THE RING ENLARGEMENT OF CERTAIN IMIDAZOLINE DERIVATIVES

by

ALBERT WILLIAM THEWS

A THESIS

submitted to

OREGON STATE COLLEGE

in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

June 1955
APPROVED:

Redacted for Privacy

Professor of Chemistry

In Charge of Major

Redacted for Privacy

Chairman of Department of Chemistry

Redacted for Privacy

Chairman of School Graduate Committee

Redacted for Privacy

Dean of Graduate School

Date thesis is presented March 24, 1955

Typed by Gladys McGinnis
ACKNOWLEDGMENT

The author wishes to express his gratitude to two people:

First, to Dr. Bert E. Christensen, for his guidance throughout the course of this research.

Second, to my wife Carol, whose sacrifices, support and encouragement, made it possible for me to carry out this investigation.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>EXPERIMENTAL</td>
<td>11</td>
</tr>
<tr>
<td>SUMMARY</td>
<td>16</td>
</tr>
<tr>
<td>BIBLIOGRAPHY</td>
<td>17</td>
</tr>
</tbody>
</table>

# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 1</td>
<td>2</td>
</tr>
<tr>
<td>Figure 2</td>
<td>4</td>
</tr>
<tr>
<td>Figure 3</td>
<td>8</td>
</tr>
<tr>
<td>Figure 4</td>
<td>10</td>
</tr>
</tbody>
</table>
THE RING ENLARGEMENT OF CERTAIN IMIDAZOLINE DERIVATIVES

INTRODUCTION

Pyrimidines are generally synthesized by the condensation of compounds of class (1) such as, $H_2N-C=NH \ (R = -OH, -SH, -SR', -NH_2, -CH_3, \text{ or phenyl})$ with intermediates of class (2) which have a (a) carbonyl beta with respect to another carbonyl (13, p. 321), carbethoxy (2, p. 393) or nitrile (14, p. 764), (b) substituted malonic esters (3, p. 364) or (c) malononitrile (6, p. 1815). Some of these reactions require a condensing agent, either an acid or a base, while others react in absence of a catalyst. Frequently the reactions are carried out in the presence of sodium ethoxide and occasionally the reaction product is a non cyclic intermediate (15, p. 1375) which requires further treatment to effect cyclization.

Hydantoins and imidazolines on the other hand are formed when intermediates of class (1) cyclize with those of class (2) which have a carbonyl alpha with respect to another carbonyl or carbalkoxy substituent as for example, as in diethyl oxalate (8, p. 1423) or biacetyl.

In the case of intermediates of class (2), in which the carbonyl is both alpha and beta to a carbethoxy, (see Figure 1) such as exists in ethyl oxalacetate or diethyl
$\alpha$-oxalylpropionate, there is a possibility for both ring systems being formed on cyclization.

FIG. I

$$\begin{array}{c}
O \quad O \\
RO-C-C-C-C-OR \\
H
\end{array}$$

Early investigators reported pyrimidines as the cyclization product of diethyl oxalacetate. For example, Pinner (12, p.1423) obtained 2-methyl-4-oxo pyrimidine-6-carboxylic acid as the reaction product of ethyl oxalacetate with acetamidine when condensed under basic conditions. Johnson (4, p.304) prepared 2-methylmercapto-4-carboxyl-5-methyl-6-oxopyrimidine from cyclization of diethyl $\alpha$-oxalylpropionate and pseudo thiomethylurea in presence of aqueous potassium hydroxide. In 1931 Backstez (1, p.323) reported the preparation of thioorotic acid upon the basic hydrolysis of the condensation product of diethyl oxalacetate with thiourea.

Muller (10, p.488), in 1897, reported the synthesis of an ester from condensation of urea with diethyl oxalacetate in acetic acid media through which bubbled hydrogen
chloride gas. The saponification of the ester yielded a salt to which he assigned a structure corresponding to uracil-4-carboxylate.

Wheeler (16, pp.358-362) later studied the same reaction and concluded that the condensation product could have been either; (1) a pyrimidone carboxylic or, (2) a substituted hydantoin. However the conversion of the uracil-4-carboxylate to a compound identical to 5,5 dibromo-barbituric acid definitely established the structure of Muller's acid as a pyrimidine derivative.

Mitchell and Nyc (9, pp.674-677) confirmed the original findings of Wheeler in regard to the acid, but were not in agreement with the pyrimidine structure assigned to the ester by Muller (10, p.488).

These investigators concluded on the basis of spectral studies that the initial cyclization product was a hydantoin. The saponification of the ester at 100° in aqueous solution resulted in a rearrangement to a pyrimidine carboxylic acid while milder treatment left the hydantoin as the major product.

The mechanism for the rearrangement was suggested in a later paper by Nyc and Mitchell (11, pp.1382-1384), who concluded that the hydantoin opened to form an unsaturated hydantoinic acid which was followed by ring closure to give a pyrimidine derivative in accordance to the following equations. (See Figure 2)
FIG. 2

\[
\begin{align*}
R-O-C-C-CH_2-CO-O-R \\
\text{H}_2N-C-NH_2
\end{align*}
\]

\[
\begin{align*}
\text{HCl} & \quad \text{HAc} \\
50^\circ C & \quad \text{KOH} \\
100^\circ C & \quad \text{KOH}
\end{align*}
\]

\[
\begin{align*}
\text{H}_2N-C-NH-C=CH-C-O^- \\
\text{C-OH} \\
\end{align*}
\]

\[
\begin{align*}
\text{O}=C & \quad \text{C}-C-O^- \\
\text{N} & \quad \text{C} \\
\end{align*}
\]

\[
\begin{align*}
\text{O}=C & \quad \text{C}-C-OH \\
\text{N} & \quad \text{C} \\
\end{align*}
\]
In order to test their hypothesis, these workers prepared 5-(carbethoxyethylidene)-hydantoin, 5-benzalhydantoin, 5-cinnamalhydantoin and subjected them to the alkaline treatment. On the basis of spectral studies these authors concluded that these hydantoins did not recyclize to yield a pyrimidine. Therefore the 5-carboxymethylidinehydantoin must have rearranged by a mechanism which did not involve the unsaturation of the substituent in the five position.

Condensations using diethyl α-oxalylpropionate were first reported by Johnson (4, pp.299-306) who noted that the reaction product obtained from an alkaline medium using pseudomethylthiourea was either the salt or ester of 5-methyl-2-methylmercapto-6-oxopyrimidine-4-carboxylate depending on amount of alkali employed. This compound was converted to thymine-4-carboxylic acid. Since the condensation was carried out in a basic medium it may be likely that the pyrimidine, in this instance, did not arise from a rearrangement of a hydantoin but by direct cyclization.

In 1949 Mentzer and Billet (7, pp.402-404), using Muller's procedure, studied the condensation of diethyl α-oxalylpropionate with urea, which was reported to yield ethyl thymine-4-carboxylate. The saponification of the ester to the acid gave a product which was identical to the acid prepared by Johnson (4, p.304). These workers however carried out their initial condensations in an acid medium in
contrast to the basic conditions employed by Johnson. Although their acids were identical, the ester which Mentzer and Billet isolated was not the same as the one prepared by the esterification of thymine-4-carboxylic acid. On the basis of spectral studies and by making comparison to the 5-carbethoxymethylenehydantoin reported by Mitchell and Nyc, these workers concluded that their initial condensation product was a hydantoin which under the influence of alkali, opens and recyclizes to a pyrimidine.

The condensation of diethyl α-oxalylpropionate with amidines, guanidines or thiourea has received scant attention. Johnson (5, pp. 291-292) attempted the condensation with guanidine in aqueous media and reports a small yield which he did not characterize. In view of the interest which has since arisen in derivatives of orotic acid, as a result of the discovery of its presence in milk, it appeared worthwhile to investigate these reactions.

Initial experiments involving the condensation of amidines with diethyl α-oxalylpropionate resulted in an oily product which was not characterized. However the condensation in anhydrous methanolic medium with guanidine free base in absence of a condensing agent yielded an insoluble product which was found to be a non cyclic guanide (I) rather than the expected cyclic derivative. The treatment of this guanide with hydrochloric acid
effected cyclization as judged by the solubility characteristics and m.p. behavior of the product II. The ultraviolet spectrum of the compound II was similar to the hydantoin which has been described earlier by Mitchell and Nyc (9, p.676). Furthermore compound II was esterified and hydrogenated at low pressures with Adams catalyst. The relatively mild conditions of hydrogenation indicated olefinic unsaturation which would not have been possible if a six membered ring had been formed in the cyclization. This observation not only confirmed the structure of the imidazoline but also fixed that of the guanide, compound I.

Since pyrimidines had been reported as cyclization products of like condensations carried out in presence of inorganic bases, compound II was heated in the presence of aqueous potassium hydroxide. Acidification of the reaction mixture yielded an acid product, III, which had a considerably higher melting point. The ultra-violet absorption spectrum of III closely resembled that reported for orotic acid (9, p.676) (see Figure 3). On this basis the pyrimidine structure was assigned to compound III.

The condensation of urea with diethyl α-oxalyl-propionate has been effected recently by Mentzer and Billet who employed an acidic medium and used hydrogen chloride as the condensing agent. Their reaction product yielded an ester which was saponified in basic medium and then acidified
FIG. 3

A = 5(4)-(2-amino-4(5)-oxo-$\Delta^2$-imidazolineidene)-2-propanoic acid
B = 2-amino-5-methyl-6-oxo-pyrimidine-4-carboxylic acid
C = ethyl-5(4)-(2-amino-4(5)-oxo-$\Delta^2$-imidazoline)-2-propionate
D = ethyl-5(4)-(2-amino-4(5)-oxo-$\Delta^2$-imidazolineidine)-2-propionate
to yield a product to which they assigned the structure thymine-4-carboxylic acid.

Although these workers also recognized their initial condensation product (the ester) as a hydantoin, no analytical data were given to support this conclusion.

This condensation has been confirmed in this laboratory, and the existence of a hydantoin intermediate has been established on the basis of analytical data and spectral data. (See Figure 4). Although the condensations with guanidine and urea gave similar products which rearranged to pyrimidine derivatives it is interesting to note that no non cyclic intermediate was observed in condensations involving urea. The tendency of guanidine to form non cyclic guanides under like conditions has been observed in other reactions.

Since condensations with thiourea and diethyl α-oxalylpropionate have not been run under the conditions here employed, this work was repeated with thiourea. Using sodium ethoxide as a condensing agent in ethanolic medium gave such a small yield of reaction product that it did not seem feasible to pursue the problem further. Condensations attempted using Muller’s (10, p.488) procedure likewise failed to yield appreciable product.
FIG. 4

A = ethyl (hydantoidene)-2-propionate
B = (hydantoidene)-2-propionic acid
C = 2,6-dioxo-5-methyl-pyrimidine-4-carboxylic acid
EXPERIMENTAL

3-Carbethoxy-2-oxobutanguanide (I): Two solutions, one containing 4.75 g (0.05 moles) in 30 ml. of absolute methanol and the other 1.15 g. (0.05 moles) of sodium in 30 ml. of absolute methanol are mixed, then filtered to remove the sodium chloride. To this solution was added 10 g. (0.05 moles) of diethyl α-oxalylpropionate and the mixture was refluxed for three hours. Upon returning to room temperature 3 ml. of glacial acetic acid was added and the reaction product was set aside in the refrigerator overnight. The crystalline product was removed by filtration, washed with a small amount of anhydrous methanol and then recrystallized from hot water; yield 5.5 g. (51%) of a white crystalline material which had no definite melting point.

Analysis Calc'd. for C_{8}H_{13}N_{2}O_{4}: C, 44.64; H, 6.09.
Found: C, 44.5; H, 6.08.

5(4)-(2-amino-4(5)-oxo-Δ^{2}-imadazolidenedene)-2-proponoic acid (II): Two grams of 3-carbethoxy-2-oxobutan-guanide (I) was dissolved in 60 ml. of 6N. hydrochloric acid and the solution was refluxed for one and one half hours. The solution was then set in a refrigerator overnight, and the product removed by filtration; yield 580 mg. of silky needles melting with decomposition from 200-212°. A second
crop of 50 mg. was obtained upon concentrating the mother liquors and allowing them to stand in a refrigerator overnight. The crude product upon recrystallization from water yielded a white crystalline powder which melted with effervescence at 234.5° -235.5°. Total yield of recrystallized product 380 mg. (24.2%).

Analysis calc'd. for C₆H₇N₃O₃: C, 42.61; H, 4.17. Found: C, 42.6, H, 4.40.

**Ethyl 5(4)-(2-amino-4(5)-oxo-Δ²-imidazolineidine) 2-propionate:** 5(4)-(2-amino-4(5)-oxo-Δ²-imidazolineidine) 2-propionic acid (II) (200 mg.) was dissolved in 9.1 ml. of 50% ethanol-concentrated sulfuric acid solution and the mixture then heated at 100° for approximately 20 minutes. The reaction vessel was then placed in an ice bath and upon cooling the pH was adjusted to approximately 8 with 6N ammonium hydroxide whereupon the ester precipitated. The product was removed by filtration and washed with several portions of cold water. Recrystallization of the crude material from 95% ethanol gave a yield of 120 mg. (51%) of a white crystalline material decomposing at 275°.

An analytical sample was prepared by recrystallization from absolute ethanol. The sample was dried in an Abderhalden over phosphorus pentoxide at 110° for two hours.

Ethyl 5(4)-(2-amino-4(5)-oxo Δ²-imidazoline)-2-propionate: Ethyl 5(4)-(2-amino-4(5)-oxo Δ²-imidazolineidene)-2-propionate (490 mg.) was dissolved in 100 ml. of glacial acetic acid. The solution was then hydrogenated at approximately 40 psi for eight hours using 100 mg. of Adams catalyst. Upon completion of the hydrogenation the solution was filtered and then concentrated to a syrup in vacuo (water pump). The pH was then adjusted to approximately 8 with 6N ammonium hydroxide whereupon the ester precipitated. The product was removed by filtration and the mother liquors were replaced in the refrigerator to produce a second crop.

The crude material was recrystallized from 95% ethanol yielding 220 mg. (45%) of a white crystalline material m.p. 227-229°. Analysis calc'd. for C₈H₁₃N₅O₃: C, 48.23; H, 6.58. Found: C, 48.1; H, 6.74.

2-Amino-5-methyl-6-oxopyrimidine-4-carboxylic acid (III): To 7.5 ml. of 1N potassium hydroxide was added 340 mg. of 5(4)-(2-amino-4(5)-oxo Δ²-imidazolineidene)-2-propanoic acid and the mixture was heated on a steam bath for 30 minutes. After the heating period the solution was cooled, acidified with 6N hydrochloric acid and set in the refrigerator to crystallize. The product was removed by filtration and recrystallized from hot water. The first crop of crystals weighed 150 mg. By concentrating the
mother liquor a second crop of 80 mg. was obtained; total yield 62%. When a sample was placed on a melting point block at 285° and the temperature raised 0.5°/minute the m.p. was 302° decomposition with effervescence.

An analytical sample was dried in an Abderhalden over phosphorus pentoxide at 110°. Analysis calc'd. for C₆H₇N₂O₃: C, 42.61; H, 4.17. Found: C, 42.5; H, 4.31.

**Ethyl hydantoidene-2-propionate:** Place 10 g. (0.05 moles) of diethyl α-oxalylpropionate, 3 g. (0.05 moles) urea and 3.8 ml. of glacial acetic acid in a flask equipped with a reflux condenser and a tube for introducing hydrochloride gas. The flask was heated on a steam bath while hydrogen chloride was bubbled through the mixture for one-half hour. The product was removed by filtration and washed with a small amount of water. The product was recrystallized from water yielding 4.3 g. (44%) of white powder melting at 181-181.5°C. Analysis calc'd. for C₈H₁₀N₂O₄: C, 48.48; H, 5.09. Found C, 48.5; H, 5.17.

**Hydantoidene-2-propionic acid:** Ethyl hydantoidene-2-propionate (340 mg.) was placed in 7.5 ml. of 1N potassium hydroxide and heated for one-half hour at 100°. The solution was then cooled, neutralized with 6N hydrochloric acid and set aside to crystallize. The product after two recrystallizations from water yielded small white needles
175 mg. (61%) which melted at 278-280°. An analytical sample was dried in an Abderhalden over phorphous pentoxide at 138° for six hours.

Analysis calc'd for C\textsubscript{6}H\textsubscript{6}N\textsubscript{2}O\textsubscript{4}: C, 42.36; H, 3.56. Found: C, 42.1; H, 3.63.

2,6-Dioxo-5-methyl-pyrimidine-4-carboxylic acid:

Hydantoidene-2-propanoic acid (1 g.) was dissolved in 23 ml. of 1 N potassium hydroxide and the solution was then evaporated almost to dryness at 100°C. Upon cooling the concentrate, it was acidified with 6N hydrochloric acid and allowed to stand in a refrigerator for several hours. The product (710 mg.) was removed by filtration and mother liquors were concentrated and cooled yielding 270 mg. additional.

The two crops were combined and recrystallized from water yielding white crystalline needles. The first crop contained 405 mg., the second 200 mg. giving 60% overall yield. The m.p. depends upon the rate of heating of the block. When a sample was placed in the block at 290° and the temperature raised 4°/minute, the sample decomposed with effervescence at 326.5-327.5°.
SUMMARY

Guanidine and ethyl α-oxalylpropionate have been condensed in an alkaline medium to yield a non cyclic guanide. The guanide has been cyclized to an imidazoline derivative and that in turn enlarged to the pyrimidine-4-carboxylic acid.

The structure of the imidazoline derivative, and consequently the isomeric pyrimidine as well as the guanide, has been determined on the basis of: (1) the ease of hydrogenation of the olefinic unsaturation in ethyl-5(4)-(2-amino-4(5)-oxo-Δ²-imidazolineidene)-2-propionate, (2) analytical data and (3) the U.V. spectral data.

The condensation of urea with ethyl α-oxalylpropionate, in an acidic medium, yielded ethyl hydantoidene-2-propionate which was hydrolyzed to the acid and then rearranged to the isomeric pyrimidine-4-carboxylic acid. The analytical data and U.V. curves are given.

Condensations of the ester with formamidine and acetamidine were attempted yielding oils which were not characterized. Thiourea gave such a small amount of product that it did not seem feasible to continue work on that phase of the problem.


