

NOTE.

The Production of Amidines from Cyanides and Ammonium Salts. By J. CYMERMAN, J. W. MINNIS, P. OXLEY, and W. F. SHORT.

IN order to ascertain whether salts other than sulphonates (*J.*, 1946, 147) and thiocyanates (*J.*, 1947, 390) can be used in the preparation of amidines, we have heated a variety of ammonium salts with two reactive cyanides, and have also investigated the stability of a number of salts of *p*-methylsulphonylbenzamidine. No amidine could be isolated when *p*-sulphonamidophenyl cyanide was heated at various temperatures within the range 200—250° with ammonium chloride, sulphate, phenoxide, picrate, sulphamate, selenate, or diammonium hydrogen phosphate. A vigorous reaction occurred at 235° with ammonium hydrogen selenate and most of the cyanide was hydrolysed to a mixture of *p*-sulphonamidobenzamide and *p*-sulphonamidobenzoic acid. The sensitive Fuller reaction (*Nature*, 1944, 154, 773; *Biochem. J.*, 1945, 39, 99) was used to detect the formation of amidine when *p*-methylsulphonylphenyl cyanide was heated for 6½ hours with various ammonium salts (3 mols.) at a series of temperatures ranging from 100° to 245°. Completely negative results were obtained with ammonium bromide, hydrogen sulphate, laurate, trichloroacetate, and diammonium hydrogen phosphate, but a positive Fuller reaction

was obtained after heating the cyanide at 170° with ammonium nitrate for 6 hours. After 6½ hours at 130° ammonium formate gave a 25% yield of *N*-formyl-*p*-methylsulphonylbenzamidine, isolated as *picrate*. *p*-Methylsulphonylbenzamidine was obtained by heating the corresponding cyanide with ammonium acetate or fluoride, variations in the reaction temperature having a marked effect on the yield of amidine (see below). *p*-Chlorobenzamidine was obtained in 61% yield by passing ammonia into a mixture of *p*-chlorophenyl cyanide, ammonium benzenesulphonate, and ammonium acetate at 130° (compare Part VIII; *J.*, 1948, 303).

N-Formyl-*p*-methylsulphonylbenzamidine.—A mixture of *p*-methylsulphonylphenyl cyanide (1.8 g.) and ammonium formate (1.9 g.; 3 mols.) was stirred and heated at 131° until the intensity of the colour reaction with Fuller's reagent reached a maximum (6½ hours). The homogeneous melt was cooled, diluted with ice-water (20 c.c.), and stirred with 10*N*-sodium hydroxide (15 c.c.) at 0°. The solid was collected, and its aqueous suspension made acid to Congo-red with hydrochloric acid. *p*-Methylsulphonylphenyl cyanide (1.1 g.), m. p. and mixed m. p. 142°, was recovered, and addition of alcoholic picric acid to the filtrate afforded *N*-formyl-*p*-methylsulphonylbenzamidinium *picrate*, m. p. 285° (Found: N, 15.65. C₁₅H₁₃O₁₀N₅S requires N, 15.4%); yield, 0.9 g., 25%.

p-Methylsulphonylbenzamidine.—(1) *p*-Methylsulphonylphenyl cyanide (1.81 g.) and ammonium fluoride (1.11 g.; 3 mols.) were heated at various temperatures for 6½ hours and the amidine, separated from the unchanged cyanide by extracting with dilute acid, was isolated as *picrate*, m. p. and mixed m. p. 263°. The effect of temperature on the yield of amidine was as follows:

Temp.	131°	153°	186°	220°
Recovered cyanide, %	100	77	72	66
Amidinium <i>picrate</i> , %	0	19	26	19

(2) *p*-Methylsulphonylphenyl cyanide (1.81 g.) and ammonium acetate (2.31 g.; 3 mols.), similarly heated for 6½ hours, both (a) alone and (b) in presence of acetamide (1.77 g.; 3 mols.), gave the following yields of amidine:

Temp.	131°	153°	186°
Recovered cyanide, %	(a) 77; (b) 66	(a) 77; (b) 66	(a) 88; (b) 83
Amidinium <i>picrate</i> , %	(a) 13; (b) 20	(a) 7; (b) 16*	(a) —; (b) 7

* After 3 hours at 153° the yield was 8%.

p-Methylsulphonylbenzamidinium Salts.—*Fluoride*. This salt was obtained by neutralising an aqueous suspension of the amidine to brilliant-yellow with hydrofluoric acid and adding acetone to precipitate the hydrated salt, m. p. 188—189° (Found, in a sample dried at 100°: N, 12.65. C₈H₁₁O₂N₂FS requires N, 12.8%). When the fluoride was heated for 10 minutes at 190—195° ammonia was evolved, and 16% of the amidine was recovered as *picrate*, m. p. and mixed m. p. 263°. After 30 minutes' heating at 200—205°, 5% of the amidine was recovered.

Acetate. Prepared from its constituents and crystallised from boiling water, this salt had m. p. 232—233° (Found: N, 11.0. C₁₀H₁₄O₄N₂S requires N, 10.9%).

Benzoate. Prepared from its constituents in aqueous alcohol and crystallised from water, the *benzoate* had m. p. 232—233° (decomp.) (Found: N, 8.8. C₁₅H₁₄O₄N₂S requires N, 8.75%). After 10 minutes' heating at 236—238°, 2% of the amidine was recovered, the rest being decomposed to *p*-methylsulphonylphenyl cyanide, m. p. and mixed m. p. 141—142°.

Trichloroacetate. This salt separated from water in crystals, m. p. 178—179° (Found: N, 7.9. C₁₀H₁₁O₄N₂Cl₃S requires N, 7.75%); it was completely decomposed when heated at 186° for 10 minutes, and the recovered cyanide had m. p. 141—142°.

The *sulphate*, prepared similarly, had m. p. 264—266° (Found: N, 11.3. C₁₆H₂₂O₈N₄S₃ requires N, 11.3%).

p-Chlorobenzamidine.—*p*-Chlorophenyl cyanide (2.8 g.), ammonium acetate (4.6 g.), and ammonium benzenesulphonate (3.5 g.) were heated at 131° for 6½ hours, ammonia being passed into the molten mixture. The product afforded unchanged *p*-chlorophenyl cyanide (0.5 g.), m. p. 95°, and *p*-chlorobenzamidinium *picrate*, m. p. 256° (decomp.), in 61% yield (4.75 g.). The *picrate* is described in Part II (*J.*, 1947, 766), and the corresponding chloride has been prepared by Ekeley, Tieszen, and Ronzio (*J. Amer. Chem. Soc.*, 1935, 57, 381).—RESEARCH LABORATORIES, MESSRS. BOOTS PURE DRUG CO., LTD., NOTTINGHAM. [Received, May 27th, 1948.]