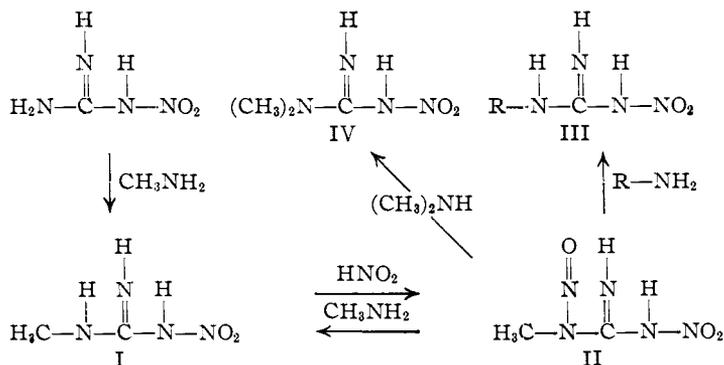


[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF TORONTO]

## Preparation and Properties of N-Methyl-N-nitroso-N'-nitroguanidine

BY A. F. MCKAY AND GEORGE F WRIGHT

It has been shown by Davis and Rosenquist<sup>1</sup> that N-nitroso-N'-alkylguanidines react with alkylamines to eliminate the nitrosamino group and form N-R,N'-R-dialkylguanidines. This reaction cannot be applied to the preparation of N-alkyl-N'-nitroguanidines because N-nitroso-N'-nitroguanidine is unknown. We have found, however, that N-methyl-N'-nitroguanidine, I, can be nitrosated with ease, and the N-methyl-N-nitroso-N'-nitroguanidine, II, reacts like Davis and Rosenquist's unsubstituted nitrosoguanidine to give N-alkyl-N'-nitroguanidines or N-phenyl-N'-nitroguanidines, III, R = methyl, *n*-butyl, isobutyl, isoamyl, dimethyl, phenyl.



The over-all reaction thus becomes an exchange of the methylamino in N-methyl-N'-nitroguanidine for other alkylamino, the dimethylamino or arylamino groups. The nitroguanidine derivatives prepared by this reaction are listed above. Diethylamine and di-*n*-propylamine do not react with N-methyl-N-nitroso-N'-nitroguanidine to give the corresponding N-dialkyl-N'-nitroguanidines IV although they do promote the decomposition of the nitrosamine with the evolution of gaseous products. Davis and Luce<sup>2</sup> also observed that of the dialkylamines only dimethylamine would react with nitroguanidine.

N-Methyl-N-nitroso-N'-nitroguanidine II reacts at or below room temperature with an aqueous solution of butylamine to give gaseous products over a fifteen-minute period and to precipitate a 51% yield of N-butyl-N'-nitroguanidine, while dimethylamine correspondingly gives a 60% yield of N-dimethylamino-N'-nitroguanidine, IV. It is possible to increase these yields by keeping the reaction at room temperature for a longer time and then cooling before filtration. Under these conditions N-isoamyl-N'-nitroguanidine, III, may

be prepared in 73% yield. However, with the higher yields the products are less pure than with the smaller yields.

The choice of which method, the one described above or that of Davis and Abrams from nitroguanidine and the amine,<sup>2,3</sup> will depend on the substituted nitroguanidine which is desired. Thus, when Davis and Abrams' method is used with aniline as the amine, the chief product is phenylurea.<sup>3</sup> On the other hand a good yield of phenylnitroguanidine can be prepared from N-methyl-N-nitroso-N'-nitroguanidine.

This choice of method is practical because the preparation<sup>3</sup> of methylnitroguanidine has been improved and simplified. In our revised procedure an aqueous alkaline solution of nitroguanidine is treated with an aqueous solution of methylammonium chloride. The precipitate which forms dissolves readily at 60–70°, and destruction of the product is diminished by decrease in the reaction time. The modification is applicable to other alkylnitroguanidines to be reported in the future.

We were somewhat surprised at the ease with which methylnitroguanidine could be nitrosated, in view of the reported failures<sup>4</sup> when attempts were made to nitrate it. We were equally unsuccessful, not only when we repeated the procedures of Davis and Elderfield, but also when we attempted the nitration in perchloric acid or with the perchlorate salt. Indeed there would seem to be some strong influence opposing the formation of methyl-dinitroguanidine. Thus, when N-methyl-N-nitroso-N'-nitroguanidine was treated with absolute nitric acid, the only reaction which occurred was the elimination of the nitroso group. The methylnitroguanidine formed in this way did not undergo nitration, but was largely recovered unchanged. An attempt to oxidize N-methyl-N-nitroso-N'-nitroguanidine with ammonium persulfate in nitric acid solution was also unsuccessful.

The investigations on N-methyl-N-nitroso-N'-nitroguanidine are being continued.

Experimental<sup>5</sup>

**N-Methyl-N'-nitroguanidine.**—An alkaline solution of 10.4 g. (0.1 mole) of nitroguanidine in 30 cc. of water containing 12 g. (0.21 mole) of potassium hydroxide was prepared. The solution was heated to 40° to dissolve the

(3) T. L. Davis and A. J. J. Abrams, *Proc. Am. Acad. Sci.*, **61**, 437 (1926).

(4) T. L. Davis and R. C. Elderfield, *THIS JOURNAL*, **55**, 731 (1933).

(5) All melting points have been corrected against known standards.

(1) T. L. Davis and E. N. Rosenquist, *THIS JOURNAL*, **59**, 2112 (1937).

(2) T. L. Davis and S. B. Luce, *ibid.*, **49**, II, 2303 (1927).

nitroguanidine and then 13.5 g. (0.2 mole) of methylamine hydrochloride was added with stirring. A viscous sludge formed and the evolution of ammonia was observed. The temperature was steadily increased to 59° over a period of eight minutes and maintained at 59-61° for twenty-three minutes. At the end of this time, during which the reaction mixture was stirred continuously, the clear solution was cooled in an ice-water-bath to 6°. The white precipitate was filtered off, washed with cold water (30 cc.) and dried in the oven at 60°. The crude product melted at 151-154° and was contaminated with a small amount of potassium chloride, yield 10 g. (84.7%). One crystallization from water (3 cc. per gram), to remove the inorganic material, raised the melting point to 157°, yield 7.8 g. Finally recrystallization from 95% ethanol (8 cc. per gram) gave the pure product melting at 160-161°. A mixed melting point with a sample of methylnitroguanidine (m. p. 159-161°) prepared by the method of Davis and Abrams<sup>3</sup> was not depressed.

**N-Methyl-N'-nitroguanidine Nitrate.**—To a suspension of 1 g. (0.0084 mole) of finely ground methylnitroguanidine in 10 cc. of carbon tetrachloride at -5° was added 0.355 cc. (0.0085 mole) of 99% nitric acid over four minutes. The gummy mass coagulated to a granular suspension after thirty minutes of stirring at -15°. It weighed 1.42 g. (93%) and melted at 79-87°. The salt could be detonated by impact between steel surfaces. The melting point varied with each preparation, and the salt is therefore not a good derivative. A sample, m. p. 91°, was analyzed.

*Anal.* Calcd. for C<sub>2</sub>H<sub>7</sub>N<sub>3</sub>O<sub>3</sub>: C, 13.2; H, 3.86; N, 38.6. Found: C, 13.2; H, 3.85; N, 38.6.

**N-Methyl-N'-nitroguanidine Perchlorate.**—A suspension of 6 g. (0.042 mole) of methylnitroguanidine in 25 cc. of 60% perchloric acid was warmed until solution was complete. The needle-like rosetts which separated on cooling were filtered off at 0° and washed with 10 cc. of 30% perchloric acid and then with 10 cc. of carbon tetrachloride. The 6.65 g. yield melted at 98-101°. A second crop (2 g., softened at 82°) was obtained by careful evaporation of the filtrate. Recrystallization of this 94% yield gave a salt melting at 104°. This salt was quite sensitive to impact; it detonated violently. It could be recovered unchanged from an ether diluate after solution in 99.3% nitric acid for thirty minutes at -15°.

*Anal.* Calcd. for C<sub>2</sub>H<sub>7</sub>N<sub>3</sub>O<sub>6</sub>Cl: C, 11.0; H, 3.20; N, 25.6. Found: C, 10.8; H, 3.26; N, 25.6.

**Attempted Nitration of Methylnitroguanidine.**—When methylnitroguanidine was dissolved in a mixture of 100.2% nitric acid and 100% perchloric acid<sup>6</sup> at 0° and the solution after one hour was poured into ethyl ether, a 91% yield of methylnitroguanidine nitrate, m. p. 80-81°, was precipitated. These results were qualitatively and almost quantitatively duplicated when the nitration medium was 1, nitric acid; 2, nitric acid plus zinc chloride; 3, nitric acid plus perboric acid; 4, nitric acid plus boron trifluoride.

**N-Methyl-N-nitroso-N'-nitroguanidine.**—Ten grams (0.08 mole) of methylnitroguanidine was dissolved in 100 cc. of water by the addition of 30 cc. of nitric acid (sp. gr. 1.42). This solution was cooled in an ice-water-bath and 12.4 g. (0.18 mole) of sodium nitrite dissolved in 20 cc. of water was added over a period of five minutes. During the addition period and for a further period of twenty minutes, the reaction mixture was mechanically stirred. The yellow crystalline product was filtered and washed with cold water. The crude product melted at 112-113° with decomposition, yield 11.25 g. (90.6%). A sample was prepared for analysis by wasteful crystallization from methanol (4.8 cc. per g.). The purified product melted at 118° with decomposition. The compound decomposes in alkaline solution with formation of gas.

*Anal.* Calcd. for C<sub>2</sub>H<sub>5</sub>N<sub>3</sub>O<sub>3</sub>: C, 16.3; H, 3.40; N, 47.6. Found: C, 16.3; H, 3.43; N, 47.5.

When a solution of the nitroso compound (1 g., 0.0068

mole) in 12.2 cc. (0.29 mole) of 99% nitric acid was prepared at -40° and allowed to stand five minutes, an aliquot gave no water-insoluble precipitate. The remainder, poured into ethyl ether, gave a white solid, presumably the nitrate salt of methylnitroguanidine. The solid was recovered by filtration and washed with water. Water caused immediate and complete hydrolysis of the nitrate salt of methylnitroguanidine. When the nitric acid was washed out, the methylnitroguanidine remained. The washed and dried product melted at 159-161° alone and on admixture with an authentic sample of methylnitroguanidine, yield 600 mg. (75%). Identical results were obtained when 0.0023 mole of zinc chloride was included with the nitric acid. An equimolar quantity of ammonium persulfate in the nitric acid solution (reaction temperature 0°) likewise gave no water-insoluble product when either zinc chloride or silver nitrate was added as a catalyst.

**N-Butyl-N'-nitroguanidine.**—An aqueous solution of 1.09 g. (0.015 mole) of *n*-butylamine in 5 cc. of water was added over a period of fifteen minutes to 2 g. (0.013 mole) of N-methyl-N-nitroso-N'-nitroguanidine with stirring. During the addition of the *n*-butylamine solution, the reaction mixture was cooled in an ice-water-bath. Vigorous gassing accompanied the addition of the amine solution. After complete addition of the amine, the reaction mixture was allowed to stand in the cold for a further three minutes. The white precipitate, which was present at this time, was filtered off and washed with cold water. The product melted at 83.5°, alone and on admixture with an authentic sample of *n*-butyl-N'-nitroguanidine; yield 1.12 g. (51.5%).

**N,N-Dimethyl-N'-nitroguanidine.**—Dimethylamine replaced butylamine in a procedure otherwise identical with that outlined above. When 1 and 2 mole equivalent of amine were mixed with N-methyl-N-nitroso-N'-nitroguanidine approximately the same yields (59.5 and 55%, respectively) were obtained. The melting point, alone and on admixture with an authentic sample of N,N-dimethyl-N'-nitroguanidine, was 193.5-195°. **N-Methyl-N'-nitroguanidine** (m. p. 158-161°), **N-isobutyl-N'-nitroguanidine** (m. p. 118-119°) and **N-isoamyl-N'-nitroguanidine** (m. p. 143-145°) were prepared in 54, 55 and 57% yields, respectively, by a procedure identical with that outlined for butylnitroguanidine. One recrystallization of N-isobutyl-N'-nitroguanidine from 40% aqueous ethanol raised the melting point to 121-122°. Likewise the melting point of N-isoamyl-N'-nitroguanidine was raised to 145-146° by one recrystallization from 60% aqueous ethanol.

**N-Isoamyl-N'-nitroguanidine** was prepared by the procedure outlined for N-butyl-N'-nitroguanidine with the one exception that the reaction mixture was allowed to stand at room temperature for forty minutes before cooling. The product, after filtration, was obtained in 73% yield, m. p. 129-133°. One crystallization from 2.5 cc. of ethanol raised the melting point to 144-145°.

**N-Phenyl-N'-nitroguanidine.**—Two grams (1.36 × 10<sup>-2</sup> mole) of N-methyl-N-nitroso-N'-nitroguanidine covered with 5 cc. of water was treated with 1.4 g. (1.5 × 10<sup>-2</sup> mole) of aniline suspended in 5 cc. of water. A slow evolution of gas occurred at room temperature. After standing overnight at room temperature a solid mass contaminated with aniline had formed. The solid was filtered off and washed with water (20 cc.) and 95% ethanol (6 cc.). The remaining white solid melted at 149-152°; yield 1.6 g. (66%). This material after one recrystallization from 95% ethanol (8 cc./g.) melted at 152-153°; yield 1.1 g.

*Anal.* Calcd. for C<sub>7</sub>H<sub>8</sub>N<sub>4</sub>O<sub>2</sub>: C, 46.6; H, 4.44; N, 31.1. Found: C, 46.3; H, 4.52; N, 31.1.

The authors wish to acknowledge the aid to one of them (A.F.M.) by a Fellowship from the National Research Council, Canada.

## Summary

Methylnitroguanidine has been prepared by an

(6) Vorländer and Schilling, *Ann.*, **310**, 369 (1900).

improved procedure and nitrosated to give N-methyl-N-nitroso-N'-nitroguanidine.

Neither this nitroso compound nor the parent methylnitroguanidine could be converted to methyl dinitroguanidine by a variety of procedures. In each instance methylnitroguanidine was recovered.

When N-methyl-N-nitroso-N'-nitroguanidine is treated with an aqueous solution of an alkylamine, the methylnitrosamino group is eliminated and replaced by an alkylamino group. This provides a convenient method for synthesis of N-alkyl-, N-aryl- and N,N-dimethyl-N'-nitroguanidines.

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## The Antibacterial Principle of *Arctium minus*. II. The Unsaturated Lactone Structure

BY CHESTER J. CAVALLITO AND FRED K. KIRCHNER

Recently, Abraham, *et al.*,<sup>1</sup> described the isolation and properties of an antibiotic from *Arctium minus* and *Onopordon tauricum* which they believe to be an isomer of the substance (I) isolated by us from the former plant.<sup>2</sup> The empirical formula for both substances is  $(C_3H_4O)_x$  in which we had tentatively assigned  $x$  as 5; however, later evidence is in agreement with  $x$  as 6 in accordance with the Oxford group for their material. Sufficient evidence is now available to indicate the nature of the groups responsible for the antibacterial activity of I.

In order to prevent formation of insoluble amorphous products from I upon standing, it is stored with refrigeration in the form of large crystals. Satisfactory cryoscopic molecular weights could be determined with freshly crystallized I in carefully purified dioxane.

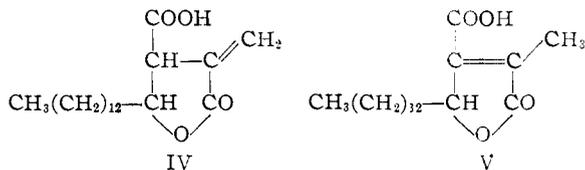
Early work<sup>2</sup> showed that I possessed one double bond reactive toward iodine bromide. Catalytic hydrogenation results in the uptake of two molar equivalents of hydrogen with formation of an amorphous tetrahydro derivative. A second double bond, conjugated to a carbonyl group, has been shown to be present.

The isopropylamine derivative previously described<sup>2</sup> was unsatisfactory for distinguishing between  $x$  as 5 or 6 in the molecular formula, hence a corresponding benzylamine derivative, II, was prepared. The nitrogen in these derivatives has basic properties and II formed a relatively water-insoluble crystalline hydrochloride. These basic derivatives show the presence of only one double bond and catalytic hydrogenation results in absorption of one molar equivalent of hydrogen with formation of an amorphous product. Although II is insoluble in sodium bicarbonate solutions, it may be dissolved in cold alcoholic sodium hydroxide. Such solutions, upon dilution with water, do not precipitate II; however, II is formed again upon acidification. These observations indicate that the amine has added to one of the double bonds in I but has not reacted with the

lactone group, as evidenced by the basic nature of II and by the remaining lactone structure. The ease of re-lactonization of II upon acidification of an alkaline solution of the substance is evidence in favor of a  $\gamma$ - or  $\delta$ -lactone, preferably the former. The double bond in I which disappeared with formation of derivative II was the one which did not react with iodine bromide. This indicates it to be  $\alpha,\beta$  to a carbonyl group and is the double bond essential for antibacterial activity, the isopropylamine derivative having no such activity. Whereas I undergoes oxidation and polymerization reactions, II is very stable. These observations all point to the presence in I of an unsaturated lactone structure of type  $\begin{array}{c} \text{---C---C---C=CH}_2 \\ | \quad | \quad | \\ \text{O} \quad \text{---CO} \end{array}$  in

which amines would add with the nitrogen attaching to the  $\beta$ -carbon atom of the unsaturated linkage. The prototype of this structure is  $\alpha$ -methylene butyrolactone (III) which has been obtained from *Erythronium americanum*.<sup>3</sup> Compound III undergoes polymerization, it readily adds dinitrophenylhydrazine, whereas the isomeric  $\alpha$ -methyl- $\Delta^{\alpha,\beta}$ -butenolide does not, and the double bond does not add iodine bromide.

Examination of the scientific literature shows that a pair of isomeric unsaturated lactones, protolichesterinic (IV) and lichesterinic (V) acids, also demonstrate considerable differences in ease of addition of amines, such as semicarbazide, IV yielding an addition product involving the double bond whereas V does not react.<sup>4</sup> Samples of IV and V were prepared and it was shown that whereas V does not react, IV yields a crystalline, basic (amphoteric) benzylamine addition product



(1) Abraham, Crowfoot, Joseph and Osborn, *Nature*, **158**, 744 (1946).

(2) Cavallito, Bailey and Kirchner, *THIS JOURNAL*, **67**, 948 (1945).

(3) Cavallito and Haskell, *ibid.*, **68**, 2332 (1946).

(4) Asano and Kanematsu, *Ber.*, **65**, 1175 (1932).