ml. of ethanol was subjected to hydrogenation at room temperature and atmospheric pressure. Approximately 5 moles of hydrogen was absorbed. After removal of the catalyst and solvent, the solid residue was recrystallized from an ethanol–ethyl acetate mixture to give 250 mg. (75%) of white crystals, m.p. 180–183.5°. That this was the hydrochloride of 2-*n*-butylpiperidine was shown by the fact that admixture of an authentic sample of the hydrochloride of 2-*n*-butylpiperidine[22] caused no depression of melting point. As further evidence of the identity of the reduction product, the N-*p*-toluenesulfonyl derivative (m.p. 40–41°) and mercurichloride derivative (m.p. 137–140° dec.) were prepared and found to show no depression of melting point on admixture of samples of these derivatives from authentic 2-*n*-butylpiperidine.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TORONTO]

Hydration of 2-Nitriminoimidazolidine

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RECEIVED NOVEMBER 25, 1953

The product obtained when nitriminoimidazolidine is decomposed by aqueous alkali has been treated with acetic anhydride and with nitrous acid. One cannot distinguish between 3-β-aminoethylnitrourea or 2-hydroxy-2-nitraminoimidazolidine as the structure of the nitriminoimidazolidine hydration product on the basis of these reactions, and must conclude that either of such ring-chain isomers may be present depending upon the environment. The same behavior is observed upon examination of the acetylation product. It is suggested that, for the purpose of nomenclature, the structure of these ring-chain isomers be assigned in consideration of behavior during potentiometric titration.

It has been shown by potentiometric titration that when 2-nitriminoimidazolidine is dissolved in dilute alkali it is converted slowly to the sodium salt of 2-nitramino-Δ^2-imidazoline.[1] At the same time, although at a slower rate, the hydration product of these tautomers is formed. Two possible structures may be assigned to this hydration product. Barton, Hall and Wright specified these structures as 3-β-aminoethyl-1-nitrourea (I) and 2-hydroxy-2-nitraminoimidazolidine (II) but were unable to discriminate on the basis of their experimental work.

It has been postulated,[2] and more recently proved,[3] that ring-chain isomerism is prevalent among β-substituted-3-ethylnitroureas or 3-ethyl nitroguanidines and their cyclic (imidazolidine) forms. Furthermore, this isomerism is sensitive to reaction environment. The present study seems further to exemplify this same behavior.

When the hydrated nitriminoimidazolidine (I or II) is dissolved in alkali and potentiometrically titrated with acid, it displays a dissociation constant of about 3×10^{-10}. Despite this low acidity the compound forms a well-defined crystalline hydrochloride. This behavior, typical of an amino acid, should designate the structure as 3-β-aminoethylnitrourea (I).

On the other hand, treatment of the hydration product (I or II) with nitrous acid does not yield gaseous nitrogen until at least 15 minutes have elapsed. By contrast a primary amine such as 1,2-diaminoethane evolves gas immediately, while a monoacyl diamine such as 1-acetamino-2-aminoethane, which is easily cyclized[4] evolves gas in about five minutes. Furthermore, the reaction of nitrous acid with the hydration product (I or II) is not simple since the solid and gaseous products differ according to the conditions of nitrosation.

When aqueous sodium nitrite solution is added very slowly to a cold solution of the hydrated nitriminoimidazolidine (I or II) in dilute hydrochloric acid, the gas (which is evolved in the later stages of the reaction) is chiefly nitrous oxide. The solid product isolable from the reaction system is found to be the hitherto-unknown 1-nitrosoimidazolidone-2 (IV) since it can further be nitrosated to give the 1,3-dinitrosoimidazolidone-2 reported by McKay, Park and Viron.[5]

When the aqueous sodium nitrite solution is added rapidly to the cold solution of hydrated nitriminoimidazolidine in hydrochloric acid, the gas, which is mostly evolved during 30 minutes (although two hours is allowed for maximum yield), is found chiefly to be nitrogen. The solid product of this reaction is the 3-β-hydroxyethylnitrourea (VI) which would have been expected if the amino group in 3-β-aminoethylnitrourea had reacted in a normal and rapid manner. Essentially the same type of gas evolution is observed when aqueous acetic rather than hydrochloric acid is used as the reaction medium. However, in this case the isolable solid product is the dehydration product from 3-β-hydroxyethylnitrourea (VI), namely, 2-nitraminooxazoline (VIII).[6] This is the only substance produced in aqueous acetic acid whether nitrite is added over a period of minutes or of hours.

Thus it may be seen that the reaction with nitrous acid cannot specify precisely whether the hydration product of 2-nitriminoimidazolidine is 2-hydroxy-2-nitraminoimidazolidine (II) or whether it is a mixture of II with 3-β-aminoethylnitrourea (I). However, under our conditions of reaction, it does not seem possible that only the chain isomer I is present, because it could not reasonably be a source of 1-nitrosoimidazolidone-2 (IV). On the other hand, the strongly-acid condition involved in slow addition of sodium nitrite in the formation of IV might be expected to promote the loss of nitrous oxide from III after it had been formed from II.

(1) S. S. Barton, R. H. Hall and G. F Wright, THIS JOURNAL, **73**, 2201 (1951).

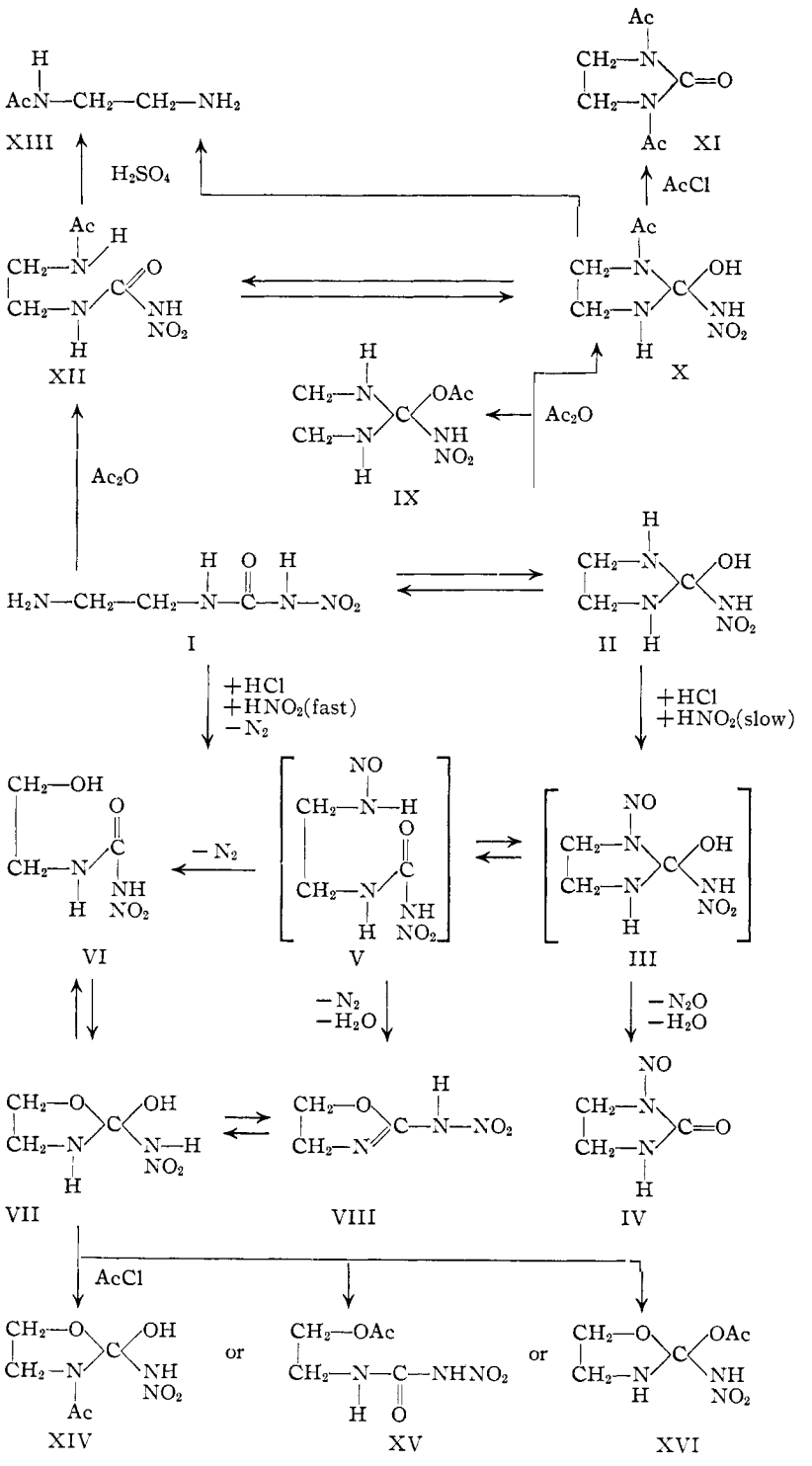
(2) R. H. Hall, A. F. McKay and G. F Wright, *ibid.*, **73**, 2205 (1951).

(3) M. W. Kirkwood and G. F Wright, *J. Org. Chem.*, **18**, 629 (1953).

(4) A. J. Hill and S. R. Aspinall, THIS JOURNAL, **61**, 822 (1939).

(5) A. F. McKay, W. R. R. Park and S. J. Viron, *ibid.*, **72**, 3659 (1950).

(6) R. H. Hall and G. F Wright, *ibid.*, **73**, 2213 (1951).



By contrast, 3-β-hydroxyethylnitrourea (VI) is formed in a medium that is strongly buffered by sodium nitrite. While this environment is favorable for conversion of the primary amino group in I to a hydroxyl group, it is at least equally favorable for the nitrosation of the secondary amino group in II. Indeed, the observation that evolution of nitrogen does not begin until 15 minutes after the reagents are mixed favors the postulation that II is initially nitrosated to III which slowly undergoes ring-opening to form V. This aliphatic nitrosamine would be expected to lose nitrogen rapidly and thus to form 3-β-hydroxyethylnitrourea (VI). Of course V also is the intermediate expected from the reaction of nitrous acid with 3-β-aminoethylnitrourea (I). Therefore, unless the delay in nitrogen evolution is significant, the reaction with nitrous acid cannot disclose the real existence of 3-β-aminoethylnitrourea. Likewise the reaction producing 2-nitraminooxazoline (VIII) does not permit a choice of I or II as the progenitor. The formation of VIII may be depicted as dehydration of VI *via* VII, or it may be formed by homopolar decomposition of V.

Acetylation of the nitriminoimidazolidine hydration product gives no information whether the monoacetyl derivative thus obtained is derived from I or II, because the properties of this acetylated substance are also those of ring-chain isomers. It may be either or both of acetaminoethylnitrourea (XII) or 1-aceto-2-hydroxy-2-nitraminoimidazolidine (X), but probably it is not 2-acetoxy-2-nitraminoimidazolidine (IX). If rearrangement does not occur the latter substance would be expected to yield 1,2-diaminoethane sulfate upon treatment with concentrated sulfuric acid. But the actual product is the salt of 1-acetamino-2-aminoethane (XIII), which is expected from either of XII or X.

Potentiometric titration shows that the acetylated product is a fairly strong acid (K_A 3 × 10^{-4}). By analogy with 1-nitro-2-amino-2-nitraminoimidazolidine[2] (K_A 3 × 10^{-6}) or 1-nitro-2-propoxy-2-nitraminoimidazolidine[6] (K_A 1 × 10^{-6}), the cyclic isomer X would not be expected to display the acid strength which actually was determined. On the other hand, this acid strength is closely comparable with that of 3-β-chloroethylnitrourea[6] (K_A 2 × 10^{-4}) which is analogous with 3-β-acetaminoethylnitrourea (XII). Therefore on the basis of potentiometric titration one would define the acetylated substance as XII.

In contrast to this behavior in aqueous media is that observed when the acetylation product is treated with acetyl chloride in acetic acid. This reagent might be expected to convert 3-β-acetaminoethylnitrourea (XII) to 1-acetamino-2-aminoethane (XIII), but not to 1,3-diacetaminoimidazolidone-2 (XI) except by transition through 1-aceto-

2-hydroxy-2-nitraminoimidazolidine. However, XI has been isolated in significant yield.

These reactions confirm the previous observation[3] that the tendency toward reversible internal addition is so great that ring-chain isomerism may be considered in the same category as labile tautomerism. Like other tautomers, or like cyclic hemiacetals, the isomer equilibrium is strongly dependent on the environment. Under these circumstances it would seem from the chemical aspect to be unimportant whether the substance were designated as one or the other isomer. However, a choice probably is important from the aspect of bibliography and index. Unfortunately a large number of compounds have recently been included in the literature by authors who have misunderstood or disregarded these tautomeric states. These entries chiefly classify ring-chain isomers as linear.[7]

The titration data mentioned in the present report show that in aqueous alkaline solution the linear classification is frequently applicable. This is not surprising because one may expect that in the case of nitroureas the equilibrium between linear and cyclic structural isomers will be preponderant with respect to the linear form. However, there are notable exceptions to the prevalence of the linear forms in alkaline solution, especially among the substituted nitroguanidines.[3] Therefore the acidic equilibrium constant is suggested as the ultimate criterion *for purposes of classification into the indexed literature* even though this classification may not be realistic insofar as the entire chemistry of a ring-chain isomer is concerned. This suggestion may also be extended to the nitrimine–nitramine tautomerism. Furthermore, in the interest of literature clarity, it is suggested that in absence of titrimetric data those compounds capable of ring-chain or nitrimine–nitramine tautomerism be classified as linear until the K_A is determined.

As an example of this designation for purposes of literature classification without regard to the essential chemistry, we may consider the compound which we have defined as 3-β-hydroxyethylnitrourea (VI) but which could also be described as the ring-isomeric form 2-hydroxy-2-nitraminoöxazolidine (VII) in view of its relationship with 2-nitraminoöxazoline (VIII, a compound also classified according to its K_A rather than its entire chemistry). Potentiometric titration of an alkaline solution of VI shows that K_A is 1×10^{-4}. Although no comparable oxazolidine has been measured, a comparison with 1-nitro-2-propoxy-2-nitraminoimidazolidine (K_A 1×10^{-6}) and with 3-β-chloroethylnitrourea (K_A 2×10^{-4}) shows that 3-β-hydroxyethylnitrourea (VI) is the proper name classification for this compound.

Since this classification does not specify the entire chemical nature of VI, the name classification of its acetyl derivative must be determined anew. However, a satisfactory titration of this derivative cannot be obtained by the ordinary procedure of solution in alkali followed by analytical addition of acid. Evidently this misbehavior is due to saponification because the product obtained by the *all-important* recovery of titrated sample is 3-β-hydroxyethylnitrourea (VI). In order to obtain a satisfactory acidity constant (K_A 1×10^{-4}) the sample is dissolved in water–acetone (2.5:1) and then is titrated with alkali. Of course the usual precaution of checking the curve by back-titration cannot be accomplished because of the saponification which produces acetic acid as well as VI. However, the relatively high acidity precludes the cyclic form XVI, while XIV is improbable on the basis of acidity and impossible on the basis of saponification to 3-β-hydroxyethylnitrourea. On the other hand, both criteria are met by XV, 3-β-acetoxyethylnitrourea, and this structure has been assigned to the substance.

(7) A. F. McKay, *Chem. Revs.*, **51**, 301 (1952).

Experimental[8]

3-β-Aminoethylnitrourea (I).—This compound, prepared by the method of Barton, *et al.*,[1] was characterized by its X-ray diffraction pattern: [10] 4.38, 3.91; [8] 4.16, 3.62, 3.14; [6] 3.36; [5] 6.17, 5.15, 3.00, 2.69; [4] 7.22, 3.52, 2.88, 2.82, 2.75; 2.27, 2.11; [3] 8.31, 2.25; [2] 2.58, 2.04; [1] 5.59, 3.74, 2.65; [0.5] 4.98, 4.41, 2.38, 2.09.

1-Nitrosoimidazolidone-2 (IV).—A solution of the ring isomer II of 3-β-aminoethylnitrourea (I) (0.74 g., 0.005 mole) in 40 ml. (0.020 mole) of 1.8% hydrochloric acid was stirrred magnetically at +4° under nitrogen in a flask connected to a rubber balloon and to the needle of a hypodermic syringe containing 1.38 g. (0.020 mole) of sodium nitrite in 10 ml. of water. The content of the syringe was forced into the reaction system uniformly during 12 hours by means of a synchronous motor-driven epicycloid cam. Toward the end of the reaction period the system began to turn yellow and the balloon expanded.

The reaction system was vacuum evaporated and the yellow gum was extracted with five 5-ml. portions of boiling ethyl acetate. The combined extract was filtered hot and vacuum evaporated leaving 0.38 g. (65%) of nitrosoimidazolidone (IV), m.p. 95–100° dec. One crystallization from hot 95% ethanol (3 ml./g.) raised this decomposition point to 101.5–101.8°.

Anal. Calcd. for $C_3H_5N_3O_2$: C, 31.3; H, 4.38; N, 36.6. Found: C, 31.7; H, 4.40; N, 36.6.

The X-ray diffraction pattern of this compound (IV) was determined: [10] 6.46, 4.62, 3.30; [9] 2.01; [7] 2.92; [6] 3.90; [5] 5.42; [2] 2.71.

1,3-Dinitrosoimidazolidone-2.—To a solution of 0.030 g. (0.00026 mole) of 1-nitrosoimidazolidone-2 in 0.5 ml. (0.0017 mole) of 20% nitric acid was added with stirring at 10° during 15 minutes a solution of 0.07 g. (0.001 mole) of sodium nitrite in 0.2 ml. of water. After several minutes the system was chilled to 0°. The bright-yellow solid (0.020 g., 53%), m.p. 131–140° dec., was filtered off. This melting point was raised to 140–141° by crystallization from 95% ethanol. A mixture melting point with the sample prepared according to McKay, Park and Viron[5] was not lowered.

3-β-Hydroxyethylnitrourea (VI).—A solution of 0.74 g. (0.005 mole) of the ring isomer (II) of 3-β-aminoethylnitrourea (I) in 9 ml. (0.010 mole) of 4% hydrochloric acid was chilled to −10° and swept with nitrogen to remove oxygen from the flask equipped with hypodermic syringe inlet and rubber balloon closure. To the magnetically-stirred solution was added a solution of 0.69 g. (0.010 mole) of sodium nitrite in 5 ml. of water during 6 minutes. Such a system did not evolve nitrogen before 14 minutes, although a system containing 1,2-diaminoethane evolved this gas at once, and 2-acetaminoethylamine evolved gas within 5 minutes. For preparative purposes the temperature of the system was allowed to rise to 0° during 25 minutes after the addition period. Stirring was continued at this temperature during 2 hours.

The system was vacuum evaporated, leaving a gummy solid which was extracted with one 10-ml. volume and three 5-ml. volumes of boiling ethyl acetate. The combined hot extract was filtered and vacuum evaporated, leaving 0.54 g. of an oily solid. This crude material was washed

(8) Melting points have been corrected against known standards. X-Ray diffraction patterns were determined with CuKα radiation (Ni filtered) and are reported as relative intensities [I/I_1].

with ethyl acetate to leave 0.15 g. (20%), m.p. 120–125°. This product was purified firstly by extraction with 100 ml. of ether. Then the filtered extract was evaporated and the residue thrice crystallized from hot ethyl acetate (5 ml./g.), m.p. 128.3–129.4°.

Anal. Calcd. for $C_3H_7O_4N_3$: C, 24.2; H, 4.74; N, 28.2. Found: C, 24.2; H, 4.87; N, 28.0.

The X-ray diffraction pattern of this compound (VI) was determined: [10] 3.73; [9] 2.87; [8] 3.93, 3.37; [6] 4.18; [4] 5.68; [2] 3.17; [0.5] 4.98, 3.03, 2.65, 2.38.

3-β-Acetoxyethylnitrourea (XV).—When 3-β-hydroxyethylnitrourea (VI) *via* its ring isomer VII is treated with acetyl chloride, it is acetylated to yield XV, m.p. 98.6–99.7°, after two crystallizations from water.

Anal. Calcd. for $C_5H_9N_3O_5$: C, 31.2; H, 4.74; N, 22.0. Found: C, 31.2; H, 4.86; N, 22.0.

This compound (XV) was characterized by its X-ray diffraction pattern: [10] 3.69, 3.56, 3.21; [9] 4.71; [7] 8.18, 4.52, 3.30; [5] 4.27; [1] 3.77, 2.70; [0.5] 10.39, 4.12.

2-Nitraminoöxazoline (VIII).—To a suspension of 0.74 g. (0.005 mole) of the ring isomer (II) of 3-β-aminoethylnitrourea (I) in 0.58 ml. (0.01 mole) of acetic acid in 40 ml. of water was added at 0° during 5 minutes a solution of 0.69 g. (0.01 mole) of sodium nitrite in 5 ml. of water. After further stirring at 0° for 45 minutes the system was vacuum-evaporated at 50°. The resulting buff-colored gum was twice extracted with 15-ml. portions of cold pure ethyl acetate. The combined extract was filtered and vacuum evaporated. The residue (0.21 g., 32%, m.p. 105–108°) was twice crystallized from 95% ethanol (7 ml./g.) and then melted at 112.8–113.4°. A mixture melting point with an authentic sample[6] was not depressed. The yield and quality of product was not altered if, alternatively, the nitrite solution was added during 12 hours.

3-β-Aminoethylnitrourea Hydrochloride.—A mixture of 1.48 g. (0.01 mole) of 3-β-aminoethylnitrourea (I) and 4.56 g. (0.015 mole) of 12% hydrochloric acid was heated gently until the solid dissolved. The warm solution was then poured into acetone. The precipitate of impure salt (1.63 g., 89%, m.p. 188–190°) was dissolved in 7.4 ml. of water, and this solution was poured into 110 ml. of acetone. The purified hydrochloride (64% recovery) melted at 190.0–190.8° with decomposition and gave a negative Franchimont test with dimethylaniline. It could be reconverted to II by neutralization of an aqueous solution to *p*H 5. The hydrochloride content was determined by precipitation of silver chloride.

Anal. Calcd. for $C_3H_9ClN_4O_3$: N, 29.7; Cl, 19.2. Found: N, 30.3; Cl, 19.2.

This compound was characterized by its X-ray diffraction pattern: [10] 7.89, 3.58; [7] 3.08, 3.02, 2.91; [5] 4.44, 3.99, 3.33; [4] 2.69; [0.5] 2.38.

3-β-Acetaminoethylnitrourea (XII).—A mixture of 14.8 g. (0.10 mole) of 3-β-aminoethylnitrourea (I), 15.2 g. (0.15 mole) of acetic anhydride and 148 ml. of glacial acetic acid was stirred at 61–68° for 1 hour. When the resulting solution was cooled, 7.11 g. (37.4%) of crude product, m.p. 170–171° dec., separated. A second crop (10 g., 53%, m.p. 162–167°) was obtained by vacuum evaporation of the filtrate. Purification of the latter by solution in hot 95% ethanol gave a 67% recovery of pure product, m.p. 172.8–173.2° dec. The substance reacted vigorously with diazomethane. It gave a strongly positive Franchimont test with dimethylaniline.

Anal. Calcd. for $C_5H_{10}N_4O_4$: C, 31.6; H, 5.30; N, 29.5. Found: C, 31.9; H, 5.32; N, 29.5.

This compound (XII) was characterized by its X-ray diffraction pattern: [10] 3.35; [9] 3.81; [8] 6.65, 2.88; [5] 6.27; [4] 5.03, 4.32, 1.96; [3] 2.13; [1] 2.75; [0.5] 5.77, 3.05, 2.62, 2.49, 2.35.

1-Acetamino-2-aminoethane (XIII).—To 3.09 g. (0.03 mole) of cooled concentrated sulfuric acid was slowly added 1.44 g. (0.0075 mole) of 3-β-acetaminoethylnitrourea (XII ⇄ X). Vigorous evolution of gas containing carbon dioxide occurred. After one day the viscous residue was diluted with 5 ml. of cold water, and 30% aqueous sodium hydroxide was added to *p*H 11. The solution was vacuum evaporated and then extracted 4 times with a total of 80 ml. of chloroform. This solution, dried with magnesium sulfate, was evaporated to leave a brown oil (0.31 g., 40%). A picrate was prepared in benzene solution. Its melting point was not depressed when it was admixed with an authentic specimen.[9] When 0.77 g. of authentic 1-acetamino-2-aminoethane was treated with sulfuric acid as described above, only 4 g. (52%) could be recovered from the reaction mixture.

1,3-Diacetoimidazolidone-2 (XI).—A mixture of 0.95 g. (0.005 mole) of 3-β-acetaminoethylnitrourea (XII ⇄ X), 1.07 ml. (0.015 mole) of acetyl chloride and 10 ml. of glacial acetic acid was heated under reflux at 60–65° for 3 hours. A mixture of 28.9 cc. of carbon dioxide and 45.6 cc. (41%) of nitrous oxide was collected over water at 26° during this time. The latter gas was identified by combustion with hydrogen. The reaction mixture was evaporated under reduced pressure to leave a semi-solid; 5 ml. of ethanol was added and the evaporation repeated. The residue, washed with 1 ml. of ethanol, weighed 0.20 g. (24%, m.p. 124–127°). This crude product was crystallized from hot ethanol (2 ml. per g.), m.p. 126.7–127.5°.

Anal. Calcd. for $C_7H_{10}N_2O_3$: C, 49.4; H, 5.92; N, 16.5. Found: C, 49.7; H, 6.16; N, 16.2.

This compound (XI) was characterized by its X-ray diffraction pattern: [10] 6.23, 3.31; [9] 3.74; [6] 3.86; [5] 7.49, 6.91, 4.06; [4] 2.94; [2] 2.91, 2.59; [1] 5.43; [0.5] 6.49, 5.73, 3.10, 2.38, 2.34, 2.29.

Electrometric Titrations.—A Coleman Model 3 electrometer was used with calomel and glass electrodes. With one exception the titrations with standard hydrochloric acid were carried out with freshly-prepared alkaline solutions, and then were back-titrated with standard alkali to demonstrate the stability of the compounds. The nitramines were recovered from the titrated liquors in 70–90% yield.

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(9) S. R. Aspinall, THIS JOURNAL, **63**, 852 (1941).