[Contribution from the Department of Chemistry, Yale University]

BETA-HYDROFORMAMINE CYANIDE: A NEW METHOD OF SYNTHESIS WHICH REVEALS ITS MOLECULAR STRUCTURE[1]

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When formaldehyde, ammonium chloride and sodium cyanide interact under the special conditions described by Klages,[1a] a colorless, crystalline substance melting at 86° is obtained which he has described as being isomeric with "methylene aminoacetonitrile" or α-hydroformamine cyanide, $C_9H_{12}N_6$, melting at 129°. This lower-melting compound was later obtained by Johnson and Rinehart,[2] and under experimental conditions that disclosed the fact that it is always a secondary product of reaction when Klages' method of synthesis is employed for preparation of the 129° product. The behavior of the two substances on hydrolysis and molecular weight determinations led Johnson and Rinehart to conclude that the two compounds are structural isomers.

In a later publication[3] it was shown that the lower-melting compound, β-hydroformamine cyanide, is decomposed upon hydrolysis by means of alcoholic hydrogen chloride into formaldehyde, ammonium chloride and a crystalline compound that behaved as the hydrochloride of a nitrogen-containing compound, but which was not identified. When the beta isomer is hydrolyzed by alkali, four of the six nitrogen atoms demanded by the formula $C_9H_{12}N_6$ are given off as volatile basic nitrogen. This observation has been confirmed and the base shown to be ammonia. The hydrochloride gave no precipitate of 1-methylamino-2,4-dinitrobenzene when Valton's method[4] for the detection of methylamine in the presence of ammonia was tried. No methylamine was present in the volatile base which the beta isomer gave upon hydrolysis and the only salt formed on leading the base into hydrochloric acid was ammonium chloride.

Liquid hydrogen cyanide in the absence of mineral acid acted as a solvent for the beta isomer, but no chemical reaction occurred, since the substance could be recovered unchanged. The presence of hydrochloric acid, however, caused a reaction leading to the formation of a colorless crystalline compound. This solid was identified as nitrilotriacetonitrile, $N(CH_2CN)_3$, by means of its melting point (124–126°), by its analysis for nitrogen, by its molecular weight determined ebullioscopically in acetone, and by the quantitative measurement of the amount of ammonia obtained when the nitrile was hydrolyzed by digestion with barium hydroxide.

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[1] This paper was presented before the Division of Organic Chemistry at the Philadelphia Meeting of the American Chemical Society, September, 1926.

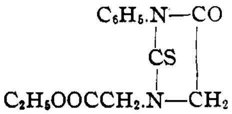
[1a] Klages, *Ber.*, **36,** 1510 (1903); *J. prakt. Chem.*, **65,** 192 (1902).

[2] Johnson and Rinehart, This Journal, **46,** 771 (1924).

[3] Rinehart and Johnson, *ibid.*, **46,** 1653 (1924).

[4] Valton, *J. Chem. Soc.*, **127,** 40 (1925).

The substance which we obtained by hydrolysis of the beta isomer and which behaved as the hydrochloride of an amine was identified as the hydrochloride of iminodiacetic acid by the esterification of the acid to give dimethyliminodiacetate hydrochloride, $HN(CH_2—COOCH_3)_2.HCl$. The acid was easily identified by its conversion into ethyl 3-phenyl-2-thiohydantoin-1-acetate (I) according to the method described by Bailey and Snyder.[5] The source of this iminodiacetic acid is very probably iminodiatetonitrile which is formed as an intermediate product of reaction when the beta isomer is ruptured by hydrolysis.



$$\begin{array}{l} C_6H_5.N—CO \\ \quad\;\; CS \qquad\; CH_2 \\ C_2H_5OOCCH_2.N—CH_2 \end{array}$$

I

Significant data were obtained when the amount of dimethyl iminodiacetate hydrochloride was compared with the weight of the beta isomer from which it was obtained by hydrolysis. The molecular ratio of ester hydrochloride to beta isomer was greater than one to one, indicating that in each mole of the latter more than one mole of the former must be present. Analytical results exclude the possibility of a ratio greater than two to one, since the beta isomer has been shown to contain only nine carbon atoms. Hence, it seems certain that two moles of iminodiacetonitrile are in some way incorporated in the molecular structure of the beta isomer.

Molecular Structure of β-Hydroformamine Cyanide

It is evident, from what has been stated above, that the following facts must fit any formula proposed for the beta isomer: (1) formaldehyde is one of the products of hydrolysis; (2) four moles of ammonia are formed from one mole of this substance by hydrolysis with alkali; (3) two molecular proportions of iminodiacetic acid result by hydrolysis with acids; (4) interaction of the beta isomer with absolute hydrogen cyanide yields nitrilotriacetonitrile.

In considering formulas that would fit the above facts, methylene-*bis*-iminodiacetonitrile, $CH_2.[N(CH_2CN)_2]_2$, at once suggested itself. Its behavior on hydrolysis would be expressed as follows: $CH_2[N(CH_2CN)_2]_2 + H_2O \longrightarrow CH_2O + 2HN(CH_2CN)_2$; $2HN(CH_2CN)_2 + 4H_2O \longrightarrow 2HN(CH_2COOH)_2 + 4NH_3$.

The reaction with hydrogen cyanide is to be expressed according to the following equation: $[(CH_2CN)_2N]_2CH_2 + HCN \longrightarrow NH(CH_2CN)_2 + N(CH_2CN)_3$.

It is obvious that the formula for methylene-*bis*-iminodiacetonitrile is $C_9H_{10}N_6$. Klages, who designated these products of reaction as isomers,[1a] apparently based his conclusion upon analytical determinations only. He did not investigate the chemical behavior of his lower-melting compound.

Klages' Analyses. C, 52.7, 52.9, 53.3; H, 5.8, 5.9, 5.6; N, 41.5, 41.2. Calcd. for $C_9H_{12}N_6$: C, 52.9; H, 5.93; N, 41.17.

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[5] Bailey and Snyder, THIS JOURNAL, **37,** 941 (1915).

At the same time, however, his results are not greatly in disagreement with the calculated values for methylene-*bis*-iminodiacetonitrile.

Calcd. for $C_9H_{10}N_6$: C, 53.4%; H, 5.0%; N, 41.58%.

The molecular-weight determination that has been made upon this compound[2] would not, of course, show so slight a difference as two hydrogen atoms. The behavior of this compound (m. p., 86°) with hydrogen sulfide, which we have previously reported as producing a dithio-amide and indicating two free cyanide groups,[3] will be seen to be out of accord with the predicted behavior of methylene-*bis*-iminodiacetonitrile, in which four free cyanide groups exist. It may be that the dithio-amide that was obtained was an intermediate product in the reaction, or it may be that the reaction stops here, due to the fact that two of the nitrile groups become masked. From the results obtained in a new research now being carried on in this Laboratory we have good reasons for believing that not all of the nitrile groups in this type of compound are necessarily reactive toward hydrogen sulfide. There is very strong evidence in support of the conclusion that two of the nitrile groups in the so-called beta isomer are not disclosed by interaction with hydrogen sulfide.[6]

Synthesis of Methylene-*bis*-Iminodiacetonitrile.—If the so-called beta isomer could actually be synthesized from formaldehyde and iminodiacetonitrile according to the equation $CH_2O + 2HN(CH_2CN)_2 \longrightarrow CH_2[N(CH_2CN)_2]_2 + H_2O$, substantial evidence as to the identity of this substance would be obtained at once. Such a reaction between iminodiacetonitrile and formaldehyde (formalin) has now been observed to take place. The product of the reaction melted after purification at 84–86° and there was no change in melting point when mixed with the substance obtained originally as a by-product by interaction of formaldehyde, ammonium chloride and sodium cyanide. The present experimental evidence, therefore, establishes the identity of this substance as *methylene-bis-iminodiacetonitrile*. Further investigations on the molecular structures of α- and β-hydroformamine cyanides and the mechanism of the interaction of ammonium chloride, formaldehyde and sodium cyanide will be carried on

In conclusion, I wish to acknowledge my indebtedness to Professor Treat B. Johnson for his aid and suggestions, and to Professor Dorothy A. Hahn of Mount Holyoke College for her kindness in furnishing me with a quantity of methylene-*bis*-iminodiacetonitrile obtained as a by-product in that Laboratory.

Experimental Part

Hydrolysis of Methylene-*bis*-iminodiacetonitrile by Means of Strong Alkali.—To 0.3495 g. of methylene-*bis*-iminodiacetonitrile in a Kjeldahl flask, 10 cc. of 50% aqueous

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[6] Dr. T. B. Johnson and Dr. E. S. Gatewood will publish later the results that have been obtained in their new work on thio-amides.

sodium hydroxide solution and 500 cc. of water were added. The solution was distilled and the distillate conducted into standard hydrochloric acid (1 cc. ≎ 0.001284 g. of nitrogen) after the manner of a Kjeldahl nitrogen determination. The following results were obtained.

A. Hydrochloric acid neutralized, 71.19 cc. Calcd. for 4 N: N, 27.72. Found: 26.15.

A regular Kjeldahl nitrogen determination was then run on the residue in the Kjeldahl flask, when the following results were obtained.

B. Calcd. for 2 N: N, 13.86. Found: 14.47.

Combining *A* and *B:*

Calcd. for 6 N: N, 41.58. Found: 40.62.

Analysis of hydrochloride formed in *A:*

Calcd. for NH_4Cl: Cl, 66.36. Calcd. for $CH_3{\cdot}NH_3{\cdot}Cl$: Cl, 52.60. Found: Cl, 65.77, 65.80.

Preparation of Nitrilotriacetonitrile from Methylene-*bis*-iminodiacetonitrile.—Five g. of the nitrile, 37 g. of absolute hydrogen cyanide prepared according to the directions of Johnson and Lane,[7] and 3 cc. of concd. hydrochloric acid were mixed in a 500cc. flask, which was then tightly stoppered and allowed to stand in a cool place. The nitrile dissolved immediately and within an hour a colorless, crystalline solid began to separate. At the end of 36 hours the excess of hydrogen cyanide was evaporated by blowing a current of air through the solution. The yellowish crystalline solid which remained was dried in a vacuum and weighed 6.136 g. When a portion of this solid was treated with warm water, an odor of hydrogen cyanide developed, indicating hydrolysis. The solid was therefore recrystallized several times from absolute alcohol, using a little Norite for decolorization, when the pure nitrile was obtained; m. p., 124–126°.

Anal. Calcd. for $N(CH_2CN)_3$: N, 41.79. Found: 41.56, 41.77.

Mol. wt. (in acetone): Calcd., 134. Found: 129, 127, 118.

Hydrolysis of Nitrilotriacetonitrile by Barium Hydroxide.—In a Kjeldahl flask 0.1698 g. of nitrilotriacetonitrile was placed and an excess of the hydroxide added. The solution was boiled and the ammonia that was evolved was absorbed in standard hydrochloric acid (1 cc. ≎ 0.001284 g. of nitrogen).

Hydrochloric acid neutralized: 41.78 cc. Calcd. for 3 N: N, 31.34. Found: 31.59.

Hydrolysis of Methylene-*bis*-iminodiacetonitrile by Means of Alcoholic Hydrogen Chloride

To 10.00 g. of the nitrile in a 500cc. flask were added 75 cc. of absolute alcohol saturated at 0° with dry hydrogen chloride, and 125 cc. of absolute alcohol. This solution was then refluxed for one and one-half hours on a steam-bath. The ammonium chloride which separated during this time was filtered from the hot solution and dried in a vacuum; it weighed 7.812 g. The filtrate was concentrated as much as possible on the water-bath, then 75 cc. of water and 25 g. of silver oxide were added to the thick, brown sirup which remained. This solution was distilled with steam. The distillate was led into concd. hydrochloric acid and the resulting solution evaporated to dryness on the water-bath. An additional 1.712 g. of ammonium chloride was obtained. The solution through which the steam had been passed was acidified with 100 cc. of concd. hydrochloric acid, filtered and finally evaporated to dryness on a steam-bath. The weight of impure iminodiacetic acid hydrochloride was 15.6 g. This substance was recrystallized twice from water, then dried in an air-bath at 110 .

Anal. Calcd. for $HN(CH_2COOH)_2.HCl$: N, 8.26; Cl, 20.94. Found: N, 8.61, 8.43; Cl, 21.01, 20.97.

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[7] Johnson and Lane, THIS JOURNAL, **43**, 354 (1921).

Preparation of Ethyl 3-Phenyl-2-thiohydantoin-1-acetate from Iminodiacetic Acid Hydrochloride.—Two g. of iminodiacetic acid hydrochloride was neutralized by 11.6 cc. of *N* sodium hydroxide solution. With this, 1.6 g. of phenylmustard oil in 20 cc. of 95% alcohol was allowed to react, according to the procedure of Bailey and Snyder.[5] Their directions were further followed in the preparation of the ester of the thiohydantoin, which was obtained in 55% yield and melted at 132–135°.

Anal. Calcd. for $C_{13}H_{14}O_3N_2S$: N, 10.07. Found: 10.39, 9.86.

Preparation of Dimethyl-iminodiacetate Hydrochloride from Methylene-*bis*-iminodiacetonitrile.—Twenty g. of the nitrile was suspended in 350 cc. of absolute methyl alcohol which was then saturated at 0° with dry hydrogen chloride. The solution was refluxed for six hours on a steam-bath, filtered hot, and then cooled for three hours in an ice-bath. The ester hydrochloride separated as a network of needles; these were filtered off and dried in a vacuum desiccator. They melted at 175–180° without further purification. The weight was 26.5 g., a yield of 68%, calculated on the basis of 2 molecular proportions of ester hydrochloride obtained from one of the nitrile.

Anal. Calcd. for $HN(CH_2COOCH_3)_2.HCl$: N, 7.09; Cl, 18.0. Found: N, 7.15; Cl, 18.17, 18.2.

Synthesis of Methylene-*bis*-iminodiacetonitrile.—In a mixture of 7.5 g. of "formalin" and 50 cc. of water was suspended 9.5 g. of iminodiacetonitrile. No heat was evolved, but the iminodiacetonitrile gradually dissolved. In several hours, white plates began to separate. After 24 hours the solid was filtered off and dried in a vacuum; the weight was 8.61 g. This solid was purified by three recrystallizations from acetone; m. p., 84–86°. It was identified as the same compound that was originally described by Klages. The melting point was not lowered by mixing the two substances.

Anal. Calcd. for $C_9H_{10}N_6$: N, 41.58. Found: 41.24, 41.57.

Summary

1. Ammonia is the only volatile base that is produced by hydrolysis of β-hydroformamine cyanide.

2. Liquid hydrogen cyanide reacts with β-hydroformamine cyanide in the presence of hydrochloric acid to form nitrilotriacetonitrile.

3. Iminodiacetic acid has been identified as one of the products formed when the beta isomer is digested with hydrochloric acid.

4. Using the dimethyl ester of iminodiacetic acid as the best method of quantitative determination, it is shown that not more than two molecular proportions of this acid are formed from one of the beta isomer by hydrolysis.

5. The experimental evidence leads to the conclusion that Klages' 86° product is not an isomer of his "methylene amino-acetonitrile" melting at 129°, but is to be assigned the empirical formula $C_9H_{10}N_6$ and expressed structurally as methylene-*bis*-iminodiacetonitrile.

6. Methylene-*bis*-iminodiacetonitrile is easily synthesized by condensation of formaldehyde with iminodiacetonitrile. It is identical with β-hydroformamine cyanide.

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