103. *Amidines. Part XI. Preparation of Amidines by Ammonolysis of* N-*Arylamidinium Salts.*

By P. Oxley and W. F. Short.

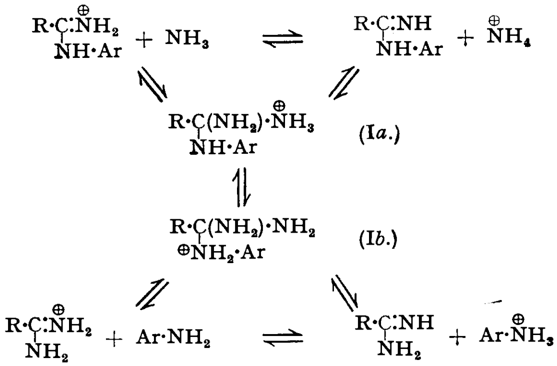
N-Arylamidinium sulphonates, obtained from cyanides and arylammonium sulphonates at *ca.* 200°, afford good yields of unsubstituted amidinium sulphonates by ammonolysis at *ca.* 140°. This is a valuable method of preparation when poor yields are obtained directly from a cyanide and an ammonium sulphonate.

This communication describes the preparation of amidines in almost quantitative yield by heating *N*-arylamidinium salts in an atmosphere of ammonia at temperatures within the range 100—160°:

$$\mathrm{R{\cdot}C(NHAr){:}\overset{\oplus}{N}H_2 + NH_3 \longrightarrow R{\cdot}C(NH_2){:}\overset{\oplus}{N}H_2 + Ar{\cdot}NH_2}$$

It is convenient to use the arylsulphonates of the *N*-arylamidines owing to the stability of the resulting unsubstituted amidinium salts and the relatively high solubility of both amidinium salts in the melt, but hydrochlorides, nitrates, acetates, and picrates have also been used. Some benzamidine (Fuller reaction) is produced by the slow ammonolysis of *N*-phenylbenzamidine in presence of phenol (1 mol.) at 140°, but the main product of the reaction is phenyl cyanide, produced by decomposition of the unsubstituted amidine. Aniline and nitrobenzene have been most frequently used as solvents in the ammonolysis of *N*-arylamidines, and although a number of other solvents has also been used (see Experimental section), alcohols seem to inhibit the reaction. It is often convenient to employ a mixture of an ammonium salt and an *N*-arylamidine in place of the reciprocal pair. The results obtained in the ammonolysis of a number of *N*-arylamidinium salts are collected in Table II, and it will be observed that high yields of unsubstituted amidinium salts are obtained at a comparatively low temperature. Since high yields of *N*-arylamidinium benzenesulphonates are almost invariably obtained from cyanides and arylammonium benzenesulphonates (see Table I) and this reaction takes place at a considerably lower temperature than that required to convert a cyanide into an amidinium benzenesulphonate by the action of ammonium benzenesulphonate, ammonolysis of *N*-arylamidinium salts is a valuable method for the preparation of unsubstituted amidines, especially in cases where the cyanide undergoes some decomposition when strongly heated, or gives a low yield of amidinium salt with ammonium benzenesulphonate.

Ammonolysis of *N*-arylamidinium salts is surprisingly facile, and although most of the reactions were carried out at 140°, it was noted in several cases that a slow reaction occurs at a much lower temperature (see Table II). Thus, *N*-*p*-tolylphenylacetamidinium benzenesulphonate, which affords a 93% yield of the unsubstituted amidinium salt after an hour with ammonia at 140°, gives a 13% yield after 116 hours in liquid ammonia (—33°). Since there is no reaction between an *N*-arylamidine and ammonia or between an *N*-arylammonium salt and an ammonium salt at this temperature, we formulate the ammonolysis as follows :



$$R\cdot\underset{NH\cdot Ar}{C}{:}\overset{\oplus}{N}H_2 + NH_3 \rightleftharpoons R\cdot\underset{NH\cdot Ar}{C}{:}NH + \overset{\oplus}{N}H_4$$

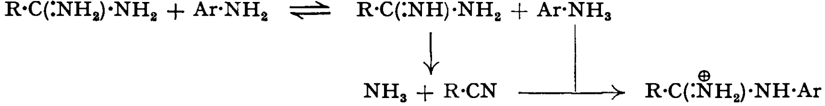
$$R\cdot\underset{NH\cdot Ar}{C}(NH_2)\cdot\overset{\oplus}{N}H_3 \quad (Ia.)$$

$$\updownarrow$$

$$R\cdot\underset{\oplus NH_2\cdot Ar}{C}(NH_2)\cdot NH_2 \quad (Ib.)$$

$$R\cdot\underset{NH_2}{C}{:}\overset{\oplus}{N}H_2 + Ar\cdot NH_2 \rightleftharpoons R\cdot\underset{NH_2}{C}{:}NH + Ar\cdot\overset{\oplus}{N}H_3$$

Decomposition of the unsubstituted amidine to a cyanide and ammonia is prevented by salt formation, and although it is probable that ammonolysis occurs by interaction between the arylamidinium ion and ammonia, the evidence does not exclude the possibility that the free arylamidine and the ammonium ion may be directly involved, and this alternative is therefore included in the scheme formulated above. The production of phenyl cyanide as main product of the interaction of *N*-phenylbenzamidine, ammonia, and phenol at 140° (above) indicates that, whilst phenol promotes ammonolysis of the substituted amidine, it is too weak an acid to prevent decomposition of the resulting benzamidine. Dissociation of the orthoamidinium ions to give the unsubstituted ion is probably promoted by the greater degree of resonance stabilisation of this ion, and since addition of a very large excess of arylamine to the reaction mixture does not appreciably affect the yield of unsubstituted amidine at temperatures up to 140°, the position of equilibrium in the reversible changes formulated above must be far on the side of the unsubstituted amidine. Moreover, no appreciable reaction between an arylamine and an unsubstituted amidinium salt could be detected up to 140°, and this recalls the observation that, whereas a number of cyanides combine with ammonia to give a small yield of amidine, yet they do not afford *N*-arylamidines with arylamines (Part VIII, *J.*, 1948, 303). If, however, an unsubstituted amidinium salt and an arylamine are heated at a higher temperature, ammonia is evolved and an *N*-arylamidinium salt is formed. The production of an *N*-arylamidinium salt under these conditions may also involve the formation of the orthoamidinium ions (I*a* and I*b*), the direction in which they dissociate at the high temperature being determined by the loss of ammonia from the system. It is also possible that the *N*-arylamidinium salt may be formed from an arylammonium salt and a cyanide produced by decomposition of the amidine (Part I; *J.*, 1946, 147) :

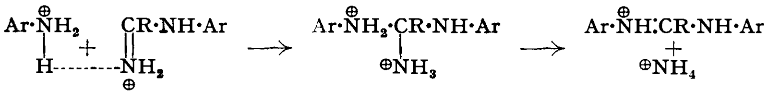


$$R\cdot C(:\overset{\oplus}{N}H_2)\cdot NH_2 + Ar\cdot NH_2 \rightleftharpoons R\cdot C(:NH)\cdot NH_2 + Ar\cdot\overset{\oplus}{N}H_3$$

$$NH_3 + R\cdot CN \longrightarrow R\cdot C(:\overset{\oplus}{N}H_2)\cdot NH\cdot Ar$$

but the production of an *NN'*-diarylamidinium salt from an *N*-arylamidine and an arylammonium salt (see below) cannot be formulated in this way. At intermediate temperatures less ammonia will be lost from the system and the product will consist of an equilibrium mixture containing substantial proportions of both the arylamidinium and unsubstituted amidinium salts, produced by arylation of the unsubstituted amidinium salt and ammonolysis of the *N*-arylamidinium salt respectively. Thus, *N*-phenylbenzamidinium benzenesulphonate dissolved in aniline affords an 88% yield of benzamidinium benzenesulphonate when heated at 100° for an hour in an atmosphere of ammonia, but at 185° an equilibrium mixture containing *ca.* 54% of benzamidine and *ca.* 27·5% of *N*-phenylbenzamidine (mainly as salts) is obtained whether one starts from benzamidinium benzenesulphonate and aniline (2 mols.), or from *N*-phenylbenzamidine, ammonium benzenesulphonate (1 mol.), aniline (1 mol.) and a trace of ammonia (equivalent to *N*-phenylbenzamidinium benzenesulphonate and a molecule of free ammonia). In either case, if the ammonia dissolved in the melt is displaced by a rapid stream of nitrogen, the product contains 23% of benzamidine, 46% of *N*-phenylbenzamidine, and 12% of *NN'*-diphenylbenzamidine. The effect of the concentration of the arylamine on the equilibrium is seen from the fact that, in contrast to the result obtained with 2 mols. of aniline, a mixture containing 74% of benzamidine and 14% of *N*-phenylbenzamidine is obtained at 185° from benzamidinium benzenesulphonate and 1 mol. of aniline, or from *N*-phenylbenzamidine and ammonium benzenesulphonate (1 mol.). The proportion of *N*-arylamidine at equilibrium appears to be determined by the basic strength of the arylamine. For example, the mixture obtained by heating *N*-*p*-chlorophenylbenzamidine, *p*-chloroaniline (1 mol.), and ammonium benzenesulphonate (1 mol.) at 185° contained only 6% of *N*-*p*-chlorophenylbenzamidinium benzenesulphonate, whereas the mixture obtained similarly from *N*-*p*-anisylbenzamidine, *p*-anisidine, and ammonium benzenesulphonate contained 39% of *N*-*p*-anisylbenzamidinium benzenesulphonate. It was therefore not surprising to find that *N*-alkylamidinium salts are more resistant to ammonolysis (see Table II) and that an *N*-phenyl-*N'*-methylbenzamidinium salt heated in ammonia at 140° yields as main product either an *N*-methylbenzamidinium salt or a benzamidinium salt according to the duration of the heating. *NN*- and *NN'*-Diarylamidinium salts undergo ammonolysis very readily, but *NNN'*-triphenylbenzamidinium benzenesulphonate is more resistant to ammonolysis than are the trialkylamidinium salts, and this may be due to the very weakly basic character of triphenylbenzamidine or to steric hindrance.

Bernthsen (*Annalen*, 1876, **184**, 354) observed that *NN'*-diarylamidinium chlorides are produced in addition to *N*-arylamidinium chlorides when methyl cyanide or phenyl cyanide is heated under pressure at 220—240° with phenyl- or *p*-tolyl-ammonium chloride (1 mol.), and sought to explain their formation on the basis of his observation that *NN'*-diphenylbenzamidinium chloride is produced by heating *N*-phenylbenzamidine and phenylammonium chloride (1 mol.) at 250°. The formation of *NN'*-diarylamidinium salts was not detected when a number of cyanides were heated with arylammonium benzenesulphonates (1 mol.) at 190—220° (Table I), but *NN'*-diphenylbenzamidinium benzenesulphonate is produced in 15% yield from phenyl cyanide and phenylammonium benzenesulphonate (1 mol.) at 270°, and *NN'*-di-*p*-tolylbenzamidinium benzenesulphonate is the main product (86%) of the interaction of phenyl cyanide with 2·5 mols. of *p*-tolylammonium benzenesulphonate at this temperature (Part I; *loc. cit.*). A mixture containing the benzenesulphonates of benzamidine (14%), *N*-phenylbenzamidine (53%), and *NN'*-diphenylbenzamidine (25%) is obtained either from *N*-phenylbenzamidine and phenylammonium benzenesulphonate (1 mol.) or from *NN'*-diphenylbenzamidine and ammonium benzenesulphonate (1 mol.) at 185°, and this is clearly the result of a balance between phenylation and ammonolytic reactions in equilibrium systems similar to those illustrated above. Contrary to Bernthsen's assumption, the production of *NN'*-diarylamidinium salts from an *N*-arylamidine and an arylammonium salt has no direct bearing on their production from cyanides and arylammonium salts, since in the latter case the intermediate *N*-arylamidine and the arylamine must both be present as salts. *N*-Phenylbenzamidinium benzenesulphonate and phenylammonium benzenesulphonate (1 mol.) do not react at 185°, but at 225° and 250° the product contains the benzenesulphonates of *N*-phenylbenzamidine (79 and 49%) and *NN'*-diphenylbenzamidine (12 and 37%). No benzamidine could be detected in the product at either temperature. These high-temperature reactions may involve dissociation of the arylammonium salt followed by reactions of the arylamine with the *N*-arylamidinium salt, or, less probably, the *NN'*-diarylamidinium salt may be formed by decomposition of a doubly charged orthoamidinium ion produced by combination of the *N*-arylamidinium and *N*-arylammonium ions :



$$\begin{matrix}\mathrm{Ar{\cdot}\overset{\oplus}{N}H_2} & \mathrm{CR{\cdot}NH{\cdot}Ar}\\ | \quad + & \| \\ \mathrm{H}\text{--------} & \mathrm{\underset{\oplus}{N}H_2}\end{matrix} \longrightarrow \begin{matrix}\mathrm{Ar{\cdot}\overset{\oplus}{N}H_2{\cdot}CR{\cdot}NH{\cdot}Ar}\\ | \\ \mathrm{{}^{\oplus}NH_3}\end{matrix} \longrightarrow \begin{matrix}\mathrm{Ar{\cdot}\overset{\oplus}{N}H{:}CR{\cdot}NH{\cdot}Ar}\\ + \\ \mathrm{{}^{\oplus}NH_4}\end{matrix}$$

EXPERIMENTAL.

Note.—Detailed descriptions of the isolation of the amidines are given only in special cases, since the methods employed followed closely those described in previous parts of this series, to which reference is made for earlier descriptions of some of the amidines (Part I, Oxley and Short, *J.*, 1946, 149; Part II, Oxley, Partridge, Robson, and Short, *ibid.*, p. 763; Part III, Oxley and Short, *J.*, 1947, 382; Part IV, Partridge and Short, *ibid.*, p. 390; Part VII, Oxley, Partridge, and Short, *ibid.*, p. 1110; Part VIII, Oxley, Partridge, and Short, *J.*, 1948, 303; Part IX, Oxley and Short, *ibid.*, p. 1514).

Preparation of N-*Substituted Amidines.*—Most of the *N*-substituted amidines used in the ammonolysis experiments were prepared by heating a cyanide with an equivalent of a *N*-arylammonium benzenesulphonate or toluene-*p*-sulphonate, following the methods described in Part I (*loc. cit.*). These experiments were conducted with 0·1—0·025 g.-mol. of cyanide, and the results are collected in Table I. Four amidines were prepared by the aluminium chloride method (Part VII) as described below, and the remainder were obtained by the methods indicated in the notes to Table II.

N-*Phenylbenzamidine.*—The temperature rose to 200° when powdered aluminium chloride (13·4 g.; 1 mol.) was added to a mixture of phenyl cyanide (10·3 g.) and aniline (9·3 g.; 1 mol.). The product was dissolved in water, and after the solution had been made alkaline with aqueous sodium hydroxide the amidine was collected in benzene. Concentration of the benzene solution afforded colourless crystals of *N*-phenylbenzamidine (15·3 g.; 78%) which had m. p. 116°, undepressed by admixture with specimens produced by other methods (Parts I, VII, and IX). *N*-Phenylbenzamidinium picrate had m. p. 148·5°, undepressed by admixture with an authentic specimen (Part IX).

N-cyclo*Hexylbenzamidine.*—Powdered aluminium chloride (13·4 g.; 1 mol.) was added to a mixture of phenyl cyanide (10·3 g.) and *cyclo*hexylamine (9·9 g.; 1 mol.). The temperature rose to 225°, and a solution of the product in hot water deposited colourless needles of N-cyclo*hexylbenzamidinium chloride*, m. p. 282° (yield 18·8 g., 79%) (Found: N, 11·5. $C_{13}H_{19}N_2Cl$ requires N, 11·7%). N-cyclo*Hexylbenzamidine* separated from light petroleum (b. p. 80—100°) in plates, m. p. 116—116·5° (Found: N, 13·8. $C_{13}H_{18}N_2$ requires N, 13·9%), and afforded a *picrate*, m. p. 143° (Found: N, 16·3. $C_{19}H_{21}O_7N_5$ requires N, 16·2%).

1 : 3-*Bis*-(p-*phenylamidinophenoxy*)*propane.**—Powdered aluminium chloride (2·67 g.; 1 mol.) was added during 10 minutes to a mixture of 1 : 3-bis-(*p*-cyanophenoxy)propane (5·56 g.) and aniline (3·72 g.; 2 mols.) previously heated to 140°. The temperature rose to 170° and, after being heated at 140° for 20 minutes, the mixture was cooled and decomposed with water (20 c.c.). The crude amidine (6·4 g.; 69%), m. p. 200—203°, was liberated with aqueous sodium hydroxide and had m. p. 206—207° after crystallisation from aqueous 2-ethoxyethanol. The amidine and its hydrochloride did not depress the m. p.s of specimens prepared by the alternative method (Table I, No. 22).

NN-*Diphenylbenzamidine.*—There was a 50° rise in temperature when aluminium chloride (13·4 g.; 1 mol.) was dissolved in a mixture of phenyl cyanide (10·3 g.) and diphenylamine (16·9 g.; 1 mol.). After being heated at 140° for an hour, the mixture was poured into water and extracted with benzene to remove unchanged cyanide and amine. The aqueous solution on being made alkaline with sodium hydroxide afforded *NN*-diphenylbenzamidine (2·5 g., 9%), m. p. 113°, undepressed by admixture with an authentic specimen (Part I). NN-*Diphenylbenzamidinium picrate* had m. p. 227° (Found: N, 14·2. $C_{25}H_{19}O_7N_5$ requires N, 14·0%).

Ammonolysis of N-*Substituted Amidines.*†—In order to avoid repetition, the results are collected in Table II. The description of the usual procedure which follows is supplemented where necessary by notes to the table. It is to be understood that identification of known compounds included not only the determination of the m. p. as quoted, but also comparison with an authentic specimen. Table III contains new salts of unsubstituted amidines prepared by ammonolysis of the *N*-substituted amidines.

The *N*-substituted amidinium salt (or a mixture of the amidine with an equivalent of an ammonium or substituted ammonium salt) was heated at *ca.* 140° (see Table II) with sufficient solvent to produce a homogeneous solution, which was kept saturated with ammonia by introducing a stream of fine bubbles of the gas from a capillary tube. Ammonia was frequently completely absorbed at the beginning of the experiment, and crystals of ammonium benzene- or toluene-*p*-sulphonate separated when nitrobenzene was used as solvent. This precipitate dissolved during the course of the experiment and the unsubstituted amidinium salt usually separated at a later stage or on cooling. More soluble amidinium salts were precipitated by adding acetone or ether. The method gave very clean products, so that one crystallisation from water or alcohol afforded the pure amidinium salt. The scale of the operations recorded in Table II was 0·002—0·02 g.-mol.

N-*Phenylbenzamidine and* cyclo*Hexylammonium Chloride.*—A solution of *N*-phenylbenzamidine (3·92 g.) and *cyclo*hexylammonium chloride (2·71 g.; 1 mol.) in aniline (5 c.c.) was heated at 140° for 2 hours, cooled, and diluted with ether (10 c.c.). The precipitate (3·38 g.), m. p. *ca.* 180°, consisted of a mixture of *N*-phenyl- and *N*-*cyclo*hexyl-benzamidinium chloride, and crystallisation from water afforded the less soluble *cyclo*hexylbenzamidinium chloride (1·52 g.; 32%) as flat needles, m. p. and mixed m. p. 282°.

Equilibrium between Reactions leading to the Ammonolysis of N-*Arylamidinium Salts and to the Arylation of Amidinium Salts at* 185°.—(A) *Systems containing benzamidine and* N-*arylbenzamidine.* (1) A mixture of *N*-phenylbenzamidine (1·96 g.) and ammonium benzenesulphonate (1·75 g.; 1 mol.) was heated at 185° for an hour, a slow stream of ammonia being passed into the mixture through a capillary tube. The product was cooled, diluted with acetone (10 c.c.), and cooled to 0°, whereupon it deposited benzamidinium benzenesulphonate (2·06 g.; 74%), m. p. and mixed m. p. 177°. The solvent was removed from the filtrate, which was then shaken with 2N-sodium hydroxide and benzene. The benzene solution was extracted with 10 × 5 c.c. of a 0·1N-sodium acetate–acetic acid buffer (pH 4·6), and the united extracts afforded *N*-phenylbenzamidine (0·27 g.; 13·8%), m. p. and mixed m. p. 115—116°, when

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* Experiment by Dr. M. W. Partridge.

† See also Boots Pure Drug Co. Ltd., Oxley and Short, B.P. 612,980 (12.6.1946).

TABLE I.

Preparation of N-*arylamidines.*

	Reaction.			Base.			
N-Arylamidine.	Temp.	Time (hrs.).	Yield (%).	M. p.	Formula.	Found, N (%).	Calc. or reqd., N (%).
(1) N-p-*Tolyl*-n-*valeramidine*	190°	5	74	70°	$C_{12}H_{18}N_2$	14·8	14·7
(2) *N*-*p*-Tolylphenylacetamidine	220	1	84	—	—	—	—
(3) *N*-Phenyl-*p*-nitrophenylacetamidine	190	2½	65	—	—	—	—
(4) *NN'*-Diphenylmalonamidine	197	¾	51	—	—	—	—
(5) N-*Phenylamidino*cyclo*hexane*	190	2	81	129	$C_{13}H_{18}N_2$	13·95	13·9
(6) N-*Phenyl*-1-*amidino*cyclo*hexene*	190	5	90	88·5	$C_{13}H_{16}N_2$	14·0	14·0
(7) *N*-*o*-Chlorophenylbenzamidine	190	4	87	116	—	—	—
(8) *N*-*p*-Chlorophenylbenzamidine	190	4	90	117	—	—	—
(9) N-p-*Bromophenylbenzamidine*	220	½	64	121·5	$C_{13}H_{11}N_2Br$	10·4	10·2
(10) N-p-*Anisylbenzamidine*	210	2	58	115·5	$C_{14}H_{14}ON_2$	12·6	12·4
(11) N-*Phenyl*-o-*chlorobenzamidine*	190	5	56	100	$C_{13}H_{11}N_2Cl$	12·1	12·15
(12) *N*-Phenyl-2 : 4-dichlorobenzamidine	190	4½	64	102	$C_{13}H_{10}N_2Cl_2$	10·6	10·6
(13) *N*-Phenyl-*p*-methylsulphonylbenzamidine	175—180	3	86·5	—	—	—	—
(14) N-*Phenyl*-p-*ethylsulphonylbenzamidine*	190	2	97	195	$C_{15}H_{16}O_2N_2S$	9·8	9·7
(15) N-*Phenyl*-p-*sulphonamidobenzamidine*	190	2½	69	226—227 *	$C_{13}H_{13}O_2N_3S$	15·3	15·3
(16) *N*-Phenyl-*p*-toluamidine	190	6	81	152·5	$C_{14}H_{14}N_2$	13·4	13·3
(17) N-p-*Tolyl*-p-*toluamidine*	190	6	84	115	$C_{15}H_{16}N_2$	12·5	12·5
(18) N-p-*Chlorophenyl*-p-*toluamidine*	190	6	94	144·5	$C_{14}H_{13}N_2Cl$	11·5	11·5
(19) *N*-*p*-Tolyl-*p*-anisamidine	200	1	90	—	—	—	—
(20) *N*-Phenylveratramidine	200	2	73	—	—	—	—
(21) 1 : 2-Bis-(*p*-phenylamidinophenoxy)ethane	210	1	92	—	—	—	—
(22) 1 : 3-*Bis*-(p-*phenylamidinophenoxy*)*propane*	210—215	¼	97	206—207	$C_{29}H_{28}O_2N_4$	12·1	12·1
(23) *N*-Phenyl-1-naphthamidine	220	⅔	69	—	—	—	—
(24) N-o-*Tolyl*-2-*naphthamidine*	210	1¼	92	158	$C_{18}H_{16}N_2$	10·8	10·8
(25) N-*Phenylnicotinamidine*	190	4	93	135	$C_{12}H_{11}N_3$	21·1	21·3
(26) N-*Phenyl*-1-*naphthylacetamidine*	190	2	76	115—116	$C_{18}H_{16}N_2$	10·75	10·8

	Picrate.				Benzenesulphonate.			
	M. p.	Formula.	Found, N (%).	Calc. or reqd., N (%).	M. p.	Formula.	Found, N (%).	Calc. or reqd., N (%)
(1)	111°	$C_{18}H_{21}O_7N_5$	16·8	16·7	—	—	—	—
(2)	—	—	—	—	158°	$C_{22}H_{24}O_3N_2S$ †	6·9	7·1
(3)	—	—	—	—	163	$C_{20}H_{19}O_5N_3S$	10·1	10·2
(4)	—	—	—	—	206	$C_{27}H_{28}O_6N_4S_2$	9·7	9·9
(5)	164	$C_{19}H_{21}O_7N_5$	16·2	16·2	—	—	—	—
(6)	165·5	$C_{19}H_{19}O_7N_5$	16·3	16·3	—	—	—	—
(7)	199	—	—	—	—	—	—	—
(8)	183	—	—	—	217	$C_{19}H_{17}O_3N_2ClS$	7·4	7·3
(9)	181	$C_{19}H_{14}O_7N_5Br$	13·8	13·9	227	$C_{19}H_{17}O_3N_2BrS$	6·6	6·5
(10)	174·5	$C_{20}H_{17}O_8N_5$	15·6	15·4	159	$C_{20}H_{20}O_4N_2S$	7·4	7·3
(11)	165	$C_{19}H_{14}O_7N_5Cl$	15·0	15·2	—	—	—	—
(12)	156·5	$C_{19}H_{13}O_7N_5Cl_2$	13·9	14·2	183—183·5	$C_{19}H_{16}O_3N_2Cl_2S$	6·4; 6·5	6·6
(13)	—	—	—	—	—	—	—	—
(14)	—	—	—	—	—	—	—	—
(15)	—	—	—	—	235	$C_{19}H_{19}O_5N_3S_2$	9·8	9·7
(16)	153	$C_{20}H_{17}O_7N_5$	15·9	15·9	—	—	—	—
(17)	182·5	$C_{21}H_{19}O_7N_5$	15·55	15·45	184	$C_{21}H_{22}O_3N_2S$	7·5	7·3
(18)	192	$C_{20}H_{16}O_7N_5Cl$	15·0	14·8	252	$C_{20}H_{19}O_3N_2ClS$	6·9	7·0
(19)	—	—	—	—	221·5	$C_{22}H_{24}O_4N_2S$ †	6·8	6·8
(20)	—	—	—	—	177	$C_{21}H_{22}O_5N_2S$	6·9	6·8
(21)	—	—	—	—	250	$C_{40}H_{38}O_8N_4S_2$	7·2; 7·3	8·0
(22)	—	—	—	—	218—219	$C_{41}H_{40}O_8N_4S_2$	7·3	7·2
(23)	—	—	—	—	186	$C_{23}H_{20}O_3N_2S$	6·9	6·9
(24)	191	$C_{24}H_{19}O_7N_5$	14·45	14·3	178	$C_{24}H_{22}O_3N_2S$	6·6	6·7
(25)	—	—	—	—	—	—	—	—
(26)	164·5	$C_{24}H_{19}O_7N_5$	14·4	14·3	—	—	—	—

* With decomposition.

† Toluene-*p*-sulphonate.

Notes to Table I.—(1) p-*Tolyl*-n-*valeramidinium chloride* had m. p. 127—128° (Found: N, 12·4. $C_{12}H_{19}N_2Cl$ requires N, 12·4%). (6) The *hydrochloride* had m. p. 196—198° (decomp.) (Found: N, 11·7. $C_{13}H_{17}N_2Cl$ requires N, 11·8%). (7) Walther and Grossmann (*J. pr. Chem.*, 1908, **78**, 491) state that the amidine and its picrate have m. p. 114—115° and 193—194°, respectively. (8) Walther (*ibid.*, 1903, **67**, 450) records m. p. 115—116° and 183° for *N*-*p*-chlorophenylbenzamidine and its picrate, respectively. (11) N-*Phenyl*-o-*chlorobenzamidinium chloride* had m. p. 147° (Found: N, 10·6. $C_{13}H_{12}N_2Cl_2$ requires N, 10·5%). (12) The m. p.s of the amidine and benzenesulphonate agree with those recorded in Part VIII. The m. p. of the picrate is given as 148—149° in Part VII. (13) The m. p.s agree with those recorded in Parts IV and VIII. N-*Phenyl*-p-*methylsulphonylbenzamidinium chloride* had m. p. 162° (Found: C, 54·2; H, 4·85. $C_{14}H_{15}O_2N_2ClS$ requires C, 54·3; H, 4·85%). (14) N-*Phenyl*-p-*ethylsulphonylbenzamidinium chloride* crystallised from water as a monohydrate, m. p. 225° (Found: N, 8·2; H_2O, 5·4. $C_{15}H_{17}O_2N_2ClS,H_2O$ requires N, 8·2; H_2O, 5·3%). (16) Lottermoser (*J. pr. Chem.*, 1896, **54**, 129) states that *N*-phenyl-*p*-toluamidine has m. p. 149°. (22) Preparation by Dr. M. W. Partridge. The yield quoted refers to the crude amidine, m. p. 180—185°. The *hydrochloride* had m. p. 287—288° (decomp.) (Found: N, 10·5. $C_{29}H_{30}O_2N_4Cl_2$ requires N, 10·4%). The amidine was also prepared by the aluminium chloride method (see below).

TABLE II.

Ammonolysis of N-*substituted amidines.*

N-Substituted amidine.	Salt.*	Solvent.	Temp.	Time (hrs.).	Yield of unsubstituted amidine, %.
(1) *N*-p-Tolyl-*n*-valeramidine	T	NH_2Ph	140°	2	96
(2) *N*-*p*-Tolylphenylacetamidine	T	NH_2Ph	140	2	93
	T	liq. NH_3	−33	116	13
(3) *N*-Phenyl-*p*-nitrophenylacetamidine	B	NH_2Ph	140	1	62
(4) *N*-Phenylamidino*cyclo*hexane	B	NHMePh	100	2	73
	B	$Ph{\cdot}NO_2$	140	1½	94
(5) *N*-Phenylbenzamidine	B	$Ph{\cdot}NO_2$	56	2	45
	B	NH_2Ph	100	1	88
	B	NH_2Ac	140	1	80
	B	None	140	1	91
	B	C_5H_5N	15	14 days	33
	B	C_5H_5N/NH_3	15	14 days	62
	B	$(CH_2{\cdot}OH)_2$	140	1	20
	T	$Ph{\cdot}NO_2$	140	1	95
	Chloride	NH_2Ph	140	1	50
	Acetate	NH_4OAc	100	½	61
(6) *N*-*o*-Chlorophenylbenzamidine	B	$Ph{\cdot}NO_2$	140	5	91·5
(7) *N*-*p*-Chlorophenylbenzamidine	Nitrate	C_5H_5N	100	2	92
(8) *N*-*p*-Bromophenylbenzamidine	B	C_5H_5N	100	2	91
(9) *N*-*p*-Anisylbenzamidine	B	C_5H_5N	15	6 days	11
(10) *N*-2-Pyridylbenzamidine	T	$2\text{-}NH_2{\cdot}C_5H_4N$	140	1½	85
(11) *N*-*p*-Nitrophenylbenzamidine	B	$Ph{\cdot}NO_2$	140	2	98
(12) *N*-*cyclo*Hexylbenzamidine	Picrate	NH_2Ph	135	2	17
(13) *N*-Phenyl-*o*-chlorobenzamidine	B	$Ph{\cdot}NO_2$	140	5	90
(14) *N*-Phenyl-2 : 4-dichlorobenzamidine	B	$Ph{\cdot}NO_2$	140	1	57·5
(15) *N*-Phenyl-*p*-methylsulphonylbenzamidine	B	NH_2Ph	140	1	93
(16) *N*-Ethyl-*p*-methylsulphonylbenzamidine	T	NH_2Ph	140	3	56
(17) *N*-*p*-Tolyl-*p*-toluamidine	B	NMe_2Ph	140	2	96
(18) *N*-*p*-Chlorophenyl-*p*-toluamidine	T	NHMePh	140	3	93
(19) *N*-*p*-Tolyl-*p*-anisamidine	T	NH_2Ph	140	2	98
(20) *N*-Phenylveratramidine	B	$Ph{\cdot}NO_2$	140	1	*ca.* 100
(21) 1 : 2-Bis-*p*-(phenylamidinophenoxy)-ethane	2B	NH_2Ph	140	1	95
(22) 1 : 3-Bis-(*p*-phenylamidinophenoxy)-propane	2B	NH_2Ph	110	6	70
(23) *N*-Phenyl-1-naphthamidine	B	NH_2Ph	140	5	94·5
(24) *N*-*o*-Tolyl-2-naphthamidine	B	$Ph{\cdot}NO_2$	140	3	93
(25) *N*-Phenylpicolinamidine	B	NH_2Ph	140	2	90
(26) *N*-Phenyl-*N′*-methylbenzamidine	B	NH_2Ph	140	1	32
(27) *N*-Phenyl-*N*-methylbenzamidine	T	$Ph{\cdot}NO_2$	140	3	98
	Picrate	NH_2Ph	140	2	60
(28) *NN′*-Diphenylbenzamidine	B	NH_2Ph	140	1	73
(29) *NN*-Diphenylbenzamidine	B	$Ph{\cdot}NO_2$	140	5	93·5
(30) *N*-Phenyl-*N′*-benzylbenzamidine	Picrate	NH_2Ph	140	1½	16
(31) *NN*-Diethyl-*p*-methylsulphonylbenzamidine	T	Quinoline	100	1⅓	40
(32) *NNN′*-Triphenylbenzamidine	B	NH_2Ph	140	3	—
(33) *NN*-Pentamethylene-*N′*-phenylbenzamidine	B	NH_2Ph	140	4½	36
(34) *N*-Methyl-*NN′*-diethylbenzamidine	B	None	135	4	17
(35) *N*-Phenyl-1-naphthylacetamidine	T	NH_2Ph	140	2	87

* B = Benzenesulphonate. T = Toluene-*p*-sulphonate.

Notes to Table II.—The preparation of a number of the *N*-substituted amidines is described in the previous section and the rest were obtained as described in earlier parts of this series as follows: Part I, No. 11; Part III, Nos. 26, 34; Part VII, Nos. 10, 16, 27, 28, 31; Part IX, Nos. 28, 30, 32, 33; Part X, No. 26. (1) *n*-Valeramidinium picrate had m. p. 195—196°, in agreement with Easson and Pyman (*J.*, 1931, 2991). (2) Phenylacetamidine and its salts are described in Parts I, IV, VII, and VIII. (5) In the first experiment using pyridine as solvent *N*-phenylbenzamidine was brought into reaction with ammonium benzenesulphonate (1 mol.); in the second experiment, the solution was also saturated with ammonia. When ammonia was passed for 2½ hours into an equimolecular mixture of *N*-phenylbenzamidine and phenol at 140°, the product contained 30% of unchanged amidine, and 48% of phenyl cyanide. The reaction mixture gave a colouration with Fuller's reagent throughout, indicating the presence of the unsubstituted amidine, but the amount was insufficient to allow benzamidine to be isolated. References to benzamidine and its salts are given in Parts I, IV, V, VII, and VIII. The benzenesulphonate had m. p. 178°, and the picrate m. p. 240°. (15) and (16) *p*-Methylsulphonylbenzamidine and its salts are described in Parts I, II, IV, and VII. (17 and (18) *p*-Toluamidine has been described by Glock (*Ber.*, 1888, **21**, 2651), Tiemann (*ibid.*, 1891, **24**, 371), Crayen (*ibid.*, p. 391), and Eitner (*ibid.*, 1893, **26**, 2839). (20) Veratramidinium picrate had m. p. 218°. Pyman and Easson (*loc. cit.*, p. 2995) give m. p. 217—218°. (21) References to the amidine and its salts are given in Part I. (22) Experiment by Dr. M. W. Partridge. For references see Parts I, IV, and VIII. (23) References to 1-naphthamidine are given in Part I. . (24) References to 2-naphthamidine are given in Parts I, IV, and VII. (25) Crude *N*-phenylpicolinamidinium benzenesulphonate, obtained by heating 2-cyanopyridine (5·2 g.) and ammonium benzenesulphonate (12·55 g.; 1 mol.) at 200° for an hour, was mixed with aniline (10 c.c.) and heated at 140° for 2 hours in a stream of ammonia. The yield is calculated on the 2-cyanopyridine. Picolinamidine and its salts are described in Parts I and IV. (26) *N*-Methylbenzamidinium benzenesulphonate (64%), m. p. and mixed m. p. 129° (Part III), was obtained by adding ether to the aniline solution obtained as filtrate from the benzamidinium benzenesulphonate. (32) The presence of benzamidine in the product was indicated by the production of a colouration with Fuller's reagent, but the amount present was too small to isolate.

TABLE III.

Amidinium salts prepared by ammonolysis.

Amidine.	Salt.	M. p.	Formula.	Found, N (%).	Calc. or reqd., N (%).
(1) *n*-Valeramidine	*Toluene*-p-*sulphonate*	134°	$C_{12}H_{20}O_3N_2S$	10·2	10·3
(2) Phenylacetamidine	*Toluene*-p-*sulphonate*	199	$C_{15}H_{18}O_3N_2S$	9·1	9·15
(3) *p*-Nitrophenylacetamidine	*Benzenesulphonate*	198·5	$C_{14}H_{15}O_5N_3S$	12·6	12·5
(4) Amidino*cyclo*hexane	*Picrate*	230—232 *	$C_{13}H_{17}O_7N_5$	19·9	19·7
(5) Benzamidine	Acetate	243 *	$C_9H_{12}O_2N_2$	15·4	15·6
(6) 2-Chlorobenzamidine	*Benzenesulphonate*	167	$C_{13}H_{13}O_3N_2ClS$	9·0	9·0
(7)	*Picrate*	217	$C_{13}H_{10}O_7N_5Cl$	18·2	18·2
(8) 2 : 4-Dichlorobenzamidine	*Benzenesulphonate*	258	$C_{13}H_{12}O_3N_2Cl_2S$	8·1	8·1
(9)	*Picrate*	205	$C_{13}H_9O_7N_5Cl_2$	16·9	16·7
(10) *p*-Toluamidine	*Benzenesulphonate*	195·5	$C_{14}H_{16}O_3N_2S$	9·7	9·6
(11)	*Toluene*-p-*sulphonate*	191	$C_{15}H_{18}O_3N_2S$	9·4	9·2
(12)	Picrate	229	$C_{14}H_{13}O_7N_5$	19·4	19·3
(13) *p*Anisamidine	*Toluene*-p-*sulphonate*	206	$C_{15}H_{18}O_4N_2S$	8·8	8·7
(14) Veratramidine	*Benzenesulphonate*	190	$C_{15}H_{18}O_5N_2S$	8·3	8·3
(15) 1 : 3-Bis-(*p*-amidinophenoxy)ethane	Bisbenzenesulphonate	*ca.* 312	$C_{28}H_{30}O_8N_4S_2$	9·0	9·1
(16) 1-Naphthamidine	Benzenesulphonate	218	$C_{17}H_{16}O_3N_2S$	8·5	8·5
(17) 1-Naphthylacetamidine	*Toluene*-p-*sulphonate*	188	$C_{19}H_{20}O_3N_2S$	7·8	7·9
	Picrate	248—249 *	$C_{18}H_{15}O_7N_5$	16·7	16·9

* Compounds having m. p.s marked with an asterisk decompose on melting.

Notes to Table III.—(3) This amidinium salt gave a strong colouration with Fuller's reagent, which is usually considered to be specific for compounds containing an unsubstituted amidino-group joined directly to an aromatic nucleus (Fuller, *Nature*, 1944, **154**, 773; *Biochem. J.*, 1945, **39**, 99). (5) Pinner ("Imidoäther," 1892, p. 156) records m. p. 229° (decomp.). (6) 2-Chlorobenzamidinium benzenesulphonate, m. p. 167°, was also obtained in 6% yield by heating *o*-chlorophenyl cyanide and ammonium benzenesulphonate (1 mol.) at 240° for 2¾ hours. (12) The m. p. of the picrate is recorded as 224—225° by Ponzio and Zamardi-Lamberti (*Gazzetta*, 1923, **53**, 818) and as 219° (decomp.) by Kirsanov and Polyakova (*Bull. Soc. chim.*, 1936, **3**, 1600). (15) The m. p. is given as >270° in Part I. (16) The m. p. recorded in Part I is 211°.

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made alkaline with aqueous sodium hydroxide. When the reaction mixture consisted of *N*-phenylbenzamidine (1·96 g.), ammonium benzenesulphonate (1·75 g.; 1 mol.), and aniline (0·93 g.; 1 mol.), the product afforded 1·49 g. (53·6%) of benzamidinium benzenesulphonate and 0·54 g. (27·6%) of *N*-phenylbenzamidine.

(2) When a mixture of benzamidinium benzenesulphonate (2·78 g.) and aniline (0·93 g.; 1 mol.) was heated at 185° for an hour, benzamidinium benzenesulphonate (1·97 g.; 71%) and *N*-phenylbenzamidine (0·28 g.; 14·3%) were isolated from the product as described in (1). When the quantity of aniline was increased to 1·86 g. (2 mols.) the amount of unchanged benzamidinium benzenesulphonate fell to 54% and the yield of *N*-phenylbenzamidine rose to 28%.

Similar experiments, each on a 0·01 g.-molar scale, were carried out with other *N*-arylbenzamidines, equimolecular quantities of the *N*-arylamidine, ammonium benzenesulphonate, and the arylamine being heated at 185° for an hour. The products, which were identified in each case by direct comparison with an authentic specimen, were separated by the method described in (1), and the results were as follows :

Ar.	*N*-Arylbenzamidine, HN:CPh·NH·Ar, %.	Benzamidinium benzenesulphonate, %.
Ph	28	54
$C_6H_4Cl(p)$	6	79
$C_6H_4\cdot OMe(p)$	39	34

The effect of reducing the concentration of dissolved ammonia was seen in an experiment in which a rapid stream of nitrogen was passed into a mixture of benzamidinium benzenesulphonate (2·78 g.) and aniline (1·86 g. ; 2 mols.) kept at 185° for an hour. Benzamidinium benzenesulphonate (23%), *N*-phenylbenzamidine (46·4%), and *NN'*-diphenylbenzamidinium chloride (11·7%), m. p. and mixed m. p. 302—304°, were isolated from the product. The disubstituted amidinium chloride separated when the benzene solution from which the *N*-phenylbenzamidine had been extracted with sodium acetate–acetic acid was shaken with 2N-hydrochloric acid.

(B) *The system containing* N-*phenylbenzamidine and* NN'-*diphenylbenzamidine.* A mixture of *NN'*-diphenylbenzamidine (2·72 g.) and ammonium benzenesulphonate (1·75 g. ; 1 mol.) was heated at 185° for 2 hours, cooled, stirred with water (10 c.c.), and neutralised to Congo-red with benzenesulphonic acid. The precipitate consisted of *NN'*-diphenylbenzamidinium benzenesulphonate (1·09 g. ; 25·3%), m. p. and mixed m. p. 213—215°. The filtrate was made alkaline with 5N-sodium hydroxide (5 c.c.), shaken with benzene (25 c.c.), and the aqueous solution (S) was separated. The benzene solution was extracted with sodium acetate–acetic acid buffer (pH 4·6; 10 × 5 c.c.) and *N*-phenylbenzamidine (1·04 g. ; 53%), m. p. and mxed m. p. 114—115°, was obtained by adding sodium hydroxide to the separated aqueous layer. The solution (S) was neutralised with acetic acid and afforded benzamidinium picrate (0·49 g. ; 14%), m. p. and mixed m. p. 337—338°, when mixed with aqueous ammonium picrate.

In the same way, *N*-phenylbenzamidine (1·96 g.) and phenylammonium benzenesulphonate (2·51 g. ; 1 mol.), heated at 185° for 2 hours, afforded *NN'*-diphenylbenzamidinium benzenesulphonate (25%), *N*-phenylbenzamidine (45%), and benzamidinium picrate (12%).

Reaction between Amidinium Benzenesulphonates and Phenylammonium Benzenesulphonate.—The reaction products were separated in each case by employing the method described in the previous section.

(1) There was no visible change when benzamidinium benzenesulphonate (1·39 g.) and phenylammonium benzenesulphonate (1·255 g. ; 1 mol.) were heated at 185° for an hour, and almost all the amidine was recovered. When the mixture was heated at 245°, phenyl cyanide was formed, and after an hour's heating 64% of the benzamidine was recovered and a 7% yield of *N*-phenylbenzamidine was obtained.

(2) *N*-Phenylbenzamidinium benzenesulphonate and ammonium benzenesulphonate did not appear to react at 185° and the product did not contain benzamidine after 2 hours' heating, since no colour reaction was obtained with Fuller's reagent. There was slight decomposition at 235° but the Fuller reaction was still negative. When the mixture was heated at 250—265° there was considerable decomposition with production of phenyl cyanide and a weak Fuller reaction was obtained.

(3) *N*-Phenylbenzamidinium benzenesulphonate (3·54 g.) and phenylammonium benzenesulphonate (2·51 g. ; 1·0 mol.) did not react at 185°, the amidine being recovered almost quantitatively. After 2½ hours at 225°, the product contained *N*-phenylbenzamidine (79%), *NN'*-diphenylbenzamidine (12%), and phenyl cyanide (trace), but no benzamidine could be detected in it by means of Fuller's reagent. Similarly, after an hour at 250° the product contained *N*-phenylbenzamidine (49%), *NN'*-diphenylbenzamidine (37%), an appreciable amount of phenyl cyanide, but no benzamidine.

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