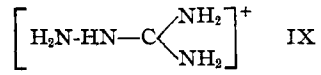
In addition Davis, Yelland and Ma[10] have shown that a carbonium ion form is possible, which may be represented for aminoguanidine as follows (IX)



IX

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

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

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

Summary

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

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

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

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

BROOKLYN, N. Y. RECEIVED AUGUST 11, 1937

[CONTRIBUTION NO. 39 FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

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

BY EUGENE LIEBER AND G. B. L. SMITH

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

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

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

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

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

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

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

deep yellow solutions, however, on careful evaporation deposit yellow crystalline crusts which are the alkylated nitrosoguanidines of 50–60% purity. They can be recovered in pure form by redissolving in water and precipitating as the nickel salts, or isolated as such directly from the reduction mixture. Due to the gelatinous nature of these salts they are somewhat difficult to purify, but on careful washing with water followed by ethyl alcohol and dry ether and drying in a vacuum desiccator the dehydrated nickel derivatives are obtained in the form of red powder or plates. They are readily combustible and explosive. It was found that these nickel salts could be analyzed readily by decomposition with strong acid and subsequent titration with standard potassium permanganate, as in the determination of nitrosoguanidine.[5]

α-Methyl- and α-ethyl-γ-aminoguanidine were prepared by the catalytic hydrogenation of the corresponding alkylnitroguanidines in 15% aqueous acetic acid. They were isolated in the form of their picrates, which were found to be identical with those prepared from the α-alkyl-γ-aminoguanidines synthesized by Kirsten and Smith.[3]

In 1933, Davis and Elderfield[6] prepared alkylnitroguanidines by nitration of alkylguanidines. They concluded that the position of the nitro group was on that of the unsubstituted amino group, *viz.*, $RNHC(=NH)NH—NO_2$, since the products were identical with those obtained by the reaction of alkylamines with nitroguanidine.[7] The proof of structure of these latter products was contingent upon a study of their hydrolysis and dearrangement products. In the present investigation the structure of the α-alkyl-γ-aminoguanidines is proved and accordingly establishes the structure of the nitro compounds from which they were produced by reduction.

Experimental

Materials.—Methylnitroguanidine was prepared by the direct nitration of methylguanidine nitrate as described by Davis and Elderfield.[6] Ethylnitroguanidine was prepared by the reaction of ethylamine with nitroguanidine as described by Davis and Abrams.[7]

α-Methyl-γ-nitrosoguanidine, Nickel Salt.—Eleven and eight-tenths grams of methylnitroguanidine and 5 g. of Raney nickel catalyst were suspended in 120 ml. of absolute methyl alcohol and reduced at 120 atmospheres hydrogen pressure and room temperature; twenty minutes were required for the absorption of one molar proportion of hydrogen. At the conclusion of the run a deep reddish-orange solution was obtained. This was treated with Norit and filtered into a 250-ml. volumetric flask. After washing the filter paper, the volume was adjusted and an aliquot portion titrated with standard potassium permanganate solution.[5] A titration yield of 59.8% was obtained. The remainder of the solution was precipitated with a mixture of nickel nitrate and sodium acetate in water solution. A very voluminous scarlet-red precipitate formed immediately. This was filtered off on a Büchner funnel, washed well with water by decantation after removal from the filter, refiltered and washed with ethyl alcohol and dry ether. It was then allowed to dry for one week in a vacuum desiccator.

Anal. Calcd. for $C_4H_{10}O_2N_8Ni$: Ni, 22.08. Found: Ni, 21.18, 22.52.

α-Ethyl-γ-nitrosoguanidine, Nickel Salt.—This was prepared as described above from 13.2 g. of ethylnitroguanidine and 5 g. of Raney nickel catalyst. The titration yield was 53.4%. The nickel salt is a bright red crystalline powder.

Anal. Calcd. for $C_6H_{14}O_2N_8Ni$: Ni, 20.19. Found: Ni, 20.22.

Titration of Nickel Salts in Strong Acid.—Since the nickel salts were found to be soluble in strong acid solution, *i. e.*, by decomposition, an analysis of the resulting solutions was attempted with standard potassium permanganate solution. Weighed samples of nickel-ethylnitrosoguanidine were allowed to digest in cold 3 *M* sulfuric acid for one hour and then titrated as described for nitrosoguanidine.[5]

Anal. $C_6H_{14}O_2N_8Ni$ taken; (a) 0.1102 g., (b) 0.1250 g. Found: (a) 0.1144 g., (b) 0.1233 g.

α-Methyl-γ-aminoguanidinium Picrate.—Five and nine-tenths grams of methylnitroguanidine and 0.5 g. of platinum oxide catalyst were suspended in 100 ml. of 15% aqueous acetic acid solution. The reduction was carried out at 130 atmospheres hydrogen pressure and room temperature. Sixty minutes were required for the absorption of three molar proportions of hydrogen. At the end of the run the solution was filtered to remove catalyst after treatment with Norit. Titration with standard potassium iodate solution[8] indicated a yield of 88.6%. A saturated solution of picric acid was added to the remainder of the solution, which immediately precipitated a voluminous yellow crystalline material, which was recrystallized from a small volume of warm water; m. p. (Dennis bar) 162°; reported,[3] m. p. 162–163°.

Anal. Calcd. for $C_9H_{11}O_7N_7$: N_2H_4, 10.09. Found: N_2H_4, 10.00, 10.12.

α-Ethyl-γ-aminoguanidinium Picrate.—Thirteen and one-half grams of ethylnitroguanidine was reduced as described above with 0.7 g. of platinum oxide catalyst in 120 ml. of 15% aqueous acetic acid solution. A titration yield of 63.8% was obtained. Addition of picric acid solution yielded a yellow crystalline picrate; m. p. found 114°, reported,[3] m. p. 114°.

We are at present engaged in extending the series of α-alkyl-γ-nitroso- and γ-aminoguanidines both by hydro-

(6) Davis and Elderfield, THIS JOURNAL, **55**, 731 (1933).

(7) Davis and Abrams, *Proc. Am. Acad. Arts Sci.*, **61**, 450 (1926).

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

genation and direct synthesis. A study of the oxidation potential of the alkylnitronitrosoguanidine system is in progress in comparison and extension of the previously reported studies of the oxidation potential of the nitronitrosoguanidine system.[9]

Summary

The reduction of α-alkyl-γ-nitroguanidines by the method of catalytic hydrogenation has been studied and the preparation of derivatives of α-alkyl-γ-nitroso- and γ-aminoguanidines is described. The structure of the alkylnitroguanidines previously based upon dearrangement and hydrolysis studies has been confirmed by comparison of the alkylaminoguanidines obtained by hydrogenation with those obtained by direct synthesis.

(9) Smith and Sabetta, THIS JOURNAL, **54**, 1034 (1932).

BROOKLYN, N. Y. RECEIVED AUGUST 16, 1937

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. XXI. Lanosterol and Agnosterol

BY RUSSELL E. MARKER AND EUGENE L. WITTLE

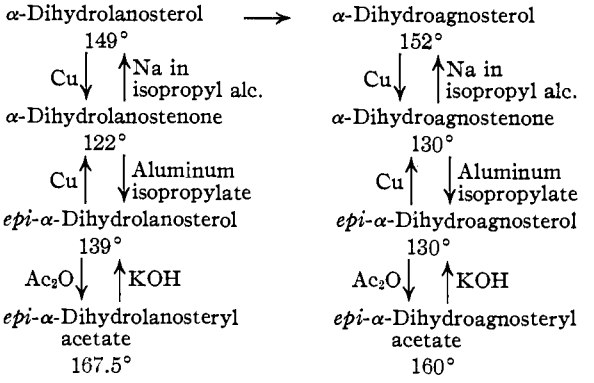
We have shown recently that α-dihydrolanosterol can be converted into a compound which is identical with α-dihydroagnosterol obtained by the catalytic reduction of agnosterol.[1] Further proof that these two compounds are the same is shown by the fact that they give the same ketone, α-dihydroagnostenone upon dehydrogenation with copper at reduced pressure. Thus lanosterol and agnosterol differ only in the number and position of the double bonds and possess the same carbon structure.

Reduction of α-dihydroagnostenone with sodium in isopropyl alcohol gave the original α-dihydroagnosterol. With aluminum isopropylate in isopropyl alcohol, the ketone gave a mixture of epimers which did not precipitate with digitonin and which could be separated by crystallization of the acetates into α-dihydroagnosteryl acetate and the more soluble *epi*-α-dihydroagnosteryl acetate. These acetates gave a marked depression in melting point when mixed. When *epi*-α-dihydroagnosterol was dehydrogenated with copper, it gave α-dihydroagnostenone, which was identical with the product obtained by the oxidation of α-dihydroagnosterol.

Reduction of α-dihydrolanostenone with aluminum isopropylate in isopropyl alcohol gave a mixture of epimers which upon crystallization of the acetates gave *epi*-α-dihydrolanosteryl acetate, and α-dihydrolanosteryl acetate. Both compounds gave the original ketone upon hydrolysis and oxidation. Neither compound precipitated with digitonin.

The fact that neither of the epimers precipitates with digitonin is of interest in showing that the ring structure differs from other sterols and also from kryptosterol,[2] which is very similar to lanosterol in properties but precipitates with digitonin.

The failure of these epimers to precipitate with digitonin lends support to the conclusion of Schulze[3] that lanosterol and agnosterol are triterpenoid rather than steroid in character.



Experimental

α-Dihydroagnostenone.—A mixture of 0.5 g. of α-dihydroagnosterol, m. p. 152°, and 0.8 g. of finely divided copper was heated at 250° under a pressure of 2 mm. for one hour. The product was then distilled and was crystallized from acetone–methyl alcohol and ethyl acetate giving 0.4 g. of material melting at 130° and crystallizing in large angular plates.

Anal. Calcd. for $C_{30}H_{48}O$: C, 84.8; H, 11.4. Found: C, 84.4; H, 11.5.

This ketone was obtained from α-dihydroagnosterol prepared by the reduction of agnosteryl acetate, and also from α-dihydroagnosterol prepared from α-dihydrolanosterol.[1]

The 2,4-dinitrophenylhydrazone crystallized in fine needles, m. p. 224°.

(1) Marker, Wittle and Mixon, THIS JOURNAL, **59**, 1368 (1937).

(2) Wieland, Pasedack and Ballouf, *Ann.*, **529**, 68 (1937).

(3) Schulze, *Z. physiol. Chem.*, **190**, 51 (1936).