1969

# The synthesis of some 2, 5-morpholinediones

Jack T. Ballinger
*Southern Illinois University Edwardsville*

# THE SYNTHESIS OF SOME 2,5-MORPHOLINEDIONES

BY

JACK T. BALLINGER

BACHELOR OF SCIENCE

This Thesis Submitted in Partial
Fulfillment of the Requirements
For the Master of Science Degree

Faculty of Chemistry
in the Graduate School
Southern Illinois University
Edwardsville Campus
August, 1969

SOUTHERN ILLINOIS UNIVERSITY

The Graduate School

8/11, 1967

I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY JACK T. BALLINGER ENTITLED THE SYNTHESIS OF SOME 2,5-MORPHOLINEDIONES BE ACCEPTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE.

Emil J. Jusa
Thesis Director

J. Edmund W Lite
Faculty Chairman

## ACKNOWLEDGEMENT

The author wishes to express his gratitude for the inspiration and guidance given him during this study by Dr. Emil F. Jason. He also wishes to express his appreciation for the aid given him by the American Oil Company in the form of time and equipment.

Typist: J. A. Marsh

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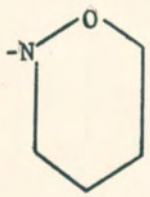
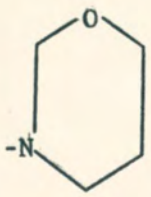
## INTRODUCTION

Oxazines (I-III) are six-membered cyclic compounds containing an oxygen and a nitrogen atom. These two hetero atoms may occupy the 1-2, the 1-3, or the 1-4 positions hence, there are three isomeric arrangements of this ring system.



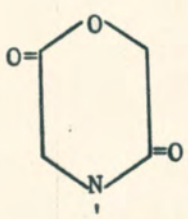
(I)



(II)

(III)

Derivatives of 1,3-oxazine (II) have been widely studied and many have been found to have considerable biological activity. It is theorized that the biological activity of 1,3-oxazine derivatives is due to an active methylene group in position 2. 1,4-oxazine (III) does not contain an active methylene site, however, its 2,5-diketo derivative (IV) does. It might be expected then that certain derivatives of compound IV would possess biological activity.

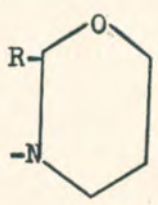


(IV)

The object of this work was (1) to synthesize 2,5-morpholinedione (IV) and some of its derivatives and (2) to explore the utility of compound IV as an intermediate in the synthesis of a variety of alpha-amino and alpha-hydroxy acids.

## DISCUSSION

In 1889, Knorr (1) was one of the first to explore the oxazine family. He mistakenly named 1,4-oxazine as "morpholine" thinking the compound to be the base for morphine. In the early 1930's, Gardner and Hammel (2) found N-substituted 1,3-oxazines to have anesthetic properties. Urbanski et. al. (3) found 2-benz-1,3-oxazine (V) to have anti-tumor activity and suggested that the biological activity was due to the active methylene group in position 2. Morpholine (III) would be speculated to have a lower degree of biological activity than 1,3-oxazine (II) because the combined oxygen and nitrogen inductive effects are not concentrated on any one methylene group. This speculation is substantiated by the fact that no biological activity has been reported for the morpholine structure itself. However, Cook et. al. (4) have shown the antibiotic lateritiin-1 to degrade to a highly substituted 2,5-morpholinedione (VI; R'=R''=$iC_3H_7$, R'''=$CH_3$). The increase in biological activity of this diketomorpholine may be due to the increased activation of the methylene groups by the carbonyl groups of the cyclic structure. It is speculated that simple alkyl and aryl substituted 2,5-morpholinedione compounds (VII) could also have chemotherapeutic properties because of their active methylene groups.

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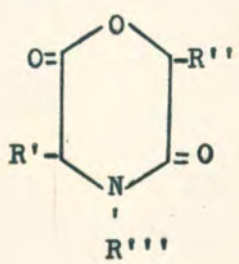
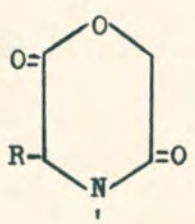



(VI)

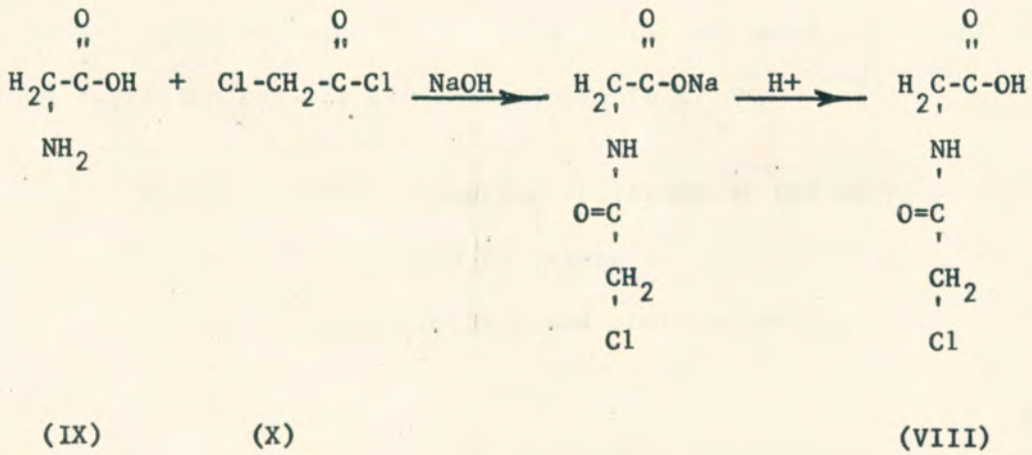



(VII)

In 1949, Cook and Cox (5) synthesized several highly substituted 2,5-morpholinediones after discovering that the antibiotic produced by lateritiin-I degraded to that type of compound. Their synthesis of 2,5-morpholinediones was patterned after that of Chadwick and Pascu (6) which involved heating the sodium salt of a bromoacylamino acid under very high vacuum whereupon a substituted 2,5-morpholinedione product sublimed. The various bromoacylamino acid intermediates were prepared using a technique developed by Fischer and Schenkel (7). which involved treating a salt of the respective amino acid with an alpha-bromo acid chloride in a cold aqueous-alkali solution.

PREPARATION OF CHLOROACETYL AMINO ACIDS:

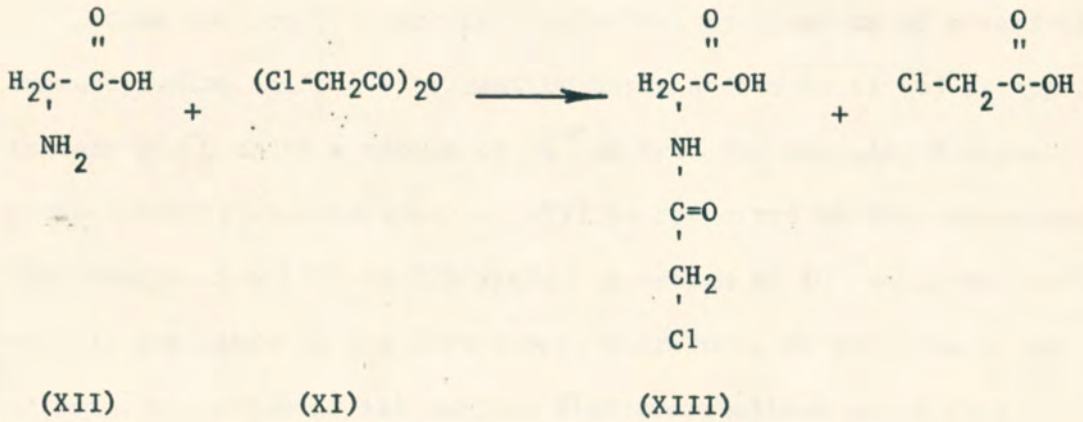
Levene et. al. (8) prepared several chloroacetyl amino acid derivatives following the scheme outlined for the preparation of chloroacetylglycine (VIII). Glycine (IX) was reacted with chloroacetyl chloride (X) in a cold aqueous sodium hydroxide solution as outlined below.




(IX) (X) (VIII)

The solution was then neutralized with acid and the product concentrated to dryness under reduced pressure. This technique gave a yield of approximately 70% for chloroacetylglycine.

Our method for the preparation of chloroacetyl amino acids utilized chloroacetic anhydride as the acetylating agent. The procedure adopted followed the one employed for the preparation of chloroacetylglycine. Chloroacetic anhydride (XI) was reacted with glycine (XII) in ethyl acetate to afford chloroacetylglycine (XIII) in 70% yield.



(XII) (XI) (XIII)

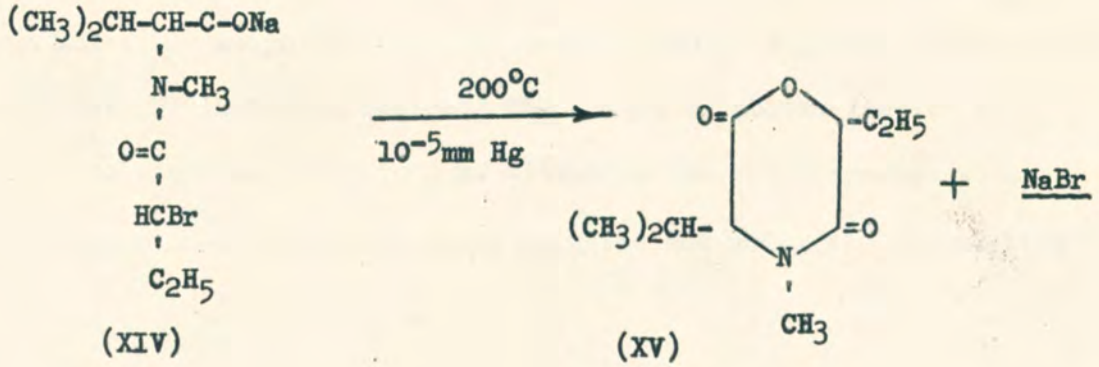
Alanine, valine, leucine, phenylalanine, and tyrosine gave the corresponding acylated derivatives in yields varying from 40 to 80%. The acylation results are shown in Table A.

Our technique for effecting acylation of the amino acids had the advantage over that employed by Levene et. al. (8) in that both the concentrating and neutralizing steps could be avoided.

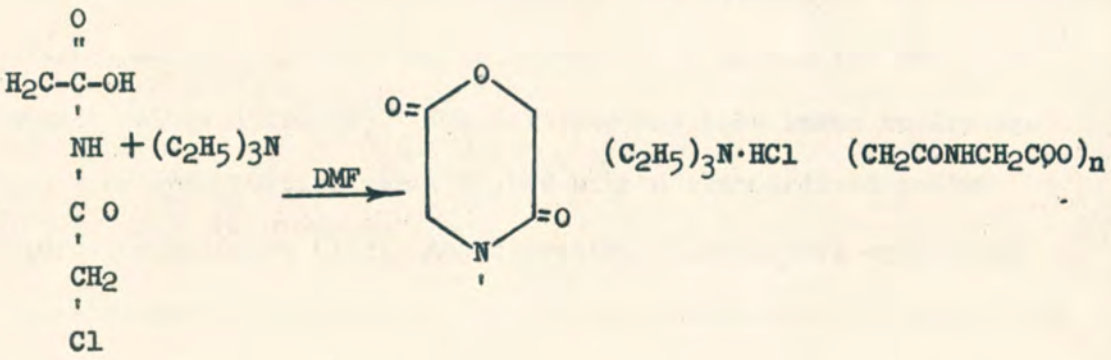
It was also found that recrystallization of "technical grade" chloroacetic anhydride from hot benzene improved the quality of the chloroacetyl amino acid derivatives. Hexane was found useful in inducing precipitation of chloroacetyl amino acid derivatives from cold ethyl acetate. The purity of the chloroacetyl amino acid derivatives was determined by titrating with a standardized sodium hydroxide solution. The chloroacetyl derivatives were found to give much sharper end points than the respective pure amino acids.

PREPARATION OF 2,5-MORPHOLINEDIONE:

Cook and Cox (5) were able to effect cyclization of a variety of bromoacylamino acids (7) by heating their sodium salts (6) at approximately 200°C under a vacuum of $10^{-5}$mm Hg. For example, N-alpha-bromo-n-butyryl-N-methylvaline (XIV) is converted to the corresponding diketomorpholine (XV) in 72% yield. A vacuum of $10^{-5}$mm Hg was not readily available in the laboratory, therefore, we were unable to effect sublimation of the various diketomorpholines using this vacuum technique.



We found that chloroacetylglycine (VIII) could be converted to 2,5-morpholinedione (XVII) by heating a dilute solution (0.05M) in dimethylformamide in the presence of triethylamine (XVI). The yield of 2,5-morpholinedione was in the neighborhood of 80% along with some polymeric product (XIX).




(VIII) (XVI) (XVII) (XVIII) (XIX)

Various solvents (acetone, ethanol, dioxane, ethylene glycol monoethyl ether, dimethylformamide, and ethyl acetate) were evaluated for the dehydrohalogenation step in cyclizing the chloroacetyl amino acid derivatives. All solvents tested were found to allow polymerization as well as the desired cyclization to occur. Dimethylformamide was selected because it gave the highest ratio of cyclized to polymerized products. Polymerization was found to give products ranging in molecular weight from approximately 2000 in ethanol to negligible polymer in dimethylformamide. The extent of polymerization from each solvent was determined by titrating the crude product with a standardized sodium hydroxide solution and using the calculation

procedure as described below and shown in Figure I (page 12). The reaction vessel solution was concentrated to approximately 10% of the original volume and the triethylamine hydrochloride was allowed to precipitate. The crude triethylamine hydrochloride (F) was quantitatively filtered out of solution and weighed. The recovered triethylamine hydrochloride weight (F) was divided by the theoretical triethylamine hydrochloride (E) quantity to obtain the per cent of dehydrohalogenation (I). The filtrate was then taken to dryness and a weighed portion was titrated with a standardized sodium hydroxide solution (IV). Any unreacted chloroacetyl amino acid (A), polymeric product (D), and/or cyclized product (C) would consume base immediately upon titration. The extent of polymerization (V) can now be ascertained by comparing the actual equivalent weight (IV) to the theoretical equivalent weight (III). For example, a larger equivalent weight than the theoretical value would indicate polymerization. Table B indicates all chloroacetyl amino acids tested to cyclize completely at very low concentrations except for chloroacetylglycine which yields approximately 20% polymer.

Triethylamine was selected as the base for the dehydrohalogenation step because its hydrochloride salt was easy to separate from both the cyclized product and the dimethylformamide. In addition, the triethylamine hydrochloride served as an excellent indication as to the extent of the dehydrohalogenation reaction. The triethylamine and other solvents were refluxed over trimellitic

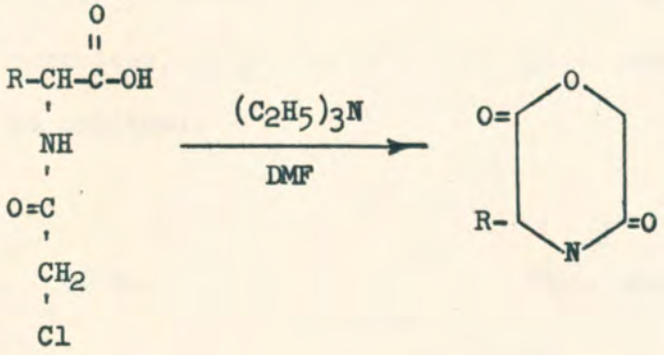
anhydride to remove impurities containing active hydrogens.

Concentration was found to be a critical factor in the cyclization of the chloroacetyl amino acid derivatives to their respective substituted 2,5-morpholinedione derivatives. A study of chloroacetylglycine concentration versus per cent yield of 2,5-morpholinedione is shown in Figure II. High chloroacetylglycine concentrations in dimethylformamide favored polymerization as opposed to cyclization. The low concentration would favor an intramolecular type condensation reaction, while an intermolecular reaction would be favored by high concentration. The optimum chloroacetylglycine concentration was found to be less than 0.05N in dimethylformamide. The percentages of 2,5-morpholinedione shown in the graph (Figure II) were calculated on the basis of triethylamine hydrochloride produced. The quantity of cyclized product was increased by utilizing a predilution technique in which the chloroacetylglycine was dissolved in dimethylformamide and this solution was slowly added to the heated dimethylformamide-triethylamine reaction vessel. This technique in effect keeps the unreacted chloroacetylglycine concentration at a minimum in the reaction vessel yet allows large quantities of material to be prepared at one time.

PREPARATION OF SUBSTITUTED 2,5-MORPHOLINEDIONES:

Alanine, valine, phenylalanine, and tyrosine were converted to their respective chloroacetyl derivatives and cyclized using the procedure developed for the preparation of 2,5-morpholinedione.

Yields varied from 60-85% (Table B) for the cyclization step.

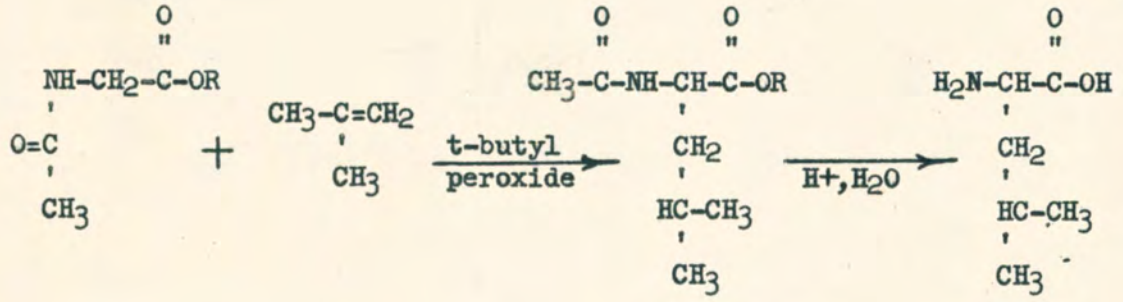



(XX) R=methyl
(XXI) R=isopropyl
(XXII) R=phenyl
(XXIII) R=p-hydroxphenyl

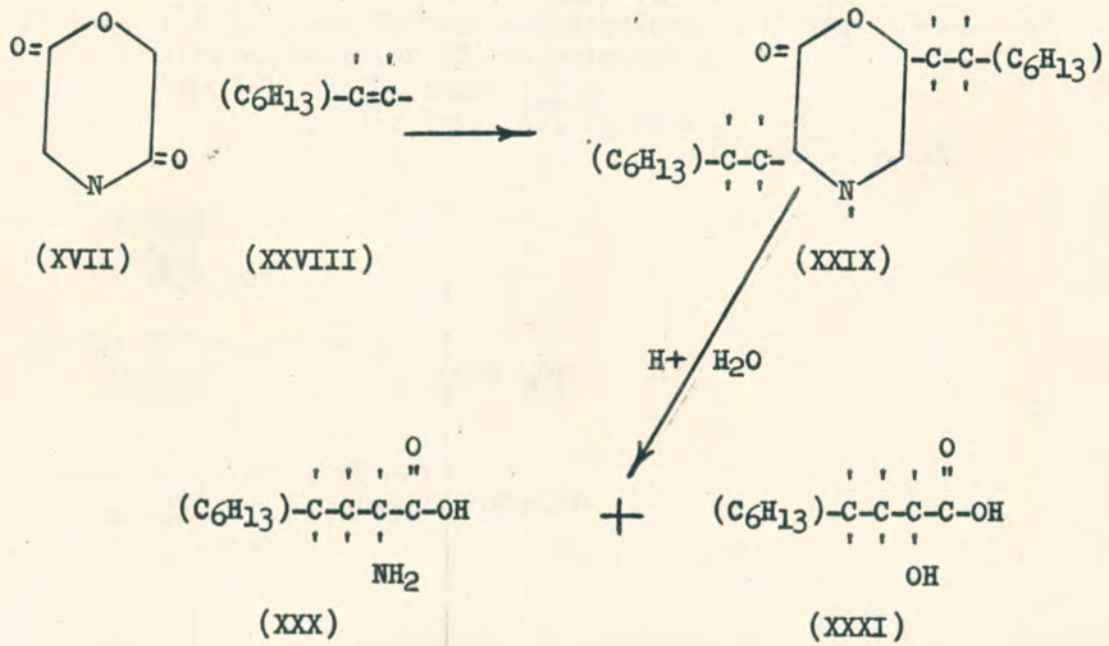
ALKYLATION OF 2,5-MORPHOLINEDIONE:

The alkylation of 2,5-morpholinedione appeared of interest to us in that substituted morpholinediones could be readily hydrolyzed to alpha-hydroxy and alpha-amino acids. Since hydrolysis is nearly quantitative, a good method for preparing a variety of alpha-hydroxy and alpha-amino acids would ensue provided we could alkylate this lactone-lactam ring system. The free-radical addition of somewhat activated methylene groups to terminal olefins has been carried out by a number of investigators (9-12). For example, Rieche, Schmitz, and Gruendemann (9) have added formamide to olefins in the presence of tertiary-butyl peroxide with the formation of amides. Elad and Rakach (10) prepared amides by the light induced addition of formamide to terminal olefins. More recently, Hey and co-workers (11) have employed peroxides to effect direct C-alkylations of acetic acid, acetyl chloride, acetic anhydride, acetamide, acyclic ketones, esters of acetic acid and others. The reactions all involve free-radical addition of these addenda to a number of terminal olefins. In work very closely related to ours, Elad and Sinnrlich (12) have carried

out the free-radical addition of glycine derivatives to olefins employing ditertiary butyl peroxide as an initiator. Employing this technique, they were able to prepare leucine in about 8% overall yield as outlined:



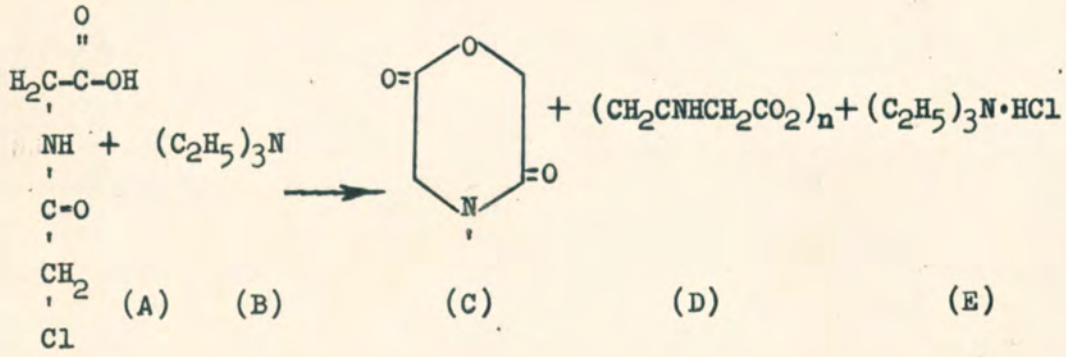

Following a procedure adapted after that of Allen and Hey (11), we reacted 2,5-morpholinedione (XVII) with octene-1 (XXVIII) in the presence of di-t-butyl peroxide and alkylation indeed took place. The alkylated 2,5-morpholinedione (XXIX) was then subjected to acid hydrolysis and the respective alpha-amino decanoic (XXX) and alpha-hydroxy decanoic acids (XXXI) were recovered in 10 to 15% yields.




(XVII) (XXVIII) (XXIX) (XXX) (XXXI)

## Figure I

### Method for Determining Extent of Cyclization




(A) (B) (C) (D) (E)

(A) chloroacetylglycine, mw=151.5, 7.5g (0.049 moles)
(B) triethylamine, mw=101.2, 10.6g (0.066 moles)
(C) 2,5-morpholinedione, mw=115.0, 5.64g (0.049 moles)
(D) polymeric product, mw=$(115.0)_n$
(E) triethylamine hydrochloride, mw=137.7 6.75g (0.049 moles)
(F) triethylamine hydrochloride product, 4.72g

I. Dehydrohalogenation

$$\frac{4.72g}{6.75g} \times 100 = 70\%$$

II. Theoretical Unreacted Chloroacetylglycine: ( Assume 30% unreacted from dehydrohalogenation (I) calculation.)

$7.5g \times 0.30 = 2.25g$ thus: $\frac{2.25g}{151.5g/eq} = 0.0149$ eq.

Theoretical Cyclized Chloroacetylglycine: ( Assume 70% reacted from dehydrohalogenation (I) calculation.)

$5.64g \times 0.70 = 3.94g$ thus: $\frac{3.94g}{115.0g/eq} = \frac{0.0343 \text{ eq.}}{0.0492 \text{ eq total}}$

6.19g total

III. Theoretical Equivalent Weight:

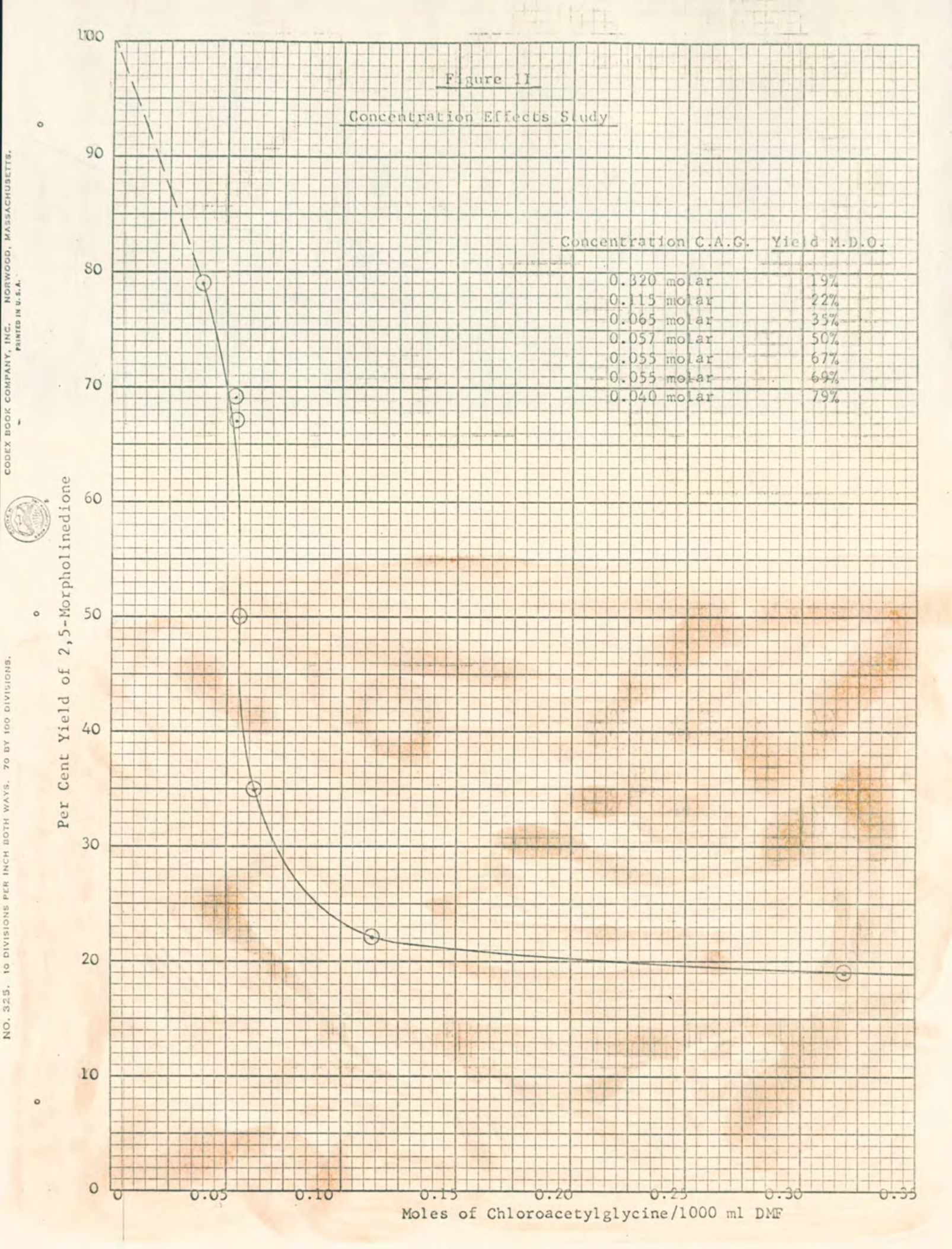
$$\frac{6.19g}{0.0492 \text{ eq}} = 126.g/eq$$

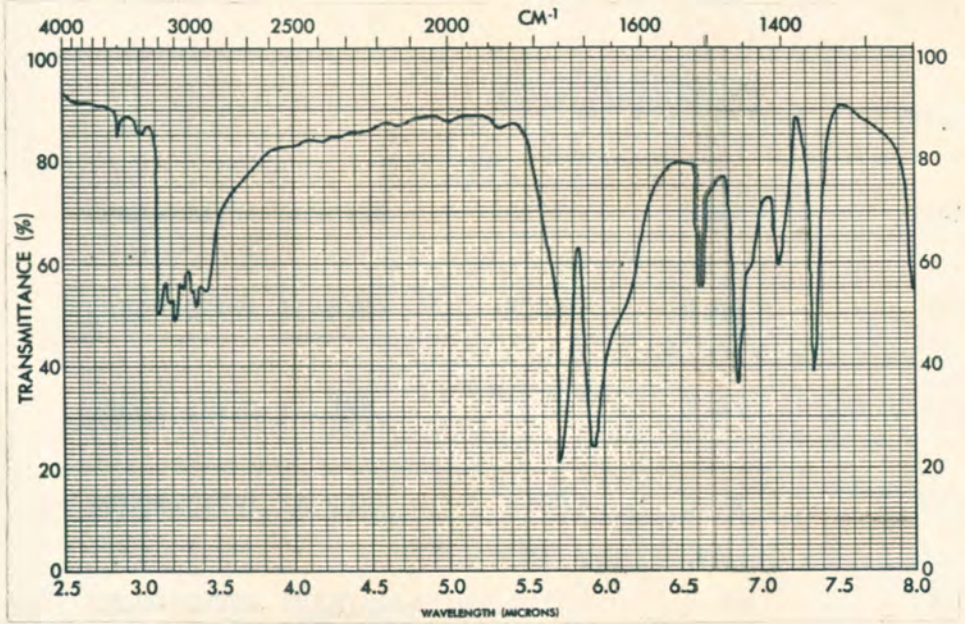
IV. Actual Equivalent Weight:

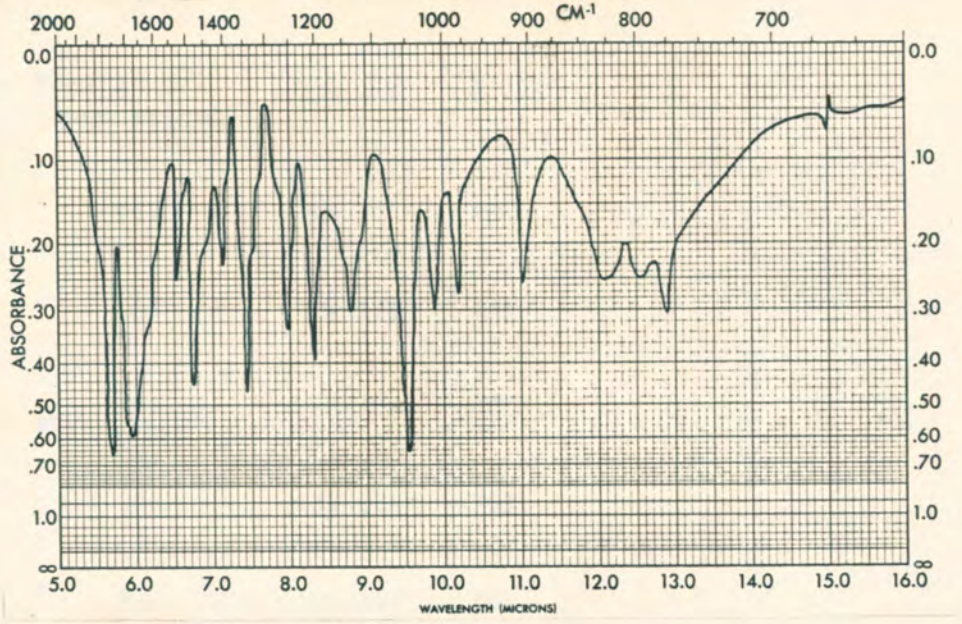
$$\frac{0.9140g}{0.05401 \times 0.113N} = 150 \text{ g/eq}$$

V. Extent of Polymerization:

$$\frac{(150g/eq - 126g/eq)}{(126g/eq)} \times 100 = 19\%$$






13a

## FIGURE III

| | | | |
|---|---|---|---|
| SAMPLE 2, 5-MORPHOLINEDIONE | CURVE NO. IR #50 | SCAN SPEED Slow | OPERATOR J.T.B. |
| | CONC. 1 Sample: 10 KBr | SLIT N | DATE 1/2/68 |
| ORIGIN | CELL PATH Potassium Bromide Pellet | REMARKS mp = 187-189°C | |
| SOLVENT | REFERENCE Air | | |

Table A

SUMMARY OF CHLOROACETYL AMINO ACID PREPARATION

| | PER CENT NITROGEN | | ACID NUMBER | | M.P. °C | YIELD |
|---|---|---|---|---|---|---|
| | Determined | Theoretical | Determined | Theoretical | | |
| CHLORACETYL GLYCINE | 9.12 | 9.24 | 149 | 152 | 96-98 | 70% |
| CHLORACETYL ALANINE | 8.40 | 8.48 | 160 | 165 | 119-121 | 55% |
| CHLORACETYL VALINE | 7.11 | 7.23 | 190 | 194 | 130-134 | 70% |
| CHLORACETYL LEUCINE | 6.60 | 6.74 | 201 | 208 | 132-134 | 70% |
| CHLORACETYL PHENYLALANINE | 5.71 | 5.86 | 234 | 242 | 125-127 | 70% |
| CHLORACETYL TYROSINE | 5.30 | 5.43 | 240 | 258 | 157-158 | 40% |

Table B

SUMMARY OF CHLOROACETYL AMINO ACID CYCLIZATIONS

| | PER CENT NITROGEN | | M.P. °C | DEHYDROHALOGENATION | CYCLIZATION |
|---|---|---|---|---|---|
| | Determined | Theoretical | | | |
| 2,5-MORPHOLINEDIONE | 12.2 | 12.2 | 189-190 | 80% | 80% |
| 3-METHYL-2,5-MORPHOLINEDIONE | 10.4 | 10.8 | 134-136 | 85% | 100% |
| 3-ISOPROPYL-2,5-MORPHOLINEDIONE | 8.5 | 8.9 | 192-193 | 70% | 100% |
| 3-PHENYL-2,5-MORPHOLINEDIONE | 6.9 | 6.8 | 138-140 | 80% | 100% |
| 3-p-HYDROXYPHENYL-2,5-MORPHOLINEDIONE | 6.3 | 6.3 | 212-214 | 60% | 100% |

## CONCLUSION

The results of this investigation indicate that the preparation of substituted 2,5-morpholinedione compounds using a dehydrohalogenation procedure in a solvent medium is dependent upon concentration effects. Large scale preparations of substituted 2,5-morpholinedione compounds must be carried out in very dilute solutions or must utilize a predilution tachnique as described in the discussion. The small amount of polymerization that takes place even at low reactant concentration presents a problem in resolving the cyclized from the polymerized product. The two products are very similar chemically and are not readily seperated. No literature references could be found for the synthesis of 2,5-morpholinedione.

2,5-morpholinedione shows promise as an intermediate in the synthesis of long-chained alpha amino and alpha hydroxy acids using a free-radical alkylation technique.

## EXPERIMENTAL

### PREPARATION OF CHLOROACETYLGLYCINE:

Approximately 66.6 grams (0.888 moles) of glycine were dissolved in 600 ml of ethyl acetate contained in a 1000 ml round bottom flask and 190 grams (1.11 moles) of benzene-recrystallized chloroacetic anhydride were added with stirring at ambient temperature. A slight excess of chloroacetic anhydride was added to compensate for water and/or other reactive contaminants. The reaction was continued for approximately two hours or until a bright yellow color developed. Approximately 100 ml of hexane were added to induce precipitation and the reaction vessel was stored in a freezer for several hours. The crude chloroacetylglycine was filtered with a Buchner filter and the filtrate returned to a freezer for additional precipitation, usually 10%.

The crude chloroacetylglycine was washed with several 40 ml portions of hot ethyl ether. The yield was normally 95 grams which corresponds to approximately 70% of the theoretical. After recrystallation from hot ethyl ether and drying in a vacuum oven, an acid number determination using a phenolphthalein end point gave 149 g/eq with a theoretical value of 152 g/eq. Elemental nitrogen analysis by the Kjeldahl method gave 9.12% while the theoretical nitrogen value is 9.24% for chloroacetylglycine. The melting range was determined to be 96-98°C compared with the literature value of 98-100°C (8).

PREPARATION OF CHLOROACETYLALANINE:

Approximately 13.6 grams of dl-alanine (0.153 moles) were dissolved in 600 ml of ethyl acetate contained in a 1000 ml round bottom flask and 37.5 grams (0.219 moles) of benzene-recrystallized chloroacetic anhydride were added with rapid stirring at ambient temperature. A slight excess of chloroacetic anhydride was added to compensate for water and/or other reactive contaminants. The reaction was allowed to continue at 50°C for approximately two hours or until the solution cleared. Any unreacted materials were filtered out immediately through a Buchner filter and approximately 2/3 of the ethyl acetate volume was removed on a Rinco evaporator. The concentrated filtrate was stored in a freezer for several hours. The precipitated chloroacetylalanine was filtered out and washed with several 20 ml portions of ethyl ether. The yield was normally 8.2 grams which corresponds to approximately 54% of theoretical based on reacted alanine. After recrystallizing from hot ethyl ether and drying in a vacuum oven, the product melted at 119-121°C. An acid number determination using a phenolphthalein end point gave 160 g/eq. with a calculated value of 165 g/eq. Elemental nitrogen analysis by the Kjeldahl method gave 8.40% while theoretical is 8.48% for chloroacetylalanine.

PREPARATION OF CHLOROACETYLVALINE:

Approximately 17.9 grams (0.153 moles) of dl-valine were dissolved in 600 ml of ethyl acetate and 40.0 grams (0.234 moles) of benzene-recrystallizated chloroacetic anhydride were added with rapid

stirring at 50°C. A slight excess of chloroacetic anhydride was added to compensate for water and/or other reactive contaminants. The reaction was continued for approximately two hours or until the solution cleared. Any unreacted materials were filtered out and approximately 2/3 of the solvent was removed by vacuum distillation. The concentrated filtrate was stored in a freezer for approximately two hours. The crude chloroacetylvaline was filtered out and the filtrate was returned to the freezer for any additional precipitation.

The crude chloroacetylvaline was washed with several 30 ml portions of hot ethyl acetate. The yield was 22 grams which corresponds to approximately 80% of the theoretical value based on the reacted valine quantity. After recrystallizing from hot ethyl acetate and drying in a vacuum oven, the product melted at 130-132°C. An acid number determination using a phenolphthalein end point gave 190 g/eq with a theoretical value of 194 g/eq. Elemental nitrogen analysis by the Kjeldahl method gave 7.11% while theoretical is 7.23% for chloroacetylvaline.

PREPARATION OF CHLOROACETYLPHENYLALAINE:

Approximately 25.3 grams (0.153 moles) of dl-phenylalanine were dissolved in 600 ml ethyl acetate contained in a 1000 ml round bottom flask and 40.0 grams (0.234 moles) of benzene-recrystallized chloroacetic anhydride were added with rapid stirring at 50°C. A slight excess of chloroacetic anhydride was added to compensate for water and/or other reactive contaminants. The reaction was continued for

approximately two hours or until the solution cleared. Any unreacted materials were filtered out and the filtrate volume was reduced to approximately 1/3 by vacuum distillation. The filtrate was stored in a freezer for approximately 24 hours and the precipitated chloroacetylphenylalanine was removed by filtration. The crude product was washed with several 30 ml portions of hot ethyl acetate. The yield was normally 25 grams which corresponds to approximately 70% of the theoretical based on reacted phenylalanine. After recrystallizing from hot ethyl acetate and drying in a vacuum oven, the product melted at 125-128°C. An acid number determination using a phenolphthalein end point gave 236 g/eq. with a calculated value of 242 g/eq. An elemental nitrogen analysis by the Kjeldahl method gave 5.70% while theoretical is 5.80% for chloroacetylphenylalanine.

PREPARATION OF CHLOROACETYLTYROSINE:

Approximately 23.0 grams (0.127 moles) of tyrosine were dissolved in 900 ml of acetone containing 10 ml of water and 40.0 grams (0.234 moles) of benzene-recrystallized chloroacetic anhydride were added with rapid stirring at 50°C. A slight excess of chloroacetic anhydride was added to compensate for the water and/or other reactive contaminants. The reaction was continued for approximately two hours or until the solution cleared. The solvent volume was reduced to 1/3 the orginal volume by vacuum distillation and the concentrated solvent was filtered immediately to remove any unreacted materials. Approximately 100 ml of ethyl acetate were added and the solvent placed in a freezer for 24 hours. The crude chloroacetyltyrosine was filtered through a

Buchner filter and washed with several small portions of ethyl acetate. The yield was normally 13 grams which corresponds to approximately 40% of theoretical yield. After washing with ethyl acetate and drying in a vacuum oven, the product melted at 157-158°C. An acid number determination using a phenolphthalein end point gave 240 g/eq. with a calculated value of 258 g/eq. An elemental nitrogen analysis by the Kjeldahl method gave 5.30% while theoretical is 5.43% for chloroacetyltyrosine.

PREPARATION OF 2,5-MORPHOLINEDIONE:

Approximately 13.8 ml (0.100 moles) of triethylamine were poured into 800 ml of dimethylformamide contained in a 1000 ml round bottom flask equipped with a reflux condenser and magnetic stirrer. The temperature was maintained between 110 and 120°C. while approximately 7.5 grams (0.049 moles) of chloroacetylglycine were added slowly. After the addition was complete the reaction was allowed to continue for approximately 3 hours. The dimethylformamide was removed by vacuum distillation until the triethylamine hydrochloride started to precipitate; precipitation occurred at approximately 100 ml total volume. The reaction vessel was allowed to stand at ambient temperature for approximately 24 hours and the triethylamine hydrochloride was allowed to precipitate. In this case, the triethylamine hydrochloride was normally 80% of the theoretical yield. The filtrate was taken to dryness by vacuum distillation and the crude morpholinedione was washed with several 5 ml portions of ethanol which normally gave approximately 3 grams of solid product.

This quantity represents approximately 70% of theoretical when normalized against the triethylamine hydrochloride yield. Triethylamine hydrochloride is soluble in cold ethanol, while the 2,5-morpholinedione is only slightly soluble. Recrystallization of the product with hot ethanol and drying in a vacuum oven gave a melting range of 189-190°C. Infrared analysis indicated two strong bands in the 5.8-6.1 micron carbonyl absorption region as shown in Figure III. Hydrolysis of the product gave glycine and alpha-hydroxyacetic acid. Elemental carbon, hydrogen, and nitrogen analysis gave 41.8% C, 4.4% H, and 12.2% N with theoretical values being 41.8% C, 4.3% H, and 12.2% N for 2,5-morpholinedione.

PREPARATION OF 3-METHYL-2,5-MORPHOLINEDIONE:

Approximately 13.8 ml (0.100 moles) of triethylamine were poured into 800 ml of dimethylformamide contained in a 1000 ml round bottom flask equipped with a reflux condenser and magnetic stirrer. The temperature was controlled between 110 and 120°C. Approximately 8.2 grams (0.050 moles) of chloroacetylalanine were added and the reaction was allowed to continue for approximately 2 hours. The dimethlformamide was removed by vacuum distillation until the triethylamine hydrochloride started to precipitate; precipitation usually occurred around 200 ml total volume. The reaction vessel was allowed to stand at ambient temperature for approximately 24 hours and the triethylamine hydrochloride was removed by filtration. In this case, the triethylamine hydrochloride was 84% of the theoretical yield. The filtrate was taken to dryness by vacuum distillation and the residue was dissolved in ethanol which normally yielded 3.0 grams of a white insoluble

product. This quantity represented 55% of the theoretical when normalized against the triethylamine hydrochloride yield. After vacuum oven drying, the product was found to melt between 134-136°C. Infrared analysis indicated two strong bands in the 5.8-6.1 micron carbonyl absorption region. Hydrolysis of the product gave alanine and alpha-hydroxyacetic acid which would be the hydroysis products for 3-methyl-2,5-morpholinedione. An elemental carbon, hydrogen, and nitrogen analysis gave 47.0% C, 5.5% H, and 10.4% N with theoretical values of 46.5% C, 5.4% H and 10.8% N for 3-methyl-2,5-morpholinedione.

PREPARATION OF 3-ISOPROPYL-2,5-MORPHOLINEDIONE:

Approximately 13.8 ml (0.100 moles) of triethylamine were poured into 800 ml of dimethylformamide contained in a 1000 ml round bottom flask equipped with a reflux condenser and magnetic stirrer. The temperature was controlled between 120-140°C. Approximately 12.9 grams (0.066 moles) of chloroacetylvaline were added and the reaction allowed to continue for approximately three hours. The dimethylformamide was removed by vacuum distillation until the triethylamine hydrochloride started to precipitate; precipitation usually occurred around 200 ml total volume. The reaction vessel was allowed to stand at ambient temperature for 24 hours and the triethylamine hydrochloride was removed by filtration. In this case, the triethylamine hydrochloride was approximately 70% of the theoretical. The filtrate was taken to dryness on a Rinco evaporator and a gravimetric determination was made on the residue. The residual material weighed 14.1 grams which was 125% of the calculated yield. This excess was probably due to residual dimethylformamide in the oily product. The 3-isopropyl-

2,5-morpholinedione product was washed with hexane and gave a melting point range of 192-193°C. An acid number titration after correcting for unreacted chloroacetylvaline gave a result of 149 g/eq with a theoretical value of 170 g/eq. An elemental carbon, hydrogen, and nitrogen analysis on a purified sample of 3-isopropyl-2,5-morpholinedione gave 54.0% C, 7.2% H, and 8.5% N with theoretical values being 53.5% C, 7.0% H, and 8.9% N for 3-isopropyl-2,5-morpholinedione.

PREPARATION OF 3-PHENYL-2,5-MORPHOLINEDIONE:

Approximately 11.6 ml (0.084 moles) of triethylamine were added to 800 ml of dimethylformamide contained in a 1000 ml round bottom flask equipped with a reflux condenser and magnetic stirrer. The temperature was maintained between 120-140°C while 16.0 grams (0.066 moles) of chloroacetylphenylalanine were added slowly. The reaction was allowed to continue for approximately two hours. The dimethylformamide was removed by vacuum distillation until the triethylamine hydrochloride started to precipitate; precipitation usually occurred around 200 ml total volume. The reaction vessel was allowed to stand at ambient temperature for approximately 24 hours and the triethylamine hydrochloride (80% of theoretical) was removed by filtration. The filtrate was taken to dryness by vacuum distillation and a portion of solids was titrated with standarized NaOH which showed the product to be almost 100% cyclized after compensating for unreacted chloroacetylphenylalanine. The solids were washed with hot ethanol which yielded 7 grams representing approximately a 70% yield. After vacuum drying, the product was fround to melt between 138-140°C. Infrared analysis indicated two strong bands in the 5.8-6.1 micron carbonyl

absorption region. Elemental carbon, hydrogen, and nitrogen analysis gave 64.9% C, 5.0% H, and 6.9% N while the theoretical values for 3-phenyl-2,5-morpholinedione are 64.4% C, 5.4% H and 6.8% N.

PREPARATION OF 3-p-HYDROXYPHENYL-2,5-MORPHOLINEDIONE:

Approximately 10.6 grams (0.066 moles) of triethylamine were poured into 800 ml of dimethylformamide contained in a 1000 ml round bottom flask equipped with a reflux condenser and magnetic stirrer. The temperature was controlled between 120-140°C. Approximately 8.7 grams (0.034 moles) of chloroacetyltyrosine were added and the reaction was allowed to continue for approximately two hours. The dimethylformamide was removed by vacuum distillation until the triethylamine hydrochloride started to precipitate; precipitation usually occured around 200 ml total volume. The reaction vessel was allowed to stand at ambient temperature for approximately 24 hours and the precipitated triethylamine hydrochloride (60% of theoretical) removed by filtration. The filtrate was taken to dryness by vacuum distillation and the residue was weighed. The residual material weighed 8.5 grams (107% of theoretical) with 3.3 grams of unreacted chloroacetyltyrosine and 4.7 grams of cyclized product. The crude product was recrystallized from cold water and gave a melting point range of 212-214°C. An acid number titration on the product after correcting for the unreacted chloroacetyltyrosine gave a result of 237 g/eq with a theoretical value of 234 g/eq. An elemental carbon, hydrogen and nitrogen analysis on a purified sample gave 60.0% C, 5.0% H and 6.3% N with theoretical values being 59.8% C, 5.0% H, and 6.3% N for 3-p-hydroxyphenyl-2,5-morpholinedione.

ALKYLATION OF 2,5-MORPHOLINEDIONE:

A mixture of 2,5-morpholinedione, 2.4 grams (0.0209 moles), octene-1, 0.60 grams (0.0054 moles), tertiary-butylperoxide, 0.40 grams (0.0027 moles) and 5 ml of ethylene glycol monoethyl ether was heated under reflux for 46 hours during which time the reaction mixture became dark brown. The solvent and other volatiles were removed by heating under an aspirator to leave a viscous syrup. To the syrup were added 8 ml 6NHCl and the reaction mixture was refluxed for 3 hours to effect hydrolysis. The cooled aqueous mixture was extracted with one 10 ml portion of chloroform and the chloroform layer was removed. The water was removed from the aqueous layer using a Rinco evaporator. The residue was dissolved in 10 ml of a 1:1 mixture of ethanol and water. To this clear solution was added approximately 5 ml of pyridine which caused the precipitation of 0.45 grams of solids. The solids were removed by filtration and treated with 5 ml of water which dissolved any glycine. The water insoluble solid 0.10 gram (10% yield) gave a positive ninhydrin test and had a decomposition range of 262-265°C. The reported melting point range for alpha-amino decanoic acid is 264°C (14).

ANALYTICAL

All infrared analyses were performed on a Perkin-Elmer Model 237 Infrared Spectrometer using the potassium bromide salt pellet technique. All elemental nitrogen determinations were performed using conventional Kjeldahl digestion, distillation, and titration techniques. The elemental carbon and hydrogen determinations were

made using a modified Coleman Model 33 Carbon-Hydrogen Analyzer. "Indicarb" was used to quantitatively absorb the carbon dioxide and a calcium sulfate scrubber was used to quantitatively remove the water from combustion. A manganese dioxide scrubber was used to remove all oxides of nitrogen from the combustion train.

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Graduate School
Southern Illinois University

Jack T. Ballinger — December 17, 1941

Address: Ivy Terrace Apartments, No. 18
East Alton, Illinois 62024

Education: Eastern Illinois University
Charleston, Illinois
Bachelor of Science in Chemistry (1963)

Thesis: The Synthesis of Some 2,5-Morpholinediones
Dr. Emil F. Jason

Publications: "Gas Chromatographic Fraction Trap-Infrared Cell", Journal of Gas Chromatography, 6, 295-297 (1968)

This Paper was presented in part at the Midwest Regional A.C.S. Meeting, Kansas State University on October 31, 1968, by Dr. E. F. Jason.

This paper was presented at the Illinois Academy of Science Meeting held at Millikin University, Decatur Illinois, on April 25, 1969, by the author.

Vita