THE CHEMISTRY OF AMINOGUANIDINE AND RELATED SUBSTANCES

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Received July 25, 1938

CONTENTS

I. INTRODUCTION

Aminoguanidine and its derivatives have been the subjects for many important, interesting, and fruitful investigations. The researches on these substances, extending over a period of about fifty years, have occupied the time and energies of a great many chemists in several countries. Thiele was the first to prepare aminoguanidine in 1892, and contributions to our knowledge of the compound have been made by Pellizzari, Hantzsch, Curtius, and other renowned chemists. Aminoguanidine and the many closely related substances have such remarkable properties that Richter in his treatise on organic chemistry uses the term *"merkwürdig"* in reference to them. In fact, many of the first compounds of certain classes have been derived from aminoguanidine as a parent substance, and the studies on aminoguanidine have contributed much to our knowledge of heterocyclic compounds, the higher hydronitrogens, the guanazyls, the azides, and nitron. Despite these facts, the importance and significance of the compound in the organic chemistry of nitrogen have been missed by many scholars.

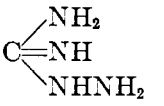
Although much important and interesting work has been carried out on aminoguanidine and related compounds, no review of the results achieved has previously been made. The lack of appreciation of the fundamental character of the work may be attributed to this fact. The papers on these subjects are rather widely scattered in the literature. Accordingly, the authors have undertaken to present a review of the chemistry of aminoguanidine and related compounds. It is their hope that the presentation will serve as a stimulus and guide to further work in the field, as many of the excellent studies are still incomplete in certain phases. Hence, one of their aims is to point out some of these gaps in our knowledge and to invite their completion. The authors believe, also, that a knowledge of aminoguanidine and related compounds is essential to a complete understanding of the organic chemistry of nitrogen. For this reason they sincerely hope that the review will be of interest to the general reader.

II. SYNTHESIS OF AMINOGUANIDINE

Several methods for the formation and preparation of aminoguanidine have been developed. These methods may be classified in three categories, as follows: (*A*) reduction, (*B*) hydrazination, and (*C*) hydrazinolysis.[1]

A. Reduction of nitro- and nitroso-guanidines

Thiele (147) was the first to prepare aminoguanidine and to suggest its probable constitution:



He obtained the compound by the reduction of nitroguanidine (24, 132, 136) with zinc dust in a solution of acetic acid (7). A modified form of his procedure has been described recently by Conard and Shriner (20). In a later paper Thiele (151) described the preparation and properties of aminoguanidinium bicarbonate and established its constitution from analytical data. The bicarbonate, owing to its insolubility, is the most convenient compound to use for recovering aminoguanidine from solution, especially when the solution contains guanidine, because this substance does not form an insoluble carbonate or bicarbonate.

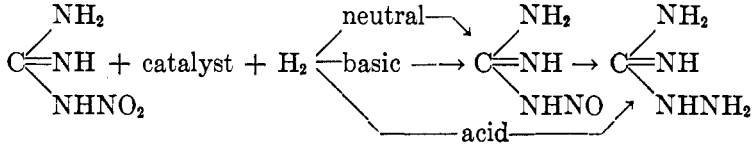
Wyler (179), in 1935 and 1938, obtained patents for the preparation of aminoguanidine by the reduction of nitroguanidine at 40°–50°C. with zinc as a reducing agent in the presence of an aqueous solution of zinc or another metal acetate. Fuller, Lieber, and Smith (51) reduced nitroguanidine in liquid ammonia solution with metallic sodium, and were able to prepare aminoguanidine in 60 per cent yield provided the reduction was carried out in the presence of a sufficient concentration of ammonium chloride. The optimum stoichiometrical ratios of sodium : ammonium chloride : nitroguanidine were 6 : 6 : 1. With smaller quantities of ammonium chloride only reddish brown products of unknown composition were obtained, and in the absence of ammonium chloride cyanamide was the only compound identified among the reduction products.

Boehringer (10), in 1903, claimed to have obtained aminoguanidine in yields as high as 80 per cent by the electrolytic reduction of nitroguanidine suspended in a dilute solution of sulfuric acid; he employed a tin cathode, a current density of 250 amperes per square meter, and a temperature of

[1] Hydrazination is a reaction in which hydrazine is added, and the term is analogous to hydration. Hydrazinolysis is a metathetical reaction with hydrazine, and the term is analogous to hydrolysis.

10°C. Workers at the Polytechnic Institute of Brooklyn have as yet failed to confirm this observation.

McGill (83) has recently suggested that aminoguanidine may be manufactured by the hydrogenation of nitroguanidine with a catalyst of nickel dispersed on kieselguhr at temperatures between 25° and 125°C. and in the *absence* of any substantial amounts of acid. A more comprehensive examination of the catalytic hydrogenation of nitroguanidine has been made by Lieber and Smith (78). Contrary to the results of McGill (83), it was found that the optimum conversion to aminoguanidine is obtained in media of relatively high acid concentration. The molar ratio of hydrogen to hydrogen acceptor obtained in the catalytic hydrogenation of nitroguanidine was found to depend upon the experimental conditions and may be summarized as follows:



In acid of such a concentration that the molar ratio of nitroguanidine to acid is 1 or higher, the reduction proceeds without the formation of nitrosoguanidine. In neutral and basic media, nitrosoguanidine is the first product of reduction and can be readily isolated in good yield. Lieber and Smith (81) have recently employed catalytic hydrogenation in the reduction of α-alkyl-γ-nitroguanidines.

Thiele (149) found that the action of zinc dust upon nitrosoguanidine dissolved in a solution of acetic acid yielded aminoguanidine, but he did not record quantitative details. Lieber and Smith (79) have studied, quantitatively, the catalytic hydrogenation of nitrosoguanidine to aminoguanidine, and have found that nitrosoguanidine is more resistant to reduction by this method than is nitroguanidine.

Thiele (147) prepared and analyzed aminoguanidinium chloride, hexachloroplatinate, nitrate, sulfate, and picrate. He also described a complex salt of copper, a beautiful violet-blue substance, and gave its formula as $(CN_4H_5)_2Cu(HNO_3)_2$, but from our present knowledge we would consider it a substituted hydrazino complex and write the formula $[(CN_4H_6)_2Cu](NO_3)_2$. G. S. Smith (130) has prepared the analogous coördination complex of nickel and has interpreted his data in a like manner. The aminoguanidinium phosphotungstate (145), tetrabromoaurate (57), hexabromotellurite (56), and tetrachloropalladinate (55) have been described, and in addition a complex compound with thiourea (5) has been prepared.

Hantzsch (58) has shown that a primary sulfate of aminoguanidine is formed in absolute sulfuric acid, aminoguanidine in this case acts as a tetraacid base. The formula of the salt may be written as $[CN_4H_{10}]$-$(HSO_4)_4$.

Aminoguanidine may be regarded as a derivative of hydrazine (*vide infra*) and it forms an especially interesting series of salts, two representatives of which are described by Thiele (147). The salts have already been referred to and are the aminoguanidinium bicarbonate and bisulfate. Kertez (unpublished notes) in this laboratory has prepared aminoguanidinium dinitrate, and Lieber (unpublished notes) has obtained the aminoguanidinium dichloride. It is, therefore, evident that aminoguanidine in these compounds possesses the property, analogous to hydrazine, *of functioning as a diacid base.* In other words, these compounds are secondary rather than primary salts.

Suida (145) has found that with acid dyes aminoguanidine forms compounds which are sparingly soluble in water. Ekeley and Swisher (35) studied the action of aminoguanidinium bicarbonate on the addition products of benzalanilines and sodium bisulfite. The reaction between molecular quantities of benzalaniline and sodium bisulfite in aqueous solution gives an unstable product which decomposes when separated from the mother solution. The aqueous solution of such a product reacts with 1 mole of aminoguanidinium bicarbonate, and primary anilinobenzylaminoguanidinium sulfite,

$$(C_6H_5NHCHC_6H_5)SO_3NH_3C(=NH)NHNH_2$$

is immediately precipitated.

G. S. Smith (129) has described a volumetric procedure for the determination of aminoguanidine, which is essentially an adaptation of the early Jamieson (72) method for hydrazine. The aminoguanidinium salt (approximately 0.1 g.) dissolved in 50 ml. of water is treated with 20 ml. of 5 *N* sulfuric acid and 50 ml. of 0.1 *N* potassium iodide; the solution is allowed to stand for 3 min. in a glass-stoppered flask; an excess of potassium iodide is added and the liberated iodine is titrated immediately with a standard solution of sodium thiosulfate.[2]

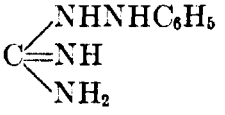
[2] In some recent studies in this laboratory Thomas G. Wheat has found that the hydrazino nitrogen in the semicarbazones of a number of aldehydes and ketones may be estimated by the Jameson technique of titration with a standard solution of potassium iodate. (See Thomas G. Wheat: Thesis, B.S. in Chemistry, Polytechnic Institute of Brooklyn, June, 1938; also G. B. L. Smith and T. G. Wheat: Ind. Eng. Chem., Anal. Ed. **11**, 200 (1939).)

B. Hydrazination

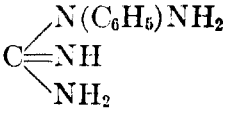
1. Cyanamide and its derivatives

Pelizarri and Gaiter (102), in 1914, improved their earlier method (101) for the preparation of aminoguanidine from cyanamide and hydrazine sulfate. Prior to this work Hofmann and Ehrhart (64) had used calcium cyanamide and hydrazine sulfate. Fantl and Silbermann (37) have recently improved this general procedure so that they obtain 90 to 95 per cent yields of aminoguanidine, starting from crude disodium cyanamide.

The preparation of a mono-substituted aminoguanidine was first recorded by Pellizzari (94). By the reaction of phenylhydrazine hydrochloride on cyanamide, in alcoholic solution, a substance was obtained which he termed "anilinoguanidine." In a more careful study of the reaction Pellizzari (95) showed that only 50 per cent of the expected anilguanidine is obtained and that an isomer, amidophenylguanidine (phenylhydrazonocarbamidine or *as*-phenylguanylhydrazine), is also formed:



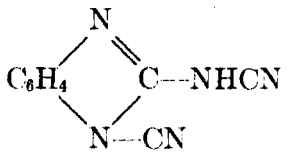
Anilguanidine



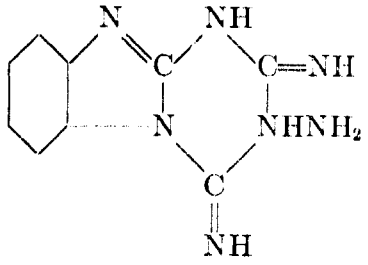
"Amidophenylguanidine"

"Amidophenylguanidine" was readily separated from its isomer by condensation with aldehydes. By using phenylhydrazinium bromide Pellizzari (96) effected a more direct separation, since the amidophenylguanidinium bromide was found to be more soluble in water and less soluble in alcohol than its isomer was. Pellizzari and Tivoli (106) attempted to prepare anilguanidine in pure form by the reaction of cyanogen chloride with phenylhydrazine. In this study anilcyanamide, $C_6H_5NHNHCN$, was first formed, and while its reaction with water gave phenylsemicarbazide, the corresponding reaction with ammonia did not take place. Instead, polymerization occurred and a substance which was believed to be dianildicyandiamide, $(C_6H_5NHNHCN)_2$, was formed. Pellizzari and Cuneo (101) showed that the reaction of cyanamide with hydrazines was a general one, and prepared a number of α-(arylamino)guanidines. A more recent application of this reaction is described by Fantl and Silbermann (37).

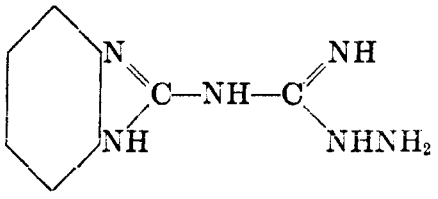
In 1921 Pellizzari (97) studied the reaction of cyanogen chloride with phenylhydrazine in aqueous solution and showed that the initial product of the reaction is *o*-phenylene-α, β-dicyanguanidine,



This substance on further reaction with hydrazine hydrate gave 3-amino-1,2,3,4-tetrahydro-2,4-diiminotriazinobenzimidazole (*o*-phenyleneamino-isomelamine).

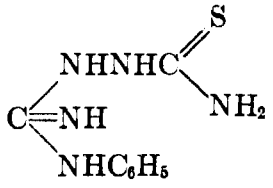


The action of alkali converts the 4-imino group to a carbonyl group. The resulting melanuric acid is unstable and loses carbon dioxide; the ring is ruptured and benzimidazoleaminoguanidine (*o*-phenyleneaminobiguanide) is formed:



o-Phenyleneaminobiguanide

Arndt and Tschenscher (4) have shown that the reaction of phenylcyanamide with thiosemicarbazide forms thiocarbamidophenylaminoguanidine (α-phenyl-γ-thioureidoguanidine):



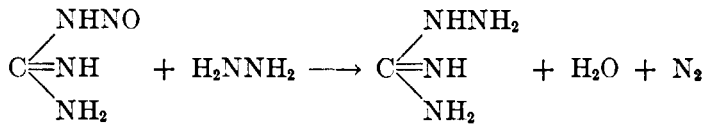
2. Dicyandiamide

The reaction of hydrazine hydrate with dicyandiamide was studied by Stollé and Krauch (143). These investigators isolated aminoguanidine, diaminoguanidine, triaminoguanidine, and aminobiguanide from the reaction mixture, besides a number of interesting nitrogen heterocyclic derivatives, which will be considered later. These former substances are no doubt the precursors of the nitrogen ring compounds.

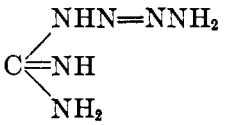
C. Hydrazinolysis

1. Nitrosoguanidine

Thiele (149), in 1893, discovered that equimolecular proportions of nitrosoguanidine (125) and hydrazine hydrate react readily, with evolution of nitrogen, to form aminoguanidine:



The intermediate, a tetrazene,



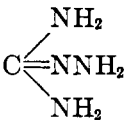
was considered to form, and immediately lose nitrogen. However, when the reaction was conducted with the ratio of 2 moles of nitrosoguanidine to 1 mole of hydrazine hydrate, a much slower reaction took place, and the product was hydrazodicarbamidine:

$$H_2NC(=NH)NHNHC(=NH)NH_2$$

The first substance formed is aminoguanidine, as indicated above. This in turn reacts with additional nitrosoguanidine to form the tetrazene

$$H_2NC(=NH)NHN=NNHC(=NH)NH_2$$

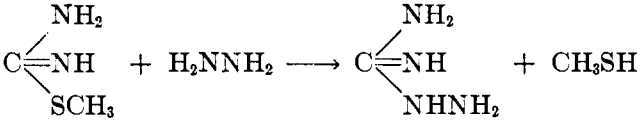
in which loss of nitrogen results in the formation of hydrazodicarbamidine. Thiele considered that this was proof that aminoguanidine did not have the "symmetrical" form:



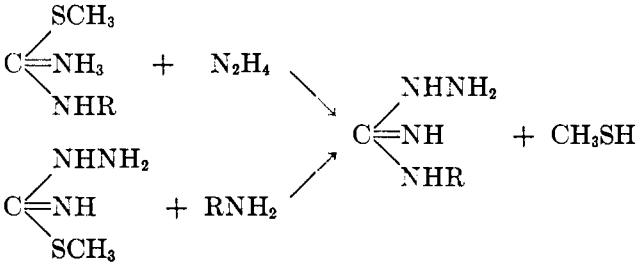
Thiele (149) suggested as an alternative mechanism for the formation of hydrazodicarbamidine that the nitrosoguanidine first "dearranged" (25, 26) to water, nitrogen, and cyanamide; that cyanamide combined with the hydrazine to form aminoguanidine; and that this compound in turn reacted with a second mole of cyanamide to form hydrazodicarbamidine. About the same time, Pellizzari (101) found that the reaction of cyanamide and hydrazine hydrochloride led to the formation of aminoguanidine.

2. Thiourea and its derivatives

Heyn (63), in 1926, received a patent on a method for the preparation of aminoguanidine and substituted aminoguanidines based on the reaction of hydrazine or substituted hydrazines with *S*-alkylisothiourea sulfates. Aminoguanidinium sulfate was prepared from hydrazine hydrate and methylisothiourea sulfate:

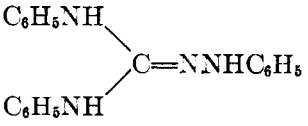


Substantially the same process was patented by Schering-Kahlbaum (126) two years later. Smith and Anzelmi (131) have confirmed the observation of Heyn (63); they obtained aminoguanidinium sulfate in quantitative yield. Kirsten and Smith (73) have prepared α-alkyl-γ-aminoguanidines by this general method and have employed the two following general schemes of synthesis:



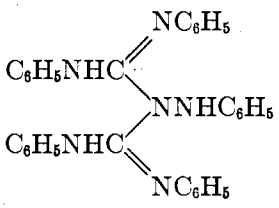
Busch and Bauer (16) have found that the reaction between hydrazine and thiourea in the presence of lead oxide or mercuric oxide does not give aminoguanidine; this reaction is prevented apparently by the oxidation of the hydrazine by the metallic oxides. However, these authors found that the reaction could be carried out in an alcoholic solution of potassium hydroxide, and they prepared a number of α,β-diaryl-γ-aminoguanidines from the respective diarylthiourea and hydrazine hydrate. These substances were found to be very strong bases, and they formed well-crystallized salts. If the reaction is carried out in the absence of alcoholic potassium hydroxide, only arylthiosemicarbazides are formed (18).

In 1888 Marchwald (86) prepared triphenylaminoguanidine



Triphenylaminoguanidine

("diphenylanilguanidine" or α,γ-diphenyl-β-(anilino)guanidine) by the action of lead oxide on an alcoholic solution of thiocarbanilide and phenylhydrazine. A little later, Marchwald and Wolff (87) prepared the same substance by the action of lead oxide with an alcoholic solution of diphenylthiosemicarbazide and aniline. Wessel (172) attempted to prepare the material by the reaction of carbodiphenylimide ($C_6H_5N{=}C{=}NC_6H_5$) with phenylhydrazine, but obtained a substance having a melting point of 204°C., whereas the compound of Marchwald and Wolff (87) melted at 160°C. Pyrolysis of triphenylaminoguanidine at elevated temperatures led to the formation of ammonia, benzene, phenylhydrazine, and a white substance believed to be identical with Wessel's (172) product, since it melted at 201°C. Its composition, $C_{32}H_{28}N_6$, was believed to correspond to a pentaphenylaminobiguanide:



Pentaphenylaminobiguanide

3. Dithioureas and thiocarbonates

A concentrated solution of hydrazine hydrate reacts with aryldithiobiurets and yields an arylthiourea and thiosemicarbazide. However, Arndt (3) and Fromm, Bruck, Runkel, and Mayer (45) found that if dilute hydrazine hydrate solutions are used, hydrogen sulfide is liberated and two isomeric (aminoguanyl)arylthioureas are formed

$$ArNHC(=S)NHC(=NH)NHNH_2$$

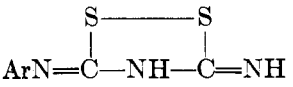
I

and

$$NH_2C(=S)NHC(=NAr)NHNH_2$$

II

I is basic and II acidic in nature. II appears to be the chief product of the reaction. Of the two isomers only I can be isolated readily in the form of well-defined salts. Thiurets (47)



are the basic oxidation products of the aryldithiobiurets discussed above. Fromm, Kayser, Brieglef, and Fohrenbach (48) studied the reaction of hydrazine with phenylthiuret and found that the initial reaction led to the formation of two isomeric (aminoguanyl) derivatives:

$$NH_2C(=S)NHC(=NC_6H_5)NHNH_2$$

III

and

$$C_6H_5NHC(=S)NHC(=NH)NHNH_2$$

IV

The (aminoguanyl)phenylthiourea (IV) appears to be the main product. Fromm and Vetter (49) and Fromm and Weller (50) studied the corresponding reaction with phenylhydrazine. Of the four isomers theoretically possible, it was shown that only two, V and VI, are formed:

$$C_6H_5NHC(=S)NHC(=NH)N(C_6H_5)NH_2$$

V

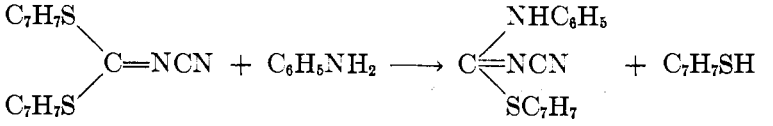
and

$$NH_2C(=S)NHC(=NC_6H_5)N(C_6H_5)NH_2$$

VI

Phenyl(aminoguanyl)phenylthiourea (V) was isolated (49) from the reaction mixture in crystalline form. Weller (50) prepared phenyl-(aminoguanyl)*p*-tolylthiourea by the reaction of phenylhydrazine on *p*-tolylthiuret.

Hantzsch and Wolvekamp (60) found that persulfocyanic acid reacts with benzyl chloride in the presence of potassium hydroxide and forms dibenzylcyanamidodithiocarbonate (VII). Subsequently, Fromm and Goncz (46) found that VII reacts with aniline to form α-phenyl-γ-benzyl-β-cyanoisothiourea (VIII):



VII VIII

This substance reacts with phenylhydrazine, and two isomeric cyano-(aminoguanido) derivatives (IX and X) are formed,

$$C_6H_5NHC(=NCN)NHNHC_6H_5$$

IX

and

$$C_6H_5NHC(=NCN)N(C_6H_5)NH_2$$

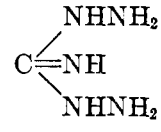
X

III. SYNTHESES OF CLOSELY RELATED COMPOUNDS

Diaminoguanidine and triaminoguanidine are closely related to aminoguanidine in properties and reactions, but they have not been so extensively studied. They are prepared by methods which involve both hydrazination and hydrazinolysis. Diaminoguanidine has also been prepared by the reduction of nitroaminoguanidine, and, only comparatively recently, by the hydrazination of the "dearrangement" products of nitroguanidine.

A. Diaminoguanidine

There are apparently only three general methods for the preparation of diaminoguanidine (α,γ-diaminoguanidine):

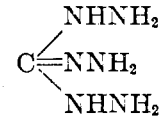


Diaminoguanidine

Stollé (139), Stollé and Hofmann (142), Pellizzari and Cantoni (100), and Pellizzari and Roncagliolio (105) prepared diaminoguanidinium chloride or bromide by allowing equimolecular proportions of cyanogen chloride or bromide to react with hydrazine in ethereal or aqueous solutions. The method was improved by Pellizzari and Gaiter (102). The isolation of diaminoguanidine from the reaction product of hydrazine hydrate and dicyandiamide (143) has been mentioned. The third method of preparation is the reduction of nitroaminoguanidine with zinc dust in a solution of acetic acid (107).

B. Triaminoguanidine

Stollé (138) first prepared triaminoguanidine



Triaminoguanidine

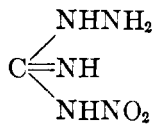
by the action of hydrazine hydrate on carbon tetrachloride at its boiling point and later (143) isolated the substance from the reaction products of hydrazine hydrate and dicyandiamide. Pellizzari and Gaiter (102) found that diaminoguanidine, aminoguanidine, or guanidine reacting with 1, 2, or 3 moles of hydrazine hydrate, respectively, gave triaminoguanidine. The reaction took place with ease in water or alcohol on heating from 2 to 5 hr. Schotte (128), in 1926, obtained a patent on the preparation of triaminoguanidine and its derivatives by treating isothiourea ethers with an excess of hydrazine or its derivatives. Prandtl and Dollfus (113) found that in aqueous solution dichloroformoxime, $Cl_2C{=}NOH$, is reduced by hydrazine to hydrocyanic acid. However, if an ethereal solution of dichloroformoxime is added, while cooling, to an ether emulsion of hydrazine hydrate, triaminoguanidine is readily formed. They explained its formation by the intermediate decomposition of dichloroformoxime to chloroformyl-nitrile oxide (chlorine isocyanate), $ClC{\equiv}NO$, which is subsequently converted to cyanogen chloride. In the presence of excess hydrazine, this forms triaminoguanidine. An alternative and more reasonable mechanism, which was suggested by one of the reviewers of this paper, may be formulated as follows:

$$Cl_2C{=}NOH + N_2H_4 \longrightarrow NH_2OH + Cl_2C{=}N_2H_2$$

$$Cl_2C{=}N_2H_2 + 2N_2H_4 \longrightarrow C(N_2H_3)_2{=}N_2H_2 + 2HCl$$

C. Nitroaminoguanidine

Phillips and Williams (107) found that hydrazine sulfate reacts with nitroguanidine to form nitroaminoguanidine



Nitroaminoguanidine

and gave as proof of its structure the reduction to the known derivative diaminoguanidine, as well as its ability to form derivatives with aldehydes and ketones (133, 173). The ultraviolet absorption of aqueous solutions of nitroaminoguanidine has recently been examined (119).

IV. REACTIONS OF AMINOGUANIDINE

The properties and reactions of aminoguanidine are profoundly different from those of guanidine. In fact, many of the properties of this substance are more nearly like those of hydrazine than those of guanidine, and aminoguanidine may be regarded as a substituted hydrazine,—guanylhydrazine. On the other hand, the guanyl group modifies the properties of hydrazine, especially in regard to basic properties, since aminoguanidine is a stronger base than hydrazine. We have no information in regard to the dearrangement of the compound. The mechanisms of some of the simpler conversions and transformations of aminoguanidine have not been definitely established.

The products of the reactions of aminoguanidine and some of its derivatives with carbonyl compounds have been studied rather extensively. Nitroaminoguanidine is potentially of importance in organic analysis as a reagent for the identification of aldehydes and ketones. Aminoguanidine and its other derivatives have not been investigated from this point of view, but some of these compounds should prove useful.

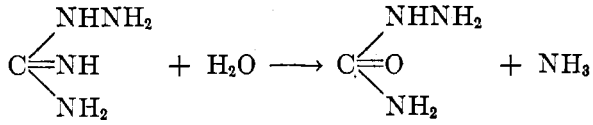
The hydrolytic reactions of aminoguanidine are of interest, but our knowledge of these reactions, particularly the reactions of the "free base," is quite fragmentary. Much the same situation exists in regard to the oxidation reactions of aminoguanidine. No physicochemical studies are recorded concerning reactions of these two types.[3]

Nitrous acid reacts with aminoguanidine, and the products formed are of great interest to workers in nitrogen chemistry. It has taken fully a quarter of a century to establish the structures of these products, and a number of investigators have contributed to these studies. We have attempted to systematize the known facts regarding the reactions of aminoguanidine with nitrous acid under different conditions.

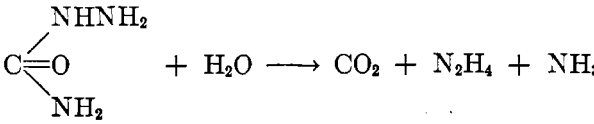
A. Hydrolytic reactions

Thiele (147) found that the hydrolysis of aminoguanidine proceeds in two stages: semicarbazide is formed in the first stage, and further hydrolysis yields hydrazine, ammonia, and carbon dioxide. The presence of semicarbazide was established by the preparation of benzaldehyde semicarbazone. This compound was identical with the product formed from the reaction of benzaldehyde, potassium cyanate, and hydrazine (23). The hydrolytic reaction of aminoguanidine may be formulated as follows:

[3] Charles Hahn, working in this laboratory, has measured the oxidation potential of the nitrosoaminoguanidine system. The system is reversible in both the acid and the alkaline region. These results will be published in the near future (see Charles Hahn: Thesis, M.S. in Chemistry, Polytechnic Institute of Brooklyn, June, 1938).



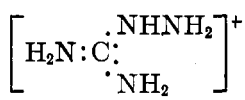
(I)



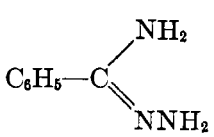
(II)

The intermediate semicarbazide was obtained in large quantities when the hydrolysis was effected with sodium carbonate instead of sodium hydroxide.

Lieber and Smith (80) have studied, quantitatively, the hydrolysis of aminoguanidine in acid and basic media. They found that, contrary to the opinions expressed in the literature (83), aminoguanidine is extremely resistant to acid hydrolysis. In dilute solutions of strong mineral acid aminoguanidine and semicarbazide were found to be resistant to hydrolysis, but in solutions of higher concentrations semicarbazide was nearly completely hydrolyzed in times and under conditions such that aminoguanidine was only slightly hydrolyzed. This is probably attributable to the strong basic properties of aminoguanidine in contrast to the weak basic properties of semicarbazide. Also, the aminoguanidinium ion probably has the following structure:[4]

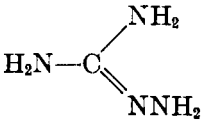


Thiele (147) attempted to prepare free aminoguanidine by precipitation of barium sulfate from a solution of aminoguanidinium sulfate with the stoichiometrical quantity of barium hydroxide. He found that the solution so obtained gradually turned reddish in the air, and, when evaporated *in vacuo*, left behind a red, crystalline material having basic properties. He did not analyze the material. In 1897 Pinner (109) found that an excess of hydrazine reacted with benzimido esters and yielded 3,6-diphenyl-1,2-dihydrotetrazine. He assumed that the following substance

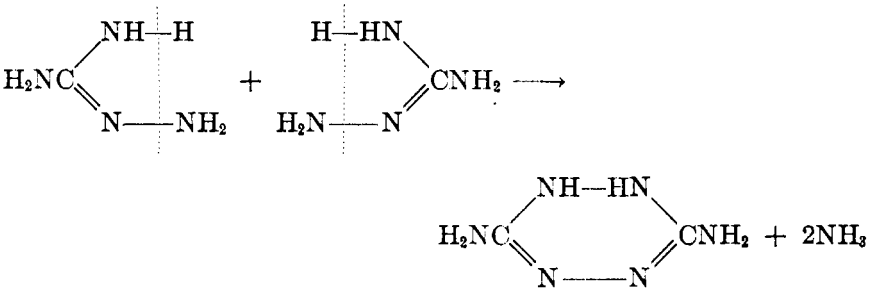


[4] See also Davis, Yelland, and Ma: J. Am. Chem. Soc. **59**, 1993 (1937).

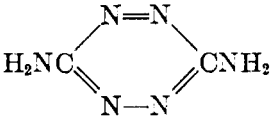
was its precursor. Ponzio and Gastaldi (110), in 1913, reasoning from the facts found by Pinner, argued that aminoguanidine, since it could also assume the form



should therefore be expected to undergo the following reaction:



and form 3,6-diamino-1,2-dihydrotetrazine. They found that if the substance was formed, it was immediately oxidized to *s*-diaminotetrazine:

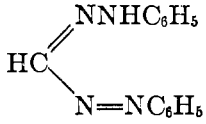


s-Diaminotetrazine

A solution of aminoguanidinium chloride, when treated with a stoichiometrical amount of a solution of potassium hydroxide and evaporated slowly over concentrated sulfuric acid, yielded reddish violet prisms with a metallic luster. This product was slightly soluble in water and gave an intense red-violet solution, from which the original product could be recrystallized if a small amount of ammonia was present. This material is fairly stable in alkaline solution, but on boiling ammonia is evolved. In acidic solutions it forms reddish orange solutions which are decolorized by heating, and on prolonged boiling nitrogen, ammonia, carbon dioxide, and hydrazine are formed. Orange crystalline salts of this material are formed. In later work Ponzio and Gastaldi (111) established the structure of *s*-diaminotetrazine through a study of its reduction products.

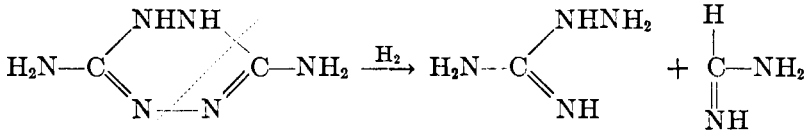
When *s*-diaminotetrazine was suspended in water and treated with hydrogen sulfide, it dissolved and sulfur was precipitated. The presence of aminoguanidine in the solution was established by its isolation as

benzaldehyde guanylhydrazone. Phenylhydrazine reduced *s*-diaminotetrazine in an alcoholic solution of acetic acid, and, when gas evolution ceaséd, diphenylformazyl hydride



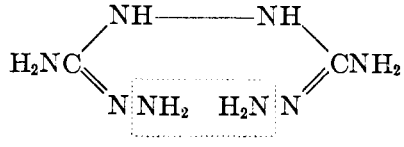
Diphenylformazyl hydride

was isolated. The mechanism of this reduction may be formulated as follows:



A B C

Continued reduction of A yields B, and the unstable ammonoformic acid (C) is hydrolyzed, giving formic acid and ammonia. The formic acid reacts with phenylhydrazine, and formylphenylhydrazine, $C_6H_5NHNHCHO$, is formed. This compound in turn reacts with the excess of phenylhydrazine and yields $C_6H_5NHNHCH{=}NNHC_6H_5$, the phenylhydrazone of formylphenylhydrazine. This substance is readily oxidized to the "formazyl" derivatives. In 1915 Ponzio and Gastaldi (112) were able to show that *s*-diaminotetrazine is obtained by the mild pyrolysis of aminoguanidinium bicarbonate. This probably accounts for the variation of the melting point of aminoguanidinium bicarbonate with the rate of heating, as found by Thiele (151). Ponzio and Gastaldi (110) suggested the following mechanism for the formation of *s*-diaminotetrazine: a small quantity of aminoguanidine decomposes to form hydrazine. Subsequently the hydrazine combines with aminoguanidine to form "hydrazinodicarbohydrazine."



The substance undergoes ring closure, through loss of hydrazine, to form *s*-diaminotetrazine.

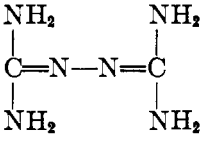
The hydrolysis of diaminoguanidine and of triaminoguanidine does not appear to have been studied. Gaiter (52) found that *s*-tetrabenzoyldiaminoguanidine on hydrolysis yields *s*-dibenzoylhydrazine and ammonia.

B. Oxidation reactions

Thiele (147) oxidized aminoguanidinium nitrate in dilute nitric acid with a solution of potassium permanganate and obtained a yellow basic substance of the composition $C_2H_6N_6$. This material was isolated as the nitrate. On hydrolysis with water, this nitrate yielded ammonium nitrate and an orange-yellow neutral compound, $C_2H_4N_4O_2$. On reduction $C_2H_4N_4O_2$ was converted to a colorless, neutral compound of the composition $C_2H_6N_4O_2$. This latter substance was $H_2NCONHNHCONH_2$, hydrazodicarbamide, since it was identical with the product obtained from the reaction of 2 moles of potassium cyanate with hydrazine sulfate. The base $C_2H_6N_6$ on reduction gave another base, $C_2H_8N_6$, and Thiele (147) therefore assigned the following structure to the oxidation product, $C_2H_6N_6$,

$$H_2NC(=NH)N=NC(=NH)NH_2$$

and called it "azodicarbamidine." Thiele (147) argued that if aminoguanidine possessed the symmetrical structure, then a base of the composition $C_2H_6N_6$ could not be formed, but would have the following composition and structure:



Thiele argued, also, that azodicarbamidine could not be formed from the guanidine, possibly resulting from the oxidation of aminoguanidine, because guanidine was not oxidized under conditions which readily led to the oxidation of aminoguanidine. Hydrolysis of azodicarbamide in the presence of hydrochloric acid yields carbon dioxide, nitrogen, and hydrazodicarbamide. This latter substance is also obtained by the reduction of azodicarbamide, as stated previously. Thiele believed that the hydrolysis of azodicarbamide resulted in the formation of ammonia, carbon dioxide, and diimide. Diimide in turn reduced azodicarbamide to hydrazodicarbamide and was itself oxidized to nitrogen.

$$H_2NCON=NCONH_2 + 2H_2O \longrightarrow 2NH_3 + N_2H_2 + CO_2$$

$$H_2NCON=NCONH_2 + N_2H_2 \longrightarrow H_2NCONHNHCONH_2 + N_2$$

Thiele (148) attempted to isolate diimide, but was able to obtain only hydrazine and nitrogen. He believed that diimide reacted with itself as follows:

$$2N_2H_2 \longrightarrow N_2H_4 + N_2$$

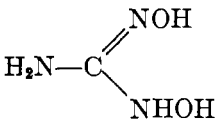
No systematic investigation of the oxidation of aminoguanidine has been recorded.

Triphenylaminoguanidine turns to a red color on standing in air. Marchwald and Wolff (87) have shown this to be due to the formation of an azo derivative:

$$C_6H_5NHC(=NC_6H_5)N=NC_6H_5$$

They isolated this substance as red needles with a metallic luster by oxidation of triphenylaminoguanidine with mercuric oxide. Hence triphenylaminoguanidine probably only exists in the unsymmetrical form as indicated by the formation of the azo derivative by oxidation. A number of other investigators have observed similar oxidation products of the derivatives of amino- and diamino-guanidines, but they have not established the constitutions of the substances so obtained. Gaiter (52) observed that *m*-nitrobenzylidenediaminoguanidinium bromide gradually turns to a red substance in the presence of light and air, and Pellizzari and Gaiter (102) found that dibenzylidenediaminoguanidinium nitrate becomes intensely red on exposure to light.

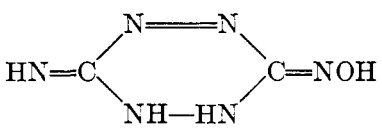
In 1905 Wieland (174) prepared dihydroxyguanidine



in the form of the hydrobromide, from cyanogen bromide and hydroxylamine in methyl alcohol. The material is stable to acids, but alkalies convert it into a deep red substance which had the constitution

$$H_2NC(=NOH)N=NC(=NOH)NH_2$$

Its relationship to azodicarbamidine, the initial product of the oxidation of aminoguanidine by acid permanganate, is clearly evident. By continued boiling with dilute acid Wieland and Bauer (175) were able to convert the azo compound to a tetrazine, "isonitrosodihydrotetrazine,"



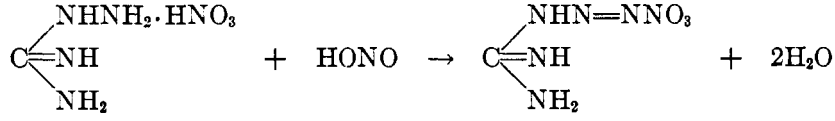
which is closely related to *s*-diaminotetrazine (110), the hydrolytic-oxidative product of free aminoguanidine.

C. Reactions of aminoguanidine with nitrous acid

The products formed by the action of nitrous acid on aminoguanidine are dependent entirely upon the conditions under which the reaction is carried out. In general, aminoguanidine reacts with nitrous acid in three ways: (*1*) If the reaction is carried out in a solution of a strong mineral acid, guanyl azide is formed; (*2*) if in aqueous solution alone, aminoguanidine and sodium nitrite form 1-guanyl-4-nitrosoaminoguanyltetrazene; and (*3*) if in a solution of acetic acid, ditetrazolyltriazene results. Of these substances guanyl azide has been the most intensively studied, and we shall discuss its formation and reactions first.

1. Formation and reactions of guanyl azide

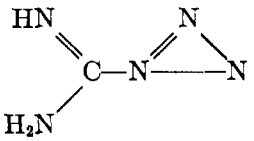
Thiele (147) was the first to prepare guanyl azide as the nitrate, but he believed that the compound was "diazoguanidine nitrate." He came to this conclusion because he considered that the reaction between nitrous acid and aminoguanidine in a solution of a strong mineral acid was a diazotization reaction and should therefore yield a diazo compound.[5] Thiele believed that the following reaction took place when aminoguanidinium nitrate, dissolved in nitric acid, was treated with sodium nitrite:



The properties of the resulting compound, however, were unusual for a diazonium compound. The substance does not decompose, even when the solution is heated; it does not give off nitrogen even if the solution is boiled; and hydrolysis with a strong alkali gives the corresponding salt of hydrazoic acid. The salts of guanyl azide have an acid reaction, but a diazonium salt with so positive a group as the guanidine residue would be expected to be neutral. The substance is not detonated by shock; on heating it undergoes rapid decomposition with evolution of light and heat but does not detonate. In spite of this strong experimental evidence, Thiele believed this substance to be a true diazoamino derivative containing the group, —NH—N=N—.

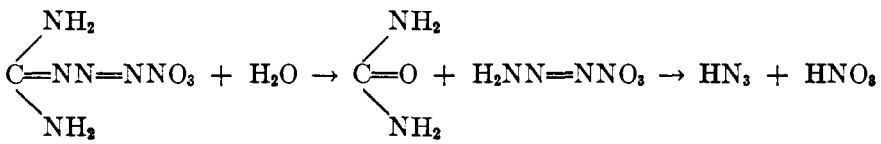
[5] The formation of guanyl azide from aminoguanidine and nitrous acid is in harmony with the view of Browne and Wilcoxon (J. Am. Chem. Soc. **48**, 683 (1936)) that hydrazoic acid may be considered a hydrazinonitrous acid, i.e., a nitrous acid of the hydrazine system. Accordingly, the reaction of nitrous acid with aminoguanidine (a hydrazinoammonocarbonic acid) is an instance of hydrazinolysis of aquonitrous acid. See also reference 41.

Alkaline hydrolysis of guanyl azide leads to the formation of hydrazoic acid (6). Thiele (147) postulated the formation of guanyl azide



Guanyl azide

as an intermediate compound and considered that its decomposition into hydrazoic acid and cyanamide was favored by the tendency of the hydrazoic acid to form salts. Thiele (147) considered that the intermediate compound "guanyl azide" (triazoguanyl) (61) was only a hypothetical product. He also reasoned that if aminoguanidine possessed the symmetrical structure, then the decomposition of the diazoguanidine would form urea instead of cyanamide, but this was not observed.



The formation of hydrazoic acid from guanyl azide certainly is one of the most interesting transformations of aminoguanidine, and Thiele (146) obtained a patent for this process. He showed that it was not necessary to isolate guanyl azide, but that if the solution obtained by the treatment of an aminoguanidinium nitrate with nitrous acid was refluxed with a solution of sodium hydroxide and then acidified, the hydrazoic acid could be separated by distillation in very high yields. Hydrolysis of guanyl azide with ammoniacal silver yields hydrazoic acid and cyanamide, even in cold solution, but ammonium hydroxide yields a new acid of the composition, CH_3N_5, which proved to be 5-aminotetrazole (*vide infra*).

Thiele's (147) so-called "diazoguanidine" of 1892 was reëxamined by Hantzsch and Vagt (59) in 1901, who showed that it was not a diazo compound at all but an azide. The fact that it formed a salt was merely due to the presence of the unmodified amino group in the guanidine

$$[N_3C(=NH)NH_2H]NO_3$$

XVI

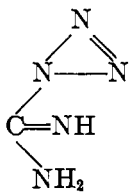
XVI is then the nitrate of carbamideimideazide, or, as recently termed by Hart (61), a nitrate of guanyl azide. The diazoguanidine cyanide (*vide infra*) of Thiele and Osborne (160) appears to favor Thiele's original view, but Hantzsch and Vagt (59) showed that other similar compounds, espe-

cially carbamyl azide, behaved in the same way. They found also that 5-aminotetrazole can be formed from hydrazoic acid and cyanamide. Accordingly, formation of this substance from Thiele's diazoguanidine, or guanyl azide, may be represented as follows:

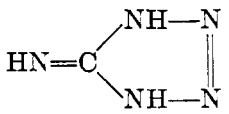
5-Aminotetrazole

Hantzsch and Vagt (59) further demonstrated that almost a complete analogy existed between the properties of guanyl azide and those of carbamyl azide, the only exception being that the latter does not form a tetrazole ring.

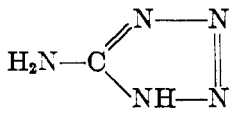
The action of solutions of weak bases (ammonium hydroxide, for example) or of solutions of weak acids on guanyl azide resulted in ring closure, perhaps a hydrolytic reaction; a new compound, CH_3N_5 (a monobasic acid), was formed. Thiele (147) gave the name "aminotetrazoic acid" to this substance, since it would form salts with barium, sodium, and silver.



XI



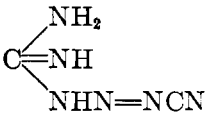
XII



XIII

Thiele at once rejected formula XI, because of the properties of the new compound. Nitrous acid converted it into a material which could not be isolated because of its explosive properties. It was a diazonium compound, however, because it coupled with dimethylaniline or β-naphthylamine to form definite azo compounds. On this basis Thiele rejected formula XII. Substances having the ring CN_4 had been prepared, and their properties had been described previously by Lossen (82) and Bladin (9). Because of the analogous behavior of CH_3N_5, Thiele (147) assigned formula XIII as representing the constitution for "aminotetrazolic acid" and termed its formation an "intramolecular diazoamino condensation." On this basis, therefore, the modern name would be 5-aminotetrazole. Potassium cyanide, "diazoguanidine nitrate," or guanyl azide react and

form a substance to which Thiele and Osborne (160, 161) assigned the formula



and which they called diazoguanidine cyanide. As the compound contains the chain N—N=N, it is the *first representative of an aliphatic diazoamino compound.* It may also be considered as a substitution product of the hypothetical $HN{=}N{-}NH_2$, "triazene." Denoting the group, $HN{=}\overset{|}{C}{-}NH_2$, as "aminoiminomethyl," Thiele and Osborne (161) accordingly named the compound "aminoiminomethylcyantriazene," but we shall refer to it by the modern name (1-guanyl-3-cyanotriazene). A number of reactions which are characteristic of the cyano group led to the formation of a whole series of substituted triazenes.

Mild hydrolysis in acidic solution converts the cyano group to the carbamyl group, $-CONH_2$, and accordingly yields "aminoiminomethyltriazenecarbamide" (1-guanyl-3-carbamyltriazene)

$$H_2NC(=NH)NHN=NCONH_2$$

Hydroxylamine converts this compound into a "triazenedicarbamidinamidoxime" or 1-guanyl-3-amidoximetriazene:

$$H_2NC(=NH)NHN=NC(=NOH)NH_2$$

This substance, on warming with water, is converted into 5-aminotetrazole and a very hygroscopic substance, which was not further identified (2). An imino-ether (a mixed ammonoaquo ester) is formed by the action of alcohol in an acidic solution,

$$H_2NC(=NH)NHN=NC(=NH)OC_2H_5$$

and this ester is hydrolyzed in the presence of hydrochloric acid, yielding an ester:

$$H_2NC(=NH)NHN=NCOOC_2H_5$$

The imino-ether is ammonolyzed to an amidine, "triazenedicarbondiamidine" or 1,3-diguanyltriazene:

$$H_2NC(=NH)NHN=NC(=NH)NH_2$$

The aliphatic diazoamino compounds prepared as described above are yellow crystalline materials. With acids they form well-characterized salts which are nearly all white and very soluble in water. The solutions

of these salts give an acidic reaction, indicating thus that the compounds are salts of weak bases. On heating the aqueous solutions of the salts, decomposition with evolution of nitrogen results. An alkaline solution of ferrous salts gives to the solutions an intense reddish violet to a red-brown color, which is quickly destroyed by oxidation in air. The melting points of these compounds are of no significance since the compounds explode, especially in a confined tube, and the temperature of their decomposition by detonation depends upon the rate of heating. They resemble the aromatic diazoamino compounds in giving off two-thirds of the triazene nitrogen on being heated with dilute acids, but they differ from them (*1*) in being decomposed by alkalies to which the aromatic compounds are unreactive, and (*2*) in being unaffected by cold concentrated acids.

Thiele and Osborne (162) also succeeded in reducing these triazenes to triazanes, i.e., hydrazoamino compounds. Like so many substances with doubly linked nitrogen, the triazenes react with sulfurous acid and form the sulfonic acids of the reduced compounds. Since the products no longer behave as a diazoamino substance, the reduction must have taken place in the triazene group. Therefore the question to be answered is whether the SO_3H group goes to the 2- or the 3-position, i.e., whether the product is

$$H_2NC(=NH)NHNHN(SO_3H)CONH_2$$

XIV

or

$$H_2NC(=NH)NHN(SO_3H)NHCONH_2$$

XV

If the resulting substance were XIV, it would be readily oxidized to a diazoamino derivative; it is, however, not easily oxidized and therefore must be XV. All attempts to replace the SO_3H group with hydrogen failed. If the substance is heated with acids, sulfuric acid is formed, but the triazane which must be produced decomposes and nitrogen, carbon monoxide, guanidine, and other products are formed.

$$NH_2C(=NH)NHNNHCONH_2 \quad (SO_3H) + H_2O \rightarrow$$

$$NH_2C(=NH)NHNHNHCONH_2 \rightarrow C(=NH)(NH_2)(NH_2) + N_2 + NH_3 + CO$$

Attempts were also made to reduce the diazoamino compounds directly. Under ordinary circumstances this gives, as it does in the aromatic series, an amine and a substituted hydrazine. But when the substance was carefully reduced with zinc dust and ammonium chloride, a colorless solution was obtained which gave no reaction for the triazene. The product must contain the nitrogen chain, since on oxidation the diazoamino compound is re-formed. The solution has strong reducing properties, and on warming readily decomposes into the same substances as are obtained by removing sulfuric acid from the sulfonic acid (XV). Thiele and Osborne (162) concluded, therefore, that in both cases the true triazane derivative

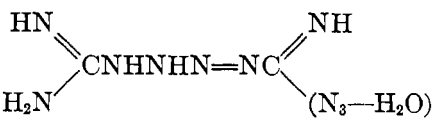
$$H_2NC(=NH)NHNHNHCONH_2$$

is formed, but that it is too unstable to be isolated. This instability of this substance makes it seem unlikely that any attempts to prepare free triazane, H_2NNHNH_2, will be successful.

2. Formation and properties of 1-guanyl-4-nitrosoaminoguanylisotetrazene

The versatility of aminoguanidine is abundantly demonstrated by the different products which it forms with nitrous acid. We have already discussed the formation of guanyl azide in a solution of a strong acid. If sodium nitrite is allowed to react with aminoguanidinium nitrate, in aqueous solution only, for 6 to 7 days at a temperature of 0°–10°C., a very different reaction product results. This product is a white crystalline compound of the composition $C_2H_7N_{10}OH$ (70). Investigations have established it as being 1-guanyl-4-nitrosoaminoguanylisotetrazene. Hofmann and Roth (70) found that the compound formed salts which were readily hydrolyzed, and that these salts were often extremely explosive; this was true particularly of the perchlorate. Four atoms of nitrogen are liberated when an aqueous solution of the compound is heated to the boiling temperature. This indicates that two diazo groups are present, one of which probably bridges the two carbon atoms as a diazoamino chain, while the other exists as an isodiazohydrate group.

Further investigation by Hofmann, Hock, and Roth (69) indicated that the probable constitution was as follows:



The nitrogen bridge between the carbon atoms comprises a diazohydrazo or *as*-tetrazene ("buzylene") group, and the compound is a substituted

isotetrazene. The radical (N_3—H_2O) was believed to be present either as a free nitrosoamino

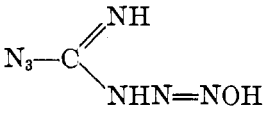
—NH—NH—NO

or as an antidiazohydrate group

—NH—N=N—OH

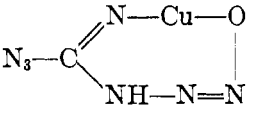
For these reasons they called the substance "guanylnitrosoaminoguanyltetrazene" or "guanyldiazoguanyltetrazene." The substance was found to be unattacked by concentrated aqueous ammonia at ordinary temperature. It is not reactive with aqueous solutions of potassium cyanide (10 per cent) or mineral acids of the same concentration. It is neutral to litmus, and with α- and β-naphthols it yields brownish to yellowish red products. It forms salts rather slowly, and therefore it was regarded as a pseudo base.

Evidence for the constitution of guanyldiazoguanyltetrazene was obtained by submitting it to alkaline hydrolysis and making a comparison of the products with those obtained from the alkaline hydrolysis of a tetrazene (hippurylphenylbuzylene) previously discovered by Curtius (22). The products obtained from guanyldiazoguanyltetrazene on hydrolysis with aqueous sodium hydroxide were ammonia, cyanamide, and triazonitrosoaminoguanidine:

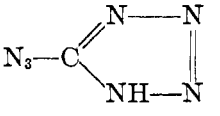


Triazonitrosoaminoguanidine

This substance could be obtained only in the form of the copper salt,



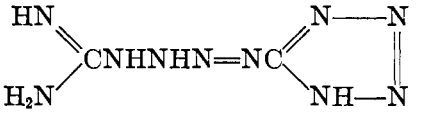
On acidification, triazonitrosoaminoguanidine was converted into tetrazolyl azide (5-azidotetrazole).



5-Azidotetrazole

This substance was described previously by Thiele and Ingle (157). In order to demonstrate (69) that the guanyldiazoguanyltetrazene, $C_2N_{10}H_8O$,

contains no tetrazole ring, an *as*-guanyltetrazolyltetrazene was prepared from aminoguanidine and diazotized 5-aminotetrazole in acetic acid solution:



as-Guanyltetrazolyltetrazene

While this substance gave the same products on alkaline hydrolysis, it differed so markedly in other physical and chemical properties from guanyldiazoguanyltetrazene, that there was no doubt that the tetrazole ring was absent from this latter substance. It is of interest to note that Thiele (147), in his early studies, had already obtained the guanyltetrazolyltetrazene, but he was not able to establish its constitution.

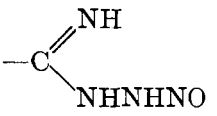
Hofmann, Hock, and Kirmreuther (68) continued the study of the structure of guanyldiazoguanyltetrazene, since the exact structure of the (N_3—H_2O) radical was still not established. The evidence (69, 70) that it did not contain a tetrazole ring has been described. The question to be answered was, "Is the radical (—C(=NH)$N_3 \cdot H_2O$) a hydrate of an azide?" These investigators found that the substance did not lose weight on drying in a vacuum over phosphorus pentoxide and that it formed salts without additional water of hydration even from aqueous solutions. It was therefore concluded that the substance did not contain water of crystallization. The following reaction characteristic of the azido group was used in testing for the presence of the azide radical:

$$RN_3 + 2HI \rightarrow N_2 + RNH_2 + I_2$$

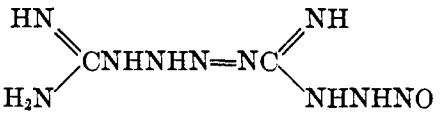
It was found that the substance $C_2H_8N_{10}O$ formed a salt of the composition $C_2H_7N_{10}I$, and the original substance could be obtained by treating the salt with aqueous ammonia or a solution of sodium acetate. The azide group was therefore absent. From the previous work it was known that the salt formation occurred through an oxygen base rather than an amino-basic linkage. Thus, for example, an excess of silver nitrate gives the salt

$$C_2H_7N_{10}OAg \cdot AgNO_3 \cdot 3H_2O$$

suggestive of the isodiazotate group. The evidence was, therefore, conclusive that the radical (N_3—H_2O) is a β-nitrosohydrazine

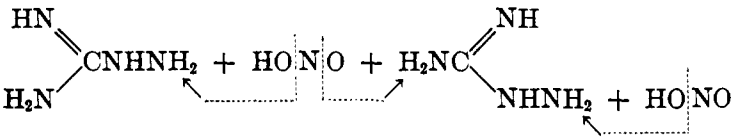


The β-position for the nitroso group is indicated by the conversion of this group to a tetrazole ring (69). The structure of guanyldiazoguanyltetrazene is, therefore, as follows:



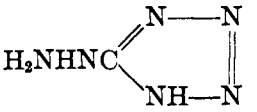
Guanyldiazoguanyltetrazene

The mechanism of its formation is indicated below:



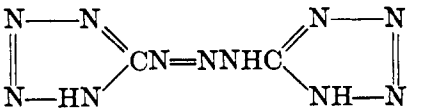
3. Formation and properties of 1,3-ditetrazolyltriazene

Hofmann and Hock (66) investigated the action of aminoguanidinium nitrate and sodium nitrate in an aqueous solution of acetic acid and found that 1,3-ditetrazolyltriazene was formed. This substance had the empirical composition, $C_2H_8N_{11}$, and was obtained in the form of almost colorless, lustrous, thin, doubly refractive plates, containing one molecule of water of crystallization. It possessed well-marked acidic properties and could be titrated to secondary salts in the presence of indicators. When boiled with dilute acids, it formed nitrogen and 5-aminotetrazole. In the presence of alkali, it gave a golden-yellow solution with β-naphthol. In dilute sulfuric acid it combined with seven atoms of oxygen from potassium permanganate. Since reduction with zinc and hydrochloric acid gave 5-aminotetrazole and tetrazolylhydrazine (5-hydrazinotetrazole)



5-Hydrazinotetrazole

the structure was concluded to be the following:



1,3-Ditetrazolyltriazene

Its formation was explained as follows: Under the environmental conditions of the reaction medium, the aminoguanidine is converted into

Thiele's (147) "guanyl azide" which, in turn, is immediately isomerized into 5-aminotetrazole. This is subsequently diazotized in part and then

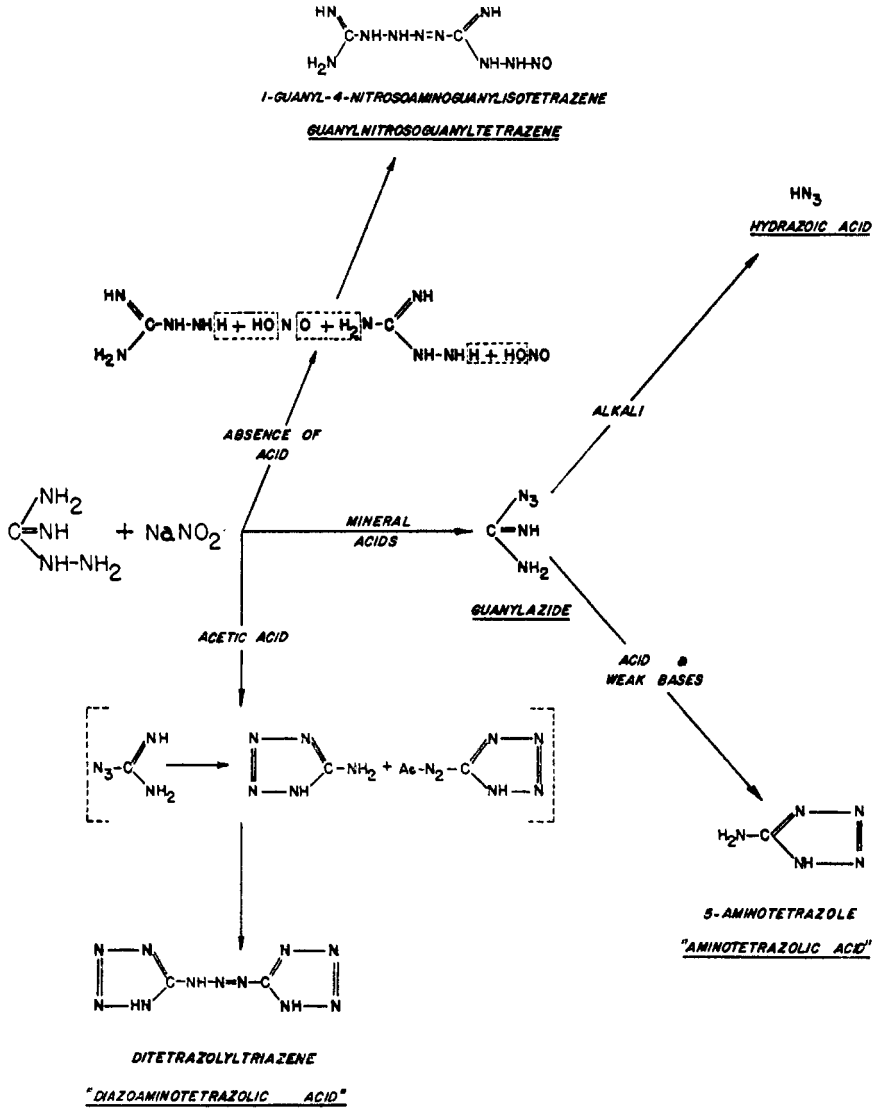


FIG. 1. Schematic summary of the reactions between aminoguanidine and nitrous acid

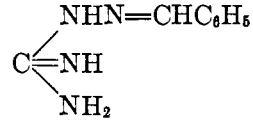
coupled with the remainder to form the very slightly soluble primary sodium salt of the 1,3-ditetrazolyltriazene.

4. Summary of the reactions between aminoguanidine and nitrous acid

The researches of Thiele (147), Hantzsch (59), and Hofmann (66, 68, 69, 70) on the reaction of aminoguanidine with sodium nitrite may be summarized as follows: (*1*) In the absence of acids guanyldiazoguanyltetrazene is formed. (*2*) In the presence of mineral acids guanyl azide is formed, which may be converted by alkali to hydrazoic acid or isomerized to aminotetrazolic acid by acids or weak alkalies. (*3*) With acetic acid diazoaminotetrazolic acid is formed.

D. Reaction with carbonyl compounds without ring formation

As a substituted hydrazine, aminoguanidine is capable of combining with aldehydes and ketones with elimination of water. Thiele (147) prepared the first compound of this type, the benzaldehyde derivative,



Benzaldehyde guanylhydrazone

by treating an aminoguanidine salt with benzaldehyde in a concentrated solution of potassium hydroxide. The guanylhydrazone separates as pearly leaflets, readily recrystallizable from toluene and having a melting point of 178°C. Thiele and Bihan (154) found later that the condensation with carbonyl derivatives took place much better in acid media. The aminoguanidine salt is treated with an aqueous or alcoholic solution of the carbonyl compound to which has been added a few drops of a mineral acid and the salt of the condensation product separates in very pure form.

Wolff (177, 178) studied the application of aminoguanidine to the formation of guanylhydrazones of the sugars. From galactose and glucose beautiful crystalline condensation products were obtained. Baeyer (8) made several terpene derivatives and isolated the picrates of the guanylhydrazones.

Thiele and Dralle (155) studied a number of condensation products of aminoguanidine with aldehydes and ketones of the aliphatic series. With monochloro- and trichloro-aldehydes the normal hydrazones were first obtained,

$$ClCH_2CH{=}NNHC(=NH)NH_2$$

and

$$Cl_3CCH{=}NNHC(=NH)NH_2$$

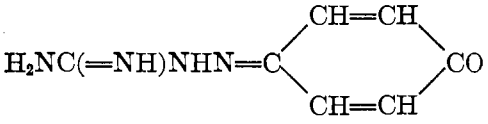
which were unstable. The trichloro product was easily converted, with loss of hydrogen chloride, into the guanylhydrazone of glyoxylic acid:

$$HOOCCH{=}NNHC(=NH)NH_2$$

α-Diketones and similar compounds were found to yield only osazones. The formation of monohydrazones with closure to six-membered rings was not observed in the aliphatic series.

Thiele and Bihan (154) studied the condensation of aminoguanidine with some aromatic aldehydes and ketones. The *o*- and *p*-hydroxybenzaldehydes and the three nitrobenzaldehyde derivatives were prepared. All these compounds exhibited properties similar to those of benzalaminoguanidine. The nitrobenzalaminoguanidines, beautiful red to yellow crystals, were found to be very strong bases. It is interesting to note that the *o*- and *p*-nitrobenzalaminoguanidines could be made by the nitration of benzalaminoguanidine.

In 1898 Thiele and Barlow (153) reported on a detailed study of the condensation of aminoguanidine with quinones. The condensation takes place readily in the presence of a trace of nitric acid. Intensively colored nitrates are formed, from which the yellow to red bases are readily isolated.



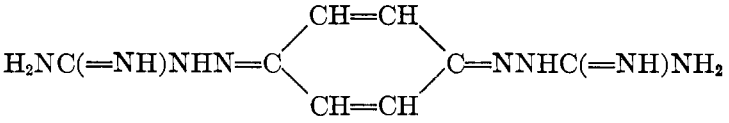
XVII

These compounds appear to exist in a tautomeric form as hydroxyazo derivatives (XVIII):

$$H_2NC(=NH)N{=}NC_6H_4OH$$

XVIII

Benzoquinone guanylhydrazone, on treatment with an additional mole of aminoguanidine salt, is easily converted into quinonebisaminoguanidine,



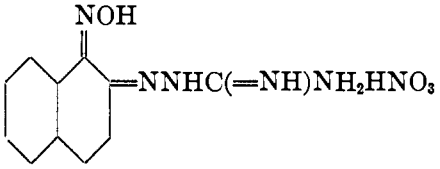
Quinonebisaminoguanidine

giving evidence for the existence of the quinone form (XVII). On reduction, both the mono- and di-derivatives are converted into guanylphenyl-

hydrazines. Benzoquinone guanylhydrazone yields 1-guanyl-2-(*p*-hydroxyphenyl)hydrazine,

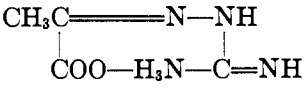
$$H_2NC(=NH)NHNHC_6H_4OH$$

which on oxidation is readily converted back to the original substance. α-Naphthoquinone was found to behave in an analogous manner to quinone. β-Naphthoquinone, however, yielded only a mono-derivative which could be distinguished from the α-quinone by its insolubility in alkali. On alkaline hydrolysis, β-naphthoquinone guanylhydrazone yields α-naphthol, indicating that the aminoguanidine residue is combined with the β-carbon atom. Quinone monoöximes were found to condense with aminoguanidine to yield very unstable derivatives. Nitroso-β-naphthol formed a well-characterized nitrate of nitroso-β-naphthol guanylhydrazone.

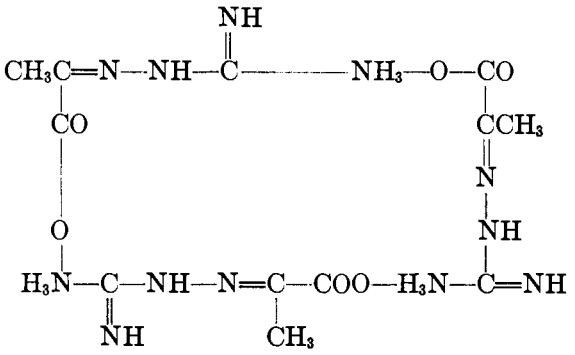


Hydrolysis in boiling water yields ammonium nitrate and a substance of the composition $C_{11}H_8N_4O$, having both acid and basic properties and forming well-crystallized salts with acids. Reduction forms a new compound of the composition $C_{11}H_8N_4$, which is only basic. No structures were given for these substances.

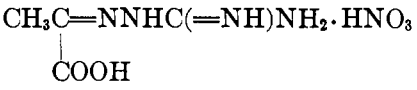
Following the pioneering work of Thiele and his students, many investigators have utilized this property of aminoguanidine for the preparation of derivatives of a large variety of substances. Doebner and Gartner (34) describe the aminoguanidine derivative of glyoxylic acid and Stoermer (137) that of phenoxyacetone; aminoguanidine derivatives have been prepared by Steinkopf and Schubart (134) for thienyl ketones, by Müller (89) for pyrrolealdehydes in a study of the constitution of the bile acids, by Rojahn and Trieloff (124) for triazolealdehydes, by Rojahn and Kühling (121) for pyrazolealdehydes, by Rojahn and Schulten (123) for thiophenealdehydes, by Rojahn and Rühl (122) for a cyclopentanone derivative, by Conard and Shriner (20) for *p*-dimethylaminobenzaldehyde, and by Degiorgi (31) for fluorenone and nitrofluorenone. Wedekind's (170) investigation of the aminoguanidine condensation product with pyruvic acid is of considerable interest. The free base was assumed to be an inner salt:



However, molecular weight determinations indicated a polymeric substance corresponding to a trimer, which was assumed to have the constitution:



The polymeric product is regenerated by mineral acids. On gentle warming with nitric acid, the normal salt



is formed with all its original properties. The condensation product forms salts in alkaline solution. By double decomposition of the ammonium salt with silver nitrate, an explosive silver salt is formed, containing silver atoms both in the carboxyl and hydrazine portions of the molecule.

The substituted aminoguanidines also form well-characterized derivatives with aldehydes and ketones. Busch and Bauer (16) describe a number of such derivatives of their diarylaminoguanidines. A very complete study of the condensation of diarylaminoguanidines with phenanthraquinone has recently been presented by De and Dutta (28). Pellizzari and Roncagliolio (103) describe the acetaldehyde, the chloral, and the acetoacetic ester derivatives of aminophenylguanidine. Pellizzari and Gaiter (102) and Gaiter (52) describe the carbonyl derivatives of diaminoguanidine. Fromm and students (45, 48, 50) describe a number of carbonyl derivatives of their (aminoguanyl)arylthioureas. Phillips and Williams (107), Whitmore, Revukas, and Smith (173), and Smith and Shoub (133) have studied extensively the carbonyl derivatives of nitroaminoguanidine.

V. SYNTHESES FROM AMINOGUANIDINE

Nitrogen and hydrogen form a series of compounds which are analogous to the hydrocarbons, the silanes, the germanes, and the boranes, but nitrogen appears to have a lesser tendency than does carbon, silicon,

germanium, or boron to enter into chain formation. Only three compounds that are true free hydronitrogens are known—ammonia, hydrazine, and hydrogen azide. Organic derivatives of other hydronitrogens have long been known, but many of them are relatively unstable.

It is therefore of important theoretical interest to observe that syntheses starting from aminoguanidine have led to the formation of nitrogen chains containing three, four, six, and seven nitrogen atoms, and these compounds have been found relatively stable. In this respect they differ markedly from the aromatic substituted hydronitrogens, many of which are relatively unstable. The properties of these substituted higher hydronitrogens, which are reviewed and discussed here, should be given more consideration than in the past in drawing general conclusions regarding the relative stability of nitrogen chain compounds.[6]

The heterocylic nitrogen compounds which are formed from aminoguanidine and from its derivatives also have properties which are unusual in many respects. Cyclizations have been accomplished by reactions of aminoguanidine with carboxylic acids, diketones, keto esters, and nitrous acid. Such reactions have involved hydrazination followed by deammonation, and pyrolysis involving deammonation, dehydrazination, removal of arylamines, and removal of hydrogen sulfide. Some of the reactions appear to be intramolecular ammonation or hydrazination. We shall discuss these heterocylic compounds in classes, grouped according to the number of nitrogen atoms in the ring and the total number of atoms in the ring.

A. The higher hydronitrogens

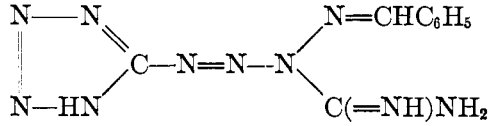
The reaction products of aromatic diazonium salts and hydrazines which form diazohydrazides or derivatives of isotetrazene, RN=NNHNHR, were shown by Fischer (38), Curtius (22), Wohl (176), and Dimroth (33) to be very unstable substances. They decompose at ordinary temperature into azides and amines, or into phenols, nitrogen, and hydrazine. No diazohydrazides could be prepared from hydrazine itself. It is, therefore, of great practical and theoretical interest to point out that the diazohydrazides obtained by Hofmann and his students from aminoguanidine (66, 69, 70) were all found to be exceptionally stable substances. In addition to the work already cited, Hofmann and Hock (67) studied the condensation of diazotized 5-aminotetrazole with hydrazines for the purpose of contributing to our knowledge of the existence and reactivity of compounds containing chains with four atoms of nitrogen, the so-called

[6] Compare, for example, Sidgwick's *Organic Chemistry of Nitrogen*, p. 457, Taylor and Baker, Oxford (1937).

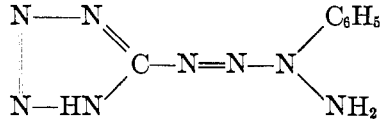
isotetrazenes or buzylenes of the structures RN=NNHNHR (the unsymmetrical tetrazenes) or RN=NN(R)NH_2.

The preparation of guanyltetrazolyltetrazene has already been described (69). It did not hydrolyze on exposure to moist air for one week at room temperature. It did not react with precipitated mercuric oxide at ordinary temperature; with Fehling's solution it evolved nitrogen; and no reaction took place with benzaldehyde. Alkaline hydrolysis produced cyanogen, nitrogen, aminoguanidine, and 5-aminotetrazole.

Diazotetrazolylbenzalaminoguanidine



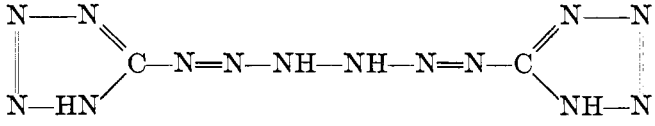
was prepared by adding diazotetrazole to a solution of benzalaminoguanidine containing acetic acid. It precipitated as an intensely orange-red substance. It was stable at room temperature and did not decompose until 132°C. Acid hydrolysis yielded nitrogen, cyanogen, benzaldehyde, and hydrazine. Most interesting was its behavior toward alkalies. Addition of concentrated sodium hydroxide precipitated orange-red needles which redissolved at 90°C. to form a reddish yellow solution capable of being kept at this temperature for a long time without decomposition. On cooling and acidifying, the original substance was recovered unchanged. Diazotetrazolylphenylhydrazide



Diazotetrazolylphenylhydrazide

prepared from 5-aminotetrazole and phenylhydrazine, was found to behave in an analogous manner.

Bisdiazotetrazolylhydrazide

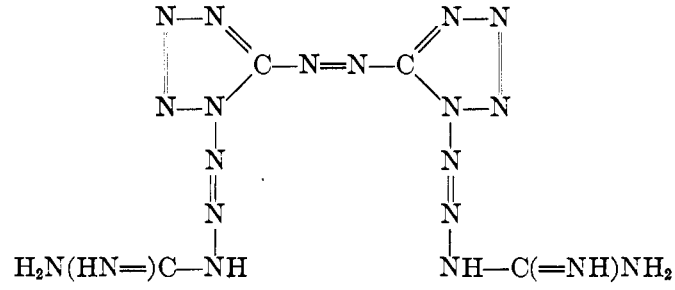


Bisdiazotetrazolylhydrazide

is of particular and considerable interest since, contrary to statements of previous workers, it represents the *first diazohydrazide isolated from hydrazine* itself and, moreover, there is present a *stable* chain of *six nitrogen atoms*.

It was prepared by adding diazotetrazole to a solution of hydrazine hydrochloride in the presence of sodium acetate at low temperature. It forms doubly refractive flakes. It is stable at 25°C., but explodes violently at 90°C. or when pressed with a glass rod. Hydrolysis in aqueous solution yields nitrogen, 5-aminotetrazole, and tetrazolyl azide, while acid hydrolysis furnishes cyanogen, nitrogen, ammonia, and tetrazolyl azide. Addition of cold concentrated alkali first yields a precipitate of intensely yellow plates of the sodium salt, which on dilution with water evolves nitrogen; 5-aminotetrazole and tetrazolyl azide remain in the solution.

Thiele (152), in a paper on azo and hydrazo derivatives of 5-aminotetrazole, reported the preparation of "azotetrazolylbisdiazoguanidine" (bis-1,1(3-guanyltriazene)-5,5-azotetrazole),



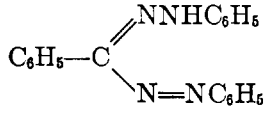
Bis-1,1(3-guanyltriazene)-5,5-azotetrazole

from guanyl azide and sodium azotetrazole. This compound is a yellow, crystalline powder. It decomposes in warm water with evolution of gas. It is of special interest because it probably is the only substance in which there are present *two chains of seven nitrogen atoms.*

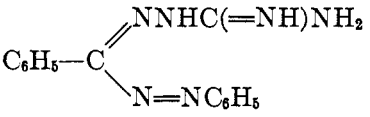
In order to demonstrate further the structure of the diazohydrazides described in the foregoing, Hofmann and Hock (67) studied the condensation of diazotetrazole with hydrazine-free substances, such as guanidine and dicyandiamidine. In both cases only the guanidine and dicyandiamidine salts of diazoaminotetrazole were isolated. This showed that when diazotetrazole was condensed with such hydrazides as aminoguanidine, the coupling took place only through the hydrazine portion of the molecule and not in the imino or amino groups.

B. The guanazyls

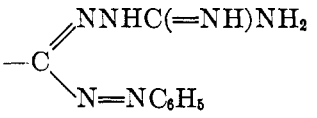
Pechmann (92), in 1894, showed that the tertiary hydrogen atom in benzaldehyde phenylhydrazone is reactive; for example, with diazobenzochloride it reacts and forms derivatives of the type



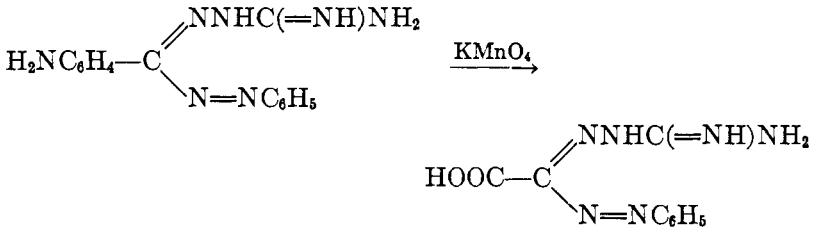
which he termed "formazylbenzoyl." The reaction takes place only in the presence of strong alkali. Wedekind (165), in 1897, investigated the effect of replacing the phenylhydrazine radical by a strongly basic substance, with the assumption that this would permit a more direct formation of the formazyl derivatives. For this purpose he used aminoguanidine. A dilute alcoholic solution of benzalaminoguanidine reacts with an aqueous solution of a diazonium salt to give



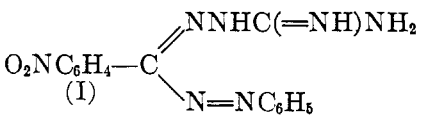
The radical



was termed "guanazyl." These compounds, orange-red to yellow in color, were found to be extremely stable. Either phenyl radical could be nitrated; the resulting nitro derivatives could be reduced to amines, which subsequently could be diazotized and coupled to other aromatic compounds to form complicated azo bodies. They are not easily oxidized; however, if an amino group is present on one of the benzene rings, the oxidation proceeds rapidly as follows:

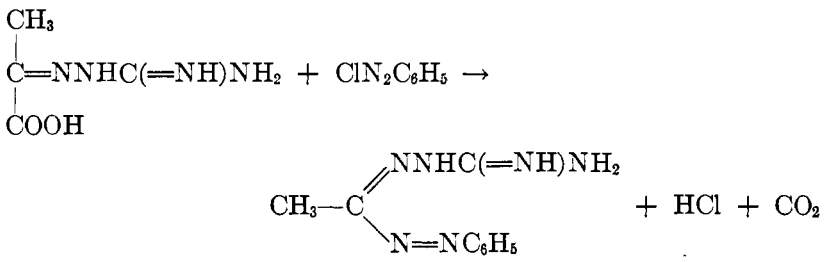


and guanazylformic acid is formed. The guanazyls do not form salts even with strong acids. Wedekind (165) also demonstrated that substituted benzalaminoguanidines react similarly; *p*-nitrobenzalaminoguanidine yields *p*-I-nitroguanazylbenzene

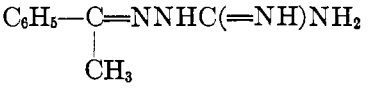


while *o*-benzalaminoguanidine (169) gave the corresponding *o*-I-hydroxyguanazylbenzene. In 1899 Wedekind (170) prepared the simplest type of

guanazyl from the reaction of the condensation product of pyruvic acid with aminoguanidine and diazobenzenechloride



The compound formed was guanazylmethane. In order to demonstrate that the diazonium chloride coupled through the hydrogen atom attached to carbon and not to nitrogen, Wedekind (170) prepared a compound of aminoguanidine in which the hydrogen atom involved was not present. Such a compound

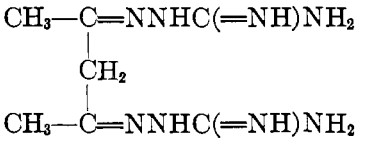


the succeeding homolog of benzalaminoguanidine, was obtained from acetophenone. This compound did not react with diazobenzochloride.

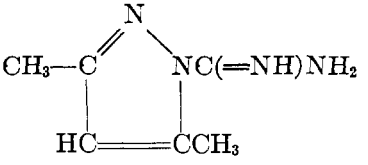
C. Heterocyclic compounds

1. Five-membered rings

(*a*) *Pyrazoles.* Thiele and Dralle (155) found that aminoguanidine reacted with acetylacetone, a β-diketone, to form the dihydrazone

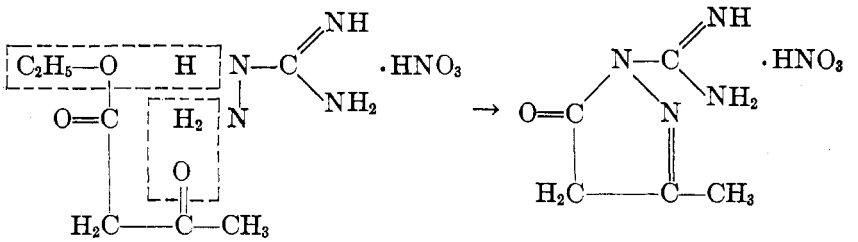


and this compound was converted to 3,5-dimethyl-2-guanylpyrazole



3,5-Dimethyl-2-guanylpyrazole

with the elimination of aminoguanidine; the formation of a monohydrazone was not observed. De and Rakshit (30) have studied the condensation of aminoguanidine and diarylaminoguanidines, $ArNHC(=NAr)NHNH_2$, with β-ketonic esters and β-diketones. In all cases well-defined pyrazole and pyrazolone derivatives were isolated. The method of carying out the reaction consists simply in mixing concentrated solutions of the reactants in water or alcohol at room temperature. On standing, the pyrazole or pyrazolone separate as insoluble products. For example, ethyl acetoacetate and aminoguanidinium nitrate yield 3-methyl-pyrazolone-1-carbamidine nitrate

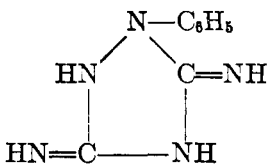


m.p. 234°C. In some cases the mono- or di-hydrazones are isolated. For example, ethyl benzoylacetate and aminoguanidinium nitrate yield ethyl benzoylacetoaminoguanidinium nitrate

$$C_6H_5C(=NNHC(=NH)NH_2)CH_2COOC_2H_5$$

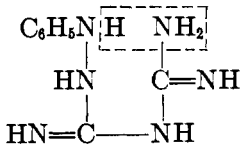
which on cyclization gives 3-phenylpyrazolone-1-carbamidine nitrate, m.p. 190°C. The original paper (30) should be consulted for details about numerous other derivatives in this series.

(*b*) *Triazoles.* Pellizzari (93), in 1891, attempted to prepare phenyl-aminobiguanide by the reaction of phenylhydrazine hydrochloride with dicyandiamide, but this product was not obtained. When equal molecular quantities of both substances were heated to 150°C., a vigorous reaction ensued with evolution of ammonia, and a base of the composition $C_8H_9N_5$ was isolated. This was shown to be phenylguanazole, or 1-phenyl-3,5-diaminodihydrotriazole

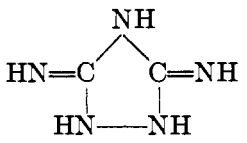


1-Phenyl-3,5-diaminodihydrotriazole

in which it was assumed that the phenylaminobiguanide

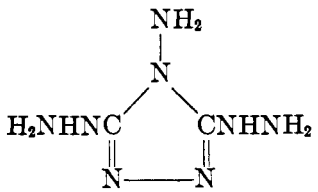


first formed subsequently lost ammonia in closure to the triazole ring. As proof of this mechanism, Pellizzari (93) showed that *as*-ethylphenylhydrazine did not give the same reaction. As additional confirmation it was found that phenylaminoguanidinium chloride reacts with either cyanamide or guanidine to give phenylguanazole. Similarly it is also formed from phenylhydrazine and biguanide. In the reaction of molar quantities of dicyandiamide with hydrazine hydrochloride in 15 parts of 90 per cent alcohol in a pressure flask at 100°C., Pellizzari (93) found that guanazole



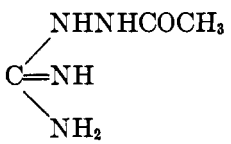
Guanazole

was the principal product. Its formation can readily be explained on the same basis given for phenylguanazole. Stollé and Krauch (143) found that the reaction of 10 g. of dicyandiamide with 25 g. of hydrazine hydrate at 67°C. gave a substance which formed rose-colored leaflets on recrystallization from alcohol. This substance was shown to have the structure

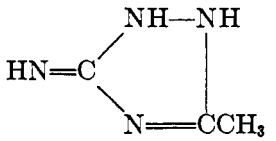


and was called "dihydrazidoaminotriazole."

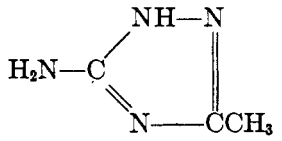
Thiele (147) found that aminoguanidine reacts with acetic acid to form, probably, acetylaminoguanidine



This substance on warming or treatment with alkali lost a molecule of water and formed an inner anhydro base:

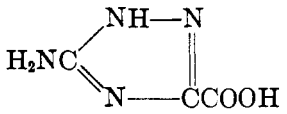


Thiele and Heidenreich (156) found that the substance $C_3H_6N_4$ had the properties of an acid. On oxidation an azo derivative was formed; other work showed that an amino group capable of diazotization was present. Accordingly the product was aminomethyltriazole.



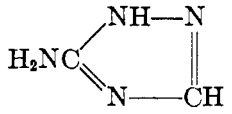
Aminomethyltriazole

Thiele and Manchot (158) showed that the reaction leading to the formation of aminomethyltriazole was general for all acid derivatives of aminoguanidine. For example, oxalylaminoguanidine is converted into aminotriazolecarboxylic acid,



Aminotriazolecarboxylic acid

and from formylaminoguanidine, aminotriazole



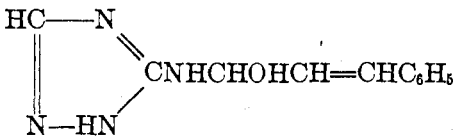
Aminotriazole

is obtained. Franklin and Bergstrom (41) have recently termed this "the elimination of water from an open-chain carbonic acid acyl hydrazide." Reilly and Madden (118) have prepared the corresponding ethyl, isopropyl, and isobutylaminotriazoles; Reilly and Drumm (116) prepared the *n*-propylaminotriazole. Manchot (84) and Manchot and Noll (85) have prepared a number of derivatives of aminotriazoles from aminoguanidine. Fantl and Silbermann (36), in repeating the preparation of methylaminotriazole by the method of Thiele and Heidenreich (156), observed that the alkaline solution took on a deep violet color. Closer

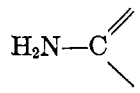
examination revealed that the coloration was due to a trace of ferric salts as an impurity in the sodium carbonate. A quantitative study showed that acetylaminoguanidine nitrate is a remarkably sensitive reagent for ferric ion, since as little as one-thousandth of a milligram of ferric iron in 1 ml. of water gives a definite violet coloration. Other cations do not appear to interfere with the color test. The application of this observation to analytical chemistry apparently has not been studied further.

The aminotriazoles show all the properties of the aromatic amines, differing only in a few respects. They exhibit both basic and acid properties, as is shown by the formation of hydrochlorides, nitrates, and picrates on the one hand, and of silver salts on the other. They are fairly stable to oxidizing agents, forming azo derivatives only. They are likewise extremely resistant to hydrolysis. Methylaminotriazole is not decomposed by dilute sulfuric acid below 180°C., but above this temperature hydrazine, carbon dioxide, ammonia, and acetic acid are formed.

The reactivity of the 5-amino group is indicated by the great ease with which the bases give condensation products with aldehydes. Reilly and Drumm (116) studied the cinnamyl and salicyl derivatives. In the latter case the condensation gave the salicylidene derivative in the usual way, but in the formation of the cinnamylidene compound an intermediate hydrate



appears to have formed. Further work will be necessary, however, to settle definitely the constitution of this substance. Of greater interest is the fact that with nitrous acid diazo compounds are formed. In 1916 Morgan and Reilly (88), by diazotization of aminotriazole and methylaminotriazole, in the presence of an oxy acid, were able to isolate the solid isodiazohydroxides, which were quite stable at 100°C., and which coupled after being acidified. That work directed attention (19) to this important heterocyclic system, which had been little investigated from the point of view of the constitution of diazonium salts. Several series of non-aromatic primary amines appear to possess in varying degrees the property of diazotizability. The requisite properties for diazotizability appear to be the presence of the group



and the possession of a certain degree of unsaturation in the cyclic system in which this carbon atom is included. But it must not be assumed that

any base having the foregoing group and belonging to an unsaturated cyclic system is necessarily diazotizable. The absence of diazotizability is noteworthy in the thiophene, furan, and pyrrole series, in spite of the close relationship between the first of these series and the aromatic compounds.

The much greater stability of diazotized aminodimethylpyrazole in comparison with the corresponding unalkylated compound (117) led Reilly and Drumm (116), Reilly and Madden (118), and Reilly and Caldwell (115) to an investigation of the diazotization of the higher aminoalkyltriazoles from aminoguanidine. It was found that the stability of the triazolediazonium salts was increased by alkyl substitution, the effect increasing with the molecular weight of the alkyl group. The comparative

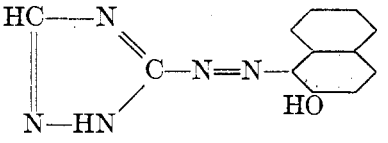
TABLE 1

Comparative stability of alkyltriazolediazonium salts

ALKYLTRIAZOLE	VOLUME OF GAS EVOLVED IN 15 MIN.		VOLUME OF GAS EVOLVED IN 20 MIN.	
	Nitrate	Chloride	Nitrate	Chloride
	ml.	*ml.*	*ml.*	*ml.*
5-Amino-1,2,4-triazole	22.0	27.7	26.8	33.1
5-Amino-3-methyl-1,2,4-triazole	19.5	22.1	23.2	28.4
5-Amino-3-ethyl-1,2,4-triazole	19.0	22.0	23.0	30.8
5-Amino-3-isopropyl-1,2,4-triazole	18.1	19.4	23.6	26.8
5-Amino-3-isobutyl-1,2,4-triazole	13.1	16.6	19.2	26.1

stability may be judged from table 1, which gives the milliliters of gas evolved from 0.002 gram-mole of the various triazolediazonium salts at 55°C. in the presence of 6 moles of acid. Compared with benzenediazonium salts, the diazonium nitrates and chlorides from these aminoalkyltriazoles show pronounced stability.

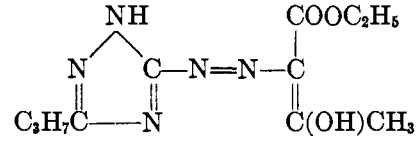
The diazonium salts readily yield azo dyes with β-naphthol, β-naphthylamine, and related aromatic substances. Unlike the purely aromatic azo-β-naphthols, 1,2,4-triazole-5-azo-β-naphthol



1,2,4-Triazole-5-azo-β-naphthol

is soluble in dilute aqueous alkali hydroxides (88). This solubility is in all probability due to the presence in the triazole ring of an imino group contiguous to the carbon atom bearing the azo complex. That the

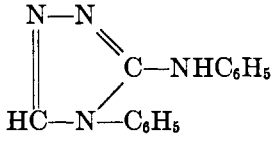
hydroxylic hydrogen of the aromatic group is not involved in this salt formation Morgan and Reilly (88) demonstrated by the fact that 1,2,4-triazole-5-azo-β-naphthylamine is also readily soluble in aqueous alkali hydroxides. The acidic character of the iminic hydrogen atom probably also plays an important part in determining the transformation of these diazonium compounds into isodiazo derivatives. They also couple with β- and γ-keto-esters and diketones to yield azo compounds. For example (116), ethyl 3-propyl-1,2,4-triazole-5-azoacetoacetate



Ethyl 3-propyl-1,2,4-triazole-5-azoacetoacetate

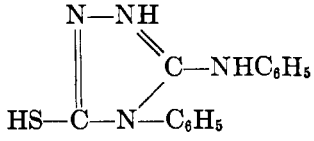
is formed from the diazonium nitrate and ethyl acetoacetate. This represents the *first time that azo-condensation products of β-diketones and keto-esters* (116) *have been isolated*, although Bülow, in 1909, had prepared similar products from diazotized aminotetrazolic acid (13). These products are of considerable interest in connection with the relation between color and constitution, as they represent azo structures in which no aromatic residue is present.

Busch and Bauer (16) found that no formyl or acetyl derivatives of their diarylaminoguanidines could be isolated, but they found that ring closure takes place directly to form derivatives of triazole. For example, diphenylaminoguanidine and formic acid yield 4-phenyl-5-aniltriazole,



4-Phenyl-5-aniltriazole

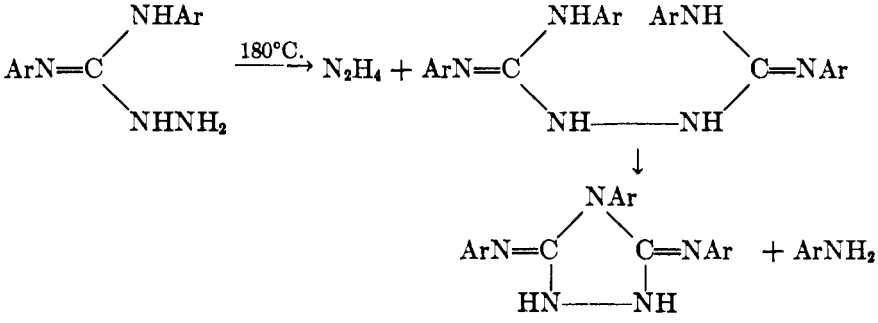
and the same product was obtained by reaction with oxalic acid, with loss of carbon dioxide (18). In the formation of diphenylaminoguanidine (16) two by-products were isolated. The first, a beautiful crystalline sulfur-containing acidic substance, was shown by Busch and Ulmer (18) to be 4-phenyl-5-anil-3-thioltriazolone



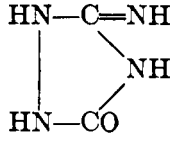
and to be formed by the reaction of diphenylaminoguanidine with excess thiocarbanilide, yielding as intermediate diphenyl(aminoguanido)phenylthiourea

$$C_6H_5NHC(=NC_6H_5)NHNHC(=S)NHC_6H_5$$

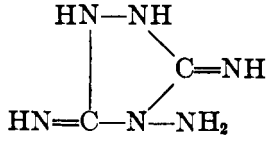
which on ring closure loses a molecule of aniline, to give the triazolone. The second substance, a sulfur-free base, was found (18) to be triphenylguanazole. Its formation by this reaction showed that the process was a general one for the preparation of triarylguanazoles:



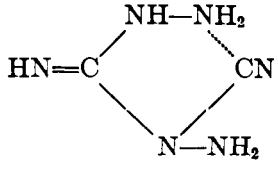
Pellizzari and Roncagliolio (104) examined the reaction of aminoguanidinium chloride with urea and found that 3-iminotriazolidene



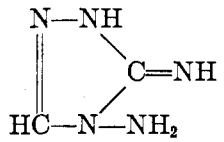
is formed. Pellizzari and Cantoni (100) found that chloro- and bromocyanogen react with hydrazine to form, besides diaminoguanidine, a cyclic derivative, which later investigation by Pellizzari (98) showed was a triazole derivative



the formation of which evidently proceeds through the formation of a cyanodiaminoguanidine

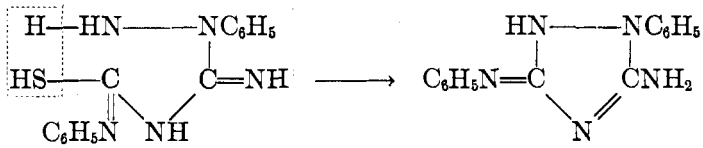


which undergoes ring closure by the intramolecular ammonation of the nitrile group. Gaiter (52) found that diaminoguanidine reacts with formic acid to yield a formyl derivative which, like the corresponding derivative of aminoguanidine, loses water to give 4-amino-3-iminotriazole

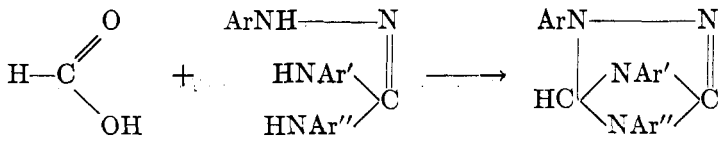


The reaction appears to be general, since with acetic acid the corresponding methylaminoiminotriazole is formed. The properties and derivatives of these substances were carefully studied by Gaiter (52).

Fromm and Göncz (46), Fromm and Vetter (49), Fromm and Weller (50), Fromm, Kayser, Brieglef, and Fohrenbach (48), Fromm, Bruck, Runkel, and Mayer (45), Fantl and Silbermann (37), and Arndt and Tschenscher (4) have very exhaustively examined the formation of triazoles from their (aminoguanido)arylthioureas. The mechanisms involving ring closure are quite complicated, and for details the original papers should be consulted. One example will suffice to illustrate the general mechanism involved. Phenyl(aminoguanido)phenylthiourea through the elimination of hydrogen sulfide forms 1-phenyl-3-anil-5-aminotriazole:

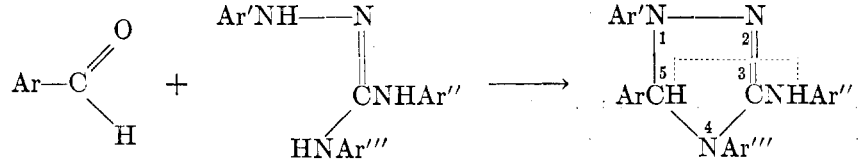


(*c*) *Nitron.* The "endoiminotriazoles" of Busch (14) are a series of triazole derivatives of practical interest to the analytical chemist. They are derived from aminoguanidine. The reactions are of further interest in that aminoguanidine appears to react in the symmetrical form only. Busch (14) found that triarylaminoguanidines condense with formic acid in the following manner:



The products are finely crystalline, mostly yellow, and possess strong basic properties. They are stable to acids, but are readily hydrolyzed to the original materials by alkalies. They form very insoluble nitrates. Busch and Mehrtens (17) also found that acids other than formic acid could not

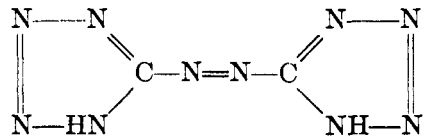
be used. If, however, phosphorus trichloride is added, the reaction proceeds smoothly, through the intermediate formation of the acid chloride. The structures of these compounds were demonstrated as follows (14). The triarylaminoguanidines combine, without difficulty, with an equimolecular quantity of an aldehyde with loss of water, to form triazoles



The structures of the resulting 1,4,5-triaryl-3-arylaminodihydrotriazoles were readily indicated by acid hydrolysis. With oxidizing agents, the two labile hydrogens, one in the 5-position and the other on the amino group, are easily removed, with the formation of a nitrogen bridge between the 3- and the 5-carbon atoms, forming the "endoiminotriazole." The application of these substances to the gravimetric determination of nitric acid has been examined by Busch (15), Desvergnes (32), and Heck and Mellon (62). Schmidt (127) has described the nitron-nitroform salt, Krauz and Turek (74) the trinitrobenzoate, and Lange (75) the difluophosphate.

(*d*) *Tetrazoles.* The formation of the tetrazole ring by the isomerization of guanyl azide has been described, and the relation of aminotetrazole to other nitrous acid transformation products of aminoguanidine has been pointed out. It is of interest to recall that, although semicarbazide forms a similar azide, Thiele and Stange (163) found that it does not isomerize to a tetrazole ring, but yields, instead, hydrazoic acid. Thiele (147), the first to prepare aminotetrazole from aminoguanidine, has described many of its salts and organic derivatives. He was the first to demonstrate that the amino group is capable of diazotization and of coupling with aromatic amines. Thiele and Marais (159) studied the chemistry of diazotized aminotetrazole, "diazotetrazolic acid." It decomposed quantitatively on warming in aqueous solution and gave 1 mole of cyanogen and 5 molecules of nitrogen. By careful reduction, tetrazolylhydrazine was prepared and isolated as the benzal derivative, from which the free tetrazolylhydrazine was obtained as yellow crystalline pellets by hydrolysis. Thiele and Ingle (157) described other derivatives and other properties of aminotetrazole. The acid hydrolysis is of considerable interest. Aminotetrazole was found to be extremely stable; boiling for 5 hr. with fuming hydrochloric acid at 160°C. caused no decomposition, and hydrolysis did not take place until a temperature of 200°C. was reached. Hydrazine, nitrogen, ammonia, and carbon dioxide were

formed. Thiele (150) obtained azotetrazole by oxidation of aminotetrazole



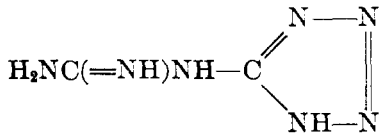
Azotetrazole

which was capable of reduction to a hydrazo derivative. On treatment of the hydrazotetrazole with bromine, an "isocyantetrabromide"

$$Br_2C{=}N{-}N{=}CBr_2$$

was obtained; it is volatile in steam, insoluble in water, and easily soluble in all organic solvents. Distillation in alkaline solution produced a substance believed to be a free halogenoid, OC=NN=CO, or its polymer. Treatment of the alkaline solution with zinc dust gave a substance, which from its hydrolysis products and odor, was thought to be "isocyan," C=N—N=C. Other derivatives of azotetrazole and hydrazotetrazole were described by Thiele (152).

In 1929 Stollé and Shick (144) found that an aqueous solution of hydrazoic acid reacts with dicyandiamide to form aminotetrazole. Using aminotetrazole prepared in this manner, Stollé (140) prepared a large number of new aminotetrazole derivatives, and gave detailed directions for each preparation. The mechanism given for the formation of aminotetrazole from hydrazoic acid and dicyandiamide is of interest here, since undoubtedly the precursor is the azide of aminobiguanide. This latter substance isomerized to guanylaminotetrazole

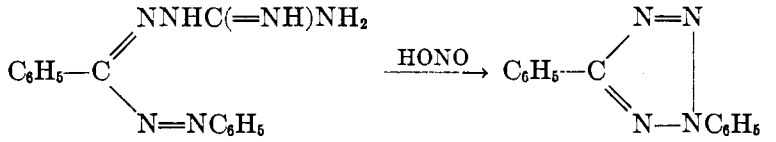


Guanylaminotetrazole

The same compound may be prepared from cyanamide and aminotetrazole. Either product on heating at 200°C. yields ammonia, carbon dioxide, and aminotetrazole. A somewhat more simple mechanism may be postulated, in which the hydrazoic acid brings about a depolymerization of the dicyandiamide to cyanamide.

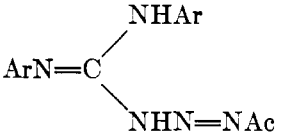
The guanazyls of Wedekind (165, 169, 170) have been described. From these Wedekind (166) found that, by treatment with nitrous acid, tetrazoles

were obtained. This is a new method for the preparation of aryl-substituted tetrazoles,



and may be regarded as a simultaneous oxidation, hydrolysis, and ring closure. The guanyl group forms water, nitrogen, and carbon dioxide. From the guanazylmethanes (170) similar tetrazoles were obtained, in which alkyl or carboxyl groups were substituted on the carbon atom of the ring. Wedekind (164, 167, 168) and Wedekind and Stauwe (171) have studied extensively the properties of these phenylated tetrazoles.

Busch and Bauer (16) attempted to prepare diazo derivatives of their diarylaminoguanidines

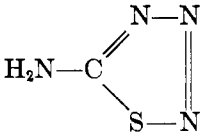


but found that they were immediately converted into tetrazoles, which from the structures of the starting material are *C*-(arylamino)aryltetrazoles.

It is interesting to point out that thiosemicarbazide,

$$H_2NC(=S)NHNH_2$$

in contrast to semicarbazide and aminoguanidine, forms no azide on reaction with nitrous acid. Freund and Schander (44) isolated a substance of the composition CH_2N_4S, which by its hydrolysis to cyanamide, sulfur, and nitrogen, was shown to have the constitution

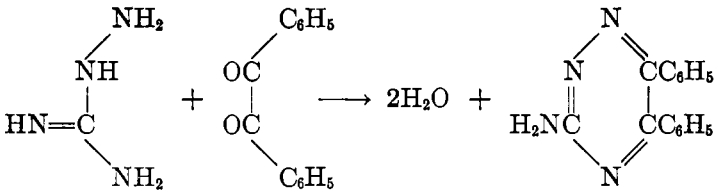


As the substance is an aminotriazole in which one of the ring nitrogens has been replaced by sulfur, it was called aminothiotriazole. (For completeness see the papers by Freund and Paradies (43) and Freund and Hempel (42).)

2. Six-membered rings

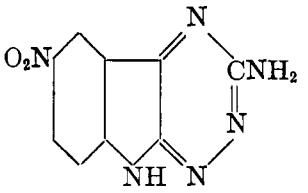
(*a*) *Asymmetric triazenes.* Thiele and Bihan found that aromatic α-diketones (154), as benzil and phenanthraquinone, reacted much less

readily with aminoguanidine to form aminotriazenes than did the aliphatic α-diketones (155). The reaction of benzil with aminoguanidine proceeds as follows



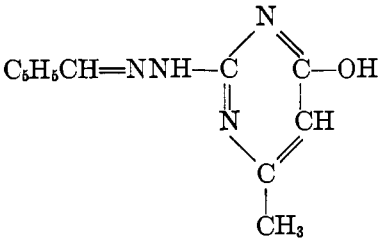
Diphenylaminotriazine

to form diphenylaminotriazine. Phenanthraquinone, under the same conditions, yields aminophenantriazine. The aminotriazines are but very slightly basic and are unreactive towards nitrous acid. In 1927 De (27) prepared the corresponding compounds from acenaphthenequinone and β-naphthoquinone. Treatment of these compounds with concentrated potassium hydroxide replaces the amino group with a hydroxyl group. The hydroxy compounds are soluble in alcohol and give a solution of deep red color and greenish fluorescence. In a more recent paper, De and Dutta (29) showed that the aminotriazines derived from aminoguanidine are dyestuffs which color wool from yellow to a reddish brown. A number of new aminotriazines were prepared, in particular those of isatin. For example, 5-nitroisatin and aminoguanidine yield 3-amino-6-nitroindotriazine:

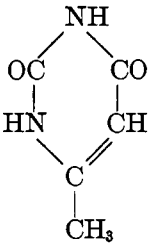


3-Amino-6-Nitroindotriazine

(*b*) *Pyrimidines.* With acetoacetic ester Thiele and Bihan (154) found that benzalaminoguanidine is transformed into a derivative of methylguanicil:



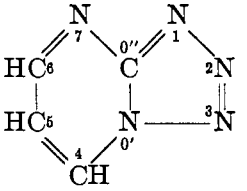
This, according to Pinner (108), may more properly be termed a "benzal-methylhydroxypyrimidinehydrazine," since on hydrolysis with acids it yields benzaldehyde, hydrazine, and methyluracil (21):



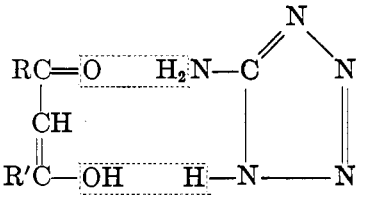
Pellizzari and Roncagliolio (103) obtained the same product by the reaction of phenylaminoguanidine and acetoacetic ester.

3. Condensed rings

Bülow (13) has extended the transformation products of aminoguanidine by examining the condensation of aminotetrazole with β-diketones and β-ketocarboxylic esters. By the removal of 2 moles of water, a new class of hetero-condensed double-nuclear compounds were formed, in which the structural unit has the following constitution:



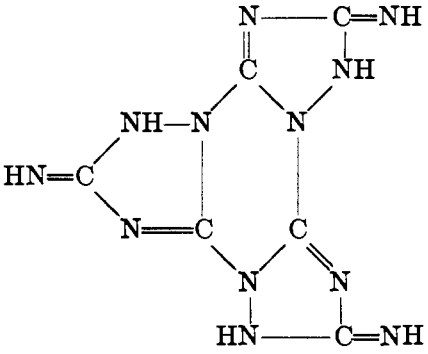
These were termed "1,2,3-tetrazole-7-0'-pyrimidines." The reaction proceeds as follows:



Condensations were carried out with acetylacetone, benzoylacetone, methylacetylacetone, and acetoacetic esters to yield products of interesting properties, which are worthy of further investigation.

The investigations of Pellizzari (93) and of Stollé and Krauch (143), on the formation of triazoles by the reaction of dicyandiamide with hydrazines, demonstrated that the precursors for the ring derivatives

were aminoguanidines and aminobiguanides. In 1911 Hofmann and Ehrhart (64) investigated the reaction of dicyandiamide and hydrazine hydrochloride in the solid state. By heating a mixture of dicyandiamide with dry hydrazine hydrochloride up to 280°C., and extracting the product with hydrochloric acid, they obtained a white powder having the composition $C_6H_8N_{12}\cdot HCl$. They termed this "melamazine." In alkaline solution, air oxidizes melamazine to a bluish violet dye, which was isolated as a barium salt. In a subsequent paper Hofmann and Ehrhart (65) reported that the substance designated as melamazine contained only six instead of eight hydrogen atoms. They assigned the following structure to their compound:



Trisdesaminoguanazole

When dicyandiamide was heated on the water bath with its own weight of hydrazine hydrate, the air oxidation produced an intensely red material, which was believed to be due to a hydrotetrazine ring which is easily oxidized to a tetrazine ring. On continued heating until no more ammonia was evolved, the tetrazine, which was not isolated, disappeared, and guanazole was formed quantitatively. When this was heated to 270°C., it lost ammonia and gave trisdesaminoguanazole. Melamazine is therefore a pyrolytic product of guanazole.

VI. USEFUL PROPERTIES OF AMINOGUANIDINE

Aminoguanidine and some of its derivatives are of practical importance, at least potentially, because of their properties as explosives and as physiological reagents. The explosive character of aminoguanidine derivatives was recognized by Thiele (147), and in recent years patents have been granted which relate to this property. Guanidine and its alkyl and aryl derivatives have been extensively investigated in regard to physiological properties, but, on the other hand, aminoguanidine and its derivatives have received very little attention.

A. Explosive properties of aminoguanidine

The explosive character of the reaction products of aminoguanidine with nitrous acid has been described (66, 67), and these derivatives are finding application in that field. This work has been reviewed by Stettbacher (136), Rinkenbach and Burton (120), Oddo (91), and Grottanelli (54). The general application of guanidine derivatives to explosives is also reviewed in a recent monograph by Stettbacher (135). A rather comprehensive patent on the use of these materials as explosives was obtained by Rathsburg (114) in 1921. An Australian patent (71) covers the use of guanyl azide picrate as an explosive. Hofmann, Hock, and Roth (69) describe the preparation of guanyl azide perchlorate from aminoguanidine, perchloric acid, and sodium nitrite. In comparison with Thiele's (147) guanyl azide nitrate, which is not detonated by rubbing or a blow, the perchlorate explodes violently.

B. Physiological behavior

Thiele (147), in his paper of 1892, evinced considerable interest concerning the physiological effects of his new compounds. Aminoguanidinium chloride was found to be a typical myo-poison. Its effect on the frog and toad was to cause a twitching of the fibrous muscles which lasted for many days. Benzalaminoguanidinium chloride was also reported to be a poison which, when present in the stomach or in the blood (100 mg. per kilogram of body weight in the blood), caused violent epileptic convulsions from which the test animals entirely recovered. The sodium salt of 5-aminotetrazole was found to be non-poisonous. Aqueous solutions of the free acid were observed to promote the growth of mouldy fungus.

Garino (53) has studied the comparative toxicity of guanidine and its amino derivatives. Guanidine is more toxic to infusoria and small crustacea than aminoguanidine, the latter more so than diaminoguanidine, and this in turn more toxic than triaminoguanidine. Eggs of *Strongylocentrotus* placed in a 0.04 *N* solution of guanidine are arrested in the morula stage; in aminoguanidine they are arrested in the blastula stage; while in triaminoguanidine they develop to the stomite stage. Similar effects were observed on the germination of lentil seeds. Experiments on guinea pigs likewise showed that, as the number of amino groups increases, the toxicity of guanidine diminishes.

A more comprehensive study of the comparative physiological action of guanidine and its amino, alkyl, and aryl derivatives has been made by Alles (1). In general, the blood pressure response consists in a fall of the blood pressure followed by a rise that may be quite prolonged. The intensity of the effect of guanidine derivatives varies; acetyl-, methyl-,

dimethyl-, ethyl-, and ethanol-guanidines have a much more marked effect than guanidine or aminoguanidine. The heart rate and amplitude of the heart beat are affected considerably, the effect being most marked with ethyl- and dimethyl-guanidines, while aminoguanidine has a less marked effect on the heart rate and amplitude of the heart beat; guanidine has no appreciable effect. The aryl derivatives of guanidine, such as *s*-diphenylguanidine and triphenylguanidine, are active in small doses, causing a fall in blood pressure and a decrease in the heart rate, the former derivative being very active in this respect. The respiratory effect is most marked with acetylguanidine. While the alkylguanidines and aminoguanidine all have considerable effect on both the respiratory rate and amplitude, the aryl derivatives are not marked in their action. The general effect of guanidine is paralysis, occasional convulsions, dyspnea, and prostration. Lettes has studied the effect of aminoguanidine on hemoclastic crisis (76) and on the blood picture (77). Aminoguanidine produces a blood picture similar to pernicious anemia. Nielsen and Widmark (90) have determined the effect of aminoguanidine on the excretion of uric acid in rats; they found no increased effect.

Certain substituted guanidines have been investigated in order to find pure substances possessing an action similar to that of insulin. A review of proposed insulin substitutes has been given by Braun (11) and by Braun, Mason, and Brown (12). Most of these compounds contain a guanidine and an amino group or two guanidine nuclei (39, 40). Conard and Shriner (20) investigated the condensation products of aminoguanidine with *p*-dimethylaminobenzaldehyde for insulin-like activity, but found no effect.

VII. SUMMARY AND CONCLUSIONS

A review has been given of the chemistry of aminoguanidine and related compounds.

1. Aminoguanidines may be synthesized by methods involving reduction of nitro- and nitroso-guanidines and by hydrazination and hydrazinolysis of compounds related to guanidine, or by a combination of these latter processes.

2. The hydrolysis of aminoguanidine in acid or basic media proceeds in simple step-wise fashion to semicarbazide and hydrazine. In contrast to semicarbazide, aminoguanidine is extremely resistant to acid hydrolysis.

3. Attempts to isolate free aminoguanidine result in the formation of *s*-diaminotetrazine. The mechanism for its formation and its relation to the simpler hydrolytic products of aminoguanidine is not clear.

4. The oxidation of aminoguanidine has been studied to only a limited extent. Permanganate ion in acid solutions yields azodicarbamidine, and

hydrolysis of this compound yields unstable "diimide," which could not be isolated.

5. The reaction with carbonyl compounds leads to well-defined guanylhydrazones, but only nitroaminoguanidine has been systematically applied to analytical organic chemistry.

6. The chemistry of the reaction of aminoguanidine with nitrous acid has been reviewed and correlated. The products obtained depend upon the conditions of the reaction media.

7. Syntheses starting from aminoguanidine lead to the formation of nitrogen chains containing three, four, six, and seven nitrogen atoms of *exceptional* stability. Their inclusion in the family of hydronitrogens must lead to some revision of the comparative stability of nitrogen chains.

8. Penta-, hexa-, and condensed heterocyclic ring compounds containing two, three, four, and five nitrogen atoms in the ring have been synthesized from aminoguanidine and its derivatives. The contribution of aminotriazoles and tetrazoles to diazotizability in non-aromatic systems has been reviewed.

9. The properties of aminoguanidine and its derivatives as explosives have been pointed out.

10. The known physiological properties of aminoguanidine have been reviewed and a comparison made with the alkyl and aryl derivatives of guanidine.

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