CHARACTERISTICS OF L-PHENYLALANINE AND ITS TETRAZOLE ANALOG

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ABSTRACT

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by Richard J. Rathsack

This research was undertaken in an effort to compare the optical behavior of L-phenylalanine and its tetrazole analog. D'Orazio (1) used the method of Lutz and Jirgensons (2,3) for studying the optical activity of L-phenylalanine, L-tyrosine and their tetrazole analogs. The amino acids were of the L-configuration and exhibited changes in rotation in acidic and basic solutions in conformity with this configuration. The tetrazole analogs exhibited rotational behavior associated with amino acids of the D-configuration.

The D,L- and L-phenylalanines were converted through a series of reactions to the D,L- and L-5-(α-amino-B-phenylethyl)tetrazoles. The amino group was first blocked with a phthaloyl group. The phthalimido derivatives were converted to the acid chloride with thionyl chloride and then treated with aqueous ammonia to form the amides. The amides were dehydrated with benzenesulfonyl chloride to form the nitriles which were treated with a metal azide to form the phthalimido tetrazoles. The phthaloyl groups were subsequently cleaved with alcoholic hydrazine.

The optical behavior of L-phenylalanine and L-5-(α-amino-B-phenylethyl)tetrazole was determined. The results

were in agreement with D'Orazio (1), in that the behavior of the L-phenylalanine was characteristic of the L-antipode while its tetrazole analog showed changes in rotation in acidic and basic solutions usually associated with the D-amino acids.

The structure and configuration of the tetrazole was verified by conversion to the starting intermediates. The degradative benzoylation of L-5-(α-amino-B-phenylethyl)-tetrazole gave L-2-(1'-benzamido-2'-phenylethyl)-5-phenyl-1,3,4-oxadiazole which subsequently was hydrolyzed with hydrochloric acid to L-phenylalanine. The recovered L-phenylalanine had the negative rotation of the starting phenylalanine but greatly reduced in magnitude. A similar result was obtained by the degradative benzoylation of L-5-(α-phthalimido-B-phenylethyl)tetrazole followed by hydrochloric acid hydrolysis. It was shown that racemization occurred during the oxadiazole formation. A possible mechanism is proposed for the racemization during the oxadiazole formation.

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3. O. Lutz and B. Jirgensons, Ber. 64, 1221-1232 (1931).

CHARACTERISTICS OF L-PHENYLALANINE
AND ITS TETRAZOLE ANALOG

By

Richard J. Rathsack

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DEDICATION

To my wife Patricia
and my son Matthew
for the many hours, days and weeks lost as a family.

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INTRODUCTION

The object of this research was to determine the specific rotations of L-phenylalanine and its tetrazole analog in various concentrations of acid and base in an effort to characterize its optical configuration. This effort was a partial reinvestigation of work previously performed by D'Orazio (1).

History

In 1848, Pasteur (2) showed that some naturally occurring amino acids are optically active by observing that asparagine rotated polarized light to the left while aspartic acid rotated it to the right. He also discovered that the addition of nitric or hydrochloric acid changed the negative rotation of asparagine to a positive value while the addition of an alkali increased the negative rotation slightly. He noted similar changes in rotation for aspartic acid. In 1880, while studying the effects of various acids upon the rotation of asparagine and aspartic acid, Landolt (3) found acetic acid to cause a large change in their rotation and sulfuric acid in an equivalent amount to exert an even greater effect. A year later, Becker (4) made a study of the specific rotations of the same compounds with increasing molecular ratios of hydrochloric acid and sodium hydroxide. He found asparagine in the presence of one equivalent of sodium hydroxide to give a specific rotation of -8.64° while in the presence of an equivalent of hydrochloric acid the specific rotation changed to +26.42°. Marshall (5) in 1896 made a similar observation on the specific rotations of aspartic acid. These investigators attributed the effects of acid and base upon the substrates as merely solvent effects. They made no attempt to relate the changes in specific rotations to any chemical reactions.

It wasn't until 1911 that other investigators (6,7,8, 9) began to distinguish the effects produced by the addition of electrolytes which might react with the optically active amino acids such as acids and bases. Wood (10) was the first to attempt a determination of dissociation constants for a number of amino acids from measurements of the optical rotatory power in the presence of various concentrations of hydrochloric acid and sodium hydroxide. In his study he found the specific rotation of leucine to be -9.84° in distilled water. When measuring the rotation in an acid solution containing a mole ratio of hydrochloric acid to leucine of 0.55, a value of +1.90° was found. This value increased with increasing mole ratios of hydrochloric acid to leucine until a mole ratio of 0.75 was reached where the specific rotation was +11.20°. Additional amounts of hydrochloric acid had little effect on the specific rotation. Similarly in an alkaline solution containing a mole ratio of sodium hydroxide to leucine of 0.54, a specific rotation of +0.58° was found. The specific rotation increased with further addition of sodium hydroxide until a mole ratio of one was reached where the specific rotation amounted to +4.00°. The effect of additional sodium hydroxide on the specific rotation of leucine was of a similar nature to the influence of hydrochloric acid.

The influence of hydrochloric acid on the specific rotations of glutamic and aspartic acids was similar to its effect on leucine. However, the influence of sodium hydroxide tended initially to decrease the specific rotation of glutamic and aspartic acids. A minimum rotation was reached when the acid salt was formed. This corresponded to a mole ratio of alkali to the acids of slightly greater than one. Increasing amounts of alkali increased the specific rotation in a manner similar to that accompanying the addition of acid. A maximum was reached at a mole ratio slightly greater than two. Further addition of alkali gave essentially no change in the specific rotation. Fischer and Raske (11) had previously made a similar observation with serine and alanine.

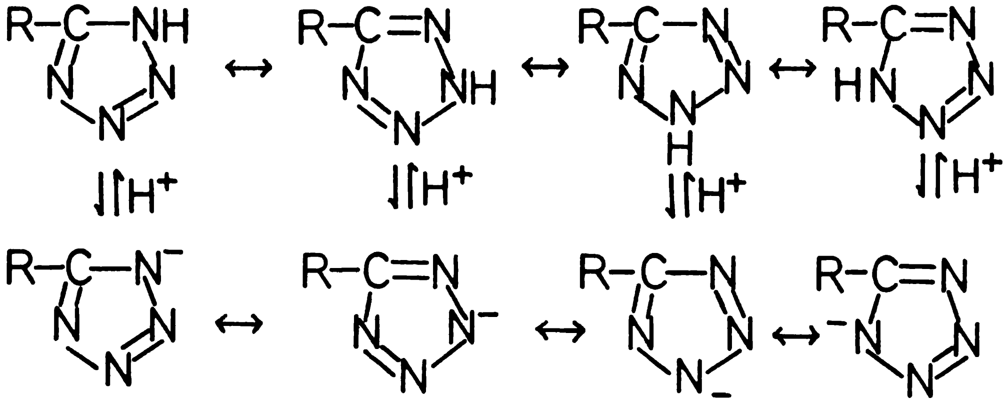
It remained, however, for Lutz and Jirgensons (12,13) to demonstrate that all naturally occurring amino acids exhibit similar behavior. These investigators used the curves which they obtained by plotting the specific rotation against the ratios of alkali or acid to the amino acids, as a means of deciding whether a given naturally occurring amino acid belonged to the D- or L-configuration series. This was achieved by comparing the curves with that of an amino acid of known configuration. The amino acid standard used for this purpose whose configuration relationship had been established by synthetic means was aspartic acid. In using this technique, the acid branch of the optical rotation curve was found to be most characteristic. If the rotation changed towards the positive direction with increasing acid concentrations, then the amino acid was designated as the L-antipode. On the other hand, if the rotation changed towards the negative direction, it was designated as the D-antipode. Their studies also indicated that the concentration of amino acid as well as the hydrochloric acid to amino acid ratio had a distinguishing effect on the magnitude of the specific rotation.

The variation of specific rotation with pH has been utilized by Levene and associates (14,15) as a means for estimating dissociation constants of various amino acids. Miller and Andrews (16) studied the optical activity of L-arginine under a variety of conditions and calculated dissociation constants. Since the specific rotation of the neutral molecule usually differs from that of the ions, and the observed rotation is an additive function of the rotations of the ions and the undissociated substances participating in electrolytic equilibrium, it has been possible in many instances to correlate the rotation curves with dissociation constants of the given substance. Curves for L-alanine, L-leucine, aspartic and glutamic acids have been obtained by Vellinger (17) from this standpoint.

Herbst and Grotta (18) investigated the effect of acid and alkali on the rotation of L-arginine and found this amino acid to exhibit the characteristics ascribed to the other amino acids of the L-configuration series.

In 1937, Akasi (19) used the technique of Lutz and Jirgensons to further characterize two amino acid derivatives, octopine and iso-octopine. Later Herbst and Swart (20) reinvestigated these effects and found somewhat different results. The curves for both compounds were qualitatively very similar but showed pronounced quantitative differences. A number of factors influence the magnitude of the specific rotation of amino acids, among these being temperature, concentration, pH, solvents and presence of salts in solutions. These factors together with the rather difficult solubility in water of some of the amino acids probably explains the lack of concordant results found in the literature on the specific rotations of the amino acids.

It has been shown that tetrazole derivatives in which there is a hydrogen atom attached to the ring nitrogens,

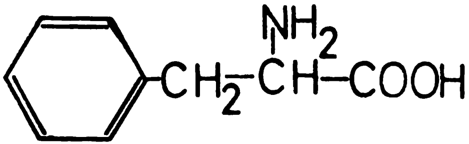


generally behave as acidic substances (21,22,23). When R is an alkyl group the tetrazole ring exhibits slightly weaker acidic properties than if R was attached to a carboxylic acid group. When R is an aryl group, the tetrazole ring exhibits slightly stronger acidic properties than if R was attached to a carboxylic acid group. Herbst and Wilson (24) showed that 5-aryltetrazoles appear to be stronger acids than the corresponding substituted benzoic acids with the exception of the *ortho* substituted compounds.

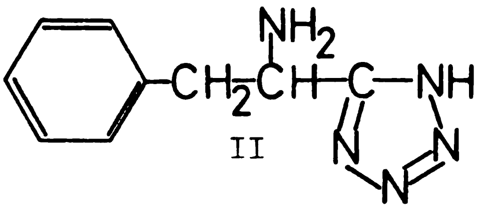
In view of the acidic character of the 5-substituted tetrazoles, a study was undertaken to compare the effects of various alkali and acid concentrations on the specific rotation of some optically active amino acids and their tetrazole analogs[1]. During this investigation, D'Orazio found that L-phenylalanine and L-tyrosine exhibited a curve which was characteristic of other amino acids of the L-configuration series. However, their tetrazole analogs gave a curve which was inverted and characteristic of the D-antipodes of the amino acids. This incongruity prompted a reinvestigation of this phenomenon.

DISCUSSION

The structures of phenylalanine (I) and its tetrazole analog (II) are quite similar. The only differences in their structures are the carboxyl and tetrazolyl groups



I



II

attached to the asymmetric carbon atom. McManus and Herbst (25) prepared the tetrazole analog of D,L-phenylalanine. They found the tetrazole analog to be very similar to the amino acid in both physical and chemical properties. The tetrazole was only slightly soluble in water but more readily soluble in dilute, aqueous acids and alkalies. Determination of the dissociation constants showed the tetrazolyl group to be a slightly weaker acid than the carboxyl group of the amino acid. They also noted that the amino group of the tetrazole analog was less basic than the amino group in the phenylalanine.

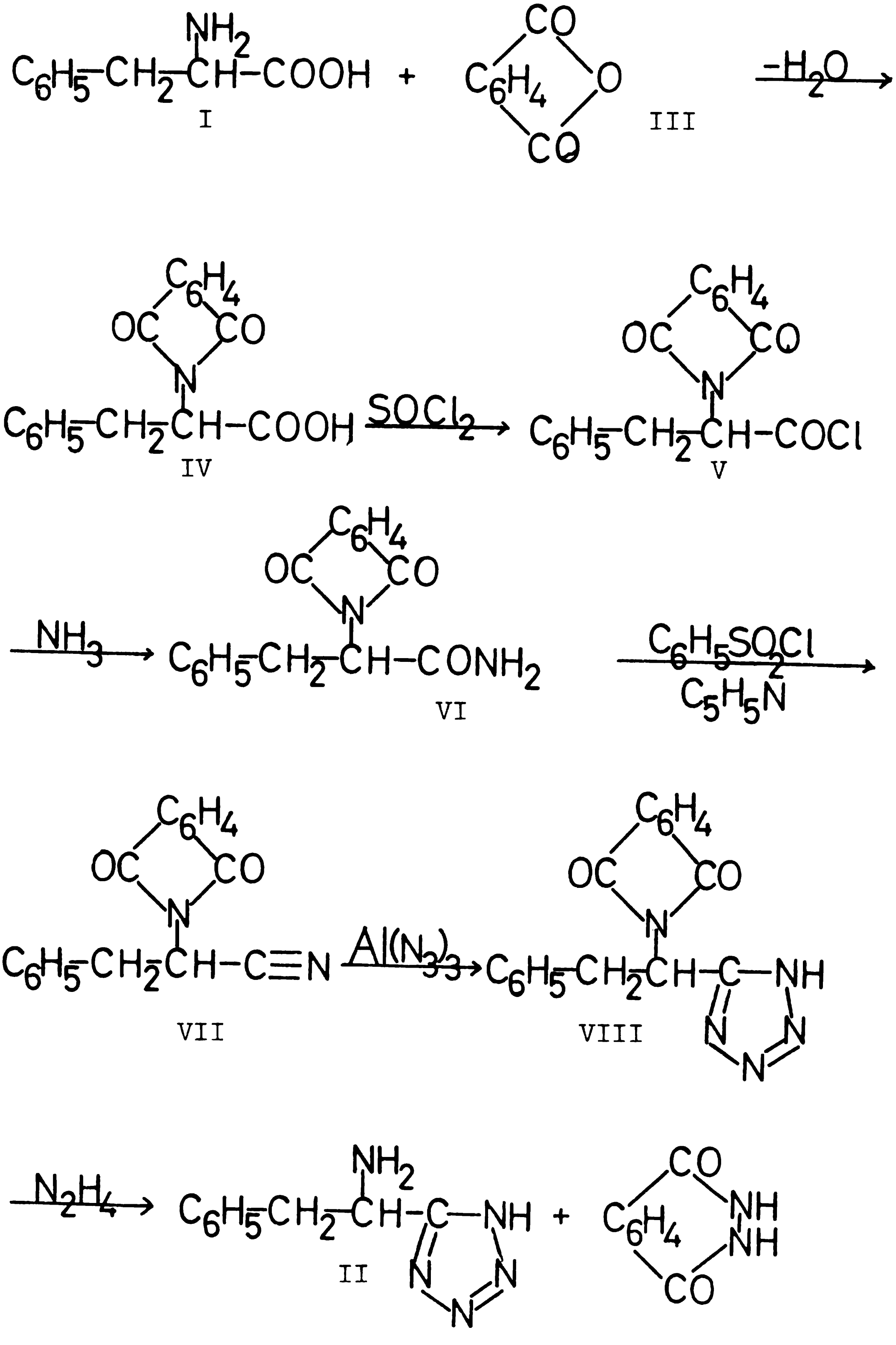
Tetrazole Preparation.

McManus and Herbst (25) synthesized the tetrazole analog by a sequence of reactions. First, they fused phthalic anhydride with phenylalanine which provided a blocking group on the amino moiety. Next, they prepared the acid chloride by treating with phosphorus pentachloride. The acid chloride was then converted to the amide by reaction with aqueous ammonia. The amide was dehydrated with benzenesulfonyl chloride in pyridine to form the nitrile. The tetrazole was subsequently prepared through the reaction of the nitrile with sodium azide.

D'Orazio (1) prepared the tetrazole analog of L-phenylalanine. He followed a scheme similar to that of McManus and Herbst (25).

Since the purpose of this research was the measurement of the optical activity of the tetrazole analog of L-phenylalanine under various conditions, it was important to prepare this compound in the most optically pure form possible. Consequently, the preparation of the tetrazole analog of D,L-phenylalanine was initially undertaken to become familiar with the synthesis.

The tetrazole analog of phenylalanine was prepared according to the scheme outlined on page 9. The phthaloyl derivative of D,L-phenylalanine was prepared by fusion of the amino acid with phthalic anhydride at 180°C. However, preparation of the phthaloyl derivative of L-phenylalanine had to be carried out at 145-150°C. to avoid racemization as demonstrated by Peterson and Niemann (26). The conversion of D,L- and L-α-phthalimido-B-phenylpropionic acids to the corresponding acid chlorides may be accomplished by reaction with phosphorus pentachloride (27,28). However, Peterson and Niemann (26) showed that the same transformation can be carried out with a milder reagent, thionyl chloride. This


I
III
$-H_2O$
IV
$SOCl_2$
V
NH_3
VI
$C_6H_5SO_2Cl$
C_5H_5N
VII
$Al(N_3)_3$
VIII
N_2H_4
II

latter method of preparation gave a ninety-four per cent yield of the L-α-phthalimido-B-phenylpropionyl chloride with retention of optical activity. The amides were then prepared by treating the acid chlorides with aqueous ammonia.

Peterson and Niemann (26) attempted to dehydrate D,L-α-phthalimido-B-phenylpropionamide to the corresponding nitrile with thionyl chloride, phosphorus oxychloride, phosphorus pentachloride in phosphorus oxychloride and phosphorus pentachloride in chloroform. In each case only the starting material could be recovered. They found, however, that benzenesulfonyl chloride in pyridine dehydrated the L-α-phthalimido-B-phenylpropionamide to the nitrile in a ninety per cent yield without evidence of significant racemization. They used a four-to-one mole ratio of the benzenesulfonyl chloride to amide. D'Orazio (1) found it possible to modify this by using a three-to-one mole ratio without appreciably affecting the yield. The D,L- and L-α-phthalimido-B-phenylpropionitriles were obtained in ninety-nine and ninety-two per cent yields, respectively, using the modified method of D'Orazio.

The tetrazole was prepared by treating the nitrile with aluminum azide. The aluminum azide was generated *in situ* from sodium azide and anhydrous aluminum chloride in anhydrous tetrahydrofuran. D'Orazio noted that difficulty was generally encountered if the aluminum chloride-tetrahydrofuran mixture became dark. Consequently, he devised the method whereby the tetrahydrofuran was initially cooled in an ice bath and then added slowly to cooled aluminum chloride. This method gave a more workable product. An eighty-four per cent yield of the tetrazole was achieved by this procedure.

The amino tetrazole was obtained by cleaving the phthaloyl group with alcoholic hydrazine hydrate. Sheenan and co-workers (28) demonstrated that the phthaloyl group may be cleaved from the L-α-phthalimido-B-phenylpropionic acid with alcoholic hydrazine hydrate. The recovered L-phenylalanine had an unchanged optical rotation.

Determination of Configuration.

Most of the measurements of optical activity in the past have involved the use of light from the sodium flame. In many instances this light source was difficult to obtain with a constant intensity of illumination and has suffered from being insufficiently monochromatic for very precise work. Within recent years, with the development of the mercury vapor lamp, the green and yellow lines (546.1 and 578 mu, respectively) of the mercury spectrum have largely replaced the sodium line (589.3 mu) as standards for accurate polarimetric work.

D'Orazio carried out his measurements of L-phenylalanine and its tetrazole analog on a Rudolph Precision Polarimeter, model 70, using a sodium light source. This polarimeter relies on the judgement of its user to adjust the analyzer until he finds the two fields of equal intensity.

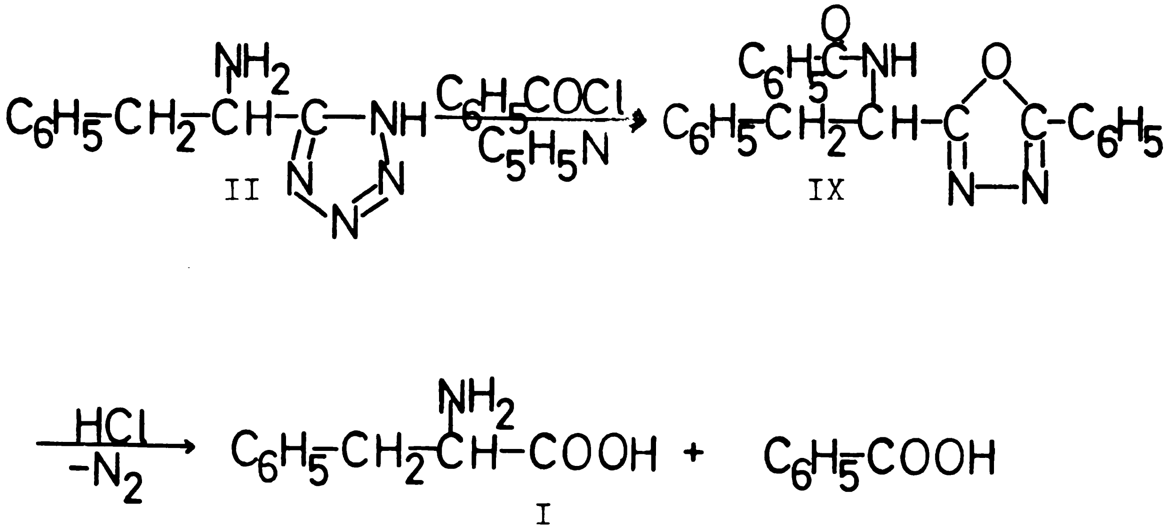
Consequently, the accuracy is subject to human error. This source of error was largely eliminated in the present work by making measurements of optical activity with a Zweiss photoelectric polarimeter using consistently the wavelength of the mercury line of 578 mu. This instrument allowed placement of the solutions in the polarimeter and direct photoelectric measurement of optical activity.

The optical activity of L-phenylalanine was measured in various concentrations of acid and base and the specific rotations determined. The results are listed in Table I. A plot of the specific rotation against the molar ratios of acid or base to amino acid was drawn. The specific rotation changed, with increasing acid concentration, toward the positive direction. According to Lutz and Jirgensons (12,13) this is characteristic of amino acids of the L-configuration. The same technique was used for the tetrazole analog. The results are given in Table II. The curve drawn for L-5-(α-amino-B-phenylethyl)tetrazole shows specific rotation becoming less positive (changing toward the negative) with increasing acid concentration. This peculiar phenomenon was also noted by D'Orazio.

Confirmation of Configuration.

Since the L-5-(α-amino-B-phenylethyl)tetrazole demonstrated behavior characteristic of a D-configuration by the method of Lutz and Jirgensons, it seemed cogent that the tetrazole be converted to the original amino acid and the specific rotation of the latter redetermined.

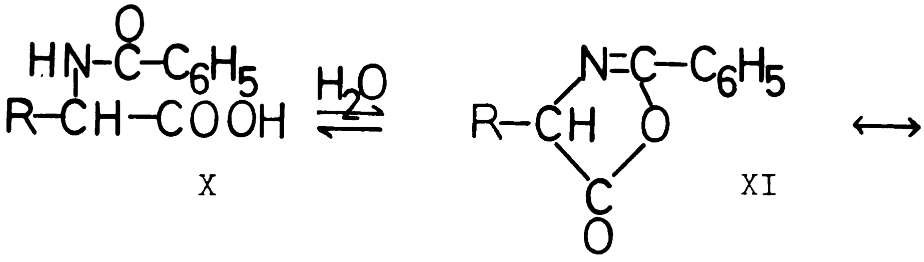
D'Orazio had converted the optically active amino tetrazole to the oxadiazole by treatment with benzoyl chloride and subsequently hydrolyzed the oxadiazole to the amino acid used as the starting material.



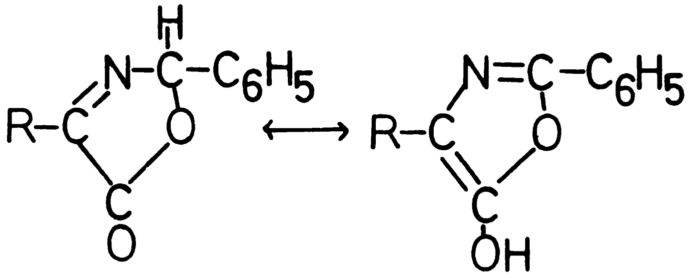
This procedure was based on work by Huisgen and co-workers (29,30,31) who found that 5-substituted tetrazoles would react, in the presence of pyridine, with a variety of acyl halides to form 2,5-disubstituted-1,3,4-oxadiazoles. D'Orazio reasoned that the recovered phenylalanine should have the same sign and magnitude of rotation as the original amino acid. The phenylalanine recovered in this fashion did have the same sign of rotation as the starting material, but the optical activity had been almost completely lost. It seemed likely that racemization occurred at some point in this process.

Degradation of α-Amino-B-phenyltetrazole.

The possibility of racemization taking place during the oxadiazole formation appears likely. It has been known that racemization takes place with acyl amino acids in an alkaline media with excess acylating agent (32). A similar

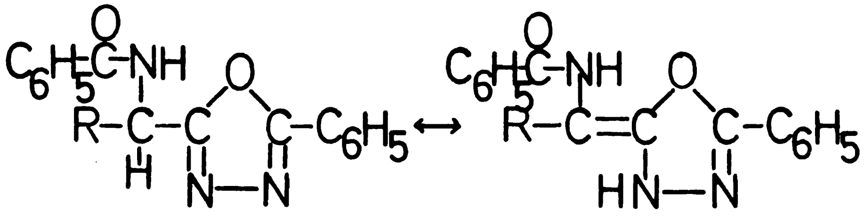


X XI



XIIa XIIb

situation may be envisioned for the racemization of an acylated amino tetrazole. Another possibility for racemization may exist after the formation of the oxadiazole. The shift of a proton in an alkaline media appears feasible



XIIIa XIIIb

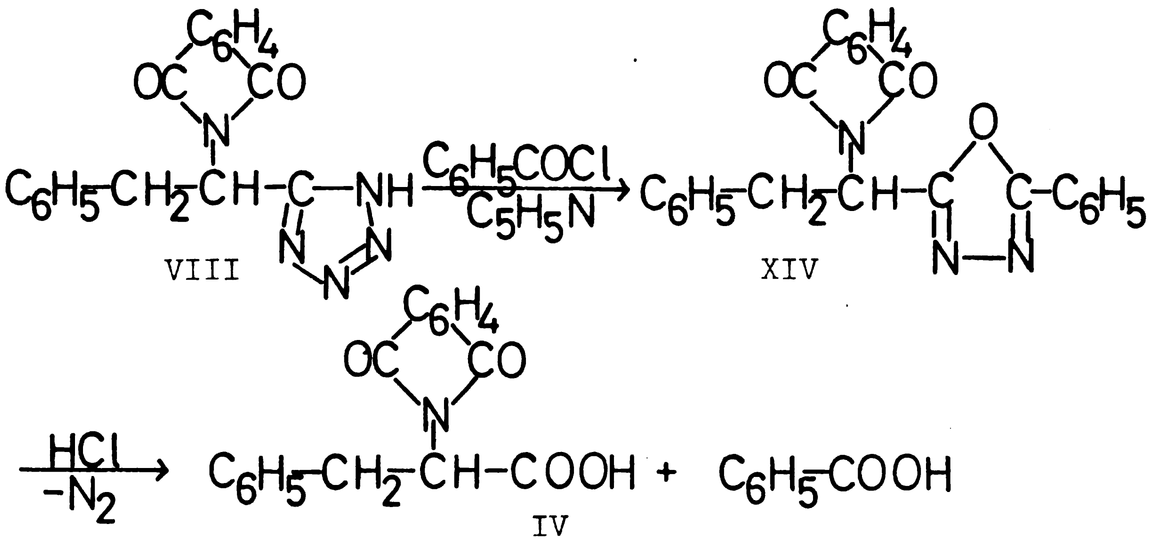
in forming the oxadiazole intermediate (XIIIb). Still another possibility to consider is racemization during the acid hydrolysis of the oxadiazole. A series of experiments was designed to determine where racemization occurred.

In the degradative benzoylation of the tetrazole, two moles of benzoyl chloride are needed per mole of tetrazole. D'Orazio carried out this reaction using two moles of benzoyl chloride per mole of amino tetrazole in a large excess of pyridine. It appears that the large excess of pyridine may have caused partial racemization of the oxadiazole. Two reaction systems were investigated with D,L-5-(α-amino-B-phenylethyl)tetrazole. The reaction was first performed according to the conditions used by D'Orazio. A second experiment was performed in a similar fashion except that equimolar quantities of benzoyl chloride and pyridine were used. The yields were eighty and seventy-five per cent, respectively. The degradative benzoylation of L-5-(α-amino-B-phenylethyl)tetrazole was carried out using equimolar quantities of benzoyl chloride and pyridine. A seventy per cent yield of L-2-(1'-benzamido-2'-phenylethyl)-5-phenyl-1,3,4-oxadiazole was obtained with a specific rotation similar to that found by D'Orazio.

D'Orazio hydrolyzed the oxadiazole to phenylalanine with concentrated hydrochloric acid at reflux during a twelve hour period. The same result was achieved by refluxing the oxadiazole with six molar hydrochloric acid over a six hour period. A seventy-seven per cent yield was obtained by this procedure while D'Orazio reported only a sixty-seven per cent yield. However, the specific rotation of the L-phenylalanine was similar to that obtained by D'Orazio. An attempt to hydrolyze the oxadiazole with three molar hydrochloric acid was unsuccessful. Although these results do not exclude the possibility of racemization during the acid hydrolysis step, they suggest this as the least likely stage for racemization.

The amino tetrazole has an unprotected amino group in which the protons on the amino-nitrogen enter into reaction during the degradative benzoylation. The possibility of eliminating participation of the benzamido group in racemization during the degradation of the amino tetrazole led us to consider the degradative benzoylation of the phthalimido tetrazole. In L-5-(α-phthalimido-B-phenylethyl)tetrazole the amino group is completely blocked with a phthaloyl moiety.

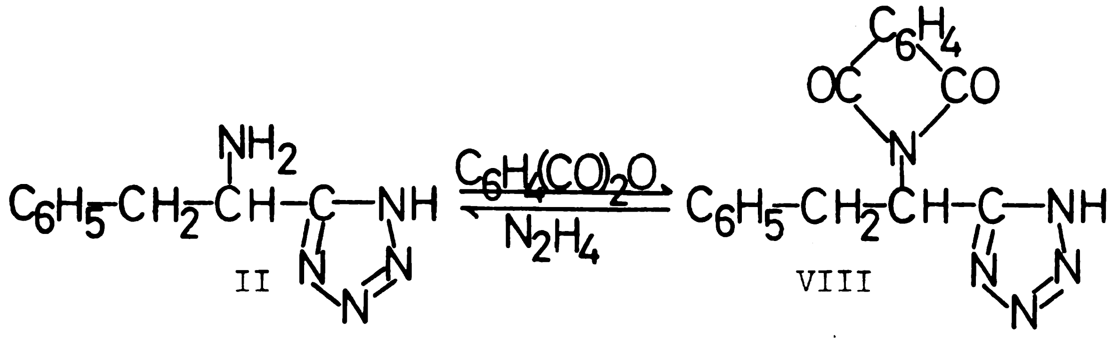
The phthalimido tetrazole was converted to the oxadiazole in a similar fashion to that used with the amino tetrazole except that only one mole of benzoyl



VIII XIV IV

chloride was needed per mole of tetrazole. The benzoyl chloride and pyridine were used in equimolar proportions. The resulting L-2-(1'-phthalimido-2'-phenylethyl)-5-phenyl-1,3,4-oxadiazole was isolated as a crystalline solid with a specific rotation of -138°. The oxadiazole was subsequently hydrolyzed with six molar hydrochloric acid to α-phthalimido-B-phenylpropionic acid having a specific rotation of -76°. The specific rotation was one-third that of the phthalimido-B-phenylpropionic acid obtained from phthalic anhydride and L-phenylalanine.

This further posed the possibility that partial racemization had occurred during cleavage of the phthaloyl group with hydrazine hydrate. To verify this possibility, the amino tetrazole was fused with phthalic anhydride in a manner similar to that used for the preparation of the phthalimido-B-phenylpropionic acid. The resulting phthalimido tetrazole was obtained with essentially no loss of rotation. Since the amino tetrazole had been prepared from the optically active phthalimido tetrazole by hydrazinolysis, the possibility of racemization during the latter step was



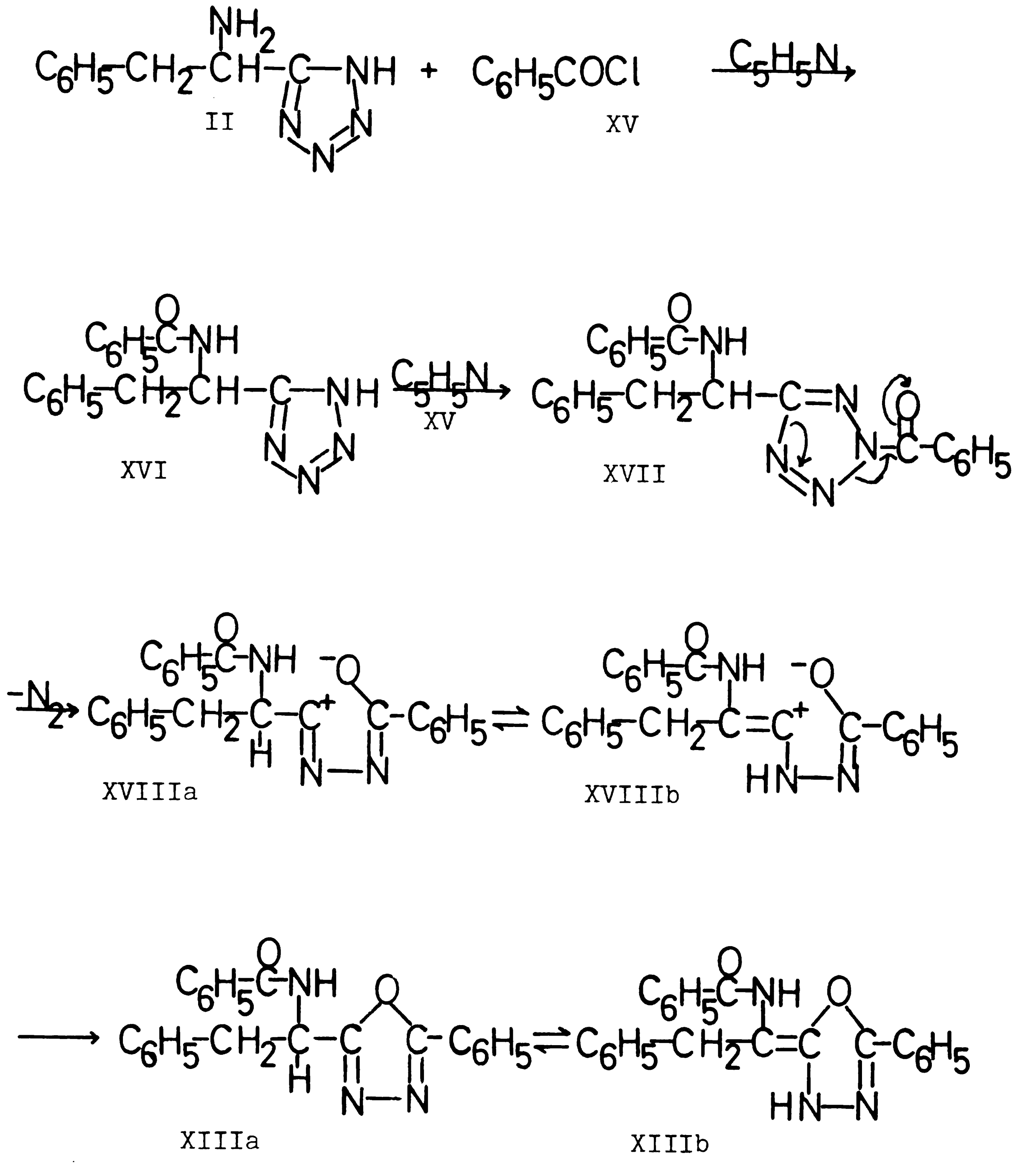
effectively eliminated.

It appears that partial racemization does occur during the oxadiazole formation.

Possible Mechanism for Racemization During Oxadiazole Formation.

A plausible mechanism for the formation of the oxadiazole is shown on the next page. The benzoyl group would initially attack the amino group forming the benzamide intermediate XVI. The second step requires the acylation of the tetrazole ring at the two position by a second molecule of benzoyl chloride. This second step has been proposed by Huisgen and co-workers (29,30,31) and substantiated by Herbst (33). The intermediate XVII shows the electron shifts resulting in the elimination of the nitrogen at the 3,4- (or 1,2-) positions of the tetrazole ring with the subsequent formation of the ionic intermediate XVIIIa. This intermediate XVIIIa can then recyclize to form the oxadiazole.

The racemization could occur during either the formation of the ionic intermediate XVIIIb or the oxadiazole intermediate XIIIb simply by a proton shift. The degree of racemization would be governed by the rate of tautomeric shift in either case.


II
XV
C_5H_5N
XVI
C_5H_5N
XV
XVII
$-N_2$
XVIIIa
XVIIIb
XIIIa
XIIIb

EXPERIMENTAL[1,2,3]

I. The Preparation of D,L-5-(α-Amino-B-phenylethyl)tetrazole.

A. D,L-α-Phthalimido-B-phenylpropionic Acid.

In a 100 ml. round-bottomed resin flask equipped with a stirrer and reflux condenser were placed 25 g. (0.152 mole) of D,L-phenylalanine and 22.4 g. (0.152 mole) of phthalic anhydride. While stirring the mixture, the flask was immersed in an oil bath heated to 180°C. for forty-five minutes. The fused melt was partially dissolved in 100 ml. of distilled methanol and filtered. The filtrate was diluted with 100 ml. of hot water, the solution heated until all the material dissolved and allowed to cool to room temperature. The colorless platelets which crystallized from solution were collected by filtration and dried under reduced pressure for four hours at 60°C. The solid material remaining from the initial methanol extraction was dissolved in an additional 100 ml. of distilled methanol and filtered. The filtrate was diluted with 100 ml. of hot water, heated until all the solid had dissolved and allowed to cool to room temperature. The yield of D,L-α-phthalimido-B-phenylpropionic acid amounted to 33.1 g. (73.8%), m.p. 178-180°C.

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[1] Elemental Analyses by the Dow Chemical Company, Midland, Michigan.

[2] Melting points were taken in open capillary tubes and are uncorrected.

[3] All infrared spectra taken as KBr pellets.

The infrared spectrum was consistent with the proposed structure.

J. Sheenan and V. Frank (27) reported a melting point of 177.5-179°C., while D'Orazio (1) reported a melting point of 175-176°C., for this product.

Analysis.

Calculated for $C_{17}H_{13}NO_4$: C, 69.2; H, 4.4; N, 4.7.

Found: C, 68.85; H, 4.49; N, 4.73.

B. D,L-α-Phthalimido-B-phenylpropionyl Chloride.

In a 300 ml. round-bottomed, three-necked flask equipped with a stirrer, reflux condenser, addition funnel and heating mantle were placed 25 g. (0.0848 mole) of D,L-α-phthalimido-B-phenylpropionic acid and 250 ml. of anhydrous benzene. The mixture was stirred and heated at reflux temperature while 10.7 g. (0.09 mole) of thionyl chloride was added drop-wise over a ten minute period. The reaction mixture was stirred and refluxed fifteen minutes before an additional 5 g. of thionyl chloride was added over a five minute period. The reaction mixture became homogeneous and clear after the second thionyl chloride addition and was refluxed an additional thirty minutes. The benzene and thionyl chloride were removed under reduced pressure. The residue was taken up in 100 ml. of fresh, anhydrous benzene. When 50 ml. of solvent was removed under reduced pressure, a white solid precipitated. It was collected by filtration and dried under reduced pressure at 60°C. for four hours. The material weighed 8.1 g.

(32.4% of theory), m.p. 175-178°C. The infrared spectrum was identical with that of the starting material.

The filtrate was evaporated to dryness leaving the acid chloride as a white solid residue, m.p. 116-119°C., which weighed 15.1 g. (57% yield). The infrared spectrum was consistent with the proposed structure. The product appeared to be slightly contaminated with the starting acid which accounts for the low melting point and chlorine value in the elemental analysis.

Sheenan and Frank (27) reported a melting point of 124-126°C. for the acid chloride, while D'Orazio (1) reported a melting point of 133-136°C.

Analysis.

Calculated for $C_{17}H_{12}NO_3Cl$:	C, 65.2; H, 3.8; N, 4.5; Cl, 11.2.
Found:	C, 66.0; H, 4.2; N, 4.4; Cl, 7.5.

C. D,L-α-Phthalimido-B-phenylpropionamide.

In a 500 ml. round-bottomed, three-necked flask equipped with a stirrer and immersed in an ice bath was placed 100 ml. of concentrated ammonium hydroxide. After stirring and cooling to 0°C., 12 g. (0.038 mole) of D,L-α-phthalimido-B-phenylpropionyl chloride was added as a solid and the mixture stirred for thirty minutes. The solid was filtered, washed with 100 ml. of cold water and dried under reduced pressure forty-eight hours at 60°C. The crude amide weighed 7.8 g. (70% yield), m.p. 232-234°C.

The infrared spectrum was consistent with the proposed structure.

Peterson and Nieman (26) reported a melting point of 236-237°C. for the amide, while D'Orazio (1) reported a melting point of 232-233°C.

Analysis.

Calculated for $C_{17}H_{14}N_2O_3$: C, 68.7; H, 4.7; N, 9.4.

Found C, 68.4; H, 4.9; N, 9.4.

D. D,L-α-Phthalimido-B-phenylpropionitrile.

In a 50 ml. round-bottomed, three-necked flask equipped with a stirrer, reflux condenser and dropping funnel were placed 5 g. (0.017 mole) of D,L-α-phthalimido-B-phenylpropionamide and 18 ml. of pyridine. To this was added 9.0 (0.051 mole) of benzenesulfonyl chloride. The mixture was refluxed fifteen minutes and then cooled to room temperature. The solution was poured into 50 ml. of ice water with vigorous stirring. The solid that precipitated was collected by filtration, washed with 50 ml. of cold water and dried under reduced pressure for four hours at 60°C. The crude nitrile weighed 4.6 g. (99% yield), m.p. 129-131°C. Recrystallization from 125 ml. of anhydrous methanol raised the melting point to 135-136°C. The infrared spectrum was consistent with the proposed structure.

Peterson and Nieman (26) reported a melting point of 134-135°C. for the nitrile as did D'Orazio (1).

Analysis.

Calculated for $C_{17}H_{12}N_2O_2$: C, 73.9; H, 4.3; N, 10.1.
Found: C, 73.8; H, 4.5; N, 9.9.

E. D,L-5-(α-Phthalimido-B-phenylethyl)tetrazole.

In a 50 ml. round-bottomed, three-necked flask equipped with a stirrer, reflux condenser, dropping funnel and heating mantle were placed 2 g. (0.007 mole) of D,L-α-phthalimido-B-phenylethylpropionitrile and 1.4 g. (0.021 mole) of sodium azide. While stirring the mixture a solution of 1.07 g. (0.008 mole) of anhydrous aluminum chloride in 20 ml. of anhydrous tetrahydrofuran was added. The solution of aluminum chloride in tetrahydrofuran was prepared by slowly adding cold tetrahydrofuran to the aluminum chloride in a flask immersed in an ice bath. The reaction mixture was stirred and refluxed twenty-four hours. The tetrahydrofuran was distilled while water was added at a rate such as to maintain a constant volume. The mixture was cooled to room temperature, filtered and the aluminum salt dried under reduced pressure for twenty-four hours at 60°C.

The dried aluminum salt was ground into fine particles and suspended in 25 ml. of water. While stirring, 3.5 ml. of 28% hydrochloric acid was added. The mixture was stirred thirty minutes. The product was collected by filtration, washed with 50 ml. of cold water and dried under reduced pressure for twenty-four hours at 60°C. The crude tetrazole weighed 2.3 g. (99% yield), m.p. 213-216°C. The infrared spectrum was consistent with the proposed structure.

McManus (25) reported a melting point of 212.5-213°C. for the tetrazole, while D'Orazio (1) reported a melting point of 213-214°C.

Analysis.

Calculated for $C_{17}H_{13}N_5O_2$: C, 63.94; H, 4.10; N, 21.93.
Found: C, 63.75; H, 4.35; N, 21.13.

F. *D,L-5-(α-Amino-B-phenylethyl)tetrazole*.

In a 50 ml. round-bottomed, single necked flask equipped with a reflux condenser and heating mantle were placed 1.0 g. (0.00314 mole) of D,L-5-(α-phthalimido-B-phenylethyl)tetrazole and 14 ml. of absolute ethanol. To this was added 4 ml. of a 1M ethanolic hydrazine solution. The mixture was refluxed two hours, cooled to room temperature and the ethanol evaporated under reduced pressure. The residue was treated with 8 ml. of 2N hydrochloric acid and the suspension was warmed on a steam bath for fifteen minutes. The warm mixture was filtered and the filtrate neutralized with concentrated ammonium hydroxide to a pH of 6. The resulting white precipitate was collected by filtration, washed with 20 ml. of water and dried under reduced pressure for twenty-four hours at 60°C. The yield of product was 0.5 g. (85%), m.p. 264-267°C. with decomposition. The infrared spectrum was consistent with the proposed structure.

McManus (25) reported a melting point of 271-272°C. with decomposition for this product, while D'Orazio (1) reported a melting point of 270-271°C. with decomposition.

II. The Preparation of L-5-(α-Amino-B-phenylethyl)tetrazole.

A. L-α-Phthalimido-B-phenylpropionic Acid.

In a 100 ml. round-bottomed, three-necked flask equipped with a stirrer, reflux condenser and stopper was placed a mixture of 16.5 g. (0.1 mole) of L-phenylalanine[1,2] and 14.8 g. (0.1 mole) of phthalic anhydride. The reaction flask was immersed in an oil bath heated to 145°C. for forty-five minutes. The melt was allowed to cool to room temperature and was dissolved in 50 ml. of methanol. The solution was filtered. An additional 50 ml. of anhydrous methanol was used in dissolving the remaining product and washing out the reaction flask. The combined methanolic solutions were diluted with 100 ml. of hot water, heated until all the solid had dissolved and allowed to cool to room temperature. The white crystalline product was collected by filtration, washed with 50 ml. of water and dried at 120°C. for four hours. The L-α-phthalimido-B-phenylpropionic acid weighed 25 g. (85% yield), m.p. 185-186°C., $[\alpha]^{25}_{578} = -222.6°$, C = 2.219 in absolute ethanol. The infrared spectrum was nearly identical with that of D,L-α-phthalimido-B-phenylpropionic acid.

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[1] Nutritional Biochemical Corporation.

[2] $[\alpha]^{25}_{578} = -34.2°$, C = 2.054 in H_2O.

Sheenan (28) reported a melting point of 183-185°C., $[\alpha]_D^{25}$ = -212°, C = 1.92 in absolute ethanol while D'Orazio (1) reported a melting point of 177-179°C., $[\alpha]_D^{25}$ = -206°, C = 1.92 in absolute ethanol for the L-α-phthalimido-B-phenylpropionic acid.

B. L-α-Phthalimido-B-phenylpropionyl Chloride.

In a 300 ml. round-bottomed, three-necked flask equipped with a reflux condenser, stirrer, addition funnel and heating mantle were placed 25 g. (0.0848 mole) of L-α-phthalimido-B-phenylpropionic acid and 100 ml. of anhydrous benzene. The mixture was stirred and heated at reflux temperature while 11.9 g. (0.1 mole) of thionyl chloride was added drop-wise over a ten minute period. The reaction mixture was refluxed for an additional hour during which 5 g. more of thionyl chloride was added to insure complete reaction. The clear solution was evaporated under reduced pressure. The residue was redissolved in 50 ml. of fresh anhydrous benzene and the benzene removed under reduced pressure. The crude acid chloride weighed 25 g. (94% yield), m.p. 81-83°C., $[\alpha]_{578}^{25}$ = -197.1°, C = 2.339 in benzene. The infrared spectrum was nearly identical to that of D,L-α-phthalimido-B-phenylpropionyl chloride.

Sheenan (28) reported a melting point of 83-84°C., $[\alpha]_D^{25}$ = -197°, C = 2.256 in benzene for the acid chloride, while D'Orazio (1) reported a melting point of 83-85°C., $[\alpha]_D^{25}$ = -198°, C = 2.256 in benzene.

C. L-α-Phthalimido-B-phenylpropionamide.

In a 500 ml. round-bottomed, two-necked flask equipped with a stirrer and immersed in an ice bath was placed 200 ml. of concentrated ammonium hydroxide. After cooling to 0°C., 25 g. (0.08 mole) of L-α-phthalimido-B-phenylpropionyl chloride was added as a solid to the cooled ammonium hydroxide solution and the mixture was stirred for thirty minutes. The product was separated by filtration, washed with 100 ml. of cold water and dried in an oven at 120°C. for sixteen hours. The crude amide weighed 20 g. (87% yield) and was recrystallized from absolute ethanol, m.p. 222-225°C. The infrared spectrum was identical with that of D,L-α-phthalimido-B-phenylpropionamide.

Peterson and Nieman (26) reported a melting point of 226-227°C. for the amide, while D'Orazio (1) reported a melting point of 217-218°C.

D. L-α-Phthalimido-B-phenylpropionitrile.

In a 250 ml. round-bottomed, single necked flask equipped with a reflux condenser and heating mantle were placed 15 g. (0.051 mole) of L-α-phthalimido-B-phenylpropionamide, 54.5 ml. of pyridine and 27 g. (0.153 mole) of benzenesulfonyl chloride. The mixture was heated to a gentle reflux for ten minutes, cooled to room temperature and poured into 100 ml. of ice water with vigorous stirring. A white solid which precipitated was collected by filtration and recrystallized from 350 ml. of absolute methanol from which it separated as colorless leaflets, yield 13 g. (92.3%), m.p. 150-152°C., $[\alpha]_{578}^{25} = -109.5°$, C = 2.387 in chloroform. The infrared spectrum was identical with that of D,L-α-phthalimido-B-phenylpropionitrile.

Peterson and Nieman (26) reported a melting point of 150-153.2°C., $[\alpha]_{D}^{25} = -103°$, C = 2.0 in chloroform for the nitrile, while D'Orazio (1) reported a melting point of 150-151°C., $[\alpha]_{D}^{25} = -102°$, C = 2.0 in chloroform.

E. L-5-(α-Phthalimido-B-phenylethyl)tetrazole.

In a 300 ml. round-bottomed, three-necked flask equipped with a reflux condenser, stirrer, addition funnel and heating mantle were placed 12 g. (0.0435 mole) of L-α-phthalimido-B-phenylpropionitrile and 8.5 g. (0.1305 mole) of sodium azide. While stirring, a solution of 6.4 g. (0.0478 mole) of anhydrous aluminum chloride in 150 ml. of dry tetrahydrofuran was added to the reaction mixture. The reaction mixture was refluxed twenty-four hours. The tetrahydrofuran was distilled while water was added at a rate such as to maintain a constant volume in the reaction flask. The reaction mixture was allowed to cool to room temperature, the solid product collected by filtration, washed with 100 ml. of cold water, and dried at 120°C. for twelve hours. The crude aluminum salt was ground into fine particles and suspended in 130 ml. of water. To this suspension was added 15 ml. of concentrated hydrochloric acid and the mixture was stirred for twenty minutes. The crude product was isolated by filtration, washed with 200 ml. of cold water and recrystallized from a mixture of 150 ml. of methanol and 150 ml. of water. The product weighed 13 g. (84% yield), m.p. 186-188°C., $[\alpha]_{578}^{25} = -205°$, C = 3.347 in absolute ethanol. The infrared spectrum was identical with that of the D,L-5-(α-phthalimido-B-phenylethyl)tetrazole.

D'Orazio (1) reported a melting point of 182-183°C., $[\alpha]_{D}^{25} = -139.9°$, C = 4.0 in absolute ethanol for the tetrazole.

F. L-5-(α-Amino-B-phenylethyl)tetrazole.

In a 250 ml. round-bottomed, single necked flask equipped with a reflux condenser and heating mantle were placed 7 g. (0.0219 mole) of L-5-(α-phthalimido-B-phenylethyl)tetrazole and 65 ml. of absolute ethanol. To this was added 27 ml. of 1M ethanolic hydrazine and the mixture refluxed two hours. The mixture was cooled to room temperature and the precipitate collected by filtration. It weighed 6.9 g. and melted at 181-184°C. The material was treated with 55 ml. of 2N hydrochloric acid and warmed on a steam bath at 50-60°C. for fifteen minutes. The hot mixture was filtered and the filtrate cooled to room temperature and adjusted to a pH of 6 with concentrated ammonium hydroxide. The tetrazole crystallized from the solution and was collected by filtration, washed with 25 ml. of cold water and dried at 120°C. for six hours. The yield of tetrazole was 3.9 g. (95%), m.p. 264-268°C. with decomposition, $[\alpha]^{25}_{578}$ = +37.0°, C = 0.654 in H_2O. The infrared spectrum was nearly identical to that of D,L-5-(α-amino-B-phenylethyl)tetrazole.

D'Orazio (1) reported a melting point of 287° with decomposition, $[\alpha]^{25}_{D}$ = +38°, C = 0.945 in H_2O for the tetrazole.

Calculated for $C_9H_{11}N_5$:	C, 57.12; H, 5.86; N, 37.02.
Found:	C, 57.40; H, 5.71; N, 35.40.

III. The Degradative Benzoylation of D,L-5-(α-Amino-B-phenylethyl)Tetrazole.

A. D,L-2-(1'-Benzamido-2'-phenylethyl)-5-phenyl-1,3,4-oxadiazole.

1) In a 100 ml. round-bottomed, single necked flask equipped with a reflux condenser and heating mantle were placed 3 g. (0.016 mole) of D,L-5-(α-amino-B-phenylethyl)-tetrazole, 4.9 g. (0.035 mole) of benzoyl chloride, 5.53 g. (0.07 mole) of pyridine and 30 ml. of anhydrous benzene. The mixture was refluxed three hours and the benzene evaporated under reduced pressure. The crude residue was recrystallized for 50 ml. of absolute ethanol. The oxadiazole weighed 4.66 g. (80% yield), m.p. 171-172°C. The infrared spectrum was consistent with the proposed structure.

D'Orazio (1) reported a melting point of 167.5-168°C. for the oxadiazole.

2) In the above mentioned apparatus were placed 3 g. (0.016 mole) of D,L-5-(α-amino-B-phenylethyl)tetrazole,

4.9 g. (0.035 mole) of benzoyl chloride, 2.8 g. (0.035 mole) of pyridine and 30 ml. of anhydrous benzene. The mixture was refluxed three hours and the benzene evaporated under reduced pressure. The crude residue was recrystallized from 50 ml. of absolute ethanol. The yield of oxadiazole was 4.42 g. (75%), m.p. 169-171°C. The infrared spectrum was identical with the infrared spectrum of the product obtained by procedure (1).

IV. Hydrolysis of D,L-2-(1'-Benzamido-2'-phenylethyl)-5-phenyl-1,3,4-oxadiazole.

In a 100 ml. round-bottomed, single necked flask equipped with a reflux condenser and heating mantle were placed 3 g. (0.0081 mole) of D,L-2-(1'-benzamido-2'-phenylethyl)-5-phenyl-1,3,4-oxadiazole and 50 ml. of 6M hydrochloric acid. The mixture was heated at reflux temperature for three hours during which the oxadiazole dissolved. The clear solution was cooled to 0°C. in an ice bath with precipitation. The precipitate of benzoic acid was collected by filtration. The benzoic acid weighed 1.93 g. (97% of theory), m.p. 120-122°C. A mixture melting point with an authentic sample of benzoic acid showed no depression.

The filtrate was evaporated under reduced pressure and the residue dissolved in 20 ml. of water. The solution was neutralized with concentrated ammonium hydroxide to a pH of 7. The mixture was allowed to stand at 38-40°C. for four hours. The product that separated was collected by filtration and dried in an oven at 120°C. for four hours. The product weighed 1 g. (74% yield), m.p. 290-293°C. with decomposition; its infrared spectrum was identical with that of D,L-phenylalanine.

D'Orazio (1) reported a melting of 310-314°C. for D,L-phenylalanine.

In a similar experiment using 50 ml. of 3M hydrochloric acid at reflux temperature for six hours the oxadiazole failed to hydrolyze.

V. The Degradative Benzoylation of L-5-(α-Amino-B-phenylethyl)tetrazole.

A. L-2-(1'-Benzamido-2'-phenylethyl)-5-phenyl-1,3,4-oxadiazole.

In a 100 ml. round-bottomed, single necked flask equipped with a reflux condenser and heating mantle were placed 3 g. (0.016 mole) of L-5-(α-amino-B-phenylethyl)-tetrazole, 4.9 g. (0.035 mole) of benzoyl chloride, 2.8 g. (0.035 mole) of pyridine and 30 ml. of anhydrous benzene. The mixture was refluxed three hours and the benzene evaporated under reduced pressure. The crude residue was recrystallized from 50 ml. of absolute ethanol. The product weighed 4.13 g. (70% yield), m.p. 186-188°C., $[\alpha]^{25}_{578} = -15.5°$, C = 2.033 in chloroform. The infrared spectrum was identical to that of D,L-2-(1'-benzamido-2'-phenylethyl)-5-phenyl-1,3,4-oxadiazole.

D'Orazio (1) reported a melting point of 191-192°C.,

$[\alpha]_D^{25}$ = -14.9°, C = 5.0 in chloroform for this product.

VI. Hydrolysis of L-2-(1'-Benzamido-2'-phenylethyl)-5-phenyl-1,3,4-oxadiazole.

In a 100 ml. round-bottomed, single necked flask equipped with a reflux condenser and heating mantle were placed 2 g. (0.0054 mole) of L-2-(1'-benzamido-2'-phenylethyl)-5-phenyl-1,3,4-oxadiazole and 50 ml. of 6M hydrochloric acid. The mixture was heated at reflux temperature for three hours. The resulting clear solution was cooled to room temperature and filtered. The white crystalline material that separated weighed 1.3 g. (99% of theory), m.p. 119-120°C. A mixture melting point with an authentic sample of benzoic acid showed no depression.

The filtrate was evaporated under reduced pressure. The crude residue was dissolved in 15 ml. of water and the solution neutralized to a pH of 6 with concentrated ammonium hydroxide. The mixture was allowed to stand at 38-40°C. for sixteen hours. The solid that had separated was filtered off and dried at 120°C. for four hours. The yield of product was 0.7 g. (77%), m.p. 284-289°C. with decomposition, $[\alpha]_{578}^{25}$ = -3.8°, C = 1.063 in H_2O. The infrared spectrum was identical with that of L-phenylalanine.

D'Orazio (1) reported a melting point of 254°C. with decomposition, $[\alpha]_D^{24}$ = -4.1°, C = 1.096 in H_2O for phenylalanine recovered from a similar series of reactions.

VII. The Degradative Benzoylation of L-5-(α-Phthalimido-B-phenylethyl)tetrazole.

L-2-(1'-Phthalimido-2'-phenylethyl)-5-phenyl-1,3,4-oxadiazole.

In a 100 ml. round-bottomed, single necked flask equipped with a reflux condenser and heating mantle were placed 5.1 g. (0.016 mole) of L-5-(α-phthalimido-B-phenylethyl)tetrazole, 2.5 g. (0.018 mole) of benzoyl chloride, 1.4 g. (0.018 mole) of pyridine and 50 ml. of anhydrous benzene. The mixture was heated at reflux temperature for three hours after which the benzene was evaporated under reduced pressure. The residue was taken up in 100 ml. of absolute ethanol. The product did not crystallize from solution. When diluted with 150 ml. of water an amorphous yellow solid precipitated. The ethanol-water solution was decanted and the yellow residue taken up in 50 ml. of acetone which was subsequently diluted with 50 ml. of water. A colorless crystalline material precipitated. The yield of oxadiazole was 3.1 g. (50%), m.p. 103-105°C., $[\alpha]^{25}_{578} = -137.8°$, C = 2.105 in absolute ethanol. The infrared spectrum was consistent with the proposed structure.

Analysis.

Calculated for $C_{24}H_{17}N_3O_3$: C, 72.1; H, 4.3; N, 10.6.

Found: C, 72.6; H, 4.5; N, 11.0.

VIII. Hydrolysis of L-2-(1'-Phthalimido-2'-phenylethyl)-5-phenyl-1,3,4-oxadiazole.

In a 100 ml. round-bottomed, single necked flask equipped with a reflux condenser and heating mantle were placed 2.5 g. (0.0064 mole) of L-2-(1'-phthalimido-2'-phenylethyl)-5-phenyl-1,3,4-oxadiazole and 35 ml. of 6M hydrochloric acid. The mixture was refluxed two hours with initial dissolution and slight precipitation at the end of the two hours. The reaction mixture was cooled to room temperature and filtered. The white solid product was dissolved in 25 ml. of absolute ethanol and diluted with 25 ml. of water. There was no crystallization after forty-eight hours. The volume was reduced fifty percent by evaporation and a colorless solid crystallized from solution. The product was collected by filtration and dried in an oven at 120°C. for four hours. The product weighed 1.3 g. (69% yield), m.p. 179-183°C., $[\alpha]^{25}_{578} = -76.2°$, C = 2.388 in absolute ethanol. The infrared spectrum was identical with that of L-α-phthalimido-B-phenylpropionic acid.

Evaporation to dryness of the filtrate gave 1.2 g. (93% of theory) of benzoic acid, m.p. 122-123°C. A mixture melting point with an authentic sample showed no depression.

IX. Synthesis of L-5-(α-Phthalimido-B-phenylethyl)tetrazole from L-5-(α-Amino-B-phenylethyl)tetrazole.

In a 100 ml. round-bottomed, three-necked flask equipped with a reflux condenser and stirrer were placed 1.6 g. (0.0084 mole) of finely ground L-5-(α-amino-B-phenylethyl)tetrazole and 1.2 g. (0.0084 mole) of finely ground phthalic anhydride. The mixture was stirred and immersed in an oil bath heated to 145°C. for one hour. The cooled melt was treated with 20 ml. of hot methanol, filtered and the filtrate diluted with 20 ml. of hot water. The product crystallized upon cooling and weighed 2.2 g. (80% yield), m.p. 185-187°C., $[\alpha]_{578}^{25} = -208.2°$, $C = 3.049$ in absolute ethanol. The infrared spectrum was identical with that of the original L-5-(α-phthalimido-B-phenylethyl)-tetrazole.

X. Specific Rotations of L-Phenylalanine and Its Tetrazole Analog in Various Concentrations of Acid and Base[1].

A. L-Phenylalanine.

Samples of L-phenylalanine[2] were dissolved in solutions containing 0.5, 1.0, 2.0 and 4.0 molar equivalents of sodium hydroxide or hydrochloric acid and the rotation of the solutions measured. The specific rotations calculated for each concentration of acid and base are given in Table I.

B. L-5-(α-Amino-B-phenylethyl)tetrazole.

The compound was prepared from L-phenylalanine[2] by the procedure outlined in Figure I. Samples of L-5-(α-amino-B-phenylethyl)tetrazole were dissolved in aqueous solutions

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[1] All measurements were carried out in a Zeiss Photoelectric Polarimeter using a 1 dm. tube and wavelength of 578 mu at 25°C.

[2] Nutritional Biochemicals Corporation.

containing 0.5, 1.0, 2.0 and 4.0 molar equivalents of sodium hydroxide or hydrochloric acid and the rotation of the solutions measured. The specific rotations calculated for each concentration of acid and base are given in Table II.

TABLE I

Specific Rotations of L-Phenylalanine in NaOH and HCl using 0.5M and 1.0M Solutions of NaOH and HCl at 25°C. The total volume of solutions were 10 ml.

Molar Ratio of HCl or NaOH to Amino Acid	Weight of Amino Acid in Grams	ml. of Acid or Base	α	$[\alpha]^{25}_{578}$
---	0.1987		-0.67	-33.7
0.5	0.2046	1.25 (0.5M HCl)	-0.44	-21.5
1.0	0.2064	2.50 (0.5M HCl)	-0.27	-13.1
2.0	0.2056	5.00 (0.5M HCl)	-0.20	- 9.7
4.0	0.2075	5.00 (1.0M HCl)	-0.18	- 8.6
0.5	0.2056	1.25 (0.5M NaOH)	-0.37	-18.0
1.0	0.2064	2.50 (0.5M NaOH)	-0.08	- 3.9
2.0	0.2059	5.00 (0.5M NaOH)	-0.01	- 0.5
4.0	0.2066	5.00 (1.0M NaOH)	-0.015	- 0.7

TABLE II

Specific Rotations of L-5-(α-Amino-B-phenylethyl)tetrazole in NaOH and HCl using 0.25M and 0.5M solutions of NaOH and HCl at 25°C. The total volume of solutions were 10 ml.

Molar Ratio of HCl or NaOH to Tetrazole	Weight of Tetrazole in Grams	ml. of Acid or Base	α	$[\alpha]_{578}^{25}$
---	0.0910		+0.335	+37.0
0.5	0.1093	1.25 (0.25M HCl)	+0.35	+32.0
1.0	0.1093	2.50 (0.25M HCl)	+0.31	+28.7
2.0	0.1005	5.00 (0.25M HCl)	+0.285	+28.3
4.0	0.1055	5.00 (0.50M HCl)	+0.29	+27.5
0.5	0.1069	1.25 (0.25M NaOH)	+0.28	+26.2
1.0	0.1008	2.50 (0.25M NaOH)	+0.175	+17.3
2.0	0.1091	5.00 (0.25M NaOH)	+0.195	+17.9
4.0	0.1051	5.00 (0.50M NaOH)	+0.175	+16.6

SUMMARY

1. The tetrazole analogs of D,L-phenylalanine and L-phenylalanine have been synthesized.

2. The method of Lutz and Jirgensons (12,13) for determining the optical configuration of amino acids has shown L-phenylalanine to be characteristic of the L-antipode. This method when applied to L-5-(α-amino-B-phenylethyl)tetrazole does not appear to be valid.

3. The degradative benzoylation of L-5-(α-amino-B-phenylethyl)tetrazole gave the L-phenylalanine with the same sign of rotation as the starting amino acid but with a greatly reduced magnitude of rotation.

4. A similar degradative benzoylation of L-5-(α-phthalimido-B-phenylethyl)tetrazole gave the L-α-phthalimido-B-phenylpropionic acid with the same rotation as the starting intermediate but with a greatly reduced magnitude of rotation.

5. The L-5-(α-amino-B-phenylethyl)tetrazole was converted to the phthalimido derivative by fusion with phthalic anhydride without loss of rotation.

6. A mechanism has been proposed to explain the racemization occurring in the degradative benzoylation of optically active tetrazole derivatives.

7. The infrared spectra of L-α-phthalimido-B-phenylpropionic acid, L-α-phthalimido-B-phenylpropionyl chloride, L-α-phthalimido-B-phenylpropionamide, L-α-phthalimido-B-phenylpropionitrile, L-5-(α-phthalimido-B-

phenylethyl)tetrazole, L-5-(α-amino-phenylethyl)tetrazole, L-2-(1'-benzamido-2'-phenylethyl)-5-phenyl-1,3,4-oxadiazole and L-2-(1'-phthalimido-2'-phenylethyl)-5-phenyl-1,3,4-oxadiazole are reported.

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FIGURE I
Specific Rotation of L-Phenylalanine

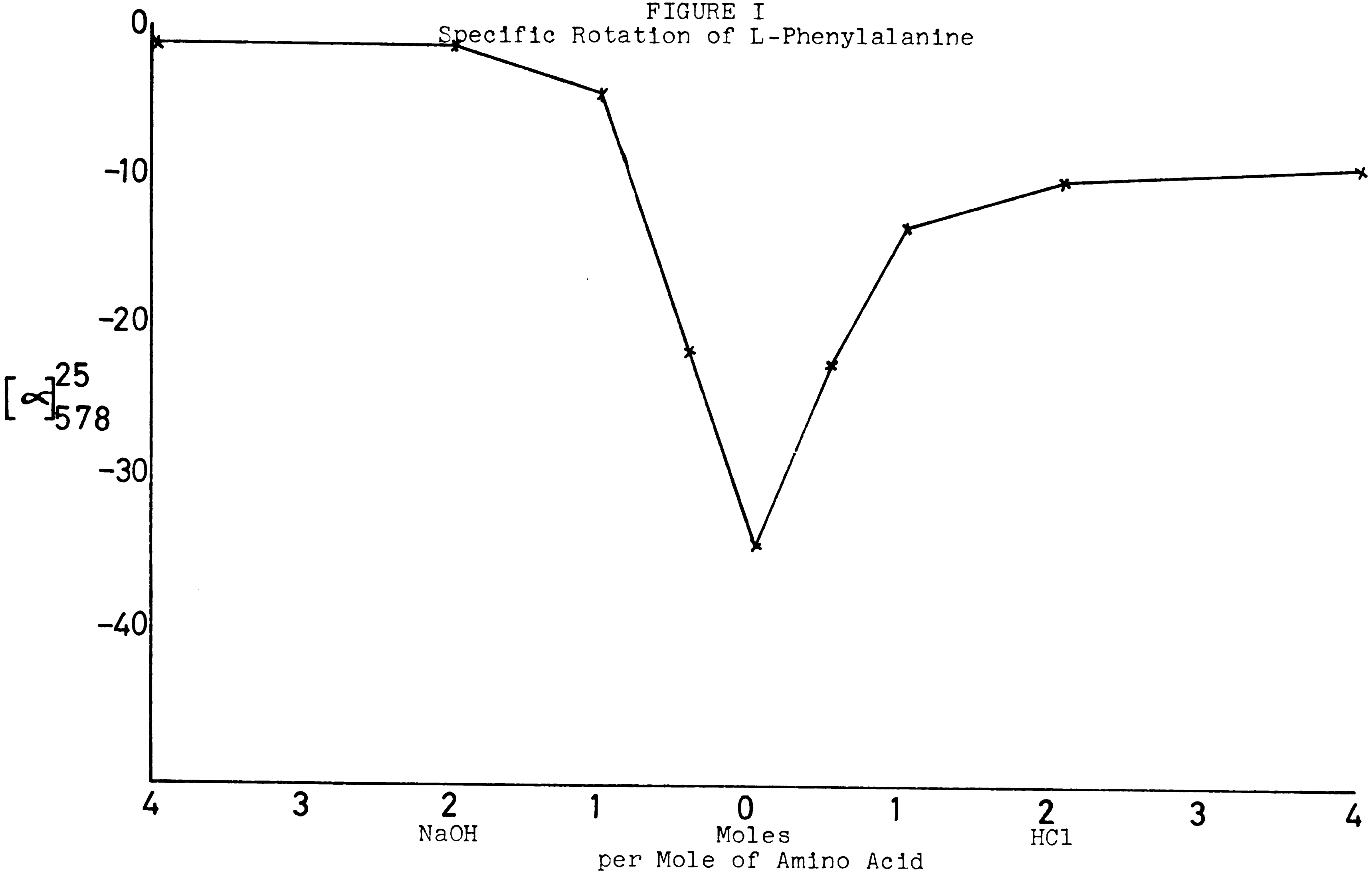

FIGURE II
Specific Rotation of L-5-(α-Amino-B-phenylethyl)tetrazole

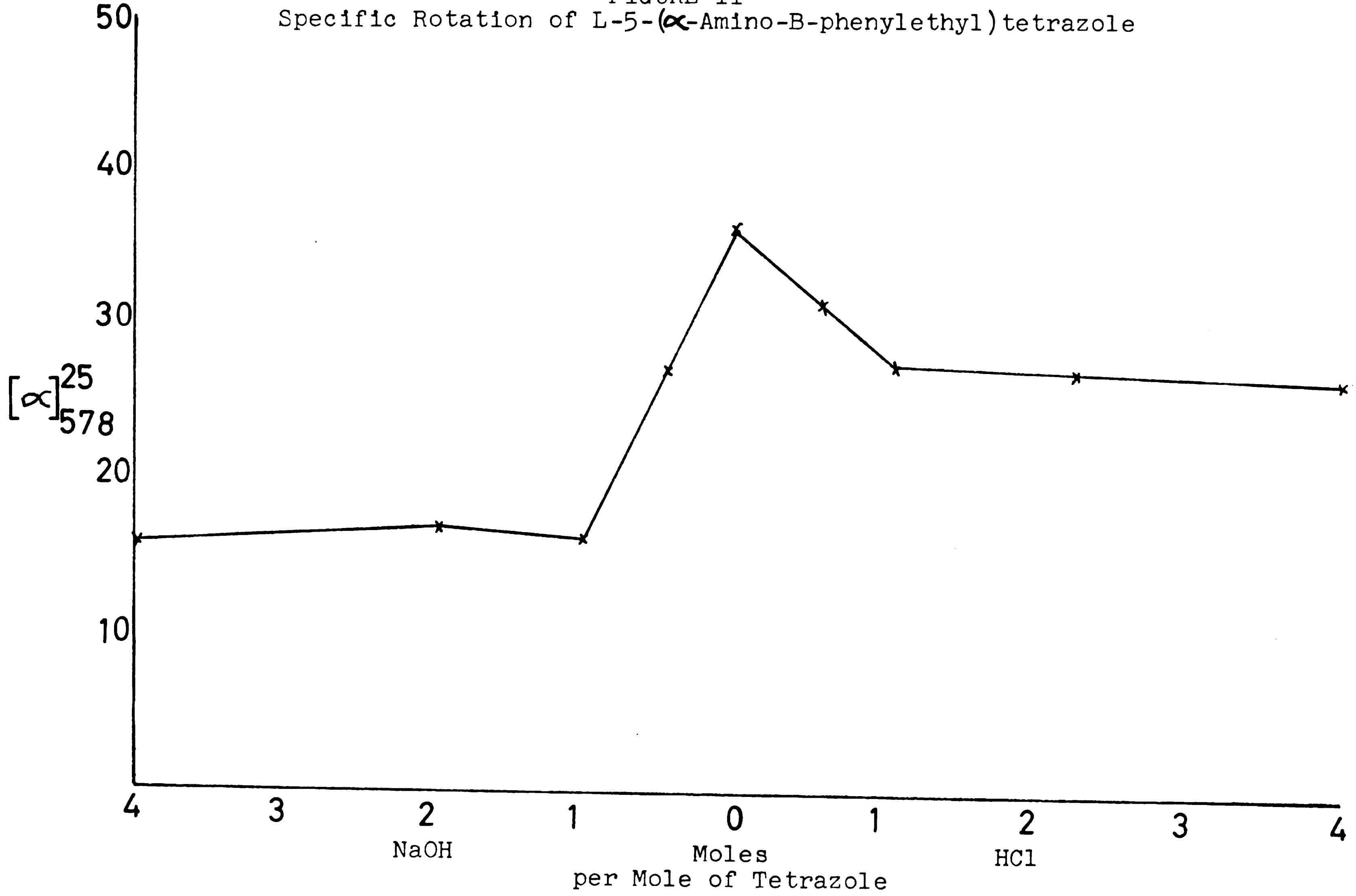

FIGURE III
Infrared Spectrum of D,L-Phenylalanine

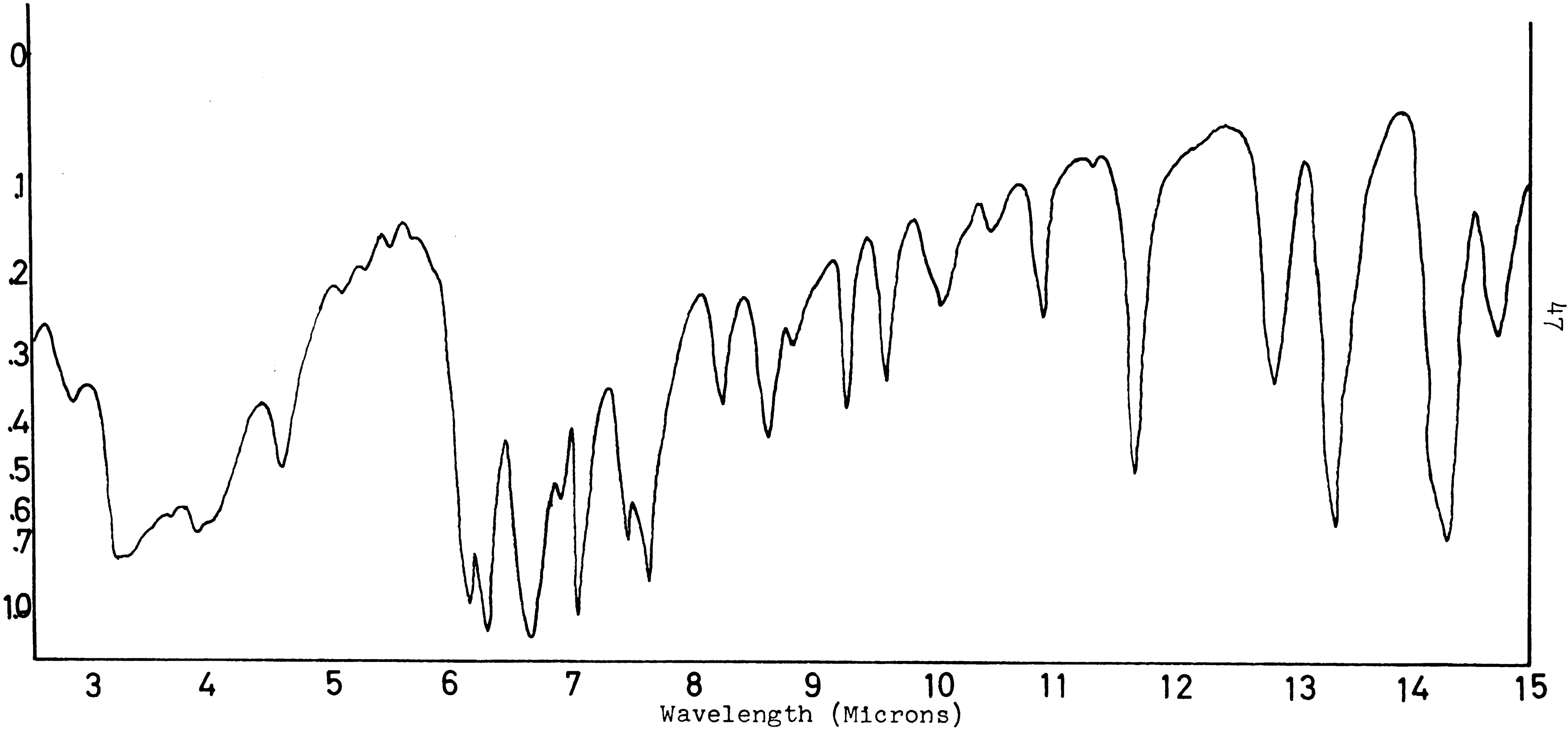

FIGURE V
Infrared Spectrum of L-α-Phthalimido-B-phenylpropionyl Chloride

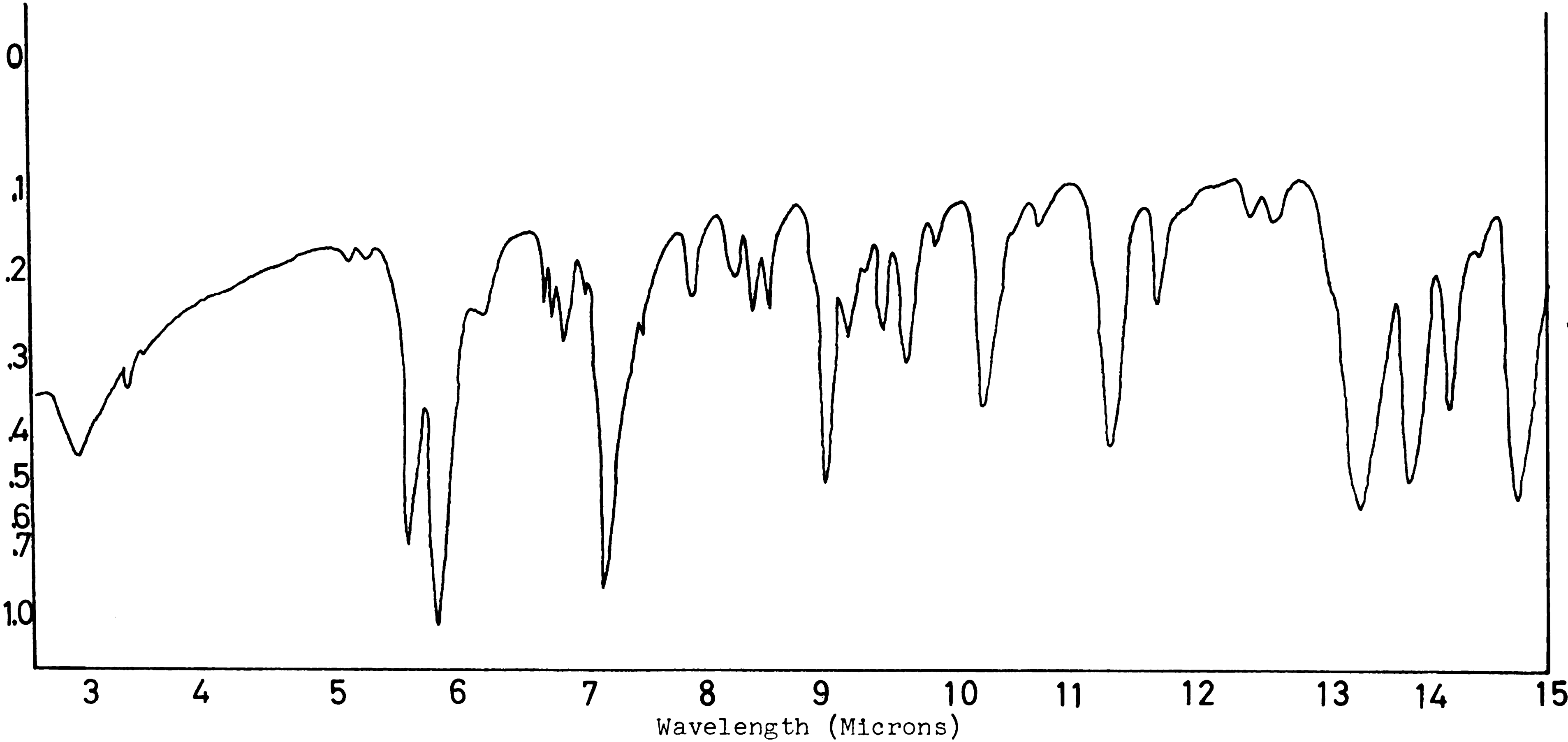

FIGURE VIII
Infrared Spectrum of L-5-(α-Phthalimido-B-phenylethyl)tetrazole

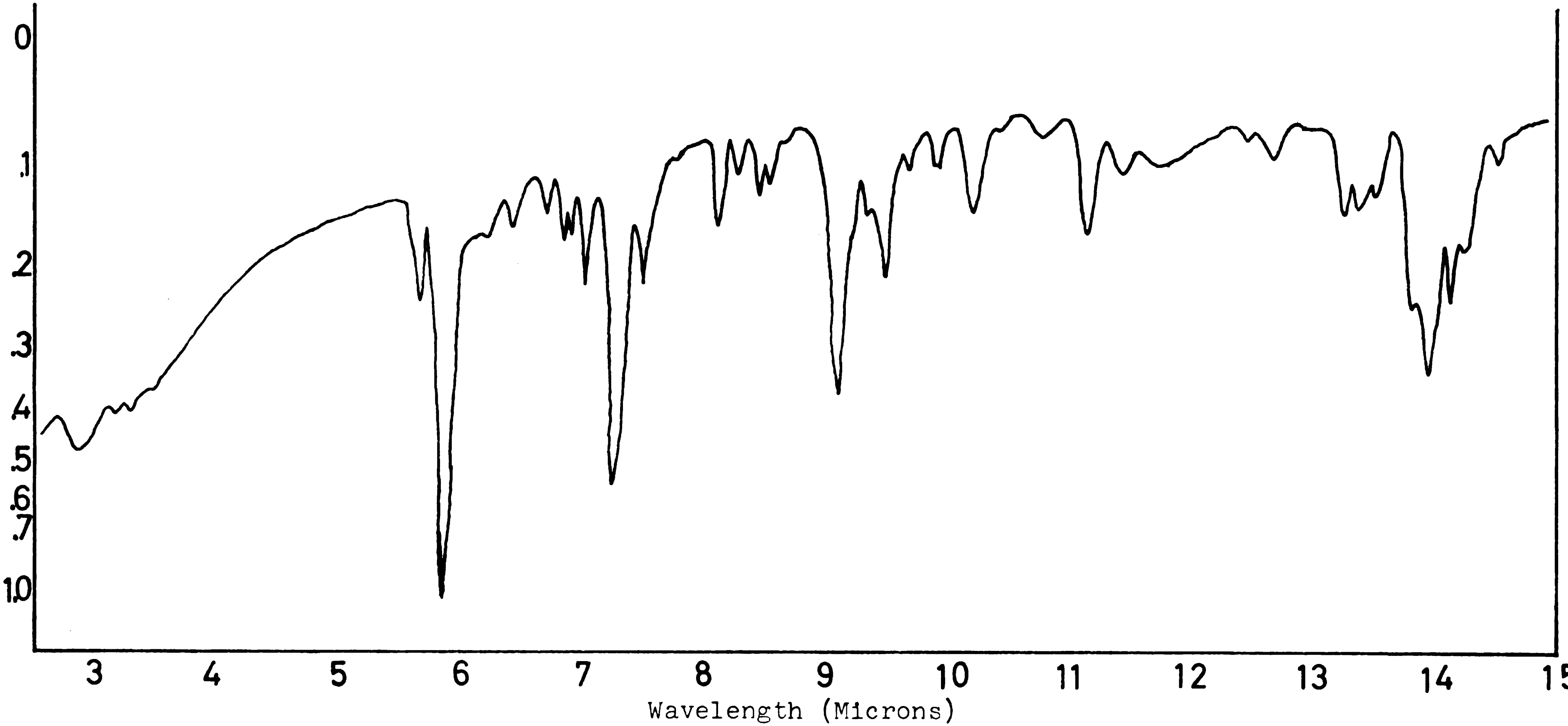

FIGURE IX
Infrared Spectrum of L-5-(α-Amino-B-phenylethyl)tetrazole

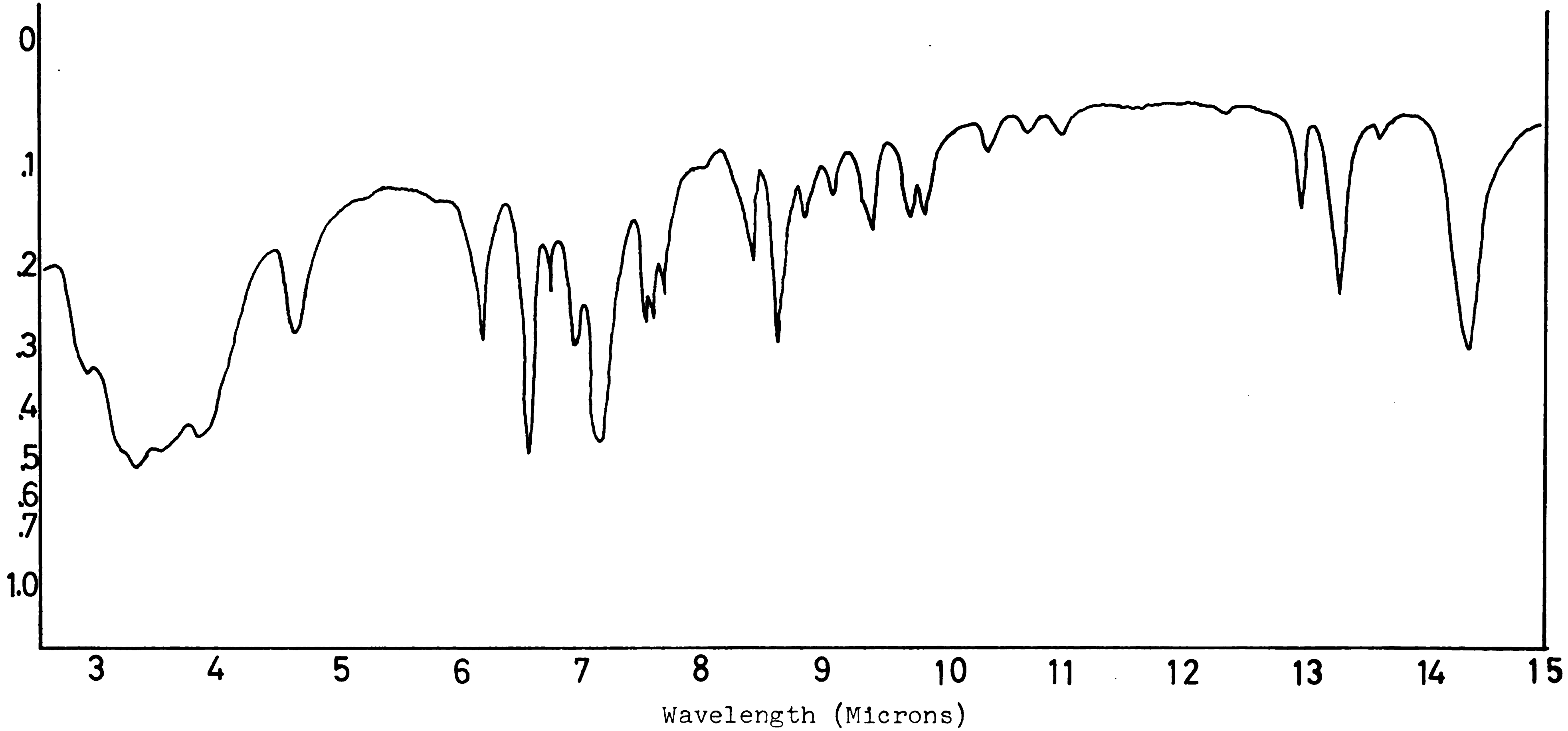

FIGURE X
Infrared Spectrum of L-2-(1'-Benzamido-2'-phenylethyl)-5-phenyl-1,3,4-oxadiazole