THE PREPARATION OF THE DERIVATIVES OF β-ALANINE

by

ARTHUR F. EMMETT

Submitted in Partial Fulfillment of
the Requirements for the Degree of
Bachelor of Science

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

August 1961

Signature of Author: Signature redacted
Department of Chemical Engineering
August 25, 1961

Certified by: Signature redacted
Thesis Supervisor

Accepted by: _____
Head of Department

Department of Chemical Engineering
Massachusetts Institute of Technology
August 25, 1961

Professor Philip Franklin
Secretary of the Faculty
Massachusetts Institute of Technology
Cambridge 39, Massachusetts

Dear Professor Franklin:

The following thesis entitled "The Preparation of the Derivatives of β-Alanine" is hereby submitted in partial fulfillment of the requirements for the Degree of Bachelor of Science in Chemical Engineering.

Respectfully submitted,

Signature redacted

Arthur F. Emmett

ACKNOWLEDGMENTS

The author wishes to thank Dr. A. A. Ashdown for his kind assistance.

TABLE OF CONTENTS

I. SUMMARY

The object of this thesis is to prepare the derivatives of the amino acid, β-alanine. The derivatives were prepared with reagents that have been used to prepare derivatives of α-amino acids. The derivatives of β-alanine that were prepared are the p-toluenesulfonamide, the benzamide, the phenyl urea, the α-naphthyl urea, and the phenylhydantoin. The titration molecular weights of all the prepared derivatives except the phenylhydantoin, which cannot be found by titration, were calculated from titration data. They closely coincided with the calculated molecular weights of the derivatives. A nitrogen determination of the phenylhydantoin suggested that the derivative contained two molecules of water of crystallization.

II. INTRODUCTION

The identification of uncharacterized compounds is an important part of the field of organic chemistry. The identification is usually effected by, first, classifying the unknown as to the type of compound, and, second, reacting the unknown with organic reagents which will give specific reactions characteristic of the functional groups present in the compound. The unidentified compound is characterized by comparing the melting points of the derivatives thus prepared with the melting points of the derivatives of known compounds of that class. The compound is identified when the melting points of the respective derivatives are the same. If the compound is completely new, a percentage composition determination, in addition to the melting points of the derivatives, is necessary to characterize the compound.

The amino acid, β-alanine, is a constituent of the protein panthothenic acid which is a growth factor in yeasts. It has been synthesized from β-propiolactone and from succinic acid. The derivatives of β-alanine, with the exception of the phenyl urea derivative have not been studied systematically, but the reagents used to prepare them in this study are the ones used to prepare the derivatives of the α-amino acids. The preparation of the known derivative and several of the new

derivatives is the object of this thesis. If the melting points of the derivatives of β-alanine are known then it could be identified much more readily should it appear in the course of any study.

III. PROCEDURE

The derivatives of β-alanine were prepared as follows:

The p-toluenesulfonyl chloride derivative was prepared by reacting β-alanine with p-toluenesulfonyl chloride in an alkali medium, to form the p-toluenesulfonamide derivative of β-alanine. The derivative was dried and a melting point taken. A weighed sample of the derivative was titrated with a standard basic solution to determine the molecular weight.

The benzoyl chloride derivative was prepared by reacting β-alanine with benzoyl chloride in an alkali medium to form the benzamide derivative of β-alanine. The derivative was dried and a melting point taken. A weighed sample of the derivative was titrated with a standard basic solution to determine the molecular weight.

The phenylisocyanate derivative was prepared by reacting β-alanine with phenylisocyanate in an alkali medium to form the phenyl urea derivative of β-alanine. The derivative was dried and a melting point taken. A weighed sample of the derivative was titrated with a standard basic solution to determine the molecular weight.

The α-naphthylisocyanate derivative was prepared by reacting β-alanine with α-naphthylisocyanate in an

alkali medium to form the α-naphthyl urea derivative of β-alanine. The derivative was dried and a melting point taken. A weighed sample of the derivative was titrated with a standard basic solution to determine the molecular weight.

The phenylhydantoin was prepared by first reacting β-alanine with phenylisocyanate in an alkali medium to form the phenylhydantoin acid and then boiling the phenylhydantoin acid in dilute hydrochloric acid, splitting out a water molecule, and forming the phenyhydantoin derivative of β-alanine, a cyclic compound. The derivative was dried and a melting point taken. A percentage composition determination was taken to determine the percentage of nitrogen in the derivative.

IV. RESULTS

The results of the experimentation are best expressed in the form of a table as follows:

compound	mp C	tit. M.W.	theo. M.W.
p-toluenesulfonamide	118	243.2	243
benzamide	93	190.9	193
α-naphthyl urea	201-203 d.	256.2	258
phenyl urea	167.5	207.1	208
phenyl hydantoin	169.5	-	190

V. DISCUSSION OF RESULTS

The results show that the derivatives of β-alanine can be prepared in the same way as α-amino acids. The molecular weight determinations have verified, within experimental error, that the products of the reactions are the desired products. The small discrepancies in the molecular weights of the products could probably be decreased with a greater degree of purification. To get closer agreement between the titration and the calculated molecular weights, the derivatives should be made in quantity and the average of a number of titrations taken.

The melting points were determined by making three runs, each time approaching the melting point region with more care until the temperature could be held quite steady at the melting point.

The six-membered ring is one of the most stable ring structures and therefore, in the case of the phenyl-hydantoin derivative, the six-membered ring structure is assumed to have been formed. A good test to ascertain that the compound is indeed the cyclic phenyl hydantoin would be a percentage composition determination of this compound. A nitrogen determination by Dr. Nagy of the M.I.T. chemical analytical laboratory showed 12.43 percent against 14.73 percent calculated. Crystallized from dilute alcohol, the compound could have two molecules of water of crystallization which would give a nitrogen percentage of 12.39.

VI. CONCLUSIONS

1. The amino acid β-alanine has derivatives corresponding to those of the α-amino acids.

2. The derivatives can, in most cases, be prepared similarly to the way in which the derivatives of the α-amino acids are prepared.

VII. RECOMMENDATIONS

1. The derivatives should be produced in enough quantity to take an average of a number of titrations to determine the molecular weight more accurately.

2. A percentage composition determination could be made on all the derivatives to ascertain that they are the desired products.

VIII. APPENDIX

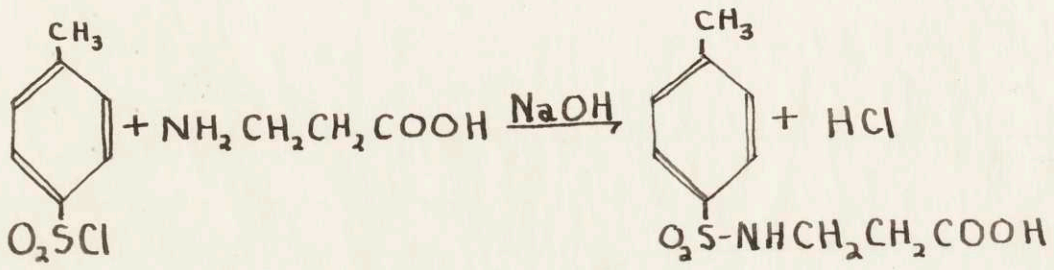
A. DETAILED PROCEDURE

1. p-Toluenesulfonamide Derivative of β-Alanine

Place 267 mg. of β-alanine in an eight-inch tube and add 7 ml. of 1 N sodium hydroxide solution. To this solution add 700 mg. of p-toluenesulfonyl chloride dissolved in 5 ml. of ether. Firmly stopper the tube and shake it frequently over a period of 3 to 4 hours or shake mechanically for 3 to 4 hours. Separate the ether and the aqueous layer and acidify the aqueous layer with dilute hydrochloric acid to a pH of 4 to 5 using Congo red or Universal indicator. The derivative separates out upon cooling. If the derivative separates as an oil, scratch the side of the vessel to induce crystallization. Filter the crystals and recrystallize from hot water.

The derivative separates as short white needles with a melting point of 118° C. A molecular weight determination of this derivative was carried out as described on page 18. The molecular weight determination verified that the product was the desired derivative.

The equation for the chemical reaction is as follows:

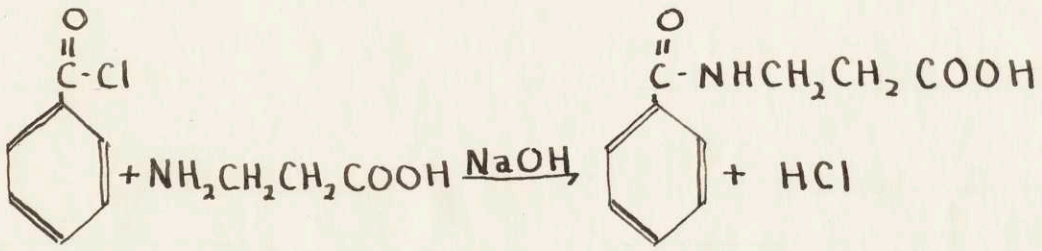


2. Benzamide Derivative of β-Alanine

Place 200 mg. of β-alanine in an eight-inch tube and add 6 ml. of 1 N sodium hydroxide solution. To this solution add 0.3 ml. of benzoyl chloride. Firmly stopper the tube and shake vigorously until the chloride is completely dissolved. Continue to shake frequently over a period of 3 to 4 hours or shake mechanically for 3 to 4 hours. The solution is then acidified with dilute hydrochloric acid to a pH of 4 to 5 using Congo red or Universal indicator. Filter the crystals and recrystallize from hot water. The crystals sometimes separate out slowly after the acid is added and scratching the tube may be necessary to induce crystallization.

The derivative separates out as white flakes with a melting point of 93° C. A molecular weight determination was carried out as described on page 18 which verified that the product was the desired derivative.

The equation for the chemical reaction is as follows:

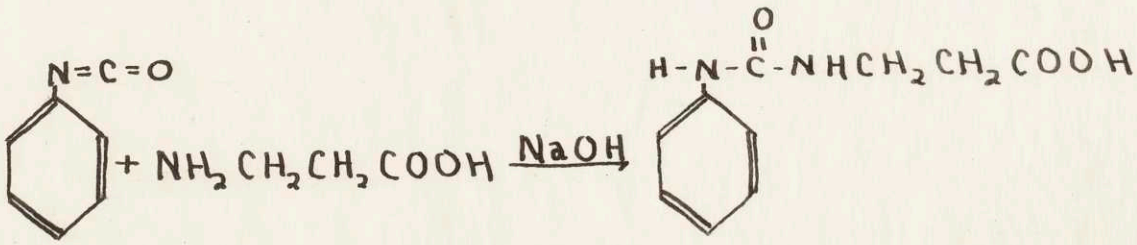


3. Phenylhydantoin Acid Derivative of β-Alanine
(Phenyl Urea Derivative of β-Alanine)

Place 267 mg. of β-alanine in an eight-inch tube and add 3 ml. of 1 N sodium hydroxide solution and 5 ml. of water. To this solution add 0.6 ml. of phenylisocyanate, stopper the tube and shake for 2 to 3 minutes. Let the mixture stand for about 45 minutes with occasional shaking. Filter the insoluble diphenyl urea and acidify the filtrate to a pH of 4 to 5 with dilute hydrochloric acid using Congo red or Universal indicator. The phenylhydantoin acid separates out upon acidification and cooling. Dissolve the phenylhydantoin acid in hot alcohol, filter, and then add a few drops of water until a permanent cloudiness results. The recrystallized phenylhydantoin acid separates out on cooling.

The derivative separates out as white flakes with a melting point of 167.5° C. A molecular weight determination was carried out as described on page 18 which verified that the product was the desired derivative.

The equation for the chemical reaction is as follows:

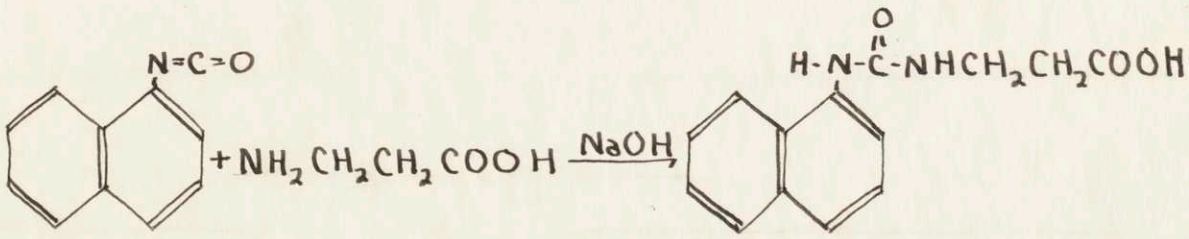


4. α-Naphthylhydantoin Acid Derivative of β-Alanine
(α-Naphthyl Urea Derivative of β-Alanine)

Place 267 mg. of β-alanine in an eight-inch tube and add 3 ml. of 1 N sodium hydroxide solution and 5 ml. of water. To this solution add 0.6 ml. of α-naphthyl-isocyanate, stopper the tube, and shake for 2 to 3 minutes. Let the mixture stand for about 45 minutes with occasional shaking. Filter the insoluble di-α-naphthyl urea and acidify the filtrate to a pH of 4 to 5 with dilute hydrochloric acid using Congo red or Universal indicator. The α-naphthylhydantoin acid separates on acidification and cooling. Dissolve the α-naphthylhydantoin acid in hot alcohol, filter, and then add a few drops of water until a permanent cloudiness results. The recrystallized α-naphthylhydantoin acid separates out on cooling.

The derivative separates out as white granular crystals with a decomposition point of 201-203° C. A molecular weight determination was carried out as described on page 18, which verified that the product was the desired derivative.

The equation for the chemical reaction is as follows:

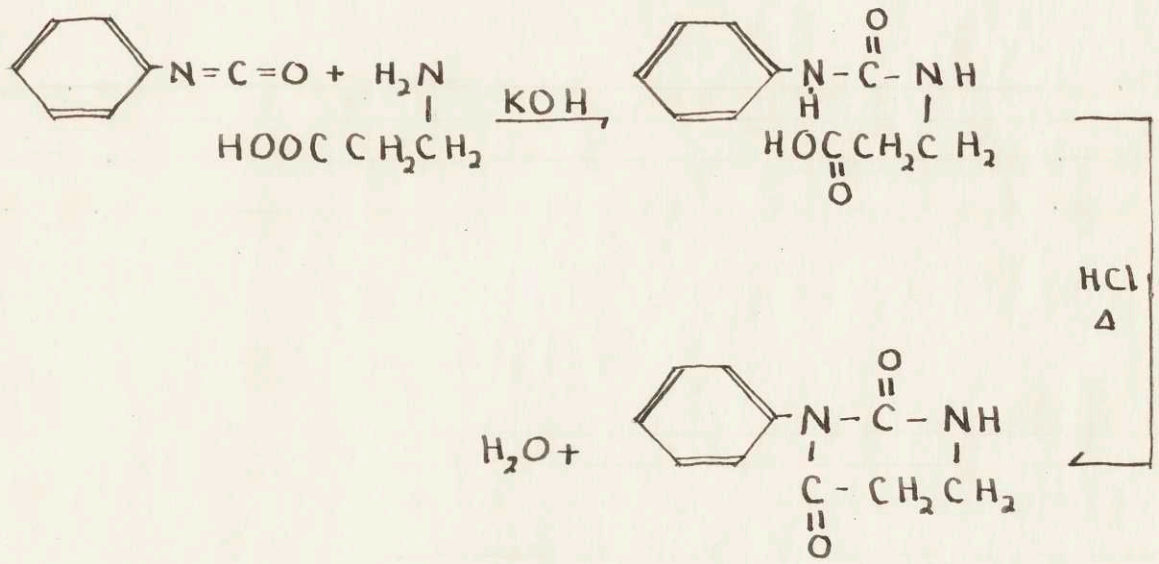


5. Phenyl hydantoin Derivative of β-Alanine

Place 200 mg. of β-alanine in an eight-inch tube and add 2 ml. of 1 N potassium hydroxide solution and 3 ml. of water. To this solution add 200 mg. of phenyl-isocyanate. Stopper the tube with a rubber stopper and shake until the odor of isocyanate disappears. Filter the insoluble diphenyl urea and acidify the filtrate with dilute hydrochloric acid to a pH of 4 to 5 using Congo red or Universal indicator. The phenylhydantoin acid separates on acidification and cooling. Filter the phenylhydantoin acid and transfer it to an eight-inch tube. Add 5 ml. of 10 per cent hydrochloric acid solution and boil gently for about 3 minutes and cool when the needles of the phenyl hydantoin separate out. Recrystallize the phenylhydantoin from dilute alcohol.

The derivative separates out as white needles with a melting point of 169.5° C. This derivative was made from a known and verified compound, phenylhydantoin acid, so that the change in melting point indicates that the desired reaction has taken place and the compound is the desired derivative. A percentage composition determination would verify that the product is the desired derivative.

The equation for the chemical reaction is as follows:



6. Molecular Weight Determination

To make certain that the products obtained were the desired derivatives, molecular weight determinations were made. The derivative is an acid and, since there are no interfering groups, titration with a standard basic solution is a method of determining the molecular weights of the products derived. The standard basic solution used was 0.1037 N sodium hydroxide. A dried sample of each derivative was weighed accurately to four decimal places. The weight of the sample taken was close to that which would require 10 ml. of the standard base to neutralize it. The derivatives were dissolved in 20 ml. of denatured alcohol except for the α-naphthyl urea derivative which was suspended in 20 ml. of alcohol as it was not soluble in the alcohol. The solutions were then diluted with distilled water. The 20 ml. of denatured alcohol required 0.5 ml. of the standard base to neutralize it and this was taken into account in the calculations. The number of ml. of the standard base required to neutralize each sample was recorded. The molecular weight of the sample can be calculated, knowing the weight of sample, the ml. of standard base, and the normality of the standard base, from the following formula:

$$\text{M.W.} = \frac{\text{wt. sample} \times 1000}{\text{ml. base} \times \text{normality base}}$$

The molecular weights obtained from the titration closely coincided with the theoretical molecular weights verifying that the products obtained were the desired derivatives.

B. SUMMARY OF DATA AND CALCULATED VALUES

p-toluenesulfonamide

1.	melting point °C	118.
2.	weight of sample	0.2218 g.
3.	ml. of NaOH	8.79
4.	theoretical molecular weight	243.
5.	titration molecular weight	243.2

benzamide

1.	melting point °C	93.
2.	weight of sample	0.1642 g.
3.	ml. of NaOH	8.3
4.	theoretical molecular weight	193.
5.	titration molecular weight	190.9

α-naphthylhydantoin acid

1.	melting point °C	201-203. d.
2.	weight of sample	0.1765 g.
3.	ml. of NaOH	6.65
4.	theoretical molecular weight	258.
5.	titration molecular weight	256.2

phenylhydantoin acid

1.	melting point °C	167.5
2.	weight of sample	0.2353 g.
3.	ml. of NaOH	10.95
4.	theoretical molecular weight	208.
5.	titration molecular weight	207.1

phenylhydantoin

1.	melting point °C	169.5

standard base solution 0.1037 N NaOH

C. SAMPLE CALCULATIONS

$$M.W. = \frac{\text{wt. sample} \times 1000}{\text{ml. base} \times \text{normality base}}$$

for the p-toluenesulfonamide derivative

$$M.W. = \frac{0.2218 \times 10000}{8.79 \times 0.1037}$$

$$= 243.2$$

D. LOCATION OF ORIGINAL DATA

The original data are located in the thesis research notebook of Arthur F. Emmett.

LITERATURE CITATIONS

1. Cheronis, N.D., and Entrikin, J.B., "Semimicro Qualitative Organic Analysis", 272-275, New York, Thomas Y. Crowell Co., 1947.

2. Fieser, L. and Fieser, M., "Organic Chemistry", 3rd edition, 422, 1009-1011, Boston, D.C. Heath and Co., 1960.

3. Shriner, R.L., Fuson, R.C., and Curtin, D.Y., "The Systematic Identification of Organic Compounds", 4th edition, 230-231, New York, John Wiley and Sons, Inc., 1956.