of benzamide at 235° and the resistance of benzenesulphonamide to hydrolysis under the conditions employed in the experiment. Addition of benzenesulphonic acid (1/15 mol.) accelerates the reaction between *p*-carboxyphenyl methyl sulphone and benzenesulphonamide (2 mols.), so that the optimum yield of *p*-cyanophenyl methyl sulphone is obtained after 50 minutes at 225°, whereas in absence of the acid the reaction is incomplete in this time, the yield being 18% lower, and the deficit appears in the form of N-p-*methylsulphonylbenzoylbenzenesulphonamide*, $Me{\cdot}SO_2{\cdot}C_6H_4{\cdot}CO{\cdot}NH{\cdot}SO_2Ph$, m. p. 215°. This compound can also be obtained from benzenesulphonamide and *p*-methylsulphonylbenzoyl chloride and it seems clear that " mixed imides " of this type are the precursors of the cyanides produced from carboxylic acids and sulphonamides (II). Two exothermic phases can be distinguished in the reaction leading to the production of *p*-nitrophenyl cyanide (see Fig.), the first representing the acid–amide exchange (I), and the second the decomposition of the mixed imide (III and IV), and by interrupting the reaction before the onset of the second exothermic stage, N-p-*nitrobenzoylbenzenesulphonamide* (69%) can be isolated from the product. N-p-*Ethylsulphonyl*- and N-o-*nitro-benzoylbenzenesulphonamide* have also been isolated as products of the reaction between benzenesulphonamide and the appropriate acid. A small yield of *N*-benzoylbenzenesulphonamide can be obtained by heating an equimolecular mixture of benzamide, benzenesulphonamide, and benzenesulphonic acid at 155° (II), and the following mechanism, analogous to that involved in Stage I, is suggested



$$\begin{array}{l} R{\cdot}CO{\cdot}NH_2 + R'{\cdot}SO_3H \longrightarrow R{\cdot}CO{\cdot}\overset{\oplus}{N}H_3\}\overset{\ominus}{S}O_3R' \\ \begin{array}{ccccc} R'{\cdot}SO_2{\cdot}NH & & CO{\cdot}R & & R'{\cdot}SO_2{\cdot}NH{\cdot}CO{\cdot}R \\ | & + & | & \longrightarrow & + \\ H & & {}^{\oplus}NH_3 & & {}^{\oplus}NH_4 \end{array} \end{array}$$

Equimolecular proportions of benzamide, benzenesulphondimethylamide, and benzenesulphonic acid react at 230—235° to give phenyl cyanide (82%) and dimethylammonium benzenesulphonate (75%), and this reaction may well proceed by the production of the mixed imide by the following mechanism



$$\begin{array}{l} Ph{\cdot}SO_2{\cdot}NMe_2 + Ph{\cdot}SO_3H \rightleftharpoons Ph{\cdot}SO_2{\cdot}\overset{\oplus}{N}HMe_2\}\overset{\ominus}{S}O_3Ph \\ \begin{array}{ccccc} Ph{\cdot}SO_2 & & NH{\cdot}CO{\cdot}Ph & & Ph{\cdot}SO_2{\cdot}NH{\cdot}CO{\cdot}Ph \\ | & + & | & \longrightarrow & + \\ {}^{\oplus}NHMe_2 & & H & & {}^{\oplus}NH_2Me_2 \end{array} \end{array}$$

In discussing the mechanism of Stages I and II we have omitted explanations based on the production of addition compounds containing hexacovalent sulphur, since, notwithstanding the existence of sulphur hexafluoride, there is, so far as we are aware, no evidence which unequivocally demands that sulphur behaves in this way in organic compounds containing the groups ·SO· and $\cdot SO_2\cdot$, and there is much evidence to the contrary (see also Rothstein, *J.*, 1940, 1550).

Wallach (*Annalen*, 1882, **214**, 211) showed that benzenesulphonamide and benzoyl chloride at 140—160° afford *N*-benzoylbenzenesulphonamide, m. p. 147°, whereas at higher temperature the main products are benzenesulphonic acid and cyaphenin. We find that if *N*-benzoylbenzenesulphonamide is heated at 190—195° so that the cyanide distils, an almost quantitative yield of phenyl cyanide is obtained and 82% of the calculated amount of benzenesulphonic acid can be isolated from the residue (as guanidine salt). *N*-*p*-Methylsulphonylbenzoylbenzenesulphonamide affords a 95% yield of *p*-cyanophenyl methyl sulphone when heated at 230° for an hour. Similarly, *N*-*o*-nitrobenzoylbenzenesulphonamide gives a 41% yield of *o*-nitrophenyl cyanide on heating, the *p*-isomer affords 81% of *p*-nitrophenyl cyanide, and a 50% yield of methyl cyanide is obtained by the dry distillation of sulphacetamide (*p*-aminobenzenesulphonylacetamide). The decomposition of the mixed imide to cyanide and sulphonic acid (IV) is therefore well established, and the isomerisation postulated (III) is analogous to that which occurs in the Beckmann transformation of oximes. An alternative mechanism involving isomerisation to $R{\cdot}C(OH){:}N{\cdot}SO_2{\cdot}R'$, followed by decomposition to $R{\cdot}CN$ and $R'{\cdot}SO_3H$, is less acceptable, since it will be shown in a subsequent communication that the reactions of the substituted imides $R{\cdot}CO{\cdot}NR''{\cdot}SO_2{\cdot}R'$ are best explained by postulating isomerisation to $R''N{:}CR{\cdot}O{\cdot}SO_2{\cdot}R'$. The fact that mixed imides cannot be obtained from an arylsulphonyl chloride and an amide is doubtless due to the production of an arylsulphonyl*iso*amide, $R'{\cdot}SO_2{\cdot}O{\cdot}CR{:}NH$, which immediately decomposes to a cyanide and a sulphonic acid (see Wolkow, *Ber.*, 1871, **4**, 290; Meister, Lucius, and Brüning, G.P. 380,323; Gwan, *J. Indian Chem. Soc.*, 1941, **18**, 164). We find that benzamide and benzenesulphonyl chloride at 125—130° afford a 78% yield of phenyl cyanide and a small amount of *benzamide benzenesulphonate*, m. p. 121·5—122°.

Stage V, the conversion of the cyanide into the amidine sulphonate, has been discussed in detail in Part I (Oxley and Short, this vol., p. 147) in which many examples of this reaction are recorded.

We find that benzoic anhydride and *p*-nitrobenzoic anhydride react with benzenesulphonamide to give the corresponding cyanide, the optimum yields being obtained when the reactants are in the proportion required by the equation

$$(R{\cdot}CO)_2O + 3R'{\cdot}SO_2{\cdot}NH_2 \longrightarrow 2R{\cdot}CN + 2R'{\cdot}SO_3H + R{\cdot}SO_3NH_4$$

It may be assumed that a mixed imide is also produced as an intermediate in this case

$$(R{\cdot}CO)_2O + R'{\cdot}SO_2{\cdot}NH_2 \longrightarrow R{\cdot}CO{\cdot}NH{\cdot}SO_2{\cdot}R' + R{\cdot}CO_2H$$

The experimental realisation of each of the stages represented by equations I, II, IV, and V does not exclude the possibility that in the normal reaction some of these stages may be short-circuited or that other intermediates may be involved. For example, we find that distillation of a mixture of benzamide and benzenesulphonic acid affords phenyl cyanide and benzoic acid each in 95% yield according to the equation

$$2Ph{\cdot}CO{\cdot}NH_2 + Ph{\cdot}SO_3H \longrightarrow Ph{\cdot}CN + Ph{\cdot}CO_2H + Ph{\cdot}SO_3NH_4$$

and at a lower temperature dibenzoylamine may be isolated from the products of the reaction. Diacylamines are known to decompose on heating as follows

$$\begin{tikzcd}
(R{\cdot}CO)_2NH \arrow[rr, leftrightarrow] \arrow[dr] & & R{\cdot}CO{\cdot}O{\cdot}CR{:}NH \arrow[dl] \\
& R{\cdot}CN + R{\cdot}CO_2H &
\end{tikzcd}$$

(see Mumm, Hesse, and Volquartz, *Ber.*, 1915, **48**, 379), and it is clear that they could be produced as intermediates in the reaction between carboxylic acids or anhydrides and sulphonamides, although we have not detected their formation. The fact that the optimum yield of phenyl cyanide is obtained from benzamide and benzenesulphonamide in presence of *ca.* 0·5 mol. of benzenesulphonic acid (above) may indicate that some dibenzoylamine is produced as an intermediate, but it will be appreciated that the ratio of benzamide to benzenesulphonamide throughout this reaction is higher than that which obtains at any stage of the reaction between benzenesulphonamide (2 mols.) and benzoic acid (I and II) which would therefore tend to produce benzoylbenzenesulphonamide. The available evidence strongly suggests that the main course of the reaction between a carboxylic acid and a sulphonamide follows equations (I)—(V).

Examples of the preparation of cyanides by this method are given in the Table. The influence of experimental conditions on the yield of cyanide has not been thoroughly investigated in all cases, so the yields recorded are not necessarily the highest obtainable. The method fails with acids which are readily decarboxylated (*e.g.*, *p*-hydroxybenzoic acid), and much decarboxylation occurs with anisic acid, which gives a poor yield of *p*-methoxyphenyl cyanide. It is convenient to employ benzene- and toluene-*p*-sulphonamides owing to their accessibility, although a somewhat lower yield (5%) of cyanide is usually obtained with toluenesulphonamide owing to the occurrence of a side reaction in which toluene is generated. There is usually no difficulty in regulating the experimental conditions so that very little amidine is formed when a cyanide is the desired product of the reaction. Thus, the maximum yield (75%) of *p*-cyanophenyl ethyl sulphone is obtained after 2—2½ hours at 210° and remains unaltered if the heating is prolonged for another 3 hours; at 225° a 75% yield of cyanide is obtained in 1¼ hours and, although the yield falls to 30% after 10 hours owing to the production of *p*-amidinophenyl ethyl sulphone benzenesulphonate, rapid formation of the amidine salt does not occur until the temperature reaches 260—270°. Amidine formation occurs more readily in the case of *p*-chlorobenzoic acid, so that after 2 hours at 225° the product contains *p*-chlorophenyl cyanide (66%) and *p*-chlorobenzamidine benzenesulphonate (20%). A free sulphonic acid and its ammonium salt are produced in the reactions resulting in the formation of a cyanide and several examples are now recorded in which an increased yield of amidine salt is obtained if the sulphonic acid is neutralised with dry ammonia before raising the temperature to accelerate reaction V. This agrees with the conclusion (Part I, *loc. cit.*) that the yield of amidine salt is proportional to the concentration of the ammonium benzenesulphonate.

	Cyanide.	Acid, g.	Benzene-sulphonamide, g.	mols.	Temp.	Time, hrs.	Yield, %.	M. p.
(1)	Phenyl cyanide	12·2	31·4	2·0	220—225°	2·0	90	—
(2)	*o*-Nitrophenyl cyanide	16·7	31·4	2·0	220—225	1·25	10·6	110°
(3)	*p*-Nitrophenyl cyanide	16·7	31·4	2·0	225	1·0	81	148—149
(4)	2 : 4-Dinitrophenyl cyanide	21·2	32·0	2·0	205—210 and 225—230	1·0 1·0	79	103
(5)	3 : 5-Dinitrophenyl cyanide	42·4	64·0	2·0	225—230	1·75	83	127
(6)	*p*-Chlorophenyl cyanide	25·0	50·0	2·0	225	2·0	66	95
(7)	2 : 4-Dichlorophenyl cyanide	19·0	39·3	2·5	225	2·0	80·7	60—61
(8)	2-*Cyanophenyl methyl sulphone*	25·0	39·25	2·0	225	1·5	83·5	103—104
(9)	3-Cyanophenyl methyl sulphone	50	78·5	2·0	225—230	1·25	61·0	103·5—104·5
(10)	4-Cyanophenyl methyl sulphone	20·0	31·4	2·0	225	1·5	75	142—143
(11)	4-Cyanophenyl ethyl sulphone	21·4	31·4	2·0	225	1·25	75	96
(12)	4-Cyanophenyl *n*-propyl sulphone	51·0	77·0	2·2	220—230	1·5	64	83—84
(13)	4 : 4′-Dicyanodiphenyl ether	6·5	15·7	4·0	220	1·5	*ca.* 45	180
(14)	4-*Cyanodiphenyl sulphone*	160	185	1·9	225	2·0	74	118
(15)	4 : 4′-Dicyanodiphenyl sulphone	40	210	10·0	225—230	2·0	76	229—231
(16)	4-*Cyanophenyl 4′-nitrobenzyl sulphone*	20·0	22·0	2·2	220—230	1·25	38	168—169
(17)	Ammonium 4-cyanobenzenesulphonate	8·0	9·0	1·4	230—270	0·4	94	—
(18)	*p*-Methoxyphenyl cyanide	15·2	31·4	2·0	220—225	7·0	10	60—61
(19)	Benzyl cyanide	27·2	75·4	2·4	225	1·0	22	—

(1) The phenyl cyanide, b. p. 189—190°, was identified by the preparation of *m*-nitrophenyl cyanide, m. p. and mixed m. p. 117°. The preparation of larger batches and the use of other sulphonamides are described in the experimental section.

(2) The reaction was strongly exothermic. The product did not depress the m. p. of authentic *o*-nitrophenyl cyanide.

(3) The reaction is exothermic and the yield falls to 70% when 50 g. of acid are used.

(4) The reaction was conducted in stages to minimise decarboxylation. Friedländer and Cohn (*Ber.*, 1902, **35**, 1265; *Monatsh.*, 1902, **23**, 559) record 104—105° as the m. p. of 2 : 4-dinitrophenyl cyanide. Bennett and Wain (*J.*, 1936, 1108) give m. p. 99·6°.

(5) Bennett and Wain (*loc. cit.*) give m. p. 127°.

(6) Meyer (*Monatsh.*, 1917, **38**, 350) gives m. p. 94—96°. A 20% yield of p-*chlorobenzamidine benzenesulphonate*, m. p. 247° (Found : N, 8·95. $C_{13}H_{13}O_3N_2ClS$ requires N, 9·0%), was obtained as by-product. Dr. J. Cymerman found that the yield of cyanide after 1¼ hours at 225° is 40% and that p-*chlorobenzamidine picrate* has m. p. 256° (decomp.) (Found : N, 18·1. $C_{13}H_{10}O_7N_5Cl$ requires N, 18·25%).

(7) Gomberg and Cone (*Annalen*, 1909, **370**, 182) give m. p. 61°.

(8) Preparation by Dr. J. W. Minnis. The cyanide (Found : N, 7·8. $C_8H_7O_2NS$ requires N, 7·7%) depressed the m. p. of 3-cyanophenyl methyl sulphone to 70—74°.

(9) Preparation by Dr. J. W. Minnis (Found : N, 7·75. Calc. for $C_8H_7O_2NS$: N, 7·7%). Fuller, Tonkin, and Walker (*J.*, 1945, 638) record m. p. 103—104°. Hydrolysis with 70% sulphuric acid gave *m*-carboxyphenyl methyl sulphone, m. p. and mixed m. p. 236—238°.

(10) Andrewes, King, and Walker (*Proc. Roy. Soc.*, 1946, *B*, **133**, 20) and Fuller, Tonkin, and Walker (*loc. cit.*) record m. p. 141°.

(11) The cyanide crystallised in glistening plates (Found : N, 7·2. Calc. for $C_9H_9O_2NS$: N, 7·2%). Fuller *et al.* (*loc. cit.*) record m. p. 94—95°.

(12) The cyanide separated from alcohol in colourless prisms (Found : N, 6·8. Calc. for $C_{10}H_{11}O_2NS$: N, 6·7%). Fuller *et al.* (*loc. cit.*) record m. p. 84—85°.

(13) The sulphonamide was mixed with 5% of benzenesulphonic acid. Ashley, Barber, Ewins, Newbery, and Self (*J.*, 1942, 113) also record m. p. 180°.

(14) Found : N, 5·8. $C_{13}H_9O_2NS$ requires N, 5·75%. Preparation by Dr. A. Koebner.

(15) Ashley *et al.* (*loc. cit.*) record m. p. 232—233°. Preparation by Dr. A. Koebner.

(16) Found : N, 9·3. $C_{14}H_{10}O_4N_2S$ requires N, 9·3%. Preparation by Dr. A. Koebner.

(17) The guanidine and the *p*-toluidine salt, obtained from the ammonium salt by double decomposition, melted at 236—237° and 241° respectively, and there was no depression on admixture with the appropriate salt prepared from authentic *p*-cyanobenzenesulphonic acid (Remsen, Hartman, and Muckenfuss, *loc. cit.*).

(18) Sulphur dioxide and carbon dioxide were evolved.

(19) The benzyl cyanide had b. p. 232—235°.

EXPERIMENTAL.*

Preparation of Acids.

o-*Carboxyphenyl Methyl Sulphone.*†—A solution containing *o*-mercaptobenzoic acid (15·4 g.) and sodium hydroxide (4 g.) in water (230 c.c.) was stirred during the addition of methyl sulphate (16 c.c.; 1·7 mols.) and a solution of sodium hydroxide (6 g.; 1·5 mols.) in water (20 c.c.). Methylation was completed by heating on the steam-bath for 2·5 hours, and the hot, filtered solution was acidified with concentrated hydrochloric acid. The yield of *o*-methylthiobenzoic acid, m. p. 168—169°, was 15 g. or 89% (cf. Friedländer, *Annalen*, 1907, **351**, 401). A solution of *o*-methylthiobenzoic acid (8·4 g.) and sodium hydroxide (2 g.; 1 mol.) in water (60 c.c.) was stirred mechanically and potassium permanganate (12 g.; equivalent to 2·3 atoms of oxygen) was added during 4 hours. After the excess of permanganate had been destroyed by sulphur dioxide the *o*-carboxyphenyl methyl sulphone was isolated in the usual way and dried at 110° for 1·5 hours; yield, 7·3 g., 73%; m. p. 134—135° (Found : S, 16·3; *M*, by titration, 199. Calc. for $C_8H_8O_4S$: S, 16·0%; *M*, 200). Arndt, Korsch, and Nachtwey (*Ber.*, 1926, **59**, 1079) record m. p. 138—140° (softening at 135°); Rule and Smith (*J.*, 1931, 1488) give m. p. 137°. In agreement with the latter authors we find that the monohydrate has m. p. 73°.

m-*Carboxyphenyl Methyl Sulphone.*†—A solution of crystalline sodium sulphite (540 g.; 2 mols.) in water (1 l.) was

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[*] See also Boots Pure Drug Co., Oxley, Robson, Koebner, and Short, B.P. Appln., 21760/6.11.1944.

[†] Preparations by Dr. J. W. Minnis.

warmed to 70—80° and slowly added with stirring to a solution of *m*-chlorosulphonylbenzoic acid (220 g.; Smiles and Stewart, *J.*, 1921, **119**, 1792) in acetone (550 c.c.), concentrated aqueous sodium carbonate being added simultaneously so that the liquid remained alkaline to Brilliant-yellow. The reaction was completed by warming for 1·5 hours, and the sulphinic acid was precipitated by acidifying the solution at 0°. Sodium carbonate was added to a mixture of the crude sulphinic acid, alcohol (1 l.), and water (1 l.) until the solution was alkaline to Brilliant-yellow; methyl iodide (62 c.c.; 1 mol.) was then added, and the mixture boiled for 2 hours. After removal of most of the alcohol by distillation, the hot residue was filtered, and the filtrate acidified. The *m*-carboxyphenyl methyl sulphone was collected, washed, and dried at 60°. Yield, 106 g., 53%. The acid had m. p. 236—238°; Smiles and Stewart (*loc. cit.*) give m. p. 230°.

p-*Nitrophenyl Methyl Sulphone*.—The following modification of Waldron and Reid's method (*J. Amer. Chem. Soc.*, 1923, **45**, 2400) is more convenient and gives better yields. A solution of potassium hydrogen sulphide, prepared from potassium hydroxide (102 g.; 1·3 mols.), alcohol (400 c.c.), and hydrogen sulphide, was added to a hot solution of *p*-chloronitrobenzene (189 g.) in alcohol (750 c.c.) so that the solution boiled gently, air having been displaced from the apparatus by a current of nitrogen. The solution was boiled for a further 15 minutes and then poured into ice-water (6 l.). After standing at 0° for 2 hours the 4 : 4'-dinitrodiphenyl disulphide was removed and washed with water. The united filtrates were stirred during the slow addition of methyl sulphate (150 g.; 1 mol.), aqueous sodium hydroxide being added so that the liquid remained alkaline to Brilliant-yellow. Stirring was continued for 2 hours and the crude *p*-nitrothioanisole, m. p. 65—70°, was then collected; yield, 125 g., 61·7%. A sample recrystallised from aqueous acetic acid had m. p. 72° as described by Waldron and Reid (*loc. cit.*). Oxidation with concentrated nitric acid afforded p-*nitrophenyl methyl sulphoxide*, which separated from water in flat needles, m. p. 155° (Found: N, 7·7. $C_7H_7O_3NS$ requires N, 7·6%). The sulphone was obtained by dissolving the sulphide (50 g.) in acetic acid (250 c.c.) and water (30 c.c.) at 50° and adding potassium permanganate (55 g.; equivalent to 3 atoms of oxygen) with cooling so that the temperature remained at 55—60°. Acetic acid (100 c.c.) was then added, and after the colour had been discharged with sulphur dioxide, the solid was removed, and the filtrate concentrated under diminished pressure. *p*-Nitrophenyl methyl sulphone, m. p. 139° (45 g., 82%), was obtained by crystallising the residue from water and recrystallisation from alcohol afforded needles, m. p. 142°. Waldron and Reid (*loc. cit.*) record m. p. 142·5°.

p-*Aminophenyl Methyl Sulphone*.—A solution of the sulphone (20 g.) in alcohol (500 c.c.) containing Raney nickel (5 g.) was shaken in hydrogen at 50—70 lb./sq. in., reduction being complete in less than an hour. The yield of *p*-aminophenyl methyl sulphone, m. p. 134°, was 15·5 g., 90%. Waldron and Reid (*loc. cit.*) obtained a 70% yield of a product, m. p. 133°, by iron-reduction. Fuller, Tonkin, and Walker (*loc. cit.*), who obtained this amine from *p*-acetamidobenzenesulphinic acid, give m. p. 133—134°.

p-*Cyanophenyl Methyl Sulphone*.—(1) Sodium toluene-*p*-sulphinate was obtained in almost quantitative yield by adding toluene-*p*-sulphonyl chloride (200 g.) and sodium bicarbonate (175 g.; 2 mols.) during 2 hours to a solution of crystalline sodium sulphite (500 g.; 1·9 mols.) in water (1 l.) which was stirred and maintained at 70—80° during the addition and for 1 hour subsequently. The sodium salt was collected by filtration at 35—40° (cf. Blomstrand, *Ber.*, 1870, **3**, 965). The crude sodium salt was dissolved in water (500 c.c.) and alcohol (500 c.c.) and boiled for 12 hours with methyl iodide (87·4 c.c.; 1·3 mols.). Unchanged methyl iodide (30 g.) was recovered by distillation, and after concentration to a small volume under diminished pressure, the solid which separated was extracted with benzene (500 c.c.). The solution was washed with water and concentrated, giving 152—161 g. (85—90%) of *p*-tolyl methyl sulphone, m. p. 89—90°. Otto (*Ber.*, 1885, **18**, 161; *Annalen*, 1895, **284**, 304) records m. p. 86—87°. Potassium permanganate (340 g., equivalent to 3·2 atoms of oxygen) was added in portions during 4—5 hours to a suspension of *p*-tolyl methyl sulphone (170 g.) in water (1 l.) maintained at 90°. When decolorisation was complete *p*-carboxyphenyl methyl sulphone, m. p. 275°, was isolated in the usual way; yield, 185—190 g., 93—95%. Fuller, Tonkin, and Walker (*J.*, 1945, 633) state that this acid has m. p. 267—268°. The acid was converted into *p*-cyanophenyl methyl sulphone, m. p. 142—143°, by heating with benzenesulphonamide as described in the Table. (2) *p*-Aminophenyl methyl sulphone was diazotised and the solution added to sodium nickel cyanide as described by Fuller, Tonkin, and Walker (*loc. cit.*), the yield of *p*-cyanophenyl methyl sulphone being 71% as stated by them.

p-*Carboxyphenyl Ethyl Sulphone*.—This sulphone was prepared from sodium toluene-*p*-sulphinate by the method described in the case of the lower homologue. *p*-Tolyl ethyl sulphone (yield 74%), m. p. 56° (Otto, *loc. cit.*, gives m. p. 55—56°), was oxidised to *p*-carboxyphenyl ethyl sulphone, m. p. 220° (yield, 71%). Monier-Williams (*J.*, 1906, **89**, 279) gives m. p. 211°.

p-*Carboxyphenyl* n-*Propyl Sulphone*.*—*p*-Tolyl *n*-propyl sulphone, m. p. 53—55°, was obtained in 75·5% yield from sodium toluene-*p*-sulphinate and propyl bromide in aqueous alcohol (cf. Otto, *J. pr. Chem.*, 1889, **40**, 562 Anm.). Addition of potassium permanganate (185 g.: equiv. to 3 atoms of oxygen) to a suspension of the sulphone (116 g.) in water (600 c.c.) at 90° during 12 hours afforded unchanged sulphone (20 g.) and 52 g. (47%) of crude acid, m. p. 190°. p-*Carboxyphenyl* n-*propyl sulphone* crystallised from 50% aqueous alcohol in colourless prisms, m. p. 191—193° (Found: C, 52·5; H, 5·3. $C_{10}H_{12}O_4S$ requires C, 52·6; H, 5·3%).

p-*Carboxyphenyl* p'-*Nitrobenzyl Sulphone*.*—A solution of sodium toluene-*p*-sulphinate (65 g.) and *p*-nitrobenzyl chloride (65 g.; 1·04 mols.) in alcohol (65 c.c.) and water (150 c.c.) was boiled under reflux for an hour and afforded p-*tolyl* p'-*nitrobenzyl sulphone* (60 g., 56·5%), m. p. 185—189° (Found: N, 5·0. $C_{14}H_{13}O_4NS$ requires N, 4·8%). Concentrated sulphuric acid (35 c.c.) was added to a boiling solution of *p*-tolyl *p'*-nitrobenzyl sulphone (60 g.) and crystalline sodium dichromate (65 g., equiv. to 3·2 atoms of oxygen) in boiling acetic acid (300 c.c.) so that the mixture remained in gentle ebullition, and after a further hour's boiling the acid was collected, washed with hot water, and purified through the ammonium salt. p-*Carboxyphenyl* p'-*nitrobenzyl sulphone* had m. p. 295—300° (Found: N, 4·5. $C_{14}H_{11}O_6NS$ requires N, 4·4%); yield, 45 g., 68%.

Preparation of Carbonamides.

Benzdimethylamide.—When a mixture of benzoic acid (6·1 g.) and benzenesulphondimethylamide (9·25 g.; 1·0 mol.) was heated at 235—240° an exothermic reaction set in after about 5 minutes and the temperature rose to 250°, falling to 235—240° during the next 10 minutes. The product, which was completely soluble in a small quantity of water, was neutralised to Congo-red with aqueous potassium hydroxide (1·0 mol. required) and then extracted with benzene. The residue obtained by evaporating the washed and dried benzene solution was distilled and afforded 6·2 g. (83%) of a fraction, b. p. 132—133°/15 mm., which solidified on cooling and had m. p. 43°, undepressed on admixture with authentic benzdimethylamide (Kon and Staudinger, *Annalen*, 1911, **384**, 114).

Nicotinamide Benzenesulphonate.—Nicotinic acid (12·3 g.) and benzenesulphonamide (31·4 g.; 2 mols.) were kept at 225° for 4·5 hours, and the product extracted with acetone. The soluble solid afforded benzenesulphonamide (9 g.) after washing with aqueous sodium carbonate. The insoluble portion (17·5 g.) was recrystallised from ethyl alcohol–acetone, giving *nicotinamide benzenesulphonate*, m. p. 157° (Found: N, 10·1. $C_{12}H_{12}O_4N_2S$ requires N, 9·9%). Guanidine benzenesulphonate, m. p. and mixed m. p. 210—212°, was precipitated when guanidine sulphate was added to an aqueous solution

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* Experiments by Dr. A. Koebner.

of the reaction product, and nicotinamide, m. p. 128—129°, was obtained by extracting the alkaline solution with chloroform. The product of the reaction did not depress the m. p. of a sample of nicotinamide benzenesulphonate, m. p. 157°, prepared from equivalent amounts of the amide and sulphonic acid in acetone.

Nicotinodiethylamide (*Nikethamide*).—(1) Nicotinic acid (12·3 g.) and benzenesulphondiethylamide (23·5 g.; 1·1 mols.) were kept at 225° for 3 hours, then dissolved in water (25 c.c.) and extracted with chloroform. The aqueous solution was made alkaline with 5N-sodium hydroxide and extracted with chloroform (2 × 50 c.c.) to give 8·8 g. (49·5%) of nikethamide, b. p. 115°/0·4 mm. (2) Nicotinic acid (12·3 g.) and toluene-*p*-sulphondiethylamide (25 g.; 1·1 mols.), heated at 250° for 1 hour, gave a 33% yield of nikethamide. (3) An 81% yield of nikethamide, b. p. 126—127°/mm., was obtained by heating nicotinic acid benzenesulphonate (7 g.) and benzenesulphondiethylamide (6 g.; 1·1 mol.) at 220° for 1 hour. *Nicotinic acid benzenesulphonate* was obtained from equivalent amounts of its constituents in hot acetone, and separated in white plates, m. p. 160° (Found: N, 5·1. $C_{12}H_{11}O_5NS$ requires N, 5·0%).

p-*Carbamylphenyl Methyl Sulphone*.—When a mixture of *p*-carboxyphenyl methyl sulphone (20 g.), benzenesulphonamide (16 g.; 1·02 mols.), and pyridine (7·9 g.; 1·0 mol.) was boiled under reflux for 3¼ hours the b. p. rose from 200° to 280°. The product was extracted successively with aqueous sodium carbonate and aqueous sodium hydroxide, which removed unchanged acid (12·9 g.) and benzenesulphonamide (2·5 g.), respectively. The residual solid was recrystallised from water and afforded p-*carbamylphenyl methyl sulphone*, m. p. and mixed m. p. 226—226·5° (Found: N, 7·2. $C_8H_9O_3NS$ requires N, 7·0%); yield, 6·7 g., or 95% on the acid consumed.

N-*Acylbenzenesulphonamides.*

p-*Aminobenzenesulphonylacetamide* (*Sulphacetamide*).—When sulphacetamide (21·2 g.) was heated at 230° and finally over a free flame and the distillate was redistilled, methyl cyanide, b. p. 76—80°, was obtained in 49% yield (identified by hydrolysis to acetic acid).

Benzoylbenzenesulphonamide.—(1) Sodium (5·75 g.; 1 atom) was stirred with a warm solution of benzamide (30·25 g.) in xylene (200 c.c.) and, when the metal had disappeared, benzenesulphonyl chloride (44·1 g.; 1 mol.) was introduced, and the mixture stirred at room temperature until it was no longer alkaline (5 hours). The product was filtered and the xylene solution afforded benzenesulphonyl chloride, b. p. 113°/9 mm. (20 g.). Benzoylbenzenesulphonamide, m. p. 147—147·2° (16 g.), was obtained from the solid by dissolving it in water, acidifying with dilute hydrochloric acid, and recrystallising the precipitate from alcohol. The benzoylbenzenesulphonamide was evidently converted into its sodio-derivative (by the sodio-benzamide), which did not react with the sulphonyl chloride. The mixed imide did not depress the m. p. of samples prepared by heating benzoyl chloride and benzenesulphonamide either alone at 135° for 3 hours (cf. Wallach, *loc. cit.*) or in presence of pyridine (1 mol.) at 95° for 2 hours.

(2) Benzamide (4·8 g.), benzenesulphonamide (6·25 g.; 1 mol.), and anhydrous benzenesulphonic acid (6·3 g.; 1 mol.) were heated at 155° for 3 hours and extracted with aqueous sodium bicarbonate. Acidification of the solution afforded benzoylbenzenesulphonamide (0·3 g., 3%), m. p. and mixed m. p. 147°. When benzoylbenzenesulphonamide (10 g.) was heated at 200°, there was a sudden exothermic reaction after *ca.* 30 minutes and the temperature soon fell to 190° owing to vigorous refluxing of phenyl cyanide. The reaction product consisted of phenyl cyanide (3·5 g., 89%) and benzenesulphonic acid (82% by titration), identified respectively as *m*-nitrophenyl cyanide, m. p. and mixed m. p. 117°, and guanidine benzenesulphonate, m. p. and mixed m. p. 211°.

N-p-*Methylsulphonylbenzoylbenzenesulphonamide*.—(1) Two tubes were each charged with *p*-carboxyphenyl methyl sulphone (10 g.) and benzenesulphonamide (15·7 g.; 2 mols.), and anhydrous benzenesulphonic acid (0·5 g.) was added to one of them. The tubes were heated in a bath at 225° for 70 minutes and then cooled rapidly. An exothermic reaction temporarily raised the internal temperature *ca.* 5° above that of the bath, and this phase occurred sooner in the tube containing the sulphonic acid. The powdered products were worked up separately by stirring with water, adding ammonia until alkaline to Brilliant-yellow, collecting the *p*-cyanophenyl methyl sulphone, m. p. 140—141°, and recrystallising it once from alcohol, whereupon the m. p. rose to 142·4—142·8°. Acidification of the ammoniacal solution and recrystallisation of the precipitate from alcohol afforded N-p-*methylsulphonylbenzoylbenzenesulphonamide*, which crystallised in long needles, m. p. 214·6—215° (Found: C, 50·2; H, 4·1; N, 4·2. $C_{14}H_{13}O_5NS_2$ requires C, 49·6; H, 3·8; N, 4·1%). The yields of cyanide and mixed imide in the experiment without added sulphonic acid were 5·62 g. (62%) and 3·5 g. (20·6%), respectively. In the experiment with added sulphonic acid, the corresponding figures were 7·27 g. (80·3%) and 0·2 g. (1·2%), respectively.

(2) *p*-Carboxyphenyl methyl sulphone (10 g.) and thionyl chloride (20 c.c.) were boiled for 3 hours, excess of thionyl chloride was removed by distillation under diminished pressure, and the crude acid chloride, m. p. 131°, was mixed with benzenesulphonamide (8 g.) and heated at 145° for 3½ hours. The product was recrystallised from alcohol, giving 4·6 g. (50·8%) of the mixed imide, m. p. 214—215°.

(3) An equimolecular mixture of *p*-carbamylphenyl methyl sulphone (3·0 g.), benzenesulphonamide (2·4 g.), and benzenesulphonic acid (2·4 g.) was kept at 198° for ½ hour and afforded 2·2 g. (81%) of *p*-cyanophenyl methyl sulphone and 0·4 g. (8%) of the mixed imide.

When *p*-methylsulphonylbenzoylbenzenesulphonamide (4 g.) was kept at 230° for 1 hour, and the product washed with dilute aqueous ammonia, *p*-cyanophenyl methyl sulphone, m. p. 138—140° (2·03 g., 95%), remained, and crystallisation from alcohol raised the m. p. to 142·5°.

N-p-*Ethylsulphonylbenzoylbenzenesulphonamide*.—*p*-Carboxyphenyl ethyl sulphone (21·4 g.) and benzenesulphonamide (31·4 g.; 2 mols.) were heated to 225° in 6 minutes, stirred at this temperature for 30 minutes, and cooled quickly. Crude ammonium benzenesulphonate (13·9 g., 79%), m. p. 270—283°, remained undissolved when the melt was extracted with acetone, and recrystallisation from aqueous acetone (charcoal) afforded glistening white plates, m. p. and mixed m. p. 285—286°, of the pure salt (Found: N, 7·9, 7·95, 8·2. Calc. for $C_6H_9O_3NS$: N, 8·0%). The ammonium salt was converted into *p*-toluidine benzenesulphonate, m. p. and mixed m. p. 203°, by reaction with *p*-toluidine hydrochloride. The acetone-soluble product was extracted successively with saturated aqueous sodium bicarbonate and dilute sodium hydroxide solution, and the residue (12·5 g., m. p. 95°) afforded 11·5 g. (59%) of pure *p*-cyanophenyl ethyl sulphone, m. p. 95—96°, on recrystallisation from aqueous alcohol. The sodium bicarbonate solution was concentrated and acidified, and the precipitate (4·5 g., 12·7%) on recrystallisation from hot water gave N-p-*ethylsulphonylbenzoylbenzenesulphonamide*, which crystallised in small needles, m. p. 189° (Found: N, 4·0, 4·0. $C_{15}H_{15}O_5NS_2$ requires N, 4·0%).

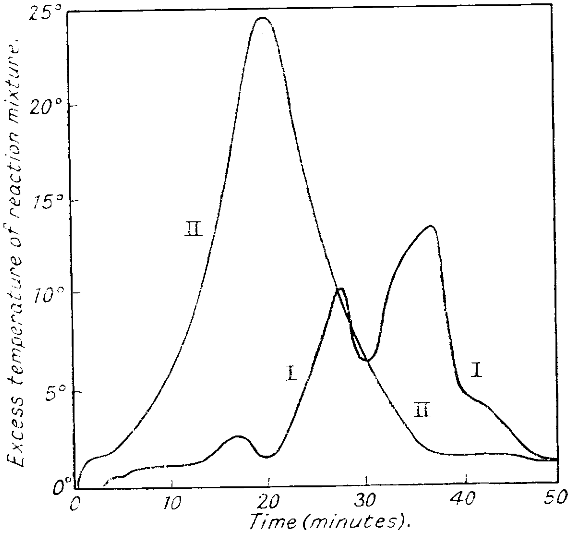
N-p-*Nitrobenzoylbenzenesulphonamide*.—(1) *p*-Nitrobenzoyl chloride (4·65 g.) and benzenesulphonamide (3·95 g.; 1 mol.) were heated at 145—150° for 5 hours and boiled with alcohol (20 c.c.) to destroy acid chloride. The solvent was removed and the powdered product was suspended in water and made alkaline to Brilliant-yellow with sodium carbonate. The filtered solution was acidified, and the precipitate, m. p. 212—214° (4·6 g., 60%), recrystallised from methanol, giving N-p-*nitrobenzoylbenzenesulphonamide*, m. p. 216—217° (Found: N, 9·1. $C_{13}H_{10}O_5N_2S$ requires N, 9·15%).

(2) A mixture of *p*-nitrobenzoic acid (6·7 g.) and benzenesulphonamide (12·6 g.) was heated to 220° in 3 minutes, and the tube containing the melt was then placed in the vapour of boiling methyl salicylate. The melt was stirred, and the temperatures of the melt and of the vapour bath were recorded at minute intervals on calibrated thermometers. The

temperature of the bath remained constant to within 0·5° throughout, and the results are shown in the Fig., in which the difference between the temperatures of the reaction mixture and the bath is plotted against the time. [The second curve was obtained when the experiment was repeated in presence of benzenesulphonic acid monohydrate (0·2 g.) and shows the acceleration produced by the acid.] It was assumed that the mixed imide is mainly produced during the first 20 minutes, and that its decomposition into cyanide and sulphonic acid is responsible for the subsequent strongly exothermic phase. The experiment was repeated on the same scale, but the tube was cooled rapidly in water 19 minutes after the temperature of the mixture attained that of the vapour bath. The powdered product was warmed with acetone (50 c.c.) and kept overnight at 0°. The solid was collected, washed with acetone (50 c.c.), and filtered, giving a solid (A), and the acetone solutions were united (B). The solid (A) was resolved by water (20 c.c.) into ammonium benzenesulphonate (2·6 g.), m. p. and mixed m. p. 279°, and *p*-nitrobenzoic acid (1·4 g.), m. p. and mixed m. p. 240°. The acetone solution (B) was diluted with water (20 c.c.), distilled to remove acetone, cooled to 50°, and rendered alkaline to Brilliant-yellow with sodium carbonate; after cooling to room temperature, the solid was collected and washed thoroughly with water. The washings were added to the sodium carbonate solution (C). The solid was separated by means of 1·7N-sodium hydroxide (15 c.c.) into benzenesulphonamide, m. p. 153—154° (4·4 g.), and *p*-nitrophenyl cyanide, m. p. 148—149° (0·8 g.). The sodium carbonate solution (C) was concentrated to 25 c.c. and acidified with hydrochloric acid, and the solid was collected, washed with a little water, and dried. This solid was extracted with hot chloroform (50 c.c. and 3 × 20 c.c.) leaving *p*-nitrobenzoic acid, m. p. 235—237° (1·0 g.). The chloroform extract was purified by crystallisation from ethanol and gave *N*-*p*-nitrobenzoylbenzenesulphonamide (4·4 g.), m. p. and mixed m. p. 213—215°. These results may be summarised as follows:

	Initial.	Recovered.	Reacted.
Benzenesulphonamide, g.-mol.	0·080	0·028	0·052
p-Nitrobenzoic acid, g.-mol.	0·0400	0·0144	0·0256

The ratio of acid to sulphonamide entering into reaction was therefore 1 : 2·03. The yield of cyanide was 0·0054 g.-mol., so that 0·0202 g.-mol. of acid was converted into mixed imide, 0·0140 g.-mol. of which was isolated, together with 0·015 g.-mol. of ammonium benzenesulphonate.



I. p-*Nitrobenzoic acid and benzenesulphonamide.*
II. p-*Nitrobenzoic acid, benzenesulphonamide, and benzenesulphonic acid.*

Decomposition of *N*-*p*-nitrobenzoylbenzenesulphonamide (5 g.) at 220° for 40 minutes gave *p*-nitrophenyl cyanide (81%), benzenesulphonic acid (86%, isolated as ammonium salt), and unchanged imide (1·4%). The reaction was first exothermic then endothermic and finally exothermic, the curve having the same shape as the final portion of that representing the reaction between *p*-nitrobenzoic acid and benzenesulphonamide (Fig.). It was found that a 66% yield of cyanide is obtained if heating is interrupted after the first exothermic reaction (18 minutes), and the significance of the subsequent endothermic phase is at present obscure.

N-o-*Nitrobenzoylbenzenesulphonamide*.—*o*-Nitrobenzoic acid (6·68 g.) and benzenesulphonamide (12·56 g.; 2 mols.) were heated in a bath at 225°, and as soon as the internal temperature reached 230° (24 minutes), the reaction was arrested by cooling in ice. The product, separated by the method used in the case of the *p*-acid, consisted of benzenesulphonamide (8·3 g.), *o*-nitrobenzoic acid (3·5 g.), ammonium benzenesulphonate (2·09 g.), and N-o-*nitrobenzoylbenzenesulphonamide* (2·73 g.), which separated from aqueous alcohol in glistening leaflets, m. p. 171° (Found: N, 9·3. $C_{13}H_{10}O_5N_2S$ requires N, 9·15%). The yield of imide was 46% on the acid consumed, or 64% on the sulphonamide consumed. When *N*-*o*-nitrobenzoylbenzenesulphonamide (2 g.) was heated in a bath at 225° and cooled quickly in ice as soon as the temperature of the melt rose sharply (8 minutes), the product contained *o*-nitrophenyl cyanide (0·16 g.), unchanged imide (1·2 g.), and benzenesulphonic acid, isolated as ammonium salt (0·21 g.); the yields of cyanide and sulphonic acid are 42 and 45·8%, respectively, calculated on the imide consumed. The temperature changes which occur during the interaction of *o*-nitrobenzoic acid and benzenesulphonamide were also recorded: the general features were similar to those observed in the case of the *p*-isomer, except that the second stage (decomposition of the imide) is much more strongly exothermic, so this part of the curve shows no inflexion. A considerable amount of tar is produced during the decomposition of the imide and impedes the isolation of pure *o*-nitrophenyl cyanide from the product.

Preparation of Cyanides.

Phenyl Cyanide.—(1) *From benzoic acid.* (*a*) Benzoic acid (122 g.) and technical benzenesulphonamide (314 g.; 2 mols.) were stirred at 220—225° for 2 hours under reflux and then distilled (bath up to 300°). The distillate was diluted with ether (25 c.c.), washed with dilute alkali and water, and dried. The fraction, b. p. 189—193°, was collected as phenyl cyanide; yield, 69 g., 67%. (*b*) Benzoic acid (122 g.), toluene-*p*-sulphonamide (342 g.; 2 mols.), and toluene-*p*-sulphonic acid monohydrate (10 g.) were heated at 240° and stirred. After 10—20 minutes, an exothermic reaction raised the temperature of the melt to *ca.* 250° and vigorous refluxing occurred. The product was then distilled under diminished pressure (100 mm.), and the distillate afforded phenyl cyanide, b. p. 188—196° (mainly 190—193°), on redistillation; yield, 74 g., 72%.

(2) *From benzoic anhydride.* Benzoic anhydride (4·5 g.) and benzenesulphonamide (9·5 g.; 3 mols.) reacted vigorously when heated at 240° for 15 minutes. The product was shaken with water, the dissolved benzenesulphonic acid titrated with alkali, and the phenyl cyanide separated. The yield of cyanide was 3·5 g. (85%), and 95% of the calculated amount of benzenesulphonic acid was produced.

(3) *From benzamide.* (*a*) A mixture of benzamide (7·26 g.) and anhydrous benzenesulphonic acid (10 g.) was heated at 280—315° so that the products distilled. The distillate, b. p. 235—236°, consisted of benzoic acid, m. p. and mixed m. p. 121° (3·5 g., 95%), and phenyl cyanide, b. p. 189—190° (2·9 g., 95%), identified as *m*-nitrophenyl cyanide, m. p. and mixed m. p. 117°.

(*b*) Benzamide (7 g.), benzenesulphonamide, and anhydrous benzenesulphonic acid (9·2 g.; 1 mol.), heated at 235° for 20 minutes, afforded ammonium benzenesulphonate (insoluble in acetone) and phenyl cyanide. The yield varied with the amount of benzenesulphonic acid as follows:

Benzenesulphonic acid (mols.)	0·04	0·25	0·5	1·0
Phenyl cyanide, %	Trace	25	53	74
Ammonium benzenesulphonate, %	Trace	25	78	77

If the reaction is carried out at a lower temperature the product also contains benzoylbenzenesulphonamide (see above).

(*c*) A mixture of benzamide (5·1 g.), benzenesulphondimethylamide (7·85 g.; 1 mol.), and anhydrous benzenesulphonic acid (6·7 g.; 1 mol.) was heated at 230—235° for 20 minutes. The product, which was completely soluble in acetone (absence of ammonium benzenesulphonate), was dissolved in *iso*propanol, and the solution on inoculation deposited dimethylammonium benzenesulphonate (6·5 g., 75%), m. p. and mixed m. p. 116°. Norton and Westenhoff (*Amer. Chem. J.*, 1888, **10**, 13) record m. p. 110°. The filtrate contained 3·5 g. (82%) of phenyl cyanide.

(*d*) Benzamide (6·05 g.) and benzamide benzenesulphonate (13·95 g.; 1 mol.) were heated at 160° for 2 hours and then dissolved in chloroform. Extraction with aqueous sodium bicarbonate afforded benzoic acid, m. p. 118—120° (1·1 g., 18%), and aqueous sodium hydroxide removed dibenzoylamine, m. p. 146—147° (1·5 g., 13·5%). The chloroform was removed by distillation, and the residue afforded benzamide, m. p. 125—127° (8·0 g., 66%), when triturated with benzene, and the benzene solution afforded crude phenyl cyanide (1·2 g., 23%) containing some benzamide.

(*e*) A 78% yield of phenyl cyanide was obtained when a mixture of benzamide (6·05 g.) and benzenesulphonyl chloride (8·8 g.; 1 mol.) was heated at 125—130° for ½ hour. The cyanide was isolated from a solution of the reaction product in dry benzene after 12 hours' keeping and removal of a solid (2 g.) by filtration. Recrystallisation from benzene gave slender needles of *benzamide benzenesulphonate*, m. p. 121·5—122° (Found: C, 56·0; H, 4·7; N, 5·2; *M*, by titration, 280. $C_{13}H_{13}O_4NS$ requires C, 55·9; H, 4·7; N, 5·0%; *M*, 279). This salt, which was also obtained from its constituents in chloroform solution, was decomposed by aqueous sodium carbonate with liberation of benzamide, m. p. and mixed m. p. 128°. Benzoic acid and phenyl cyanide were produced when the salt was heated at 225°:

$$2\mathrm{Ph{\cdot}CO{\cdot}}\overset{\oplus}{\mathrm{N}}\mathrm{H_3}\}\mathrm{S}\overset{\ominus}{\mathrm{O}}_3\mathrm{Ph} \longrightarrow \mathrm{Ph{\cdot}CN} + \mathrm{Ph{\cdot}CO_2H} + \mathrm{Ph{\cdot}SO_3H} + \mathrm{Ph{\cdot}SO_3NH_4}.$$

p-*Nitrophenyl Cyanide.*—*p*-Nitrobenzoic anhydride (26·5 g.) and toluene-*p*-sulphonamide (43 g.; 3 mols.), heated at 225° for ½ hour, afforded *p*-nitrophenyl cyanide (16 g., 64·5%), m. p. 149°.

p-*Cyanobenzenesulphonic Acid.*—*p*-Sulphonamidobenzoic acid (8 g.) and benzenesulphonamide (9 g.; 1·4 mols.) afforded a clear melt after being heated at *ca.* 230° for 15 minutes, and after a further 5—10 minutes there was an exothermic reaction which raised the temperature to 270°. The reaction product was triturated with acetone to remove benzenesulphonic acid and benzenesulphonamide, and the residual ammonium *p*-cyanobenzenesulphonate (7·5 g., 94%) was purified by recrystallisation from dilute ammonium chloride solution; m. p. above 290°. The guanidine salt, m. p. 236—237°, and *p*-toluidine salt, m. p. 241°, prepared from the ammonium salt by double decomposition, did not depress the m. p. of samples prepared from authentic *p*-cyanobenzenesulphonic acid (Remsen, Hartman, and Muckenfuss, *loc. cit.*). Ammonium *p*-cyanobenzenesulphonate was also prepared from *p*-sulphonamidobenzoic acid and 1—1·1 mols. of toluene-*p*-sulphonamide, benzenesulphonmethylamide, or benzenesulphondimethylamide under the same conditions, the yields being 94, 80, and 67·5%, respectively, and the reaction product was crystallised directly from aqueous ammonium chloride.

3-*Cyanopyridine.*—Nicotinic acid benzenesulphonate (14·05 g.) and benzenesulphonamide (19 g.; 2·4 mols.) were heated at 230° for 40 minutes and the powdered product was stirred with dry acetone. Ammonium benzenesulphonate (78%) remained undissolved, and when the residue obtained by evaporating the acetone solution was dissolved in 5N-sodium hydroxide and extracted with chloroform, 3-cyanopyridine, m. p. and mixed m. p. 49—50°, was obtained in 75% yield (9·8 g.). Its *benzenesulphonate* had m. p. 132° (Found: N, 10·6. $C_{12}H_{10}O_3N_2S$ requires N, 10·7%).

Preparation of Amidines.

p-*Amidinophenyl Methyl Sulphone.*—A mixture of *p*-carboxyphenyl methyl sulphone (14 g.) and benzenesulphonamide (22 g.; 2 mols.) was kept at 220—225° for 1·25 hours with mechanical stirring. Dry ammonia was then passed over the surface of the melt until no more was absorbed. The stream of gas was then stopped, and the temperature was raised to 255—260° during 10 minutes and kept thereat for 2 hours. The product was dissolved in hot water (42 c.c.), the solution then being cooled to 60° and poured into a mixture of ice (105 g.) and 36% aqueous sodium hydroxide (35 c.c.) with vigorous stirring. The precipitate was collected, washed with a little ice-water, suspended in water (52 c.c.), brought to pH 6·5 with hydrochloric acid, and filtered. The residue (2·2 g.) was *p*-cyanophenyl methyl sulphone, m. p. 139—142°, and sodium hydroxide precipitated the crude amidine (7·8 g.) from the filtrate. The amidine was washed with ice-water, suspended in water (90 c.c.), and brought to pH 6·5—7·0 with hydrochloric acid; the solution was stirred with charcoal (0·5 g.) and filtered, and the filtrate was evaporated to dryness on the steam-bath. The residue was powdered, washed with a little acetone, and dried at 100°, giving almost pure *p*-amidinophenyl methyl sulphone hydrochloride, m. p. 290—291° (7·84 g., 60%). The pure amidine hydrochloride has m. p. 294° (see Part I). The yield of amidine hydrochloride fell to 7·6 g. (48·7%) when the stream of ammonia was omitted, all other conditions remaining unaltered, and to 5·8 g. (35%) when toluene-*p*-sulphonamide was used in place of benzenesulphonamide.

p-*Amidinophenyl Ethyl Sulphone.*—(1) A mixture of *p*-carboxyphenyl ethyl sulphone (22 g.) and benzenesulphonamide (40 g.; 2·5 mols.) was melted and stirred at 235° ± 5° for 3 hours and the product was extracted with boiling acetone to remove *p*-cyanophenyl ethyl sulphone (7 g., 32%; m. p. 95°) and excess of benzenesulphonamide. The amidine was liberated from the residue and converted into the hydrochloride as described in the previous example. *p*-Amidinophenyl ethyl sulphone hydrochloride separated from aqueous acetone in rhombs, m. p. 253° (Found: N, 11·45. Calc. for $C_9H_{13}O_2N_2ClS$: N, 11·3%); yield, 12·5 g., 49%. Fuller, Tonkin, and Walker (*loc. cit.*) record m. p. 246—247°.

(2) *p*-Cyanophenyl ethyl sulphone (23 g.) and ammonium benzenesulphonate (25 g.; 1·2 mols.) were stirred at 245° for 4 hours and the powdered product was extracted with acetone to remove unchanged cyanide (8·9 g.). The residue was recrystallised from boiling water (75 c.c.) in presence of charcoal, giving 23 g. (52·5%) of p-*amidinophenyl ethyl sulphone benzenesulphonate*, which crystallised in plates, m. p. 240° (Found: N, 7·65. $C_{15}H_{18}O_5N_2S_2$ requires N, 7·6%).

p-*Nitrobenzamidine.*—Rouiller (*loc. cit.*) obtained *p*-nitrobenzamidine benzenesulphonate and *p*-nitrophenyl cyanide in 31 and 27% yield respectively by heating *p*-nitrobenzoic acid and benzenesulphonamide (2 mols.) at 220° for 5 hours, and we found that the yield could be increased by neutralising the sulphonic acid with ammonia. Thus, *p*-nitrobenzoic acid (3·34 g.) and benzenesulphonamide (6·28 g.) were kept at 220—225° for 1·25 hours, and, after passage of dry ammonia for 0·5 hour, the temperature was raised to 255—260° and kept thereat for 2 hours. The cooled reaction product was triturated with ice and 5N-sodium hydroxide (10 c.c.), and the solid was collected, washed with water, and neutralised with dilute hydrochloric acid. The insoluble portion afforded *p*-nitrophenyl cyanide, m. p. 149° (33%), when extracted with acetone, and *p*-nitrobenzamidine, m. p. 213° (43·5%), was precipitated from the solution of the hydrochloride by adding 10N-sodium hydroxide. Pinner and Gradenwitz (*Annalen*, 1897, **298**, 47) record m. p. 215°. p-*Nitrobenzamidine picrate* had m. p. 240° (Found : N, 21·5. $C_{13}H_{10}O_9N_6$ requires N, 21·3%). *p*-Chlorobenzenesulphonamide was also used in the preparation of this amidine.

3 : 4-*Dichlorobenzamidine.*—A mixture of 3 : 4-dichlorobenzoic acid (3·82 g.) and benzenesulphonamide (6·28 g.; 2 mols.) was maintained at 220—225° for 1·75 hours, a stream of dry ammonia being passed over the melt during the last 0·5 hour, and the temperature was then kept at 260° for 2 hours. The powdered product was extracted with cold acetone (120 c.c.) which removed 3 : 4-dichlorophenyl cyanide, m. p. 70—71° (1·1 g., 29%). Kraay (*Rec. Trav. chim.*, 1930, **49**, 1084) states that 3 : 4-dichlorophenyl cyanide has m. p. 71·8—72·1°. The portion insoluble in acetone was washed with water and recrystallised from alcohol, giving 3·68 g. (53%) of 3 : 4-*dichlorobenzamidine benzenesulphonate*, m. p. 240—241° (Found : N, 8·2. $C_{13}H_{12}O_3N_2Cl_2S$ requires N, 8·1%). 3 : 4-*Dichlorobenzamidine* separated from benzene in leaflets, m. p. 94—95° (Found : N, 15·0. $C_7H_6N_2Cl_2$ requires N, 14·8%), and afforded a *hydrochloride* which crystallised from alcohol–ether in prisms, m. p. 239·5° (Found : N, 12·3. $C_7H_7N_2Cl_3$ requires N, 12·4%). When the preparation was carried out without introducing the stream of ammonia the yield of 3 : 4-dichlorobenzamidine benzenesulphonate fell to 35%.

4 : 4′-*Diamidinodiphenyl Ether.*—A mixture of 4 : 4′-dicarboxydiphenyl ether (2·58 g.), benzenesulphonamide (6·28 g.; 4 mols.), and benzenesulphonic acid (0·1 g.) was heated at 240° until a homogeneous melt was obtained (0·5 hour) and was then kept at 220—225° for 1 hour. After passage of dry ammonia at 220° for 15 minutes, the melt was kept at 260—265° for 2·25 hours, and the amidine, isolated in the usual way, had m. p. 213—214° (decomp.) alone or mixed with an authentic specimen (Ashley, *et al.*, *loc. cit.*); yield 1·05 g., 42%.

RESEARCH LABORATORIES, MESSRS. BOOTS PURE DRUG CO. LTD.,
NOTTINGHAM.

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