

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Addition of Hydroxylamine to ω -Nitrostyrene, Furylnitroethylene and Nitroolefins

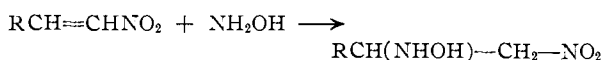
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The addition of hydroxylamine to unsaturated nitro compounds of the nitroolefin type was shown to be a general reaction. The stability of the substituted hydroxylamines of the type $R-CH(NHOH)CH_2NO_2$ decreases as R is varied from phenyl to 2-furyl to alkyl. The chemistry of a representative member, N-(1-phenyl-2-nitroethyl)-hydroxylamine, was studied.

The recent studies of the addition of amines,¹⁻⁴ mercaptans,⁵ nitroparaffins⁶ and various other nucleophilic reagents^{3,7} to nitroolefins make it appear that this reaction is general. The relationship of hydroxylamine to these reagents suggests that it also should behave similarly. Harries and co-workers⁸ showed that hydroxylamine added to conjugated systems which contained a carbonyl group. Thus, hydroxylamine was found to add to the double bond in phorone and mesityl oxide. Posner,⁷ while studying the addition of hydroxylamine to members of the cinnamic acid series, investigated certain other olefins. ω -Nitrostyrene, the only nitro compound studied, was found to add hydroxylamine with great ease while these other unsaturated compounds failed to do so: styrene, ω -bromostyrene, stilbene, allyl alcohol and amylenene.

The present work was concerned with the addition of hydroxylamine to various unsaturated nitro compounds, the stability of the products and the chemistry of a representative member. This addition was observed to proceed in yields of 50-80%



where R represents phenyl, 2-furyl, ethyl and methyl. The products of this reaction and derivatives thereof are listed in Table I.

hydroxylamine was stable over the period of a year. N-(1-Furyl-2-nitroethyl)-hydroxylamine turned dark within five months. N-(1-Ethyl-2-nitroethyl)-hydroxylamine showed no change in refractive index over a period of three weeks when kept at 5°, but decomposition did occur after seven weeks.

This evidence indicates that the aromatic system exerts a stabilizing influence to the product even though the hydroxylamine group is one atom removed from the ring.

The stability of the aliphatic hydroxylamines can be compared to that of analogous amines. Heath and Rose,¹ in their study of the addition of aromatic amines and ammonia to nitroalkenes, have pointed out that the stability of the product is a function of the base strength of the nucleophilic reagent. Thus, aromatic amines form more stable products than aliphatic amines or ammonia. Hydroxylamine, then, should form products of intermediate stability, since its base strength is intermediate between ammonia and aniline. This was found to be true (see Table II). Decomposition probably involves a reverse Michael reaction and polymerization of the nitroalkene by the more strongly basic amine formed.

The chemistry of the (nitroalkyl)-hydroxylamines has been confined to the qualitative oxidation⁷ of these compounds with Tollens and Fehling reagents. New reactions of N-(1-phenyl-2-nitro-

TABLE I
PROPERTIES OF THE HYDROXYLAMINES, $RCH(NHOH)CH_2NO_2$

R	Compound					Nitrogen, %		Derivative				
	B. p., °C.	Mm.	n_D^{20}	d_{20}^{20}	Yield, %	Mol. formula	Calcd.	Found	M. p., °C.	Mol. formula	Nitrogen, % Calcd.	Found
Phenyl	^a		80	$C_8H_{10}N_2O_3$	•	•	129-129.5°	$C_{15}H_{15}N_3O_4$	13.95	14.15
2-Furyl	^b		81	$C_6H_8N_2O_4$	16.27	16.12	139.5-140°	$C_{13}H_{13}N_3O_5$	14.42	14.41
Ethyl	103.5-104	2	1.4740	1.202	52.8	$C_4H_{10}N_2O_3$	20.88	20.48	95 dec. ^d	$C_{11}H_{13}N_3O_3S$	15.60	15.89
Methyl	92-92.5	0.9	1.4769	1.269	49.8	$C_3H_8N_2O_3$	23.32	22.93	134 dec. ^d	$C_{10}H_{13}N_3O_3S$	16.45	16.35

^a M. p. 98.5-99° (ref. 7 gives 99-100°). ^b M. p. 62.5-64°. ^c Phenyl isocyanate. ^d Phenyl isothiocyanate. ^e Analyzed previously (ref. 7).

The stability of these hydroxylamines was found to decrease as R changed from phenyl to 2-furyl to alkyl. Thus N-(1-phenyl-2-nitroethyl)-

- (1) R. L. Heath and J. D. Rose, *J. Chem. Soc.*, 1486 (1947).
- (2) H. Wieland and E. Sakellarios, *Ber.*, **52**, 898 (1919).
- (3) D. E. Worrall, *THIS JOURNAL*, **49**, 1598 (1927).
- (4) J. Loevenich and H. Gerber, *Ber.*, **63**, 1707 (1930); J. Loevenich, J. Koch and U. Pucknat, *ibid.*, **63**, 636 (1930).
- (5) R. L. Heath and A. Lambert, *J. Chem. Soc.*, 1477 (1947).
- (6) A. Lambert and H. A. Piggott, *ibid.*, 1489 (1947).
- (7) T. Posner, *Ann.*, **389**, 1 (1912).
- (8) C. Harries and L. Jablonski, *Ber.*, **31**, 1371 (1898); C. Harries and F. Lehmann, *ibid.*, **30**, 234 (1897); C. Harries and U. Ferrari, *ibid.*, **36**, 656 (1903).

TABLE II

Nitroalkene	Amine	pK_b , ^a	Stability ^b
1-Nitro-1-propene	Aniline	9.42	Apparently stable ^c
1-Nitro-1-butene	Hydroxylamine	7.97	3 weeks
2-Nitro-2-butene	Ammonia	4.76	48 hours ^c
2-Nitro-2-butene	Diethylamine	2.90	12 hours ^c

^a I. M. Kolthoff and V. A. Stenger, "Volumetric Analysis," 2nd Ed., Vol. I, Interscience Publishers, Inc., New York, N. Y., 1942, p. 283. ^b Length of time elapsed before decomposition occurred. ^c Ref. 1.

ethyl)-hydroxylamine were investigated in this study. Generally, these reactions involved only one of the two functional groups.

m.p. 145° (dec.). A consistent analysis was not achieved because of rapid decomposition on heating. This substance also was formed from the 95°-compound on storage. Darkening accompanied the decomposition but rinsing with chloroform removed most of the color and left a residue melting at 146° (dec.). This substance also gave a blue ferric chloride color test and reduced ammoniacal silver nitrate.

Phenylthiocarbamo-N-(1-methyl-2-nitroethylhydroxamic) Acid.—This compound was prepared analogously. The white solid obtained, after washing with chloroform and ether, melted at 135° (dec.). Darkening occurred at 104°. Ferric chloride solution caused an intense blue coloration. On storage of this compound it darkened somewhat in two weeks and 10 weeks later it was found to have changed into a substance of m.p. 148° (dec.). A mixture of this and the 146°-material (above) decomposed at 138°.

Reactions of N-(1-Phenyl-2-nitroethyl)-hydroxylamine. Phenylcarbamoyl-N-(1-phenyl-2-nitroethylhydroxamic) Acid.—To 1 g. of N-(1-phenyl-2-nitroethyl)-hydroxylamine in 1 ml. of dried dioxane, 0.59 g. of phenyl isocyanate was added. The reaction mixture became solid and was filtered; yield 0.75 g. The solid was recrystallized from acetone and dried in a vacuum oven at 50° for a few days, m.p. 129–129.5°.

Anal. Calcd. for $C_{15}H_{15}N_3O_4$: N, 13.95. Found: N, 14.15.

The product reduces ammoniacal silver nitrate in the cold and a methanol solution gives an intense blue color with 1% ferric chloride. It was stable on storage.

N-(1-Phenyl-2-nitroethyl)-hydroxylammonium Chloride.—Three grams of N-(1-phenyl-2-nitroethyl)-hydroxylamine was dissolved in a minimum quantity of anhydrous dioxane and absolute ethyl ether added until the cloud point. The mixture was saturated with anhydrous hydrogen chloride and the product precipitated by the addition of anhydrous ether. The yield was 3.46 g. (99.2%), m.p. 110.5–112°.

Anal. Calcd. for $C_8H_{11}ClN_2O_3$: Cl, 16.22. Found: Cl, 16.28.

N-(1-Phenyl-2-nitroethyl)-phenylnitron.—Method was adapted from Bamberger.¹⁵ To 5.30 g. of freshly distilled benzaldehyde in 50 ml. of 95% ethanol was added 9.10 g. of N-(1-phenyl-2-nitroethyl)-hydroxylamine. The mixture was stirred. Shortly after solution occurred, a white solid separated which was removed and dried in a desiccator. The yield of crude product was 9.5 g. (70.5%), m.p. 79.5–81°. After recrystallization from ligroin-chloroform mixture, the white solid melted at 80–81°.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: N, 10.37. Found: N, 10.63.

N,N'-Styrenebisbenzamide.—Five grams (0.027 mole) of N-(1-phenyl-2-nitroethyl)-hydroxylamine in 50 ml. of anhydrous methanol with 60 mg. of platinum oxide catalyst was treated with hydrogen at 27 lb./in.². When the hydrogen pressure became constant, the mixture was filtered to remove the platinum and evaporated to a small volume. After the addition of 1.25 g. (0.054 mole) of sodium hydroxide in 10 ml. of water, the mixture was treated with 7.5 g. (0.054 mole) of benzoyl chloride. Filtration and washing of the precipitate with ether produced 5.4 g. (58.1%) of a white solid. The solid was recrystallized twice from 95% ethanol, m.p.: 220.5–221.5°. Reported melting points vary¹⁶: 217°, 218–219°, 225.5°.

Anal. Calcd. for $C_{22}H_{20}N_2O_3$: N, 8.14. Found: N, 8.21.

Acetic N-(1-Phenyl-2-nitroethyl)-acetohydroxamic Anhydride. Method I.—Two grams of N-(1-phenyl-2-nitroethyl)-hydroxylamine was dissolved in 10 ml. of acetic anhydride. After standing overnight, the solution was heated on a steam-bath for five minutes and then poured into water. A white solid separated on hydrolysis of the acetic anhydride. The yield was 2.5 g. (86%), m.p. 143–145°. On recrystallization from methanol and twice from benzene, the melting point was 131–132°. An alcoholic solution did not give a color with ferric chloride. The product was soluble in aqueous sodium hydroxide.

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: N, 10.52. Found: N, 10.27.

Method II.—To 2 g. (0.011 mole) of N-(1-phenyl-2-nitroethyl)-hydroxylamine dissolved in 5 ml. of anhydrous

dioxane and 1.74 g. (0.022 mole) of anhydrous pyridine, 1.7 g. (0.022 mole) of acetyl chloride in 2 ml. of anhydrous dioxane was added with cooling and shaking. After standing at room temperature for 15 minutes, the mixture was poured into an ice-water mixture. The yield was 2.6 g. (89%), m.p. 143–145°.

Treatment with Alkali.—N-(1-Phenyl-2-nitroethyl)-hydroxylamine (4.55 g.) was dissolved in 25 ml. of water containing an equivalent quantity (1.2 g.) of sodium hydroxide. The resulting solution was added dropwise into an agitated solution of 15 ml. of concd. sulfuric acid in 15 ml. of water. No gas was evolved. Neutralization produced 4.1 g. of white solid, m.p. 94–96°. It was not an aldehyde but was the original hydroxylamine. Recrystallization from chloroform-methanol raised the m.p. to 96–97°. A mixed melting point with N-(1-phenyl-2-nitroethyl)-hydroxylamine was not depressed. The results were the same when dilute and concentrated sulfuric acid solutions were used.

Attempted Isolation of *aci*-N-(1-Phenyl-2-nitroethyl)-hydroxylamine.—The method used was adapted from Fraser and Kon.¹⁷ One gram of N-(1-phenyl-2-nitroethyl)-hydroxylamine was dissolved in 5 ml. of water containing three equivalents (0.68 g.) of sodium hydroxide. After one hour at room temperature, the mixture was cooled to 2° and neutralized with cold, dilute acetic acid. Upon standing, 1 g. of an orange-brown solid separated of m.p. 95.5–98.5° after crystallization from chloroform. The solid gave no color with ferric chloride and reduced ammoniacal silver nitrate in the cold. A mixed melting point with N-(1-phenyl-2-nitroethyl)-hydroxylamine was not depressed.

N-(1-Phenyl-2-nitroethyl)-benzenesulfonylhydroxamic Acid.—To 9.1 g. of N-(1-phenyl-2-nitroethyl)-hydroxylamine dissolved in 25 ml. of anhydrous pyridine and cooled to –10° in an ice-salt-bath, 8.8 g. of chilled benzenesulfonyl chloride was added in small portions. The mixture was shaken during this process, after which it was left for one hour at 0° and then was poured into ice-water; yield 16.8 g. The product was recrystallized from 95% ethanol, m.p. 94–95°, after desiccation over sulfuric acid.

Anal. Calcd. for $C_{14}H_{14}N_2O_6S \cdot C_6H_5N$: N, 10.47. Found: N, 10.48.

Proof of Pyridine of Crystallization.—Five grams of the above product, m.p. 94–95°, was dissolved in 15 ml. of water containing 0.6 g. of sodium hydroxide. The solution was extracted with ether and the ether extract was dried over magnesium sulfate, filtered and the ether evaporated. The liquid thus obtained was treated with methyl iodide producing 0.4 g. of a solid which melted at 115.5–117° with decomposition after recrystallization from absolute ethanol (N-methylpyridinium iodide, m.p. 117°).

Action of Alkali on N-(1-Phenyl-2-nitroethyl)-benzenesulfonylhydroxamic Acid.—Method taken from Piloty.¹⁸ To 14.5 g. of N-(1-phenyl-2-nitroethyl)-benzenesulfonylhydroxamic acid (solvated), dissolved in 25 ml. of water containing 3.6 g. (0.09 mole) of sodium hydroxide, carbon dioxide gas was added until precipitation was complete. The yield was 6.5 g. (quantitative). The solid was insoluble in cold chloroform. It was recrystallized from water and then from chloroform, m.p. 94.5–95.5° (ω -nitroacetophenone oxime, m.p. 96°).¹⁰ One gram of the yellow needles was refluxed with 6 N hydrochloric acid. Cooling produced white crystals which were recrystallized from chloroform, m.p. 105–105.5° (ω -nitroacetophenone, m.p. 105–105.5°).¹⁹

Oxidation by Hypochlorous Acid.—To a solution of 0.03 mole (5 g.) of N-(1-phenyl-2-nitroethyl)-hydroxylamine in 20 ml. of water containing 0.03 mole of hydrochloric acid was added a suspension of 0.014 mole of calcium hypochlorite in 10 ml. of water, followed by an excess of dilute hydrochloric acid. The mixture was stirred for one hour and allowed to stand overnight. The yellow-tinted white solid weighed 1.7 g., m.p. 104–105° (ω -nitroacetophenone, m.p. 105–105.5°).¹⁹

Oxidation by Chromic Acid.—To 9.1 g. of N-(1-phenyl-2-nitroethyl)-hydroxylamine, dissolved in 120 ml. of 6 N sulfuric acid and diluted to 200 ml., was added a solution of 14.9 g. of sodium dichromate dihydrate in 100 ml. of water with cooling so that the temperature did not exceed 0°. The precipitate produced was collected on a filter, washed with several portions of water and air-dried. The yield of

(15) E. Bamberger, *Ber.*, **27**, 1548 (1894).

(16) F. Feist and H. Arnstein, *ibid.*, **28**, 426 (1895); G. Ruggeri and G. Rigoli, *Gazz. chim. ital.*, **54**, 552 (1924); H. Reihlen, E. Weinbrenner and G. V. Hessling, *Ann.*, **494**, 158 (1932).

(17) H. B. Fraser and G. A. R. Kon, *J. Chem. Soc.*, 604 (1934).

(18) O. Piloty, *Ber.*, **29**, 1566 (1896).

(19) J. Thiele and S. Haecckel, *Ann.*, **325**, 11 (1902).

white solid, tinted green, was 7.0 g. The solid was washed with portions of ether until the melting point was constant, 128.5–129° with decomposition. Wieland¹¹ reports styrene pseudo-nitrosite to melt at 129° with decomposition. Fusion of the solid converted it into a bright green liquid which rapidly decomposes into a yellow oil. The molecular weight was determined by the Rast camphor method. Calcd. for C₈H₈N₂O₂: mol. wt., 180. Found: mol. wt., 235 (average of two determinations). The camphor solution exhibited a transitory bright green color on fusion.

ω-Nitroacetophenone Oxime.—Extraction of 7 g. of styrene pseudo-nitrosite with hot chloroform produced 6.1 g. of an oily solid which melted at 94.5–95.5° after recrystallization from carbon tetrachloride. Recrystallization of the styrene pseudo-nitrosite from hot water also produced white needles melting at 94.5–95.5°. The oxime is reported to melt at 96°. ¹⁰

ω-Nitroacetophenone.—Refluxing a portion of either ω-nitroacetophenone oxime or styrene pseudo-nitrosite with dilute hydrochloric acid gave rise to white needles melting at 104.5–105.5° (literature, ¹⁹ m.p. 105–105.5°).

Reaction of N-(1-Phenyl-2-nitroethyl)-hydroxylamine with Benzoyl Chloride.—To 2 g. (0.011 mole) of N-(1-phenyl-2-nitroethyl)-hydroxylamine dissolved in 10 ml. of anhydrous pyridine, 2.8 g. (0.022 mole) of benzoyl chloride was added. The mixture was shaken and kept chilled. After 10 minutes, the mixture was poured into 50 ml. of cold water. A brown oil was obtained which was washed twice with water and

then was dissolved in a minimum volume of methanol. After standing overnight, a solid separated which, on filtration and washing with cold methanol, yielded 1.1 g. of white solid. The yield was approximately the same when three equivalents of benzoyl chloride were used. The solid was recrystallized from methanol and then several times from benzene, m.p. 155.5–156°.

Anal. Calcd. for C₂₀H₂₂N₂O₆: C, 70.46; H, 4.48; N, 5.67. Found: C, 70.31; H, 4.36; N, 5.60.

A methanolic solution did not give a color with 1% ferric chloride. The compound was insoluble in 5% sodium hydroxide after 30 minutes. After a longer period the solid is soluble. Neutralization of the alkali with hydrochloric acid and treatment with 1% ferric chloride produced an intense red-violet coloration. Strong alkaline hydrolysis of 4.4 g. of the benzoylated product produced 2.4 g. of purified benzoic acid (m.p. 120.5–121.5°) corresponding to 2.2 moles of benzoic acid per mole of benzoylated product.

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EVANSTON, ILLINOIS


[CONTRIBUTION FROM ABBOTT LABORATORIES]

The Mannich Reaction of Diphenylacetonitrile. Products and Derivatives

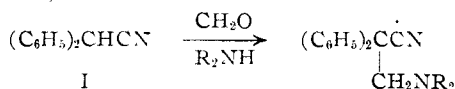
By HAROLD E. ZAUGG, BRUCE W. HORROM AND MAYNETTE R. VERNSTEN

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Mannich type products have been prepared by the reaction of diphenylacetonitrile and formaldehyde with six secondary amines. Three of these α,α-diphenyl-β-substituted-amino-propionitriles have been hydrolyzed to the corresponding β-amino acids. A number of cleavage reactions of α,α-diphenyl-β-dimethylaminopropionitrile and of the corresponding carboxylic acid are described. Ester and amide derivatives of the dimethylamino acid have been prepared as general analogs of the active analgesic, Methadon.

Zief and Mason¹ have reported the reaction between benzyl cyanide and morpholinomethanol to give the expected amino nitrile C₆H₅CH(CN)CH₂N . However, attempts to prepare the picrate resulted in cleavage of the molecule by a reverse Mannich reaction.

In the present work, the reaction of the analogous diphenylacetonitrile (I) and formaldehyde with the six secondary amines, dimethylamine, diethylamine, pyrrolidine, piperidine, morpholine and N-methylpiperazine, respectively, is reported.² In all cases the expected products (II) were obtained, the first three in fair to good yields even at low reaction temperatures (40°) but the last three only in poor yields even at higher temperatures (80–120°).



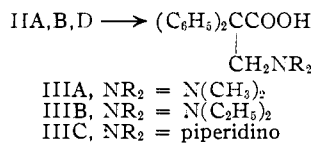
IIA, NR₂ = N(CH₃)₂; IID, NR₂ = piperidino
IIB, NR₂ = N(C₂H₅)₂; IIE, NR₂ = morpholino
IIC, NR₂ = pyrrolidino; IIF, NR₂ = N-methylpiperazino

In contrast to the instability of the salts of the Mannich product of benzyl cyanide observed by

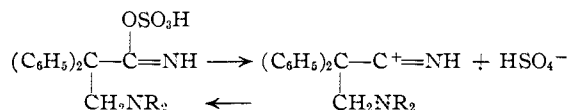
(1) M. Zief and J. P. Mason, *J. Org. Chem.*, **8**, 1 (1943).

(2) After most of this work was completed, M. Bockmühl and G. Ehrhart, *Ann.*, **561**, 52 (1948), reported the reaction of diphenylacetonitrile and formaldehyde with dimethylamine. However, few details were given and the product was not investigated extensively.

Zief and Mason, the product IIA obtained from dimethylamine formed a stable crystalline hydrochloride which underwent nearly quantitative reversal only on prolonged heating in water. On the other hand, when 75% sulfuric acid at 140° was employed as the hydrolytic agent, the corresponding β-amino acid IIIA was produced in a 64% yield. In like manner, the diethylamino (IIB) and piperidino (IID) nitriles were readily hydrolyzed to the corresponding carboxylic acids, IIIB and IIIC, respectively. The reason for this apparent anomaly—reversal in weakly acid or



neutral solution and conversion of the nitrile to the carboxyl group in strong acid—probably lies in the intermediate formation in strong sulfuric acid of the following salt-like addition product³



This would have the effect of reducing the polariz-

(3) Compare J. J. Ritter and P. P. Minieri, *THIS JOURNAL*, **70**, 4045 (1948).