# PROCESS for AMINOGUANIDINE

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**P**OR the past fifty years the preparation of aminoguanidine and its derivatives has been a problem of only theoretical interest. The free amine is hygroscopic and unstable, hydrolyzing readily in the presence of dilute bases. However, it is quite basic in character and forms salts by addition to common acids. The bicarbonate is the only insoluble salt, and the compound is generally isolated in this form.

Aminoguanidine was made by Thiele in 1892 (1, 27) by reduction of nitroguanidine with zinc dust and acetic acid, with a yield of 65% or less. A modification of this reaction was reported by Conard and Shriner (3) and Stefanowski with Janiszewski (26). Wyler (29) in 1935 was granted a patent using zinc acetate instead of acetic acid with zinc dust, with yields claimed to be 90%. We were unable to obtain better than 50%. Yields of 60-70% of aminoguanidine were obtained by the reduction of nitroguanidine with sodium and liquid ammonia in the presence of ammonium chloride (14). Lieber and Smith (12-15) studied thoroughly the production of aminoguanidine by hydrogen and a catalyst from nitroguanidine. McGill (17) obtained a patent in 1936 for a somewhat similar method.

Various methods have been published on the synthesis of aminoguanidine with hydrazine as reagent. They are divided into hydrazination, or the addition of hydrazine to a compound, and hydrazinolysis. Pelizarri and Gaiter reacted cyanamide with hydrazine sulfate (19, 20). Similar reactions were carried out by Hofmann and Ehrhart (9) and Fantl and Silbermann ( $\theta$ ). Thiele (28) in 1893 prepared aminoguanidine by reacting equimolecular amounts of nitrosoguanidine and hydrazine hydrate. In 1927 Heyn (7) prepared aminoguanidine by the reaction of 3-alkyl isothiourea sulfate and hydrazine. Schering-Kahlbaum (21), Smith and Anzelmi (23), and Kirsten and Smith (11) investigated the same reaction; the latter prepared substituted aminoguanidinium salts.

Boehringer (2) patented an electrolytic reduction of nitroguanidine, using a tin cathode and very little acid. This is the process studied here and improved. The nitroguanidine is easily made from dicyandiamide (Dicy). The latter material is obtained by the hydrolysis of calcium cyanamide at  $60-65^{\circ}$  C. The reaction sequences may be represented as:



## **GUANIDINIUM NITRATE**

One mole equivalent of Dicy was fused with slightly over 2mole equivalents of commercial ammonium nitrate (4), resulting ▶ ▶ In making dyes from aminoguanidine it was first necessary to elaborate a process for its preparation. This involved the electrolytic reduction of nitroguanidine. The nitroguanidine resulted from the dehydration with sulfuric acid of guanidinium nitrate which, in turn, was derived from dicyandiamide by heating with ammonium nitrate. Yields of 73% nitroguanidine were obtained, based on the dicyandiamide used. Yields on the reduction process for converting nitroguanidine to the sulfate and recovering the product as the bicarbonate were around 50%.

in a 90% yield of guanidinium nitrate. The crude material was converted immediately into the nitro compound by sulfurie acid dehydration (5). The nitrate is fairly soluble in water; the nitro compound is only slightly soluble cold but more so hot. Hence the nitroguanidine is easily purified by recrystallization from water.

The following was the procedure for a typical run. Four moles (420 grams) of Dicy and 11 moles (880 grams) of ammonium nitrate were mixed and ground well. This mixture was charged into a 2-liter round-bottom flask heated by an oil bath. The temperature at the start was 120° C. and at the end of half an hour was 160° C. This temperature was maintained for 4 hours without stirring. However, Smith, Sabetta, and Steinbach (25) reported that after 1 hour of fusion the yield of by-products, melamine and ammelide, is greatly increased, and that on heating over an hour, less product was recovered. The mixture at first melted and then set as the reaction proceeded. The final solid was guanidinium nitrate.

To purify the product, the flask was allowed to cool to  $100^{\circ}$  C., and the contents were extracted with 4 liters of hot water. Small quantities of melamine and ammelide were present, but since they are insoluble, they could be filtered out. The materials remaining in solution were guanidinium nitrate and ammonium nitrate; an excess of the latter was used because it greatly increases the yield. The solution was evaporated until the water content was very small, as indicated by rapid crystallization from the boiling solution and the tendency to set. This material could have been purified by recrystallization from a small volume of water, but the pure product was not necessary for the next reaction.

### NITROGUANIDINE

The crude guanidinium nitrate was dehydrated by dissolving it in 1500 ml. of 96% sulfuric acid. The acid was cooled by an ice-salt mixture surrounding the 4-liter beaker in which the reaction took place. It was stirred vigorously while the temperature was kept below 20° C., the rate of addition of guanidinium nitrate being used to regulate the temperature. Later Ludlow (16) found in this laboratory that, even if the temperature rises to 26° C., no decrease in yield is apparent. This allows the use of tap water as a cooling medium. Ludlow also found that maximum conversion was reached at the end of an hour.

The reaction mass is diluted at this stage, and the insoluble crystals of nitroguanidine are filtered off. Here Ludlow found that orystals with much better filtering characteristics could be obtained by pouring the mass into water held at a maximum of  $40^{\circ}$  C. than by pouring it over ice as directed in "Organic Syntheses" (5). The product was purified by recrystallization from water and gave long needle-shaped crystals. The yield was 760 grams, melting at 232° C. (reported, 231-232° C., 18), or 73% based on the Dicy used.



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Nitro- guani-	95%						Aminc dine	guani Bicar-
dine,	H2SO4,	Amper-	Volt	age	Temp.,	Time.	bonate	Yield
Grams	Grams	age	Begin	End	° C. '	Hr.	Grama	%
104	150	10	7.0	15	17	16	40	30
104	200	10	6.5	8.5	16	15.75	57	42
104	200	10	6.5	8.5	16	18	60	44.2
104	250	10	6.7	8.5	16	18	48	35.3
104	300	10	6.0	8.0	15.5	18	54	39.7
104	200	15	8.5	10.7	16.5	12	78.5	57.7
104	200	20	9.5	12.5	17	9	62	45.6
104	200	20	9.0	12.0	17	9.75	66	48.5
52	150	15	9.0	11.0	16	6.25	34	50
26	125	15	9.7	10.7	16.5	3	17	50
52	150	15	9.0	11.5	16	7.5	38.6	56.8
52	150	15	8.5	10.5	25	5.5	21	31
52	150	15	8.5	10.5	25	5.5	22.3	32.8
52	150	15	9.0	11.0	20	6	32.6	48
52	150	15	9.0	11.0	20	6	34	50.1
52	150	15	10.0	12.0	13	7	38.7	57
52	150	15	10.0	11.0	10	8.5	41.3	61
52	150	15	10.0	12.2	5	10.5	43.6	64.2
104	200	15	8.3	10.7	16.5	12	72	53
104	200	15	8.3	10.7	16.5	12	73	53.6

A cheaper method for the preparation of nitroguanidine uses calcium cyanamide and ammonium nitrate as raw materials rather than the more costly Dicy (22).

#### AMINOGUANIDINE

The basis for the electrolytic cell was suggested by the procedure for reducing nitrourea to semicarbazide (10). Smith and Sabetta (24) reported that the reduction of nitroguanidine to nitrosoguanidine in neutral or basic media is reversible. Lieber and Smith (15) determined that aminoguanidine is very resistant to hydrolysis in an acid medium; they reported earlier (15) that in acid media the nitroso derivative is not formed by catalytic reduction.

A cell was constructed from a hard rubber battery box (Figures 1 and 2). The partitions separating the cells had been removed as well as the risers from the bottom. A diaphragm was made from birch veneer,  $\frac{1}{2}$  inch thick, and was cemented in place

with a melted plastic. This plastic was made by heating equal molal quantities of ethylene glycol and phthalic anhydride to  $200^{\circ}$  C. for 24 hours (8). This material withstood the action of the dilute sulfuric acid very satisfactorily.

The cathode was a layer of mercury on the floor of the cathode chamber. This layer was thick enough to cover the bottom completely without breaking. Electrical contact to this mercury was made by heavy copper wire, sealed in the end of an 8-mm. glass tube with the plastic. The wire was bent at right angles to the tube at the point at which it projected from the tube. The tube was clamped in such a way that it dipped into the mercury, and the copper wire was completely covered. A small amount of mercury was placed inside the tube, and the negative lead from the generator dipped into the mercury (Figure 1).

A sheet of lead, 1/s inch thick, was employed as the anode. It was bent at 90° along each of two parallel lines, so that it would line the anode cell on the three outside walls. A small piece was left projecting upward, to which the positive lead from the generator was attached. The diaphragm was cemented in the cell so as to make the cathode side have twice the volume of the anode compartment. The cell was cooled by tap water running through 10 feet of 10-mm. Pyrex tubing in the cathode chamber and 6 feet of similar tubing in the anode side (Figure 1). Since nitroguanidine is not soluble in the catholyte, a rapid motor stirrer was used to agitate the suspension. For runs at cell temperatures lower than that of tap water, an alcohol-water solution was pumped intermittently through the cooling coils and copper tubing in an ice-salt mixture. An ammeter was connected in series with the cell and a voltmeter across the leads just outside of the cell (Figure 2). Direct current was supplied by a rotary converter (Figures 1 and 2). The over-all resistance of the cell when filled with 8% sulfuric acid was only 0.6 ohm, calculated from the voltage necessary to force the required current through the cell.

#### EXPERIMENTAL REDUCTIONS

Forty experimental reductions were made in the electrolytic cell. Twenty representative runs were used to furnish the data for Table 1. The following procedure was found most satisfactory for this reduction:

The cell was assembled, and the proper electrical connections ere made to the anode and cathode. Two liters of water were were made to the anode and cathode. poured into the cathode compartment and one liter into the anode side. Ninety grams of concentrated sulfuric acid (95%) were added to the anode compartment and 150 grams to the cathode cell. The stirrer was started and the cooling water turned on. When the temperature of the cathode chamber turned on. When the temperature of the cathour enames of the cathour enames of the direct our part of the direct o The direct-current generator was started to this compartment. and the resistance of the field adjusted to put 15 amperes of curthe temperature 15.5° C. The nitroguanidine was in suspension at first, but as it was reduced to the very soluble amino derivative, a clear solution finally resulted. After 71/, hours the solution had become clear and excess hydrogen began to bubble off. No hydrogen came off during the initial stages of the reduction and very little during the final part. The reduction was conand very little during the final part. By this time the temperature tinued an additional 15 minutes. By this time the temperature had reached 16° C. and the voltage was 11.5 volts, the current having been held constant at 15 amperes for the entire reaction.

The cathode solution was sucked into a calibrated flask, and 1 cc. was withdrawn and titrated with a standard base to phenolphthalein end point. After neutralization with the calculated amount of calcium carbonate, the solution was filtered to remove







Figure 2. Diagram of Electrolytic Cell and Hook-up

the calcium sulfate, evaporated to 300 ml., and filtered again to remove the remaining hydrated calcium sulfate. The solution now contained the aminoguanidine in the form of the sulfate. Water was added to bring the final volume up to 600 ml., and 42 grams of sodium bicarbonate were dissolved in it with rapid stirring; the solution turned from clear to a brown-pink color. In about one minute all of the bicarbonate had dissolved, and in a few additional seconds the fine white precipitate of aminoa few additional seconds the fine white precipitate of amino-guanidine bicarbonate had begun to form. After standing over-night, the precipitate was filtered and the cake washed with water and methyl alcohol. After air drying the yield was 38.6 grams, or 56.8% based on the nitroguanidine used. Aminoguanidine bicarbonate was analyzed for nitrogen con-tent by the Dumas procedure, and showed 41.20 and 41.23%. By calculation NH<sub>3</sub>C(NH)NHNH<sub>2</sub>.H<sub>3</sub>CO<sub>2</sub> has 41.18% N<sub>2</sub>. A sample melted at 177.6° C. (reported, 177-178° C., 14).

The values for sulfuric acid given in Table I were the amounts used in the cathode solution, and that in the anode was enough to produce a similar concentration of acid. An excess of acid is needed during the reduction because acid concentration decreases in the cathode compartment as the amine salt is formed. If



too little acid is used, the resistance of the cell is greater and more heat is produced; consequently the cooling of the cell is more difficult. Too concentrated an acid medium results in a lower cell resistance; but more sulfuric acid has to be subsequently removed by calcium sulfate precipitation, and the aminoguanidine is decomposed as it forms. Enough acid to produce an 8% solution at the beginning of a 1-mole reduction, or a 4% solution at the end, was the optimum proportion.

The amperage is also an important factor. Too small a current gives a reduced yield; too great a current causes a similar decrease in amount of product recoverable, probably because of the excess heat produced. The voltage is governed by the amperage desired and the resistance of the cell itself. From Table I an optimum current of 15 amperes seems to be indicated for this particular cell.

Lower temperatures give better yields of desired product (Table I). However, then it was necessary to continue the reaction for a longer time in order to produce a clear solution, an indication that all of the nitroguanidine previously in suspension had reacted. At this lower temperature the resistance is greater and the current efficiency is decreased (Figure 3). The latter effect is partially caused by the decreased solubility of nitroguanidine in water. Hydrogen escaped during the entire reduction when the temperature was 10° C. and especially at 5° C. Curves in Figure 3 were plotted from the data in Table I.

#### CALCULATION OF CURRENT EFFICIENCY

To evaluate the current efficiency, a calculation made from that of the typical run described under "Experimental Reductions" is as follows: A yield of 38.6 grams of aminoguanidine bicarbonate was recovered. Dividing this value by the molecular weight (136), the moles of product are obtained. Since six hydrogens are necessary to balance the reduction of 1 mole

# $H_2NC(NH)NH(NO_2) + 6H = H_2NC(NH)NHNH_2 + 2H_2O$

the number of moles multiplied by six times Faraday's number (96,500) gives the coulombs of electricity actually used:

$$(38.3 \times 6 \times 96,500)/136 = 164,30$$

coulombs Since the cell was operated at 15 amperes for  $7^{1}/_{2}$  hours,

 $15 \times 7.5 \times 3600 = 405,000$  coulombs were put into the cell. The output divided by the input times 100 gives the current efficiency:

 $(164.300 \times 100)/405.000 = 40.5\%$ 

This type of calculation was used to give curve 2 of Figure 3.



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## ACKNOWLEDGMENT

Appreciation is expressed to American Cyanamid Corporation for certain chemicals which aided this investigation. This report is abstracted from a part of the Ph.D. thesis of R. P. Carter.

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# Azo Dyes from Aminoguanidine

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**REVIOUS** attempts to diazotize and couple aliphatic amines generally have been unsuccessful. Ordinary reagents and procedures for aromatic diazotization have given no similar diazonium compounds in the aliphatic series (6). Indirect methods have been tried on ordinary aliphatic amines (7) but with no success. However,

> > Aminoguanidine has been diazotized and hotcoupled with various intermediates to furnish a whole new series of azo dyes which possess of good dyeing properties on animal fibers such as silk and wool, particularly in conjunction with a mordant. The dyes are of various shades with the browns and oranges predominating. The coupling of the aminoguanidine diazonium hydroxide or of its isomer is carried out in a hot aqueous solution under controlled conditions of pH to give the various dyes. The latter are soluble in alkaline solution, but they are precipitated by acids.

The substance is stable at room temperature, but explodes violently when heated to about 130° C. or even when cold if struck sharply. Bases decompose it with the production of ammonia, cyanamide, and other materials. Acids form salts; with hydrochloric acid the formula C<sub>2</sub>N<sub>10</sub>H<sub>7</sub>Cl was obtained. These properties were given by

aminoguanidine can be subjected to the action of sodium nitrite in the absence of free acid and a diazonium compound be obtained; this work was done by Hofmann and Roth (4, 5) in Germany in 1910, but prior to the present research little or no use was made of the compound produced. Hofmann, Hock, and Kirmreuther (3) repeated the work and gave a more detailed report. Their method was to treat aminoguanidine nitrate with an excess of neutral sodium nitrite in an aqueous medium at room temperature. After the solution had stood for 40 hours, the reaction was complete and aminoguanidine diazonium hydroxide precipitated in almost quantitative yields. The same investigators reported color reactions produced by the diazonium material, but their method required a week for the color to develop. No dye formation or precipitation was reported.

The diazonium material was analyzed by several methods (3). Hofmann's theory that it is in equilibrium with the nitrosoamine, as shown below, was based upon its insolubility in water and other common solvents:

# $H_{2}NC(NH)NHNHN=NC(NH)NHN=NOH \rightleftharpoons$ Diazonium hydroxide

#### H<sub>2</sub>NC(NH)NHNHN-NC(NH)NHNHNO Nitrosoamine

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Hofmann and were confirmed in the present work. Different products have been obtained from the diazotization

of aminoguanidine, depending on the pH of the solution:

If aminoguanidine is treated with free mineral acid plus sodium nitrite, the product is guanyl azide (13, 14):

 $NH_{1}C(NH)NHNH_{2} + HNO_{2} \rightarrow NH_{2}C(NH)N_{2} + 2H_{2}O$ 

2. If diazotization is carried out in the presence of acetic acid and sodium acetate, diazoaminotetrazolic acid results (9):

 $2NH_2C(NH)NHNH_2 + 3HNO_2 \rightarrow$ 



3. In neutral aqueous solutions, guanylnitrosoaminoguanyl tetrazene is formed (9):

# $2NH_2C(NH)NHNH_2(HNO_3) + 2NaNO_2 \rightarrow$ $NH_2C(NH)NHNHN:NC(NH)NHNHN:O + 2N_BNO_2$

The product from the latter reaction or its isomeric diazonium hydroxide serves as the reagent in the coupling reactions to give the dyes dealt with in this paper.

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