

### 549. *The Basic Strengths of Methylated Guanidines.*

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All the possible methyl-substituted guanidines have been prepared and their dissociation constants measured. Contrary to a previous report, they are all very strong bases.

AN interesting anomaly in the base strengths of substituted guanidines was reported by Davis and Elderfield (*J. Amer. Chem. Soc.*, 1932, **54**, 1499). They found that, like the parent substance, the *N*-methyl, *NN*-dimethyl-, and *NN'N''*-trimethyl derivatives were bases comparable in strength with the inorganic hydroxides, but the *NN'*-dialkylguanidines were much weaker, having a  $pK_a$  of about 10.3. Pauling ("The Nature of the Chemical Bond," 1940, p. 213) has attempted an explanation of this anomaly in terms of the resonance theory; he predicted that the *NNN'N'*-tetramethyl derivative should be an even weaker base (Gilman, "Organic Chemistry," 1943, Vol. 2, p. 1966). Referring to his arguments, Wheland ("The Theory of Resonance," 1944, p. 180) commented: "An ingenious explanation of these facts has been given by Pauling, but the problem might repay further experimental investigation." This investigation has now been carried out with the surprising result that the anomaly to be explained does not exist at all.

To obtain as much information as possible on the effect of methyl substitution on guanidines, the eight methylated guanidines have been prepared and their  $pK_a$  values determined. Difficulties were experienced in some of the preparations. All the guanidines have been synthesised before, mainly by the life-long work of Schenk (*Arch. Pharm.*, 1909, **247**, 466, 490; *Z. physiol. Chem.*, 1912, **77**, 328; 1925, **150**, 121; Schenk and Graevenitz, *ibid.*, 1924, **141**, 132; Schenk and Kirchhof, *ibid.*, 1926, **153**, 150), but the more highly substituted ones were isolated only as chloroplatinates, chloroaurates, or picrates. Our attempts to convert the picrates into other salts were not successful; we therefore evolved methods for the direct preparation of simple salts. The reaction of the appropriate thiuronium salts with ammonia, methylamine, or dimethylamine provided unambiguous syntheses for every methylated guanidine.

## EXPERIMENTAL.

M. p.s are corrected. Microanalyses by E. Bielski.

*Preparation of the Guanidines.*—Methylguanidinium sulphate, m. p. 240°, and *NN*-dimethylguanidinium sulphate, m. p. 295—297°, were prepared by Clarke and Phillips's method (*J. Amer. Chem. Soc.*, 1923, **45**, 1755) in 82 and 75% yield from 5-methylthiuronium sulphate by the action of methylamine and dimethylamine, respectively. Clarke and Phillips report m. p.s 239° and 285—288° respectively. In view of our higher m. p. for the dimethyl compound, its identity was established by the preparation of the picrate, m. p. 224—225°; Davis and Elderfield (*loc. cit.*) report m. p. 224°.

Attempts were made to extend this method to the higher homologues but were abandoned because no crystalline thiuronium sulphates could be obtained from any of the methylated thioureas by treatment with methyl sulphate. The action of methyl iodide, however, yielded well-characterised thiuronium salts from which the guanidines were obtained as the hydriodides. Their crystallisation from the oily reaction mixtures was difficult and was achieved only by careful treatment with anhydrous ethanol and ether. Once crystalline, although mostly very hygroscopic, they recrystallised readily.

*NN*'-Dimethylguanidine.—*SNN*'-Trimethylthiuronium iodide (4.2 g.) (Schenk, *loc. cit.*, 1912) was heated at 65—75° for 2 hours with ethanolic ammonia (6.0 c.c.; 10%). Methanethiol was evolved. The reaction mixture was evaporated to dryness under reduced pressure and the residual oil was dissolved in anhydrous ethanol. Addition of ether gave a crop of ammonium iodide, and the mother-liquor, on addition of more ether, deposited an oil which gradually solidified. Two recrystallisations from ethanol-ether gave deliquescent plates of the *hydriodide*, m. p. 103.5—105° (22%) (Found: N, 19.55.  $C_3H_{10}N_3I$  requires N, 19.55%).

The same compound was also prepared by the following method (cf. Schenk, *loc. cit.*, 1909): Freshly sublimed cyanogen iodide (7.6 g.) was dissolved in anhydrous ethanolic methylamine solution (45 c.c.; 10%). The reaction vessel was firmly stoppered and set aside for 48 hours. The initially brown mixture was then colourless. Removal of the solvent under reduced pressure yielded a crop of crystals which were recrystallised three times from anhydrous ethanol-ether to give the *hydriodide* (5.4 g., 48%), m. p. 104—105.5°.

By treatment with silver nitrate, *NN*'-dimethylguanidinium iodide was converted into the *nitrate*, m. p. 102—104° (from aqueous ethanol) (Found: N, 37.3.  $C_3H_{10}O_3N_4$  requires N, 37.3%). When shaken with silver sulphate in water, the *hydriodide* gave the *sulphate*, m. p. 298—300° (decomp.) (from water) (Found: N, 30.65.  $C_6H_{20}O_4SN_6$  requires N, 30.85%). The picrate melted at 178—179°; Schenk (*loc. cit.*, 1912) reports m. p. 178°. The same picrate was also obtained from the reaction of *SN*-dimethylthiuronium iodide with methylamine, but the *hydriodide* did not crystallise.

*NNN*'-Trimethylguanidine.—*SN*-Dimethylthiuronium iodide (23.5 g.) (Schenk, *loc. cit.*, 1912) and aqueous dimethylamine (60 c.c.; 16%) were heated at 100° for 3 hours and then worked up as above to give the *hydriodide* (8.7 g., 41%), m. p. 202.5—204° (Found: N, 18.25.  $C_6H_{12}N_3I$  requires N, 18.35%). The picrate, m. p. 151—151.5°, crystallised from ethanol (Found: N, 25.35. Calc. for  $C_{10}H_{14}O_7N_6$ : N, 25.45%) (Schenk and Kirchoff, *loc. cit.*, m. p. 151—152°).

*NNN*''-Trimethylguanidine.—*SNN*'-Trimethylthiuronium iodide (22.0 g.) and aqueous methylamine solution (18 c.c.; 30%), worked up as above, gave the *hydriodide* (14.8 g., 73%), recrystallised from a large volume of alcohol, m. p. >300° (Found: N, 18.35%). The sulphate, m. p. >300°, was obtained in nearly quantitative yield by shaking this salt with silver sulphate and crystallisation from aqueous ethanol. The picrate melted at 214—215° (Davis and Elderfield, *loc. cit.*, 214.5°).

*NNNN*'-Tetramethylguanidine.—*SNNN*'-Tetramethylthiuronium iodide (30 g.) (obtained as a glass, Schenk, *loc. cit.*, 1912) and ethanolic methylamine solution (27 c.c.; 30%) were heated for 1 hour on the water-bath and worked up as above to give the *hydriodide* (13.0 g., 46%), m. p. 120—120.5° (Found: N, 17.15.  $C_5H_{14}N_4I$  requires N, 17.3%). Schenk, using higher temperatures, did not obtain this guanidine by this method. The picrate melted at 159—160° (Schenk, 158—160°).

*NNNN*'-Tetramethylguanidine.—Pentamethylthiuronium iodide (20.8 g.) (Delépine, *Bull. Soc. chim.*, 1910, **7**, 992), dissolved in the minimum amount of water, was warmed for 2 hours at 100° with concentrated ammonia solution (20 c.c.). The mixture was worked up as above, to give the *hydriodide* (7.5 g., 40%), hygroscopic crystals, m. p. 131—131.5° (Found: N, 17.0%). The picrate melted at 130—131°; Schenk (*loc. cit.*, 1912) reports 130°.

*Pentamethylguanidine.*—Pentamethylthiuronium iodide (24 g.) and methylamine (7.0 g.) in anhydrous ethanol (50 c.c.) were heated to 65—70° for 2 hours and worked up as above, to give the *hydriodide* (5.2 g., 21%), m. p. 136—138° (Found: C, 30.1; H, 6.65; N, 15.0.  $C_6H_{14}N_5I, \frac{1}{2}C_2H_5OH$  requires C, 30.0; H, 6.8; N, 15.0%). The picrate melted at 163—165°; Lecher and Graf (*Annalen*, 1924, **438**, 154) have also described the *hydriodide* but did not record its m. p.; for the picrate they report (*Ber.*, 1923, **56**, 1329) m. p. 165—166° (corr.).

*pK<sub>a</sub> Measurements.*—The dissociation constants were measured by potentiometric titration, following closely, in experimental details and in calculation, Hall and Sprinkle's determination of the *pK<sub>a</sub>* of guanidine (*J. Amer. Chem. Soc.*, 1932, **54**, 3475), except that a glass electrode ("Alki," Cambridge Instrument Co.) was used instead of a hydrogen electrode. The pH values were determined with a Leeds and Northrup Universal pH Potentiometer Assembly (No. 7663-A-1) adjusted to glycine buffers of pH 11.14 and 12.66. Hall and Sprinkle titrated a 2*N*-solution but, some of our compounds being insufficiently soluble, we adopted *N*-solutions for all the measurements, with some loss of accuracy. *NNN*'-Trimethylguanidinium iodide would not even give a *N*-solution but the sulphate was sufficiently soluble. The solutions were made up in carbon dioxide-free water and were titrated in a stream of nitrogen. Corrections were not applied for the potassium-ion error of the glass electrode, or for the

hydrogen-ion activity coefficients because reliable data were not available for these corrections. In view of these facts, and of the high pH involved, the results are not regarded as very accurate: the error may be as high as 0.2 pH unit.

## DISCUSSION.

The experimental results are recorded in the Table. The  $pK_a$  value of guanidine agrees well with Hall and Sprinkle's more accurately measured and corrected value of 13.6<sub>5</sub> (*loc. cit.*). The results listed in the Table show that all the methylated guanidines are very strong bases, the base strengths being only slightly affected by methyl substitution. The symmetrical dimethyl derivative is no exception. There seems to be little doubt that our compound was really *NN'*-dimethylguanidine: it was prepared in two different ways and three of its salts (sulphate, nitrate, and iodide) gave correct analyses. The high  $pK_a$  value in itself indicates that the compound is a guanidine. But it seems also certain that Davis and Elderfield's compound was not identical with our *NN'*-dimethylguanidine: not only their  $pK_a$  value but also the melting points of their sulphate (264—265°) and nitrate (68°) differed widely from ours (298—300° and 102—104°, respectively). We conclude therefore that the compound of which Davis and Elderfield reported the base strength was not *NN'*-dimethylguanidine.

From the scanty details given by the American authors we were not able to establish the identity of their compound. They state that it was prepared by Kaess and Gruszkiewicz's method (*Ber.*, 1902, **35**, 3599). These authors obtained, by the reaction of cyanogen chloride and methylamine in dry ether, a solid, of no definite melting point, which gave correct analysis figures for a *di*hydrochloride of dimethylguanidine. This in itself throws serious doubt on the identity of their compound for guanidines are theoretically not expected, and have never been found, to be diacid bases. Methylamine hydrochloride would undoubtedly be precipitated in this reaction and would have been part of their product; the rest might have been methylcyanamide hydrochloride. Davis and Elderfield give no indication of how this product was converted into a nitrate and a sulphate, and we were not able therefore to repeat their preparation. The possibility that their salts were molecular addition compounds of methylamine salts and methylcyanamide was investigated, but we were unable to prepare crystalline products by mixing these ingredients.

Guanidine.	Salt used.	$pK_a$ at 25°.
(Unsubstituted) .....	Sulphate	13.6
<i>N</i> -Methyl .....	"	13.4
<i>NN</i> -Dimethyl .....	"	13.4
<i>NN'</i> -Dimethyl .....	Iodide	13.6
<i>NNN'</i> -Trimethyl .....	"	13.6
<i>NN'N''</i> -Trimethyl .....	Sulphate	13.9
<i>NNN'N'</i> -Tetramethyl .....	Iodide	13.6
<i>NNN'N''</i> -Tetramethyl .....	"	13.9
Pentamethyl .....	"	13.8

The fact that all the  $pK_a$  values were measured under identical conditions makes it probable that, even if the absolute values do not differ by much more than the experimental error, the *relative* values are subject to less error. We therefore regard the differences between the  $pK_a$  values as significant and feel justified in discussing them. The variations are in the expected directions. Methyl groups are base-strengthening but a substitution which destroys the equivalence of the three nitrogens in guanidine will be base-weakening because it reduces the resonance energy of the ion. It is not surprising therefore that the introduction of one methyl group lowers the  $pK_a$  value of guanidine. The combined effect of several methyl groups compensates for this effect but it is notable that in each pair of isomers the one with the more even distribution of substituents is the stronger base.