gestion of 3 g. of the solid with hot dilute aqueous ammonia gave 1.79 g. of nearly pure **HMX** (V); m.p. 278° (safety shield should be used). After heating another 3-g. portion with 50% acetic acid containing 1% of nitric acid on a steam-bath for 15 hours, 2.44 g. remained with m.p. 270°. From this 0.12 g. of pure RDX was isolated as transparent rhombs; m.p. 204–205° (cor.), alone and when mixed with an authentic specimen.

ANN ARBOR, MICH. RECEIVED DECEMBER 11, 1950

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

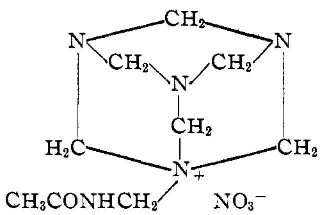
Structure Determination and Synthesis of 1-Acetamidomethylhexamine Nitrate[1]

BY W. E. BACHMANN, E. L. JENNER AND L. B. SCOTT

A compound formed by the action of acetic anhydride on hexamine mononitrate is shown to be 1-acetamidomethylhexamine nitrate. Several new syntheses of the compound are described.

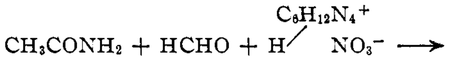
By the action of acetic anhydride on hexamine mononitrate Linstead, Kuehl and Leavitt[2] obtained a beautifully crystalline compound of unknown structure. Later, excellent directions for its preparation were devised by Carmack, Kuehl, Leavitt and Connor,[3] who reported that the empirical formulas $C_9H_{18}N_6O_4$ and $C_{15}H_{30}N_{10}O_7$ agreed best with the analytical values. The presence of a nitrate ion was indicated in the spectrum and the acetate ion was detected in the alkaline hydrolysate of the compound by the color test with lanthanum nitrate.

A determination of the nitrate ion by precipitation with nitron gave us an equivalent weight of 275, which was in agreement with the empirical formula $C_9H_{18}N_6O_4$. Assuming the presence of a hexamine nucleus $C_6H_{12}N_4$, there remained C_3H_6NO after subtraction of the hexamine moiety and a nitrate group. Since C_3H_6NO must contain an acetyl group (to account for the acetic acid produced on hydrolysis), only the grouping CH_3N remained after subtraction of CH_3CO. This could only be $-NHCH_2$ and the group attached to the hexamine molecule must be either $CH_3CONHCH_2-$ or CH_3COCH_2NH-, of which the first appeared to be the logical choice. On the basis of these speculations the compound has the structure (I) of the quaternary salt, 1-acetamidomethylhexamine nitrate

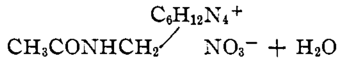


I

If the proposed structure is correct, the compound could probably be prepared from hexamine mononitrate, formaldehyde and acetamide according to the formulation



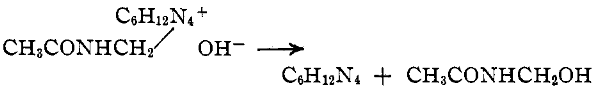
$$CH_3CONH_2 + HCHO + \overset{C_6H_{12}N_4^+}{H\diagup}\ NO_3^- \longrightarrow$$



$$\overset{C_6H_{12}N_4^+}{CH_3CONHCH_2\diagup}\ NO_3^- + H_2O$$

Experiment showed this to be the case; the quaternary salt which crystallized from a solution of acetamide and hexamine mononitrate in formalin was identical in all respects with the compound prepared from acetic anhydride and hexamine mononitrate.

It had been reported that the compound reacted with one equivalent of alkali at room temperature and a second equivalent at elevated temperature. We have investigated the reaction with one equivalent of alkali more closely. In agreement with the structure the aqueous solution of the salt is neutral; when 0.1 *N* sodium hydroxide was added to the aqueous solution of the quaternary salt containing phenolphthalein, a pink color was soon formed. The color faded quickly but reappeared when more alkali was added. More time was required for the fading as more of the compound had reacted. The half-way point was reached in about one-half hour; complete neutralization of one equivalent of alkali required about 12 hours. These results suggested that the quaternary hydroxide was unstable and decomposed in the following manner into hexamine and N-methylolacetamide.



$$\overset{C_6H_{12}N_4^+}{CH_3CONHCH_2\diagup}\ OH^- \longrightarrow C_6H_{12}N_4 + CH_3CONHCH_2OH$$

From the mixture hexamine and sodium nitrate were isolated in good yield. The N-methylolacetamide could not be obtained crystalline; on sublimation of the fraction containing it acetamide was obtained. Clearly the reaction with a second equivalent of alkali at elevated temperature involved the hydrolysis of the acetamide. In agreement with the proposed formula, the compound yielded exactly one mole equivalent of acetic acid on saponification.

The neutralization reaction suggested another synthesis of the quaternary salt, which was realized; namely, the reaction of N-methylolacetamide with hexamine mononitrate. The salt was obtained also from acetamide, paraformaldehyde and hexamine in acetic acid followed by addition of nitric acid; from hexamine mononitrate and acetamide in acetic acid followed by addition of water (the requisite formaldehyde must have been derived from hydrolysis of part of the hexamine); from hex-

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(1) This investigation was carried out under a contract recommended by the NDRC between the OSRD and the Regents of the University of Michigan, 1940–1945. This material has been released by the Security Review Branch of the Department of Defense.

(2) R. P. Linstead, F. A. Kuehl and J. Leavitt, private communication.

(3) M. Carmack, F. A. Kuehl, J. Leavitt and R. Connor, private communication.

amine, ammonium nitrate, acetic acid and acetic anhydride.

The last named synthesis was suggested from a study of the anomalous solubility of ammonium nitrate in acetic acid containing hexamine. Approximately 5 g. of ammonium nitrate is soluble in one liter of acetic acid at 26°; 184 g. (2.3 gram moles) of ammonium nitrate is soluble in a liter of acetic acid containing two grams moles of hexamine. The solubility of ammonium nitrate increases approximately mole for mole with the quantity of hexamine in the solution.

Solutions which contain more than about 1.8 gram moles each of hexamine and ammonium nitrate are supersaturated with respect to hexamine mononitrate; seeding of the solution with this salt will result in precipitation. Solutions containing as little as one gram mole each of hexamine and ammonium nitrate are supersaturated with respect to crystals of hexamine mononitrate monoacetate. The crystals lose the molecule of acetic acid when exposed to air. In virtue of the formation of hexamine mononitrate, these solutions must contain ammonium acetate; and it is readily apparent why the addition of acetic anhydride can give rise to I, for it reacts with ammonium acetate to form the requisite acetamide.[4]

Pyridine also increased the solubility of ammonium nitrate in acetic acid but not to the same extent as did hexamine. The solubility of potassium nitrate in acetic acid was increased by the addition of hexamine.

1-Acetamidomethylhexamine chloride was obtained from the nitrate by reaction with nitron chloride. The propionyl analog of I was prepared by the various methods used for I. We found that when hexamine mononitrate was dissolved in 37% formalin, stout colorless crystals soon appeared which may be the methylol derivative, $HOCH_2\text{-}C_6H_{12}N_4^+NO_3^-$. The compound decomposed rapidly in water into hexamine nitrate and formaldehyde. As was expected the compound gave the quaternary salt I when treated with acetamide.

Experimental

Preparation of 1-Acetamidomethylhexamine Nitrate (I): (a) **From Hexamine Mononitrate.**—A solution of 1.2 g. of acetamide, 4 g. of hexamine mononitrate and 4 cc. of 37% formalin was allowed to stand at room temperature. After 20 hours, when the mixture was seeded with a crystal of I, 1.55 g. of I separated; m.p. 178–180° (183–184° when placed in the bath at 175°). An additional 0.92 g. of large transparent colorless plates of I were obtained by addition of 15 cc. of ethanol to the filtrate.

In another run 16 cc. of ethanol was added to a mixture of 1.2 g. of acetamide, 4 g. of hexamine mononitrate, 2 cc. of formalin and 2 cc. of water which had stood for 24 hours. After five days 3 g. of large colorless plates of I was present.

N-Methylolacetamide, prepared from acetamide and formalin by the procedure of Einhorn and Ladisch,[5] crystallized from ethyl acetate containing a few drops of acetone in colorless needles; m.p. 54–56° (reported, 50–52°). A mixture of 0.45 g. of crystalline N-methylolacetamide, 1 g. of hexamine mononitrate and 1 cc. of acetic acid was warmed for ten minutes on a steam-bath with occasional swirling. One cc. of water was added and then 4 cc. of ethanol. On cooling, the solution deposited 0.9 g. of thick plates of I; m.p. 174–176°. Additional I separated gradually from the filtrate. The product was also obtained without the use of acetic acid.

A rapid method of preparing crude N-methylolacetamide (not crystalline) consisted in heating on a steam-bath with occasional swirling a mixture of 3 g. of paraformaldehyde, 5.9 g. of acetamide and a drop of pyridine; in about 45 minutes a clear viscous liquid was obtained which was suitable for the preparation of I.

(b) **From Hexamine.**—A mixture of 5.9 g. of acetamide, 3 g. of paraformaldehyde, 14 g. of hexamine and 22 cc. of acetic acid was warmed on a steam-bath until a clear solution resulted (ten minutes) and then for 20 minutes more. Part of the acetic acid was removed in a current of air; then 7 cc. of 70% nitric acid was added, followed by 60 cc. of ethanol. The first crop of I (11.8 g.) was recrystallized by adding 45 cc. of ethanol to a solution of I in 11.8 cc. of water. Ammonium nitrate can be added in place of nitric acid in the last step to furnish the nitrate ion.

In another method a solution of 1.2 g. of acetamide, 2.8 g. of hexamine, 1.2 cc. of acetic acid and 4 cc. of 37% formalin was allowed to stand at room temperature for two days; then 1.3 cc. of 70% nitric acid was added, followed by 15 cc. of alcohol. I crystallized slowly in large transparent plates; yield 2.5 g.

In still another method 200 cc. of an acetic acid solution of 28 g. (0.2 g. mole) of hexamine and 16 g. (0.2 g. mole) of ammonium nitrate was treated at 35° with 45 cc. (0.45 g. mole) of acetic anhydride in the course of five minutes. After five hours at room temperature, 300 cc. of ether was added to the mixture. Colorless crystals of I precipitated immediately and was collected on a filter after one-half hour; weight 32 g. Pure I (21 g.) was obtained by dissolving the product in an equal weight of water and adding four volumes of ethanol.

The product obtained by the above described methods was shown to be identical with that of Linstead, Kuehl and Leavitt[2] by m.p., mixed m.p., microscopic comparison and chemical properties.

Experiments Related to the Structure Proof of I. (a) **Titration.**—An aqueous solution of 11.8 g. of 1-acetamidomethylhexamine nitrate was titrated with 0.1 *N* sodium hydroxide with phenolphthalein as indicator. The behavior during titration has already been described; a permanent end-point was obtained after 12 hours. Calcd. for $C_9H_{18}N_6O_4$: equiv. wt., 274. Found: equiv. wt., 276.

The titrated solution was evaporated to dryness at room temperature in a current of air and the residue was digested with chloroform. The residue weighed 3.62 g.; calcd. (as sodium nitrate), 3.66. From the chloroform solution, by evaporation and digestion of the residue with acetone to dissolve a liquid portion, was obtained 5 g. (calculated, 6 g.) of crystalline hexamine. Sublimation of the uncrystallizable product isolated from the acetone solution yielded acetamide.

(b) **Reaction with Nitron Chloride.**—Determination of the nitron nitrate which precipitated on addition of nitron chloride to a solution of I gave an equivalent weight of 275 (calcd., 274). Evaporation of the aqueous filtrate and crystallization of the residue from alcohol yielded 1-acetamidomethylhexamine chloride as broad colorless needles; m.p. 188–189°.

1-Propionamidomethylhexamine Nitrate.—A mixture of 0.46 g. of propionamide and 4 g. of hexamine mononitrate in 4 cc. of 37% formalin was warmed slightly and then allowed to stand at room temperature. Precipitation of the product began after three hours and was complete in two days; yield of beautifully crystalline product, 2.4 g. Alternately, a mixture of 7.3 g. of propionamide, 3 g. of paraformaldehyde and a solution of 20 g. of hexamine in 20 cc. of propionic acid was warmed on a steam-bath for 30 minutes; then 10 cc. of 70% nitric acid was added. On standing at room temperature for 12 hours 12.5 g. of 1-propionamidomethylhexamine nitrate crystallized; m.p. 178–180°. Addition of ethanol to the filtrate precipitated an additional 5.7 g. of the same product. By the method of Carmack, Leavitt, Kuehl and Connor for I except that propionic acid and its anhydride were used, 52 g. of the product was obtained from 33.6 g. of hexamine; the product began to precipitate from the mixture in a short time. The 1-propionamidomethylhexamine nitrate crystallized from water, after addition of ethanol, in large colorless plates; m.p. 178–180° or higher. The compound is less soluble than I; it

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(4) E. Aristoff, J. A. Graham, R. H. Meen, G. S. Myers and G. F Wright. *Can. J. Research*, **B27**, 520 (1949), obtained an 81% yield of acetamide from ammonium acetate and acetic anhydride. They also reported some reactions of 1-acetamidomethylhexamine nitrate.

(5) A. Einhorn and C. Ladisch, *Ann.*, **343**, 265 (1905).

requires 1.5 cc. of water for 1 g. When put in the bath at 176° it has m.p. 183–184°. There was no depression in m.p. when mixed with I. By titration with alkali a neutral equivalent of 292 was obtained; calculated, 288.

Reaction of Hexamine and Ammonium Nitrate in Acetic Acid.—A warm solution of 8 g. (0.1 g. mole) of ammonium nitrate and 14 g. (0.1 gram mole) of hexamine in 50 cc. of acetic acid deposited 1.8 g. of stout colorless rods of hexamine mononitrate.

A solution of 80 g. of ammonium nitrate and 140 g. of hexamine in sufficient acetic acid to make a liter of solution deposited colorless crystals of hexamine mononitrate monoacetate after 12 or more hours; neutral equivalent, 262 (calcd., 263). When dried at 70° the transparent crystals changed to a white powder, which proved to be hexamine mononitrate.

ANN ARBOR, MICH. RECEIVED DECEMBER 11, 1950

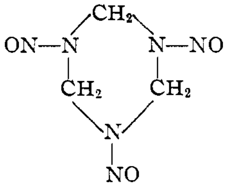
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

The Nitrosation of Hexamethylenetetramine and Related Compounds[1]

BY W. E. BACHMANN AND N. C. DENO

The nature of the product formed in the reaction between hexamethylenetetramine and nitrous acid depends on the *p*H of the solution. At *p*H 1 trinitrosotrimethylenetriamine is formed exclusively; at *p*H 3 and higher, the product is dinitrosopentamethylenetetramine. New eight-membered ring N-nitroso compounds were formed by the action of a mixture of nitrosyl chloride and acetic anhydride on known compounds derived from hexamethylenetetramine.

In connection with studies on the nitration of hexamethylenetetramine, the analogous nitrosation was investigated. From the reaction between hexamethylenetetramine and nitrous acid two compounds have been obtained by previous investigators[2]: 1,3,5-trinitroso-1,3,5-triazacyclohexane (I) (trinitrosotrimethylenetriamine) and 1,5-methylene-3,7-dinitroso-1,3,5,7-tetrazacyclooctane (II) (dinitrosopentamethylenetetramine).



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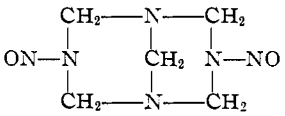

II

Mayer[2] prepared the trinitroso compound (I) by adding a solution of sodium nitrite all in one portion to an aqueous solution of hexamethylenetetramine and excess hydrochloric acid, his purpose being to have a *large amount* of nitrous acid present. To obtain the dinitroso compound (II), Mayer added hydrochloric acid slowly to an aqueous solution of hexamethylenetetramine and sodium nitrite so that *no excess* nitrous acid was present during the reaction. Results which are contrary to Mayer's principles were obtained by Downing[3] and by ourselves. Downing obtained chiefly the dinitroso compound (and not the trinitroso compound that would be expected from Mayer's views) when he added a solution of sodium nitrite (4.8 mole equivalents) all in one portion to a solution of hexamethylenetetramine (1 mole equivalent) and hydrochloric acid (4.1 mole equivalents), and we obtained the trinitroso compound (and not the dinitroso derivative) from exactly the same amounts of reagent used by Downing by adding the sodium nitrite slowly to the other two reagents. All of these apparently conflicting results become clear and consistent with the discovery that the chief factor that determines the nature of the product is the *p*H of the solution. At a *p*H of 1 the trinitroso compound is formed exclusively; at *p*H 2 a mixture of the trinitroso and dinitroso compounds is produced; and in the *p*H range of 3–6 the dinitroso compound is formed exclusively. Table I shows these results, which were obtained by adding hydrochloric acid and a solution of sodium nitrite simultaneously to a solution of hexamethylenetetramine at 2–5° at controlled *p*H values. Provided the proper *p*H is maintained, it is immaterial whether the reagents are mixed all at once or brought into reaction in portions.

TABLE I

INFLUENCE OF *p*H ON THE PRODUCT OF NITROSATION OF HEXAMETHYLENETETRAMINE

*p*H	Weight,[a] g.	Yield, %	M.p.,[b] °C.	Product
1	4.4	50	104.5–106	Trinitroso
2	5.0	..	96–200	Di and trinitroso
3	7.1	76	203.5	Dinitroso
4	6.7	72	207	Dinitroso

[a] From a solution of 7 g. of hexamethylenetetramine in 200 cc. of ice and water, to which were added simultaneously a solution of 15 g. of sodium nitrite (4.3 mole equivalents) in 50 cc. of water and 6 *N* hydrochloric acid at the rate required to maintain the desired *p*H. For the runs at *p*H 3 and 4, potassium hydrogen phthalate was used also. The mixtures were held at 0° for the following periods before filtration: *p*H 1, thirty minutes; *p*H 2, forty-five minutes; *p*H 3, one hour; *p*H 4, five days. [b] M.p. of pure trinitrosotrimethylenetriamine, 106–107°; of dinitrosopentamethylenetetramine, 207 to 215°.

The effect of the *p*H of the solution is emphasized further in the results shown in Table II. In each of these experiments the sodium nitrite solution was added all in one portion to the other reagents, but the products differed because of the differences in the acidity of the mixtures.

When acetic acid was employed, the product was the dinitroso compound over a wide range of conditions (Table III) because the *p*H was in range of 3–6 under the conditions employed.

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[1] This investigation was carried out under a contract recommended by the NDRC between the OSRD and the Reagents of the University of Michigan, 1944. This material has been released by the Security Review Branch of the Department of Defense.

[2] F. Mayer, *Ber.*, **21**, 2883 (1888); P. Griess and G. Harrow, *ibid.*, **21**, 2737 (1888); R. Cambier and A. Brochet, *Compt. rend.*, **120**, 105 (1895); P. Duden and M. Scharff, *Ann.*, **288**, 218 (1895). The last paper presents evidence for the correct structures of the compounds.

[3] D. C. Downing, private communication, 1942.