

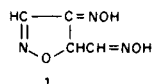
1-Hydroxyimidazole 3-Oxide and Some 2-Substituted Derivatives

Kenyon Hayes

Norwich Pharmacal Company, Division of Morton-Norwich Products, Inc.
Norwich, New York 13815

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In a study of the condensation of 5-nitro-2-furaldehyde with glyoxime in strongly acidic media, a major contaminant of the expected 2-(5-nitro-2-furyl)-1-hydroxyimidazole 3-oxide was an explosive, white, methanol soluble material which decomposed at 180-182°, without prior sublimation. The substance was soluble in aqueous bicarbonate. It showed infrared absorption at 1215 cm^{-1} , indicative for an *N* oxide. This material analyzed as $\text{C}_4\text{H}_5\text{N}_3\text{O}_3$ and the observed neutral equivalent was 140. It was noted that Miolati (1) had reported a substance of this composition and similar characteristics derived from glyoxal and hydroxylamine hydrochloride to which he tentatively assigned the isoxazole structure 1.

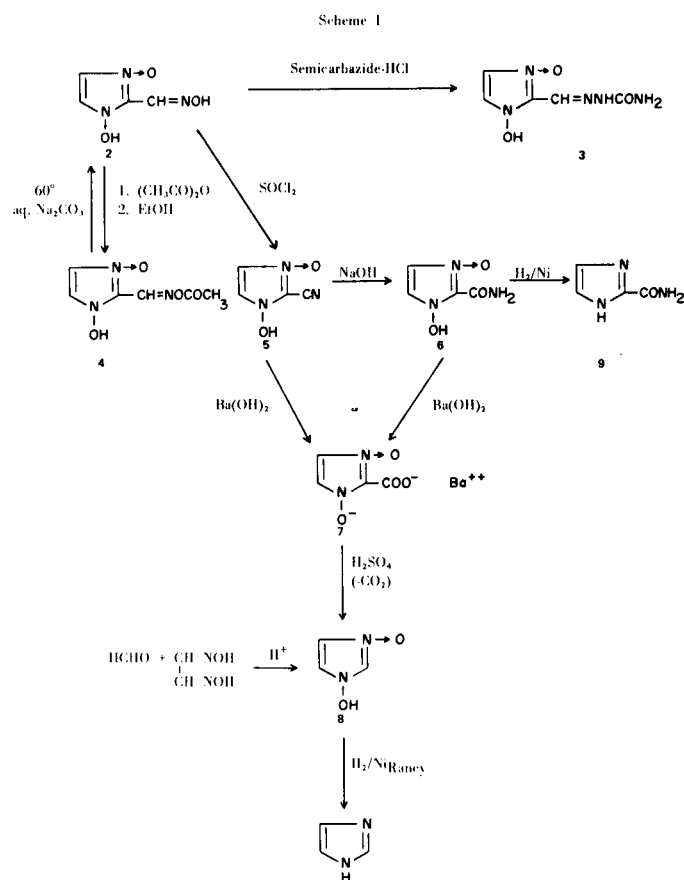


Synthesis by Miolati's procedure confirmed the identity with the unknown obtained here.

G. LaParola (2) in studying the condensation of aromatic aldehydes with dimethylglyoxime under acidic conditions had shown that the products were 1-hydroxyimidazole 3-oxide derivatives by their ready reduction to imidazoles. More recently this has been confirmed by J. Wright (3) and K. Bodendorff and H. Towliati (4) for closely related condensations.

Thus it seemed probable that Miolati's 1 was 1-hydroxyimidazole-2-carboxaldoxime 3-oxide (2). The nmr spectrum of 2 in deuterated dimethyl sulfoxide exhibited a sharp singlet at 7.40 δ with an area of two protons, assigned to the 4,5-imidazole positions; a sharp singlet at 8.00 δ with an area of one proton, assigned to the formyl hydrogen; and a two proton area, exchangeable with deuterium oxide, at 12 to 13 δ dependent on concentration and temperature, assigned to the hydroxylamine functions. This supports structure 2.

After this work had been completed Franchetti and Grifantini (5) assigned structure 2 to a by-product of decomposition point 180-181° obtained by reaction of glyoxime on *o*-nitrobenzaldehyde in ethanolic hydrogen chloride. They based the structure on elemental composition and the nmr spectrum of the hydrochloride salt.



Structure 2 was confirmed by the chemical degradations outlined in Scheme 1.

Action of excess semicarbazide hydrochloride on 2 displaced only one hydroxylamine to give the monosemicarbazone 3, whereas 1 should produce a bissemicarbazone. Acetylation with acetic anhydride followed by alcoholysis produced a monoacetate, soluble in aqueous bicarbonate indicating retention of the acidic 1-hydroxyimidazole 3-oxide function. This was the oxime acetate 4. Heating 4 at 60° in aqueous sodium carbonate regenerated 2, with no trace of nitrile formation by infrared analysis. Thus the aldoxime 2 had the *syn* configuration. The nitrile 5 was formed by the action of thionyl chloride in dioxane

on **2**. The nitrile yielded the amide **6** on treatment with aqueous caustic at room temperature. The amide **6** on catalytic reduction produced a carboxamidoimidazole **9**, which differed in the melting characteristics of the base and its mono-picrate from those reported by Balaban (6) for 4(5)-carboxamidoimidazole. The amide **6** has the properties later reported for 2-carboxamidoimidazole by P. Lont *et al.* (7). Hydrolysis of either **5** or **6** with aqueous caustic at 100°, followed by acidification, produced what was presumed to be 2-carboxy-1-hydroxyimidazole 3-oxide. This, however, decarboxylated so readily that it was not obtained pure. It was best isolated as the sesquihydrate of the barium salt **7**. Treatment of the barium salt **7** with dilute sulfuric acid, and removal of the barium sulfate at pH 8, followed by reacidification produced a white solid which appeared to be the 2-carboxylic acid but again contaminated with a product of decarboxylation. Recrystallization from boiling water completed the decarboxylation to give a new substance of melting point 189°. Elemental analysis fitted the empirical formula $C_3H_4N_2O_2$. It seemed probable that this was 1-hydroxyimidazole 3-oxide **8**. Condensation of formaldehyde and glyoxime under acidic conditions produced a material identical with **8** by mixture melting point, infrared spectra and elemental analysis. The structure of **8** was conclusively proved by its reduction to imidazole employing hydrogen over Raney nickel in methanol. The latter route is a very convenient procedure for the preparation of imidazole. Franchetti *et al.* (8) have prepared and described **8**.

EXPERIMENTAL (9)

1-Hydroxyimidazole-2-carboxaldoxime 3-Oxide (**2**) (1).

In an open beaker set on a magnetically stirred hot plate were placed 600 g. (4.14 moles) of 40% glyoxal (Matheson, Coleman, Bell), 440 g. (4.22 mole) of hydroxylamine hydrochloride (Alfa Inorganics), and 500 ml. of water. The solution was heated at 50-55° for 5 hours. Glyoxime first precipitated but redissolved. The orange solution was cooled to room temperature and the pH brought to 2 by addition of 370 ml. of concentrated ammonium hydroxide. The voluminous precipitate was filtered, and washed with 2 x 100 ml. of water and with 75 ml. of methanol. After air drying the solid was slurried with 400 ml. of ether to remove any glyoxime. The filtered solid was dissolved in 500 ml. of water and 80 ml. of concentrated ammonium hydroxide. The solution was light yellow after treatment with 10 g. of Norit. The product was precipitated by adding 105 ml. of concentrated hydrochloric acid (pH 2-3) with cooling, collected, washed with water and methanol, and dried at 70°, yield 105 g. (35.2%), m.p. 185.0-185.5° dec. Miolati reported the dec. pt. as 177°.

An analytical sample was prepared by solution in DMSO (15 ml. per g.), filtering to clarify and reprecipitation with water (25 ml. per g.). The dec. pt. was unchanged.

Anal. Calcd. for $C_4H_5N_3O_3$: C, 33.57; H, 3.52; N, 29.37. Found: C, 33.40, 33.47; H, 3.46, 3.36; N, 29.15, 29.32.

Compound **2** has been obtained in a polymorphic form of fluffy, felted needles exhibiting the same dec. pt. and nmr spectrum in DMSO, but quite a different infrared absorption as a Nujol mull. 1-Hydroxyimidazole-2-carboxaldehyde 3-Oxide Semicarbazone (**3**).

In 400 ml. of water were dissolved 13.5 g. (0.12 mole) of semicarbazide hydrochloride and 5.8 g. (0.04 mole) of **2** by heating to boiling. A precipitate formed during the heating at pH 2. After 30 minutes the pH was raised to 5 by addition of 10 g. of sodium acetate to facilitate ketone semicarbazone formation. Boiling 1 hour at pH 5 did not increase the amount of solid, so 8.5 ml. concentrated hydrochloric acid (to pH 2) was added and boiling continued for 1-1/2 hours. After cooling the solid was collected. The crude **3** was stirred with 240 ml. of 2% aqueous caustic and filtered from a little (1.0 g.) insoluble material, identified as hydrazodicarbonyl amide by m.p. and infrared absorption spectrum. Acidification of the clear filtrate to pH 3 with concentrated hydrochloric acid produced a fine white precipitate. After boiling 20 minutes to coalesce the solid it was filtered, washed with water and methanol, and dried at 75°, yield, 6.5 g. (88.0%); m.p. darkens without melting above 260°.

Anal. Calcd. for $C_5H_7N_5O_3$: C, 32.43; H, 3.81; N, 37.83. Found: C, 32.23, 32.26; H, 3.83, 3.77; N, 37.55, 37.70.

1-Hydroxyimidazole-2-carboxaldoxime 3-Oxide Acetate (**4**).

Three-tenths of a mole (42.9 g.) of **2** was added to 200 ml. of acetic anhydride containing 10 drops of pyridine. The solution warmed spontaneously and was held at 35-40° for 95 minutes, when 400 ml. of anhydrous ethanol (SDA #32) was added with cooling. White crystals were slowly deposited on standing in the dark for 3 days. These were filtered and washed with methanol. The 65 g. of crude **4** were dissolved in an ice-cold solution of 55 g. of sodium bicarbonate in 550 ml. of water. The neutral solution was treated with Norit, and filtered, and the oxime acetate reprecipitated by acidifying with concentrated hydrochloric acid to pH 2 while cooling below 10°. The granular white solid was filtered, washed with water and methanol, and dried by aspirating on the funnel (in a mass **4** explodes when heated to 95°), yield, 43.7 g. (78.8%), m.p. sinters 145°, resolidified, remelts 178-182°. For analysis a sample was recrystallized from acetic acid (25 ml. per g.); dried over phosphorus pentoxide.

Anal. Calcd. for $C_6H_7N_3O_4$: C, 38.92; H, 3.81; N, 22.70. Found: C, 38.90; H, 3.87; N, 22.62.

Action of Aqueous Sodium Carbonate on **4**.

One g. of the oxime acetate **4** dissolved in 5 ml. of saturated aqueous sodium carbonate was heated at 60-75° for 1 hour. Concentrated hydrochloric acid was added to pH 2 and the resultant white precipitate collected, washed with water and methanol, and dried at 80° to constant weight, 0.60 g. The infrared spectrum indicated this was the pure needle form of the oxime **2**, thus **2** is of the syn configuration.

2-Cyano-1-hydroxyimidazole 3-Oxide (**5**).

In an open beaker were placed 80 ml. of thionyl chloride and 335 ml. of *p*-dioxane. Finely powdered **2** (103 g., 0.719 mole) was added in portions with good stirring during 25 minutes. During this addition the suspension was cooled to hold between 35-45°. The suspension was then heated to 55-60° until sulfur dioxide evolution ceased (45 minutes). The thin, yellow suspension was cooled in an ice bath and concentrated ammonium hydroxide added dropwise with vigorous stirring, while holding below 25°, until the pH rose to 2 (125 ml. of ammonium hydroxide). The voluminous white precipitate was filtered and washed with *p*-dioxane (2 x 50

ml.). The crude product was slurried with 200 ml. of water to remove ammonium chloride, filtered, and boiled with 125 ml. of methanol. After filtering hot the solid was dried at 80°, yield, 49.6 g. (55.2%), m.p. 191° dec.

An analytical sample was prepared by repeating the water and hot methanol extractions; dec. pt. unchanged. The infrared spectrum of a Nujol mull showed a strong nitrile band at 2240 cm^{-1} .

Anal. Calcd. for $\text{C}_4\text{H}_3\text{N}_3\text{O}_2$: C, 38.40; H, 2.42; N, 33.60. Found: C, 38.56; H, 2.54; N, 33.41.

2-Carboxamido-1-hydroxyimidazole 3-Oxide (6).

The nitrile **5** (12.5 g., 0.10 mole) was added to a solution of 5.5 g. of sodium hydroxide in 40 ml. of water, cooling intermittently to keep below 30°. The nitrile dissolved gradually and a fine precipitate formed. After 17 hours at room temperature the suspension was warmed to 40-45° for 2 hours. The white solid was collected and washed with water. The crude **6**, after drying, was boiled with 100 ml. of methanol, filtered hot, washed with water and methanol, and dried at 80°, yield, 12.2 g. (85.4%), m.p. sublimes > 200°, dec. 243-244°. For an analytical sample the water and hot methanol extractions were repeated. M.p. unchanged.

Anal. Calcd. for $\text{C}_4\text{H}_5\text{N}_3\text{O}_3$: C, 33.57; H, 3.52; N, 29.37. Found: C, 33.43; H, 3.50; N, 29.32.

2-Carboxamidoimidazole (9).

The amide **6** (14.3 g., 0.1 mole) in 300 ml. of methanol was hydrogenated with Raney nickel at 3 atmospheres and room temperature in a Parr shaker. In 2.5 hours, 92% of the theoretical 2 moles of hydrogen were absorbed. The product was separated from the catalyst by hot filtration followed by repeated extraction of the catalyst with 300 ml. of boiling 50% aqueous ethanol. The combined crystals were dried, yield, 9.2 g. (83%), m.p. sublimes above 180°, does not melt to 295°. For analysis a sample was dissolved in 10% aqueous hydrochloric acid, charcoaled and precipitated with ammonium hydroxide. The needles were collected, washed with water and methanol, and dried over phosphorus pentoxide.

Anal. Calcd. for $\text{C}_4\text{H}_5\text{N}_3\text{O}$: C, 43.24; H, 4.54; N, 37.83. Found: C, 43.07; H, 4.53; N, 37.90.

The picrate was prepared by boiling **9** with excess picric acid in 50% aqueous ethanol, filtering hot, cooling and collecting the yellow needles. M.p., sublimes above 180°, melts 272-273°.

Anal. Calcd. for $\text{C}_{10}\text{H}_8\text{N}_6\text{O}_8$: C, 35.30; H, 2.37; N, 24.70. Found: C, 35.13; H, 2.28; N, 24.53.

Neutral Barium Salt of 2-Carboxy-1-hydroxyimidazole 3-Oxide (7).

A. From 2-Carboxamido-1-hydroxyimidazole 3-Oxide.

To a suspension of barium hydroxide octahydrate (12.6 g., 0.04 mole) in 100 ml. of water was added 4.3 g. (0.03 mole) of **6**. The suspension was boiled until ammonia evolution ceased (4 hours). The suspension was cooled and brought to pH 3 by adding concentrated hydrochloric acid (3.0 ml.). The white solid was filtered and washed with water. The crude **7** was boiled with 100 ml. of water containing 0.5 ml. of acetic acid and filtered hot. After washing with water and methanol it was dried at 80°, yield, 6.4 g. (69.5%) of sesquihydrate of **7**.

An analytical sample was prepared by dissolving 0.8 g. of **7** and 0.6 g. of barium chloride in 10 ml. of water containing 0.5 ml. of concentrated hydrochloric acid. To the clear solution was added 2 ml. of acetic acid and concentrated ammonium hydroxide to pH 5. The white precipitate was washed with methanol and water and dried at 80°. The infrared spectrum showed a broad band at 3400-3150 cm^{-1} indicating water of hydration.

Anal. Calcd. for $\text{C}_4\text{H}_2\text{BaN}_2\text{O}_4 \cdot 1\frac{1}{2}\text{H}_2\text{O}$: C, 15.65; H, 1.64; N, 9.15. Found: C, 15.90; H, 1.50; N, 9.11.

B. From 2-Cyano-1-hydroxyimidazole 3-Oxide.

To a warm solution of 40 g. of barium hydroxide octahydrate in 250 ml. of water was added 12.5 g. (0.10 mole) of **5**. The nitrile dissolved and a white precipitate formed immediately thereafter. The suspension was stirred and heated at 50-60° until a sample showed by infrared spectrum the absence of amide absorption at 1650 and 1110 cm^{-1} (10 hours). The suspension was cooled, all solid dissolved by adding 23 ml. of concentrated hydrochloric acid and immediately reprecipitated at pH 5 using acetic acid-ammonium hydroxide buffer. The white solid was filtered, washed with water and methanol, and dried at 80°, yield, 19.7 g. (64.1%).

1-Hydroxyimidazole 3-Oxide (8).

A. From Barium 1-Hydroxyimidazole-2-carboxylate 3-Oxide.

The barium salt **7** (6.13 g., 0.02 mole) was stirred with 10 ml. of 20% sulfuric acid for 7 minutes. Carbon dioxide was evolved. Concentrated ammonium hydroxide (3.3 ml.) was added to pH 8. The barium sulfate was filtered using hardened filter paper and washed with two 2.5-ml. portions of water. The yellow filtrate and washes were acidified to pH 3 with concentrated hydrochloric acid. White crystals formed in a few minutes and the suspension evolved carbon dioxide. It was filtered rapidly, washed with a little water, and air-dried on filter paper, 1.3 g. The crude material was probably the 2-carboxylic acid in great part. It was boiled with 6 ml. of deionized water until carbon dioxide evolution ceased (20 minutes), filtered hot and crystallized by cooling in the refrigerator for 3 hours. The material was collected, washed with methanol, and dried *in vacuo* at 60°, yield, 0.5 g. (25%), m.p. 189-190°.

Anal. Calcd. for $\text{C}_3\text{H}_4\text{N}_2\text{O}_2$: C, 36.00; H, 4.03; N, 27.99. Found: C, 35.95; H, 4.01; N, 27.64.

B. From Glyoxime and Formaldehyde.

A solution of 88.0 g. (1.0 mole) of glyoxime, 105 g. (1.05 mole) of 30% formalin, 45 ml. of concentrated hydrochloric acid, and 300 ml. of methanol was heated at 45-55° for 48 hours. The clear yellow solution was cooled and brought to pH 4 with 50% aqueous caustic. A white solid formed rapidly and was collected after cooling 1 hour in an ice bath, and washed with water and methanol. The dried crude **8** was crystallized from boiling water (5 ml. per g.) to yield 44.2 g. (44.2%) of **8**, m.p. 189-191°. Franchetti *et al.* (**8**) report the m.p. 178-180°.

Anal. Calcd. for $\text{C}_3\text{H}_4\text{N}_2\text{O}_2$: C, 36.00; H, 4.03; N, 27.99. Found: C, 36.07; H, 4.07; N, 27.97.

Heating an equimolar mixture of 40% aqueous glyoxal, 30% formalin and hydroxylammonium sulfate in methanol with 70% methanesulfonic acid as catalyst for 6 hours at 60° gives **8** in yields of 65-70%.

Mixture melting point and infrared spectra showed the products from Methods A and B to be identical.

Catalytic Reduction of 1-Hydroxyimidazole 3-Oxide to Imidazole.

To a suspension of about 10 g. of Raney nickel (W. R. Grace No. 28 aq. paste) in 100 ml. of methanol was added 10.0 g. (0.10 mole) of **8**. This was hydrogenated in a Parr shaker at 45 psi and room temperature. In 1 hour 95% of the theoretical hydrogen was absorbed and hydrogenation ceased. After filtering the catalyst the methanol was removed in a Roto-vap under vacuum. The residue was refluxed with 35 ml. of benzene under a Dean-

Stark water trap until anhydrous. The clear benzene solution was cooled at 10° until crystallization was complete. The white product was collected and air dried on filter paper to constant weight, yield, 6.4 g. (94%), m.p. 88-89° with sublimation. A mixture melting point with an authentic sample of imidazole was not depressed and the infrared spectra were identical.

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- (9) I am indebted to Mrs. P. Curtis and Dr. J. Michels for obtaining and interpreting the nmr curve. A Varian A60 instrument was employed. Melting points were observed on a Fisher-Johns hot stage calibrated to U.S.P. Melting Point Standards and are corrected. Infrared spectra were determined as Nujol mulls on NaCl plates in a Perkin-Elmer Infracord 137. I am indebted to Mr. G. Gustin and Mr. M. Tefft for the elemental analyses.