

tained in a check experiment where it appeared that the low-boiling material was chiefly reduction product.

E. Di-isopropyl Ketone and Propylmagnesium Bromide.—From 57 g. of ketone we obtained 19.6 g. of di-isopropyl carbinol boiling at 134–138° and 34.3 g. of propyl di-isopropyl carbinol^{2b} boiling at 100° (50 mm.).

Summary

From a study of the reaction between certain aliphatic ketones and some alkylmagnesium halides it is pointed out that there is no definite and exact correlation between an increase in the complexity of the alkyl groups present and the amount of reduction observed. Further it is shown that the synthesis of tertiary aliphatic carbinols containing both straight and branched chain alkyl groups and where the branches are in the α -position to the carbinol carbon atom, should be carried out by the interaction of branched chain ketones and primary straight chain Grignard reagents.

BUFFALO, N. Y.

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY,
MASSACHUSETTS INSTITUTE OF TECHNOLOGY, NO. 77]

THE DETERMINATION OF THE IONIZATION CONSTANTS OF GUANIDINE AND SOME OF ITS ALKYLATED DERIVATIVES¹

BY TENNEY L. DAVIS AND ROBERT C. ELDERFIELD²

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Guanidine seemingly occupies a unique position among organic bases, for, with the possible exception of the quaternary ammonium and the substituted idonium bases, it alone approximates the strong fixed alkalis in basic strength. Notwithstanding, the study of its ionization appears to have been largely neglected, while the extent to which the presence of substituents influences its dissociation has attracted no attention whatsoever. In the course of other work which will be reported shortly, information regarding this point was desired, and the results of such an investigation are here presented.

Ostwald³ made careful measurements of the conductivity of aqueous solutions of guanidine, but there appears to have been no calculation of an ionization constant from these data. Such a calculation shows that guanidonium hydroxide apparently behaves as a strong base. Bredig⁴

¹ The material from which this paper is constructed forms part of a thesis submitted by Robert C. Elderfield to the Faculty of the Massachusetts Institute of Technology in partial fulfilment of the requirements for the degree of Doctor of Philosophy in June, 1930. The results here presented were given as part of a paper on the aliphatic guanidines and nitroguanidines by Tenney L. Davis before the Organic Division of the American Chemical Society at the Atlanta meeting in April, 1930.

² The Rockefeller Institute for Medical Research, New York City.

³ Ostwald, *J. prakt. Chem.*, [2] **33**, 352 (1886).

⁴ Bredig, *Z. physik. Chem.*, **13**, 208 (1894).

determined the conductivity of guanidine hydrochloride solutions of various concentrations, and, from calculations based on his data, guanidine again is a strong electrolyte. However, Morell and Bellars⁵ determined the ratio of the strength of guanidonium hydroxide to that of sodium hydroxide by three methods, *viz.*: by observing the rate of change of the angle of rotation of a hyoscyamine solution in the presence of the two bases, the ratio was found to be 0.78 : 1; by relative rates of saponification of ethyl acetate, 0.85 : 1, and for barium hydroxide, 0.926 : 1; and by depression of the freezing point of water, 0.81 : 1. Veley⁶ measured the hydrolysis of guanidine hydrochloride colorimetrically with methyl orange, and obtained a value for $K_B = 1.1 \times 10^{-8}$ at 15°. This, however, is apparently in error. Matignon⁷ determined the heat of neutralization of guanidine to be 14.12 Kg. cal. per gram mole, slightly divergent from the constant value for strong bases.

The present experiments dealt with guanidine and eleven substituted guanidines possessing varying types of substitution as well as of substituents. It appears that guanidine itself is a base of the order of strength of potassium hydroxide. Titration curves of the two are identical within the limits of accuracy of this work. With the exception of the symmetrical di-alkyl derivatives, introduction of aliphatic substituents is without effect on the basicity of the parent compound. Thus, in mono-alkyl, unsymmetrical di-alkyl, and symmetrical tri-alkylguanidines, the character and position of the substituents appears to exert a negligible influence on the ionization. In phenylguanidine, the only aromatic one studied, as would be expected the introduction of the phenyl group diminishes the basic properties. In the case of the symmetrical di-alkylguanidines, a curious anomaly appears. These substances are markedly weaker in basic properties than the others, but here again, the character of the substituents seems to exert a negligible influence. Hence the statement may be made that in the cases studied the ionization of the alkylated guanidines is determined solely by the position of the substituents, and is independent of the character of the latter.

Description of Experiments

For the determination of the basic strength of the compounds under consideration, the method chosen was that embracing the use of titration curves. The apparatus used consisted of a 250-cc. wide-mouthed Erlenmeyer flask fitted with a three-holed stopper slotted at one place on the periphery. Through the holes were passed a glass tube for the hydrogen half-cell, the buret tip, and a saturated potassium chloride bridge. The latter led to another 250-cc. wide-mouthed Erlenmeyer serving as a potassium chloride reservoir which in turn was joined to a saturated calomel half-cell by means of a

⁵ Morell and Bellars, *J. Chem. Soc.*, **91**, 1012 (1907).

⁶ Veley, *ibid.*, **93**, 660 (1908).

⁷ Matignon, *Ann. chim. phys.*, [6] **28**, 88 (1893).

second saturated potassium chloride bridge. The hydrogen half-cell was of the Hildebrand type. The whole apparatus was immersed in a thermostat held at $25 \pm 2^\circ$. The potentiometer system was of the standard type using a student type potentiometer and a portable galvanometer. The accuracy of the measurements is about 0.05 P_H units. The saturated calomel half-cell was checked from time to time against a 0.05 molal potassium acid phthalate solution.

In order to prepare a solution of any guanidine, the sulfate was used as starting material. These are well crystallizable salts easily obtainable in a high degree of purity. An exactly 0.05 normal solution of the sulfate under examination was prepared and 100 cc. of this solution was placed in the titration vessel. A stream of hydrogen was then passed through to sweep out any carbon dioxide. To the solution was added 0.1 normal barium hydroxide in quantity exactly sufficient to precipitate all the sulfate and thus give a solution of the free base. The latter was then titrated with 0.1 normal hydrochloric acid without filtering off the precipitated barium sulfate. For reference purposes an exactly similar titration was made using potassium sulfate.

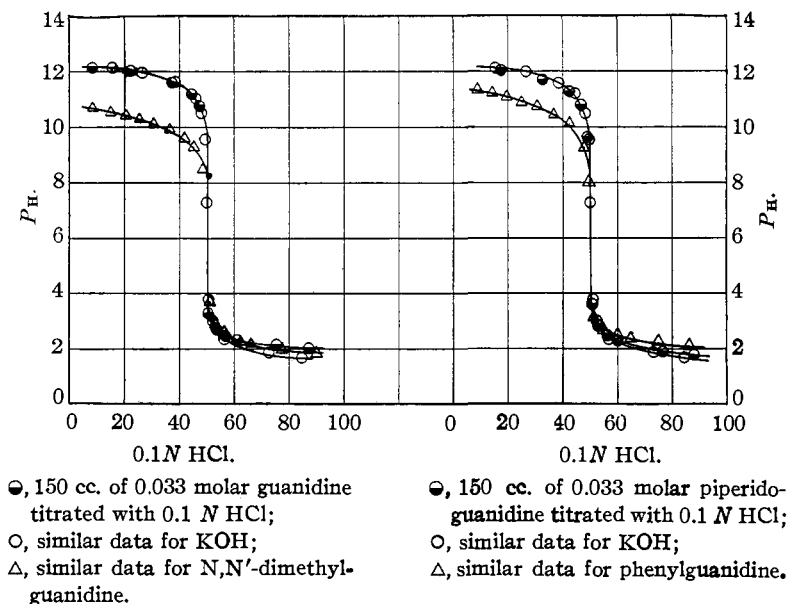


Fig. 1.

The results thus obtained are summarized in Table I. In the cases of the highly ionized strong bases no attempt was made to calculate an ionization constant, as the evidence clearly justified the assumption of complete ionization. The curves were merely plotted on the same graph with that of potassium hydroxide, typical examples of which are shown in Fig. 1. The others coincided equally as well within the limits of experimental error. In the case of the weaker bases, the constants were determined by the usual method from the titration curves. Typical curves for these substances are also shown in Fig. 1.

TABLE I
RESULTS OF EXPERIMENTS

Guanidine	K × 10 ⁻⁴	Sulfate				Nitrate				Picrate			
		M. p., °C.	Recryst. from	Analysis, % SO ₄ Calcd.	Found	M. p., °C.	Recryst. from	Analysis, % N Calcd.	Found	M. p., °C.	Recryst. from	Analysis, % N Calcd.	Found
Guanidine ^a	Large	300 dec.	Alc.-Aq.			212	Aq.			310 dec.	Alc.		
Methyl-	Large	238-9 dec.	MeOH-Aq.			150	Aq.			200	Alc.-Aq.		
<i>n</i> -Butyl-	Large	206	MeOH-BuOH	29.28	29.34	69	Alc.	31.46	31.22	154.5	Alc.-Aq.	24.42	24.46
<i>n</i> -Heptyl-	Large	244 dec.	Alc.-Ether	23.32	23.21	86	Aq.	25.61	25.41	140.5	Alc.-Aq.	22.79	22.62
Benzyl- ^b	Large	204	MeOH	24.25	24.15	165	Aq.	26.40	26.46	185.5	Alc.	21.21	21.77
Piperido-	Large	Above 270	Aq.			154 dec.	Aq.	29.63	29.45	244.5	Alc.		
NN-Dimethyl-	Large	285-7 dec.	Alc.-Aq.			141	Aq.			224	Alc.-Aq.		
NN'-Dimethyl-	1.95	264-5 dec.	Alc.-Aq.	35.51	35.48	68	Aq.	37.32	37.49	178	Alc.-Aq.		
NN'-Diethyl-	2.00	234-5 dec.	Alc.-Ether	29.28	29.43					141	Alc.-Aq.		
NN'-Di- <i>n</i> -amyl-	1.78	190-1 dec.	Alc.-Ether	19.35	19.26					108	Benzene	19.63	19.71
NN'N'-Tri-													
methyl-	Large	Above 345	Alc.-Ether	32.01	32.19	276	Alc.	34.15	34.46	214.5	Alc.-Aq.	25.46	25.85
Phenyl-	5.89	205	Water							222	Alc.		

^a After this work had been completed an article by Hall [THIS JOURNAL, 52, 5125 (1930)] appeared wherein the pK_H value for guanidine as determined by titration in acetic acid is given as 13.5, thus confirming the conclusions here reached.

^b Benzyl guanidine bicarbonate is very characteristic, being extremely insoluble in cold water and more readily in hot from which it is deposited in long thick needles. *Anal.* CO₂ (Geissler alkalimeter). Calcd.: 20.95. Found: CO₂, 20.62.

Preparation of Materials.—The guanidine salts were prepared from guanidine carbonate which was in turn prepared from nitroguanidine and ammonium carbonate.⁸ The mono-alkyl and NN-dialkylguanidines were prepared according to Clarke and Phillips⁹ the sulfates thus obtained being metathesized into the nitrates by means of barium nitrate. The NN'-dialkylguanidines were prepared according to Kaess and Gruszkiewicz.¹⁰ NN'N'-Trimethylguanidine was prepared according to Hoffmann¹¹ Phenylguanidine was prepared by the method of Smith¹² The melting points of the various derivatives together with analyses of those previously undescribed in the literature are shown in Table I.

n-Heptylamine.—This was prepared by the interaction of *n*-heptyl bromide and ammonia, which preparation does not seem to have been described in the literature; 92 g. of *n*-heptyl bromide (b. p. 176–178°) was dissolved in 800 cc. of methyl alcohol, and the mixture saturated with ammonia and allowed to stand at room temperature one week. After breaking up the amine hydrobromides with sodium hydroxide, the amines were fractionated in a current of nitrogen. The yields were: *n*-heptylamine, b. p. 155–158°, 28 g.; di-*n*-heptylamine, b. p. 270–275°, 20 g.; tri-*n*-heptylamine, trace.

Summary

1. The ionization of twelve alkylated guanidines of varying types of substitution has been studied.
2. Basic strength in this series of compounds, wherever aliphatic substituents occur, appears to be a function only of the positions of the substituents. A phenyl group diminishes the basicity.
3. Twenty new substituted guanidine salts are described.
4. General details for the synthesis of amines have been given in the preparation of *n*-heptylamine.

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⁸ Davis and Abrams, *Proc. Am. Acad.*, **61**, 437 (1926).

⁹ Clarke and Phillips, *THIS JOURNAL*, **45**, 1755 (1923).

¹⁰ Kaess and Gruszkiewicz, *Ber.*, **35**, 3598 (1902).

¹¹ Hoffmann, *ibid.*, **2**, 600 (1869); Schenck, *Arch. Pharm.*, **247**, 466 (1909).

¹² Smith, *THIS JOURNAL*, **51**, 476 (1929).