[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

# PREPARATION AND REACTIONS OF α-HYDROXYLAMINO NITRILES

CHARLES D. HURD AND J. M. LONGFELLOW[1]

*Received January 8, 1951*

In 1892–1894 von Miller, Ploechl, and their coworkers (1) reported the addition of hydrogen cyanide to aliphatic oximes and the hydrolysis of the α-hydroxylamino nitriles thus obtained to α-hydroxylamino acids. A few subsequent papers (2, 3) have appeared but work in this field has been largely neglected except for α-hydroxylaminoisobutyronitrile. The last compound has been investigated by several workers (4) because it is the starting point of Piloty's synthesis of porphyrexide. In these studies 20–29% yields were obtained using acetone oxime and a diluted hydrogen cyanide, about three-fifths of the oxime being recovered. If absolute hydrogen cyanide was used, as recommended by von Miller and Ploechl, an oil was formed from which practically no hydroxylaminoisobutyronitrile was obtained.

In the present investigations the reactions of butyraldehyde oxime and heptanal oxime with absolute hydrogen cyanide yielded up to 75% and 37% of the expected nitriles, respectively; but the nitriles were seldom obtained in satisfactory purity by this reaction. The best yields were obtained if the operation was interrupted when it changed in color from golden yellow to orange. At later changes of color from orange to red no nitrile could be isolated. Continued reaction gave rise to black viscous oils and, ultimately, black, coke-like solids. Reactions in these later stages were quite vigorous.

Confirming von Miller and Ploechl (1a), we found that neither of the benzaldoximes reacted to form an adduct with hydrogen cyanide, even under a variety of conditions. Also, β-2-furaldoxime forms no adduct. Propionaldehyde 2,4-dinitrophenylhydrazone was insoluble in hydrogen cyanide and did not react.

Butyraldehyde oxime, in contrast, was found to add hydrogen cyanide even from a solution in acetic acid. Furthermore, 2-hydroxylaminovaleronitrile was prepared conveniently and in excellent yield by the reaction of butyraldehyde, hydroxylammonium chloride, sodium cyanide, and potassium dihydrogen phosphate in aqueous solution. Unfortunately, this last procedure is not general. Although propionaldehyde reacted under these conditions to give 2-hydroxylaminobutyronitrile, heptanal gave only its oxime and none of the nitrile. Formaldehyde reacted under these conditions to give a liquid product which decomposed vigorously at room temperature. Acetone gave only a tar.

The yield of 2-hydroxylaminoöctanenitrile from heptanal oxime was increased to 55% by the use of an equivalent of pyridine and an excess of hydrogen cyanide. Small amounts of pyridine (1 or 2%) were not effective. Similarly, pyridine promoted reaction of acetone oxime and hydrogen cyanide to give a 38% yield of α-hydroxylaminoisobutyronitrile, a significant increase over the

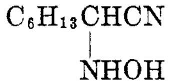
---

[1] Holder of Fellowship sponsored by Swift and Company, 1946–1949.

yields of 20–29% previously reported (4). Replacement of pyridine by ethylamine in the solution of acetone oxime in hydrogen cyanide produced a rapid formation of red oil from which no α-hydroxylaminoisobutyronitrile was recovered. Other workers have noted the effectiveness of pyridine in promoting the reaction of hydrogen cyanide with acyl chlorides (5) and with sulfur or selenium (6).

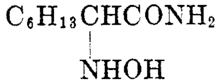
*Hydrolysis of the nitriles.* von Miller and Ploechl hydrolyzed α-hydroxylamino nitriles to the corresponding acids (1b) by the use of concentrated hydrochloric acid for several hours at 25°. 2-Hydroxylaminobutyric acid was isolated in 50% yield. The corresponding derivatives of valeric, caproic, and caprylic acids were obtained also (no yields stated), but they could not isolate 2-hydroxylaminopropionic acid. We obtained 2-hydroxylaminovaleric acid by this procedure in low and variable yields, the highest being 29%. Several modifications tried did not improve the yield.

While these investigators obtained 2-hydroxylaminoöctanoic acid from 2-hydroxylaminoöctanenitrile (I) as stated above, we found that a solution of this nitrile in concentrated hydrochloric acid at 25–40° gave within 12 hours a precipitate of 2-hydroxylaminoöctanamide hydrochloride from which the amide (II) was liberated by treatment with aqueous ammonia. The amide was condensed with benzaldehyde to give phenyl-N-(1-carbamylheptyl)nitrone (III). Oxidation of the amide hydrochloride in aqueous solution with potassium permanganate gave 2-oximinoöctanamide (IV) in somewhat better yields than when it was prepared by treating 2-hydroxylaminoöctanenitrile with concentrated sulfuric acid (1b).



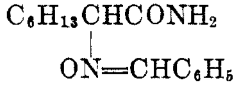
$C_6H_{13}\underset{\substack{|\\ NHOH}}{C}HCN$

I



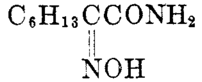
$C_6H_{13}\underset{\substack{|\\ NHOH}}{C}HCONH_2$

II



$C_6H_{13}\underset{\substack{|\\ ON{=}CHC_6H_5}}{C}HCONH_2$

III



$C_6H_{13}\underset{\substack{\|\\ NOH}}{C}CONH_2$

IV

## EXPERIMENTAL

Microanalyses for carbon, hydrogen, and nitrogen were performed by Misses V. Hobbs, J. Sorenson, and C. Brauer.

*2-Hydroxylaminovaleronitrile.* A. *Method of von Miller and Ploechl* (*1b*). The best yield was obtained by the following procedure, in which the processing of the product departs somewhat from the original method. Butyraldehyde oxime (89.6 g., b.p. 57.5–60° at 16 mm.) was evenly divided into four 50-ml. flasks, and to each flask was added about 20 ml. of hydrogen cyanide. The clear colorless solution acquired a slight green tinge after 15 hours at 20°. Nine hours later it was yellowish. At the end of 26 hours, the reaction mixture had set up to a semi-solid slurry. The flask contents were combined and dissolved in 200 ml. of warm ether. The yellow solution was chilled to −10° for one hour. To the semi-solid paste was added an additional 250 ml. of cold ether. After 15 minutes, the mixture was filtered and the white fibrous solid washed with petroleum pentane. After drying, the solid weighed 34.5 g., m.p. 87–92°.

The combined filtrates were diluted with 250 ml. of pentane, cooled for three hours at

−78° and filtered; weight, after air-drying, 38 g., m.p. 86–90°, fibrous, papery, white solid with slight green hue.

From portions of this 72 g. (67%) of crude 2-hydroxylaminovaleronitrile, pure samples of m.p. 102° were obtained by repeated precipitations from ether with petroleum pentane.

If the reaction mixture of hydrogen cyanide and butyraldehyde oxime (which did not always set up to a slurry as in the example described) was permitted to react beyond the optimum time as evidenced by bright yellow color, ether-insoluble red, tarry oils resulted from which little or no nitrile could be isolated. The time for later color changes (green, golden yellow, red, black) varied widely. On keeping the reaction mixture for two or three weeks at room temperature, black, coke-like solids resulted.

B. *By emulsification of hydrogen cyanide and butyraldehyde oxime in petroleum pentane.* To an ice-cold solution of 20 g. of butyraldehyde oxime (b.p. 145–146° at 750 mm.) in 55 ml. of petroleum pentane was added 10 ml. of hydrogen cyanide. The mixture was stirred to maintain emulsification. After 24 hours of stirring at 0°, a second 10 ml. of hydrogen cyanide was added. Stirring was continued. After 48 hours a solid appeared, and after 60 hours the mixture was a sludge of white, fibrous solid in a yellow liquid. The solid was air-dried; 28 g., m.p. 80–87°. By precipitation from ether with pentane, there was obtained 25 g. of 2-hydroxylaminovaleronitrile, m.p. 95.5–98.5° (75%).

C. *From butyraldehyde.* To a stirred solution (0 to 3°) of 70 g. (1 mole) of hydroxylammonium chloride in 300 ml. of water was added 72 g. (1 mole) of butyraldehyde (freshly distilled, b.p. 72–74°). To it was added dropwise a solution of 50 g. of sodium cyanide and 10 g. of sodium carbonate in 150 ml. of water. The mixture was stirred and kept cold for three hours, after which 50 g. of solid sodium cyanide and a slurry of 136 g. of potassium dihydrogen phosphate in 400 ml. of water was added. Stirring and cooling was continued, but the ice was not replenished. After nine more hours, the bath temperature was 30°, and a granular precipitate had separated. The stirred mixture was again chilled and filtered. This solid (72 g.) was washed thoroughly with petroleum pentane and dried: weight, 64 g. It discolored slightly at 80° but melted at 96–98.5°.

The residual reaction mixture was diluted with 2 l. of water and was extracted with ether. The extract was dried over sodium sulfate and diluted with petroleum hexane. There first precipitated 16.6 g. of colorless 2-hydroxylaminovaleronitrile, m.p. 95–97°, then 4.7 g. of yellow to red nitrile melting at 78–84°. Total yield of colorless nitrile was 80.6 g. (70.6%).

Initial addition of butyraldehyde to equivalent quantities of hydroxylammonium chloride and sodium cyanide in aqueous solution, followed thereafter by the procedure described above, resulted in lower yields and poorer quality.

Replacement of the sodium cyanide and potassium dihydrogen phosphate by an equivalent amount of sodium cyanide and a 1:1 solution of hydrogen cyanide in acetic acid resulted in lower yields of the nitrile (37%) but the product was of satisfactory purity, m.p. 93–97°.

D. *By reaction of butyraldehyde oxime and hydrogen cyanide in acetic acid.* Crude butyraldehyde oxime (75 g.) was dissolved in 50 ml. of a 1:1 solution of hydrogen cyanide in acetic acid in a stoppered flask and the solution was left for 36 hours at 25°. The flask pressure increased sufficiently to force out the stopper. In three more hours a precipitate began to form which greatly increased the total volume. Two hours later the fibrous, white, papery 2-hydroxylaminovaleronitrile was collected, washed with petroleum pentane, and dried; weight 34.5 g., m.p. 92–96°.

*2-Hydroxylaminovaleric acid.* Following the directions of von Miller and Ploechl (1b), there was obtained 2-hydroxylaminovaleric acid, m.p. 166–167° (dec.). The reported melting point was 156°. Otherwise, the properties checked those listed for it. In addition, it was observed that 2 g. of the acid suspended in pyridine dissolved exothermically on addition of 1.5 g. of acetic anhydride, but the 2 ml. of liquid product could not be induced to crystallize.

The yields in this reaction were low and variable, the highest being 29%. In their method the solution of the nitrile in concentrated hydrochloric acid was allowed to stand at 25°, then was concentrated at 100° until separation of ammonium chloride, then cooled, filtered, and brought to weak acidity with ammonia. These modifications were tried in the present work, but unsuccessfully: concentration of the solution under diminished pressure, alcoholysis of the nitrile in the presence of sulfuric or hydrobromic acids, hydrolysis of the nitrile with barium hydroxide solution, treatment of the nitrile in water with an anion exchange resin (Amberlite IR-4-B.A.G.) or a cation exchange resin (Amberlite IR-100-H).

*2-Hydroxylaminobutyronitrile.* A 50% yield of 2-hydroxylaminobutyronitrile, m.p. 84–86°, was obtained from propionaldehyde by a procedure similar to above procedure C. One portion of the product, packed loosely in a cardboard box and stored at 20–25° for two weeks, showed no visible change. A second portion, packed firmly in an amber jar closed loosely with a screw cap, had turned into a black sirupy tar after nine days at 25–30°.

*2-Hydroxylaminoöctanenitrile.* A. *By the method of von Miller and Ploechl* (1b). A solution of 9.3 g. of heptanal oxime (b.p. 105–106° at 18 mm.) in hydrogen cyanide was shaken for 30 hours. When the solution became yellow, it was evaporated. A waxy solid remained which was taken up in ether and reprecipitated by dilution with petroleum pentane and partial evaporation; yield 3.4 g. (30%), m.p. 60–68°. The m.p. was raised to 76–78° by a second such treatment but von Miller and Ploechl gave 92–93°.

Permitting the reaction mixture to stand for two days or more resulted in the formation of tars. During this further reaction, stoppers were frequently blown from the reaction flasks, and the contents ejected. In one experiment 2 g. of the oxime and 20 ml. of hydrogen cyanide were left for five weeks in a tightly stoppered flask. After four days, the solution was black and viscous. At the end of five weeks, the side of the flask had been blown out and there remained in the flask 10.3 g. of a black, friable, cokelike solid, 2 g. of which was extractable with methanol.

B. *In the presence of pyridine.* To a cooled solution of 12 g. of heptanal oxime in 8 g. of pyridine was added 25 ml. of hydrogen cyanide. A solid (probably oxime) precipitated, then slowly dissolved to give a clear water-white solution. The solution was left at room temperature for 19 hours, at which time it was orange-yellow and contained a few crystals. After 29 hours the reaction mixture was aspirated (water pump) for one-half hour in a closed vessel to remove hydrogen cyanide. The solid mat which formed was washed well with cold water, pressed dry and then taken up in ether and separated from the 5–6 ml. of aqueous phase. On dilution with petroleum hexane, a fibrous solid began to form at once. The solution was concentrated slightly by evaporation in a stream of air, then was filtered. The solid was pressed under a rubber sheet on the funnel, and the filtrate was concentrated under reduced pressure until a second heavy, matted precipitate formed. The latter was also pressed dry. Evaporation of the second filtrate gave a third crop of nitrile, but evaporation of the third filtrate left 5 g. of red oil. The combined solids were reprecipitated from ether by hexane and dried in a vacuum desiccator over paraffin wax; weight, 8.0 g., m.p. 85.5–87°. Two reprecipitations by this method gave nitrile of m.p. 86–87.5°. The melting point was not changed by further reprecipitations from ether or by recrystallization from water.

*2-Hydroxylaminoöctanamide hydrochloride.* Five grams of 2-hydroxylaminoöctanenitrile (m.p. 85.5–87°) and 20 ml. of concentrated hydrochloric acid (sp. gr. 1.19), previously cooled to 0°, were mixed. Most of the nitrile dissolved. As the mixture warmed to room temperature, it formed a green solution. After three hours at 20°, it was placed in a water-bath at 40° in a Dewar flask. The bath temperature dropped to 31° in 12 hours and the flask then contained a heavy white precipitate. The solution was cooled in ice for three hours, then was filtered. The 5.5 g. of air-dried solid was dissolved in 20 ml. of warm glacial acetic acid containing 10 ml. of ether. On cooling, filtering, and washing with ether, there was obtained 4.4 g. of white, crystalline hydrochloride, decomposing at 131–135°. This portion was analyzed by titration to the phenolphthalein end point. Dilution of the mother liquor with ether precipitated an additional 0.6 g. (total 5.0 g., 77%).

*Anal.* Calc'd for $C_{18}H_{19}ClN_2O_2$: Neut. equiv., 210.6. Found: Neut. equiv., 206.2, 207.5.

*2-Hydroxylaminoöctanamide.* Cold (0°) concentrated aqueous ammonia (6 ml.) was mixed with 3 g. of the hydrochloride. The stiff slurry was diluted with 6 ml. of ice-water. After two hours at room temperature, the mixture was cooled in ice and filtered (2.6 g.). The white solid amide was very sparingly soluble in ether but was soluble in alcohol, hot ethyl acetate, and hot water. Recrystallization from ethyl acetate gave 1.7 g. (65%) of m.p. 91–92°.

*Anal.* Calc'd for $C_{18}H_{18}N_2O_2$: C, 55.14; H, 10.41; N, 16.08.
Found: C, 55.76; H, 10.32; N, 16.28.

*2-Oximinoöctanamide.* A. *From 2-hydroxylaminoöctanamide hydrochloride.* To a vigorously stirred solution of 2.1 g. of the amide hydrochloride in 100 ml. of water was added gradually a solution of 0.63 g. of potassium permanganate. The permanganate reduced rapidly as it was added, forming a white solid. When the last few drops were added, the suspension took on a muddy tan color, which was decolorized by adding about 0.5 g. of sodium bisulfite. The mixture was cooled in an ice-bath and filtered. The white product was recrystallized twice from 300-ml. portions of hot water giving 1.2 g (66%) of 2-oximinoöctanamide, m.p. 136–137°.

*Anal.* Calc'd for $C_{18}H_{16}N_2O_2$: C, 55.78; H, 9.36; N, 16.27.
Found: C, 55.89; H, 9.48; N, 16.03.

B. *From 2-hydroxylaminoöctanenitrile.* To 34.4 g. of concentrated sulfuric acid was added, in portions, 7.0 g. of 2-hydroxylaminoöctanenitrile (m.p. 85–87°). The nitrile dissolved and the solution became warm. The final solution, which was green in color, was permitted to stand at room temperature for two days, then poured into 200 ml. of water and neutralized with an excess of solid barium carbonate. It was diluted to 500 ml. with water, heated, and filtered. On cooling the filtrate, there precipitated 0.4 g. of white crystals, m.p. 125–136°. Another 0.14 g. was obtained by extracting the residual solids with 800 ml. of hot water. These two crops were combined and crystallized from 200 ml. of hot water; yield, 0.30 g., m.p. 135–136° [von Miller and Ploechl (1b) obtained by this procedure 2-oximinoöctanamide, m.p. 138–139°, in yield not stated].

*Phenyl-N-(1-carbamylheptyl)nitrone.* A mixture of 1.3 g. of 2-hydroxylaminoöctanamide and 0.8 g. of benzaldehyde, heated on the steam-bath, formed a clear melt which solidified on cooling. This solid was crushed and extracted with ether. The insoluble residue (1.2 g.) melted at 115–118°. An analytical sample, prepared by twice recrystallizing from a mixture of benzene and petroleum pentane, melted at 115–116°.

*Anal.* Calc'd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45.
Found: C, 68.95; H, 8.29.

*2-Hydroxylaminoöctanoic acid.* Concentrated hydrochloric acid (20 drops) was added to a solution of 5.0 g. of 2-hydroxylaminoöctanamide hydrochloride in 50 ml. of water. The flask was sealed by a wired-on rubber stopper and maintained at 80–85° for one week. On cooling and filtering, there was obtained 1.35 g. of white solid, m.p. 155–158°. Two recrystallizations from ethanol brought the m.p. to 160–162°.

*Anal.* Calc'd for $C_8H_{17}NO_3$: N, 7.99. Found: N, 8.05, 8.11.

*$\alpha$-Hydroxylaminoisobutyronitrile.* To a solution of 33 g. of acetone oxime (m.p. 59–61°) in 40 g. of pyridine was added 50 ml. of hydrogen cyanide. A clear colorless solution resulted, which was faintly yellow after 21 hours and was orange after 28 hours. The solution was then evaporated in a stream of air for two hours. The residue was taken up in 400 ml. of ether, cooled to −78°, filtered from a small amount of orange gum, and the filtrate was concentrated to 350 ml. under reduced pressure. It was diluted with 350 ml. of petroleum hexane and concentrated to 400 ml. at reduced pressure. The white, powdery nitrile which separated weighed 17 g. (38%); m.p. 95–97°.

## SUMMARY

Propionaldehyde and butyraldehyde reacted in aqueous solution with a mixture of hydroxylammonium chloride, sodium cyanide, and sodium dihydrogen phos-

phate, to give, respectively, 2-hydroxylaminobutyronitrile and 2-hydroxylaminovaleronitrile in excellent yields; but the reaction was not general for formaldehyde, acetone, or heptanal.

The yield of α-hydroxylamino nitriles formed by addition of hydrogen cyanide to heptanal oxime or acetone oxime was substantially improved by the presence of large quantities of pyridine. Hydrolysis of 2-hydroxylaminovaleronitrile by the method described by von Miller and Ploechl gave α-hydroxylaminovaleric acid in low and variable yield. Other hydrolytic conditions tried were unsuccessful.

Acid hydrolysis of 2-hydroxylaminoöctanenitrile yielded 2-hydroxylaminooctanamide hydrochloride, from which the free amide was obtainable.

Oxidation of 2-hydroxylaminoöctanamide hydrochloride in aqueous solution with potassium permanganate yielded 2-oximinoöctanamide. Condensation of benzaldehyde with 2-hydroxylaminoöctanamide produced phenyl-N-(1-carbamylheptyl)nitrone.

EVANSTON, ILLINOIS

## REFERENCES

(1) VON MILLER, PLOECHL, *et al.*, (a) *Ber.*, **25**, 2020 (1892); (b) *Ber.*, **26**, 1545 (1893); (c) *Ber.*, **27**, 1281 (1894).
(2) MUENCH, *Ber.*, **29**, 62 (1896).
(3) STEINKOPF, *Ber.*, **46**, 98 (1913).
(4) KUHN AND FRANK, *Ber.*, **68**, 1528 (1935); ADICKES, *J. prakt. Chem.*, **161**, 271 (1943); PORTER AND HELLERMANN, *J. Am. Chem. Soc.*, **61**, 754 (1939); **66**, 1652 (1944); LILLEVIK, *et al.*, *J. Org. Chem.*, **7**, 164 (1942).
(5) JANDERS AND SCHOLZ, *Z. physik. Chem.*, **192**, 163 (1943).
(6) MCCROSKY, BERGSTROM, AND WAITKINS, *J. Am. Chem. Soc.*, **64**, 722 (1942).