

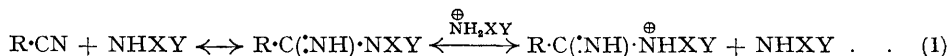
**76.** *Amidines. Part VIII. Preparation of Amidines from Cyanides, Ammonia or an Amine, and an Ammonium or Substituted-ammonium Salt.*

By P. OXLEY, M. W. PARTRIDGE, and W. F. SHORT.

Amidines and their *N*-substituted derivatives may be prepared by heating a cyanide, ammonia or a primary or secondary amine, and the corresponding ammonium or substituted-ammonium salt, especially a sulphonate, at a suitable temperature within the range 150—220°.

THE production of amidines by the addition of ammonia or an amine to a cyanide has been recorded with ethyl cyanotartrate (Curtis and Nickell, *J. Amer. Chem. Soc.*, 1913, **35**, 887) and trichloromethyl cyanide (I.G., G.P., 671,785), and the enhanced activity of the cyano-group in these compounds may be attributed to the inductive effect of the polar substituents (cf. Part I, *J.*, 1946, 147). It has been stated (Drew and Kelly, *J.*, 1941, 630) that a diamidine is formed by addition of ammonia to 3 : 6-dihydroxy-*o*-phenylene dicyanide, but it seemed unlikely that the cyano-group in this compound would be activated, and, moreover, the production of a diamidine would be opposed by the steric effect of the *o*-substituents. Mr. F. F. Whitmont has now shown that the compound produced from this cyano-phenol and cold alcoholic ammonia is in fact the diammonium salt and not 3 : 6-dihydroxyphthalodiamidine.

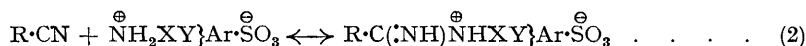
We have now shown that an equilibrium mixture containing approximately 1% of amidine is obtained by the decomposition of *p*-methylsulphonylbenzamidine at 180° or by heating *p*-methylsulphonylphenyl cyanide in an atmosphere of ammonia at this temperature. Amidines were also obtained in the yields shown in parentheses when this cyanide was heated at 180° with dimethylamine (0.7%), 2-aminopyridine (11%), or piperidine (24%). Similarly, phenyl cyanide and piperidine afforded *NN*-pentamethylenebenzamidine (1.5%) after 3 hours at 180°. Combination of cyanides with typical aromatic amines, such as aniline, has so far not been detected (see below). It seemed probable that by selecting a suitable reaction temperature many cyanides would combine with ammonia or amines to yield amidines but that only in exceptional cases would sufficient amidine be present at equilibrium to make the reaction of value as a method of preparation. Since amidines are usually stronger bases than ammonia or amines, it seemed probable that if the reaction were carried out in presence of an ammonium salt, an amidinium salt would be formed, and, provided that the temperature was lower than that at which this salt dissociates (Part I, *loc. cit.*), the equilibrium would be disturbed and conversion of the cyanide into the amidine would be promoted :



In agreement with this conclusion, an 83% yield of *p*-methylsulphonylbenzamidinium benzenesulphonate was obtained when *p*-methylsulphonylphenyl cyanide and ammonium benzenesulphonate (1 mol.) were heated in an atmosphere of ammonia for 2½ hours at 180°, and a number of amidines and *N*-substituted amidines have been prepared in a similar manner. The reaction appears to be controlled by a number of factors, some of which act in opposition. Thus, although the presence of a more strongly anionoid nitrogen atom in the base would facilitate addition to the cyanide, this increase in the strength of the base would decrease the proportion of

amidine converted into salt, with a correspondingly smaller displacement of the equilibrium between the cyanide, base, and amidine (1). When dissociation of the amidinium salt takes place, the relative volatility of the base and of the amidine will have an influence on the reaction. Ammonium and substituted-ammonium sulphonates are preferably employed as salts owing to the stability of the corresponding amidinium sulphonates, but other salts, including chlorides and thiocyanates, have given satisfactory results in a number of cases. The relative efficiency of various salts also depends to some extent on their miscibility with the molten cyanide, and when solidification of the reaction mixture occurs owing to the separation of the amidinium salt, the reaction is impeded, especially when the base is a gas. The addition of a solvent was sometimes beneficial in these cases; for example, *p*-methylsulphonylbenzamidine was obtained in only 15% yield from the corresponding cyanide, ammonium chloride, and ammonia at 180°, and the addition of acetamide increased the yield to 43% under otherwise identical conditions. Urea and substituted ureas can be used as solvent and as a source of ammonia or amine. Thus, *p*-methylsulphonylbenzamidine (43%) was obtained from the cyanide, ammonium chloride, and urea at 180°, and *NN*-dimethyl-*p*-methylsulphonylbenzamidine (32%) was similarly obtained from the cyanide, *NN*-dimethylurea, and dimethylammonium chloride.

It must be emphasized that reaction (1) is quite distinct from that which takes place between a cyanide and an ammonium sulphonate (Part I, *loc. cit.*; Part VII, *J.*, 1947, 1110) :



Thus, when arylammonium salts are used in reaction (2) good yields of amidinium salts are obtained, but, under the same conditions, cyanides do not add arylamines to yield free *N*-arylamidines, in spite of the fact that these amidines are stable at the temperature employed. For example, although *N*-phenyl-*p*-methylsulphonylbenzamidine suffered no appreciable decomposition when heated at 180° for 3 hours, no detectable quantity of this amidine was formed from *p*-methylsulphonylphenyl cyanide and aniline under these conditions, but the use of anilinium benzenesulphonate in place of aniline gave an 86.5% yield of the amidinium benzenesulphonate. Similarly, although Bernthsen (*Annalen*, 1877, **184**, 341; 1878, **192**, 4) found that phenyl cyanide does not react with aniline or diphenylamine at 280–360°, yet *N*-phenyl- and *NN*-diphenylbenzamidinium salts are readily prepared by using phenyl- and diphenyl-ammonium salts respectively (see Part I, *loc. cit.*). We found that trichloromethyl cyanide did not react with aniline in benzene solution under conditions which, as stated by the I.G. (*loc. cit.*), give an almost quantitative yield of trichloroacetamidine when ammonia is used in place of aniline. A further distinction between the reactions is observed in the case of *o*-substituted phenyl cyanides which afford very poor yields in reaction (1) but moderately good yields in reaction (2). Reaction (1) usually takes place at a considerably lower temperature. Thus, whereas *p*-methylsulphonylphenyl cyanide and ammonium benzenesulphonate (1 mol.) afforded traces of amidinium salt after 2½ hours at 180°, *ca.* 3% after 2 hours at 220°, and 61% after 2 hours at 250°, an 83% yield was obtained in 2½ hours at 180° in the presence of ammonia. Our rejection of the hypothesis that reaction (2) involves dissociation of the ammonium salt (Part I, *loc. cit.*) is therefore now supported by further evidence.

In an inconclusive attempt to obtain additional evidence that reaction (1) does in fact involve the addition of ammonia or an amine to the cyanide and not simply its reaction with the ammonium salt, it was found that *p*-methylsulphonylbenzamidine and its *NN*-dimethyl derivative were both produced when *p*-methylsulphonylphenyl cyanide was heated either with ammonia and dimethylammonium benzenesulphonate or with dimethylamine and ammonium benzenesulphonate. The influence of experimental conditions on the ratio of the two amidines formed indicated that the controlling factors are the relative strengths of the four bases concerned and the stability of the free amidines. For example, when the cyanide and ammonium benzenesulphonate (1 mol.) were heated at 180° for 3 hours in a slow stream of dimethylamine, *p*-methylsulphonylbenzamidine and its *NN*-dimethyl derivative were produced in 0.03 and 79% yield, respectively. Under the same conditions, the cyanide, dimethylammonium benzenesulphonate, and ammonia afforded 62% of the unsubstituted amidine and 17% of the *NN*-dimethylamidine, but when the amount of ammonia was limited to 1 mol., the volume of the gas phase decreased by 27% and the yields of unsubstituted and substituted amidine were 32 and 52%, respectively. The decrease in the volume of gas would be accounted for if the substituted amidine and dimethylamine have approximately the same basic strength, so that some of the amidine is displaced from its salt by the amine.

During the preparation of amidines by heating cyanides with ammonium thiocyanate (Part

IV, J., 1947, 390) ammonia is freely evolved, and it is probable that a reaction analogous to reaction (1) takes place. Many cyanides appear to react more readily with ammonium thiocyanate than with ammonia in presence of an ammonium salt and, although this may be due solely to physical factors, it is possible that a reaction of type (2) takes place simultaneously.

#### EXPERIMENTAL.

*Note.*—The yields of amidines recorded are not necessarily the highest obtainable since a systematic examination of the effect of conditions on the yield of amidine was not made in all cases. Detailed descriptions of the isolation of the amidines are given in special cases only, since the methods employed followed closely those described in previous parts of this series, to which reference is made for earlier descriptions of many of the amidines (Part I, Oxley and Short, *J.*, 1946, 149; Part II, Oxley, Partridge, Robson, and Short, *ibid.*, p. 763; Part IV, Partridge and Short, *J.*, 1947, 390; Part VII, Oxley, Partridge, and Short, *ibid.*, p. 1110).

*Trichloromethyl Cyanide and Ammonia.*—Dry ammonia was passed for 2 hours at 0° into a solution of trichloromethyl cyanide (7 g.; b. p. 84–84.5°) in benzene (20 c.c.) and the solvent was then removed in a vacuum below 0°. The product was an oil and was therefore neutralised to bromocresol-purple with ethanolic picric acid, and concentration of the solution afforded slender yellow needles of *trichloroacetamidinium picrate*, which changed into stout needles at 220–223° and had m. p. 273–275° (decomp.) (Found: N, 17.8.  $C_8H_6O_7N_5Cl_3$  requires N, 17.9%). Trichloroacetamidine was obtained as a solid, m. p. 41–42°, by the I.G. (*loc. cit.*) but was not analysed.

*Trichloromethyl Cyanide and Aniline.*—These reagents (1 mol. each) were recovered unchanged after a benzene solution of them had been kept at 20° for an hour.

*Trichloromethyl Cyanide and Ethylenediamine.*—A solution of trichloromethyl cyanide (5.78 g.) in dry benzene (10 c.c.) was added dropwise to a stirred solution of anhydrous ethylenediamine (1.2 g.; 1.0 mol.) in benzene (10 c.c.) at 0°. After the mixture had been stirred at 0° for 15 minutes and at 20° for 30 minutes, the solid (4.4 g.; 63%), m. p. 94–96°, was collected, and crystallised from benzene (15 c.c.) in rods, m. p. 97–98° (slight decomp.) (Found: N, 15.9.  $C_6H_8N_4Cl_3$  requires N, 16.05%.  $C_4H_8N_2Cl_3$  requires N, 14.9%). In agreement with the I.G. (*loc. cit.*), who give m. p. 88–90° but record no analysis, the compound is therefore *NN-ethylenebis-trichloroacetamidine* and not 2-trichloromethyl-4:5-dihydroglyoxaline. The *bispicrate* crystallised from methanol in needles, m. p. 178° (decomp.) (Found: N, 17.4.  $C_{18}H_{14}O_{14}N_{10}Cl_6$  requires N, 17.35%). The *bistoluene-p-sulphonate* separated from isopropanol in plates, m. p. 254° (decomp.) (Found: N, 7.9.  $C_{20}H_{24}O_8N_4Cl_6S_2$  requires N, 8.1%), and from water in small plates, m. p. 210° (Found: N, 8.0%).

*Phenyl Cyanide and Piperidine.*—Phenyl cyanide (5.2 g.) and piperidine (4.25 g.; 1 mol.) were heated at 180° for 3 hours in a sealed tube, and the product was separated into a basic and a neutral fraction. Phenyl cyanide, b. p. 56°/5 mm. (4.6 g.; 88.5%), was recovered, and distillation of the basic fraction gave piperidine and a fraction, b. p. 114°/1 mm., which afforded *NN-pentamethylenebenzamidinium picrate* (0.32 g., 1.5%), m. p. and mixed m. p. 173–174° (Part IV).

*3:6-Dihydroxy-o-phenylene Dicyanide and Ammonia.\**—The yellow needles prepared from the dicyanide and cold alcoholic ammonia, as described by Drew and Kelly (*loc. cit.*), blackened and decomposed between 200° and 280° without melting. An aqueous solution of this compound had a greenish-blue fluorescence, was alkaline to brilliant-yellow but not to Titan-yellow, afforded ammonia with cold aqueous sodium hydroxide, and did not respond to Fuller's amidine reagent (*Nature*, 1944, **154**, 773). When acetic acid (0.2 c.c.) was added to a solution of the yellow compound (147 mg.) in water and the white needles so obtained were dried in a vacuum at room temperature, they darkened at 230–250° without melting (Found: N, 17.25. Calc. for  $C_8H_4O_2N_2$ : N, 17.5%). Thiele and Meisenheimer (*Ber.*, 1900, **33**, 675) state that 3:6-dihydroxy-*o*-phenylene dicyanide darkens at ca. 230°. Acetylation of this regenerated dicyanide (53 mg.) with acetic anhydride (0.4 c.c.) in dry pyridine (0.8 c.c.) for 12 hours afforded 3:6-diacetoxy-*o*-phenylene dicyanide, m. p. 166–168° (Found: N, 11.7.  $C_{12}H_8O_4N_2$  requires N, 11.5%), identical with a specimen prepared from authentic 3:6-dihydroxy-*o*-phenylene dicyanide. It is therefore clear that the yellow compound is the diammonium salt of 3:6-dihydroxy-*o*-phenylene dicyanide and not the corresponding diamidine.

*p-Methylsulphonylphenyl Cyanide and Ammonia.*—(a) *p*-Methylsulphonylphenyl cyanide (5 g.) was heated at 180° for 3 hours in an atmosphere of ammonia, and the product was cooled, suspended in water (5 c.c.), and neutralised to brilliant-yellow with hydrochloric acid. The solid was collected, washed with water (2 × 3 c.c.), and separated by acetone into a soluble portion consisting of *p*-methylsulphonylphenyl cyanide, m. p. 142° (4.52 g., 91%), and the almost insoluble 2:4:6-tris-*p*-methylsulphonylphenyl-1:3:5-triazine (Found: N, 7.8. Calc. for  $C_{24}H_{21}O_6N_3S_3$ : N, 7.7%) (0.35 g. or 6.9%; Part VII). When sodium picrate was added to the amidinium chloride solution and washings, *p*-methylsulphonylbenzamidinium picrate, m. p. 261–262° (Part IV), was obtained (0.14 g., 1.2%).

(b) *p*-Methylsulphonylbenzamidine (4.94 g.) was heated at 180° for 3 hours in an atmosphere of ammonia, and the product afforded *p*-methylsulphonylphenyl cyanide, m. p. and mixed m. p. 142° (3.10 g., 68.7%), 2:4:6-tris-*p*-methylsulphonylphenyl-1:3:5-triazine, m. p. > 360° (1.26 g., 27.9%), and *p*-methylsulphonylbenzamidinium picrate, m. p. 260° (0.11 g., 1.1%), or 262° after recrystallisation from ethanol. A small quantity of the cyanide, m. p. 139–140°, sublimed from the reaction mixture. In another experiment, the amidine (0.618 g.) was heated at 180° for 3 hours and the ammonia evolved was collected in 0.1N-hydrochloric acid, the residual gas being displaced by a stream of dry air. The ammonia evolved neutralised 30.45 ml. of 0.1N-acid and represented decomposition of 97.6% of the amidine. Unchanged amidine, the cyanide, and the triazine were identified in the residue.

(c) When the cyanide (1.8 g.) and urea (2.4 g.; 4 mols.) were stirred at 180° for 2 hours, the product on being worked up as described above afforded 0.08 g. (2%) of *p*-methylsulphonylbenzamidinium picrate, m. p. and mixed m. p. 262°.

\* Experiments by Mr. F. F. Whitmont.

*p*-Methylsulphonylphenyl Cyanide and Dimethylamine.—A steady stream of dimethylamine was passed into the molten cyanide (4.5 g.) at 180° for 3 hours and the unchanged cyanide (4.4 g., 98%) and amidine were separated as described in the previous section. The yield of *NN*-dimethyl-*p*-methylsulphonylbenzamidinium picrate, m. p. and mixed m. p. 187—189° (Part IV), was 0.08 g. (0.7%).

*p*-Methylsulphonylphenyl Cyanide and 2-Aminopyridine.—A mixture of the cyanide (9.05 g.) and 2-aminopyridine (4.7 g.; 1 mol.) was kept at 180° for an hour and afforded unchanged cyanide (7.5 g.; 83%) and *N*-2-pyridyl-*p*-methylsulphonylbenzamidinium picrate (1.5 g., 11%), m. p. and mixed m. p. 169—170° (Part VII).

*p*-Methylsulphonylphenyl Cyanide and Piperidine.—The cyanide (9.05 g.) and amine (8.5 g.; 2 mols.) were heated in a sealed tube for 18 hours at 175—180° and afforded 6.7 g. (74%) of recovered cyanide, m. p. 140—142°, and 3.1 g. (24%) of crude amidine, which gave 5.1 g. of pure *NN*-pentamethylene-*p*-methylsulphonylbenzamidinium picrate, m. p. and mixed m. p. 199—199.5° (Part VII).

*p*-Methylsulphonylphenyl Cyanide and Aniline.—The formation of amidine could not be detected, and the cyanide, m. p. 142°, was recovered quantitatively when *p*-methylsulphonylphenyl cyanide (4.5 g.) and aniline (9.3 g.; 4 mols.) were heated at 180° for 3 hours. *N*-Phenyl-*p*-methylsulphonylbenzamidinium picrate (Part IV), was recovered unchanged after heating at 180° for 3 hours.

2 : 4-Dichlorophenyl Cyanide and Aniline.—After 2 : 4-dichlorophenyl cyanide (Gomberg and Cone, *Annalen*, 1909, 370, 182) (1.72 g.) and aniline (0.93 g.; 1 mol.) had been heated at 180° for 5 hours, 99% of the cyanide, m. p. and mixed m. p. 59—60°, was recovered and no amidine could be detected in the product. A mixture of the cyanide (3.44 g.) and anilinium benzenesulphonate (5.02 g.; 1 mol.) was heated at 190° for 4½ hours, and crystallisation of the product from water gave colourless prisms of *N*-phenyl-2 : 4-dichlorobenzamidinium benzenesulphonate, m. p. 183—183.5° (Found : N, 6.4, 6.5. C<sub>13</sub>H<sub>16</sub>O<sub>3</sub>N<sub>2</sub>Cl<sub>2</sub>S requires N, 6.6%). The amidine separated from light petroleum (b. p. 100—120°) in needles, m. p. 102° (Found : N, 10.6. C<sub>13</sub>H<sub>16</sub>O<sub>3</sub>N<sub>2</sub>Cl<sub>2</sub> requires N, 10.6%), and afforded a picrate, m. p. 156.5° (Found : N, 13.9. C<sub>13</sub>H<sub>13</sub>O<sub>7</sub>N<sub>5</sub>Cl<sub>2</sub> requires N, 14.2%).

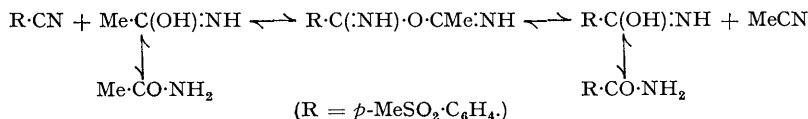
*Preparation of Amidines from Cyanides, Ammonia or an Amine, and an Ammonium Salt.*

*p*-Methylsulphonylbenzamidinium.—(a) *p*-Methylsulphonylphenyl cyanide (9.05 g.) and ammonium benzenesulphonate (8.8 g.; 1 mol.) were heated at 180° for 2½ hours, a stream of dry ammonia being passed into the mixture, which solidified during the course of the reaction. The product was triturated with acetone to remove unchanged cyanide (1.45 g., 16%), and the insoluble portion was crystallised from hot water, giving 14.8 g. (83%) of *p*-methylsulphonylbenzamidinium benzenesulphonate, m. p. and mixed m. p. 253° (Part I). When the mixture was heated at 153° the yield of amidinium salt was 42 and 65% after 8.5 and 15½ hours, respectively. Addition of various "fluxes" to an equimolecular mixture of the cyanide and ammonium benzenesulphonate, so that the mixture remained homogeneous during the passage of ammonia, resulted in reduced yields in this instance, as shown in the table.

Flux.	Mols.	Temp.	Time, hrs.	Amidine, %.	Recovered cyanide, %.
Guanidinium benzenesulphonate	1.0	180°	5	79	—
<i>N</i> -Methylpyridinium benzenesulphonate	1.6	160	15.5	65	—
	1.6	160	4	51	31
Acetamide	3.4	180	2	39	58
Triethylammonium benzenesulphonate	0.8	160	2	Trace *	90

\* The product gave a positive reaction with the Fuller reagent.

(b) (i) No amidine could be detected with Fuller's reagent in the mixture obtained by heating the cyanide and ammonium chloride (4 mols.) at 180° for 3½ hours. (ii) When dry ammonia was passed for 2½ hours into a mixture of the cyanide (9.05 g.) and ammonium chloride (2.7 g.; 1 mol.) at 180°, *p*-methylsulphonylbenzamidinium picrate (3.2 g.), m. p. and mixed m. p. 265°, was obtained in 15% yield, and 62% of the cyanide was recovered. (iii) A solid began to separate after *ca.* 2½ hours when ammonia was passed into the homogeneous solution obtained by heating the cyanide (4.5 g.), ammonium chloride (1.5 g.; 1.1 mols.), and acetamide at 180°. The operation was interrupted after 5 hours, the product was cooled and triturated with acetone, and the insoluble solid was collected by filtration. The filtrate was evaporated, and the residue crystallised from methanol, giving crude *p*-methylsulphonylphenyl cyanide (0.25 g.; 6%), m. p. 136—138°. The acetone-insoluble solid was stirred with cold water and an insoluble portion was removed by filtration. *p*-Methylsulphonylbenzamidinium toluene-*p*-sulphonate (4 g.; 43%), m. p. and mixed m. p. 293° (Part VII), separated when aqueous ammonium toluene-*p*-sulphonate was added to the filtrate. The solid insoluble in cold water was crystallised from hot water and afforded *p*-methylsulphonylbenzamidinium chloride (2.1 g., 42%), m. p. and mixed m. p. 226—227° (Part II). Since all the substances used in this reaction were dry, it is probable that this amide is produced by an exchange of functions between acetamide and the cyanide, possibly by the mechanism :



(c) *p*-Methylsulphonylphenyl cyanide (9 g.) and ammonium thiocyanate (3.8 g.; 1 mol.) were heated at 180° for 1½ hours in a stream of ammonia; the amidine was isolated and converted into *p*-methylsulphonylbenzamidinium chloride (8.6 g.; 74%), m. p. and mixed m. p. 295°. 2 : 4 : 6-Tris-*p*-methylsulphonylphenyl-1 : 3 : 5-triazine (1 g.) was obtained from the neutral portion of the product.

*p*-Methylsulphonylbenzamidinium (3.2 g.; 54%), m. p. and mixed m. p. 201—202° (decomp.), was isolated from the mixture obtained by heating the cyanide (5.4 g.), ammonium thiocyanate (2.3 g.; 1 mol.), and urea (9 g.; 5 mols.) at 180° for 1½ hours.

(d) Dry ammonia was passed for 2½ hours into a mixture of the cyanide (9.05 g.) and ammonium methanesulphonate (5.7 g.; 1 mol.) heated at 180°, and the unchanged cyanide (0.5 g.; 6%) was extracted from the product by trituration with acetone. The residue was dissolved in a solution of ammonium benzenesulphonate (20 g.) in hot water (50 c.c.), and the *p*-methylsulphonylbenzamidinium benzenesulphonate (14.2 g.; 81%) which separated on cooling had m. p. and mixed m. p. 253°.

(e) *Ammonium p-hydroxybenzenesulphonate*, prepared from its constituents, separated from water in colourless plates, m. p. 270—271° (decomp.) (Found: N, 7.4.  $C_6H_5O_2NS$  requires N, 7.3%). When the cyanide (5.43 g.) and this salt (5.73 g.; 1 mol.) were heated at 195° for 1½ hours in an atmosphere of ammonia, the product contained unchanged cyanide (4.4 g.; 81%), m. p. 140—141°, and the amidine, which was isolated as toluene-*p*-sulphonate (2 g.; 18.3%), m. p. and mixed m. p. 293—294° (Part VII).

*NN-Dimethyl-p-methylsulphonylbenzamidinium*.—In the following experiments the reaction product contained unchanged *p*-methylsulphonylphenyl cyanide, 2 : 4 : 6-tris-*p*-methylsulphonylphenyl-1 : 3 : 5-triazine, *p*-methylsulphonylbenzamidinium benzenesulphonate, and its *NN*-dimethyl derivative. The amidines were separated by taking advantage of the distinct solubility of the substituted amidine in aqueous alkali (cf. Part IV). The unsubstituted amidine was extracted from the insoluble portion with dilute hydrochloric acid, and the residual cyanide and triazine were separated by extracting the cyanide with acetone.

(a) *p*-Methylsulphonylphenyl cyanide (9 g.) and ammonium benzenesulphonate (8.75 g.; 1 mol.) were heated at 180° and stirred for 3 hours, a slow stream of dry dimethylamine being passed into the mixture. A homogeneous melt was produced after 20 minutes, persisted for *ca.* 40 minutes, and then became increasingly turbid. When a hot solution of the product in water (40 c.c.) was poured into a mixture of 10*N*-sodium hydroxide (20 c.c.) and ice (20 g.), dimethylamine was evolved, and the solid which separated was collected after an hour and washed with a little ice-water, and the united filtrates were kept. The solid (3.04 g.) was suspended in water, acidified to Congo-red with dilute hydrochloric acid (2 drops), and the whole filtered. The solution gave no colouration with Fuller's reagent and afforded no precipitate with aqueous sodium picrate. The solid was separated by acetone into unchanged cyanide, m. p. and mixed m. p. 141—142° (1.96 g.; 21.8%), and the triazine (1.07 g.; 11.9%). The original filtrate was extracted with chloroform (6 × 100 c.c.), the solution dried ( $K_2CO_3$ ) and evaporated, and the residual gum (5.9 g.) dissolved in water (25 c.c.), neutralised to brilliant-yellow with dilute hydrochloric acid, and diluted to 50 ml. The *NN*-disubstituted amidine gave no colouration with Fuller's reagent, and the *p*-methylsulphonylbenzamidinium chloride in 1 ml. of the solution was determined colorimetrically (Fuller, *Biochem. J.*, 1945, **39**, 99) and found to be equivalent to 3.3 mg. in the whole solution. The remaining solution (49 ml.) was evaporated on the steam-bath and the residue, dried at 100°, was equivalent to 6.87 g. of the *NN*-dimethylbenzamidinium chloride in 50 ml. of solution. The amidinium chloride was purified with considerable loss by dissolving it in the minimum quantity of 1 : 1 aqueous acetone (charcoal) and pouring the filtered solution into a large excess of acetone, and was obtained in colourless plates, m. p. 274—275° (decomp.), undepressed on admixture with an authentic specimen.

(b) A stream of dry ammonia was passed for 3 hours into a mechanically stirred mixture of *p*-methylsulphonylphenyl cyanide (9 g.) and dimethylammonium benzenesulphonate (11.5 g.; 1 mol.) kept at 180° in the vapour of phenol. The clear melt became increasingly turbid during the last two hours' heating. A hot solution of the product in water (40 c.c.) was poured into 10*N*-sodium hydroxide (20 c.c.) and ice (20 g.), and the solid (A) was collected after 2½ hours and washed with water (3 × 5 c.c.) and chloroform (3 × 5 c.c.). The aqueous filtrate was extracted with chloroform (6 × 50 c.c.), and the united chloroform solutions were dried ( $K_2CO_3$ ) and evaporated, giving a pale yellow gum (3.4 g.). A small amount of a flocculent solid remained undissolved when this gum was added to water (5 c.c.), and was collected, washed with water (5 c.c.), and added to the solid (A). The filtrate, which gave a faint colouration with Fuller's reagent, was neutralised to brilliant-yellow with alcoholic picric acid, cooled to 0°, and filtered. The *NN*-dimethyl-*p*-methylsulphonylbenzamidinium picrate so obtained (2.95 g.) had m. p. 185—186°, alone or on admixture with an authentic specimen, m. p. 189.5° (Part IV). The solid (A) was suspended in water (10 c.c.), and dilute hydrochloric acid was added until the solution was neutral to brilliant-yellow. The insoluble solid (B) was then removed, the filtrate was poured into 10*N*-sodium hydroxide (5 c.c.) and ice (10 g.), and filtered after an hour. The solid was washed with water, suspended in water (20 c.c.), and neutralised to Congo-red with aqueous benzenesulphonic acid. The resulting solution was warmed with charcoal, filtered, and evaporated to dryness under diminished pressure. The residual *p*-methylsulphonylbenzamidinium benzenesulphonate (8.5 g.) had m. p. 250—251°, undepressed on admixture with an authentic specimen (Part I). The solid (B) was separated by acetone into *p*-methylsulphonylphenyl cyanide, m. p. and mixed m. p. 138—140° (1 g.; 11.1%), and the triazine (0.93 g.; 10.3%).

(c) In this experiment the cyanide (6.8 g.) and dimethylammonium benzenesulphonate (8.66 g.; 1 mol.) were heated and stirred at 180° for 3 hours, and dry ammonia (900 c.c. at 19° and 762 mm.; 1 mol.) was passed to and fro over the reaction mixture. At the end of 3 hours the volume of the residual gas was 657 c.c. (19°/762 mm.). Recovered cyanide (1.2 g.), triazine (0.5 g.), *p*-methylsulphonylbenzamidinium benzenesulphonate (3.2 g.), and *NN*-dimethyl-*p*-methylsulphonylbenzamidinium picrate (6.4 g.) were isolated and identified as described in (b).

(d) When the cyanide (4.5 g.) and dimethylammonium benzenesulphonate (5.8 g.; 1 mol.) were heated at 180° for 3 hours and the cold mixture was extracted with acetone, dimethylammonium benzenesulphonate, m. p. 110° (5.3 g.; 92%), remained and the solution afforded unchanged cyanide (4.36 g.; 97%). No picrate could be obtained from the mother-liquor, indicating that there is no appreciable formation of amidine at 180°. This is in accord with the observation (Part VII) that the cyanide and diethylammonium benzenesulphonate give only 7% of the corresponding *NN*-diethylamidine at 224°.

NN'-Dibenzyl-*p*-methylsulphonylbenzamidine.—*p*-Methylsulphonylphenyl cyanide (9 g.), ammonium benzenesulphonate (8.8 g.; 1 mol.), and benzylamine (10.7 g.; 2 mols.) were heated at 180° for 2 hours, and the cold product was stirred with dilute hydrochloric acid. The oil which separated was dissolved in chloroform, and the solution was washed with a little water to remove benzylammonium chloride, shaken with aqueous sodium hydroxide to decompose the hydrochlorides, and then evaporated. The residue was dissolved in dilute hydrochloric acid and ammonia was added to the solution to precipitate NN'-dibenzyl-*p*-methylsulphonylbenzamidine, which crystallised from methanol in needles, m. p. 129—131° (Found: N, 7.4. C<sub>22</sub>H<sub>22</sub>O<sub>2</sub>N<sub>2</sub>S requires N, 7.4%); yield, 1.2 g. (6.35%).

*p*-Nitrobenzamidine.—(a) *p*-Nitrophenyl cyanide (4.95 g.) and ammonium benzenesulphonate (5.85 g.; 1 mol.) were heated at 180° for 2 hours, during which a stream of dry ammonia was passed into the mixture. Acetone extracted unchanged cyanide (35%) from the product, and crystallisation of the insoluble fraction from water afforded *p*-nitrobenzamidinium benzenesulphonate (52%), m. p. and mixed m. p. 258—259° (Part I). Rouiller (*Amer. Chem. J.*, 1912, 47, 483) records m. p. 250°.

(b) *p*-Nitrophenyl cyanide (1.5 g.), benzenesulphonic acid monohydrate (1.9 g.; 1.1 mol.), and urea (2.4 g.; 4 mols.), heated at 180° for 1½ hours so that water vapour and ammonia were allowed to escape, afforded a 27% yield of *p*-nitrobenzamidinium benzenesulphonate, m. p. and mixed m. p. 258°, and 54% of the cyanide was recovered.

3 : 5-Dinitrobenzamidine.—A stream of dry ammonia was passed into a molten mixture of 3 : 5-dinitrophenyl cyanide (3.86 g.) and ammonium benzenesulphonate (3.5 g.; 1 mol.) which was kept at 195°. After 15 minutes' heating the mixture had solidified and was then cooled, triturated with acetone, and filtered. The solid was crystallised from water and gave 3 : 5-dinitrobenzamidinium benzenesulphonate, m. p. 265° (Found: N, 15.3. C<sub>13</sub>H<sub>12</sub>O<sub>7</sub>N<sub>4</sub>S requires N, 15.2%); yield, 61%. 3 : 5-Dinitrobenzamidinium picrate had m. p. 271° (Found: N, 22.4. C<sub>13</sub>H<sub>8</sub>O<sub>11</sub>N<sub>7</sub> requires N, 22.3%).

2 : 4-Dinitrobenzamidine, 2 : 4-Dichlorobenzamidine, and 2 : 6-Dimethoxybenzamidine.—When the corresponding cyanides and ammonium benzenesulphonate (1 mol.) were heated at 180° for 3 hours in an atmosphere of ammonia, the products all gave colourations with Fuller's reagent, but the amount of amidines produced was small and they were not isolated.

4 : 4'-Diamidino-*ay*-diphenoxypropane.—Dry ammonia was passed for 24 hours into a mechanically stirred mixture of 4 : 4'-dicyano-*ay*-diphenoxypropane (28 g.) and ammonium benzenesulphonate (35 g.; 2 mols.) heated in a bath at 210—212°. The amidinium chloride, isolated in the usual way (Part IV), had m. p. and mixed m. p. 294° (18.8 g., 48%).

4 : 4'-Diamidinostilbene.\*—4 : 4'-Dicyanostilbene (46 g.) and ammonium benzenesulphonate (70 g.; 2 mols.) were heated at 270—275° and a stream of ammonia was passed into the melt for 3 hours with vigorous stirring. The amidinium sulphonate was separated from unchanged cyanide (14 g.; 30%) by solution in boiling water, and the amidine was liberated with 5*N*-sodium hydroxide and converted into 4 : 4'-diamidinostilbene dihydrochloride dihydrate, m. p. 372—375° (decomp.) (Found: N, 14.9; Cl, 18.8. Calc. for C<sub>14</sub>H<sub>14</sub>N<sub>4</sub>Cl<sub>2</sub>·2H<sub>2</sub>O : N, 15.0; Cl, 19.0%). The m. p. depends upon the rate of heating (cf. Part IV); yield, 45.5 g. (61%).

2-Amidinopyridine.—2-Cyanopyridine (4.2 g.), ammonium benzenesulphonate (7 g.; 1 mol.), and urea (9.6 g.; 4 mols.) were heated at 180° and stirred for 2 hours. The mixture was cooled, triturated with water (50 c.c.), and then extracted with chloroform (3 × 10 c.c.). The aqueous solution was made alkaline with 10*N*-sodium hydroxide at 0° and the amidine was extracted with chloroform (7 × 20 c.c.). The chloroform solution was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated, and saturated alcoholic picric acid was added to the residue until the mixture was neutral to brilliant-yellow; it was then cooled to 0° and filtered, giving 3.4 g. (24%) of the picrate of 2-amidinopyridine, m. p. 202—203°. Recrystallisation from methanol raised the m. p. to 207—208°, not depressed on admixture with an authentic specimen (Part I).

Phenylacetamidine.—Benzyl cyanide (11.7 g.) and ammonium benzenesulphonate (3.5 g.; 0.2 mol.) were heated at 195° for 8 hours, during which a steady stream of ammonia was passed into the mixture. The cooled product was diluted with acetone and filtered, and the solid was washed with acetone and crystallised from water, giving phenylacetamidinium benzenesulphonate, m. p. and mixed m. p. 186° (Part IV); yield, 15%.

*N*-cyclohexylphenylacetamidine.—(a) The product obtained by heating benzyl cyanide (11.7 g.), cyclohexylamine (19.8 g.; 2 mols.), and ammonium chloride (5.4 g.; 1 mol.) at 180° for 8 hours was triturated with water (20 c.c.) and the mixture was made acid to Congo-red with 5*N*-hydrochloric acid. The solid was collected, washed with benzene, and crystallised from alcohol, giving 18.9 g. (75%) of *N*-cyclohexylphenylacetamidinium chloride, m. p. 290—292° (decomp.). A second recrystallisation from alcohol afforded the pure compound, m. p. and mixed m. p. 303—304° (decomp.) (Part VII).

(b) An 84% yield of the amidinium chloride, m. p. and mixed m. p. 302—303° (decomp.), was obtained by heating benzyl cyanide (11.7 g.), cyclohexylamine (9.9 g.; 1 mol.), and cyclohexylammonium chloride (13.5 g.; 1 mol.) at 180° for 8 hours.

(c) Benzyl cyanide (11.7 g.), cyclohexylamine (19.8 g.; 2 mols.), and pyridinium benzenesulphonate (23.7 g.; 1 mol.) were heated under reflux at 180° for 4 hours, and the bases were then liberated with ice-cold 2.5*N*-sodium hydroxide and collected in chloroform. The chloroform solution was washed with 2.5*N*-sodium hydroxide (2 × 20 c.c.) and water (5 c.c.), dried (K<sub>2</sub>CO<sub>3</sub>), and evaporated. Pyridine was removed by distilling the mixture of bases at 2 mm. until the temperature reached 82°, and the residue was then warmed with 3.3*N*-hydrochloric acid (15 c.c.). The solution was cooled, and the solid was collected and washed with benzene, giving 2.2 g. (8.8%) of *N*-cyclohexylphenylacetamidinium chloride, m. p. 290—292° (decomp.).

*N*-cyclohexyl-1-amidino-*n*-heptane.—*n*-Heptyl cyanide (2.5 g.), cyclohexylamine (1 g.; 0.5 mol.), and cyclohexylammonium toluene-*p*-sulphonate (5.4 g.; 1 mol.) were heated at 190—195° for 5 hours under a reflux condenser. The product was dissolved in chloroform, and after the solution had been washed several times with 2*N*-sodium hydroxide, chloroform was removed by distillation.

\* Experiment by Mr. S. W. Stroud.

2N-Hydrochloric acid was added to the residue until the mixture was acid to Congo-red, and the solid was then collected and crystallised from water, giving the hydrochloride of *N*-cyclohexyl-1-amidino-*n*-heptane, m. p. and mixed m. p. 200° (Part VII); yield, 0.63 g. (12%).

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[Received, April 10th, 1947.]

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