[CONTRIBUTION NO. 38 FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

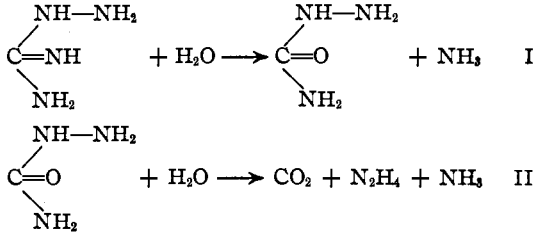
Reduction of Nitroguanidine. X. The Hydrolysis of Aminoguanidine in Acid and Basic Media[1,2]

BY EUGENE LIEBER AND G. B. L. SMITH

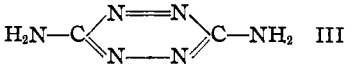
Introduction

The impression is existent in the literature, without experimental foundation, that aminoguanidine undergoes hydrolysis readily in acid solution. McGill,[3] in a process for the manufacture of aminoguanidine by hydrogenation of nitroguanidine, warns against even the presence of carbonic acid and devotes many of his claims to reductions in the presence of buffering materials. In the isolation of aminoguanidine salts after reduction of nitroguanidine with zinc and acetic acid by the method of Thiele,[4] the precaution is often given of concentrating by evaporation under vacuum at room temperature, because of the ease of hydrolysis of the aminoguanidine. However, Lieber and Smith[1c] found that the optimum conversion of nitroguanidine to aminoguanidine by hydrogenation took place in media of relatively high acid concentration, while the data at high temperature (up to 200° in 15% aqueous acetic acid solution) indicated a stability for aminoguanidine in acid media not generally appreciated. On the other hand, reduction of nitroguanidine in basic media gave little or no aminoguanidine and only ammonia, guanidine and hydrazine could be detected. This parallels the results found by Fuller, Lieber and Smith[5] for the reduction of nitroguanidine by sodium in liquid ammonia. Aminoguanidine was isolated only after reduction of nitroguanidine in the presence of a relatively high concentration of an acid (ammonium chloride). The facts, therefore, indicate that aminoguanidine is readily susceptible to alkaline, but resistant to acid, hydrolysis.

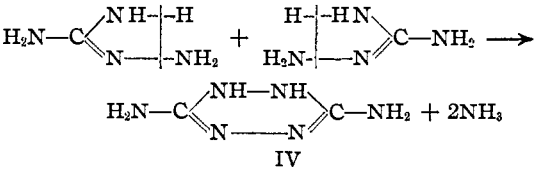
No quantitative studies on the hydrolytic decomposition of aminoguanidine in acid or basic media have been published. Anzelmi,[6] in the determination of the nitrogen in aminoguanidine, by the Kjeldahl method, showed that only one-half of the total nitrogen was obtained. Thiele,[4] in his initial publication, demonstrated qualitatively that the hydrolysis of aminoguanidine proceeds in two stages



The intermediate product of stage I, semicarbazide, was isolated in the form of a benzal derivative and was shown to be identical with the reaction product of potassium cyanate and hydrazine with benzaldehyde. The intermediate semicarbazide was obtained in large quantities by carrying out the hydrolysis with sodium carbonate instead of with sodium hydroxide. Thiele[4] had also attempted to isolate free aminoguanidine by precipitation of the sulfate with the calculated quantity of barium hydroxide. He found that the solution so obtained gradually turned reddish in the air, and when evaporated *in vacuo* left behind a red, crystalline mass exhibiting an alkaline reaction. He did not analyze the material. Ponzio and Gastaldi[7] examined this behavior of aminoguanidine and were able to demonstrate the formation of *sym*-diaminotetrazine (III)



by treating aminoguanidine salts with alkali. The reaction which they assumed to take place may be indicated as follows



The resulting C-diamino-N-dihydrotetrazine (IV) could not be isolated but was oxidized simul-

(1) This paper is an abstract of a part of the thesis submitted by Eugene Lieber to the Graduate Faculty of the Polytechnic Institute of Brooklyn in June, 1937, in partial fulfilment of the requirements for the degree of Doctor of Philosophy. For other abstracts from this thesis see THIS JOURNAL, (a) **57**, 2479 (1935); (b) **58**, 1417 (1936); (c) **58**, 2170 (1936); (d) **59**, 1834 (1937).

(2) Presented before the Division of Organic Chemistry at the Rochester meeting of the American Chemical Society, September 6–10, 1937.

(3) McGill, U. S. Patent 2,033,203; March 10, 1936.

(4) Thiele, *Ann.*, **270**, 35 (1892).

(5) Fuller, Lieber and Smith, THIS JOURNAL, **59**, 1150 (1937).

(6) Anzelmi, B.S. Thesis, The Polytechnic Institute of Brooklyn, 1933.

(7) Ponzio and Gastaldi, *Gazz. chim. ital.* [II] **48**, 129 (1918).

taneously to form (III). No quantitative data on the hydrolysis of this latter substance have been reported; however, Ponzio and Gastaldi[7] found that on boiling in an alkaline solution ammonia was evolved, while prolonged heating in solutions of acids produced nitrogen, ammonia, hydrazine formic and carbonic acids.

In the present study the relative stability of aminoguanidine to acid and basic hydrolysis was studied quantitatively by treating weighed quantities of the sulfate under a reflux with known volumes of standard acid and alkali and determining the quantity of ammonia formed as a measure of the percentage hydrolysis. Since semicarbazide was shown by Thiele[4] to be an intermediate product of hydrolysis, parallel studies were also carried out with this substance since it was believed that this would furnish some clue as to the over-all rate of decomposition. Additional data on the stability of aminoguanidine were obtained by studying the hydrogenation of nitroguanidine to aminoguanidine at high pressure in acid and neutral media. In the latter case, since aminoguanidine is a strong base, this was equivalent to reduction in basic solution.

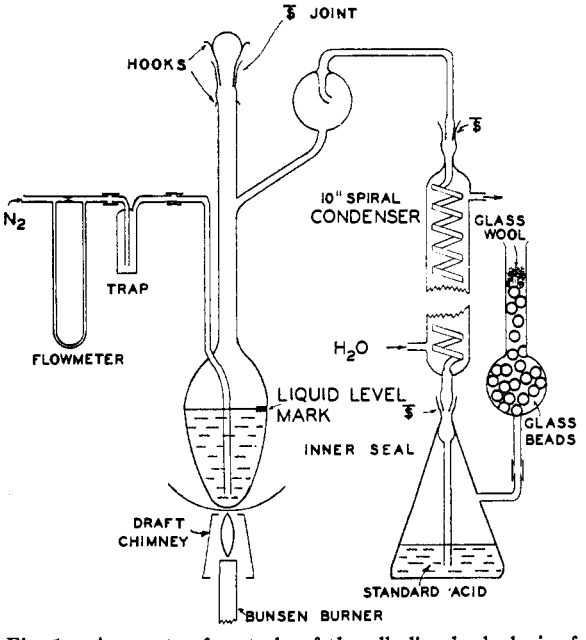


Fig. 1.—Apparatus for study of the alkaline hydrolysis of aminoguanidine.

Experimental

The Alkaline Hydrolysis of Aminoguanidine.—The apparatus used for the study of the alkaline hydrolysis is illustrated by Fig. 1. The following procedure was used in carrying out a run. A known volume of standard sulfuric acid was introduced into the Erlenmeyer receiving flask through the calcium chloride tube filled with glass beads. A few drops of methyl red indicator was added with an additional 25 to 50 ml. of water and the whole assembled upon the spiral condenser by means of the ground glass joint. Six-tenths gram of aminoguanidine sulfate or semicarbazide hydrochloride was dissolved in 100 ml. of the standard alkali and added to the modified Kjeldahl flask by means of a funnel, an additional 100 ml. of the alkali solution being used for washing. The ground glass cap was now fitted to the distilling flask and fastened with rubber bands by means of the glass hooks. All joints were lubricated with stopcock grease before each three-hour run. The nitrogen tank was connected to the distilling flask by means of a rubber tube, and a small stream of bubbles allowed to flow through. This was maintained constant for every run by means of the capillary flowmeter. A non-luminous Bunsen flame was adjusted to a height of approximately 2.5 cm., the tip just touching the gauze. Once adjusted the flame was kept constant for all runs. The time of hydrolysis was noted from the start of gentle ebullition. This required about ten minutes starting cold. At the end of the first hour of reaction, the burner was turned off and the nitrogen tube removed. The ground glass cap was taken off and the neck of the distilling flask immediately washed down with cold distilled water back to the liquid level mark shown on the modified Kjeldahl flask (about 10–15 ml. of the liquid was distilled off during sixty minutes). The contents of the receiving flask and scrubber were washed carefully into another flask, recharged and fitted as before. For the second and third hour of the reaction, only five minutes was required to warm the liquid to ebullition. The amount of standard acid consumed during each period of hydrolysis was determined by back titration with standard alkali in the usual manner. The complete experimental data obtained are summarized in Table I and Fig. 2.

TABLE I

HYDROLYSIS OF AMINOGUANIDINE AND SEMICARBAZIDE IN ALKALINE SOLUTION

NaOH *N*	Time, Hrs.	% Hydrolysis Aminoguanidine	% Hydrolysis Semicarbazide
0.126	1	27.1	2.2
.126	1	27.7	3.3
.126	2	36.8	7.7
.126	2	35.0	8.7
.126	3	44.6	13.1
.126	3	39.7	15.3
.513	1	27.7	14.2
.513	2	42.2	31.7
.513	3	50.0	44.8
.995	1	33.7	45.9
.995	2	51.2	67.7
.995	3	62.0	76.5
1.981	1	46.4	82.0
1.981	2	65.7	89.7
1.981	3	74.8	90.7

The Acid Hydrolysis of Aminoguanidine. Procedure.—Experiments on the acid hydrolysis of aminoguanidine and semicarbazide were carried out in an ordinary reflux

apparatus comprising a round-bottomed flask surmounted by an upright water-cooled condenser. A sample of 0.600 g. of aminoguanidine sulfate or semicarbazide hydrochloride was dissolved in 200 ml. (or 100 ml. for the very high normality acids) of the desired acid strength and refluxed vigorously. At the conclusion of the desired hydrolysis period, the reaction flask was immersed immediately in an ice-water bath and cooled to room temperature. A few drops of phenolphthalein indicator were added and the solution neutralized slowly, to avoid undue heating, with 10 *N* sodium hydroxide solution (to prevent a too large increase in volume). During the neutralization the reaction mixture was cooled in an ice-bath to avoid heating. When only *faintly acid*, it was washed into the ammonia distillation apparatus described below.

Determination of the Ammonia Formed.—The apparatus used for the determination of the extent of hydrolysis was the same as that illustrated by Fig. 1, except that the nitrogen inlet tube was discarded. The distillation flask was dried thoroughly and set into place with the receiver containing the measured volume of standard acid and methyl red indicator. A glass-bead absorption tube as shown in Fig. 1 was also used to prevent any possible escape of ammonia. Seven grams of magnesium oxide was added to the distilling flask together with some glass beads followed by the neutralized reaction mixture. It was found by trial (using known quantities of an ammonium salt) that thirty minutes of vigorous distillation was sufficient to liberate all of the ammonia present. At the conclusion of the distillation, the receiver was rinsed carefully into an Erlenmeyer flask and the acid consumed determined by back titration with standard sodium hydroxide.

Blank Experiments.—Blank experiments were conducted by vigorously distilling a solution of 0.600 g. of aminoguanidine sulfate or semicarbazide hydrochloride, respectively, in 200 ml. of water, for thirty minutes in the presence of 7 g. of magnesium oxide in the manner described above. Aminoguanidine gave an average blank of 4.3 ml. of 0.1018 *N* sulfuric acid, while with semicarbazide, the blank was practically zero.

Experimental Data.—The preliminary experimental data obtained on the acid hydrolysis of aminoguanidine and semicarbazide are summarized in Table II.

TABLE II

ACID HYDROLYSIS OF AMINOGUANIDINE AND SEMICARBAZIDE PRELIMINARY EXPERIMENTS

Substance	H_2SO_4, *N*	Time, hrs.	%, hydrolysis
Aminoguanidine	0.1018	1	0.0
Aminoguanidine	.5080	1	.0
Aminoguanidine	.9937	1	.0
Aminoguanidine	1.9600	1	1.0
Aminoguanidine	3.9240	1	0.5
Aminoguanidine	0.9937	2	.0
Aminoguanidine	.9937	3	.0
Aminoguanidine	.9937	4	.0
Aminoguanidine	.9937	5	1.2
Aminoguanidine	.9937	6	0.8
Semicarbazide	.1018	1	4.3
Semicarbazide	.5080	1	4.5

It was evident from the data presented in Table II that in order to get any appreciable acid hydrolysis much more drastic conditions involving time of hydrolysis and acid strength were necessary. To test this two experiments were run simultaneously. Aminoguanidine sulfate and semicarbazide hydrochloride, respectively, were refluxed vigorously for seventeen hours in 3.924 *N* sulfuric acid. After the determination of the ammonia formed, in the manner described above, aminoguanidine showed a per cent. hydrolysis of 5.2, while semicarbazide was 94.5% hydrolyzed. In order to check these results a series of experiments was run using solutions of acids whose concentrations were increased gradually. The reactions were allowed to continue for seventeen hours. Figure 3 summarizes the data obtained, while Table III gives a comparison between the acid and basic hydrolysis of aminoguanidine and semicarbazide.

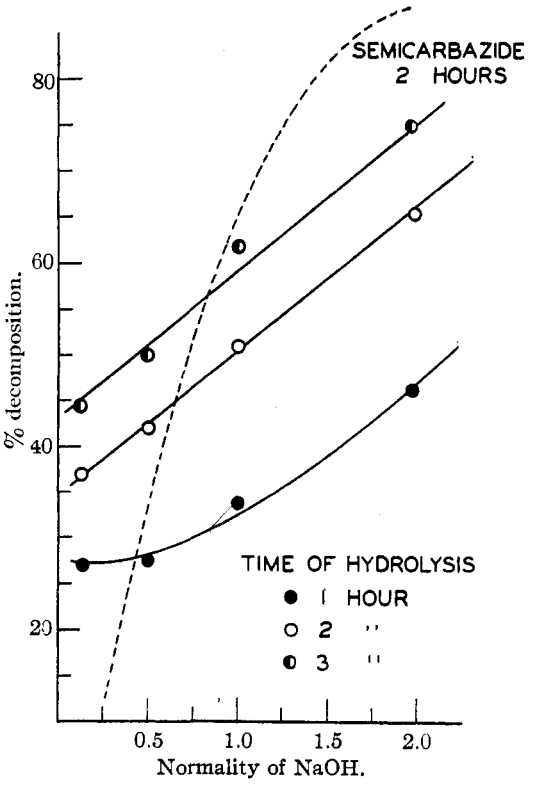


Fig. 2.—Alkaline hydrolysis of aminoguanidine.

Hydrogenation of Nitroguanidine in Acid and Basic Media.—The procedure described by Lieber and Smith[1c] was followed for the hydrogenation of nitroguanidine at 125 atmospheres pressure. In two series of runs the solvents were, respectively, water and a 15% solution of acetic

TABLE III

HYDROLYSIS OF AMINOGUANIDINE AND SEMICARBAZIDE IN ACID AND BASIC MEDIA

Time, hrs.	Normality of NaOH	Normality of H_2SO_4	% decomposition in NaOH	% decomposition in H_2SO_4
1	0.126	0.1018	27.1 (2.2)[a]	0.0 (4.3)
1	.513	.508	27.7	.0
1	.995	.994	33.7	.0
1	1.981	1.960	46.4 (82.0)	1.0
2	0.995	0.994	51.2	0.0
3	.995	.994	62.0	.0
5		.994		1.2
17		3.924		5.2 (94.5)

[a] Values in ( ) are for semicarbazide.

acid in water. The reduction mixture consisted of 10.4 g. of nitroguanidine, 0.5 g. of platinum oxide catalyst and 120 ml. of solvent. The reductions were carried out at 25, 75 and 125°, respectively.

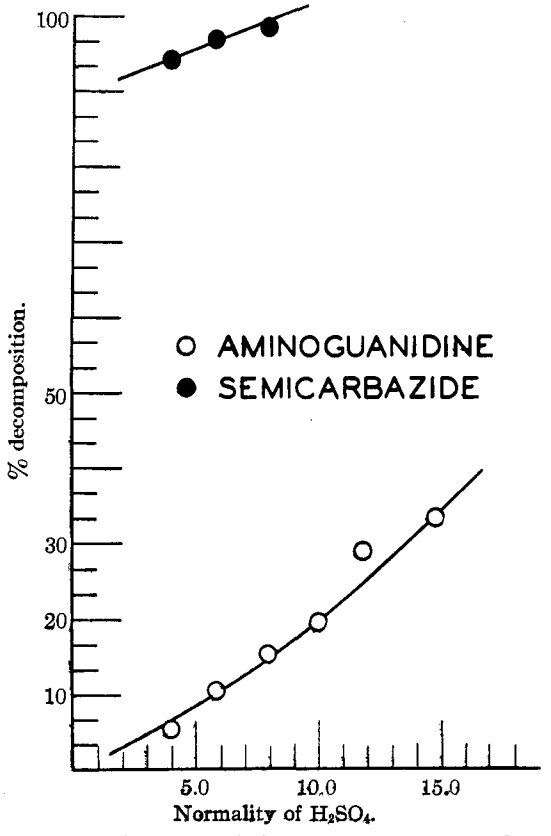


Fig. 3.—Acid hydrolysis for 17 hours vigorous reflux.

At the conclusion of a run, the reduction mixture was filtered to remove the catalyst and adjusted to a volume of 500 ml. The yield of aminoguanidine was then determined by titration of an aliquot portion with standard potassium iodate solution by the method of Jamieson.[8] The data obtained are summarized by Fig. 4. The isolation and identification of aminoguanidine from such reduction mixtures has been described elsewhere.[1c]

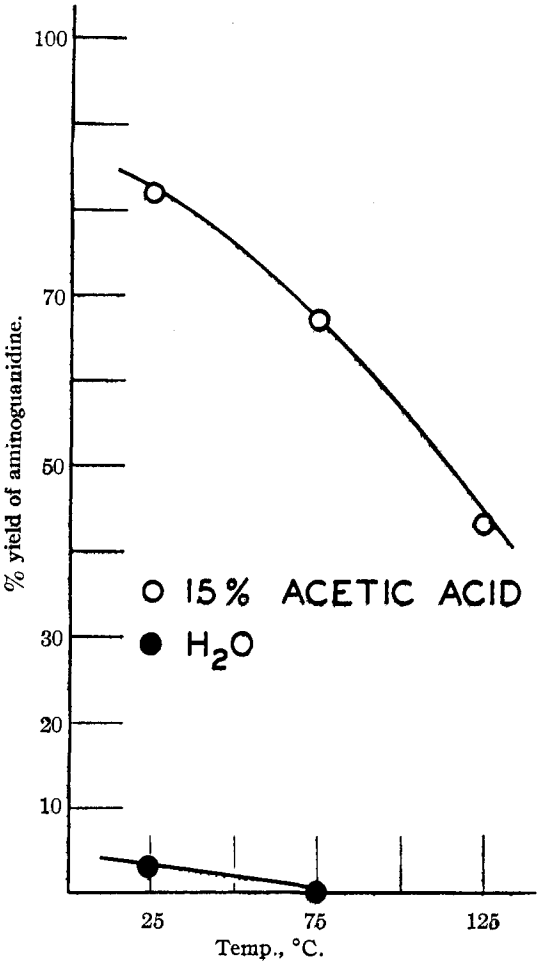
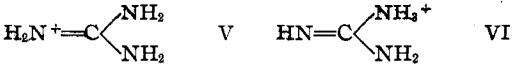


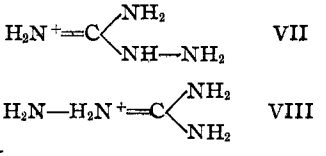
Fig. 4.—Hydrogenation of nitroguanidine at 125 atm. with PtO_2 catalyst.

Discussion

The structure of the guanidine cation has been shown clearly by Lecher and Graf[9] to be (V) and not (VI)



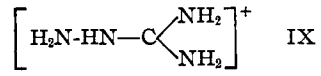
Application to aminoguanidine would then represent the aminoguanidinium ion as follows, in which two forms are possible



(8) Jamieson, "Volumetric Iodate Methods," Chemical Catalog Co., New York, N. Y., 1926, p. 36.

(9) Lecher and Graf, *Ann.*, **438**, 154 (1924); **445**, 61 (1925).

In addition Davis, Yelland and Ma[10] have shown that a carbonium ion form is possible, which may be represented for aminoguanidine as follows (IX)



IX

On the basis of the data presented in this paper, an aminoguanidinium ion of form (VII) appears to be the most logical in lack of more pertinent evidence. Since semicarbazide has been shown[4] to be the initial product of hydrolysis in basic media, it is this imino group which is first subject to attack. It can therefore be assumed that conversion of the imino nitrogen to the onium form imparts to it resistance to replacement by hydrolysis.

Since the remarkable stability of aminoguanidine to acid hydrolysis is undoubtedly related to its basic properties, a forthcoming paper will relate to the determination of the basicity of aminoguanidine and a comparison with several related substances. The relation of *sym*-diaminotetrazine (III) to the mechanism of the hydrolysis of aminoguanidine first postulated by Thiele[4] is being studied and will be reported subsequently.

(10) Davis, Yelland and Ma, THIS JOURNAL, **59**, 1993 (1937).

Summary

1. It has been demonstrated that aminoguanidine is extremely resistant to acid hydrolysis. Aminoguanidine is not hydrolyzed in acid solutions of concentrations and in times comparable to extensive alkaline hydrolysis.

2. At low acid concentrations both aminoguanidine and semicarbazide were found to be resistant to hydrolysis, but with increasing acid concentration and time of hydrolysis, semicarbazide is decomposed practically quantitatively under conditions in which aminoguanidine is unaffected.

3. For normalities of sodium hydroxide below 0.2 *N*, the rate of hydrolysis of aminoguanidine is very much faster than for semicarbazide, while for concentrations above this, the reverse was found to be true.

4. The relationship of the hydrolytic data for aminoguanidine and semicarbazide to a possible "aminoguanidinium ion" has been discussed.

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Reduction of Nitroguanidine. XI. The Reduction of alpha-Alkyl-gamma-nitroguanidines[1]

BY EUGENE LIEBER AND G. B. L. SMITH

There are no data in the literature[2] on the reduction of alkyl or aryl substituted nitroguanidines. Kirsten and Smith[3] prepared α-methyl-, α-ethyl- and α-*n*-butyl-γ-aminoguanidines by two general synthetic procedures involving the hydrazinolysis of S-methyl-N-alkyl-isothioureas and the reaction of S-methyl-N-amino-isothioureas with primary alkylamines. Their method definitely established the constitution of what may be considered as the final reduction products of the α-alkyl-γ-nitroguanidines.

The present investigation has demonstrated that the method of catalytic hydrogenation is a convenient means for the preparation of reduction products of the α-alkyl-γ-nitroguanidines. As in the hydrogenation of nitroguanidine,[4] it was found that the mechanism of the reduction is dependent on the environmental conditions of the solvent media. In neutral or basic media, the α-alkyl-γ-nitrosoguanidine is the first product of reduction, while in acid media, the reduction proceeds directly to the formation of α-alkyl-γ-aminoguanidines *without the appearance of the intermediate nitroso stage.* α-Methyl- and α-ethyl-γ-nitrosoguanidine were prepared by the catalytic hydrogenation of the corresponding alkylnitroguanidines in absolute methyl alcohol. Unlike nitrosoguanidine,[5] the alkylated derivatives are extremely soluble in water and ethyl alcohol and are impossible to isolate in pure form by direct crystallization from these solvents. The

(1) This paper is an abstract of a part of the thesis submitted by Mr. Lieber, to the Graduate Faculty of the Polytechnic Institute of Brooklyn, in partial fulfilment of the requirements for the degree of Doctor of Philosophy in June, 1937. For previous abstracts from this thesis see THIS JOURNAL, **59**, 2283 (1937).

(2) After submission of this paper to the Editor it was learned, by private communication from Professor Tenney L. Davis, that he had isolated in pure form α-methyl-γ-nitrosoguanidine by reduction of the corresponding methylnitroguanidine.

(3) Kirsten and Smith, THIS JOURNAL, **58**, 800 (1936).

(4) Lieber and Smith, *ibid.*, (a) **57**, 2479 (1935); (b) **58**, 2170 (1936).

(5) Sabetta, Himmelfarb and Smith, *ibid.*, **57**, 2478 (1935).