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The Synthesis of 3-Hydroxy-4-Imidazolidiones

Victor L. Rizzo

THE SYNTHESIS OF 3-HYDROXY-4-IMIDAZOLIDINONES

by

Victor L. Rizzo

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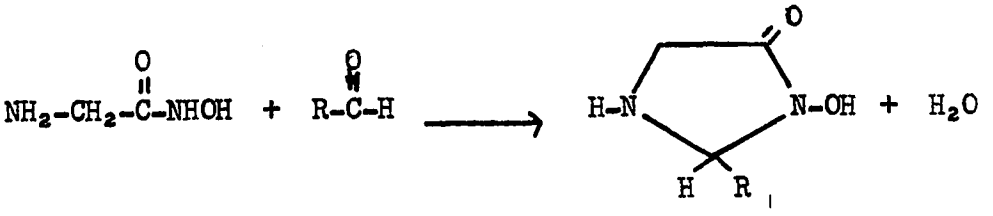
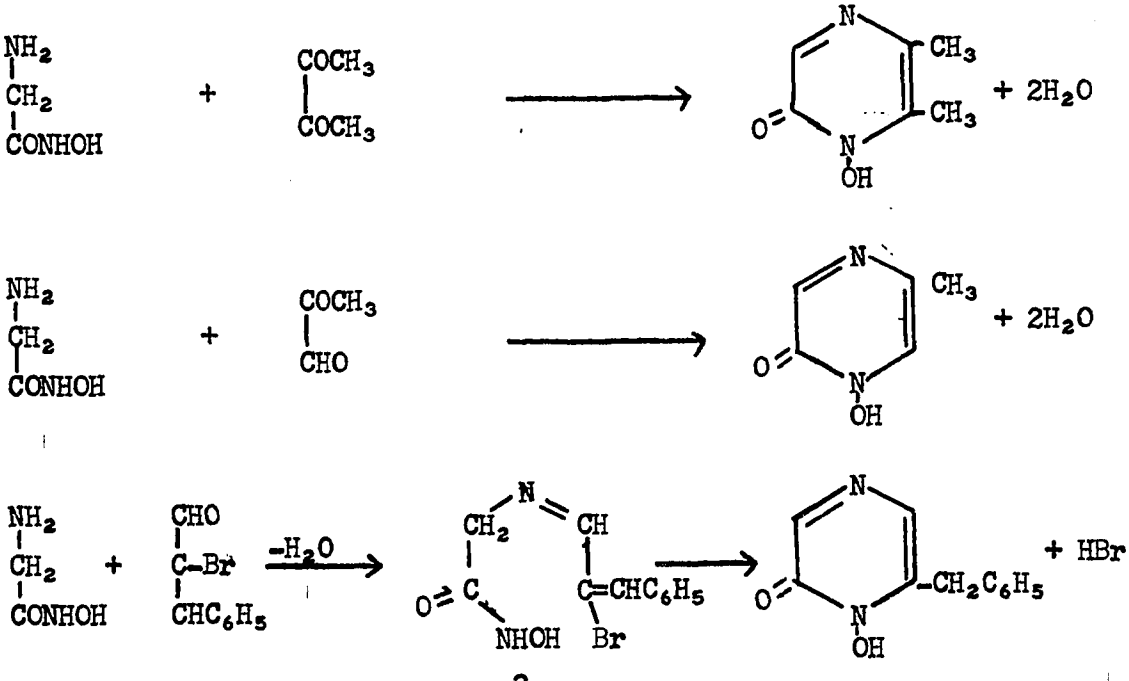
INTRODUCTION

The purpose of this investigation was to determine if an α-amino-hydroxamic acid would react in the presence of an aldehyde to give a cyclic hydroxamic acid having a 3-hydroxy-4-imidazolidinone structure.

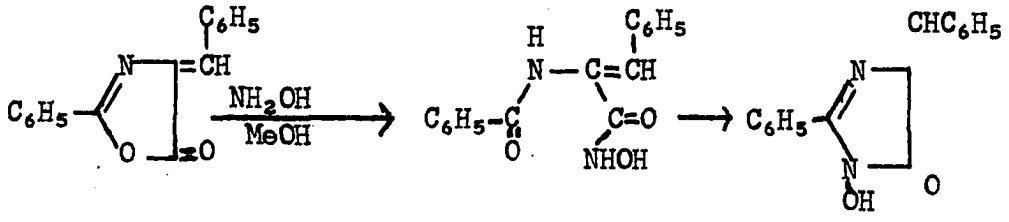


Prior to the establishment of the structure of aspergillic acid as a pyrazine cyclic hydroxamic acid by Dutcher and Wintersteiner[1] very little work had been done in the area of cyclic hydroxamic acids.

Many of the cyclic hydroxamic acids that are known have been prepared from aliphatic α-amino-hydroxamic acids.[2,3]



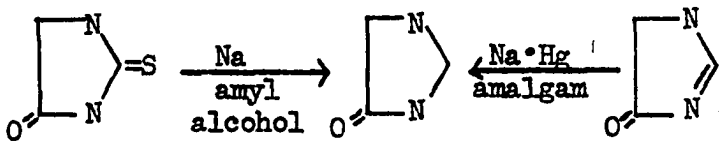
Shaw and McDowell[4] synthesized a five membered cyclic hydroxamic acid which they prepared from 2-phenyl-4-benzylidine-5-oxazalone in the following manner.



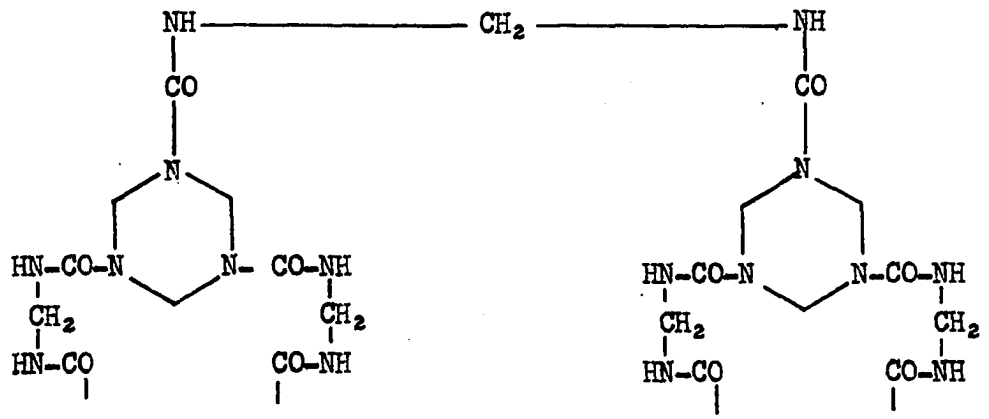
Aspergillic acid and its analogs as well as numerous acyclic hydroxamic acids have been found to be biologically active.[5,6] Aspergillic acid and its analogs are very good antibacterial agents. It is believed that 3-hydroxy-4-imidazolidinones will also exhibit biological activity.

HISTORICAL

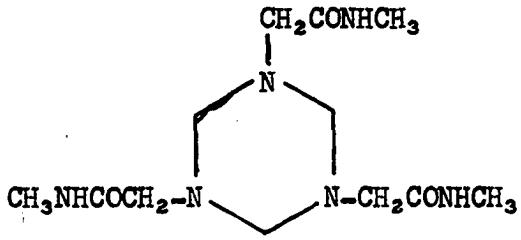
The number of reported 4-imidazolidinones is relatively small as is the number of methods of preparing them. Thiohydantoins have been reduced in the presence of sodium and amyl alcohol to give 4-imidazolidinone.[7] 4-Imidazolidinones have also been prepared by the reduction of 4(5)-imidazolones with sodium amalgam.[8]



In 1946 Marvel[9] studied the reaction of amino acid amides with formaldehyde. He found that glycinamide reacted with formaldehyde to give a polymeric gel. He proposed that the amine portion would react to form a methylene-imine derivative which would trimerize to a cyclic trimethylenetriamine compound and that the amido group would react with formaldehyde to form methylene bis amide links between the rings.



When an amino acid amide is substituted on the amide nitrogen Marvel found that a cyclic trimer resulted. Glycine methylamide gave the following product as indicated by analysis and molecular weight.



In addition to glycinamide and glycine methylamide, sarcosinamide was also reacted with formaldehyde. The product which was obtained from this reaction was a viscous oil believed to be a low molecular weight linear polymer.

EXPERIMENTAL

General

All melting points are given in degrees centigrade, are corrected and are determined after drying in a drying pistol under reduced pressure at a temperature of 78° for several hours. Infrared spectra were obtained using a Beckman I.R.-8 spectrophotometer. Nuclear magnetic resonance spectra (nmr) were obtained with a Varian A-60 spectrophotometer using deuterated dimethylsulfoxide as a solvent and tetramethylsilane as an internal reference. Mass spectral data were determined on an Atlas CH4 mass spectrometer and interpreted by Dr. Marvin Grostic of The Upjohn Company. All analyses were carried out by Galbraith Microanalytical Laboratories.

Preparation of α-Amino-Hydroxamic Acids[10]

GLYCINE HYDROXAMIC ACID (I). --Ethyl glycinate hydrochloride, 46.3 g (0.33 mole), was dissolved in 125 ml of absolute methanol with slight heating. A solution of potassium hydroxide, 18.6 g (0.33 mole), in 75 ml of absolute methanol was prepared. The two solutions were cooled below 40°, mixed together, cooled in the refrigerator for several hours, and filtered.

Hydroxylamine hydrochloride, 33.4 g (0.48 mole), was dissolved in 150 ml of absolute methanol with heating. A solution of potassium hydroxide, 28.6 g (0.48 mole), in 75 ml of absolute methanol was prepared. The two solutions were cooled below 40°, mixed together,

cooled for several hours in a refrigerator, and filtered.

The solutions of the free ester and free hydroxylamine were mixed together, allowed to remain in the refrigerator overnight, and concentrated to about 200 ml of solution. The reaction mixture was further cooled in the refrigerator overnight and 20.5 g of crude product removed by filtration. The crude product was purified by adding enough distilled water to cover the product, heating on a steam bath, cooling, removing the product by filtration, and drying in a vacuum desiccator overnight. Water soluble impurities should have been removed without excessive loss of hydroxamic acid by this procedure. The yield was 14.0 g (46.7%) of a white powdery compound, mp 140-141° (dec.); lit.[11] mp 140° (dec.).

ETHYL SARCOSINATE HYDROCHLORIDE (II). --Sarcosine, 50.0 g (0.56 mole), was suspended in 500 ml of absolute ethanol in an ice bath. Anhydrous hydrogen chloride was bubbled into the stirred suspension until the solution was saturated. The reaction flask was stoppered loosely and the mixture allowed to react overnight with stirring. The reactants had gone into solution and the reaction was considered completed. The solution was concentrated by rotary evaporation under reduced pressure to approximately 250 ml and placed in a refrigerator for several hours. The product was collected on a sintered glass filter, recrystallized from absolute ethanol, and dried. The yield was 34.0 g (39.6%) of a white crystalline product, mp 119-121°; lit.[12] mp 121-122°.

SARCOSINE HYDROXAMIC ACID (III). --Ethyl sarcosinate hydrochloride, 3.17 g (0.20 mole), was dissolved in 70 ml of absolute methanol. A solution of potassium hydroxide, 11.2 g (0.20 mole), in 70 ml of absolute methanol was prepared. The two solutions were mixed, cooled for several hours in the refrigerator, and the solution filtered.

Hydroxylamine hydrochloride, 21.0 g (0.30 mole), was dissolved in 140 ml of absolute methanol with heating. A solution of potassium hydroxide, 16.8 g (0.30 mole), in 70 ml of absolute methanol was prepared. The two solutions were cooled below 40°, mixed, cooled for several hours in a refrigerator, and filtered.

The solutions of free amine and free ester were mixed and the resulting solution placed in a refrigerator overnight. The reaction mixture was concentrated to about 200 ml and placed in the refrigerator overnight. A white product, 16.0 g, was removed by filtration and purified by the same procedure as glycine hydroxamic acid. The yield was 14.0 g (66.6%), mp 139-141° (dec.).

An analytical sample was prepared by recrystallization of 7.0 g of the purified product in 20 ml of distilled water. The yield was 2.0 g, mp 140-141° (dec.); $\nu_{max.}$ (Nujol) 2685, 2400, 1630, 1305, 1155, 1060, 983, 935, 894, 867, and 785 cm^{-1}.

Anal. Calcd. for $C_3H_8N_2O_2$: C, 34.61; H, 7.75; N, 26.91. Found: C, 34.85; H, 7.77; N, 26.84.

O-BENZYLSARCOSINE HYDROXAMIC ACID (IV). --Ethyl sarcosinate hydrochloride, 12.0 g (0.079 mole), was dissolved in 50 ml of absolute methanol. To this solution was added a solution of 4.4 g (0.079 mole), of potassium hydroxide in 50 ml of absolute methanol. The

resulting solution was cooled in the refrigerator for several hours and the salt removed by vacuum filtration. Benzyloxyamine[13-15] was prepared from its hydrochloride, 20.0 g (0.0125 mole), by neutralizing the hydrochloride with excess base, extracting with ethyl ether, and drying over anhydrous magnesium sulfate. The ether solution of the free amine was added to 100 ml of absolute methanol and most of the ether removed by evaporation under reduced pressure. The solution of the free amine was added to the solution of the free ester and allowed to react overnight in a refrigerator. The solution was concentrated to about 75 ml and placed in the freezer overnight. A yield of 5.0 g (33.0%) of the crude product having a melting point of 97-100° was obtained. A white crystalline product, mp 104-106°, was obtained by recrystallization from an ethanol water solution; $V_{max.}$ (Nujol) 3080, 3030, 2580, 2325, 1660, 1602, 1580, 1518, 1450, 1310, 1262, 1242, 1198, 1154, 1081, 1060, 1050, 1027, 1008, 985, 844, 766, 737, 693, and 625 cm^{-1}.

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.62; H, 7.36; N, 14.33.

Preparation of 3-Hydroxy-4-Imidazolidinones

2-(4-CHLOROPHENYL)-3-HYDROXY-4-IMIDAZOLIDINONE (V). --Glycine hydroxamic acid, 1.8 g (0.02 mole), and p-chlorobenzaldehyde, 2.81 g (0.02 mole), were added to 60 ml of absolute ethanol and the reaction refluxed with stirring for four hours during which time the reactants had gone into solution. The reaction mixture was filtered to remove

any insoluble impurities, the volume of solvent reduced, and the solution cooled in the refrigerator. White fluffy crystals of crude product, 3.0 g (70.9%); mp 148-153° (dec.), were obtained. The product was recrystallized from absolute ethanol and gave an analytical sample which melted at 155-156° (dec.); $V_{max.}$ (Nujol) 3080, 3030, 2580, 2325, 1660, 1602, 1580, 1518, 1450, 1310, 1262, 1242, 1198, 1154, 1081, 1060, 1050, 1027, 1008, 985, 844, 766, 737, 693, and 625 cm^{-1}.

Anal. Calcd. for $C_9H_9N_2O_2Cl$: C, 50.84; H, 4.27; N, 13.17. Found: C, 50.83; H, 4.33; N, 12.97.

2-(2-CHLOROPHENYL)-3-HYDROXY-4-IMIDAZOLIDINONE (VI). -- Glycine hydroxamic acid, 0.90 g (0.01 mole), and o-chlorobenzaldehyde, 1.40 g (0.01 mole), were added to 50 ml of absolute ethanol and the reaction mixture refluxed for two hours with stirring during which time the reactants had gone into solution. The reaction mixture was filtered, the volume of solvent reduced by evaporation under reduced pressure, and the solution cooled in a refrigerator. A crude white crystalline solid, 1.5 g (70.5%); mp 154-156° (dec.), was separated by filtration. The product was recrystallized from absolute ethanol, mp 157-158° (dec.); $V_{max.}$ (Nujol) 3235, 1700, 1300, 1270, 1070, 1048, 1030, 910, and 753 cm^{-1}.

Anal. Calcd. for $C_9H_9N_2O_2Cl$: C, 50.84; H, 4.27; N, 13.17. Found: C, 50.67; H, 4.44; N, 13.32.

2-(2,4-DICHLOROPHENYL)-3-HYDROXY-4-IMIDAZOLIDINONE (VII). -- Glycine hydroxamic acid, 0.90 g (0.01 mole), and 2,4-dichlorobenzaldehyde, 1.75 g (0.01 mole), were added to 50 ml of absolute ethanol.

The reaction mixture was refluxed for a period of two hours with stirring, filtered, the volume of solvent reduced, and the solution cooled in a refrigerator. A crude white product was collected by vacuum filtration, 1.9 g (77%); mp 150-151° (dec.). The product was recrystallized from absolute ethanol, mp 151-152° (dec.); $V_{max.}$ (Nujol) 3250, 1695, 1590, 1550, 1302, 1230, 1202, 1145, 1080, 1056, 1040, 957, 905, 861, 830, and 803 cm^{-1}.

Anal. Calcd. for $C_9H_8N_2O_2Cl_2$: C, 43.75; H, 3.26; N, 11.34. Found: C, 43.82; H, 3.23; N, 11.20.

2-PHENYL-3-HYDROXY-4-IMIDAZOLIDINONE (VIII). --Glycine hydroxamic acid, 1.35 g (0.015 mole), and benzaldehyde, 1.56 g (0.015 mole), were added to 50 ml of absolute ethanol and the mixture refluxed with stirring for two hours. The solution was filtered, concentrated, cooled, and the resulting white cystals, 2.3 g (81%); mp 147-150° (dec.), were removed by filtration. The crude product was recrystallized from absolute ethanol to give an analytical sample, mp 149-150° (dec.); $V_{max.}$ (Nujol) 3250, 1700, 1300, 1278, 1260, 1085, 1064, 945, 903, 871, 750, and 696 cm^{-1}.

Anal. Calcd. for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.50; H, 5.78; N, 15.51.

2-(4-METHOXYPHENYL)-3-HYDROXY-4-IMIDAZOLIDINONE (IX). -- Glycine hydroxamic acid, 0.90 g (0.01 mole), and p-methoxybenzaldehyde, 1.36 g (0.01 mole), were added to 50 ml of absolute ethanol and the mixture refluxed for a period of two and a half hours. A crude white product was removed by filtration, 1.9 g (91.5%); mp 172-174° (dec.).

The product was sparingly soluble in absolute ethanol, but by refluxing with a large amount of solvent the product went into solution and recrystallized out very readily upon cooling, mp 171-172° (dec.); $\nu_{max.}$ (Nujol) 3350, 1730, 1700, 1605, 1510, 1415, 1300, 1270, 1240, 1185, 1169, 1110, 1080, 1055, 1020, 940, 921, 860, 825, and 674 cm^{-1}.

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.56; H, 5.93; N, 13.29.

2-(4-NITROPHENYL)-3-HYDROXY-4-IMIDAZOLIDINONE (X) -- Glycine hydroxamic acid , 1.80 g (0.02 mole), and p-nitrobenzaldehyde, 3.02 g (0.02 mole), were added to 80 ml of absolute ethanol and the reaction mixture refluxed for a period of two hours. The solution was filtered, concentrated, cooled, and a light yellow crude product, 3.3 g (74%); mp 155-156° (dec.), collected by filtration. The product was recrystallized from absolute ethanol, mp 156-157° (dec.); $\nu_{max.}$ (Nujol) 3300, 3250, 1715, 1680, 1520, 1345, 1287, 1105, 1052, 1010, 940, 850, 790, 748, and 700 cm^{-1}.

Anal. Calcd. for $C_9H_9N_3O_4$: C, 48.43; H, 4.06; N, 18.83. Found: C, 48.27; H, 4.05; N, 18.64.

2-(2-NITROPHENYL)-3-HYDROXY-4-IMIDAZOLIDINONE (XI). -- Glycine hydroxamic acid, 0.90 g (0.01 mole), and o-nitrobenzaldehyde, 1.51 g (0.01 mole), were added to 60 ml of absolute ethanol and the reaction mixture refluxed for a period of two hours. The reaction mixture was filtered, concentrated, and cooled. A crude white crystalline product was obtained, 2.0 g (90%); mp 160-161° (dec.). The crude product was recrystallized from absolute ethanol to give an analytical sample, mp 160-161° (dec.); $\nu_{max.}$ (Nujol) 3190, 1695,

1600, 1360, 1350, 1340, 1300, 1070, 912, 864, 840, 787, 745, 710, and 682 cm^{-1}.

Anal. Calcd. for $C_9H_9N_3O_4$: C, 48.43; H, 4.06; N, 18.83. Found: C, 48.42; H, 4.10; N, 18.84.

2-METHYL-3-HYDROXY-4-IMIDAZOLIDINONE (XII). --Glycine hydroxamic acid, 1.80 g (0.02 mole), and acetaldehyde, 0.88 g (0.02 mole), were added to 60 ml of absolute ethanol. The reaction mixture was refluxed for two hours, filtered, concentrated, and cooled. A crude white crystalline product, 1.8 g (78%); mp 146-148° (dec.), was obtained. The crude product was recrystallized from absolute ethanol, mp 148-149° (dec.); $V_{max.}$ (Nujol) 3220, 1680, 1305, 1210, 1130, 1083, 1046, 1020, 965, 855, 768, 669, and 650 cm^{-1}.

Anal. Calcd. for $C_4H_8N_2O_2$: C, 41.37; H, 6.94; N, 24.13. Found: C, 41.59; H, 7.14; N, 23.90.

2-(4-CHLOROPHENYL)-3-HYDROXYL-5-BENZYL-4-IMIDAZOLIDINONE (XIII).--Phenylalanine hydroxamic acid, 1.0 g (0.0056 mole), and p-chlorobenzaldehyde, 0.78 g (0.0056 mole), were added to 60 ml of absolute ethanol. The reaction mixture was refluxed for two and a half hours, filtered, concentrated, and cooled. A crude white crystalline product was obtained, 1.25 g (74.5%); mp 154-156° (dec.). The product was recrystallized from absolute ethanol for analysis, mp 158-159° (dec.); $V_{max.}$ (Nujol) 3300, 1700, 1530, 1475, 1405, 1300, 1287, 1250, 1170, 1095, 1080, 1060, 1035, 1009, 961, 940, 902, 873, 828, 818, 748, and 705 cm^{-1}.

Anal. Calcd. for $C_{16}H_{15}N_2O_2Cl$: C, 63.47; H, 4.99; N, 9.25. Found: C, 63.31; H, 4.95; N, 9.09.

1-METHYL-2-(4-CHLOROPHENYL)-3-HYDROXY-4-IMIDAZOLIDINONE (XIV). -- Sarcosine hydroxamic acid, 1.05 g (0.01 mole), and p-chlorobenzaldehyde, 1.40 g (0.01 mole), were refluxed with 60 ml of absolute ethanol for one and a half hours. The reaction mixture was filtered, concentrated, and cooled. The crude white product which crystallized out of solution, 1.7 g (75%); mp 142-145° (dec.), was collected by filtration. This was recrystallized from absolute ethanol, mp 143-144° (dec.); $V_{max.}$ (Nujol) 1690, 1295, 1121, 1073, 1020, 847, and 797 cm^{-1}.

Anal. Calcd. for $C_{10}H_{11}N_2O_2Cl$: C, 52.99; H, 4.89; N, 12.36. Found: C, 53.14; H, 4.82; N, 12.23.

1-METHYL-3-HYDROXY-4-IMIDAZOLIDINONE (XV). --Sarcosine hydroxamic acid, 1.05 g (0.01 mole), and paraformaldehyde, 0.30 g (0.01 mole), were refluxed in 60 ml of absolute ethanol with stirring for twelve hours. The solution was filtered, concentrated, and cooled. A crude white product , 0.9 g (77%); mp 115-116° (dec.), was collected by filtration. The product was recrystallized from absolute ethanol for analysis, mp 115-116° (dec.); $V_{max.}$ (Nujol) 1690, 1295, 1121, 1073, 1020, 847, and 797 cm^{-1}.

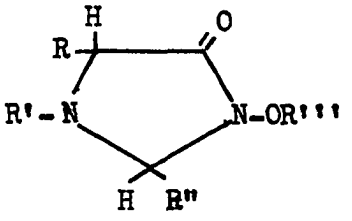
Anal. Calcd. for $C_4H_8N_2O_2$: C, 41.37; H, 6.94; N, 24.13. Found: C, 41.19; H, 6.96; N, 24.27.

1-METHYL-2-(4-CHLOROPHENYL)-3-BENZYLOXY-4-IMIDAZOLIDINONE (XVI). -- O-Benzylsarcosine hydroxamic acid, 1.99 g (0.01 mole), and p-chlorobenzaldehyde, 1.40 g (0.01 mole), were refluxed with 60 ml of absolute ethanol overnight with stirring. The solution was filtered, concen-

trated, and cooled. A crude white product, 2.5 g (79%); mp 96-98°, was collected by filtration. The crude product was recrystallized from absolute ethanol, mp 99-100°; $\nu_{max.}$ (Nujol) 1725, 1650, 1600, 1320, 1290, 1278, 1258, 1150, 1080, 1063, 1023, 1012, 968, 908, 840, 830, 800, 750, 718, and 696 cm^{-1}.

Anal. Calcd. for $C_{17}H_{17}N_2O_2Cl$: C, 64.46; H, 5.41; N, 8.84. Found: C, 64.62; H, 5.63; N, 9.01.

TABLE I.
INFRARED SPECTRAL DATA[a,b]
OF IMIDAZOLIDINONES[16]



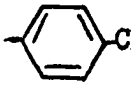
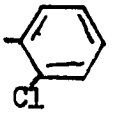
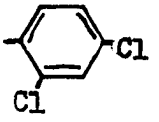
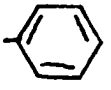
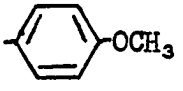
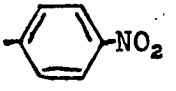
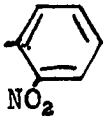
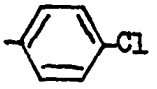
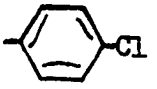
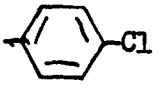
Compound Number	R	R'	R''	R'''	H -N-	O -C-
V	H	H		H	3200 (m)	1675 (s)
VI	H	H		H	3235 (m)	1700 (s)
VII	H	H		H	3250 (m)	1680 (s)
VIII	H	H		H	3250 (m)	1700 (s)
IX	H	H		H	3350 (m)	1700 (s)
X	H	H		H	3300 (m)	1715 (s)
XI	H	H		H	3190 (m)	1695 (s)
XII	H	H	CH_3	H	3220 (s)	1680 (s)

TABLE I.
continued

Compound Number	R	R'	R''	R'''	H -N-	O -C-
XIII	Benzyl	H		H	3300 (m)	1700 (s)
XIV	H	CH_3		H	--------	1690 (s)
XV	H	CH_3	H	H	--------	1690 (s)
XVI	H	CH_3		Benzyl	--------	1725 (s)

(a) Infrared spectra were determined as Nujol mulls and absorption maxima expressed in cm^{-1}.

(b) s = strong absorption, m = medium absorption.

TABLE II.
NUCLEAR MAGNETIC RESONANCE SPECTRAL DATA[a]

Compound Number	Relative Peak Area Ratio[b]	Assignment	τ Value[c]	Peak Area Ratio After D_2O Exchange[b]
V	2	CH_2	6.62	2
	1	NH	6.70	0
	1	CH	4.76	1
	4	C_6H_4	2.60	4
	?	OH	----	-
VI	2	CH_2	6.62	2
	1	NH	5.2-6.6	0
	1	CH	4.30	1
	4	C_6H_4	2.64	4
	1	OH	0.4-1.0	0
VII	2	CH_2	6.68[c]	2
	1	NH	6.6-7.0	0
	1	CH	4.38	1
	3	C_6H_3	2.54	3
	1	OH	0.5	0
VIII	2	CH_2	6.66	2
	1	NH	5.9-6.7	0
	1	CH	4.80	1
	5	C_6H_5	2.66	5
	1	OH	0.4-1.0	0
X	2	CH_2	6.58	2
	1	NH	5.4-6.6	0
	1	CH	4.52	1
	4	C_6H_4	2.10[c]	4
	1	OH	0.4	0
XI	2	CH_2	6.62	2
	?	NH	----	-
	1	CH	4.00	1
	4	C_6H_4	2.36[c]	4
	?	OH	----	-

TABLE II.
continued

Compound Number	Relative Peak Area Ratio [b]	Assignment	τ Value [c]	Peak Area Ratio After D_2O Exchange [b]
XII	3	CH_3	8.77[c]	3
	2	CH_2	6.80[c]	2
	1	CH	5.70[c]	D_2O
	1	NH	4.0-5.4[c]	0
	1	OH	4.0-5.4[c]	0
XIII	2	CH_2	7.00[c]	2
	1	NH	6.6-7.2[c]	0
	1	CH	6.26[c]	1
	1	CH	4.80[c]	1
	9	C_6H_5-C_6H_4	2.80	9
	1	OH	0.52	0
XIV	3	CH_3	7.80	3
	2	CH_2	6.68[c]	2
	1	CH	5.30[c]	1
	4	C_6H_4	2.60	4
	1	OH	0.54	0
XV	3	CH_3	7.64	3
	2	CH_2	6.90	2
	2	CH_2	5.90	2
	1	OH	0.4-2.0	0
XVI	3	CH_3	7.80	3
	2	CH_2	6.62[c]	2
	2	CH_2	5.38[c]	2
	1	CH	5.22	1
	5	C_6H_5	2.80[c]	5
	4	C_6H_4	2.58	4

(a) The nmr of these compounds were determined in deuterated dimethylsulfoxide.

(b) The values given for the peak area ratios are rounded to whole numbers.

(c) The values given represent the center of a multiplet.

TABLE III.
MASS SPECTRAL DATA [a]

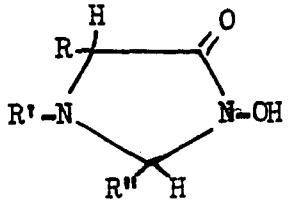
Compound Number	Isotope	$\frac{M}{e}^+$	$\frac{M}{e}^+ -$ OH	$\frac{M}{e}^+ -$ -CO-NOH-
VI	Cl^{35}	212	195	153
	Cl^{37}	214	197	155
XIV	Cl^{35}	226	209	167
	Cl^{37}	228	211	169

(a) The spectral data is given in terms of the mass to charge ratio of the parent species minus one electron, M/e^+, and the parent species minus an indicated fragment.

DISCUSSION

Evaluation of Preparative Procedures

Eleven new 3-hydroxy-4-imidazolidinones and an O-benzyl derivative, variations of structure 1, have been prepared by refluxing an α-amino-hydroxamic acid with various aldehydes in absolute ethanol, Table I. In addition, two unreported hydroxamic acids, sarcosine hydroxamic acid and O-benzylsarcosine hydroxamic acid, have been prepared.



Structure 1

The yields of crude imidazolidinones obtained were between 70% and 91.5%. With additional care in working up the reaction mixtures, higher yields may be realized. It was found after investigating a wide variety of solvents that ethanol was the best solvent for recrystallization. On the basis of thin layer chromotography using Silica Gel-G and absolute methanol as the developing solvent, only one isomer could be detected for each product. Ferric chloride tests with all of the imidazolidinones prepared gave a deep red color except the O-benzyl derivative, XVI.

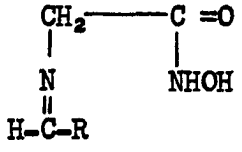
Evaluation of Chemical and Physical Data

The reaction of an aliphatic α-amino-hydroxamic acid with an aldehyde is unreported in the literature as are the compounds

synthesized in this investigation. The proposed products are based on reactions which are indirectly related to the one carried out in this investigation.

The determination of the structure was made on the basis of elemental analysis, nmr spectra, infrared spectra, molecular weight determination by mass spectroscopy, and chemical evidence obtained through the use of various derivatives of glycine hydroxamic acid.

There are numerous ways in which an aldehyde could have possibly reacted with an α-amino-hydroxamic acid. The first possibility which was investigated was that the amine portion of the molecule would react to form a Schiff base. However, the Schiff base, structure 2, was ruled out on the basis of the following evidence. It was found

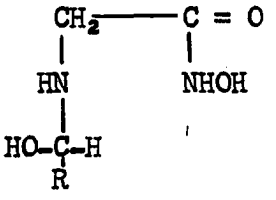


Structure 2

that the Schiff bases prepared from either p-chlorobenzaldehyde or p-nitrobenzaldehyde and aniline gave nmr spectra in which the methine protons were found at τ = 1.76 and 1.64. The methine protons in all the compounds prepared showed resonance between τ = 4.00 and 5.90. On the basis of this evidence and the fact that sarcosine hydroxamic acid reacted with aldehydes to form compounds which could not be Schiff bases, structure 2 is considered improbable. Harmon and Parsons found that these resonance peaks were characteristic of a cyclic rather than linear structure in the pyrimido-pyrimidine

series.[17] This was also reported by McDonagh and Smith.[18]

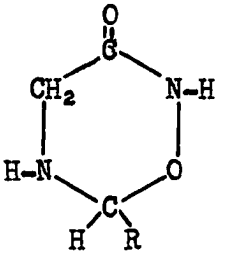
There was also the possibility that water was not lost in the reaction of an aldehyde with the amine portion of the molecule.



Structure 3

Elemental analysis and integration of the nmr spectra of the compounds indicated that structure 3 was not correct.

Another possibility was that oxadiazoles having structure 4 might be formed in this reaction.

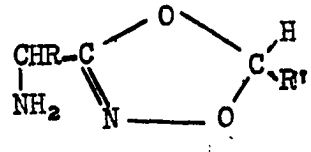


Structure 4

Sarcosine derivatives, XIV and XV, did not show an absorption for N-H bonds in their infrared spectra. Mass spectra of VI and XIV indicated that a fragment of mass seventeen was lost which would correspond to a hydroxyl group. To prevent a reaction involving cyclization through the oxygen atom, a benzyl group was substituted for the hydroxyl proton in sarcosine hydroxamic acid. A product which is believed to be a 4-imidazolidinone was obtained. This evidence

would tend to indicate that structure 4 was not correct.

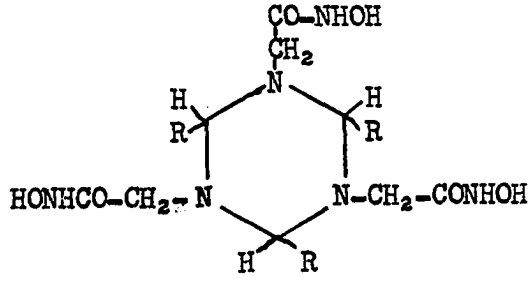
Hydroxamic acids are known to react with aldehydes through the hydroxamic acid portion of the molecule.[19] If α-amino-hydroxamic acids reacted analegously they would form compounds of structure 5.



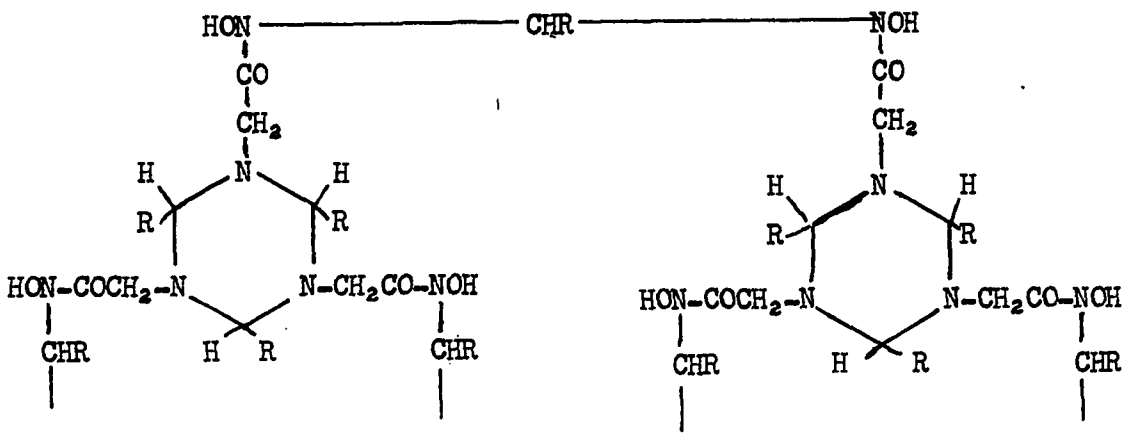
Structure 5

The compounds prepared exhibited a carbonyl stretching band in their infrared spectra. The nmr spectra of the compounds did not correspond to structure 5. Two different exchangeable protons are indicated by the nmr spectra, whereas structure 5 should show two equivalent exchangeable protons in its nmr spectra. In addition the O-benzyl derivative of sarcosine hydroxamic acid would prohibit cyclization through the oxygen atom.

The work of Marvel[9] on the reactions of amino acid amides with formaldehyde indicated that a cyclic trimer or a polymer might be a possible structure. Elemental analysis and molecular weight determination by mass spectroscopy would tend to rule out either of these possibilities.



Structure 6



Structure 7

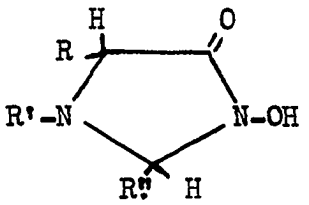
If the compound had structure 6 one would expect the molecular weights of VI and XIV to be 637.5 amu and 679.5 amu respectively. The molecular weights were determined by mass spectra to be 212.5 amu and 226.5 amu respectively. There were no peaks in the higher molecular weight region to indicate the presence of a compound having structure 6.

A cyclic polymer, structure 7, would have a mole ratio of hydroxamic acid to aldehyde of 1:1.5. This would not agree with the 1:1 mole ratio determined by elemental analysis.

From the elemental analysis data and the molecular weight determination several conclusions can be made as to the structure of the compounds. The mole ratio of aldehyde to hydroxamic acid is 1:1, thus eliminating any structure not having this ratio. The molecular weight determination indicates that the compounds are formed by the

reaction of one mole of aldehyde with one mole of hydroxamic acid.

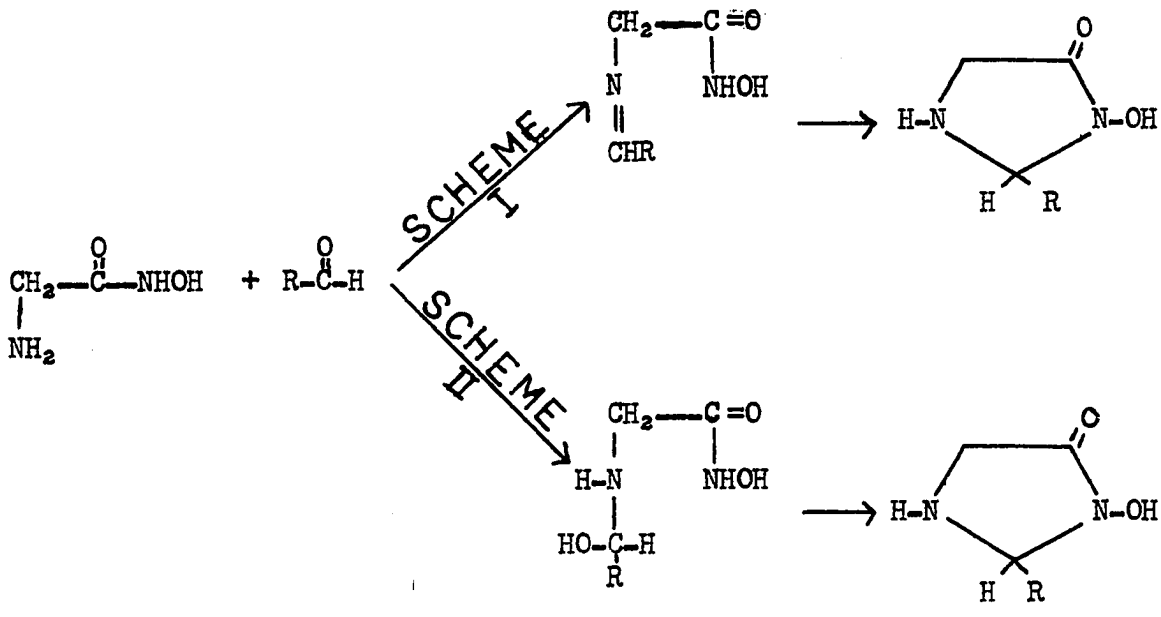
Of all the possible structures examined only that of the 3-hydroxy-4-imidazolidinones is in agreement with the physical and chemical evidence presented.



Structure 1

Possible Reaction Sequence

Originally it was believed that the reaction proceeded through a Schiff base intermediate which underwent ring chain isomerism to form a cyclized product as described in scheme I.[20] However, the fact that sarcosine hydroxamic acid is capable of undergoing this reaction also would tend to rule out the Schiff base intermediate or else suggest that two routes are possible in the formation of the 3-hydroxy-4-imidazolidinone compounds. A second reaction sequence is postulated which would also include sarcosine hydroxamic acid.[21]



SUMMARY

The synthesis of a number of 3-hydroxy-4-imidazolidinones has been accomplished which are representative of a new class of compounds. The method of preparation involved the reaction of an α-amino-hydroxamic acid with an aldehyde in absolute ethanol heated under reflux. Only glycine hydroxamic acid, phenylalanine hydroxamic acid, and sarcosine hydroxamic acid were used. It is believed, however, that the reaction is a general one and is not limited to the α-amino-hydroxamic acids or the aldehydes used in this investigation.

Elemental analyses, nmr spectra, infrared spectra, mass spectra, and chemical evidence obtained through the use of various derivatives of glycine hydroxamic acids are in agreement with the assigned structures.

In addition two unreported α-amino-hydroxamic acids, sarcosine hydroxamic acid and O-benzylsarcosine hydroxamic acid, have been prepared in conjunction with this investigation.

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VITA

Victor L. Rizzo was born in Chicago, Illinois on March 17, 1943. The author received his high school education at Iron Mountain High School, Iron Mountain, Michigan. He received a B.S. degree in chemistry in June, 1965, from Michigan Technological University. The author began his graduate studies at Western Michigan University in August of 1965. He was awarded a teaching assistantship during his first year. During his second year, the author received a research assistantship from the National Institute of Health. He is a member of the American Chemical Society.