

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.

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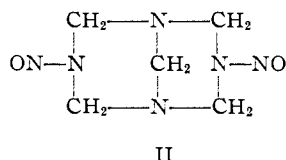
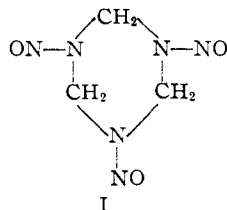
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

## The Nitrosation of Hexamethylenetetramine and Related Compounds<sup>1</sup>

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 pH of the solution. At pH 1 trinitrosotrimethylenetriamine is formed exclusively; at pH 3 and higher, the product is dinitroso-pentamethylenetetramine. 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<sup>2</sup>: 1,3,5-trinitroso-1,3,5-triazacyclohexane (I) (trinitrosotrimethylenetriamine) and 1,5-methylene-3,7-dinitroso-1,3,5,7-tetraazacyclooctane (II) (dinitrosopentamethylenetetramine).



Mayer<sup>2</sup> 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<sup>3</sup> 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

(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.

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 pH of the solution. At a pH of 1 the trinitroso compound is formed exclusively; at pH 2 a mixture of the trinitroso and dinitroso compounds is produced; and in the pH 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 pH values. Provided the proper pH is maintained, it

TABLE I  
INFLUENCE OF pH ON THE PRODUCT OF NITROSATION OF  
HEXAMETHYLENETETRAMINE

pH	Weight, g.	Yield, %	M.p., <sup>b</sup> °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

<sup>a</sup> 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 pH. For the runs at pH 3 and 4, potassium hydrogen phthalate was used also. The mixtures were held at 0° for the following periods before filtration: pH 1, thirty minutes; pH 2, forty-five minutes; pH 3, one hour; pH 4, five days. <sup>b</sup> M.p. of pure trinitrosotrimethylenetriamine, 106–107°; of dinitroso-pentamethylenetetramine, 207 to 215°.

is immaterial whether the reagents are mixed all at once or brought into reaction in portions.

The effect of the pH 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 pH was in range of 3–6 under the conditions employed.

TABLE II  
NITROSATION OF HEXAMETHYLENETETRAMINE IN HYDRO-  
CHLORIC ACID

Hex- amine	Ratio of reagents in moles		Weight, <sup>a</sup> g.	M.p., °C.	Product
	HCl	NaNO <sub>2</sub>			
1	6	1	1.2	106-107	Trinitroso
1	6	3	3.6	106-107	Trinitroso
1	3	3	6.0	155-204	Di and trinitroso
1	3	6	7.1	207-209	Dinitroso

<sup>a</sup> From 7 g. of hexamethylenetetramine in 50 cc. of water, which was added to the hydrochloric acid (13 cc. concentrated acid for 3 mole ratio) and 400 g. of ice, followed by addition in one portion of the sodium nitrite (10.4 g. for 3 mole ratio) in 50 cc. of water; product collected after one hour.

TABLE III  
NITROSATION IN ACETIC ACID

Hex- amine	Ratio of reagents in moles		Weight, <sup>a</sup> g.	M.p., °C.	Product
	AcOH	NaNO <sub>2</sub>			
1	6	3	5.0	206-209	Dinitroso
1	3	6	3.8	207-209	Dinitroso
1	6	6	6.2	207-209	Dinitroso
1	33	6	5.7	206-208	Dinitroso
1	<sup>b</sup>	6	6.6	215	Dinitroso

<sup>a</sup> To an ice-cold solution of 7 g. of hexamethylenetetramine and the acetic acid (9.7 cc. for 3 mole ratio) in 450 cc. of water was added an ice-cold solution of sodium nitrite (10.4 g. for 3 mole ratio) in 50 cc. of water; the product was collected by filtration after one hour. <sup>b</sup> Acetic acid was added in portions over a period of days to the other two reagents in amounts necessary to keep the pH between 6 and 7.

A pH of 1 is best for the preparation of trinitrosotrimethylenetriamine (I). The yield of practically pure product is 50% (mole for mole basis). The optimum pH for a good yield (76%) of dinitrosopentamethylenetetramine at a convenient rate is 3-4.

On the basis of our findings it is possible to understand the reasons for certain statements of other investigators. Thus, Griess and Harrow<sup>2</sup> cautioned against the use of too great an excess of mineral acid in preparing the dinitroso compound and Downing<sup>3</sup> reported that his trinitroso compound was contaminated with the dinitroso derivative if the quantity of hydrochloric acid was reduced.

Two nitro compounds, which can be prepared from hexamethylenetetramine, were nitrosated successfully by a mixture of nitrosyl chloride and acetic anhydride. 1,5-Methylene-3,7-dinitro-1,3,5,7-tetraazacyclooctane (III),<sup>4</sup> the dinitro analog of II, was simultaneously nitrosated and acetylated with loss of the bridge methylene group to 1-acetyl-3,7-dinitro-5-nitroso-1,3,5,7-tetraazacyclooctane (IV) in 60% yield. The structure of IV was demonstrated by oxidation to the known 1-acetyl-3,5,7-trinitro-1,3,5,7-tetraazacyclooctane (V). The oxidation of the nitroso group to the nitro group was accomplished with nitric acid and with a mixture of nitric acid and hydrogen peroxide, which was used by

Brockman, Downing and Wright<sup>5</sup> to oxidize I to RDX.

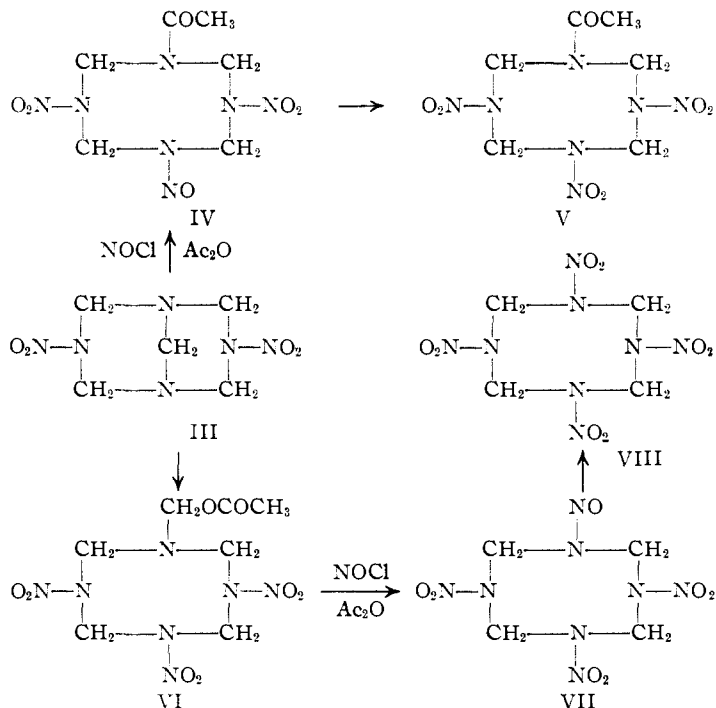
Nitrosyl chloride and acetic anhydride replaced the acetoxymethyl group of 1-acetoxymethyl-3,5,7-trinitro-1,3,5,7-tetraazacyclooctane (VI) by a nitroso group and produced 1-nitroso-3,5,7-trinitro-1,3,5,7-tetraazacyclooctane (VII). The structure of this new product was established by oxidation to the known 1,3,5,7-tetranitro-1,3,5,7-tetraazacyclooctane (HMX) (VIII) in excellent yield.

### Experimental

**Reaction of 1,5-Methylene-3,7-dinitro-1,3,5,7-tetraazacyclooctane (III) with Nitrosyl Chloride and Acetic Anhydride.**—A suspension of 0.5 g. of III<sup>4,6</sup> in a solution of 3 cc. of nitrosyl chloride<sup>7</sup> and 10 cc. of acetic anhydride was stirred at 25° for 15 hours. The clear solution was added to 30 cc. of water and the mixture was allowed to stand until precipitation of the colorless crystalline product was complete; yield 0.39 g. (60%); m.p. 175-180°. After recrystallization from acetone the 1-acetyl-3,7-dinitro-5-nitroso-1,3,5,7-tetraazacyclooctane (IV) began to melt with frothing at 180° when heated fairly rapidly; at 190° it had volatilized completely by decomposition to gaseous products. There was no formation of the reddish color which is characteristic of the decomposition of III.

*Anal.* Calcd. for C<sub>8</sub>H<sub>11</sub>N<sub>7</sub>O<sub>6</sub>: C, 26.00; H, 3.97; N, 35.30. Found: C, 26.15; H, 4.08; N, 34.60.

**Oxidation of 1-Acetyl-3,7-dinitro-5-nitroso-1,3,5,7-tetraazacyclooctane (IV).**—Forty-six mg. of IV was added in portions to a solution of 0.2 cc. of 30% hydrogen peroxide in 2 cc. of 98% nitric acid at -50°; the temperature was allowed to rise to 0° in the course of 30 minutes and was kept there for 12 hours. The 1-acetyl-3,5,7-trinitro-1,3,5,7-tetraazacyclooctane (V) (0.39 mg.; m.p. 214-218°) ob-



tained on drowning melted at 220° (reported,<sup>8</sup> 224.2-

(5) F. J. Brockman, D. C. Downing and G. F. Wright, *ibid.*, **B27**, 469 (1949).

(6) W. E. Bachmann, W. J. Horton, E. L. Jenner, N. W. MacNaughton and L. B. Scott, *THIS JOURNAL*, **73**, 2769 (1951).

(7) W. E. Bachmann and R. Hoffman, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 251.

(8) E. Aristoff, J. A. Graham, R. H. Meen, G. S. Myers and G. F. Wright, *Can. J. Research*, **B27**, 520 (1949).

(4) W. J. Chute, D. C. Downing, A. F. McKay, G. S. Myers and G. F. Wright, *Can. J. Research*, **B27**, 218 (1949).

224.7°) after one recrystallization from acetone-absolute alcohol. Dr. A. T. Blomquist and Dr. W. C. McCrone of Cornell University showed it to be identical with an authentic specimen<sup>5</sup> by crystallographic measurements.

Treatment of 20 mg. of IV with 2 cc. of 98% nitric acid alone at 40° for ten minutes yielded 7 mg. of V.

**Action of Nitrosyl Chloride and Acetic Anhydride on VI.**—A suspension of 0.5 g. of 1-acetoxymethyl-3,5,7-trinitro-1,3,5,7-tetrazacyclooctane (VI) (prepared from III and acetic anhydride and nitric acid)<sup>9</sup> in 5 cc. of acetic anhydride at 0° was treated with a chilled solution of 5 cc. of nitrosyl chloride in 5 cc. of acetic anhydride. After the suspension had been stirred for one hour at 0° and for 12 hours at room temperature, 0.25 g. of unchanged VI was re-

(9) W. E. Bachmann and E. L. Jenner, *THIS JOURNAL*, **73**, 2773 (1951).

moved by filtration; addition of the filtrate to 20 cc. of ice and water precipitated 115 mg. of product (m.p. 192–205°). The 1-nitroso-3,5,7-trinitro-1,3,5,7-tetrazacyclooctane (VII) crystallized from acetone-absolute alcohol in colorless needles; m.p. 236–237°. The highest m.p. obtained was 243.2–243.3°; the compound decomposed suddenly into gaseous products.

*Anal.* Calcd. for  $C_8H_8N_8O_7$ : C, 17.1; H, 2.9; N, 40.0. Found: C, 17.6; H, 3.0; N, 39.9.

**Oxidation of VII to HMX (VIII).**—Oxidation of 40 mg. of VII by 0.15 cc. of 30% hydrogen peroxide and 2 cc. of 98% nitric acid was carried out as described for the oxidation of IV. The HMX (35 mg.) obtained on drowning the mixture melted at 281° alone and when mixed with an authentic specimen.<sup>6</sup>

ANN ARBOR, MICH.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF FORDHAM UNIVERSITY]

## The Willgerodt Reaction in the Heterocyclic Series. II. Some Compounds of the $\alpha$ - and $\beta$ -Thienyl Series

BY JOSEPH A. BLANCHETTE AND ELLIS V. BROWN

The Willgerodt reaction in the thiophene series has been extended with a view to determining its scope. Alkyl substituted  $\alpha$ -thienyl methyl ketones,  $\beta$ -thienyl methyl ketone,  $\alpha$ -formyl-,  $\alpha$ -vinyl-,  $\alpha$ -acetyl- and  $\alpha$ -(1-hydroxyethyl)-thiophenes have yielded the respective amides. Several new acetamides and acetic acids of the thiophene series are characterized and a method for the preparation of 3-methyl-2-thienyl methyl ketone, which does not involve separation of the 3 and 4 isomers, is described.

We have recently reported<sup>1</sup> a study of the Willgerodt reaction with a series of 2,5-dimethyl-3-thienyl aliphatic ketones. It had previously been shown<sup>1,2</sup> that 2-thienyl methyl ketone does not react under the conditions of the Willgerodt reaction although the introduction of  $\alpha, \alpha'$ -methyl groups into thiophene alkyl ketones allowed us to obtain the expected amides. In view of these facts, the effect of substituents and their position seemed to be of major importance in the application of this reaction to thiophene compounds.

This paper deals with the further application of the Willgerodt reaction to thiophene compounds in an attempt to determine the necessary groups and position for a favorable reaction. We have conducted our investigation with the aim of determining the limiting conditions necessary for a successful reaction. As an addition to the previous study both  $\alpha$ -methyl groups were replaced by ethyl groups. The 2,5-diethyl-3-thienyl methyl ketone gave the expected 2,5-diethyl-3-thienylacetamide in satisfactory yields.

$\alpha$ -Thienyl ketones which react to give the respective amides are 5-methyl-2-thienyl methyl ketone, 5-ethyl-2-thienyl methyl ketone and 2,3-dimethyl-5-thienyl methyl ketone. Recently Ford, Prescott and Colingsworth<sup>2b</sup> applied the Kindler modification to 5-*t*-butyl-2-thienyl methyl ketone obtaining a derivative of 5-*t*-butyl-2-thienylacetic acid and, in view of the failure of 2-acetothienone to react, speculated that the reactive hydrogen in the 5-position must be replaced by an alkyl group before the Willgerodt reaction can take place. This does not seem to be the case as we have con-

verted both 3,4-dimethyl-2-thienyl methyl ketone and 3-methyl-2-thienyl methyl ketone to the corresponding acetamides. To circumvent the isomeric mixture obtained from direct acetylation of 3-methylthiophene, the latter ketone was prepared by a five-step process. 3-Methylthiophene was converted to 2-bromo-3-methylthiophene by the action of N-bromosuccinimide. 2-Bromo-3-methylthiophene was treated with magnesium and then carbonated to yield 3-methyl-2-thienyl-carboxylic acid. This acid was treated with thionyl chloride and then converted to the ketone with dimethylcadmium by the method of Gilman and Nelson<sup>3</sup> in 85% yield. The melting point of the 3-methyl-2-thienylcarboxylic acid was in agreement with that reported in the literature.<sup>4</sup>

At this point it seemed plausible to assume that at least one ring position, either  $\alpha$  or  $\beta$ , must contain an alkyl substituent for reaction to occur. However, 2-vinylthiophene was found to give 2-thienylacetamide in yields of 25–30% despite an otherwise completely unsubstituted ring. The failure of 2-acetothienone to react may therefore be due to some peculiarity of this particular molecule rather than to the unsubstituted character of the ring. Further support for this assumption was sought from other monosubstituted thiophenes with different functional groups at the 2-position.

2-Thienylcarboxaldehyde<sup>5</sup> gave 2-thienylcarboxamide<sup>5</sup> in excellent yields and a mixed melting point with an authentic sample of this amide, prepared from 2-cyanothiophene, showed no de-

(3) H. Gilman and J. F. Nelson, *Rec. trav. chim.*, **55**, 518 (1936).

(4) W. Steinkopf and H. Jacob, *Ann.*, **515**, 273 (1935); L. E. Levi, *Ber.*, **19**, 657 (1886); L. Gattermann, *Ann.*, **244**, 58 (1888); I. J. Rinkes, *Rec. trav. chim.*, **52**, 1052 (1933).

(5) K. Wiberg, "Organic Syntheses," Vol. 29, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 87.

(6) W. Steinkopf, "Chemie Des Thiophens," J. W. Edwards, Ann Arbor, Mich., 1944, p. 85.

(1) E. V. Brown and J. A. Blanchette, *THIS JOURNAL*, **72**, 3414 (1950).

(2) (a) E. Schwenk and D. Papa, *J. Org. Chem.*, **11**, 798 (1946); (b) J. H. Ford, G. C. Prescott and D. R. Colingsworth, *THIS JOURNAL*, **72**, 2109 (1950).