The Mannich Reaction of Certain Dinitro Alcohols with Glycine and Ethanolamine[1]

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The reaction of dinitro alcohols, such as 2,2-dinitro-1,3-propanediol and sodium 2,2-dinitroethanol with glycine results in the formation of a 3,3,5,5-tetranitropiperidine. However, ring closure does not occur when ethyl glycine hydrochloride is reacted with sodium dinitroethanol. Instead 5,5-dinitro-3-azavalerate is formed. Ethanolamine reacts with the above nitroalcohols to give 5,5-dinitro-3-aza-1-pentanol.

The Mannich-type reaction with nitro paraffins was first investigated by Henry[2] who established that N-hydroxymethylpiperidine condensed with nitromethane and nitroethane yielding, respectively, 2-nitro-1,3-bis-(N-piperidyl)-propane and 2-nitro-2-methyl-1,3-bis-(N-piperidyl)-propane. A large number of papers[3-6] have since been published on this type of reaction, and recently Senkus[7] and Lambert[8] have shown that nitro alcohols derivable from nitro paraffins and formaldehyde or acetaldehyde will react directly with amines or N-methylolamines to give the Mannich-type base.

In this work the reaction of 2,2-dinitro-1,3-propanediol (I) with glycine (IIa) was investigated, since the literature indicated that the Mannich-type reaction had not been studied with *gem*-dinitro paraffins. It was expected that compound I would condense with two equivalents of IIa to form 5,5-dinitro-3,7-diazanonanedioic acid. This was, however, not the case and I reacted with IIa, its hydrochloride or its ethyl ester hydrochloride[9] IIb to yield 1-carbomethoxymethyl-3,3,5,5-tetranitropiperidine (IIIa) and 1-carboxymethyl-3,3,5,5-tetranitropiperidine (IIIb).

(HOCH₂)₂=C(NO₂)₂
+
R₂NCH₂CO₂R'

$pH\ 4$

I

IIa, R = R' = H
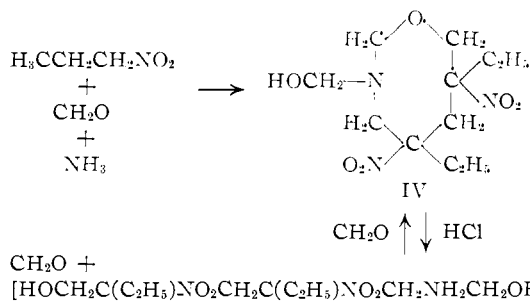b, R = H, R' = C₂H₅

IIIa, R = C₂H₅
b, R = H
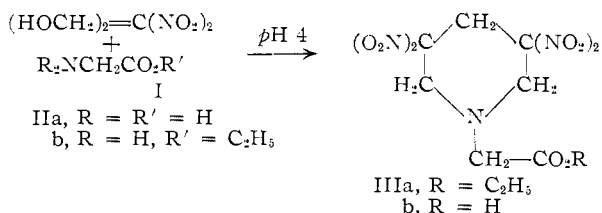
The reaction procedure consisted of heating an aqueous solution of I and the glycine derivative to 70° and recovering the product by filtration. Removal of the precipitate as it formed during the reaction of I with IIb gave the ester IIIa as the only product. However, if the precipitate was allowed to remain in the acidic reaction mixture for several hours part of IIIa was hydrolyzed to the acid IIIb. The latter was separated by recrystallization from 50% ethanol, while the ester was recovered from the alcohol insoluble residue by recrystallizations from carbon tetrachloride.

Numerous reactions between I and IIb showed that the pH, the reaction temperature, and the mole ratio of the reactants have a pronounced effect on this reaction. An aqueous mixture of the two reactants showed a pH of 4.0 and any attempt to neutralize the solution with base caused tar formation. The optimum reaction temperature was about 70°; higher temperatures gave a tar as the only product while lower temperatures decreased the yields. A ratio of two moles of ester IIb to 1 mole of diol I gave a better yield than either a 1-to-1 ratio or a 1-to-2 ratio. The highest yield of IIIa obtained was 20% and even though the recovery of some starting material after a reaction time of 18 hours indicated that the reaction was incomplete, a longer reaction time led to an increase in the amount of tar instead of the desired product. The use of absolute ethanol as a solvent in place of water reduced the yield to 12%.

Glycine (IIa) reacted with I to give a 52% yield of IIIb. Again the best yields were obtained when the mole ratio of IIa to I was 2:1. The optimum temperature was 70°, the optimum pH 4.0, and the optimum reaction time about eight hours. A pH below 4.0 lowered the yield to 18%.

The formation of piperidine derivatives in the Mannich reaction[10] is not uncommon especially when ammonia or a primary amine and formaldehyde are reacting with a methyl ketone or compounds having reactive hydrogens in the 1,3-position. However, only two examples are reported in which cyclization occurred with a nitro paraffin. Senkus[11] prepared hexahydropyrimidines by treating nitroethane with formaldehyde and isopropylamine, and Urbansky[12] obtained a cyclic ether (IV) from the reaction of 1-nitropropane with ammonia

H₃CCH₂CH₂NO₂
+
CH₂O
+
NH₃

IV

$CH_2O \uparrow \downarrow HCl$

CH₂O +
[HOCH₂C(C₂H₅)NO₂CH₂C(C₂H₅)NO₂CH₂NH₂CH₂OH] +Cl⁻

(1) (a) Abstracted from a thesis by Wayne May submitted to the Faculty of the Graduate School of Purdue University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. (b) Presented before the Division of Organic Chemistry at the Los Angeles Meeting of the American Chemical Society, March, 1953.

(2) L. Henry, *Bull. acad. roy. Belg.*, [3] 32, 33 (1896); *Ber.*, 38, 2027 (1905).

(3) Th. Mousset, *Bull. acad. roy. Belg.*, [4], 622 (1901).

(4) P. Duden, *et al.*, *Ber.*, 38, 2036 (1905).

(5) H. Cerf de Mauney, *Bull. soc. chim.*, [5] 4, 1451, 1460 (1937).

(6) M. Zief and J. P. Mason, *J. Org. Chem.*, 8, 1 (1943).

(7) M. Senkus, THIS JOURNAL, 68, 10 (1946).

(8) A. Lambert and J. D. Rose, *J. Chem. Soc.*, 1511 (1947).

(9) Ethylglycine itself cannot be used because it polymerizes too readily.

(10) See, for example, F. F. Blicke, "Organic Reactions," Vol. I, R. Adams, *et al.*, Editors, John Wiley and Sons, Inc., 1947, p. 326; H. S. Mosher, "Heterocyclic Compounds," Vol. I, R. C. Elderfield, Editor, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 658.
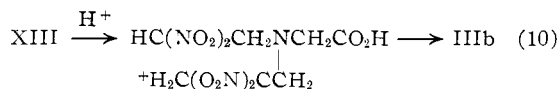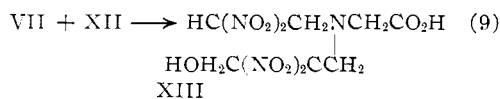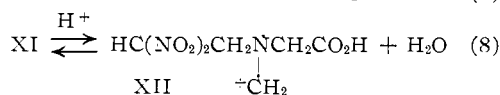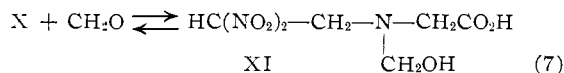
(11) M. Senkus, THIS JOURNAL, 68, 1611 (1946).

(12) T. Urbansky, *J. Chem. Soc.*, 924 (1947).

and formaldehyde. Upon heating with hydrochloric acid ring opening took place which was taken as evidence of a cyclic ether structure.

When the acid IIIb was heated for 12 hours with concd. hydrochloric acid it was recovered unchanged indicating the absence of a cyclic ether structure and substantiating the proposed formation of a substituted piperidine in the reaction.

In contrast to their stability to acid, compounds IIIa and IIIb decompose in basic media with the formation of tars. Elemental analysis and a molecular weight determination of IIIa by potentiometric titration were consistent with the assigned piperidine structure. Potentiometric titration of the acid IIIb did not give a shar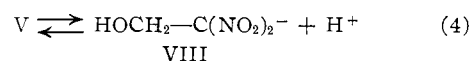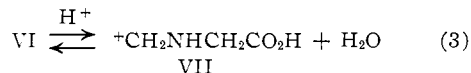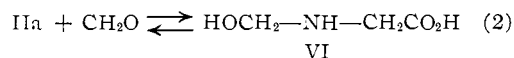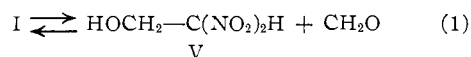p end-point, but the acid could be esterified to the same ester (IIIa) obtained from the reaction of I with IIb. The absence of a primary or secondary amine grouping was indicated by the failure of several attempts to prepare a p-toluenesulfonamide derivative. The infrared spectrum of both the acid and its ester showed well-defined absorption maxima for the gem-dinitro group at 6.3, 7.6 and 11.8 μ, and for the carboxyl group at 5.8 μ.

The formation of the piperidine ring might involve the following sequence of equations. They are proposed as only one of the possible paths

$$I \rightleftarrows HOCH_2—C(NO_2)_2H + CH_2O \qquad (1)$$
$$V$$

$$IIa + CH_2O \rightleftarrows HOCH_2—NH—CH_2CO_2H \qquad (2)$$
$$VI$$

$$VI \overset{H^+}{\rightleftarrows} {}^+CH_2NHCH_2CO_2H + H_2O \qquad (3)$$
$$VII$$

$$V \rightleftarrows HOCH_2—C(NO_2)_2{}^- + H^+ \qquad (4)$$
$$VIII$$

$$VII + VIII \longrightarrow HOCH_2C(NO_2)_2CH_2NHCH_2CO_2H \qquad (5)$$
$$IX$$

$$IX \rightleftarrows HC(NO_2)_2—CH_2—NHCH_2CO_2H + CH_2O \qquad (6)$$
$$X$$

$$X + CH_2O \rightleftarrows HC(NO_2)_2—CH_2—N—CH_2CO_2H \qquad (7)$$
$$\qquad\qquad\qquad XI \qquad\qquad |$$
$$\qquad\qquad\qquad\qquad\qquad CH_2OH$$

$$XI \overset{H^+}{\rightleftarrows} HC(NO_2)_2CH_2NCH_2CO_2H + H_2O \qquad (8)$$
$$\qquad\qquad XII \qquad |$$
$$\qquad\qquad\qquad {}^+CH_2$$

$$VII + XII \longrightarrow HC(NO_2)_2CH_2NCH_2CO_2H \qquad (9)$$
$$\qquad\qquad\qquad HOH_2C(NO_2)_2C\overset{|}{C}H_2$$
$$\qquad\qquad\qquad XIII$$

$$XIII \overset{H^+}{\longrightarrow} HC(NO_2)_2CH_2NCH_2CO_2H \longrightarrow IIIb \qquad (10)$$
$$\qquad\qquad\qquad\qquad {}^+H_2C(O_2N)_2C\overset{|}{C}H_2$$
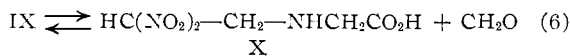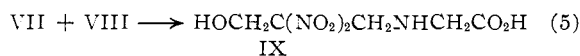
Step 1 is in agreement with the experimental evidence of Senkus[7] and was further verified in this investigation by the reaction of sodium dinitroethanol (XIV) with glycine hydrochloride at a pH of 4.0 yielding the same acid (IIIb). The reaction failed in a pH range of 7 to 4. Step 2 is supported by the work of Alexander[13] who showed that the same rate constant is obtained when an N-methyl-

(13) E. R. Alexander and E. S. Underhill, This Journal, 71, 4014 (1949).

olamine is used in place of the corresponding amine and formaldehyde in the Mannich reaction. Steps 3, 4, 5 and 6 lead to the intermediate X according to the mechanism proposed by Lieberman and Wagner for Mannich reactions.[14] Compound X actually was obtained as the ethyl ester XV from the reaction of sodium dinitroethanol (XIV) with ethyl glycine hydrochloride at a pH of 5–6. This ester decomposed on standing but could be converted to the stable ethyl 3,5,5-trinitro-azavalerate (XVI) upon treatment with a mixture of concd. sulfuric acid and fuming nitric acid.

$$HC(NO_2)_2—CH_2—NHCH_2COOEt \overset{HNO_3}{\longrightarrow}$$
$$XV$$

$$HC(NO_2)_2—CH_2—N(NO_2)CH_2CO_2Et$$
$$XVI$$
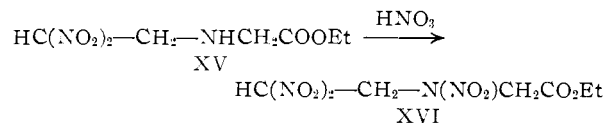
The structure of XVI was substantiated by elemental analysis and by its conversion to ethyl 5-bromo-3,5,5-trinitro-3-azavalerate by treatment of the sodium salt with bromine. Attempts to hydrolyze XVI by refluxing with concd. hydrochloric acid resulted only in decomposition with evolution of oxides of nitrogen. Compound XVI would not undergo further condensation with formaldehyde alone.

The reaction of ethanolamine with compounds I or XIV did not lead to cyclization. With both compounds, 5,5-dinitro-3-aza-1-pentanol (XVII) was obtained in good yield when the pH was kept at 6–7. In an effort to obtain a derivative of XVII it was treated with acetyl chloride. However, this

$$HC(NO_2)_2—H_2C—NHCH_2CH_2OH \overset{CH_3COCl}{\longrightarrow}$$
$$XVII$$

$$CH_3CONHCH_2CH_2OH$$
$$XVIII$$
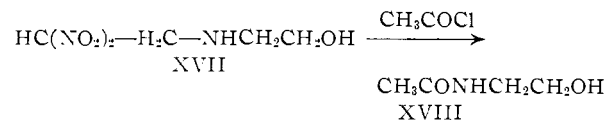
caused acetolysis of the Mannich-type base yielding N-acetyl-2-aminoethanol (XVIII).

Experimental[15]

1-Carbethoxymethyl-3,3,5,5-tetranitropiperidine (IIIa). (a) From 2,2-Dinitro-1,3-propanediol.—Ethyl glycine hydrochloride was prepared from glycine according to the procedure of Harries.[16] A mixture of 6 g. (0.036 mole) of 2,2-dinitro-1,3-propanediol,[17] 10.2 g. (0.073 mole) of ethyl glycine hydrochloride and 20 ml. of water was heated to 65–70° with stirring. After about 15 minutes a precipitate formed in the solution and was removed by filtration. While maintaining the temperature at 65–70°, any additional solid was filtered at approximately 30-minute intervals until no further precipitation occurred (8 hours). The product was recrystallized from carbon tetrachloride to give 1.3 g. (20%) of light yellow crystals, m.p. 126-127°.

Anal. Calcd. for $C_9H_{13}N_5O_{10}$: C, 30.77; H, 3.70; N, 19.94; neut. equiv., 351. Found: C, 31.00; H, 3.75; N, 19.78; neut. equiv., 345.

(b) From 1-Carboxymethyl-3,3,5,5-tetranitropiperidine. —A mixture of 4 ml. of absolute ethanol, 0.2 ml. of concentrated sulfuric acid (96%) and 0.2 g. of 1-carboxymethyl-3,3,-5,5-tetranitropiperidine was heated for 8 hours at 70°. On cooling, a precipitate formed in the solution. This solid was filtered, recrystallized from carbon tetrachloride and identified as 1-carbethoxymethyl-3,3,5,5-tetranitropiperidine by means of a mixed melting point (125°).

(14) S. V. Lieberman and E. C. Wagner, *J. Org. Chem.*, 14, 1001 (1949).

(15) All melting points are uncorrected.

(16) C. Harries and M. Weiss, *Ann.*, 327, 365 (1903).

(17) H. Feuer, G. B. Bachman and J. P. Kispersky, This Journal, 73, 1360 (1951).

1-Carboxymethyl-3,3,5,5-tetranitropiperidine (IIIb).
(a) From 2,2-dinitro-1,3-propanediol.—To 3.6 g. (0.045 mole) of glycine dissolved in 30 ml. of water was added 4 g. (0.024 mole) of 2,2-dinitro-1,3-propanediol. While stirring, the mixture was heated to 65–70° and held at that temperature for 5 hours. At the end of that time the solid which had precipitated from the solution was filtered and recrystallized from 50% alcohol to give 2.0 g. (52%) of 1-carboxymethyl-3,3,5,5-tetranitropiperidine as white crystals, m.p. 145–146°.

Anal. Calcd. for $C_7H_9N_5O_{10}$: C, 26.00; H, 2.78; N, 21.67. Found: C, 26.40; H, 3.18; N, 21.78.

(b) From Sodium Dinitroethanol. Preparation of Sodium Dinitroethanol (XIV).—A solution of 5 g. (0.03 mole) of 2,2-dinitro-1,3-propanediol in 25 ml. of absolute methanol was cooled in an ice-bath to 5°. While stirring, sodium methoxide (0.75 g. of sodium in 10 ml. of absolute methanol) was added slowly. The yellow precipitate of sodium dinitroethanol which formed during the addition of base was filtered, washed with a small amount of methanol and dried under vacuum. The yellow solid, sodium dinitroethanol, melted at 132° and exploded when heated to 135–136°.

To a solution of 5 g. (0.032 mole) of sodium dinitroethanol in 30 ml. of water was added 3.5 g. (0.031 mole) of glycine hydrochloride. After stirring for about 10 minutes at 25°, the solution darkened and the temperature tended to rise but was kept at 30° or below by intermittent cooling with an ice-bath. This initial reaction soon subsided and over a period of several hours a solid gradually precipitated from the solution. This precipitate was filtered and recrystallized from 50% alcohol to give 1.3 g. (25%) of 1-carboxymethyl-3,3,5,5-tetranitropiperidine, m.p. 147°. A mixed melting point with an authentic sample prepared as in (a) gave no lowering.

(c) From 1-Carbethoxymethyl-3,3,5,5-tetranitropiperidine.—To a solution of 0.5 ml. of concentrated hydrochloric acid (36.5%) in 5 ml. of water was added 0.5 g. of 1-carbethoxymethyl-3,3,5,5-tetranitropiperidine and the mixture heated for 18 hours at 70°. The white solid was filtered, recrystallized from 50% alcohol and identified as 1-carboxymethyl-3,3,5,5-tetranitropiperidine by means of a mixed melting point (145°).

Ethyl 5,5-Dinitro-3-azavalerate (XV).—In a 100-ml. round-bottom flask equipped with a stirrer and a thermometer, 5 g. (0.032 mole) of sodium dinitroethanol was added to 5 g. (0.035 mole) of ethyl glycine hydrochloride dissolved in 50 ml. of water. After stirring for about 30 minutes at 25°, a large amount of solid formed in the solution and was filtered. A solid continued to form in the reaction mixture and was filtered at frequent intervals until the precipitation ceased (2 hours). Recrystallization from ethyl acetate gave 4.5 g. (65%) of ethyl 5,5-dinitro-3-azavalerate as yellow plate-like crystals, m.p. 102–103° dec.

Anal. Calcd. for $C_6H_{11}N_3O_6$: C, 32.6; H, 5.01; N, 19.0; neut. equiv., 221. Found: C, 33.0; H, 5.19; N, 19.26; neut. equiv., 229.

Ethyl 3,5,5-Trinitro-3-azavalerate (XVI).—To a mixture of 7 ml. of fuming nitric acid (sp. gr. about 1.5) and 7 ml. of concentrated sulfuric acid (96%) cooled in an ice-bath was added slowly 5 g. (0.023 mole) of ethyl 5,5-dinitro-3-azavalerate. The solution was warmed slowly to 55–60° and held at that temperature for 5 minutes. After allowing it to cool slowly to 30°, the mixture was poured into a beaker of chipped ice. The white oil which precipitated from the aqueous solution became solid after about ten minutes of stirring. The product was filtered and recrystallized from

carbon tetrachloride to give 3.7 g. (60%) of ethyl 3,5,5-trinitro-3-azavalerate, m.p. 41–42°.

Anal. Calcd. for $C_6H_{10}N_4O_8$: C, 27.07; H, 3.79; N, 21.05; neut. equiv., 266. Found: C, 26.98; H, 3.78; N, 21.00; neut. equiv., 257.

Ethyl 5-Bromo-3,5,5-trinitro-3-azavalerate.—To a slurry of 1 g. (0.0037 mole) of ethyl 3,5,5-trinitro-3-azavalerate in 5 ml. of ether at 5° was added slowly sodium methoxide (0.1 g. of sodium in 3 ml. of methanol). The light yellow sodium salt which formed was filtered, washed with a little methanol and dried; it decomposed at 87–88°.

While cooling in an ice-bath, 0.14 g. (0.0017 mole) of bromine dissolved in 5 ml. of chloroform was added slowly to 0.5 g. (0.0017 mole) of the sodium salt of ethyl 3,5,5-trinitro-3-azavalerate suspended in 10 ml. of ether. The mixture was allowed to stand for 15 minutes and then filtered to remove the inorganic salt. The ether filtrate was evaporated under vacuum to give a yellow-white solid. Recrystallization from carbon tetrachloride gave 0.49 g. (80%) of ethyl 5-bromo-3,5,5-trinitro-3-azavalerate as a white solid, m.p. 57–58°.

Anal. Calcd. for $C_6H_9N_4O_8Br$: C, 20.87; H, 2.61; N, 16.20. Found: C, 21.00; H, 3.12; N, 15.81.

5,5-Dinitro-3-aza-1-pentanol (XVII). **(a) From 2,2-Dinitro-1,3-propanediol.**—To a solution of 1.85 g. (0.03 mole) of ethanolamine in 25 ml. of water was added 5 g. (0.28 mole) of 2,2-dinitro-1,3-propanediol. The temperature rose from 28° to 35° and the precipitate which formed almost immediately was filtered. The reaction was allowed to continue for three more hours but only a small amount of additional product formed. The solid was recrystallized from water to give 4.2 g. (82%) of light yellow crystals of 5,5-dinitro-3-aza-1-pentanol, m.p. 115–116° dec.

Anal. Calcd. for $C_4H_9N_3O_5$: C, 26.81; H, 5.06; N, 23.46; neut. equiv., 179. Found: C, 26.95; H, 5.45; N, 23.41; neut. equiv., 172.

(b) From Sodium Dinitroethanol.—To a solution of 0.38 g. (0.0063 mole) of ethanolamine in 15 ml. of water was added 1 g. (0.0063 mole) of sodium dinitroethanol. The pH of this solution was 11. When it was neutralized slowly to a pH of 7–8 with concentrated hydrochloric acid a precipitate formed. This was filtered and recrystallized from water to give 0.76 g. (69%) of 5,5-dinitro-3-aza-1-pentanol, m.p. 117°. A mixed melting point with a sample prepared as in (a) gave no lowering.

Reaction of 5,5-Dinitro-3-aza-1-pentanol with Acetyl Chloride.—A mixture of 1 g. (0.0056 mole) of 5,5-dinitro-3-aza-1-pentanol and 5 g. (0.06 mole) of acetyl chloride was allowed to stand at 25° for 12 hours with occasional swirling of the mixture. At the end of this time, the white solid was filtered, dissolved in water and neutralized with dilute sodium hydroxide. The aqueous solution was distilled under vacuum to give a white solid residue, the organic portion of which was recrystallized from acetone to give N-acetyl-β-aminoethanol as white needles, m.p. 62–63° (lit. value[18] 63–65°). An authentic sample was prepared from ethanolamine and acetyl chloride and a mixed melting point gave no lowering.

Lafayette, Ind.

(18) S. Fraenkel and M. Cornelius, *Ber.*, **51**, 1654 (1918).