279. *Amidines. Part XV. Preparation of Diguanides and Guanidines from Cyanoguanidine and Ammonium Sulphonates.*

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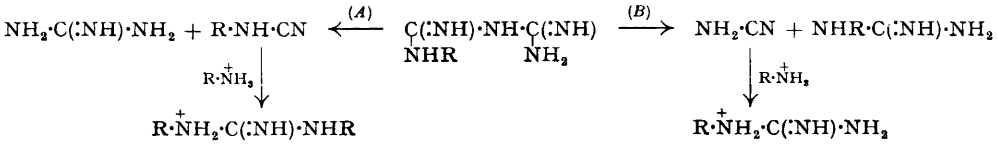
A number of diguanides and guanidines have been prepared by fusion of cyanoguanidine with ammonium sulphonates. The mechanism of the reaction is discussed.

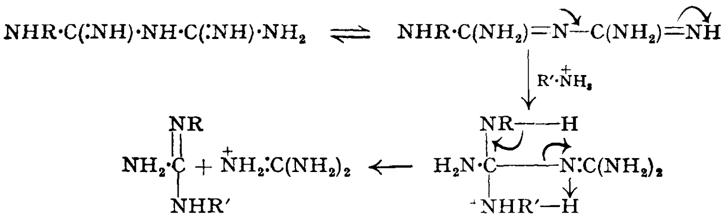
Considerable experimental evidence is available in support of the view that the formation of guanidine by fusion of cyanoguanidine (" dicyandiamide ") with ammonium salts involves the production of a diguanide salt which subsequently yields two molecules of a guanidine salt by reaction with a second molecule of the ammonium salt (Davis, *J. Amer. Chem. Soc.*, 1921, **43**, 2234; Blair and Braham, *ibid.*, 1922, **44**, 2346; Smith, Sabetta, and Steinbach, *Ind. Eng. Chem.*, 1931, **23**, 1124; Mannelli, *Ann. Chim. Appl.*, 1933, **23**, 235). The production of some guanidine by depolymerisation of cyanoguanidine to cyanamide which then reacts with an ammonium salt (Werner and Bell, *J.*, 1920, **117**, 1133; also Sugino, *J. Chem. Soc. Japan*, 1939, **60**, 351; *Chem. Abs.*, 1940, **34**, 2273) is not excluded but there is no direct evidence for the participation of cyanamide and most of the guanidine salt is undoubtedly produced from the diguanide salt. Much less attention has been given to the preparation of substituted diguanides and guanidines by fusion of cyanoguanidine with amine salts (Smolka and Friedreich, *Monatsh.*, 1888, **9**, 230; Lumière and Perrin, *Bull. Soc. chim.*, 1905, **33**, 205; Slotta and Tschesche, *Ber.*, 1929, **62**, 1400; Bobeck, *Annalen*, 1931, **487**, 295).

Sugino (*loc. cit.*, p. 411) suggested that the diguanide produced in the first stage of this reaction decomposes to a guanidine and a cyanamide, the latter subsequently being converted into a guanidine by the ammonium salt:



Fission of the diguanide is analogous to the decomposition of a hemi-acetal:

and the proportion of the diguanide decomposed in the alternative directions (*A* and *B*) can be correlated with the basic strength of the resulting guanidines. We have observed in several cases that the decomposition of diguanide salts is facilitated by the presence of a base, indicating that the diguanide is more readily decomposed than its salts. Thus, *iso*propyldiguanide toluene-*p*-sulphonate and *m*-chloroaniline afforded guanidine and *iso*propylguanidine at a temperature at which the diguanide salt is stable in absence of chloroaniline. Moreover, we find that cyanoguanidine and sulphanilamide toluene-*p*-sulphonate afford *p*-sulphonamidophenyldiguanide (44%), whereas the use of free sulphanilamide leads to the production of sulphanilylguanidine (Buttle, Dewing, Foster, Gray, Smith, and Stephenson, *Biochem. J.*, 1938, **32**, 1101; Dewing and Smith, *Nature*, 1941, **148**, 24; White, Bratton, Litchfield, and Marshall, *J. Pharmacol.*, 1941, **72**, 113). No diguanide was obtained from cyanoguanidine and 2-aminopyridinium toluene-*p*-sulphonate, owing presumably to acceleration of its decomposition by the second basic centre in the molecule. Although diguanide salts decompose at higher temperatures in the same way as the free bases, the only evidence for the production of a substituted cyanamide during the preparation of guanidines from cyanoguanidine and substituted ammonium salts is Sugino's observation that a condensation product of phenylcyanamide and cyanamide, probably 6-amino-2 : 4-dianilino-1 : 3 : 5-triazine, is formed as by-product when N^1-phenyldiguanide is heated with ammonium chloride. Cooper, Partridge, and Short (*J.*, 1950, 395) advanced reasons for the view that decomposition of diamidides to amidines by ammonium salts involves a 1 : 4-addition, and the production of guanidines from diguanides may well follow a parallel course. The relative activity of the different conjugated systems in the diguanide and the direction in which the addition complexes decompose will be controlled by the substituents and will determine the proportions in which the different substituted guanidines are formed. The following selected example is given to illustrate the general scheme:



The nature of the anion in the ammonium salt has a considerable influence on the yield of diguanide and guanidine obtained from cyanoguanidine, an effect which may sometimes be attributed mainly to lowering of the fusion temperature (Ewan and Young, *J. Soc. Chem. Ind.*, 1921, **40**, 109T; Sugino, *loc. cit.*). For example, diguanide is obtained in 21—23% yield when ammonium chloride is used (Bamberger and Dieckmann, *Ber.*, 1892, **25**, 545), whereas a 45% yield is obtained with ammonium iodide (Ostrogovich, *Bul. Soc. Stiinte Bucuresti*, 1910, **19**, 641; *Chem. Abs.*, 1911, **5**, 2102). Ammonium thiocyanate (Werner and Bell, *loc. cit.*) and ammonium nitrate (Sprengstoffwerke in Spandau, G.P. 222,522; Davis, *J. Amer. Chem. Soc.*, 1921, **43**, 669, 2234; Blair and Braham, *ibid.*, 1922, **44**, 2342) are especially effective in the preparation of guanidine from cyanoguanidine. We have prepared a number of diguanides from cyanoguanidine and ammonium sulphonates (1 mol.) at 140—160° and the results are collected in Table II. The yields, although reproducible, vary considerably with the N^1-substituent, the best results being obtained with N^1-aryldiguanides. Cyanoguanidine and ammonium sulphonates (2 mols.) at *ca.* 200° afford guanidine sulphonates, and the use of sulphonates is specially advantageous in the preparation of guanidine itself, since it is obtained practically free from the amorphous by-products (ammelide, ammeline, melamine) with which it is invariably contaminated when the ammonium salt of an inorganic acid is employed. Alkylguanidines are conveniently prepared in the same way, an alkylammonium sulphonate being used. The method is less satisfactory for the preparation of arylguanidines, since fission of the diguanide in the alternative direction (cf. *A*, above) is then appreciable and the *N*-arylguanidine is contaminated with an N^1N^3-diarylguanidine, $HN{:}C(NHAr)_2$, and with guanidine, so that the yield is poor.

EXPERIMENTAL.*

Preparation of Ammonium Sulphonates.—The ammonium salts recorded in Table I were prepared from equivalent quantities of their constituents.

Preparation of Diguanides.—An equimolecular mixture of cyanoguanidine and the ammonium sulphonate (usually 0·01—0·05 g.-mol.) was heated in a vapour-bath, with occasional stirring, to the

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* See also B.P. 593,675, 610,379.

TABLE I.

Amine salts.

Amine.	Salt.†	Solvent for crystn.	Form.	M. p.	Formula.	Analyses. Found, N, %.	Analyses. Reqd., N, %.
(1) Diethylamine ...	T	$COMe_2$	Flat needles	103°	$C_{11}H_{19}O_3NS$	5·7	5·7
(2) Piperidine	T	$COMe_2$	Flat needles	126	$C_{12}H_{19}O_3NS$	5·4	5·45
(3) *cyclo*Hexylamine	T	Pr^iOH	Flat needles	184	$C_{13}H_{21}O_3NS$	5·1	5·2
(4) Benzylamine ...	T	Pr^iOH	Rect. plates	185·5	$C_{14}H_{17}O_3NS$	5·05	5·0
(5) Methylaniline ...	B	Pr^iOH-Et_2O	Plates	82—83	$C_{13}H_{15}O_3NS$	5·3	5·3
(6) Sulphanilamide	B	MeOH	Prisms	255 (decomp.)	$C_{21}H_{14}O_5N_2S_2$	8·5	8·5
(7) Diphenylamine	T	C_6H_6	Flat needles	134·5	$C_{19}H_{19}O_3NS$	4·2	4·1

† B = benzenesulphonate; T = toluene-*p*-sulphonate.

(1) Norton and Otten (*Amer. Chem. J.*, 1888, **10**, 140) record m. p. 88°.
(4) Noller and Liang (*J. Amer. Chem. Soc.*, 1932, **54**, 670) record m. p. 184·5—185·5°.
(7) Norton and Otten (*loc. cit.*) state that diphenylammonium toluene-*p*-sulphonate has m. p. 64°.

TABLE II.

Synthesis of Diguanides.

*N*¹-Substituent(s) in diguanide.	Ammonium sulphonate.*	Reaction temp.	Reaction time (mins.).	Yield, %.
(1) None	B	140°	60	30
(2) ,, ...	M	140	60	18
(3) Me	B	160	20	37
(4) Pr^i	T	160	90	79
(5) *cyclo*Hexyl	T	140	60	36
(6) CH_2Ph	T	140	30	78
(7) Ph	B	160	15	75
(8) ,, ...	M	140	15	96
(9) p-$C_6H_4{\cdot}SO_2{\cdot}NH_2$	B	160	20	44
(10) Me_2	T	160	10	75
(11) Et_2	T	140	120	39
(12) $-[CH_2]_5-$	T	140	120	62
(13) Me, Ph	B	140	40	95
(14) Ph_2	T	140	30	73

*N*¹-Substituent(s) in diguanide.	Toluene-*p*-sulphonate.				Picrate.			
	M. p.	Formula.	Found, N, %.	Reqd., N, %.	M. p.	Formula.	Found, N, %.	Reqd., N, %.
(1) None	232—233° †	$C_9H_{15}O_3N_5S$	25·8	25·6	238° †	$C_8H_{10}O_7N_8$	33·9	33·9
(2) ,, ...	—	—	—	—	—	—	—	—
(3) Me	—	—	—	—	—	—	—	—
(4) Pr^i	161—161·5	$C_{12}H_{21}O_3N_5S$	22·4	22·2	165·5	$C_{11}H_{16}O_7N_8$	30·1	30·1
(5) *cyclo*Hexyl	158	$C_{15}H_{25}O_3N_5S$	19·7	19·7	158·5	$C_{14}H_{20}O_7N_8$	27·5	27·2
(6) CH_2Ph	142—143	$C_{16}H_{21}O_3N_5S$	18·7	19·3	150	$C_{15}H_{16}O_7N_8$	26·5	26·7
(7) Ph	—	—	—	—	184	$C_{14}H_{14}O_7N_8$	27·6	27·6
(8) ,, ...	—	—	—	—	—	—	—	—
(9) p-$C_6H_4{\cdot}SO_2{\cdot}NH_2$	—	—	—	—	—	—	—	—
(10) Me_2	150	$C_{11}H_{19}O_3N_5S$	23·3	23·3	—	—	—	—
(11) Et_2	142	$C_{13}H_{23}O_3N_5S$	21·2	21·3	147	$C_{12}H_{18}O_7N_8$	29·0	29·0
(12) $-[CH_2]_5-$	177	$C_{14}H_{23}O_3N_5S$	20·3	20·5	178	$C_{13}H_{18}O_7N_8$	28·2	28·1
(13) Me, Ph	—	—	—	—	169·5	$C_{15}H_{16}O_7N_8$	26·6	26·7
(14) Ph_2	210·5	$C_{21}H_{23}O_3N_5S$	16·5	16·5	—	—	—	—

* B = Benzenesulphonate; M = methanesulphonate; T = toluene-*p*-sulphonate.

† With decomp.

(1) The yields were 29 and 28% after ⅔ and 1½ hours respectively. (3) N¹-*Methyldiguanide benzenesulphonate* separated from *iso*propanol in plates, m. p. 146° (Found: N, 25·6. $C_9H_{15}O_3N_5S$ requires N, 25·6%). The form of methylguanidine benzenesulphonate having m. p. 138·5° (see below) was also isolated from the reaction product in 43% yield. (7) *N*¹-Phenyldiguanide had m. p. 145—146°. Cohn (*J. pr. Chem.*, 1911, **84**, 396) states that the base and the picrate have m. p. 144—146° and 176—179°, respectively. N¹-*Phenyldiguanide benzenesulphonate* crystallised from ethanol in prisms, m. p. 181° (Found: N, 20·9. $C_{14}H_{17}O_3N_5S$ requires N, 20·9%). (8) N¹-*Phenyldiguanide methanesulphonate* separated from ethanol in prisms, m. p. 198—199° (decomp.) (Found: C, 39·8; H, 5·7. $C_9H_{15}O_3N_5S$ requires C, 39·6; H, 5·5%). (9) N¹-p-*Sulphonamidophenyldiguanide benzenesulphonate* crystallised from water in plates, m. p. 205—206° (decomp.) (Found: N, 20·2. $C_{14}H_{18}O_5N_6S_2$ requires N, 20·3%). (12) The toluene-*p*-sulphonate separated from water as a *monohydrate* (Found: Loss at 100°, 5·2, 5·0. $C_{14}H_{23}O_3N_5S,H_2O$ requires H_2O, 5·0%). (13) N¹-*Methyl*-N¹-*phenyldiguanide benzenesulphonate* crystallised from *iso*propanol in prisms, m. p. 147·5° (Found: N, 20·2. $C_{15}H_{19}O_3N_5S$ requires N, 20·1%).

temperature recorded in Table II. The mixture usually melted completely and there was an exothermic reaction which raised the internal temperature 5—15° above that of the bath for a few minutes. The mixture sometimes solidified immediately (Nos. 7, 8, 9, 14) or on cooling (Nos. 4, 10, 13), and the resulting diguanide sulphonate could usually be isolated by crystallisation from water or alcohol. In cases where the salt was both readily soluble and obtained in low yield, the reaction product was dissolved in water and precipitated with an excess of aqueous copper toluene-*p*-sulphonate and ammonia; the resulting very sparingly soluble, pink, crystalline copper toluene-*p*-sulphonate complexes were suspended in hot water and decomposed with hydrogen sulphide. The copper sulphide was removed and the filtrate was concentrated to obtain the diguanide toluene-*p*-sulphonate. The diguanide picrates were obtained from the sulphonates and ammonium or lithium picrate solution and were purified by crystallisation from water.

Preparation of Guanidines.—*Guanidine.* (1) Cyanoguanidine (2 g.) and ammonium benzenesulphonate (10 g., 2·3 mols.) were heated at 260° for ½ hour, and the cold product was crystallised from water, giving guanidine benzenesulphonate, m. p. 211° (9·8 g., 95%). Karrer and Epprecht (*Helv. Chim. Acta*, 1941, **24**, 311) record m. p. 212°. (2) When a mixture of cyanoguanidine (8·4 g.) and ammonium benzenesulphonate (17·5 g., 1 mol.) was heated in a bath at 160°, the internal temperature rose in 10 minutes to 190°, and then fell again. The mixture was heated for an hour in all and then crystallised from water, giving guanidine benzenesulphonate, m. p. 210—211° (19·8 g., or 88% based on the ammonium salt). (3) Cyanoguanidine (4·2 g.) and ammonium phenol-*p*-sulphonate (20 g., 2·05 mols.) were heated at 200° for 1¼ hours and then crystallised from *iso*propanol. *Guanidine phenol-*p*-sulphonate*, m. p. 201—201·5° (Found: N, 18·2. $C_7H_{11}O_4N_3S$ requires N, 18·0%), was obtained in 92% yield (21·5 g.). (4) Cyanoguanidine (4·2 g.) and ammonium toluene-*p*-sulphonate (20 g., 2·1 mols.) afforded guanidine toluene-*p*-sulphonate, m. p. 231—231·5° (22·4 g., 97%), when heated at 210° for ¼ hour and then at 225° for ¼ hour. The pure salt was obtained when the reaction product was crystallised from water (Found: N, 18·3. Calc. for $C_8H_{13}O_3N_3S$: N, 18·2%). Remsen and Garner (*Amer. Chem. J.*, 1901, **25**, 185) give m. p. 206° for this salt; Perrot (*Bull. Soc. chim.*, 1946, **13**, 557) records m. p. 230°. (5) *Guanidine methanesulphonate* was obtained in 90% yield when cyanoguanidine (42 g.) and ammonium methanesulphonate (120 g., 2·1 mols.) were heated at 210° for ½ hour; after crystallisation from methanol, the salt had m. p. 207° (Found: N, 27·0. Calc. for $C_2H_9O_3N_3S$: N, 27·1%). Perrot (*loc. cit.*) records m. p. 206—207°.

N-*Methylguanidine.* Cyanoguanidine (4·2 g.) and methylammonium benzenesulphonate (21 g., 2·2 mols.) were heated at 210° for 25 minutes, and the cooled product was crystallised from *iso*propanol, giving N-*methylguanidine benzenesulphonate*, m. p. 128° (Found: N, 18·2. $C_8H_{13}O_3N_3S$ requires N, 18·2%). A second *form* of the benzenesulphonate, crystallising from *iso*propanol in long needles, m. p. 138·5° (Found: C, 41·7; H, 5·6; N, 18·3. $C_8H_{13}O_3N_3S$ requires C, 41·6; H, 5·7; N, 18·2%), was obtained from cyanoguanidine and methylammonium benzenesulphonate (1 mol.) at 160° (Table II). A mixture of the two forms melted sharply at 128°. The benzenesulphonate, m. p. 138·5°, afforded a pale yellow picrate, crystallising in long, slender, flat needles, m. p. 202°, apparently identical with the α-picrate described by Lecher (*Annalen*, 1927, **455**, 156, 164). The picrate prepared from the benzenesulphonate, m. p. 128°, also had m. p. 202° but crystallised in dark orange rods which appeared to be identical with Lecher's β-form.

NN-*Dimethylguanidine.* A mixture of cyanoguanidine (2·1 g.) and dimethylammonium toluene-*p*-sulphonate (11·5 g., 2·1 mols.) was kept at 200° for 1 hour and then crystallised from *iso*propanol, giving NN-*dimethylguanidine toluene-*p*-sulphonate* (8·1 g., 60%), m. p. 179° (Found: N, 16·4. $C_{10}H_{17}O_3N_3S$ requires N, 16·2%).

N-iso*Propylguanidine.* (1) The product obtained by heating cyanoguanidine (2·1 g.) and *iso*propylammonium toluene-*p*-sulphonate (11·55 g., 2·1 mols.) at 200° for 2 hours was dissolved in warm *iso*propanol (25 c.c.). The solution deposited guanidine toluene-*p*-sulphonate (2·0 g.), m. p. and mixed m. p. 231°, and the residue obtained by evaporating the filtrate to dryness was crystallised from water, giving iso*propylguanidine toluene-*p*-sulphonate* (6·3 g., 46%), m. p. 120° (Found: C, 47·3; H, 6·9; N, 15·7. $C_{11}H_{19}O_3N_3S$ requires C, 48·4; H, 7·0; N, 15·4%). (2) A mixture of N^1-*iso*propyldiguanide toluene-*p*-sulphonate (2·1 g.) and *m*-chloroaniline (0·85 g.) afforded guanidine toluene-*p*-sulphonate (0·32 g., 21%), m. p. 231°, and *N*-*iso*propylguanidine toluene-*p*-sulphonate (1·22 g., 67%), m. p. 115—118°, after being heated at 160° for 16 hours. There was no reaction when N^1-*iso*propyldiguanide toluene-*p*-sulphonate and *iso*propylammonium toluene-*p*-sulphonate (1 mol.) were heated at 160° for 2 hours.

N-cyclo*Hexylguanidine.* (1) The product obtained by heating cyanoguanidine (4·2 g.) and *cyclo*hexylammonium toluene-*p*-sulphonate (13·55 g., 1 mol.) at 200° for 1 hour gave guanidine toluene-*p*-sulphonate (3 g.), m. p. 231°, on crystallisation from *iso*propanol. The solid obtained by diluting the filtrate with ether was crystallised from water or acetone and afforded colourless plates of N-cyclo*hexylguanidine toluene-*p*-sulphonate* (4·6, 26%) m. p. 136—136·5° (Found: N, 13·6. $C_{14}H_{23}O_3N_3S$ requires N, 13·4%). The *picrate* separated from water in needles, m. p. 230° (Found: N, 22·75. $C_{13}H_{18}O_7N_6$ requires N, 22·7%). (2) A mixture of cyanoguanidine (2·1 g.) and *cyclo*hexylammonium toluene-*p*-sulphonate (13·55 g., 2 mols.) similarly gave 0·9 g. and 3·3 g. of the toluene-*p*-sulphonates of guanidine and *N*-*cyclo*hexylguanidine, respectively.

N-*Phenylguanidine.* A mixture of cyanoguanidine (4·2 g.) and phenylammonium benzenesulphonate (12·55 g., 1·0 mol.) was heated at 200° for an hour, and then digested with water (100 c.c.) at 100° until the insoluble gum solidified. The mixture was cooled, the crude *NN'*-diphenylguanidine benzenesulphonate (2·6 g.) was collected, the filtrate was evaporated to dryness, and the residue was extracted with acetone, leaving guanidine benzenesulphonate (4·8 g., 44%), m. p. and mixed m. p. 212°. The solid obtained by evaporating the acetone solution was crystallised from a little water and gave rectangular prisms of N-*phenylguanidine benzenesulphonate*, m. p. 155° (Found: N, 14·6. $C_{13}H_{15}O_3N_3S$ requires

N, 14·7%). The picrate crystallised from water in long needles, m. p. 227·5° (Found: N, 23·2. Calc. for $C_{13}H_{12}O_7N_6$: N, 23·1%). Kämpf (*Ber.*, 1904, **37**, 1682) records m. p. 221—222°. The crude *NN'*-diphenylguanidine benzenesulphonate was converted into the *picrate*, m. p. 171° (Found: N, 19·3. $C_{19}H_{16}O_7N_6$ requires N, 19·1%), and the *nitrate*, m. p. *ca.* 190° (decomp.) (Found: N, 20·7. $C_{13}H_{14}O_3N_4$ requires N, 20·4%)

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