[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

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

BY CHARLES D. HURD AND JOHN PATTERSON

RECEIVED AUGUST 11, 1952

The addition of hydroxylamine to unsaturated nitro compounds of the nitroölefin 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] nitroparaffins[6] and various other nucleophilic reagents[3,7] to nitroölefins 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-workers[8] 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 amylene.

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%

$$RCH{=}CHNO_2 + NH_2OH \longrightarrow RCH(NHOH){-}CH_2{-}NO_2$$

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 oxidation[7] of these compounds with Tollens and Fehling reagents. New reactions of N-(1-phenyl-2-nitroethyl)-hydroxylamine were investigated in this study. Generally, these reactions involved only one of the two functional groups.

TABLE I

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

	Compound								Derivative			
R	B.p., °C.	Mm.	$n^{20}D$	d^{20}_{20}	Yield, %	Mol. formula	Nitrogen, % Calcd.	Found	M.p., °C.	Mol. formula	Nitrogen, % Calcd.	Found
Phenyl	[a]		....	...	80	$C_8H_{10}N_2O_3$	[e]	[e]	129–129.5[c]	$C_{15}H_{15}N_3O_4$	13.95	14.15
2-Furyl	[b]		....	...	81	$C_6H_8N_2O_4$	16.27	16.12	139.5–140[c]	$C_{13}H_{13}N_3O_5$	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]	$C_{11}H_{15}N_3O_3S$	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)-

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.

(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).

The hydroxylamine function seems to exert a stabilizing effect on the nitro group. Although the sodium salt of the *aci*-nitro group was formed readily, attempts to isolate the *aci*-nitro form or to convert the sodium salt into an aldehyde by use of mineral acid were fruitless. The starting material was recovered instead.

Since the hydroxylamino group in these compounds is more stable than in simple alkylhydroxylamines, it was of interest to test for the usual hydroxylamine reactions and they were found to proceed smoothly. Thus, N-(1-phenyl-2-nitroethyl)-hydroxylamine reacted with phenyl isocyanate to give phenylcarbamo-N-(1-phenyl-2-nitroethylhydroxamic) acid; with hydrochloric acid to give N-(1-phenyl-2-nitroethyl)-hydroxylammonium chloride; with benzaldehyde to give phenyl-N-(1-phenyl-2-nitroethyl)-nitrone; and with acetic anhydride or with acetyl chloride and pyridine to give acetic N-(1-phenyl-2-nitroethyl)-acetohydroxamic anhydride. Alkali solubility of the last product and non-reaction with ferric chloride indicated that acetylation occurred on the hydroxylamine function.

Benzoyl chloride produced a derivative of N-(1-phenyl-2-nitroethyl)-hydroxylamine which points to a reaction involving three parts of benzoyl chloride. Two of them reacted at the hydroxylamine function to produce a N-substituted benzoic benzohydroxamic anhydride, similar to the acetylation reaction. The third benzoyl group probably formed a benzoic *aci*-nitro anhydride, since the product was no longer soluble in alkali and therefore did not possess a free nitro group. The structure can be represented as

$$C_6H_5CO-N(OCOC_6H_5)-CHPh-CH=N(O)-O-COC_6H_5$$

Rearrangement of the *aci*-nitro benzoic anhydride to the hydroxamic acid, as was observed by Jones[9] with nitroethane and benzoyl chloride, is ruled out here, since the product would have been a strong acid.

Catalytic reduction with platinum oxide and hydrogen produced styrenediamine, $H_2NCHPh-CH_2NH_2$, which was isolated as the dibenzoyl derivative, N,N′-styrenebisbenzamide.

Treatment with benzenesulfonyl chloride in pyridine gave rise to N-(1-phenyl-2-nitroethyl)-benzenesulfonohydroxamic acid which crystallized with a molecule of pyridine. Solution of the hydroxamic acid with alkali and neutralization with carbon dioxide yielded ω-nitroacetophenone oxime

$$NaOH + C_6H_5SO_2N(OH)-CHPh-CH_2NO_2 \longrightarrow C_6H_5SO_2Na + HON=CPh-CH_2NO_2 + H_2O$$

The ease of oxidation was readily demonstrated by use of cold ammoniacal silver nitrate. A hypochlorous–hydrochloric acid mixture gave rise to ω-nitroacetophenone. Oxidation with chromic acid produced a green-tinted white solid which possessed the same properties as styrene pseudo-nitrosite, obtained by Sommer[10] by the action of arsenic and concentrated nitric acid on styrene and by Wieland[11] on treatment of styrene in glacial acetic acid with concentrated sodium nitrate. On fusion, it changed to a transitory bright green colored oil which rapidly decomposed into a yellow oil. Refluxing the pseudo-nitrosite with chloroform or water yielded ω-nitroacetophenone oxime, while boiling with dilute hydrochloric acid produced ω-nitroacetophenone. Molecular weight by the Rast camphor method was found to be 235. During the fusion in camphor, a bright green solution was obtained which rapidly turned yellow. This explains the value of 235, which is between 180 for the nitroso compound indicated below and 360 for its dimer. These facts indicate that the oxidation product is a nitroso dimer which, on heating or on solution in solvents such as water, chloroform or camphor, dissociates and rearranges to the ω-nitroacetophenone oxime

$$2C_6H_5CH(NHOH)CH_2NO_2 + 2[O] \longrightarrow [C_6H_5CH(NO)CH_2NO_2]_2 + 2H_2O$$

$$[C_6H_5CH(NO)CH_2NO_2]_2 \rightleftarrows 2C_6H_5CH(NO)CH_2NO_2 \longrightarrow 2C_6H_5-C(=NOH)-CH_2NO_2$$

Experimental

Melting points and boiling points are uncorrected.

Preparation of Unsaturated Nitro Compounds.—ω-Nitrostyrene was prepared as described by Gilman.[12] 1-Furyl-2-nitroethylene was synthesized by a modification of the method of Thiele and Landers.[13] The method was essentially that used for the preparation of ω-nitrostyrene. 1-Nitro-1-propene and 1-nitro-1-butene were prepared from the nitro alcohols by the method of Buckley and Scaife.[14]

Reactions with Hydroxylamine.—The method used for nitrostyrene, a modification of Posner's method,[7] was used also for the furan analog. To 0.1 mole of the nitro compound, dissolved in 25–50 ml. of methanol, was added 0.1 mole of hydroxylamine in 50 ml. of methanol. The mixture was refluxed for 30 minutes, then the solvent was removed by a stream of air. Crystallization of the phenyl compound was from a 9:1 chloroform–methanol solution. Crystallization of the furyl compound (light yellow color when crude, white when pure) was from chloroform or 95% ethanol or ethyl ether. It turned dark within 5 months. Data are given in Table I.

To make N-(1-ethyl-2-nitroethyl)-hydroxylamine and N-(1-methyl-2-nitroethyl)-hydroxylamine 0.34 mole of the nitroalkene was added to a suspension of 0.34 mole of pure hydroxylamine in 50 ml. of anhydrous ethyl ether at such a rate that gentle reflux was maintained. After 30 minutes the ether was removed and the residue distilled at 2 mm. to give the colorless liquid fractions described in Table I.

Phenylcarbamo-N-(1-furyl-2-nitroethylhydroxamic) Acid.—To 0.5 g. of N-(1-furyl-2-nitroethyl)-hydroxylamine in 1 ml. of anhydrous dioxane, 0.04 g. of phenyl isocyanate was added. After standing for two hours, 0.5 g. of a white solid was obtained which browned on air drying. Recrystallization from 95% ethanol (Norit A) produced white crystals melting at 139.5–140° with decomposition. The product gave a deep blue color with 1% ferric chloride and reduced ammoniacal silver nitrate in the cold. This compound did not decompose in six months.

Phenylthiocarbamo-N-(1-ethyl-2-nitroethylhydroxamic) acid was prepared by mixing equal volumes of phenyl isothiocyanate and N-(1-ethyl-2-nitroethyl)-hydroxylamine in chloroform. The white solid obtained after washing with chloroform and ether melted at 95° with decomposition and gave the analysis shown in Table I. It gave a blue ferric chloride color reaction. Attempts at recrystallization from a chloroform–acetone solvent produced a new compound,

(9) L. W. Jones, *Am. Chem. J.*, **20**, 1 (1898).

(10) E. A. Sommer, *Ber.*, **28**, 1329 (1895).

(11) H. Wieland, *ibid.*, **36**, 2558 (1903).

(12) H. Gilman, "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 413.

(13) J. Thiele and H. Landers, *Ann.*, **369**, 303 (1909).

(14) G. D. Buckley and C. W. Scaife, *J. Chem. Soc.*, 1471 (1947).

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. Phenylcarbamo-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)-phenylnitrone.—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 vary[16]: 217°, 218–219°, 225.5°.

Anal. Calcd. for $C_{22}H_{20}N_2O_2$: 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 $C_{12}H_{14}N_2O_5$: 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)-benzenesulfonohydroxamic 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 $C_{14}H_{14}N_2O_5S \cdot C_5H_5N$: 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)-benzenesulfonohydroxamic Acid.—Method taken from Piloty.[18] To 14.5 g. of N-(1-phenyl-2-nitroethyl)-benzenesulfonohydroxamic 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. Haeckel, *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. Wieland[11] 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 $C_8H_8N_2O_3$: 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 $C_{29}H_{22}N_2O_6$: 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.

Acknowledgment.—Micro combustions for C, H and N were performed by J. Sorenson and C. White. This work was supported by a Commercial Solvents Corporation fellowship held by one of us (J. P.) during 1950–1951.

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

RECEIVED AUGUST 7, 1952

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 Mason[1] have reported the reaction between benzyl cyanide and morpholinomethanol to give the expected amino nitrile $C_6H_5CH(CN)CH_2N$⟨O⟩ 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°).

$$(C_6H_5)_2CHCN \xrightarrow[R_2NH]{CH_2O} (C_6H_5)_2C(CN)CH_2NR_2$$

I

IIA, NR_2 = $N(CH_3)_2$; IID, NR_2 = piperidino
IIB, NR_2 = $N(C_2H_5)_2$; IIE, NR_2 = morpholino
IIC, NR_2 = pyrrolidino; IIF, NR_2 = N-methylpiperazino

In contrast to the instability of the salts of the Mannich product of benzyl cyanide observed by 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 product[3]

$$\text{IIA,B,D} \longrightarrow (C_6H_5)_2C(CH_2NR_2)COOH$$

IIIA, NR_2 = $N(CH_3)_2$
IIIB, NR_2 = $N(C_2H_5)_2$
IIIC, NR_2 = piperidino

$$(C_6H_5)_2C(OSO_3H)C(CH_2NR_2)=NH \longrightarrow (C_6H_5)_2C(CH_2NR_2)C^+=NH + HSO_4^- \longrightarrow (C_6H_5)_2C(CH_2NR_2)C(CH_2NR_2)=NH$$

This would have the effect of reducing the polariz-

(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.

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