THE REACTION OF NITRAMINES WITH HYDROCHLORIC ACID[1]

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ABSTRACT

A facile process for the conversion of N-(β-nitraminoethyl)-N′-substituted-N″-nitroguanidines into the reactive N-(β-chloroethyl)-N′-substituted-N″-nitroguanidines has been developed. N-(β-Nitraminoethyl)-N′-phenyl-N″-nitroguanidine on standing in concentrated hydrochloric acid solution gives a mixture of N-(β-chloroethyl)-N′-phenyl-N″-nitroguanidine and 1-nitro-2-phenylamino-2-imidazoline. N-(β-Chloroethyl)-N′-diethyl-N″-nitroguanidine, which is prepared in a similar manner, is unstable at room temperature and it slowly cyclizes to give 1-nitro-2-diethylamino-2-imidazoline. Some new nitroguanidine derivatives formed from the reaction of amines with methylnitrosonitroguanidine also are described.

It was previously (2) shown that alkyl nitramines in dilute acid solutions decomposed to give alkyl cations. Thus methylnitramine in dilute hydrochloric acid solution gave a 50% yield of methyl chloride from the reaction of the intermediate methyl cation with the chloride ion. The mechanism of this reaction indicated the possibility of substituting the chloro group for a nitramino group in good yield by treating an aliphatic nitramine with an excess of concentrated hydrochloric acid. This assumption was realized (8) with N-β-nitraminoethyl-N′-nitroguanidine on treatment with concentrated hydrochloric acid when a 92.6% yield of the expected N-β-chloroethyl-N′-nitroguanidine was obtained. Since this reaction provided a simple method of obtaining the reactive and highly substituted N-β-chloroethyl-N′-nitroguanidines, it was investigated further.

N-(β-Nitraminoethyl)-N′-phenyl-N″-nitroguanidine (I) in concentrated hydrochloric acid solution gave a 74.2% yield of N-(β-chloroethyl)-N′-phenyl-N″-nitroguanidine (III). The filtrate after neutralization in the cold with sodium hydroxide solution gave a 20.4% yield of 1-nitro-2-phenylamino-2-imidazoline (or the tautomeric 1-nitro-2-phenyliminoimidazolidine) (IV). These products are easily explained on the basis of the formation of an intermediate alkyl cation II as shown below. The similarity of the reactions depicted here to those previously outlined for the reaction of acetyl chloride with N-(β-nitraminoethyl)-N′-substituted-N″-nitroguanidines (4, 7, 9, 10) will be apparent. As stressed before (7) the main reason for the complexity ascribed to some of the acetyl chloride – nitramine reactions was the variety of products isolated. Some of these products undoubtedly arose from secondary reactions during the involved isolation procedures. The products from the reaction of the N-(β-nitraminoethyl)-N′-substituted-N″-nitroguanidine with concentrated hydrochloric acid solution can be separated with ease, which eliminates this difficulty.

The structure of N-(β-chloroethyl)-N′-phenyl-N″-nitroguanidine (III) was

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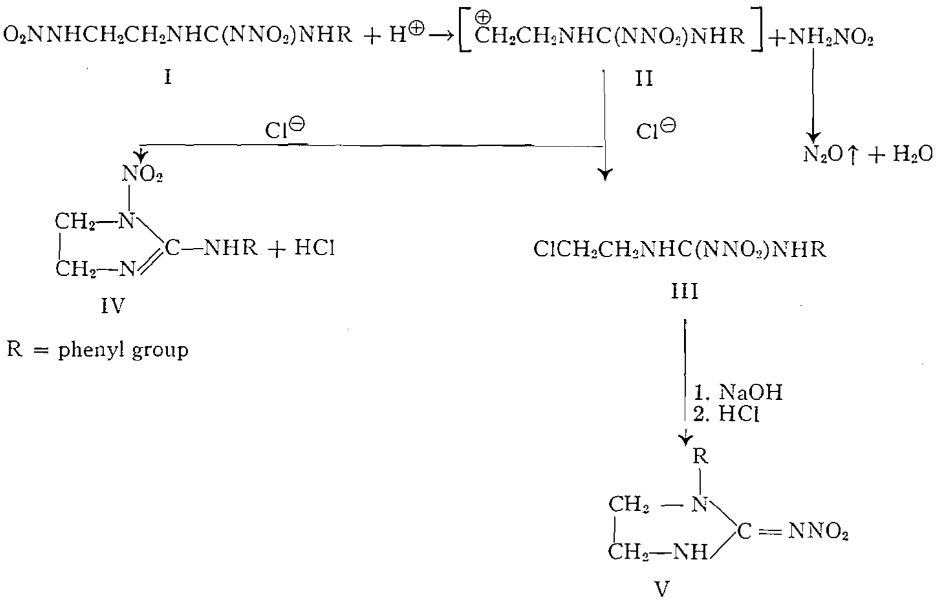
[1] *Manuscript received March 21, 1955.*
Contribution from Defence Research Chemical Laboratories, Ottawa, Ontario, and L. G. Ryan Research Laboratory of Monsanto Canada Limited, Ville LaSalle, Quebec. Issued as D.R.C.L. Report No. 140.



R = phenyl group

confirmed by its infrared spectrum and by its conversion to the known 1-phenyl-2-nitriminoimidazolidine (V) (12). 1-Phenyl-2-nitriminoimidazolidine was previously (12) referred to as the tautomeric 1-phenyl-2-nitramino-2-imidazoline. The reason for this change in nomenclature has been discussed recently (13).

A more highly substituted compound N-(β-nitraminoethyl)-N′-diethyl-N″-nitroguanidine also was allowed to stand at room temperature in hydrochloric acid solution. The product from this reaction melted at 96–97° C. and it was identified as N-(β-chloroethyl)-N′-diethyl-N″-nitroguanidine by analysis and by its chemical properties. When N-(β-chloroethyl)-N′-diethyl-N″-nitroguanidine was heated with water it cyclized to 1-nitro-2-diethylamino-2-imidazoline. The latter compound was isolated as its picrate. On standing in a vial the crystalline N-(β-chloroethyl)-N′-diethyl-N″-nitroguanidine changed into a viscous oil with entrained gas bubbles. This oil was dissolved in water and then treated with a saturated solution of picric acid. A 69% yield of 1-nitro-2-diethylamino-2-imidazolinium picrate was obtained. Thus the original crystalline N-(β-chloroethyl)-N′-diethyl-N″-nitroguanidine cyclized on standing at room temperature. The presence of gas bubbles in the viscous oil suggests that some decomposition also occurred.

Some new nitroguanidine derivatives have been prepared by the reaction of amines with methylnitrosonitroguanidine (6, 14). These are described in the Experimental section.

EXPERIMENTAL[2]

N-Methyl-N-nitroso-N′-nitroguanidine

This compound (m.p. 118° C. with decomp.) was prepared as previously described (11).

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[2] *All melting points were taken on a Kofler block. Microanalyses by Micro-Tech Laboratories, Skokie, Illinois.*

N-Acetyl Ethylenediamine

N-Acetyl ethylenediamine was prepared by the method of Hill and Aspinall (1, 5). Ninety-five per cent ethylenediamine (570 gm., 9.0 moles) was mixed with 264 gm. (3.0 moles) of ethyl acetate and left at room temperature for eight days. The ethyl alcohol and excess amine were removed by distillation *in vacuo*. The residue on distillation *in vacuo* gave 233.3 gm. (69.9%) of N-acetyl ethylenediamine, b.p. 99–103° C. (0.5 mm.). This distillate soon solidified after which it melted at 49.5° C. The melting point given in the literature (5) is 51° C. The residual solid (62.6 gm.) in the distillation flask melted sharply at 173–174.5° C. after one crystallization from 95% ethanol (2.4 cc./gm.). A melting point of 175° C. is given in the literature (5) for N,N'-diacetyl ethylenediamine.

N-(β-Acetylaminoethyl)-N'-nitroguanidine

To 32.7 gm. (0.032 mole) of monoacetylethylenediamine in 35 cc. of water was added portionwise 15.7 gm. (0.0107 mole) of methylnitrosonitroguanidine over a period of 25 min. During the addition period the temperature was held at 22–27° C. A creamy-white solid separated which was removed by filtration and washed with water, yield 11.24 gm. (56.2%). One crystallization from 95% ethanol (9 cc./gm.) raised the melting point from 134° C. to 150.5–151.5° C. Calc. for $C_5H_{11}N_5O_3$: C, 31.75; H, 5.82; N, 37.03%. Found: C, 31.54; H, 5.87; N, 37.28%.

Monocarbethoxyethylenediamine

Monocarbethoxyethylenediamine (b.p. 135–137°C. (23 mm.); ($n_D^{24.8}$ 1.455; $d_4^{24.8}$ 1.029) was prepared in 40% yield by the method of Moore *et al.* (15).

N-(N-Carbethoxy-β-aminoethyl)-N'-nitroguanidine

To 7.5 gm. (0.0568 mole) of monocarbethoxyethylenediamine in 30 cc. of water was added gradually with stirring 2.79 gm. (0.019 mole) of methylnitrosonitroguanidine over a period of 32 min. During the addition period and an additional half hour of stirring, the temperature was held at 30–35° C. The white solid (m.p. 165.0° C.) was removed by filtration and washed with water, yield 3.34 gm. (80.2%). One crystallization from absolute ethanol (44.3 cc./gm.) raised the melting point to 165.5° C. Calc. for $C_6H_{13}N_5O_4$: C, 32.88; H, 5.93; N, 31.96%. Found: C, 33.05; H, 6.22; N, 32.22%.

N-(β-Nitraminoethyl)-N'-diethyl-N''-nitroguanidine

Five grams (0.029 mole) of 1-nitro-2-nitriminoimidazolidine were covered with 20 cc. of diethylamine and then allowed to stand at room temperature for three days. This reaction mixture was acidified and then placed in the refrigerator for two days. The crystals were removed by filtration and washed with ether and ethanol, yield 3.05 gm. (43.1%). Two crystallizations from 95% ethanol raised the melting point from 133–135° C. with decomposition to 152.5° C. with decomposition. The Franchimont test using dimethylaniline was negative. Calc. for $C_7H_{16}N_6O_4$: C, 33.85; H, 6.45; N, 33.85%. Found: C, 33.86; H, 6.48; N, 33.81%.

N-(β-Nitraminoethyl)-N′-phenyl-N″-nitroguanidine

N-(β-Nitraminoethyl)-N′-phenyl-N″-nitroguanidine (m.p. 139.5–140.5° C.) was prepared in 96% yield as previously described (10).

Reaction of N-(β-Nitraminoethyl)-N′-phenyl-N″-nitroguanidine with Hydrochloric Acid Solution

N-(β-Nitraminoethyl)-N′-phenyl-N″-nitroguanidine (4.97 gm., 0.018 mole) was suspended in 10 cc. of concentrated hydrochloric acid solution and left at room temperature for 48 hr. After the reaction mixture was diluted with 10 cc. of water, it was placed in the refrigerator for 12 hr. The crystals (m.p. 101–102° C., resolidified at 112° C. and then decomposed at 160–163° C.) were removed by filtration and washed with water, yield 3.245 gm. (74.2%). Two crystallizations from methanol at room temperature by the addition of water increased the melting point to 112–113° C. with resolidification at 117–118° C. and decomposition at 160–163° C. Calc. for $C_9H_{11}ClN_4O_2$: C, 44.54; H, 4.56; Cl, 14.62; N, 23.09%. Found: C, 44.75; H, 4.65; Cl, 14.92; N, 22.80%. This product possessing a double melting point was further identified as N-(β-chloroethyl)-N′-phenyl-N″-nitroguanidine by cyclization to the known 1-phenyl-2-nitriminoimidazolidine (12). N-(β-Chloroethyl)-N′-phenyl-N″-nitroguanidine (500 mgm., 0.002 mole) was refluxed for one minute with 117 mgm. (0.0027 mole) of potassium hydroxide in 2 cc. of 95% methanol. On cooling, colorless crystals (m.p. 164–168° C.) separated, yield 394 mgm. (92.7%). One crystallization from 95% methanol raised the melting point to 168–168.5° C. The melting point was unchanged on admixture with an authentic sample of 1-phenyl-2-nitriminoimidazolidine (m.p. 168–169° C.).

The mother liquor from the N-(β-chloroethyl)-N′-phenyl-N″-nitroguanidine gave 140 mgm. of the original N-(β-nitraminoethyl)-N′-phenyl-N″-nitroguanidine (m.p. 138–139° C.). The latter compound was identified by a mixed melting point determination with an authentic sample of N-(β-nitraminoethyl)-N′-phenyl-N″-nitroguanidine (m.p. 139.5–140.5° C.).

The original filtrate from the first crop of crystals on neutralization with 10% sodium hydroxide solution gave 602 mgm. (20.45%) of crystals (m.p. 129–130° C.). One crystallization from ethanol raised the melting point to 138–139° C. (m.p. 132.5–133.5° C. by the capillary method). This compound gave a deep green color with dimethylaniline in the Franchimont test (3). Calc. for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.89; N, 27.17%. Found: C, 52.49; H, 4.99; N, 27.00%. This compound gave a picrate (m.p. 146–147° C.) when treated in the usual manner, yield 80.5%. This picrate was identified as 1-nitro-2-phenylamino-2-imidazolinium picrate by a mixed melting point determination with an authentic sample (10).

Reaction of N-(β-Nitraminoethyl)-N′-diethyl-N″-nitroguanidine with Hydrochloric Acid Solution

N-(β-Nitraminoethyl)-N′-diethyl-N″-nitroguanidine (5.0 mgm., 0.020 mole) was covered with 15 cc. of concentrated hydrochloric acid solution and left at room temperature for 19 hr. The clear solution was diluted with one volume of water and then placed in the refrigerator for several hours. During neutralization of the cold solution with 10% sodium hydroxide solution, colorless crystals separated, yield 2.53 gm. (53.51%). Another 534 mgm. (total yield 66.39%) of crystalline material was obtained from the mother liquor on evaporation. The melting point (96–97° C.) of the crude material was not changed by crystallization from absolute methanol. Calc. for $C_7H_{15}ClN_4O_2$: C, 37.76; H, 6.74; Cl, 15.94; N, 25.18%. Found: C, 38.02; H, 6.66; Cl, 16.15; N, 25.00%.

A sample (377 mgm., 0.0015 mole) of this N-(β-chloroethyl)-N′-diethyl-N″-nitroguanidine was converted to 1-nitro-2-diethylamino-2-imidazoline by refluxing for 15 min. with 10 cc. of water. The aqueous solution on addition of a saturated aqueous picric acid solution gave a yellow picrate, yield 337 mgm. (47.9%). The picrate melted at 128.5° C. Calc. for $C_{13}H_{17}N_7O_9$: C, 37.58; H, 4.12; N, 23.60%. Found: C, 37.43; H, 4.01; N, 23.20%.

The crystalline N-(β-chloroethyl)-N′-diethyl-N″-nitroguanidine changed into a viscous liquid containing gas bubbles on standing for a few weeks at room temperature. A sample (207 mgm., 0.0009 mole) of this oil gave a 69.9% yield of the picrate melting at 128.5° C. on treatment with an alcoholic solution of picric acid. This picrate did not depress the melting point of the above-described picrate of 1-nitro-2-diethylamino-2-imidazoline.

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